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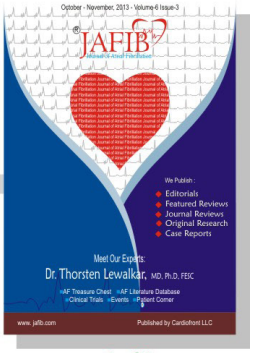

The Challenge of Chamber Stiffness Determination in Chronic Atrial Fibrillation vs. Normal Sinus Rhythm: Echocardiographic Prediction with Simultaneous Hemodynamic Validation

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Abstract

Echocardiographic diastolic function (DF) assessment remains a challenge in atrial fibrillation (AF), because indexes such as E/A cannot be used and because chronic, rate controlled AF causes chamber remodeling. To determine if echocardiography can accurately characterize diastolic chamber properties we compared 15 chronic AF subjects to 15, age matched normal sinus rhythm (NSR) subjects using simultaneous echocardiography-cardiac catheterization (391 beats analyzed). Conventional DF parameters (DT, Epeak, AT, Edur, E-VTI, E/E') and validated, E-wave derived, kinematic modeling based chamber stiffness parameter (k), were compared. For validation, chamber stiffness (dP/dV) was independently determined from simultaneous, multi-beat P-V loop data. Results show that neither AT, Epeak nor E-VTI differentiated between groups. Although DT, Edur and E/E' did differentiate between groups (DTNSR vs. DTAF $p < 0.001$, EdurNSR vs. EdurAF $p < 0.001$, E/E'NSR vs. E/E'AF $p < 0.05$), the model derived chamber stiffness parameter k was the only parameter specific for chamber stiffness, (kNSR vs. kAF $p < 0.005$). The invasive gold standard determined end-diastolic stiffness in NSR was indistinguishable from end-diastolic (i.e. diastatic) stiffness in AF ($p = 0.84$). Importantly, the analysis provided mechanistic insight by showing that diastatic stiffness in AF was significantly greater than diastatic stiffness in NSR ($p < 0.05$). We conclude that passive (diastatic) chamber stiffness is increased in normal LVEF chronic, rate controlled AF hearts relative to normal LVEF NSR controls and that in addition to DT, the E-wave derived, chamber stiffness specific index k, differentiates between AF vs. NSR groups, even when invasively determined end-diastolic chamber stiffness fails to do so.

Introduction

Atrial fibrillation (AF) is strongly associated with heart failure, coronary artery disease (CAD), valvular heart disease, diabetes mellitus, and hypertension.[1,2] If present when AF manifests they are viewed as risk factors. However, the actual causal relationship between these comorbidities and AF is incompletely understood. The ultimate relationship is certainly more complex than the term 'risk factor' implies. The mechanisms by which risk factors cause AF and the long-term consequences of AF on diastolic chamber properties remain topics of investigation.[3,4] The 'epidemic' of heart failure with normal ejection fraction[5,6,7] has cast a spotlight on diastolic function (DF) and its determinants such as chamber stiffness, whose gold-standard method of measurement requires invasive, simultaneous, LV pressure and volume change ($\Delta P/\Delta V$) data. Doppler echocardiography is the standard method for DF assessment; with E-wave deceleration time (DT) being the most common chamber stiffness correlate.[8] DF can also be analyzed via the Parametrized Diastolic Filling (PDF) formalism (Appendix 1) which provides unique E-wave derived chamber stiffness (k), chamber relaxation/viscoelasticity (c) and load (xo) parameters.[9] Importantly, k is specific for chamber stiffness whereas E-wave DT is jointly determined by LV chamber stiffness (k) and LV relaxation/viscoelasticity (c).[10]

The chamber stiffness gold standard is the end-diastolic pressure-volume relation (ED-PVR). Load-varying ED-PV data can be fit using exponential, power law, or linear functions.[11] The slope, dP/dV of the ED-PVR is a relative index that defines chamber stiffness, whereas LVEDP itself is an absolute index.[12]

We hypothesized that because echocardiography can compute only relative rather than absolute pressure related indexes, it should be able to determine whether chamber stiffness is altered in AF compared to NSR. To test this hypothesis we compared conventional and PDF model-derived E-wave based chamber stiffness metrics between groups. For independent validation we analyzed simultaneous

Key Words:
Echocardiography, Atrial Fibrillation, Diastasis, Diastolic Function, Pdf Formalism

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micromanometric pressure-volume data.

