Slovenian Medical Journal

Early atrial ectopic beats and atrial conduction delay predict atrial fibrillation

Zgodnji preddvorni ektopični utripi in upočasnjen preddvorni prevod napovedujejo preddvorno fibrilacijo

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Abstract

Background: Atrial fibrillation/flutter (AF/AFl) is commonly diagnosed arrhythmia, associated with increased morbidity and mortality. Therefore, we have to improve our early AF/AFl diagnostics. Several studies indicated association between conduction delay, excessive atrial ectopic beats (AEBs) and AF/AFl onset. Association with some other AEB features is less clear.

Objective: To validate the role of early AEBs from Holter-ECG in relation to documented AF/AFl events.

Methods and Results: We enrolled 14 consecutive patients (6 female, median 60.5 years) with documented AF/AFl during or within 6 months after Holter-ECG (AF-group). Control group consisted of 10 clinically similar consecutive patients (5 female, median 64.5 years), without any evidence of AF/AFl, but with comparable burden of AEBs. Holter-ECGs were examined with 3-channel Holter system (Schiller, Darwin2 software). 24-hour data were analyzed for number and/or burden (%) of: a) AF/AFl, b) AEBs, c) early-AEBs (coupling interval cut-off <530 ms), d) AEB pairs, triplets, runs, and e) bigeminy. In addition, P-wave duration (cut-off <130 ms), PQ, QRS, and QTc were measured. AF-group had higher burden of early-AEBs (p<0.03) and longer P-waves (p<0.05) than controls. In both groups, non-conducted and aberrantly-conducted early-AEBs, AEBs in bigeminy, pairs, triplets and runs were found, as-well-as no difference for PQ, QRS, and QTc (p=NS). The majority of 243 AF/AFl events started during day-time and in 83% with early-AEBs. Before AF onset, outbursts of early-AEBs were encountered in 58% of patients.

Conclusion: A higher burden of early AES in the Holter ECG and a longer P-wave duration predict the occurrence of AF/AU.

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Keywords: atrial fibrillation; atrial ectopic beats; electrocardiogram; holter-monitoring

Ključne besede: atrijska fibrilacija; preddvorni ektopični utripi; elektrokardiogram; holtersko monitoriranje

Received / Prispelo: 27. 3. 2024 | **Accepted / Sprejeto:** 18. 11. 2024

Cite as / Citirajte kot: Šinkovec M, Antolič B, Rauber M, Ambrožič J, Cvijić M, Klemen L, et al. Early atrial ectopic beats and atrial conduction delay predict atrial fibrillation. Zdrav Vestn. 2025;94(1–2):3–15. **DOI:** https://doi.org/10.6016/ZdravVestn.3532

Izvleček

Izhodišča: Preddvorna fibrilacija/undulacija (AF/AU) je pogosta motnja srčnega ritma, ki je povezana z višjo umrljivostjo in obolevnostjo. Zato jo je treba čim prej diagnosticirati. Rezultati več raziskav kažejo na povezavo med upočasnjenim preddvornim prevodom, velikim številom preddvornih ektopičnih utripov (AES) in pojavom AF/AU. Manj jasna je povezava z nekaterimi drugimi značilnostmi AES.

Cilj raziskave: Vrednotiti smo želeli pomen zgodnjih AES pri holterskem elektrokardiogramu (EKG) v povezavi z zabeleženimi epizodami AF/AU.

Metode in rezultati: V pilotsko raziskavo smo vključili 14 zaporednih bolnikov (6 žensk, mediana starost 60,5 leta) z dokumentirano AF/AU v zapisu holterskega EKG ali do 6 mesecev po njem (skupina z AF/AU). V kontrolni skupini je bilo 10 zaporednih bolnikov s podobno klinično sliko (5 žensk, mediana starost 64,5 leat) brez AF/AU v anamnezi, vendar s podobnim bremenom AES. Holterski EKG smo beležili s 3-kanalnim sistemom (Schiller, Darwin2 software). V 24-urnih zapisih EKG smo analizirali število in/ali breme (%) naslednjih parametrov: a) AF/AU, b) AES, c) zgodnjih AES (vezni interval < 530 ms), d) AES v parih, tripletih in salvah in e) prisotnost bigeminije; poleg tega pa še trajanje vala P (normalna vrednost < 130 ms), PQ, QRS in QTc. Skupina z AF/AU je imela večje breme zgodnjih AES (p< 0,03) in daljši val P (p< 0,05) kot kontrolna skupina. V obeh skupinah smo zabeležili neprevedene in aberantno prevedene AES, AES v bigeminiji, parih, tripletih in salvah. Prav tako ni bilo razlike v trajanju PQ, QRS in QTc (p=NS). Večina od 243 primerov AF/AU se je sprožila v dnevnem času, v 83 % z zgodnjo AES. Pri 58 % smo zabeležili pred pojavom AF/AU porast števila zgodnjih AES.

