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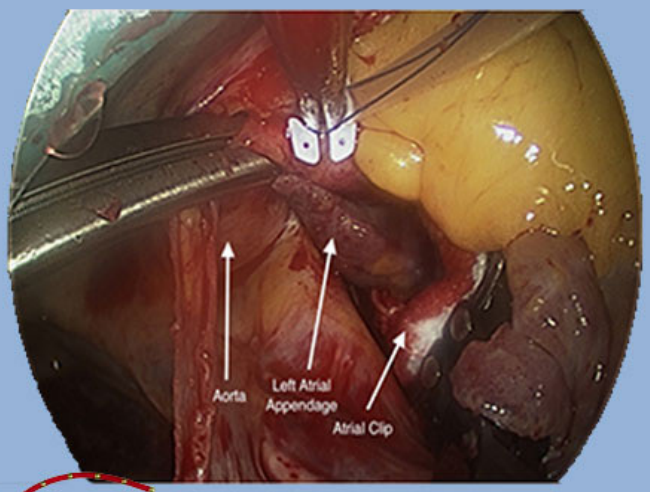

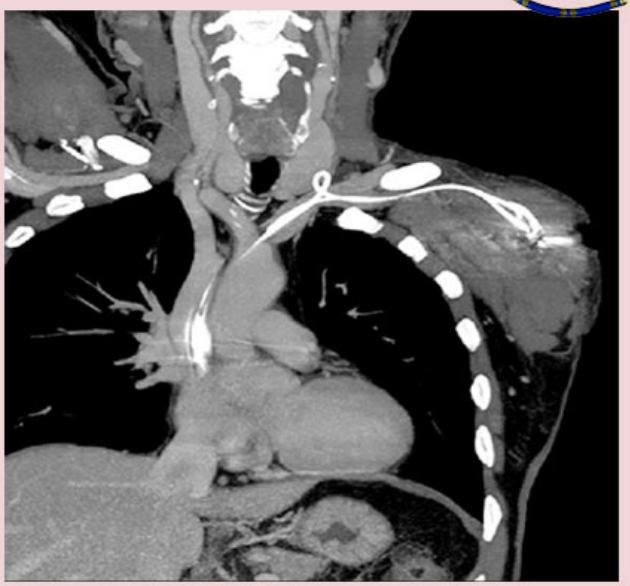

Meet the Expert Doctor

Dr. Jonathan Kalman, MD

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Editorial

Journal of Atrial Fibrillation

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Quality measures in Atrial Fibrillation therapy – AF ablation and Get with the Guidelines AFIB registries

Dear Colleagues

Welcome to the summer issue of JAFIB. Hope everyone had a chance to enjoy the season and related travels. As MACRA and Pay for Performance continue to evolve to be the guiding force on physician reimbursement, quality becomes an important piece we need to focus on. It doesn't mean that we are not providing quality care to our patients now, but we need a special effort to document our quality work through various registries and quality bench marks. AF ablation has become an important area of focus for all the professional societies including HRS, ACC and AHA. One such effort is the recently released NCDR's AFib registry. It's relatively comprehensive dataset that attempts to track outcomes and quality in a systematic way. Eventhough, it may not be very extensive and lead to long term follow up, it is a good start.

The Heart Rhythm Society recently announced their collaboration with the American Heart Association on the Get with the Guidelines®- AFIB Registry. Get With The Guidelines®-AFIB is apparently designed to assist hospital care teams for providing the latest evidence-based treatment for their AFib patients. At the same time, it is supposed to offer a means of monitoring the quality of AFib care in U.S. hospitals and building a database for continued research and further quality improvement. There is not much debate that these efforts help improve patient care and are a proven platform for improving outcomes but at what cost to the hospitals and physicians.

In a practicing environment that places a significant burden of documentation on physicians this once again adds a great deal of work. It doesn't mean we should not embrace this important initiative, what it means is we should figure out a smart and efficient way of gathering this data. This is where effective physician-hospital partnerships are critical to the success of these programs. Typically depending on the volume of AF patients each institution cares for, it may require one or two FTEs to handle the work load and the hospitals should get ready in bringing additional resources to implement these programs. On the other hand the professional societies should make a continued effort to make these registries as less cumbersome and more meaningful for patient care as possible. There should be continued opportunities in improving the education and awareness in AF.

We continue to encourage you to submit your original research, literature reviews, state-of-the-art papers, case reports, meta analyses to the journal for consideration of publication. We assure you a faster turn around and reasonable time line for publication.

Have a great summer.
Best wishes

Dhanunjaya (DJ)Lakkireddy
MD, FACC, FHRS
Associate-Editor, JAFIB

Andrea Natale
MD, FACC, FHRS, FESC
Editor-in-Chief, JAFIB

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Safety And Necessity Of Thermal Esophageal Probes During Radiofrequency Ablation For The Treatment Of Atrial Fibrillation

Antonio Fasano, Prof Emeritus, , Luca Anfuso, MD, Stefano. Bozzi, MD, Claudio Pandozi, Prof

San Filippo Neri Hospital, Rome, Italy.

Abstract

Backbround Radiofrequency ablation is extensively used to achieve pulmonary veins isolation for the cure of atrial fibrillation. Luminal esophageal temperature can be monitored by means of suitable probes to prevent the onset of lesions.

Objective: To compute the thermal field generated by the ablation, to investigate the interaction between the electromagnetic field and the probe sensors, and to provide a safe interpretation of the temperature detected by the probe, supported by clinical data.

Methods: A mathematical model is formulated and the thermal and electromagnetic fields are computed. Experiments have been performed to assess the the influence of the ablator on the probe sensors. Clinical data have been collected during RF isolation of pulmonary veins in patients with atrial fibrillation.

Results: The direct interaction between the radiofrequency source and the probe sensors is found to be negligible. Numerical simulations show that the outer esophageal wall can be much warmer than the lumen. Theoretical heating curves are compared with the clinical data selecting the maximal slope as the reference quantity. The clinical values range between 0.01°C/s and 0.15°C/s agree with the computed predictions and demonstrate that reducing the esophagus-atrium distance by 1mm causes a slope increase of 0.06°C/s.

Conclusion: The use of esophageal thermal probes is absolutely safe and necessary in order to prevent the occurrence of thermal lesions. The model is reliable, and describes effectively the generated thermal field. The external esophageal temperature can be considerably higher than the luminal one.

Introduction

Radio Frequency Ablation (RFA) for Pulmonary Veins Isolation (PVI) is a largely applied procedure for the cure of Atrial Fibrillation (AF). It is well known that radio frequency (RF) can produce Esophageal Thermal Lesions (ETLs), from mild forms, to intramural hematomas, or ulcerations which can be asymptomatic or hemorrhagic and in some rare cases (e.g. atrial esophageal fistulae) can have lethal consequences. Altogether ETL incidence is slightly below 20%.[1,2] Documentation of fistulae occurrence is relatively abundant.[3,4,5,6,7,8] A detailed analysis of complications connected to RFA can be found in the reports[9,10,11] and frequency of complications in the overviews.[12,13,4,15] The Luminal Esophageal Temperature (LET) increase is usually very modest, but temperatures well beyond 40°C, which can occur when the esophagus-heart distance is reduced, can represent a serious risk.[16] A correlation of LET and measured distance between esophagus and the ablated PVs has previously been reported[17] and several papers[18,19] illustrate the esophagus anatomy and its implications on RFA.

The complexity of this framework confirms that LET monitoring, which offers the possibility of switching off power supply if temperature exceeds a safety threshold, is of crucial importance. Here we are going to discuss various aspects related to the thermal field generated during RF- PVI procedures based on numerical simulations and of experimental data.

The fact that during RFA only a relatively small LET variation is normally expected has somehow suggested that LET measurements can be optional. Somebody has even conjectured that esophageal thermal probes may contribute to the formation of ETLs[20] because of power absorption by the metallic sensors. On the contrary, recent papers[21,17] emphasize the importance of LET measurement.

In the sequel we will illustrate an experiment showing that the steel rings of a temperature esophageal probe do not catch any sizeable power, confirming the theoretical result of a recent paper.[22] In any case, it must be remembered that the thermal sensors measure their own temperature, thus signaling any alarming situation, independently of its cause.

Next we shall use a mathematical model in order to compute the thermal field during a typical RF ablation for PVI and we provide some clinical data collected during RFA to support the conclusions based on the model. Our main intention is not only to furnish

Key Words:
Atrial Fibrillation, Esophageal Lesions, Esophageal Temperature Monitoring, Atrial Fibrillation Ablation.

Disclosures:
Antonio Fasano is Scientific and R&D Manager at FIAB, Italy (Sensitherm/Esotherm manufacturer), Stefano Bozzi and Luca Anfuso are senior researchers at FIAB, Italy.

Corresponding Author:
Claudio Pandozi,
San Filippo Neri Hospital,
Rome, Italy.

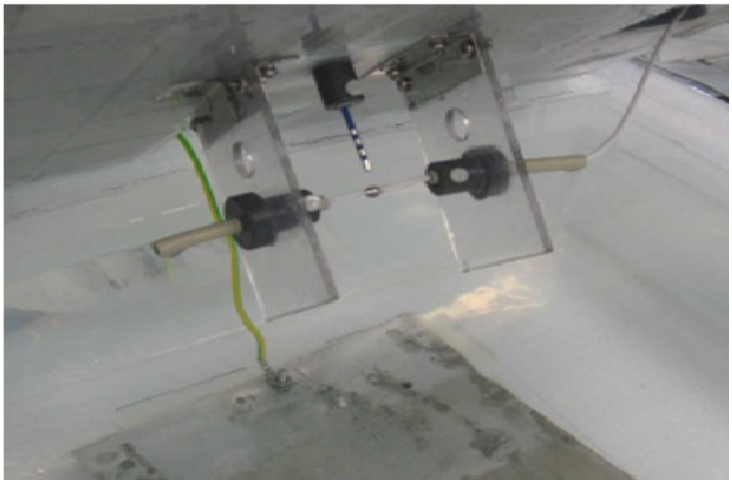

Figure 1: Apparatus for direct exposure of the sensor to the RF field

further scientific justification of the fact that esophageal thermal probes are totally harmless, but that they are an absolutely necessary tool to prevent esophageal lesions, as largely confirmed by clinical practise.[23,24,25] In addition we will point out that LET measurements have to be correctly interpreted by the clinicians in order to determine a really safe switch off temperature.

Methods

Exposing Metallic Sensors To RF Sources

The following experiment has been performed at FIAB Laboratories. A RF ablator was placed in a slowly stirred saline solution (1.9%) kept at 38°C and it was set to deliver a power of 50W. A movable frame was placed in front of it (Figure 1), bearing (in three different sets of experiments)

- a thermocouple
- a thermocouple welded to a steel ring (as in the Esotherm probe)
- the same element coated with a 30 μm thick Teflon layer

In each experiment the temperature was recorded at the following distances (mm) 10, 5, 4, 3, 2, 1 for an exposure of 1 min (preceded and followed by a 30 second pause). The outcome is illustrated in the Results section.

Mathematical Model

Already in the mathematical model developed in previous papers,[26,27] with no esophageal probe, it was recognized that a rather rough geometrical representation of the interested domain was

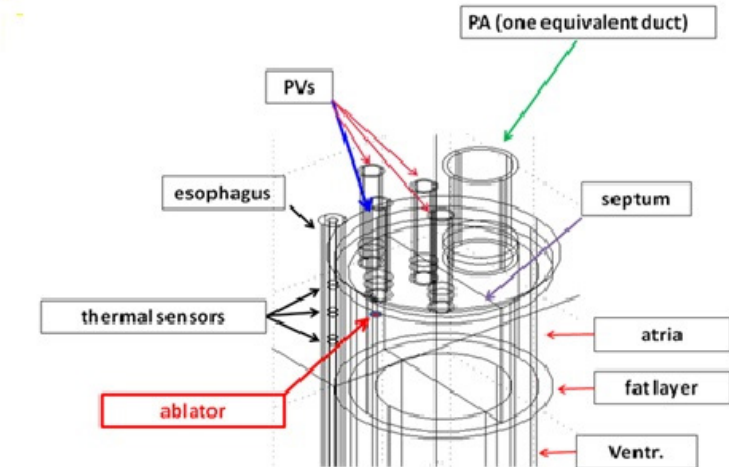

Figure 2: Detail of the computational domain showing the thermal sensors and the ablator

Table 1: Thermal and electrical coefficients (from [26])

	ρ (density) (kg m−3)	c (spec. heat) (J kg^{-1} K^{-1})	k (therm. cond.) (W m^{-1} K^{-1})	σ (electrical conductivity) (S/m)
Steel (sensors)	8000	480	15	7.4E+6
Esophagus	1000	3700	0.4	0.61
Connective	1000	3200	0.4	0.61
Fat	900	2200	0.2	0.02
Heart	1200	3200	0.7	0.61
Blood	1000	4180	0.54	0.99

sufficient to compute the thermal field during RFA within a reasonable approximation. In particular it is not necessary to reproduce the actual organs shape, nor the pulsatile nature of blood flow. Here too we take a naive scheme as follows (Figure 2): the heart is a four-chamber immobile cylinder (external diameter 80mm), longitudinally divided by a septum of negligible thickness, impervious to blood and perfectly transmitting heat. Ventricles (internal height 70mm) are thicker than atria (internal height 50mm): we took respective thickness of 15mm, 3 mm. We must stress that the choice of the latter values is not critical (as pointed out in[26]), unless reducing the atrial thickness is accompanied by a reduction of the esophagus-electrode distance. [28,29] The whole cylinder is coated by a fat layer (1mm thick). Blood flows freely and with constant cross sectional discharge in each atrium-ventricle pair (no valves). Four vessels enter the left atrium (with the average size of PVs), while all other chambers are connected with just one efferent or afferent pipe. Esophagus is sketched as a cylinder parallel to the heart (thickness 2.5mm) with the lumen occupied by a 4 mm diameter probe (the probe is actually thinner, and 4mm is slightly exceeding the diameter of the steel rings, still with the idea of deriving a conservative estimate of the power absorbed by the rings). The presence of the probe has been disregarded in other papers, but millimeters here do matter, as we shall see. In particular we plan to check the behavior of electric and thermal fields on the probe steel sensors. The distance between the outer esophagus wall and the fat coating is 3mm.The intermediate region is occupied by connective tissue, the surrounding domain has the form of a square box (20cm side) whose vertical axis coincides with the esophagus generatrix closest to the heart. Our cylindrical heart has equal distances from the top and the bottom face of the cube. Such a geometry is sketched in Figure 2. One of the PVs is placed so to face the esophagus and we examine the case in which the RF source is located there, in order to consider the most critical case for the possible occurrence of ETL. The thermal and electrical properties of the various elements are listed in Table 1.

For our purposes Pennes' equation

$$\rho c \frac{\partial T}{\partial t} - k\Delta T = \rho_b c_b \omega (T_b - T) + Q \quad (1)$$

is certainly appropriate to describe heat transfer. Here T is temperature, ρ is density, c the specific heat. The subscript b refers to blood. In the present context, since the expected temperature range is not very large, the perfusion coefficient ω can be taken constant in each tissue, according to Table 2.

Table 2: Perfusion rate (sec-1) ω for various tissues[30]

Heart	Fat	Connective	Esophagus
0.017	$5.5.10^{-4}$	6.10^{-4}	3.10^{-3}

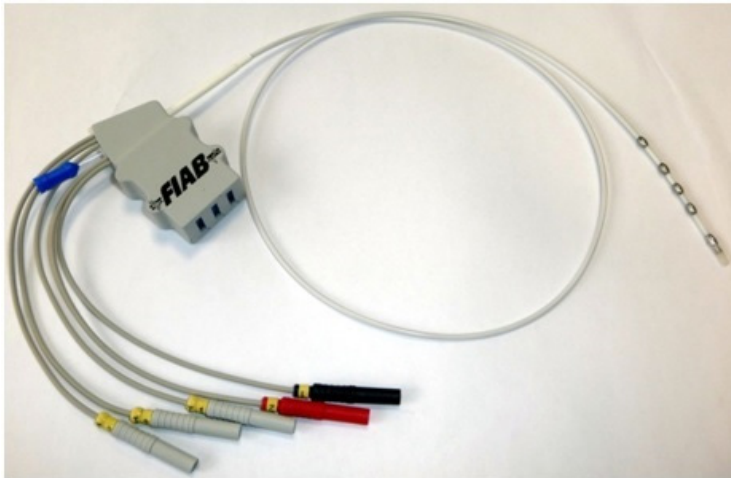

Figure 3: The probe Esotherm/Sensitherm (FIAB, Italy)

The source term Q expresses power deposition from electromagnetic field, while metabolic heat supply rate can be neglected.

Heat flux continuity is taken at the interface between different tissues. At the external boundary a no flux condition is imposed (as a compensation to the fact that metabolic heat has been ignored). Concerning the electric field there is a large agreement in the literature that the quasi-steady approximation is largely justified, since the typical RF wavelength is of the order of one kilometer. Accordingly, the electric potential V is assumed to satisfy Laplace's equation

(2) $\Delta V = 0$

with continuity of the normal derivative at interfaces, and the condition V = 0 imposed on the dispersive electrode, identified with the cube face opposite to the heart with respect to the esophagus (so that the electric field is driven towards the esophageal region). A zero current condition is imposed on the other faces. The electric field is $\bar{E} = -\nabla V$, the current density is $\sigma \bar{E}$ (σ is the electric conductivity, depending on the material), and the deposited power per unit volume in equation (1) is $Q = {}^1/_2 \sigma E^2$.

Clinical Procedures

In this study we enrolled 14 patients scheduled for RF catheter ablation of symptomatic, paroxysmal or persistent AF. Transesophageal echocardiography was performed within 48 hours before the ablation procedure to rule out left atrial thrombi in every patient. AF ablation was monitored by LET in every patient. Written informed consent was obtained from all patients included in the study. Irrigated-tip radiofrequency ablation was performed with the CARTO 3 (BiosenseWebster, DiamondBar,CA) electroanatomic mapping system with a ThermoCool catheter (Biosense Webster). All left atrial ablation procedures were performed with the patient in sedation using propofol infusion and via single transseptal access to the left atrium. A shell of the left atrium was created and isolation of the ipsilateral pulmonary veins was performed using a point-by-point method. The activated clotting time was maintained between 250 and 300 seconds during all the procedure. Additional ablations were performed at the discretion of the operator, with a maximum of 35W and a maximum irrigation rate of 30 mL/min. Maximal energy delivery at the posterior wall was reduced to 25 W. To monitor LET, an intraluminal temperature probe (Esotherm/SensiTherm, FIAB, Italy) was used (Figure 3). The location of the probe was adapted according to the site of ablation. RF energy was discontinued when the temperature of the esophagus probe reached 39°C. Figure 4 exhibits an example of the position of temperature probe in relation to the ablation catheter during RF delivering.

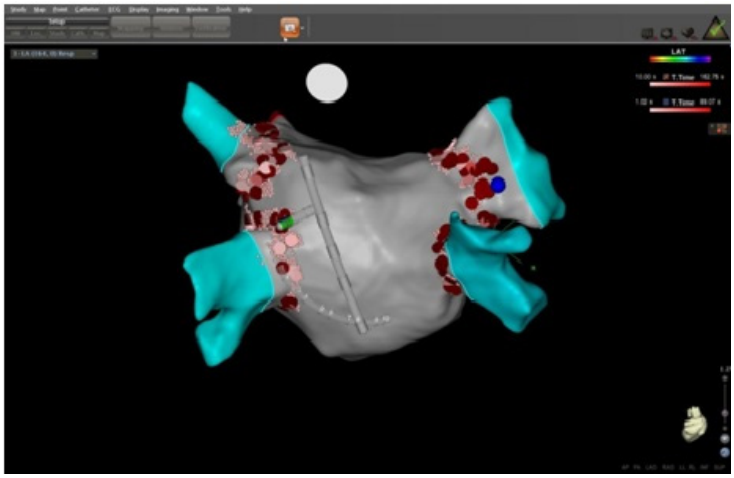

Figure 4: 3D imaging showing the relative position between esophageal probe and ablation catheter

Results

The thermal response of elements exposed to a 50W RF field at 500KH for 60 sec at various distances is reported in Figure 5

At distances larger than 1 mm the elements exhibit quite similar temperature increase. The bare thermocouple reaches a slightly larger maximal temperature. The effect of Teflon coating is generally negligible. Only at the distance of 1 mm the uncoated ring heats up one degree more than in the other cases. The Teflon coating has a strong electrical shield effect due to its extremely low electrical conductivity (order 10^{-24}S/m, compared to ~8.106S/m for stainless steel), but it has very little influence on temperature (its thermal conductivity is only 50 times less than stainless steel). Thus the 1 degree difference has to be attributed to the eddy currents induced in the uncoated ring at a distance of 1 mm. This definitely shows that the much feared antenna effect has nothing to do with the Sensitherm probe in any practical application.

Coming to the computation of the thermal field during RF applications, we first deal with the electric field generated by an applicator with a single irrigated electrode with an applied potential

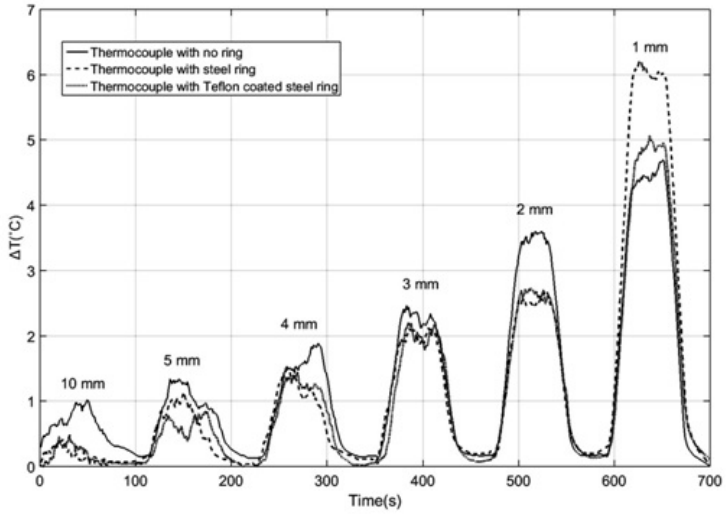

Figure 5: Comparison of the thermal response of the three systems to a 1 min exposure to a 50W RF source

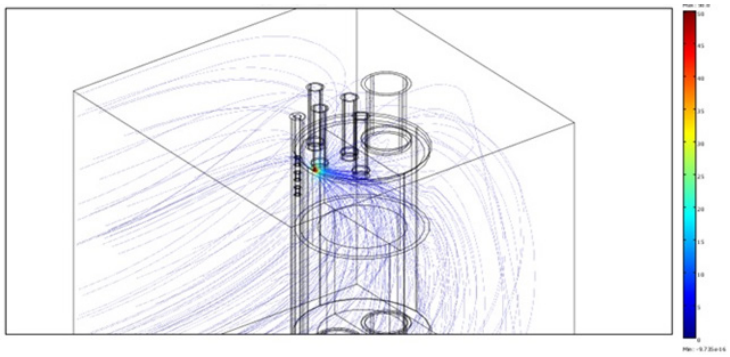

Figure 6A: 3-D view of the lines of the electric field

of 50V and a power 30.9W.

In Figure 6a we report a 3-D view of the electric field, strongly diverted by blood. Figure 6b shows the detail of the lines attracted by the steel sensors, though in a region where the field is so weak that no sizeable power is deposited. Indeed the power dissipated on the central sensor turns out to be less than 10^{-7} W. In terms of temperature variation, considering that the ring volume is of the order of 100 mm^3, it corresponds to a temperature increase which is far below the sensitivity of the apparatus.

The figures above emphasize a concentration of the streamlines within the atrium, due to the larger electrical conductivity of blood, which actually carries away a large fraction of the delivered energy. The figures 7a and 7b provide a view (in 3-D, panel a, and on a vertical

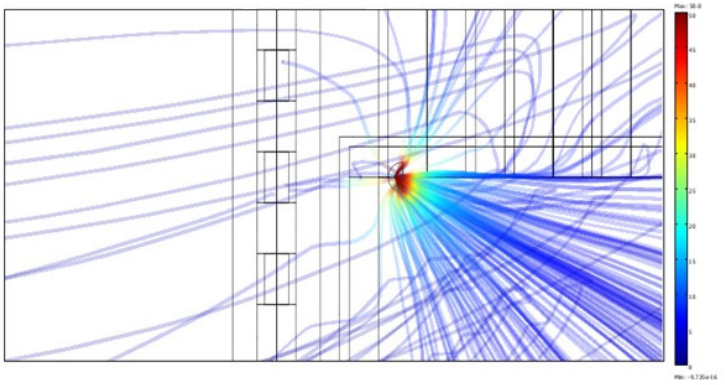

Figure 6B: Electric field (front view). The field is extremely weak in the sensors region

cross section, panel b), of the hot regions after a 1-min application.

The peak occurs at a distance of ~1 mm from the electrode, the strong heat removal being caused both by catheter irrigation and by blood flow. The mild gradient profile at the left is in correspondence to the esophageal wall facing the electrode. The strong thermal protection provided by the fat layer is clearly visible.

The temperature is lower in the region underneath the RF source, owing to the cooling action of blood flow. Figure 8 illustrates the temperature profile after a 60 sec. application (lower curve) and after a second application of equal duration, preceded by a 60 sec. pause. The temperature time evolution during a 240 sec. procedure (four alternated 1min intervals of application and pause) is reported in figure 9. No switch off procedure is simulated.

The farther we go from the emitting source the larger is the delay between the power switch off and the temperature decrease. After the first application the temperature in E2 keeps raising for about ten more seconds, up to 47°C. The temperature in E1 is not yet

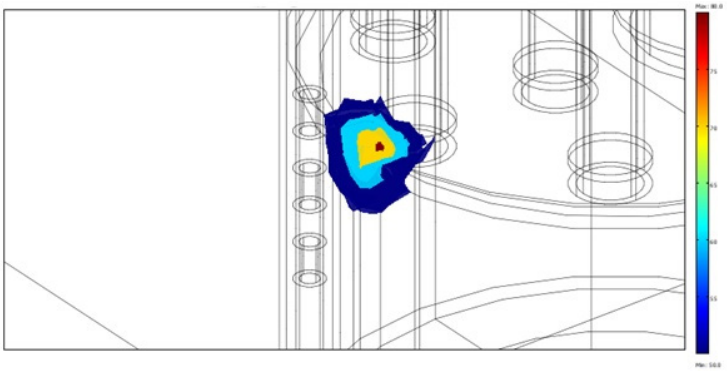

Figure 7A: 3-D view of isotherms 50, 60, 70, 80 degrees

decreasing when the second application is initiated. Maximal and minimal temperatures are likewise shifted in time.

Since the esophagus and connective tissue thermal diffusivities are rather close to each other (about 1.1 and $1.2.10^{-7} m^2/s$ respectively), it is possible to guess what happens if the thickness of either tissue is reduced by simply interpolating between the curves E1-E2-F. For instance, if the esophagus thickness is reduced to 2mm (20% reduction) leaving the connective thickness unchanged, the maximal luminal temperature is expected to increase to ~41°C (20% of the difference between the maximal internal and the maximal external temperature in Figure 6). If instead the connective thickness is increased by 0.5mm so to leave the esophagus lumen at the same location, then the luminal temperature will remain ~39.5°C, while the external temperature will decrease by ~1°C.

Here are some observations of clinical interest:

• On the curve E1 we can read the maximal luminal temperature, while the associated LET will generally be slightly less, being comprised between the temperature in E1 and the one at the opposite point in the lumen (see Figure 8b below: the maximal expected deviation is about 0.4°C).

• When the temperature in E1 attains the value of 39.5°C, the external point E2 has experienced the maximal temperature 47°C some thirty seconds earlier and has remained above 45°C for about fifty seconds.

Consequently one should be aware that it may happen that while LET measure suggests that one is working within a safe temperature range, the esophagus outer surface can be in danger of thermal lesion. This fact should suggest much care in selecting a really safe switch off temperature.

It is also interesting to explore the spatial temperature profile along

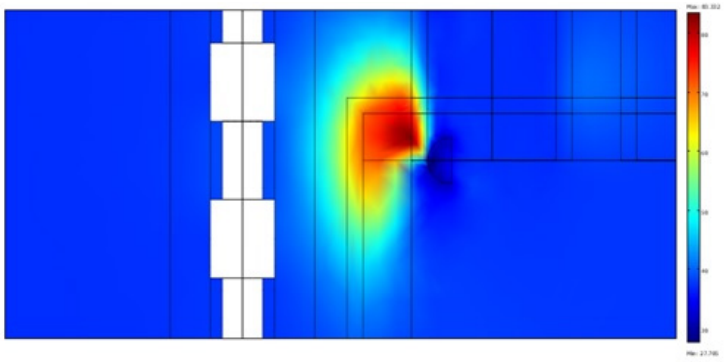

Figure 7B: Vertical cross section of the hot regions

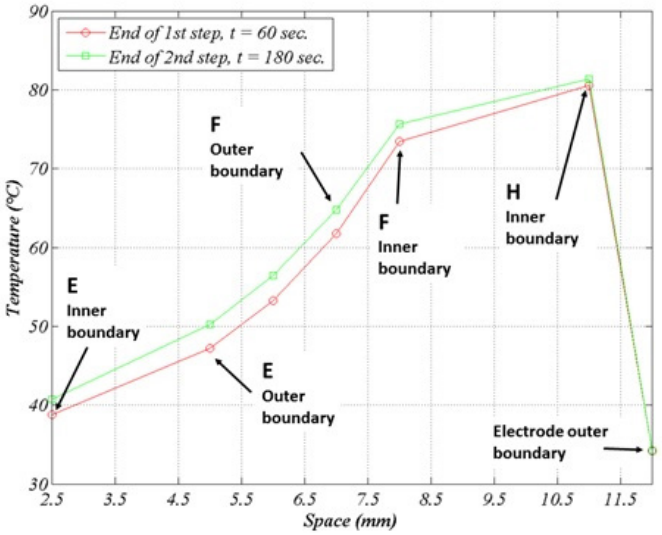

Figure 8: Schematic radial temperature profile after 60 sec (lower graph) and after 180 sec. (60 sec. on, 60 sec. off, 60 sec. on). Physical regions: esophagus (E) (2.5,5), connective (5,7), fat (F) (7,8), atrium (8,11), irrigated electrode tip (12)

the probe, for instance after the first application (Figure 10a, 10b).

The profile is rather flat near the maximum, but it falls down by ~1°C at a distance of ~1cm. This is the expected difference between the temperature recorded by the distal sensors and the median one, when the probe is ideally positioned, and it gives an idea of the error in LET measurement when it is not. A slight asymmetry can be noted, since temperature is moderately larger above than below the central point. Such a deviation is generated by the similar asymmetry in the thermal field shown in Figure 7b.

Clinical Data

To be concise, in Figures 11a, 11b we show two of the many recorded LET heating curves, obtained during various AF ablation procedures at S.Filippo Neri (Rome), with the corresponding value of the parameter α_{exp}, representing the maximal slope. For greater clarity we have reported only one of the three temperatures detected by the probe sensors. Results confirm a great variability of the temperature behavior, with no appreciable correlation between maximal slope and maximal temperature, since the latter is related with operation

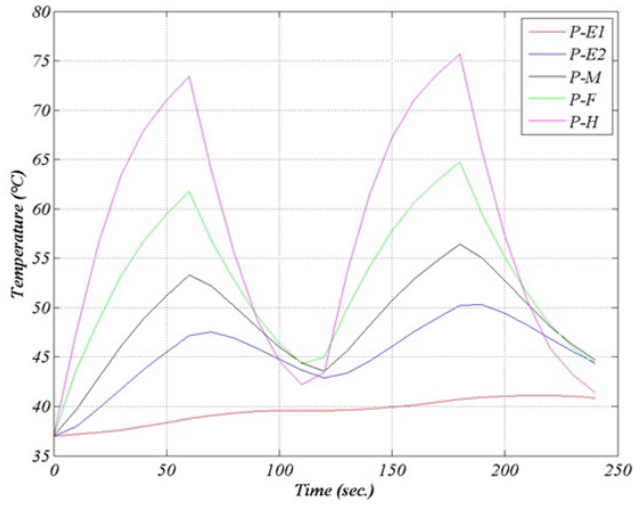

Figure 9: Temperature time evolution (two 1-min applications with 1-min pause. (E1, E2 inner and outer esophagus wall, M, F, H like in the previous figure)

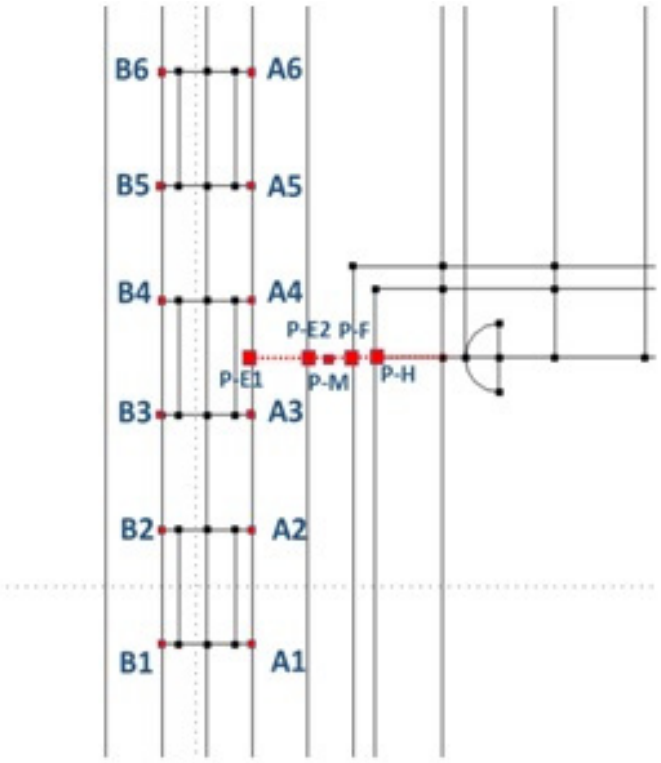

Figure 10A: Points at which temperature is shown

modalities. In many cases the maximal slope is close to the one predicted by our simulations. Larger (smaller) slopes are attributable to a shorter (longer) distance between the patient's esophagus and the ablator. Different slopes observed in the same patients are due to different locations of the ablator and/or different pressures exerted.

Discussion

We have computed the thermal and the electric fields generated by an irrigated RF emitting catheter in the left atrium, having LET as a specific target. Calculations are based on a mathematical model with a simplified geometry, which keeps into account the presence of an esophageal probe. We have compared LET with the temperature at the external esophageal wall, finding that the latter can be considerably higher and growing faster in the early stage of the treatment. This circumstance emphasizes the importance of the selection of the alarm temperature. We have been also dealing with the question of power deposition on the metallic sensors of the probe, both from the numerical and the experimental point of view, showing that the presence of metallic sensors produces no measurable perturbation. Indeed, out of the atrium the electric field is very weak, also because of the diverting action of blood flowing through the heart. We have discussed how the presented numerical simulation can be extrapolated to cases in which inter-organs distances are different from the ones in the chosen geometry. We have compared our results with a set of experimental data collected at S. Filippo Neri Hospital in Rome, selecting the maximal LET increasing rate as a significant quantity for comparison. In the large majority of cases such a parameter falls in a range which is in accordance with numerical predictions. Thus, it can be concluded that the model agrees rather well with the experimental data.

Comparing numerical simulations with clinical data is not a straightforward matter. The extreme variability of the configuration

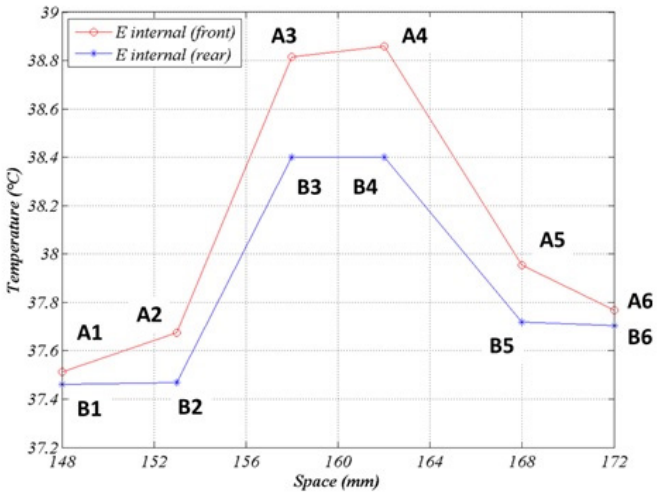

Figure 10B: Temperature profile along the probe after 60 sec. Points A1-A6 lie on the internal esophagus generatrix close to the emitting electrode. Points B1-B6 are symmetric to A1-A6 with respect to the esophagus axis

of the involved organs and of the patient's reaction is not the only reason. Of course, the actual location of the RF ablator, which is moved several times during a procedure, is an important element in the evolution of the thermal field. Another parameter that can be very influential is the pressure exerted by the ablator tip on the tissue. In one paper [31] the contact force applied was estimated to be in the range 10-40 g, which can proportionally displace tissues, making the ablator tip closer to the esophagus. Even a 2mm displacement can have a considerable influence on LET, introducing an important element of uncertainty. Further investigation is necessary, and is being carried out, to assess the influence of contact force on ETL occurrence. The presence of a switch off temperature threshold is a further complication, since a time shift in the attainment of such a temperature implies a deep modification of the thermal field after switch off. The time elapsed between the alarm and the actual interruption of the power supply is another random variable. A ten second delay while temperature is raising at the rate of 0.1°C/s introduces an extra temperature increase actually bound to exceed 1°C. Moreover, the duration of each application can be different. In these conditions the parameter which in our opinion can be sensibly compared is the maximal slope α during LET raise. Therefore we focused on that quantity. From Figure 9 we deduce the theoretical value α_{num} = 0.05°C/s and we note that the maximal slope β_{num} of the curve E2 (β_{num} = 0.20°C/s), actually represents an upper bound for α_{exp}, which normally ranges between 0.01°C/s and 0.15°C/s. Simulations suggest that if the esophagus-RF source distance is decreased by 1mm the slope under consideration increases by 0.06°C/s, which makes experimental results clearly interpretable in the model framework.

It is an old debate that metallic bodies deployed in biological tissues and exposed to a RF source may exhibit the so-called "antenna effect" with consequent abnormal heating, but such a phenomenon requires actually quite powerful fields and sufficiently large masses. For instance, a paper [32] reports about lesions surrounding metallic clips (larger than the Sensitherm sensors) during a RF ablation in the liver, but the power used there was 200W (five to eight times the one employed for PVI), and the effect was not visible at a distance of 2 cm from the ablator tip. One could deduce that in the case of RF-PVI a small metallic body placed anywhere outside the heart is

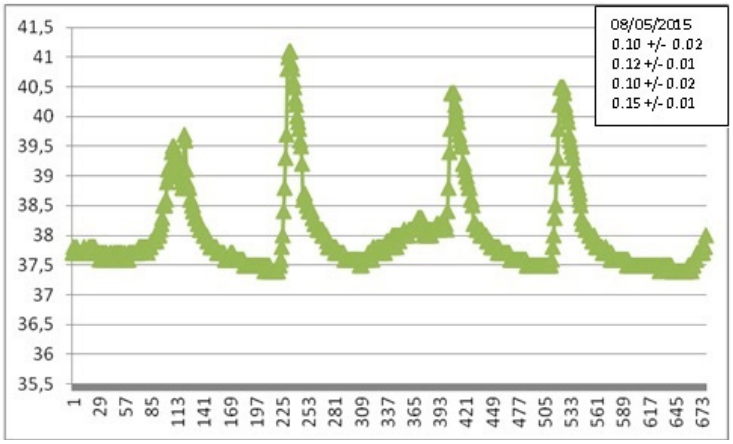

Figure 11A: Selected experimental LET curve: temperature (°C) vs. time (sec). The corresponding value of α_{exp} is shown in the side case

totally harmless. Indeed on the basis of our model we have confirmed that the electric field generated during RF-PVI decays very rapidly away from the ablator, becoming very weak in the esophageal region, also because of effective energy removal by the blood circulating in the heart.

For what it concerns the conjecture of the contribution of esophageal thermal probe to the ETL formation there are some caveats. The debate about the use of probes for LET measurement has been revived by the just appeared paper, [31] reporting the outcome of the comparison between 40 procedures performed with the FIAB-Sensitherm probe (Figure 1) and an equal number of treatments carried out in similar conditions but with no esophageal thermal sensors. Since 12 lesions were found in the first group and only one in the second, the suggested conclusion was obvious. Nevertheless, the large majority of the "lesions" (10 out of 13) were actually simple erythemas and the results presented clearly suggest that their origin is rather attributable to an irritation of mechanical nature, caused by the long exposure of esophageal mucosa to a foreign object, particularly in conditions of heating beyond 40°C. Moreover, an experiment analogous to that of Müller et al.[31] has been performed on two groups of 80 patients each in another paper, [25] reaching precisely the opposite conclusion: no esophageal injuries among the patients with LET monitoring and 6 in the other group. Finally we remind that it has been recently pointed out that ETLs can be produced not by RF ablation, but rather by the procedure of transesophageal echocardiography sometimes preceding RF application.[33,34]

In a forthcoming paper we intend to perform a parallel analysis on cryo-ablation procedures, which exhibits very peculiar aspects owing the larger thermal excursions. Indeed cryo-ablation is recognized to present similar risk as RFA. LET monitoring turns out to be of extreme importance when esophagus is potentially exposed to severe cooling35,36.

Study Limitations

Contact force catheters were not used in the clinical procedures to measure the force applied by the ablator tip on the tissue. We are now performing a new study using exclusively contact force catheters (Thermocool SmarTouch catheter, Biosense –Webster).

Conclusions

On the basis of theoretical and experimental investigations we have shown that monitoring the luminal esophageal temperature by means of an esophageal probe is not only quite safe, but highly

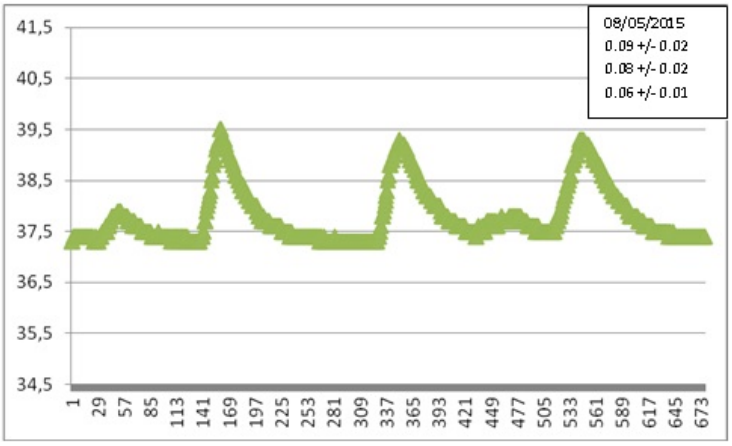

Figure 11B: **Selected experimental LET curve: temperature (°C) vs. time (sec). The corresponding value of α_{exp} is shown in the side case**

advisable. From the detected data it is possible to infer the temperature attained at the external esophageal wall, an element to be brought to the attention of clinicians.

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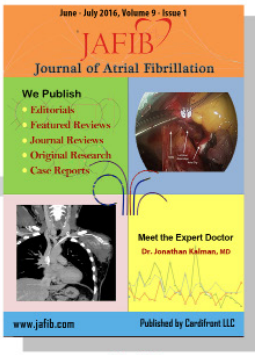

The Role Of NOACs in Atrial Fibrillation Management: A Qualitative Study

Katherine Kirley, MD, MS[1], Goutham Rao, MD[2], Victoria Bauer, BS[3,4], Christopher Masi, MD, PhD[3,5]

[1]American Medical Association, Chicago, IL. [2]Case Western Reserve University School of Medicine. [3]Ambulatory Primary Care Innovations Group (APCIG), NorthShore University HealthSystem, Evanston, IL. [4]Department of Family Medicine, NorthShore/University of Chicago Pritzker School of Medicine. [5]Department of Internal Medicine, NorthShore/University of Chicago Pritzer School of Medicine.

Abstract

Patients with atrial fibrillation (AF) benefit from anticoagulation to reduce stroke risk. However, 30-60% of patients with AF are not anticoagulated. This study explored physicians' reasons for under-treatment of AF, focusing on the role of the novel oral anticoagulants (NOACs). We interviewed primary care physicians and cardiologists involved in AF management in a variety of practice settings. We conducted interviews using a semi-structured format and analyzed the data using the Framework Method. Four themes emerged. First, the likelihood of physicians to prescribe NOACs depends upon their willingness to try new medications and their successful experience with them. Second, physicians typically balance the benefits and risks of anticoagulation in AF patients, although not always accurately. Third, patient convenience and preferences, as well as physician convenience, are important when considering anticoagulation. Finally, concerns regarding the out-of-pocket cost of NOACs deter many physicians from prescribing them. The persistence of under-treatment in AF despite the availability of effective therapies suggests that new strategies are needed to improve physician knowledge and practice. These strategies should enhance physician awareness of AF under-treatment, emphasize accurate assessment of bleeding risk among AF patients, compare the safety, efficacy, and convenience of NOACs relative to warfarin, and address physician concerns regarding the out-of-pocket cost of NOACs. Guidelines and decision supports which promote physician knowledge in these areas have the potential to increase oral anticoagulant use and reduce preventable morbidity and mortality.

