**Patterns of Left Atrial Activation and Evaluation of Atrial Asynchrony in Patients with Atrial Fibrillation and Normal Controls: Factors beyond Left Atrial Dimensions**

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Referat: Left atrial (LA) remodeling characterized by slower and asynchronous conduction is crucial for the maintenance of atrial fibrillation (AF). We propose a simple and quick method to evaluate the LA asynchrony.

One hundred and thirty patients with AF (AF group) and 70 patients without a history of AF (non-AF controls) were examined prospectively using pulsed-wave tissue Doppler (PW-TDI). The time intervals from the onset of P-wave to the A´ (P-A´) velocity in PW-TDI were measured at 4 different left atrial sites next to the mitral annulus (septal, lateral, anterior and inferior). To assess the LA asynchrony, the differences between the longest and the shortest P-A´ (DLS-PA´) as well as the standard deviation (SD-4PA´) of all 4 values were calculated.

Both groups were matched for the baseline characteristics including the LA diameter. AF group had longer DLS-PA´ as compared to non-AF controls: 37 ± 16 msec. vs. 28 ± 13 msec.; P=0.0001. SD-4PA´was also bigger in AF group: 17 ± 7 msec. vs. 13 ± 5 msec.; P=0.0001. Furthermore, distinct patterns of LA activation were observed. Most AF patients exhibit an upward LA activation (86.5%) with an

inferior breakthrough into the LA, whereas the non-AF controls presented with a downward LA activation (65.5%) spreading from the LA roof downwards. ROC analysis revealed that P-A´ at anterior LA successfully discriminated patients with AF from the non-AF controls (AUC 0.85, P<0.0001). Furthermore, P-A´ anterior > 55 msec. discriminated between AF patients and non-AF controls with 85% sensitivity; 81% specificity; positive predictive value of 0.898 and negative predictive value of 0.707.

In conclusion, patients with AF showed: greater LA asynchrony in PW-TDI; an upward LA activation; and a prolonged activation time at the anterior left atrium. Prolongation of P-A´ anteriorly > 55 msec. discriminated between AF and non-AF controls with high sensitivity and specificity.

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# 1 Introduction

## *1.1. Mechanisms of initiation and perpetuation of atrial fibrillation*

Atrial fibrillation (AF) is frequently triggered by foci predominately located inside the pulmonary veins. [1,2] This concept led to the establishment of the electrical isolation of the pulmonary veins as a new effective treatment for patients with AF. [3] However, the higher recurrences rates even after repeated pulmonary vein isolation suggest an insufficient understanding of the puzzling nature of this arrhythmia. [4-7]

At present, there is bulking evidence for the complex AF pathophysiology in which different mechanisms may contribute. One theory proposed that AF results from multiple wandering atrial wavelets. [8,9] The leading-circle model demands that reentry circuits can spontaneously establish in the LA. The wavelength (WL) of the leading circle depends on the refractory period (RP) and the propagation velocity (CV) usually described by the equation WL=RP x CV. The smaller the wavelength of the reentry circuit, the larger is the number of the wavelets that can simultaneously exist. [10,11] Moreover, bigger left atria can accommodate a larger number of coexisting reentry wavelets. Therefore, the left atrial dilatation, the shortened LA refractory time, and the prolonged intra-atrial conduction are important prerequisites and hallmarks of persistent AF. The shortening of the atrial RP promotes also the perpetuation of the spiral rotor waves which is regarded as an alternative mechanism for AF perpetuation. The slowing of the intra-atrial conduction can be caused by functional (loss of Na channel function, mutation of the connexin genes) or structural atrial changes (fibrosis and anisotropic conduction properties). [12,13] In addition, the role of the Bachmann’s bundle in the pathophysiology of AF was demonstrated in animal experiments. Using epicardial and endocardial mapping during induced AF in canine hearts, Kumagai et al. showed that AF was maintained from multiple unstable re-entry circuits using the Bachmann's bundle as a part of their re-entry pathway. A single site catheter ablation of Bachmann's bundle can successfully eliminate AF in animal experiments. [14,15] Furthermore, there are evidences that atrial synchronous pacing at Bachmann's bundle can be effective in preventing the initiation of AF with pacing. [16] Patients with history of paroxysmal AF were less likely to develop persistent AF during follow-up if paced at the region of Bachmann's bundle as compared to right atrial appendage pacing. [17]

### *1.2. Left atrial remodeling in atrial fibrillation*

Extensive experimental and clinical data suggest that certain electrical and structural changes in the LA can develop in result of the AF itself. [18,19] These alterations, commonly referred as atrial remodeling, are considered to play a crucial role in the self-perpetuation of the AF. Importantly, restauration and maintenance of sinus rhythm may result in reversal of the LA remodeling.

Acute electrophysiological adaptive responses ensue shortly after the onset of AF and are caused by rapid alterations of the ion currents. [20-22] However, certain structural changes (inflammation, apoptosis, necrosis and fibrosis) can develop over time in the atria of patients with AF. The precise signaling pathways that regulate these structural changes are not well understood but involve established profibrotic factors such as angiotensin II, transforming growth factor-β1 (TGF-β1) and platelet-derived growth factor (PDGF). [23-28] Atrial fibrosis can be quantified indirectly by contrast-enhanced cardiac magnetic resonance or by electro-anatomical voltage mapping. [29-34]

A hallmark of LA structural remodeling is the LA dilatation which is a predictor for progression to chronic AF and therapeutic failure as well. [35-37] However, AF is associated not only with enlargement but also with non-uniform changes in the left atrial geometry. [38] Several recent studies in AF patients demonstrated that the LA shape changes to a more spherical one in result of increasing antero-posterior LA diameter. These increased LA “sphericity” correlates with poorer outcomes after catheter ablation of AF and suggests a more advanced LA remodeling. [39,40]

### *1.3. Echocardiographic assessment of the left atrial remodeling in atrial fibrillation*

Left atrial size measured as LA diameter or LA volume is historically the oldest and simplest surrogate parameter of LA remodeling as well as an independent predictor for AF. [41,42] More recently, the LA emptying fraction was used to evaluate the transport function of the LA. [43,44] Additionally, pulsed-wave tissue Doppler (PW-TDI) measurements of the transmitral flow, as well as the blood flow in the pulmonary veins, can be useful to assess the LV diastolic function and the LA transport function. Numerous PW-TDI parameters have been shown to correlate with the outcomes after electrical cardioversion and catheter ablation of AF. [45,46] On the other hand, tissue Doppler method can provide additional insight into the nature of the LA remodeling because it allows the characterization of the intrinsic LA tissue velocities. An excellent correlation between the mitral annulus A´ velocity and different parameters characterizing the left atrial function was demonstrated in number of studies. [47,48] However, the magnitude of the A´ velocity is angle-dependent and can be affected by the tethering effects of the neighboring myocardium. Previous studies have demonstrated the superiority of atrial strain and strain rate PW-TDI for segmental evaluation of the LA function in the setting of AF. [49-52] In spite of the advantages it offers, the routine use of strain and strain rate for assessment of LA function is still limited by the time consuming offline measurements and significant expertise needed for the interpretation of the strain curves.

On the other hand, PW-TDI offers a quick and reliable approach to perform simple measurements of the LA activation. It features a good temporal resolution and eliminates the need for offline measurements using expensive software. Previous studies reported that PW-TDI can be used to measure the interval from the onset of the sinus P-wave to the peak A´ velocity at the lateral mitral annulus (MA). These studies assumed that the time of the local electrical LA activation matches the time of the local mechanical contraction. Based on this assumption, the interval from the onset of the P-wave to the onset of the A´ velocity in PW-TDI at lateral mitral annulus was introduced as a representation of the total intra-atrial conduction (TACT). [53,54] It was demonstrated that prolonged TACT was associated with new-onset AF, AF after open heart surgery, and AF recurrences after both electrical cardioversion and catheter ablation. [55-57] An important limitation of these investigations is that *TACT has never been confirmed by direct measurements of the true electrical conduction* in the LA. Moreover, all studies assumed that the activation of the lateral MA should be the latest atrial activation site.

### *1.4. Pathophysiology of interatrial conduction in atrial fibrillation*

Left atrial activation in humans occurs predominantly through the Bachmann's bundle which passes from the superior right atrium to the antero-superior portion of the left atrium. [58] Additionally, the bundles around fossa ovalis as well as the coronary sinus muscular coat serve as electrical connection between both atria. Notably, a block in Bachmann's bundle can change the course of interatrial conduction through the septum and the coronary sinus (CS) resulting in biphasic P-waves in the inferior leads. It can also cause electromechanical atrial dysfunction. [59] Studies demonstrated that ECG evidence of Bachmann's bundle block was associated with occurrence of AF. [60] Interestingly, a post-mortem study showed that Bachmann's bundle was absent in the hearts of a significant proportion of patients with AF. [61]

Anatomical studies showed that the CS musculature merges with the right atrial myocardium at CS ostium as well as with the LA myocardium at the lateral MA. [62,63] Antz et al. proved in an animal experiment that the CS activation reflects the electrical activation of the LA. [64] Therefore, the velocity of the electrical CS activation in distal direction can be used to validate the PW-TDI measurements of the TACT in AF patients and non-AF controls.

# 2 Objectives and methods

## *2.1 Study objectives*

At first, we sought to validate the TACT interval by comparing it with the actual electrical activation of the left atrium measured directly by a catheter inserted into the coronary sinus.

