Atrial fibrillation-induced atrial contractile dysfunction: a tachycardiomyopathy of a different sort

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Received 2 July 2001; accepted 24 August 2001

Abstract

Objective: Although AF-induced atrial contractile dysfunction has significant clinical implications the underlying intracellular mechanisms are poorly understood. Methods: From the right atrial appendages of 59 consecutive patients undergoing mitral valve surgery (31 in SR, 28 in chronic AF) thin muscle preparations (diameter<0.7 mm) were isolated. Isometric force of contraction was measured in the presence of different concentrations of Ca\textsuperscript{2+} and isoprenaline. To assess the function of the sarcoplasmic reticulum, the force–frequency relationship and the post-rest potentiation were studied. The myocardial density of the ryanodine-sensitive calcium release channel (CRC) of the sarcoplasmic reticulum was determined by [H]ryanodine binding. Myocardial content of SR-Ca\textsuperscript{2+}-ATPase (SERCA), phospholamban (Plb), calsequestrin (Cals) and the Na\textsuperscript{+}/Ca\textsuperscript{2+}-exchanger (NCX) were analyzed by Western blot analysis. Adenylyl cyclase activity was measured with a radiolabeled bioassay using \textsuperscript{32}P[ATP as a tracer. Results: In 72 muscle preparations of SR patients contractile force was 10.9\pm1.8 mN/mm\textsuperscript{2} compared to 3.3\pm0.9 mN/mm\textsuperscript{2} (n=48, P<0.01) in AF patients. The positive inotropic effect of isoprenaline was diminished but the stimulatory effect on relaxation and the adenylyl cyclase were not altered in AF patients. The force–frequency relation and the post-rest potentiation were enhanced in atrial myocardium of AF patients. The protein levels of CRC, SERCA, Plb, and Cals were not different between the two groups. In contrast, the Na\textsuperscript{+}/Ca\textsuperscript{2+}-exchanger was upregulated by 67\% in atria of AF patients. Conclusions: AF-induced atrial contractile dysfunction is not due to \beta-adrenergic desensitization or dysfunction of the sarcoplasmic reticulum and thus is based on different cellular mechanisms than a ventricular tachycardia-induced cardiomyopathy. Instead, downregulation or altered function of the L-type Ca\textsuperscript{2+}-channel and an increased Ca\textsuperscript{2+} extrusion via the Na\textsuperscript{+}/Ca\textsuperscript{2+}-exchanger seem to be responsible for the depressed contractility in remodeled atria. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Arrhythmia (mechanisms); Atrial function; Contractile function; SR (function)

1. Introduction

The rapid and irregular atrial contractions during atrial fibrillation (AF) result in a depression of atrial transport function and contribute to the reduction of ventricular filling and cardiac output. The main clinical relevance of the loss of synchronized atrial contraction is the development of atrial thrombi presumably due to increased stasis of blood near the atrial wall. Accordingly, AF is a common cause of cerebral embolism, accounting for approximately 15\% of all strokes [1]. Therefore, maintenance of sinus rhythm (SR) is of primary importance in the treatment of AF. Echocardiographic studies in patients have shown that after cardioversion, contractile function of the atria is...
impaired. The degree of contractile dysfunction correlates with the previous duration of AF and the complete recovery of atrial function can take months [2]. The post-fibrillatory atrial contractile dysfunction favors the development of atrial thrombi after cardioversion to SR and therefore contributes to the thromboembolic risk associated with AF [3].

Studies in goats with sustained AF have shown that AF is associated with alterations of the cellular ultrastructure [4]. These data suggest that the contractile abnormalities in remodeled atria are caused by a loss of myofibrils and fragmentation of the sarcoplasmic reticulum. In a previous study we demonstrated that the contribution of myolysis to the AF-induced atrial contractile dysfunction is rather limited [5]. In experimental and clinical studies, the Na+/H+-exchange inhibitor HOE642 [6] and verapamil [7,8] were shown to delay the effects of AF on the atrial contractility indicating that they were mediated by Ca2+-overload during AF. Several studies demonstrated that altered Ca2+-metabolism indeed contributed to atrial dysfunction. In dogs with sustained atrial tachycardia atrial contractility has been shown to be reduced on the cellular level [9] and a pronounced reduction of the L-type Ca2+ current (IcA,1) was reported [10]. Recently, a reduced ICaL was also reported in human atrial cardiomyocytes of patients with chronic AF [11,12]. Also, altered expression of sarcoplasmic reticulum Ca2+-handling proteins [13] or alterations in the β-adrenergic signal transduction might contribute to the changes in Ca2+-metabolism in fibrillating atria. In addition, β-adrenergic desensitization and dysfunction of the sarcoplasmic reticulum have been described as the main pathophysiological alterations in experimental tachycardia-induced cardiomyopathy on the ventricular level [14–16].