Introduction

Atrial fibrillation (AF) affects 2.3 million Americans, and is associated with a five-fold increase in the risk of stroke.[1,2] This risk can be reduced by 64% with use of an oral anticoagulant such as warfarin.[3] Guidelines from several organizations recommend anticoagulation for all AF patients except those at very low risk for stroke.[4,5] Furthermore, the rate of anticoagulation of AF patients is a quality measure endorsed by the National Quality Forum.[6] Despite these recommendations, 30-60% of patients with AF do not receive anticoagulation when it is indicated. Under-treatment of AF results in thousands of preventable ischemic strokes in the U.S. each year.[7,8,9,10] Under-treatment specifically by family physicians has been documented.[11]

Within the past five years, the FDA approved four novel oral anticoagulants (NOACs) for AF treatment: dabigatran, rivaroxaban, apixaban, and edoxaban.[12,13,14,15] These agents offer several advantages over warfarin, including straightforward dosing regimens, no requirement for monitoring, and lower risk of intracranial hemorrhage.[11,12,13,14] Given these advantages, rapid adoption of NOACs might be expected to alleviate the AF under-treatment problem. Though NOACs are being rapidly adopted for new AF patients, under-treatment remains a serious challenge.[16,17,18]

In an effort to address this gap in the quality of AF care, comprehensive educational programs for AF patients are being rolled out. Perhaps the best-known effort is the American Heart Association's Get With the Guidelines–AFIB program which has been introduced to assist hospitals with registry building and other AF-related performance improvement activities.[19] However, these programs address NOACs and warfarin together as equivalent treatment options without recognizing that NOACs could play a different role from warfarin in AF management. Currently, little information is available regarding physicians' opinions of NOACs and their role in AF management. Because such knowledge is needed to inform the development of AF educational programs for family physicians and other primary care physicians as well as specialists,

Key Words:
Atrial Fibrillation, Anticoagulation, NOACs.

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Corresponding Author:
Christopher Masi,
Suite 136, 1001 University Place,
Evanston, IL 60201.

we conducted a qualitative study of physicians' decision-making processes regarding anticoagulation management in AF, with a specific focus on the role of NOACs.

Material And Methods

Study Design

To address the many unanswered questions about physician knowledge, attitudes, and practices regarding NOAC use, we chose a qualitative study design which facilitated exploration of a broad range of perspectives. Specifically, we used the Framework Method of qualitative analysis,[20] which permitted us to integrate newly discovered concepts into existing conceptual frameworks. The study design was approved by the NorthShore University HealthSystem institutional review board.

Sampling, Recruitment, And Data Collection

Purposive sampling was used. A list of potential participants was assembled from the extended professional networks of the primary author and co-authors. Physicians were then recruited with the goal of including participants from a range of specialties (family medicine, internal medicine, cardiology, and electrophysiology), experience levels, and practice settings. Written informed consent was obtained prior to each interview. Recruitment concluded when thematic saturation was achieved.

A semi-structured interview guide (Table 1) was developed based on a review of the oral anticoagulation literature. The guide provided an overall structure to the interviews. Questions were open-ended with follow-up questions prompted by participants' responses. Participants were free to introduce and discuss points not outlined in the guide. Individual interviews were conducted by the primary author (KK). The interviews were digitally recorded and professionally transcribed.

Data Analysis

Implementation of the Framework Method began with data familiarization; the primary author (KK) and co-authors (GR and CM) read each transcript and made notes of initial impressions. Each author developed a potential list of codes, then met to develop an initial consensus code list. Each transcript was then re-read and independently coded by two authors. The authors met to iteratively perform comparative coding to refine the code list according to patterns that emerged from re-reading and discussing the transcripts. The codes were grouped and organized into an analytic framework in the form of themes and sub-themes. The transcript data were indexed according to this framework using NVivo 10 software (QSR International, Doncaster, Australia). Indexed data were organized into a framework matrix, which was reviewed by all authors and used to develop final interpretations of the data.

Table 1: Semi-structured interview guide

Opening statement: Thank you for meeting with me to discuss anticoagulation in atrial fibrillation.
1. Describe your practice and your patient population.
2. Do you manage patients with atrial fibrillation frequently?
3. When you consider whether or not to prescribe a medication for a patient, what factors influence your decision?
4. When you manage patients with atrial fibrillation, how do you go about deciding whether or not to anticoagulate?
5. Please tell me what you know about the novel oral anticoagulants, also known as NOACs.
6. What are your colleagues saying about NOACs?
7. Can you describe an example of a patient for whom you prescribed a NOAC?
8. What are your impressions regarding the benefits of NOACs compared to warfarin?
9. What are your impressions regarding the risks of the NOACs compared to warfarin?
10. Is there anything else about NOACs or atrial fibrillation you would like to share with me?

Results

Participants

Interviews were conducted with seven physicians (five men and two women). Three were family physicians, one was an internist, two were cardiologists, and one was a cardiologist sub-specializing in electrophysiology. Participants' practice settings included community private practice, community residency practice, and academic practice at a tertiary care center.

Themes

Themes that emerged from our interviews were grouped into four categories: the impact of knowledge and experience on prescribing practices, methods used to weigh risks and benefits of anticoagulation, medication barriers and facilitators, and the high cost of NOACs.

Theme 1: Knowledge and Experience Influence Prescribing

Knowledge regarding the safety and efficacy of oral anticoagulants, as well as experience prescribing them, were clear practice drivers. Table 2. Several primary care physicians indicated they were less familiar with NOACs compared to warfarin and were therefore less likely to prescribe NOACs. They also expressed a willingness to defer to the recommendations of cardiologists regarding initiation of NOACs. When asked about this, one PCP said, "I think a lot of us will send them to cardiology." On the other hand, some of the PCPs and all of the cardiologists were comfortable prescribing NOACs and this typically reflected the extent of their experience with these medications. Referring to his colleagues, one cardiologist said, "They've started to become very comfortable with these novel agents."

Related to knowledge, an important sub-theme was anxiety related to novelty. Newness of medications was viewed by many as inherently negative, and novel medications were considered more likely to be associated with unforeseen adverse events. Some physicians questioned the quality of evidence used to support the use of NOACs. Other physicians reported hesitancy prescribing NOACs due to concerns regarding clinical trial methodology and the FDA approval process, which some viewed as hasty: "I think the United States is very aggressive [in bringing] new medications to market."

Prior experience with new medications influenced current prescribing practices both negatively and positively. For example, one participant said, "I have been burned with enough medications

Table 2: Example Quotes Describing Physician Experience and Knowledge

Anxiety around novelty (risk aversion, reliability of new evidence) "Not a first user. Cause I want to see what plays out. ....a wise man, physician, once told me, don't be the first or the last to prescribe new medication." "And, and I think, honestly that's a, that's a pretty good approach (to be risk averse) for a physician in general." "I think the United States is very aggressive (in bringing) new medications to market." "The good thing about a lot of the new medications especially in cardiology is that they've gone through these mega-trials. It's very hard to get a cardiovascular medication approved without, you know, a ten thousand patient trial."
Prior Negative Experiences "I have been burned with enough medications that have gone off the market."
Familiarity, comfort level "So I have a handful [of medications] that I'm just used to prescribing..... Although I'm sure if I read about other ones, if I actually looked into other ones, I'd like other ones better." "It requires understanding, learning these medications, talking with people who had more experience with them, and then kind of going out on that ledge of starting a new medication you may not have learned about during your training."

that have gone off the market." On the other hand, physicians with successful experience prescribing NOACs were more likely to continue prescribing them: "All you have to do is write a prescription and counsel the patient. It's so easy to start these medications."

Theme 2: Formal and Informal Methods Used to Weigh Risks and Benefits

Balancing the benefits and risks of oral anticoagulation is critical when deciding how to manage patients with AF. Table 3. Participants typically reported that their first step in this calculation was estimating the patient's risk of stroke, usually with the $CHADS_2$ or CHA_2DS_2-VASc calculators. All physicians reported using at least one of these calculators when considering benefits of OACs. Participants then discussed their methods for estimating bleeding risk. A variety of approaches was described, with most physicians making informal assessments based on past medical history and co-morbidities: "You have patients with chronic renal disease where their platelets don't work well and they're gonna be more of a bleeding risk, and you know, a host of things – underlying liver disease." Concerns about fall risk were significant and often tilted the balance against warfarin or NOACs: "If someone has fallen multiple times, even if they haven't bled from the fall and nothing bad has happened, I will just switch them to aspirin usually." Only one physician reported using the HAS-BLED score or any other formal strategy to estimate bleeding risk.

Additional factors were important when calculating the benefit/risk estimate. For example, participants often assumed that the bleeding risk in elderly patients outweighed the benefits of anticoagulation. Referring to older patients, one PCP said, "We think they've got lots of comorbidities, we think they're likely to bleed, and therefore we don't try to put them on an anticoagulant." However, a cardiologist who frequently prescribed OACs noted that older patients may benefit more from OACs than younger patients, who tend to have fewer comorbidities and a lower stroke risk.

Characteristics of the various anticoagulants were important in deciding whether to anticoagulate and which agent to use. Medication side effects were mentioned by many physicians. The irreversibility of the NOACs was a concern for some physicians, and the majority felt that the reversibility of warfarin was one of the few benefits that it offered in comparison to NOACs: "I think that the biggest thing that everybody, myself included, is [concerned about is] that there's no antidote [for NOACs]."

When comparing efficacy of stroke prevention, physicians indicated NOACs were at least as efficacious as warfarin. A few were skeptical that any NOAC was substantially better than warfarin, while others felt that the reported increased efficacies of apixaban and dabigatran were meaningful.

Theme 3: Important Barriers and Facilitators Related to Anticoagulation and Anticoagulant Choice

Several barriers and facilitators were described as important when deciding whether to start an oral anticoagulant and which OAC to use. Table 4. An important sub-theme concerned the frequent laboratory monitoring associated with warfarin: "It [is] very time consuming. That's probably the one thing that soured me on warfarin." However, almost all participants reported utilizing anticoagulation clinics, which significantly reduced their personal burden of managing warfarin and increased their willingness to prescribe it. The lack of need to monitor NOACs was very appealing and the majority of participants commented that it was the best feature of the NOACs: "I think the biggest [benefit] is the ease of use, where you don't have to monitor."

Convenience for the patient was also important to physicians, who believed that most patients found laboratory monitoring troublesome, particularly at the time of warfarin initiation. Some expressed concern that the need for frequent testing contributes to medication non-adherence and may increase the risk of stroke. One physician said, "I have people who are like, 'I don't want to be on [warfarin]'" while another said, "If someone was not carefully weighing it, one could say, 'Oh, I don't want that.' And that would feel easier in the moment but that might not be the best outcome."

Patient preferences and pre-conceived ideas were commonly described as both barriers and facilitators of OAC use. Physicians reported frequently encountering resistance from patients when recommending an oral anticoagulant. Patients' concerns were sometimes viewed as legitimate (i.e. concerns about bleeding risk or side effects), and sometimes viewed as unrealistic or irrational (i.e. anecdotes about acquaintances' experiences or general aversion to medications). On the other hand, multiple physicians reported patients requesting a NOAC after viewing television commercials. Some patients had positive impressions of oral anticoagulants based on acquaintances' experiences, and were therefore more open to their use. Despite frequently encountering resistance to anticoagulation, most physicians reported that patients usually choose to follow the physician's recommendation.

Theme 4: Cost Influences Prescribing

All participants discussed out-of-pocket cost as an important factor when considering treatment with NOACs. Table 5. Two physicians reported that the majority of their patients had lower incomes so

Table 3: Example Quotes Describing Clinical Benefits and Risks

Risk of stroke	"Our practice tends to be to anticoagulate anybody without a contraindication with a $CHADS_2$VASc of 1 or greater"
Risk of bleeding	"If someone has fallen multiple times, even if they haven't bled from the fall and nothing bad has happened, I will just switch them to aspirin usually." "You have patients with chronic renal disease where their platelets don't work well and they're gonna be more of a bleeding risk, and you know, a host of things - underlying liver disease."
Benefit/Risk assessment	"If you look in their old records and someone fell like two times this year, but their $CHADS_2$ score says that they should be anticoagulated, then I would think long and hard about doing that." "The patients that are aged eighty-five and older tend to be the lowest percentage of patients that are given Coumadin. And that's because you see somebody frail and you think they're gonna bleed and you don't prescribe them. But they are actually the people who benefit the most."
Risks of NOACs	"I think that the biggest thing that everybody, myself included, is [concerned about is] that there's no antidote [for NOACs]."

Table 4: Example Quotes Describing Barriers and Facilitators of Prescribing

Convenience/Inconvenience for the provider	"Oh, Jesus, yeah. I mean ten years ago we were shown every single INR, and then had to control them. It was very time consuming. That's probably one thing that soured me on warfarin." "So I think the biggest [benefit of NOACs] is the ease of use, where you don't have to monitor."
Negative feelings toward warfarin	"I hate having people on [warfarin]." "I have people who are like, 'I don't want to be on [warfarin].'"
Patient Preferences	"No one wants to take a drug, and no one wants to be on a pill if they don't have to... So if someone was not carefully weighing it, one could easily just say, 'Oh, I don't want that.' And that would feel easier in the moment, but that might not be the best outcome that they would choose for themselves if they're looking at it more objectively." "Sometimes it's a time factor, and you fight with them for a couple different times and you just give up. Fine, here."

they rarely prescribed NOACs. Similarly, physicians reported being less likely to prescribe NOACs to patients with Medicare insurance due to uncertainty regarding coverage. Participants also indicated that the high out-of-pocket cost of NOACs can negatively impact medication adherence. One said, "If they can't afford it they're not gonna take it. They're not gonna take it properly or they're gonna take it every other day or cut a pill when they shouldn't." In contrast, physicians were more likely to prescribe NOACs for patients with private or supplemental insurance. Frustration arising from the frequent need to obtain prior authorizations for NOAC coverage, even among privately insured patients, was mentioned by several participants.

When asked whether NOACs might be associated with lower society-level costs, several physicians said this might be the case. However, for all physicians, the out-of-pocket cost to each patient remained a more important determinant of NOAC use than potential savings at the societal level.

Discussion

We found that physician prescribing practices in the setting of AF depended principally upon: 1) knowledge and experience, 2) clinical benefits and risks, 3) barriers and facilitators of prescribing, and 4) medication cost. Associated with each of these themes were sub-themes which help explain the persistent under-treatment of AF and provide guidance regarding ways to address this problem.

A key sub-theme regarding knowledge and experience was physician apprehension regarding new medications. This is not surprising, given that quite a few aggressively marketed new medications have been withdrawn after serious adverse effects were identified. The story of refecoxib (Vioxx) is a well-known example.[21] Physicians also described the impact of negative personal experiences with new medications, including anticoagulants. Additionally, we found a general skepticism about the evidence supporting new medications, including NOACs. The quality of research sponsored by pharmaceutical companies has been called into question in recent years, which may underlie this skepticism.[22] Newer medications are viewed, especially by primary care physicians, as inherently riskier. Because the potential risks of NOACs include life-threatening hemorrhage and possibly cardiovascular events, physicians may be even more hesitant to prescribe these new medications relative to other new medications with less worrisome potential risks.[23]

Table 5: Example Quotes Describing Cost

Cost of medication "Some patients can't really afford [NOACs], I think they're something like 90 bucks a month or something. So I wouldn't switch anyone over basically because of the cost difference."
Insurance coverage "A lot depends on the demographics of your practice and the insurance issues within your patient population." "I deal with mostly an insured population. You know, so it's less of an issue for me" "Except that patients on Medicare who are these patients, ah, you know, might have to pay more out of pocket if they don't have a secondary insurance."
Cost influencing adherence "If they can't afford it they're not gonna take it. They're not gonna take it properly or they're gonna take it every other day or cut a pill when they shouldn't." "Because if they're not going to afford it, a lot of times those patients aren't gonna go to their doctor and be like, I can't afford this, can I try something else? There's the concern that they're just gonna be like, I'm not gonna take this."
Cost-effectiveness "My gut sense is it's (NOACs) cleaner and from a system standpoint it probably is more cost effective or efficient." "My colleagues are saying, and I agree, that, you know, we should, we should probably be prescribing them more because no one's looking at really this, this monitoring cost, which is significant. Time and money, you know." "The individual still matters more to me than the public health" "There's a lot of things that we do in medicine that would be cost effective from a more like national or global standpoint. But when it comes time to patient care, patients don't care about that."

Discussion of strategies for assessing the clinical benefits and risks of anticoagulation was revealing. Physicians reported relatively consistent methods for assessing stroke risk among their patients, but there was substantial variation in processes for assessing bleeding risk. This was expected because current clinical guidelines provide specific instructions for assessing stroke risk but little guidance for assessing bleeding risk.[24,25] Most physicians compared their estimation of a given patient's stroke risk directly to the patient's bleeding risk, as if they were equally serious outcomes. However, ischemic stroke has substantially higher rates of morbidity and mortality than major bleeding.[26] The majority of participants acknowledged this fact when pressed. Yet, most participants failed to take this differential risk of morbidity and mortality into account in their decision-making processes. It appears that AF under-treatment persists in part due to substantial variation in assessment of bleeding risk and a tendency among physicians to treat strokes and hemorrhages as equivalent adverse events.

Much time during interviews was spent discussing facilitators and barriers related to prescribing oral anticoagulants. Universally, physicians felt that the most compelling reason to use a NOAC was convenience. The idea that some NOACs might be more efficacious for stroke prevention was less compelling for physicians than the increased convenience. It is possible that the convenience of NOACs is allowing them to reach a share of the AF population previously not anticoagulated due to warfarin's inconvenience. This may explain the recently reported increases in both the rate of NOAC prescribing and the proportion of AF patients receiving anticoagulation.[17]

Out-of-pocket cost emerged as an important barrier to prescribing NOACs. PCPs and specialists were aware that NOACs are more expensive than warfarin, and they expressed concern that paying for these medicines could present a financial hardship that impacts medication adherence. As a result, some physicians were hesitant to prescribe NOACs for patients with limited resources or public insurance. While most physicians recognized that NOAC use may be associated with lower societal costs, this was perceived as a less important factor in prescribing than cost control at the individual level.

We believe our findings have significant implications for clinical practice and education, particularly among primary care physicians. Our findings regarding physician knowledge, familiarity, and comfort with NOACs are consistent with other studies which have demonstrated incomplete knowledge among primary care physicians of guidelines for cardiovascular disease prevention in general.[27,28] Important components of an educational program could include, among others, an overview of the risks of atrial fibrillation and the anticoagulation under-treatment problem, accurate assessment of bleeding and stroke risk, the benefits and disadvantages of anticoagulation options, and prescription and insurance coverage guidelines for the available NOACs. An educational program could be embedded in a broader quality improvement initiative, in which nurses and other practice personnel are involved as well as primary care physicians. Similar efforts have been used recently to successfully improve adherence to cardiovascular guidelines in primary care.[29]

A limitation of this study is the relatively small number of study participants. However, the diverse perspectives of primary care physicians and cardiologists yielded a rich data set from which we

identified four substantial themes. Social desirability bias is a potential limitation given that physicians may not be inclined to discuss their lack of familiarity with new medications. We attempted to limit this risk by asking open-ended questions and maintaining a non-judgmental demeanor during the interviews. In addition, it is unclear whether our findings can be generalized to PCPs and cardiologists in other practice settings or other parts of the country. To address this, we recently pilot-tested a survey among all PCPs and cardiologists in our health system and plan to administer this survey nationally.

Conclusions

Under-use of oral anticoagulants in the management of AF continues to be common despite the availability of effective therapies. We found that physicians are more likely to prescribe anticoagulants, including NOACs, when they have achieved a comfort level through education and experience, when they believe the benefits of treatment outweigh the risks, and when they feel that treatment will not impose undue financial burden. Systematic educational and quality improvement efforts, of the type already used successfully to improve adherence to guidelines for cardiovascular risk management, are needed to help correct the under-treatment problem and reduce morbidity and mortality associated with stroke.

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Myocardial Biopsy In "Idiopathic» Atrial Fibrillation And Other Arrhythmias: Nosological Diagnosis, Clinical And Morphological Parallels, And Treatment

O.V.Blagova,[1] A.V.Nedostup,[1] E.A.Kogan,[1] V.A.Sulimov,[1] S.A.Abugov,[2] A.G.Kupriyanova,[3] V.A.Zaydenov,[3] A.E.Donnikov,[4] E.V.Zaklyazminskaya,[2] E.A.Okisheva[1]

[1]Sechenov First Moscow State Medical University 119992, Moscow, B.Pirogovskaya str., 6. [2]Petrovsky Russian Scientific Center of Surgery. RAMS. [3]Shumakov Scientific Center of Transplantation and Artificial Organs. [4]Kulakov Scientific Center for Obstetrics, Gynecology and Perinatology.

Abstract

Background: The nosological nature of "idiopathic" arrhythmias and the effect of etiotropic and pathogenetic treatment are often unknown.

Methods And Results: 19 patients (42.6±11.3 years, 9 women) with atrial fibrillation (n = 16), supraventricular (n = 10) and ventricular (n = 4) premature beats, supraventricular (n = 2) and ventricular tachycardia (n = 1), left bundle branch block (n= 2), AV block (n = 2) without structural heart changes. Viruses were identified (polymerase chain reaction, PCR) along with measurement of anti-heart antibodies (AHA) and endomyocardial biopsy (EMB).

EMB allowed to establish diagnosis in all patients: 1) infectious-immune myocarditis (n = 11, parvovirus-positive in 1), 2) parvovirus-positive endomyocarditis (n = 1), 3) systemic (n = 2) and myocardial (n = 1) vasculitis, 4) Fabry's disease (n = 1), 5) arrhythmogenic right ventricular dysplasia (n = 1), 6) unspecified genetic cardiomyopathy (n = 2, herpes virus 6 one positive). Level of AHA had the greatest significance for myocarditis diagnostics. All patients with myocarditis/vasculitis had background therapy: acyclovir (n = 10), IV immunoglobulin (n = 2), meloxicam (n = 12), hydroxychloroquine (n = 15), steroids (n = 14, 31.1±12.5 mg/day), azathioprine 150 mg/day (n = 2). Median follow-up was 4 years. Treatment significantly reduced the rate of arrhythmias (8 [5;8] to 3 [1.25;7.75] points); disappearance of bundle branch block was noted.

Conclusion: EMB allowed to diagnose immune-mediated inflammatory diseases in 78.9% patients with 'idiopathic' arrhythmias and genetic diseases in 21.1%. Background therapy of myocarditis improved the antiarrhythmic efficiency, and allowed the best premed for interventional treatment.

Background

Methods of diagnosis and treatment of arrhythmias are actively developing, therefore etiology often goes on the back burner. As Ivan Pavlov had noted, "The etiology is the weakest part of medicine." The concept of "idiopathic" arrhythmia has being mentioned in literature for at least 50 years (including "lone atrial fibrillation"[1]); it means arrhythmias in patients (usually younger than 60 years) without structural heart changes ("with a healthy heart".) A more rigorous definition considers that causes scope has come to the end, but it also includes unexplained arrhythmias, or primary electrical heart disease. Incidence of idiopathic arrhythmias ranges from 3-17% to 20-45% for atrial fibrillation (AF),[2,3] and from 5% to 10-30% for ventricular arrhythmias.[4] The absence of obvious cause does not mean a favorable course and prognosis.[5,6]

Attempts to establish the etiology of «idiopathic» arrhythmias using myocardial biopsy are few, and their results are contradictory: in isolated works myocarditis in AF was revealed in 66% of atrial biopsies and 22-25% of ventricular biopsies.[7,8] In ventricular arrhythmias signs of myocarditis, cardiomyopathy and normal findings were 0-80%.[9,10] Attempts to speculate about the inflammatory etiology of «idiopathic» arrhythmias only due increased blood C-reactive protein (CRP) and cytokines are inconsistent. Genetic channelopathies can be the other causes of «idiopathic» arrhythmias. Options of causal and pathogenetic treatment of idiopathic arrhythmia remain unclear.

Study Objective

To establish the nosological nature of "idiopathic" arrhythmias

Key Words:
Idiopathic Arrhythmias, Lone Atrial Fibrillation, Endomyocardial Biopsy, Myocarditis, Myocardial Vasculitis, Immunosuppressive Therapy.

Disclosures:
None.

Corresponding Author:
Blagova Olga,
Sechenov First Moscow State Medical University 119992,
Moscow.

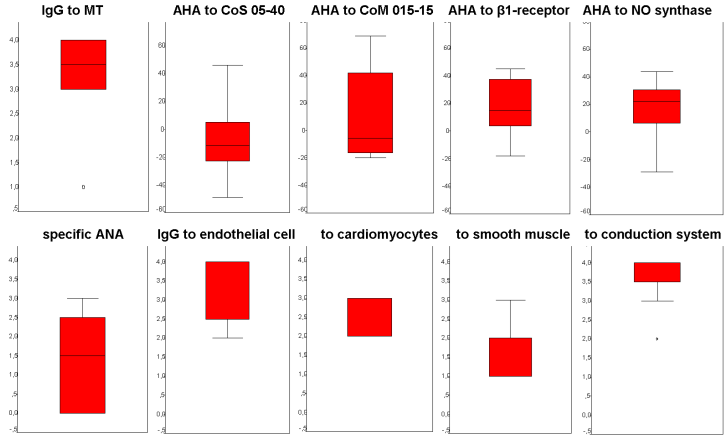

Figure 1: Median of increase of different types of anti-heart antibodies. The abscissa is the level of titer increase (x fold). AHA, anti-heart antibodies, MT, myocardial tissue, ANA, anti-nuclear antibodies

with endomyocardial biopsy of the right ventricle and to evaluate the effect of etiotropic and pathogenetic treatment.

Materials And Methods

Stugy included 19 patients of 24-60 years (mean age 42.6 ±11.3 years, 9 women) with different arrhythmias and conduction abnormalities (Table 1), and without: left ventricular hypertrophy (>14 mm), dilatation with reduced contractility, myocardial infarction, endocarditis, history of open heart surgery, valvular heart disease, hypertrophic and various types of restrictive cardiomyopathies, diffuse connective tissue diseases and vasculitis, thyrotoxic and hypertensive heart. Hypertension (53.6%) and grade 1 obesity (26.3%) were not considered as a leading cause of arrhythmia. All patients underwent standard screening (including thyroid function), and following additional tests:

1) IgG to herpes viruses, Coxsakie B viruses and genome of herpes viruses types 1,2,6, Epstein-Barr virus, herpes zoster, cytomegalovirus in the blood (PCR);

2) anti-heart antibodies (AHA) by direct and indirect ELISA in 3 laboratories: IgM and IgG to myocardial antigen (normal 1:100); IgG to cardiomyocytes cytoplasmic protein CoS05-40 and membrane protein CoM015-15; IgG to NO-synthase; IgG to β1-adrenergic receptor (n = 8, normal -30 to +20); anti-endothelial cell IgG, anti-cardiomyocyte IgG, anti-smooth muscle IgG, conduction heart system (normal 1:40), and antigen-specific anti-nuclear antibodies (ANA) with bovine heart (normally absent). We used pure FITC (fluorescein isothiocyanate)-labelled anti-human IgG and luminescent anti-human serum. Accounting was performed with fluorescent microscope Leica (Laborlux and DM4000V) at x 400 and 600;

3) endomyocardial biopsy (EMB) of the 5 sites in the right ventricle. Samples underwent PCR (including parvovirus B19 identifying), morphological study with hematoxylin-eosin, Van Gieson, periodic acid-Schiff (PAS) reaction staining, in some cases, electron microscopy.

Moreover, geneticist consultation and DNA (deoxyribonucleic acid) diagnosis (n = 4), treadmill test (n = 5), transesophageal (n = 5) and intracardiac electrophysiological study (n = 3), myocardial scintigraphy with 99mTc-MIBI (n = 10), magnetic resonance imaging (MRI, n = 3), cardiac multi-slice computer tomography (CT, n = 3), coronary angiography (n = 6), and skin biopsy (n = 1) were performed when appropriate. Paroxismal tachycardias (incl. AF and sustained ventricular tachycardia, VT), atrioventricular (AV) block and bundle brunch blocks were identified in ECG and/or Holter monitoring. The premature ventricular beats (PVB) and premature atrial beats (PAB) assessed by means of Holter monitoring.

SPSS 11.5 for Microsoft Windows was used for statistical analysis. Quantitative signs are presented as M+6 (average + one standard deviation) or as median with indication of the first and the third quartiles. Kolmogorov-Smirnoff test was applied for normalcy of distribution check. Criteria of Student, Mann-Whitney and Wilcoxon were used for estimation of differences significance. Differences have been considered significant in case of $p<0.05$. Local ethics committee approved this study and all patients signed written informed consent.

Results

Arrhythmia was the first disease sign in 73.7% of patients, acute onset was observed in 52.6%, relationship with infection - in 36.8%, disease duration less than a year - in 14.8%. Average duration of arrhythmia was 6 years (72 months, 30 to 144), average age of arrhythmia's onset was 34.8 ± 10.4 years, age of AF onset – 36.2 ±10.8 years. Patients received an average of 5 antiarrhythmic drugs (AAD, 1 to 8), including 14 patients who received amiodarone. At enrollment, one patient had permanent pacemaker due to AV block, 3 patients had a history of radio frequency ablation (RFA, 2 - due to paroxysmal AV tachycardia, one - due to stable VT; three patients (15.8%) had syncope.

Minimal levels of acute-phase reactants were found in 21.1% patients; T-wave changes on the ECG - in 73.7%, isolated left atrial enlargement - in 52.6% (Table 1), diffuse uneven or focal perfusion impairment on scintigraphy - in 50%. Only one patient (with AF and premature ventricular beats, PVB) revealed 70% stenosis of the right

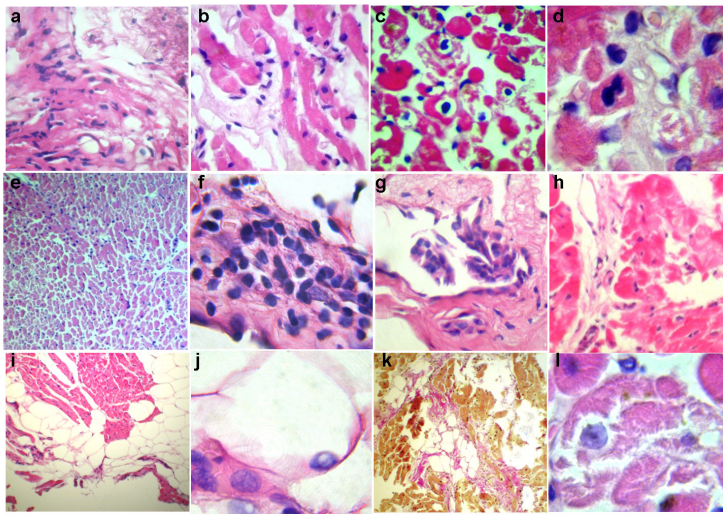

Figure 2: Key morphological changes in patients with myocarditis. Stained with hematoxylin and eosin (a-j, l) and Van Gieson (k). Large (a-d, f-h, j, l) and low (e, i, k) magnification. interstitial lymphohistiocytic infiltration > 14 cells (a, b, e), focal lysis (b, l) and necrosis (h) of cardiomyocytes, immune cytolysis with emperipolesis (intracellular lymphocytes locations are indicated by arrows) and loss of cardiomyocytes (c), mitosis in cardiomyocytes (d) significant endothelial thickening, swelling with focal proliferation (including villous proliferation, g) and infiltration (f), subendocardial and intramyocardial lipomatosis (i, k) with nuclei debris (j), focal fibrosis (k)

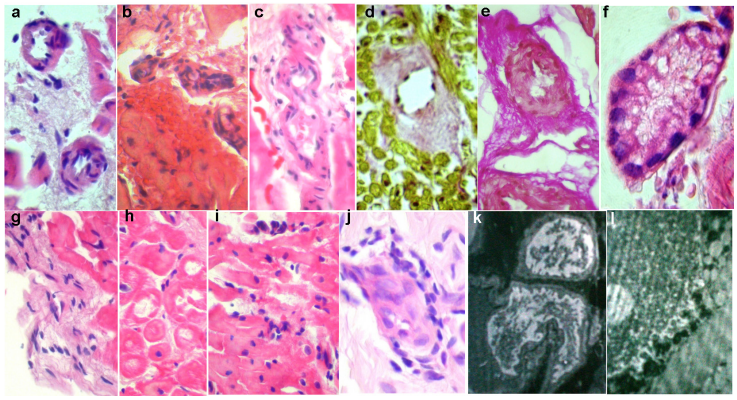

Figure 3: Key morphological changes in patients with vasculitis. EMB: light microscopy (a-i), and electron microscopy (k, l). Skin biopsy (j). Stained with hematoxylin and eosin (a-c, e-j) and Van Gieson (d). Large magnification. Cardiomyocytes with cytoplasmic homogenization, foci of myolysis with formation of cytoplasmic clefts (h), lymphohistiocytic myocardial (i) and endocardial (g) infiltration with deposits of eosinophils, vessels with endothelial proliferation, luminal stenosis, perivascular infiltrates (a-c) and sclerosis (d, e), microvessel ectasia with swollen endothelium and thrombotic lumen occlusion with loose clots (f). Skin: leukoclastic vasculitis (j). Explanation of electron-diffraction photographs - see text

coronary artery in the absence of angina pectoris and stress-induced ischemia. One patient had late contrast enhacenment (CT) and fat inclusions in the myocardium (MRI).

Cardiotropic virus genome (Epstein-Barr virus and herpes virus type 6, HHV6) was detected in the blood in two patients. Anti-herpes IgG levels were 2-3 times higher in 70-80% patients, anti-Coxsackie IgG levels - 2 times higher in 50% patients. Titers of anti-myocardial IgG were increased 3-4 times higher (Fig. 1). Extended analysis revealed that anti-endothelial cell IgG and anti-conduction system IgG had the highest titers, anti-cardiomyocyte IgG increased in a lesser extent. Levels of anti-smooth muscle IgG were normal that suggested selectivity of autoimmune reactions. Two thirds of patients had positive specific ANA (in the absence of standard ANA). Level of natural autoantibodies tended to slight increase. Increased AHA levels seen as sign of possible myocarditis, and one of the indication for EMB.

Biopsy results are shown in Table 2: no patient had normal histology. Different combinations of morphological features allowed nosological diagnosis in all patients (Table 3).

1. Chronic infectious-immune myocarditis based on lymphohistiocytic infiltration, including perivascular infiltration, was diagnosed in 11 patients, and in 8 patients it was active (Fig. 2). These patients included one with hemodynamically significant coronary atherosclerosis (Fig. 2a). Parvovirus B19 was identified in 2 patients. Twelve patients (almost exclusively with signs of myocarditis) had adipocytes concentrates under endocardium or in myocardial wall (Fig. 2i) with rare nuclei debris (Fig. 2j). Lipomatosis was considered as a marker and irreversible substrate of arrhythmias. Endocardium sclerosis and thickening, small focal interstitial sclerosis reflected duration of inflammation. In 2 patients morphological diagnosis was "lupus-myocarditis" (similarly with autoimmune "lupus-hepatitis"): it was characterized by signs of immune cytolysis (peripolesis and emperipolesis, Fig. 2b), vasculitis with perivascular bulbous sclerosis (Fig. 3d), and in one case - mitosis in cardiomyocytes (Fig. 2c). Immune cytolysis (with nuclear antigens exposure that may interact with intracellular lymphocytes) was morphological confirmation of antinuclear antibodies development: levels of specific ANA, other AHA in these patients were the highest (1:160-1:320), including anti-cardiomyocyte IgG. They had a history of autoimmune thyroiditis and polyvalent allergy, higher titers of anti-DNA IgG, anti-anticardiolipin IgM, and fibrinogen.

2. Chronic viral-immune (parvovirus B19) endomyocarditis with predominant endocardial infiltration but without eosinophils and neutrophils (Fig. 2f). Unusually low titer of anti-endothelial cell IgG (1:40) probably reflects massive AHA release in the immune complexes into the endothelium from the blood. Arrhythmias significantly varied (AF, atrial tachycardias, premature atrial beats PAB, PVB, and unsustained VT) and were resistant to all AAD. The second parvovirus-positive patient with myocarditis had minimal signs of endocarditis (Fig. 3f). Seven patients showed signs of active productive vasculitis (Fig. 3,a-c), other 7 patients had vessels sclerosis with significant lumen narrowing (Fig. 3,d-e). No patients had necrotising vasculitis. In 3 patients vasculitis was the leading morphological sign that was reflected in diagnosis.

3. Systemic vasculitis with cardiac injury: myocarditis with predominant productive vasculitis without necrosis and secondary (ischemic?) myocardial degeneration with foci of myolysis in one patient (Fig. 3h). In patient with more active vasculitis, systemic disease was confirmed by biopsy of the clear skin (leukoclastic vasculitis, Fig. 3j) without general clinical signs, or anti-neutrophil cytoplasmic antibodies (ANCA). Mild transient eosinophilia (6%), as well as eosinophils in the infiltrates (Fig. 3i), signs of endocarditis (Fig. 3g), and single blood clots in the myocardial microvasculature allowed to consider hypersensitive vasculitis and Loeffler's endomyocarditis. Daily paroxysmal AF was resistant to all AAD and combined with polytopic extrasystoles. The patient with less active vasculitis and myocarditis had a history of atopic asthma, hemorrhagic rash episode, hay fever, eosinophilia up to 20%, and typical angina with unchanged coronary arteries and paroxysmal AF. Periods of exacerbation alternated with long and often spontaneous remission. At the time of biopsy, eosinophils and ANCA were normal

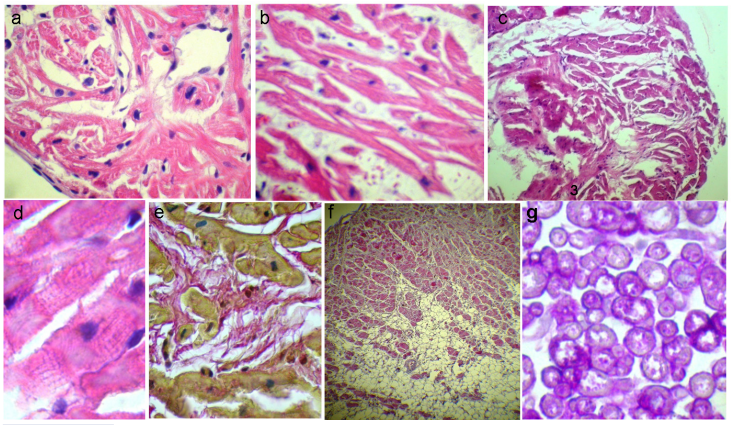

Figure 4: Key morphological changes in patients with genetic cardiomyopathies. Stained with hematoxylin and eosin (a-d, f), Van Gieson (e), and PAS-reaction (g). Large (a, b, d, e) and low (c, f, g) magnification. Disarray of cardiomyocytes with glomerular structures formation, cells arborization (disarray, a-c), cardiomyocytes with disappearance of the cross-striation and small intranuclear inclusions (d), mild interstitial sclerosis (e), accumulation of PAS-positive membrane-bound substance in cardiomyocytes (g)

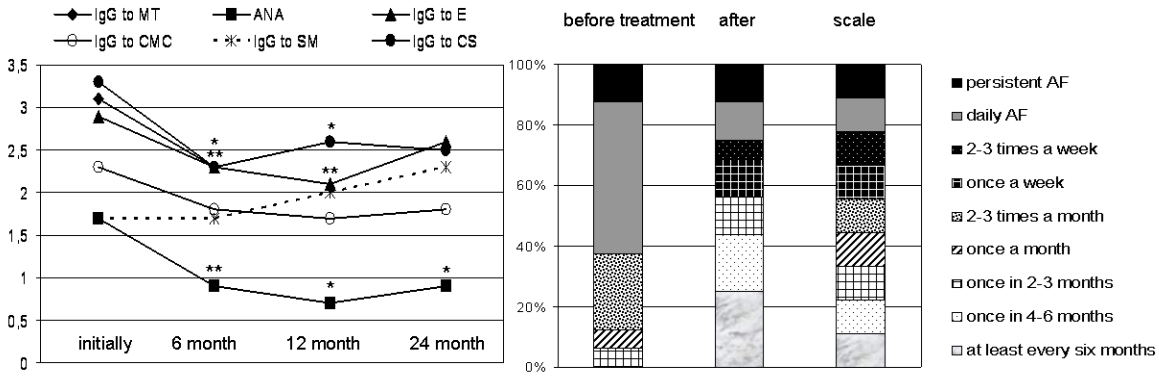

Figure 5: **Dynamics of anti-heart antibodies and the frequency of atrial fibrillation during therapy. Left - titers IgG to anti-myocardial tissue (MT), anti-cardiomyocytes (CMC), anti-smooth muscle (SM), anti-endothelial cells (E), anti-conducting system (CS) antibodies and specific anti-nuclear antibodies (ANA), measured as multiplies of normal; * significance of differences compared with baseline value with p <0.05, ** - p <0.01. Right - frequency of AF paroxysms during complex treatment (estimates after 6 months from the start of basic therapy)**

that did not allow to diagnose "gross" vasculitis (eg, Churg-Strauss syndrome).

4. Myocardial vasculitis (with minimal signs of myocarditis) in one patient was isolated (Fig. 3b) with concomitant thickening and sclerosis of the endocardium. Signs of the disease included transient (stress-induced) complete LBBB and stress-induced ischemia on myocardial perfusion scintigraphy without coronary atherosclerosis. Low titer of anti-endothelial cell IgG (1:80; antibodies' fixing in the vascular and endocardial endothelium?) was combined with specific ANA (1:80).

5. Unspecified genetic cardiomyopathy was diagnosed in two patients. Diagnose was based on the disarray of cardiomyocytes (Fig. 4,a-c) without clinical signs of hypertrophic cardiomyopathy. One of these patients (HHV6-positive in the blood and myocardium) also had small (viral?) inclusions in cardiomyocytes (Fig. 4d) and tender focal cardiosclerosis (Fig. 4e) thay may suggest history of myocarditis. Clinically, possible genetic nature of the disease was confirmed by AF development at the age of 16 years, and moderate mental retardation. At the same time, AF paroxysms recurred during sore throats and frequent acute respiratory viral infections. Titer of anti-endothelial cell IgG was increase up to 1:320, and titer of anti-myocardial IgG - up to 1:300. The second patient (with transient left bundle brunch block (LBBB) and history of paroxysmal supraventricular tachycardia) had fatty tissue in the myocardium, but no fibro-fatty replacement, and ventricular arrhythmias.

6. Fabry disease. EMB in patient of 32 years with persistent AF, AV block and minimal left ventricular hypertrophy revealed central myolysis foci in cardiomyocytes, PAS-positive substance in the membrane of cardiomyocytes (Fig. 4g), suggesting that storage disease. Also differential diagnosis included myocarditis, "athlete's heart" and mesenchymal dysplasia syndrome. Geneticist suggested Fabry disease taking into account biopsy data, which was confirmed by biochemical (level of A-galactosidase 5.1 nM/mg/h, normally - 48.6-150.3) and genetic (Glu283Lys (Q283E) mutation in the gene X-Gal) studies. Increased titer of anti-smooth muscle IgG up to 1:160 may reflect involvement of small vessels with accumulation of the globotriaosilceramid. Titers of other AHA were normal.

7. Morphological features of arrhythmogenic right ventricular dysplasia (ARVD) were observed in patients with frequent PVC and history of RFA of sustained right ventricular tachycardia, and included: subendocardial adipocytes up to 50% separating myocardium into segments; fibrotic septa with architectonics abnormalities of the myocardium and fibrosis area up to 25%; sclerosis and thickening of the endocardium, as well as no signs of myocarditis (Fig. 4f). Fat inclusions in the right ventricle on MRI supported ARVD. At the same time, patient had a history of ovarian dysfunction, subfebrile episode regarded as myocarditis, positive effects of NSAIDs; ECG revealed small negative T-waves in V1-V4, which lability allowed suggesting myocarditis. Levels of AHA remained normal.

Thus, EMB allowed to diagnose different immune-mediated inflammatory heart diseases in 78.9% patients and genetic – in 21.1% patients (Table 3), and their ratio was about 4:1.

