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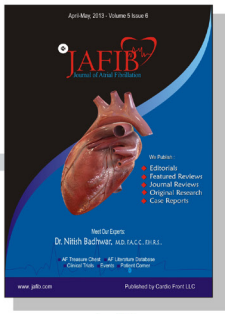

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Ischemic Conditioning and Atrial Fibrillation: Hope for a NewTherapy?

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Abstract

Atrial fibrillation (AF) is the most common sustained arrhythmia. It is accompanied by both structural and ion channel remodeling which underlie the propensity to perpetuate AF. The prevalence of AF is expected to increase as population ages and as more patients survive myocardial infarction. Despite pharmacological and nonpharmacological (such as ablation) therapies for AF, more effective therapy is needed. Ischemic or pharmacological conditioning offers a potential novel approaches to patients with AF. This review will focus on the basic biology of ischemic pre- and postconditioning, patho-physiology of AF, potentially novel AF treatment approaches based on conditioning, and clinical situations that may be amenable to a conditioning strategy.

Introduction

As the most common sustained arrhythmia, AF represents an enormous healthcare burden,[1] which is anticipated to increase in coming years.[2] Progress has been made in management, yet there continues to be a significant need for safer, more effective, and durable treatments.

Current drug therapy continues to have limited efficacy in maintaining sinus rhythm and presents concerns over adverse effects.[3] This dilemma is illustrated by the fact that amiodarone is the most effective anti-arrhythmic drug, but only has a long term efficacy of 50-70%[4] with a wide range of adverse effects that often limit its tolerability.[5] This has led to the search for alternatives such as dronedarone, which has been disappointing in terms of efficacy.[6]

Transcatheter ablation represents an exciting new frontier in rhythm management, but it also has limited efficacy[7, 8] and carries risk of procedural complication[9, 10] These issues highlight the need for novel approaches. In this manuscript, we will describe the role of ischemia in the pathophysiology of AF and discuss the mechanisms of ischemic conditioning and hypothesize how conditioning may protect against AF.

Pathogenesis of Atrial Fibrillation

Atrial Fibrillation and Clinical Risk Factors

Paroxysmal AF is defined as AF lasting at least 30 seconds but less than 7 days with spontaneous termination. In contrast, persistent AF lasts longer than 7 days, requires cardioversion and is not self-terminating. Chronic or permanent AF does not terminate and the clinical decision is then to keep the patient in AF.[11] Patients who initially present with paroxysmal AF - usually progress to more chronic forms over time.[12] Clinical risk factors for AF include advanced age,[13] ischemia,[14] after car-

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diac surgery,[15] hypertension, heart failure including both systolic and diastolic heart failure. Channelopathies like long-QT syndromes or Brugada syndrome can also be associated with AF. High catecholamine states can also precipitate AF. In a subset of patients no risk factors or structural heart disease can be identified. These patients are considered having "lone AF".

Triggers

Haissaguerre and his group identified the pulmonary veins as important triggers for AF (16). Some studies of the pulmonary veins showed cells with spontaneous activity.[16,17] Investigation of pulmonary vein cells using patch clamp technique revealed a reduced action potential duration and Vmax favoring reentry by slowing conduction velocity. Focal foci were also found near the superior or inferior caval veins or adjacent to the coronary sinus os. Other triggers include sympathetic and parasympathetic stimulation and acute atrial stretch.

Basic mechanisms underlying ectopic impulse formation include enhanced automaticity as well as early and delayed afterdepolarization. While normal atrial cells do not exhibit automaticity, abnormal atrial cells exhibiting If may be overwhelmed by a large IK1. A change in the balance of IK1 (decrease) and If (increase) can cause enhanced automaticity of atrial cells with ectopic firing. Early afterdepolarization can occur with prolonged action potentials when ICaL has recovered enough to cause a second depolarization. This might be the cause of AF seen in patients with long-QT syndrome.Delayed afterdepolarization results from Ca overload. ICaL triggers Ca release from the sarcoplasmic reticulum during systole. During resting membrane potential and before the depolarized portion of action potential, the Na-Ca exchanger can operate in forward mode causing entry of 3 Na ions while extruding 1 Ca ion causing a net positive depolarization current. This mechanism might be seen in patients in AF caused by digitalis intoxication.

