Novel insights in pathophysiology of postoperative atrial fibrillation

Rohit K. Kharbanda, MD, a,b Mathijs S. van Schie, MSc, a Yannick J. H. J. Taverne, MD, PhD b Natasja M. S. de Groot, MD, PhD a and Ad J. J. C. Bogers, MD, PhD b

ABSTRACT

Objectives: Atrial extrasystoles are usually benign; however, they can also trigger atrial fibrillation. It is most likely that if atrial extrasystoles provoke a larger amount of conduction disorders and a greater degree of endo-epicardial asynchrony, the risk of postoperative atrial fibrillation increases. To test this hypothesis, we investigated the effect of programmed atrial extrasystoles on endo-epicardial conduction and postoperative atrial fibrillation.

Methods: Twelve patients (58% male, age 68 ± 7 years) underwent simultaneous endo-epicardial mapping (256 electrodes) of the right atrium during sinus rhythm and programmed atrial extrasystoles provoked from the right atrial free wall. Areas of conduction block were defined as conduction delays of ≥12 milliseconds and endo-epicardial synchrony as activation time differences of exact opposite electrodes of ≥15 milliseconds.

Results: Endo-epicardial mapping data of all programmed atrial extrasystoles were analyzed and compared with sinus rhythm (median preceding cycle length = 531 milliseconds [701-992]). All programmed atrial extrasystoles were aberrant (severe, moderate, and mildly aberrant, respectively, n = 6, 3, and 3) and had a mean prematurity index of 50.1 ± 11.9%. The amount of endo-epicardial asynchrony (1% [1-2] vs 6.7 [2.7-16.9], P = .006) and conduction block (1.4% [0.6-2.6] vs 8.5% [4.2-10.4], P = .006) both increased during programmed atrial extrasystoles. Interestingly, conduction block during programmed atrial extrasystoles was more severe in patients (n = 4, 33.3%) who developed postoperative atrial fibrillation (5.1% [2.9-8.8] vs 11.3% [10.1-12.1], P = .004).

Conclusions: Atrial conduction disorders and endo-epicardial asynchrony, which play an important role in arrhythmogenesis, are enhanced during programmed atrial extrasystoles compared with sinus rhythm. The findings of this pilot study provide a possible explanation for enhanced vulnerability for postoperative atrial fibrillation to induce postoperative atrial fibrillation in patients after cardiac surgery. (JTCVS Open 2021;6:120-9)

It is well known that postoperative atrial fibrillation (AF) is the most common complication following cardiac surgery and is associated with a prolonged hospital stay and increased risk of other complications, such as hemodynamic instability and thromboembolic events.1 The underlying mechanism of postoperative AF is considered to be a multifactorial combination of pre-existing (e.g., age and cardiovascular risk factors), intraoperative (e.g., type of surgery), and postoperative

From the Departments of aCardiology and bCardiothoracic Surgery, Erasmus Medical Center, Rotterdam, The Netherlands.
Dr de Groot is supported by funding grants from CVON-AFFIP (914726), NWO-Vidi (91717339), Biosense Webster USA (ICD 783454), and Medical Delta. Dr Kharbanda is supported by a grant from the Dutch Heart Foundation (2019T091). Received for publication Jan 8, 2021; accepted for publication Jan 8, 2021; available ahead of print April 5, 2021. Address for reprints: Natasja M. S. de Groot, MD, PhD, Unit Translational Electrophysiology, Department of Cardiology, Erasmus Medical Center, Doctor Molewaterplein 40, 3015 GD Rotterdam, The Netherlands (E-mail: n.m.s.degroot@erasmusmc.nl). 2666-2736
Copyright © 2021 The Authors. Published by Elsevier Inc. on behalf of The American Association for Thoracic Surgery. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/). https://doi.org/10.1016/j.xjon.2021.01.014

Video clip is available online.
Abbreviations and Acronyms

AES = atrial extrasystoles  
AF = atrial fibrillation  
CB = conduction block  
CD = conduction delay  
EEA = endo-epicardial asynchrony  
RA = right atrial/atrium

Simultaneous Endo-Epicardial Mapping of the RA

Simultaneous endo-epicardial high-density and resolution mapping of the RA was performed before the commencement of extracorporeal circulation, as previously described in detail,10 Two multielectrode arrays, each containing 128 electrodes with a diameter of 0.45 mm and with 2 mm inter-electrode spacing, were attached on 2 bendable spatulas and positioned on the exact opposite side of each other. A temporary bipolar pacemaker wire was stitched to the free wall of the RA serving as a temporal reference electrode. The indifferent electrode was connected to a steel wire stitched in the subcutaneous tissue. The endocardial electrode array was introduced in the RA in the auricular purse string suture for the venous cannula. Simultaneous endo-epicardial mapping of the mid-RA was performed, as depicted in the left panel of Figure 1. Simultaneous endo-epicardial mapping was performed during sinus rhythm (SR) followed by programmed electrical stimulation at the RA free wall. Recorded data included a surface electrocardiogram lead, calibration signal of 2 mV and 1000 milliseconds, bipolar reference electrogram, and 253 endo- and epicardial unipolar electrograms. Recordings were analog-to-digital converted (16-bits), sampled with a rate of 1 kHz, amplified (gain 1000), and filtered (bandwidth 0.5-400 Hz).