Further, we sought to determine the LA activation sequence. Having in mind the ovoid LA shape and asymmetrical changes in LA geometry observed in patients with AF, we hypothesized that the lateral mitral annulus may not always be the latest activation spot. Using PW-TDI, P wave to A´ times were measured at 4 (septal, lateral, inferior and anterior) distinct LA sites and were ranked from shortest to longest P-A´ interval.

At last, we sought to evaluate the LA asynchrony by calculating the difference between the longest and the shortest P-A´ as well as the standard deviation of all four P-A´ intervals. Further, LA asynchrony in patients with AF was compared with a matched control group of patients without history of AF.

## *2.2 Methods*

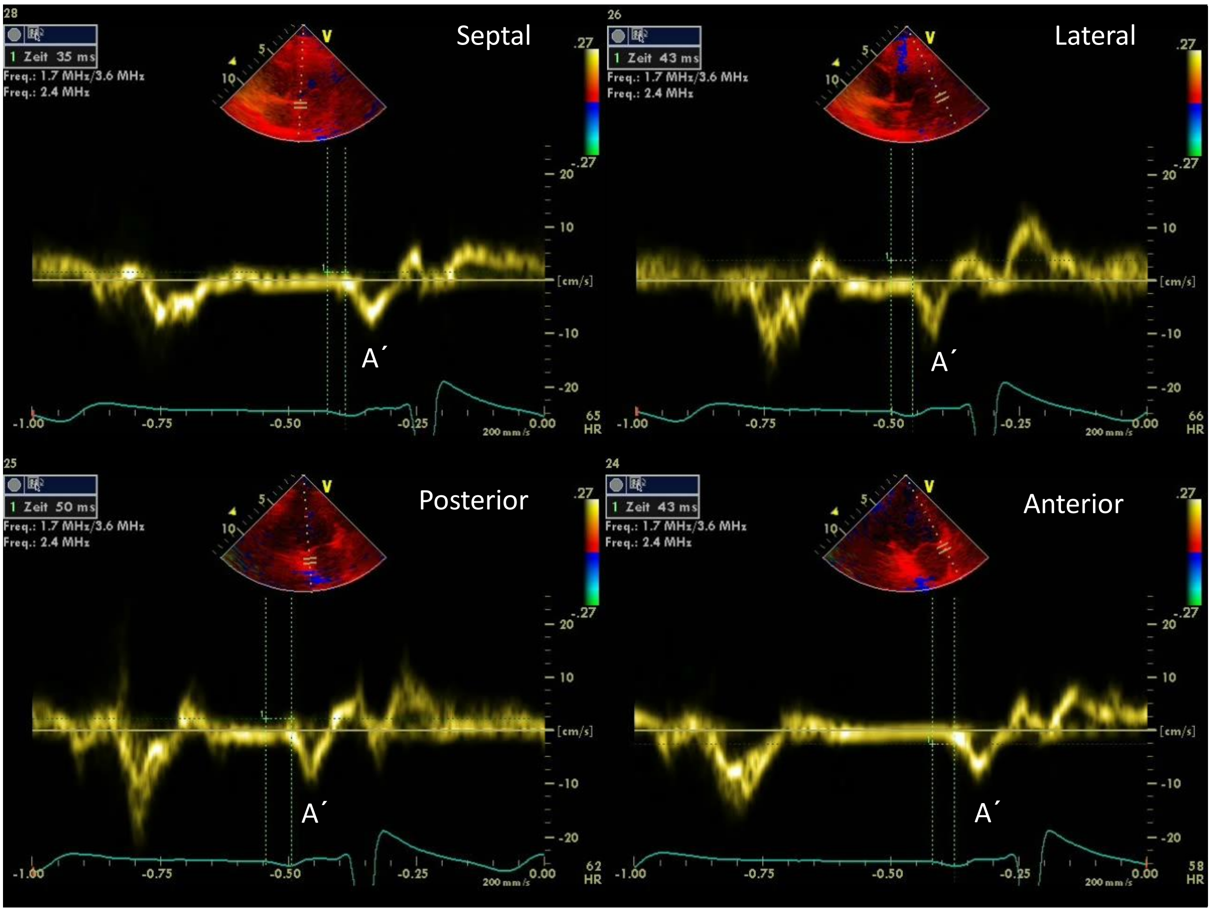
A total of 200 consecutive patients were enrolled in the study from September 2014 and September 2015. One hundred and thirty patients were referred for CA of documented AF (paroxysmal or persistent). All of them were in sinus rhythm at the time of admission. The non-AF control group consisted of 70 patients referred for electrophysiological study (EPS) and CA because of other arrhythmias. Exclusion criteria were any previous CA, impaired left ventricular ejection fraction, severe valvular disorders, sever mitral valve calcification, continuous pacemaker stimulation or intraventricular conduction delay, overt preexcitation, history of palpitations without ECG documentation, history of electrical cardioversion within last 4 weeks, pregnancy, age < 18 years. Patients with poor image quality were also discarded from analysis.

### 2.2.1 Echocardiography

Two-dimensional transthoracic echocardiography on the day of admission was performed in left lateral patient position using a commercially available ultrasound system (Vivid 7, General Electric, Milwaukee, WI, USA) equipped with 3.5 MHz transducer. Recordings were made in parasternal long- and short-axis, as well as apical four-chamber and two-chamber views. All images were ECG-triggered and stored as cineloop for off-line analysis.

Left ventricular (LV) wall thickness, LV dimensions, and LA diameter were measured from the grey scale images in parastermal long axis (PLAX) view. LA diameter was indexed for the body surface area (LAi). LV ejection fraction was measured in four-chamber and two-chamber views using the Simpson's method. LV diastolic function was evaluated using pulsed-wave (PW) Doppler recording of the mitral valve flow (E-wave, A-wave, deceleration time of the E-wave). LA volumes were measured from apical four- and two-chamber views and the LA emptying fraction was calculated according the following formula: LA emptying fraction % = (LA max volume – LA minimum volume)/LA maximum volume x 100. The valves morphology and function were assessed according to the guidelines of the American Society of Echocardiography.

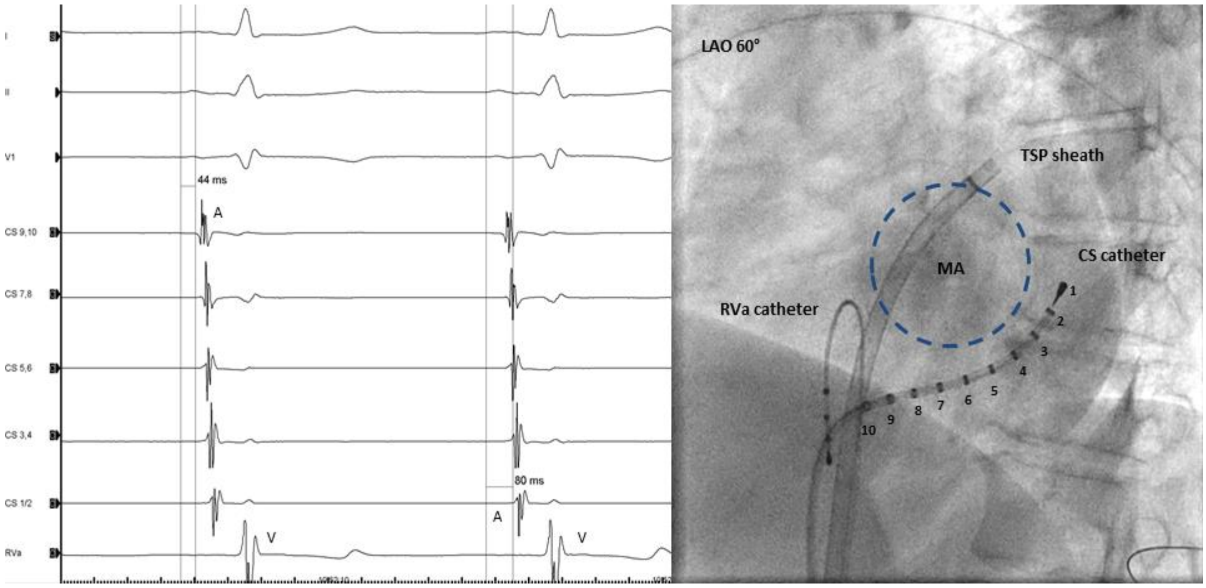
Further, we performed pulsed-wave tissue Doppler imaging (PW-TDI) from apical 4-chamber and 2-chamber views. The region of interest was adjusted at 3.5 mm and was placed at the level of septal, lateral, anterior and posterior LA just above the MA as well as at the lateral tricuspid annulus. The gain was minimized to obtain clear Doppler signals with minimal background noise. All PW-TDI measurements were performed at end of expiration. Particular attention was paid on the alignment of the region of interest with the atrial wall. P-wave onset was easily distinguishable if amplified and registered at lower rates (25 mm/s), however, the P-wave was usually blurred at 200 mm/s. Therefore, we set the marker at the beginning of the P-wave at 25 mm/s and changed the sweep speed to 200 mm/s afterwards to measure the distance to the beginning of the A` velocity at each site. (as shown on the figure below).




The P-A´ intervals were measured only for sinus beats, whereas P-waves of different morphology were discarded. All intervals were measured for at least 3 cardiac cycles and averaged.

