Loss of atrial contractility is primary cause of atrial dilatation during first days of atrial fibrillation

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Schotten, Ulrich, Sunniva de Haan, Hans-Ruprecht Neuberger, Sabine Eijshouts, Yuri Blaauw, Robert Tieleman, and Maurits Allessie. Loss of atrial contractility is primary cause of atrial dilatation during first days of atrial fibrillation. Am J Physiol Heart Circ Physiol 287: H2324–H2331, 2004. First published July 15, 2004; doi:10.1152/ajpheart.00581.2004.—Atrial fibrillation (AF) induces a progressive dilatation of the atria which in turn might promote the arrhythmia. The mechanism of atrial dilatation during AF is not known. To test the hypothesis that loss of atrial contractile function is a primary cause of atrial dilatation during the first days of AF, eight goats were chronically instrumented with epicardial electrodes, a pressure transducer in the right atrium, and piezoelectric crystals to measure right atrial diameter. AF was induced with the use of repetitive burst pacing. Atrial contractility was assessed during sinus rhythm, atrial pacing (160-, 300-, and 400-ms cycle length), and electrically induced AF. The compliance of the fibrillating right atrium was measured during unloading the atria with diuretics and loading with 1 liter of saline. All measurements were repeated after 6, 12, and 24 h of AF and then once a day during the first 5 days of AF. Recovery of the observed changes after spontaneous cardioversion was also studied. After 5 days of AF, atrial contractility during sinus rhythm or slow atrial pacing was greatly reduced. During rapid pacing (160 ms) or AF, the amplitude of the atrial pressure waves had declined to 20% of control. The compliance of the fibrillating atria increased twofold, whereas the right atrial pressure was unchanged. As a result, the mean right atrial diameter increased by ~12%. All changes were reversible within 3 days of sinus rhythm. We conclude that atrial dilatation during the first days of AF is due to an increase in atrial compliance caused by loss of atrial contractility during AF. Atrial compliance and size are restored when atrial contractility recovers after cardioversion of AF. A relationship between atrial size and atrial fibrillation (AF) was first proposed by Fraser and Turner in 1955 (1), who showed that AF was more common in patients with enlarged atria than in patients with normal atrial size. In the 1990s, large prospective trials established left atrial enlargement as an independent risk factor for the development of AF (13, 14). Today, it is generally accepted that AF is not only a consequence but also a cause of atrial dilatation. In patients with “lone AF,” Sanfilippo et al. (9) demonstrated that AF resulted in progressive atrial dilatation, which in turn, might contribute to the self-perpetuating nature of the arrhythmia. The mechanism of atrial dilatation related to AF is still unclear. It has been proposed that mild impairment of ventricular pump function due to the high ventricular rate during AF might increase end-diastolic ventricular and atrial pressures (12). An alternative explanation might be that the pronounced atrial contractile dysfunction of the atria induced by AF (6, 7, 10) underlies the dilatation of fibrillating atria. In theory, loss of contractility in fibrillating atria is expected to increase atrial compliance and size. In isolated canine hearts, AF did not result in significant changes of atrial compliance (5). In contrast, in anesthetized dogs (15) and pigs (4) atrial compliance was found to decrease during the transition from sinus rhythm (SR) to AF. Because during AF fibrillatory contractions continuously spread over the atrial myocardium, the compliance of the fibrillating atrium is generally lower than the diastolic atrial compliance during SR (11). However, the long-term effect of a loss of atrial contractility due to AF on compliance and size of fibrillating atria has not been studied yet.