Mapping Data Analysis

Custom-made software was used to analyze the mapping data as previously described in detail.10 Color-coded activation maps of both the endo- and epicardial layer were constructed by annotating the steepest negative slope of atrial potentials recorded at every electrode.

Atrial Conduction Disorders

Consistent with previous mapping studies, areas of conduction delay (CD) and conduction block (CB) were defined as interelectrode differences in local activation times of, respectively, 7-11 milliseconds and ≥12 milliseconds.11 These cutoff values correspond with effective conduction velocities of, respectively, 18 to 28 cm/s for CD and <18 cm/s for CB. Areas of uninterrupted CD and CB lines were defined as continuous CDCB lines. In addition, the median and maximal length of all CB and continuous CDCB lines were calculated.

Endo-epicardial Asynchrony

As demonstrated in the middle and right panel of Figure 1, local endo-epicardial activation time differences were determined by selecting the median of the time delays within the exact opposite electrode and its 8 surrounding electrodes. The longest time delay for every endo-epicardial electrode pair is then selected for the asynchrony map demonstrating local degree of EEA. Consistent with previous studies, EEA was defined as transmural difference in electrical activation of ≥15 milliseconds between every endo-epicardial electrode pair.10,11

Classification of Programmed AES

Prematurity index of programmed AES was expressed as the ratio between the coupling interval of the programmed AES and the preceding SR cycle length. In general, we aimed to achieve a mean prematurity index of approximately 50%. Depending on the degree of shift in wavefront direction during programmed electrical stimulation compared with SR, patterns of activation during programmed AES were classified as mildly, moderately, or severely aberrant (respectively, 0-45°, 135-180°, or 90° shift).6,7

Statistical Analysis

Normally distributed continuous variables are expressed as mean ± standard deviation and skewed variables as median with interquartile range. Categorical data are presented as numbers and percentages and compared with the $\chi^2$ test. Comparison of conduction disorders between the endo- and epicardium was performed with the Wilcoxon signed rank test. Normally distributed continuous variables are expressed as mean ± standard deviation and skewed variables as median with interquartile range. Categorical data are presented as numbers and percentages and compared with the $\chi^2$ test. Comparison of conduction disorders between the endo- and epicardium was performed with the Wilcoxon signed rank test.
test. Association of clinical characteristics and electrophysiological parameters were analyzed with the Wilcoxon rank-sum test. Statistical analyses were performed using IBM SPSS Statistics, version 21 (IBM Corp, Armonk, NY).

RESULTS
Study Population
Baseline characteristics of the 12 enrolled patients (68 ± 7 years, 7 male) are summarized in Table 1. One half of the patients had ischemic heart disease (n = 6) and 4 (33.3%) had a history of paroxysmal AF. Seven patients underwent coronary artery bypass grafting (n = 1, concomitant mitral valve repair), 4 patients underwent aortic valve replacement (n = 1 concomitant mitral valve repair and n = 1 concomitant mitral and tricuspid valve repair), and 1 patient underwent a Cox-maze IV procedure. None of the patients had dilated RA, and the majority had normal left ventricular function (n = 7, 58.3%). Postoperative AF occurred in 4 patients (33.3%) of whom 2 with new-onset postoperative AF.

Characteristics of Programmed AES
All programmed AES were aberrant (6 severely, 3 moderately, and 3 mildly aberrant) and had a mean prematurity index of 50.1 ± 11.9%. The preceding median coupling interval and median cycle length during SR recording were, respectively, 531 milliseconds [345-787] and 843 milliseconds [701-992].

Endo- and Epicardial Conduction Disorders
Table 2 summarizes the amount and extensiveness of conduction disorders during both SR and programmed AES. During SR, the total amount of CB and continuous CDCB observed in both the endo- and epicardium together was 1.4% [0.6-2.6] and 1.9% [0.9-4.1], respectively. This resulted in a median length of 4 mm [4-6] for CB and 8 mm [6.5-12] for continuous CDCB. There were no differences observed in amount and extensiveness of conduction disorders between the endo- and epicardial layer separately during SR (Table E1, all P > .156).

