

Left atrial vascular and metabolic remodeling in pig models of atrial fibrillation

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SUMMARY

The normal heartbeat originates in the sinus node. From there, the activation wave spreads over both upper chambers (atria), and also reaches the atrioventricular (AV) node, the only electrical connection between the upper chambers and the lower chambers (ventricles). Because conduction within the AV node is slow, there is a delay between atrial and ventricular activation. This delay allows the atria to empty themselves into the ventricles, before the ventricular contraction starts. During the ventricular contraction, blood is pumped by the right ventricle into the pulmonary artery and by the left ventricle into the aorta. There are numerous cardiac arrhythmias in which the activation sequence of the heart is disturbed. Of these arrhythmias, atrial fibrillation (AF) is the most common in clinical practice. In some patients, this arrhythmia occurs in the absence of other heart disease, so-called 'lone AF', but many patient have heart disease, for example heart failure' that predisposes to AF. During AF, activation waves in the atrium propagate rapidly (up to 600 times per minute) and irregularly, and organized atrial contraction is lost. Some of the atrial activations conduct through the AV node to the ventricles, leading to a fast (up to 180 beats per minute) and irregular ventricular rate. Patients with AF experience this rapid, irregular ventricular rate as palpitations, and their exercise tolerance is reduced because this rate cannot be properly regulated during physical exertion. In addition, on the long term AF patients have an increased tendency to develop blood clots, especially in the left atrium, leading to a higher risk of debilitating strokes and increased mortality.

In the beginning of the disease process, AF is often paroxysmal, meaning that AF occurs in episodes that terminate spontaneously. In many patients, the duration of these episodes gradually increase, until AF does not terminate spontaneously anymore (persistent AF). At this stage, sinus rhythm can often be restored by treatment with antiarrhythmic drugs. Eventually however, these drugs lose their efficacy and AF cannot be terminated by anti-arrhythmic drug treatment (permanent AF). During the progression of the disease, AF itself leads to atrial 'remodeling'; changes in the atrial tissue that makes the arrhythmia more stable. Several key players in this process have already been identified and characterized extensively. A fast process of 'electrical remodeling' occurs rapidly, in the first hours to days of AF, and entails the shortening of the atrial action potential, allowing a higher activation frequency. A much slower process of 'structural remodeling', developing over months to years, changes the structure of the atrial tissue, increasing the size of atrial muscle cells (hypertrophy) and the amount of connective tissue (fibrosis) in between muscle cells. The latter in particular is thought to represent obstacles to conduction, increasing the complexity of fibrillatory conduction and therefore the stability of AF. Although these 'culprits' are well known, the treatment strategies to prevent the progression of AF are still unsatisfactory. One of the central problems is

that we do not know exactly which factors cause electrical and structural remodeling. One of the candidate factors is the energy balance of the atrial myocardium. In a cardiac muscle cell (myocyte), the molecule adenosine triphosphate (ATP) delivers the energy that is required for contraction, electrical activity and other metabolic processes. An estimated 2% of the cellular ATP pool is utilized during each heartbeat. The rapid rates of electrical and contractile activity during AF will increase ATP consumption. This increased demand needs to be matched by increased ATP production, and the required oxygen and nutrients have to be supplied by the atrial vasculature. If the energy demand by the myocardium cannot be met, a state of supply/demand ischemia develops. The metabolic challenge presented by AF can be met by scaling back energy demand and by increasing energy supply, and there are several indications that both phenomena occur as a result of AF. Still, there is ample evidence that these adaptations fall short of redressing this disbalance, that may represent a driving force for atrial electrical as well as structural remodeling.

The general aim of this thesis is to investigate the metabolic and vascular consequences of AF itself, and of an important risk factor for AF, congestive heart failure (CHF). Characterizing and understanding the role of these processes may help in finding therapeutic approaches and targets that could inhibit the progression of AF.

As an animal model, we have chosen pigs, which are known to be similar to humans with respect to coronary anatomy, coronary blood flow regulation and metabolism. We studied animals early in the disease process, in the first few weeks, a phase in which we expected the metabolic and vascular derangement and adaptations to be most pronounced. First, we studied a pig model of CHF (chapter 2). Clinically, CHF is a major independent risk factor for AF, with approximately 50% of patient with severe CHF developing AF. In the pig model, we induced CHF by rapid ventricular pacing. After 5 weeks, we observed that the degree to which both atrial and ventricular coronary vessels could dilate (i.e. increase blood flow to the cardiac muscle) was decreased. This in itself would reduce that capacity of the coronary vessels to accommodate fluctuation in energy and oxygen demand. However, during pacing (i.e. increased heart rate), we did not observe an increase in atrial lactate production, which would be a tell-tale sign of supply-demand ischemia. On the other hand, we demonstrate that atrial contractility has decreased dramatically in this model. Thus, the hypertrophied atria in this model still receive adequate coronary blood flow, but this does not translate to useful external work (contractility). In other words, the atrial oxygen efficiency (the amount of work delivered per amount of oxygen supplied) has decreased dramatically. In failing hearts, the atrial contraction becomes more important to overall cardiac function. The loss of the atrial contraction may contribute to reduced exercise capacity and exacerbation of heart failure, even before AF develops.

