Cellular changes in atrial fibrillation

Jolanda van der Velden, Nadiya A. Narolska and Ger J.M. Stienen
Laboratory for Physiology, Institute for Cardiovascular Research, VU University Medical Center,
Amsterdam, The Netherlands

Correspondence: J. van der Velden, Laboratory for Physiology, Institute for Cardiovascular Research, VU University Medical Center, van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands. Tel: +31 20 4448113; fax: +31 20 4448255; e-mail: J.vandervelden@vumc.nl

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
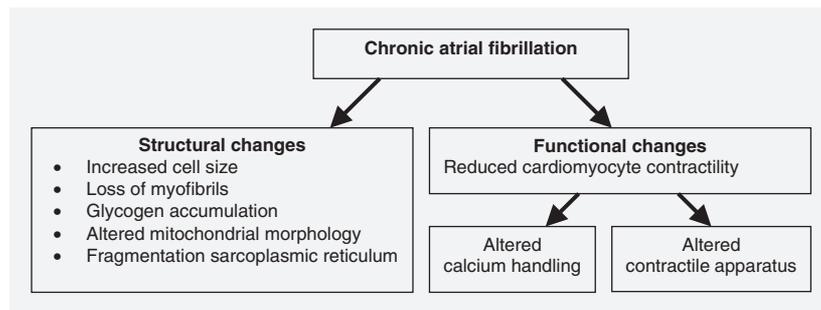
Refresher corner

Jolanda van der Velden, Nadiya A. Narolska and Ger J. M. Stienen

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

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.

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].

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
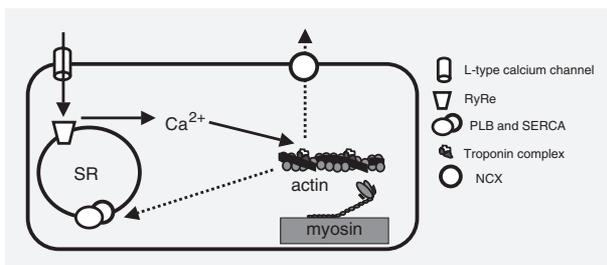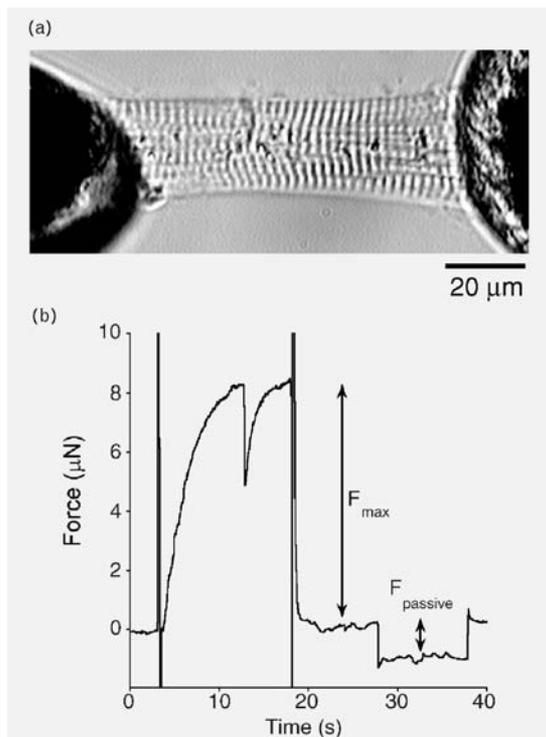
Figure 3. Force measurements in a human atrial cardio-myocyte.(a) A single human cardiomyocyte was glued between a force transducer and piezoelectric motor and force was measured at different calcium concentrations. (b) Force registration at maximal calcium concentration. F_{max}, maximal activated force; $F_{passive}$, 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 cardiomyo-cytes (*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 dysfunc-tion induced by atrial fibrillation.