![FIGURE 1](image_url)

**FIGURE 1.** Simultaneous endo-epicardial mapping of the RA was performed using two 128-electrode arrays secured exactly opposite of each other on 2 spatulas (left panel). Color-coded activation maps of the endo- and epicardium are shown in the middle panel. Black arrows display the main trajectories of the electrical wavefronts. To calculate EEA, for each electrode, the median time delay within the exact opposite electrode and its eight surrounding electrodes was selected. The longest time delay for every endo-epicardial electrode pair is then selected to express local degree of EEA, defined as transmural difference in electrical activation of ≥15 milliseconds between every endo-epicardial electrode pair. Ao, Aorta; SCV, superior caval vein; RA, right atrium; RV, right ventricle; ICV, inferior caval vein; Epi, epicardium; Endo, endocardium; EEA, endo-epicardial asynchrony.

| TABLE 1. Patient characteristics |
|----------------------------------|
| Number of patients | 12 |
| Age, y | 68 ± 7 [51-78] |
| Male | 7 (58.3) |
| Underlying heart disease | n (%) |
| IHD | 6 (50) |
| VHD | 4 (33.3) |
| I/VHD | 1 (8.3) |
| Lone AF | 1 (8.3) |
| Surgical procedure | n (%) |
| CABG | 6 (50) |
| CABG + MVR | 1 (8.3) |
| AVR | 2 (16.6) |
| AVR + MVR | 1 (8.3) |
| AVR + MVR + TVR | 1 (8.3) |
| Cox-Maze IV | 1 (8.3) |
| History of AF | 4 (33.3) |
| Paroxysmal | |
| Cardiovascular risk factors | BMI, kg/m² | 28.6 ± 3.8 [23.7-36.3] |
| Hypertension | 8 (66.7) |
| Dyslipidemia | 4 (33.3) |
| Diabetes mellitus | 4 (33.3) |
| Left ventricular function | Normal | 7 (58.3) |
| Mild/moderate dysfunction | 5 (41.7) |

Numbers in brackets are ranges. IHD, Ischemic heart disease; VHD, valvular heart disease; I/VHD, ischemic and valvular heart disease; AF, atrial fibrillation; CABG, coronary artery bypass grafting; MVR, mitral valve repair; AVR, aortic valve replacement; TVR, tricuspid valve repair; BMI, body mass index.
The upper panel of Figure 2 shows typical endo-epicardial activation maps of one single SR beat and programmed AES obtained from the same patient. A substantial increase in CB, indicated by thick black lines, is demonstrated during programmed AES compared with SR. The lower panel of Figure 2 shows the effect of programmed atrial stimulation on the amount of CB for each patient separately. During programmed AES, the total amount of CB and continuous CDCB in both layers together significantly increased from 1.4% [0.6-2.6] to 8.5% [4.2-10.4] and from 1.9% [0.9-4.1] to 10.7% [5.7-15.1] respectively (both \( P < .005 \)). Characteristics of conduction disorders during programmed AES did not differ between the endo- and epicardial layer separately (Table E1, all \( P > .167 \)), except for a greater maximal conduction time at the endocardium (29.5 milliseconds [18.5-37.5] vs 23 milliseconds [16.3-23], \( P = .033 \)).

### Endo-Epicardial Asynchrony

In the upper panel of Figure 3, endo-epicardial activation maps and corresponding EEA maps demonstrate the incremental effect of programmed AES on electrical asynchrony between both atrial layers. In the lower panel of Figure 3, differences in amount of EEA during SR (light green) and programmed AES (dark green) are shown for each patient separately. Overall, programmed AES provoked a significant increase in EEA from 1% [1-2] during SR to 6.7% [2.7-16.9] during programmed AES (\( P = .006 \)). The severity of EEA during programmed AES, expressed in

### TABLE 2. Characteristics of conduction disorders during sinus rhythm and programmed AES

|                      | SR               | P-AES             | \( P \) value |
|----------------------|------------------|-------------------|--------------|
| % CB                 | 1.4 [0.6-2.6]    | 8.5 [4.2-10.4]    | .005         |
| Length CB lines      | 4 [4-6]          | 4.5 [4-6]         | .570         |
| Max length CB lines  | 10 [6.5-16.5]    | 21 [15-25]        | .026         |
| % Continuous CDCB    | 1.9 [0.9-4.1]    | 10.7 [5.7-15.1]   | .004         |
| Length continuous CDCB | 8 [6.5-12]   | 11 [8.3-20]       | .239         |
| Maximal length continuous CDCB | 10 [11-29] | 28 [16.5-35.5] | .196 |
| Maximal conduction time | 19.5 [15-29.8] | 29.5 [23-37.8] | .059 |
| % EEA                | 1 [1-2]          | 6.7 [2.7-16.9]    | .006         |
| Median endo-epicardial delay | 16.5 [0-19] | 20 [16.3-20.8] | .050 |
| Maximal endo-epicardial delay | 18.3 [0-25.8] | 24 [19.5-33.9] | .036 |

Length of lines is expressed in millimeters and conduction time in milliseconds. \( P \) values below .05 as statistically significant indicated in bold. SR, Sinus rhythm; P-AES, programmed atrial extra systoles; CB, conduction block; CDCB, conduction delay-conduction block; EEA, endo-epicardial asynchrony.