Maintenance of Atrial Fibrillation

After an initiating trigger, perpetuation of atrial fibrillation is usually dependent on the presence of a vulnerable substrate to maintain the rhythm. Once initiated, electromechanical remodeling promotes the maintenance of AF - often referred to as atrial fibrillation begetting atrial fibrillation.

AF can be maintained by persistent triggers or reentrant activity. Different models describe reentrant activity. In the leading circle model the wavelength and size of the reentrant circuit is determined by the refractory period and the conduction velocity.[18,19] The shorter the wavelength of the circuit the more reentrant wavelets can be accommodated in the atria. Therefore, the shorter the refractory period and the slower the conduction velocity, conditions found in persistent AF with fibrosis, the more chronic AF gets. The rotor model describes a rotor circulating around a core .[8,9] AF persists as long as enough wavefronts are available at the same time in both atria. In contrast to the reentrant wavelet model perpetual firing from one or more foci can maintain atrial fibrillation.[20]

Anatomical as well as electrophysiological properties within the atria play a role in maintaining AF. The abrupt change in fiber orientation between the pulmonary vein and atrial juncture may facilitate reentry by causing unidirectional block.[21] Fiber orientation and fibrosis of the posterior wall may facilitate unidirectional block and reentry.[22] Studies of the pulmonary veins have shown specialized cells with automatic activity[23] and the resting potential of pulmonary vein cells with a reduced AP can cause slowed conduction favoring reentry[24, 25]

Electromechanical Remodeling

AF leads both to mechanical as well as electrical remodeling. These changes in the substrate of the atria facilitate the continuation of AF and likely cause the transition from paroxysmal to chronic AF. The two important electrical changes in AF are a decrease in AP duration and shortening of the AP plateau.[26-29] The basis of these changes is the altered physiology of ion channels with ICaL playing a central role. Initially, rapid activation leads to increased calcium Ca++ influx activating mechanisms to limit Ca influx. As a result, ICaL is reduced. Also an increase in IK1 and IKAch can be seen in chronic human AF. These changes result in both shortening of AP duration and shorten-

ing of the AP plateau. These effects can be seen within 24hours of the onset of AF. The shortened AP promotes the continuation of AF by shortening the wave length in the leading circle model or stabilizing the core in the rotor model.

Fibrosis is of key importance in mechanical remodeling. Hypertensive heart disease, dilated cardiomyopathy, and coronary disease are associated with fibrosis involving the atria. Fibrosis does interfere with the homogenous excitation wavefront propagation and can promote ectopic impulse formation. Fibroblasts separate myocardial bundles causing a discontinuous zig-zag type conduction pattern which results in conduction slowing. Conduction slowing, electrical coupling between fibroblasts and myocytes as well as conduction block favor reentrant formation. These reentrant circuits may only be a few millimeters in diameter. Reactive interstitial fibrosis may be caused by the underlying heart disease but there is evidence that AF itself contributes in the remodeling process.[30] Apoptosis may contribute to structural changes of the atria. A8 small number of apoptotic cells can be found in human hearts with chronic fibrillation.[31] The Renin-angiotensin-aldosterone (RAS) system may play a role in the structural changes occurring in AF supported by some experimental evidence. The RAS activates protein kinases causing myocyte hypertrophy as we, after AFas fibroblast proliferation.[32] In patients with AF expression of ACE and AT1 can be increased .[33] By contributing to structural remodeling, AF itself creates positive feedback making permanent AF more likely.

Ischemic Conditioning-Basic Mechanisms

Ischemic pre- and post-conditioning provides potent cardioprotection in animals and humans.[34-39] Ischemic preconditioning (IPC) is triggered by a brief period of ischemia prior to an infarct that causes, after that sustained ischemia.IPC has been shown to have protective benefits of limiting myocardial infarction and protecting against arrhythmias.[34-41] Brief ischemia/reperfusion during early reperfusion is also cardioprotective and is known as ischemic postconditioning (IPost). The extent of the protective effect of IPost is similar to that of IPC, with nearly equivalent reduction in the infarct size. In order for the protection of IPost to occur, brief ischemia/reperfusion must be applied immediately after sustained ischemia at the beginning of reperfusion.

Both pre- and post-conditioning appear to share similar signaling mechanisms via RISK (reperfusion injury survival kinases). Thus, pharmacological conditioning might be applied to mimic the protection achieved by the triggering ischemia/reperfusion.