### *2.2.2 Electrophysiological study*

All patients gave an informed consent for the EPS and CA and were prepared according to the practice in our center. A 10-poles steerable catheter (2-5-2 mm interelectrode distance) was inserted into the coronary sinus (CS). The proximal pole (10) of the catheter was placed at the CS ostium based on its fluoroscopic position in left anterior oblique (LAO) view. The time from the onset of the P-wave to the local sharp CS signal in milliseconds was measured at the proximal CS (electrode pair 9-10) and distal CS (electrode pair 1-2). (as shown on the figure below)




In patients scheduled for CA of AF a left atrial access was obtained through a transseptal puncture. A circumferential pulmonary vein isolation using irrigated catheters was successfully performed in all of them. Electroanatomical mapping systems (Carto 3; Biosense Webster, Diamond bar, CA or EnSite Velocity; Endocardial Solutions, St. Paul, MN) were used for creation of the anatomy of the pulmonary veins and LA as well as for visualization of the catheters.

### *2.2.3 Statistical methods*

Data analysis was performed with SPSS statistical software V.21. Continuous variables are reported as mean (SD) and categorical variables are presented as numbers (percentage). Differences between groups were tested using parametric (Student's t-test) and non-parametric (Fisher, Chi-square, Mann-Whitney) tests. The standard deviation of the all four P-A´ intervals (SD-4PA´) was calculated for each patient. Bivariate Pearson correlation was performed to test for significant correlations between the P-CS and P-A´ intervals. The predictive accuracy of the variables was evaluated using receiver operator characteristics (ROC) curve. Sensitivity, specificity, positive and negative predictive values were calculated. Value of $P < 0.05$ was considered statistically significant.

## 3 Publication

Dinov B, Knopp H, Löbe S, Nedios S, Bode K, Schönbauer R, Sommer P, Bollmann A, Arya A, Hindricks G. Patterns of left atrial activation and evaluation of atrial dyssynchrony in patients with atrial fibrillation and normal controls: factors beyond the left atrial dimensions. Heart Rhythm. 2016 Sep;13(9):1829-36.

# Patterns of left atrial activation and evaluation of atrial dyssynchrony in patients with atrial fibrillation and normal controls: Factors beyond the left atrial dimensions

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**BACKGROUND** Left atrial (LA) remodeling causing slower and asynchronous conduction is crucial for the maintenance of atrial fibrillation (AF).

**OBJECTIVE** We propose a simple and quick method to evaluate the LA asynchrony.

**METHODS** One hundred thirty patients with AF (AF group) and 70 patients without a history of AF (controls) were examined prospectively using pulsed-wave tissue Doppler imaging. The time intervals from the onset of the P wave to the onset of the A′ wave (P-A′ intervals) were measured at 4 sites at the mitral annulus: septal, lateral, anterior, and posterior. To assess the LA asynchrony, the differences between the longest and the shortest P-A′ interval as well as the standard deviation of all 4 P-A′ intervals were calculated.

**RESULTS** Both groups were matched for the baseline characteristics. The AF group had longer differences between the longest and the shortest P-A′ than did controls (37 ± 16 ms vs 28 ± 13 ms; $P = .0001$). The standard deviation of all 4 P-A′ intervals was also higher in the AF group (17 ± 7 ms vs 13 ± 5 ms; $P = .0001$). Furthermore, distinct patterns of LA activation were observed with most patients with AF showing upward LA activation (86.5%) whereas normal controls were showing downward LA activation (65.5%). Receiver operating characteristic analysis revealed that P-A′ anterior successfully discriminated patients with AF from controls (area under the curve 0.85; $P < .0001$). Furthermore, P-A′ anterior > 55 ms discriminated between patients with AF and controls with a sensitivity of 85% a specificity of 81%, a positive predictive value of 0.898, and a negative predictive value of 0.707.

**CONCLUSION** Patients with AF showed greater LA asynchrony in pulsed-wave tissue Doppler imaging, upward LA activation, and a prolonged activation time at the anterior mitral annulus. Prolongation of P-A′ anterior discriminated between patients with AF and controls with high sensitivity and specificity.

**KEYWORDS** Atrial; Asynchrony; Atrial fibrillation; PW-TDI

(Heart Rhythm 2016;13:1829–1836) 

## Introduction

Earlier risk stratification for atrial fibrillation (AF) is important to prevent devastating AF-associated events such as stroke. Numerous clinical and echocardiographic parameters were found to be associated with an increased likelihood of new-onset AF. However, even the most widely used prognostic variables have low diagnostic yield, suggesting a multifactorial pathogenesis of AF.

Although pulmonary vein foci are widely accepted as drivers of paroxysmal AF, multiple mechanisms can contribute to AF maintenance. Experimental studies[1–4] showed that along with shortening of the atrial refractory period, slowing of intra-atrial conduction is a common hallmark of the AF-associated left atrial (LA) remodeling. Previous studies[5,6] suggested that the total atrial activation time (TACT) measured at the lateral mitral annulus (MA) using pulsed-wave tissue Doppler imaging (PW-TDI) is an independent predictor of AF. Some recent studies[7,8] also demonstrated that TACT is associated with an increased probability of AF recurrences after electrical cardioversion and catheter ablation (CA) of AF.

In this article, we propose a more elaborate method to assess the LA asynchronous activation and conduction delay using PW-TDI. We test whether the measurement of local atrial contraction at 4 LA sites can be useful to distinguish patients with AF from those without a history of AF (controls).

## Methods

We *prospectively* studied a total of 200 patients from September 2014 to September 2015. One hundred thirty patients had documented AF (both paroxysmal and

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persistent) and were referred for CA. All of them were in sinus rhythm at the time of admission. They were compared with a control group of 70 patients without a history of AF referred for the electrophysiology study (EPS) and CA because of other arrhythmias. Exclusion criteria were previous CA for supraventricular or ventricular arrhythmias, impaired left ventricular (LV) ejection fraction, severe valvular disorders, pacemaker stimulation or intraventricular conduction delay, overt preexcitation, history of palpitations without electrocardiographic documentation, history of electrical cardioversion within 4 weeks, and age $<18$ years. All patients gave a written informed consent for ablation. The study was approved by the institutional committee on human research.

## Echocardiography

Two-dimensional transthoracic echocardiography on the day of admission was performed using a commercially available ultrasound system (Vivid 7, General Electric, Milwaukee, WI) equipped with 3.5-MHz transducer. Recordings were done in parasternal long- and short-axis views as well as in apical 4- and 2-chamber views. All images were electrocardiogram triggered and stored as cine loops for off-line analysis.

LV wall thickness, LV dimensions, and LA diameter were measured from the gray scale images in the left parasternal long-axis view. LA diameter was corrected for the body surface area (LA diameter index). LV ejection fraction was measured in 4- and 2-chamber views using Simpson's method. LV diastolic function was evaluated using pulsed-wave Doppler recording of the mitral valve flow (E wave, A wave, and deceleration time of the E wave). LA volumes were measured from apical 4- and 2-chamber views, and the LA emptying fraction was calculated using the following formula: LA emptying fraction (%) = [(LA maximum volume – LA minimum volume)/LA maximum volume] × 100. The valvular morphology and function were assessed according to the guidelines of the American Society of Echocardiography. In addition, we performed PW-TDI in apical 4- and 2-chamber views. The sample volume was placed at the level of the septal, lateral, anterior, and posterior LA just above the MA, as well as at the lateral tricuspid annulus.

We measured time duration from the onset of the P wave to the first activation of the above-mentioned landmarks. The onset of the P wave was easily distinguishable if amplified and registered at lower rates (25 mm/s); however, the onset of the P wave was usually blurred at 200 mm/s. Therefore, we set a marker at the beginning of the P wave at 25 mm/s and changed the speed to 200 mm/s afterward to measure the distance to the A′ wave. Particular attention was paid to measure the time intervals from the onset of the surface P wave to the onset of the local A′ wave (P-A′) only of sinus beats, and P waves of different morphology were discarded. All intervals were measured in at least 3 cardiac cycles and averaged. Particular attention was paid on the quality of the image acquisitions, and patients with insufficient image quality were excluded from the study (Figure 1).

## EPS and CA

All patients gave an informed consent for the EPS and CA and prepared according to the practice in our center. In all cases, a decapolar steerable catheter (2-5-2 mm) was inserted in the coronary sinus (CS). The proximal pole of the catheter (electrode pair 9-10) was placed in the vicinity of the CS ostium on the basis of its fluoroscopic position in the left anterior oblique view. The time from the onset of the sinus P wave to the local sharp CS signal was measured at the proximal CS (electrode pair 9-10) and the distal CS (electrode pair 1-2).

In patients scheduled for CA of AF, an LA access was obtained through a transseptal puncture. A circumferential pulmonary vein isolation using irrigated catheters was successfully performed in all. Electroanatomic mapping systems (CARTO 3, Biosense Webster Inc., Diamond bar, CA, or EnSite Velocity, Endocardial Solutions, Inc., St. Paul, MN) were used for the creation of pulmonary veins and LA anatomy and for the visualization of catheters. After the completion of circumferential ablation, voltage maps of the LA in sinus rhythm were constructed and the areas showing low-amplitude signals ($<0.5$ mV) were annotated as low-voltage areas. Additional linear ablation in these areas to connect them with electrically unexcitable hallmarks was performed as previously described.[9]

## Statistical analysis

Data analysis was performed with SPSS version 21 (IBM, Armonk, NY, USA). Continuous variables are presented as mean ± SD, and categorical variables are presented as number (percentage). Differences between groups were tested using parametric (Student *t* test) and nonparametric (Fisher exact, $\chi^2$, and Mann-Whitney) tests. The standard deviation of all 4 P-A′ intervals (SD-4PA′) was calculated for each patient. A bivariate Pearson correlation was performed to test for significant correlations between the proximal CS and P-A′ intervals. The predictive accuracy of the variables was evaluated using the receiver operating characteristic (ROC) curve. Sensitivity, specificity, and positive and negative predictive values were calculated. A $P$ value of $<.05$ was considered statistically significant.

