Contents

Arrhythmia and metabolism

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The observation that plasma free fatty acid concentrations are increased during and immediately after myocardial infarction was made several decades ago [1]. Clinical observations showed that plasma free fatty acid concentrations greater than those that could bind to the two primary affinity-binding sites on albumin were associated with an increase in the incidence of ventricular arrhythmias during myocardial infarction [2]. Subsequently, it was proposed that certain arrhythmias have a metabolic basis [3]. The oxygen-wasting effects of increased provision of free fatty acids to the acutely ischemic myocardium were found to be augmented by impairment of the uptake or utilization of glucose [4]. These early findings led to the views that provision of glucose is ''good'' [5] and that the presence of increased circulating free fatty acid concentrations is ''bad'' [3] for the ischemic myocardium.

During ischemia, β-oxidation of long-chain fatty acids in mitochondria is inhibited and there is an intracellular accumulation of metabolites such as long-chain acyl carnitine and acyl coenzyme A. The metabolites that accumulate during ischemia-reperfusion may, indirectly, lead to ionic disturbances; in particular, they may alter both sodium and calcium homeostasis and contribute to electrical dysfunction. Increases in intracellular sodium (Na^+_i), which have been demonstrated during ischemia-reperfusion [6], may indeed have functional and proarrhythmogenic consequences [7], because increases in Na^+_i in turn generate Ca^{2+} loading via reverse Na^+–Ca^{2+} exchange. Interestingly, it has been shown that trimetazidine, which inhibits fatty acid oxidation in the heart [8], also significantly reduces the increase in Na^+_i during ischemia and early reperfusion [6]. The most plausible underlying mechanisms for the gain in Na^+_i during ischemia are a decrease in Na^+ extrusion via Na^+/K^+-ATPase or an influx of Na^+ via Na^+–H^+ exchange and the voltage-gated Na^+ channel, or both. Na^+–H^+ exchange activity may be rapidly inhibited by extracellular acidosis during total ischemia, which suggests that voltage-gated Na^+ channels may have a significant role as mediators of ischemic Na^+ loading [9]. A large proportion of these channels become rapidly non recruitable in ischemic tissues after resting membrane potential depolarization, and action potentials initially shorten and subsequently cease with exhaustion of cellular ATP. Na^+ influx continues, however, through non inactivated voltage-gated sodium channels, giving rise to persistent window currents [10,11]. Moreover, the slowly inactivating component of the Na^+ current also increases substantially during ischemia, amplifying Na^+ influx [11,12]. In this context, it has been shown that long-chain acyl carnitine, which accumulates in the cell membrane during ischemia, markedly increases the slowly inactivating component of the Na^+ current [12]. Experimental data also indicate that acyl carnitine, like ouabain, produces a reversible inhibition of the Na^+/K^+ pump current [13] and thereby a decrease in Na^+ extrusion. Therefore, specific myocardial metabolic modulation such as with trimetazidine, which limits the accumulation of long-chain acyl carnitine during ischemia [14], may well limit the increase in Na^+_i via slowly inactivating the sodium channels and causing a relative increase in Na^+/K^+ pump function. This would be particularly important in reducing ionic disturbances and the susceptibility of the myocardium to malignant arrhythmogenic events.

The experimental evidence summarized above probably represents only a few aspects of the fascinating machinery that may underlie the metabolic signals of arrhythmia. This issue of *Heart and Metabolism* will highlight the importance of metabolic disturbances, associated either with an imbalance of metabolic substrates or, as most recently reported, with genetic mutations that can alter the function of a key

regulatory enzyme of cardiac energy metabolism [15] and downstream effectors such as cardiac ion channels [16] and, possibly, other ion transporters. ■

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Metabolic signals of arrhythmia

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Abstract

Cardiac arrhythmias represent a major cause of mortality in the Western world. Recent research has advanced our understanding of the cellular and molecular mechanisms of arrhythmogenesis and has demonstrated that some of the causes of arrhythmias may occur as a result of perturbations in cardiac energy metabolism. These alterations in cardiac energy metabolism can have direct effects on the activity of ion channels and exchangers involved in ionic homeostasis, which can subsequently promote arrhythmogenesis. In addition, a mutation in AMP-activated protein kinase – a kinase that has a major role in the regulation of cardiac energy metabolism – has been implicated in causing ventricular pre-excitation and/or progressive conduction system disease, further highlighting the involvement of metabolism in contributing to cardiac arrhythmogenesis. Pharmacological modulation of specific metabolic pathways may therefore represent a novel approach for the clinical treatment and prevention of certain types of arrhythmias.
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Keywords: Arrhythmia, cardiac energy metabolism, ion channels, AMPK, PRKAG2

Introduction

The correct conduction of electrical signals within the heart relies on the precise spatial and temporal control of action potential propagation throughout the myocardium. It comes as no surprise that any disruption in this highly orchestrated rhythmic process can potentially lead to life-threatening electrical abnormalities or arrhythmias. Indeed, arrhythmias are one of the major causes of cardiac-related deaths in the Western world.

Depending on the underlying reason, arrhythmias may be generated in many different regions of the heart. The most common type of arrhythmia is atrial fibrillation, which has an incidence of 6% in people older than 65 years [1]; other types of arrhythmia include congenital long QT syndrome and familial Wolff–Parkinson–White (WPW) syndrome [2]. It is now apparent that the underlying trigger for many types of arrhythmias may not be purely electrical in nature, but that alterations in cellular metabolism also contribute to abnormal ionic homeostasis leading to increased susceptibility of the myocardium to arrhythmogenic events. Thus the attenuation of metabolic disturbances may offer a novel therapeutic strategy in several types of arrhythmia, such as those precipitated by ischemia-reperfusion injury and familial WPW syndrome, in which metabolism has a causative role. Because of the relative clinical importance of the proarrhythmogenic events that are probably generated in response to the metabolic disturbances that occur in ischemia-reperfusion and familial WPW

syndrome, we have focused this review on these two topics.

Ischemic metabolism and arrhythmogenesis

The most common trigger for fatal arrhythmias is the underlying pathology of acute coronary syndrome. Myocardial ischemia has a major role in the pathophysiology of heart disease and is a major health concern worldwide. The slowing or cessation of blood flow to regions of the heart resulting from coronary artery occlusion induces ischemia and provides the ideal conditions for the genesis of arrhythmias. It is now apparent that both ionic and metabolic disturbances act in concert to trigger proarrhythmic activity within the myocardium.

During severe ischemia, oxidative metabolism effectively ceases and ATP is produced primarily from glucose via anaerobic glycolysis. Although the benefit of a continued supply of ATP via glycolysis is essential to myocardial cell function and survival, the hydrolysis of glycolytically derived ATP in the absence of glucose oxidation results in an accumulation of protons and lactate that may cause cardiac dysfunction and/or arrhythmias, either during ischemia or after reperfusion [3,4]. One reason why this dysfunction occurs is that the already diminished supply of ATP is redirected from myocardial contraction towards the clearance of the glycolytic byproducts. If the ischemic episode is too severe, then ATP concentrations may decrease sufficiently to alter ionic homeostasis, leading to proarrhythmic activity. Indeed, the ST-segment elevation often observed on the electrocardiogram in the ischemic heart is believed to result from excess opening of ATP-sensitive potassium channels [5]. A limited supply of ATP may also lead to the impaired clearance of sodium ions via the action of Na^+/K^+-ATPase. Furthermore, upon reperfusion, the accumulated protons are removed from the cardiac myocyte by the Na^+–H^+ exchanger NHE1, in exchange for Na^+ ions, which further increases the intracellular Na^+ concentration. This increase in intracellular Na^+ activates the Na^+–Ca^{2+} exchanger in the reverse mode, thus promoting increased accumulation of Ca^{2+} within the cardiac myocyte. The resultant Ca^{2+} overload is believed to be a major cause of contractile dysfunction of cardiac arrhythmias after reperfusion of an ischemic myocardium [6].

In addition to alterations in the supply of ATP during ischemia, there are other metabolic signals that can contribute to arrhythmias. As metabolism is switched from β-oxidation of fatty acids to glycolytic production of ATP during ischemia, an intracellular build-up of lipid metabolites such as lysophosphatidylcholine* has been shown to increase the persistent activity of the normally transient voltage-gated sodium channel [7], which may also contribute to action potential prolongation and Na^+ loading in myocytes. Furthermore, esterified fatty acids such as long-chain acyl coenzyme A also accumulate in the ischemic myocardium, and our recent research (Embo J 2006, in press) suggests that these metabolites increase reverse-mode Na^+–Ca^{2+} exchange activity, further exacerbating Ca^{2+} overload, contractile dysfunction, or cardiac arrhythmias.

Reperfusion of reversibly injured myocardial tissue improves functional recovery, but there are also negative consequences associated with restoring blood flow to the ischemic region. For example, reperfusion of the ischemic myocardium results improved mitochondria function and a rapid production of reactive oxygen species, which further exacerbates existing ionic imbalances [8]. Therefore the metabolic generation of reactive oxygen species is also believed to have a major role in cardiac arrhythmogenesis.

Collectively, the metabolites that are generated during ischemia and/or reperfusion, or both, will alter both sodium and calcium homeostasis and contribute to electrical dysfunction. This resulting heterogeneity of the action potential duration and dispersion of refractoriness will lead to an increased potential for re-entrant-type arrhythmias [9]. Therefore, it is clear that the alterations in cardiac energy metabolism that occur during ischemia-reperfusion have a major impact on many ion channels and exchangers involved in ionic homeostasis, highlighting the importance of metabolism in the control of arrhythmogenesis.

Alterations in AMP-activated protein kinase activity and arrhythmogenesis

In addition to the metabolic disturbances that occur during ischemia-reperfusion, there are also genetic mutations that can alter the function of specific proteins, eventually leading to arrhythmias. A number of these proteins are ion channels [10,11]; however, several mutations in one enzyme that has a major role in the regulation of cardiac energy metabolism have been identified as being a major contributor to ventricular pre-excitation or progressive conduction system disease, or both. This enzyme is AMP-activated protein kinase (AMPK)*. The identification of this key regulator of cardiac energy metabolism as being centrally involved in a specific arrhythmia further supports the notion that metabolism plays a major part in the regulation of arrhythmogenesis.

AMPK is a heterotrimeric protein (consisting of an α–β–γ complex) that regulates both whole-body and cellular utilization of energy [12]. Early reports showed that AMPK is activated by metabolic stresses that

deplete cellular ATP [13] and responds by readjusting energy production and expenditure in order to re-establish the supply of ATP. AMPK has a major role in regulating cardiac energy metabolism [3], but specific mutations in the γ_2 gene of AMPK (PRKAG2)* have recently been shown to alter AMPK activity in the heart [14–17]. These PRKAG2 mutations also appear to be directly responsible for a glycogen storage cardiomyopathy characterized by ventricular pre- excitation (WPW syndrome), progressive conduction system disease [18–22], and, in specialized cases, cardiac hypertrophy [23,24]. This triad of cardiac abnormalities has been termed the PRKAG2 cardiac syndrome [23,24].

The exact cause of this ventricular pre-excitation in patients with the PRKAG2 cardiac syndrome has not been firmly established, but it has been suggested that conduction system abnormalities observed in this disease originate from glycogen-filled myocytes causing the formation of pre-excitation muscular bypass tracts between the atrial and ventricular chambers [18,20]. Such tracts are used as a retrograde limb of the re-entrant circuit, and appear to result in a macro-re-entrant arrhythmia. The finding that a mutation in a major regulator of cardiac energy metabolism leads to arrhythmias further supports the concept that alterations in cardiac energy metabolism, independent of ischemia-reperfusion, may be sufficient to signal arrhythmogenic activity.

Although metabolic alterations occurring in response to abnormal AMPK activity clearly produce glycogen-filled myocytes that may act as bypass tracts, there are also other possible mechanisms by which alterations in AMPK activity may contribute to the arrhythmogenic activity. Indeed, we have shown that the cardiac Na^+ channel is also regulated by activated AMPK [2,25], and suggested that there may be other ion channels that are regulated by AMPK, which could contribute to the observed arrhythmogenic activity in patients with some PRKAG2 mutations [25]. Future research will undoubtedly clarify the targets of the mutated form of AMPK and help establish the precise mechanism by which the ventricular pre-excitation and progressive conduction system disease originate in patients who are afflicted with the PRKAG2 cardiac syndrome.