However, several important features differentiate the two kinds of conditioning. First, IPC requires that the trigger ischemia/reperfusion or pharmacological agonist be applied before the sustained ischemia. Thus, for cardioprotective effect of preconditioning to be exerted therapeutically, one will need to anticipate the occurrence of sustained ischemia/reperfusion. The occurrence of sustained ischemia would be difficult to predict clinically in patients. On the other hand, IPost is exerted after sustained ischemia has already begun. Its protective effect can be achieved by applying triggering ischemia/reperfusion or pharmacological agents after prolonged ischemia, obviating the need to anticipate clinical events. Second, the protective effect of IPost requires several repetitive episodes of brief ischemia and reperfusion especially in pigs [42] and is limited to sustained ischemia of 45 minutes or less.[43] Third, while RISK enzymes mediate protection in both kinds of conditioning, connexin 43 (Cx43) is not important in mediating the protection of IPost. This potentially important insight was obtained in Cx43 knockout mice in which the protection of IPC or of pharmacological preconditioning by diazoxide is lost while that of IPost is preserved. Fourth, signaling mechanism for IPC appears to be more complex. During the trigger phase, preconditioning ischemia activates a number of G protein-coupled receptors such as adenosine, bradykinin and -opioid receptors.[44] This is followed by activation of EGF and TNF- receptors that in turn stimulate survival kinases (similar to the RISK involved in IPost). The trigger phase of IPC is followed by the mediator phase during which actual protection against ischemia-induced injury is exerted. Various mediators activated by the trigger phase's survival kinases include phosphor-Ser9-glycogen synthase kinase-3 (phosphor-GSK-3), mitochondrial ATP-sensitive K+ channel 10 (mitoKATP) and Cx43. It is thought that mitoKATP channels and phosphor-GSK-3 converge on

and inhibit the mitochondrial permeability transition pore with the latter being the final mediator of necrosis. Finally, while IPC has been shown to reduce arrhythmias caused by sustained ischemia, the protection against arrhythmias by IPost is less well studied.

Ischemic Conditioning in Humans

It is a well-described phenomenon that cardiac tissue has the adaptive ability to become more tolerant to the toxic effects of prolonged ischemia with intermittent ischemia and subsequent reperfusion[34-39] This adaptability can be intentionally stimulated with the therapeutic delivery of brief periods of ischemia. Classically, short episodes, usually 3-5 minutes of ischemia, are delivered before a larger ischemic insult with subsequent reperfusion, and are termed IPC. The cardiac benefits of IPC in humans are decreased frequency of ventricular arrhythmias and limitation of infarct size.[34-41, 45, 46]

Recent studies have demonstrated that similar benefits may also be seen with the delivery of short episodes of ischemia after a larger ischemic insult i.e. IPost.[47, 48] In addition, the benefit of ischemic conditioning may not only be derived by ischemic conditioning of cardiac tissue, but there is evidence that ischemic conditioning of remote organs can result in benefits to the heart. To date, data are limited on the benefit of ischemic conditioning with respect to AF.

Ischemic Pre Conditioning

There is an extensive literature describing the benefits of ischemic conditioning in animal studies, however, the clinical uses of direct cardiac ischemic conditioning in humans have been limited by the invasive nature of its delivery. The cardiac operating theater is a natural setting to evaluate the potential for direct ischemic conditioning.Multiple small studies have evaluated the ability of ischemic conditioning to reduce the release of cardiac biomarkers, and to reduce the requirement of inotropes post surgically.[49]

With regard to arrhythmias, data are more limited. One group from Finland has been particularly active in assessing effect of IPC on arrhythmias in CABG patients. Their most recent cohort (50) evaluated forty five patients with three vessel CAD undergoing CABG and randomized them in 1:1 fashion to two rounds of IPC immediately after cardiopulmonary bypass and run pump to vent the still normothermic heart. Immediately post-operatively (<2 hrs), there was a significant decrease in ventricular extrasystoles in patients treated with IPC. Clinical follow-up was limited to 5 days, over which time a significant reduction in incidence of VT and SVT was seen that peaked on postoperative day three. There was no description of the types of SVT's seen. The same group of investigators demonstrated that IPC results a significant suppression of heart 12 rate variability after CABG, suggesting that cardiac autonomic function is involved in the IPC mechanism.[51]