Zaključek: Večje breme zgodnjih AES v holterskem EKG in daljše trajanje vala P napovedujejo pojav AF/AU.

1 Introduction

Atrial fibrillation (AF) is a commonly diagnosed arrhythmia in clinical practice. It is associated with an increased risk of stroke, heart failure, and cognitive decline, contributing to high morbidity and mortality rates in these patients (1,2). Therefore, in clinical practice, it is important to improve our early AF diagnostics with a view toward early AF treatment (3,4).

Atrial ectopic beats (AEBs) are common in the general population (5,6). However, several studies and meta-analyses in recent years indicated an association between excessive AEBs and AF (7,8,9), stroke (8,10) pacemaker implantation (11), and mortality (8,11,12). In addition, standard ECG data had been recently reviewed, confirming a strong predictive value of atrial and AV-conduction delay parameters for AF onset (13,14). From clinical practice, it is evident that some patients with excessive AEBs will develop AF and others will not, possibly depending on the severity of atrial cardiomyopathy (15). The diagnostic value of some additional AEB features (except high AEB burden) that could reveal patients with AF remains partially studied.

Therefore, this pilot observational case-control study was aimed to validate some AEB features and conduction delay markers from Holter-ECG recordings with documented AF.

2 Methods

2.1 Patients

Between September 2022 and October 2023, we recruited consecutive patients of both genders from the waiting list for catheter ablation of AF at our institution (AF-group). All had documented paroxysmal AF/atrial flutter (AF/AFl) during or within 6 months after Holter recordings. The control group consisted of clinically similar consecutive patients from the same time period, without any evidence of AF, without antiarrhythmic drug treatment, but with a comparable burden of AEBs. They were selected from outpatients' lists with available Holter and clinical data. The study was approved by the National Ethics Committee of the Republic of Slovenia (KME 0120-65/2022/6). An informed consent was obtained from all study participants prior to investigations.

2.2 Methods, ECG parameters, and definitions

We used the Holter system (Schiller, Medilog AR Professional) with EASI 5-electrode set-up for 3 orthogonal lead tracings (16). Continuous ECG data were stored for later automatic analysis, review, and manual measurements (Darwin2 Professional Software). We analysed 24-hour data for: a) the number and burden of all AEBs presented as singles, pairs, and triplets (the burden was defined as % of all beats during sinus rhythm), b) early-AEBs burden of >50 %, and <50 % (from all AEBs), c) number of pairs, triplets and non-sustained (<30 s) AEB runs of (4–8 beats and >8 beats), d) presence or absence of AEB bigeminy (at least 3 consecutive AEBs coupled with sinus beats), e) number and onset time of AF/AFl events, f) AF/AFl burden (% of time in AF/AFl), and g) number of sustained atrial tachycardias (AT). In addition, we manually measured durations of P-wave, PQ-interval, QRS, at heart rate of 55–65/min, and analysed automatic measurements of QTc (Fridericia correction, 5-minute average). AF and flutter events were analysed together since these arrhythmias frequently interchanged between each other in the same subject. AF/AFl was defined according to current international guidelines (1,2). AF was a varying, low amplitude, rapid (300–500 beats/min) atrial rhythm with chaotic ventricular response. AFl was a rapid atrial rhythm with a constant rate (220–350 beats/min), "flutter" P-wave morphology, and regular ventricular response. AT was regular atrial rhythm at a constant rate of >100 beats/min with discrete altered P waves and longer PR-interval than during sinus rhythm. We defined that early-AEBs fire before completed atrial repolarisation, which is at an AEB coupling interval of <500 ms in those with a P-wave duration of <130 ms, and <530 ms in those with a P-wave duration >130 ms (Figures 1 and 2). In case of uncertainty in the Holter-ECG analysis, the decision was made by consent.