We hypothesized that during the first days of AF, the loss of atrial contractility would result in an increase of atrial compliance and thereby serve as main cause of atrial dilatation. In the present study we measured the time course of changes in contractility, compliance, and size of fibrillating atria of chronically instrumented goats during the first 5 days of AF. MATERIALS AND METHODS

Animal model. In eight goats (43–63 kg wt), a left intercostal thoracotomy was made during general anesthesia (1–2% halothane–65% N2O–33% O2). Small silicon patches containing three silver electrodes (2 mm diameter) were sutured on the upper free wall of the right and left atria and the left ventricular apex. A pair of ultrasonic piezoelectric crystals was used to measure right atrial diameter. One crystal was placed between the aorta and the auricle and the other was sutured on the middle of the right atrial free wall (Fig. 1). A tip pressure transducer was implanted in the right atrium via the right jugular vein. Two to three weeks after the goats recovered from surgery, AF was induced by burst pacing with the use of an automatic fibrillation pacemaker (16). The study was conducted in conformity with the principles of the American Physiological Society and was approved by the ethical committee of the University Maastricht.

Study protocol. Before AF was induced, the baseline electrophysiological and contractile properties, as well as right atrial pressure, size, and compliance, were determined. Afterward, AF was maintained for 5 days. During these 5 days, the maintenance of AF was briefly interrupted at 6, 12, 24, 48, 72, 96, and 120 h of AF. Thirty minutes after spontaneous termination of AF, the atrial contractile function was studied at different pacing rates. Twenty minutes after reinduction of AF, right atrial pressure, size, and compliance were measured. After 5 days of AF, the recovery of atrial contractility, size, and compliance was studied for 5 days.

Electrophysiological and contractile measurements. Median AF cycle length (AFCL) was measured from a bipolar atrial electrogram.
The respiratory cycle length of the goats studied was 2.5 to 4.5 s with expiration taking two to three times longer than inspiration. To minimize the effect of inspiration on the measured atrial pressure and size, mean atrial pressure ($P_{mean}$) and diameter ($D_{mean}$) during AF were calculated by averaging the recorded pressure and diameter data during expiration of three to six consecutive respiratory cycles (total recording time 10 s). The maximal ($D_{max}$) and the minimal atrial diameters ($D_{min}$) during each ventricular contraction cycle were also averaged from the same recordings. Contractility of the fibrillating atrium ($\Delta P_{open}$, $\Delta P_{closed}$, and $\Delta D_{open}$) was measured using the same criteria as during rapid atrial pacing with a cycle length of 160 ms. Compliance curves of the fibrillating atrium were calculated as described by Kihara et al. (2) and Nagano et al. (8) with minor modifications. Atrial pressure-volume data were recorded during 2 to 3 s of AF (4 to 5 contraction cycles during expiration) without medication, after unloading the atria with a loop diuretic (30 min after administration of 125 mg furosemide), and after loading the atria with 1 liter of saline infused within 10 min. The compliance curve was obtained by fitting the merged pressure diameter data to the exponential function $P = offset + a*e^{-b*d}$, where $a$ is the elastic constant and $b$ the stiffness constant of the fibrillating atrium. For each atrial diameter the fibrillating atrium can be calculated as the reciprocal steepestness of the compliance curve. The point of the compliance curve at $D_{mean}$ was taken as the “working point.” We calculated the compliance at $D_{mean}$ at baseline (compliance$_{basal}$) and at the working point on the compliance curve of each particular experiment (compliance$_{work}$).

**RESULTS**

Time course of contractile remodeling. Figure 2, left, shows representative PV loops recorded during SR and during rapid atrial pacing at a cycle length of 400 and 300 ms. In Fig. 2, right, the time course of AF-induced atrial contractile dysfunction (contractile remodeling) is depicted. At baseline, AWI was highest during pacing at 300 ms (40.0 ± 8.7 mm·mmHg) and lowest during SR (4.4 ± 1.2 mm·mmHg). Both during SR and atrial pacing AWI declined during the first days of AF. After 24 h of AF, AWI was reduced by >50%, and after 3 days the atrial loop was almost closed, indicating that atrial contractile function was nearly completely abolished. After resumption of SR, it took ~2 days for atrial contractile function to recover.

