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Atrial thrombogenesis in atrial fibrillation

Results from atrial fibrillation models and AF-patients

Pathophysiology of atrial thrombogenesis

The left atrial appendage (LAA) is the classical origin of atrial thrombi. The LAA is approximately 1.2–4.5 cm in length; however, there is a huge variability in length and shape. During atrial fibrillation (AF), in addition to the occurrence of hypercoagulability and stasis of blood, the occurrence of prothrombotic endothelial changes are of central significance in the development of atrial thrombi within the LAA [12, 17]. AF induces stasis of the blood, hypercoagulability state, and activation of platelets [27]. At the level of atrial tissue, increased cytosolic calcium via activation of calcium-dependent proteases and phosphatases leads to the destruction of contractile filaments, to an impaired function of mitochondria, and to hypertrophy of atrial myocytes ([15]; ◘ **Fig. 1**). Besides calcium overload, AF causes increased generation of reactive oxygen species (ROS). Effects of oxidative stress on atrial myocardium have been shown in vitro and in vivo [4, 8, 13, 26, 29]. In sum, these processes cause increased synthesis of prothrombotic tissue factors at the endocardium of the left atrium (endothelial alteration) such as plasminogen activator inhibitor

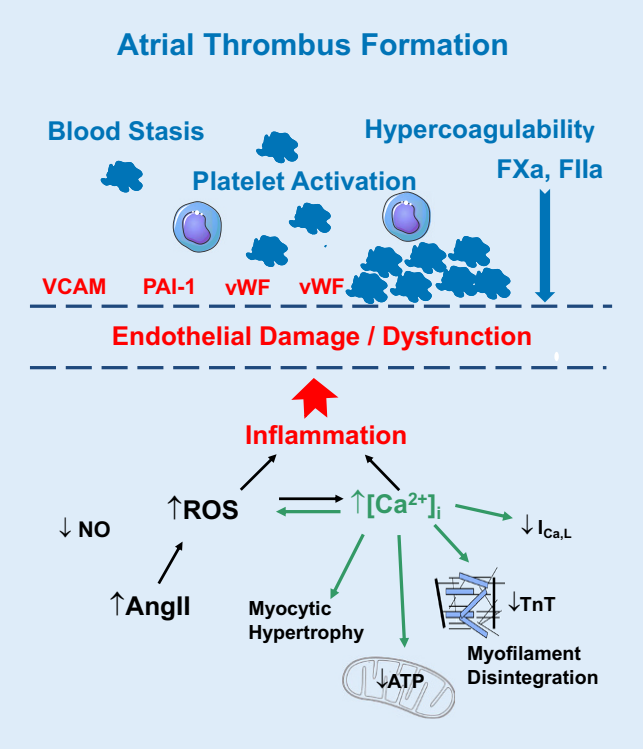

Fig. 1 ▲ Concept of prothrombotic endocardial remodeling as described in the European Heart Rhythm Association consensus report on atrial cardiomyopathies. Several molecular mechanisms and pathway lead to expression of prothrombotic proteins at the endocardial surface of the left atrium. *VCAM* vascular cell adhesion molecule 1, *PAI-1* plasminogen activator inhibitor 1, *vWF* von Willebrand factor, *ROS* reactive oxygen species, *ATP* adenosine triphosphate, *AngII* angiotensin II, *NO* nitric oxide, *TnT* troponin T, $I_{Ca,L}$ calcium influx through L-type channel

The original version of this article was revised: The title was incomplete.