2.3 Statistics

We used a t-test for normally distributed metric data, the Mann-Whitney rank-sums test for non-normally distributed data, and a Chi-squared test for proportion analysis. Anderson-Darling normality test was applied. Value P < 0.05 was considered significant.

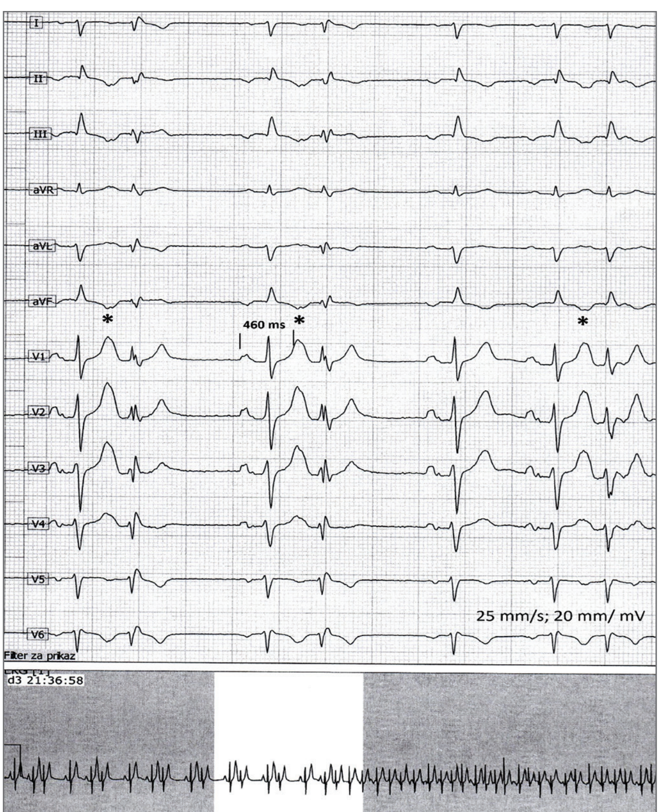

Figure 1: Frequent early atrial ectopic beats (*) in bigeminy, conducted with aberrancy, before induction of atrial fibrillation. The coupling interval of atrial ectopic beat is about 460 ms.
Source: archive of the Department of Cardiology, University Medical Centre Ljubljana.

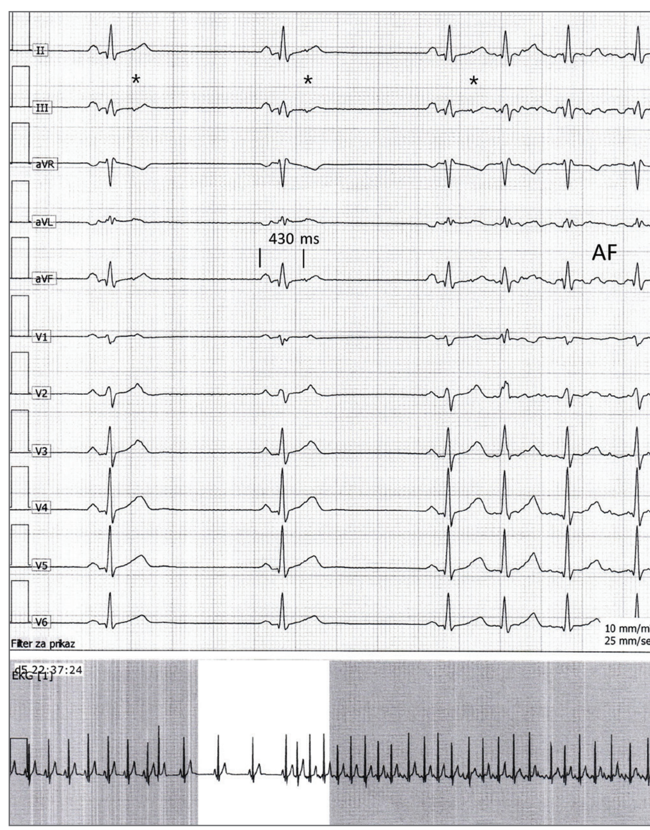

Figure 2: Non-conducted early atrial ectopic beats (*) in bigeminy, with coupling interval of 430 ms. The last one is conducted aberrantly and followed by atrial fibrillation (AF).
Source: archive of the Department of Cardiology, University Medical Centre Ljubljana.