The present study was designed to investigate the cellular mechanisms of postfibrillatory atrial contractile dysfunction. Additionally, we aimed to study whether the pathophysiological mechanisms underlying ventricular tachycardiomypathy also account for the AF-induced atrial contractile dysfunction.

2. Methods

2.1. Patients

Right atrial appendages were obtained from 59 consecutive patients undergoing mitral valve surgery. At the time of operation 28 patients were in chronic AF (>3 months), the others were in SR and had no history of AF (n=31). The clinical characteristics of the patients are given in Table 1. Hemodynamic parameters did not differ between the two patient groups, but Ca2+-antagonists and digitalis were more frequently taken by AF patients for control of their ventricular rate. The study conforms with the principles outlined in the Declaration of Helsinki. All patients gave written informed consent and the study was approved by an institutional ethical committee.

2.2. Contraction experiments

Immediately after surgical resection, the atrial tissue was placed in a 4°C cold Tyrode’s solution (pH 7.4, gassed with 5% CO2/95% O2) and transferred to the laboratory. Thin myocardial muscle bundles of a length between 3 and 6 mm were prepared under stereomicroscopic control (diameters: SR (n=72): 0.47±0.09 mm, AF (n=48): 0.45±0.10 mm; n.s.), connected to force transducers and placed in an organ bath with prewarmed bathing solution (37°C). The muscle strips were electrically stimulated with rectangular impulses at 1 Hz (5 ms duration, 5–10% above threshold). After an equilibration period of 30 min, the muscles were stretched by increasing the resting tension from 2 mN stepwise by 0.5 mN until the muscle length providing maximal active force generation was reached (Lmax). Resting tension at Lmax was 3.2±0.6 mN (n=72) in SR and 3.4±0.8 mN (n=48) in AF (n.s.). To assess the relaxation properties of the muscle preparations the time to 90% relaxation was measured.

In a subgroup of muscle preparations the effects of isoprenaline on force of contraction and time to 90% relaxation was studied. For this purpose isoprenaline was cumulatively added to the organ bath. After wash-out of isoprenaline a concentration–response curve of Ca2+ was studied.

In another set of experiments the force–frequency relationship (FFR) was studied by increasing the stimulation frequency from 0.5 to 3 Hz.

In a third subgroup we studied the post-rest potentiation of contractile force as an index for the capacity of the sarcoplasmic reticulum to store Ca2+. Electrical stimulation at 1 Hz was interrupted for 2 s to 5 min and the contractile force of the first post-rest contraction was measured. In SR patients post-rest potentiation was also measured after adding 100 nM of nifedipine or 10 nM of ryanodine in the bathing solution.

2.3. Adenylyl cyclase activity

Adenylyl cyclase (AC) activity was determined as described previously [17]. Briefly, enzyme activity was determined in assays (100 μl) containing 1 mM Na2-ATP ([32P]ATP, 1 μCi) as tracer substrate. The reaction was started by the addition of the homogenates (75 μg protein) to the reaction mixture and stopped after 20 min by the addition of 100 μl 1 M HCl and subsequent heating to 95°C for 5 min. After chromatographic purification the [32P]cAMP fraction was counted in a β-counter (Canberra-Packard).
Table 1
Patients — hemodynamic and clinical data

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<tr>
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<th>Sinus rhythm (n=31)</th>
<th>Atrial fibrillation (n=28)</th>
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<tr>
<td>Age (years)</td>
<td>55±8</td>
<td>57±7</td>
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<tr>
<td>Gender (m/f)</td>
<td>(13/18)</td>
<td>(13/15)</td>
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<tr>
<td>Cardiac index (l/min per m²)</td>
<td>3.0±0.6</td>
<td>2.8±0.8</td>
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<td>Mean pulmonary capillary wedge pressure (mmHg)</td>
<td>12±6</td>
<td>15±6</td>
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<tr>
<td>Mean right atrial pressure (mmHg)</td>
<td>5.6±2.1</td>
<td>7.9±2.3</td>
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Medication (n)

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<tr>
<td>Diuretics</td>
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<td>Beta-blockers</td>
<td>7</td>
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<tr>
<td>Digitalis</td>
<td>8</td>
</tr>
<tr>
<td>ACE-Inhibitors</td>
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<tr>
<td>Ca²⁺-Antagonists</td>
<td>9</td>
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<tr>
<td></td>
<td>16</td>
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<td></td>
<td>6</td>
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<td>17*</td>
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<tr>
<td></td>
<td>15</td>
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<td>16*</td>
</tr>
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</table>

*P<0.05.