Future research

Recent evidence suggests an important role for oxi-dative 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 super-oxide radicals ($O_2^{-\bullet}$), hydroperoxyl radicals ($HO_2^{\bullet}$), nitric oxide, and peroxynitrite ($ONOO^-$). Collec-tively, these radicals cause a loss of biological func-tion 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 fibril-lation. 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 contrib-ute 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. ■

REFERENCES

1. Ausma J, Wijffels M, Thone F, et al. Structural changes of atrial myocardium due to sustained atrial fibrillation in the goat. *Circulation*. 1997;96:3157–3163.
2. Ausma J, van der Velden HM, Lenders MH, et al. Reverse structural and gap-junctional remodeling after prolonged at-rial fibrillation in the goat. *Circulation*. 2003;107:2051–2058.
3. Manning WJ, Silverman DL, Katz SE, et al. Impaired left atrial mechanical function after cardioversion: relation to the dura-tion of atrial fibrillation. *J Am Coll Cardiol*. 1994;23:135–140.
4. Brundel BJJM, Ausma J, van Gelder IC, et al. Activation of proteolysis by calpains and structural changes in human paroxysmal and persistent atrial fibrillation. *Cardiovasc Res*. 2002;54:380–389.
5. Bers DM. Cardiac excitation–contraction coupling. *Nature*. 2002;415:198–205.
6. Schotten U, Ausma J, Stellbrink C, et al. Cellular mechanisms of depressed atrial contractility in patients with chronic atrial fibrillation. *Circulation*. 2001;103:691–698.
7. Logan WF, Rowlands DJ, Howitt G, et al. Left atrial activity following cardioversion. *Lancet*. 1965;10:471–473.
8. Schotten U, Greiser M, Benke D, et al. Atrial fibrillation-induced atrial contractile dysfunction: a tachycardiomyopathy of a different sort. *Cardiovasc Res*. 2002;53:192–201.
9. Christ T, Boknik P, Wöhrl, et al. L-type Ca^{2+} current down-regulation in chronic human atrial fibrillation is associated with increased activity of protein phosphatases. *Circulation* 2004; 110:2651–2657.

Refresher corner

Jolanda van der Velden, Nadiya A. Narolska and Ger J. M. Stienen

10. Narolska NA, van Loon RB, Boontje NM, et al. Myocardial contraction is 5-fold more economical in ventricular than in atrial human tissue. *Cardiovasc Res*. 2005;65:221–229.
11. Mihm MJ, Yu F, Carnes CA, et al. Impaired myofibrillar energetics and oxidative injury during human atrial fibrillation. *Circulation*. 2001;104:174–180.
12. Narolska NA, Eiras S, van Loon RB, et al. Myosin heavy chain composition and the economy of contraction in healthy and diseased human myocardium. *J Muscle Res Cell Motil*. 2005;26:39–48.
13. Braunwald E, Frahm CJ. Studies on Starling's law of the heart IV Observations of the hemodynamic functions of the left atrium in man. *Circulation*. 1961;24:633.
14. Morano I. Tuning the human heart molecular motors by myosin light chains. *J Mol Med*. 1999;77:544–555.
15. Eiras S, Narolska NA, van Loon RB, et al. Alterations in contractile protein composition and function in human atrial dilatation and atrial fibrillation. *J Mol Cell Cardiol*. 2006; In press.
16. Carnes CA, Chung MK, Nakayama T, et al. Ascorbate attenuates atrial pacing-induced peroxynitrite formation and electrical remodeling and decreases the incidence of postoperative atrial fibrillation. *Circ Res*. 2001;89:E32–E38.
17. Shiroshita-Takeshita A, Schram G, Lavoie J, et al. Effect of simvastatin and antioxidant vitamins on atrial fibrillation promotion by atrial-tachycardia remodeling in dogs. *Circulation*. 2004;110:2313–2319.
18. Kim YM, Guzik TJ, Zhang YH, et al. A myocardial Nox2 containing NAD(P)H oxidase contributes to oxidative stress in human atrial fibrillation. *Circ Res*. 2005;97:629–636.