Considering the ED-PVR in the setting of chronic atrial fibrillation (AF) raises a concern. In normal sinus rhythm (NSR), the ED-PVR includes the effect of both (atrial and ventricular) chambers and therefore includes atrial contractile properties. In rate controlled AF, the ED-PVR lacks atrial contractile effects and relies only on diastatic chamber effects. Thus, comparison of NSR vs. AF stiffness that relies on end-diastole incorporates chamber properties confounded by atrial contraction, thereby masking potential differences in passive ventricular diastatic chamber stiffness (see Figure 1). Indeed, in NSR, stiffness measured at end-diastole is always greater than stiffness at diastasis.[13,14] Importantly, the D-PVR and the ED-PVR are distinguishable and distinct relations.[14] Accordingly, chamber stiffness was computed at two distinct physiologic portions of (NSR) P-V loops, as the slope of the ED-PVR and the slope of the diastatic pressure-volume relation (D-PVR).[14]

Materials and Methods

Subject Selection

Thirty datasets were selected from the Cardiovascular Biophysics Laboratory database.[15] All subjects were referred for elective cardiac catheterization and coronary angiography to rule out suspected coronary artery disease. All participants provided informed consent prior to the procedure using a protocol approved by the Washington University Human Research Protection Office (HRPO).

Fifteen subjects were in NSR, 15 subjects had chronic AF (average duration 7.2±4.2 years) and were in AF during data acquisition. Selection criteria for the NSR group were: no active ischemia, normal valvular function, normal LV ejection fraction (LVEF≥50%), no history of myocardial infarction, peripheral vascular disease, or bundle branch block, and clear diastatic intervals following E-waves. Selection criteria for the AF group were similar, with the exception

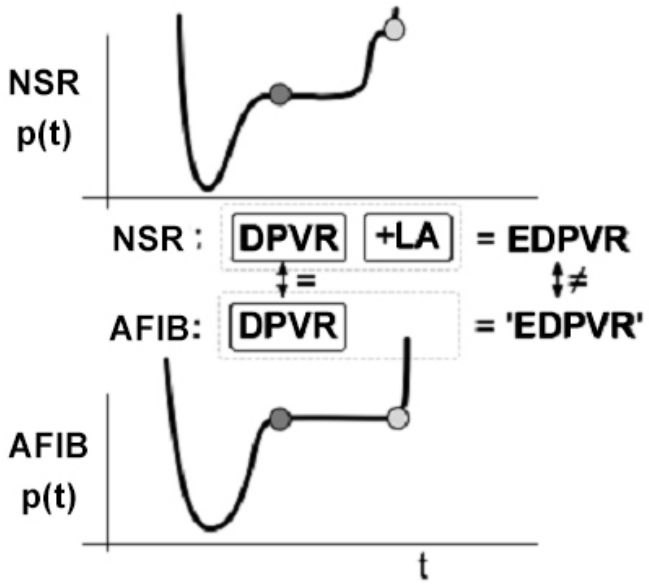

Figure 1: **Schematic of LV pressure in NSR and AF. In NSR, end-diastolic pressure and volume are jointly determined by diastolic LV chamber and systolic LA properties. In AF, diastasis and end-diastole inscribe the same pressure and volume values. Thus comparison of NSR vs. AF chamber stiffness requires comparison of diastatic rather than end-diastolic hemodynamics. See text for details.**

that four of the 15 AF subjects had LVEF somewhat < 50%. No subjects were in heart failure, and all subjects were normotensive at the time of data acquisition. Because our intent is to compare grouped averages primarily differentiated by AF vs. NSR physiology, we specifically included a range of LV end-diastolic pressures (LVEDP) encountered in practice, including elevated LVEDP. See Table 1.