Under these experimental conditions AC activity was linear with respect to incubation time (up to 30 min) and protein concentration (up to 150 μg/assay) indicating that determination of AC activity using 75 μg protein and 20 min incubation time was within the linear range.

2.4. [³H]Ryanodine radioligand binding

A homogenate of atrial tissue was incubated with different concentrations of [³H]ryanodine ranging from 0.3 to 40 nM [18]. Free calcium concentration was adjusted to 10⁻⁴ M according to the calculations of Fabiato [19]. The reaction was stopped by rapid filtration of the homogenates through Whatman GF/C filters and the retained radioactivity was counted in a β-counter. Nonspecific radioactivity was determined by the addition of 10 μM of unlabeled ryanodine to the binding assay.

2.5. Western blot analysis

To quantify the Na⁺/Ca²⁺-exchanger, SR-Ca²⁺-ATPase, phospholamban, and calsequestrin, electrophoresis of homogenate aliquots was carried out using polyacrylamide gels [18]. After tank blotting the nitrocellulose (0.45 μm) was exposed to primary antibody solution followed by radioactive labeling with the secondary antibody. The nitrocellulose membranes were cut and single band signals were quantified in a γ-counter. Table 2 shows the details of the Western blot conditions.

For all proteins investigated there was a linear correlation between the amount of protein subjected to gel electrophoresis and the radioactive signals. The protein content of the homogenates was measured by the method of Bradford [20].

2.6. Statistical analysis

All data are expressed as means±S.D. Kᵣ-values and EC₅₀-values are given with 95% confidence intervals. Statistical significance of mean differences was determined by unpaired Student’s t-test (for comparison of two groups) or by one-way analysis of variance (ANOVA) and Newman–Keuls post test for comparison of multiple groups. A P-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Inotropic effects of Ca²⁺ and isoprenaline

The baseline force of contraction was reduced in the AF
of isoprenaline (P<0.01). In the AF patients neither at baseline conditions (252±22 ms) nor in the presence of 1 μM of isoprenaline (194±18 ms) TR$_{90}$ was significantly different compared to the SR patients. The concentration of isoprenaline eliciting a half-maximal shortening of TR$_{90}$ (positive lusitropic potency) was similar in both groups (SR: EC$_{50}$=6.1(3.2–12.1) nM, AF: EC$_{50}$=7.1(3.2–13.4) nM, n.s.). Subgroup analysis revealed that differences in medication did not influence contractile force of the muscle preparations or their response to positive inotropes.

3.2. Adenyl cyclase

Fig. 2 shows the results of the AC activity assays. Baseline AC activity was the same in SR and AF patients. Isoprenaline (1 μM) stimulated AC activity by a factor of three in both patient groups. AC activity in the presence of 5 mM MnCl$_2$, resulting in maximal activation of the enzyme, exceeded the activity exerted by isoprenaline and also did not differ between the patient groups.

3.3. Force–frequency relationship

In SR patients FFR was positive up to a stimulation frequency of 2.0 Hz (Fig. 3). At higher frequencies contractile force declined slightly. In AF patients the FFR was also positive but shifted to higher frequencies. The half-maximal response was reached at 0.9(0.6–1.6) Hz in SR patients, whereas in AF patients 1.7(1.2–2.4) Hz (P<0.05) was needed to elicit the same effect. Also, the relative increase in contractile force was more pronounced in AF patients. Compared to the force at 0.5 Hz the maximal force was increased to 242±39% (at 2.5 Hz), whereas in SR patients only 167±26% (at 2.0 Hz, P<0.05) were reached. TR$_{90}$, as a measure of the relaxation behavior, did not differ between the two groups.

3.4. Post-rest potentiation

Fig. 4 shows representative experiments on post-rest contractile force (rest interval 10 s). In the SR patient force of contraction of the first post-rest twitch was increased by 40% compared to steady state force of contraction (post-rest potentiation). Ryanodine abolished post-rest potentiation in the same patient. In AF patients the steady state force of contraction was lower than in the SR patients, but post-rest potentiation of contractile force was fully preserved. Similarly, when muscle preparations of SR patients were exposed to nifedipine, steady state force of contraction was low, but the post-rest potentiation was less affected.