At the end of the study, we obtained results of electron microscopy

Table 1: **Patients distribution by arrhythmia type and clinic date**

N	Type of arrhythmia	age	sex	CRP	L	EDV	IVS	LA	EF
1	paroxysmal AF	24	M	0	5.0	4.4	7	32	71
2	paroxysmal AF	38	F	0	5.3	4.7	7	65	59
3	persistent AF	50	M	0	6.1	5.2	10	69	56
4	persistent AF	45	M	0	5.8	4.9	8	63	65
5	paroxysmal AF + SVT + PAB	54	F	0.8	6.8	4.4	8	38	70
6	paroxysmal AF + SVT + PAB	33	F	0	7.3	4.1	6	42	58
7	paroxysmal AF + SVT + PAB	29	M	0	7.5	4.8	9	51	66
8	paroxysmal AF + PAB +RBBB	64	F	0	4.6	4.7	10	63	58
9	paroxysmal AF + PAB	50	M	0	6.2	5.3	8	67	58
10	paroxysmal AF + PAB	60	F	0	6.9	4.9	9	35	64
11	paroxysmal AF + PAB	32	M	0	5.4	4.8	9	60	62
12	persistent AF + AV block +RBBB	32	M	0	5.7	4.8	14	203	68
13	persistent AF + AV block	45	F	0	7.7	5.2	9	42	73
14	paroxysmal AF + PAB + PVB + 1st degree AV block	46	M	0	6.8	5.3	10	59	73
15	paroxysmal AF + PAB + PVB + unsustained VT	54	F	0	5.2	4.5	8	46	72
16	paroxysmal AF + PAB + PVB + unsustained VT	49	M	0.1	7.0	5.0	9	80	69
17	PVB + VT	31	F	0	6.1	4.6	10	40	58
18	transient LBBB + SVT	46	F	0	4.1	4.9	10	52	63
19	transient LBBB	34	M	0	4.4	5.4	7	62	56

AF – atrial fibrillation, SVT – paroxysmal supraventricular tachycardia, PAB – premature atrial beats, RBBB – right bundle branch block, LBBB – left bundle branch block, AV – atrioventricular, PVB – premature ventricular beats, VT – ventricular tachycardia, CRP – C-reactive protein (mg/dl), L - leukocytes in the blood (x109/ml), EDV – end-diastolic volume of left ventricle (ml), IVS - interventricular septum (mm), LA – left atria (ml), EF – ejection fraction of left ventricle (%)

Table 2: Results of endomyocardial biopsy

PCR results / morphological changes	n	%
parvovirus B19 / herpes simplex virus type 6 (PCR)	2/1 (of 18)	16.7%
endocardium sclerosis / thickening	8	42.1%
lymphohistiocytic infiltration in endocardium	2	10.5%
subendocardial / interstitial lipomatosis	12	63.2%
interstitial lymphohistiocytic infiltration (>14 and 7-10)	11/3	73.7%
necrosis / myolysis / apoptosis of cardiomyocytes	6	31.6%
immune cytolysis (emperipolesis, peripolesis)	2	10.5%
mitosis in cardiomyocytes	1	5.3%
disarray of cardiomyocytes	2	10.5%
dystrophy / hypertrophy of cardiomyocytes	14/7	73.7/36.8%
productive vasculitis / arteriosclerosis / angiopathy	7/7/1	36.8/36.8/5.3%
interstitial edema / swelling	12	63.2%
interstitial sclerosis	14	73.7%
fat (up to 50%) + fibrosis (up to 25%) + cell reorganization	1	5.3%
PAS-positive substance in cardiomyocytes	1	5.3%
no changes	0	0
Total	19	100%

in three patients with myocarditis (Fig. 3,k-l): lysosomal myolysis, microbodies in cardiomyocytes, mitochondrial wrinkling, cristae adhesion, absence of matrix; vascular endothelium swelling, thickening of the microvessels basic membrane, precipitate on the endothelium surface, increased pinocytosis. The most marked changes were revealed in the mitochondria that are, apparently, both play a key role in the pathogenesis of metabolic disorders, and also are potential target for drug exposure.

Comparison of the results of non-invasive and morphological studies showed that AHA had the highest diagnostic value (Table 4). We found not only correlation between the diagnosis and specific ANA ($r = 0.65$; $p < 0.01$), but also a clear correlation between immune and morphological activity of myocarditis. In patients without viral genome, specificity of ANA was 100%. Other signs had a high specificity but low sensitivity. Following factors were the most important for diagnosis of the genetic nature of arrhythmias: age younger than 40 years (sensitivity 75%, negative predictive value of 88.9%), isolated nature of arrhythmia (75% and 90.9%, respectively), family history and possible genetic markers (specificity and positive predictive value of 100%), and early repolarization syndrome (specificity 78.6%, negative predictive value of 84.6%).

Drug treatment included selection of the most effective AAD and basic myocarditis therapy. IC class AADs were the most effective: aethacizine, allapinine (including combination with sotalol), propafenone; 4 patients received amiodarone, 3 patients (with treatment-resistant AF) - β-blocker. Warfarin was prescribed in 9 patients.

Antiviral therapy (acyclovir, 750 mg/day IV and/or 1.6-2.0 g/day per os for 10-21 days) was administered to 10 patients with viral genome in the blood/myocardium or high titers of antiherpetic antibodies. Epstein-Barr virus was eliminated from the blood, but not the herpes virus type 6. Parvovirus-positive patients underwent IV infusion of immunoglobulin, 10 and 12.5 g, respectively.

All patients with verified myocarditis received hydroxychloroquine 200 mg/day for 15.0 [7.0; 24.0] months. Steroids were administered

Table 3: Distribution of patients according to nosological diagnosis based on EMB

initial diagnosis	diagnosis according to EMB	n	% patients	
myocarditis?	chronic / subacute infectious-immune myocarditis, including	11	57.89%	
	virus-positive (parvo B19 in myocardium/ EBV in the blood)	2		
	active / borderline	8/3		
	lupus-myocarditis	2		78.9%
	chronic viral autoimmune endomyocarditis (parvo B19)	1	5.26%	
	systemic vasculitis, including	2	10.53%	
myocarditis with predominant vasculitis?	hypersensitive	1		
	myocardial vasculitis (with minimal signs of myocarditis)	1	5.26%	
myocarditis? genetic cardiomyopathy?	viral (HHV6) + genetic cardiomyopathy	1	5.26%	
	genetic cardiomyopathy	1	5.26%	21.1%
	Fabry disease	1	5.26%	
myocarditis? ARVD?	arrhythmogenic right ventricular dysplasia	1	5.26%	
Total		19	100%	

to 14 patients: mean dose was 31.1 ± 12.5 mg/day, maintenance dose 6.2 ± 2.2 mg/day, median duration of therapy - 18.0 [4.0, 25.5] months. Patients with systemic vasculitis had pulse therapy with metylprednisone 1000 mg No. 3 (n=1) or azathioprine 150 mg/day (n=2).

Median follow-up of patients was 4 years (48.0 [31.0, 62.0] months). The level of all AHA, except anti-cardiomyocyte IgG and anti-smooth muscle IgG, decreased significantly in six months (Fig. 5); in 1 and 2 years effect of treatment remained, but weakened (with decreasing doses and drug withdrawal). In 4 women side effects caused early steroid dose decline: peripheral myopathy in two patients and severe sweats and hot flashes in 2 cases. More frequent intercurrent infections were observed only with azathioprine. Causes of exacerbations were "common" infection in 10 patients, amiodarone-induced thyrotoxicosis - in 3 patients, dose reduction or drug withdrawal -in 9 patients. Median number of exacerbations per patient during follow-up was 3 [14 3], and they required to increase the dose of steroids by 1/3-1/2 from baseline.

In 16 patients AF at baseline was resistant to AAD (daily paroxysmal AF or sustained AF more than in 60% patients, Fig. 5). Basic therapy in 14 patients with myocarditis resulted in significant decrease of median AF episodes from 8 [5; 8] to 3 [1.25; 7.75] (see scale in Fig. 5): more than 40% patients had AF paroxysms once a month or less. After persistent suppression of inflammatory activity, 4 patients underwent RFA of pulmonary vein with complete AAD withdrawal. In 2 patients AF remained constant. In other patients satisfactory antiarrhythmic effect was achieved with drug therapy. In one patient with vasculitis, tachycardia-dependent LBBB disappeared but recurred after steroids withdrawal. A patient with ARVD had ICD implantation, a patient with Fabry disease – pacemaker implantation.

Discussion

Despite the predominance of supraventricular arrhythmias (AF in 16 patients, only in 3 - in combination with PVC), right ventricular EMB was informative in 100% of patients, including 2 patients with isolated LBBB. In literature, there are only two consistent

Table 4: The sensitivity and specificity of various clinical, laboratory and instrumental signs in the diagnosis of myocarditis

diagnostic signs	sensitivity	specificity	+	-
anamnestic triad	16.7%	100%	100%	25%
duration of history < 1 year	21.4%	100%	100%	26.6%
acute onset	64.3%	75%	90%	37.5%
onset correlation with infection	50%	75%	87.5%	30%
history of sore throat / tonsillitis	50%	75%	87.5%	30%
systemic immune signs	35.7%	100%	100%	30.8%
microvascular angina / ischemia	35.7%	100%	100%	30.8%
increased level of anti-O-streptolysin	21.4%	100%	100%	26.4%
increased CRP	14.3%	100%	100%	25%
non-specific inflammatory signs	35.7%	75%	83.3%	25%
viral genome in blood	7.1%	75%	50%	18.8%
specific ANA	78.6%	66.7%	91.7%	40%
anti-endothelial cell IgG ≥ 1:160	78.6%	66.7%	91.7%	40%
anti-cardiomyocyte IgG ≥ 1:160	64.3%	100%	100%	37.5%
anti-conduction system IgG ≥1:160	92.9%	66.7%	92.9%	66.7%
isolated atriomegaly	64.3%	75%	90%	37.5%
pericardial effusion	21.4%	75%	75%	21.4%
DND of RP (scintigraphy)	22.2%	0	66.7%	0
local perfusion disorders (scintigraphy)	33.3%	100%	100%	14.3%

«+», positive predictive value, «-», negative predictive value, DND, diffuse non-uniform distribution, RP, radiopharmaceutical

articles discussing biopsies in resistant to treatment "idiopathic" AF performed in 1991 and 1997.[7,8] Biopsy of interatrial septum revealed signs of myocarditis in 66% of cases, while in ventricles myocarditis was found only in 22% of patients in the first article and in 25% - in the second article. The number of patients in both studies by A.Frustaci was 26. There are no other published biopsy data in "idiopathic" AF.

This study showed a greater frequency of myocarditis in ventricular biopsy specimens (78.9%) compared with those of atrial biopsies by A.Frustaci, and in 60% active myocarditis was revealed. We suggest that the cause was in patients' selection: EMB was performed only in those with high levels of anti-heart antibodies. Our patients had significantly longer history of arrhythmias and consistently more frequent fibrosis (73.7% compared to 57.2% by A.Frustaci). Biopsy also allowed to differ genetic disease including ARVD from myocarditis in 4 patients: frequency of errors in the diagnosis of ARVD in such patients is known to reach 50%.[11] Disarray was revealed in 2 patients, and in the absence of hypertrophic cardiomyopathy clinical signs clearly indicated the genetic nature of the disease. One can expect signs of cardiomyopathy progression of in these patients over time.

There are no published data on the high frequency of subendocardial lipomatosis (63.2%) and productive vasculitis (36.8%) in "idiopathic" arrhythmias. Both signs correlated with inflammatory infiltration ($r = 0.88$, $p < 0.001$ and $r = 0.58$, $p < 0.05$, respectively). There are only a few mentions of isolated myocardial vasculitis as the cause of life-threatening arrhythmias[12] and "idiopathic» PVBs.[13] Perhaps, adipose tissue is formed instead of ceased cardiomyocytes, from stem cells that present in the myocardium.[14,15] Therefore, data on the lipogenesis mechanism in ARVD are interesting: nuclear translocation of plakoglobin suppresses the signaling pathway involved in the development of the right ventricle outflow tract, and leads to induction of stem cells transformation into adipocytes.[16] The activation of stem cells may be confirmed by mitosis identification in lupus-myocarditis: myocardium is a tissue with very low level of regeneration (about 0.05% of the cells), but in diseases the intensity of this process increases 10-70-fold.

In one patient with "idiopathic" arrhythmia we observed such active endocarditis that had never been previously described, although the possibility of viral valves infection was confirmed experimentally and clinically.[17] Immune endocarditis (Libman-Sacks, as part of systemic vasculitis) is also known. Some of our patients, of course, are associated with systemic diseases but do not reach all criteria; this may be due to genetically determined response features.

We proved high significance of AHA in the diagnosis of myocarditis that is fundamentally important. Data on the increased level of AHA in "idiopathic" arrhythmias and conduction abnormalities have been obtained previously,[18] but the case of AHA development was unclear. Some study proved correlation between titer of anti-endothelial cell IgG and severity of humoral rejection of the transplanted heart .[19] Significantly higher frequency of AHA compared with control (15.7%) in patients with ventricular (64.2%) and supraventricular arrhythmias (44.0%), as well as high frequency of myocarditis (81%) in these patients were proved only in 2012.[20] Anti-β1-receptor antibodies had 90% positive predictive value regarding histological changes.

In Russian articles significantly higher AHA titers in patients compared to healthy donors along with no between patients with coronary artery disease, myocarditis and cardiomyopathy were described.[21] The role of abzymes - catalytic anti-DNA antibodies that can cause double-stranded DNA hydrolysis and detorsion, and thus have a direct cytotoxic effect – was studied. Two-fold increase in their level in patients with immune myocarditis was confirmed ,[22] as well as correlation with severity of the disease: high level in malignant myocarditis, normal level in benign myocarditis (with increase of catalytic activity in 1/3 of patients) and post-myocarditis cardiosclerosis (without increase of activity). Thus, normal level of these antibodies does not exclude myocarditis that we observed in our study but suggests less activity.

The sensitivity of acute-phase proteins, including CRP, was very low: in majority of patients with active myocarditis they remained within normal limits. Primary chronic disease was observed in 57.1% (including patients with lupus-myocarditis and active endocarditis).

According to the diagnosed myocarditis, background therapy was administered to all patients. Clinical effect was seen in patients with baseline ineffectiveness of antiarrhythmic therapy. Formally, these patients had indications for RFA, but unrecognized myocarditis significantly reduces its effectiveness. In addition, 4 patients with all formal indications for RFA achieved satisfactory antiarrhythmic effect without surgery.

Doses of steroids in the treatment of myocarditis, especially its arrhythmic type, have not been studied. In some patients with "idiopathic" arrhythmias and verified myocarditis aggressive therapy was used.[7, 8, 10, 23] In low doses, prednisone shows predominantly anti-inflammatory but not immunosuppressive properties. However, metipred 16 mg/day in 104 patients with "idiopathic" AF and elevated CRP in combination with constant propafenone therapy resulted in significantly less AF recurrences compared to the control group (9.6% and 50%, respectively), and AF transformation to permanent form (2% and 29%, respectively) with mean follow-up about 2 years.[24] Nature of AF also remained unclear.

Our study showed that clinical effect in myocarditis can be

achieved with different regimens of background therapy (from hydroxychloroquine monotherapy to combination of metipred pulse therapy with azathioprine), and intensity of this effect depended not only on the disease activity, but also on the duration of the disease and irreversible structural changes in the myocardium (fibrosis, lipomatosis).

Conclusions

Thus, EMB confirmed nosological diagnosis in all patients with "idiopathic" arrhythmias (predominantly AF, as well as PVBs and LBBB). Prevalence of immuno-mediated inflammatory diseases (78.9%) over genetic diseases (21.1%) was found; in one case their combination can not be excluded. Level of various anti-heart antibodies, including specific ANA, had the greatest diagnostic value among noninvasive markers. Lack of correlation of arrhythmia onset with infection, acute onset, and coronary atherosclerosis and hypertension could not rule out myocarditis; more than half of the patients had primary chronic myocarditis. Antiviral and immunosuppressive therapy tailored according to myocarditis severity, could improve the effectiveness of antiarrhythmic therapy in patients resistant to AAD or prepare them for the RFA.

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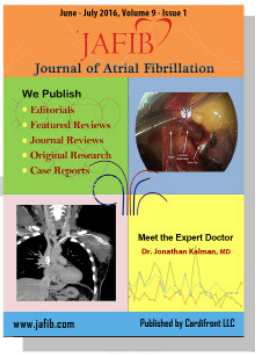

Assessment Of Sinoatrial Node Function In Patients With Persistent And Long-Standing Persistent Forms Of Atrial Fibrillation After Maze III Procedure Combined With Mitral Valve operation

Kulikov Aleksei A, Bokeria Leo A

A.N. Bakoulev Scientific Center for Cardiovascular Surgery.

Abstract

Research objective: Assessment of sinoatrial node function after Maze III procedure combined with a mitral valve operation.

Methods: 100 patients were included in the research with persistent and long-standing persistent forms of atrial fibrillation (AF) and need of operative treatment concerning valve disease.

The following preoperative preparation methods were executed to all patients: 1. Electrocardiogram in 12 standard assignments; 2. Two-dimensional echocardiographic with assessment of systolic and diastolic functions of the left ventricle, size of the left atrium and grade of valve disease; 3. Transesophageal echocardiography for exclusion of blood clots in the left atrium and left atrial appendage; 4. Coronary angiography for exclusion of coronary heart disease; 5. Computer tomography for examination of cardiac chambers and anatomic characteristics of pulmonary veins.

Electric cardioversion in X-ray operating room conditions was performed on all patients. After successful restoration of sinus rhythm, electrophysiological examination (EP) of heart was carried out. Then, on the first or second day after EP study, Maze III procedure combined with a mitral valve operation was performed.

Results: Following the results of Maze III procedure combined with correction of valve disease, disposal of AF was observed in 95% of patients. 46% of patients had stable sinus rhythm to the moment of discharge from the hospital. 24% of patients had atrial rhythm with the maximum heart rate of 80-110 bpm (according to results of 24-hour Holter monitoring). For 25% of patients, it was necessary to implant a pacemaker. According to results of EP study, 13% of these patients suffered from sick sinus syndrome before operation. For 9% of the remaining 12% of patients, the indications for pacemaker implantation were atrioventricular nodal rhythm with low heart rate and pauses more than 3 sec long. For 1% of patients the indication was second degree AV block (type 2) and second degree SA block (type 2); for 1% the indication was complete heart block, and for 1% it was atrial rhythm and pauses more than 3 sec long.

13% of patients with an atrial rhythm and normal heart rate developed typical atrial flutter (AFL) in the early postoperative period. For all of them the RF catheter ablation with linear ablation of the right atrial isthmus and creation of isthmus block was effective, and further recurrence of AFL was not observed.

Conclusions: In the early postoperative period Maze III procedure combined with a mitral valve operation proved to be an effective surgical technique of treatment of persistent and long-standing persistent forms of AF. Only 12% of patients had dysfunction of sinus node work due to iatrogenesis.

Introduction

For treatment of persistent and long-standing persistent forms of atrial fibrillation combined with mitral valve operation several surgical techniques are used. The Maze procedure is based on the principle of prevention of atrial fibrillation by interruption of all potential re-entry ways. To direct an impulse from sinus node to AV-node multiple cuts are made in such a way, that do not allow the critical volume of atrial tissue to support fibrillation process, thus preserving atrial contraction. This procedure has several major functional advantages over other surgical techniques, allowing to reach almost at all patients four therapeutic objectives: control of heart rate, restoration and maintenance of sinus rhythm, thromboembolic complications risk decreasing and restoration of normal heart hemodynamics. In our research we used operation modification - cryomodification of Maze III procedure by means of the Atricure device in combination with RFA of the right atrium. It is a method of choice in treatment of atrial fibrillation refractory to medicamentous therapy. [1, 2, 3, 4, 5, 6, 7] Despite of the use of the combined technic, at several patients dysfunction of sinus node (SND) was observed. It manifested itself by a wide range of electrophysiological anomalies. On a surface ECG dysfunction of sinus node shown itself as a severe form of sinus bradycardia, sinus pauses or a sinus arrest, sinoatrial exit block, atrial tachyarrhythmias, the alternating episodes of bradiarrhythmias and tachyarrhythmias

Key Words:

Sinoatrial, Atrial Fibrillation, Maze III Procedure.

Disclosures:
None.

Corresponding Author:
Alex Kulikov,
A.N. Bakoulev Scientific Center for Cardiovascular Surgery,
Moscow,
Russia.

Table 1: Patient characteristics

Characteristics	Values
Number	100
Men (%)	48
Age (years)	59,3±10,2
AF duration (years)	4±4,2
Antiarrhythmic therapy (drugs/patient)	3±0,45
Electrical cardioversion (n)	15
Valvular affection (years)	21,8±12.8
Tricuspid valve insufficiency (n)	80, (80)
NYHA class	
I (n)	14, (14)
II (n)	20, (20)
III (n)	66, (66)
F-waves (mV)	0,15±0,09
Left ventricular ejection fraction (%)	61±8,6
Size of the left atrium (cm)	5,1±1,5
Cardiothoracic index (%)	58,6±4,7
Thromboembolic anamnesis (n)	12, (12)
Aorto-coronary artery bypass graft surgery (n)	9, (9)
Arterial hypertension (n)	16, (16)
Diabetes (n)	5, (5)

Note. Values are means ± SD or % unless otherwise is indicated

and the inadequate response of heart rate to emotional or physical activity.

The main aims of this long prospective research were: 1) to identify the type and frequency of postoperative electrophysiological manifesting of sinus node dysfunction; 2) to estimate dynamics of sinus node function in postoperative period; 3) to estimate the possible reasons of these pathological changes after Maze III procedure at patients with valve pathologies and lack of electrophysiological symptoms of sinus node dysfunction at a preoperative stage.

Invasive electrophysiology study is commonly used for a sinus node function assessment. However, there are only few reports about the use of this method at a significant amount of patients with mitral and tricuspid valve disease and persistent and long-standing persistent forms of atrial fibrillation before Maze III procedure combined with mitral valve operation.

On the basis of the conducted research the complex assessment of the sinus node function, function of the atrioventricular conduction system (atrioventricular node and His-Purkinje system) and electrophysiological parameters of atriums at patients with mitral and tricuspid valve disease and persistent and long-standing persistent forms of atrial fibrillation is given.

Material And Methods

100 patients were included in the research with persistent and long-standing persistent forms of atrial fibrillation (AF) and need of operative treatment concerning valve disease.

The following preoperative preparation methods were executed to all patients: 1. Electrocardiogram in 12 standard assignments; 2. Two-dimensional echocardiography with assessment of systolic and diastolic functions of the left ventricle, size of the left atrium and grade of valve disease; 3. Transesophageal echocardiography for exclusion of blood clots in the left atrium and left atrial appendage; 4. Coronary angiography for exclusion of coronary heart disease; 5. Computer tomography for examination of cardiac chambers and

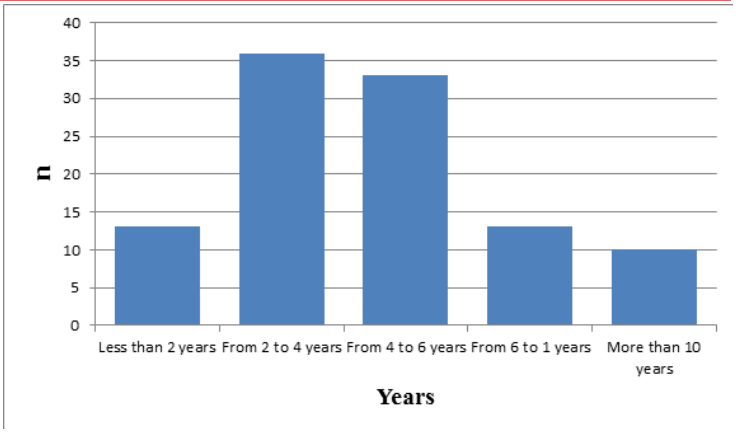

Figure 1: Distribution of AF duration (n=100)

anatomic characteristics of pulmonary veins.

Electric cardioversion in X-ray operating room conditions was performed on all patients. After successful restoration of sinus rhythm, electrophysiological examination (EP) of heart was carried out. Then, on the first or second day after EP study, Maze III procedure combined with a mitral valve operation was performed.

Electrical Cardioversion

Electrical cardioversion was performed in a X-ray operating room, fully equipped for tracking the vital functions of a patient (an electrocardiogram, measurements of arterial blood pressure, frequencies of breath and saturation of blood by oxygen) and for carrying out resuscitation actions (a defibrillator, artificial respiration unit and an electropacemaker in case of development of heart blockades).

Two electrodes on a thorax surface were imposed, one electrode was located to the right of the chest under a clavicle, and the second — in the area of the apex of the heart, centered in the sixth — seventh intercostal space on the anterior axillary line.

The defibrillator generating a bipolar impulse was used. Electric discharge was begun with 200 J, and if necessary, the force of each following discharge was increased on 50 J.

After cardioversion sinus rhythm was successfully restored to all patients.

Electrophysiological Examination (EP)

All antiarrhythmic drugs were cancelled for 5 half-lives before EP. Usually, under local anesthesia of 0,5 % Novocain solution the left or right femoral vein and the left subclavian vein were punctured. Through them four electrodes for carrying out the EP study were positioned.

The first quadripolar electrode was positioned in the high right atrium (HRA). Thus, the distal couple of poles could be used for stimulation, and proximal - for registration of activity of HRA.

The second electrode (quadripolar) was established in the apex of the right ventricle for diagnostic stimulation and recording EG of the right ventricle.

The third quadripolar electrode was placed in a projection of His bundle.

The fourth ten-polar electrode was set in the coronary sinus (CS) for registration of activity of right and left atriums.

The refractory periods of atriums were studied from three points: HRA, AV-node area and CS.

After positioning the catheters we registered patient's own heart rhythm for 5-10 minutes. Then we began with stimulation of HRA

Table 2: EP study results

	Data	Normal values
P-P (msec)	1000,4±300,3	600-1000
P (msec)	128,0±24,2	<120
PQ (msec)	220,1±36,5	140-210
QRS (msec)	118,6±20,1	70-110
QT (msec)	435,2±98,3	350-440
AH (msec)	88,2±34,8	60-125
HV (msec)	48,3±15,5	35-55
Atrial conduction time (msec)	84,7±27,3	24-50
Intra-atrial conduction time (msec)	106,3±18,4	
SNRT (msec)	1426,2±346,4	<1500
CSNRT (msec)	425,7±147,1	350-525
Sinoatrial Conduction Time (msec)	174,4±72,8	<215
Atrial FRP (HRA) (msec)	290,0±45,4	
Atrial RRP (HRA) (msec)	360,3±24,0	
Atrial ERP (HRA) (msec)	258±33,6	180-330
Atrial FRP (CS) (msec)	278±24,2	
Atrial RRP (CS) (msec)	323±25,6	
Atrial ERP (CS) (msec)	231,5±37,1	180-330
AV node FRP (msec)	256±33,7	
AV node RRP (msec)	380,9±130,4	
AV node ERP (msec)	225,6±25,2	250-400
Antegrade Wenckebach point (msec)	365,0±86,5	350-460

Normal values are given according to Mark E. Josephson ["Clinical Cardiac Electrophysiology: Techniques and Interpretations", 1979]

with a frequency of 5-10 bmp. higher than patient's own rhythm. After 1 min. we stopped pacing and registered post-stimulation activity of sinus node. Then resumed stimulation with a frequency of 10 bpm exceeding the previous, and had all the procedure repeated. Thus, the increasing stimulation of atriums was led up to the frequency of 150-160 bpm. If at that time no paroxysm of tachycardia or second-degree atrioventricular block was registered, the frequency of stimulation continued to be increased until atrioventricular block is reached.

Afterwards we carried out single extrastimul pacing of atriums. Two frequencies of pacing were used (100 and 120 bpm.). The coupling interval of extrastimul was reduced by 10 msec each time, before reaching the refractory period of atriums.

The sinus node function was estimated by definition of sinus node recovery time (SNRT) - measurement of the duration of a post-stimulation pause between the last stimulated complex and the first atrium complex caused by a spontaneous impulse from the sinus node. Pacing began with a frequency exceeding a sinus rhythm for 10-20% and continued for 60 sec. The maximum value of a post-stimulation pause was assumed as SNRT. Also corrected sinus node recovery time (CSNRT) as difference between SNRT and sinus cycle length was calculated. The sinus node function was considered normal if the maximum SNRT didn't exceed 1500 msec, and CSNRT — 525 msec.

The sinoatrial conduction time (SACT) was measured as a difference of a value of an incomplete compensatory pause as a result of discharge of sinus node from a premature atrial beat and a value of a spontaneous atrial cycle.

Cryomodification Of Maze III Procedure In Combination With Rfa Of The Right Atrium During Mitral Valve Surgery

For the surgical treatment of atrial fibrillation at all patients cryomodification of the operation Maze III procedure on a classical technique was executed. Several of the surgical incisions were replaced with linear ablation using bipolar radiofrequency energy by Atricure device.

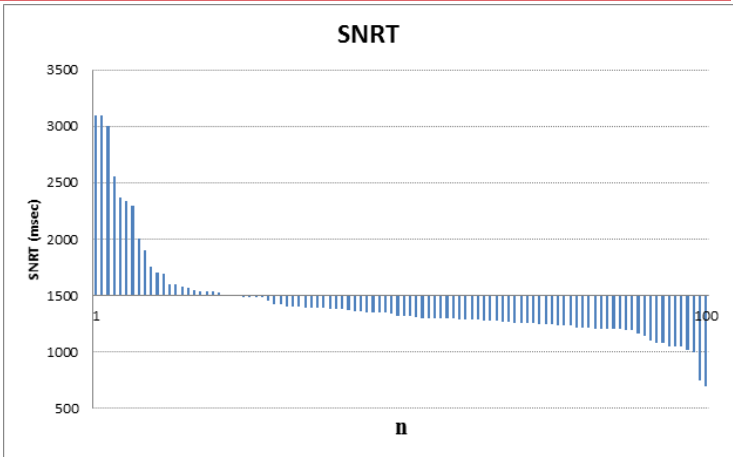

Figure 2: Distribution of CSNRT values in the research. The normal value is supposed to be less than 1500 msec

Operation was combined with valve surgery. At all patients correction of mitral valve defect was made (at 44 patients – valve replacement and at 56 – valve repair) and at 80% of patients tricuspid valve repair was executed.

Statistical Analysis

Statistical analysis was carried out by nonparametric methods. When comparing constant figures the Mann-Whitney test was applied, and in the analysis of reliability of reactions of these figures in dynamic supervision in each of groups Vilkokson's test was used. When comparing dichotomizing figures the bilateral test of Fischer was applied. In all cases of the comparative analysis of figures were considered reliable at $p<0,05$. At multiple comparisons the Bonferonni adjustment on number of the groups included in comparison was considered. The correlation analysis between variables was carried out on Spirmen's method.

Results

Patient Characteristics

Research included 100 adult patients (48 men (48%) and 52 women (52%)) with persistent and long-standing persistent forms of atrial fibrillation and valve pathologies (see tab. 1). Average age of patients – 59,3±10,2 years with dispersion from 21 to 77 years. Existence of AF was confirmed by a surface electrocardiogram in 12 standard assignments or 24-hour Holter ECG monitoring.

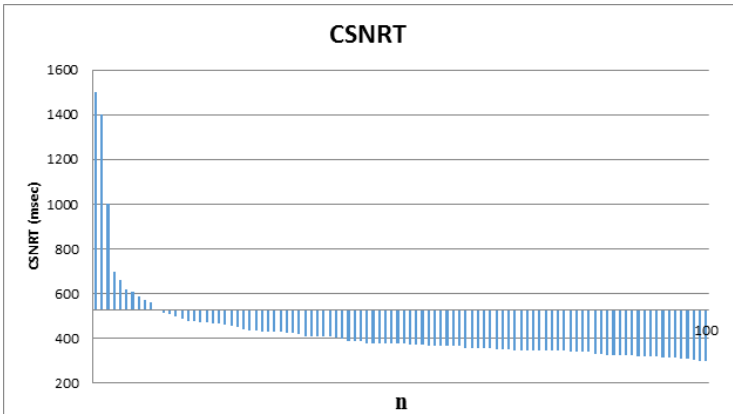

Figure 3: Distribution of CSNRT values in the research. The normal value is supposed to be less than 525 msec

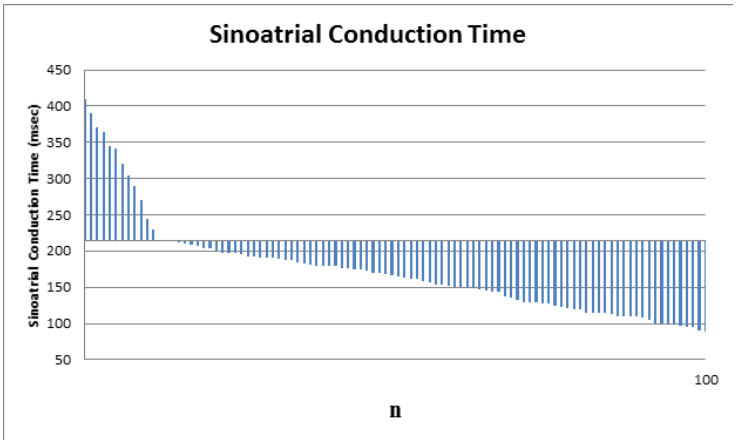

Figure 4: Distribution of Sinoatrial Conduction Time values in the research. The normal value is supposed to be less than 215 msec

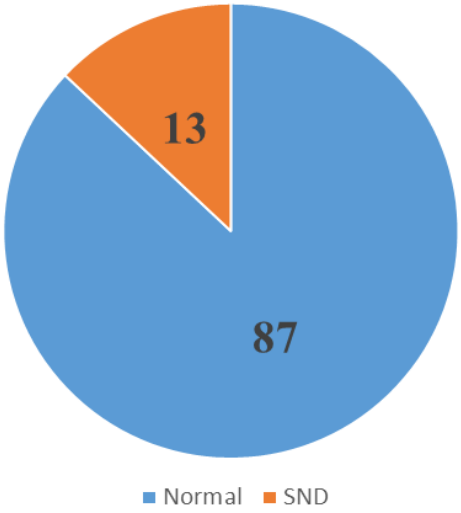

Figure 5: Distribution of SND

Duration of AF from 1 year to 17 years, with average 4±4,2 years (see fig. 1). To all patients antiarrhythmic therapy was tried out, but proved to be ineffective. At 15% of patients attempts of restoration of a sinus rhythm by means of the electric cardioversion were applied, however it was not possible to control a normal sinus rhythm in long perspective. All patients had an organic pathology of the mitral valve with an average duration in 21,8±12.8 years. Also at 80% of patients tricuspid valve insufficiency was revealed. The functional class of heart failure on NYHA 2,7±0,75. The average size of the left atrium was 5,1±1,5 cm, average left ventricular ejection fraction - 61±8,6%, and a cardiothoracic index - 58,6±4,7%. 12% of patients had the anamnesis of thromboembolic complications. 9% of 100 patients had aorto-coronary artery bypass graft surgery earlier, 16% of patients had arterial hypertension and 5% – diabetes.

Electrophysiological Examination Results

During the research all the patients retained normal sinus rhythm with a frequency from 45 to 94 bpm (see tab. 2). The average duration of P wave 128,0±24,2 ms, PQ interval - 220,1±36,5 ms, QRS complex width - 118,6±20,1 ms. The time of carrying out an impulse from sinus node to His bundle (AH interval) and from His bundle to ventricles (HV interval) made 88,2±34,8 ms and 48,3±15,5 ms respectively. Average atrial conduction delay was 84,7±27,3 ms. Average intra-atrial conduction delay was 106,3±18,4 ms. Average sinus node recovery time (SNRT) was 1426,2±346,4 ms, corrected sinus node recovery time (CSNRT) - 425,7±147,1 ms, and sinoatrial conduction time - 174,4±72,8 ms. The value of the functional refractory period (FRP) of the right atirum made 290,0±45,4 ms. The average relative refractory period (RRP) of the right atrium - 360,3±24,0 ms. And the average effective refractory period (ERP) of the right atrium - 258±33,6. For the left atrium indicators of refractory periods were: FRP - 278±24,2 ms, RRP - 323±25,6 ms and ERP - 231,5±37,1 ms. Average values of a refractory periods of AV-node: FRP - 256±33,7 ms, RRP - 380,9±130,4 ms and ERP - 225,6±25,2 ms. Antegrade Wenckebach point was 365,0±86,5 ms. Average retrograde ERP of AV-node - 316,2±76,4 ms.

At 11% of patients pathological lengthening of CSNRT – 900,3±300,6 msec was revealed. And at 13% - pathological lengthening of sinoatrial conduction time (SACT) – 340,2±80 msec (see fig. 2-4). At 11% of patients pathological lengthening of SACT was followed by pathological lengthening of CSNRT, but at 2% of patients other signs sinus node dysfunction (SND), except lengthening of SACT was not discovered.

Thus, total 13% of patients with AF and sinus node dysfunction (SND) were initially diagnosed (see figure 5).

The study of refractivity of various areas of the atria has shown that the ERP of AV-node was minimum in comparison with other areas and had mean value 225,6±25,2 msec. The longest ERP was found in the HRA area - 258±33,6 msec, that is significantly higher, than in the AV-node ($p<0,01$). In the area of the coronary sinus the ERP had intermediate value, on average 231,5±37,1 msec. This is significantly lower, than the ERP in HRA ($p<0,01$), but no statistically significant differences were found from the value of ERP of the AV-node (see figure 6).

The mean duration of PQ interval was 220,1±36,5 mm. The mean atrial conduction time was 84,7±27,3 msec, the mean AV-node conduction in the anterograde direction (AH) and the mean time of conduction of His-Purkinje system (HV) - 88,2±34,8 msec and 48,3±15,5 msec respectively. Thus, the lengthening of PQ interval was a consequence of the impulse conduction delay through the atria and AV-node.

Therefore, it is possible to draw a conclusion that patients with AF had decrease in functional ability of the AV-node.

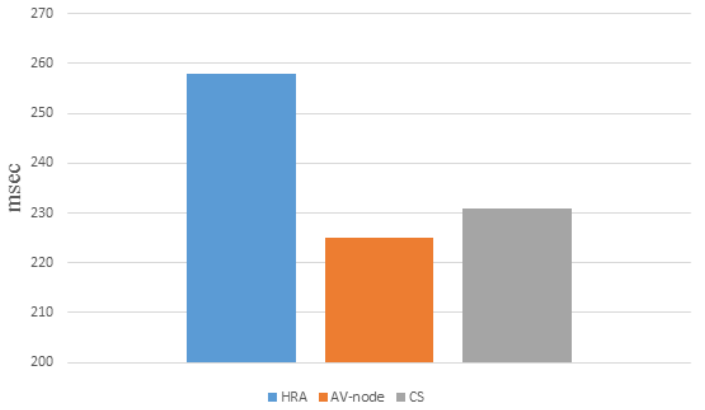

Figure 6: Duration of the effective refractory periods of various areas of atria. HRA – high right atrium, CS – coronary sinus, AV-node – atrioventricular node

Cryomodification Of Maze III Procedure In Combination With Rfa Of The Right Atrium During Mitral Valve Surgery Results

Consequently, by results of Maze III procedure with valve disease correction disposal of AF was observed at 95% of patients. At 46% of patients at the moment of discharge from the hospital the stable sinus rhythm remained. At 24% of patients the atrial rhythm with the maximum heart rate 80-110 bpm was observed (by the results of 24-hour Holter ECG monitoring). 25% of patients needed permanent pacemaker implantation. At the same time, by results of EP-study, initially before surgical treatment 13% of patients suffered from sinus node dysfunction. From the remained 12% at 9% of patients the indication for pacemaker implantation were the nodal rhythm with low heart rate and pauses more than 3 sec long, one patient had episodes of transient AV block (second degree, second type) and SA block (second degree, second type), one patient had a complete heart block and at the last one – atrial rhythm with pauses more than 3 sec long.

At 13% of patients with the atrial rhythm and normal heart rate in the early postoperative period typical atrial flutter has developed. To all of them the radio-frequency ablation of cavo-tricuspid isthmus with creation of the bidirectional block was performed, and further recurrence of atrial flutter wasn't observed.

Discussion

The mechanisms involved in development of sinus node dysfunction after Maze III procedure are: 1) direct consequence of the surgical treatment; 2) the general postoperative complications of the open-heart surgery. Anyway, sinoatrial node can be either directly damaged or its function can be lowered because of the external reasons, without direct damage of the sinus node tissue. The surgical factors directly changing anatomy and functional ability of sinoatrial node or an adjacent myocardium (or all together), include a mechanical trauma, injury of the sinoatrial node arteries, ischemia or necrosis. [8, 9, 10, 11]

Influence of the surgical cuts applied during Maze III procedure on the atrial innervation, humoral homeostasis and the subsequent rhythm effect is still not fully studied. The main concern is caused by changes of integrative ability of sinus node area, autonomous nervous regulation and blood supply. Arterial supply of sinus node can be more variable, than it was supposed earlier, that makes critical all the area of the vena cava superior. [12]

Anyway, violation of a blood supply of the sinus node artery can contribute to its dysfunction, but most likely does not take essential part in pathogenesis, especially in case of cryomodification of Maze III procedure, which allows protecting the anatomic region of sinus node. Nevertheless, the process of generation of an electric impulse in the atria is difficult and is connected not only with one center of automatism. Experimental and clinical evidences force us to assume that the functional part of sinus node isn't so well defined as it was supposed earlier. [8, 13-15]

Conclusions

In our research after cryomodification of Maze III procedure in combination with RFA of the right atrium during mitral valve surgery 46 (46%) patients have been discharge from the hospital with the stable sinus rhythm and 24 more (24%) had the atrial rhythm with adequate chronotropic characteristics.

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Concomitant Left Atrial Appendage Clipping During Minimally Invasive Mitral Valve Surgery: Technically Feasible and Safe

Ashraf Alqaqa MD[1], Shabiah Martin MD[2], Aiman Hamdan MD, FACC[1], Fayez Shamoon MD, FACC[1], Kourosh T. Asgarian DO[2]

[1]Department of Cardiology, St Josephs Medical Center, Paterson, NJ,USA. [2]Department of Cardiothoracic surgery, St Josephs Medical Center, Paterson, NJ,USA.

Abstract

Background: It is believed that most of thrombi form in the left atrial appendage (LAA)before they emboli. Different surgical and percutaneouse approaches were suggested to manage the LAA. In this study we are evaluating the safety of clipping the LAA via minithoractotomy approach.

Method: All consecutive patients who had minimally invasive mitral valve surgery with concomitant LAA clipping between December 2012 and February 2014 were included in the study. LAA exclusion was performed using AtriClip® LAA Exclusion System (Cincinnati, Ohio, AtriCure®). The patient s' clinical characteristics, intraoperative complications, and in-hospital coarse were obtained by reviewing the medical records.

Result: Total of 22 patients(50% males) were included in the study. The median ages was 66.0 years (IQR: 50.8 to 81.3). Eight(36%) had mitral valve replacement and the rest had mitral repair surgery. Five(23%) patients needed blood product transfusion during the surgery. No clip related bleeding was observed and no perioperative mortality was recorded.

Conclusion: During minimally invasive mitral valve surgery, Concomitant exclusion of the left atrial appendage using AtriClip® can be performed rapidly and safely.

Introduction

Although the left atrial appendage (LAA) is not the only site of intracardiac thrombus formation, it is the main site where most thrombi form prior to embolization.[1] Several approaches to this problem have been suggested, either by excising or excluding the left atrial appendage (LAA) in patients who are at high risk of stroke. This is particularly relevant for , patients whom chronic anticoagulation is contraindicated. Furthermore, management of the LAA is recommended by American College of Cardiology in patients who are undergoing mitral valve surgery.[2,3]

LAA clipping is a new US FDA- approved technique which has been increasingly used to exclude the LAA from the circulation during cardiac surgery in patients who have atrial fibrillation or have high CHADS2 risk score.[2-4] The atrial clip has usually been deployed via median sternotomy incision.[4-7] Herein we examine the safety and feasibility of epicardial clipping of the LAA via a mini-thoracotomy approach during minimally invasive mitral valve surgery.

Key Words:

Left Atrial Appendage,Mitral Valve Surgery,Transesophageal Echocardiogram.

Disclosures:
None.

Corresponding Author:
Ashraf Alqaqa,
Department of Cardiology
St Josephs Medical Center, 703 Main Street,Paterson, NJ 07503.

Methods

Setting

This study was conducted in a 700 bed, tertiary care teaching hospital in the northeastern US. Because the study used only pre-existing post-operative records, the study was declared exempt by the St. Joseph's Healthcare System Institutional Review Board.

Patients And Protocol

All consecutive patients who had no previous history of cardiac surgery and had minimally invasive mitral valve surgery with concomitant LAA exclusion using The AtriClip® LAA Exclusion System (Cincinnati, Ohio, AtriCure®) were included. The AtriClip® is composed of two rods, which are made from titanium and interconnected with nitinol hinges. The clip is covered in a braided polyester lining.[4-6]

Patient demographics, clinical characteristics, intra-operative complications, and in-hospital course were collected by reviewing the medical records. Transesophageal echocardiogram (TEE) was used intraoperatively to exclude left atrial thrombus.

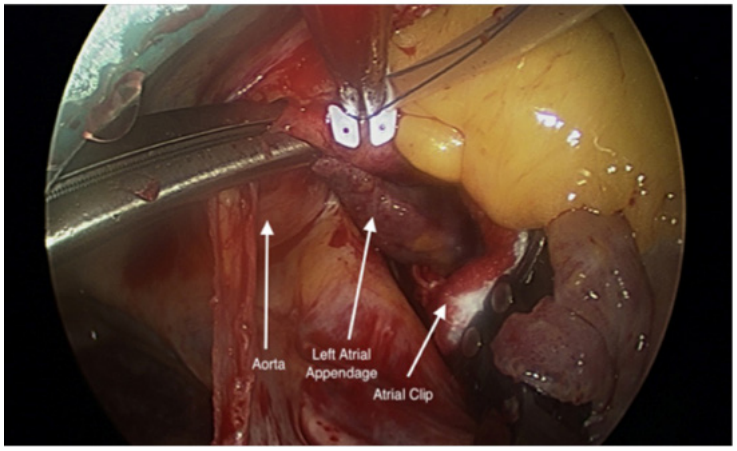

Figure 1: By mobilizing the ascending aorta, the base of the LAA can be visualized posterior to the aorta in the coronal junction of the transverse sinus. The atrial clip is advanced through the coronal junction of transverse sinus and placed over the base of the LAA

Technique Of Laa Clip Placement Via Right Minithoracotmy

First, the femoral artery and vein are exposed and unroofed. The anterior portion of each vessel is exposed only with minimal dissection. This provides more support during cannulation and reduces potential risk of seroma formation. A five to six centimeter right minithoracotomy incision is then made in the fourth intercostal space in the midaxillary line. An Alexis soft tissue retractor is placed, and a small chest tube incision is made in the ninth intercostal space. A stay stitch is then placed in the tendonious portion of the diaphragm and pulled out through the chest tube incision. This retracts the diaphragm down and provides better exposure to the entire heart and pericardium. The pericardium is then opened and the cardiac structures are examined.