The upper panel of Figure 2 shows typical endo-epicardial activation maps of a single SR beat and programmed AES obtained from the same patient. A substantial increase in CB, indicated by thick black lines, is demonstrated during programmed AES compared with SR. The lower panel of Figure 2 shows the effect of programmed atrial stimulation on the amount of CB for each patient separately. During programmed AES, the total amount of CB and continuous CDCB in both layers together significantly increased from 1.4% [0.6-2.6] to 8.5% [4.2-10.4] and from 1.9% [0.9-4.1] to 10.7% [5.7-15.1] respectively (both \( P < .005 \)). Characteristics of conduction disorders during programmed AES did not differ between the endo- and epicardial layer separately (Table E1, all \( P > .167 \)), except for a greater maximal conduction time at the endocardium (29.5 milliseconds [18.5-37.5] vs 23 milliseconds [16.3-23], \( P = .033 \)).

### Endo-Epicardial Asynchrony

In the upper panel of Figure 3, endo-epicardial activation maps and corresponding EEA maps demonstrate the incremental effect of programmed AES on electrical asynchrony between both atrial layers. In the lower panel of Figure 3, differences in amount of EEA during SR (light green) and programmed AES (dark green) are shown for each patient separately. Overall, programmed AES provoked a significant increase in EEA from 1% [1-2] during SR to 6.7% [2.7-16.9] during programmed AES (\( P = .006 \)). The severity of EEA during programmed AES, expressed in

![FIGURE 2. Upper panel: Typical endo-epicardial activation maps of a SR beat (left) and P-AES (right) obtained from the same patient. Black arrows display the main trajectories of the electrical wavefronts and local activation times are depicted at its head and tail. Thick black lines indicate lines of conduction block. The lower panel shows the effect of programmed right atrial stimulation on the amount of conduction block (y-axis) for each patient (x-axis) separately. Increase in total activation time and amount of conduction block is observed during P-AES compared with SR. SR, Sinus rhythm; LAT, local activation times; Epi, epicardium, Endo, endocardium; P-AES, programmed atrial extrasystoles.](image-url)
median and maximal endo-epicardial delay, also increased from 16.5 to 20 milliseconds ($P = .05$) and 18.3 to 24 ms ($P = .036$), respectively.

**Postoperative AF**

Differences in characteristics of programmed AES between patients with and without postoperative AF are summarized in Table 3. Programmed AES caused significantly more conduction disorders and EEA in patients who developed postoperative AF compared with patients without postoperative AF. Not only was the prevalence of CB (5.1% [2.9-8.8] vs 11.3% [10.1-12.1], $P = .004$) and continuous CDCB (6.7% [5.2-11.6] vs 16% [14.1-18.5], $P = .004$) significantly greater in patients with postoperative AF, but also the length of continuous CDCB lines (9.5 mm [8-11] vs 22 mm [15.3-23.5], $P = .008$).

Despite the clinically relevant EEA provoked by programmed AES in patients who encountered postoperative AF (4.5% vs 16%), it did not reach statistical significance ($P = .109$). Median and maximal endo-epicardial delay measured between both atrial layers, however, was significantly greater in patients with postoperative AF (respectively, $P = .048$ and $P = .016$). Cardiopulmonary bypass- and aortic crossclamp time were similar between both groups (both $P > .109$).

**DISCUSSION**

**Key Findings**

Simultaneous endo-epicardial mapping of the RA during SR and programmed RA stimulation revealed that programmed AES originating from the free wall of the RA

| TABLE 3. Differences in characteristics of programmed AES between patients with and without POAF |
|----------------------------------|----------------------------------|----------------------------------|
|                                  | No POAF                          | POAF                             | $P$ value |
| % CB                             | 5.1 [2.9-8.8]                    | 11.3 [10.1-12.1]                 | **.004**  |
| Length CB lines                  | 4 [2.5-5.5]                      | 5.5 [5-7.5]                      | .073      |
| Max length CB lines              | 21 [9.5-22]                      | 22 [18-33.5]                     | .368      |
| % Continuous CDCB                | 6.7 [5.2-11.6]                   | 16 [14.1-18.5]                   | **.004**  |
| Length continuous CDCB           | 9.5 [8-11]                       | 22 [15.3-23.5]                   | **.008**  |
| Maximal length continuous CDCB   | 21 [14.5-31.5]                   | 42 [28.5-57]                     | **.028**  |
| Maximal conduction time          | 24.5 [18.5-29.8]                 | 38.5 [37.3-47.3]                 | **.004**  |
| % EEA                            | 4.5 [2.6-7.6]                    | 16.0 [7.1-31.4]                  | .109      |
| Median endo-epicardial delay     | 17.3 [15.6-20]                   | 22 [20-24.8]                     | **.048**  |
| Maximal endo-epicardial delay    | 22 [16.8-24]                     | 36 [27-42]                       | **.016**  |