The extent of the post-rest potentiation depended on the rest interval in both SR and the AF patients (Fig. 5). In the SR group maximal post-rest potentiation was reached at a rest-interval of 10 s, whereas in AF 30 s rest-interval provoked the maximal post-rest response. The increase in...
Fig. 2. Effect of the extracellular Ca\(^{2+}\) concentration and the \(\beta\)-adrenoceptor agonist isoprenaline on force of contraction (mN/mm\(^2\)) (upper panel) and time to 90% relaxation (mid panel) of isolated muscle preparations of 12 patients in SR (18 muscle preparations) and 12 AF patients (17 muscle preparations). *\(P<0.05\). Lower panel: AC activity in homogenates of right atrial myocardium. Neither at baseline conditions, nor in the presence of isoprenaline (1 \(\mu\)M) or Mn\(^{2+}\) (5 mM), activity of the enzyme differed between the two groups (\(n=12\) in each group).
post-rest force of contraction compared to the steady state contraction was more pronounced in the AF patients (275±42% vs. steady state) compared to the SR group (151±18% vs. steady state, \(P<0.01\)). Ryanodine abolished the post-rest response (rest decay). Similar to the behavior of atrial myocardium of AF patients, also in SR patients the post-rest potentiation was enhanced, when the L-type Ca\(^{2+}\) channel was blocked with nifedipine. The maximal response occurred after 30 s of rest and reached 297±58% compared to the steady state contractile force (n.s. vs. AF).

3.5. Expression of Ca\(^{2+}\)-handling proteins

Representative autoradiographs of right atrial myocardium are depicted in Fig. 6. There was no significant difference in protein levels of SR-Ca\(^{2+}\)-ATPase, calsequestrin, and phospholamban in atrial myocardium of AF and SR patients (Table 3). Fig. 6 also shows a
Table 3

<table>
<thead>
<tr>
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<th>SR (n=13)</th>
<th>AF (n=13)</th>
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<tbody>
<tr>
<td>SR Ca&lt;sup&gt;2+&lt;/sup&gt;-ATPase/protein</td>
<td>22 604±2994</td>
<td>22 407±2870</td>
</tr>
<tr>
<td>Calsequestrin/protein</td>
<td>3581±495</td>
<td>3459±454</td>
</tr>
<tr>
<td>Phospholamban/protein</td>
<td>16 543±2190</td>
<td>14 558±2712</td>
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Protein expression given in cpm of bound secondary antibody per mg protein; no significant differences were observed between SR and AF patients.

Fig. 5. Force of contraction of the first post-rest twitch normalized to the steady state force of contraction as a function of the rest interval in 15 preparations from 15 patients (SR and AF group). In 10 SR patients the experiment was performed after the addition of 10 nM of ryanodine (10 muscle preparations). In 13 patients 100 nM of nifedipine was given in the organ bath (13 muscle preparations).

Fig. 6. Representative Western blot analysis of calcium transport proteins in atrial myocardium of patients in SR or in AF. STD=Standard sample which was used as a standard on all blots to promote comparability of determination from the different blots. Representative saturation binding of [3H]ryanodine to a homogenate of atrial myocardium of one SR patient and one patient in AF.

Fig. 7. Protein expression of the Na<sup>+</sup>/Ca<sup>2+</sup>-exchanger in right atrial myocardium of patients with SR or AF (n=13 in each group). Above: Representative autoradiography. STD=standard sample. Below: Scatter graph showing the results of all single determinations. The Na<sup>+</sup>/Ca<sup>2+</sup>-exchanger expression was increased in AF patients by ~67% (P<0.01).

Fig. 8. Representative [3H]ryanodine binding experiment in one SR and one AF patient. In both groups specific [3H]ryanodine binding was saturable and of high-affinity. In atrial myocardium of SR patients, the [3H]ryanodine binding site density was 133±23 fmol/mg protein (n=13) compared to 123±24 fmol/mg in AF patients (n=13; n.s.). The affinity of the radioligand to the binding sites also did not differ between the different patient groups (K<sub>D</sub>-values: SR: 1.3(0.4–3.3) nM, AF: 1.6(0.5–3.7) nM, n.s.). In contrast, as shown in Fig. 7, the Na<sup>+</sup>/Ca<sup>2+</sup>-exchanger was significantly upregulated by 67% in atrial myocardium of AF patients.