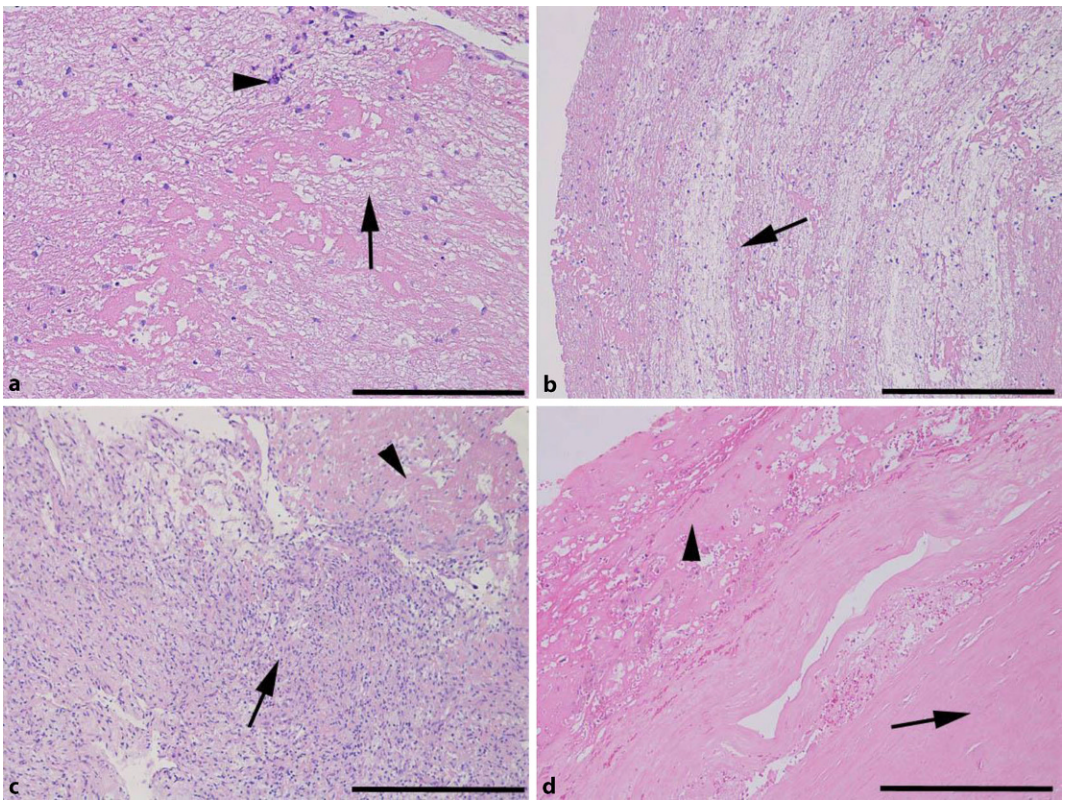

Fig. 2 ▲ Histopathology of an atrial mural thrombus. **a** A recent thrombus which is characterized by a complex network of fibrin (*arrow*) entrapping platelets and blood cells (*arrowhead*). **b** Sometimes, a recent thrombus is organized into layers (*arrow*) of fibrin, platelets, and blood cells, parallel to the endocardium. **c** An organizing thrombus where the original structure is replaced by proliferating and collagen synthetizing myofibroblasts (*arrow*). The arrowhead indicates some residual fibrin clots. **d** A late-stage organized thrombus which is constituted by hyaline and noncellular fibrous tissue (*arrow*). Sometimes a more recent thrombosis may be detectable on the surface (*arrowhead*). Staining: **a**–**d** hematoxylin–eosin. Original magnifications: **a** ×20 (bar is 200 µm), **b**–**d** ×10 (bar is 400 µm)

(PAI) 1, von Willebrand factor (vWF), and adhesion molecules (ICAM, VCAM, selectins) [5, 16, 20].

There is clinical evidence that AF-induced thrombogenicity of the left atrium is much greater compared with the right atrium [9]. This helps to explain why AF induces predominantly systemic emboli and stroke rather than pulmonary emboli. Of note, studies revealed the impact of angiotensin II on the adhesiveness of the left atrial endothelium, characterized by increased expression of adhesion molecules (VCAM, ICAM). Besides AF, concomitant cardiovascular diseases like hypertension, heart failure, diabetes mellitus, etc. (parameters of the CHA2DS2-VASc score) have the potential to activate molecular pathways such as angiotensin-II-dependent signaling pathway to contribute to an increased incidence of atrial thrombi. Thus, to some extent the process of endocardial remodeling is independent of the atrial rhythm.

Increasing evidence points to a link between elevated angiotensin II levels, systemic inflammation, and prothrombotic state in AF. In this way elevated concentrations of inflammatory markers (e. g., C-reactive protein [CRP], interleukin [IL]-6; [11, 19]) might mediate an outside-in inflammatory signaling. Interesting, the circulating IL-6 level was associated with increased left atrial size, supporting a link between the cytokine and atrial remodeling [18, 24]. However, the precise mechanism by which IL-6 and CRP induces AF remodeling is uncertain. In addition, in the last few years it has been shown that coagulation factors such as thrombin, factor X or factor VII exert important cellular effects that are induced by binding of the clotting factors to proteinase-activated receptors (PAR; [3]). Four receptors (PAR1 to PAR4) are currently known and belong to the subfamily of G protein—coupled receptors with seven transmembrane domains. Activated coagulation factor X (FXa) occupies a central position in the coagulation system. Together with activated factor V (FVa), phospholipids, and calcium ions, it forms the prothrombinase complex at which activation of prothrombin (FII) to thrombin (FIIa) occurs. Thus, FXa might act as a mediator of inflammatory signaling in human atrial tissue slices via activation of PAR1 and PAR2. Most importantly, the synergistic action of FXa and atrial tachyarrhythmia resulted in a potentiated response involving the increase of inflammatory and oxidative stress molecules, which create an inflammatory, prothrombotic status in atrial endocardium [5].