Table 1: Clinical data and results of our observations.

	AF group	Control group	P value
N (Female)	14 (6)	10 (5)	NS
Average age (years) (median, range)	60.5 (45-72)	64.5 (58-72)	NS
CHA_2DS_2-VASc	1.5 (0-4)	2 (0-6)	NS
Increased LAVI (>34 ml/m^2)	7/14	3/10	NS
*Antiarrhythmic drugs	6/14	0/10	
Number of Holter-ECG recordings	26 (1-4/patient)	10 (1/patient)	
Duration of all Holter-ECG recordings (hours)	2427	400	
AF/AFl number of events	243	0	
24-hour AF burden (%) (median, range)	10 (0-67)	0	
24-hour AEB burden (%) (median, range)	0.39 (0.0001-6.3)	1.14 (0.13-7.23)	<0.03
24-hour AEB number (median, range)	381 (3-3937)	1219 (125-7998)	<0.01
**>50 % eAEB burden	9/14	1/10	<0.03
24-hour AEB runs (median, range)	3 (0-151)	2 (1-59)	NS
24-hour AEB pairs, triplets (median, range)	6 (0-174)	9 (2-233)	NS
AEB bigeminy	23/26	6/10	NS
AEB aberrant conduction	21/26	7/10	NS
P-wave duration (ms) (mean ± SD)	143 ± 20.3	129 ± 13.0	<0.05
PQ duration (ms) (mean ± SD)	183 ± 40.2	172 ± 18.5	NS
QRS duration (ms) (mean ± SD)	100 ± 13.4	98 ± 12.4	NS
QTc duration (Fridericia) (mean ± SD	438 ± 21	426 ± 23	NS

Legend:
* Propafenone, flecainide, sotalol, amiodarone
** More than 50% of atrial ectopic beats are early (eAEBs); AEB coupling interval of <500–530 ms was considered "early"
LAVI – left atrial volume index; normal values are according to Lang et al. (2015) (17).

3 Results

3.1 Patients

We included 14 patients (6 female, median age of 60.5 years (45–72, range)) (Table 1). Twelve patients had documented AF/AFl events during Holter-ECG monitoring, and two patients 2 weeks and 4 months after the monitoring, respectively. The control group consisted of 10 clinically similar patients (5 female, median age of 64.5 years (58–72, range)) without any evidence of AF, without antiarrhythmic drug treatment, but with a comparable burden of AEBs (Table 1).

