

Electrical and Contractile Remodeling During the First Days of Atrial Fibrillation Go Hand in Hand

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Background—The mechanisms of the atrial contractile dysfunction induced by atrial fibrillation (AF) are not completely understood. In particular, the relation between the atrial dysfunction and electrical remodeling has not yet been studied.

Methods and Results—Seven goats were chronically instrumented with electrodes sutured to the atria and with ultrasonic piezoelectric crystals to record the atrial diameters. A pressure transducer was implanted in the right atrium. After 5 minutes, 3 hours, and throughout the first 5 days of artificially maintained AF, atrial contractile function was measured and the atrial effective refractory period (AERP) was monitored for comparison. Also, the positive inotropic effects of the L-type Ca^{2+} -channel agonist BayY5959 and short trains of rapid atrial pacing were studied. After resumption of sinus rhythm, the recovery of atrial contractile function was followed. After 5 minutes of AF, atrial contractility was decreased by $\approx 55\%$ but recovered completely within 10 minutes. Five days of AF nearly completely abolished the atrial contractile function, and recovery took 2 days. During the first days of AF, the development of the contractile dysfunction followed the same time course as the shortening of AERP (electrical remodeling). In remodeled atria, BayY5959 increased atrial contractility to the same extent as it prolonged AERP. The inotropic effect of short trains of rapid atrial pacing was similar in normal and remodeled atria.

Conclusions—Depending on the duration of AF, different mechanisms contribute to the AF-induced atrial hypocontractility. Atrial contractile remodeling during several days of AF goes hand in hand with electrical remodeling and might be caused by a reduction of the L-type Ca^{2+} -current. (*Circulation*. 2003;107:1433-1439.)

Key Words: arrhythmia ■ atrium ■ contractility ■ remodeling

An important clinical implication of the loss of synchronized atrial contractions during atrial fibrillation (AF) is the high risk of thrombus formation and stroke. The atrial emptying function is impaired not only during AF but also after the cardioversion to sinus rhythm (SR). The degree of atrial contractile dysfunction and the time required for recovery depend on the duration of AF.¹ During the first days to weeks after cardioversion to SR, new thrombus formation has been demonstrated to contribute to the thromboembolic risk associated with AF.²

Experimental and clinical studies have shown that brief episodes of AF may already cause a significant impairment of atrial contractility.³⁻⁵ The loss of atrial function is thought to be triggered by Ca^{2+} overload during AF and might be mediated by a decrease in the release of Ca^{2+} from the sarcoplasmic reticulum.⁶ However, these studies focused on relatively short episodes (several minutes to hours) of AF or rapid atrial pacing. Less is known about the effect of prolonged AF on atrial contractile function. Neither the exact time course of the atrial contractile dysfunction nor the relation with electrical remodeling caused by a downregulation of the L-type Ca^{2+} current (I_{CaL})⁷ has yet been elucidated.

In the present study, we used the goat model of persistent AF⁸ to test the hypothesis that electrical and contractile remodeling are closely related. The AF-induced changes in atrial contractility were compared with changes in electrophysiological properties of the atrium.

Methods

Animal Model

In 7 goats (Dutch land race, weight, 45 to 61 kg), a left intercostal thoracotomy was made under general anesthesia. Five silicon patches, each containing 4 silver electrodes (diameter=2 mm), were sutured to the upper and lower free walls of the right and left atria and to the left ventricular apex. A pair of ultrasonic piezoelectric crystals was sutured to both the right and left atria. One crystal was placed between the aorta and the auricle, and the other was fixed in the middle of the free wall of the atrium (Figure 1). A tip pressure transducer was implanted transvenously in the right atrium. After recovery from surgery (2 to 3 weeks), AF was induced by burst pacing with an automatic fibrillation pacemaker.⁸ The study was performed according to institutional guidelines and was approved by the local ethics committee.

Study Protocol

Before the induction of AF, baseline electrophysiological and contractile properties of both atria were measured. In 3 consecutive

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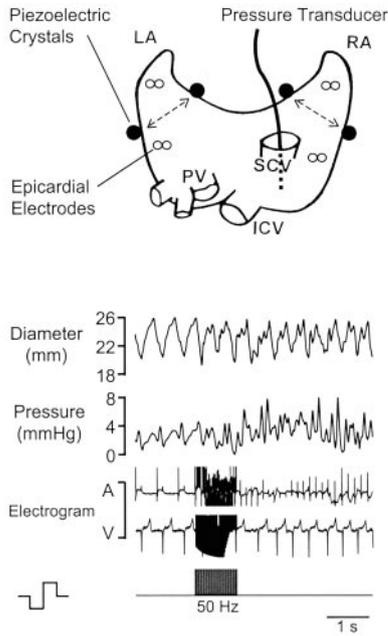