Data Acquisition

The high fidelity, simultaneous echocardiographic transmitral flow and pressure-volume data recording method has been previously described.[14] Briefly, immediately prior to arterial access a complete 2-D echo-Doppler study is performed according to ASE criteria.[16] After arterial access and placement of a 64-cm, 6-Fr sheath (Arrow, Reading, PA), a 6-Fr micromanometer conductance catheter (SPC-560, SPC-562, or SSD-1034, Millar Instruments, Houston, TX) was directed across the aortic valve under fluoroscopic control. Pressure and volume signals were processed through clinical amplifier systems (Quinton Diagnostics, General Electric, CD Leycom) and recorded by a custom PC via a standard interface (Sigma-5). Simultaneous transmitral Doppler images were obtained.[16] Using a clinical imaging system (Acuson, Sequoia C256, Mountain View, CA or Philips, Model iE33, Eindhoven, the Netherlands). Following data acquisition, end-systolic and end-diastolic volumes (ESV, EDV) were determined by calibrated quantitative ventriculography.

Load Variation

As previously described,[14] respiratory physiologic load variation was present in all 30 datasets. In 10 out of 15 NSR subjects, additional physiologic load variation derived data included the recovery phase of the Valsalva maneuver. In the remaining 5 NSR subjects, additional load variation data included cardiac cycles following either catheter generated or isolated spontaneous premature ventricular contractions (PVC).

Data Analysis

After ventriculography-based calibration of volume, LV pressures and volumes at both diastasis (PD, VD) and end diastole (PED, VED) were determined for 8-12 cardiac cycles with a custom LabView interface (National Instruments, Austin, TX). For AF subjects, only cardiac cycles with R-R intervals generating essentially constant diastatic pressures and volumes following E-waves were included. Because of the time delay inherent in electro-mechanical coupling, end-diastole was identified by ECG R-wave peaks. ECG

Table 1: **The clinical descriptors of NSR and AF groups.**

Clinical Descriptors	NSR Group	AF Group	Significance
N	15	15	N.A.
Age (y)	62±9	61±9	0.65
Gender (M/F) ((M/F)(male/female)	7/8	12/3	N.A.
Heart Rate (bpm)	66±7	76±9	<0.005
Ejection Fraction (LVEF) (%) *	76±12	55±17	<0.0005
Height (cm)	170±9	178±11	N.S.
Weight (kg)	88±12	99±19	N.S.

Data are presented as mean ± standard deviation.
LVEF left ventricular ejection fraction (via calibrated ventriculography)
NSR normal sinus rhythm.
AF atrial fibrillation.
N.S. not significant
N.A. not applicable

P-wave peaks identified end-diastasis for NSR, and by ECG R-wave peaks in AF subjects.

Echocardiographic Analysis

Approximately 5 (continuous) Doppler transmitral E-wave contours per subject were selected and analyzed using the triangle shape approximations,[17] yielding peak E-wave velocity (Epeak), deceleration time (DT), velocity-time integral (E-VTI), E/E', and peak A-wave velocity (Apeak).

The parameterized diastolic filling (PDF) formalism, (See Appendix 1) was also used to analyze E-waves[9,18] to yield kAF, kNSR respectively. Specifically, k is the analog of invasively determined chamber stiffness.[19]

Multiple Beat Estimates of Stiffness

To construct the ED-PVR, and D-PVR VED, PED and VD, PD were measured at physiologically varying load states as previously described.[14] Thus for each subject the ED-PVR was generated by the best-fit linear regression to the 8-12 measured (VED, PED) locus of points (see Figure 2). Previous work[14] showed that linear or exponential fits yielded similar goodness of fit (by mean square error), and therefore linear regression was used. The D-PVR was generated similarly using (VD, PD) data. For the AF group, end-diastatic and end-diastolic data was identical, hence only a D-PVR was generated.