Figure 3 illustrates the quantification of atrial contractility during rapid atrial pacing at a cycle length of 160 ms. Figure 3, top, shows the cyclic changes in atrial pressure and diameter at baseline. Four atrial contractions are marked in gray (Fig. 3, left). The corresponding pressure-diameter diagrams are shown in Fig. 3, right. Contractions 1 and 3 occurred during ventricular contraction when the AV valve was closed. Therefore, no significant ejection of blood into the right ventricle occurred, and at the end of the contraction atrial diameter was the same as at the onset of the atrial contraction. Only $\Delta P_{closed}$ was used for quantification of atrial contractility. Contractions 2 and 4 occurred during ventricular diastole when the AV valve is open. During these contractions, blood was pumped from the atria into the ventricles and the right atrial diameter decreased. Both $\Delta P_{open}$ and $\Delta D_{open}$ were measured. After 3 days of AF, the amplitude of the pressure waves and the atrial wall excor-
Compliance and size of fibrillating atrium

During rapid atrial pacing is shown. During the first 5 days of AF, the elasticity constant decreased to <5% of the baseline value, whereas the stiffness constant increased approximately twofold. These changes were completely reversible within 2 days after cardioversion of AF. The offset of the monoeponential compliance curve ranged from 0.2 to 2.7 mmHg and did not change significantly throughout the experiment. In Fig. 6A, representative compliances curves during baseline (acute AF) and after AF lasting 2 and 5 days are depicted. The lines mark $P_{\text{mean}}$ and $D_{\text{mean}}$, indicating the working point on the compliance curve (solid circles). Whereas $P_{\text{mean}}$ did not change, the compliance curve flattened at low atrial diameters, i.e., atrial compliance increased. This caused a rightward shift of the working point on the atrial compliance curve and $D_{\text{mean}}$ increased from 20 to 22.7 mm. Over a broad range of atrial diameters, atrial compliance increased during the first days of AF (Fig. 6B). The compliance at the baseline diameter (compliance$_{\text{base}}$, open triangles) increased twofold. However, in all experiments compliance declined with increasing atrial diameter due to the increasing tension of myocardial muscle fibers. Because $D_{\text{mean}}$ increased during 5 days of AF, the compliance at the working point (compliance$_{\text{work}}$) depends on both the loss of contractility and on the increase of atrial size. In the example given in Fig. 6, the decrease of compliance due to the atrial dilatation just compensated for the increase of compliance due to loss of contractility. Figure 7 shows the changes of atrial compliance at the baseline atrial diameter, the atrial compliance at the working point, $P_{\text{mean}}$, and the diameter during 5 days of AF and during recovery. Compliance$_{\text{base}}$ increased twofold reflecting the progressive flattening of the compliance curve at low atrial diameters. At the working point of the compliance curve, however, the compliance did not significantly change. The increase of $D_{\text{mean}}$ by ~11.8 ± 4.7% within 5 days of AF was mainly caused by an increase of $D_{\text{min}}$ (+23.7 ± 5.1% after 5 days of AF). In contrast, $D_{\text{max}}$ only slightly increased (+4.5 ± 1.9% after 5 days of AF). All changes were reversible within 3 days of SR.

**Discussion**

In the present study, we describe the effects of atrial contractile remodeling on atrial pressure, compliance, and size during the first days of AF. The progressive loss of atrial contractility causes a rightward shift of the working point due to a flattening of the atrial compliance curve. Thus atrial dilatation during the first days of AF is a direct consequence of the loss of atrial contractility. All changes in contractility, compliance, and size were completely reversible within 3 days of SR.

Atrial wall excursions during SR, atrial pacing, and AF. The atrial PV loop during SR consists of an a loop representing the active atrial contraction and a v loop, which is due to passive filling and emptying of the atria during ventricular contraction and relaxation. During atrial pacing the phase of passive atrial emptying becomes shorter. Because the preload of the atrial contraction is higher than during SR, the a loop is more prominent.
During rapid atrial pacing (160 ms) and 2:1 or 3:1 AV block, the shape and strength of atrial contractions depend on the timing between atrial and ventricular contraction. During the ventricular diastole, when the AV valve is open, a simultaneous increase in atrial pressure and decrease in diameter indicate an active atrial contraction ejecting blood into the ventricle. During the ventricular systole, when the AV valve is closed, no blood is ejected into the ventricles and atrial contraction only results in an increase in atrial pressure.