4. Discussion

Although the postfibrillatory atrial contractile dysfunction is of significant clinical relevance the underlying cellular mechanisms are not completely understood. In a previous study we demonstrated that the isometric force of contraction of isolated atrial myocardium of patients with prolonged AF is reduced by 75% compared to a control...
group in SR [5]. Of interest, the contractile reserve in these muscle preparations was only slightly reduced indicating that a loss of myofilaments is not the main mechanism of post-fibrillatory atrial contractile dysfunction. The impaired activation of the myofilaments might be due to impaired myofibrillar energetics [21] but could also be explained by an altered Ca$^{2+}$ metabolism of the atrial cardiomyocytes. Sun et al. showed that 3 min of rapid pacing were sufficient to reduce the Ca$^{2+}$ transient in atrial canine cardiomyocytes [22]. Prolonged atrial tachycardia in dogs (rapid atrial pacing for 6 weeks) results in a reduction of the Ca$^{2+}$ transient by 50% [9]. In diseased ventricular myocardium a similar reduction in the Ca$^{2+}$ transient is due to a dysfunction of the sarcoplasmic reticulum probably caused by changes in the expression of Ca$^{2+}$ handling proteins [18,23,24]. Also, an upregulation of the Na$^+$/Ca$^{2+}$-exchanger was suggested to contribute to the depressed Ca$^{2+}$ transient [25].

Another important mechanism controlling the generated force is the β-adrenergic signal transduction pathway [26]. Like in a ventricular tachycardiomyopathy, dysfunction of the β-adrenergic signal transduction pathway might impair the inotropic response of the atria to physiological variations in sympathetic tone.

The present study was undertaken to investigate whether the atrial dysfunction resulting from AF is due to the same intracellular mechanisms as the ventricular tachycardiomyopathy. We showed that neither β-adrenergic desensitization nor dysfunction of the sarcoplasmic reticulum can adequately explain the post-AF atrial contractile dysfunction. Instead, downregulation or altered function of the L-type Ca$^{2+}$ channel and possibly an upregulation of the Na$^+$/Ca$^{2+}$-exchanger are responsible for the depressed atrial contractility in AF patients. Since subgroup analysis revealed no effect of medication on force of contraction or responsiveness of the muscle bundles to positive inotropes the observed differences are most probably caused by the arrhythmia itself and not due to the drug therapy.

4.1. No desensitization of the β-adrenergic signal transduction pathway

Downregulation of β-adrenoceptors [26] and an upregulation of the inhibitory G protein [27] have been shown to cause β-adrenergic desensitization in human failing myocardium and in a canine model of tachycardia-induced heart failure [14]. Since atrial contractile dysfunction can also be provoked by rapid atrial pacing [9] it has been classified as a tachycardia-induced atrial cardiomyopathy [28]. Our previous and the present study show that the positive inotropic effect of isoprenaline is clearly reduced in atrial myocardium of AF patients. However, a reduced inotropic response to β-adrenergic stimulation does not necessarily mean that the β-adrenergic signal transduction is impaired. Since the positive inotropic effect of catecholamines is mainly due to protein kinase A mediated phosphorylation of the L-type Ca$^{2+}$ channel, changes in protein expression or function of this ion channel could also explain the diminished inotropic effect of isoprenaline. In this case, a β-adrenergic response not mediated by the L-type Ca$^{2+}$ channel would be unchanged. In our present study the positive lusitropic effect of isoprenaline was found to be preserved in atrial myocardium of AF patients. The increase in speed of relaxation is governed by phosphorylation of phospholamban and a consecutive activation of the SR-Ca$^{2+}$-ATPase, i.e. not dependent on L-type Ca$^{2+}$ channel function. Therefore, the preserved effect of isoprenaline on relaxation indicates that the β-adrenergic signaling is not impaired. Also, isoprenaline-activated, and maximal catalytic capacity of the AC was unaltered in AF patients. These data provide direct evidence that the β-adrenergic signal transduction pathway itself is not desensitized in atrial myocardium of AF patients. Rather, the diminished positive inotropic effect of isoprenaline is due to the well established reduction of $I_{\text{Cal}}$ [11] in atrial cardiomyocytes of AF patients.

4.2. The function of the sarcoplasmic reticulum is preserved

In human failing myocardium as well as in animal models of tachycardia-induced heart failure changes in intracellular Ca$^{2+}$ handling result in prolonged relaxation and impaired systolic force development especially at higher rates. As a result the FFR becomes flat or even inverted [29].