Figure 1. Top, Chronic instrumentation: piezoelectric crystals were sutured to atrial epicardium as indicated. Right atrial pressure was measured with an implantable pressure transducer. LA indicates left atrium; RA, right atrium; SCV, superior caval vein; ICV, inferior caval vein. Bottom, Simultaneous recording of right atrial diameter and pressure. AF was induced by burst stimulation of atria as previously described.⁸

protocols, the effects of 5 minutes, 3 hours, and 5 days of AF were studied. After spontaneous cardioversion of 5 minutes of AF, the atria were paced at 400-ms cycle length, and the atrial effective refractory period (AERP) and atrial contractility were monitored for 30 minutes. After 3 hours of AF, atrial contractility and AERP were monitored during the subsequent 48 hours. During the 5-day protocol, the maintenance of AF was interrupted after 6, 12, and 24 hours as well as after 2, 3, 4, and 5 days of AF. During the first 30 minutes

after termination of AF, atrial contractile function and AERP were studied at different pacing rates. After 5 days of AF, the recovery of atrial contractility was studied for 5 days. To study the mechanism of the AF-induced atrial contractile dysfunction, the positive inotropic effect of the L-type Ca^{2+} -channel agonist BayY5959 was tested (1 mg/kg IV over a period of 10 minutes). This dosage produced a maximal prolongation of AERP (data not shown). The transient hypercontractility induced by a short train of rapid pacing has been demonstrated to reflect the Ca^{2+} -reuptake and storage function of the sarcoplasmic reticulum.⁹ Thus, we also studied the positive inotropic effect of 20 seconds of rapid atrial pacing.

Electrophysiological and Contractile Measurements

The AERP was measured during unipolar pacing at 4 sites (upper and lower right and left atrial free walls) by interpolating single premature stimuli at 4 times threshold. The longest coupling interval that did not result in propagated atrial response was taken to be the AERP.

Atrial contractility was assessed during SR and during atrial pacing at the upper right atrial wall at a cycle length of 250, 300, 350, 400, and 450 ms. The distance between the pair of piezoelectric crystals on the right and left atria was measured with a commercially available sonomicrometer system (Sonometrics) and was taken as the atrial mediolateral diameter. In the right atrium, we also measured the atrial systolic pressure amplitude (ΔP) and the maximal pressure rise velocity ($\Delta P/dt_{max}$) of the a wave. The atrial systolic shortening amplitude (ΔD) was defined as the difference between the atrial diameter at the onset of the a wave (D_0) and the minimal atrial diameter (Figure 2).⁴ The ratio $\Delta D/D_0$ was taken as fractional shortening. Right atrial pressure diameter loops were obtained by plotting right atrial pressure against its mediolateral diameter. These surrogate “pressure-volume (PV) loops” are the result of both right atrial and ventricular contraction. The atrial part of the PV loop (a loop) starts at the onset of the a wave and ends when the same atrial diameter is reached again (Figure 2). The area enclosed by this part of the atrial PV loop was taken as the atrial work index (AWI).

Statistical Analysis

Data are expressed as mean \pm SD. Time constants are given with 95% CIs. Statistical significance was determined with the unpaired Student’s *t* test or by 1-way ANOVA for comparison of multiple groups. Recovery of contractile function was analyzed by nonlinear