Summary

It is becoming clear that alterations in cardiac energy metabolism can have a major role in the development of cardiac arrhythmias, but it is currently unknown whether pharmacological restoration of cardiac metabolism will be an effective approach to the treatment of arrhythmogenesis. Although the approach of ''metabolic modulation'' for the treatment of cardiac arrhythmias is in its infancy, there is clear evidence that modifications to the downstream effector ion channels, and exchangers, or both, that are disturbed by metabolic alterations may have clear benefit for the treatment of certain arrhythmias. For example, drugs that ameliorate the function of the Na^+–H^+ and the Na^+–Ca^{2+} exchangers are good candidates for novel antiarrhythmic agents [26,27]. In addition, modulation of AMPK activity in patients with the PRKAG2 mutations that cause familial WPW syndrome may help prevent the accumulation of glycogen or prevent the ventricular pre-excitation and progressive conduction system disease. Together, these new strategies may one day lead to improved treatment of patients who develop cardiac arrhythmias that are related to ischemia-reperfusion or the PRKAG2 cardiac syndrome. ■

* See glossary for definition of these terms.

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Metabolic gene defects and risk of arrhythmia

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Abstract

Inherited single-gene disorders offer unique insights into the role of metabolic processes in arrhythmogenesis. Although many metabolic defects result in cardiomyopathy as a physiologic compensation, it is clear that specific perturbations are associated with particular arrhythmias. Metabolic gene defects may cause arrhythmia through many different pathways, including developmental effects on cardiac patterning, pathologic disruption of specific myocardial cell types, and the perturbation of several cellular processes. Understanding the precise pathways linking individual gene defects with discrete clinical arrhythmias will shed light, not only on monogenic disease, but also on common disorders such as ischemia or diabetes.

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Keywords: Glycogen, fatty acid, mitochondrial, atrial fibrillation, ventricular tachycardia

Introduction

Myocardial metabolism can adapt to a wide range of substrates, but the precise pattern of substrate utilization is dependent on availability, oxygen delivery, workload, and physiologic regulation. As a consequence of these constraints, and the demands on myocardial functional reserve throughout life, many single-gene metabolic defects cause cardiomyocyte dysfunction, including arrhythmia [1,2].

Specific metabolic gene defects associated with arrhythmia

Lipid metabolism

At rest, free fatty acids constitute the predominant myocardial substrate, so it is not surprising that several inherited disorders of fatty acid oxidation present with early onset cardiomyopathy and arrhythmias. Abnormal carnitine transport into cells or into mitochondria, in addition to defects in several mitochondrial enzymes required for fatty acid oxidation, can result in cardiomyopathies (*Table I*) [3,4]. Overt cardiac involvement is present in more than 50% of those with defects of fatty acid oxidation. Presentation is usually precipitated by fasting, depletion of glycogen stores, and consequent dependence on fatty acid as an energy substrate. In typical acute metabolic crises, characterized by hypoglycemia, lactic acidosis, hepatic dysfunction, blunted ketone formation, and hypotonia, ventricular tachycardia is the most common arrhythmia [3]. However, other arrhythmias may be prominent in a substantial minority of cases, irrespective of overt evidence of cardiomyopathy. Sinus node dysfunction, paroxysmal supraventricular arrhythmias, atrioventricular block, and intraventricular conduction abnormalities all have been reported [3]. It is difficult to make definitive correlations in such rare disorders, but there may be a propensity to specific arrhythmias with different defects. The majority of fatty acid oxidation disorders are recognized in the first 2–3 years of life, but there are well-documented cases that have presented in adulthood [5].

Table I. Metabolic gene defects associated with arrhythmias.

Disorder	OMIM	Gene defect	Mode of inheritance	Arrhythmias	Comments	References
Lipid metabolism						
CPT-II	608836	Carnitine palmitoyltransferase*	AR	VT, AVB		[3,4]
CACT deficiency	212138	SLC25A20, carnitine–acylcarnitine translocase*	AR	VT, SVT, AVB		[3,4]
MCAD	201450	Medium-chain acyl dehydrogenase*	AR	VT	Late onset reported	[3–5]
LCAD	201460	Long-chain acyl dehydrogenase	AR	VT		[3]
VLCAD	201475	Very-long-chain acyl dehydrogenase	AR	VT, AVB		[3]
MADD	231680	Multiple acyl CoA dehydrogenase deficiency	AR	VT, SVT		[3]
Barth	302060	Tafazzin*	XLD	VT, SCD		[6,7]
Glycogen storage						
Pompe	232200	Lysosomal acid glucosidase*	AR	PE, CD	MLVT, EFE, several forms	[1,2,9]
McArdle's	232600	Glycogen phosphorylase*	AR	AVB, CD	DCM	[1,2]
Brancher	232500	Amylo-1,4-1,6-transglucosidase*	AD, AR	AVB, SCD	DCM	[1,2]
Debrancher	232400	Amylo-1,6-glucosidase*	AR	AVB	DCM	[1,2]
PRKAG2	602743	AMP-activated protein kinase γ-2 subunit*	AD	PE, AVB	MLVT	[10–12]
Danon	300257	Lysosome-associated membrane protein 2*	XLD	AVB	MLVT	[10]
Glycosphingolipid storage						
Fabry	301500	β-Galactosidase A*	XLD	AF, VT	MLVT, RF	[2,13]
Mitochondrial						
KSS	530000	Variable deletion	Mitochondrial	AVB, PE	LVH/DCM	[15]

AD, autosomal dominant; AF, atrial fibrillation; AR, autosomal recessive; AVB, atrioventricular block; CD, diffuse conduction disease; DCM, dilated cardiomyopathy; EFE, endocardial fibroelastosis; KSS, Kear–Sayre syndrome; LVH, left ventricular hypertrophy; MLVT, massive left ventricular wall thickening; OMIM, Online Mendelian Inheritance in Man(http://www.ncbi.nlm.nih.gov/omim/); PE, pre-excitation; RF, renal failure; SCD, sudden cardiac death; SVT, supraventricular tachycardia; VT, ventricular tachycardia; XLD, X-linked dominant.

Barth's syndrome is characterized by cardiomyopathy, skeletal myopathy, neutropenia, organic aciduria, and growth retardation. Ventricular arrhythmia and cardiac arrest are typical [6]. The syndrome is caused by mutations in tafazzin [7], a gene of unknown function with a suspected role in mitochondrial phospholipid metabolism [8].

Storage disorders

Many of the classic metabolic storage disorders are associated with cardiac involvement (*Table I*) [2]. Neurologic or respiratory failure is often the cause of early death. Cardiac manifestations, including massive left ventricular wall thickening (a combination of deposition and true hypertrophy) and valvular involvement, although present to some degree in all cases, may emerge as a problem only later in life in those who survive as a result of therapeutic intervention or less penetrant alleles [1,2]. Prominent evidence of atrioventricular conduction disease, often with ventricular pre-excitation, is seen in all these diseases, and atrial arrhythmias are also a frequent problem.

Glycogen storage

Pompe's disease typically results in massive thickening of the ventricular wall in childhood, sometimes with endocardial fibroelastosis [1,2]. There is usually evidence of ventricular pre-excitation, in addition to bizarre fractionation of the entire surface electrogram [9]. Ectopy is commonly seen, but arrhythmias do not dominate the clinical course and death is usually from cardiorespiratory failure. Defects in glycogen phosphorylase (McArdle's disease), brancher or

debrancher enzymes, all are reported to cause atrioventricular conduction system disease and dilated cardiomyopathy with disproportionate wall thickening [2]. In these disorders, heart failure and sudden death are seen occasionally.

Dominant mutations in the γ2 subunit of the AMP-activated protein kinase gene (PRKAG2)* have recently been shown to result in massive myocardial thickening, atrioventricular conduction system disease, and ventricular pre-excitation [10]. Affected families had previously been included under the rubric of hypertrophic cardiomyopathy on the basis of their inheritance patterns, adult onset, and echocardiographic features [11]. Atrial fibrillation and atrial flutter are common, but high-grade atrioventricular block is the dominant clinical arrhythmia [11]. Clinical studies suggest that, in many cases, asymptomatic individuals are maximally pre-excited at rest, and therefore are probably dependent on accessory atrioventricular connections from an early age. Syncope and sudden death are reported in families with PRKAG2 mutations, but the mechanism is not always clear.

Danon disease has previously been classified as a glycogen storage disorder, despite the inconsistent presence of glycogen on biopsy [12]. The identification of mutations in the lysosomal-associated membrane protein, LAMP2, confirmed this as a vacuolar myopathy. The clinical course is malignant, complicated by ventricular arrhythmias and intractable heart failure.

Glycosphingolipid storage*

Andersen–Fabry disease is an X-linked storage disorder characterized by angiokeratoma, acroparesthesias, abdominal pain, and renal and cardiac disease [2]. Female heterozygotes often exhibit much less penetrant forms of the disease, and cardiac-specific, late-onset variants exist [13]. In these *formes frustes*, the incidence of cardiovascular symptoms in males and females is similar. Ventricular thickening is common, especially in males, and correlates with the risk of non sustained ventricular tachycardia [14]. Atrial fibrillation is the most frequent arrhythmia. Atrioventricular conduction system disease and pre-excitation are less common than in many other storage disorders.

Other storage disorders

Cardiac involvement is the rule rather than an exception with a host of other rare storage disorders, including mucopolysaccharidoses, mucolipidoses, gangliosidoses, and neuronal ceroid lipofuscinosis [2]. The majority of these conditions are recessive and lethal in childhood. Reports of arrhythmias are rare, but are dominated by atrioventricular block.

Mitochondrial disorders

Specific mitochondrial DNA defects have quite variable effects as a result of differences in the extent of tissue heteroplasmy for mutant mitochondria. However, cardiac involvement is a central feature of several of the classic mitochondrial syndromes [1]. Cardiac expression of these defects is usually in the form of cardiomyopathy. Atrioventricular conduction disease is a common feature of Kearns–Sayre syndrome and accessory atrioventricular connections are also reported [15]. In several autosomal disorders in which left ventricular hypertrophy, cardiomyopathy, or conduction system disease are prominent, the mutated genes have recently been implicated in mitochondrial function. These include myotonic dystrophy and Friedreich's ataxia [16].

Metabolic mechanisms of arrhythmogenesis

The reproducible clinical effects of most inherited metabolic diseases suggest a precise relationship between perturbations of metabolism and specific arrhythmias. Discrete metabolic defects may act via developmental patterning events, on distinct myocardial cell types or through particular signaling pathways to cause specific arrhythmias.

Inherited metabolic defects act at several time points throughout development, adolescence, and adulthood. The patterning of cardiac form and function are closely intertwined, and subtle physiologic perturbations may lead to both abnormal myocyte specification and macroscopic anatomic abnormalities [17]. The strong association between atrioventricular conduction abnormalities and ventricular pre-excitation seen across several metabolic gene defects suggests that patterning of the atrioventricular ring is particularly susceptible [2,10,18].

Several cell types exist within the myocardial syncytium. Perhaps the most obvious cell-specific pathology seen with several metabolic gene defects is atrioventricular block (*Table I*). This may reflect not only the role of calcium transport and conductance in the action potentials of these cells, but also many other attributes. Distinctive intercellular junctions, membrane turnover, or unique sarcomeric protein isoforms may predispose the conduction system in metabolic disorders. Differential sensitivity to metabolic defects also extends to other cell types, such as ventricular myocytes, which appear particularly affected by defects in fatty acid oxidation [3]. ''Passive'' storage itself may be quite localized, and many other intracellular processes are highly regionalized throughout the heart [19]. Differential effects across apico–basal or endocardial–epicardial gradients result in myocardial heterogeneity, a major substrate for re-entrant arrhythmias.