Very recently, Spronk et al. [28] showed that thrombin via PAR1-receptor-dependent signaling induces inflam-

matory and fibrotic effects in atrial tissue from adult rats. Moreover, the authors suggest that hypercoagulability might promote the development of an AF substrate. The hypothesis was verified in goats with persistent AF and a hypercoagulable state resulting from AF, in which an inhibition of FXa attenuated atrial fibrosis and the complexity of AF substrate compared to control animals [23].

Thus, a highly complex interaction emerges between concomitant diseases, clotting factors, and AF at the endothelium. Since human in vivo biopsies are prohibitory for ethical reasons, there is a need for in vitro or in vivo animal models to define the exact pathophysiology of atrial thrombogenesis.

In vitro model of endocardial remodeling

From human atrial appendages obtained during open heart surgery, 350 µm thin tissue slices can be kept in culture in a petri dish for up to 24 h when placed on top of the membrane of tissue culture inserts. To simulate AF, a pair of custom-built carbon electrodes are submersed at the opposite ends of a petri dish and connected to a stimulation unit. Pacing of the tissue slices can be performed within serum-free Dulbecco's Modified Eagle's Medium (DMEM) up to 24 h at 37 °C at rates of 0.6 and 4.0 Hz (10 V/cm, 5 ms bipolar pulse). Furthermore, several humoral factors can be applied to the culture during the pacing period to determine signal transduction and molecular biology. Using this in vitro model, it was shown that a few hours of rapid atrial pacing are sufficient to elevate expression of angiotensin-converting enzyme (ACE; [6, 16]), induce oxidative stress [4], diminish nitric oxide, and increase adhesion molecule expression [5, 16]. All these factor mediate tissue remodeling and exert direct arrhythmogenic effects. Interestingly, recent experiments also revealed gender-dependent differences in tissue remodeling, which appear to be related to the amount of 17β-estradiol [7].

Abstract · Zusammenfassung

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Atrial thrombogenesis in atrial fibrillation. Results from atrial fibrillation models and AF-patients

Abstract

Atrial fibrillation (AF) is the most common cause of thromboembolic complications. The risk of suffering a thromboembolic complication depends on the accompanying cardiac risk factors and the patient's age. For patients who have an increased risk, which is now classified using the CHA2DS2-VASc score, initiation of long-term oral anticoagulation is the first-line treatment. In AF, thrombi arise in the left atrial appendage. The present review will summarize the basic pathophysiology of thrombogenesis in AF and will provide the molecular basis of a process called prothrombotic endocardial remodeling. Despite oral anticoagulation being a central component of therapy, the present results can be used to support concomitant therapy with statins, angiotensin II blockers, etc. to inhibit atrial thromogenesis.

Keywords

Endocardium · Anticoagulation · Angiotensin II · Therapy · Stroke

Atriale Thrombogenese bei Vorhofflimmern. Ergebnisse von Vorhofflimmermodellen und AF-Patienten

Zusammenfassung

Systemische Embolien und Schlaganfälle treten häufig bei Patienten mit Vorhofflimmern (AF, „atrial fibrillation") auf. Das Risiko für thromboembolische Komplikationen hängt von begleitenden kardialen Risikofaktoren und dem Alter der Patienten ab. Risikobewertungen, wie der CHA2DS2-VASc-Score, wurden entwickelt, um eine gewisse Vorhersage treffen zu können, welcher Patient mit Vorhofflimmern gefährdet ist, einen Insult zu erleiden. Für diese Patienten ist eine orale Langzeit-Antikoagulation die First-Line-Therapie. Beim Vorhofflimmern entstehen die Tromben im linken Vorhofohr. Der vorliegende Review fasst die Pathophysiologie zusammen, die in In-vitro- und In-vivo-Modellen zur atrialen Thrombogenese gesammelt wurden und liefert die molekulare Basis für einen Prozess, genannt prothrombotisches endokardiales Remodeling. Auch wenn eine zentrale Komponente der Therapie die orale Antikoagulation ist, können die vorliegenden Ergebnisse dazu dienen, eine begleitende Therapie mit Statinen, Angiotensin-II-Blockern u. ä. auch für eine Hemmung der atrialen Thrombogenese zu nutzen.

