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Chronic Atrial Dilation, Electrical Remodeling, and Atrial Fibrillation in the Goat

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OBJECTIVES This study was designed to investigate the mutual effects of chronic atrial dilation and electrical remodeling on the characteristics of atrial fibrillation (AF).

BACKGROUND Both electrical remodeling and atrial dilation promote the inducibility and perpetuation of AF.

METHODS In seven goats AF was induced during 48 h by burst pacing, both at baseline and after four weeks of slow idioventricular rhythm (total AV block). Atrial size and refractory period (AERP) were monitored together with the duration and cycle length of AF paroxysms (AFCL). After four weeks of total atrioventricular (AV) block, the conduction in both atria was mapped during AF. Six non-instrumented goats served as controls.

RESULTS At baseline, AF-induced electrical remodeling shortened AERP and AFCL to the same extent (from 185 ± 9 ms to 149 ± 14 ms [$p < 0.05$] and from 154 ± 11 ms to 121 ± 5 ms [$p < 0.05$], respectively). After four weeks of AV block the right atrial diameter had increased by 13.2 ± 3.0% ($p < 0.01$). Surprisingly, in dilated atria electrical remodeling still shortened the AERP (from 165 ± 9 ms to 132 ± 15 ms [$p < 0.05$]) but failed to shorten the AFCL (140 ± 19 ms vs. 139 ± 11 ms [$p = 0.98$]). Mapping revealed a higher incidence of intra-atrial conduction delays during AF. Histologic analysis showed no atrial fibrosis but did reveal a positive correlation between the size of atrial myocytes and the incidence of intra-atrial conduction block ($r = 0.60$, $p = 0.03$).

CONCLUSIONS In a goat model of chronic atrial dilation, AF-induced electrical remodeling was unchanged. However, AFCL no longer shortened during electrical remodeling. Thus, in dilated atria a wider excitable gap exists during AF, probably caused by intra-atrial conduction defects and a higher contribution of anatomically defined re-entrant circuits. (J Am Coll Cardiol 2006; 47:644–53) © 2006 by the American College of Cardiology Foundation

Perpetuation of atrial fibrillation (AF) is promoted by an atrial substrate that favors initiation and continuation of re-entering wavelets. Most patients with AF have structural heart disease often leading to more or less dilation of the atria. Large clinical trials have identified atrial dilation as an independent risk factor for the development of AF (hazard ratio 1.4 per 5 mm increment in left atrial size) (1,2). An increase in atrial size increases the possible number of multiple wavelets during AF. Furthermore, an elevated intra-atrial pressure will increase the atrial wall stress, which may result in local intra-atrial conduction disturbances (3). In addition, atrial dilation may promote focal arrhythmias that trigger self-perpetuating AF or maintain irregular atrial activation (fibrillatory conduction) (4,5). During the first months of atrial fibrillation, the atrial substrate becomes modified by electrical, contractile, and structural remodeling. This may further dilate the atria, impair conduction, and stabilize AF.

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Recently we showed that in goats with chronic atrioventricular (AV) block, paroxysms of AF become progressively longer when the atria are slowly dilating (6). Whereas atrial dilation did not change the atrial refractory period, mapping during rapid pacing unmasked the presence of a higher degree of intra-atrial conduction disturbances. In the present study, we compared the time course and degree of electrical remodeling in dilated and non-dilated atria and studied the interaction between electrical remodeling and dilation on the cycle length and persistence of AF.

METHODS

Animal model. Sixteen female goats weighing 51.9 ± 3.6 kg were used for this study. Animal handling was performed according to the European directive on laboratory animals (86/609/EEC), and the study protocol was approved by the ethics committee of the University of Maastricht. Seven goats were chronically instrumented. Under general anesthesia (10 to 15 mg/kg intravenous thiopental; 1% halothane, and a 1:2 mixture of O_2 and N_2O) two bipolar screw-in leads were implanted transvenously in the anterolateral and posteroseptal wall of the right atrium. At the tip of each lead a pair of piezoelectric crystals (diameter 2 mm; Sonometrics, London, Canada) was mounted, together with two silver electrodes (1.2 × 4 mm) to record atrial electro-

Abbreviations and Acronyms

AERP = atrial effective refractory period
AF = atrial fibrillation
AFCL = atrial fibrillation cycle length
AV = atrioventricular
CT = conduction time
EGAF = excitable gap during atrial fibrillation
LA = left atrium
RA = right atrium
RPAF = refractory period during atrial fibrillation

grams. A third unmodified lead was screwed into the right ventricular apex. Three silver plates (diameter 15 mm) were implanted subcutaneously to serve as indifferent electrodes.

Electrophysiologic measurements. Two weeks after lead implantation, the size of the right atrium (RA) was measured together with the normal electrophysiologic properties of the atrium. The atrial effective refractory period of the RA was determined at pacing intervals (S1-S1) between 400 and 200 ms. The longest S1-S2 interval (4× threshold, 2-ms steps) not resulting in a propagated response was taken as the atrial effective refractory period (AERP). The stability of AF was determined by measuring the duration of AF paroxysms induced by repetitive burst pacing during a period of 1 h. The median AF cycle length and the fifth percentile were determined from at least 100 consecutive AF intervals. After this baseline study, atrial fibrillation was induced for 48 h by burst pacing, and the degree of