To our knowledge, no human clinical trials have demonstrated an effect of IPC with respect to AF. Other potential benefits of ischemic conditioning include: decreased heart rate after surgery, and decreased systemic vascular resistance after surgery.[52] All of these peri-cardiac surgery trials have been limited by small numbers of patients and limited follow-up. Any benefits seen appeared to be limited in duration and any long-term data are lacking. One study from Japan evaluated the electrophysiologic responses to repeated coronary balloon inflation and deflation in the setting of percutaneous coronary intervention for treatment of acute ST-segment elevation myocardial infarction.[53] These data pointed to a possible anti-arrhythmic mechanism underpinning the benefit of ischemic conditioning by demonstrating a significant decrease in the QT dispersion with repeated balloon inflation and dilation. Numbers were too small to draw conclusions, but anecdotally, patient's with frequent PVC's were suppressed or disappeared with progressive ballooning. Atrial arrhythmias were not seen during this study.

Ischemic Post Conditioning

Some of the same protective benefits of direct IPC may also be derived from postconditioning.[54] Ischemic post-conditioning has even been shown to convert VF to sinus rhythm in perfused rat hearts.[55] However, the clinical benefits of postconditioning was recently thrown into doubt with the publication of a study showing no benefit from post conditioning in patients undergoing PCI for

STEMI.[56] This study demonstrated no difference in infarct size or LVEF and revealed a significantly lower myocardial salvage after post-conditioning was performed.

Remote Ischemic Conditioning

Remote ischemic pre-conditioning (RIPC) refers to the protective effects to the heart seen by delivery of short periods of ischemia to remote organs. The promise is that its benefit may be delivered non-invasively. Animal models of short periods of ischemia to limbs and kidneys are protective to the heart after cardiac reperfusion.[57-60] Human studies have evaluated the effect of non-invasive limb ischemia prior to elective PCI and demonstrated reduced release of Trop I.[61] ECG changes were seen less frequently in patients receiving RIPC, however subsequent follow-up did not evaluate for presence of arrhythmias.

The benefit of RIPC has also been evaluated in the setting of acute myocardial infarction as a complement to percutaneous coronary intervention (PCI) .[62] Repeated inflation with a blood pressure cuff to induce transient limb ischemia resulted in a significant improvement in the degree of myocardial salvage as assessed by myocardial perfusion imaging 30 days after infarction. There was no reduction in MACE (coronary death, reinfarction, and heart failure). Presence of arrhythmias was not assessed.

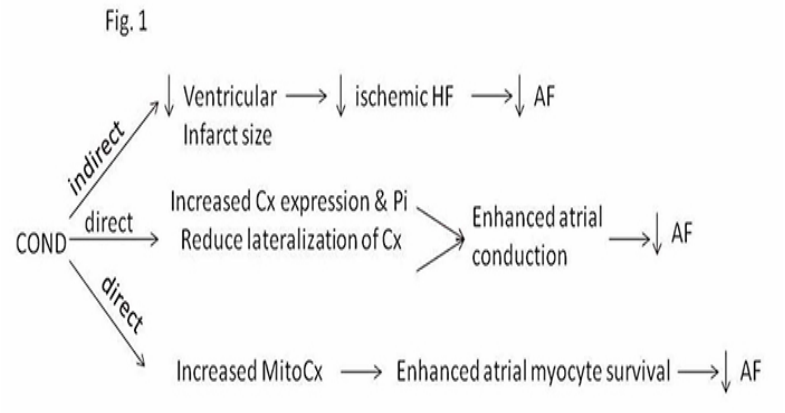
Several small trials have also evaluated RIPC in patients undergoing CABG and demonstrated conflicting data. A meta-analysis of these studies concluded that there was a 36% (95%CI = -0.62 to -0.12) reduction in the amount of Troponin I or T released after RIPC, with slightly greater reduction in patients with multi-vessel disease. Postoperativ change in creatinine and length of hospital stay were unchanged.[63]

A recent meta-analysis of RIPC concluded that while RIPC may reduce the incidence and degree of peri-procedural infarction and troponin release, there is insufficient evidence at this time to suggest the RIPC can reduce mortality or MACE .[64] Little appears to be known about RIPC and AF or other arrhythmias.