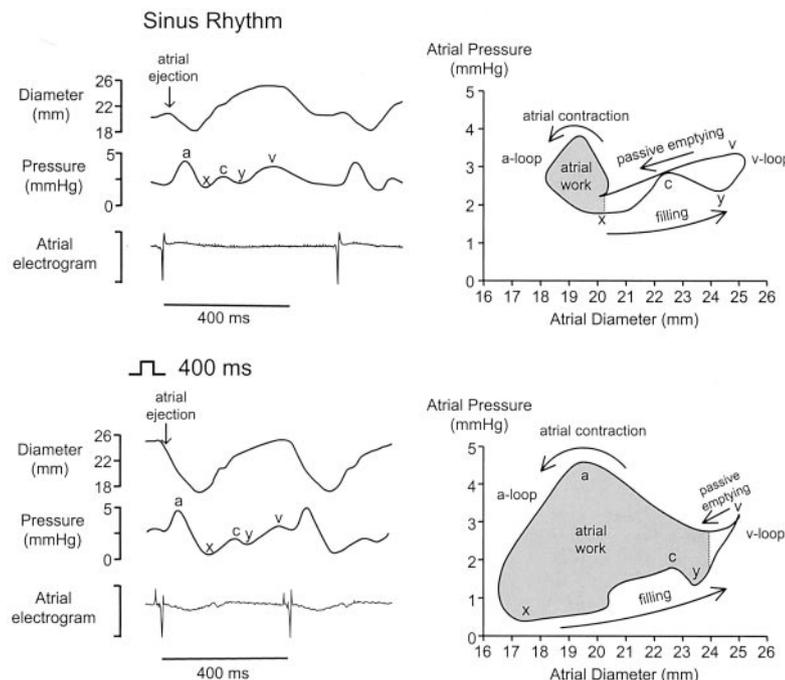


Figure 2. Right atrial diameter and pressure recordings and PV loops during SR (top) and during slow atrial pacing at upper right atrium at a cycle length of 400 ms (bottom). Area enclosed by active part of loop (a loop) is marked in gray and was taken as AWI.

least-squares regression of the data to a 1- or 2-phase exponential association curve. A value of $P < 0.05$ was considered statistically significant.

Results

Atrial Contraction Cycle

Figure 2 (top left) shows the changes in right atrial diameter and pressure during an atrial contraction cycle in SR. Shortly after the atrial depolarization, the atrial pressure increases (a wave) and the diameter declines (atrial ejection). The onset of the ventricular contraction is marked by the closure of the tricuspid valve (c wave). During ventricular systole, blood accumulates in the atria, and atrial pressure and diameter increase (v wave). During early ventricular diastole, the atria empty passively into the ventricles, causing a decline in atrial pressure and diameter. Thus, the atrial PV loop (top right) consists of 2 parts. The a loop represents atrial contraction. The v loop reflects passive filling and emptying of the atria during contraction and early relaxation of the ventricle.

During atrial pacing (cycle length, 400 ms), the atria are still filled at the onset of atrial contraction, and the v loop is small. Because of the high preload, the resulting atrial a wave and the atrial ejection are more pronounced than during SR. As a result, the AWI (gray area) is higher than during SR.

Atrial Hypocontractility Induced by Short-Lasting AF

Figure 3 (top) shows the effect of AF on atrial contractility 15 seconds and 10 minutes after spontaneous termination of AF lasting 5 minutes, 3 hours, 24 hours, or 5 days. Figure 3 (bottom) shows the statistical data of the recovery of atrial contractile function during the first 30 minutes after spontaneous cardioversion. Even 5 minutes of AF significantly impaired atrial contractility. Fifteen seconds after spontaneous cardioversion, AWI was reduced by $\approx 55\%$. However, atrial function recovered completely within 10 minutes of SR. Fifteen seconds after termination of AF lasting for 3 hours, atrial contractility was reduced by $\approx 95\%$. Again, during the first minutes after cardioversion, AWI increased rapidly, but atrial contractility recovered only partly during the first 10 minutes after cardioversion. Rather, AWI remained significantly depressed throughout the first 30 minutes after cardioversion. AF episodes of longer duration were associated with a more pronounced degree of this longer-lasting atrial contractile dysfunction. Whereas after 3 hours of AF, $\approx 70\%$ of atrial contractility was restored during the first minutes after cardioversion, after 5 days of AF, no early recovery of atrial contractile function occurred, and even 30 minutes after cardioversion, atrial contractility was depressed by $>90\%$.

Time Course of Electrical and Contractile Remodeling

The post-AF atrial contractile dysfunction was assessed during right atrial pacing (400 ms) 30 minutes after spontaneous cardioversion of AF (Figure 4). With increasing duration of AF, the amplitude of the a wave and the atrial systolic shortening progressively declined (top left). At the same time, the area enclosed by the right atrial PV loop decreased (top right). After 12 hours of AF, AWI was reduced by 50%, and after 2 days, the loop was almost closed,