Length of lines is expressed in millimeters and conduction time in milliseconds. $P$ values below .05 as statistically significant indicated in bold. POAF, Postoperative atrial fibrillation; CB, conduction block; CDCB, conduction delay-conduction block; EEA, endo-epicardial asynchrony.
(1) provoked a substantial increase in endo- and epicardial conduction disorders, (2) enhanced electrical asynchrony between both layers up to 44 milliseconds and covering 36% of the mapping area and (3) provoked more conduction disorders and EEA in patients who developed postoperative AF compared with patients who remained postoperatively in SR. The findings of this pilot study provide a possible explanation for enhanced vulnerability for postoperative AES to induce postoperative AF in patients after cardiac surgery and are summarized in Figure 4.

Effect of (Programmed) Right AES on Endo-Epicardial Conduction

Previous intraoperative mapping studies examined the effect of spontaneous AES on atrial conduction and showed an increase in epicardial conduction disorders, especially during aberrant AES. Simultaneous endo-epicardial mapping of the RA during spontaneous AES revealed that this increase in conduction disorders may be unequally expressed between the endo- and epicardium giving rise to EEA. An important limitation of these studies is lack of information on the origin of the AES. To overcome this limitation, in the present study, programmed premature atrial stimulation was performed at the RA free wall as we assume that excessive surgical manipulation in combination with surgical incisions in the RA appendage and purse-string suture induced local ischemia, are likely to provoke AES originating from the RA free wall in patients after cardiac surgery. In addition, enhanced anisotropic properties of the RA tissue may reinforce conduction disorders and EEA during AES thereby increasing the vulnerability of the atria for arrhythmias. AES that provoke a larger amount of conduction disorders and a higher degree of EEA are more likely to induce postoperative AF episodes, which is supported by the present pilot study showing more pronounced conduction disorders during programmed AES in patients who developed postoperative AF compared with patients who remained in SR.

It is generally assumed that the complex architecture and anatomy of both atria play an important role in arrhythmogenesis. Fiber orientation and atrial wall thickness may vary between different atrial regions. Even at one specific site, differences in fiber orientation between the endo- and epicardium may be observed. Any premature AES

![FIGURE 4. Left panel: This pilot study revealed that P-AES originating from the free wall of the RA (1) provoked a substantial increase in endo- and epicardial conduction disorders, (2) enhanced electrical asynchrony between both layers up to 44 milliseconds, and (3) provoked more conduction disorders and EEA in patients who developed POAF compared with patients who remained postoperatively in SR. Right panel: Typical endo-epicardial activation maps of a sinus rhythm beat (left) and programmed AES (right) obtained from the same patient are shown. Black arrows display the main trajectories of the electrical wavefronts and local activation times are depicted at the head and tail. Thick black lines indicate lines of conduction block. Enhanced electrical disturbances can be observed during programmed AES compared with sinus rhythm. These findings may explain why postoperative AES may induce POAF.](image-url)
originating from an anisotropic region may provoke significant conduction disorders that may affect the endo- and epicardium unequally. This may provoke or aggravate EEA in the atrial wall, thereby possibly initiating transmural reentry. Spach and colleagues demonstrated that programmed premature atrial stimulation in isolated anisotropic muscle fibers resulted in dissociated conduction that causes unidirectional CB, thereby providing a potential substrate for re-entry.

Schuessler and colleagues have investigated endo-epicardial conduction at the RA appendage of canines during SR and programmed premature atrial stimulation. Endo-epicardial asynchrony was greater during programmed AES with a greater prematurity index and increased mostly with prematurely aberrant AES, which is in line with previous studies from our group. Premature AES provoked EEA up to 30 milliseconds. Subsequently, they induced tachyarrhythmia by an extra-stimulus during intravenous acetylcholine administration. A 3-dimensional pathway using a free-running muscle bundle between the endo- and epicardium was part of the induced reentry circuit with a cycle length as short as approximately 60 milliseconds. Recently, endo-epicardial optical mapping combined with high-resolution 3-dimensional gadolinium-enhanced magnetic resonance imaging (80 μm³ resolution) demonstrated similar re-entry loops using transmural pectinate muscles in ex vivo human RA. These findings provide a possible explanation for the underlying mechanism of postoperative AES inducing episodes of postoperative AF.

**Factors Contributing to Enhanced Arrhythmogenicity of AES**

The arrhythmogenicity of an AES is determined by AES-related characteristics (eg, prematurity), anatomical features (eg, 3-dimensional fiber orientation, fibrosis), and alterations in the cardiac autonomic tone (eg, enhanced sympathetic or parasympathetic activity).