Carbon dioxide(CO2) is then introduced into the chest. Intravenous heparin is given to achieve an activated clotting time (ACT) greater than 450. Then, femoral artery and vein cannulas are placed and positioned under TEE guidance. Cardiopulmonary bypass is initiated. The aorta is cross clamped using a Chitwood clamp and the heart is arrested using antegrade and retrograde cardioplegia. The transverse sinus is exposed and examined in order to visualize the left atrial appendage (LAA). This is done to assess the location and size of the LAA and its base. The base of the LAA is measured with the AtriClip sizer (AtriCure®). The mitral valve is then exposed through the right superior and inferior pulmonary veins. Watersons groove is not dissected. The interatrial septum is left undisturbed so it can be retracted and allow for better exposure of the mitral valve and left atrium. The left atrium is retracted with a Cardiovation left atrial retractor (Edwards Life Sciences). The mitral valve portion of the operation is then completed and the atrium is closed. The LAA is not addressed until after the LA is closed. This is because it is difficult to safely expose the LAA with the atrial retractor in place. The LAA is again exposed through the transverse sinus. The AtriClip® is then slid through the transverse sinus until the pericardium on the opposite (left) side is seen. The Atriclip® is placed over the LAA with the help of endoforceps (Fig-1). The LAA is eased into the transverse sinus and pulled towards the right chest. The clip is then released and assessed to assure it is at the base of the LAA (Fig-2). The clip is deployed just before opening the aortic cross-clamp and while the heart is still immobilized.

The heart is then de-aired and the CO_2 is stopped. The cross-clamp is then removed, the patient is ventilated and weaned off cardiopulmonary bypass. The mitral valve and LAA are evaluated by TEE. Particular attention is paid to determine flow into the LAA and that the clip is at the base of the LAA. The patient is then de-cannulated.

One pericardial and one right pleural drain are placed through the original ninth intercostal space chest tube incision. The mini thoracotomy and groin incisions are then closed. The coronary sinus catheter is removed. TEE is performed to assess the success of the LAA(Fig-3A) with no color flow. (Fig-3B)

Statistical Analysis

Baseline characteristics are presented as a median (interquartile range (IQR)). The thromboembolic risk after surgery for mitral regurgitation is estimated to be 1.9 ± 0.4% at 30 days.[7] The minimum event rate that a 22 patient might be expected would be 0.42. This study was not powered to evaluate stroke prevention.

Results

Total of 22 patients were included in our study. The median age was 66.0 years (IQR: 50.8 to 81.3). Eight (36%) patients had mitral valve replacement (Three patients had severe mitral stenosis, 1 patient had infective endocarditis, and 4 with severe mitral regurgitation, which were un-repairable due to severe annular calcification). The rest of the patients had mitral valve repair surgery to treat severe degenerative mitral regurgitation. The ACC guidelines recommend management of the LAA during mitral valve surgery. All patients had concomitant

Table 1: Clinical characteristics

Clinical characteristic	
Age Median(IQR)	66.0 yrs (50.8 to 81.3)
Male	11(50%)
BMI	26.4(23.0 to 32.0)
White ethnicity	15(68%)
HTN	15(68%)
DM	4(18%)
CHF(NYHA>2)	13(59%)
Renal Failure	2(11%)
Ever smoked	3(14%)
On aspirin	8(37%)
History of PCI	2(9%)
Urgent surgery	11(50%)
Dyslipidemia	9(41%)

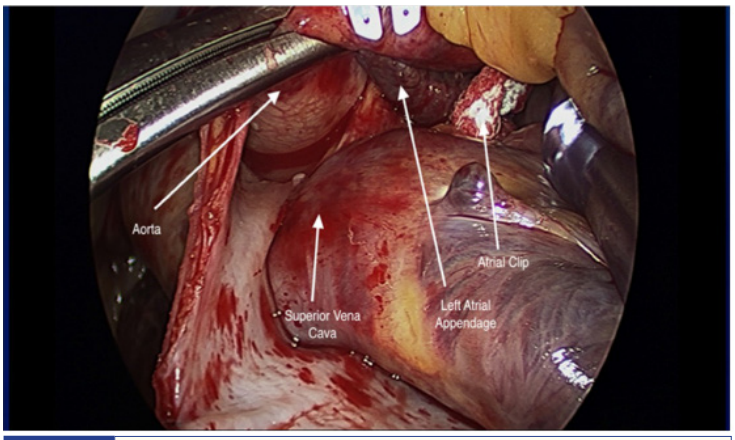

Figure 2: Once the clip is secured at the base and judged satisfactory by the primary surgeon, the LAA is clipped using appropriately sized clip

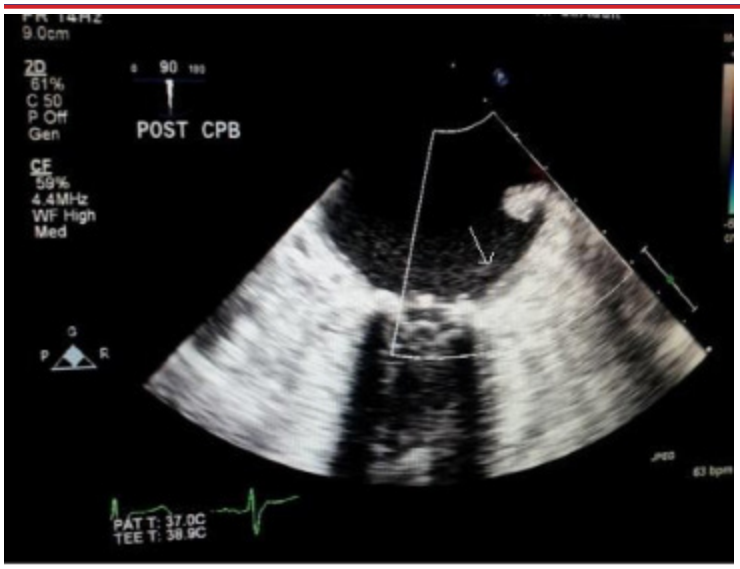

Figure 3A: TEE image shows complete obliteration of the LAA post clipping (Arrow)

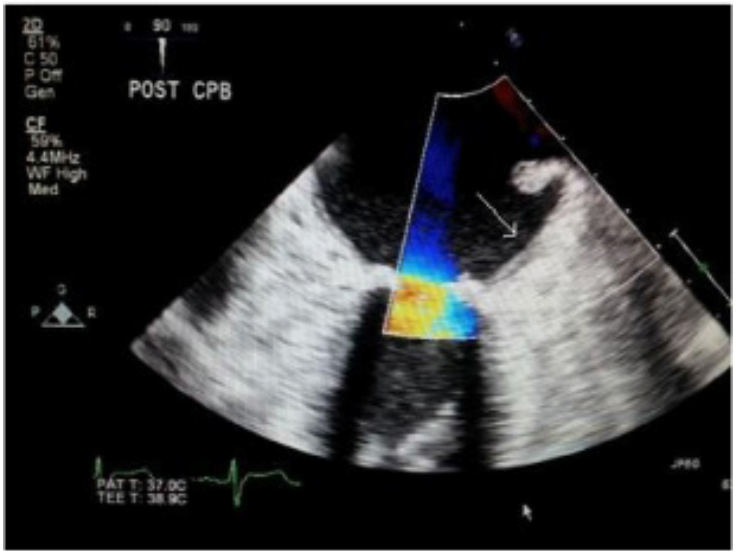

Figure 3B: TEE image shows no color flow across the LAA orifice post clipping (Arrow)

LAA clipping as recommended by the ACC guidelines. Table-1 shows the different clinical characteristics of the cohort.

Intra-Operative And Postoperative Course

All patients had transesophageal echocardiogram(TEE), confirming the absence of left atrial thrombus before the surgery. All patients had minimally invasive mitral valve surgery through right mini-thoracotomy incision. All patients were operated on by the same surgeon. All patients were on-pump during the surgery. Bioprosthetic mitral valve was used in all patients who required valve replacement.

Intraoperatively, 5 patients required blood product transfusion. All patients had successful clipping of the LAA from the first time and no repositioning was needed. Two patients had re-operation to evacuate chest wall hematoma. Both patients were males, have hypertension, and underwent annuloplasty surgery; however, there was no in-hospital mortality.

IQR:interqurtile range;BMI: body mass index; HTN: hypertension; DM: diabetes mellitus; CHF: congestive heart failure; PCI percutaneous coronary intervention.

Discussion

LAA surgical excision or exclusion (by stapling or suturing) are frequently performed as a concomitant procedure during atrial fibrillation cardiac surgery or mitral valve surgery. However, those procedures have been associated with high failure rates and increased risk of bleeding.[8-11]

LAA clipping is one of the interesting recent technologies used to epicardially exclude the left atrial appendage from the circulatory system during cardiac surgery. This has been suggested to decrease the cardioembolic stroke rates, especially in patients who have atrial fibrillation or high CHADS2 score.[4-6] Moreover, recent reports have postulated that epicardial clippings will electrically isolate the LAA and decrease the recurrence rate of atrial fibrillation.[12]

Table 2: Intra-operative data

Intra-operative data	
Valve replacement	8(37%)
Aortic Cross clamp time (min)	71.0(IQR 62.3 to 80.0)
Cardiopulmonary bypass time(min)	92.5 (IQR 81.0 to 105.0)
Blood product needed during the surgery	5(23%)

Preclinical studies had shown that the epicardial exclusion of the LAA is safe and can be achieved without inserting foreign body into the left atrium.[4] The first human application of the LAA clip was reported by Salzberg et. al in 2010 in patients who underwent cardiac surgery via median sternotomy approach.[5] Ailawadi and coworkers also reported successful clipping of the LAA in 70 patients using the AtriClip in patients undergoing elective cardiac surgery via median sternotomy.[6]

We are reporting the first human application of the atrial clip through sternal-sparing, direct vision, right-sided minithoracotomy as a concomitant procedure in patients who are undergoing mitral valve surgery. The clipping was achieved rapidly and safely with no intraoperative complications. And no inhospital mortality.

Clipping the LAA appendage during minimally invasive mitral valve surgery can be achieved with relative ease and without significant increase in the time of the surgery. This approach may change the surgeons management approach and could expand the practice of clipping the LAA in this subset of patients. In addition, it could offer a less invasive management option to those patients with atrial fibrillation who have contraindication for chronic anticoagulation.

Limitation

This is a small retrospective study, which should be replicated using a prospective design of a larger number. It is not powered to evaluate stroke prevention and no outpatient follow up was done. There was also no subsequent follow-up of the success of the procedure by either TEE or CT post-operatively.

IQR:interqurtile range

Conclusions

Occluding the LAA using AtriClip device during minimally invasive mitral surgery can be achieved safely and rapidly. Applying the LAA clip via min-thoracotomy approach offers a new and safe approach for patients who are at high risk of cardio-embolic stroke and undergoing cardiac surgery.

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Safety And Utility Of Cardiac MRI In A Patient With Pericardial Effusion And A Recently Implanted Conventional Pacemaker

Hussam Ali, MD, FESC[1], Gianluca Epicoco,[1] MD, Antonio Sorgente,MD, PhD, FHRS[2], Pierpaolo Lupo,MD[1], Riccardo Cappato,MD, FHRS, FESC[3]

[1]Arrhythmia & Electrophysiology Unit II, Humanitas Gavazzeni Clinics, Bergamo, Italy. [2]Heart & Vascular Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi (UAE). [3]Arrhythmia & Electrophysiology Research Center, Humanitas Clinical & Research Center, Rozzano (Milan), Italy.

Abstract

Cardiac MRI is usually not recommended in the acute phase after pacemaker implantation, particularly for conventional devices. This case concerns a 66-year-old patient who developed significant pericardial effusion subacutely after implantation of a dual-chamber, conventional pacemaker. Cardiac MRI was planned to elucidate the characteristics of the pericardial effusion and was performed under controlled conditions without any consequences. Images analysis was very helpful to reveal the non-hemorrhagic nature of the pericardial effusion and correct endocardial position of the leads. In conclusion, cardiac MRI might be feasible and useful, under controlled conditions, in selected non-pacing dependent patients with conventional pacemakers.

Introduction

A 66-year-old man with paroxysmal atrial fibrillation and sick sinus syndrome was referred to our center for pacemaker implantation. Basal trans-thoracic echocardiogram showed no structural abnormalities. The patient underwent uneventful implantation of a dual-chamber, conventional (non-MRI conditional), pacemaker (Medtronic/Adapta). Atrial and ventricular active fixation leads were implanted in the right appendage and ventricular apex, respectively. Before discharge, device interrogation and chest x-ray confirmed optimal parameters and positioning of the both leads. Two weeks later, the patient presented with chest discomfort and exertional dyspnea. Vital signs were stable, and 12-lead ECG showed normal sinus rhythm. Echocardiogram demonstrated abundant pericardial effusion (the asterisk in Fig.1A) without echocardiographic evidence of hemodynamic instability. Fluoroscopy check, chest x-ray, and device interrogation showed correct location and functioning of the pacemaker system.

To elucidate the underlying mechanism of this pericardial effusion, whether it was secondary to a breach in the myocardial wall or a reactive inflammatory process in the presence of active fixation leads; a cardiac MRI was planned. After discussion with our radiologists, this imaging technique was preferred to CT imaging since it may provide better visualization of the pericardial sac, and characterization of soft tissues and pericardial effusions.[1,2] Considering the theoretical risk of recent leads torsion /movement, MRI is usually not recommended in the acute phase after device implantation, particularly for non-MRI conditional devices.[3] However, cardiac MRI was programmed in this case through an ongoing strict protocol by our equip that tests MRI safety/efficacy in non-pacing dependent patients with conventional devices under controlled conditions. After detailed discussion with the patient and obtaining his informed consent, 1.5 Tesla cardiac MRI was performed three weeks after the implantation. During MRI, the pacemaker was programmed to backup VVI pacing (40 bpm) with continuous electrocardiographic and saturation monitoring, and in the presence of a senior electrophysiologist during the entire exam. The MRI exam was accomplished without any consequences regarding both the patient and the pacemaker functioning.

Images analysis revealed non-hemorrhagic nature of the pericardial effusion, and correct endocardial position of the right ventricular lead tip (the arrows in Fig.1B/C). Successively, and due to the persistent, abundant and symptomatic pericardial effusion despite pharmacological therapy; elective pericardiocentesis was planned. The analysis of the pericardial fluid confirmed the cardiac MRI findings and the non-hemorrhagic nature of the effusion. An echocardiogram performed two weeks after the drainage showed only minimal posterior effusion (the asterisk in Fig.1D).

Conclusions

In conclusion, cardiac MRI might be feasible and useful, under

Key Words:
Cardiac MRI, Conventional Pacemaker, Pericardial Effusion.

Disclosures:
None.

Corresponding Author:
Hussam Ali,
Arrhythmia & Electrophysiology Unit II,
Humanitas Gavazzeni Clinics, Via M. Gavazzeni 21, 24125 Bergamo, Italy.

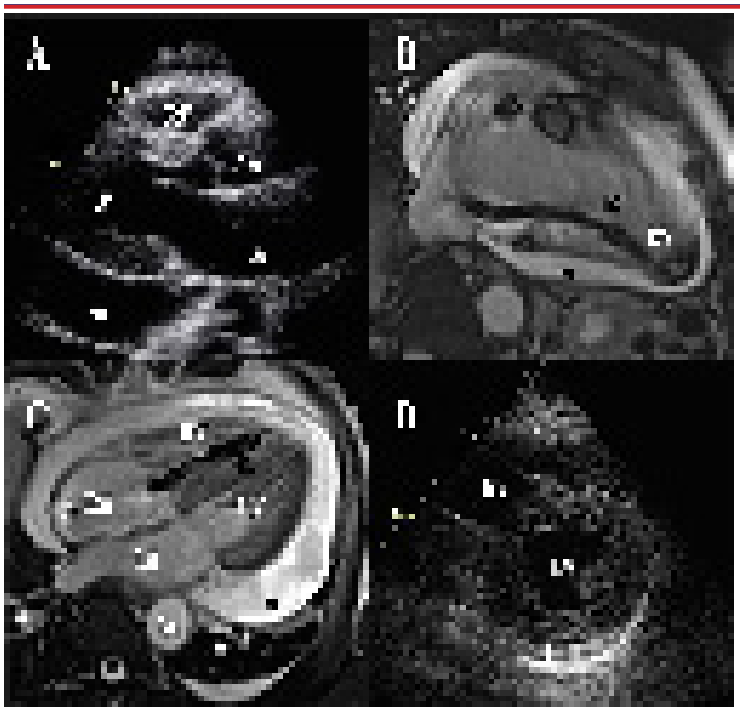

Figure 1: **A: An echocardiogram image showing abundant pericardial effusion (the asterisk). B and C: Cardiac MRI showing the pericardial effusion (the asterisk) and correct intracardiac location of the ventricular lead tip (the arrow). D: Echocardiogram control two weeks after pericardiocentesis showing minimal residual pericardial effusion (the asterisk). Ao = aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle**

controlled conditions, in selected non-pacing dependent patients with conventional pacemakers to characterize the nature of pericardial effusion and the position of intracardiac leads. A careful risk-benefit analysis should be individualized for each case, and the patient should be informed about the potential risks and alternative options.

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Internal Jugular Vein Complete Thrombosis After Dual Chamber Pacemaker Implant

Angelo Placci, Maria Mattioli, Maria Francesca Notarangelo, Gianluca Gonzi, Marco Zardini

Parma University Hospital, Parma, Italy.

Abstract

Venous thrombosis after pacemaker implant is a known, although often underrecognized condition that can challenge system revision or upgrading, leading occasionally to thromboembolic complications. Several factors are considered to promote thrombus formation. Among them, alteration of blood flow mechanics due to the presence of catheters in the vessel lumen may itself play a pivotal role. Hereby we present the case of a 65-year old men who underwent a dual-chamber pacemaker implant in another institute for sick sinus syndrome by means of left cephalic venous access. About two months later he started experiencing neck swelling, pain and dysphagia. Six months later, ultrasonography and CT-scan revealed complete jugular vein thrombosis caused by a lead loop at the level of the left subclavian vein. Of note, thrombosis occurred despite proper oral anticoagulation with warfarin undertaken for coexisting atrial fibrillation. It's important to keep in mind this possible complication of pacemaker implant to allow for early diagnosis and better treatment chances. This case report is an example of how proximal catheter displacement may promote thrombus formation, probably by affecting blood flow mechanics, even in spite of proper oral anticoagulation.

Case Report

A 65-year old men underwent a dual chamber pacemaker implant (Boston Advantio DR) in another hospital center due to sick sinus syndrome. The atrial and ventricular passive fixation leads were inserted by cut down approach by means of the left cephalic vein. No periprocedural complication was reported, and electric parameters (pacing threshold, impendance, and sensing) were optimal. At discharge, warfarin was started because of persistent atrial fibrillation.

A few months later the patient complained of pain and left latero-cervical neck swelling. Only six months later doppler ultrasonography and CT scan revealed left internal jugular vein (IJV) thrombosis caused by a lead loop occurring at the origin of the left subclavian vein [Figure 1, 2]. Pacing and sensing parameters were stable. The patient underwent an unsuccessful lead extraction procedure; therefore, a new contralateral implant was performed by means of subclavian vein access. Although taken into account, the hypothesis of a hypercoagulability state was deemed as low due to absence of thrombotic disease at young age both in the patient's and in his familial history. In the literature, to our knowledge, only a few cases of IJV thrombosis following a permanent pacemaker implant were reported.[1-5]

Key Words:
Venous Thrombosis, Pacemaker Implantation, Pacemaker Implantation Complications.

Disclosures:
None.

Corresponding Author:
Maria Mattioli,
UO Cardiologia,
Azienda Ospedaliero-Universitaria di Parma
Via Gramsci 14, 43126 – Parma, Italy.

Comment

Venous thrombosis after pacemaker implant is a known, although underdiagnosed condition that can challenge system revision or upgrading, and poses a threat of possible thromboembolic complications.[4] Numerous cases of venous complications due to pacemaker leads have been reported, namely stenosis, occlusions, and superior vena cava syndrome, the catheter itself acting as a nidus for clot formation, as happens for other intravascular devices (e.g. central venous catheters). Available epidemiologic studies show an incidence of pacemaker-related venous complications around 14-38%.[6,7] Most cases (97%) are asymptomatic, thus revealing that this condition is broadly underdiagnosed. The clinical spectrum is variable, ranging from asymptomatic forms, usually unmasked during venography at time of system revision or upgrading, to lateral neck swelling and pain or, in extreme cases, pulmonary embolism.

Although numerous risk factors were proposed (i.e. number of leads, age of leads, lead material, personal history of previous thrombosis, systemic infetion),[5] attempts to define precise risk factors are, to date, inconclusive.

Factors involved in the pathogenesis of upper extremity and internal jugular deep venous thrombosis include hypercoagulable states, but alteration in flow mechanics caused by the presence in the vessel lumen of the lead itself[8] is considered to play a pivotal role in

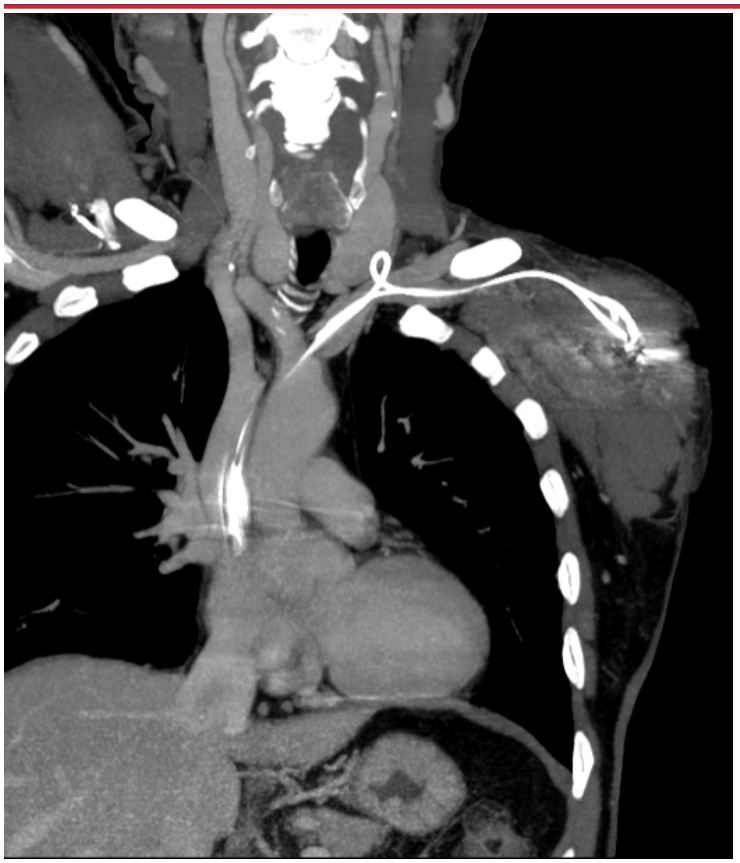

Figure 1: Neck and thoracic contrast tomography showing a lead loop at the origin of the left subclavian vein

thrombus formation. Endothelial dysfunction due to inflammation by continuous lead trauma may further act as a procoagulant factor. Moreover, ligation of the access vein (cephalic vein) can initiate thrombus formation and promote further propagation.

This case report enphasizes that it is important to remind that homolateral pain, dysphagia and lateral neck tumour after a pacemaker implant can suggest internal jugular vein thrombosis, a condition requiring early diagnosis to restore blood flow using antithrombotic drugs to allow better chances of successful lead extraction. In this particular case, since no alteration in routine post-implantation tests were reported, we assumed that the displacement of the pacemaker lead and its subsequent wire loop became a nidus for clot formation and propagation, possibly by promoting blood stasis even in a patient undergoing proper anticoagulant therapy.

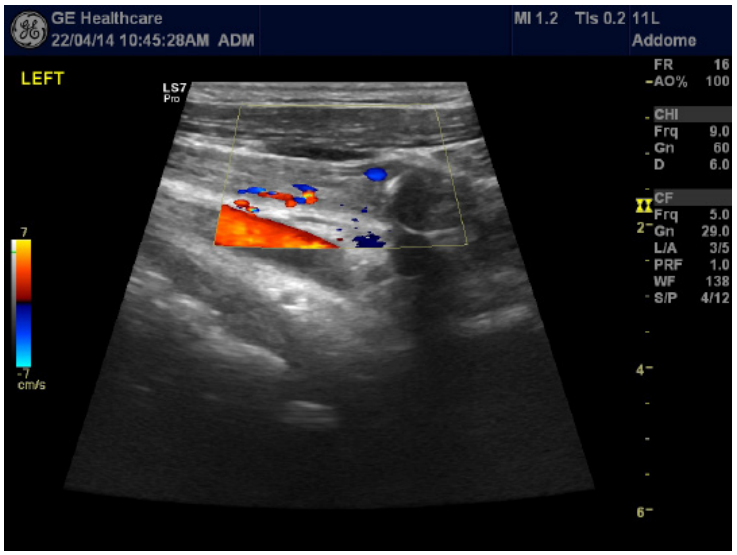

Figure 2: Doppler ultrasonography showing internal jugular vein thrombosis

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Junctional Beats During Cryo-Ablation Of The Slow Pathway For The Elimination Of Atrioventricular Nodal Reentrant Tachycardia

Murat Sucu, Vedat Davutoglu, Esra Polat

Gaziantep University Medical Faculty Department of Cardiology Gaziantep Turkey.

Abstract

The patient was a 39-year-old female with recurrent paroxysmal, regular narrow QRS complex tachycardia. Atrioventricular nodal reentrant tachycardia (AVNRT) was induced. The cryo-ablation attempts (-80 °C, 240 second) were performed in the inferior–posterior triangle of Koch. We observed several junctional beats during cryo-ablation. After successful cryo-ablation, AVNRT induction was repeatedly checked during a waiting period of 30 minutes without recurrence. In our case we demonstrated that junctional beats can be observed during cryo-ablation. We believe this to be the first description of junctional beats occurring during cryo-ablation of AVNRT.

Case Report

The patient was a 39-year-old female with recurrent paroxysmal, regular narrow QRS complex tachycardia. The patient had signed informed consent before the baseline electrophysiology study and patient was investigated in the fasting state without sedation. All anti-arrhythmic drugs were discontinued for at least five half-life periods. Surface electrocardiography (ECG) and endocardial electrocardiograms were recorded on a multichannel recording system (Pruka Cardiolab, GE HealthCare, Milwaukee, WI, USA). Two 6 F diagnostic quadripolar catheters were inserted percutaneously via the right femoral vein and positioned in the high right atrium, His-bundle region. A 6 F decapolar catheter was inserted via right femoral vein and placed inside the coronary sinus. A standard electrophysiology study was performed. Baseline surface electrocardiogram was normal and intracardiac intervals revealed an HV interval of 44 ms after programmed atrial stimulus. The tachycardia cycle length was 260 ms, and earliest retrograde atrial activation at the His bundle catheter. AVNRT was induced and diagnosed on the basis of standard diagnostic criteria. Dual AV nodal physiology was determined by a sudden AH or HA jump of at least 50 ms in response to programmed atrial or ventricular extra stimulation or demonstration of dual AV node physiology with earliest retrograde atrial activation at the His bundle catheter, measured ventricular atrial (VA) time<70 milliseconds during tachycardia. A combination of intracardiac electrocardiograms and anatomical approaches was conducted to identify target sites for ablation of the slow pathway in the triangle of Koch. Cryo-ablation was performed using a 7 Fr cryocatheter (Freezor® Xtra, CryoCath Technologies, Quebec, Canada) with a 6 mm-tip electrode. Cryo-mapping was carried out first at a temperature of -30°C for a maximal duration of 30 seconds to test the electrophysiological effect on the target sites using programmed stimulation that reproducibly demonstrated dual nodal physiology or induced AVNRT.

Four corresponding cryo-ablation attempts (-80°C, 240 seconds) were performed in the inferior–posterior triangle of Koch. If AVNRT was still inducible, cryo-ablation was interrupted and cryo-mapping was performed at the new target sites. We observed several junctional beats during each attempt at cryo-ablation, cryo-ablation, and immediately we stopped cryo-ablation application (Figure 1). When junctional beats occurred during cryo-ablation, the catheter was moved more posteriorly, resulting in successful ablation without complication. After successful cryo-ablation, AVNRT induction was repeatedly checked during a waiting period of 30 minutes.

Discussion

Radiofrequency (RF) ablation of the slow pathway has become first-line therapy for the treatment of AVNRT. Cryo-ablation provides a useful, safe technique for slow pathway ablation. The ability of cryo-ablation to test the functionality of specific ablation sites before production of a permanent lesion may eliminate accidental AV block.[1] During cryo-ablation, usually accelerated junctional tachycardia is not seen and therefore cannot guide lesion delivery.

In every attempt within 80-100 second of cryo-ablation we observed junctional beats in all four cryo-ablations but we did not see junctional beats during cryo-mapping. When junctional beats occurred during cryo-ablation we terminated and the catheter was moved more posteriorly. As it is well known that during cryoablation

Key Words:
AVNRT, Cryoablation, Junctional Beat.

Disclosures:
None.

Corresponding Author:
Murat Sucu
Gaziantep University Medical Faculty Department of Cardiology
Gaziantep Turkey.

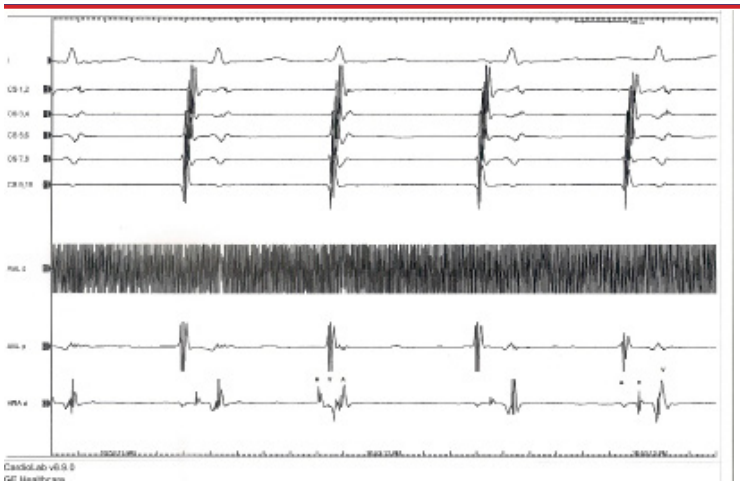

Figure 1: **The panel is arranged from top to bottom as leads D1, coronary sinus (CS 9,10 proximal, CS 1,2 distal) and ablation catheter (Abl) in the triangle of Koch's high right atrium (HRA) catheter in the His bundle area. A junctional beat on cryo-ablation (the third beat). (A: atrial electrogram, V: ventricular electrogram, H: His electrogram)**

catheter movement is difficult since the catheter is freezing, the junctional beats can not be attributed to the mechanical effect of catheter movement. Taken together, in our view, the junctional beats in our case likely did not stem from mechanical effect of the His catheter.

We believe this is the first report of junctional beats occurring during cryo-ablation of AVNRT. The accelerated junctional tachycardia was seen on re-warming in during cryo-ablation.[1,2] Nguyen et al. reported transient accelerated junctional rhythm late after para-Hisian accessory pathway cryo-ablation.[2] Recently, Drago et al. have reported in the post ablative period, junctional arrhythmias occurred in 2 patients, and they claimed that probably it was due to a direct trauma or inflammatory reaction very close to the compact AV node.[2] In our case we demonstrated that junctional beats can be observed during cryo-ablation. The implication and pathophysiologic mechanism of this event need to be clarified in further studies.

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Recurrent Atrial Fibrillation After Catheter Ablation: Considerations For Repeat Ablation And Strategies To Optimize Success

Andrew E. Darby, MD, FHRS

Assistant Professor, University of Virginia, Charlottesville, VA.

Abstract

Recurrent AF after catheter ablation occurs in at least 20 to 40% of patients. Repeat ablation is primarily considered for those with symptomatic AF recurrences (often drug-refactory) occurring at least 3 months or more post-ablation. Pulmonary vein reconnection is almost universally encountered, and repeat isolation of electrically connected pulmonary veins should be the primary ablation strategy. Beyond repeat PVI and possible ablation of non-PV triggers, there is little to no evidence that additional substrate modification improves outcomes. In addition to repeat ablation, it is critical to address and treat comorbid conditions which increase arrhythmia risk post-ablation. Specifically, obesity, hypertension, and sleep-disordered breathing should be targeted and modified to increase the likelihood of success.

Introduction

Catheter ablation of atrial fibrillation (AF) has become an increasingly frequent procedure per-formed in electrophysiology laboratories worldwide. It is most often performed for maintenance of sinus rhythm in patients with symptomatic, drug-refractory paroxysmal or persistent AF or as an initial rhythm control strategy in lieu of anti-arrhythmic drug therapy in patients with paroxys-mal AF.[1] The increased efficacy of catheter ablation over anti-arrhythmic drug therapy to main-tain sinus rhythm has been demonstrated in a number of randomized, controlled trials and meta-analyses.[2-12] Unfortunately, recurrent atrial fibrillation or atrial tachycardia after an index AF ab-lation procedure results in repeat ablation in 20 to 40% of patients.[13] A number of dilemmas are presented by patients with recurrent AF after catheter ablation: Which patients should be con-sidered for a second procedure and when should repeat ablation be performed? What is the op-timal approach to ablation in a patient undergoing a repeat procedure? What additional interven-tions may reduce the likelihood of recurrence post-ablation? The purpose of this review is to summarize the available relevant data surrounding repeat ablation for atrial fibrillation and identi-fy areas needing further investigation.

Key Words:
Atrial Fibrillation Ablation, Repeat Catheter Ablation, Pulmonary Vein Reconnection, Atrial Fibrillation Lifestyle Modification.

Disclosures:
None.

Corresponding Author:
Andrew E. Darby,
Assistant Professor
University of Virginia Health System
Charlottesville, VA 22908.

Rationale For Repeat Catheter Ablation

The primary ablation strategy for AF is creation of electrical isolation of all pulmonary veins (PVs) with demonstration of bidirectional (entrance and exit) conduction block post-ablation.[1] The most commonly reported finding at repeat catheter ablation is resumption of con-duction to (and from) previously targeted pulmonary veins.[14-17] Durable PV isolation (PVI) may be so difficult to achieve after a single AF ablation that some have reported recovery of conduc-tion in 1 or more PVs in all patients undergoing repeat ablation.[18-19] Amazingly, pulmonary vein reconnection has been identified in up to 92% of patients undergoing a third or greater proce-dure.[20] Electrical isolation of the pulmonary veins is more likely to be permanent after a repeat ablation procedure. Consequently, one rationale for repeat ablation is to "finish" what was started during the first procedure and attempt to ensure permanent electrical isolation of all pulmonary veins. In addition, studies have shown incremental success with higher rates of long-term free-dom from AF with repeat ablation possibly resulting from a higher rate of permanent PV isola-tion.[12,19,21]

Timing Of Repeat Catheter Ablation

Among patients with recurrent arrhythmias post-ablation, there are a number of consid-erations impacting patient management. First, the patient's symptoms should heavily influence subsequent management strategies. Patients with minimal to no symptoms who are adequately rate-controlled may be suitable for a rate-control and anticoagulation strategy rather than con-tinuing to pursue sinus rhythm. The timing of recurrence is also important when considering a repeat procedure. Recurrent arrhythmias within the first two to three months post-ablation may resolve spontaneously or not recur after cardioversion so a repeat procedure is often deferred in this timeframe.[1] The mechanism of recurrent arrhythmia (AF versus atrial

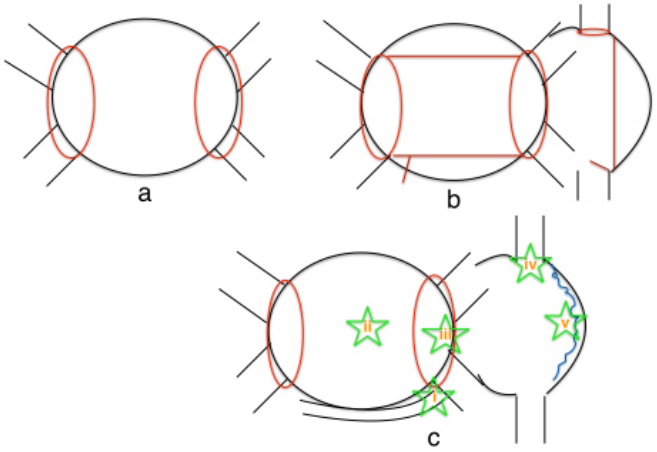

Figure 1: **Potential ablation strategies during repeat AF procedures: a) repeat pulmonary vein isolation only with confirmation of entrance and exit block from each vein; b) pulmonary vein isolation with ad-ditional linear lesions (posterior wall isolation with linear lesions connecting the superior and infe-rior pulmonary veins; mitral isthmus ablation; +/- right atrial linear lesions); c) pulmonary vein iso-lation and ablation of non-pulmonary vein triggers (i = coronary sinus; ii = LA posterior wall (and left atrial appendage, not pictured); iii = fossa ovalis/interatrial septum; iv = crista terminalis/right atrium; v = superior vena cava)**

tachycardia/flutter) may also play a role in decision-making. Patients typically considered for repeat ablation have recurrent, symptomatic AF more than 3 months after initial ablation. Early repeat ablation may be considered for recurrent arrhythmia (particularly atrial tachycardia or atrial flutter) that is diffi-cult to manage medically and recurs despite cardioversion. Recurrent atrial flutter or tachycar-dia post-ablation may be better managed with a repeat procedure as such arrhythmias can be difficult to rate control, frequently recur after cardioversion, and are often due to gaps in areas of prior ablation and have a relatively high success rate with repeat ablation. The focus of this re-view is recurrent atrial fibrillation after catheter ablation and not management of post-ablation atrial flutter or tachycardia.

An additional consideration is the likelihood of success with repeat catheter ablation. Factors shown to negatively impact recurrence rates include left atrial properties (volume, fibro-sis), associated systemic disease (hypertension, obstructive sleep apnea), concomitant heart disease (particularly mitral valve disease and hypertrophic cardiomyopathy), and duration of atrial fibrillation (e.g., longstanding persistent AF has a higher recurrence rate than paroxysmal AF, table 1).[1] Patients with multiple negative prognostic factors for recurrence perhaps are best managed medically (if possible) rather than exposed to the risks of ablation with low likelihood of success. It would not be appropriate to pursue repeat ablation in asymptomatic patients with the hope of obviating need for long-term oral anticoagulation when the CHA2DS2-VASc score indi-cates a moderate to high risk of stroke. Repeat catheter ablation is most commonly accepted for patients with well-documented arrhythmia recurrences who are symptomatic (despite a trial of anti-arrhythmic drug therapy) and are more than 3 months removed from the initial proce-dure.[1]

Strategies For Repeat Catheter Ablation

When AF recurs after PVI and PV reconnection is identified at repeat ablation it seems prudent to re-isolate any reconnected PVs. If the PVs have reconnected, however, how does one know that PV reconnection is the cause of recurrent arrhythmia? Going a step further, should additional ablation beyond repeat PVI be performed? If the PVs have not reconnected what ablation strategy should be employed? Considerations include using different energy deliv-ery sources to repeat PVI (e.g., using cryoablation if radiofrequency was used initially), creation of linear lesions in the left and/or right atrium, isolation of the superior vena cava or coronary si-nus, ablation at atrial sites with fractionated electrograms during AF, ablation at sites of vagal in-puts to the atria, and targeting non-PV triggers (figure 1). It is important to note there are no randomized controlled trials addressing these issues in patients with recurrent AF. The data re-porting outcomes with repeat AF ablation are derived from retrospective and observational co-hort and case-control studies. The most recent consensus statement on catheter ablation of AF suggests the first step when performing a repeat procedure is to check each PV for electrical reconduction followed by reisolation of PVs as necessary as there is data showing reasonably good outcomes with repeat PVI alone.[1,15] If there is little to no evidence of PV reconduction, non-PV foci should be sought and consideration should be given to modification of the ar-rhythmogenic substrate although no particular linear lesion set or alternative ablation approach is recommended in the guidelines.[1]

Techniques To Enhance Durability Of Pulmonary Vein Isolation

As pulmonary vein reconnection is near universal among patients undergoing repeat ab-lation, it is prudent when re-isolating PVs to employ techniques shown to increase the likelihood of durable PVI. This is more likely to occur with the delivery of contiguous, transmural lesions regardless of the energy deliver system. It is postulated that improved acute lesion delivery will translate to enhanced long-term outcomes. A number of procedural techniques have been ad-vocated to improve the likelihood of transmural lesion formation thereby increasing the likelihood of durable PVI and (hopefully) freedom from arrhythmia. General anesthesia compared to con-scious sedation lowers reconnection rates among patients with recurrences who underwent re-peat ablation (19 vs 42%).[22] Efforts to minimize respiratory motion, particularly using high-frequency jet ventilation, have also been shown to improve freedom from AF at 1 year post-ablation.[23] Catheter stability may be further enhanced by manipulation through a steerable sheath, and use of such technology has been shown to improve short-term AF freedom rates post-ablation.[24] Ablation using multi-pore irrigated tip catheter technologies results in lower peri-procedural PV reconnection rates compared to standard irrigated tip catheters.[25] Contact force sensing technologies provide continuous feedback regarding catheter contact force and stability, and ablating with a contact force > 10 grams is associated with a lower likelihood of acute pul-monary vein reconnection and improved outcomes at 1 year.[26,27] Pulmonary vein reconnection rates were no different between standard radiofrequency ablation (using an open-irrigation RF catheter) and the first generation cryoballoon system among patients presenting for repeat abla-tion in a small study of 50 patients with paroxysmal AF.[28]

Rigorous testing to confirm bidirectional (entrance and exit) conduction block post-ablation improves long-term success rates.[29] A reasonable post-ablation wait period to assess for acute PV electrical reconnection seems to improve outcomes, and a study of 181 patients sug-gests waiting at least 35 minutes after acute isolation is the optimal observation time.[30]

Assessing for non-capture along the circumferential lesion set is

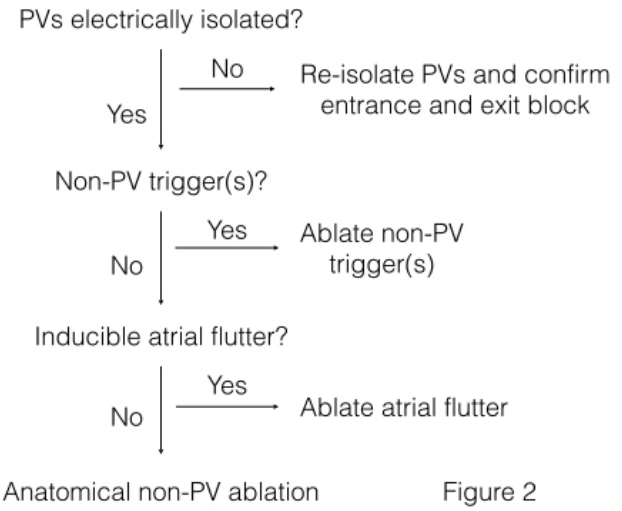

Figure 2: Rational approach to a repeat AF ablation procedure

one method for testing the integ-rity of the ablation line, and re-ablating sites of pace capture resulted in greater AF freedom (83 vs 52%) at 1-year follow-up in a prospective study.[31] Administration of adenosine to assess for dormant conduction can be useful for identifying gaps in the ablation line and pulmonary veins with higher risk of reconnection.[32] Additional ablation of acutely reconnected pulmonary veins after adenosine administration may or may not improve long-term outcomes as data is mixed.[33,34]

It is important to note that none of these approaches has been systematically studied to determine their true impact on promoting durable pulmonary vein isolation. It is also worth noting that absence of AF recurrence does not necessarily indicate permanent pulmonary vein isola-tion, and PV reconnection noted at repeat procedure may be incidental and not causative with regard to arrhythmia recurrence. That being said our initial approach during a repeat AF ablation procedure is to first and foremost ensure pulmonary vein isolation by ablating any reconnected pulmonary veins and confirming bidirectional conduction block (figures 2 and 3). Our standard approach is to use a contact force sensing catheter within a steerable sheath guided by an elec-troanatomic mapping system and intracardiac echocardiography. A circular mapping catheter is used to confirm bidirectional conduction block, and adenosine is routinely administered with re-ablation of any sites exhibiting dormant conduction. A comprehensive EP study is then per-formed to assess for other inducible arrhythmias or non-PV triggers with additional ablation as needed.