Schlüsselwörter

Endokard · Antikoagulation · Angiotensin II · Therapie · Schlaganfall

In vivo models of atrial thrombogenesis

Transgenic mice with cardiomyocytes-directed overexpression of the transcriptional repressor CREM-IbΔC-X (CREM-TG) have recently been shown to constitute a useful experimental model of AF and atrial thrombogenesis [7]. Interestingly, mice develop thrombi in both atria. In a recent study, inflammatory and prothrombotic alterations were evaluated in the left (LA) and right atria (RA) from CREM-TG mice at the age of 20 weeks and compared to wild-type controls. Analogous to the observations in AF patients with distinct endocardial dysfunction, this model also exhibited diminished amounts of eNOS-mRNA in both atria. The prothrombotic state was characterized by the increased PAI-1/tPA ratio (pro- and anticoagulatory molecules) as well as by the downregulation of TFPI (tissue factor pathway inhibitor). Importantly, CREM-TG mice developed progressive atrial dilatation detectable at a very early age [21–23] which may be responsible for blood stasis in atria. Moreover, the inflammatory phenotype with a preserved antithrombotic capacity was present in atria of CREM-TG mice before onset of arrhythmia and thrombi generation. Interestingly, the inflammatory pheno-

Table 1 Baseline characteristics of patients undergoing tissue Doppler analysis

	Control ($n = 38$)	Paroxysmal AF ($n = 46$)	*P* value
Age, years	54 ± 17	58 ± 11	NS
Male sex, %	76	65	NS
CAD, %	21.1	6.5	0.05
Diabetes mellitus, %	5.3	6.5	NS
Art. hypertension, %	31.6	47.8	NS
Med, %			
– *AT2 blocker*	13.2	17.4	NS
– *ACE inhibitor*	26.1	26.3	NS
– *Ca blocker*	5.3	26.1	0.01
– *β-blocker*	28.9	69.6	0.0001
Heart rate, bpm	71 ± 11	66 ± 12	0.04
PR interval, ms	161 ± 18	174 ± 24	0.01
QRS-D, ms	91 ± 10	96 ± 14	NS
LAD, mm	38 ± 10	42 ± 8	NS
LVEF, %	61 ± 5	59 ± 6	NS
E/A	0.9 ± 0.3	1.3 ± 0.8	0.04

LAD left atrial diameter, *LVEF* left ventricular ejection fraction, *E/A* ratio of the early and late transmitral flow, *CAD* coronary artery disease, *AF* atrial fibrillation, *Art. hypertension* , *Med* medication, *PR* interval time interval between P-wave to R-wave in the electrocardiogram, *QRS-D* duration of the QRS-interval in the electrocardiogram, *AT2* angiotensin 2, *ACE* angiotensin-converting enzyme, *NS* not significant

Table 2 Analysis of late diastolic velocities of the mitral annulus at different left atrial regions

	Peak systolic value			Peak early diastolic			Peak late diastolic		
	PAF ($n = 46$)	Control ($n = 38$)	*P*	PAF ($n = 46$)	Control ($n = 38$)	*P*	PAF ($n = 46$)	Control ($n = 38$)	*P*
LA lateral									
Wall velocity, cm/s	5.4 ± 2.2	6.4 ± 2.4	–	–4.5 ± 1.9	–4.5 ± 2.1	–	–5.8 ± 2.7	–2.6 ± 3.3	–
Strain, %	36 ± 26	83 ± 51	0.0001	–20 ± 25	–38 ± 46	–	–14 ± 14	–29 ± 19	0.001
Strain rate, s^{-1}	2.1 ± 1.9	3.7 ± 2.1	0.002	–2.3 ± 1.3	–3.8 ± 2.6	0.006	–2.1 ± 2.3	–4.5 ± 2	0.0001
LA inferior									
Wall velocity, cm/s	3.8 ± 2.2	4.3 ± 1.5	–	–3.9 ± 1.9	–4 ± 2	–	–3 ± 1.5	–5.4 ± 1.9	–
Strain, %	37 ± 24	58 ± 31	0.004	–24 ± 20	–31 ± 33	–	–16 ± 9	–39 ± 85	0.0001
Strain rate, s^{-1}	2.2 ± 2.4	3.2 ± 1.6	0.03	–2.3 ± 2.1	–2.4 ± 1.4	–	–2.7 ± 1.9	–3.4 ± 1.5	–
LA anterior									
Wall velocity, cm/s	4.5 ± 1.5	5.5 ± 2	0.04	–4.5 ± 2.9	–4.7 ± 1.7	–	4.6 ± 2.6	–5.8 ± 2	–
Strain, %	31 ± 13	49 ± 36	0.03	–18 ± 17	–29 ± 30	–	–11 ± 6	–25 ± 12	0.0001
Strain rate, s^{-1}	1.7 ± 0.6	3.5 ± 4.1	0.0001	–2.1 ± 1.3	–2.9 ± 1.2	0.04	–1.8 ± 1.2	–3.9 ± 1.4	0.0001
LA posterior									
Wall velocity, cm/s	6.3 ± 2.8	–4.5 ± 1.6	–	–3.7 ± 1.8	–6.5 ± 2.8	–	–6.2 ± 1.9	5.3 ± 1.9	–
Strain, %	44 ± 17	60 ± 30	–	–25 ± 24	–40 ± 35	–	–13 ± 10	–21 ± 10	0.03
Strain rate, s^{-1}	2.9 ± 0.9	3.5 ± 1.6	0.01	–2.6 ± 1.1	–2.9 ± 2.4	–	–2.8 ± 1.7	–3.3 ± 2.8	–