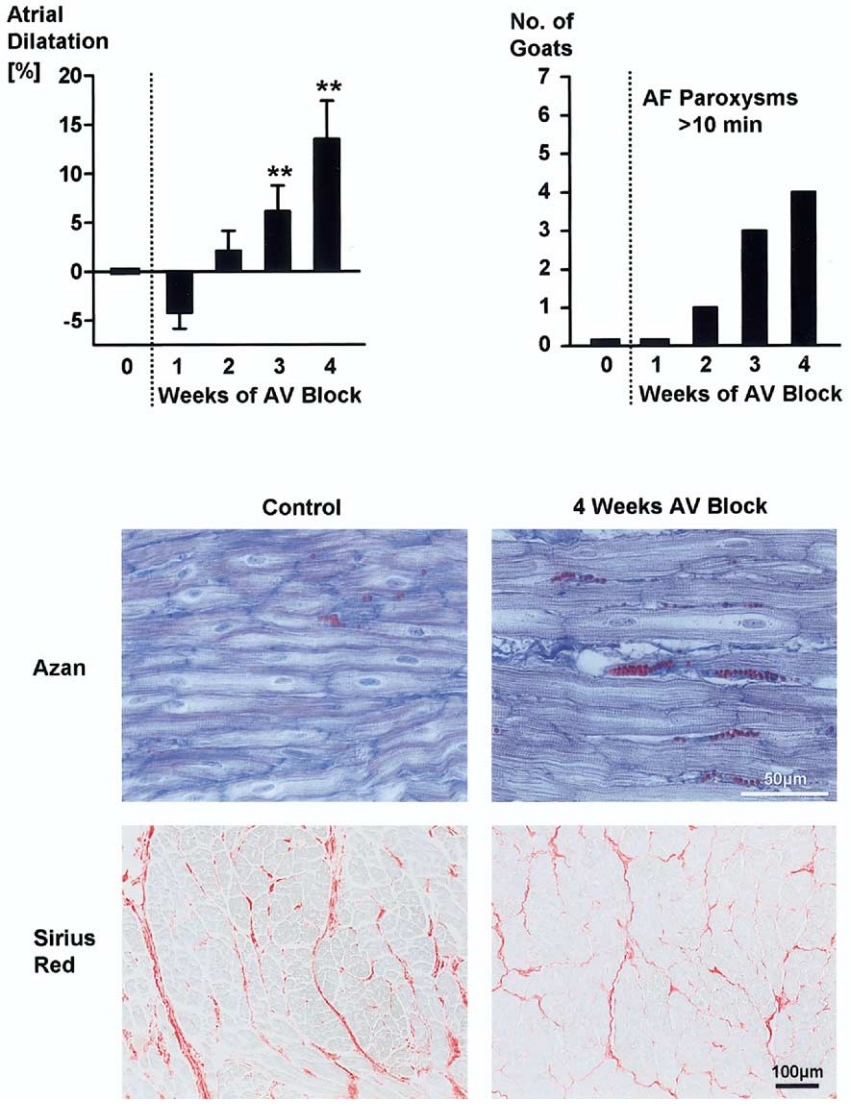

Figure 1. (Top left) Relative changes in right atrium (RA) size measured during the first four weeks of total atrioventricular (AV) block. The average RA diameter was measured during five consecutive ventricular cycles from the distance between the tips of two screw-in leads (ultrasound crystals). Immediately after His bundle ablation **(dotted line)**, the atrial diameter decreased owing to the lower ventricular rate. The size of the atria then progressively increased, resulting in 13.2 ± 3.0% dilation after four weeks of AV-block. $^{**}p < 0.01$. **(Top right)** Time course of the increase in duration of atrial fibrillation (AF) paroxysms. In four of seven animals, the AF episodes lasted longer than 10 min after four weeks of idioventricular rhythm. **(Lower panels)** Photomicrographs from sections of the left atrium. A modified azan stain was used to determine cell size, and Sirius red was used to visualize collagen. After four weeks of AV block, the atrial myocytes were clearly enlarged and the amount of collagen was not increased.

Table 1. Comparison of AF-Induced Electrical Remodeling and its Effect on AFCL in Normal and Dilated Atria

	Baseline (Normal Atria)								4 Weeks AV Block (Dilated Atria)							
	Sinus Rhythm				After 48 h AF				Sinus Rhythm				After 48 h AF			
Goat	AERP 200 (ms)	AERP 350 (ms)	AFCL p50 (ms)	AFD (s)	AERP 200 (ms)	AERP 350 (ms)	AFCL p50 (ms)	AFD (s)	Atrial Dilation (%)	AERP 200 (ms)	AERP 350 (ms)	AFCL p50 (ms)	AFD (s)	AERP 200 (ms)	AERP 350 (ms)	AFCL p50 (ms)	AFD (s)
1	—	222	200	1	142	181	115	1	16.0	147	146	130	2,472	118	—	123	>24 h
2	—	200	165	44	—	—	145	>24 h	16.1	170	208	143	>24 h	—	—	—‖	—
3	168	180	129	2	144	122	121	1	12.5	136	150	120	5,447	—	—	108	>24 h
4	160	194	170	3	—	—	118	8	12.9	166	184	194	2	156	158	233	402
5	152	184	132	1	152	180	120	1	11.0	134	160	105	1	114	124	113	1,408
6	148	168	118	18	148	148	102	3	25.1	—	170	142	14,099	—	152	132	>24 h
7	146	148	164	22	122	114	129	38	−1.3	120	140	141	36	94	92	131	2,195
Mean	154.8	185.1	154	5	141.6	149*	121.4*	13	13.2	145.5	165.4	139.3	382‡	120.5*	131.5*	140	9,638†§
SEM	4.1	8.9	10.9		5.2	14.0	5.0		3.0	7.9	9.1	10.5		13.0	15.1	19.0	

*$p < 0.05$ vs. sinus rhythm. †$p < 0.01$ vs. sinus rhythm. ‡$p < 0.05$ vs. baseline. §$p < 0.01$ vs. baseline. ‖AF was cardioverted after 24 h (AFCL 139 ms).
AERP = atrial effective refractory period; AF = atrial fibrillation; AFCL p50 = median atrial fibrillation cycle length; AFD = duration of induced atrial fibrillation episodes; mean AFD is given as geometric mean; SEM = standard error of the mean.