Metabolic defects are understood to induce arrhythmia through an increasing number of cellular mechanisms [20]. The function of many ion channels is closely coupled with cellular metabolic function through cyclic nucleotides gating and other mechanisms. Calcium cycling in each intracellular compartment is distinctly affected by particular metabolic pathway perturbations. Syncytial coupling is mediated by gap junctions, which are regulated by intracellular substrate concentration, local calcium and pH [21]. Subtle defects in the posttranslational modification of ion channels and other transmembrane proteins may interfere with the ability of these molecules to reach the sarcolemma [22]. Normal metabolism is required for the activation of some ion channels, acting as a long-term regulator of membrane conductances [23]. Understanding the precise pathways linking individual gene defects with discrete clinical arrhythmias will shed light, not only on monogenic disease, but also on the common disorders such as ischemia or diabetes. ■

* See glossary for definition of these terms.

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Imaging and arrhythmia

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Abstract

Imaging is becoming increasingly important in the management of cardiac arrhythmias as treatment moves away from long-term medication to curative radiofrequency ablation (RFA). With the complexity of the arrhythmias being treated in cardiac catheterization laboratories, information from echocardiography, computed tomography, and magnetic resonance imaging (MRI) are increasingly being used in planning before the procedure, in addition to helping guide the procedures. These imaging techniques can provide information about patient-specific cardiac anatomy. In addition, MRI can provide information about myocardial motion and myocardial tissue characteristics. In the future, arrhythmia ablations may be performed entirely under MRI guidance, without the harmful effects of X-rays, and with the added benefit of real-time anatomical views.
■ *Heart Metab.* 2006;33:13–16.

Keywords: Arrhythmia, echocardiography, computed tomography, magnetic resonance imaging

Introduction

There has been a major change in the treatment of arrhythmias over the past 20 years. Most of these conditions can now be treated, and often cured, by radiofrequency ablation (RFA) [1,2]. This alleviates the need for long-term drug treatment and is often preferred by patients. There follows a brief description of the different imaging techniques used for RFA and, in particular, MRI, which is one of the newer and more promising techniques in this field.

X-ray fluoroscopy

Radiofrequency ablation procedures are traditionally carried out under X-ray fluoroscopic guidance.

Advantages:

- gives clear images of the entire length of the catheters;
- provides high temporal resolution of at least 25 frames per second;
- is an easy-to-use technology that is widely available and known by operators.

Disadvantages:

- is a projection imaging modality, and more than one view is necessary to gain an appreciation of the 3-dimensional location and path of catheters. Therefore, there is a need either to move the X-ray c-arm to obtain different projections or to use a bi-plane X-ray system;
- the anatomical context of the acquired images can be difficult to interpret, because soft tissues, such as the heart and blood vessels, are not visible during X-ray exposure;
- X-ray imaging delivers a dose of radiation to the patient and those carrying out the procedure. This can be significant for prolonged procedures and in pediatric cases [3].

Echocardiography

Echocardiography is used as an adjunct to assess cardiac anatomy and function before an RFA procedure, and to look for the presence of complications

such as pericardial effusion after a procedure. Intracardiac echocardiography is becoming adopted for use during the procedure [4].

Advantages:

- intra-cardiac echocardiography allows real-time visualization of patient-specific cardiac anatomy and the ablation catheter – particularly useful for assessing contact between the two;
- the technique does not involve administration of a dose of X-ray radiation.

Disadvantages:

- cost – the probes are expensive and, in some countries, can be used only once;
- an additional large sheath is required for vascular access;
- at present this technique provides only 2-dimensional information, although 3-dimensional systems are being developed.

Electroanatomic mapping systems

The mainstay of the planning of RFA procedures is electrical mapping of the heart. However, increasingly, the anatomical shape of the vessels and chambers of the heart has become important, especially in ablation of atrial fibrillation. In the past few years, a number of electroanatomic systems have been developed, such as CARTO [5] and EnSite [6], that bring together the 3-dimensional representation of the anatomy and the electrical mapping.

Advantages:

- there is potentially little or no dose of X-ray radiation;
- a 3-dimensional representation of the surface of the heart is obtained;
- combined electrical and anatomical information are provided;
- the technique affords the ability to mark, and thus return to, the position of the ablation catheter on the surface of the heart.

Disadvantages:

- cost – particularly with the CARTO system, which requires dedicated catheters;
- additional time is needed to build an anatomical surface by contact mapping of the cardiac chamber;
- there may be errors in the anatomical surface that is depicted by this technique, which can make the heart rather spherical, although this can be improved by importing computed tomographic information;
- there is no correction for respiratory motion.

Computed tomography

Computed tomography is very helpful in the preplanning for atrial fibrillation ablation, as it provides images of the pulmonary veins and left atrium that have a high spatial resolution. It can also be combined with electroanatomic systems such as CARTO [7] or, as has been done more recently, with real-time X-ray fluoroscopic images [8].

Advantages:

- the technique gives consistent high spatial resolution images of the heart;
- it is relatively fast and the images are easy to acquire;
- it provides 3-dimensional information.

Disadvantages:

- the technique involves an additional dose of X-ray radiation that can be substantial;
- as imaging is performed hours, and even days, before the procedure, it does not take into account any changes to the shape and size of the heart that can take place before or during the procedure;
- when the technique is combined with electroanatomic systems or X-ray fluoroscopy, no correction is made for respiratory motion.

Magnetic resonance imaging

Magnetic resonance imaging can provide anatomical information similar to that obtained with computed tomography. The recent emergence of hybrid X-ray and magnetic resonance imaging systems (XMR) has opened up new interventional guidance strategies for the ablation of arrhythmias [9]. As the hybrid, these systems are also useful tools in the process of development of interventions that are fully guided by MRI.

Advantages:

- provides high-quality anatomical information;
- affords excellent 3-dimensional visualization of cardiovascular structures;
- it is possible to obtain functional information such as cardiac wall motion;

- gadolinium late enhancement allows visualization of ablation lesions and myocardial scarring;
- there is no ionizing radiation.

Disadvantages:

- devices that are used during RFA, such as catheters, are not designed to be MRI-visible or MRI-compatible, as they often contain ferromagnetic materials or long electrical conductors. Much effort is being directed into making electrophysiology catheters that are both MRI-compatible and MRI-visible, although the routine use of such devices in patients remains to be established;
- the MRI technique can be noisy, and access to patients can be restricted;
- there is limited availability of XMR systems, and not many operators are accustomed to working in this environment.

My colleagues and I have developed an XMR guidance system for cardiovascular interventions, in particular for RFA. This system allows us to use both magnetic resonance and X-ray imaging for guidance [10]. A key step in the development of this system is to register magnetic resonance and X-ray images that are acquired during the procedure. This allows the overlay of cardiovascular anatomy recently acquired by MRI onto X-ray images, and the reconstruction of the position of catheters seen during X-ray fluoroscopy in this anatomy (*Figure 1*). Using this technique, we are also able to mark the position of ablation lesions on the 3-dimensional surface by automatically tracking the catheter tip. We are therefore able to delineate linear ablation lines (*Figure 2*).

Planned improvements to the technique include correction of the position of the MRI-derived surface to account for respiratory motion. It has been possible to take electrical information from electrical mapping systems and display this on our MRI-derived surface (*Figure 3*). Further improvements should allow fast interpolation of sparse electrical data points so that similar electroanatomic surfaces can be built using standard electrophysiology electrodes [11]. MRI-derived myocardial wall motion information has also been combined with electrical maps derived during the same procedure [12]. This information is being used to help build computer models that, in the future, may allow us to get electrical maps from motion data (*Figure 3*) [13]. Finally, in common with others, we are developing the tools needed to carry out the entire ablation procedure under MRI guidance. ■

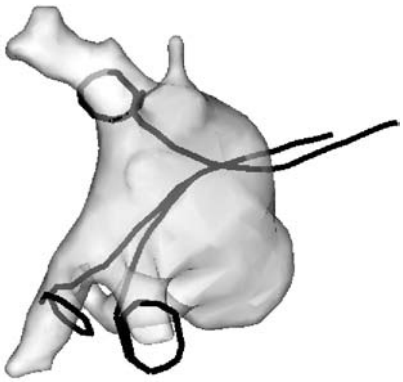

Figure 1. Magnetic resonance imaging (MRI) view of the left atrial endocardial surface showing the position of a helix ablation catheter during pulmonary vein isolation. The catheter position was derived using hybrid X-ray/MRI registration technology.

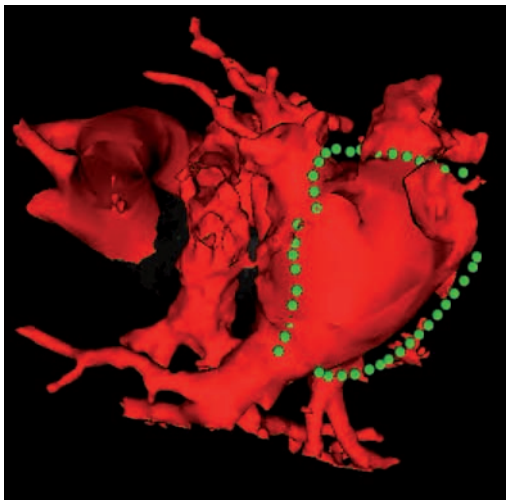

Figure 2. Magnetic resonance imaging (MRI) view of the left atrial endocardial surface (red) with the location of linear ablation points shown (green). The ablation points were marked onto the surface using hybrid X-ray/MRI registration technology during the course of the intervention.

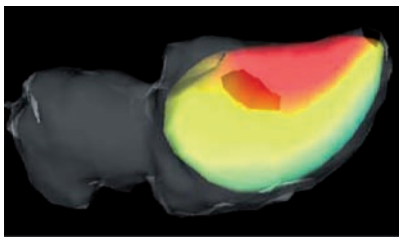

Figure 3. Magnetic resonance imaging (MRI) view of the left ventricular endocardial surface showing the mapped electrical activity during early systole. The electrical data were measured using the EnSite system and fused with the MRI data using hybrid X-ray/MRI registration technology.

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New therapeutic approaches in atrial fibrillation

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Abstract

In patients with atrial fibrillation, a decision must be made whether to accept the arrhythmia (rate-control strategy) or to pursue restoration and subsequent maintenance of sinus rhythm (rhythm-control strategy). Previous randomized trials have shown no difference between these strategies with respect to morbidity, mortality, or quality of life. However, new non pharmacological rhythm-control treatment strategies have emerged and have improved the likelihood of long-term maintenance of sinus rhythm tremendously.

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Keywords: Atrial fibrillation, antiarrhythmic drugs, anticoagulation, radiofrequency ablation, treatment

Introduction

From two large randomized trials [1,2] it has been learned that, in patients with atrial fibrillation who are not severely symptomatic, a rate-control strategy is not inferior to a rhythm-control strategy. A subanalysis in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management trial, however, demonstrated that a successful rhythm-control strategy was associated with improved survival [3]. Furthermore, the optimal heart rate during atrial fibrillation remains unknown and is currently being investigated in a large multicenter trial [4]. These facts, and the improving success rate of new treatment strategies to cure atrial fibrillation, further the discussion of rate versus rhythm control. New insights will be briefly discussed here, including the issue of prevention of thromboembolic complications.

New antiarrhythmic drugs

The classic Vaughan-Williams classes I, II, and III drugs used for prevention of atrial fibrillation are frequently ineffective. For instance, in the Rate Control Efficacy in Permanent Atrial Fibrillation trial, maintenance of sinus rhythm at study completion in the rhythm-control group was only 39% [2]. In addition, these drugs have serious potential cardiac and non cardiac side effects. Other more effective and safer drugs have therefore been investigated in preclinical and clinical trials. First, class III drugs have emerged that have a mechanism of action similar to that of amiodarone, but do not have the side effects. These drugs include azimilide, dronedarone, tedisamil, and SSR149744C [5–8]. Secondly, atrial-selective ion channel blockers, including AZD7009, AVE0118, and RSD1235, are a promising new group of antiarrhythmic drugs [9–11]. Finally, drugs preventing structural remodeling, inflammation, and fibrosis (''upstream antiarrhythmic drugs''), including ACE inhibitors, angiotensin receptor blockers, statins, and aldosterone blockers, may target the underlying substrate and therefore prevent atrial fibrillation [12–15].