Refractory periods of adjacent cardiomyocytes may vary and are influenced by several factors, such as heart rate and autonomic tone. When the prematurity of AES increases, it is more likely that the electrical wavefront encounters areas with differences in excitability of atrial tissue which may promote development of AF. This effect may be enhanced by changes in autonomic tone. As the cardiac autonomic nervous system is heterogeneously distributed between both atria, changes in sympathetic and parasympathetic tone may enhance dispersion of atrial refractoriness and promote differences in local conduction velocities. It is generally believed that, enhanced sympathetic tone increases calcium loading, thereby enhancing triggered activity, while enhanced parasympathetic tone slows conduction velocity, shortens the refractory period and increases dispersion of atrial refractoriness, thereby facilitating re-entry.

Conduction velocity is also dependent on the 3-dimensional anatomical features of the area where the AES originates. To initiate an endo-epicardial reentry circuit at an area with significant EEA, transmural muscle fibers connecting the endo- and epicardium are a prerequisite. This 3-dimensional architecture can also be disrupted by structural remodeling caused by ageing, coronary- or valvular heart disease or tachyarrhythmia-induced electrical remodeling. Furthermore, when a small atrial muscle bundle has to excite a relatively large heterogeneous area, sink-to-source mismatch may occur resulting in slowing of atrial conduction and breaking of wavefronts, which may initiate re-entry.

**Premature AES After Cardiac Surgery, Common or Not?**

The relationship between frequent AES and greater incidence of AF has been demonstrated in different populations. There are only a few studies investigating the role of premature AES in initiation of postoperative AF after cardiac surgery. After Frost and colleagues had demonstrated that premature AES could initiate postoperative AF, several studies demonstrated that the incidence of postoperative AF could be reduced by atrial overdrive pacing thereby suppressing atrial premature depolarizations. Blommaert and colleagues introduced an algorithm for dynamic overdrive pacing which reacts to premature AES by increasing its frequency. A significant reduction in the incidence of postoperative AF was observed in the pacing group compared to controls (10% vs 27% respectively, \( P = .036 \)). The aforementioned studies evaluated the performance of atrial overdrive pacing suppressing premature AES to prevent postoperative AF. However, there are only a few studies investigating the incidence of premature AES in relation to postoperative AF.
artery bypass grafting, it was initiated by premature AES in 81% of the patients. Previously, the same research group already demonstrated that a greater preoperative burden of premature AES is associated with a greater risk of postoperative AF. Recently, Hashimoto and colleagues observed significantly more premature AES/24 hours in patients who developed new-onset postoperative AF compared with patients who remained in SR (4128 ± 7186 vs 69 ± 221, P < .001) after off-pump coronary artery bypass. In line with the findings of Jidéus and colleagues and Frost and colleagues, frequent premature AES (>47 per 24 hours) appeared to be a predictor for postoperative AF. Yaksh and colleagues were the first to determine whether postoperative AES burden is associated with postoperative AF using postoperative telemetry data of 29 patients with postoperative AF and controls. Patients with postoperative AF showed a greater burden of premature AES compared with controls (0.9% vs 0.2%, P = .001). Moreover, AES triggering AF episodes were more often premature (P < .001).

Limitations
This proof-of-concept study is mainly limited by the low sample size, and the results should therefore be interpreted with caution. Future larger studies are required to substantiate our findings. We could not address whether AES also enhance electrical disturbances in the left atrium. Due to safety reasons, simultaneous endo-epicardial mapping of the left atrium can only be performed under specific circumstances and was therefore not performed in the present pilot study. Moreover, to determine the effect of AES on endo-epicardial conduction in both atria, total simultaneous endo-epicardial mapping should be performed which is technically impossible. Future studies focusing on both atria are required to further unravel the arrhythmogenic effects of AES originating from different sites.

CONCLUSIONS
The exact mechanistic role of AES in initiating postoperative AF is unknown. In the present pilot study, premature programmed AES at the RA aggravated endo-epicardial conduction disorders and electrical asynchrony between both layers occurring up to 44 milliseconds and covering 36% of the mapping area (Video 1). Enhanced conduction disorders and EEA provoked by premature AES are potential mechanisms for intramural re-entry, which may result in postoperative AF. Larger studies are needed to assess whether intraoperative cardiac mapping including programmed atrial stimulation may predict development of postoperative AF.

Conflict of Interest Statement
The authors reported no conflicts of interest.

The Journal policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

The authors thank F. R. N. van Schaagen, C. Kik, MD, J. A. Bekkers, MD, PhD, F. B. S. Oei, MD, PhD, P.C. van de Woestijne, MD, A. Heida, MD, R. Starrevelt, MSc, L. N. van Staveren, MD, and W. F. B. van der Does, MD, for their contributions to this work.