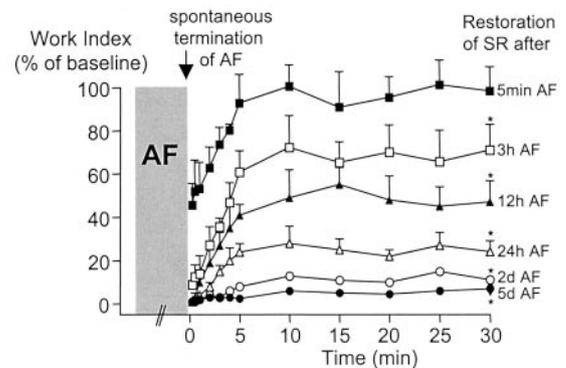
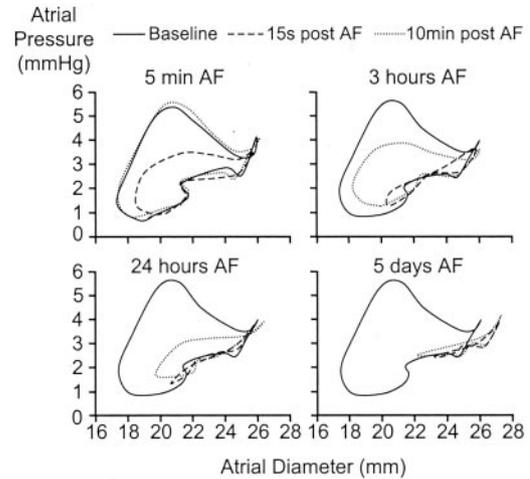


Figure 3. Early recovery of atrial contractility after spontaneous termination of AF. Top, Right atrial PV loops at baseline and 15 seconds and 10 minutes after termination of AF. All loops were recorded at 400-ms cycle length. Bottom, Statistical data from $n=7$ goats. $*P < 0.05$ vs baseline.

indicating that the atrial contractile function was nearly completely abolished.

Figure 4 (bottom left) compares the time courses of the atrial contractile dysfunction and electrical remodeling (shortening of the AERP). Both during the first 5 days of AF and after resumption of SR, the changes in AWI and AERP followed exactly the same time course. The AWI correlated positively with AERP ($r=0.878$, $P < 0.01$) (bottom right).

Tables 1 and 2 show the numerical data of electrical and contractile remodeling during 5 days of AF and its recovery. During the 5 days of AF, right atrial ΔP and $\Delta P/dt_{max}$ declined to $<5\%$ of control. In the right and left atria, the atrial fractional shortening declined to $\approx 45\%$ of the baseline value. Right and left atrial diameters (D_0) increased to $108.3 \pm 1.1\%$ and $108.5 \pm 1.2\%$ of baseline, respectively ($P < 0.05$), which was reversible within 2 to 3 days of SR. Neither the time course nor the extent of contractile remodeling differed between right and left atria (Figure 5, top). In both atria, the fractional shortening correlated positively with the shortening of the AERP during the first days of AF (Figure 5, bottom).

Rate Adaptation of Atrial Contractility

Incremental atrial pacing with a cycle length between 450 and 250 ms increased the size of the atrial PV loop (Figure 6). At

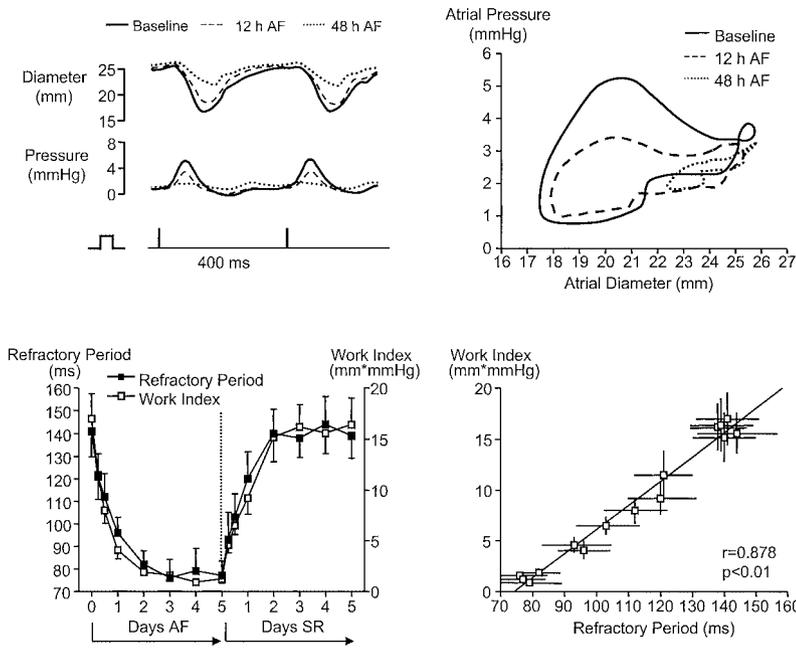


Figure 4. Time course of electrical and contractile remodeling during first days of AF. Atrial contractile function and AERP were recorded 30 minutes after spontaneous cardioversion during atrial pacing at a cycle length of 400 ms. Top, Right atrial pressure and diameter recordings at baseline and after 12 and 48 hours of AF (left) and respective PV loops (right). Bottom left, Time course of electrical and contractile remodeling and reversibility. Bottom right, Correlation between right AWI and refractory period. n=7 goats.