Because of the random nature of AF, the contraction pattern of the fibrillating atrium is chaotic. The shape and strength of the contractions depend on variations in preload, fibrillatory rate, and afterload. Nevertheless, as during rapid atrial pacing, two types of contractions can be distinguished. When the AV valve is open, blood is ejected from the atria into the ventricles, and the atrial diameter shortens during the atrial pressure wave.

In contrast, when the AV valves are closed, no blood is ejected into the ventricles and atrial contraction only results in an increase in atrial pressure.

Atrial contractility measured either during rapid atrial pacing or AF markedly declined during the first 5 days of AF. After 5 days, AF pressure and shortening amplitude of the atria were decreased to <20%. However, this might not only reflect a decrease in atrial intrinsic contractility during AF. Mapping studies (3) in the goat have shown that during acute AF, single propagation wavefronts spread over the right atrial wall. This observation is in line with our finding that each atrial activation during AF is followed by one single pressure wave in the right atrium. After several days of AF the shortening of the AFCL from 152 ± 13 to 85 ± 10 ms results in a pronounced decrease of the path length of the electrical activation allowing 4 to 6 reentry circuits to coexist in the right atrium (3).
circumstances, some areas of the right atrial myocardium will contract while others relax. Changes in atrial pressure and diameter are no longer expected to occur as single contractions of the fibrillating atrium. To overcome this limitation of our methods we also measured atrial contractility during rapid atrial pacing at a cycle length of 160 ms. Under these conditions, the atria are activated regularly with a frequency only slightly below the frequency of AF. Atrial contractility measured during rapid atrial pacing clearly declined during the first days of AF exactly to the same extent as the contractility measured during AF (to \( \approx 20\% \) of baseline). This observation suggests that the decrease of pressure and shortening amplitude of the fibrillating atrium during the first days of AF is mainly due to the loss of intrinsic atrial contractility.

**Time course of contractile remodeling.** In a previous study (10), we investigated the time course of atrial contractile remodeling during AF in the same model. It turned out that within 2 to 3 days of AF the atrial PV loop recorded during SR or slow atrial pacing was almost completely closed. At that time the atrial work index was reduced to \(<10\%\) of the normal value. This loss of atrial contractility was present during both SR and right atrial pacing with a cycle length ranging from 450 to 250 ms. The present study extends this finding to higher atrial frequencies. The time course and extent of atrial contractile remodeling assessed during AF or rapid atrial pacing were roughly the same as when atrial contractile function was measured during SR or atrial pacing at a cycle length of 400 or 300 ms. The recovery of the contractile function was complete after 2 days of SR, indicating that contractile remodeling recovers approximately as quickly as it develops.

**Effect of contractile remodeling on atrial compliance and size.** As a result of the progressive loss of atrial contractility during AF, the pressure-diameter diagram of the fibrillating atrium becomes narrower and the curvature of the compliance curve increases. This change in shape of the compliance curve reflects the decrease of the elasticity constant of the fibrillating atria while the stiffness constant increases. With the progressive loss of atrial contractility, the atrial wall becomes stiffer.
and less elastic because stretch of the atrial wall is no longer damped by the muscle bundles but directly transferred to the more rigid strands of connective tissue. At the baseline atrial diameter, increasing stiffness of the atrial wall leads to flattening of the compliance curve causing the rightward shift of the working point and thus an increase in atrial size. After cardioversion atrial size normalizes as contractility recovers. The changes in atrial contractility and size follow exactly the same time course, suggesting that during the first days of AF, atrial dilatation is mainly related to the loss of atrial contractility. This hypothesis is also supported by the observation that right atrial $D_{\text{max}}$ increases by only $\sim 4.5\%$ during 5 days of AF.