electrophysiologic atrial remodeling was measured (7). The goats were then left in sinus rhythm, and after complete reversal of electrical remodeling (two days) total AV block was created by transcutaneous radiofrequency ablation of the His bundle. The resulting slow idioventricular rhythm ranged between 33 and 67 beats/min. In case the ventricular rate was lower than 40 beats/min, the ventricles were paced at 45 beats/min. Starting two days after His bundle ablation, the atrial diameter was measured once a week together with the average duration of AF paroxysms induced by burst pacing during 1 h. After four weeks of total AV block, when the atria were moderately dilated, the atria were electrically remodeled again by maintaining AF for 48 h. Special attention was paid to the effects of electrical remodeling on atrial refractory period, AF cycle length, and duration of AF paroxysms. After complete reversal of electrical remodeling (more than two days of sinus rhythm), the animals were killed and the right and left atria were mapped (see the following text).

In two goats, the refractory period and temporal excitable gap during AF were measured by slow fixed-rate pacing (1 Hz) (8). After four weeks of AV block and two days of electrical remodeling, 600 consecutive stimuli (4× threshold) with a fixed interval of 1 s were applied through one of the right atrial leads. A bipolar electrogram was recorded close to the pacing site. From this electrogram, the random coupling intervals between the fibrillation waves and the stimuli (AF-S) were measured together with the associated AF cycle length (AFCL). The coupling interval that captured the fibrillating atria in 50% of cases was taken as the RP_{AF}. The temporal excitable gap was calculated by subtracting the RP_{AF} from the local median AFCL.

Atrial conduction during AF was mapped under general anesthesia after exposing the heart through a left thoracotomy. A spoon-shaped mapping electrode (diameter 4 cm, 242 unipolar electrodes, interelectrode spacing 2.4 mm) was placed on the free wall of the right and left atria. Atrial fibrillation episodes, lasting longer than 30 s, were induced by burst pacing, and the activation pattern during 4 s of AF was mapped. Intra-atrial conduction block was defined as a local conduction time (CT) between neighboring electrodes of >24 ms (apparent conduction velocity <10 cm/s). A CT of >8 ms (conduction velocity <30 cm/s) was defined as slow conduction (6). Because normal conduction velocity in caprine atria is about 100 cm/s, using these criteria will underestimate rather than overestimate the amount of intra-atrial conduction disturbances.

Three non-instrumented goats with chronic AV block were used for additional mapping studies. Six non-instrumented goats in sinus rhythm served as a control group. Hemodynamic measurements were made using a Swan-Ganz catheter with a pressure transducer at the tip (Sentron, Zoetermeer, the Netherlands).

Histology. After mapping, the heart was excised from the chest, the remnants of the main vessels were cut, and the blood was removed. The heart was then weighed and fixed

in buffered formalin. Samples of the trabeculated parts of both atria were embedded in paraffin. Four-μm sections were stained by a modified azan stain to determine myocyte dimensions or by Sirius red for quantification of collagen (9). The relative collagen content was defined as the area positive for Sirius red divided by the total tissue area. Of each section, an area of 2.4 mm^2 was examined. Pericardial, endocardial, and perivascular fibrosis was excluded from the measurements.

Statistics. Results are expressed as mean values ± standard error of the mean (SEM). The duration of AF episodes is expressed as the geometric mean ± geometric SEM. An unpaired *t* test was used to determine differences between two groups. Multiple groups were compared by analysis of variance (ANOVA). A p value of <0.05 was considered statistically significant.

RESULTS

Atrial dilation due to complete AV block. After four weeks of idioventricular rhythm, heart weight was increased compared to the control group (343 ± 16 g [n = 7] vs. 266 ± 31 g [n = 6]; $p < 0.05$). Body weight was the same in both groups. In the instrumented goats, His bundle ablation slowed the ventricular rate from 113.7 ± 4.5 beats/min to 53.5 ± 2.7 beats/min ($p < 0.01$). The atrial rate slightly increased but normalized within one to two weeks. After four weeks of idioventricular rhythm, the atrial rate and left ventricular systolic pressure were unchanged (106.8 ± 4.7 beats/min vs. 113.7 ± 4.5 beats/min; p = 0.32; and 135.0 ± 12.2 mm Hg vs. 129.8 ± 7.6 mm Hg; p = 0.71). Right atrial pressure increased from 5.7 ± 0.7 mm Hg to 8.8 ± 0.7 mm Hg ($p < 0.01$), pulmonary wedge pressure from 7.4 ± 1.1 mm Hg to 11.1 ± 0.8 mm Hg ($p < 0.05$), and left ventricular end-diastolic pressure from 8.6 ± 1.2 mm Hg to 12.5 ± 1.2 mm Hg (p = 0.06). The amount of atrial dilation was 13.2 ± 3.0% (absolute increase 3.7 ± 1.1 mm; p = 0.02) (Fig. 1). Histologic analysis of the atrial wall showed that the right and left atrial myocytes were clearly enlarged. The average cell length and diameter were 110 ± 7 μm and 16.5 ± 1.2 μm, respectively, versus 88 ± 2 μm and 13.2 ± 0.8 μm, respectively, in control animals ($p < 0.05$; p = 0.06; respectively). The relative tissue area occupied by collagen was smaller after four weeks of AV block (8.0 ± 0.6% vs. 12.2 ± 0.6%; $p < 0.01$). However, because of the increased volume of the myocytes, the absolute collagen content of the atrial wall remained unchanged.