PAF paroxysmal atrial fibrillation, *LA* left atrium

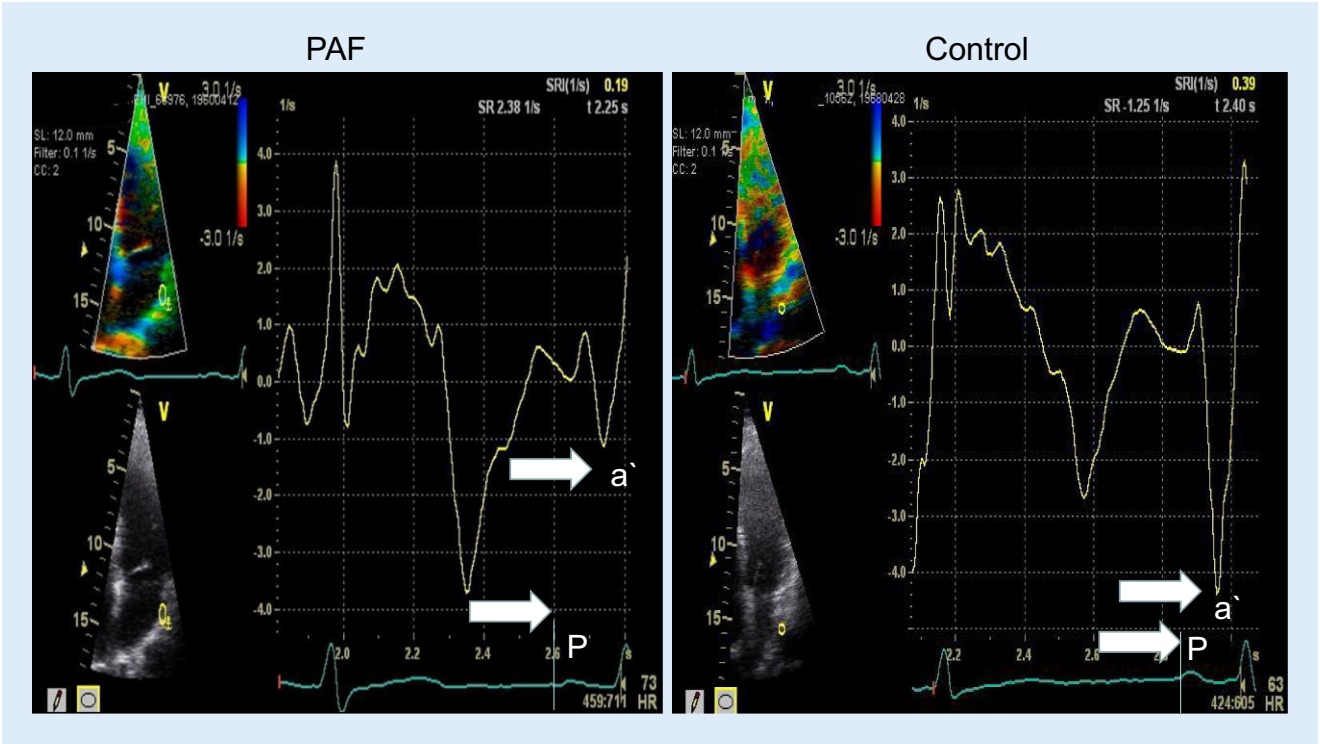

Fig. 3 ▲ Recording of strain rate at the lateral left atrial wall in patients with paroxysmal atrial fibrillation (*PAF*) and in a control patient with sinus rhythm. Differences in strain rates are clearly visible (marked with an *arrow*; a'). The surface P-wave is also marked (*arrow*, P). Time between P-wave onset and a' was used to calculate the electromechanical time index in each patient

type was much more pronounced in the RA and is reflected by a significant increase in the expression level of adhesion molecules ICAM-1 and selectin P. In conclusion, CREM-TG mice represent a valuable model for studying atrial thrombogenesis and assessing therapeutic approaches preventing embolic episodes through systemic and pulmonary circulation.