For NSR subjects chamber stiffness was determined from both ED-PVR and D-PVR slopes (dP/dVNSR-ED, dP/dVNSR-D respectively) whereas, for AF subjects chamber stiffness was computed from the D-PVR slope (dP/dVAF). It is generally accepted that LV relaxation is complete after an elapsed time of 3.5 tau after peak –dP/dt. To minimize the possible effect of insufficient time to achieve relaxation in generating the D-PVR we took care to use P, V data recorded at the END of diastasis, both in NSR (ECG P-wave) and in AF (ECG R-wave). Tau values for all subjects indicate that on average in NSR 6 tau intervals elapsed between peak -dP/dt and end-diastasis, while at least 4 tau intervals elapsed between peak -dP/dt and end-diastasis in AF.

Medications

Among the AF group of 15 subjects, most were prescribed several medications. The breakdown by type of medication is:

13 were on anticoagulants/antithrombotics (Coumadin, Aspirin, Heparin, Pradaxa),

8 were on beta blockers (Metoprolol, Coreg, Atenolol, Imdur, Sotalol),

7 were on lipid lowering agents (Zocor, Tricor, Lipitor, Gemfibrozil),

7 were on ACE inhibitor or ARB (Altace, Lisinopril, Cozaar, Quinapril),

6 were on calcium channel blockers (Norvasc, Diltiazem),

6 were on diuretics (Lasix, HCTZ, Triamterene),

5 were on digoxin.

Statistical Analysis

For each subject, parameters were averaged for the beats selected. Within the NSR group PD, VD and dP/dVNSR-D were compared to PED, VED and dP/dVNSR-ED by paired t-test. Comparisons of dP/dV, DT, k, and other parameters between NSR and AF groups were carried out by Student's t-test using MS-Excel (Microsoft, Redmond, WA).

Results

Absolute Index (Volume and Pressure) Comparison

NSR diastatic volumes and pressures were significantly smaller than corresponding NSR end-diastolic pressures and volumes (VD vs. VED: 118±31ml vs. 153±26ml $p<0.001$; PD: 13±3mmHg vs. 19±5mmHg $p<0.001$). Diastatic (same as end-diastolic) pressures and volumes in the AF group were indistinguishable from end-diastolic pressures and volumes in the NSR group (AF VD vs. NSR VED: 169±56ml vs. 153±26ml, $p=0.96$; AF PD vs. NSR PED: 18±4 mmHg vs. 19±5 mmHg, $p=0.51$). See Table 2 for additional hemodynamic details.

Relative Index (Chamber Stiffness) Comparison

Invasive Measures of Chamber Stiffness

Concordant with previous findings,[14] chamber stiffness in the NSR group at end-diastole, from the ED-PVR (dP/dVNSR-ED) was significantly greater than stiffness measured at diastasis, from the D-PVR (dP/dVNSR-D) (0.16±0.10 mmHg/ml vs. 0.10±0.07