Pharmachological Adjuvants

Several drugs had been shown to offer benefits similar to those of preconditioning: opiods, certain volatile anesthetics, and even certain noble gases have demonstrated the ability to induce tolerance to the effects of ischemia.[65-71] Fascinatingly, one study demonstrated interaction between pharmachologic agents and RISP when 15 troponin reduction was present when RIPC was delivered in the presence of isoflourane anesthesia, but this benefit was absent during propofol anesthesia.[72]

Figure 1: An Overall Model of Conditioning again AF

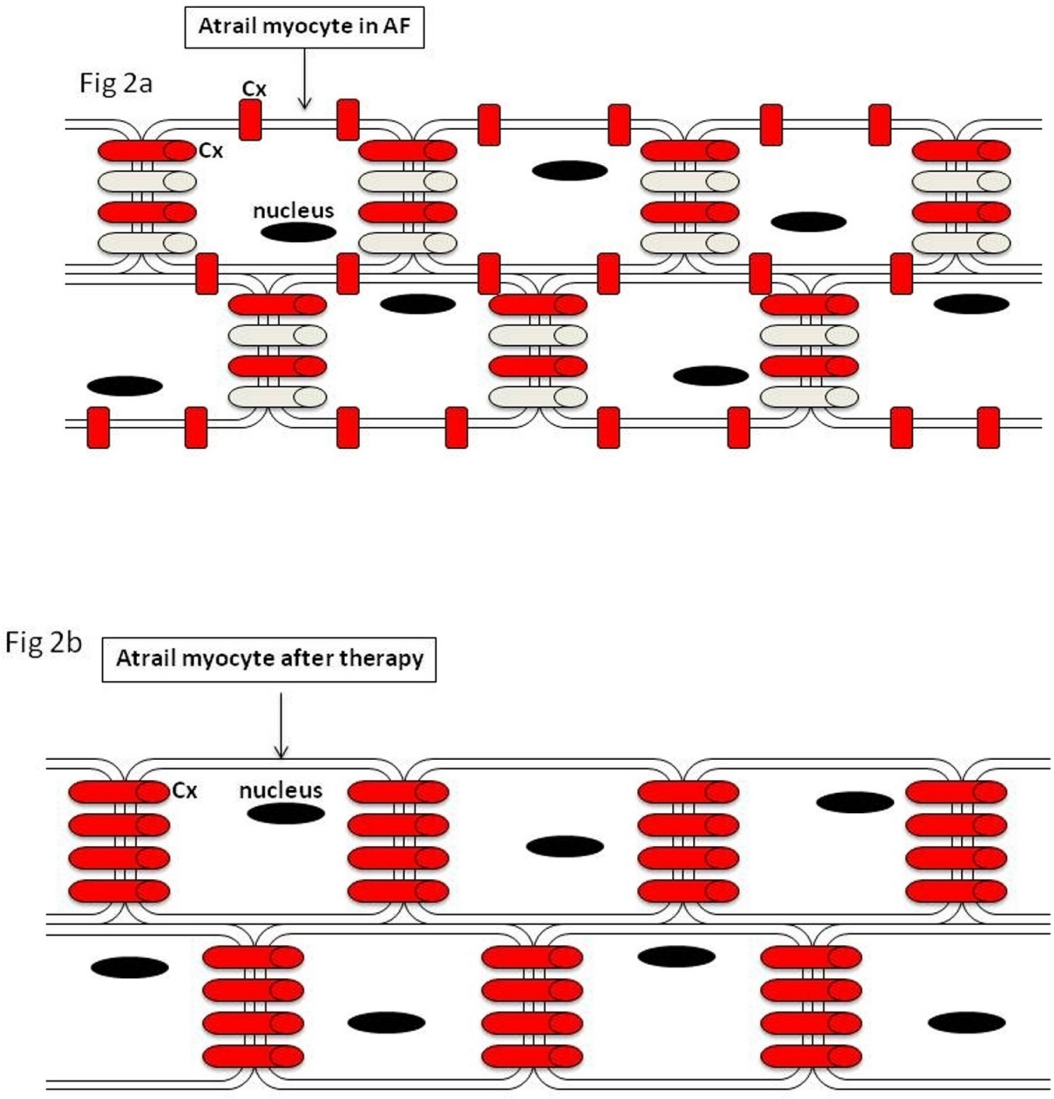


Both direct and indirect mechanisms are proposed to protect against occurrence of AF. Indirectly, conditioning (COND) can reduce ventricular infarct size and protect from ischemic heart failure-associated AF. Directly, COND may enhance atrial conduction and atrial myocyte survival. The increased Cx expression appears to be caused by its reduced degradation due to IPC; the increase Cx phosphorylation (Cx-Pi) is due to reduced dephosphorylation. Together, these two changes in Cx enhance electricalcoupling during the sustained ischemia. Enhanced atrial myocyte survival may reduce fibrotic replacement and atrial structural remodeling in AF.