Anticoagulation

Atrial fibrillation is associated with a 5-fold increased risk of stroke. As the risk of ischemic stroke in patients

with atrial fibrillation is related to lack of or inadequate anticoagulation, regardless of rhythm management strategy [1], restoration of sinus rhythm does not obviate the use of anticoagulant drugs in patients with increased risk of ischemic stroke. Coumarins increase the risk of hemorrhagic stroke and require frequent adjustments to the dosage. Therefore alternatives are sought.

The direct thrombin antagonist, ximelagatran, has been shown to be equally effective in prevention of stroke when compared with coumarins [16,17]. The main advantage of ximelagatran over coumarins is the predictable dose–response relationship; however, because of hepatotoxicity, production of ximelagatran has been discontinued. New, similar drugs such as dabigatran are currently under investigation.

The AMADEUS (The Atrial fibrillation trial of Monitored, Adjusted Dose Vitamin K antagonist, comparing Efficacy and safety with Unadjusted SanOrg 34006/idraparinux) trial comparing the heparin analog, idraparinux, with warfarin in patients with atrial fibrillation was terminated prematurely because more bleeding complications were observed in the group treated with idraparinux.

The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events, comparing the combination treatment of clopidogrel and aspirin with warfarin in patients with atrial fibrillation and at least one risk factor for stroke, was also stopped because the efficacy was clearly in favor of anticoagulation [18]. Furthermore, there was also no reduction in bleeding in the group treated with clopidogrel plus aspirin. Thus, up to now, alternatives for coumarins are not available, and data on new drugs are eagerly awaited.

Radiofrequency ablation and surgery

In recent years, invasive techniques have been developed in treating atrial fibrillation. Originally, linear ablations were performed, mimicking the surgical MAZE procedure. However, since the observation was made that the pulmonary veins have an important role in the initiation and maintenance of atrial fibrillation [19], there has been a rapid development of techniques targeting the pulmonary veins, using either a transvenous endocardial approach or a surgical epicardial approach. The most widely used methods are segmental ablation, targeting myocardial tissue in the myocardial sleeves around the pulmonary veins [19], and circumferential pulmonary vein isolation, completely encircling the pulmonary veins [20].

Wazni et al [21] compared pulmonary vein isolation and the use of antiarrhythmic drugs as treatment of first choice in patients with atrial fibrillation. After 1 year of follow-up, 63% of the patients receiving antiarrhythmic drugs had experienced one or more recurrences of atrial fibrillation, compared with only 13% of patients who had undergone venous ablation. Pulmonary vein isolation is especially effective in patients with paroxysmal atrial fibrillation [22]. New data also show promising results in patients with heart failure [23] and chronic atrial fibrillation [24].

However, in the abovementioned studies, follow-up was short and the patients were relatively young (mean age approximately 55 years). Only a small proportion had clinically significant structural heart disease, including the patients with heart failure [24]. Therefore, these individuals differed essentially from the typical 70-year-old patient with atrial fibrillation and hypertension or coronary heart disease. Furthermore, radiofrequency ablation in the left atrium is associated with important risks, including stroke, pulmonary vein stenosis, tamponade, and formation of an atrio–esophageal fistula [25]. Therefore, in the search for better success rates and fewer complications, techniques implementing new energy sources [26] and new approaches are being developed and investigated, including epicardial ablation procedures by (minimally invasive) surgery [27–29]. The first results are very promising and will further current discussion as to the most favorable treatment for patients with atrial fibrillation. ■

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Modulation of metabolic changes in patients with heart failure by selective inhibition of 3-ketoacyl coenzyme A thiolase

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Abstract

A direct approach to manipulating cardiac energy metabolism consists of modifying substrate utilization by the heart. Pharmacological agents that directly inhibit fatty acid oxidation include inhibitors of 3-ketoacyl coenzyme A thiolase, the last enzyme involved in β-oxidation. The most extensively investigated agent of this group of drugs is trimetazidine. Clinical studies have shown that trimetazidine can substantially increase the ischemic threshold in patients with effort angina. However, the results of current research also support the concept that shifting the energy substrate preference away from fatty acid metabolism and toward glucose metabolism by the use of trimetazidine could be an effective adjunctive treatment in patients with heart failure, in terms of improvement in left ventricular and endothelial function and glucose metabolism. The recent literature on the protective effects of this new class of drugs on left ventricular dysfunction is reviewed and discussed.
■ *Heart Metab.* 2006;33:21–24.

Keywords: Trimetazidine, heart failure, left ventricular function, glucose metabolism, free fatty acids

Introduction

Wasting of subcutaneous fat and skeletal muscle are relatively common in heart failure and suggest an increased utilization of non carbohydrate substrates for energy production [1]. In fact, fasting blood ketone bodies [2], and fat oxidation during exercise [3], have been shown to be increased in patients with heart failure. Insulin resistance has been found to be associated with heart failure [4] and the consequent impaired suppression of lipolysis could determine the development of ketosis. Experimental studies have shown that sodium dichloroacetate stimulates pyruvate dehydrogenase activity by inhibiting pyruvate dehydrogenase kinase [5]. Stimulation of pyruvate dehydrogenase activity leads to enhanced glycolysis of glucose and utilization of lactate by the myocardium for aerobic respiration. Myocardial consumption of free fatty acids is simultaneously inhibited, with the overall effect of a change of substrate utilization from predominantly non esterified free fatty acids to glucose and lactate [6], finally resulting in improved left ventricular mechanical efficiency [7].

A number of different approaches have been used to manipulate energy metabolism in the heart. These involve both indirect measures and the use of agents that act directly on the heart to shift energy substrate utilization away from fatty acid metabolism and towards glucose metabolism, which is more efficient in terms of ATP production per mole of oxygen utilized. One approach consists of directly modifying

substrate utilization by the heart. Trimetazidine 1 (2,3,4, trimethoxybenzyl-piperazine dihydrochloride) has been shown to affect myocardial substrate utilization by inhibiting oxidative phosphorylation and by shifting energy production from free fatty acid to glucose oxidation [8]. Despite experimental evidence indicating that this effect is predominantly caused by a selective block of long-chain 3-ketoacyl coenzyme A thiolase [9], the last enzyme involved in β-oxidation, this issue remains controversial [10,11]. Recent studies have outlined the potential benefits of this agent on regional and global myocardial dysfunction. These beneficial effects can be explained by the fact that, by increasing the utilization of glucose and lactate, which are more efficient fuels for aerobic respiration, the efficiency of oxygen consumption of the myocardium can be improved by 16–26% [12].

In this paper we will review and summarize the reported evidence on the protective effects of trimetazidine on left ventricular dysfunction and its potential clinical application in patients with heart failure.

Effects of metabolic modulation with trimetazidine in left ventricular dysfunction

On the basis of the hypothesis that trimetazidine could act as a metabolic modulator in the protection of ischemic myocardium, Brottier and colleagues [13] assessed the value of long-term treatment with trimetazidine in patients with severe ischemic cardiomyopathy who were already receiving conventional therapy. Twenty patients were allocated randomly to groups receive to either placebo or trimetazidine. At 6-month follow-up, all the patients receiving trimetazidine reported a clinically considerable improvement in symptoms and showed a greater ejection fraction than those receiving placebo. The investigators concluded their study, recommending the use of trimetazidine as a complementary therapeutic tool in patients with severe ischemic cardiomyopathy.

On the basis of these findings, the effects of trimetazidine on dobutamine-induced left ventricular dysfunction in patients with angiographically proven coronary artery disease were assessed [14]. Patients were blindly and randomly assigned to a 15-day period of treatment with either placebo or trimetazidine; they were then crossed over to the other regimen for another 15 days. At the end of each period of treatment, a stress echo test with dobutamine was performed. Both in the resting condition and at peak infusion of dobutamine, the wall motion score index was significantly lower with trimetazidine therapy than with placebo. Furthermore, trimetazidine induced an increase in both the dose of dobutamine administered and the duration of dobutamine infusion before the development of ischemia. These results indicated that trimetazidine may not only protect from dobutamine-induced ischemic dysfunction, but could also improve resting regional left ventricular function, as shown by the significantly decreased peak and resting wall motion score index, during the active treatment period. A subsequent study confirmed these preliminary results [15].

At that point it became a priority to gain an understanding both of the mechanisms beyond the observed improvement in resting left ventricular function induced by trimetazidine and of whether this effect could also be operative in patients for whom left ventricular dysfunction represented the main clinical problem.

Modulation of myocardial metabolism by trimetazidine in postischemic heart failure

Keeping in mind the concept that trimetazidine should, therefore, be able to promote the utilization of glucose and non fatty substrates by the mitochondria, attention was focused on heart failure, in which maintenance of metabolic efficiency is a crucial issue.

In diabetic patients with ischemic dilated cardiomyopathy, the effects of the addition of trimetazidine to standard treatment were assessed, as judged by symptoms, exercise tolerance, and left ventricular function [16]. Thirteen such patients who were receiving conventional therapy were randomly allocated in a double-blind fashion, first to receive either placebo or trimetazidine, each arm lasting 15 days, and then again to receive placebo or trimetazidine for two additional periods of 6 months. In both the short and the long term, trimetazidine showed a significant beneficial effect on left ventricular function and control of symptoms, compared with placebo (*Figure 1*). The observed short-term benefit of trimetazidine was maintained in the long term and contrasted with the natural history of the disease, as shown by the mild but consistent decrease in ejection fraction while patients were receiving placebo. These results paved the way to additional studies, which have invariably confirmed the positive effects of trimetazidine in patients with postischemic left ventricular dysfunction [17–19].

Modulation of myocardial metabolism by trimetazidine in heart failure of different etiologies

The beneficial effect of trimetazidine on left ventricular function has been attributed to preservation of intracellular concentrations of phosphocreatine and ATP [20]. Previous clinical studies using

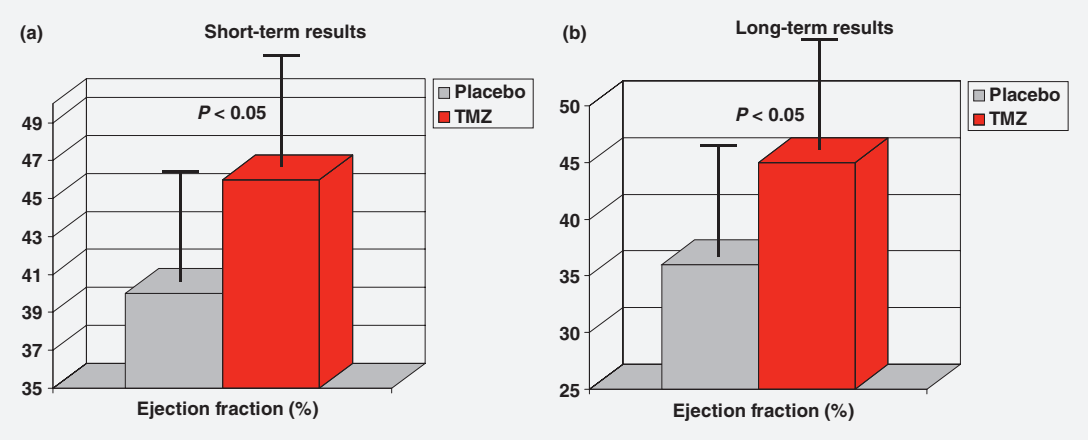

Figure 1. (a) Short-term and (b) long-term effects of trimetazidine (■) and placebo (□) on ejection fraction in diabetic patients with postischemic cardiomyopathy. The histograms demonstrate the significant beneficial effects (mean ± 1 SD) of trimetazidine compared with placebo. (Modified from Fragasso et al. [16], with permission.).

phosphorus-31 magnetic resonance spectroscopy to measure phosphocreatine : ATP (PCr : ATP) ratios in human myocardium have shown that this ratio is reduced in failing human myocardium [21]. The PCr : ATP ratio is a measure of myocardial energetics and its reduction may be related to an imbalance between myocardial oxygen supply and demand [22], and a reduction in the total creatine pool, a phenomenon known to occur in heart failure [23]. In a recent study performed in patients with heart failure of different etiologies who were receiving full standard medical treatment, we observed that the trimetazidine-induced improvements in functional class and left ventricular function were associated with an improvement in the PCr : ATP ratio, supporting the hypothesis that trimetazidine probably preserves the intracellular concentrations of myocardial high-energy phosphate [24]. These results appear to be of particular interest, especially in view of previous evidence indicating the PCr : ATP ratio is a significant predictor of mortality [25].