# Results

## Baseline characteristics

The mean age of our cohort was 58 ± 13 years, and 87 patients (43.5%) were women. Thirty patients (15%) presented with persistent AF. Both groups were matched for the baseline clinical characteristics (Table 1). Importantly, age, LV ejection fraction, LV septum thickness, LA diameter, and LA diameter index did not differ significantly between the groups.

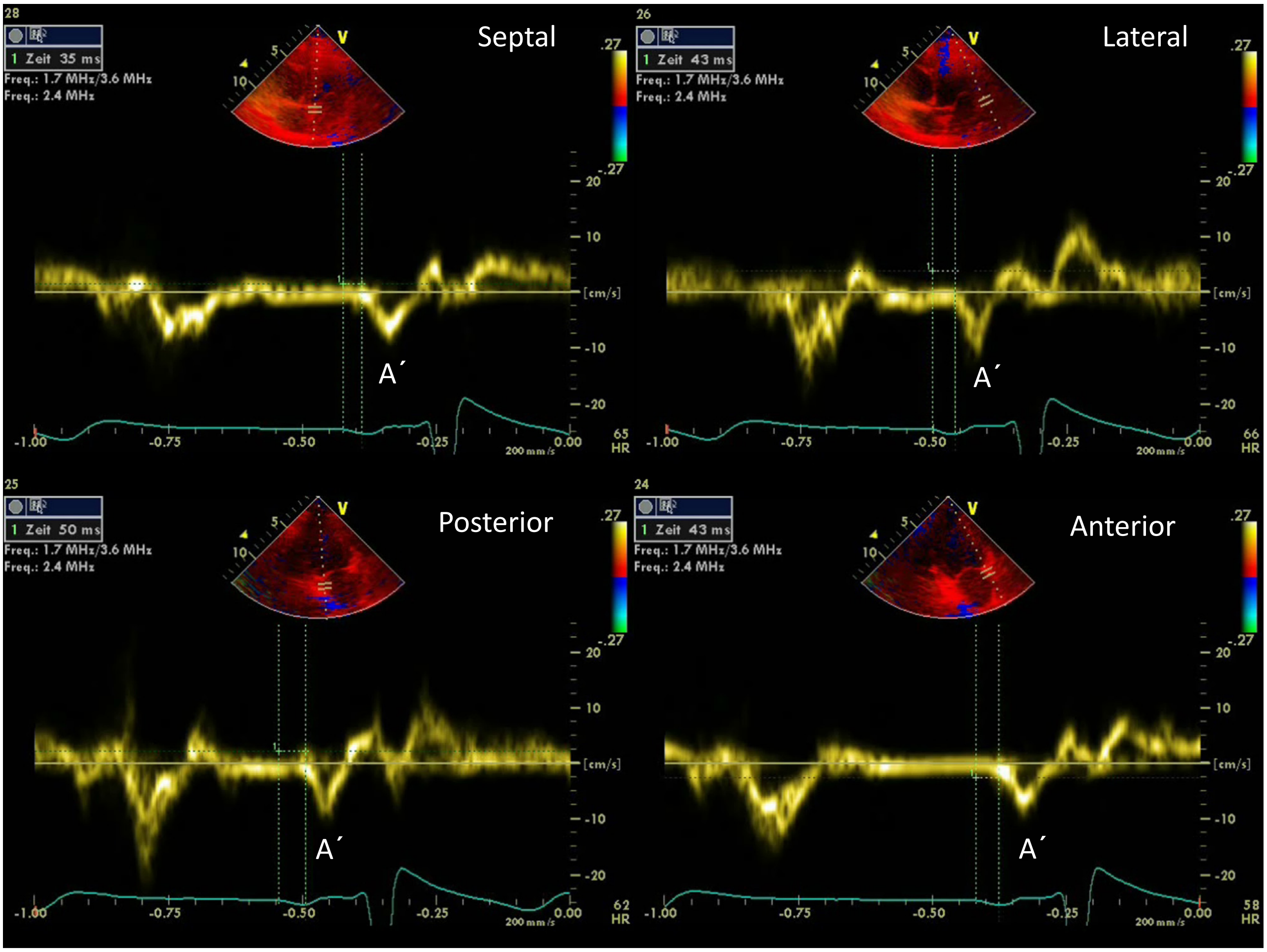



**Figure 1** Pulsed-wave tissue Doppler imaging (PW-TDI) measurements of time intervals from the onset of the surface P wave to the onset of the local A′ wave (P-A′). PW-TDI is performed in the apical 4- and 2-chamber views. The sample volume is placed at the level of septal, lateral, anterior, and posterior left atria just above the mitral annulus. The P-A′ intervals at each of the aforementioned points of the mitral annulus are measured.

## Correlations between PW-TDI and CS activation measurements

Patients with AF showed a significantly slower conduction to septal and lateral MA positions (septal: 36 ± 16 vs 43 ± 19; $P = .005$; lateral: 59 ± 17 vs 73 ± 23; $P = .0001$) (Table 2). In the overall cohort, the P-A′ at the lateral MA showed a positive, strong, and significant correlation with the proximal CS activation time at the distal pole of the CS catheter (Pearson $r = 0.708$; $P = .0001$ for P-A′ lateral and proximal coronary sinus [electrode pair 1-2]) (Figure 2).

**Table 1** Baseline clinical characteristics

| Characteristic | Controls (n = 70) | Patients with AF (n = 130) | *P* |
|---|---|---|---|
| Age (y) | 57 ± 13 | 59 ± 12 | .155 |
| Sex: female | 32 (45.7) | 55 (42.3) | .657 |
| Hypertension | 40 (57.1) | 91 (70) | .086 |
| Diabetes | 10 (14.3) | 16 (12.3) | .667 |
| CAD | 3 (4.3) | 15 (11.5) | .120 |
| Persistent AF | | 30 (23) | |
| β-Blockers | 33 (47.1) | 110 (84.6) | .0001 |
| AAD class III | 1 (1.4) | 38 (29.2) | .0001 |
| AAD class IC, n (%) | 0 | 16 (12.2) | .002 |
| Dronedarone | 0 | 4 (3.1) | .301 |

Values are presented as mean ± SD or as n (%).

AAD = antiarrhythmic drug; AF = atrial fibrillation; CAD = coronary artery disease.

## LA asynchrony in AF and control groups

Compared with controls, patients with AF had significantly longer P-A′ intervals in all 4 LA sites, but not in the P-A′ interval at the lateral tricuspid annulus. The difference between the longest and the shortest P-A′ (DLS-PA′) was higher in the AF group than in the control group (37 ± 16 ms vs 28 ± 13 ms; $P = .0001$). Furthermore, SD-4PA′ was significantly higher in the AF group (17 ± 7 ms vs 13 ± 5 ms; $P = .0001$) (Table 2). In patients not taking amiodarone, the findings were consistent with the results for the overall cohort. There was a significant difference in DLS-PA′ between the AF and control groups (36 ± 15 ms vs 28 ± 13 ms; $P = .0001$). Similarly, SD-4PA′ was significantly higher in the AF group (17 ± 7 ms vs 13 ± 5 ms; $P = .0001$) (Table 3).

## Patterns of LA activation in AF and control groups

P-A′ at the lateral tricuspid annulus was the shortest interval, consistent with earliest right atrial activation (Table 2).

**Table 2** Echocardiographic and electrophysiological characteristics

| Characteristic | Controls (n = 70) | Patients with AF (n = 130) | *P* |
|---|---|---|---|
| LA (PLAX view) (mm) | 38.9 ± 6.3 | 40.7 ± 6.1 | .062 |
| LA index (mm/m$^2$) | 20.0 ± 3.2 | 20.3 ± 3.2 | .688 |
| LA emptying fraction (%) | 63 ± 14 | 51 ± 18 | .001 |
| IVS (mm) | 11.1 ± 2.5 | 11.2 ± 2.2 | .904 |
| LVEDD (mm) | 48.7 ± 5.9 | 49.1 ± 6.4 | .662 |
| LVESD (mm) | 29.2 ± 5.8 | 29.3 ± 6.4 | .869 |
| LV EF (%) | 63.7 ± 6.3 | 63.7 ± 6.8 | .987 |
| E/A ratio | 1.04 ± 0.36 | 1.23 ± 0.53 | .008 |
| DT (ms) | 233 ± 63 | 230 ± 59 | .761 |
| TA P-A′ (ms) | 28 ± 18 | 30 ± 19 | .368 |
| MA P-A′ sept (ms) | 36 ± 16 | 43 ± 19 | .005 |
| MA P-A′ lat (ms) | 59 ± 17 | 73 ± 23 | .0001 |
| MA P-A′ post (ms) | 53 ± 16 | 55 ± 19 | .347 |
| MA P-A′ ant (ms) | 46 ± 18 | 71 ± 23 | .0001 |
| LSD P-A′ (ms) | 28 ± 13 | 37 ± 16 | .0001 |
| SD-4PA′ | 13 ± 5 | 17 ± 7 | .0001 |
| P-CS 9-10 (ms) | 45 ± 17 | 56 ± 20 | .001 |
| P-CS 1-2 (ms) | 73 ± 16 | 85 ± 22 | .003 |

Values are presented as mean ± SD.