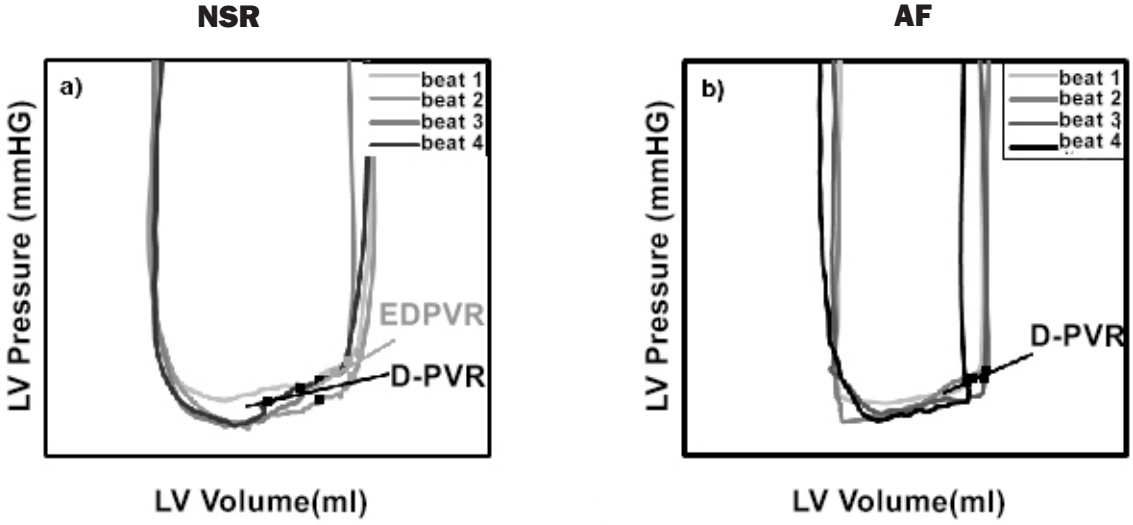

Figure 2: In-vivo pressure-volume loops showing diastatic pressure-volume relation (D-PVR) and end-diastolic pressure-volume relation (ED-PVR) from selected NSR subject (panel a) and D-PVR for selected AF subject (panel b). For clarity only 4 of 10 analyzed beats are shown. Black line, D-PVR via linear regression for all 10 beats. Gray line, ED-PVR in NSR subject via linear regression for all 10 beats. See text for details.

mmHg/ml p<0.001). Between AF and NSR groups, comparing the hemodynamics at the same phase of diastole, revealed that diastatic chamber stiffness, dP/dVAF-D was significantly higher than diastatic chamber stiffness dP/dVNSR-D (0.16±0.08 mmHg/ml vs. 0.10±0.07 mmHg/ml, p<0.05) in NSR.

Noninvasive Measures of Chamber Stiffness

E-wave deceleration time (DT) was significantly shorter in AF than in NSR (170±21 msec vs. 210±26msec, p<0.001). The PDF stiffness parameter in AF was significantly higher than in NSR (kAF vs. kNSR: 249±75/s2 vs. 183±35/s2, p<0.005). Higher k means increased stiffness.

Discussion

Noninvasive Indexes

We assessed E-wave derived chamber stiffness (DT, k)[8,19,20] in NSR and AF groups. To validate E-wave predicted stiffness we used chamber stiffness from simultaneous catheterization-derived multiple beat P-V data.

The PDF derived chamber stiffness k and DT both showed significant difference between the AF and NSR groups, with the AF group having increased stiffness. The shorter DT in the AF group is not due to the higher average heart rate (HR) of the AF group because all AF E-waves were followed by a diastatic interval. As long as diastasis is present, E-wave DT remains essentially unchanged as HR increases[21] while diastasis shortens. In addition, it is relevant that E-wave DT is determined jointly by stiffness and relaxation (kPDF and cPDF in PDF formalism terminology) rather than stiffness alone,[10] and therefore kPDF is the physiologically more specific index of stiffness than DT.

Table 2: Hemodynamic and echocardiographic data in NSR and AF groups.

	NSR (n=15)	AF (n=15)	p	p NSRED vs. NSRD
Hemodynamic Parameters:				
PED (mmHg)	19±5	18±4	0.51	<0.001
VED (ml)	153±26	169±56	0.96	<0.001
PD (mmHg)	13±3	18±4	<0.005	
VD (ml)	118±31	169±56	<0.005	
dP/dVED (mmHg/ml)	0.16±0.10	0.16±0.08	0.84	<0.001
dP/dVD (mmHg/ml)	0.10±0.07	0.16±0.08	<0.05	
Echocardiographic Parameters				
Peak E-wave velocity (Epeak) (cm/s)	76±17	90±28	0.12	
E-wave acceleration time (AT) (ms)	92±9	87±17	0.32	
E-wave deceleration time (DT) (ms)	210±26	170±21	<0.001	
E-wave duration time (Edur) (ms)	302±30	257±34	<0.001	
kPDF (1/s2)	183±35	249±75	<0.005	
E-VTI (cm)	11.2±0.03	11.4±0.04	0.93	
E/E'	4.7±1.8	6.0±1.9	<0.05	

Data are presented as mean ± standard deviation.