During the first four weeks of slow idioventricular rhythm, the average duration of pacing-induced AF paroxysms progressively prolonged from 5 s to 382 s ($p < 0.05$) and in four of seven animals persisted for more than 10 min (Fig. 1,

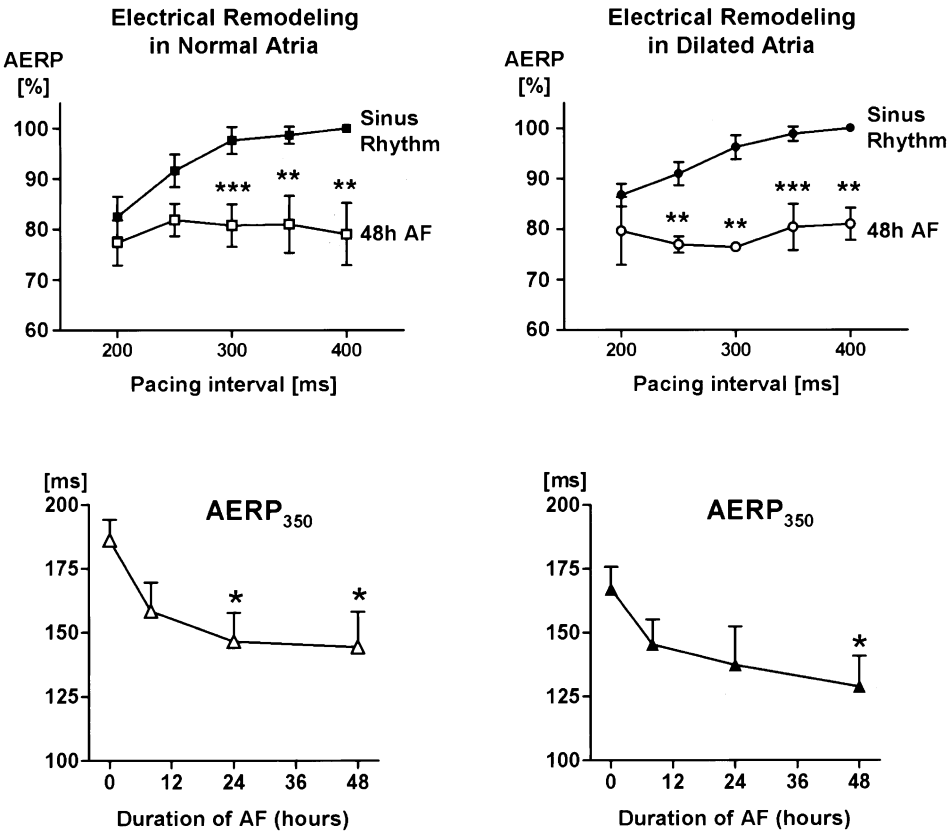

Figure 2. (Upper panels) Effects of 48 h of atrial fibrillation (AF) on atrial effective refractory period (AERP) in normal and dilated atria at pacing intervals between 400 and 200 ms (n = 7). In dilated atria, electrical remodeling shortened the AERP to a similar extent as in normal atria. **(Lower panels)** The time course of electrical remodeling (changes in $AERP_{350}$) during the first 48 h of AF in normal and dilated atria. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

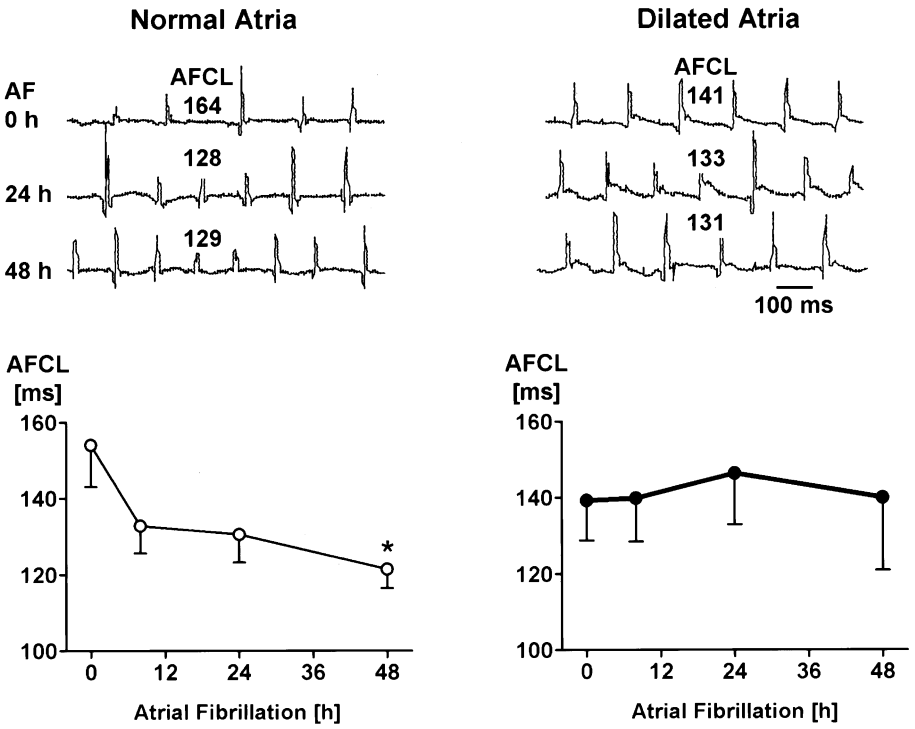

Figure 3. (Top) Bipolar electrograms from the right atrial wall after 0, 24, and 48 h of atrial fibrillation (AF) in dilated and nondilated atria. The numbers indicate the median AF cycle length (AFCL). **(Bottom)** Effects of electrical remodeling on AFCL during the first 48 h of AF (n = 7). *p < 0.05.

Table 1). Spontaneous atrial ectopic beats or paroxysms of AF were never observed.