AF = atrial fibrillation; ant = anterior; DT = deceleration time; E/A = early/late diastolic filling velocities; IVS = interventricular septum; LA = left atrial; lat = lateral; LSD = longest-shortest difference; LVEDD = left ventricular end-diastolic diameter; LV EF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; MA = mitral annulus; P-A′ = time interval from the onset of the P wave to the onset of the A′ wave; P-CS 1-2 = proximal coronary sinus (electrode pair 1-2); P-CS 9-10 = proximal coronary sinus (electrode pair 9-10); PLAX = parastermal long axis; post = posterior; SD-4PA′ = standard deviation of all 4 P-A′ intervals; sept = septal; TA = tricuspid annulus.

Furthermore, 3 patterns of LA activation were observed with regard to the timing of P-A′ intervals in the LA: predominantly upward activation with P-A′ interval posteriorly shorter than

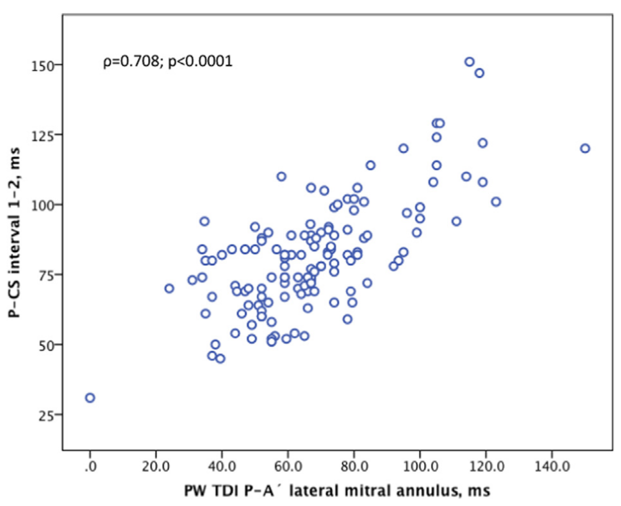



**Figure 2** Correlation between the electrical activation in the distal coronary sinus and the pulsed-wave tissue Doppler imaging (PW-TDI) measured mechanical contraction at the lateral mitral annulus (time intervals from the onset of the surface P wave to the onset of the local A′ wave [P-A′]). The figure depicts a linear positive correlation between the time to the local mechanical LA activation measured using PW-TDI at the lateral mitral annulus and the electrical activation measured invasively at the distant pole of the coronary sinus catheter. P-CS 1-2 = proximal coronary sinus (electrode pair 1-2).

**Table 3** Echocardiographic and electrophysiological characteristics of patients not taking amiodarone

| Characteristic | Controls (n = 69) | Patients with AF (n = 92) | *P* |
|---|---|---|---|
| LA (PLAX view) (mm) | 38.9 ± 6.3 | 40.3 ± 6.3 | .199 |
| LV EF (%) | 63.8 ± 6.3 | 63.0 ± 6.7 | .473 |
| TA P-A′ (ms) | 27.9 ± 18 | 28.7 ± 18 | .783 |
| MA P-A′ sept (ms) | 35 ± 16 | 42 ± 20 | .030 |
| MA P-A′ lat (ms) | 59 ± 17 | 72 ± 23 | .0001 |
| MA P-A′ post (ms) | 53 ± 16 | 54 ± 19 | .681 |
| MA P-A′ ant (ms) | 46 ± 18 | 69 ± 22 | .0001 |
| LSD P-A′ (ms) | 28 ± 13 | 36 ± 15 | .0001 |
| SD-4PA′ | 13 ± 5 | 17 ± 7 | .001 |
| P-CS 9-10 (ms) | 45 ± 17 | 56 ± 18 | .002 |
| P-CS 1-2 (ms) | 73 ± 16 | 84 ± 21 | .009 |

Values are presented as mean ± SD.

AF = atrial fibrillation; ant = anterior; LA = left atrial; lat = lateral; LSD = longest-shortest difference; LV EF = left ventricular ejection fraction; MA = mitral annulus; P-A′ = time interval from the onset of the P wave to the onset of the A′ wave; P-CS 1-2 = proximal coronary sinus (electrode pair 1-2); P-CS 9-10 = proximal coronary sinus (electrode pair 9-10); PLAX = parastermal long axis; post = posterior; SD-4PA′ = standard deviation of all 4 P-A′ intervals; sept = septal; TA = tricuspid annulus.

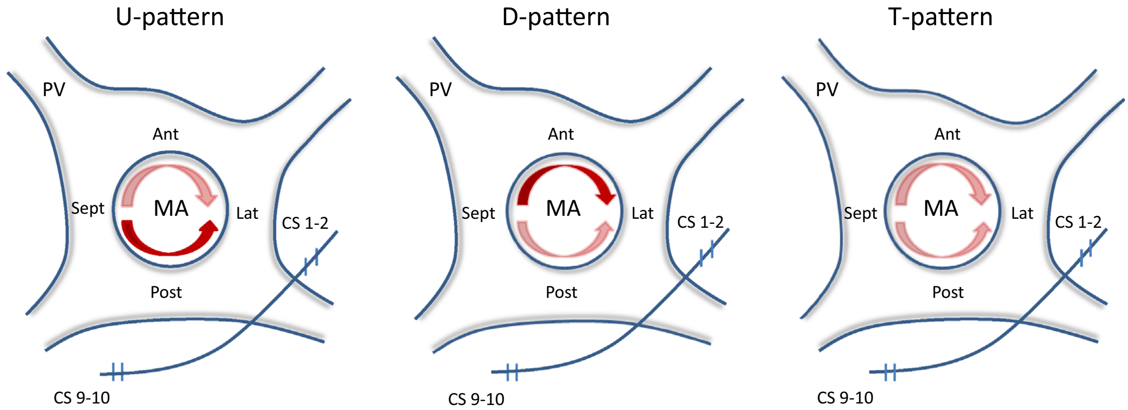
P-A′ interval anteriorly (U pattern); predominantly downward activation with P-A′ interval anteriorly shorter than P-A′ interval posteriorly (D pattern); and transitional pattern with P-A′ interval anteriorly that equals P-A′ interval posteriorly (T pattern). In patients with AF, the most frequently observed was the U pattern in 114 patients (87%), followed by the D pattern in 14 patients (10.8%) and the T pattern in 2 patients (1.5%). In the control group, the most frequently observed was the D pattern in 48 patients (68.6%), followed by the U pattern in 15 patients (21.4%) and the T pattern in 7 patients (10%). There was a significant difference in activation patterns between the AF and control groups ($P = .0001$) (Figure 3).

## P-A′ anterior as a predictor of AF

Figure 4 presents the ROC curves to discriminate between patients with AF and controls for each P-A′, and Figure 5 presents the ROC curves for SD-4PA′ and DLS-PA′. P-A′ measured at the anterior MA has the largest area under the curve (AUC 0.847; 95% confidence interval 0.788–0.907; $P < .0001$) of all. The cutoff value for P-A′ anteriorly > 55 ms discriminates patients with AF from controls with a sensitivity of 81.5% and a specificity of 82.8%. For a P-A′ of 55 ms, the positive predictive value is 0.898 and the negative predictive value is 0.707. These results remained consistent after the exclusion of patients pretreated with amiodarone as P-A′ remained the best discriminator for AF (AUC 0.836; 95% confidence interval 0.769–0.902; $P < .0001$). In patients not taking amiodarone, P-A′ anteriorly > 55 ms discriminates between patients with AF and controls with a sensitivity of 83.7% and a specificity of 77%.

## Discussion

The study prospectively investigated atrial activation times in patients with AF and controls by using PW-TDI. In




| Group | U-pattern | D-pattern | T-pattern | P |
|---|---|---|---|---|
| Atrial fibrillation | 114 (87.7 %) | 14 (10.8 %) | 2 (1.5 %) | 0.0001 |
| Control | 15 (21.4 %) | 48 (68.6 %) | 7 (10 %) | |

**Figure 3** Patterns of left atrial (LA) activation in patients with atrial fibrillation (AF) and controls. Differences in activation patterns between patients with documented AF and those with without documented AF. The D pattern stands for downward LA activation predominantly through the Bachmann bundle (most common pattern in controls). The U pattern stands for upward LA activation consistent with predominant activation through the coronary sinus, suggesting Bachmann bundle's block (typical pattern for patients with AF). The T pattern features transitional LA activation with equal time intervals from the onset of the surface P wave to the onset of the local A′ wave anteriorly and posteriorly. Ant = anterior; CS 1-2 = coronary sinus (electrode pair 1-2); CS 9-10 = coronary sinus (electrode pair 9-10); Lat = lateral; MA = mitral annulus; Post = posterior; PV = pulmonary vein; Sept = septal.

contrast to all previous reports that studied TACT, we obtained local atrial activation times (P-A′) at 4 sites at the MA as well as at the tricuspid annulus. To our knowledge, this is the first study to compare these intervals with those of a matched control group of patients without AF. Importantly, this is also the first study that directly correlated the PW-TDI measurements with the actual electrical activation along MA using the catheter placed in the CS.