AF	atrial fibrillation
NSR	normal sinus rhythm
NSRED	end-diastolic values for NSR group
NSRD	diastatic values for NSR group
PED	left ventricular end-diastolic pressure
VED	left ventricular end-diastolic volume
PD	left ventricular diastatic pressure
VD	left ventricular diastatic volume
Epeak	peak E-wave velocity
AT	E-wave acceleration time
DT	E-wave deceleration time
Edur	E-wave duration
kPDF	Kinematic model-based, E-wave derived chamber stiffness
E-VTI	E-wave velocity-time integral
E/E'	ratio of Epeak and Peak E'-wave velocity
N.A.	not applicable

Invasive Indexes

Stiffness measures use end-diastolic P-V data. In chambers with chronic AF, however, end-diastole and diastasis (when R-R intervals are sufficiently long) are physiologically and hemodynamically the same (same point on the P-V plane). This is not the case in NSR. This and previous work [14] shows that in NSR, the diastatic and end-diastolic PVR are physiologically distinct and distinguishable. The feature responsible for this distinction is atrial systole, which expands the ventricle beyond its diastatic, equilibrium volume. This stiffens the chamber at end-diastole with the concomitant confounding of the ED-PVR by atrial systolic properties.

In NSR diastatic stiffness, is consistently lower than at end-diastole, after atrial systole. As a result, end-diastolic stiffness between AF and NSR groups would systematically overestimate NSR stiffness relative to AF stiffness. Indeed in the current work, AF chamber stiffness (0.16±0.08 mmHg/ml) is indistinguishable from NSR chamber stiffness (0.16±0.10 mmHg/ml) measured at end-diastole (p=0.84). The AF chamber stiffness (0.16±0.08 mmHg/ml) measured at diastasis is significantly (p<0.05) higher than diastatic NSR chamber stiffness (0.10±0.07 mmHg/ml). These are concordant with the simultaneous, and independent chamber stiffness findings from E-wave DT and the PDF formalism parameter k. Hence, when diastatic phases are not matched, and are merely referred to as 'diastolic chamber stiffness' the significant differences between AF and NSR stiffness is lost (dP/dVAF-D vs. dP/dVNSR-ED: 0.16±0.08 mmHg/ml vs. 0.16±0.10 mmHg/ml, p=0.84).

Although elucidation of mechanisms is beyond the scope of the current work, the likeliest explanation for the increased diastatic stiffness observed in chronic AF vs. NSR is chamber remodeling.[22,23,24,25]

Equilibrium Volume

Diastasis defines the hemodynamic/physiologic P-V point for passive chamber stiffness measurement. Elastic elements, displaced from equilibrium by systole, recoil toward their equilibrium diastatic position and power suction-initiated early rapid filling. At diastasis there is no bulk tissue or fluid movement and the chamber is momentarily static; there is no atrioventricular pressure gradient, no net force, and no net flow. As previously detailed,[26,27] diastasis defines the in-vivo equilibrium chamber volume, and represents the most relaxed and passive in-vivo state. Displacement above equilibrium volume by atrial systole loads elastic elements and couples the contracted atrium itself in series with a now, passively stretched ventricle, generating a state stiffer than the relaxed diastatic state .[14] Thus while conventionally one uses end-diastole for chamber stiffness, measuring stiffness at the equilibrium (diastatic) volume provides a physiologically more accurate measure of actual passive stiffness.

Chamber Stiffness in Sinus Rhythm and Atrial Fibrillation

There are few studies that compare DF between AF and NSR groups. Pozzoli et al followed heart failure subjects over 2 years and compared DF parameters between 18 subjects that developed chronic

AF, and 34 control subjects in NSR.[28] While they found values of DT consistent with the current study, and a decrease in DT between AF and NSR subjects, the difference was not significant. However all of their subjects had systolic heart failure (average EF=25%). In contrast, all NSR subjects in the current study had normal EF, and this may help explain the more significant DT difference between groups observed in the current study. Furthermore, Pozzoli et al did not include simultaneous, invasive measures of chamber stiffness to support their echocardiographic DT based findings.