Electrical remodeling in dilated and non-dilated atria. In Table 1 and Figure 2, the effects of 48 h of AF on right atrial refractoriness before and after four weeks of AV block are compared. There was no difference in amount or time course of AF-induced electrical remodeling between normal and dilated atria. The shortening and loss of rate-adaptation of the AERP were the same. However, electrical remodeling had a greater effect on AF stability in dilated atria. Whereas two days of electrical remodeling increased the mean AF duration in normal atria about three-fold (from 5 to 13 s; p = 0.44), in dilated atria AF paroxysms were prolonged more than 20 times (from 6 to 7 min to almost 3 h; p < 0.01) (Table 1). Apart from this stronger effect on the stability of AF, there was yet another striking difference. Whereas shortening of atrial refractoriness normally leads to a proportional shortening in AF cycle length (in agreement with functional re-entry), in dilated atria electrical remodeling no longer resulted in shortening of the AF cycle length (Fig. 3). In non-dilated atria, the median AFCL shortened during the first 48 h of AF from 154 ± 11 ms to 121 ± 5 ms (p < 0.05). In dilated atria, the AF-cycle length was not changed by electrical remodeling (140 ± 19 ms vs. 139 ± 11ms; p = 0.98). The temporal variation in AF cycle length increased by atrial dilation. Figure 4 shows the AFCL histogram of a goat before and after four weeks of AV block (top) together with the variation in AFCL (difference between 5th and 50th percentile) in all animals (bottom). After four weeks of idioventricular rhythm the average p50-p5 was 44 ± 7 ms compared with 29 ± 4 ms during control (p < 0.05). Also the relative irregularity in AFCL ([p50-p5]/p50) became significantly higher after atrial dilation (0.32 ± 0.04 vs. 0.22 ± 0.02; p < 0.01).

The longer median AFCL and higher temporal variation in AFCL implies a widening of the excitable gap in dilated atria. This was directly tested in two goats by fixed-rate pacing at 1 Hz (8). Figure 5 shows an example with a median AFCL of 218 ms. In the left panel, the random coupling intervals (AF-S) of 600 consecutive stimuli are plotted against the associated AFCL. At AF-S coupling intervals of <120 ms, AFCL was not affected by the stimuli and varied between 154 (p5) and 280 ms (p95). However, at longer AF-S coupling intervals the normal distribution of AFCL became disturbed. Because of local capture of the fibrillating atria, long AF cycle lengths no longer occurred and the AFCL was determined by the AF-S interval. A stimulus with an AF-S interval of 163 ms captured the atria in 50% of the cases (Fig. 5, right panel). Taking this as the average refractory period during AF (median AFCL-RP_{AF}) the mean excitable gap (EG_{AF}) was calculated to be 55 ms. This is considerably higher than the average of 29 ± 2 ms determined by the same technique in non-dilated atria (8).

Mapping of atrial fibrillation. To test the hypothesis that the higher stability of AF after four weeks of AV block is due to the development of intra-atrial conduction disturbances, the free walls of the right and left atria were mapped during electrically induced paroxysms of AF. The median AFCL was similar in normal and dilated atria (RA: 127 ± 15 ms vs. 123 ± 13 ms; left atrium [LA]: 137 ± 5 ms vs.

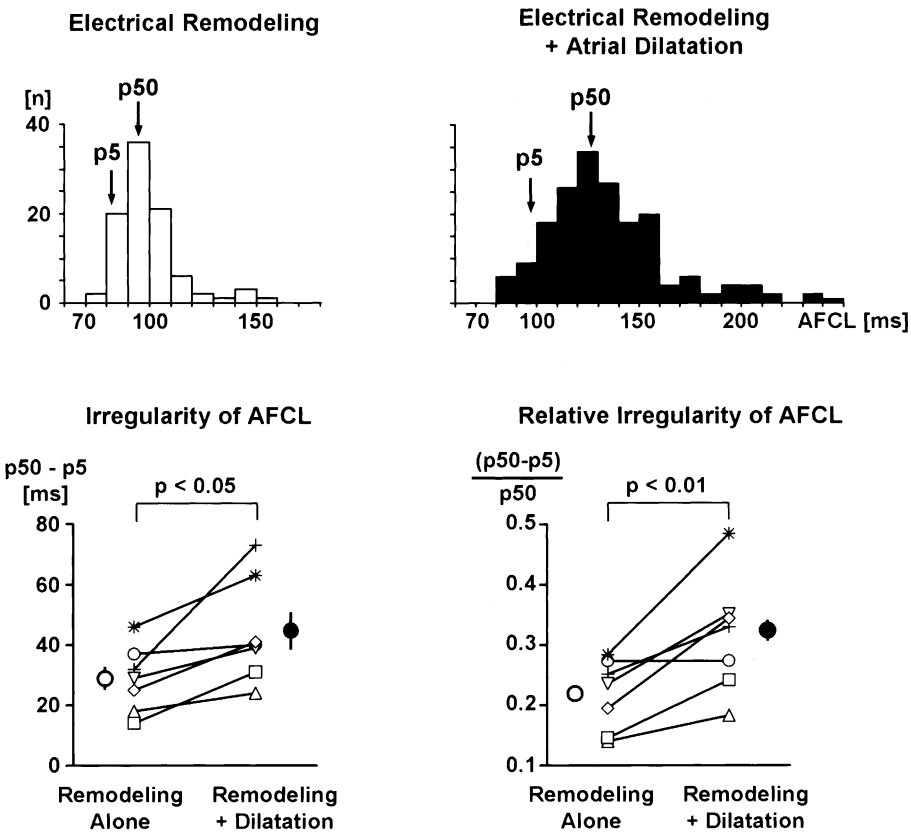

Figure 4. (Top) Example of an atrial fibrillation cycle length (AFCL) histogram in electrically remodeled atria before and after four weeks of atrioventricular (AV) block. In dilated atria the median AFCL was longer (shift to the right) and the temporal variation was higher (wider histogram). **(Bottom)** The absolute and relative irregularity in AFCL in seven goats. In six of seven goats the absolute and relative beat-to-beat variation in AFCL was increased after four weeks of AV block.