References
1. Greengberg JW, Lancaster TS, Schuessler RB, Melby SJ. Postoperative atrial fibrillation following cardiac surgery: a persistent complication. *Euro J Cardio Surg*. 2017;52:665-72.
2. Dobrev D, Aguilar M, Heijman J, Guichard JB, Nattel S. Postoperative atrial fibrillation: mechanisms, manifestations and management. *Nat Rev Cardiol*. 2019;16:417-36.
3. Blommaert D, Gonzalez M, Mucumbitsi J, Garné O, Efrard P, Bache M, et al. Effective prevention of atrial fibrillation by continuous atrial overdrive pacing after coronary artery bypass surgery. *J Am Coll Cardiol*. 2000;35:1411-5.
4. Taylor AD, Groen JG, Thorn SL, Lewis CT, Marshall AJ. New insights into onset mechanisms of atrial fibrillation and flutter after coronary artery bypass graft surgery. *Heart*. 2002;88:499-504.
5. Jidéus L, Kees K, Joachimsson PO, Ericson M, Nilsson L, Blomstrom-Lundqvist C. The role of premature atrial contractions as the main triggers of postoperative atrial fibrillation. *J Electrocardiol*. 2006;39:48-54.
6. Teuwen CP, Kik C, van der Does L, Lanters EAH, Knops P, Mousw EMJP, et al. Quantification of the arrhythmogenic effects of spontaneous atrial extrasystole using high-resolution epicardial mapping. *Circ Arrhythm Electrophysiol*. 2018;11:e005745.
7. van der Does L, Kharbanda RK, Teuwen CP, Knops P, Kik C, Bogers AJJC, et al. Atrial ectopy increases asynchronous activation of the endo- and epicardium at the right atrium. *J Clin Med*. 2020;9:558.
8. Olgin JE, Kalman JM, Fitzpatrick AP, Lesh MD. Role of right atrial endocardial structures as barriers to conduction during human type I atrial flutter. *Activation and entrainment mapping guided by intracardiac echocardiography*. *Circulation*. 1995;92:1839-48.
9. Papageorgiou P, Monahan K, Boyle NG, Seifert MJ, Beswick P, Zedebe J, et al. Site-dependent intra-atrial conduction delay. Relationship to initiation of atrial fibrillation. *Circulation*. 1996;94:384-9.
10. Kharbanda RK, Knops P, van der Does LJME, Kik C, Verheugen Y, Roos-Serote MC, et al. Simultaneous endo-epicardial mapping of the human right atrium: unravelling atrial excitation. *J Am Heart Assoc*. 2020;9:e017069.
11. de Groot N, van der Does L, Yaksh A, Lanters E, Teuwen C, Knops P, et al. Direct proof of endo-epicardial asynchrony of the atrial wall during atrial fibrillation in humans. *Circ Arrhythm Electrophysiol*. 2016;9:e003648,
12. Spach MS, Dolber PC, Heidtage JF. Interaction of inhomogeneities of repolarization with anisotropic propagation in dog atria. A mechanism for both preventing and initiating reentry. *Circ Res*. 1989;65:1612-31.
13. Schuessler RB, Kawamoto T, Hand DE, Misuno M, Bromberg BI, Cox JL, et al. Simultaneous epicardial and endocardial activation sequence mapping in the isolated canine right atrium. *Circulation*. 1993;88:250-63.
14. Hansen BJ, Zhao J, Csepes TA, Moore BT, Li N, Jayne LA, et al. Atrial fibrillation driven by micro-anatomic intramural re-entry revealed by simultaneous subepicardial and sub-endocardial optical mapping in explanted human hearts. *Eur Heart J*. 2015;36:2390-401.
15. Starovas S, Nakagawa H, Poo SS, Scherer BJ, Lazzara R, Jackman WM. The role of the autonomic ganglia in atrial fibrillation. *JACC Clin Electrophysiol*. 2015;1:1-13.
16. Spach MS, Miller WT III, Dolber PC, Koosym J, Sommer JR, Mosher CE Jr. The functional role of structural complexities in the propagation of depolarization in the atrium of the dog. Cardiac conduction disturbances due to discontinuities of effective axial resistivity. *Circ Res*. 1982;50:175-91.
17. Allessie M, Auer N, Schott U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res*. 2002;54:230-46.
18. Kawara T, Derksen R, de Groot JR, Coronel R, Tasseron S, Linnenbank AC, et al. Activation delay after premature stimulation in chronically diseased human myocardium relates to the architecture of interstitial fibrosis. *Circulation*. 2001;104:3069-75.
19. Angel N, Li L, Macleod RS, Marrouche N, Ranjan R, Dosdall DJ. Diverse fibrosis architecture and premature stimulation facilitate initiation of reentrant activity following chronic atrial fibrillation. *J Cardiovasc Electrophysiol*. 2015;26:1352-60.