Takagaki et al, compared myocardial compliance in sheep before and after induction of atrial fibrillation.[29] This is the only other AF vs. NSR invasive study where chamber stiffness was compared. Interestingly, they found no difference in invasive ED-PVR results between AF and NSR. However, they compared 'end-diastole' in AF with 'end-diastole' in NSR. End-diastole in (rate controlled) AF allows achievement of diastasis, and therefore a comparison of the D-PVR between AF and NSR sheep in the Takagaki et al study would have been more appropriate. Indeed, we found that chamber stiffness between AF and NSR groups showed no significant difference when end-diastole was used, but showed significant difference when diastasis was employed. By using end-diastole, Takagaki et al likely over-estimated the NSR chamber stiffness relative to AF Another important difference between the Takagaki study and the present work is that our subjects had chronic AF of several years duration – and therefore sufficient time for chamber remodeling - whereas the Takagaki study measured compliance before and after induction of AF.

Study Limitations

The conductance catheter method of volume determination has known limitations related to noise, saturation and calibration that we have previously acknowledged.[14,15,16,19] Only physiologically consistent P-V loops were selected and averaged. If the two absolute measures (ESV, EDV) have slight systematic differences, resulting in a systematic volume calibration offset, the absolute values of the slopes could be innacurate. However, comparison of slopes between groups remain valid, because a systematic offset would affect all measurements equally. Indeed the absolute location of the D-PVR or ED-PVR in the pressure-volume axes should not affect the slope of the pressure-volume relation.

As previously,[14] the P-V measurements in NSR subjects utilized ECG R- and P-waves having an interobserver dependence of <5%.

Load Variation Approach

An average of 7 beats per subject in NSR and 19 beats per subject in AF were used to construct respective D-PVR because in NSR, the observed physiologic load variation was primarily the result of respiration, with PVC or Valsalva also utilized. For PVC and Valsalva the D-PVR was measured during the compensatory period. Although the amount of load variation after these maneuvers is modest, the P-V relationship constructed from an average of 7 beats in NSR is sufficient.[14] In contrast we used only respiratory variation in AF patients to determine D-PVR, so a greater number of cardiac cycles per subject was included in the analysis. Previous D-PVR work,[14] demonstrated that even though the heart may respond differently to Valsalva maneuver and PVC, the D-PVR and ED-PVR measurements using the two load-varying methods do not differ significantly.

In P-V relationship determining physiology experiments, inotropic state may be varied by pharmacologic means. Data obtained during the course of cardiac catheterization and the associated informed consent procedure did not allow for interventions involving external (non-physiologic) inotropic agents. This limitation is obviated by the fact that load variation was entirely physiologic and did not activate reflex mechanisms associated with pharmacologic interventions.

HR Limitation

The D-PVR requires the presence of diastasis and therefore a suitable HR. In the current study HR was such that every analyzed cardiac cycle in AF or NSR had a clear, diastatic pressure interval and an E-wave followed by diastasis.

Conclusions:

We determined if echocardiography is able to reliably characterize chamber properties in AF vs. NSR. Conventional DF parameters (DT, Epeak, AT, Edur, E-VTI, E/E',) and E-wave derived, stiffness specific PDF parameter (k), were computed. Although AT, Epeak and E-VTI failed to differentiate between groups, DT, Edur and E/E' and stiffness parameter k showed that AF hearts are stiffer than NSR hearts. In contrast, chamber stiffness from simultaneous ED-PVR data showed no difference between groups! We resolved the discordance and gained mechanistic insight when we found that diastatic stiffness in the AF group is significantly greater than diastatic stiffness in NSR group. We conclude that passive (diastatic) chamber stiffness is increased in normal LVEF chronic, rate controlled AF hearts relative to normal LVEF, NSR hearts and that in addition to DT, the E-wave derived, chamber stiffness specific index k, differentiates between AF vs. NSR groups, even when invasive hemodynamic P-V loop derived end-diastolic chamber stiffness fails to do so.

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