## Correlation between mechanical and electrical LA activation

Previous studies[5–8] reported that the TACT measured using PW-TDI represents the LA conduction delay and was associated with a history of AF as well as with AF recurrences after cardioversion, CA, and cardiac surgery. Assuming a link between electrical activation and mechanical contraction, these previous studies accepted for granted an unproven concept that the onset of A′-wave velocity in PW-TDI at the MA represents the onset of both mechanical and electrical LA activation. Although this theory appears to be plausible, we made an effort to validate it through the correlation of the P-A′ measured using PW-TDI and the actual electrical activation of the CS. Indeed, earlier anatomical studies[10,11] showed that CS musculature merges with the right atrial myocardium at the CS ostium and with the LA myocardium at the lateral MA. In addition, Antz et al[12] proved in an animal experiment that CS activation reflects the electrical activation of the LA. They also showed that CS musculature can serve as an electrical connection between the right atrium and the lateral LA. Although not simultaneously measured, we found that P-A′ at the lateral MA featured a strong, positive, linear correlation with the electrical activation of the distal CS. Therefore, although not proved for each MA segment, we assumed that the P-A′ can be used with a reasonable approximation for the LA electrical activation at different LA sites.

## Advantages of PW-TDI over atrial strain to assess the temporal LA activation

Recent studies[13–15] have demonstrated the feasibility of atrial strain for the evaluation of the timing of intra-atrial conduction delay and LA asynchrony. However, it requires off-line measurements and significant expertise in the interpretation of the strain curves. Moreover, all current software options were designed to conduct LV analysis. In contrast, the PW-TDI method offers a simple, quick, and reliable approach to assess the LA activation sequence. It features a good temporal resolution and eliminates the need for off-line measurements using expensive software.

## Patterns of LA activation and possible mechanisms of asynchronous LA activation

In this study, we proved that patients with AF have different LA activation patterns as well as longer LA activation times as compared with controls. To our knowledge, this is the first study to demonstrate that most patients with AF feature a specific upward LA activation pattern with latest local

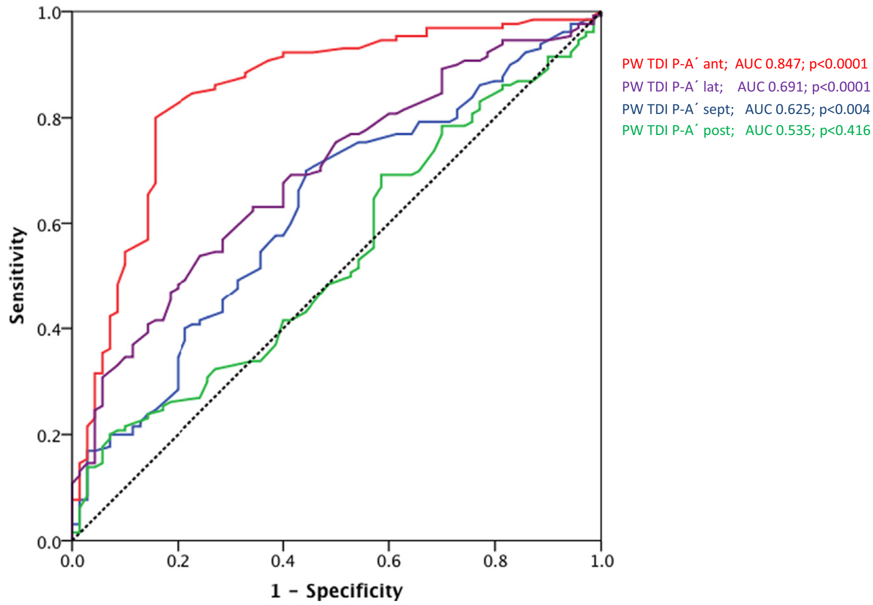



**Figure 4** Receiver operating characteristic curves for each time interval from the onset of the surface P wave to the onset of the local A′ wave (P-A′) with the corresponding area under the curve (AUC) for discriminating between patients with atrial fibrillation and controls. See text for further discussion. Ant = anterior; Lat = lateral; Post = posterior; PW-TDI = pulsed-wave tissue Doppler imaging; Sept = septal.

activation at the anterior MA. In contrast, in patients without a history of AF, the predominant LA activation pattern features earlier activation at the septum and anterior MA. We hypothesize that significantly prolonged P-A′ anteriorly in AF is a result of a block in the Bachmann bundle that connects the right atrium with the anterosuperior part of the LA. Since in human hearts the Bachmann's bundle is the preferential electrical connection between both atria, a block in this route can change the course of interatrial conduction through the septum and the CS resulting in an upward LA activation, explaining the pattern observed in most patients with AF. Indeed, previous studies[16–19] confirmed that the biphasic P wave in the inferior leads as expression of interatrial conduction block is associated with AF. A postmortem study[20] showed that the Bachmann bundle was absent in a significant proportion of the hearts of patients with AF. Aging and certain diseases can affect the intra-atrial conduction across the Bachmann bundle, causing a significant interatrial delay and nonphysiological and asynchronous LA electrical activation and contraction.[21]

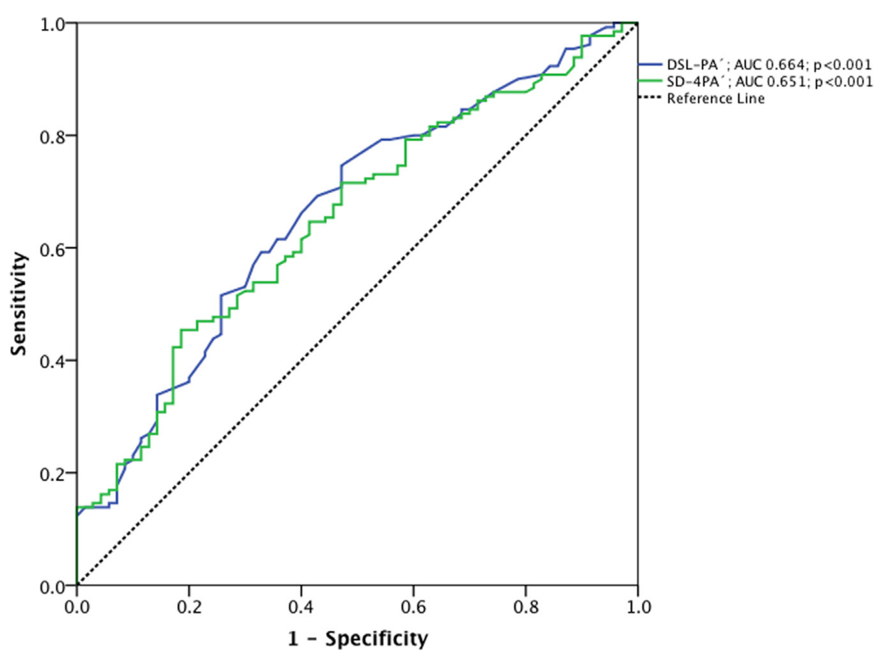



**Figure 5** Receiver operating characteristic curves for the standard deviation of all 4 P-A′ intervals (SD-4PA′) and differences between the longest and the shortest P-A′ interval (DLS-PA′) with the corresponding area under the curve (AUC) for discriminating between patients with atrial fibrillation and controls. See text for further discussion.

The role of the Bachmann bundle in the pathophysiology of AF was demonstrated in animal experiments. Using epicardial and endocardial mapping during induced AF in canine hearts, Kumagai and co-workers[22,23] showed that AF was maintained from multiple unstable reentry circuits using the Bachmann bundle as a part of their reentry pathway. A single site CA of the Bachmann bundle can successfully eliminate AF in animal experiments. Furthermore, there are evidences that atrial synchronous pacing at the Bachmann bundle can be effective in preventing the initiation of AF with pacing.[24] Patients with a history of paroxysmal AF were less likely to develop persistent AF during follow-up if paced at the region of the Bachmann bundle as compared to right atrial appendage.[25]

### Asymmetrical LA enlargement or Bachmann bundle block

It is widely accepted that LA dilatation is strongly associated with AF. In the present study, although both AF and control groups were matched for all baseline characteristics including LA dimension, both groups differ significantly with respect to PW-TDI activation intervals and LA asynchrony. This suggests that LA dilatation is not the only mechanism responsible for the delayed intra-atrial activation and asynchrony. In a previous study, De Vos et al[6] reported that the TACT that had an AUC of 0.74 and a cutoff value of 165 ms had a sensitivity and specificity of 67% and 77% for the occurrence of new-onset AF. In comparison, the P-A′ at the anterior MA had a superior predictive value for AF with an AUC of 0.85 as well as a higher sensitivity and specificity of $>80\%$ for a cutoff value of $>55$ ms. We hypothesize that this value identifies susceptible patients with conduction delay in the Bachmann bundle. In contrast, the prolongation of the P-A′ at the anterior MA can be explained with changes in LA symmetry. Nedios et al[26] investigated changes in LA geometry in 3-dimensional computed tomography reconstructions of the LA and proved that LA asymmetry, and especially the increase in anterior LA volume, was an independent predictor of AF recurrence after CA of AF.

### Influence of right atrial conduction

P-A′ intervals can be influenced by the right atrial conduction time. Therefore, in addition to the P-A′ intervals, the intervals from the P wave to the lateral tricuspid annulus (P-TA′ lateral) were measured. Since P-TA′ lateral intervals were similar in both patients with AF and controls ($P = .368$), we suggested that the effects of the intrinsic intra–right atrial conduction on the P-A′ intervals should be negligible.