baseline, AWI was 4.8 ± 0.8 mm \times mm Hg during SR and reached a maximum at a pacing interval of 300 ms (45.1 ± 5.6 mm \times mm Hg). During the first days of AF, atrial contractility declined progressively at all pacing rates. However, the positive rate adaptation was preserved until, after 5 days of AF, atrial contractility was nearly completely lost at all rates.

Effect of Transient Rapid Atrial Pacing on Atrial Contractility

Twenty seconds of rapid atrial pacing (cycle length of 180 ms) induced a short-lasting increase in atrial contractility in normal and remodeled atria (Figure 7, top). In the control goat, the first beat after the cessation of the tachycardia was twice as strong as during steady state. The work index was increased by 11.8 ± 4.9 mm \times mm Hg. After 3 days of AF, the

steady-state atrial contraction was nearly completely lost, but immediately after the cessation of 20 seconds of rapid pacing, the work index was increased to a similar extent as under control conditions ($+12.1 \pm 2.9$ mm \times mm Hg, $P=NS$).

Effect of BayY5959

After 3 days of AF, the L-type Ca^{2+} -channel agonist BayY5959 partly restored atrial contractility (Figure 7, bottom). The AWI increased from 0.8 ± 0.4 to 7.9 ± 1.6 mm \times mm Hg (n=5 goats), which was $46.3 \pm 5.2\%$ of atrial contractility lost during 3 days of AF. At the same time, AERP was prolonged from 80.8 ± 10.3 to 117.6 ± 20.6 ms, $50.2 \pm 3.7\%$ of the AERP shortening induced by 3 days of AF. Thus, BayY5959 increased AWI to a similar extent as it prolonged AERP. There was a strong correlation between AWI and AERP measured at control and before and after the

TABLE 1. Electrical and Contractile Remodeling in Right and Left Atria During the First 5 Days of AF

	Atrial Fibrillation					
	Baseline	6 Hours	12 Hours	24 Hours	2 Days	5 Days
AERP, ms						
Right	141 \pm 12	121 \pm 10*	112 \pm 10*	96 \pm 7*	82 \pm 6*	77 \pm 7*
Left	132 \pm 19	118 \pm 19	105 \pm 12*	85 \pm 12*	72 \pm 13*	72 \pm 13*
AWI, mm \times mm Hg						
Right	17.0 \pm 2.6	11.5 \pm 2.4*	8.0 \pm 1.3*	4.1 \pm 0.9*	1.9 \pm 0.3*	1.2 \pm 0.4*
ΔP , mm Hg						
Right	2.5 \pm 0.4	1.5 \pm 0.3*	1.2 \pm 0.3*	0.7 \pm 0.1*	0.3 \pm 0.1*	0.1 \pm 0.1*
$\Delta P/dt_{max}$, mm Hg/s						
Right	90 \pm 15	60 \pm 12*	43 \pm 12*	19 \pm 8*	13 \pm 5*	0 \pm 3*
$\Delta D/D_0$, %						
Right	21.4 \pm 3.5	16.4 \pm 2.6*	16.1 \pm 2.7*	15.0 \pm 2.6*	12.4 \pm 1.9*	9.3 \pm 1.0*
Left	24.7 \pm 2.4	18.2 \pm 3.3*	16.2 \pm 2.8*	14.8 \pm 2.2*	13.9 \pm 2.5*	10.9 \pm 2.0*

* $P < 0.05$ vs baseline.

TABLE 2. Reverse Electrical and Contractile Remodeling in Right and Left Atria After 5 Days of AF

	5 Days AF	Sinus Rhythm				
		6 Hours	12 Hours	24 Hours	2 Days	5 Days
AERP, ms						
Right	77±7	93±12	103±10*	120±12*	140±11*	139±10*
Left	72±13	88±18	100±13*	121±15*	138±17*	136±15*
AWI, mm×mm Hg						
Right	1.2±0.4	4.6±0.8*	6.5±0.9*	9.2±1.6*	15.2±2.4*	16.4±2.6*
ΔP, mm Hg						
Right	0.1±0.1	0.3±0.2	1.1±0.3*	1.7±0.2*	2.4±0.3*	2.4±0.4*
ΔP/dt _{max} , mm Hg/s						
Right	0±3	13±9	38±10*	67±9*	92±13*	88±14*
ΔD/D ₀ , %						
Right	9.3±1.0	12.8±1.2*	12.7±1.6*	17.4±2.7*	19.9±3.0*	19.7±3.0*
Left	10.9±2.0	14.6±3.6	15.4±3.6	20.1±2.9*	23.4±3.1*	23.2±3.2*

*P<0.05 vs 5 days AF.

administration of BayY5959 after 3 days of AF ($r=0.931$, $P<0.01$).