20. Teuwen CP, Korevaar TIM, Coolsen RL, van der Wel T, Houck CA, Evertz R, et al. Frequent atrial extrasystolic beats predict atrial fibrillation in patients with congenital heart defects. *Europace*. 2018;20:25-32.

21. Chong BH, Pong V, Lam KE, Liu S, Zuo ML, Lau YF, et al. Frequent premature atrial complexes predict new occurrence of atrial fibrillation and adverse cardiovascular events. *Europace*. 2012;14:942-7.

22. Frost L, Christiansen EH, Molgaard H, Jacobsen CJ, Allermand H, Thomsen PE. Premature atrial beat eliciting atrial fibrillation after coronary artery bypass grafting. *J Electrocardiol*. 1995;28:297-305.

23. Murgatroyd FD, Nitzsche R, Slade AK, Limousin M, Rosset N, Camm AJ, et al. A new pacing algorithm for overdrive suppression of atrial fibrillation. Chorus Multicentre Study Group. *Pacing Clin Electrophysiol*. 1994;17:1966-73.

24. Greenberg MD, Katz NM, Iuliano S, Tempesta BJ, Solomon AJ. Atrial pacing for the prevention of atrial fibrillation after cardiovascular surgery. *J Am Coll Cardiol*. 2000;35:1416-22.

25. Takeda M, Furuse A, Kotsuka Y. Use of temporary atrial pacing in management of patients after cardiac surgery. *Cardiovasc Surg*. 1996;4:623-7.

26. Ramdat Misier A, Beukema WP, Oude Luttikhuis HA. Multisite or alternate site pacing for the prevention of atrial fibrillation. *Am J Cardiol*. 1999;83:237D-40D.

27. Hashimoto M, Yamauchi A, Inoue S. Premature atrial contraction as a predictor of postoperative atrial fibrillation. *Asian Cardiovasc Thorac Ann*. 2015;23:153-6.

28. Judeus L, Blomstrom P, Nilsson L, Stridsberg M, Hansell P. Blomstrom-Landqvist C. Tachyarrhythmias and triggering factors for atrial fibrillation after coronary artery bypass operations. *Ann Thorac Surg*. 2000;69:1064-9.

29. Frost L, Molgaard H, Christiansen EH, Jacobsen CJ, Allermand H, Thomsen PE. Low vagal tone and supraventricular ectopic activity predict atrial fibrillation and flutter after coronary artery bypass grafting. *Eur Heart J*. 1995;16:825-31.

30. Yaksh A, Kik C, Knops P, van Ettinger MJ, Bogers AJ, de Groot NM. Early, de novo atrial fibrillation after coronary artery bypass grafting: facts and features. *Am Heart J*. 2017;184:62-70.

**Key Words:** atrial fibrillation, electropathology, electrophysiology, cardiac mapping
**TABLE E1. Differences in conduction disorders between the endo- and epicardium**

|                               | SR P-AES                  | Endo         | Epi           | P value | Endo         | Epi           | P value |
|-------------------------------|---------------------------|--------------|---------------|---------|--------------|---------------|---------|
|                               |                           | % CB         | Length CB lines | Max length CB lines | % Continuous CDCB | Length continuous CDCB | Max length continuous CDCB | Maximal conduction time |
|                               |                           | 1.6 [0.5-2.9] | 4 [3.3-7.5]    | 9 [5-11.5]        | 2.3 [0.6-3.6]    | 8 [8-12.3]     | 11 [8.5-29]       | 17.5 [15-25.8]        |
|                               |                           | 0.9 [0.1-2.4] | 2 [0.5-4.8]    | 5 [1-11.5]        | 2.1 [0.1-3.7]    | 8 [1-12.8]     | 14 [1-21]         | 15 [11.8-25.8]       |
|                               |                           | .239         | .156           | .167               | .875              | .529           | .694               | .610               |
|                               |                           | 7.7 [3.7-11.0]| 6 [4-10.3]     | 19 [8.5-22]       | 8.6 [5.8-16.5]   | 15.5 [8.3-21.5] | 24 [16-31.5]      | 29.5 [18.5-37.5]     |
|                               |                           | 7.7 [2.5-9.3] | 3.5 [2.3-5.5]  | 13 [5.5-18]       | 9.9 [5.9-16.5]   | 11.5 [8.5-14.5] | 26 [14-31.5]      | 23 [16.3-31]        |
|                               |                           | .433         | .213           | .167               | .638              | .328           | .362               | .033               |

Length of lines is expressed in millimeters and conduction time in milliseconds. *P* values below .05 as statistically significant indicated in bold. SR, Sinus rhythm; P-AES, programmed atrial extra systoles; Endo, endocardium; Epi, epicardium; CB, conduction block; CDCB, conduction delay-conduction block.