### Study limitations

Since PW-TDI measurement requires sinus rhythm at the time of echocardiography, more patients in the cohort had paroxysmal AF than chronic AF. Although unsatisfactory echocardiographic conditions can influence the quality of the images, it was possible to obtain reliable PW-TDI curves even in cases of poor acoustic windows. In addition, cardiac translational and rotational movements as well as the passive deformation due to traction of the adjacent segments can influence the measurements at different MA sites. High-density local activation times mapping (LAT) mapping could provide a more direct measurement of activation times; however, it is invasive, time-consuming, and prone to other inherent limitations. More patients in the AF group received amiodarone that can influence the intra-atrial conduction and the conduction velocity through the Bachmann bundle and, respectively, P-A′ intervals. Since patients with impaired LV systolic function, severe hypertrophy, and valvular abnormalities were excluded from the study, the results may not be valid for patients with these conditions. PW-TDI measurement at the lateral tricuspid annulus is a surrogate marker of the activation times at the lateral right atrium and alone may not be sensitive enough to detect slowing of right atrial activation. Finally, it is uncertain whether the observed changes in the LA activation are a cause or a consequence of AF.

## Conclusion

Patients with AF showed greater LA asynchrony in PW-TDI independent of the LA dimensions as well as an upward LA activation and a prolonged activation time at the anterior MA. Prolongation of the P-A′ at the anterior MA discriminates between patients with AF and controls with high sensitivity and specificity. This method can be useful to identity patients at risk of the occurrence of new AF.

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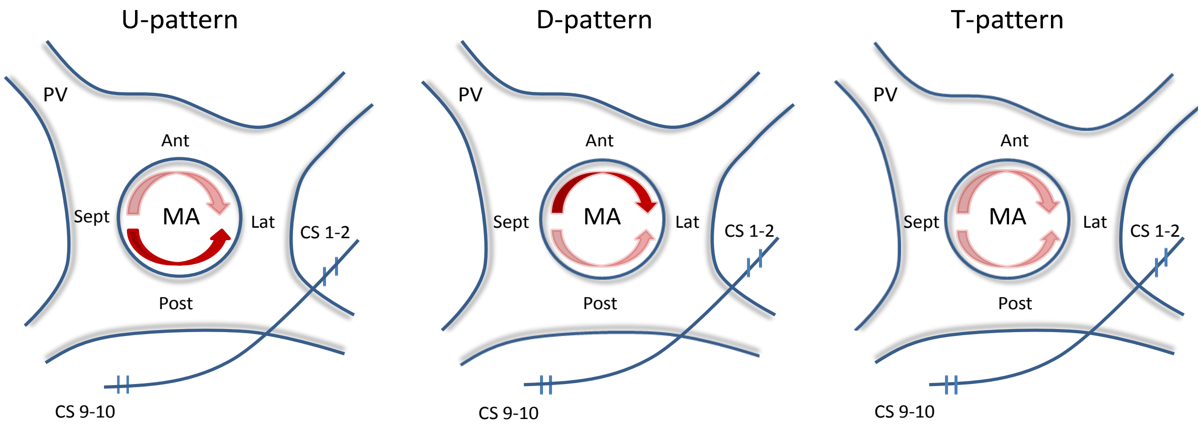
# 4 Discussion

The current work prospectively investigated the LA activation and asynchrony in patients with AF using PW-TDI and a matched control group of patients without history of AF. In previous studies PW-TDI was used to measure the total atrial conduction time at the lateral mitral annulus. Prolongation of TACT has been shown to correlate with unfavorable outcomes after electrical cardioversion, RF catheter ablation of AF, and new-onset of AF. [52-57] In contrast to the previously published studies, we measured the local atrial conduction times (P-A´) at four distinct left atrial sites as well as at the lateral tricuspid annulus, and the intervals in patients with AF were compared with the intervals in a control group without AF.

Although the assumption that TACT is a measurement of the electrical activation of the atria is plausible, it has not been proven yet. Apart from the local atrial activation, the magnitude and the timing of the A´ velocity in PW-TDI can be influenced by multiple confounding factors. To validate the reliability of the PW-TDI derived TACT, a multipolar catheter was placed into the coronary sinus to measure directly the electrical activation at the lateral mitral annulus, and these measurements were correlated with the corresponding P-A´ measured by PW-TDI at lateral LA. Demonstrating a strong, positive, linear correlation between the P-A´ at lateral LA and the electrical activation at distal CS poles (Pearson correlation r=0.708), we suggested that the P-A´ intervals can be used with a reasonable approximation as a measurement of the local LA electrical activation.

Furthermore, we found that patients in the AF group demonstrated longer LA activation times in comparison to the non-AF control group. Although both groups shared similar baseline characteristics, AF patients featured greater difference between the longest and the shortest P-A´ intervals as well as a greater standard deviation of the 4 P-A´ intervals. These findings suggest that, independently from the LA size, AF patients have more pronounced LA asynchrony compared to normal controls.

Notably, after ranking the P-A´ intervals from the shortest to the longest, we observed three distinct LA activation patterns: U (upward), D (downward) and T (transitional). Most patients with AF (88%) featured a U-pattern with an earliest activation observed at the septum and inferior LA, and latest local activation at the anterior LA. In contrast to them, most patients in the non-AF group (69%) exhibit a D-pattern with an earlier activation at septum and anterior MA, followed by the posterior and lateral LA. Some patients in the non-AF group featured equal local activation




| Group | U-pattern | D-pattern | T-pattern | P |
|---|---|---|---|---|
| Atrial fibrillation | 114 (87.7 %) | 14 (10.8 %) | 2 (1.5 %) | 0.0001 |
| Control | 15 (21.4 %) | 48 (68.6 %) | 7 (10 %) | |

times posteriorly and anteriorly: T (transitional) pattern (shown on the figure below).

Based on the knowledge about the electrical activation of the LA, we hypothesize that a block in the Bachmann's bundle may explain the significantly prolonged P-A´ interval anteriorly as well as the more pronounced LA asynchrony in AF patients. Since in human hearts the Bachmann's bundle is the preferential electrical route, connecting RA with the antero-superior LA, a block in this bundle can change the course of the interatrial conduction inferiorly through the coronary sinus. Therefore, a shift in the interatrial conduction from antero-septal to infero-posterior LA may occur, resulting in an upward LA activation in AF patients. Indeed, previous studies demonstrated that the presence of Bachmann's bundle block in surface ECG was associated with AF. [60,65-67] A post-mortem study showed that Bachmann's bundle was absent in a significant proportion of the hearts of patients with AF. [61] Aging and certain diseases can affect the intra-atrial conduction across the Bachmann's bundle causing a significant interatrial delay and non-physiological, asynchronous LA electrical activation. [68,69] This could partly explain the increasing prevalence of AF with aging and in certain illnesses.

It is widely accepted that LA dilatation is strongly associated with AF. In the present study, although the AF and the non-AF patients were matched for all baseline characteristics, both groups differ significantly in respect of PW-TDI activation intervals and LA asynchrony indexes. This observation suggests that LA dilatation is not the only mechanism responsible for the delayed LA activation and asynchrony. In a previous study, De Vos et al. reported that TACT had AUC of 0.74 and a cutoff value of 165 msec. had sensitivity and specificity of 67% and 77% for predicting the occurrence of new-onset AF. [53] In our patient cohort, the P-A´

measured at the anterior MA had a higher AUC of 0.85, and the cutoff value > 55 msec. showed superior sensitivity and specificity of over 80% for discriminating the AF from non-AF patients. We hypothesize, that this value can identify patients with conduction delay in the Bachmann’s bundle which are susceptible to AF. Another possible explanation for the prolonged anterior P-A´ can be the asymmetrical change of LA shape. Recently, Nedios et al. investigated changes in LA geometry in 3D computer tomographic reconstructions of LA and proved that LA asymmetry, specifically the increase of the anterior LA volume, was an independent predictor for AF recurrence after catheter ablation. [39]

To exclude a possible interference of the right atrial conduction time, we measured the intervals from the P wave to the lateral tricuspid annulus (P-TA´ lat) in addition to the P-LA´ intervals. However, we could not observe any significant difference in the P-TA´ lateral between the AF patients and the non-AF controls. Therefore, we assumed that the effects of the intra-right atrial conduction on the P-LA´ intervals should be negligible.

## 5 Limitations

Since PW-TDI measurement required sinus rhythm at the time of the echocardiography, more patients in the AF cohort had paroxysmal than chronic AF. Although unsatisfactory echocardiographic conditions can influence the quality of the images, it was possible to obtain reliable PW-TDI curves even in cases of poor acoustic windows. Since the A´ velocity is angle-dependent, it can be influenced by the tethering of the adjacent segments. Therefore, we chose to omit it from the analysis and to study the P-A´ intervals instead, because the beginning of the A´ velocity is relatively angle-independent. Since patients with impaired LV systolic function, severe hypertrophy and valve abnormalities were excluded from the study, the results may not be valid for patients with these conditions. Finally, it remains uncertain if the observed changes in the LA activation are a cause or a consequence of AF.