Different Time Domains During Recovery of Atrial Contractile Function

Figure 8 shows a direct comparison between the time courses of recovery of the atrial function after 5 minutes, 3 hours, and 5 days of AF. The recovery of contractile function after 5 minutes of AF took several minutes, whereas after 5 days of AF, it required 2 days. After 3 hours of AF, the recovery was biphasic, $t_{1/2}$ of the early recovery being not significantly different from $t_{1/2}$ after 5 minutes AF (Table 3). The delayed

recovery followed the same time course as the recovery of the contractile function after 5 days of AF. In both time domains, recovery of AERP shortening occurred with the same time constant as recovery of contractile function (Table 3).

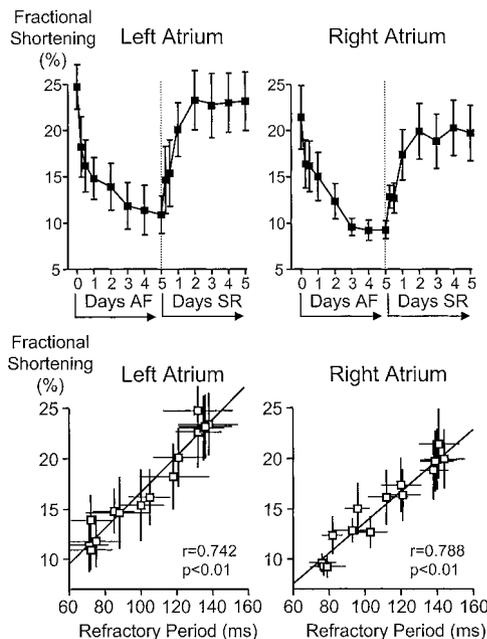


Figure 5. Top, Changes in fractional shortening of left and right atria during 5 days of AF and recovery. Bottom, Correlation between fractional shortening and refractory period. $n=7$ goats.

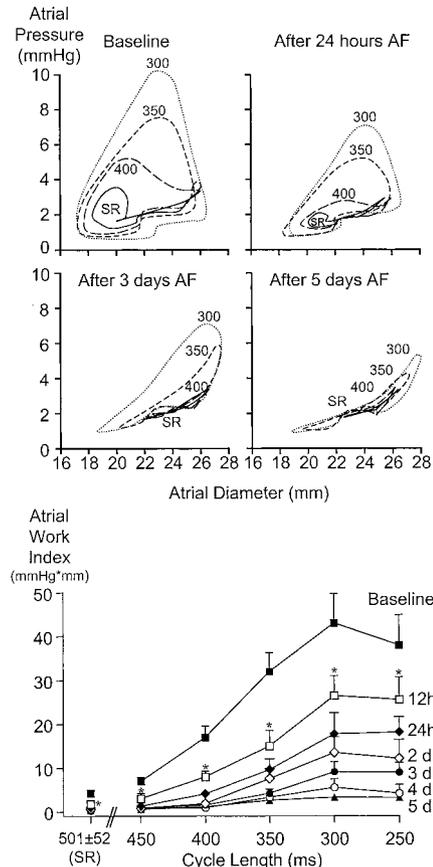


Figure 6. Effect of different pacing rates on atrial contractile function at different stages of remodeling process. Top, Representative PV loops recorded during SR and during pacing at 400-, 350-, and 300-ms cycle length. Bottom, Statistical data from 7 goats. *P<0.05 vs baseline.