On the basis of the results of that pilot study, we tested whether trimetazidine, added to usual treatment, could also be beneficial in a more consistent group of patients with systolic-dysfunction heart failure of different etiologies [26]. Compared with patients receiving conventional treatment alone, those receiving trimetazidine exhibited improvement in functional class, exercise tolerance, quality of life, and left ventricular function (ejection fraction; *Figure 2*), and used reduced amounts of diuretic drugs and of digoxin. The plasma concentration of B-type natriuretic peptide was also significantly reduced in the patients receiving trimetazidine, compared with those given conventional therapy alone.

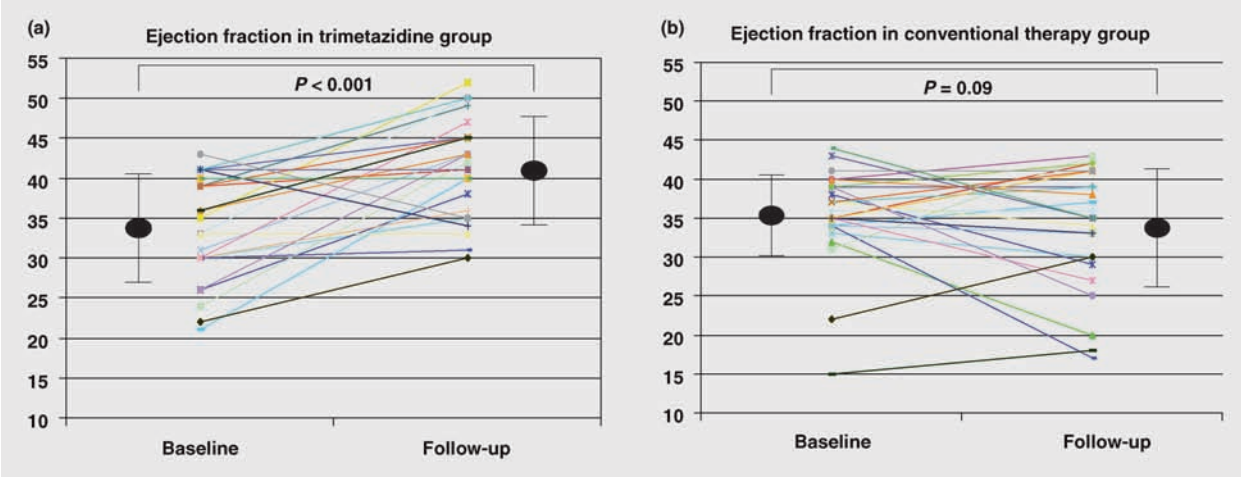

Figure 2. Long-term effects of (a) trimetazidine and (b) placebo on ejection fraction in patients with heart failure of different etiologies. The figure shows a clear beneficial effect on ejection fraction (individual values and mean ± 1 SD) of trimetazidine compared with placebo. (Modified from Fragasso et al [26], with permission.).

These data confirm that selective inhibition of 3-ketoacyl coenzyme A thiolase by trimetazidine represents a new therapeutic window in the treatment of patients with systolic-dysfunction heart failure of different etiologies, not only that secondary to ischemic heart disease.

Conclusions

Metabolic modulators such as trimetazidine could have an important role in the therapeutic strategy for patients with heart failure. Shifting the energy substrate preference away from fatty acid metabolism and toward glucose metabolism by the use of trimetazidine could also be an effective adjunctive treatment in patients with heart failure, in terms of improving their left ventricular metabolism and function. These effects seem to operate in heart failure syndromes regardless of their etiopathogenetic cause, and are not confined to those of ischemic origin. Although it seems highly likely that these benefits would translate into improved survival, a multicenter trial is required to ascertained whether this is indeed the case. The time has come to test this huge potential therapeutic advancement in heart failure syndromes, which still suffer very high rates of morbility and mortality. ■

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Anderson–Fabry disease: an important differential diagnosis in patients with unexplained left ventricular hypertrophy

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Abstract

Anderson–Fabry disease is an X-linked lysosomal storage disorder that results in a deficiency of the enzyme α-galactosidase A. Previously believed to be rare, Anderson–Fabry disease is present in 4–5% of men with unexplained left ventricular hypertrophy or cryptogenic stroke. In this case report, a female patient with Anderson–Fabry disease and left ventricular hypertrophy is described. In addition to highlighting the importance of cardiac disease in female heterozygotes, the case also illustrates the importance of taking a careful family history in establishing the diagnosis of Anderson–Fabry disease within an affected family.

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Keywords: Anderson–Fabry disease, left ventricular hypertrophy, women

Case report

Mrs X presented for the first time in 1995 when she was assessed by her general practitioner for hormone replacement therapy. She complained of no cardiac symptoms and was normotensive, but a routine electrocardiogram was abnormal, with evidence of left ventricular hypertrophy. Subsequent echocardiography confirmed the presence of concentric left ventricular hypertrophy. No further evaluation or management was suggested.

In 2004, Mrs X started to experience chest pain and dyspnea when walking up stairs and inclines. On systematic questioning she complained of tinnitus. A careful family pedigree was taken (*Figure 1*). Her sister in Australia had been diagnosed with hypertrophic cardiomyopathy and had a son in his mid-30s with end-stage renal disease. Mrs X's mother, sister, and daughter had a history of deafness. In 2003, her brother had presented at the age of 70 years with presyncopal ventricular tachycardia associated with a small increase in serum, troponin. Coronary angiography demonstrated no flow-limiting stenosis and he received an internal cardioverter defibrillator. He subsequently presented with an episode of transient right hemiplegia and syncope with transient amnesia.

Clinical examination of Mrs X revealed a regular pulse of 60 beats/min and a blood pressure of 130/80 mm Hg. No other abnormalities were found. The electrocardiogram (*Figure 2*) demonstrated left atrial enlargement and left ventricular hypertrophy, with repolarization abnormalities in leads I, II, aVL, and V4–6. Echocardiography demonstrated concentric left ventricular hypertrophy, with a maximum left ventricular wall thickness of 18 mm and mild right ventricular hypertrophy (*Figure 3*). Conventional measures of systolic function were normal, but the Doppler study suggested the presence of increased left ventricular filling pressure. There was

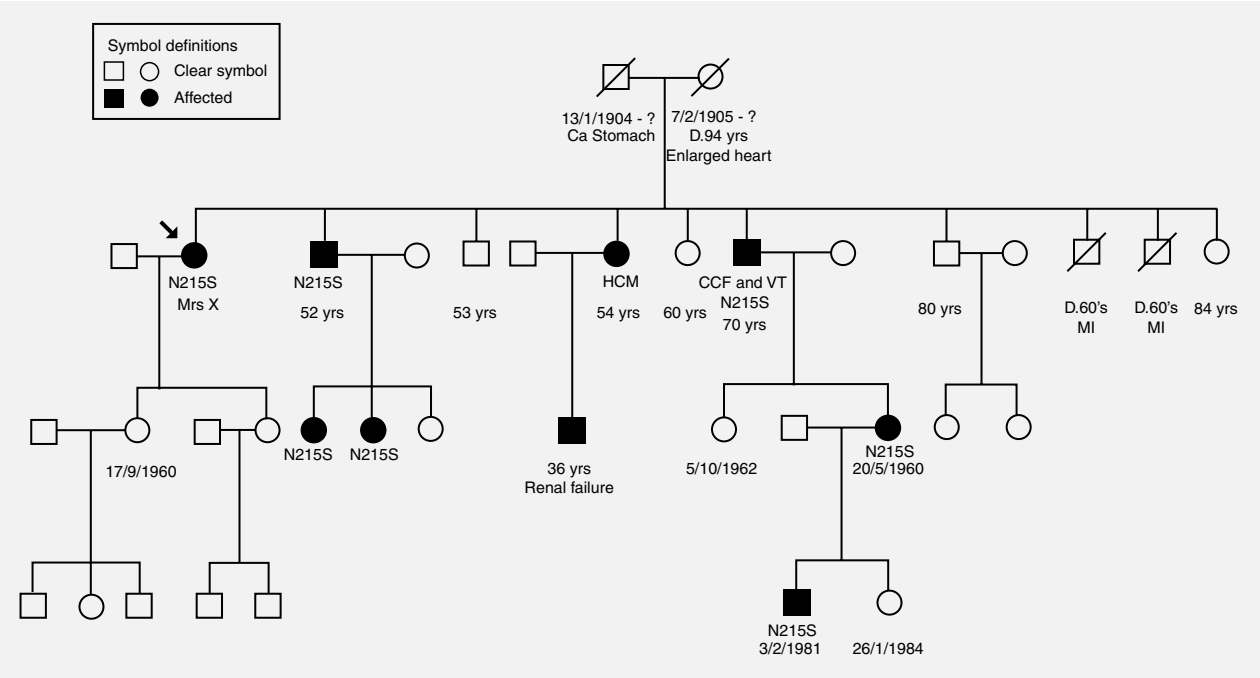

Figure 1. Family pedigree. At the time of presentation, there was a family history of cardiomyopathy and renal disease. The results of genotyping are shown (carriers of N215S mutation). Open symbols, clear; solid symbols, affected.

incomplete systolic anterior motion of the mitral valve, without evidence of left ventricular outflow tract obstruction and obliteration of the mid-ventricular cavity in systole. The left atrium was mildly dilated, at 45 mm.

In view of the concentric distribution of hypertrophy and the family history of deafness, cardiomyopathy, and renal disease, plasma α-galactosidase A was measured and found to be within the diagnostic range for Anderson–Fabry disease (2.14 nmol/h per ml; normal range 4–21.9 nmol/h per ml). Subsequent genetic analysis demonstrated that Mrs X was heterozygous for an AAT→AGT mutation at codon 215 of exon 5, resulting in an $Asn^{215}Ser$ (N215S) substitution.

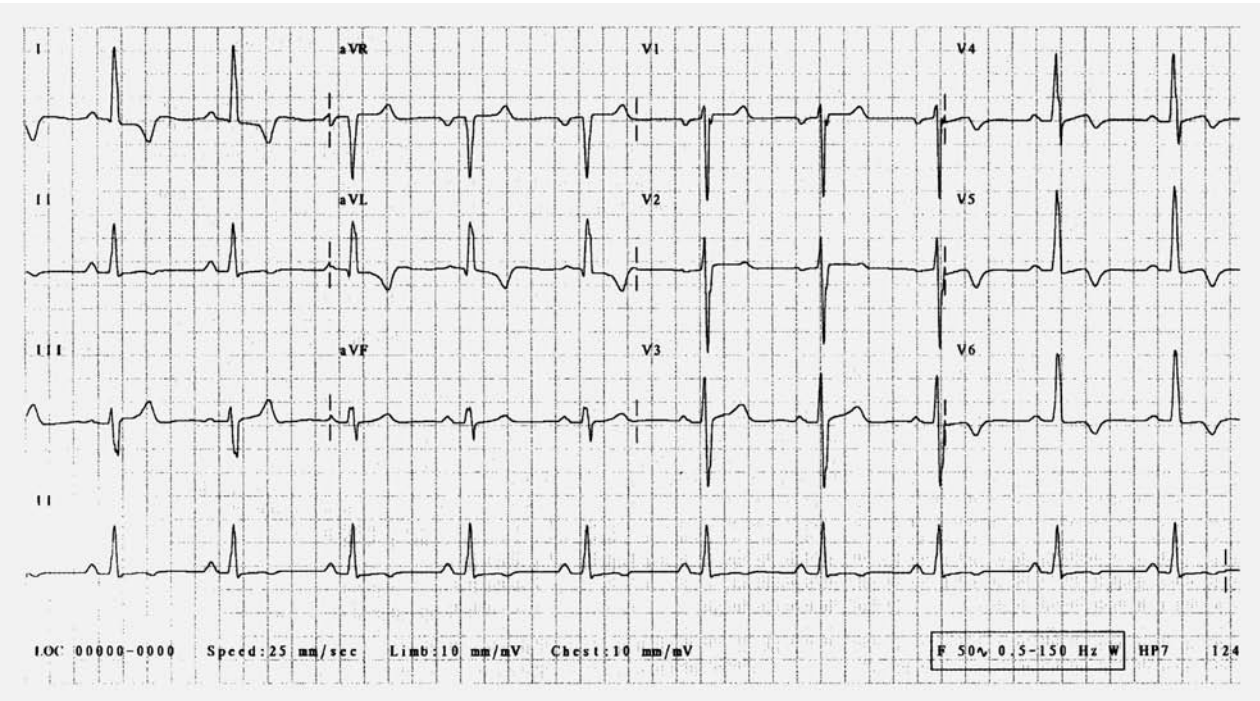

Figure 2. Standard 12-lead electrocardiogram demonstrating left ventricular hypertrophy and left atrial enlargement.