146 ± 8 ms; p = 0.80). A total of 104 s of AF were analyzed, 48 s in the control group (n = 6) and 56 s in the AV block group (n = 7). Figure 6 shows a typical example for each group. In dilated atria, crowding of isochrones occurred more frequently with a higher incidence of local conduction delays. In Figure 7 the percentage of slow conduction (CT between neighboring electrodes >8 ms) and block (conduction delay >24 ms) are plotted. The amount of conduction delay and conduction block was higher in dilated than in non-dilated atria (RA: 19.4 ± 4.3% and 12.3 ± 3.1% vs. 12.0 ± 4.2% and 7.0 ± 2.7%; LA: 18.0 ± 3.7% and 12.6 ± 3.0% vs. 9.4 ± 2.9% and 4.6 ± 1.9%; p = 0.05; p < 0.05; respectively). There was no difference between the right and left atria (p = 0.62; p = 0.71). In the lower panels of Figure 7 the amount of conduction disturbances is correlated with the atrial cell length in normal (filled circles) and dilated atria (open circles). A moderate but statistically significant correlation was found between atrial cell size and the amount of conduction block (r = 0.60; p < 0.05).

DISCUSSION

Electrical remodeling in dilated atria. In the present study, complete AV block was created to induce slowly progressive dilation of the atria without concomitant heart failure. Atrial fibrillation was maintained during 48 h to compare its electrophysiologic effects in normal and dilated atria. Atrial fibrillation-induced electrical remodeling occurred to the same extent and with the same time course in dilated and non-dilated atria. This contrasts with observations in a dog model of heart failure where atrial tachycardia shortened the AERP less in dogs with atrial enlargement (10). Thus, heart failure seems to reduce atrial electrical remodeling by means other than an increase in atrial size.

Effects of electrical remodeling on AFCL. Whereas in normal atria the shortening of atrial refractoriness during the first days of AF is paralleled by a shortening in AFCL, in dilated atria the AFCL was not affected by electrical remodeling. This implies a wider temporal excitable gap during AF and explains the broader AFCL histograms in dilated atria (Fig. 4). In one goat with chronic AV block, in which the atrial refractory period could be directly measured, the excitable gap during AF was about twice as long as previously reported in non-dilated atria (Fig. 5) (8). One possible explanation for a widening of the excitable gap is a shift from functional to anatomically determined circuits. In an ovine model of atrial flutter around a Y-shaped lesion, electrical remodeling caused only a minor shortening in flutter cycle length (from 194 ms to 183 ms) but a clear

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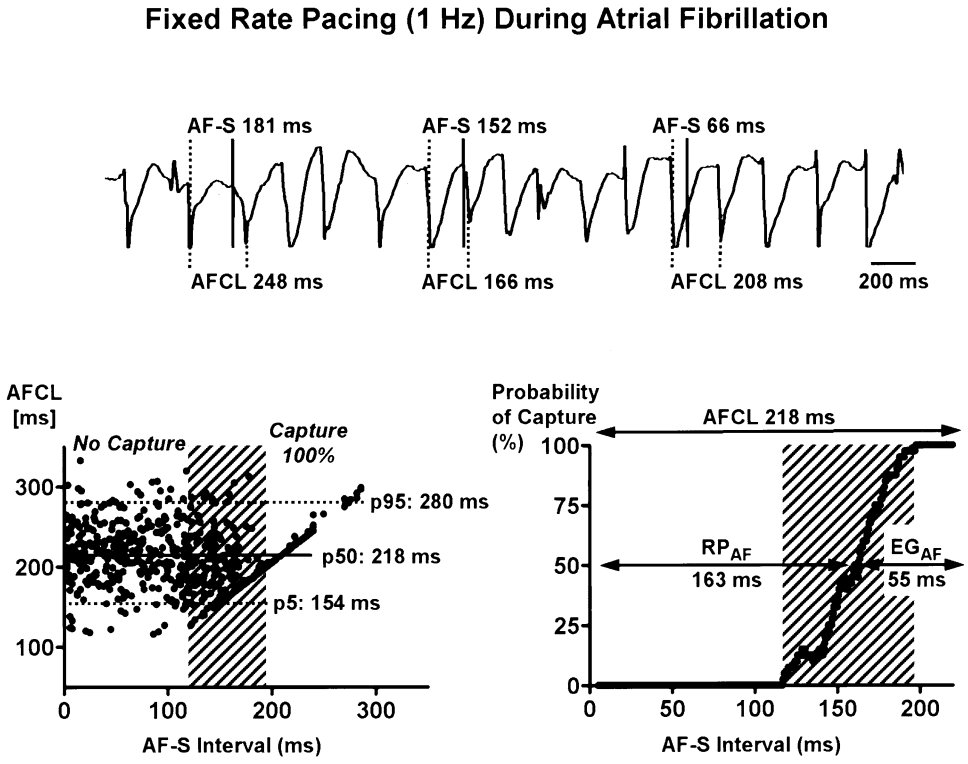

Figure 5. Measurement of the refractory period (RP_{AF}) and temporal excitable gap (EG_{AF}) during atrial fibrillation by slow fixed-rate pacing (8). After four weeks of atrioventricular block and two days of electrical remodeling, 600 stimuli with an interval of 1 s were applied to the fibrillating atria. From a bipolar electrogram close to the pacing site, the random intervals between the fibrillation waves and the stimuli (AF-S intervals) were measured together with the associated atrial fibrillation cycle length (AFCL). Capture was defined as atrial activation within 15 ms after the stimulus. The probability of local capture of the fibrillating atria followed an S-shaped curve **(lower right panel)**. At coupling intervals of <117 ms, capture did not occur, whereas at AF-S intervals of >197 ms the atria were captured 100% of the time. The hatched columns in the **lower panels** indicate the range of the measured refractory periods. The AF-S interval resulting in 50% capture was taken as the RP_{AF} (163 ms). The average temporal excitable gap was calculated by subtracting the RP_{AF} from the median AFCL (218 − 163 ms = 55 ms).