Options Beyond Pulmonary Vein Isolation: Ablation Of Non-Pulmonary Vein Triggers And Substrate Modification

As pulmonary vein electrical reconnection is a common finding at repeat ablation, it seems prudent to re-isolate any reconnected PVs as an initial repeat ablation strategy as men-tioned above. The decision to pursue additional ablation beyond PVI is difficult, and there is little data to guide whether additional ablation, if any, should be performed during a repeat procedure. Several studies have reported improved outcomes with a strategy of PVI and additional ablation of spontaneous or inducible non-pulmonary vein AF triggers.[15,16,20,35,36] One of these studies reported outcomes among 169 patients with recurrent AF despite 2 or more prior ablation proce-dures.[20] Astonishingly, only 8% of patients had all PVs isolated at baseline despite more than 1 prior ablation. Non-pulmonary vein triggers were rigorously sought with incremental doses of isoproterenol (3, 6, 12, and 20 μg/min and/or burst atrial pacing to provoke AF followed by cardi-oversion with or without low-dose isoproterenol). The majority of AF triggers localized to the pulmonary veins, although other triggers were identified (Eustachian ridge and crista terminalis; coronary sinus; SVC; LA posterior wall; left atrial appendage; interatrial septum). With a strategy of repeat PVI and targeting non-PV triggers, 81% of patients had arrhythmia control at up to 1-year follow-up.

Beyond PVI and ablation of non-PV triggers, there is very little data to guide whether ad-ditional substrate modification should be performed during a repeat ablation procedure. On one hand, it could be argued that recurrent AF is a failure of the initial strategy so a different strategy (i.e., substrate modification) should be attempted. Alternatively, one could postulate that the primary goal of repeat ablation is to ensure durable PVI, and non-PV based ablation strategies should be reserved for patients without PV reconnection. Extensive ablation may come with the costs of altering atrial contractile properties, increasing the risk for procedural complications, and placing the patient at risk for iatrogenic atrial flutter(s) if bidirectional block is not achieved across linear lesions.[37] Ultimately, the critical question is how important the PVs are in driving a given patient's arrhythmia. Comparing the cycle length of PV triggers to the cycle length in the coro-nary sinus during AF may provide some indication as to the role of the PVs in supporting a patient's arrhythmia.[38] Pulmonary vein electrogram frequency tends to be much higher than the coronary sinus early in the disease process (suggesting PV isolation will result in a high likelihood of arrhythmia control), whereas the PV electrogram frequency is often lower than the coronary sinus as the disease process becomes more advanced (suggesting non-PV sources may be of increased importance and PV isolation alone may not result in optimal outcome).

There are no randomized controlled trials evaluating the efficacy of substrate modifica-tion techniques in patients with recurrent AF. The available data for non-PV based ablation come from patients undergoing de novo ablation procedures. Substrate modification techniques such as left atrial linear ablation, focal impulse or rotor modulation, ablation of complex fraction-ated atrial electrograms (CFAEs), and ganglionated plexi modification have been evaluated pri-marily in patients undergoing initial ablation for persistent and longstanding persistent AF. Ex-trapolation of these results to patients undergoing repeat ablation should be done with caution. Electrical isolation of the LA posterior wall has been evaluated primarily in patients with persistent AF with mixed results.[39,40] Ablation of areas with complex fractionated activity (CFAEs) have been investigated in patients with paroxysmal and persistent AF. Nademanee et al. targeted CFAEs defined as sites with low-amplitude potentials and continuous electrical activity or cycle length < 120 ms and reported a success rate of 91% at 1-year follow-up.[41] A more recent study evaluated adjunctive ablation of CFAE sites (identified with an automated mapping system) ver-sus ablation of sites with continuous electrical activity.[42] At 1-year follow-up, freedom from ar-rhythmia, although modest, was higher with CFAE ablation compared with ablation of sites with continuous electrical activity (50 vs 28%). Adjunctive CFAE ablation has not been uniformly demonstrated to improve outcomes as one study randomly assigned 156 patients to PVI plus ablation of inducible non-PV triggers versus one of two additional strategies: PVI + empiric abla-tion of common non-

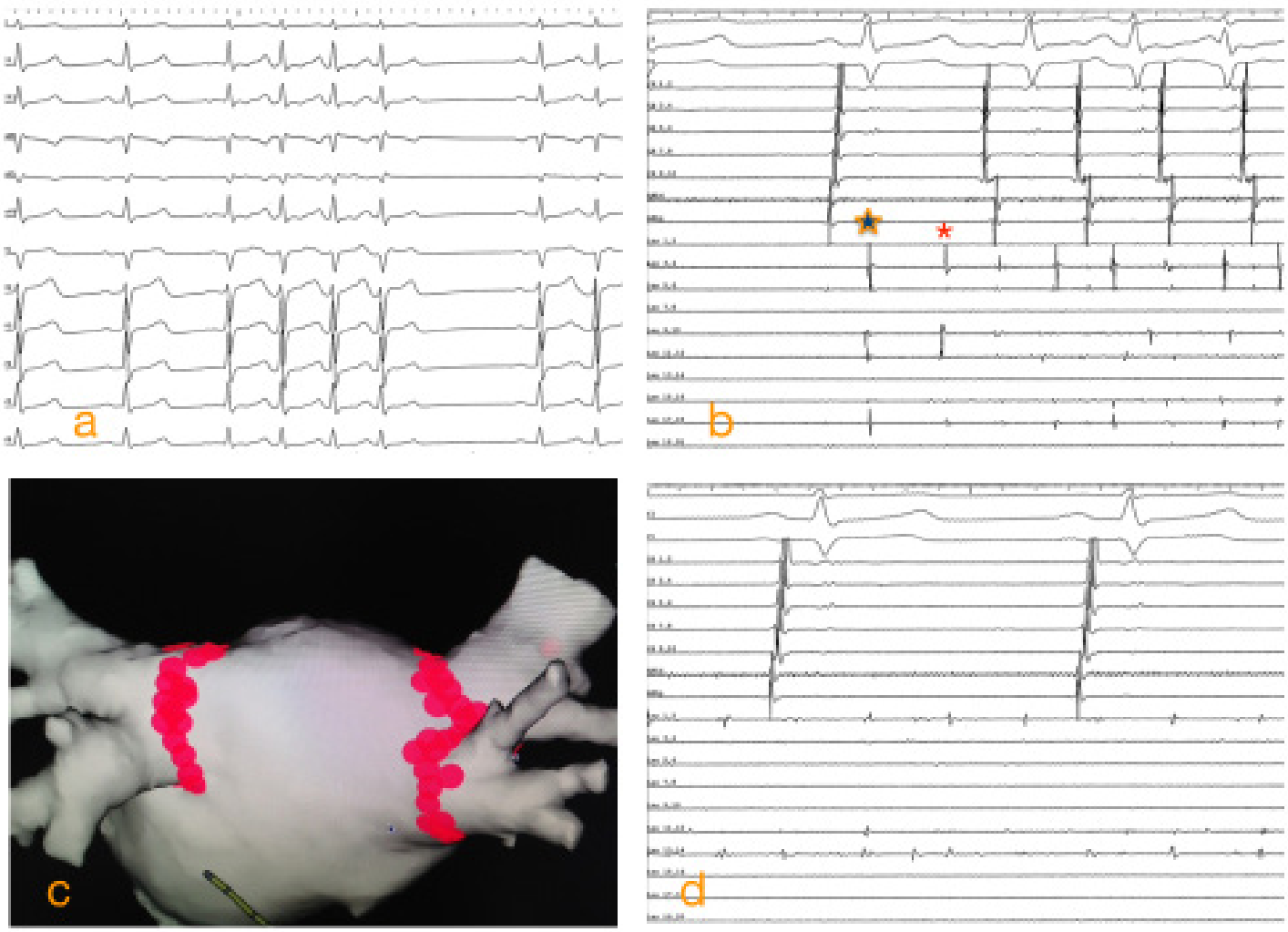

Figure 3: **Illustrative case of a 47 year-old man undergoing repeat catheter ablation for atrial fibrillation. Paroxysmal AF had been diagnosed 2 years prior, and the patient underwent catheter ablation approximately 12 months earlier at another institution. He was AF free for nearly 9 months but then began having recurrent symptoms with paroxysmal AF documented. a) baseline rhythm at the start of the procedure under general anesthesia; frequent short bursts of AF noted; b) dis-played are 3 surface ECG leads and intracardiac recordings from a decapolar catheter in the coronary sinus (labeled cs 9,10 through cs 1,2) and a circular mapping catheter (labeled Las 19,20 through Las 1,2) placed in the right superior pulmonary vein; note the delayed pulmonary vein potential (star) and initiation of AF triggered by spontaneous firing from the RSPV (asterisk); the other 3 PVs remained electrically isolated from the prior procedure; c) electroanatomic map with a posterior view of the left atrium; the RSPV was re-isolated using RF ablation and addition-al tags were placed at sites around the remaining pulmonary veins were there was bipolar volt-age < 0.2 mV and no pace capture; 4) the circular mapping catheter in the right superior pulmo-nary vein demonstrates AF in the RSPV with exit block while the atria remain in sinus rhythm**

PV AF trigger sites or PVI + ablation of left atrial CFAE sites.[43] Ablation of CFAE sites did not result in improved arrhythmia control at 1-year follow-up. In addition, a more recent randomized trial (STAR AF II) further assessed the role of adjunctive CFAE and linear ablation among patients with persistent atrial fibrillation.[44] At 18 months follow-up, 59% of PVI only patients were free from recurrent arrhythmia as opposed to 49% of patients who underwent PVI + CFAE ablation and 46% of patients who underwent PVI + empiric linear ablation.

The autonomic nervous system may play a role in initiating and maintaining AF through several mechanisms: facilitating spontaneous premature atrial depolarizations; shortening of atrial and PV effective refractory periods; and increasing heterogeneity of refractoriness. Con-sequently, a number of authors have investigated the role of adjunctive ganglionated plexus (GP) ablation. A randomized trial involving 67 patients with paroxysmal AF assigned to PVI ver-sus PVI plus GP ablation showed improved outcomes at 10 month follow-up (45.5 vs 73.5%).[45] This is an area of active investigation and additional data involving a larger number of patients is needed to determine if GP ablation truly improves outcomes.

Recent studies have reported the presence of stable reentrant circuits ("rotors") within the atria of AF patients which may provide an additional target during AF ablation.[46-48] The CON-FIRM trial reported initial experience in 92 patients treated either with FIRM-guided ablation with PVI versus PVI alone.[49] FIRM ablation was associated with slowing or termination of AF in 86% of patients, and over follow-up 82% of FIRM patients remained free of AF compared with 45% in the PVI-only group. More recently, two additional studies evaluated the efficacy of FIRM abla-tion on early and long-term outcomes and reported less optimistic results. One study reported 6-month outcomes among 29 patients (20 persistent, 9 longstanding persistent) undergoing FIRM-identified rotor ablation alone.[50] Single-procedure freedom from atrial tachyarrhythmias without anti-arrhythmic drugs was 17%. The other study reported

Table 1: Risk factors for atrial fibrillation recurrence after ablation

Age	Increased risk of recurrence with advancing age
AF duration and type	(Longstanding persistent > persistent > paroxysmal)
Cardiac structural changes	Left atrial dilatation; left ventricular function; hypertrophic cardiomyopathy; valvular heart disease
Clinical features	Hypertension; obesity; obstructive sleep apnea/sleep disordered breathing; metabolic syndrome; thyroid disease

outcomes among 43 patients (56% paroxysmal) who underwent FIRM ablation and PVI.[51] At 18 month follow-up only 21% of patients were free from arrhythmia off antiarrhythmic drugs.

Additional studies have evaluated the benefit of assessing for low-voltage areas at the time of ablation and performing additional substrate modification of these sites. A study involving 178 patients (65% persistent) found low voltage abnormalities in 35% and 10% of persistent and paroxysmal patients, respectively.[52] Low voltage areas were defined as sites with ≥ 3 adjacent points with bipolar voltage < 0.5 mV. Catheter ablation of low voltage areas in addition to PVI resulted in 12-month arrhythmia freedom of 70% compared with 27% among 26 patients with low voltage abnormalities who did not undergo further substrate modification. Another study as-sessed outcomes among 85 patients who underwent PVI and ablation of low voltage areas as-sociated with either fractionated or discrete rapid local activity within or along the border zones of low voltage areas compared with 42 "control" patients with persistent AF who underwent PVI alone.[53] Arrhythmia freedom at 13 months was 69% among patients who underwent ablation of low voltage areas compared with 47% in the PVI-alone control group.

Substrate modification techniques (i.e., linear ablation; targeting of CFAEs or low voltage areas) have yielded conflicting results among patients undergoing de novo ablation and have not been studied and are of unclear benefit in patients undergoing repeat AF ablation. Given that the majority of studies investigating non-PV based ablation have shown little to no improvement over PVI alone (e.g., STAR AF II), it is hard to advocate for extensive atrial ablation. The majority of evidence suggests repeat PVI (if the PVs have reconnected) and ablation of non-PV triggers seems to be the most effective strategy. If the PVs have not reconnected, it seems reasonable to perform a comprehensive EP study to assess for inducible atrial flutter(s) or atrial tachycar-dia(s) and reserve substrate modification for patients in whom the PVs have not reconnected and other arrhythmias are not inducible. If linear ablation is performed it is imperative that bidi-rectional block be confirmed to avoid creating the substrate for iatrogenic atrial arrhythmias.

Repeat AF Ablation: Cryoablation Versus Radiofrequency?

When patients have recurrent AF after ablation is a certain energy delivery system pre-ferred for repeat PVI? If cryoablation was used in the index procedure, should radiofrequency (RF) be employed in a subsequent procedure or vice versa? There is limited data addressing this subject but one interesting study is worth mention. Pokushalov et al. randomly assigned 80 patients with recurrent paroxysmal AF after a first PVI using radiofrequency ablation to repeat PVI with either cryoablation or RF.[54] Study participants had implantable loop recorders to moni-tor for recurrence. At 1-year follow-up more patients randomized to repeat ablation with RF (58%) were AF-free compared with those who underwent cryoablation (43%). This finding sug-gests repeat PVI with RF, as opposed to cryoablation, results in improved outcomes although this study is small and the results should be validated in a larger number of patients.

Pre-Procedural And Intra-Procedural Imaging To Guide Ablation

Ideally pre-procedural imaging could be used to identify sites of PV reconnection or pro-vide clues to the mechanism of recurrent arrhythmia to guide repeat ablation. Late gadolinium-enhanced (LGE) MRI has been used to identify gaps in lesion sets which may be targeted acute-ly or with repeat ablation.[55-57] One study involving 15 patients undergoing repeat ablation for AF found pre-ablation late gadolinium-enhanced MRI accurately identified gaps in areas of prior ab-lation resulted in shorter procedure times by allowing more targeted ablation.[58] In addition, as previously mentioned there is some evidence suggesting improved outcomes if areas of low voltage are targeted in addition to PVI. If this is validated in subsequent studies and found bene-ficial in patients undergoing repeat ablation, LGE-MRI may be useful for pre-procedure planning by helping identify abnormal substrate which could be targeted for ablation.

A critical step forward may be noninvasive imaging of electrical activation to identify the processes essential to maintaining an individual's arrhythmia. Identification of focal drivers or rotational activities prior to entering the electrophysiology laboratory may facilitate a tailored abla-tion strategy more likely to be successful than empirically applying the same lesion sets to each patient regardless of arrhythmia mechanism. Medtronic, Inc. and CardioInsight's ECVUETM is a noninvasive system which captures body surface electrical data to create and visualize epicardi-al 3D electroanatomic maps. The system has proven successful in mapping and ablation of persistent AF in a multicenter study.[59] In the study, 118 persistent AF patients underwent pre-ablation body surface mapping with data used to guide ablation of AF drivers. Acute success (AF termination) was achieved in 64% with driver-based ablation alone. At mean 6 months' fol-low-up, 83% of patients were AF free including recurrent atrial tachycardia in 38%. Although ad-ditional work needs to be done to validate the accuracy of noninvasive electrical mapping, the concepts and available data are intriguing. Noninvasive electrical mapping may become a valu-able pre-ablation tool for both de novo and repeat AF ablation procedures by potentially identify-ing areas critical to a patient's AF mechanism(s) prior to entry into the EP laboratory.

Ancillary Interventions To Minimize AF Recurrence

In addition to procedural interventions to treat AF, one should also screen for and modify any comorbid conditions which may increase the likelihood of AF recurrence (table 1). Specifi-cally, it is prudent to address obesity; sleep-disordered breathing/obstructive sleep apnea; hyper-tension; smoking and alcohol consumption. Obesity is a clearly defined risk factor for AF.[60] It increases the risk of hypertension, metabolic syndrome/diabetes mellitus, and obstructive sleep apnea (OSA), all of which have also been associated with development of atrial fibrillation. Weight reduction has been shown to reduce AF symptom burden and severity.[61] Obstructive sleep apnea independently increases the risk of incident atrial fibrillation and increases the risk of recurrent AF after ablation.[62,63] OSA promotes atrial structural and electrical remodeling includ-ing atrial enlargement and low-voltage areas with conduction abnormalities.[64] Treatment of OSA with continuous positive airway pressure (CPAP) improves arrhythmia-free survival post-catheter ablation.[63] A recent study demonstrated aggressive risk factor modification including weight reduction (initial goal to reduce body weight by 10% followed by target BMI < 25 kg/m^2); blood pressure management with target

< 130/80 mmHg; aggressive lipid and glycemic control; treatment of obstructive sleep apnea if the apnea-hypopnea index (AHI) was > 30/hour; and ab-stinence from smoking and alcohol significantly improved arrhythmia-free survival.[65] Additional research is needed to define optimal targets for management of AF risk factors, but it is clear that treatment of comorbid conditions optimizes AF control.

Conclusions

Recurrent AF after catheter ablation occurs in at least 20 to 40% of patients. Repeat ab-lation is primarily considered for those with symptomatic AF recurrences (often drug-refactory) occurring at least 3 months or more post-ablation. Pulmonary vein reconnection is almost uni-versally encountered, and repeat isolation of electrically connected pulmonary veins should be the primary ablation strategy. Beyond repeat PVI and possible ablation of non-PV triggers, there is little to no evidence that additional substrate modification improves outcomes. If substrate modification and linear lesions are created, however, it is imperative to confirm bidirectional con-duction block to avoid creating substrate for iatrogenic atrial arrhythmias. In addition to repeat ablation, it is critical to treat the "whole" patient by addressing comorbid conditions which in-crease arrhythmia risk post-ablation. Specifically, obesity, hypertension, and sleep-disordered breathing should be targeted and modified to increase the likelihood of success.

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Surgical Ablation of Atrial Fibrillation: is Electrical Isolation of the Pulmonary Veins a Must?

Bart Maesen, MD, PhD,[1] Ines Van Loo, MD,[2] Laurent Pison, MD, PhD,[3] Mark La Meir, MD, PhD[1,2]

[1]Department of Cardio-Thoracic Surgery, Maastricht University Medical Center, Maastricht, The Netherlands. [2]Department of Cardiac Surgery, Universitair Ziekenhuis Brussel, Brussels, Belgium. [3]Department of Cardiology, aastricht University Medical Center, Maastricht, The Netherlands.

Abstract

Ablation of atrial fibrillation (AF) is a well-established treatment option for patients with symptomatic AF refractory to antiarrhythmic drugs. The cornerstone of catheter ablation is electrical isolation of the pulmonary veins, since the pulmonary veins are the most common location for triggers of AF. Electrical reconnection of the pulmonary veins is associated with arrhythmia recurrence and therefore diminishes long-term success of catheter ablation of AF. Therefore, durable pulmonary vein isolation remains a condition sine qua non for catheter ablation of AF. The Cox-Maze procedure is considered an effective surgical cure of AF, however it has never been widely adopted due to its procedural complexity. Since the development of minimal invasive techniques for surgical AF treatment, surgical ablation of AF has regained interest. Most of the minimal invasive surgical AF ablations performed around the globe include pulmonary vein isolation as a part of the procedure. In this review, we explore the necessity of electrical isolation of the pulmonary veins in surgical AF ablation.

Historical Perspective

Although the exact pathophysiology of atrial fibrillation (AF) remains unknown, different mechanisms driving the arrhythmia have been proposed. Generally it is accepted that AF requires both a trigger and a substrate capable of perpetuating AF. Mechanisms driving AF can be classified as 'hierarchical' or 'anarchical'.[1] In a hierarchical organization a single source, ranging form local automaticity or triggered activity to local reentrant circuits, drives AF. Contrary to hierarchical AF, anarchical AF indicates that multiple non-localized sources, like reentry circuits or multiple wavelets, act anarchically to drive. Also interactions of several of these mechanisms could be responsible for the initiation and perpetuation of AF.

The multiple wavelet hypothesis, introduced by Moe and coworkers, is a classic example of anarchical AF.[2] In this conceptual model, AF is sustained by the co-existence of multiple wavelets meandering over both atria, given that the atria are big enough (atrial mass) and the refractory period short enough.[2,3] Early 1980s, the only interventional treatment for AF was ablation of the atrio-ventricular node and implantation of a ventricular pacemaker.[4] The Cox-Maze procedure was the first curative attempt in AF treatment and was performed for the first time on 25 September 1987 at the Barnes Hospital in St. Louis, USA by James Cox.[5] The operation consisted of an extensive cut-and-sew incision set in both atria with the goal of blocking macro-reentrant conduction and (re)directing propagation from the sino-atrial node throughout both atria. The concept of this procedure was based on epicardial mapping in patients with paroxysmal AF who were undergoing surgical correction of the Wolff-Parkinson-White syndrome.[6] In this study, Cox et al. demonstrated that, during human AF, mainly multiple wave fronts and macro-reentrant circuits occur.[6] The numerous atrial transections were designed in such way that macro-reentrant circuits no longer could prevail. It is remarkable that, although this surgical procedure was designed long before any knowledge of the arrhythmogenicity of the pulmonary veins (PVs) existed, it did include electrical isolation of the PVs and the posterior left atrial wall (box lesion) as a part of the surgical procedure.[5] As such, success of the Cox-Maze procedure cannot solely be attributed to the prevention of multiple waves to co-exist, but might also be partly due to abolished AF triggers.

The initiation of paroxysms of AF by repetitive discharges originating in the PVs is a typical example of a hierarchical type of AF. In 1998, Haïssaguerre et al. demonstrated that 90% of the triggers responsible for the onset paroxysmal AF were located in and around the orifices of the PVs and that these foci responded well to catheter based radio-frequency (RF) ablation therapy.[7] Later, it was shown that the ectopic activity presumably was a consequence of micro-reentry promoted by the presence of heterogeneity in refractoriness and anisotropic conduction at the atrial junction

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Corresponding Author:
Mark La Meir,
UZ Brussels
Centre for Cardiovascular Diseases
(Louis Tielemans Pavilion +1)
101, Laarbeeklaan
B - 1090 Jette Belgium.

with the PVs and within the PVs.[8,9] These findings have important implications: as frequent discharges of a few focal sources can lead to progressive pathologic changes in the atrial substrate,[10] thereby entraining AF,[11] and ablation of these foci suppresses the trigger and reduces the potential degeneration of the atrial substrate,[7] the underlying mechanism driving human paroxysmal AF seems to be that of multiple foci adjacent to or in the PVs.[12] Since this pioneering work of Haïssaguerre et al.,[7] PV isolation has been regarded as the cornerstone for the treatment of paroxysmal AF and even of persistent AF. However, the underlying mechanism of persistent AF maintenance is not fully understood and might be due to

(1) cellular proarrhythmic mechanisms, like automaticity or triggers;

(2) spiral wave reentry or rotors;

(3) multiple wavelet reentry where the fibrillation process is actually driven by waves and no localized sources of AF exist; or

(4) a combination of all, different in each patient.[1] This might explain the pour outcomes reported in (single procedure) PV isolation for persistent AF.[13] After recognition of the PVs as a dominant source of triggers initiating AF, more foci were found at other locations in right and left atria. Amongst them were the ligament of Marshall,[14] the proximal superior vena cava[15] and the left atrial appendage.[16]

Based on the success of compartmentalization in open surgical ablation, addition of left atrial linear lesions to PV isolation were introduced in catheter ablation of AF.[17] For example the mitral isthmus line, a linear line from the lateral mitral annulus to the left inferior PV, was added by Jaïs et al. based on anatomical studies suggesting that preferential propagation is closely correlated to muscle fiber orientation along the posterior LA and circumferentially around the mitral annulus.[18, 19] Another example of substrate modification was the introduction of a linear lesion connecting both superior PVs, the so-called 'roof line' ablation.[20]

In 2004, Nademanee et al. proposed a different substrate-based approach for the treatment of AF. They identified and ablated areas with bipolar complex fractionated electrograms (CFAE),[21] based on the earlier described finding by Konings et al. that unipolar CFAE are found in regions of conduction slowing and conduction block.[22] The authors suggested that ablation of CFAE-sites alter or eliminate random reentry paths preventing fibrillation wavelets to reenter the ablated areas.[21] Although PV isolation was not performed, PVs were identified as key areas where CFAEs were located.[21]

A new method for analyzing AF propagation was introduced by Narayan et al. in 2012. The authors unmasked sustained electrical rotors and/or repetitive focal activation in 97% of mapped human AF (combination of paroxysmal and persistent AF) by using a 64-pole basket catheter and a novel algorithm that produces a video of the computed activation process.[23] These localized sources were low in number, stable in position, mostly located in the left atrium and they controlled surrounding fibrillatory conduction.[24] Catheter ablation at the center of these localized sources terminated or consistently slowed persistent or paroxysmal AF in 86% of patients prior to PV isolation.[24] Of notice, in a recent extension of that report, more rotors and less focal sources were reported compared to earlier reports,[23, 24] which the authors attributed to 'improved software', among other things.[25] This might reflect a high dependence on a special software algorithm enabling the detection of rotors driving human AF.

Even more recently, Haissaguerre et al. used electrograms generated by body surface mapping and biatrial geometry relative from a computed tomography (CT) scan to reconstruct the propagation pattern of fibrillating atria in a noninvasive way.[26] Signal-analysis processing combining filtering, wavelet transform, and phase mapping was used to identify drivers (focal or reentrant activity) in 103 patients with persistent AF.[27] Contrary to Narayan et al.,[23, 24] the authors reported more driver locations, substantial meandering, and periodic occurrence of unstable reentries requiring statistical density maps to identify them.[27] Also here, RF ablation at the driver location resulted in acute AF termination in 75% of persistent AF and 15% of long-lasting AF patients.[27] In this strategy, ipsilateral PV isolation was only performed if drivers were found in the PVs or if the endpoint was not reached.

As discussed before, surgical ablation of AF started with the Cox-Maze III operation, a surgical procedure through median sternotomy on cardio-pulmonary bypass (CPB) in which compartmentalization was created by cutting and sewing in order to interrupt and eliminate macro re-entrant circuits.[5] Later, the Cox-Maze III procedure was changed to the Cox-Maze IV procedure: based on the findings of Haïssaguerre[7] the pulmonary veins were isolated bilaterally, most incision sets were replaced by bipolar RF ablation and cryosurgery was applied at the valve annuli.[4, 28] The Cox-Maze IV can be performed either through a median sternotomy or through a right mini-thoracotomy.[28] Although the right atrial ablations can be performed on the beating heart, CPB is still required for the left atrial lesion set.[28] Several changes to the Cox-Maze procedure have been developed, mainly based on the application of other (and now obsolete) energy sources like microwave, laser, and high-frequency ultrasound.[4] Nitta et al. developed the radial incision procedure, an alternative approach to preserve a more physiologic atrial transport function.[29] This procedure consisted of atrial incisions radiating from the sinus node to allow a more physiologic atrial activation sequence and to preserve blood supply to most atrial segments.[30]

The last decades, new technologies enabled the creation of transmural lesions using minimal invasive surgery (MIS) for treatment of stand-alone AF.[31] Most widely used are the RF bipolar clamp devices that allow PV isolation by applying RF energy between the two jaws of the clamp. In addition, creation of a 'box'-lesion and left atrial appendage (LAA) removal or exclusion, usually with ganglionic plexi ablation, is performed via video-assisted MIS.[31-34] The advantage of these MIS approaches, next to the fact that they are truly minimal invasive, is that they can be performed on the beating heart (off-pump).[31-34] The difference, however, between these techniques and the Cox-Maze III lesion set is that the epicardial off-pump techniques lack the possibility of a mitral isthmus line as this lesion cannot be created solely from the epicardium.[35, 36] Therefore, Edgerton et al. developed the 'Dallas lesion set', an epicardial minimal invasive approach in which the mitral isthmus line is replaced by a connecting lesion -using unipolar RF energy- from the left fibrous trigone at the anterior mitral valve annulus across the anterior dome of the atrium to the 'roof' line.[35]

Although much more efficient as unipolar, even bipolar RF energy cannot guarantee transmural lesions.[37] To overcome this shortcoming and to tackle the problem of the mitral isthmus line, a combination of a transvenous endocardial and thoracoscopic epicardial approach in a single procedure, the so-called 'hybrid AF ablation', has been successfully put forward as an alternative.[38] Almost all of the surgical ablation procedures for the treatment of concomitant and stand-alone AF include PV isolation using RF or cryo-energy.

Is Pulmonary Vein Isolation Mandatory In Catheter Ablation Of AF?

In the initial report on PV trigger ablation for the treatment of paroxysms of AF, Haïssaguerre et al. reported 80% acute success and 62% freedom of AF in a follow-up period of 8±6 months after ablation.[7] Since then PV isolation is considered to be the cornerstone of catheter-based ablation of AF.[12] Initial PV isolation consisted of electrical isolation of the PV myocardium close to the PV ostia, but identification of triggers in the PV antrum and recognition of PV stenosis resulted in a shift towards wider antral PV isolation techniques (e.g. wide area circumferential ablation or WACA).[39-41]

It has been demonstrated that PV isolation is more effective in maintaining sinus rhythm compared to medical therapy.[42] However, catheter-based PV isolation has been reported to be successful in patients with paroxysmal AF, although repeat PV isolation procedures are needed, but far less successful in patients with persistent or longstanding persistent AF.[43-48] Teunissen et al. recently reported on the five-year freedom of atrial tachyarrhythmia after PV isolation.[47] PV isolation restored and maintained long-term sinus rhythm in 48.6% for paroxysmal AF, but only 33.1% in persistent AF and 23.5% in longstanding persistent AF.[47] When allowing multiple re-isolations, freedom of AF increased to 67.8% for paroxysmal AF, but remained disappointing for persistent AF (46.2%) and longstanding persistent AF (38.2%).[47]

The consensus that complete electrical isolation of PVs is a necessity stems from the finding that AF recurrences after PV isolation for paroxysmal AF are almost always associated with electrical PV reconnection based on conduction gaps.[49] The need for durable PV isolation is clearly demonstrated by the results of the Gap-AF–AFNET 1 trial.[50] In this study, 233 patients were randomized to complete and intentional incomplete PV isolation.[50] After 3 months, rhythm follow-up showed that patients with incomplete PV isolation had far more AF recurrences then patients with complete PV isolation (62,2% vs 79.2%).[50] More surprising was the finding that at invasive reevaluation at 3 months the rate of electrical PV reconnection in patients with acute complete PV isolation was up to 70%.[50] This illustrates that initial acute PV isolation using catheter-based RF ablation techniques does not per se translates into a durable PV isolation. What about the second most frequently used catheter-based ablation technology, cryo-energy? Kuck et al recently compared cryoballoon ablation to RF ablation in a large randomized multicenter trial, the 'fire and ice trial' and demonstrated non-inferiority of cryo-ablation to RF ablation.[51] In a report on redo procedures for recurrent AF in 29 out of 131 patients who initially underwent a successful cryoballoon PV isolation, PV reconnection was again found to be the underlying mechanism (PV reconduction in 2.45 + 0.7 veins in each patient).[52] Some techniques have been evaluated to reduce the amount of PV reconnection. Recently, a large randomized trial demonstrated that in patients with dormant PV conduction additional adenosine-guided ablation resulted in a higher freedom of AF compared to no additional ablation (69.4% vs 42.3%).[53] In patients without dormant PV conduction, AF freedom was only 55.7%, suggesting that adenosine is unable to identify all veins that might reconnect.[53] Theoretically, waiting longer after PV isolation could help to reveal early PV reconnection. Bänsch et al. demonstrated that although this resulted in the detection of more gaps, ablation of these gaps did not result in higher freedom of AF in follow-up.[54] Furthermore, demonstration of bidirectional block has been suggested to improve results of PV isolation.[55] Electroporation is a promising technique but still needs to be evaluated in clinical practice.[56]

As discussed before, the short and long term results of PV isolation are less convincing in patients with persistent and longstanding persistent AF.[44-48] As a result, additional substrate modifications, such as linear lesions or ablation of CFAEs, have been proposed for catheter-based ablation of persistent AF.[18, 21, 57] The initial report on CFAE ablation by Nademanee et al. presented very high acute (98%) and 1-year follow-up (91%) freedom of AF rates.[21] In this study, no PV isolation was performed. Does this finding challenge the need for PV isolation? It might, but although PV isolation was not performed, the PVs were identified as key areas for CFAEs.[21] Estner et al. compared CFAE ablation with PV isolation in combination with CFAE ablation in patients with persistent AF.[58] In the CFAE ablation only group, sinus rhythm off AAD was present in 9% after a mean follow-up time of 13 + 10 months, compared to 41% in the CFAE plus PVI ablation group.[58] Moreover, Oral et al. randomized patients with long-lasting persistent AF who did not convert to sinus rhythm after PV isolation to CFAE ablation or no further ablation and failed to demonstrate an add-on value of CFAE ablation to PV isolation.[59] Because of the dynamic nature of CFAEs and the inability of current algorithms to adequately define CFAEs, it remains challenging to identify sites critical for AF termination.[60, 61]

Also addition of linear lesions has been reported with varying success. For example, Gaita et al. randomized patients with paroxysmal or persistent/permanent AF to 2 different ablation schemes: PV isolation and PV isolation plus left linear lesions.[62] The authors reported that addition of linear lesions is more effective in maintaining sinus rhythm off anti-arrhythmic drugs).[62] In contrast, several recent randomized trials failed to show any benefit of additional substrate modifications techniques over PV isolation alone.[63-65] Of interest is the STAR AF 2 trial, a large randomized trial evaluating currently used substrate modifications techniques.[63] Verma et al. randomized 589 patients with persistent atrial fibrillation to PV isolation alone, PV isolation in combination with CFAE ablation or PV isolation with linear lesions across the left atrial roof and mitral valve isthmus.[63] The authors failed to show any benefit in AF freedom between the 3 techniques, independent of AAD-allowance or repeat procedures.[63]

The poor results of additional substrate modification in patients with non-paroxysmal forms of AF should be interpreted with caution, however, as they might be due to the relative incapacity of catheter-based unipolar RF to create transmural lesions.[66] As such, it would be interesting to (re-)evaluate these 3 techniques in patients were effective PV isolation has been proven by electrophysiological testing at a fixed time point after the initial procedure.

In 2012, Narayan et al. proposed a new ablation technique, focal impulse and rotor modulation (FIRM), based on the hypothesis that localized sources or rotors sustain human AF.[23] When comparing FIRM in addition to PV isolation with PV isolation alone, FIRM-guided cases had higher freedom from AF (82.4% vs. 44.9%).[67] These promising results were confirmed in a 3-year follow up report.[68] However, in these studies FIRM ablation was always performed in combination with PV isolation. Recently, Gianni et al reported that FIRM ablation as a sole therapy, so without PV isolation, in patients with non-paroxysmal AF did not result in AF termination.[69] After a mean follow-up of 5.7 months, single-procedure freedom from atrial

arrhythmia was 17% without AADs, 28% allowing AADs.[69]

In conclusion, PV isolation is not only mandatory in catheter ablation of AF; it forms the cornerstone of this therapy. Whether additional substrate modification techniques, in combination with PV isolation or as a sole therapy, are able to improve freedom of AF is unclear at this stage.

Is Pulmonary Vein Isolation Mandatory In Surgical Ablation Of AF?

The fact that all surgical AF ablation techniques include PV isolation makes it difficult to question its need in AF surgery. There are, however, some indirect arguments to support its necessity.

There a few differences between surgical and catheter ablation techniques for ablation of AF. First, a variety of different lesion sets are performed, including right atrial lesions, extensive left atrial lesions including full isolation of the posterior left atrium (box-lesion), addition of a trigonum or mitral isthmus line and left atrial appendage exclusion. In theory, those additional lesions might be responsible for AF termination even if the PVs are not fully electrically isolated. The left atrial appendage, for example, harbors triggers that can play a role in initiation or recurrence of AF.[16, 70] Next to the prevention of cloths, surgical exclusion of the left atrial appendage performed by amputation, stapler or epicardial occluding device (clip), will also electrically isolate the left atrial appendage, thereby preventing its triggers to persist. An endocardial left atrial appendage occluding device, however, will not result in electrical isolation. Secondly, the devices used to perform AF ablation are different. In several stand-alone or concomitant surgical AF procedures, cryo-ablation is performed on the arrested heart, thereby preventing the heat sink effect of endocardial (warm) blood. Also, in surgical treatment of AF, bipolar RF devices can be used to perform PV isolation (both on the beating and the arrested heart) and to create linear lesion on the arrested heart. Those bipolar devices differ from unipolar devices in the fact that RF energy is applied from two sides with the target tissue in between. In a porcine animal study, ablation of the PVs and the left atrial appendage using a bipolar RF clamp resulted in 100% acute isolation and at 30 days.[71] Microscopic evaluation of the ablation lines showed that all lesions were transmural in a total of 209 samples.[71] Bugge et al compared a bipolar clamping device with a handheld unipolar device in a sheep model and showed that in atrial tissue continuous transmural lesions were achieved more often with the bipolar than with the unipolar device (92.3 vs. 33.3%).[37] Off course these results coming from animal studies cannot be translated one-on-one into clinical practice, but they at least suggest the superiority of bipolar compared to unipolar RF devices in creating transmural lesions. As such, it might be more representative to study the success of substrate modification techniques in addition to PV isolation in AF patients who undergo surgical PV isolation using bipolar RF devices, rather than in patients undergoing percutaneous PV isolation.

There are some indirect arguments that PV isolation is mandatory in AF surgery. Surgical PV isolation using bipolar RF devices is at least as effective as catheter ablation.[72-74] De Maat et al. reported that video-assisted PV isolation in patients with paroxysmal AF resulted in 69% freedom from atrial arrhythmias off AAD after a mean follow-up of 5 years.[75] These results do not prove that PV isolation is a must in surgical AF ablation, but they do show that surgical PV isolation is an adequate therapy to treat paroxysmal AF. In non-paroxysmal forms of AF, additional lesions are often required to maintain sinus rhythm. In permanent AF patients with left atrial dilatation and valvular disease, PV isolation seems necessary but not sufficient to regain sinus rhythm.[76] Gaita et al. assigned patients undergoing valve surgery to 3 different groups: cryo-isolation of the PV's only, cryo-isolation of the PV's in combination with interconnecting lines between the PV ostia and the right and left lower PVs down to the mitral annulus (reversed 'U' lesion) and cryo-isolation of the PV's in combination with interconnecting lines between the PV ostia and the left lower PV down to the mitral annulus ('7' lesion).[76] A subset of patients underwent an electrophysiological study at 3 months.[76] First of all, the 'U' lesion was never achieved; in general only 65% of linear lesions or PV isolation using cryo-energy was achieved in this patient population.[76] Complete PV isolation alone resulted in 25% sinus rhythm, whereas PV isolation in combination with a complete '7' lesion (intended '7' lesion or incomplete 'reversed U' lesion) resulted in 86% sinus rhythm at 2 years off AAD.[76] In a mixed population of paroxysmal and persistent AF patients undergoing the Cox-Maze IV procedure, higher freedom of AF at 3 and 6 months and a trend towards higher freedom of AF at 12 months was reported in patients where, in addition to PV isolation, a complete posterior left atrial isolation ('box-lesion') was performed compared to a line between the inferior PVs only.[77] This suggests that in certain patients, the posterior left atrium harbors triggers that (re-)initiate AF, and that in those patients PV isolation alone is not sufficient.[77] Off course, full posterior left atrial isolation also results in reduction of the available conducting critical mass. In contrast, in a large randomized multicenter study involving patients with persistent and longstanding persistent AF, Gillinov et al. reported no differences in freedom of AF at 1 year between patients undergoing PV isolation alone compared to patients undergoing a biatrial Cox-Maze procedure.[78] However, the reported success rate of the maze group is in this study is lower than expected.[79] Furthermore, a variety of bipolar and unipolar radiofrequency and cryothermy was used (bipolar PV isolation was only performed in 43%).[78]

Electrophysiological evaluation after bipolar RF PV isolation has been scarcely performed. Kron et al performed an electrophysiological study in 13 patients (69% paroxysmal AF) with recurrent atrial tachyarrhythmias at a mean of 214±162 days after minimal invasive surgical ablation of the PVs using bipolar RF, the parasympathetic ganglionated plexi and the ligament of Marshall.[80] In these 13 failures, 50% of examined PVs reconnected; in 7/8 patients with recurrent AF either 2 or 3 PVs were reconnected and in 6/8 patients, the left superior PV was reconnected.[80] Zeng et al. reported on 8 patients (3 paroxysmal AF, 5 persistent AF) with recurrent atrial arrhythmias after minimal invasive PV isolation using bipolar RF and left atrial appendage exclusion by stapler.[81] An electrophysiological study revealed gaps at the PVs in 4 patients with recurrent AF, an ectopic focus between the left atrial appendage and left superior PV in a patient with atrial tachycardia, perimitral atrial flutters in 2 patients and a left atrial roof flutter in the remaining patient.[81] Trumello et al. performed percutaneous ablation on 36 patients with previous surgical ablation (7 biatrial maze, 18 left atrial ablation and 11 PV isolation).[82] Among other findings, 15 patients had reconnection around the PVs.[82] The authors underlined the importance of an appropriate energy source as two-thirds of patients with gaps around the PVs were initially treated using unipolar RF only.[82] Velagic et al reported on repeat catheter ablation in 14 patients out of 64

patients treated with a hybrid AF ablation including PV isolation with bipolar RF.[83] In all patients, conduction block of the PVs was confirmed by endocardial mapping with a Lasso catheter. [83] In only 5 patients PV reconnection was found and only 1 vein per patient reconnected.[83] Although these findings are not direct proof, they do strongly support the need for durable PV isolation in surgical AF ablation.

Hybrid AF ablation may help to detect and immediately treat conduction gaps that are not identified during epicardial ablation. The concept of hybrid AF ablation, as discussed before, consists of combining the advantages of an epicardial and endocardial approach.[38] It can be performed as a staged procedure or in one single procedure. On et al. reported on 97 patients (10.1% paroxysmal AF, 21.5% persistent AF, 68.3% long-standing persistent AF) who underwent staged hybrid AF ablation.[84] Surgery consisted of thoracoscopic PV isolation with a box lesion, ganglionated plexus ablation, division of the Marshall ligament and left atrial auricle resection.[84] In 61 patients an electrophysiological study was performed 5 days after surgery: cavotricuspid isthmus ablation was routinely performed in 56 patients, and mitral isthmus ablation and septal ablation because of preoperative atrial flutter.[84] In 15 patients PV conduction gaps were detected requiring additional ablation.[84] Using this staged approach, the freedom of AF after 1 year was 74% off AAD.[84] Pison et al reported on 26 patients (42% persistent AF) undergoing hybrid AF ablation in a single procedure.[38] Combining thoracoscopic surgical ablation (consisting of PV isolation, a box lesion +/- additional lesions) with endocardial validation and touch-up (if needed) of the epicardial lesions resulted in a single procedure success rate of 83% at 1 year, off AAD.[38] During the hybrid procedure, endocardial touch-up was necessary in 23% of patients because the epicardial lesions were not transmural, illustrating the immediate advantage of this approach.[38] Using meticulous rhythm follow-up, 4 failures were identified.[38] Of this 4 patients, 2 underwent an electrophysiological study: 1 conduction gap in the roofline and 1 atrial flutter but no reconnection of the PVs was documented.[38] In theory, endocardial validation of epicardial ablation lesions is superior to epicardial testing for several reasons. First, because of edema, epicardial testing of surgical ablation lines can lead to false negative results. Secondly, it can be challenging to adequately pace in between instead of on the performed ablation lines. Also, the border between conducting and non-conducting tissue at the distal sleeve of the pulmonary vein cannot be determined without sophisticated mapping techniques. Third, there is a timeframe of at least 30 minutes between epicardial PV isolation and endocardial validation, which can help to unmask incomplete PV isolation. Last, endocardial testing of PV isolation allows electrophysiological mapping using validated techniques (e.g. Lasso catheter). Probably these advantages result in a more durable PV isolation and thereby contribute to a higher rate of AF freedom.

Conclusion

PV isolation remains the cornerstone in AF ablation. In catheter ablation, durable PV isolation is mandatory as recurrences of AF go hand in hand with PV reconnection. In surgical ablation of AF, the necessity of PV isolation is more difficult to demonstrate, as reports on redo procedures after surgery are scarce. However, there are no obvious reasons why surgical ablation would differ from catheter ablation in necessitating PV isolation. Surgical ablation of AF seems superior to catheter ablation of AF, especially in the treatment of non-paroxysmal forms of AF. This seems, at least in part, to be due to the use of bipolar radiofrequency devices. As such, more durable PV isolation is to be expected in surgical AF ablation. Therefore the efficacy of additional substrate modification techniques should also be evaluated in patients undergoing surgical AF ablation, and not only in patients undergoing percutaneous ablation.