In the present study the FFR was positive in atria of SR and AF patients. In AF patients the response of the depressed contractions to an increase in rate was even more pronounced than in SR patients. Since a dysfunction of the sarcoplasmic reticulum inhibits an increase in contractile force at higher stimulation rates it is not very likely that AF-induced atrial contractile dysfunction is due to impaired Ca$^{2+}$ handling of the sarcoplasmic reticulum. Alternatively, the enhancement and the rightward shift of the FFR in AF patients can be explained by a Ca$^{2+}$ depletion of the atrial cardiomyocytes during slow rates. At higher stimulation rates the increased Ca$^{2+}$ influx restores the intracellular Ca$^{2+}$ load and contractility is improved.

Dysfunction of the sarcoplasmic reticulum has been reported to impair the diastolic function of isolated myocardium [30]. In atrial myocardium of AF patients relaxation was not prolonged in the absence of isoprenaline, at high stimulation frequencies, or during maximal stimulation of contractile force with high extracellular Ca$^{2+}$ concentrations. This absence of slowed relaxation also favors the hypothesis that the Ca$^{2+}$ reuptake function of the sarcoplasmic reticulum is preserved in atrial myocardium of AF patients.

Post-rest potentiation of contractile force is a marker for the capacity of the sarcoplasmic reticulum to store Ca$^{2+}$
[31]. Ryanodine inhibits the repetitive storage and release of Ca²⁺ by the sarcoplasmic reticulum and completely abolished the post-rest potentiation. In atrial myocardium of AF patients the post-rest potentiation was more pronounced than in SR patients indicating that force of contraction was not limited by a disturbed reuptake of Ca²⁺ by the sarcoplasmic reticulum. This observation is in accordance with our finding that the protein expression of the Ca²⁺ release channel of the sarcoplasmic reticulum, the SR-Ca²⁺-ATPase, phospholamban and calsequestrin was unaltered in atrial myocardium of AF patients.

The L-type Ca²⁺ channel agonist BayK8644 was shown to inhibit post-rest potentiation in ferret ventricular muscle by activating the physical linkage between the L-type Ca²⁺ channel and the Ca²⁺ release channel of the sarcoplasmic reticulum. The resulting opening of the Ca²⁺ release channel accelerates the Ca²⁺ release of the sarcoplasmic reticulum during the rest interval [32]. In atrial myocardium of AF patients a downregulation or depressed function of the L-type Ca²⁺ channel might inhibit this interaction between the L-type Ca²⁺ channel and the ryanodine receptor. This would decrease the leakage of Ca²⁺ out of the sarcoplasmic reticulum during rest and might explain why the post-rest potentiation is enhanced in atrial myocardium of AF patients. This hypothesis is supported by our observation that, when atrial muscle preparations of SR patients were exposed to nifedipine, the post-rest potentiation was enhanced to a similar extent as in AF patients.

4.4. What causes the AF-induced atrial contractile dysfunction?

Our previous study on the AF-induced changes in atrial contractility had demonstrated that downregulation or dysfunction of the L-type Ca²⁺ channel is a main mechanism for the atrial dysfunction [5]. In contrast, myolysis can only explain a small part of it. The present study adds some new aspects to this concept: (1) β-adrenergic desensitization does not contribute to the AF-induced atrial contractile dysfunction. (2) Neither biochemical nor physiological experiments provided any indication that the Ca²⁺ reuptake function of the sarcoplasmic reticulum is impaired in atrial myocardium of AF patients. (3) Potentially, the upregulation of the Na⁺/Ca²⁺-exchanger worsens the Ca²⁺ depletion in atrial cardiomyocytes of AF patients and thereby contributes to the atrial contractile dysfunction after cardioversion of AF.

Furthermore, our data demonstrate that clear differences exist in pathophysiological mechanisms underlying a tachycardia-induced cardiomyopathy of the ventricles and the AF-induced tachycardia-induced cardiomyopathy of the atria. The main pathophysiological alterations attributed to classical ventricular tachycardia-induced cardiomyopathy — β-adrenergic desensitization and dysfunction of the sarcoplasmic reticulum — do not occur in atrial myocardium of AF patients indicating that adaptation processes upon the same stimulus may be very different in atria and ventricles.

Acknowledgements

This work was supported by a grant from the Academy of Science of North-Rhine Westfalia, Germany.

References