Appearance of atrial thrombi in AF patients

From a histopathological point of view, atrial thrombi (whether left or right) are basically nonspecific. Their structure largely depends on how old the thrombotic event is. In fact, recent atrial mural clots consist of a complex network of fibrin where platelets and blood cells are entrapped (**Fig. 2a**). Very often, especially if the thrombosis is recurrent, distinct layering of fibrin, blood cells, and platelets may become detectable (so-called "lines of Zahn", **Fig. 2b**). With passage of time, the thrombus body may undergo organization, usually starting from its base. Thrombus organization implies a progressive replacement of the above-mentioned fibrin network by myofibroblasts (**Fig. 2c**), which subsequently start synthesizing procollagen fibers that in the extracellular spaces, organize into collagen type I fibers in order to create a firm background (*interstitium*). As this organization proceeds, the thrombus surface may undergo endothelization. In late stages, the mural thrombus usually turns into a hyaline fibrous structure that is tightly adherent to the atrial wall (**Fig. 2d**) and difficult to remove from its recesses. Structurally, recent atrial thrombi may be broad-based ("membranous") with negligible risk of emboli detachment, or at the opposite end of the spectrum, polypoid and friable with a higher tendency to embolize. Occasionally, polypoid thrombi may be superimposed on membranous atrial mural clots [25]. Abe et al. [1] provided a classification of LA thrombus morphology based on transesophageal findings: (1) "movable ball" type, i. e., the thrombus is ball-shaped and moves with the heartbeat; (2) "fixed ball" type, i. e., the thrombus is ball-shaped but does not move with the heartbeat; and (3) "mountain" type, i. e., the thrombus is mountain-shaped with a broad base and does not move with the heartbeat. They found that "movable ball" type thrombi showed a significantly higher embolism than the other two kinds of clot. It is easy to deduce that fully organized thrombi are much less prone to embolization.

Effect of ACE inhibitors/ARBs on atrial contractility and thrombus formation

There are some indirect hints in the literature showing that ACE inhibitor therapy or angiotensin-receptor blockers (ARBs) might reduce occurrence of stroke in AF patients. Several studies have shown that upstream therapy using statins, mineralocorticoid receptor blockers, ARBs, and ACE inhibitors might be useful at least in primary prevention of AF and its sequelae [10, 14]. In particular, patients with arterial hypertension and congestive heart failure appear to benefit. The RACE-3 trial for secondary prevention