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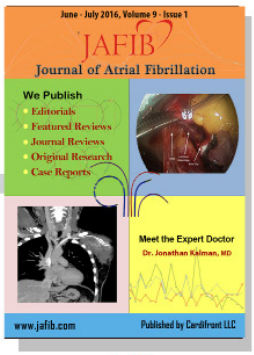

Influence Of Novel Electrocardiographic Features Of Provocable Brugada ECG In Arrhythmogenic Cardiomyopathy And Its Exclusion By Lead AVR

Stefan Peters

St.Elisabeth Hospital gGmbH Salzgitter, Germany.

Abstract

In 19 patients (14 females, mean age 49.1 ± 11.3 years) with typical arrhythmogenic cardiomyopathy and provocable type I Brugada ECG pattern by ajmaline administration were analysed by novel electrocardiographic features as having "true" or "false" Brugada syndrome. Three patients turned out as having false Brugada syndrome, the diagnosis is pure arrhythmogenic cardiomyopathy.

In 16 patients, however, true Brugada syndrome could be provoked. In these patients the diagnosis was arrhythmogenic cardiomyopathy associated by provocable Brugada syndrome.

Introduction

In a large collective of 385 patients (212 males, mean age 46.3 ± 11.1 years) with typical arrhythmogenic cardiomyopathy lead aVR was analysed. A morphology of large Q wave of 3mm or more, a small R wave of 2mm or less, and T-wave inversion turned out to be the best predictor of arrhythmogenic cardiomyopathy.

In 1498 healthy probands (859 males in an age range of 18 – 85 years) the same morphologic parameters were analysed. Similar results were obtained in 284 probands (18.9%). Specificity and positive predictive value were low, but negative predictive value was nearly 100%.

An association between arrhythmogenic cardiomyopathy and Brugada syndrome seems to be a matter of fact.[1,2,3]

A continuum between these both diseases has been described.[4] Causal gene mutations have been confirmed in plakophilin-2,[5] desmoglein-2[6] and desmoplakin.[7]

To differentiate true or false provocable Brugada syndrome novel electrocardiographic features have been presented [8] as follows:

- concave (coved) ST-segment morphology with negative symmetrical T-waves
- QRS-ST at least 2mm high in lead V1
- ST-segment morphology shows progressive decline
- the ratio between the peak height of QRS-ST after 80ms is greater than 1
- the duration of the QRS in leads V1 and V2 is greater than in the middle and left precordial leads
- type-1 Brugada syndrome ECG may be seen in a single lead, V1 or V2, but never exclusively in V3

We analysed 19 patients (14 females, mean age 49.1 ± 11.3 years) with typical diagnosis of arrhythmogenic cardiomyopathy and provocable Brugada syndrome by ajmaline administration.

In three patients without novel electrocardiographic criteria we could rule out true provocable type I Brugada –ECG pattern. These patients ends up in the diagnosis of pure arrhythmogenic cardiomyopathy.

In 16 patients with novel electrocardiographic criteria demonstrated true provocable type I Brugada ECG pattern. These patients ends up in a combination of arrhythmogenic cardiomyopathy and Brugada syndrome supporting the continuum between these two cardiac entities.

In order to diagnose or to exclude arrhythmogenic cardiomyopathy we like to focus the interest to lead aVR. Lead aVR is the only lead which points directly to the right ventricle.

In a large collective of 385 patients (212 males, mean age 46.3 ± 11.1 years) with typical arrhythmogenic cardiomyopathy the morphology of lead aVR was analysed.

In 97% of cases large Q wave of 3mm or more, small R wave of 2mm or less and T-wave inversion were found. In a control collective of the University Hospital of Glasgow, U.K. (Prof. Peter Macfarlane, Cardiology and Electrocardiography) of 1498 probands (859 males in an age range of 18 – 85 years) the same morphologic parameters were analysed. Similar results were obtained in 284 healthy probands

Key Words:
ECG, AVR, Cardiomyopathy.

Disclosures:
None.

Corresponding Author:
Stefan Peters
Chief Cardiologist
St.Elisabeth Hospital gGmbH Salzgitter
Liebenhaller Str. 20
38259 Salzgitter
Germany.

(18.9%).

Specificity and positive predictive value were low, but negative predictive value was nearly 100% (9).

Lead aVR is an excellent tool to exclude arrhythmogenic cardiomyopathy as demonstrated in different publications.[10, 11]

Conclusions

In conclusion, there are new tools to confirm provocable true Brugada syndrome in arrhythmogenic cardiomyopathy to reveal a continuum between these two entities and to definitely exclude arrhythmogenic cardiomyopathy by electrocardiographic means.

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Interactive In-Vitro Training In Physics Of Radiofrequency Ablation For Physicians And Medical Engineering Students

Haber T,[1] Kleister G,[1] Selman B,[1] Härtig J,[2] Melichercik J,[2] Ismer B[1]

[1]Peter Osypka Institute for Pacing and Ablation at Offenburg University of Applied Sciences. [2]MediClin Heart Center Lahr/ Baden, Germany.

Abstract

Radiofrequency (RF) ablation requires a complex set of devices as well as profound electrophysiological experience and substantial knowledge of physical science basics. To establish RF ablation in-vitro teaching-system, six workstations were equipped with computer-controlled RF ablation generators. Universal connection boxes allow ablation-essays with catheters of different make and model. Special wetlabs were developed combining a basin containing isotonic saline solution with a thermostat and a pump to simulate blood flow. This hands-on teaching system can be used to demonstrate differences in lesion-forming dependent on tip-electrodes, sensor technology and ablation techniques, influence of blood flow and electrode-angle to the myocardium. It was also utilized to reproduce industrial in-vitro tests.

Introduction

Radiofrequency ablation is the most popular method in the treatment of supraventricular reentrant and focal tachyarrhythmia, atrial fibrillation and an increasing number of ventricular tachycardias. Many studies from clinical practice have demonstrated impressively the effectiveness of this method in terms of improvement of quality of life, morbidity and mortality of affected patients. A highly complex set of peripheral support systems is required to perform the treatment. The most important thing – however – is the experience of the attending physician and company staff.

Therefore, despite of numerous developments in the last years, which helped to markedly increase success rate, RF ablation is still a complex procedure requiring the operator's electrophysiological experience and expertise, as well as profound physical science basics knowledge. Besides the medical aspects, various complex and interdependent technical parameters concerning desired lesion size, catheter geometry as well as temperature and power settings have to be considered.

While theory and practice of ablation therapy is being discussed in scientific papers, we found a lack of in-vitro hands-on teaching systems and software to provide practical exercises. Electrophysiologists as well as company staff are usually gaining the necessary experience and skills in the context of their profession and specialization. In addition, the increase in knowledge in the field of arrhythmias, electrophysiological diagnosis and therapy and a high rate of innovation in this area require further education. Thus, there is a need to school young physicians, company staff and medical engineering students the essential physical science basics of RF ablation.

Key Words:
Education, Radiofrequency Ablation, Electrophysiology.

Disclosures:
None.

Corresponding Author:
Tobias Haber,
Peter Osypka Institute for Pacing and Ablation,
Offenburg,
Germany.

Aims

We aimed to school young physicians, company staff and medical engineering students the essential physical science basics of RF ablation. Under didactic aspects, in-vitro experiments in small training groups allow deeper understanding of the physical processes during RF ablation to facilitate a structured knowledge acquisition by studying in-vitro the effects observed in clinical routine.

Training In Radiofrequency Catheter Ablation

To enable a practical in-vitro teaching system for radiofrequency catheter ablation, we established an environment to simulate relevant conditions affecting lesion size using the pork model. The system offers the possibility to demonstrate the effects of different tip electrodes and generator settings and provides exercises in the sensitive handling of the various ablation catheters.

For that purpose, we constructed special wetlabs combining a basin containing isotonic saline solution with a thermostat and a pump to simulate an adjustable blood flow (Fig. 1). In these wetlabs, limited to in-vitro situations, ablation experiments can easily be performed.

Six identical workstations were equipped with this self designed wetlab simulating the blood`s temperature and flow and an own computer-controlled industrial RF ablation generator, allowing temperature- and power-controlled in-vitro RF ablations without or with open or closed cooling.

The software of the Osypka HAT 300s RF ablation generator allows an excellent didactic data analysis through continuous

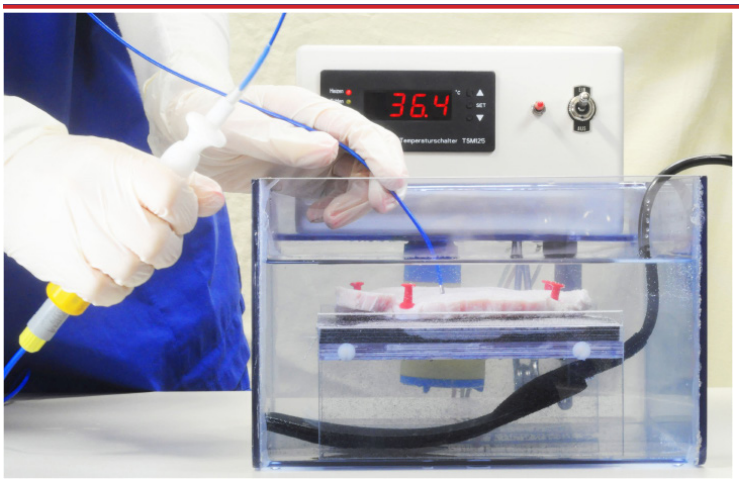

Figure 1: Demonstration of in-vitro RF ablation on pork in the wetlab containing isotonic saline solution, heated to body temperature and simulating the cooling influence of the blood flow

graphical and tabular recording and real-time-displaying of all relevant physical parameters, affecting the results of the in-vitro procedures (Fig. 2). Special screenshot and video capture software was installed on each workstation for easy documentation of parameters like radiofrequency power, temperature and impedance during the

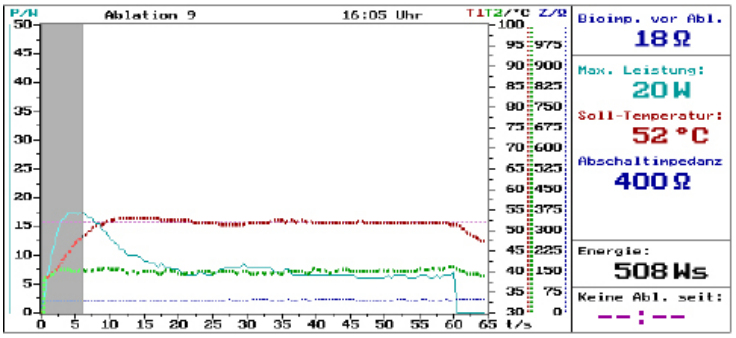

Figure 2: Demonstration of a dual-temperature-sensor in-vitro RF ablation. All relevant parameters are presented as diagrams: the courses of output power, the temperatures of both sensors and impedance. Furthermore, the applied energy as well as impedance before and after delivery of RF energy is displayed

treatments. Any workstation's screen can be displayed on additional large scale monitors for discussions of the observed effects in the training group.

By establishing special connection boxes, in-vitro experiments with catheters of different make and model can be performed. Thus, fundamental processes during RF ablation can be demonstrated and the special characteristics of different types of catheters and procedures can be revealed.

Using this equipment the participants can learn, interactively, by measurements and visualization

Figure 3: Identical Cerablate RF ablation catheters (Osypka AG) with 8 mm tip electrode of different materials. Top: standard platinum-iridium tip electrode; Bottom: novel massive-gold tip electrode; Middle: steering handle, identical for both catheters

Figure 4: Comparison of lesions generated with 8 mm massive gold (left) and platinum-iridium electrode (right) using identical generator settings (T =65 °C) and contact force

- differences between temperature and power controlled RF ablation
- differences in lesion size and geometry using standard 4 mm and 8 mm tip
- influence of the specific tip electrode angle to the myocardium on lesion size
- advantages and catheter handling using dual sensor technology

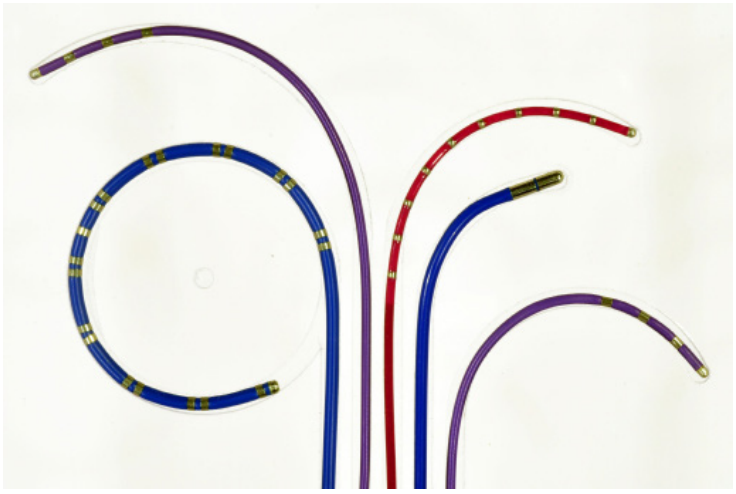

Figure 5: Plexiglass template, fixing a set of different diagnostic and therapeutic (ablation) catheters in the wetlab, in order to record artificial electrograms for test purposes

- differences between open [1-4] and closed irrigated tip RF ablation
- influences of blood flow and cooling rate on lesion size
- effects of different tip materials on lesion size
- intracardiac electrogram recording

During delivery of the radio frequency energy, the courses of power, one or two sensor temperatures and electrode impedance will be continuously displayed on each workstation monitor. It can by documented by screenshots and procedure protocol for every experiment. Furthermore, curve progressions can also be displayed on four large scale monitors for interactive discussions between professional teacher and the trainees.

The training system was also used to investigate the influence of different catheter tip materials on lesion size. For example, we compared geometrical lesion size of identical catheters, differing in 8 mm massive gold and standard platinum-iridium tip electrode (Osypka AG) only (Fig. 3).

Compared to platinum-iridium, gold tip electrodes exhibit an almost four-fold thermal conductivity (3.17 versus 0.72 W/cm K).

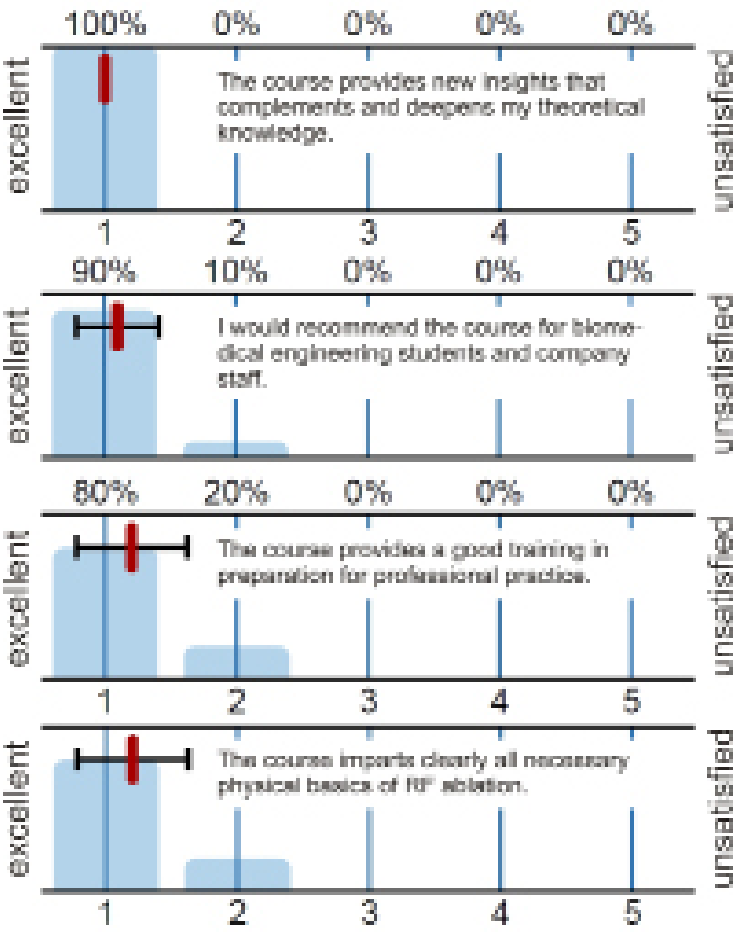

Figure 6: Excerpt from evaluation of the RF ablation hands-on teaching system

Thus, due to better cooling of the gold tip by blood flow, increasing RF power results in significantly larger and deeper lesion, as expected.[5]

Results of such experiments can also be used to reproduce in-vitro tests of new RF ablation catheters.

Results of these investigations, using identical RF ablation parameters, are shown in Table 1. Significant differences were found concerning lesion size by depth and diameter (Fig. 4). Using temperature-controlled RF ablation, the massive gold electrode tip showed an RF energy increase of up to 173% compared to platinum-iridium tip (Table 1). These results promise a reduction of ablation time, number of lesions and - consequently – decrease of fluoroscopy time.

The wetlabs can be equipped with a simplified plexiglass template to simulate different electrode arrays for electrophysiologic electrogram recording (Fig. 5). Connecting the output of a heart rhythm simulator to the wetlab, recording and particular filtering of intracardiac electrograms can de demonstrated by multi-channel EP-lab. Using this feature, the wetlab can also be used for tests and troubleshooting with diagnostic catheters, e.g. for elimination of noise.

During hands-on trainings for young electrophysiologists as well as for students of the biomedical engineering study path at Offenburg University of Applied Sciences, the in-vitro training system in physics of RF ablation provided excellent conditions to become acquainted with the theoretical and practical aspects of this method. This hands-on teaching system provides didactic simulations on the technical basics of the method. It allows a structured acquisition of practical knowledge. This ensures that physicians, company staff and

Table 1: Comparison between energy deliveries after 60 s RF ablations by platinum-iridium and massive gold electrode tips at different target temperatures using the Stockert SmartAblate G4 RF ablation generator (Stockert GmbH, Freiburg, Germany)

Catheter tip material	Energy (J) T = 45 °C	Energy (J) T = 55 °C	Energy (J) T = 65 °C
Platinum-Iridium tip	117	246	394
Gold tip	202	546	1075
Difference (%)	62	122	173

biomedical engineering students receive a practical training, based on the needs of the clinical routine.

Evaluation of the didactic benefit was done by 10 of 12 trainees absolving the RF ablation physical basics course. On a scale between excellent (1) and unsatisfied (5), mean ranking was 1,2 of 10 different questions. Examples are shown in figure 6. Furthermore, this RF ablation teaching system was honoured for innovation in didactic of University education by a fellowship of the Association for the Promotion of Science and Humanities in Germany.

Finally the teaching system has proven to be a suitable environment for testing and evaluating of new catheters.

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Arguments to Apply Epinephrine for Pocket Hematoma Reduction. The MAITRE Study

Nikolay Ilov, MD, Anatoly Nechepurenko, MD, Albert Abdulkadyrov, Damir Paskeev, Elena Damrina, Elena Kulikova, Marina Terent'eva, Dinara Stompel, Dmitry Tarasov, MD

Federal Center for Cardiovascular Surgery, Astrakhan, Russia. Presented in Venice Arrhythmias 2015, Venice, Italy.

Abstract

Pocket hematoma (PH) is a common complication of implantations of cardiac electrophysiological devices with occurring at a particularly high rate in patients on oral anticoagulation or antiplatelet treatment. Different pharmacological agents with hemostatic effect are used to avoid PH. We supposed that the vasoconstrictor effects of epinephrine may reduce bleeding extent and be effective in prevention of PH. Maitre is the first clinical trial conducted with an aim to show the safety and efficacy of epinephrine in PH prophylaxis. We randomized 133 patients to receive either epinephrine or saline solution, which were added to a local anesthetic administered during pacemaker implantation. In cases of diffuse bleeding a method of pocket drainage was effectively used. Results showed that risk of PH was significantly higher in the group receiving epinephrine. We conclude that a local epinephrine effect may lead to a false impression of adequate hemostasis and force a surgeon to refuse from drainage insertion.

Introduction

Pocket hematoma (PH) is a known complication of pacemaker implantation procedure. PH is followed by local discomfort related to infiltration of hypodermic tissue.[1] In some cases it may demand surgical revision which increases a risk of device-related infection and prolongs hospitalization.[2, 3] The results of conducted research indicate different PH rates. Makeev et al. (1999) according to the analysis of 700 implantation procedures concluded that it's a rare complication with a rate of 0.5%.[4] European authors usually point out a higher PH rate reaching a value of 5%.[5]

Known risk factors of PH include procedure type (primary implantation or redo procedure), operator experience,[6] size of implanting device, site of pocket formation, number of implanting leads, venous access type (subclavian or cephalic access).[7] Moreover a risk of PH is connected with patient's medications. It has been shown that anticoagulation (AC) therapy significantly increases PH rate to 3.5%-16%.[8] Chen et al. carried out a retrospective analysis of 1093 implantations of different devices and showed that double antiplatelet (AP) therapy, bridging anticoagulation and even moderate thrombocytopenia considerably increased the risk of PH.[9]

Key Words:
Epinephrine, Electrophysiological, Pocket Hematoma, Dual Antiplatelet.

Disclosures:
None.

Corresponding Author:
Nikolay Ilov.
414024 N. Ostrovskogo,
46-25, Astrakhan, Russia.

A question of PH prophylaxis is relevant for patients with constant administration of AC and/or AP therapy. It's often suggested to perform pacemaker surgeries with partial or full interruption of these drugs.[10] Our opinion is that in most cases it may bear a potential danger for patient health. It may be especially harmful after valve replacement surgery and PCI.

It is considered that careful surgical technique, earlier pocket formation,[11] electrocautery use and cephalic access may decrease the risk of PH.[12] Some centers recommend drain insertion into the device pocket,[13] and different pharmacological agents with hemostatic effect are used to avoid PH.[14] Epinephrine is one such drug. Vasoconstrictor effects caused by alpha-adrenoreceptors localized in the skin, mucous membranes and bodily organs are thought to strengthen potential and reduce bleeding extent. These advantages of epinephrine are widely and effectively used in ophthalmologic and stomatologic practice and may be useful during implantations of electrophysiological devices (EPDs). We couldn't find any publications devoted to this topic. Lack of clinical trials and evidence-based recommendations has led us to conduct this trial.

Materials And Methods

Maitre is a single-centered, double blind, randomized, placebo-controlled trial in two parallel groups of patients with indications for primary pacemaker implantation. The aim of our study was to study the safety of epinephrine's systemic and local effects and to estimate its influence on pocket hematoma prophylaxis.

The study protocol was approved by the Ethic Committee of Federal Centre for Cardiovascular Surgery (Astrakhan, Russia). We enrolled 133 patients who met inclusion and exclusion criteria (Table 1).

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• a signed informed consent for participation in the study	• individual epinephrine and/or lidocaine intolerance
	• known contraindications for studied drugs administration
	• severe arterial hypertension: SBP ≥ 200 mm Hg and/or DBP ≥ 110 mm Hg
	• unstable IHD
• men and women aged from 40 to 70 with indications for single and dual-chamber pacemaker	• disturbances in any hemostasis mechanisms: number of thrombocytes, PT, fibrinogen, INR, tourniquet test;
	• LV EF (Simpson) <35%
	• pregnancy and lactation
	• chronic kidney insufficiency: creatinine level higher than 110 icromoles per liter

Randomization

The type of solution (saline or epinephrine) as well as the name of the operator were previously coded in numbers. Generated using Excel random number generation functions. The patients were randomized in group A (75 patients) or in group B (58 patients). In spite of quantitative difference in the number of patients assigned to each group, the formed groups were comparable on main clinical and demographic characteristics (Table 2). According to the results of randomization a medical nurse added a 0.4% solution of epinephrine for group A or a saline solution (placebo) for group B to a local anesthetic (usually lidocaine). The operator therefore had no knowledge about anesthetic solution contents. A registration card was started for each patient.

Pacemaker Implantation Technique

A patient was administered a 1.0 gr cephazolin solution I/V before a procedure. A choice of implanting pacemaker type (single or dual-chamber) was made according to the Russian National Recommendations for performing of electrophysiological, catheter procedures and implanting EPDs (2013). The procedure was performed under the local anesthesia using a commonly accepted standard with pacemaker implantation in the right or in the left subclavian area. Moderate sedation wasn't administered. The choice of pocket location, venous access, lead fixation type and pacemaker mode was made by a surgeon depending on a specific case. Cephalic access and subcutaneous pacemaker placement were preferable. Electrocautery was routinely used in all implantations. Drainage was used in case of diffuse bleeding.

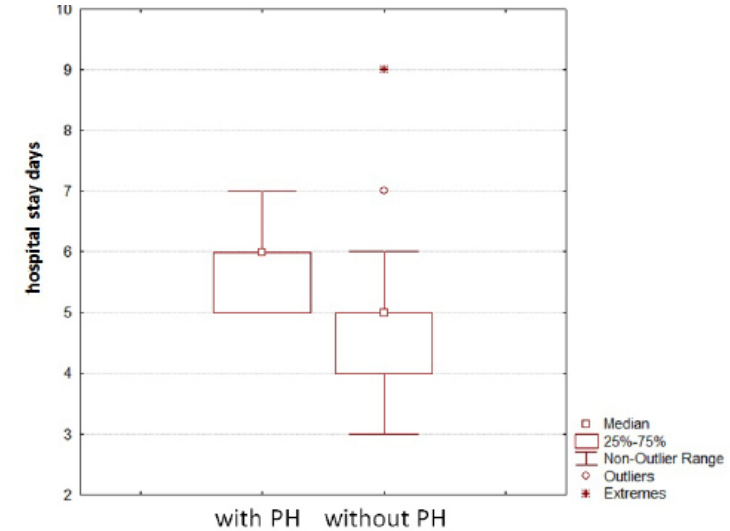

Figure 1: PH associated length of hospital stay

Table 2: Clinical and demographic characteristics of studied patients

	Group A (Epinephrine)	Group B (Saline Solution)	P-value
Number of patients	75	58	p > 0,1
male/female	43/32 (57%/43%)	29/29 (50%/50%)	p > 0,1
Average Age	60 (55;65)	62 (56; 65)	p > 0,1
BMI	29,2 (26,4; 33,1)	30,7 (26,8; 34,7)	p > 0,1
Diabetes mellitus	5 (7%)	6 (10%)	p > 0,1
LV EF Simpson, %	58 (53; 61)	58 (53; 60)	p > 0,1
AP treatment	12 (16%)	8 (14%)	p > 0,1
AC treatment	22 (29%)	22 (38%)	p > 0,1
AP + AC treatment	2 (3%)	1 (2%)	p > 0,1
Without AC/AP treatment	39 (52%)	27 (47%)	p > 0,1

Patients Follow-Up

A 1 day bed rest and a 2-hour cold and compression therapy were prescribed for all patients. Patients didn't receive bridging anticoagulation and we didn't stop AP and/or AC therapy before and after pacemaker surgery. It was forbidden to administer any hemostatic drugs for the first two days after implantation. Antibiotics continued in case of severe bleeding from the device pocket and necessity to coutinue drainage.

Study Endpoints

Primary Endpoint: PH which was identified after two physicians' investigation by palpated infiltration, smoothing the pacemaker contour. PH was also assessed by ultrasound study routinely performed for all patients on the 3rd-5th day after implantation.

Secondary Endpoints: Death from any cause, cerebral vascular events, bleeding, pericarditis, tamponade, infectious complications, drainage insertion during the procedure, drainage prolongation, hospital stay days.

After an implantation procedure with blind use of epinephrine or saline solution a surgeon was asked to guess the used solution thereby giving a subjective evaluation of the bleeding extent.

Early End Of Study

The study could come to an early end for a patient in case of his/

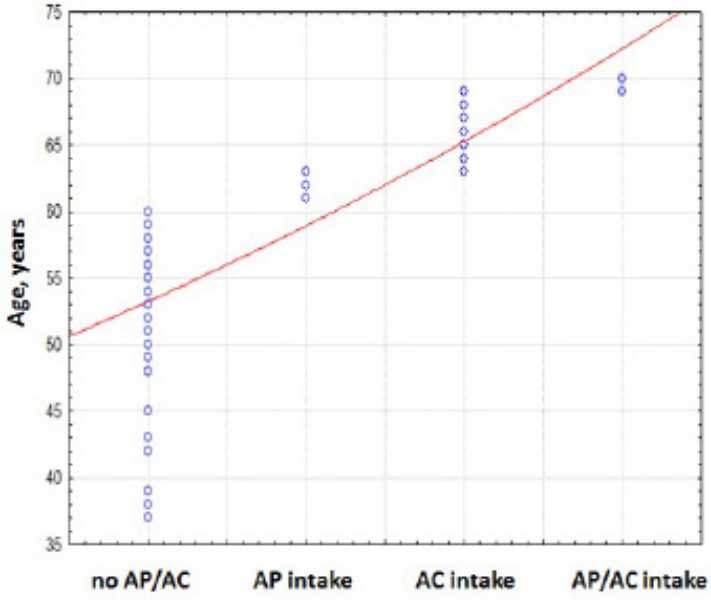

Figure 2: Age-depended anti-clotting agents administration

Table 3: Operative details

	Group A	Group B	P
Single-chamber pacemaker	23 (31%)	19 (34%)	p > 0,1
Dual-chamber pacemaker	52 (69%)	39 (66%)	p > 0,1
Subcutaneous device pocket	62 (83%)	54 (93%)	p > 0,1
Subfascial device pocket	10 (13%)	4 (7%)	p > 0,1
Subpectoral device pocket	3 (4%)	0	p > 0,1
Cephalic venous access	29 (39%)	38 (66%)	p > 0,1
Subclavian venous access	41 (55%)	18 (31%)	p > 0,1
Cephalic + subclavian venous access	5 (6%)	2 (3%)	p > 0,1

her refusal to participate; according to the decision of a researcher in case of violation of the study protocol or non-related to PH need to perform surgical revision.

Statistical Analysis

Module Statistica 7,0 (Statsoft) was used to carry out a statistical analysis. Central tendencies were described as Median (IQR 25%; 75%). Data comparison and association analysis were provided by nonparametric methods with the p-value of 0.05 designated as the threshold for statistical significance.

Results

We randomized 133 patients who met the inclusion criteria. Average procedure time was 38 (35; 60) min. Both groups were comparable on gender, age and clinical features as well as on heart failure status and AP/AC administration (Table 3). Patients were discharged from hospital on the 5th (4; 5) day. All of them were recommended to communicate immediately with a surgeon in case of any skin changes at the site of the device pocket.

Three patients (2 from group A and 1 from group B) stopped a trial early due to necessity of surgical revision (lead dislodgement diagnosed three days after implantation).

Primary Endpoint

We observed primary endpoint (PH) in 7 cases, 6 of them occurred in group A (86%). PH risk was 0.09 (9 %) in group A and 0.02 (2%) in group B (OR = 5, 95%; CI: 2.1-7.3, p=0.003). Anesthetic solution content was the only significant difference in the characteristics of these patients (Table 4).

Secondary Endpoints

Lead dislodgement was observed in 5 patients (4%) and demanded surgical revision within the first three days (3 patients) or later (2 patients). Pneumothorax following pleural draining was registered in 2 patients. These complications had an equal rate in both groups (p>0.1).

A drain was inserted in 43 procedures (32%), 25% of them in group A and 44% - in group B (p=0.04). Pocket drainage duration didn't exceed 2 days and was on average 1 day in both groups (p>0.05).

There was no significant difference in length of hospital stay (5 (4; 5) days in group A and 5 (4; 6) days in group B, p=0.3). This parameter increased in case of PH reaching a value of 6 (5; 6) days. A positive correlation between the number of hospital stay days and any complication occurrence was observed (r = 0.18 при p=0.04), in case of PH it was also significant (r = 0.24, p=0.04). Other secondary endpoints didn't occur.

Discussion

What is PH?

The fact is that we have no common definition of PH. There is no doubt that this fact complicates the analysis of data from different studies.[15] Niederhuber J. E. (2012) suggested that PH is a palpable swelling of the device pocket exceeding the size of implanted EPD. It was recommended to refer to ultrasound investigation in a disputable case.[16] The primary point of BRUISE CONTROL (the Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial, 2013) was "clinically significant" PH which the researchers defined as PH demanding surgical reoperation with prolongation of hospitalization or interruption of oral ACs.[8] These signs are found to be significant by other authors.[12]

Table 4: Characteristics of the patients with PH

Patients	1	2	3	4	5	6	7
Study Group	A	B	A	A	A	A	A
Age	64	64	64	66	64	57	69
Gender	male	female	male	male	male	male	male
BMI	34,5	27,2	28,4	21,6	42,9	31,7	34,1
AP/AC treatment	-	AC	AC	AC	-	AC	AC
Pacemaker type*	DCh	DCh	SCh	DCh	DCh	SCh	SCh
Site of device pocket**	SC	SC	SF	SC	SC	SC	SC
Venous access***	C	S	C	S	S	S	C

*DCh – dual-chamber, SCh – single-chamber; **SC-subcutaneous, SF-subfascial; ***C-cephalic, S-subclavian

In our trial the vast majority of PHs (6 of 7 patients) didn't demand active surgical strategy which corresponds to the published data.[8,12] No doubt a necessity to perform reoperation has to be evaluated with a risk of infectious complications taken into consideration.[17] Either insufficient reduction of PH size or PH expansion with the symptom of local tenderness are widespread criteria for such a strategy.[18] We observed similar manifestations in one case with subsequent pocket puncture and evacuation of its liquid content.

The hospital stay in our study (5 days) seems to be too long for US and Europe but it's common in Russia. Our study demonstrated an increased number of hospital stay days in cases of PH which was supported by the statistical analysis (Figure 1).

In this randomized trial we evaluated the safety of epinephrine used as a component of local anesthesia and estimated its influence on PH prophylaxis. We showed that PH is a rare complication with rate of about 5%. Analyzing the characteristics of patients with PH participating in our study we found that these were older than those who didn't have PH (64 (64; 66) years vs 60 (54; 64) years old (Mann-Whitney U-test: U[7; 123]= 233.5; p=0.042). The results of correlation analysis prove the role of age in PH occurrence rate (r=0.18 при p=0.04). The possible explanation of this is a positive correlation between patient age and AC or dual AC+AP therapy administration (r=0.22 при p=0.04) - Figure 2.

Five of seven PH (71%) were registered in our trial in patients with AC administered before implantation. PH risk in this group was tripled compared to those who didn't receive any anti-clotting agents (10.6% vs 3%, p=0.04). It has been shown that AC and AP administration is one of the main causes of PH after pacemaker surgery. Kutinsky I.B. et al (2014) showed a high range of PH rate (11.1% and 24.2% at AP mono and dual therapy, 6.9% at AC therapy).[12] No patient taking AP agents had PH in our trial. It may be explained by drainage insertion in almost half of the implantation procedures performed for this group of patients.

In fact, there is no consensus about drainage use with pacemaker implantation. One of the arguments against such approach is a probable increasing risk of pocket infection (PI) after pacemaker

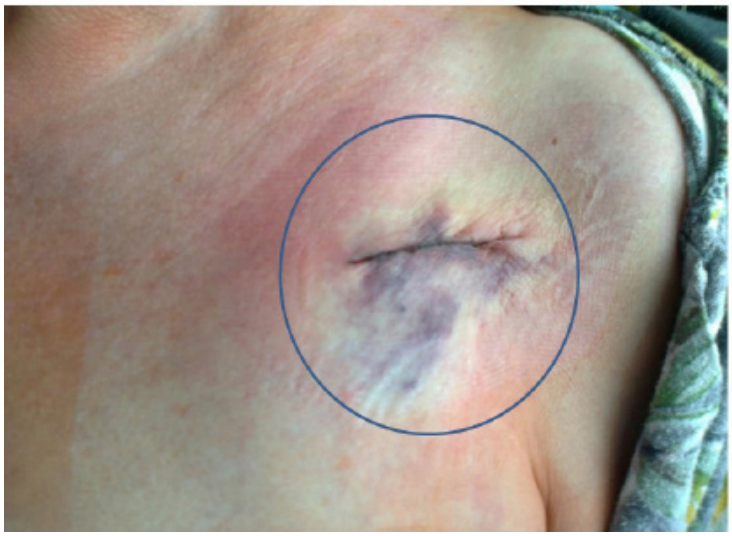

Figure 3: Epinephrine skin effect

surgery. Meanwhile about 4500 EPDs have been implanted in our center. A strategy to insert drainage in case of diffuse bleeding has been used for all these procedures with a total draining time no more than 3 days along with antibiotic administration for this period. We do believe that pocket draining has to be used especially in cases of subfascial or subpectoral pocket localization, which has been shown in this trial (r = 0.28 при p = 0.03). The PI rate in our center is annually about 0.4% and we didn't observe any correlation between drainage insertion and post implantation infection.

Influence Of Epinephrine On PH Prophylaxis

Our trial showed that use of epinephrine as a component of local anesthetic solution is safe during pacemaker surgery. We didn't observe any systemic effects of epinephrine with respect to blood pressure or heart rate increasing. In 3 cases we observed circular skin paleness above the pacemaker pocket which resolved in 2 or 3 days (Figure 3). We estimated it as a local vasopressor effect of epinephrine.

In spite of our expectations our trial didn't prove a positive influence of epinephrine on PH prophylaxis. A risk of PH was statistically higher in group A, in most cases of registered PHs drainage wasn't performed (in 5 from 7 patients, 71%). These were patients from group A and a surgeon's decision to refuse drainage was made due to lack of diffuse bleeding during implantation. Drainage was used in almost half of all the procedures in group B (44%) and in a quarter of implantations in group A (p=0.04) – Figure 4.

Local vasopressor effect of epinephrine were consistent with results of a surgeon poll a surgeon poll after the procedure. Surgeons correctly pointed out the patient group in 78% of implantations. We consider that a local epinephrine effect may lead to a false impression of an adequate hemostasis and provide false reassurance regarding the potential need for drain placement. It may explain a higher rate of PH in group A.

Patients Follow-Up

The studied patients had follow-up at 3, 6, 12 and 18 months after implantation. They were informed about necessity to contact a surgeon in cases of any pocket or wound compromise. We have observed no PI even in patients with PHs. There wasn't any necessity to perform reoperation for them.

Study Limitations

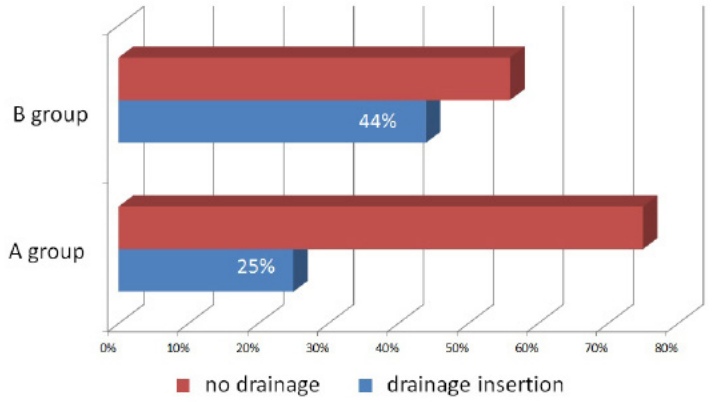

Figure 4: Secondary End-point - Pocket draining duration, n=43 (32%)

The evidence level of this trial is limited by the number of patients and single center participation.

Conclusions

Epinephrine administration as a component of local anesthetic solution during pacemaker implantation is safe and doesn't lead to any serious adverse effects. Meanwhile it doesn't decrease the risk of PH formation which is probably connected with local vasopressor epinephrine effects and delayed capillary bleeding in device pocket. The efficacy of pocket drainage in cases of diffuse bleeding has to be evaluated in future randomized trials.

Acknowledgments

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Symptom/Rhythm Correlation With Patient Owned Device: Insights Into Practice And Challenges

Mohammed Shurrab, MD,MSc,[1,2] Anatoly Langer, MD,[3] Eugene Crystal, MD,[1] David Newman MD[1]

[1]Arrhythmia Services, Schulich Heart Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada. [2]Arrhythmia Services, Cardiology Department, An-Najah National University Hospital, Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, Palestine. [3]Cardiology Department, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada.

Abstract

Capturing symptom/rhythm correlation is crucial in patients who have rhythm-related symptoms. Evolving technology has led from 24 hour and 14 day Holter monitors to now external loop recorders to capture symptom/rhythm correlation. In patients with very infrequent and short-lived symptoms, the only recourse is an implantable recording device. Recently, patient activated recording devices have become available. These have the potential to significantly increase the duration for monitoring symptom/rhythm correlations. We report cases of using such devices to demonstrate some of the uses and challenges of this new ECG recording technology.

Introduction

Patients who have rhythm-related symptoms usually have a need to record symptoms and rhythms in the same time frame. The use of an ambulatory ECG or Holter monitor for symptom evaluation has a diagnostic yield proportional to symptom frequency and with evolving technology has led from 24 hour to now 14 day Holter monitors to capture symptom/rhythm correlation. The arrival of external loop recording devices in the late 1980's increased the diagnostic yield to approximately a 25% range,[1] again related to the symptom frequency and the ability of the patient to tolerate continuous or intermittently applied skin electrodes.

In patients who absolutely require the recording of rhythm prior to infrequent but short-lived symptoms, the only recourse is an implantable recording device. In the last years, patient activated recording devices have become available. These have the potential to significantly increase the duration during which patients may have a tool for monitoring symptom/rhythm correlations. As well, given their ability to be used in the very long term, such devices offer an opportunity to consider longitudinal assessment of drug effects. Such devices can be used in the long term for atrial fibrillation detection in groups deemed to be at risk for such an arrhythmia based on epidemiological (age plus hypertension) or clinical features (post CVA with normal carotid Doppler assessment).[2-4]

We report four typical cases of using such devices to demonstrate some of the uses and challenges of this new and potentially disruptive advance in patient and marketing driven ECG recording technology.

Key Words:
Recording Device, Ambulatory ECG, Diagnosis, Symptom/Rhythm Correlation.

Disclosures:

David Newman, Anatoly Langer are members of board of directors of cardiocom.

Corresponding Author:
Mohammed Shurrab,
Arrhythmia Services, Schulich Heart Centre, Sunnybrook Health Sciences Centre,
2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada.

Device Description

A handheld ECG device that captures a modified lead II ECG recording was used. The device has two contact electrodes for each thumb and records a modified lead II ECG which is uploaded to a central recording site or can be recorded to the patient's desktop. Record duration is 30 seconds (with storage of up to 20 recordings). The validity of a thumb electrode record to accurately reflect a modified lead II has been established.[5] Patients are capable of making records whenever symptoms occur. Further details about the current iteration of this device can be found at the manufacturer's URL (http://www.theheartcheck.com/products/pen_device.html).

Case 1

A 52-year-old triathlete presented with a five-year history of sudden onset/offset rapid heart palpitations. Episode duration was minutes at a time causing significant symptoms at peak exercise while training. Over the years three, 2-week external loop recorders (ELR) failed to correlate symptoms with rhythms. The patient was bothered by his rare rhythm related events but never pre-syncopal and was not offered an implantable monitor. Using a home athletic heart rate monitor, he recorded his heart rate changes during symptoms. After a cool down period he engaged in vigorous exercise. A sudden step increase in

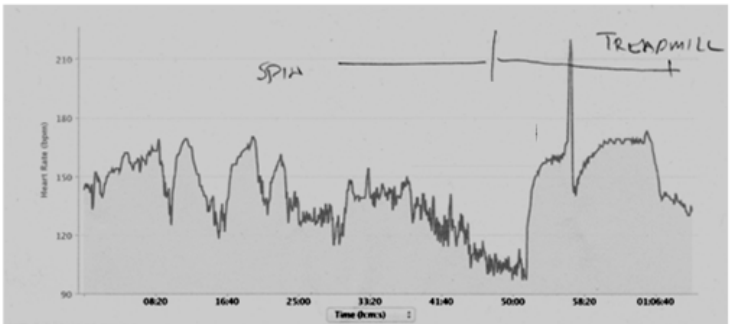

Figure 1A: Patient home exercise heart rate device showing exercise induction of symptoms coincident with a step rise in heart rate

heart rate to 230 bpm followed by an equally sudden decrement back to basal rate 160 bpm was seen (Fig 1a). Based on this, he underwent diagnostic electrophysiology study in January 2010. This revealed intermittent dual AV node physiology with isolated atrial ectopy at extremes of stimulation with ISOPROTERENOL infusion. Since no significant inducible rhythm was ever documented it was opted not to perform empiric slow pathway ablation.[6]

He acquired a hand held ECG device in March 2014 and 10 months later was able to induce and record index symptoms followed by a recording of rhythm when he returned to normal (Fig 1b). The rhythm recorded is suggestive of typical atrioventricular nodal re-entrant tachycardia (AVNRT) as a cause of symptoms with a small retrograde deflection seen after each QRS at a rate of 200 bpm. He was booked for redo procedure with planned empiric slow pathway ablation to be performed even if no arrhythmia was induced.[6-8]

Case 2

A 29-year-old man, morbidly obese otherwise healthy, presented to Emergency Room with rapid atrial fibrillation. By history he was thought to have a rapid regular rhythm that then degenerated to an irregular rhythm. Resting and stress echocardiograms, as well as Holter monitoring, were unrevealing. On September 19, 2004, an electrophysiogical study documented a difficult to induce typical AVNRT at rate of 250 bpm. An uncomplicated slow pathway ablation procedure was performed with the unproven hypothesis that typicalAVNRT preceded bouts of atrial fibrillation.