Indirect Benefit of Pre- or Post-Conditioning on Atrial Fibrillation

Very little is known about the potential benefit of ischemic conditioning against the occurrence of AF. Since ischemic heart disease such as myocardial infarction and heart failure increase the prevalence of AF, a reduction in the size of ventricular infarction will decrease the extent of subsequent adverse ventricular remodeling and may thus reduce the propensity to AF (Fig. 1). Although unknown, it is possible that reduced atrial infarction in patients with STEMI or NSTEMI will decrease atrial fibrosis and structural remodeling in that tissue. This could secondarily reduce the occurrence of AF. Since both pre- and post-conditioning can decrease ventricular infarct size, ischemic or pharmacological conditioning can be exploited as a new therapy to prevent AF.

Figure 2: Pre Comditioning to Enhance Cx-Mediated Electrical Coupling



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Potential Direct Conditioning Against Atrial Fibrillation

Very little is known about potential direct conditioning against the occurrence of AF.Given the pivotal role of connexin (Cx) in electrical coupling between cardiomyocytes, and in mediating the protection of preconditioning[40, 73-75] Cx may be important in preconditioning against AF. We propose a potential mechanism by which increased 16 cell-end expression of Cx with a concomitant reduced lateralization via IPC may suppress AF (Fig. 2).

Cx40 is mainly found in atrial myoytes while Cx43 is the predominant isoform of Cx in ventricular cardiomyocytes.[76, 77] Both Cx43 and Cx40 are expressed in atrial myocytes and appear to mediate gap junction function in that tissue. Cx 43 has been well-characterized and is implicated in mediating the protective effect of IPC.[75] It is mainly localized to the sarcolemma and the intercalated discs where six connexins assemble into a so-called connexon or hemichannel. Two opposing connexons, one each from adjacent cells, form a pore through which ions and molecules less than 1000 Da can flow down their concentration gradients. Clusters of such pores form a gap junction. It has been suggested that gap junctions are responsible for both electrical coupling (permitting ions) and chemical coupling (permitting larger molecules as defined by Lucifer Yellow dye). It has been suggested that IPC may have a differential effect on these two proposed types of coupling via the Cx hemichannels: further suppression of chemical coupling and partial preservation of electrical coupling during the sustained ischemia. Loss of electrical coupling occurs early during ischemia (10-20 min after onset of ischemia) as shown by extra- and intracellular electrodes in isolated papillary muscles while chemical coupling via gap junction as assessed by Lucifer yellow and ethidium bromide persists for 30-60 min during ischemia. Despite this difference in time course of loss of electrical vs. chemical coupling, the underlying process and mechanism are not known. It is difficult to ascertain which biological molecules are spread via the so-called chemical coupling between myocytes. It is further suggested 17 that IPC-induced suppression of chemical coupling would inhibit the spread of any "death signal" from one myocyte to another while preservation of electrical coupling would enhance conduction and decrease heterogeneity of excitability. While this concept may be appealing, Na+ as an ion should be spread via electrical coupling but may contribute to neighboring myocyte's Na overload that in turn results in Ca overload and cell death. That IPC can protect isolated cardiac myocytes suggests gap junctionmediated coupling is not necessary for the protection against cell death. Accumulating evidence demonstrates an important role of the mitochondrial Cx against cell death. [75,78, 79] Mitochondrial Cx is increased by ischemia and positively enhances the function of mitoKATP channel which can help trigger IPC by increasing reactive oxygen species (ROS) and PKC- activation. MitoKATP channels can also be the mediator protecting against cell death during the sustained ischemia. Taken together, Cx plays an important role against myocyte death during preconditioning.