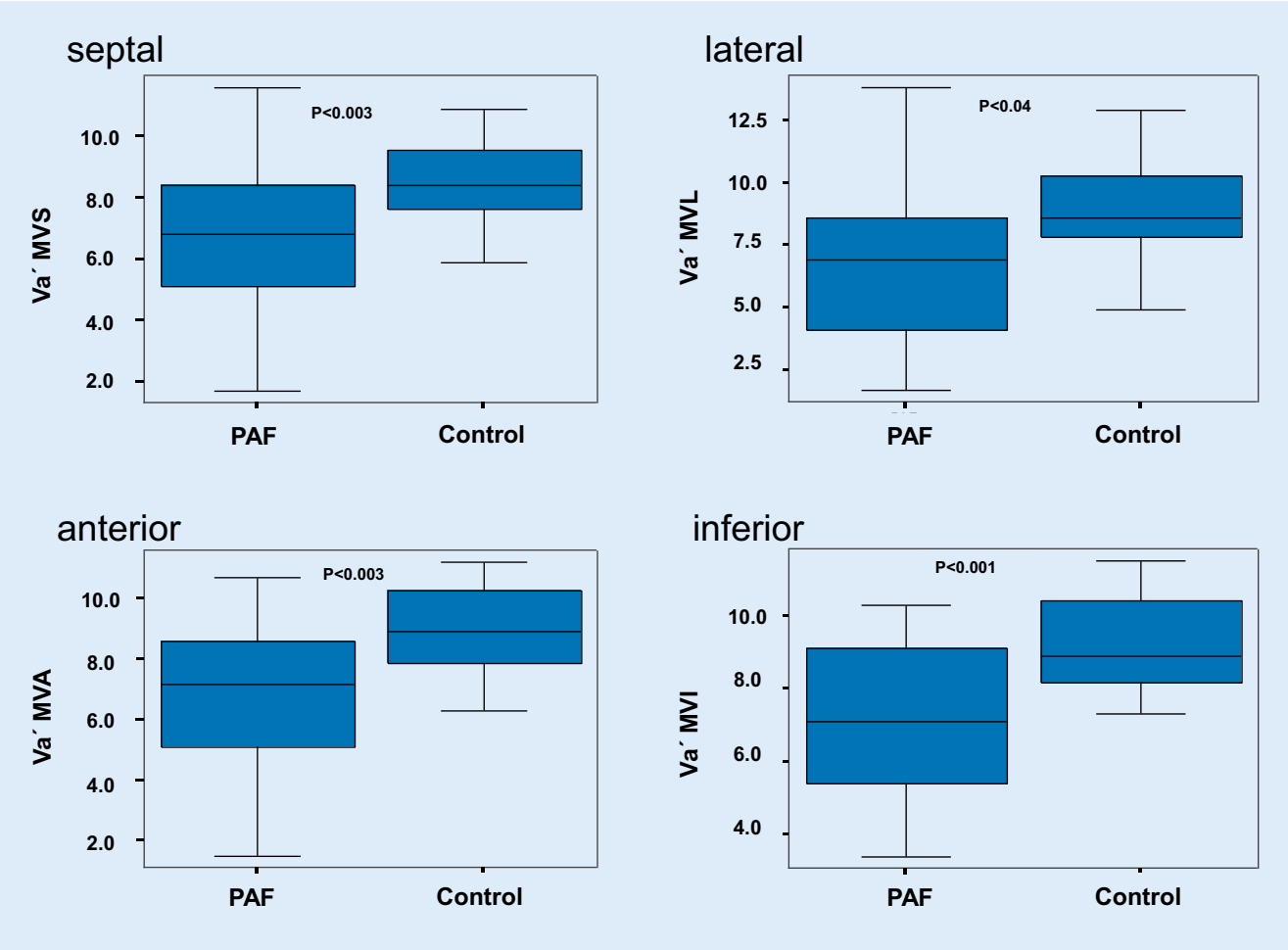

Fig. 4 ▲ Analysis of late diastolic velocities of the mitral annulus at different left atrial regions. Values are provided in box plots. Additional information is included in **Table 2**. *PAF* paroxysmal atrial fibrillation

could show that the combination of all substances mentioned above can reduce the recurrence rate of AF [2]. Inhibition of angiotensin II and oxidative stress might directly protect atrial myocytes and their contractile performance.

The purpose of our prospective trial was to evaluate atrial mechanical function in patients with paroxysmal AF using tissue Doppler analysis (TDA) and to examine the relationship between electrical impulse propagation and mechanical function. In our study, 84 patients (56 ± 14 years; 59 men; 25 women) were examined with TDA, 46 patients had paroxysmal AF and 38 patients were in normal sinus rhythm without any history of AF, and therefore, served as controls. At the time of TDA all patients were in sinus rhythm (**Table 1**). With TDA the velocity (V), strain (S), and strain rate were measured in the medial segment of each wall of the left atrium (anterior, posterior, inferior, and lateral wall) and in the mitral valve annulus. Thereafter, an electromechanical time index was defined as the period from the onset of the P-wave in the surface ECG to the peak of the late diastolic velocities of the left atrial wall segments (a'). Tissue Doppler imaging results suggest that ACE inhibitor and angiotensin II inhibitor therapy (AT2-Anta) increase contractile performance of the atria in patients with paroxysmal AF. Mitral annulus late diastolic velocity (lateral, septal, anterior, and inferior) was significantly reduced in patients with paroxysmal AF, and velocity, strain and strain rate were significantly decreased in all analyzed left atrial segments of these patients (**Fig. 3**). In addition to the prolonged PR interval on the surface ECG, there was a significant prolongation of the averaged electromechanical time index in patients with paroxysmal AF (AF: 138 ± 27 ms vs. 119 ± 17 ms; $p < 0.0001$). In summary, paroxysmal AF was associated with reduced mitral annulus velocity and reduced atrial strain and strain rate (**Table 2**). Paroxysmal AF was also associated with a prolonged electromechanical time index (P wave-a'; **Fig. 4**). Therapy with calcium channel blockers impaired atrial mechanical tissue Doppler parameters (**Fig. 5**). In contrast, therapy with angiotensin II antagonists was associated with an increased velocity of the left inferior wall and the systolic strain rate of the left lateral wall. Thus, a hint for the presence of substantial structural remodeling of atrial tissue might be diagnosed using the surface P-wave duration since the P wave is prolonged in patients prone to AF. Furthermore, the developed electromechanical index using the P wave-a' may serve as an easy ac-