widening (+46%) of the excitable gap (11). The cycle length of conduction around rings of rabbit atrial myocardium was also not affected by shortening of the AERP. In contrast, functionally determined circuits became smaller (and their cycle length shorter) when the refractory period was shortened (12). Ikeda et al. (13) described the effects of anatomic obstacles on the meandering of re-entrant wave fronts. When atrial refractoriness was abbreviated by acetylcholine, the excitable gap of a re-entrant impulse around an anatomic obstacle increased, whereas in isolated canine atria acetylcholine accelerated the rate of re-entrant wave fronts. Also in ventricular tissue, shortening of the effective refractory period reduced the core of functional circuits, thereby shortening the re-entrant cycle length (14). Gray et al. (15) induced atrial arrhythmias in isolated right atria of sheep by burst pacing. Functionally determined re-entrant waves became anchored to anatomic structures such as the crista terminalis or the pectinate muscles. Addition of acetylcholine shortened the lines of functional conduction block as well as the re-entrant cycle length.

These observations support the notion that a shortening in AFCL by electrical remodeling should be taken as evidence that AF is predominantly maintained by functional re-entrant circuits (7). In contrast, the lack of response of the median AFCL to a shortening in refractory period, suggests that other mechanisms (such as anatomic circuits) are operative.

Instead of self-perpetuating multiple re-entry, a single rapidly firing focus can also "drive" the atria in an irregular way (fibrillatory conduction). Although the absence of spontaneous atrial ectopy in the goat makes this mechanism rather unlikely, the possibility that a micro–re-entrant circuit outside the mapping area may have served as a "driver" of AF cannot be excluded.

Intra-atrial conduction disturbances in dilated atria. Mapping of AF showed spatial heterogeneities in conduction and a higher incidence of conduction disturbances in dilated atria. Because atrial conduction during slow pacing was normal, these conduction disturbances were functional in nature and rate dependent (6). Disturbances in conduction are usually attributed to increased interstitial deposition of collagen (fibrosis) (16–18). However, in a previous study no atrial fibrosis or redistribution of connexins was observed after four weeks of AV block (6). In the present study, we found a correlation between the length of atrial cells and conduction disturbances during AF (Fig. 7). Computer studies of anisotropic conduction showed that an increase in cell size resulted in local conduction disturbances. It was postulated that cell size was a

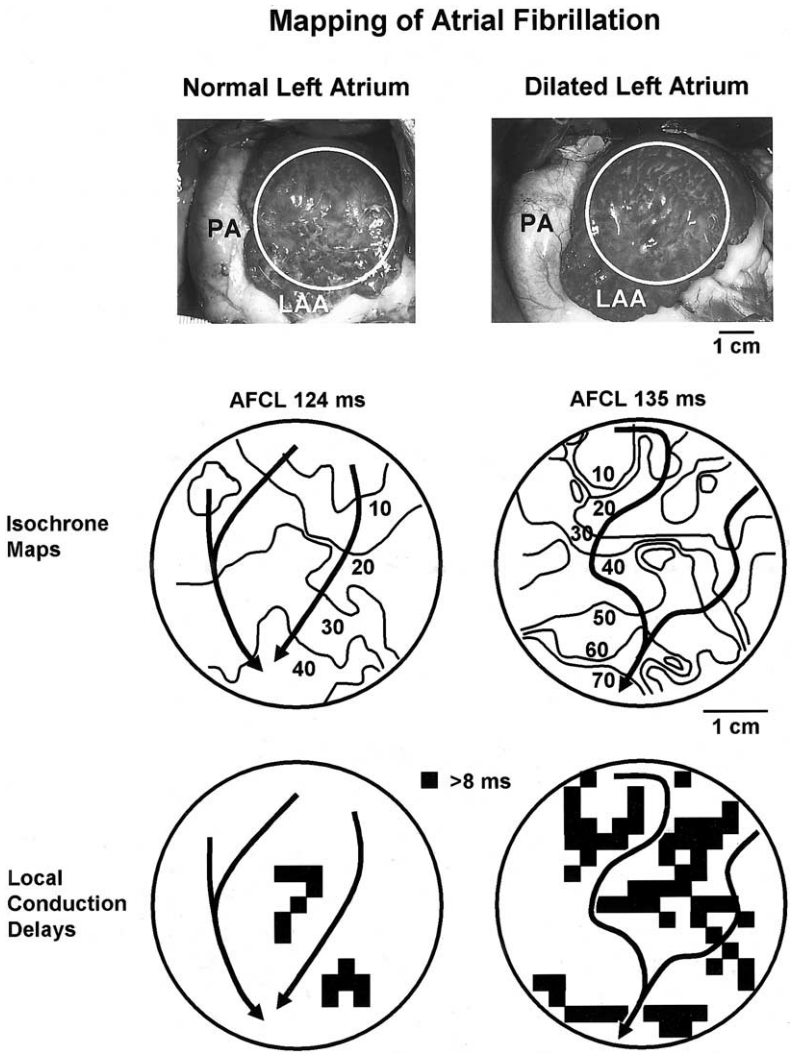

Figure 6. Fibrillation maps recorded from the free wall of the left atrium during control **(left)** and after four weeks of atrioventricular block **(right)**. In dilated atria, fibrillation waves were less uniform and local crowding of isochrones occurred more frequently. Local conduction delays of >8 ms between neighboring electrodes are mapped in the **lower panels**. A higher degree of dissociation of fibrillation waves by lines of conduction delays was observed in dilated atria. LAA = left atrial appendage; PA = pulmonary artery.

more important determinant of conduction than the distribution of gap junctions (19). Another possible explanation for the heterogeneity in conduction in dilated atria is that the higher intra-atrial pressure increases atrial wall stress more in thinner than in thicker parts (20). This may lead to preferential depression of conduction between the pectinate muscles, increasing non-uniform tissue anisotropy and facilitating lines of conduction block for re-entry (15,21). The spatial distribution of AF cycle lengths was more heterogeneous in dilated atria. A similar finding was reported in a dog model of chronic mitral regurgitation (22). Local differences in AF frequency thus may result not only from spatial differences in refractoriness but also from intra-atrial conduction disturbances.