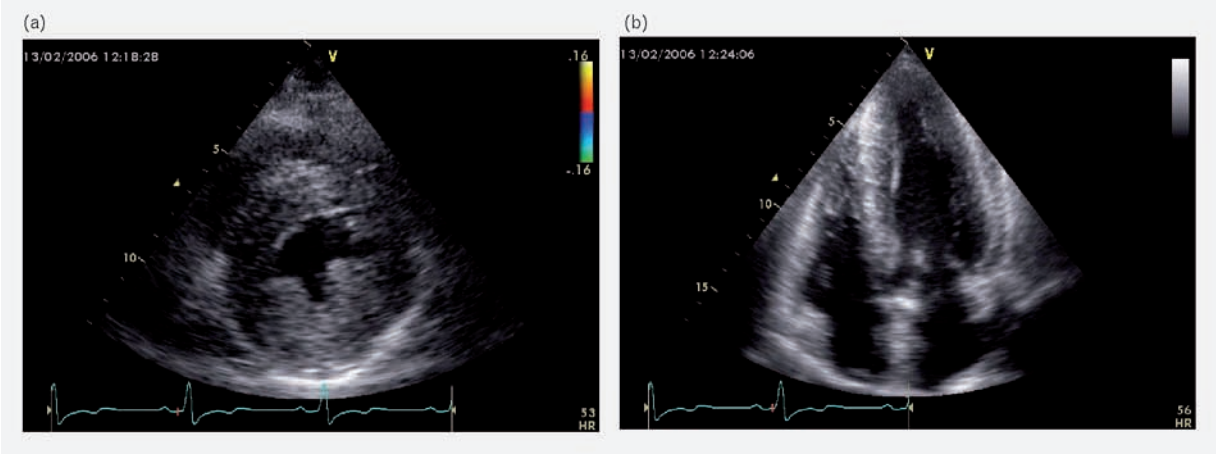

Figure 3. (a) Two-dimensional echocardiogram showing short-axis view of the left ventricle at mitral valve level. There is concentric left ventricular hypertrophy, with enlargement of the papillary muscles. (b) Two-dimensional echocardiogram showing apical four-chamber view. There is hypertrophy of both the left and right ventricles.

The same mutation was identified in other affected family members (*Figure 1*).

Because of her chest pains, Mrs X was advised to undergo coronary angiography, but she declined to do so. Further evaluation demonstrated a glomerular filtration rate of 81 ml/min and hearing loss to all frequencies on the left. In view of her mild renal impairment, tinnitus, and significant cardiac disease, she was commenced on treatment with agalsidase alfa (Replagal) in 2005.

Discussion

Anderson–Fabry disease is caused by mutations in the gene encoding the lysosomal enzyme α-galactosidase A [1,2]. This results in reduced or absent α-galactosidase A activity and intra-lysosomal accumulation of neutral glycosphingolipids, mainly globotriaosylceramide (Gb3), in various organ systems. Anderson–Fabry disease is characterized by progressive clinical manifestations and premature death from renal disease, stroke, and cardiac disease [1–4].

Historically, Anderson–Fabry disease has been believed to be a rare disease, but a recent study using an α-galactosidase A assay on blood spots from 37 104 consecutive Italian male neonates, has demonstrated a prevalence of 0.03% and an incidence of α-galactosidase A deficiency of 1 in 3100, with an 11 : 1 ratio of patients with the later-onset as opposed to the classic phenotype [5]. These data are in accordance with findings of studies that have reported a prevalence of 0.2–1.2% in patients with end-stage renal disease on hemodialysis and 4.9% in men with cryptogenic stroke [6,7]. The prevalence of Anderson–Fabry disease in men with unexplained left ventricular hypertrophy is reported to be at least 3–4% and may be greater in studies that have used endomyocardial biopsy as a screening tool [8–10].

Although many symptoms occur in childhood, a correct diagnosis can be delayed by as much as 14 years in males and 16 years in females (Fabry Outcome Survey) [2]. In males, symptoms often start in the first decade of life with acroparesthesias and pain, febrile crises, hypohidrosis, heat intolerance, gastrointestinal disturbance, and the development of cutaneous angiokeratomata. From the second decade onwards, patients develop proteinuria and neurological manifestations, including vestibular and hearing disturbance, and autonomic dysfunction. Cardiac involvement is present early in life, but is not detected clinically until the third or fourth decade [1–4]. The main causes of death are end-stage renal disease, heart failure, arrhythmia, and stroke.

The "cardiac variant"

A number of reports have suggested that some patients with residual α-galactosidase activity (approximately 1–5% of normal values) present in middle age with left ventricular hypertrophy and conduction disease, in the absence of other classical disease manifestations [1,8,9]. Patients with this so-called "cardiac variant" may have proteinuria, but are said not to develop end-stage renal disease. Contemporary studies have suggested that the term "cardiac variant of Anderson–Fabry disease" is a misnomer, as rigorous clinical characterization usually reveals disease in other organs. Nevertheless, clinical presentation in patients with residual activity may be dominated by cardiovascular signs and symptoms.

Genetics of Anderson–Fabry disease

Anderson–Fabry disease results from mutations in the α-galactosidase gene, located on the long arm of the X chromosome (Xq22.1) [1,11–14]. The gene consists of seven exons that encode a 101 kDa homodimeric

glycoprotein that exists in a number of natural forms defined by different sialic acid residues on carbohydrate chains. More than 200 mutations have been described in all seven exons, the majority of which are missense point mutations [1,12–14].

Reduced enzyme activity occurs by several mechanisms, including abnormal/unstable protein folding, perturbation of the active binding site, and defects in enzyme tracking to the lysosome [1,14,15]. More than 90% of the described mutations are associated with the classical phenotype [1] and fewer than 20 are associated with the so-called cardiac phenotype. The N215S mutation that was responsible for disease in Mrs X is a missense mutation that results in abnormal glycosylation [14,15]. In the first descriptions of this mutation, the clinical phenotype was typically mild. As can be seen in this case study, however, expression varies enormously between individuals.

Disease in females

Disease manifestations were believed to be rare or mild in female carriers, but data from the Fabry Outcome Survey and other sources show that most affected women have signs or symptoms of disease, with a similar prevalence of fatigue and neurological and gastrointestinal symptoms as in men [2–4]. Despite a lower prevalence of left ventricular hypertrophy, females have a similar prevalence of cardiac symptoms such as angina, dyspnea, and palpitations. The frequency of symptoms and signs related to Anderson–Fabry disease increases with age in both men and women, and it has been suggested that females with Anderson–Fabry disease have a 15-year reduction in their lifespan when compared with the general population [3].

The findings of a twin study have suggested that the mechanism of non random X inactivation (lyonization) may result in disease expression in females [16]. This hypothesis was further strengthened by a recent study that demonstrated a higher Mainz Severity Score (a validated score for disease severity) in females with non random X inactivation demonstrated in peripheral blood, compared with those without [11].

Enzyme replacement therapy

There are two recombinant enzyme preparations approved for the treatment of Anderson–Fabry disease in Europe: agalsidase-alpha (produced in human fibroblasts) and agalsidase-beta (produced in a Chinese hamster ovarian cell line). Enzyme uptake is mediated by mannose-6-phosphate, mannose, and asialoglycoprotein receptors. Several studies have shown that these preparations can improve neurological and renal function, in addition to quality of life [17–21]. A phase 3 trial using agalsidase-alpha has demonstrated an improvement in duration of the QRS complex [17] and Gb3 clearance from vascular endothelial cells [18]. Case reports and observational clinical studies have shown improvements in left ventricular size and function with both treatments [22–24].

As Anderson–Fabry disease is an X-linked disease, sex has a major influence on cardiac involvement. Although definitive proof of the long-term beneficial effects of enzyme replacement therapy in men and women with disease are awaited, Mrs X was considered to have sufficient organ involvement to warrant treatment.

Conclusions

Cardiovascular disease accounts for much of the morbidity associated with Anderson–Fabry disease in men and women. This case illustrates the importance of Anderson–Fabry disease as a cause for otherwise unexplained cardiac hypertrophy in both men and women. It also shows how careful systematic questioning and a detailed family pedigree can provide clues to the diagnosis.

Conflict of interest

Dr Elliott acts as a consultant for Genzyme Inc. and Shire Human Genetics Therapies. He is a member of the International Board of The Fabry Outcome Survey (FOS). ■

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Cellular changes in atrial fibrillation

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Abstract

Chronic atrial fibrillation represents one of the main risk factors for the occurrence of thromboembolic events. At present it is clear that thrombus formation is triggered, not only by irregular rhythm, but also by reduced intrinsic atrial contractility. Apart from the thromboembolic risk, reduced atrial contractility might contribute to reduced cardiac output in patients with ventricular heart disease. Hence, the clinical importance of atrial dysfunction induced by atrial fibrillation prompts research into the underlying mechanisms involved in reduced atrial contractility that may serve to develop new therapeutic strategies. This review addresses both structural and functional cellular alterations involved in contractile dysfunction associated with chronic atrial fibrillation.
■ *Heart Metab.* 2006;33:31–34.

Keywords: Atrial fibrillation, contractility, cardiomyocyte function, contractile proteins

Introduction

Atrial fibrillation, the most common sustained cardiac arrhythmia in humans, is characterized by severe electrophysiological and structural changes. A profound cellular remodeling process takes place during persistent atrial fibrillation, which is reversible after cardioversion [1,2]. However, upon cardioversion, reversal of the atrial contractile dysfunction that is induced by atrial fibrillation varies with the duration of the atrial fibrillation before cardioversion, and may take weeks to months [3].

Reduced atrial contractility may be caused by ultrastructural and functional changes (*Figure 1*). The structural alterations involved in cellular remodeling in response to chronic atrial fibrillation include loss of myofibrils (myolysis) [1,4], accumulation of glycogen, changes in mitochondrial shape and size, and fragmentation of the sarcoplasmic reticulum [1]. These ultrastructural changes are representative for dedifferentiated cardiac tissue as observed during cardiac development. Apart from ultrastructural changes, impaired cardiomyocyte function may also contribute to reduced atrial contraction induced by chronic atrial fibrillation. This may also be detrimental after cardioversion, when the normal electric rhythm is restored.