## 6 Conclusions

Tissue Doppler can be reliably used to assess the LA asynchrony. Patients with atrial fibrillation showed greater LA asynchrony in PW-TDI independently from the LA dimensions. Left atrial activation showed 3 distinct patterns of activation with the upward LA activation being the most frequently observed in patients with AF. Patients with AF demonstrated a prolonged P-A´ activation time at the anterior MA. A cutoff value for P-A´ at anterior left atrium > 55 msec. discriminates between patients with AF and controls with high sensitivity and specificity. This method can be eventually useful to identity patients at risk for occurrence of new-onset atrial fibrillation.

## 7 Synopsis

Dissertation zur Erlangung des akademischen Grades Dr. med.

**Titel: Patterns of left atrial activation and evaluation of atrial asynchrony in patients with atrial fibrillation and normal controls: Factors beyond left atrial dimensions**


Eingereicht von Herrn Borislav Dinov

Angefertigt im Herzzentrum; Universität Leipzig

Betreut von Prof. Dr. med. Gerhard Hindricks



Eingereicht im Dezember 2016


Synopsis

I. Extensive experimental and clinical data suggest that certain electrical and structural changes develop in the atria of patients with atrial fibrillation (AF). These alterations are commonly referred as atrial remodeling and are considered to play a crucial role in the self-perpetuation of this arrhythmia.

   a. A hallmark of LA structural remodeling is the LA dilatation which is a predictor for progression to chronic AF and therapeutic failure as well. However, AF is associated not only with LA enlargement but also with *asymmetrical changes* in the left atrial geometry.

   b. Furthermore, the electrical remodeling is characterized by *slower and asynchronous inter- and intra-atrial conduction* that also contributes to the maintenance of AF. Some studies suggested a role of the conduction block in the Bachmann's bundle, connecting the right and left atrium, in the AF pathophysiology and LA remodeling.

II. Echocardiography and especially the tissue Doppler method can provide additional insight into the nature of the LA remodeling, because it allows the characterization of the intrinsic LA velocities.

a. Using pulsed-wave tissue Doppler (PW-TDI) is possible to measure the interval from the onset of the surface P wave to the A´ velocity at the lateral mitral annulus as a representation of the total interatrial conduction time (TACT). In number of studies, it was demonstrated that prolonged TACT was associated with new-onset AF, AF after open heart surgery, and AF recurrences after electrical cardioversion and catheter ablation.

b. An important limitation of the previous studies is that TACT has never been validated by direct measurements of the true electrical conduction in the LA. Moreover, it was assumed that the activation of the lateral MA must be the latest LA activation site.

III. In this study, we sought to evaluate the feasibility of the PW-TDI as a simple and quick method to evaluate the LA asynchrony. For the purpose, we measured the time intervals from the onset of P-wave to the A´ (P-A´) in PW-TDI at 4 different left atrial sites next to mitral annulus (septal, lateral, anterior and inferior) in patients referred for electrophysiological study and catheter ablation because of atrial fibrillation or other arrhythmias.

a. The differences between the longest and shortest P-A´ (DLS-PA´), as well as the standard deviation (SD-4PA´) of all 4 values were calculated as indexes for LA asynchrony. Importantly, LA asynchrony in patients with AF was compared with a matched control group of patients without history of AF.

b. Moreover, the TACT was validated by comparing it with the actual electrical activation of the left atrium measured directly in the coronary sinus. For this purpose, the intervals between the onset of the P-wave and the local LA activation at the distal electrode pair of a catheter inserted in the coronary sinus were measured.

c. Having in mind the ovoid LA shape and asymmetrical changes in LA geometry observed in patients with AF, we hypothesized that the lateral mitral annulus may not always be the latest activation spot. Therefore, we sought to determine the latest LA activation site exhibiting the longest P-A´ interval, as well as to describe the sequence of LA activation in AF patients and non-AF controls.

IV. One hundred and thirty patients with AF (AF group) and 70 patients without a history of AF (non-AF control group) were examined prospectively using PW-TDI.

a. Both groups were matched for the baseline characteristics, including LA diameter. The P-A´ interval measured with PW-TDI at the lateral LA showed a strong, positive, linear correlation with the P-A activation at the distal poles of the CS catheter at the lateral MA: Pearson r=0.708; P=0.0001.

b. Asynchrony in the AF group was more pronounced in comparison to the non-AF control group. Patients in the AF group had longer DLS-PA´

as compared to controls: 37±16 msec. vs. 28±13 msec.; P=0.0001, as well as bigger SD-4PA´: 17±7 msec. vs. 13±5 msec.; P=0.0001.

c. Furthermore, distinct patterns of LA activation were observed. Most AF patients (86.5%) showed an upward LA activation with inferior LA breakthrough, whereas the non-AF controls exhibited mostly a downward LA activation (65.5%), spreading from LA roof downwards.

d. ROC analysis revealed that P-A´ at anterior LA successfully discriminated patients with AF from the non-AF controls (AUC 0.85, P<0.0001). A cut off value for P-A´ anterior > 55 msec. discriminated between AF patients and controls with 85% sensitivity; 81% specificity; positive predictive value of 0.898, and negative predictive value of 0.707.

V. In conclusion, PW-TDI can be reliably used to assess the LA asynchrony. Patients with atrial fibrillation showed greater LA asynchrony in PW-TDI independently from the LA dimensions. For the first time, we described that LA activation showed 3 distinct patterns with the upward LA activation being the most frequently observed in patients with AF. Patients with AF demonstrated a prolonged P-A´ activation time at the anterior left atrium. P-A´ at anterior LA > 55 msec. discriminates between patients with AF and non-AF controls with high sensitivity and specificity. This method can be useful to identity patients at risk for occurrence of new-onset atrial fibrillation, as well as to assess the severity of the LA remodeling in order to improve the selection of patients for catheter ablation.

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## 9 Selbstständigkeitserklärung

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt an der Entstehung der vorliegenden Arbeit beteiligt waren.

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*1)* **Dinov B**, Bode K, Koenig S, Oebel S, Sommer P, Bollmann A, Hindricks G, Arya A. Signal-Averaged Electrocardiography as a Noninvasive Tool for Evaluating the Outcomes After Radiofrequency Catheter Ablation of Ventricular Tachycardia in Patients With Ischemic Heart Disease: Reassessment of an Old Tool. **Circulation Arrhythm Electrophysiol.** 2016 Sep;9(9). pii: e003673.

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3) **Dinov B**, Knopp H, Löbe S, Nedios S, Bode K, Schönbauer R, Sommer P, Bollmann A, Arya A, Hindricks G: Patterns of left atrial activation and evaluation of atrial dyssynchrony in patients with atrial fibrillation and normal controls: Factors beyond the left atrial dimensions. **Heart Rhythm**. 2016;13(9):1829-36.

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5) Kosiuk J, **Dinov B,** Bollmann A, Koutalas E, Mussigbrodt A, Sommer P, Arya A, Richter S, Hindricks G, Breithardt OA: Association between ventricular arrhythmias and myocardial mechanical dispersion assessed by strain analysis in patients with nonischemic cardiomyopathy. **Clin Res Cardiol**. 2015;104(12):1072-7.

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7) **Dinov B**, Arya A, Schratter A, Schirripa V, Fiedler L, Sommer P, Bollmann A, Rolf S, Piorkowski C, Hindricks G: Catheter ablation of ventricular tachycardia and mortality in patients with nonischemic dilated cardiomyopathy: can noninducibility after ablation be a predictor for reduced mortality**? Circulation Arrhythm Electrophysiol.** 2015 Jun;8(3):598-605.

8) Müssigbrodt A, **Dinov B**, Bertagnoli L, Sommer P, Richter S, Breithardt OA, Rolf S, Bollmann A, Hindricks G, Arya A: Precordial QRS amplitude ratio predicts long-term outcome after catheter ablation of electrical storm due to ventricular tachycardias in patients with arrhythmogenic right ventricular cardiomyopathy **J Electrocardiol.** 2015;48(1):86-92.

9) **Dinov B**, Arya A, Bertagnolli L, Schirripa V, Schoene K, Sommer P, Bollmann A, Rolf S, Hindricks G: Early referral for ablation of scar-related ventricular tachycardia is associated with improved acute and long-term outcomes: results from the Heart Center of Leipzig ventricular tachycardia registry **Circulation Arrhythm Electrophysiol.** 2014;7(6):1144-51.

10) **Dinov B**, Kosiuk J, Kircher S, Bollmann A, Acou WJ, Arya A, Hindricks G, Rolf S. Impact of metabolic syndrome on left atrial electroanatomical remodeling and outcomes after radiofrequency ablation of nonvalvular atrial fibrillation. **Circulation Arrhythm Electrophysiol**. 2014;7(3):483-9.

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12) **Dinov B**, Schönbauer R, Wojdyla-Hordynska A, Braunschweig F, Richter S, Altmann D, Sommer P, Gaspar T, Bollmann A, Wetzel U, Rolf S, Piorkowski C, Hindricks G, Arya A: Long-term efficacy of single procedure remote magnetic catheter navigation for ablation of ischemic ventricular tachycardia: a retrospective study. **J Cardiovasc Electrophysiol**. 2012;23(5):499-50.

***Konferenzen; Ausgewählte Vorträge und Posters***

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**European Society of Cardiology Congress, Rome, 2016**

S. Nedios, S. Loebe, H. Knopp, P. Sommer, A. Bollmann, A. Arya, G. Hindricks, **B. Dinov**: Left atrial activation changes and asymmetric anatomical remodeling in patients with atrial fibrillation: results of a prospective study using pulsed-wave tissue Doppler imaging.

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