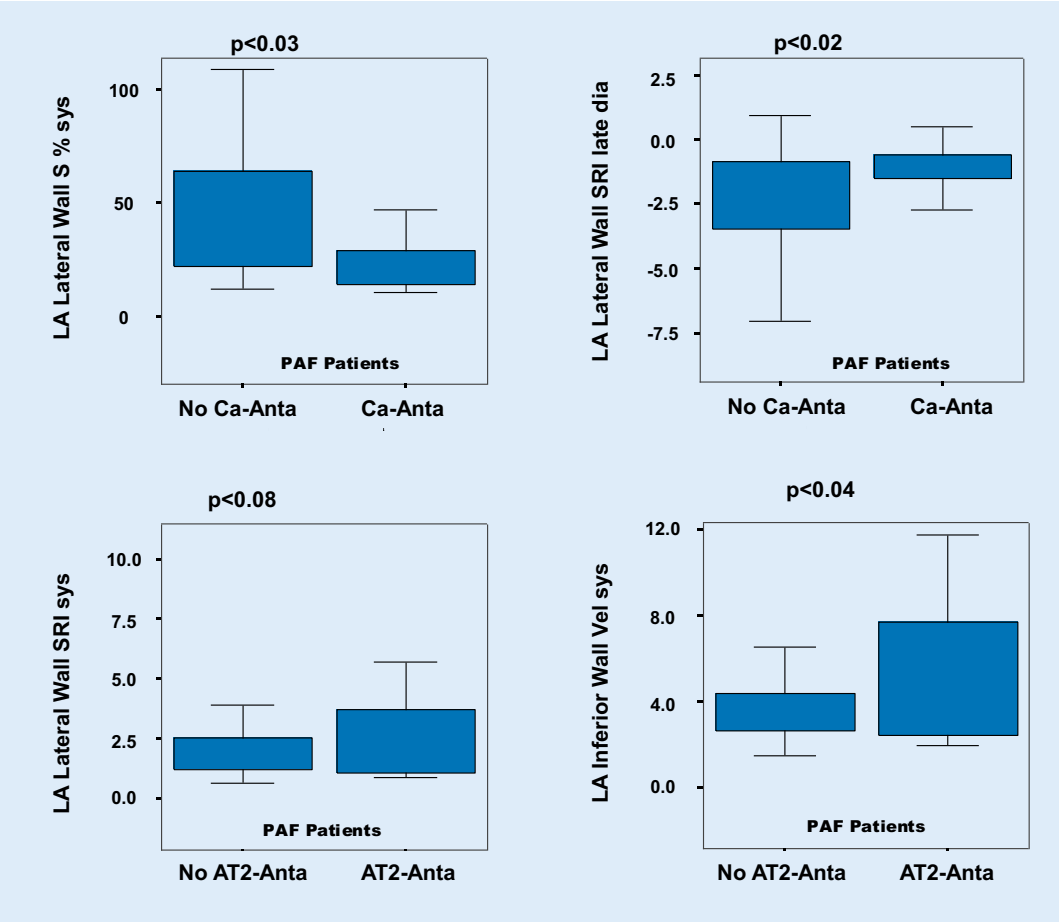

Fig. 5 ◀ Impact of medical therapy on tissue Doppler parameters strain (*S*), strain rate (*SRI*), and velocity (*Vel*) in the left atrium in patients with atrial fibrillation (AF). Angiotensin II inhibitor therapy (*AT2-Anta*) improved the contractile performance whereas calcium-antagonist (*Ca-Anta*) had a negative effect. *PAF* paroxysmal atrial fibrillation, *LA* left atrium

cessible marker to indirectly characterize specific tissue pathologies.

Conclusion

Activation of the clotting system, low blood flow, and endothelial damage cause atrial thrombogenesis in AF. The molecular pathway responsible for induction of adhesion molecules at the endocardial surface depends primarily on oxidative stress and inflammation. Imaging technologies like Doppler modalities appear helpful to determine the contractile performance of the atrial tissue, which remains impaired even in phases of sinus rhythm between AF episodes. Thus, these modalities and biomarkers should be further assessed and validated in larger clinical trials.

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Compliance with ethical guidelines

Conflict of interest. M. Hammwöhner: Speaker fees from Astra Zeneca, Boehringer Ingelheim, Bayer Health Care, BMS/Pfizer, Daiichi-Sankyo. A. Goette: Speaker fees from Astra Zeneca, Berlin Chemie, Boehringer Ingelheim, Bayer Health Care, BMS/Pfizer, Daiichi-Sankyo. A. Bukowska, D. Corradi and W. Mahardhika declare that they have no competing interests.

This article does not contain any studies with animals performed by any of the authors.

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