Factors involved in cardiomyocyte function

Cardiomyocyte contractility is determined by the amount of calcium released into the cytosol and the responsiveness of the contractile apparatus to calcium. During an action potential, voltage-dependent L-type calcium channels are opened and calcium enters the cell (*Figure 2*). This calcium influx induces the release of calcium stored inside the sarcoplasmic reticulum via the ryanodine receptor into the cytosol: the calcium-induced calcium release mechanism [5]. The cardiomyocyte contracts when a molecular interaction takes place between the contractile proteins, actin and myosin, which is triggered by the increase in cytosolic calcium and is driven by the energy from ATP hydrolysis. Calcium binds to the troponin complex, inducing cardiomyocyte contraction by the formation of crossbridges between the thin (actin) and thick (myosin) myofilaments. Relaxation results from detachment of calcium from the troponin complex and removal of calcium from the cell via the

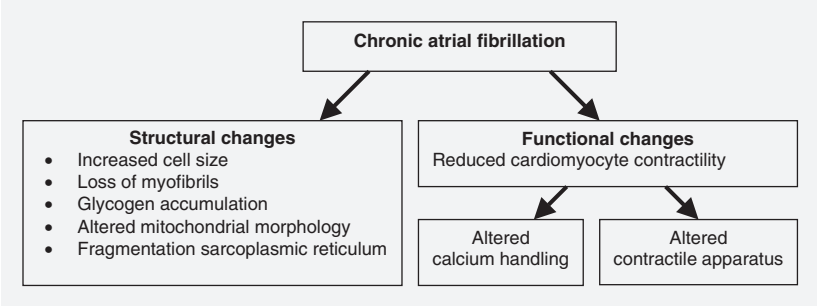

Figure 1. Factors involved in reduced atrial contractility.

sarcolemmal Na^+–Ca^{2+} exchanger and back into the sarcoplasmic reticulum via the sarcoplasmic reticulum Ca^{2+}-ATPase, the activity of which is regulated by an associated protein, phospholamban. Depressed cardiomyocyte contractility may originate from impaired calcium handling, myofilament contraction, or both, as a result of alterations in the regulatory proteins involved.

Reduced cardiomyocyte contractility in chronic atrial fibrillation

The contractile force measured in atrial muscle strips from patients with persistent atrial fibrillation (that is, of at least 3 months' duration) was reduced by 75% in comparison with that in patients in sinus rhythm [6]. The reduction in force development could be partly explained by myolysis (reduction in contractile proteins). Although contractile remodeling of the atria has been recognized for several decades [7], the intrinsic cellular mechanisms responsible for contractile dysfunction induced by atrial fibrillation remain poorly understood.

Altered calcium handling contributes significantly to this contractile dysfunction, and mainly involves alterations in transmembrane calcium transport, rather than changes in calcium handling by the sarcoplasmic reticulum. A decreased function of the L-type calcium channels most probably explains reduced availability of cytosolic calcium during activation [6,8]. Impairment of the L-type calcium current is probably caused by altered phosphorylation of the channels involved, as a result of increased phosphatase activity [9]. In addition, upregulation of the Na^+–Ca^{2+} exchanger might increase removal of calcium from the cell, further diminishing the amount of calcium available for contraction [8]. Calcium storage in the sarcoplasmic reticulum seems to be preserved, as no changes have been found in the expression of sarcoplasmic reticulum calcium ATPase, phospholamban, and the ryanodine receptor [8].

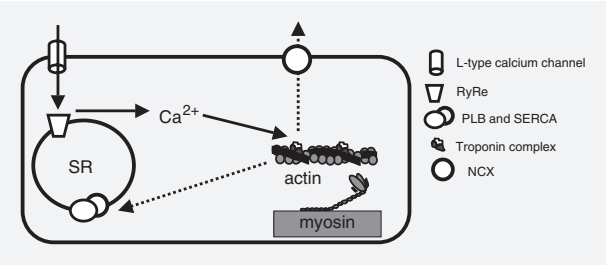

Figure 2. Calcium handling and contractile proteins involved in cardiomyocyte contraction. NCX, Na^+–Ca^{2+} exchanger; PLB, phospholamban; RyRe, ryanodine receptor; SERCA, sarcoplasmic reticulum calcium ATPase; SR, sarcoplasmic reticulum.

In addition to impaired calcium handling, a reduction in the force-generating capacity of the contractile apparatus may contribute to reduced cellular contractility. Recent studies on the composition of contractile proteins, comparing patients with chronic atrial fibrillation and those in sinus rhythm, revealed several changes, in the status of both the expression and the phosphorylation of contractile proteins.

Each myosin molecule is composed of two heavy chains (MHC), each with two light chains (LC-1 and LC-2). Human atrial tissue predominantly expresses the faster (higher ATPase activity) α-MHC, but also contains the slower β-MHC [10]. The relative expression of β-MHC is increased in patients with chronic atrial fibrillation [11,12]. Despite a reduction in speed of contraction, the shift from α- to β-MHC may be beneficial because less energy is required to maintain pump function at rest. However, as the contribution of atrial contraction to cardiac output becomes more important in patients with ventricular dysfunction [13], reduced velocity of atrial contraction may impair ventricular filling and reduce cardiac output in patients with heart failure.

The essential light chain (LC-1) and regulatory light chain (LC-2) tune the function of the myosin head [14] and influence the maximum force-generating capacity and its sensitivity to calcium. In patients with atrial fibrillation, a decrease was observed in the expression of both atrial light chains normalized to actin, suggesting a loss (~25%) of atrial light chains in patients with atrial fibrillation [15]. Increased proteolysis of light chains may be the result of increased calpain activity, as observed in human atrial

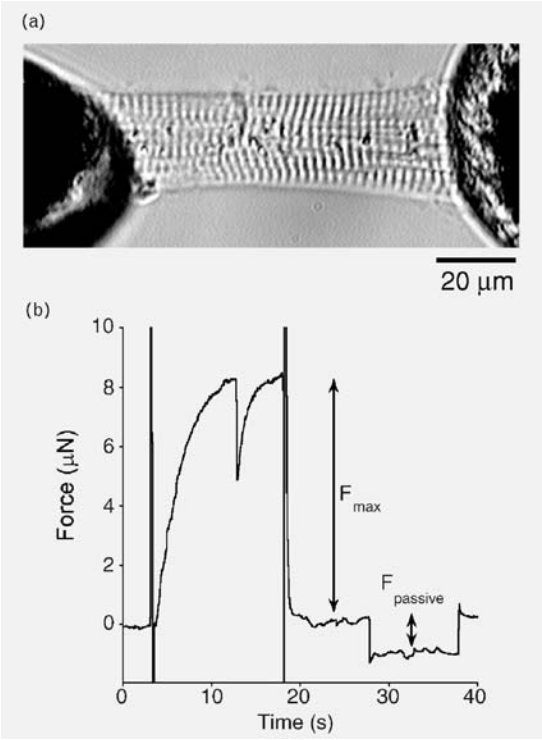

Figure 3. Force measurements in a human atrial cardiomyocyte.(a) A single human cardiomyocyte was glued between a force transducer and piezoelectric motor and force was measured at different calcium concentrations. (b) Force registration at maximal calcium concentration. F_{max}, maximal activated force; $F_{passive}$, passive force at low calcium concentration.

fibrillation [4]. In contrast, desmin content in the patients with atrial fibrillation was markedly increased, as was evident from a large increase (70%) in the desmin : actin ratio [15]. In addition, the phosphorylation status of troponin T was increased in human atrial fibrillation. Studies in rodent myocardium indicated a central role for protein kinase C-mediated phosphorylation of the troponin T in decreasing maximal force. Force measurements in permeabilized atrial cardiomyocytes (*Figure 3*) showed a reduction of 33% in the maximum force-generating capacity in human atrial fibrillation and a decrease in contraction. Thus, apart from myolysis and impaired calcium handling, a reduction in velocity of contraction and in the maximal force-generating capacity of the contractile apparatus may contribute to the contractile dysfunction induced by atrial fibrillation.

Future research

Recent evidence suggests an important role for oxidative stress in reducing myocardial function during atrial fibrillation [11,16–18]. Mihm et al. [11] showed an increased prevalence of protein oxidation, protein nitration, and protein carbonyl formation in patients with atrial fibrillation. Kim et al. [18] showed that myocardial activation of NAD(P)H oxidase and uncoupling of nitric oxide synthase have important roles in patients with paroxysmal and permanent atrial fibrillation. The major reactive oxygen species and their derivatives, reactive nitrogen species, are superoxide radicals ($O_2^{-\bullet}$), hydroperoxyl radicals ($HO_2^{\bullet}$), nitric oxide, and peroxynitrite ($ONOO^-$). Collectively, these radicals cause a loss of biological function through oxidation of the protein backbone or amino acid side chains, or both, which may lead to protein fragmentation and the formation of protein–protein crosslinkages, respectively. However, little is known about the target proteins and the functional implications of oxidative modifications in atrial fibrillation. Hence the prevention of protein oxidation provides new therapeutic strategies directed towards the prevention of structural remodeling and reduced contractility.

Summary

Upon cardioversion of chronic atrial fibrillation, both structural and functional cellular alterations contribute to a reduction in atrial contractile function. Atrial dysfunction induced by atrial fibrillation increases the risk of development of thromboembolisms and impairs ventricular filling and cardiac output in patients with ventricular heart disease. Insight to the mechanisms underlying the atrial remodeling that is induced by atrial fibrillation will provide a basis for new therapeutic strategies. ■

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Featured research

Abstracts and commentaries

The circadian clock within the cardiomyocyte is essential for responsiveness of the heart to fatty acids

Durgan DJ, Trexler NA, Egbejimi O, et al. *J Biol Chem*. 2006; In press.

It has long been appreciated that both experimental animals and humans exhibit diurnal variations in several cardiovascular parameters, including blood pressure, heart rate, electrical properties of the heart, and cardiac output. These rhythms have been ascribed primarily to fluctuations in neurohumoral influence during the day, which in turn are due to both environmental factors and the central circadian clock within the suprachiasmatic nucleus. Diurnal variations in physiological cardiovascular parameters have been attributed to the same factors (eg, sympathetic activity) responsible for diurnal variations in fatal cardiovascular events, which have an increased incidence in the early hours of the morning. However, few studies have investigated whether the intrinsic properties of the heart fluctuate during the day, or whether a loss of synchronization between the presence of a stimulus (eg, increased sympathetic activity in the early hours in the morning) and responsiveness of the heart plays a part in the instigation of contractile dysfunction.

One extracellular influence to which the heart must adapt rapidly is a change in circulating fatty acid concentrations. Fatty acids are the primary fuel source for the normal myocardium. However, fatty acids are more than just a fuel for cardiomyocytes, as they act as both structural and signaling precursors [1]. Consequently, a balance between fatty acid availability and rates of fatty acid β-oxidation must be maintained. If the latter fails, detrimental fatty acid derivatives accumulate within the myocardium, which has been linked to the pathogenesis of various cardiomyopathies. A major way in which the heart prevents accumulation of intracellular fatty acids during periods of increased availability is through induction of fatty-acid-responsive genes that promote β-oxidation. Increasing evidence exists in support of the hypothesis that the circadian clock *intrinsic to* the cardiomyocyte has a critical role in synchronizing cardiac metabolism with the environment. Circadian clocks are intracellular transcriptional mechanisms composed of positive and negative feedback loops, with a free running period of approximately 24 h. This molecular mechanism confers the selective advantage of anticipation, permitting the cell to respond rapidly to a given stimulus at the appropriate time of the day. The purpose of this study was to test the hypothesis that the circadian clock within the cardiomyocyte mediates diurnal variations in the responsiveness of the heart to fatty acids.

Commentary

Two strategies were used in this research: investigation of the responsiveness of cardiomyocytes to fatty acid ex vivo, and disruption of the circadian clock within the heart in vivo, through disruptions of either the light/dark cycle or metabolic genetics. Oscillations in metabolic genes were observed in vitro only under conditions in which the circadian clock was operational; furthermore, they exhibited the same temporal pattern as observed in the intact heart in vivo, when compared with circadian clock genes. Using oscillations of circadian clock genes as a marker of the subjective time perceived by the cardiomyocytes, experiments showed that diurnal variations in the responsiveness of cardiomyocytes to fatty acids persisted ex vivo. Furthermore, disruption of the circadian clock within the heart, either through manipulation of the light/dark cycle or through use of genetically modified mice, severely impaired the responsiveness of the myocardium to fatty acids. A mismatch between fatty acid availability and fatty acid oxidation rates results in accumulation of detrimental intracellular fatty acid derivatives. In

addition to β-oxidation, one way in which a cell prevents the accumulation of such derivatives is through their storage as triglyceride.