Interplay between electrical remodeling and atrial dilation. In the present study, we found no differences in AF-induced electrical remodeling between dilated and non-dilated atria. Yet the duration of AF paroxysms was increased by electrical remodeling much more in dilated atria. The AFCL histograms in dilated atria were wider, indicating a higher beat-to-beat variability and a larger excitable gap. An increased temporal variation in AFCL may be explained by a shift from primarily functional re-entry to a mixture of functional and anatomically determined circuits. The short AF intervals, determined by the local refractory period are most likely the result of functional re-entry, whereas long AFCL may result from re-entry around dilation-induced lines of intra-atrial conduction block (23). The synergistic action of electrical remodeling and atrial dilation on AF duration thus may be explained by their independent action on two determinants of AF: a shortening of atrial refractoriness (electrical remodeling) and lines of intra-atrial conduction block (atrial dilation).

However, there are alternative explanations which should be considered. 1) Stretch-induced rapid automaticity or a stable (micro–re-entrant) "mother-rotor" anchored at sites of local conduction delays may act as a driver for the rest of

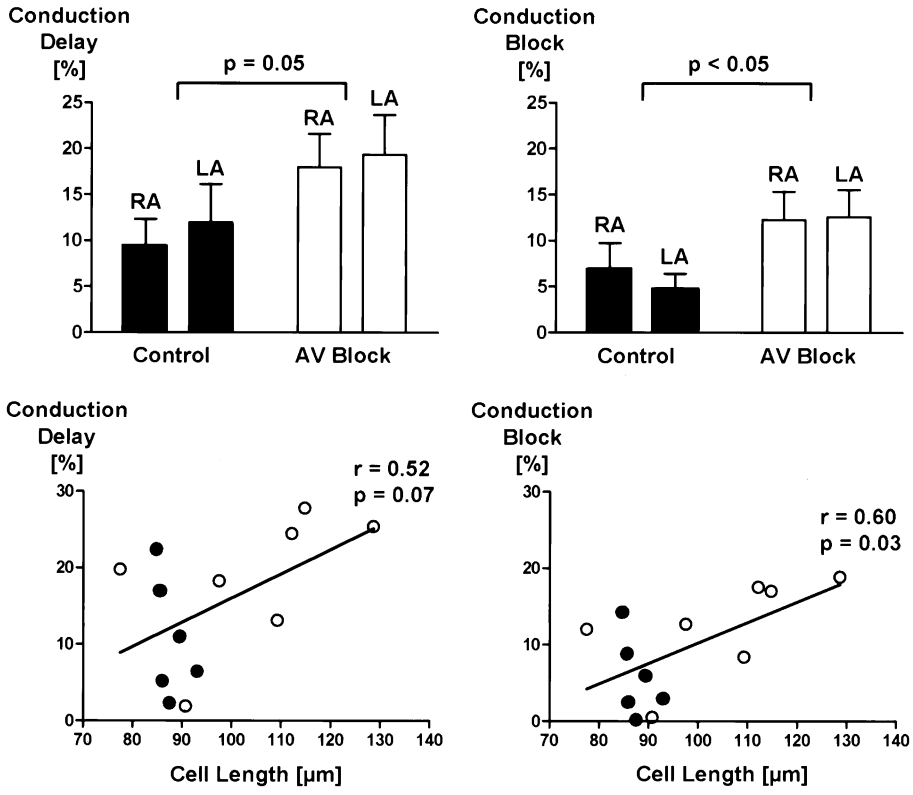

Figure 7. (Top) Percentage of local conduction delays (>8 ms/2.4 mm) and conduction block (>24 ms/2.4 mm) in the right atrial (RA) and left atrial (RA) walls of six control and seven atrioventricular (AV)-blocked goats. In dilated atria, conduction disturbances during atrial fibrillation were about twice as frequent as in non-dilated atria. **(Bottom)** The amount of intra-atrial conduction delay and block plotted against the mean atrial cell length in the control group (n = 6; **filled circles**) and in seven goats with chronic AV block **(open circles)**. A moderate but statistically significant correlation was found between atrial cell size and intra-atrial conduction block (r = 0.60; p = 0.03).

the atria that is not captured 1:1 owing to the high focal rate (fibrillatory conduction) (4). 2) Electrical remodeling may increase AF stability more in dilated than in non-dilated atria, because the L-type calcium current becomes more important for impulse conduction in case of electrical discontinuities between enlarged atrial cells (19). The reduction of $I_{Ca(L)}$ by AF-induced electrical remodeling (24) might impair atrial conduction and stabilize AF more in dilated atria than expected from the shortening in refractoriness.

Study limitations and clinical implications. Mapping of the free walls of the RA and LA was performed under general anesthesia and only in non-remodeled atria. This does not exactly reflect the situation in awake animals subjected to 48 h of AF. Although we tried to explain atrial conduction disturbances on the basis of atrial architecture, we did not directly correlate conduction disturbances with changes in the structure of the atrial myocardium. We also did not compare the effects of class I and class III drugs in dilated and non-dilated atria. Our hypothesis that in dilated atria AF is dominated by anatomically determined re-entry is mainly based on indirect evidence. To conclude that different mechanisms are operative during AF in dilated and non-dilated atria, more studies will be needed.

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