Fig. 5. Effect of contractile remodeling on the compliance curve of the fibrillating atrium. A: RA pressure and diameter at baseline without medication (Med), 30 min after administration of furosemide, and after infusion of 1 liter of saline within 10 min (left). Right, the merged pressure diameter data are shown. $a$, elastic constant; $b$, stiffness. $B$: same recordings after 5 days of AF. Changes of elasticity ($C$) and stiffness ($D$) constant during the first 5 days of AF and during recovery ($n = 8$ goats) are shown. *$P < 0.05$ vs. baseline.
contrast, $D_{\text{min}}$, which is more dependent on atrial contractile function, increases by $\sim 24\%$.

**Limitations and clinical relevance.** This study emphasizes the causal role of loss of atrial contractility in atrial dilatation during the first days of AF. Echocardiographic studies have shown, however, that atrial dilatation during prolonged AF is a progressive process that may continue for months to years (9). Thus, during prolonged AF, additional mechanisms apart from loss of atrial contraction must also contribute to atrial dilatation. Cellular hypertrophy as well as elongation and new synthesis of connective tissue fibers might contribute to the long-term increase in atrial dimensions. Loss of atrial contractility (regardless the underlying mechanism) may facilitate these processes. In paralyzed atria, atrial stretch will be transferred to the passive filaments of the atrial wall, which may enhance elongation of collagen fibers.

Although the present study clearly demonstrates that loss of atrial contractility facilitates atrial dilatation, it is questionable whether increasing atrial contractility would delay or even prevent the slow increase in atrial size during AF. Positive inotropic stimulation of fibrillating atria might increase the metabolic burden of the atrial myocardium, which possibly would (on the long term) enhance atrial structural remodeling and weaken the atrial myocardial wall.

During AF, the atrial refractory period progressively shortens (electrical remodeling), which significantly contributes to increasing stability of AF with time. Electrical remodeling is mainly a consequence of downregulation of the L-type Ca$^{2+}$ inward current ($I_{\text{Ca,L}}$) in atrial cardiomyocytes (17). In a recent study (10), we demonstrated that electrical remodeling follows the same time course as the decrease in atrial contractility. This suggests that (like electrical remodeling) contractile remodelling is also a consequence of reduced $I_{\text{Ca,L}}$. In contrast, loading

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Fig. 6. A: representative RA compliance curves during baseline, after 2 days, and after 5 days of AF. $P_{\text{mean}}$, mean atrial pressure. $D_{\text{mean}}$, mean atrial diameter. ●, Working point on the compliance curves. B: atrial compliance as a function of atrial diameter of the same experiments. Over a broad range of diameters, atrial compliance was higher after 2 and 5 days of AF than at baseline. The compliance at the baseline atrial diameter ($\text{compliance}_{\text{base}} = \cdot$) increased twofold. At high atrial diameters, the difference in compliance was less pronounced. The compliance at the working point ($\text{compliance}_{\text{work}} = \bullet$) did not change during the first 5 days of AF.

Fig. 7. Changes of the atrial compliance at the baseline atrial diameter ($A$; $\text{compliance}_{\text{base}}$), the atrial compliance at the working point ($B$; $\text{compliance}_{\text{work}}$), $P_{\text{mean}}$ ($C$), and the atrial diameter ($D$) during 5 days of AF and during recovery. In $D$, maximal diameter ($D_{\text{max}}$), $D_{\text{mean}}$, and minimal atrial diameters ($D_{\text{min}}$) are normalized to the mean atrial diameter at baseline ($n = 8$ goats). *$P < 0.05$ vs. baseline.
the sarcoplasmic reticulum with $\text{Ca}^{2+}$ using trains of rapid atrial pacing resulted in the same increase of the atrial contractile force of the first post-tachycardia beat in normal and AF goats, indicating that the function of the sarcoplasmic reticulum and the myofilaments is not severely affected in the goat model of AF.

Thus the present study implies a double pathophysiological role of $I_{\text{Ca,L}}$ downregulation in AF. First, it contributes to the shortening of atrial refractoriness and the increase in stability of the arrhythmia with time. Second, during the first days of AF, it underlies loss of atrial contractility and thereby gives rise to progressive dilatation of fibrillating atria, which might (independently from a shortening of refractoriness) contribute to the progressive nature of the arrhythmia.

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