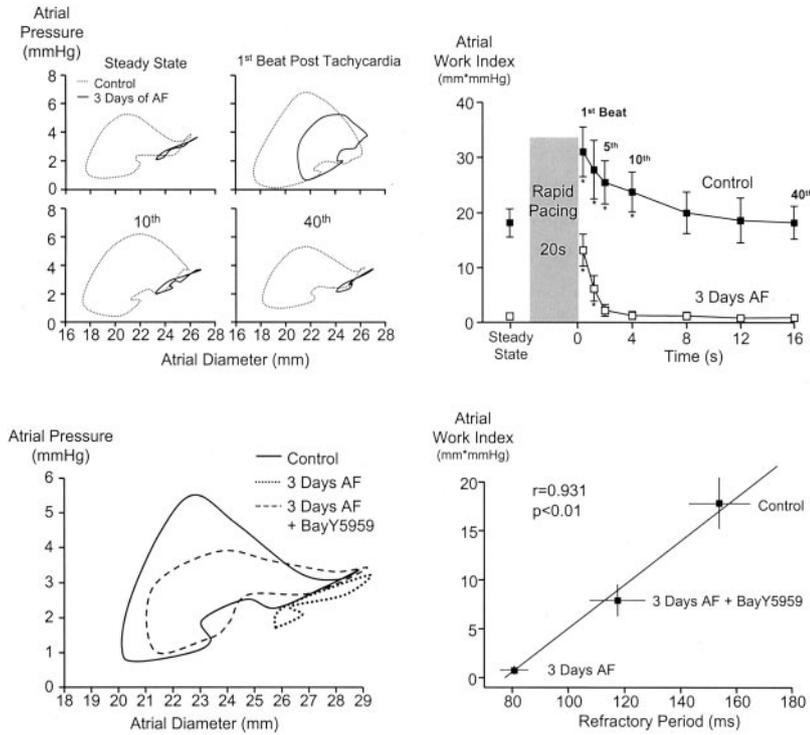


Figure 7. Top, Effect of 20 seconds of rapid atrial pacing (180-ms cycle length) on atrial contractility at baseline and after 3 days of AF. PV loops were recorded at 400-ms cycle length. n=7 goats. *P<0.05 vs steady state. Bottom, In remodeled atria, BayY5959 partly restored atrial contractility and prolonged AERP (atrial pacing, 400 ms). AWI and AERP measured during control and before and after application of BayY5959 after 3 days of AF were significantly correlated. n=5 goats.

Discussion

The present study provides the first evaluation of the time course of contractile remodeling during the first days of AF. The loss of atrial contractility followed exactly the same time course as the shortening of the atrial refractory period. This strongly suggests that AF-induced electrical and contractile remodeling is a result of the same cellular mechanisms. Our study also demonstrated that atrial hypocontractility caused by short episodes of AF (5 minutes) has much faster onset and offset kinetics than the atrial contractile dysfunction after several days of AF.

Atrial PV Loop

The atrial PV loop during SR consists of the a loop representing the active atrial contraction and the v loop, which is a result of the passive filling and emptying of the atria during ventricular contraction and relaxation. The latter reflects the reservoir function of the atria.¹⁰ During slow overdrive pacing, the phase of passive atrial emptying becomes shorter and fuses with the active atrial shortening. Although less

clearly distinguishable, both the atrial pump function and the reservoir function are still present under these conditions as well. This becomes obvious when the atrial contraction is completely abolished after 3 days of AF. At that time, the amplitude and pressure rise velocity of the a wave and AWI were all reduced to <10% of control. In contrast, atrial fractional shortening was reduced to only ≈45% of baseline. This is because the atria are still filling and emptying passively during ventricular contraction and relaxation. Although the reduced atrial fractional shortening certainly reflects atrial contractile dysfunction, the reservoir function of the atria still causes significant excursions of the atrial wall. This might explain the seemingly conflicting results between a pronounced reduction in atrial cellular contractility after 6 weeks of rapid atrial pacing in dogs (−70%)¹¹ and the rather moderate reduction of the atrial fractional shortening (−19.3%) in the same model.¹²

Transient Atrial Hypocontractility Versus Contractile Remodeling

Our study confirms previous observations that after brief episodes of AF, a transient phase of atrial hypocontractility exists.^{3–6} This transient atrial hypocontractility had much shorter onset and offset

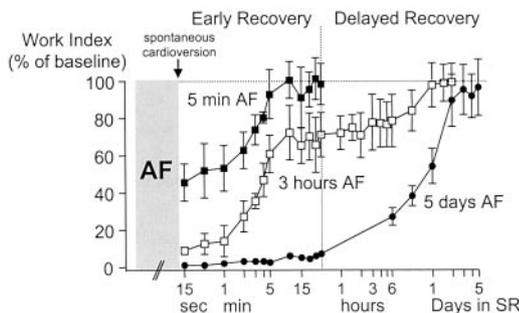


Figure 8. Different time domains of recovery of contractile function after termination of AF of 5 minutes, 3 hours, and 5 days in duration. Atrial contractility was measured at 400-ms cycle length. n=7 goats.