The authors report here that impairment of the circadian clock within the cardiomyocyte not only attenuated the induction of enzymes promoting β-oxidation, but also markedly attenuated triglyceride synthesis during fasting. Accumulation of detrimental fatty acid derivatives is not only a possible source of arrhythmia and contractile dysfunction, but is also associated with hallmarks of type 2 diabetes mellitus and the metabolic syndrome. This study is the first to ascribe a functional role for the circadian clock within the cardiomyocytes of the heart in vivo. Whether alterations in the circadian clock contribute to the progression of cardiovascular disease will require further investigation.

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Danielle Feuvray

Guidelines on the management of stable angina pectoris: executive summary: the Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology

Fox K, Garcia AA, Ardissini D, et al. *Eur Heart J*. 2006;27:1341–1381.

The new European guidelines are a welcome and comprehensive overview of the management of stable angina pectoris. They review the definition and pathophysiology, epidemiology, natural history and prognosis, diagnosis, and treatment, with clear algorithms covering the initial evaluation and medical management. Metabolic agents are reviewed and their antianginal efficacy confirmed. They are recommended as add-on treatment to hemodynamic agents or as a substitution when conventional drugs are not tolerated. The recent Cochrane Collaboration report [1] has also confirmed the effectiveness of the metabolic approach with trimetazidine in stable angina as monotherapy or in combination.

The lack of adverse effects with trimetazidine emphasizes its role when hemodynamic agents are limited by adverse effects, especially in the elderly. The important improvement in impaired left ventricular function may have prognostic implications, but these need to be confirmed in a large-scale trial comparing trimetazidine with placebo, in addition to currently established evidence-based therapy.

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Graham Jackson

Tissue distribution of 18F-FDG-labeled peripheral haematopoietic stem cells after intracoronary administration in patients with myocardial infarction

Kang WJ, Kang HJ, Kim HS, Chung JK, Lee MC, Lee DS. *J Nucl Med*. 2006;47:1295–1301.

Adult stem cell therapy is expected to improve left ventricular function in patients with myocardial infarction. Because of the low risk of arrhythmia and the maximal concentration at the target tissue, intracoronary infusion of stem cells is preferred. The aim of this study was to investigate the homing and tissue distribution of intracoronarily injected peripheral hematopoietic stem cells labeled with [^{18}F]2-fluoro-2-deoxyglucose (FDG). Seventeen patients with myocardial infarction were included as the intracoronary injection group (14 men, three women; ages 58 ± 12 years). Three patients underwent intravenous stem cell injection as the intravenous injection group (three men, no women; ages 50 ± 20 years). After mobilization with granulocyte colony-stimulating factor, peripheral stem cells were collected by means of apheresis. [^{18}F]-FDG labeling of stem cells was performed for 40 min with gentle intermittent mixing at 37 °C. The mean labeling efficiency was 72% (range 46–95%), and 44.4–175 MBq (1.2–5 mCi) of [^{18}F]-FDG-labeled stem cells were injected via an intracoronary catheter after stenting in infarct-related arteries. Images obtained by positron emission tomography (PET)/computed tomography were obtained with a 3-dimensional acquisition mode, 2 h after intracoronary infusion. Two hours after intracoronary infusion, 1.5% (range 0.2–3.3%) of injected stem cells accumulated at the infarcted myocardium. Outside the myocardium, spleen, liver, bladder, and bone marrow showed a high accumulation of stem cells. The delayed image of a patient up to 20 h showed a prolonged residence of stem cells at the myocardium. Intravenous injection of stem cells showed a high initial uptake by the lungs, with no myocardial activity. We have shown that [^{18}F]-FDG-labeled stem cell

PET could be used to assess the tissue distribution of stem cells and to measure their amount at a target tissue. [^{18}F]-FDG-labeled stem cell PET can be used to measure and optimize the amount of stem cells injected.

Comments

Stem cell therapy for acute myocardial infarction has entered the stage of large-scale clinical trials. Earlier, small studies have shown that stem cell therapy may lead to decreased infarct size, improved regional and global function, decreased cardiac volumes, and improved perfusion in the infarct area. These early promising results have now provided the justification for larger randomized and blinded trials to address the efficacy of cellular therapy.

To evaluate the effects of stem cell therapy, assessment of the homing, distribution, and differentiation of cells are important. These factors may largely influence the ultimate clinical outcome in patients. In the present study, the authors successfully labelled the stem cells with FDG before their administration to patients who had suffered an infarct; using PET, they were able to visualize the presence of the labelled stem cells clearly. Moreover, they were able to measure the distribution and to quantify the percent injected dose of stem cells in the myocardium.

One of the interesting results of the study was that intravenous administration of stem cells, in contrast to the intracoronary route, did not result in any measurable uptake of labeled stem cells. As an example, *Figure 1* shows one of the figures from the paper, showing the uptake of FDG-labelled cells in the myocardium.

Thus, this technique of labeling stem cells with FDG gives quantitative information on cell homing and distribution, and may be used to optimize methods of administration and calculation of the dose of stem cells, and to predict the clinical outcome of treatment

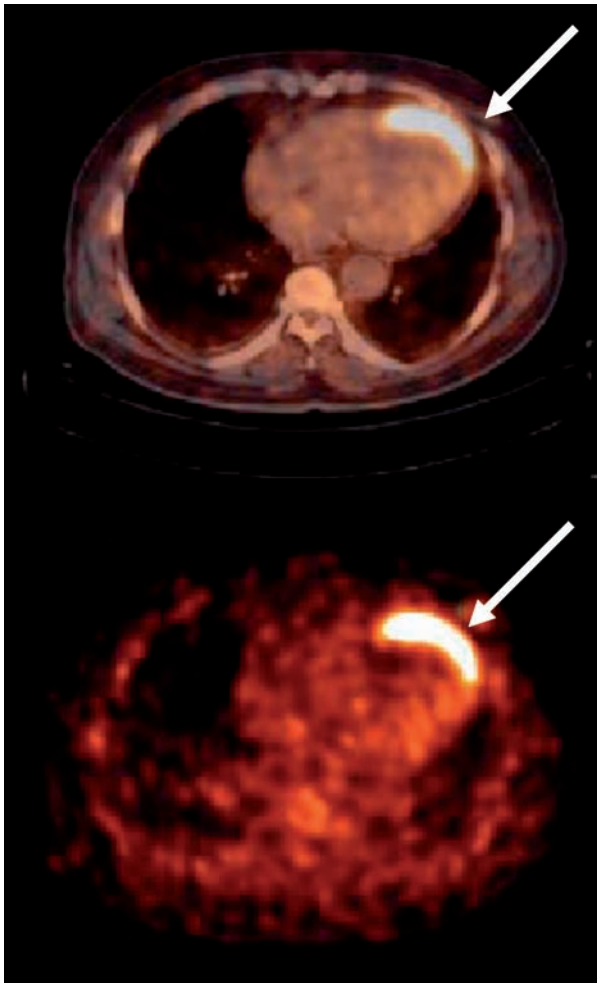

Figure 1. Positron emission tomography/computed tomography image of a patient after myocardial infarction. The arrow shows the distribution of FDG-labeled stem cells in the myocardium after intracoronary injection.

Frans Visser

Glossary

Gary D. Lopaschuk

Alpha-galactosidase A

Fabry disease is caused by a mutation in the enzyme alpha-galactosidase-A. A mutation in the alpha-galactosidase A gene that controls this enzyme causes insufficient breakdown of lipids, which build up to harmful levels in the eyes, kidneys, autonomic nervous system and cardiovascular system. Lipid storage may lead to impaired arterial circulation and increased risk of heart attack or stroke. The heart may also become enlarged and the kidneys may also be affected.

AMP-activated protein kinase (AMPK)

AMP-activated protein kinase (AMPK) is a widely distributed cellular kinase that is activated during times of metabolic stress. It has been termed a cellular ''fuel gauge'', and primarily functions to turn off energy consuming pathways and turn on energy producing pathways during metabolic stress.

AMPK-activated protein kinase gamma subunit (PRKAG2)

The AMPK enzyme is composed of three subunits, an alpha, beta and gamma subunit. These subunits also exist in a number of different isoforms. PRKAG2 is the gene that encodes the gamma2 subunit of AMP-activated protein kinase (AMPK).

Amylo-1,6-glucosidase

Amylo-1,6-glucosidase is an enzyme that catalyzes the hydrolysis of glycogen at specific branch points in its glucose residue chains. It is sometimes called a ''debrancher enzyme''. Mutations in this gene cause glycogen storage disease. Forbes disease is an inherited mutation that results in an amylo-1,6-glucosidase deficiency. This enzyme deficiency causes excess amounts of an abnormal glycogen to be deposited in the liver, muscles and, in some cases, the heart.

Carnitine palmitoyltransferase

Carnitine palmitoyltransferase (CPT) is an important enzyme involved in the transport of fatty acids across membranes, particularly the mitochondrial membrane. CPT 1 is one isoform of CPT that is a key enzyme transporting fatty acids into the mitochondria. Mutations in this enzyme can result in serious energetic deficiencies in muscle.

Globotraosylceramide (Gb3)

Globotraosylceramide (Gb3) is a glycosphingolipid with glucosylceramide as its base cerebroside. Fabry disease is an inherited deficiency of the enzyme, alpha-galactosidase A, which is normally responsible for the breakdown of globotriaosylceramide (Gb3). The subsequent abnormal level of Gb3 causes the symptoms of Fabry disease described above.

Glycogen Phosphorylase

Glycogen phosphorylase is one of the enzymes that break up glycogen into glucose subunits. Glycogen is left with one less glucose molecule. McCardle's disease is a condition caused by an inborn glycogen phosphorylase deficiency. Symptoms include muscular pain, fatigability, and muscle cramping following exercise. Unlike other types of glycogenosis the disease is not fatal and the missing enzyme does not impair the functioning of other body systems.

Glycosphingoplipid

Glycosphingolipids are a subtype of glycerol containing lipids (glycolipids) that contain the amino alcohol sphingosine. The class of glycosphingolipids include a group of specialized glycolipids including cerebrosides, gangliosides and globosides.

Long Chain Acyl CoA Dehydrogenase

Long chain acyl CoA dehydrogenase (LCAD) is the first enzyme involved in the ß-oxidation of fatty acids in mitochondria. ß-oxidation of fatty acid oxidation is a major source of energy for the heart. Mutations in the LCAD gene can lead to serious cardiomyopathies due to inadequate production of energy.

Glossary

Gary D. Lopaschuk

Lysophospholipid

Phospholipids are important components of all cellular membranes in organisms. They consist of a glycerol backbone, a polar head group and two fatty acid moieties linked to the glycerol backbone. If one of these fatty acids is removed, a lysophospholipid is formed. These lysophospholipids can disrupt the normal membrane and the normal function of the proteins contained in the membrane.

Lysosomal acid glucosidase

Lysosomal acid glucosidase is a glycogen-degrading lysosomal enzyme. Pompe disease is a hereditary metabolic disorder caused by the complete or partial deficiency of lysosomal acid glucosidase. This enzyme deficiency causes excess amounts of glycogen to accumulate in the lysosomes of many cell types but predominantly in muscle cells. The resulting cellular damage manifests as muscle weakness and/or respiratory difficulty.

Lysosome associated membrane protein 2

Danon disease, a lysosomal glycogen storage disease, occurs as a result of a lysosome associated membrane protein 2 (LAMP 2) deficiency. Danon disease is associated with a severe cardiomyopathy and variable skeletal muscle weakness are constant features and mental retardation is very frequently associated.

Mutations in the AMPK-activated protein kinase gamma subunit (PRKAG2)

Mutations in PRKAG2 have recently been shown to cause cardiac hypertrophy, cardiac glycogen accumulation, Wolff-Parkinson White syndrome and conduction system disease causing pre-excitation. Dominant mutations in PRKAG2 have recently been shown to result in massive myocardial thickening, AV conduction system disease and ventricular pre-excitation.

Tafazzin

Tafazzin is a protein highly expressed in cardiac and skeletal muscle that is involved in the metabolism of specialized lipids. Mutations of the tafazzin gene are associated with a number of clinical disorders including dilated cardiomyopathy.