In the intact myocardium, electrical coupling mediated by Cx may be important in mediating the protective effect of preconditioning on arrhytmias. IPC can attenuate the prolongation of transmural conduction time during ischemia as measured by microelectrodes in isolated right ventricle walls .[80] The anti-arrhythmic effects of IPC were correlated with delayed electrical uncoupling between myocytes[81, 82] In a porcine model of AF, forced overexpression of Cx43 by gene transfer improves atrial conduction with increased probability of sinus rhythm .[83] It is of interest that Cx43 gene transfer can improve conduction and reduce ventricular tachycardia in Yorkshire pigs after myocardial infarction.[84] A parallel pattern now emerges such that Cx 18 enhancement at its intercalated disk location is of anti-arrhythmic benefit on both ventricular and atrial arrhythmias. Small molecule drugs have been developed to increase gap junction conduction with improvement in ischemia and mitral valve disease-related AF. Such agents have little or no benefit in other AF models, however.In patients with AF, metoprolol treatment could partially reverse the lateralization of Cx43 and antagonized the attendant transverse conduction velocity.[85] Since IPC appears to protect against electrical uncoupling via a better Cx-mediated gap junction function, it is possible that IPC or drugs that mimic the anti-arrhythmic effect of IPC can be exploited to suppress AF (Fig. 2).

Finally, while IPC or IPost is speculated to impact on Cx, a conditioning strategy may also modulate other ion channels implicated in pathogenesis or maintenance of AF. For example, conditioning may induce an increase of IK1 and/or a decrease in If. In this scenario, conditioning may reduce automaticity of atrial cells with less ectopic firing. Conditioning may also reduce spontaneous firing or propagation of the pulmonary vein cells. Channels important in the pulmonary vein myocytes may be targets for IPC or IPost.

Future Directions- Possible Use of Ischemic Conditioning in Patients

Despite improvements in pharmacological and non-pharmacological therapies for AF, more effective therapy is needed. This review focused on the basic biology of ischemic pre- and post-conditioning, patho-physiology of AF, and potentially new pathways for AF [19] treatment approach based on conditioning. If ischemic conditioning can be developed as a new therapy for AF, what are the clinical conditions that may be amenable to conditioning? Given the prevalence of post-operative AF following both cardiac and non-cardiac surgeries, a preconditioning stimulus before surgery may reduce the incidence of post-operative AF. Examples of such a stimulus include a pharmacological preconditioning agent or remote IPC. The latter can be achieved by repetitive episodes of limb ischemia and reperfusion such as those achieved by application of a tourniquet. Clinical conditioning strategies may include administration of an agent during reperfusion phase of cardioplegia or during percutaneous coronary intervention. It mayalso be possible to use remote conditioning during early phase of reperfusion to mimic the protection of IPost. The ongoing RICO-Trial (Effect of remote ischemic conditioning on AF and outcome after coronary artery bypass grafting) is a randomized control trial that is evaluating the efficacy of remote pre- and post-conditioning in patients undergoing cardiac bypass grafting with incidence of post-operative AF as the primary endpoint.[86] Pre conditioning will consist of 3 x 5 minute ischemic episodes via tourniquet to an upper limb after the induction of anesthesia and before bypass. The post ischemic treatment consists of similar 3 x 5 minute episodes of upper limb ischemia after aortic cross clamping has occurred. Follow up will be out to one year.These results are pending. Finally, as we understand more about the pathogenesis ofAF, it is possible that daily administration or ingestion of a conditioning drug may prevent AF.

Limitations Sense

This review is intended to be hypothesis-driven, proposing that conditioning may be a new therapeutic strategy to prevent or reduce AF. It is based on the many salutary effects of conditioning in the cardiovascular system. Although evidence exists for IPC against arrhythmias, there is no experimental study to show that IPC or IPost can condition against AF. The hypothetical mechanisms proposed are based on potential links between known effects of conditioning in the heart, existing knowledge of Cx in atrial myocyte coupling, and the established role of Cx in IPC. Future investigations areneeded to test the proposed pathways.

Conclusions

Despite pharmacological and non-pharmacological advances in the treatment of AF, new therapy for this most common sustained arrhythmia is needed. Ischemic conditioning, already known to protect from infarction and ventricular arrhythmias, represents a potential novel approach to patients with AF. Modulating the expression or phosphorylation of Cx may be the target of conditioning that can be accomplished by ischemic or pharmacological conditioning.

Disclosures

No disclosures relevant to this article were made by the authors.

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