TABLE 3. Time Constants of Recovery of Contractile and Electrical Function in Different Time Domains

	3 Hours AF			
	5 Minutes AF	Early Recovery	Delayed Recovery	5 Days AF
AWI	2.1 (1.6–3.2)	2.0 (1.5–2.9)	802 (655–1207)	987 (777–1398)
AERP	2.3 (1.5–3.9)	ND	893 (722–1194)	801 (678–1161)

ND indicates not done. Within the respective time domains, the time required for 50% recovery (t_{1/2} in min) of AWI and AERP were not different. n=7 goats.

kinetics than the atrial contractile dysfunction after 2 days of AF. Because in a previous study, even 3 repetitive cycles of AF for 5 days did not have a cumulative effect on AF duration or changes in refractoriness,¹³ it is unlikely that repetitive induction of AF in the 3 consecutive protocols underlies these differences in kinetics. Rather, the slower kinetics of the AF-induced atrial contractile dysfunction induced by several days of AF reflect a different cellular mechanism causing the contractile dysfunction. Thus, minutes after termination of AF, atrial contractile function is depressed by both the rapidly reversible hypocontractility and contractile remodeling. Measurements of atrial contractility immediately after termination of AF might therefore overestimate the degree of contractile remodeling. To avoid this confounding factor, we waited 30 minutes after cardioversion of AF before atrial contractile remodeling was assessed.

Time Course and Mechanisms of Contractile Remodeling

Echocardiographic studies in patients showed that the transmitral a wave velocity was clearly lower after 6 weeks of AF than after 2 weeks.¹ In contrast, in the dog, the left atrial fractional shortening was diminished by $\approx 18\%$ after 2 weeks of rapid atrial pacing and did not decrease any further after 4 or 6 weeks of rapid pacing.¹² In the present study, we followed the exact time course of contractile remodeling in the chronically instrumented goat model of AF. It turned out that within 2 days of AF, the atrial contractile function was almost completely abolished. Comparison of the fractional shortening of right and left atria revealed no differences in extent or time course of contractile remodeling.

The development of AF-induced atrial contractile dysfunction and its reversal followed exactly the same time course as the shortening of the refractory period (electrical remodeling). Obviously, the 2 phenomena are very closely linked, indicating that electrical and contractile remodeling may share common mechanisms. Electrical remodeling was shown to be caused primarily by a reduction of I_{CaL} ,⁷ which might explain the pronounced decrease in atrial contractility. This hypothesis is supported by our observation that in remodeled atria, the L-type Ca^{2+} -channel agonist BayY5959 increased atrial contractility to the same extent as it prolonged the refractory period. In contrast, the Ca^{2+} -reuptake and storage function of the sarcoplasmic reticulum was not affected. The increase in atrial contractility induced by 20 seconds of rapid atrial pacing was similar in normal and in remodeled atria, suggesting that atrial contractile function in remodeled atria is not limited by dysfunction of the sarcoplasmic reticulum.

Limitations and Clinical Relevance

Recent work has shown that in humans too, AF-induced electrical remodeling is completely reversible within a few days.¹⁴ This is true even after prolonged duration of AF (months to years). In contrast, recovery of the contractile function after cardioversion in these patients takes weeks.¹ This discrepancy strongly suggests that apart from a reduction of I_{CaL} , additional mechanisms contribute to the contractile dysfunction of atrial myocardium in patients with chronic AF. One possibility is that atrial myolysis explains the loss of contractility after chronic AF. However, in right atrial muscle preparations of patients with chronic AF, the sarcomere content and the contractile reserve were reduced by only $\approx 15\%$, indicating that the contribution of

myolysis to the atrial dysfunction in AF patients is limited.¹⁵ Mihm et al¹⁶ suggested that altered energetics of the myofibrils resulting from oxidative modification of the myofibrillar proteins also contributes to the loss of atrial contractility. In addition, slowing of the transfer of Ca^{2+} from nonjunctional to junctional parts of the sarcoplasmic reticulum and a depressed release function of the ryanodine receptor could reduce atrial contractile function.¹⁷

Our results emphasize that prevention of the atrial contractile dysfunction might reduce the thromboembolic risk after cardioversion. Some benefit in this respect was demonstrated by verapamil^{4,5} and the Na^+/H^+ -exchange inhibitor HOE642 during short-lasting AF.³ No therapeutic strategy exists for prevention of atrial contractile dysfunction after prolonged AF, and anticoagulant therapy has to be continued after cardioversion for some time.

Acknowledgments

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