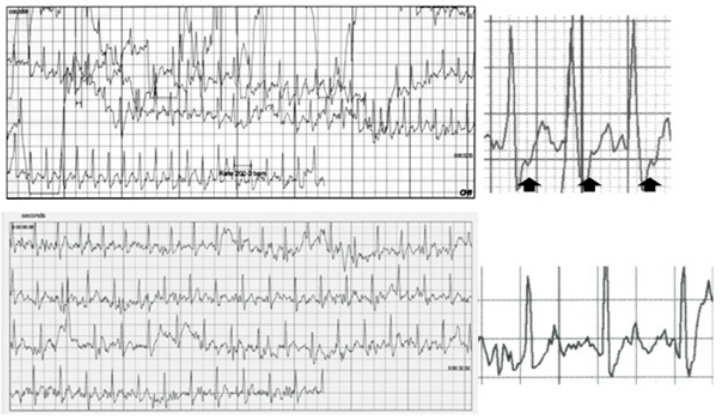

Figure 1B: Upper panel: Symptomatic suddent-onset rate of 200 bpm. Insert shows suggestion of retrograde atrial activity just after each QRS. Lower panel: Recording after termination of symptoms. Insert shows enlargement of selected QRS complexes with no obvious evidence of retrograde atrial activity. Blow up insert shows enlargement of QRS complexes without obvious or retrograde atrial activity consistently seen

He did well for the next 9 years. In September 2013, he had bouts of symptoms suggestive of typical atrial fibrillation that were not documented. ECG evidence of atrial fibrillation was detected in November 2013 with ongoing infrequent episodes.

He was offered and declined pulmonary vein isolation (PVI) procedure and given his symptom burden and the perceived risk-benefit ratio opted for medical management instead opted for medical management. He declines a beta blocker so flecainide monotherapy was started along with aggressive efforts towards weight control. Sleep studies showed no OSA. He acquired an ECG recording device to record recurrent arrhythmia symptoms symptoms while on flecainide (Fig 2). Recurrent bouts of atrial fibrillation were recorded. His symptoms were not radically different, and the arrhythmia was not showing signs of organization. A beta-blocker was added, and he eventually underwent uncomplicated pulmonary vein isolation (PVI). He continues to use the same ECG recording device in follow-up.

Case 3

A 35-year-old presented with longstanding proximal perimembranous restrictive VSD, which produces a high velocity peri-cuspal small left-to-right shunt. On MRI, the shunt jet causes prolapse of the right coronary cusp into the right ventricle (RV). The RV was normal in size and function, and the QP/QS ratio was calculated at 1.8, consistent with a left-to-right shunt.

He had longstanding highly symptomatic ventricular ectopy, which 12-lead ECG suggested was localized to the right ventricular outflow tract (left bundle branch morphology, inferior axis, transition lead V3, coupling interval 390 ms). Ectopy was shown on the Holter monitor to be isolated, typically less than 500 beats per 24 hours with no diurnal variation. Symptom – rhythm correlation using a home ECG recording revealed that some but not all symptoms were related to ectopy. His highly symptomatic but infrequent ectopy was a source of psychological stress, mitigated in his view by the ability to obtain and document a signal of on-going reassurance from an ECG recording apparatus. He had been offered and declined an ablation for rhythm the emergency room. He had intolerence or inefficacy with trials of rhythm suppression and symptom control with bisoprolol, sotalol, verapamil and diltiazem. Flecainide starting at 50 mg BID and titrated to a 100 mg dose improved his symptoms with no significant QRS prolongation. He continues to monitor for

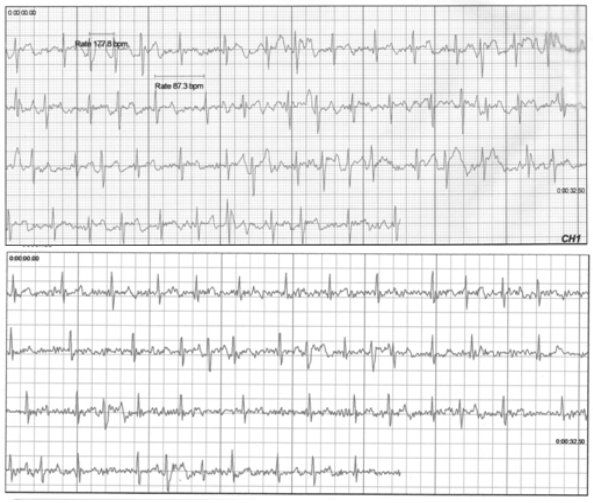

Figure 2: Upper panel: Atrial fibrillation. Lower panel: similar symptoms while on Flecainide 100 mg bid; recorded atrial fibrillation with no suggestion of organization of the arrhythmia

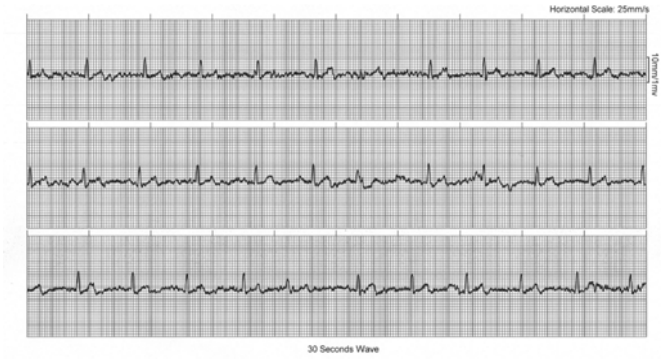

Figure 3: Ongoing rhythm documentation showing no significant QRS prolongation, symptom-rhythm correlation and no clear signal of pro-arrhythmia

recurrent symptoms, and to date there has been no evidence of pro-arrhythmic effect from his therapy.

Case 4

A 54-year-old man presented with infrequent paroxysmal atrial fibrillation in the setting of mild treated hypertension, absence of structural heart disease and inducible ischemia, and with normal BMI and a normal sleep study. Episodes of sustained arrhythmia were rare, occurring only once in 3 years. He was offered and declined a PVI ablation or continuous medical therapy for prevention of highly bothersome but infrequent bouts of arrhythmia. He preferred a pill-in-the-pocket oral pharmaco-conversion approach to management with an intent to take flecainide 300 mg as a single oral dose in the event of arrhythmia recurrence.[9] He received a recording device in February 2013. With this device he frequently documented bouts of nonsustained atrial tachycardia. He has found reassurance in being taught how to recognize their reoccurrence and is satisfied with his sense of control of rhythm and symptoms (Fig 4).

Discussion

The era of new devices for arrhythmia detection and subsequent monitoring has arrived. The embrace by some patients (or their concerned families) of novel technologies has started. The use of such devices, directly marketed to patients, may exceed clinical experience, familiarity or even proven clinical evidence of efficacy in outcomes such as symptom control and appropriate health resource utilization. Importantly, it remains to be seen how such devices might influence therapeutic decisions.

There is certainly the possibility that the use of such devices may in some patients encourage and promote a technologically driven somatoform behaviour. Alternatively for many patients it may provide a tool to enhance autonomy, offering reassurance and a sense of control. Furthermore, the use of such devices may offer an important tool for drug monitoring, assessment of therapeutic efficacy, mitigation of diagnostic ambiguity. In these ways their use may promote more appropriate health resource utilization. The four cases presented here illustrate many of these issues. In Case 1, the device helped in the decisionmaking process for empiric slow pathway ablation.[6-8] Cases 2 and 4 highlight the potential role such devices may have for pharmacological surveillance with the documentation of rhythm recurrence while on flecainide, a potentially pro-arrhythmic medication. Although not used for this purpose in the highlighted cases, such devices have been speculated to have a role in areas of concern for drug induced malignant arrhythmia with a QT signal that can be followed over time. This strategy may promote for pharmaco-surveillance for agents with very rare but potentially devastating long QT effects, such as certain psychotropic medications or macrolide antibiotics.[2,10]

Case 3 outlines the use of the device to inform patient driven decisions to use an outpatient oral pharmaco-conversion approach for rhythm control of atrial fibrillation. There is a burgeoning literature on long-term recording devices to identify atrial fibrillation in post stroke patients. Long-term (30 day) external loop recorder devices have a 20% diagnostic yield in such patients.[11] Longer term implanted devices increase the diagnostic yield by virtue of longer time of recording to 60% in two years.[12] Such devices, however, are cumbersome and require an invasive procedure. Alternatively a simple software program operating on a handheld device may allow a much longer duration of overall screening and thereby promote rates of arrhythmia detection. Such a system has been used for a population-based survey of a circumscribed community in patients over the age of 75 with a diagnostic prevalence of atrial fibrillation measured at 1.5%. Similarly, in a patient population of adults over the age of 75 taking prescription medications, 1% of patients were found to have silent AF.[13]

At the same time there have been advances in devices to record and generate an irregularity signal, but as cases 1 and 3 demonstrate, documenting changes in heart rate or providing a statement of irregularity may not be adequate or equivalent to the utility of having an actual ECG signal.

For cardioembolic stroke prevention due to atrial fibrillation, the alternative is a presumption of atrial fibrillation based on Holter atrial ectopy counts. Such methods have decreased diagnostic precision in predicting atrial ffibrillation to the 30-40% range in post-stroke patients.[14,15] The safety of new anticoagulation may allow such relatively poor diagnostic precision to still be useful as a surrogate for the decision for anticoagulation therapy in post stroke patients however this is an area of ongoing research that may be replaced by long term home ECG monitors used in this study.

There are some challenges related to the use and interpretation of the recording devices. The devices' utility depends on patient self-recordings. As a result they require patient attention and certain awareness, which might be challenging when the patient is distressed with the arrhythmic event at the time of the recording. Providing patients with a recording system to monitor their own dysrhythmias can lead to neurotic behavior. Patients can become quite anxious over

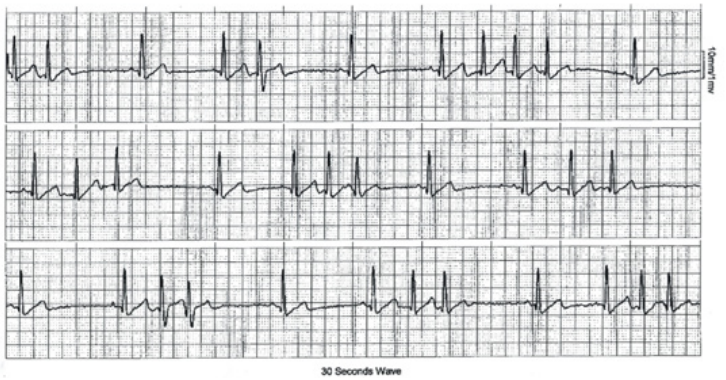

Figure 4: The patient feels better control of rhythm and symptoms with a pill-in-the-pocket- oral pharmaco-conversion approach. Frequently documented bouts of nonsustained atrial tachycardia were recorded, no delivery of oral pharmaco-conversion therapies used

their heart health and may have a worsened psychological quality of life.

While interpreting tracings from these devices, physicians sometimes face a significant number of tracings with artifact that are difficult to interpret. The large number of recordings can be cumbersome for providers to sift through. Without an automated automated recording/evaluation system such as those included with Holter monitors and loop recorders, providers may find themselves overwhelmed with data. There are a few recording devices in the market that are conceptually similar to our device. AliveCor is a similar device using only lead 1 for recording. This is not an ECG device but rather a sensor that records a single lead using paddle electrodes which can be mounted onto a mobile device. The recordings are transmitted to the mobile device via Bluetooth. Unlike the device discussed in our report, AliveCor does not currently include ECG analysis software; operators can only scan ECG documents produced by the accompanying application. Ultimately, the evolution of these devices might improve many of the current limitations in the near future.

Current machines have a cost to the patient directly or their insurer. The devices used in this study cost $250 CDN, and it is possible that the increased use of such devices will lead to new discussions on equitability of access to health technology. Such a discussion already occurs in Canada in other areas, such as mental health, prescription medication use, and access to healthcare in remote areas mental health care, medication prescriptions use and access to health care in remote areas. These technologies will force further discussion in two directions:

1. Better research to show proof in healthcare utilization benefits and other benefits that are clinically relevant but more difficult to evaluate (e.g. health-related quality of life, measures of autonomy and control, etc.).
2. Ongoing discussions on costs of healthcare delivery with a device that is directly marketed to patients and families by for-profit companies.

Conclusions

The cases presented illustrate the utility of patient-activated home recording devices in the diagnosis of arrhythmias and long-term monitoring of safety related to antiarrhythmic medications. They further highlight some of the challenges pertaining to utilization of these novel devices in routine electrophysiology practice and offer insights into the future of symptom/rhythm correlation.

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Clinical Use And Limitations Of Non-Invasive Electrophysiological Tests In Patients With Atrial Fibrillation

Valentina D.A. Corino,[1] Luca T. Mainardi,[1] Frida Sandberg,[2,3] Leif Sörnmo,[2,3] Pyotr G. Platonov[3,4,5]

[1]Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Italy. [2]Department of Biomedical Engineering, Lund University, Lund, Sweden. [3]Center for Integrative Electrocardiology at Lund University (CIEL), Lund, Sweden [4] Department of Cardiology, Clinical Sciences, Lund University, Lund, Sweden. [5]Arrhythmia Clinic, Skåne University Hospital, Lund, Sweden.

Abstract

Atrial fibrillation (AF) is a complex arrhythmia, that has been studied non-invasively assessing atrial refractory period, atrioventricular node (AV) node refractory period, and ventricular response. The AV node plays a fundamental role as it filters many of the numerous irregular atrial impulses bombarding the node. Despite its importance, the electrophysiological (EP) characteristics of the AV node are not routinely evaluated since conventional EP techniques for assessment of refractory period or conduction velocity of the AV node are not applicable in AF. Since rate-control drugs control ventricular response through their effect on the AV node, noninvasive assessment of AV node electrophysiology may be useful. The RR series, though being highly irregular, contains information that can be used for risk stratification and prediction of outcome. In particular, RR irregularity measures during AF have been shown to be related to clinical outcome. This paper reviews the attempts done to noninvasively characterize the AV node and the ventricular response, highlighting clinical applications and limitations of the noninvasive techniques.

Introduction

Atrial fibrillation (AF) is a complex arrhythmia, characterized by irregular atrial depolarization and, consequently, an irregular heart rate that prevents many of the commonly used approaches to evaluate for example autonomic tone or atrioventricular (AV) node properties. However, much effort has been spent on understanding the information that can be extracted in patients with AF.[1,2] In AF, there are three main characteristics of the heart that have been studied non-invasively: i) atrial refractory period ii) AV node refractory period, iii) ventricular response.

It has been shown that shortening of the atrial refractory period is associated with increase risk of AF.[3,4] To non-invasively assess the atrial refractory period, the atrial fibrillatory rate (AFR), being closely related to the atrial fibrillatory cycle length (an indirect estimate of the atrial refractory period), is often studied. AFR has been validated against intracardiac recordings and extensively studied in clinical contexts.[5–7] The interested reader is referred to a recent review[8] for more details on AFR.

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Atrial Fibrillation,Electrophysiological, Arrhythmia.

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Corresponding Author:
Valentina D.A. Corino
Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano
Via Golgi 39, 20133, Milano, Italy.

The AV node plays a fundamental role in AF as a regulator of the ventricular response. Rate-control drugs commonly act on atrial and/or AV node properties to reduce the ventricular rate. During drug development, cardiac electrophysiological (EP) effects of antiarrhythmic drugs are usually assessed invasively in EP studies performed in sinus rhythm. However, an atrial pacing protocol cannot be applied in patients with AF, and thus the EP effects of drugs on the AV node are still not completely understood in AF. When optimizing therapy, non-invasive assessment of the effect of a drug on AV nodal electrophysiology in patients with AF may help in choosing the best therapy. During the early clinical phases of drug development, non-invasive characterization of the AV node may facilitate data collection from large patient cohorts and favor patient-tailored therapy. Various studies have attempted to assess AV nodal refractory period[9–13] as well as to characterize AV nodal function.[14–22]

Even if the ventricular response during AF is highly irregular, it contains information that can be used for risk stratification and prediction of outcome, for example quantified by the RR irregularity measures.[23–28]

FRP: Functional Refractory Period. Mesor represents the average FRP on the 24-hour; Amplitude represents the maximum excursion over the Mesor. * $p < 0.002$ CHF vs. No CHF.

This paper reviews the work on noninvasively characterizing AF patients. On one hand, we describe AV node characterization, highlighting clinical applications but also limitations of the noninvasive technique. On the other hand, we describe the

Table 1: Effect of heart condition on the circadian behavior of FRP

Study		Mesor (ms)	Amplitude (ms)	Time of peak
Hayano et al.[13]	No CHF	575	63	2:40 a.m.
	CHF	560	35*	2:10 a.m.
Khand et al.[12]	NYHA I-II	532	104	3:30 a.m
	NYHA III-IV	552	66	3:30 a.m

FRP: functional refractory period. Mesor represents the average FRP on the 24-hour; Amplitude represents the maximum excursion over the Mesor. * p < 0.002 CHF vs. No CHF.

ventricular response, highlighting the association between reduced RR irregularity and clinical outcome as well as the effect of commonly used drugs on irregularity.

Av Node Electrophysiological Measures

Classical Invasive Measures

To evaluate AV node characteristics during an EP study, various pacing protocols can be applied. The S1S2 protocol is commonly used: a basic cycle length is chosen and a fixed number of S1S1 cycles is given, followed by a premature S2 stimulus, creating a shorter S1S2 interval. Being the driving stimuli applied at one or several atrial sites (A) while simultaneously recording the His (H) electrogram, A1A2 is shortened until A2 is not followed by His activation (H2). Shortening of A1A2 results in prolongation of A2H2,. Two important quantities can be defined: the effective refractory period (ERP), equal to the longest A1A2, resulting in AV nodal block, and the functional refractory period (FRP), equal to the shortest achievable H1H2 interval. Finally, during an EP study, the existence of dual AV nodal pathway can be easily identified by the so-called jump that can be observed in the A2H2 value.

Non-Invasive Measures

Noninvasive estimation of AV characteristics can rely on the analysis of surface ECG: from this signal the RR intervals can be derived and used as a surrogate of the H1H2 interval. The estimation of the functional refractory period of the AV node in AF has been attempted in different phenomenological studies. The FRP, defined as the shortest H1H2 interval, was estimated as the shortest RR interval in some phenomenological studies.[9–11] Talajic et al. showed in dogs that the shortest RR interval in AF correlated well with the FRP estimated invasively during an EP study in sinus rhythm, and therefore used the shortest RR interval as a surrogate measurement of the FRP. A disadvantage with this method is, however, its sensitivity to outlier RR intervals due to falsely detected or missed beats. A more robust FRP estimation was later obtained by using the 5th percentile of the RR series.[12]

Hayano et al. [13] used the 1.0-s intercept of the lower envelope of the Poincarè plot and the degree of scatter above the envelope as surrogate measurements of AV node refractoriness and concealed AV conduction, respectively. The method is based on the Poincarè plot, where each RR interval is plotted against the previous one. Briefly, the scattergram plane is divided vertically into eight consecutive bins in the preceding RR interval; in each bin, the minimum value of the subsequent RR interval is determined, and the eight minimum values thus obtained are linearly regressed on the average preceding RR interval for each bin. With this method the possible dependence between consecutive RR intervals is taken into account. However, the measurements produced by this approach depend of RR interval bin size, and therefore a comparison of results needs to be made with caution.

Table 2: Results from the studies assessing prognostic value of ventricular response

Study	N	Mean age (years)	Follow-up (years)	End point	Clinical characteristics	Prognostic measure
Cygankiewicz et al.[25]	155	69 ± 10	4.1	total mortality (cardiac, non cardiac)	heart failure in NYHA class II and III	ApEn<1.68 SE<6.44
Frey et al.[26]	35		1		advanced heart failure	SDANN <100ms
Platonov et al.[23]	68	69 ± 8	2	total mortality	congestive heart failure	pNN20<87
Stein et al.[27]	21		9.1	mortality and progression to mitral valve surgery	chronic nonischemic mitral regurgitation	SDANN
Yamada et al. [28]	107	64 ± 9	2.75	death (cardiac, fatal stroke, all-cause)	chronic AF	ApEn<1.83

The above-mentioned studies do not account for the dual pathways of the AV node. Recently, statistical model-based analysis, combining ventricular response and information on atrial activity derived from the surface ECG (Figure 1), was proposed for evaluating essential AV nodal characteristics in AF. The method estimates five parameters which characterize the AV node in patients with AF, with emphasis put on the refractory periods of the two AV nodal pathways, and the probability of an impulse to not pass through the fast pathway, i.e. to pass through the slow pathway.[16–18] The AV node is treated as a lumped structure that accounts for both temporal and spatial summation of the electrical activity of the cells. Atrial impulses are treated as if they arrive randomly to the AV node, with a mean arrival rate proportional to atrial fibrillatory rate (AFR), determined from the f-wave pattern.[29] Impulses arriving to the AV node are assumed to produce ventricular activations unless blocked by a refractory AV node. The slow and the fast AV nodal pathways are characterized by their absolute refractory period (aRP) and relative refractory period (rRP); slow or fast pathway is indicated by appending the letter s or f. All atrial impulses arriving to the AV node before the end of the aRP are blocked, whereas no impulses arriving after the end of the maximally prolonged refractory period (aRP+rRP) are blocked. The definition of aRP defines the shortest possible time between conducted impulses and hence may serve as an indirect estimate of the functional refractory. The rRP accounts not only for relative refractoriness but also for concealed conduction. The probability of an impulse to pass through the slow pathway provides global information on the impulse pattern, but not on the pathway selected by each individual impulse. A detailed description of the method and the technique for estimating the parameters can be found in.[16–18]

Non-Invasive Ep Tests On Av Node For Circadian Rhythm Assessment

Circadian rhythm assessment can be accomplished through the use of cosinor analysis in which a single-component cosinor with a 24-h period is fitted to the RR series to determine whether a circadian variation exists. The following variables are studied: the midline estimating statistics of rhythm (mesor); the amplitude, i.e., a measure of half the extent of predictable variation within a cycle and the time of peak estimated rhythm.

Khand [12] investigated the circadian rhythm of FRP as an index of autonomic function in patients with chronic AF and varying severity of heart failure. They found that the diurnal change in hourly 5th

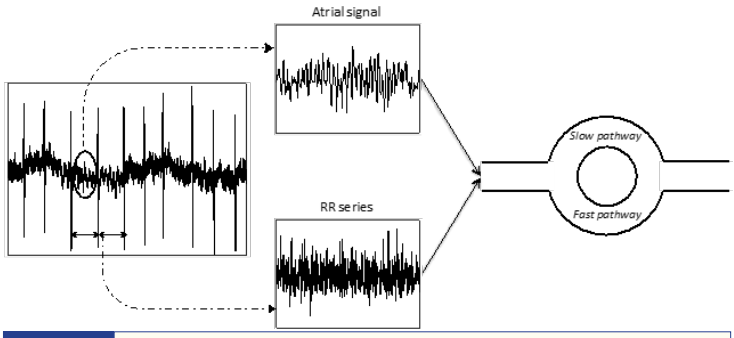

Figure 1: Scheme of the method for assessing AV node characteristics: the ECG is processed to produce the RR series and the atrial signal that form together the basis for estimation of the AV node parameters

percentile of the RR intervals was correlated to the NYHA class of heart failure (classes III and IV heart failure vs. classes I and II). Hayano[13] assessed the circadian changes in AV nodal properties in AF patients with or without congestive heart failure. The results showed that both AV node refractoriness and the degree of concealed AV conduction in AF are associated with circadian rhythms, attenuated in patients with congestive heart failure. In both studies a smaller circadian variation of the FRP was observed in patients with severe heart failure[12] or in patients with CHF,[13] even if not statistically significant.

Non-Invasive Ep Tests On Av Node For Drug Effect Evaluation

The evaluation of drug effect on AV nodal electrophysiology in AF, without the need for cardiac catheterization, may be useful during drug development or when optimizing the therapy. We used our recently proposed method[16, 17] on data from patients with AF taking different drugs. The results showed that the parameter estimates reflect the expected changes in AV nodal properties for the investigated drugs. To illustrate the use of the method, Figure 2 shows the response of six patients to two different antiarrhythmic drugs: a beta blocker (metoprolol) and calcium channel blocker (verapamil) in a controlled setting, i.e., data from the "RATe control in Atrial Fibrillation" (RATAF) study.[30] It can be noted that in patients (a) and (b) both drugs act in the same way: the RR fitted models with both drugs are right-shifted and broader when compared to baseline, and the FRP is prolonged. In patients (c) and (d), as well as in patients (e) and (f), there is one drug acting more on the AV node, making the RR fitted model right-shifted, thus prolonging the FRP. The method provides an estimate of the probability of an atrial impulse passing through the slow pathway–an estimate which provides information on whether a drug changes the pathway in which the impulses pass through. The availability of a noninvasive and rapid test of different drugs on patients can help in defining the therapy.

Figure 3 shows the percentage of prolongation with respect to the baseline value of the refractory period of the slow (a) and fast (b) pathway in different cohorts of patients with AF. It can be observed that the effect of all drugs is similar on both pathways. All of the estimated FRP prolongations were in agreement with the results previously reported in invasive studies performed in sinus rhythm. In particular, in EP studies tecadenoson was found to prolong the ERP of the AV node and to slow down its conduction.[31] Esmolol was found to prolong refractoriness and conduction time in both pathways during AV nodal reentrant tachycardia.[32] In,[19] the

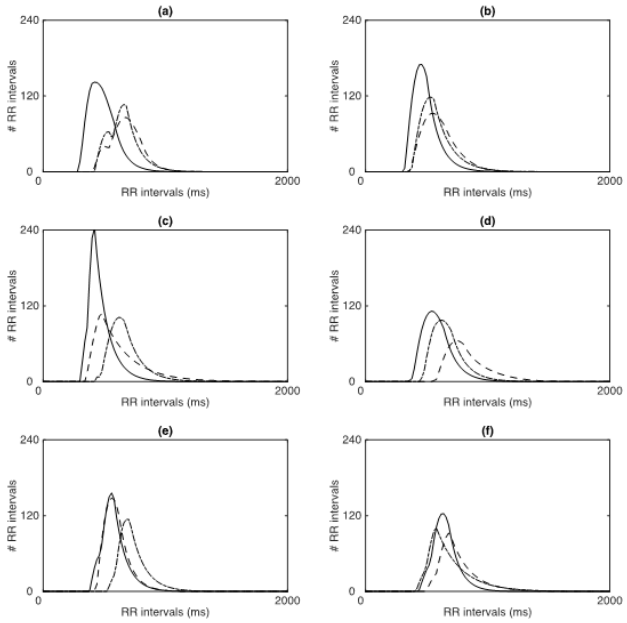

Figure 2: Response of six patients to two different rate-control drugs: a beta blocker (metoprolol, dotted line) and a calcium channel blocker (verapamil, dashed line) response are compared to baseline behavior (solid line). (a)-(b) both drugs act in the same way, right-shifting the RR fitted model; (c)-(e) verapamil seems to affect the RR fitted model more than metoprolol; (d)-(f) metoprolol seems to affect the RR fitted model more than verapamil (see text for details)

noninvasive estimate of FRP was prolonged during tecadenoson and esmolol administration. Both pathways were equally influenced, suggesting either prolonged effective refractory period or prolonged AV conduction, or both. In addition, tecadenoson reduced heart rate without significantly changing atrial rate, suggesting that this drug mainly affects the AV node properties. In previous invasive studies, calcium channel blockers and beta blockers were found to prolong the FRP, the prolongation in calcium channel blockers being greater than in beta blockers (metoprolol [33] and carvedilol[34] vs. verapamil[35] and diltiazem[36]); this result was observed also in.[21]

Ventricular response

Variability measures and irregularity entropy-based measures have been successfully applied. Variability measures are related to the dispersion of data, providing an estimate of overall heart rate variability, as well as long-term and short-term components of heart rate variability.[37] Irregularity measures are related to the degree of unpredictability of the data fluctuations, reflecting the likelihood that a certain pattern is repeated. Approximate entropy (ApEn)[38] and sample entropy (SampEn)[39] are the most commonly used measures.

Long-term prognosis based on RR series

Reduced RR variability/irregularity in AF has been associated to poor clinical outcome or death. The first two studies that addressed this issue analyzed patients with AF and advanced heart failure[26] and chronic non-ischemic mitral regurgitation,[27] respectively. Both these studies showed that lower RR variability was associated with poor outcome; in particular, the standard deviation of the mean RR intervals during 5-min periods (SDANN) was identified as the parameter linked to outcome. Another study[28] involving 107 consecutive patients with chronic AF followed up for 2.5 years (in mean) did not confirm the independent prognostic value of SDANN,

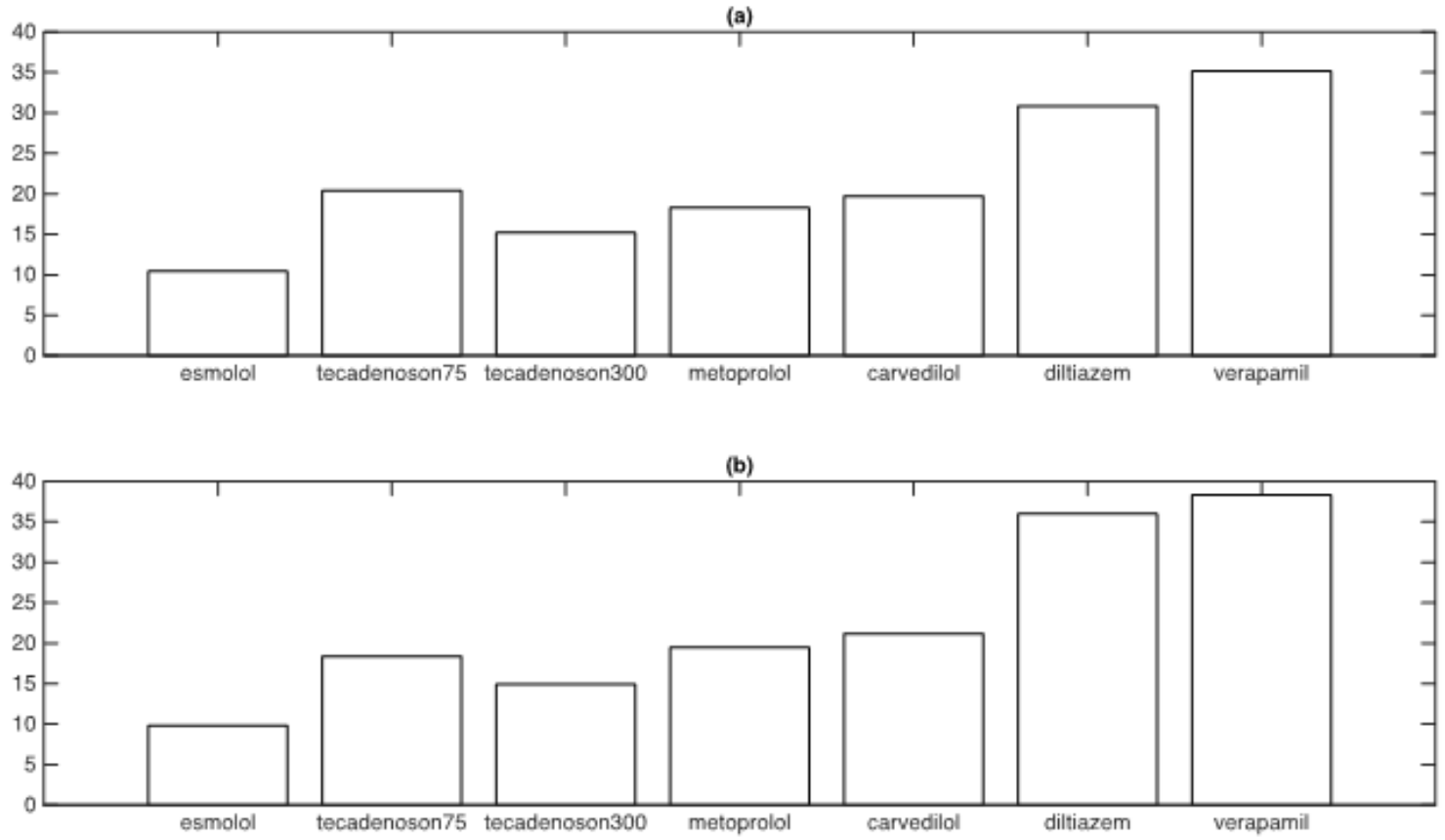

Figure 3: **Percentage of prolongation in respect to baseline of FRP of the slow (a) and fast (b) pathway estimated using the method in 16, 17 in patients with AF, taking different drugs**

whereas a reduced RR irregularity measured as ApEn was predictive of cardiac mortality after adjustment for clinical covariables.

Recently, the association between RR irregularity during AF and clinical outcome was assessed in the patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) study, presenting AF at baseline. RR variability was assessed using pNNx, i.e., the percentage of interval differences of successive NN intervals greater than x ms, with x varying from 10 to 50 ms in steps of 10 ms. At the end of the 2-year follow-up, 19 patients died (28%). In univariate analysis, pNN10-30 were lower in patients who died during follow-up. pNN20 was an independent predictor of all cause mortality after adjustment for significant clinical covariates in multivariate Cox analysis.[23] ApEn was not confirmed as predictive of clinical outcome: this may be due to the worse clinical characteristics of the patients enrolled in the MADIT-II study, all having congestive heart failure.

The association between variability and irregularity measures to clinical outcome was assessed in the patients enrolled in the MUSIC (Muerte SUbita en Insufficiencia Cardiaca) study, presenting AF at baseline. None of the variability measures was significantly different between survivors and non-survivors. On the contrary, the irregularity parameters were significantly lower in non-survivors than in survivors across all-mortality outcome parameters, i.e., total mortality as well as cardiac, sudden and congestive heart failure related mortality. ApEn was found to be a significant predictor of total mortality, sudden death and heart failure death in the univariate analysis as well as after adjustment for significant clinical covariates, including rate-control drugs, in a multivariate model.[25]

As noted from Table 2, summarizing the results of the above-mentioned studies, there is no uniform finding regarding the specific variability or irregularity measure linked to clinical outcome. However, these results suggest that reduced variability or irregularity is correlated with poor outcome in patients with AF.

Unanswered questions and future directions

We are still far from a clear understanding of mechanisms underlying variability and irregularity of ventricular response during AF and its relationship to clinical outcome. Noninvasive assessment of AV nodal characteristics may improve our understanding of AV node function during AF and the effects of antiarrhythmic drugs on AV conduction. Different methodologies for assessing the properties of the RR series have been proposed over the years. Some methods are sensitive to the influence of outliers in the RR series,[9] or require that a bin size is defined.[13] Still the main limitation of all these studies[9,13,18,19,21] is that direct validation of non-invasive estimates of AV node properties in clinical settings during AF remains to be done. Testing the methodology[16,17] in different groups of patients confirmed the hypothesis that the estimates of AV nodal refractory periods reflect overall changes in AV nodal properties previously reported on in studies accomplished invasively during sinus rhythm. Non-invasive assessment of AV node properties during AF appears to have potential for assessment of drug effects during AF and bringing our understanding of electrophysiological processes occurring in the AV node during AF on a new level.

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Symptoms In Atrial Fibrillation: A Contemporary Review And Future Directions

Steven T. Heidt, BS,[1] Anna Kratz, PhD,[2] Kayvan Najarian, PhD,[3] Afton L. Hassett, PsyD,[4] Hakan Oral, MD,[1] Richard Gonzalez, PhD,[5] Brahmajee K. Nallamothu, MD, MPH,[1] Daniel Clauw, MD,[4] Hamid Ghanbari, MD, MPH[1]

[1]University of Michigan– Department of Cardiovascular Medicine. [2]University of Michigan – Department of Physical Medicine and Rehabilitation. [3]University of Michigan – Department of Computational Medicine and Bioinformatics. [4]University of Michigan – Department of Anesthesiology. [5]University of Michigan – Department of Psychology.

Abstract

Atrial fibrillation (AF) is the most prevalent arrhythmia leading to hospital admissions in the United States. The majority of patients with AF report symptoms associated with this condition that can lead to a decrease in health related quality of life (HRQOL) and functional status. Therefore, along with reducing the risk of stroke and mortality, improvements in such symptoms are important therapeutic goals in the management of patients with AF. Our current understanding of how AF and symptoms are linked is hampered by the dominant assessment paradigm, where symptoms thought to be associated with AF are measured at a single point in time (frequently at a clinic visit). Unfortunately, this "static" snapshot does not capture the variability of symptoms and heart rhythm within a person over time and does not shed light on how symptoms are related to heart rhythm. This focused review summarizes current methods for assessing symptoms including generic and AF-specific HRQOL and functional status tools. It also describes gaps in the current assessment paradigm and where future research using mobile applications and digital technology might be able to assist with patient care.

Introduction

Atrial fibrillation (AF) is the most prevalent arrhythmia leading to hospital admissions in the United States.[1] Its incidence is associated with an increase in the risk of stroke, congestive heart failure, and overall mortality.[2-4] The national incremental cost of AF to the health care system has been estimated from $6.0 to $26.0 billion.[5] Moreover, the number of patients diagnosed with AF is expected to increase to more than 15 million by 2050.[6]

The onset of AF may or may not be signaled by the onset of symptoms. The majority of patients with AF report symptoms associated with the condition sometime throughout the disease process; however, a sizable proportion of patients (12-42.5%) remain completely asymptomatic during each presentation of AF.[7-9] The most common symptoms reported are dyspnea, chest pain, dizziness, fatigue, and palpitations. Paradoxically, recent studies using implantable cardiac monitors and arrhythmia-detecting pacemakers have revealed that patients in sinus rhythm also report symptoms of AF. These symptoms, whether reported during a period of AF or not, are related to lower functional status and health related quality of life (HRQOL) in the majority of patients with AF.[10-12] In turn, low functional status and HRQOL are strong predictors of all-cause and cardiovascular hospitalizations in patients with AF.[13] Furthermore, symptoms contribute to the increase in invasive cardiovascular procedures, medication use, and health care resources utilization. Therefore, improvement of symptoms is an important therapeutic goal in itself and is also related to lower risk of stroke and mortality in patients with AF.[14]

There are several treatment strategies that target improvement of AF symptoms. The goals of these therapies are to either restore normal sinus rhythm (NSR) or achieve heart rate control with medications and invasive cardiac procedures. Several studies have evaluated the effect of restoring NSR or achieving adequate heart rate control on symptoms and generally have shown that improving rhythm does not improve symptoms.[11, 15-19] Paradoxically, even without evidence for improvement of symptoms when rhythm is restored in patients with AF, a significant number of patients undergo pharmacological and interventional therapies to restore sinus rhythm in an effort to improve symptoms.[20] Further, there is little empirical data to guide clinicians in regard to which symptoms are directly related to AF and should be a focus of the management of AF, versus other symptoms that might be generally unrelated to AF. Our understanding of how

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None.

Corresponding Author:
Steven T. Heidt
University of Michigan - Department of Cardiovascular Medicine
24 Frank Lloyd Wright Drive
Lobby A, Suite 3700, Room 3201
Ann Arbor, MI 48106.

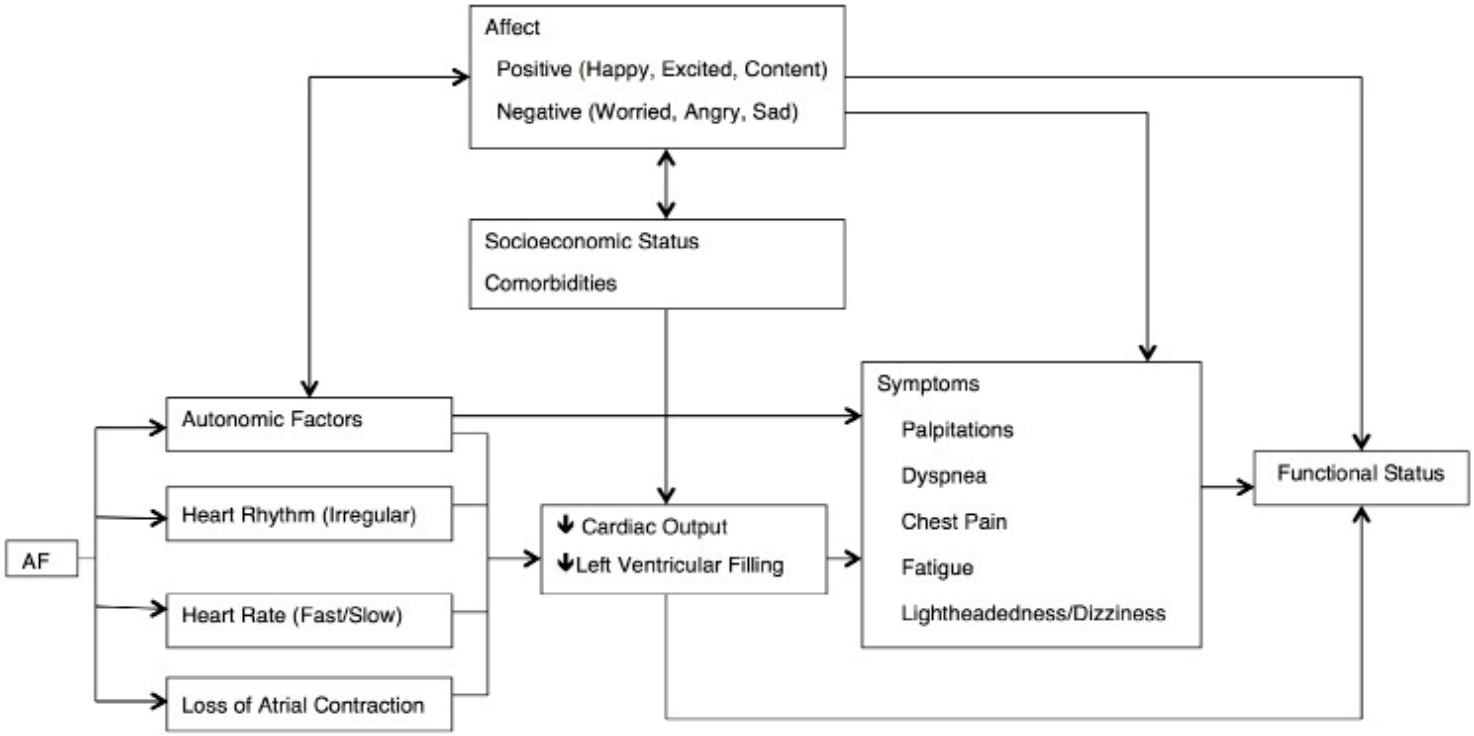

Figure 1: **Conceptual Model of Relationship between Heart Rhythm, Symptoms, Affect, and Functional Status**

Functional status of AF patients is influenced by a variety of factors including disease processes, symptom severity and frequency, and psychological affect. These elements may contribute to functional status individually or in combination with other factors

AF and symptoms are linked is hampered by the dominant assessment paradigm, where symptoms thought to be associated with AF – dyspnea, chest pain, palpitations, dizziness, fatigue – are measured at a single point in time (frequently at a clinic visit). Unfortunately, this "static snapshot" does not capture the daily variability of symptoms and heart rhythm and does not shed light on how symptoms are related to heart rhythm. AF can be a highly dynamic disease and a resting heart rhythm and rate during a clinical visit does not provide information about the patient's heart rate, AF burden, and symptoms during activities of daily living. Also, this static snapshot ignores significant features within the ECG recording (especially those that serve as surrogates for autonomic function) that may better predict symptoms in AF.

This focused review will summarize our current knowledge of symptoms, symptom measurement, HRQOL, and functional status in AF and guide future research efforts aimed at improving the assessment, understanding, and treatment of symptoms in patients with AF.

Review Criteria

Articles selected for this review were chosen based on the authors' knowledge of the AF literature and a structured search using the Medline®/PubMed® database (http://www.ncbi.nlm.nih.gov/pubmed) and Google Scholar (https://scholar.google.com). Our review was deemed complete in May 2016, and encompassed literature regarding AF published between 1964 and 2016. Search terms used alone or in combination included "atrial fibrillation," "quality of life," "assessment," "arrhythmia," "ECG," "demographics," "psychological," "perception," "somatization," "monitor," "Holter," "event," "implantable loop," "ambulatory cardiac telemetry," "pacemaker," and "implantable defibrillator." All abstracts were considered, and articles of interest were reviewed in full. Reference sections were explored to identify cited articles of interest. Google Scholar's "cited by" tool was beneficial in identifying follow-up articles to novel investigations. No preference was given to a specific study type: clinical trials, observational studies, cross-sectional investigations, and other reports of other research efforts were equally considered. This report is intended to be informative rather than exhaustive, and presents major findings related to HRQOL assessment in AF and factors that may influence perception of AF related symptoms.