Subsequently, we assessed metabolic and vascular alterations that occur because of AF itself. As a relatively early time point, we chose one week of AF (maintained by rapid atrial pacing). From these pigs, we isolated atrial small muscular arteries, the arteries that normally determine blood flow to the myocardium. Because virtually nothing was known about the behavior of these blood vessels and their reaction to AF, we performed a basic characterization of vascular function (chapter 4). We observed that both the reaction to vasodilators and vasoconstrictors was enhanced after one week of AF. This implies that coronary vessels, and thus coronary blood flow, react more strongly to factors that regulate vascular tone. To some extent, these alterations are similar to the (adaptive) changes that occur during exercise training. Further studies will have to determine whether these alterations in vascular function persist during the time course of AF, or whether vascular dysfunction eventually develops.

At the same point in time, we determined a number of metabolic parameters in tissue and assessed the function of isolated mitochondria. On the hand, we demonstrate a number of changes that can be interpreted as adaptations to increased energy demand, metabolic stress and calcium overload (increased mitochondrial respiratory control, decreased production of reactive oxygen species and faster calcium buffering). On the other hand, we observed potential counterproductive, maladaptive changes, including reduced tissue levels of energy carriers (ATP and PCr), possibly reduced energy producing capacity (a reduction in the mitochondrial membrane constituent cardiolipins) and reduced mitochondrial calcium storage capacity during oxidation of fatty acids. The work we have performed in this study represents only a snapshot of metabolic changes during the pathogenesis of AF. While the time course of metabolic remodeling will have to be studied more closely, our observations do support the view that AF presents a major metabolic stress for atrial myocytes.

Finally, we have studied vascular structure at two time points, after 1 and 5 weeks of AF. First we show an increase at both time points of HIF1 α expression, a classic marker of oxygen shortage. HIF1 α activates the transcription of VEGF, one of the key factors in the formation of new blood vessels. Indeed, expression of VEGF was increased after 5 weeks of AF. Increased expression of VEGF would normally lead to the formation of new blood vessels to supply the tissue in which oxygen shortage occurs. However, when we determined the distribution of capillaries (the small vessels where oxygen supply to the tissue takes place), a paradoxical decrease in the number of vessels was apparent after 5 weeks of AF. This suggests that newly formed capillaries are not sufficiently stabilized and quickly disappear. At this point, we do not have a mechanistic explanation for the loss of capillaries from the atrial myocardium, despite hypoxic signaling. However, this phenomenon implies the capacity of the remodeled atria to respond to fluctuations in energy demand is

limited and that it remains vulnerable to supply/ demand ischemia.

ARABIC SUMMARY

الخلاصة

اضطراب النظم القلبي أو اختلال النظم القلبي هي الاختلافات التي تطرأ على دقات القلب وعلى نُظم نقل الشارة الكهربائية في عضلة القلب. تختلف اضطرابات النظم القلبي فيما بينها فمنها الأكثر خطورةً والأقل خطورةً على حياة المريض. إحدى حالات اضطراب النظم القلبي هو الرجفان الأذيني. يعتبر الرجفان الأذيني إحدى حالات اضطراب النظم القلبي الأكثر شيوعاً عند مرضى القلب، تكمن خطورة هذا المرض في كونه مسبب رئيسي في السكتة الدماغية.

هناك عدة عوامل تجعل الإنسان أكثر عرضة لمرض الرجفان الأذيني، على سبيل المثال تشوهات الهيكل الأذيني الذي يعتبر السبب الرئيسي في حدوث الرجفان الأذيني. حتى الآن العوامل المسببة بحدوث تشوهات الهيكل الأذيني غير معروفة كلياً.

لذلك كان الهدف العام من هذه الأطروحة هو دراسة وفهم الآليات والعوامل التي تشارك في حدوث تشوهات الهيكل الأذيني. فهم هذه الآليات يمكن أن يساعد في إيجاد النهج والأهداف العلاجية التي من شأنها وقف مظاهر الرجفان الأذيني. إحدى أبرز الفرضيات لحدوث تشوهات الهيكل الأذيني هي نتيجة إختلال توازن الأوكسجين في الأذين الأيسر.

لذلك لقد قمت في هذه الأطروحة بدراسة الأوعية الدموية وإعادة التمثيل الغذائي ولا سيما في الأذين الأيسر في ثلاثة نماذج من الخنازير. أولاً نموذج خنزير لديه قصور القلب الاحتقاني حيث تمت دراسة الأوعية الدموية وحركة إنقباض الأذين الأيسر، ثانياً نموذج خنزير لديه رجفان أذيني قصير المدى حيث قمت هنا بدراسة وظيفة وهيك الشرايين التاجية للأذين الأيسر كما قمت أيضاً بدراسة التمثيل الغذائي، هيك، ووظيفة الميتوكوندريا. ثالثاً وأخيراً نموذج خنزير لديه رجفان أذيني طويل المدى حيث تم تقييم بنية الأوعية الدموية في الأذين الأيسر.

تم العثور في مجموعة قصور القلب الاحتقاني على انخفاض في حركة إنقباض الأذين، تضخم في خلايا الأذين الأيسر، انخفاض في احتياطي تدفق الدم في الشريان التاجي المؤدي إلى الأذين الأيسر وانخفاض في كثافة الأوعية الدموية في الأذين الأيسر. في مجموعة الرجفان الأذيني قصير المدى تم العثور على انخفاض في وظيفة التمثيل الغذائي ونقص الأوكسجين في الأذين الأيسر لكن هذا النقص لم يكن نتيجة تغيير في وظيفة الشرايين التاجية للأذين الأيسر وإنما كان بسبب الزيادة في معدل حركة الأذين الأيسر خلال الرجفان الأذيني.