Conceptual Model Of Symptoms In Patients With AF

Symptoms related to AF are likely to be multifactorial as a result of both direct and indirect effects of the arrhythmia, as well as interactive effects with affect (aspects of which are independent from arrhythmia). We have adopted a recent conceptual model of symptoms in AF that reflects this complex relationship and addresses the interaction between physiological factors, affect, symptoms, and functional status (Figure 1).[21] The model identifies physiological manifestations of AF and affect as separate but related entities, combining to influence symptom perception and ultimately functional status. This reciprocal relationship has led to increased investigation of both psychological and physiological factors contributing to the AF experience in recent years.

There is a paucity of data on the physiological mechanisms by which AF causes some symptoms.[22] The postulated mechanisms for the common symptoms associated with AF include impaired myocardial perfusion, alterations in sympathetic nervous system function, impaired ventricular diastolic filling, and decreased cardiac output.[23-26] Remarkably, despite the lack of evidence for improvement of symptoms after treatment of patients with AF, [11,15-19] a significant number of patients undergo pharmacological and interventional therapies to restore sinus rhythm in an effort to improve symptoms.[20] One potential reason for the lack of concordance between clinical

practice and research findings is that clinical trials have been limited by the static assessments of heart rhythm and symptoms obtained during a clinical encounter.

Asymptomatic AF: Accounting For Symptom Dissociation

Historically, investigations measuring the success rates of AF-targeting operations such as ablation, cardioversion, and the Cox-Maze procedure were based on freedom from symptoms of AF during the follow-up period. Others used brief clinic electrocardiograms or limited Holter monitor recordings to get a clearer picture of post-procedural heart rhythm. Unfortunately, many of these studies failed to properly account for asymptomatic recurrences of AF, which still create the opportunity for deep vein thrombosis, pulmonary embolism, and stroke.[27] Studies using implantable cardiac monitoring systems have shed light on the true prevalence of AF, and have found that AF recurs far more often than symptom presentation may suggest. In one of the first studies to measure asymptomatic disease, Page et al discovered that in patients with symptomatic paroxysmal AF followed for 12 months, asymptomatic atrial tachyarrhythmia occurred 12 times more often that symptomatic tachyarrhythmia.[28] Later studies expanded upon this finding, estimating that even in patients with some symptomatic disease, asymptomatic AF was far more prevalent, accounting for 54-94% of all AF arrhythmias.[8, 29-31] Asymptomatic AF is especially prevalent in patients who have undergone some form of interventional procedure to treat AF. Verma and colleagues found that the ratio of asymptomatic to symptomatic events increased from 1.1 to 3.7 following catheter ablation.[7]

The use of implantable cardiac monitoring devices has done more than reveal the prevalence of asymptomatic AF: it has allowed us to search for correlations between heart rhythm and AF symptoms. Two separate studies attempting to determine the predictive value of AF symptoms to heart rhythm offered disappointing results, estimating the positive predictive value at only 17-21%.[8, 31] On the other hand, these studies have allowed us to learn that a large proportion of patients report AF symptoms when not in a device-confirmed episode of AF. Results from varied paroxysmal AF populations found that of all symptom reports, 45-79% were actually these "false positives."[8, 29, 31] Precipitating factors of non-AF arrhythmic symptoms have yet to be elucidated. Regardless of actual heart rhythm during symptom presentation, symptom measurement and management remain key in the treatment of AF.

Measuring Functional Status And HRQOL In AF Patients

Of all AF patients, about 15% to 20% report a decreased exercise tolerance associated with their condition.[32] It is therefore of clinical interest to measure functional status in patients with AF both as a means of measuring symptom burden and as an outcome measure for therapeutic interventions.[21] The most commonly used subjective measures of functional status in AF are the New York Heart Association (NYHA) classification, the Canadian Cardiovascular Society classification, the Duke Activity Scale Index, and the Goldman Specific Activity Scale. More objective measures include the 6-minute walk test or an exercise stress test.[33] However, these published measures have not been specifically designed or validated in patients with AF. Further, they are collected at a single point in time without considering the variability in heart rhythm, symptoms, affect and functional status.

There are several different global measures used for evaluation of HRQOL in patients with AF, although the EuroQol 5-Dimension

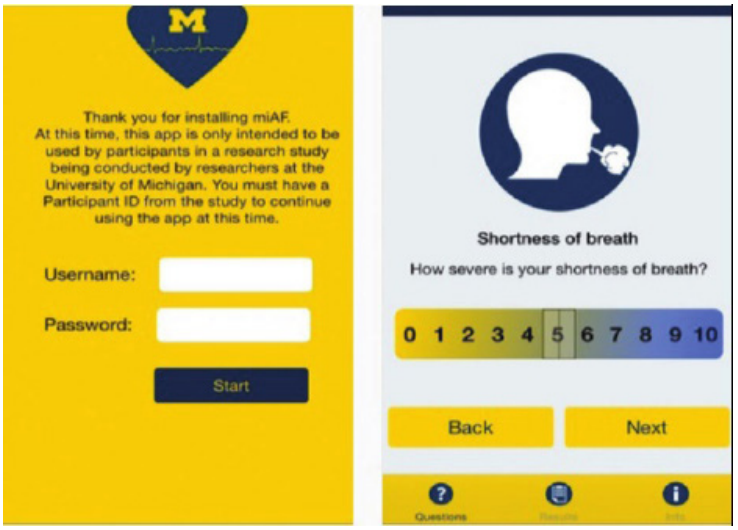

Figure 2: miAfib Mobile Application

Representation of the miAfib mobile application interface used by study participants in a small institutional trial. The mobile application allows study participants to record symptoms and emotional affect at any time; when paired with ambulatory ECG readings, investigators may begin to associate alterations in heart rhythm with symptoms and changes in affect.

(EQ-5D) Assessment and the Short-Form Health Survey (SF-36) are the most frequently administered.[34, 35] An in-depth analysis of these generic HRQOL instruments is presented in Table 1. The EQ-5D assesses five specific domains regarding health status: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[34] In total, the assessment contains six questions; one for each health domain and the Visual Analogue Scale, which asks the patient to rate their perceived level of health from "worst imaginable" to "best imaginable" on a scale of zero to one hundred.[34] Responders select from one of three values on the health-domain specific questions: "no problem," "some or moderate problems," or "extreme problems." Based on these answers, one of 245 disease states can be assigned, which include "unconscious," "dead," and "worse than dead."[34] Using these disease state classifications, patients can be assigned "Quality-Adjusted Life Years" for cost and health utility analyses.[36] Later interpretations of the EQ-5D (EQ-5D-5L) have increased the number of responses on the health-domain questions to five, thereby improving granularity.

The SF-36 questionnaire is likely the most widely used tool to assess HRQOL in the general population. It was found to be valid, reliable, and acceptable for public use in 1992, and has since been used in general patient practice and numerous clinical trials, including those for AF.[35] The SF-36 assesses eight specific disease domains, including physical functioning, social functioning, role limitations (both physical and emotional), mental health, vitality, pain, and general health perception. The questionnaire also queries health change, which is not scored and serves to quantify changes in health status over the course of a particular treatment. Disease domains are stratified into physical or mental component scores (PCS/MCS), which can be used to assess overall physical or mental health. On average, the SF-36 takes patients about five minutes to complete, and the non-monotonous make-up of the questions may decrease participant fatigue and improve completion rates. In the years since its validation, three shorter interpretations of the SF-36 have been developed and validated, the SF-12, the SF-8, and the SF-6.[37, 38] These briefer forms take less time to complete, and like the SF-36, they can be completed as part of a routine clinic visit. Additional

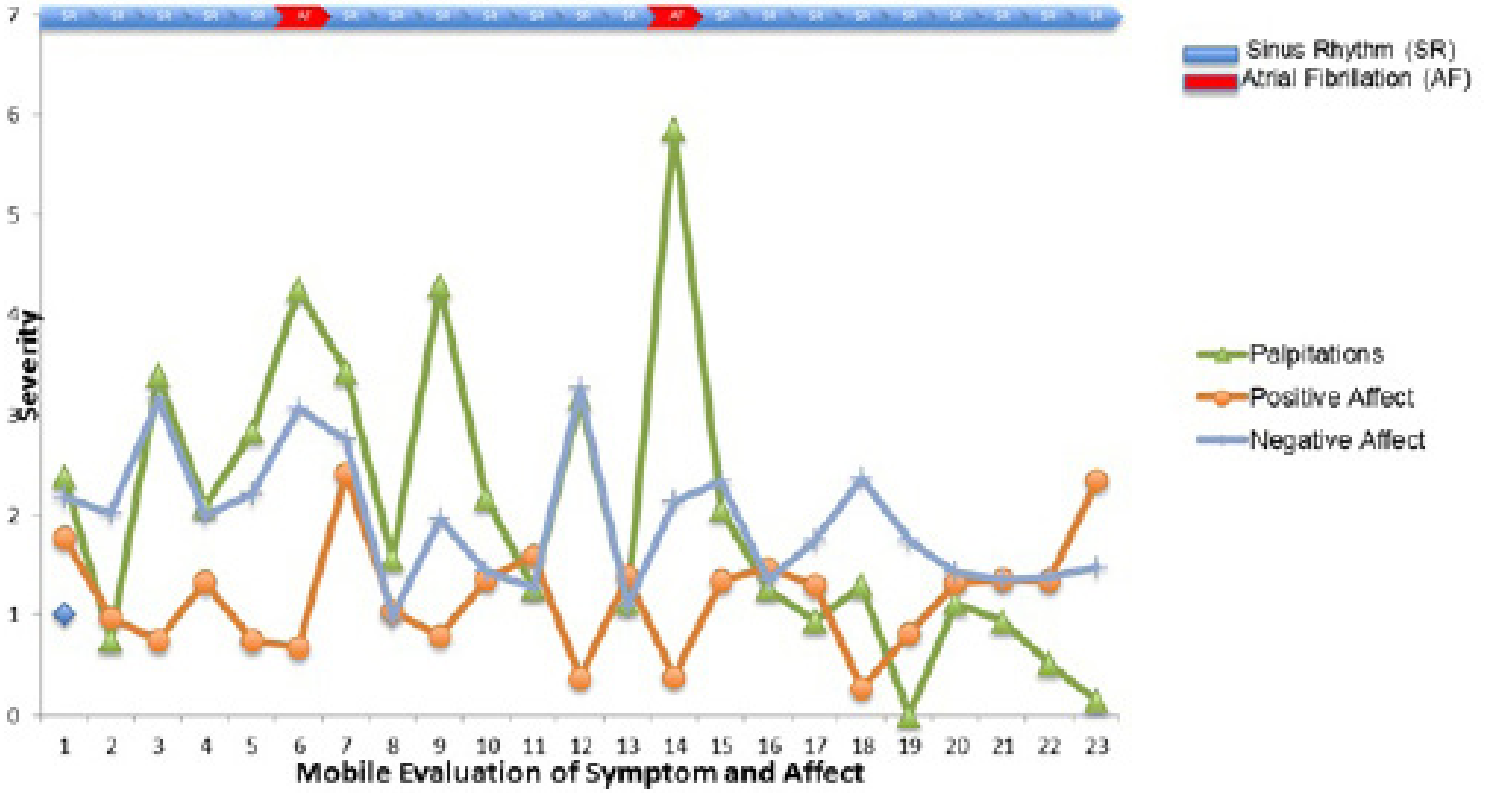

Figure 3: **Relationship between Heart Rhythm, Affect, and Palpitations**

Representation of results obtained from the miAfib mobile application, documenting rhythm status, presence of palpitations, and emotional affect. Palpitations were not always associated with presence of AF, and emotional state varied throughout the observation period.

versions of the SF-36 and the SF-12 have been validated in recent years, showing improvements in general wording and precision in the role-functioning scales (both emotional and physical).[39, 40] These new forms are now recommended for general use in most situations.

Generic HRQOL assessments like the SF-36 and the EQ-5D are extremely effective in determining general levels of HRQOL in a variety of patient populations. Although brief and suited for use in clinical situations, they lack the specificity needed to distinguish between different disease states. Because patients with AF are likely to have a variety of other cardiovascular conditions, such as coronary artery disease or heart failure, determining the true effect of AF on HRQOL is challenging when using generic measures. In addition, these instruments have been shown to improperly account for HRQOL in women, the elderly, and the unemployed, among other groups.[35] For optimal determination of HRQOL in the AF population, it is recommended that generic measures be used alongside AF-specific measures.

AF-Specific HRQOL Instruments

In order to meet the need for AF-specific instruments to assess HRQOL, AF-specific measurements have come into widespread use in the past few years. Although AF-specific instruments are not as generalizable to the general population or as extensively validated, they offer a clearer picture of what AF patients experience on a regular basis. AF-specific measurements generally assess symptom severity, AF burden, and impact of treatments, among other characteristics. Most of these instruments have been validated against general HRQOL assessments, and are often used alongside general measures in clinical trials to obtain a full picture of HRQOL. The most commonly used instruments are presented in Table 2.[41-45]

The Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) Questionnaire has become the most commonly used AF-specific HRQOL measure in recent years.[42] It has been developed and validated for measurement of symptoms, daily activities, treatment concern, and treatment satisfaction. Patients are categorized by symptom severity: asymptomatic, mild, moderate, or severe. It is accurate in discriminating between AF patient groups (i.e. those with paroxysmal or persistent AF) and is sensitive to changes in AF-related HRQOL over time. In the validation study, patients who were treated with radiofrequency ablation showed significant HRQOL improvements over those treated with pharmacological treatment and those who received no AF treatment.[42] This finding indicates that AFEQT is beneficial in assessing treatment-specific changes to HRQOL, which is of particular importance for investigators selecting an AF-specific instrument for clinical trial use.

AF-Specific Classification Tools and Symptom Scales

As opposed to generic or disease specific HRQOL measures, classification tools and symptom scales offer a chance to quantify the impact of AF on a patient's health condition without considering overall HRQOL. These instruments are often used in clinical practice, when there is not enough time in a regular patient interaction to complete longer HRQOL assessments. The classification tools described in this section include the European Heart Rhythm Association (EHRA) Classification and the Canadian Cardiovascular Society Severity in Atrial Fibrillation (CCS-SAF) Scale.[46-48] Similar to the NYHA scale in patients with congestive heart failure, these classification systems allow a provider to quickly designate AF patients into specific classes, which can then be used as a guide for future treatment options.[49] Patient-completed symptom scales such as the University of Toronto Atrial Fibrillation Symptom Severity (AFSS) tool and the Symptom Checklist (SCL) have been used for

decades to immediately assess the frequency, duration, and severity of AF-related symptoms.[50, 51] They are often paired with generic HRQOL tools to create a broader picture of the overall effects of AF. These classification systems and scales, along with pertinent characteristics and advantages, are presented in Table 3.[46-48, 50-52]

The EHRA classification is a clinician-completed tool and assigns patients with AF into one of four symptom distinct categories: 1-no symptoms; 2-mild symptoms which do not affect daily activities; 3-moderate symptoms which affect daily activities; and 4-severe symptoms which cause a discontinuation of daily activities.[47] The classification was validated in 2014, though a poor discriminatory ability between groups two and three prompted a reclassification of patients in group two: those whose symptoms were not considered "troublesome" are assigned to group 2A; those with troublesome symptoms are assigned to group 2B.[46] This new classification system is known as the modified EHRA (mEHRA). Both tools are valid and reliable for differentiating between AF patients of varying symptom severity, but the mEHRA offers more granularity. The Canadian Cardiovascular Society Severity of Atrial Fibrillation (CCS-SAF) scale was created as a concise, symptom-based severity scale intended for routine clinical use in patients with AF.[53] The CCS-SAF scale provides a potentially clinically useful scale for practitioners to assess patient status and to communicate the severity of the functional consequences of the patient's symptoms from AF. It closely approximates patient-reported subjective measures of quality of life in AF and may be practical for clinical use.[48] The SAF class, derived from CCS-SAF, is imperfectly correlated to generic QOL measures in the SF-36 and AFSS. This presumably occurs because the SAF class captures, by design, all components of the AF syndrome (including, for example, symptom severity during AF, adverse effects of treatment administered, and the physical and psychological consequences of the disease state), whereas the generic QOL measures capture only components of the AF "illness burden."[48] Though not as regularly utilized as the NYHA classifications, we anticipate that the EHRA, mEHRA, and CCS-SAF scales will become commonplace in clinical practice.

Patient completed symptom scales have been extensively used in clinical trials and in the validation of AF-specific HRQOL instruments. Although they are not descriptive enough to encompass all facets of HRQOL, these tools are helpful in determining the effect of pharmacological or interventional treatments on the symptoms of AF. The SCL encompasses frequency and severity of AF symptoms and has been shown to be beneficial in evaluating patients with atrial fibrillation and other types of tachyarrhythmia.[51] The AFSS is a 14-item assessment that also investigates symptom frequency, duration, and severity, but is limited to atrial fibrillation patients only.[50] The AFS/B is a relatively new symptom scale that assesses both AF severity and burden; as compared to other tools, both the patient and provider assess symptoms.[52] Not surprisingly, the correlation of patient-reported symptoms to HRQOL was stronger than that of the physician's, underscoring the need for patient-completed outcome measures.

While the breadth of available classification systems and symptom scales allows the use of specific tools for distinct patient populations, the lack of consensus on one specific tool is apparent. It is imperative that we continue to further validate the available tools in different populations and develop new measures for assessment of patients with AF should the need arise.

Demographics Influencing Symptom Assessment In AF

Large population-based assessments of HRQOL outside of the AF population tell us that older patients often report lower levels of HRQOL when compared with their younger counterparts.[54, 55] This finding can be explained by the fact that older patients are more likely to have additional underlying chronic diseases, which hinder them more than younger patients with fewer diagnoses. Along these lines, many studies have found that older age negatively affected HRQOL in those with permanent AF.[19, 50, 56] Some other assessments of HRQOL show an interesting discordance with this trend: although older AF patients reported lower levels of physical functioning, both younger and older patients recorded similar mental functioning levels and overall HRQOL scores. Reynolds et al found that elderly AF patients reported decreased levels of physical functioning, but ranked higher on mental HRQOL scores than their younger counterparts.[57] This finding is consistent with well-established findings in the general population that levels of negative affect tend to decrease, while levels of positive affect tend to increase with age. This could also stem from younger patients perceiving the diagnosis of AF to be more intrusive to their execution of daily activities.[58-60] In addition, younger patients reported higher levels of symptom severity, possibly stemming from anxiety over having a new diagnosis.[61] Data from the ORBIT-AF trial regarding demographic differences in AF presentation and HRQOL showed that patients with a new AF diagnosis recorded lower HRQOL scores on the AFEQT.[9] Older patients may place less emphasis on their symptoms of AF, or attribute non-specific symptoms of chest pain or dyspnea to separate cardiac diagnoses, such as coronary artery disease or congestive heart failure, or even attribute such symptoms to growing older. One study of exercise tolerance in the elderly found that elderly AF patients had no depreciation of quality of life when compared with a separate control group of older patients, but this finding has been heavily refuted and can be attributed to a low participant number.[17] Studies measuring the relationship between age and AF must take into account that while their participants may report lower levels of physical functioning, they may not perceive AF to have a great impact on overall HRQOL.

When validating the SF-36 instrument, the investigators found that females in the general population scored significantly lower than men in all aspects of the assessment, including physical, mental, and overall HRQOL.[35] Numerous AF clinical trials, cross-sectional investigations, and prospective studies have found that women score lower than men on at least one aspect of a generic HRQOL assessment.[9, 19, 50, 57, 62-64] It should be noted that even in some clinical trial control groups, healthy men report greater HRQOL than healthy women.[62] Although there is debate over the exact cause of decreased scores on HRQOL assessments, increased symptom reporting among females may offer some clarification.[65, 66] Women often report greater AF severity, frequency, and burden than men on questionnaire measures.[50, 52, 56, 57] When evaluated with continuous ambulatory monitors or an event/loop recorder, women report more undocumented episodes of AF, meaning symptom reports do not correlate with time-stamped ECG recordings.[67] A 2016 study of HRQOL in female AF patients showcased all of these findings, as women recorded fewer asymptomatic AF events, recorded an increased number of AF symptoms (even when not correlated with ECG-documented AF), and lower overall HRQOL as measured by the AFEQT.[9]

Increased symptom reports in women have been linked with

Table 1: Analysis of Generic HRQOL Instruments

Generic HRQOL Instrument	Number of Questions and Scoring Method	HRQOL Domains Assessed	Length of Recall Period	Specific Advantages
EQ-5D[34]	- 6 total questions - Patients are assigned one of 245 disease states based on responses	- Mobility - Self-care - Usual Activities - Pain/Discomfort -Anxiety/Depression	Present day	- Extensive validation - Widespread use in clinical situations - Extremely brief - Stratification by QALY
SF-36[35]	- 36 total questions - Questions within each domain are scored on a 0-100 scale (Health Change is unscored) -Physical (PCS) and Mental (MCS) Component subscores (0-100) may be calculated	- Physical Functioning - Social Functioning - Role limitations (physical problems) - Role limitations (emotional problems) - Mental health - Vitality - Pain - General Health Perception - Health Change	Up to four weeks	- Extensive validation - Widespread use in clinical situations - Relatively brief - PCS/MCS subscores

*EQ-5D: EuroQol Five Dimension. SF-36: Medical Outcomes Survey Short Form 36. QALY: Quality-Adjusted Life Year

depression, anxiety, and somatization tendencies, which may also explain decreases in mental well-being and overall HRQOL.[63, 68] Regardless of the underlying physiological or psychological mechanism, increases in AF symptom severity, frequency, or duration drive more women than men to seek medical treatment.[13,63,67] Suttorp et al found that women had a higher rate of AF recurrence after pharmacological or interventional treatment; however, the investigators defined AF recurrence as any report of symptomatic AF, failing to account for asymptomatic AF.[69] Knowing that women report symptoms more commonly than men, and that both groups report symptoms in normal sinus rhythm, it is unlikely that a significant difference in AF recurrence rate exists between these groups. Although most investigators are aware of the tendency for females to score lower on HRQOL measures and report more AF-related symptoms than men, some studies still fail to adjust for female sex in multivariate models, leading to potentially confounded results.

Association Between Affect and Symptoms

There is growing evidence that affect is associated with cardiovascular health.[70] Negative emotional states have been associated with acute cardiac dysfunction, myocardial ischemia, and increased long term cardiovascular mortality.[71] These negative emotional states and specifically anxiety and depression have also been linked to more severe symptoms in patients with AF.[70, 72-74] Anxiety in the AF population is fairly widespread, and may affect all types of patients. Studies examining the prevalence of anxiety in the AF population have found that while women report higher rates compared to men, the prevalence of anxiety is consistent across age groups.[64, 75, 76] Increased symptom prevalence in women may cause greater feelings of anxiety, perhaps because of a belief that their disease is more serious as compared to the male population. Increased levels of anxiety often manifest as lower rankings of HRQOL and increased reports of symptom frequency and severity.[64,77,78] In a landmark study assessing the relationship between personality traits and lower levels of HRQOL, Ong et al. discussed the role of anxiety sensitivity, or the tendency to associate anxiety-related sensations as signifying immediate harm or catastrophe. The authors found that anxiety sensitivity was related to symptom preoccupation; furthermore, both anxiety sensitivity and symptom preoccupation led to decreased mental and physical HRQOL and increased symptom severity.[79] Patients who are more sensitive to anxiety provoking events (such as symptoms of atrial fibrillation) may be more likely to worry about these symptoms, which manifests as decreased perception of HRQOL. Other investigators have shown that illness perception can fuel negative thoughts about AF and its symptoms, and attempts to educate patients about the true nature of AF may remedy erroneous and anxiety-provoking beliefs.[80, 81]

The prevalence of depression among the AF population is similar to that of anxiety, with similar detrimental effects on HRQOL. Women are more likely to be affected than men, and rank lower on HRQOL scales as a result.[64, 82] Ong et al. cited depression as a mediating factor for decreased HRQOL in women, suggesting that because women are more commonly affected by depression, this tendency influences HRQOL scores.[82] While depression may contribute to AF-related HRQOL in some women, additional underlying factors are likely to be present in others. Regardless of sex, patients with depression are more likely to be affected by symptoms.[83] The presence of depression may perpetuate with an AF diagnosis: Dabrowski et al showed that AF patients with depression also had lower levels of activity and overall energy, negatively impacting HRQOL.[84] AF patients who were unemployed also reported lower levels of HRQOL, which may be explained by the prevalence of depression among those without full-time jobs.[64, 85] Investigations measuring anxiety and depression at baseline and follow-up have found that AF treatments are generally ineffective at improving these psychological conditions, and recurrence rates of AF after cardioversion are higher in those with depression.[61, 64, 86]

Compared to anxiety and depression, somatization has been less well examined as a potential contributor to HRQOL in the AF population. Defined as the tendency to experience non-specific, recurrent medical symptoms due to underlying psychological distress, somatization may be present in patients who report AF symptoms as especially frequent or particularly severe. AF studies assessing somatization most commonly use the Somatosensory Amplification Scale, a validated, brief tool that reliably identifies patients who amplify symptoms based on clinical or subclinical psychological conditions.[87] Paquette et al determined that along with depression and anxiety, AF patients with high levels of somatization scored lower on the mental health subscale of the SF-36, reported decreased functional capacity, and experienced increased symptom frequency and severity when compared to those with low levels of somatization.[63] An additional study found that even after adjusting for age, sex, and other demographic factors, somatizing patients still scored higher on the AFSS in terms of symptom severity.[88] Assessment for somatization plays an important role in interventional studies that define an "AF recurrence" as the first time a subject experiences an AF symptom post-procedure. Aside from not accounting for asymptomatic AF, this definition may lead to an overestimation of AF recurrences in specific demographic groups. In order to provide

Table 2: Analysis of AF-Specific HRQOL Instruments

AF-Specific HRQOL Instrument	Number of Questions/Scoring Method	HRQOL Domains Assessed	Length of Recall Period	Validation Strategy	Specific Advantages
AF-QoL[41]	-18 total questions -0 to 100 scoring scale, 100 indicating best HRQOL -Domain scores may be calculated	-Physical Functioning -Psychological Functioning -Sexual Activity	-One month	-Validated against SF-36	-Good discriminatory power -Sensitive to change for follow-up assessment -Domain scoring for specific assessment
AFEQT[42]	-20 total questions -0 to 100 scoring scale, 100 indicating no limitation or disability from AF. -Domain scores may be calculated	-Symptoms -Daily Activities -Treatment Concern -Treatment Satisfaction	-4 weeks	-Validated against SF-36, EQ-5D, AFSS, and SCL	-Good discriminatory power -Sensitive to change for follow-up assessment -Patient input via treatment concern and satisfaction domains -Domain scoring for specific assessment
ASTA[43]	-9 total questions -Patient scores are not coded to specific 0-100 scales. -Higher scores indicate greater symptom burden or arrhythmia impact	-Symptom Burden -Arrhythmia Impact	-3 month episode recall	-Validated against SF-36 and SCL	-Brief assessment -May be used in patients with non-AF tachyarrhythmias
AFSympTM [44]	-11 total questions -Domain scores may be calculated	-Heart Symptoms -Tiredness -Chest Discomfort	-1 week	-Validated against SF-36, AFSS, AFImpact	-Developed for use across cultural contexts -Valid for use in all AF patient groups (paroxysmal, persistent, and permanent) -Electronic tool
AFQLQ[45]	-26 total questions -Domain scores may be calculated	-Variety and frequency of symptoms -Severity of symptoms -Limitations of daily and special activities and mental anxiety related to AF	-Not available (written in Japanese)	-Not available (written in Japanese)	-Sensitive to change for follow-up assessment -Previous clinical trial use -Domain scoring for specific assessment

*AF-QoL: Quality of Life Questionnaire for Patients with Atrial Fibrillation. AFEQT: Atrial Fibrillation Effect on QualiTy of Life Questionnaire. AFSS: Atrial Fibrillation Symptom Severity Scale. SCL: Symptom Checklist. ASTA: Arrhythmia-Specific Questionnaire in Tachycardia and Arrhythmia. AFQLQ: Atrial Fibrillation Quality of Life Questionnaire.

a clearer characterization of the psychological makeup of patient populations under study, investigators should consider administering some form of somatosensory scale along with validated depression and anxiety measures.

Socioeconomic Status

Regardless of disease type, patients with higher educational levels have been shown to possess increased levels of health literacy, better equipping them to seek out, use, and understand health information.[89, 90] In the AF population, it is known that older patients, those with less formal education, and those with decreased health literacy all possess lower levels of disease-specific knowledge.[91-93] Aside from the potential clinical implications associated with decreased AF knowledge, a lack of understanding of AF and its complications may impact symptom perception. To our knowledge, only one study has examined the impact of educational level on AF symptom perception. Goli et al. determined that in a prospective cohort of AF patients, those with low levels of educational achievement (less than a high school diploma) were more likely to report severe symptoms of AF.[88] These patients may believe that their disease is more intrusive or potentially harmful than others who are more informed about the course of the non-lethal arrhythmia. Initial unadjusted analyses found that non-Caucasian race and unemployment also significantly influenced AF symptom severity though did not remain significant after adjustment for confounding variables including age and comorbid conditions.[88] Investigations assessing HRQOL in the AF population must account for the influence of educational level on AF symptom perception. Clinical trials lacking a standardized educational session regarding the course and complications of AF may be introducing an additional confounding element into the analysis, allowing patients to draw their own conclusions about the prognosis of AF.

Influence Of Comorbid Conditions

The advent of disease specific tools has, to an extent, allowed investigators to analyze the effects of treatments or interventional techniques on the patient experience of AF. AF patients are often afflicted with multiple cardiovascular conditions, especially in the older population and, on general HRQOL assessments, patients with cardiovascular disease score lower than healthy controls; it follows that those with multiple diagnoses will report lower HRQOL than those with only a single diagnosis.[10,94] Yet, studies assessing the impact of comorbid conditions on HRQOL in patients with AF offer mixed results. The FRACTAL investigators found that AF patients with additional cardiovascular conditions recorded lower HRQOL as compared to those with AF alone.[57] An additional study found that AF patients with severe underlying cardiovascular disease reported lower HRQOL as compared to patients with more manageable conditions.[19] Conversely, Dorian et al found that a range of cardiovascular parameters had no significant impact on HRQOL, including NYHA class, coronary artery disease, hypertension, left ventricular function, AF frequency, or AF duration.[50] Regardless of the impact of other conditions, the classification of AF as paroxysmal, persistent, or permanent may have a greater influence on both general and disease-specific AF assessments. Numerous investigations have shown that patients with paroxysmal disease report more frequent, invasive, and severe symptoms of AF than those with persistent or permanent disease; however, increased symptom reports do not always correlate with decreased perception of HRQOL.[95, 96] When developing and validating the Canadian Cardiovascular Society Severity of Atrial Fibrillation Scale, investigators found that persistent or permanent AF patients had lower HRQOL than those with paroxysmal AF.[48] Other studies have found that those affected by paroxysmal, persistent, or permanent AF have similar levels of HRQOL.[64] These results may be influenced by the subject's rhythm at the time of assessment: prior research has shown that AF patients in sinus rhythm while completing an HRQOL measure score higher than those in AF.[97] Clinical trial investigators should strive to evaluate rhythm throughout the HRQOL instrument administration process.

Limitations Of Traditional Assessments Of Symptoms, Affect, And Functional Status

Current approaches to the assessment of symptoms during clinical

Table 3: Analysis of AF-Specific Classification Tools/Symptom Scales

Classification Tool/Symptom Scale	Patient or Provider Completed?	Classifications or Scoring Method	Length of Recall Period	Validation Strategy	Specific Advantages
EHRA[47]	Provider	-4 total classifications -Patients classified based on AF's impact on ability to complete daily activities	-Immediate Assessment	-Validated against AFEQT and EQ-5D	-Simple classification system for efficient bedside use
mEHRA[46]	Provider	-5 total classifications -Patients classified based on AF's impact on ability to complete daily activities -Subset of patients scored based on "troublesome" nature of symptoms	-Immediate Assessment	-Validated against AFEQT and EQ-5D	-Increased granularity compared to standard EHRA
CCS-SAF[48]	Provider	-5 total classifications -Patients classified based on symptom's perceived impact on overall HRQOL	-Immediate Assessment	-Validated against SF-36 and AFSS	-More detailed classifications as compared to EHRA/mEHRA -Assesses symptom severity with respect to HRQOL
AFSS[50]	Patient	-14 total questions assessing symptom severity, frequency, and duration -Objective and subjective measure of AF symptom impact	-	-	-Patient -reported outcome measure
SCL[51]	Patient	-Separate assessments of symptom severity and burden. -Higher scores indicate more frequent/severe symptoms	-	-	-Patient -reported outcome measure
AFS/B[52]	**Patient**	-4 classifications of symptom and burden severity -14 total questions: Eight focus on symptoms in daily life, six focus on AF frequency, duration, and healthcare use	-Current Status	-Validated against SF-12 (V2)	-Both patient and provider complete instrument.

*Authors were unable to determine validation strategies or recall lengths for the AFSS and SCL. §EHRA: European Heart Rhythm Association Classification. mEHRA: Modified European Heart Rhythm Association Classification. CCS-SAF: Canadian Cardiovascular Society Symptoms Severity in Atrial Fibrillation. AFSS: Atrial Fibrillation Symptom Severity. SCL: Symptom Checklist. AFS/B: Atrial Fibrillation Symptom and Burden.

visits are problematic for several reasons. These data are traditionally collected via recall that requires participants to summarize their experiences over some time period (i.e. since the last clinic visit). Therefore the events that are easily recalled are more likely to be reported during the retrospective reporting of events.[98] The recall of an event can also be influenced by other events occurring after the event to be recalled (retroactive reconstruction), individual's beliefs about the condition (effort after meaning), and affect.[99] Another concern is that the assessments of symptoms, affect, and functional status are not performed objectively in patient's natural settings, therefore limiting their generalizability and ecological validity.[100] This emphasis on retrospective assessment prevents the study of dynamic changes in symptoms over time and their interaction with heart rhythm, affect, and functional status. There is a need for time sensitive study designs with repeated assessments of rhythm, symptoms, and affect to capture the daily variability in symptoms and that can increase our understanding of the dynamic interplay between physiology, psychology, patient reported symptoms, and moment-to-moment functioning in daily life.

Mobile Application To Assess Symptoms And Affect In Patients With AF (miAfib app)

Investigating the temporal sequence of affect and cardiac dysfunction represents significant methodological challenges that are not addressed with one-time assessments of affect during clinic visits. The prospective real-time assessments regarding how a person feels over a period of time have demonstrated an association between negative affect, acute cardiac dysfunction, and poor long-term survival. Despite the evidence suggesting an association between affect and symptoms in cardiovascular disease, there have not been studies evaluating their relationship in patients with AF.

Developments in mobile technology have created opportunities for people to assess their symptoms during times (real time) and in places or situations (real world) when they are most needed. Mobile technology is ideal for the recording of symptoms because these devices are relatively small and convenient for people to carry as they go about their daily lives. We have developed a novel mobile application (miAfib) to assess symptoms (chest pain, palpitation, shortness of breath, fatigue, dizziness/lightheadedness), and positive (happy, excited, content) and negative (worried, angry, sad) affect on multiple occasions throughout the day. The application is based on the iOS platform for iPhone and is available through the app store for download by study participants (Figure 2). We designed a study website (www.miAfib.com) to assist participants with mobile application set up and study details.

We conducted a feasibility trial to examine the user adherence, acceptance, and experiences over a 21-day period. The protocol was approved by IRB and informed written consent was obtained. For initial feasibility testing, we recruited 10 patients with paroxysmal AF for 21 days. At the end of the trial, we conducted a structured interview asking the patients to complete a questionnaire consisting of five point Likert scaled questions (strongly agree to strongly disagree) designed to measure ease of use ("I found the app easy to use"), convenience and integration into daily practice ("I found the app fit into my routine"), and future intention to use the application ("I intend to use the app in the future"). Participants completed 1.70±0.84 assessments per day. All of these entries contained complete information. Descriptive statistics showed that users found the application easy to use (M=4.67±0.52), intended to use the application in the future (M=4.83±0.41), and easily integrated the application into their daily routines (M=4.50±0.55). These descriptive data suggest that the application was easy to use and users would consider its continued use. The relationship between heart rhythm, affect and palpitations during multiple evaluations is shown in Figure 3.

Future Directions

There is a complex and poorly understood interplay between symptoms, heart rhythm, affect and functional status in patients with AF. Our understanding of this relationship has been hampered by our current assessment paradigm that is focused on evaluations at one point in time (typically a clinical visit). Mobile and sensor technologies offer novel methods for evaluating symptoms and functional status in patients with AF and can give us a unique and never-before-seen window into this disease. Future research is

needed to evaluate the role of these technologies in evaluation and treatment of patients with AF.

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A Foreign Material Image In The Coronary Sinus During Coronary Sinus Angiography

[1]Mustafa Yildiz, MD, PhD, Prof, [2]Gokhan Kahveci, MD, [2]Yunus Emiroglu, MD, [3]Okan Erdogan, MD, Prof.

[1]Department of Cardiology, Istanbul University Cardiology Institue, Istanbul, Turkey. [2]Department of Cardiology, Kartal Kosuyolu Heart Training and Research Hospital, Istanbul, Turkey. [3]Department of Cardiology, Marmara University Medical Faculty, Istanbul, Turkey.

Introduction

A 63-year-old man with history of bedside temporary pacemaker lead insertion a year ago was hospitalized for cardiac resynchronization and defibrillator device implantation. After insertion of the right ventricular shocking lead we tried to engage the ostium of the coronary sinus (CS) and injected some dye to delineate its anatomy. Unfortunately, the proximal portion of the main CS was occluded. In addition, 2 fixed and rounded neighboring foreign materials were incidentally detected within its opacified portion (Fig. 1A, arrow indicates foreign material). A subsequent multislice computed tomography (Fig. 1B, Fig. 1C * indicates foreign material) confirmed CS occlusion and foreign metallic materials (Hounsfield unit: 2686) resembling metallic electrodes most probably originating from the previous inserted temporary pacemaker lead. We suggested that the forceful blunt insertion of the firm lead tip dissected the CS wall and cretaed a subintimal pouche. Further blood accumulation and formation of intense coagulum externally compressed the wall and occluded the lumen of the CS. When the temporary pacing lead that was partly encapsulated and fixed by the fibrocoagulative tissue was forcefully pulled out, the metallic electrodes overlying the lead tip might have been teared off and retained within the CS. This interesting and rare case highlights an unusual cause of CS occlusion and unexpected complication of temporary pacemaker lead insertion. One must be sure that no fragments have been retained or embolized when removing the pacing leads from the body.[1]

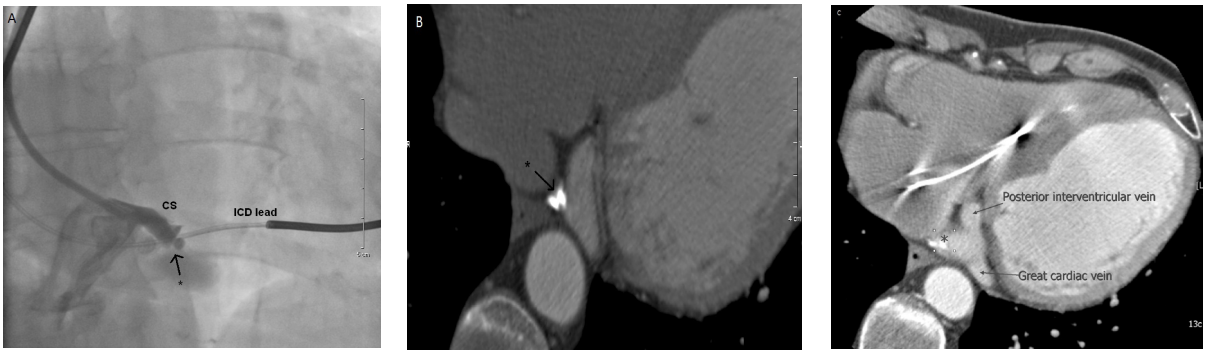

Figure 1: A foreign material was seen in the coronary sinus angiography (Fig. 1A). A subsequent multislice computed tomography confirmed CS occlusion and foreign metallic materials (Fig. 1B, Fig. 1C; * indicates foreign material)

Key Words:
Coronary Sinus, Angiography, Foreign Material.

Disclosures:
None.

Corresponding Author:
Mustafa Yildiz,
Cardiologist, Internal medicine Specialist and Physiologist
Department of Cardiology, Istanbul University Cardiology Institue,
Istanbul,
Turkey.

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Dr. Dhanunjaya Lakkireddy, MD, F.A.C.C, FHRS

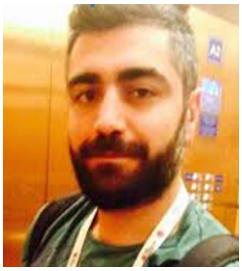
A board certified electrophysiology expert and practices at Mid-America Cardiology and The University of Kansas Hospital Clinics in Kansas City, KS, USA

Dr. Dogac Oksen, MD

Dogac Oksen, MD is clinical cardiologist and investigator, currently working at Istanbul University Institute of Cardiology, Istanbul, Turkey. He has achieved Doctor of Medicine degree at Cerrahpasa Medical Faculty. His scientific focuses are interventional cardiology, arrhythmia cardiac electrophysiology and catheter based treatment of arrhythmias

Dr. Mattias Duytschaever, MD

Department of Cardiology, Sint-Jan Hospital Bruges; Ruddershove 10, 8000 Bruges, Belgium

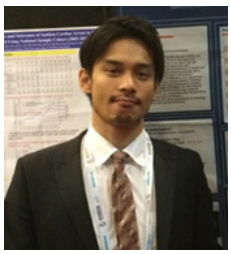


Dr. Tolga Aksu, FESC, FEHRA

He is an Associate Professor of Cardiology. He is working Department of Cardiology and Director of Clinical Electrophysiology at the Kocaeli Derince Education and Research Hospital in Turkey. Dr. Aksu clinically interested in invasive electrophysiology, device implantation and catheter ablation therapies. Special interest areas are Atrial fibrillation and cardioneuroablation. Dr. Aksu has published more than 100 national and international scientific publications. Also, He is in Editorial Board of some international academical journals.

Dr. George Louridas, MD

Emeritus Professor of Cardiology, Aristotle University, Thessaloniki Greece, Director of Cardiac Catheterization Laboratory, AHEPA Hospital (1983-2006), Director of Department of Cardiology, AHEPA Hospital (1996-2006).



Dr. Kyoichiro Yazaki, MD

Affiliation: Ogikubo Hospital, Department of Cardiology,Cardiovascular Center, Tokyo, Japan.
Clinical research of electrophysiology, catheter ablation, and Device therapy are of my interests

Dr. Ashraf Alqaqa, MD, FACC

Dr. Farhad Farokhi received his medical degree from the Kansas City University of Medicine & Biosciences. He finished his internal medicine residency at the Grandview Hospital in Dayton, OH. He currently holds board certification in Cardiovascular Disease and Clinical Cardiac Electrophysiology from the American Osteopathic Board of Internal Medicine, Internal Medicine from the American Osteopathic Board of Internal Medicine, and Echocardiography from the American Society of Echocardiography. Dr. Farokhi's clinical interests include Atrial Fibrillation, Catheter Ablation, Ventricular Arrhythmia, and Left Atrial Appendage Closure (LARIAT).

Dr. Hickey

Dr. Hickey is an Associate Professor of Nursing at Columbia University Medical Center and holds a joint appointment in the Division of Cardiology (electrophysiology) as both a family and adult nurse practitioner. Her interdisciplinary research, clinical practice and scholarship is focused in the areas of cardiac genetics, the clinical care of those with chronic cardiac conditions and arrhythmias, and the prevention of sudden cardiac death. Her current grant awards include a R01 from the National Institute of Nursing Research (iHEART) focusing on arrhythmia telehealth monitoring in those with atrial fibrillation, her newly awarded (multiple-PI) P30 award with Dr. Suzanne Bakken is focusing on improving symptom self-management for underserved populations with or at risk for chronic health conditions.

Dr. Andres Enriquez, MD

Dr. Enriquez received his medical degree from the Universidad de Concepcion, in Chile. He specialized in Internal Medicine, Cardiology and Cardiac Electrophysiology at Pontificia Universidad Catolica de Chile in Santiago.

Between 2013 and 2015 he moved to Canada to continue his electrophysiology training at Queen's University, Kingston, Ontario.

He currently resides in Philadelphia with her wife Karen and is a second-year fellow in the Advanced Clinical Electrophysiology program at the Hospital of the University of Pennsylvania, under the mentorship of Dr. Francis Marchlinski.

Dr. Enriquez interests include electrocardiology, clinical electorphysiology catheter ablation and cardiac devices.

Dr. Ryan Dean White. MD

Dr. Ryan Dean White, MD, medical degree from the University of Missouri and currently training in internal medicine at Indiana University School of Medicine in Indianapolis, Indiana.

Dr. James R Edgerton, MD, FACC, FACS, FHRS

The Heart Hospital

Dr. Jackson J. Liang, MD

Clinical Cardiac Electrophysiology Fellow
Hospital of the University of Pennsylvania

Dr. Gianluca Rigatelli, MD, PhD, EBIR, FACP, FACC, FESC, FSCAI, Vice-Director

Cardiovascular Diagnosis and Endoluminal Interventions
Director, Section of Adult Congenital Heart Interventions
Rovigo General Hospital, Viale Tre Martiri
45100 Rovigo, Italy