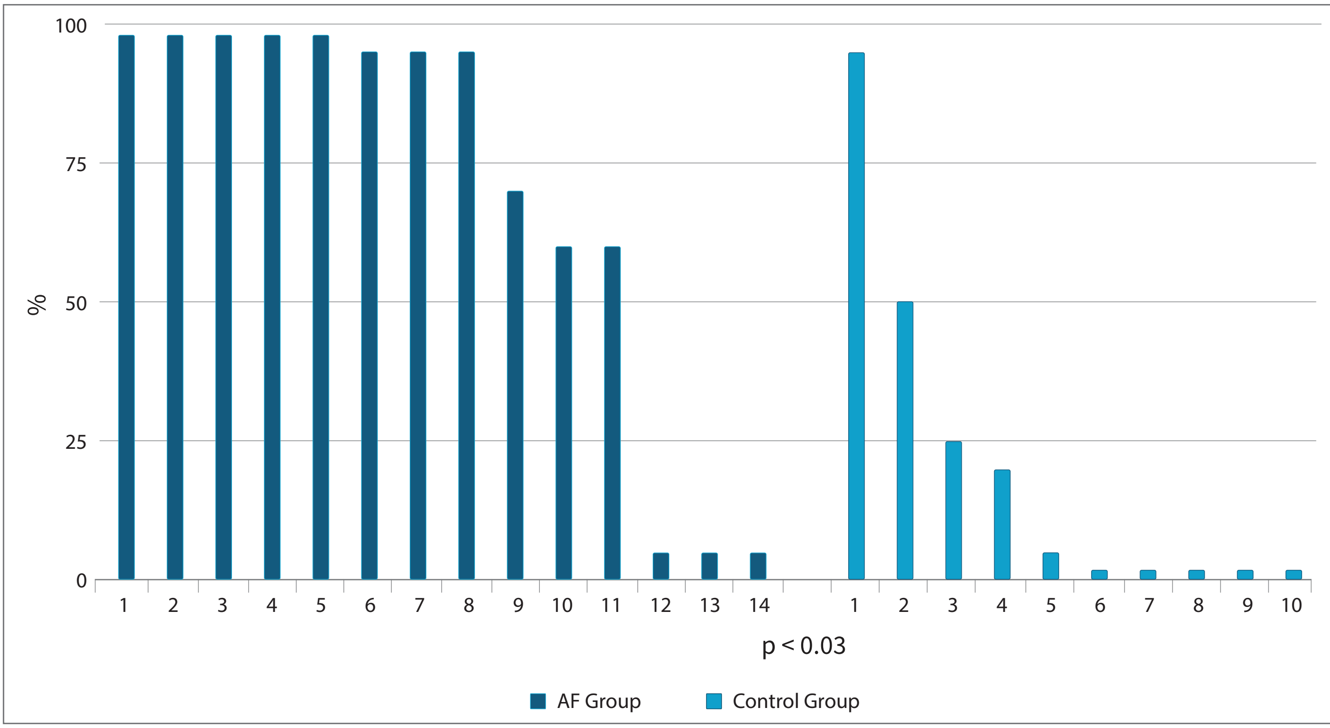

Figure 3: Patients from the AF group had a significantly higher burden of early AEBs than the controls.

In the AF group, 26 continuous ECG recordings were analysed (1–4 recordings per patient, median 195.8 hours (23–279, range, together 2427 hours). In the control group, we analysed 10 recordings of a median of 23.4 hours per patient (19–143 range), together 400 hours.

3.2 ECG parameters

The results are shown in Table 1. We identified 243 AF/AFl events. Patients from the AFgroup had asignificantly higher burden of early,AEBs than controls ($p < 0.03$) (Figure 3), as well as longer P-wave duration ($p < 0.05$). In both groups, some early AEBs were conducted to ventricles with aberrancy or were even non-conducted (Figures 1 and 2). The repetitive forms of AEBs in bigeminy or trigeminy were frequently found in both groups, as well as were AEBs in pairs, triplets and runs. Sustained AT was not associated with AF/AFl induction since it has been found in controls only. AF was induced with early AEBs in the majority of patients (10/12, 83%) (Figures 1 and 2); in some, it was the second beat in the row, after the late first AEB (2/12, 17%). The AF/AFl started most frequently during the day and particularly in the evening (Figure 4). As expected, some early AEBs were related to higher heart rates (not shown). Before AF onset, the increasing numbers of singles, pairs, triplets and runs of early AEBs were encountered in 7/12 (58%) patients, like an outburst of an "electrical storm". A short AF/AFl event typically preceded the more sustained AF/AFl event.

The prolonged P-wave and PQ interval durations were frequently observed with longer AEB coupling intervals and more regular activity of AF/AFl events (Figure 5). In 5/14 (36%) patients from the AF group and in 1/10 (10 %) control, night-time QT-interval > 454 ms was documented (P = NS), and one patient had short PQ-interval (< 120 ms). Late AEBs were mainly related to slow repetitive ectopic activity and non-sustained atrial rhythms and were unrelated to AF/AFl onset (not shown).

4 Discussion

4.1 Early atrial ectopic activity

In this pilot case-control observational study, we demonstrated an association between early-AEB burden and AF/AFl events ($p < 0.03$). The arrhythmogenic potential of early AEBs may be explained with firing before completed atrial repolarization. The cut-off values for early AEBs were arbitrarily derived from Holmquist et al. (2009) (18), who reported data on

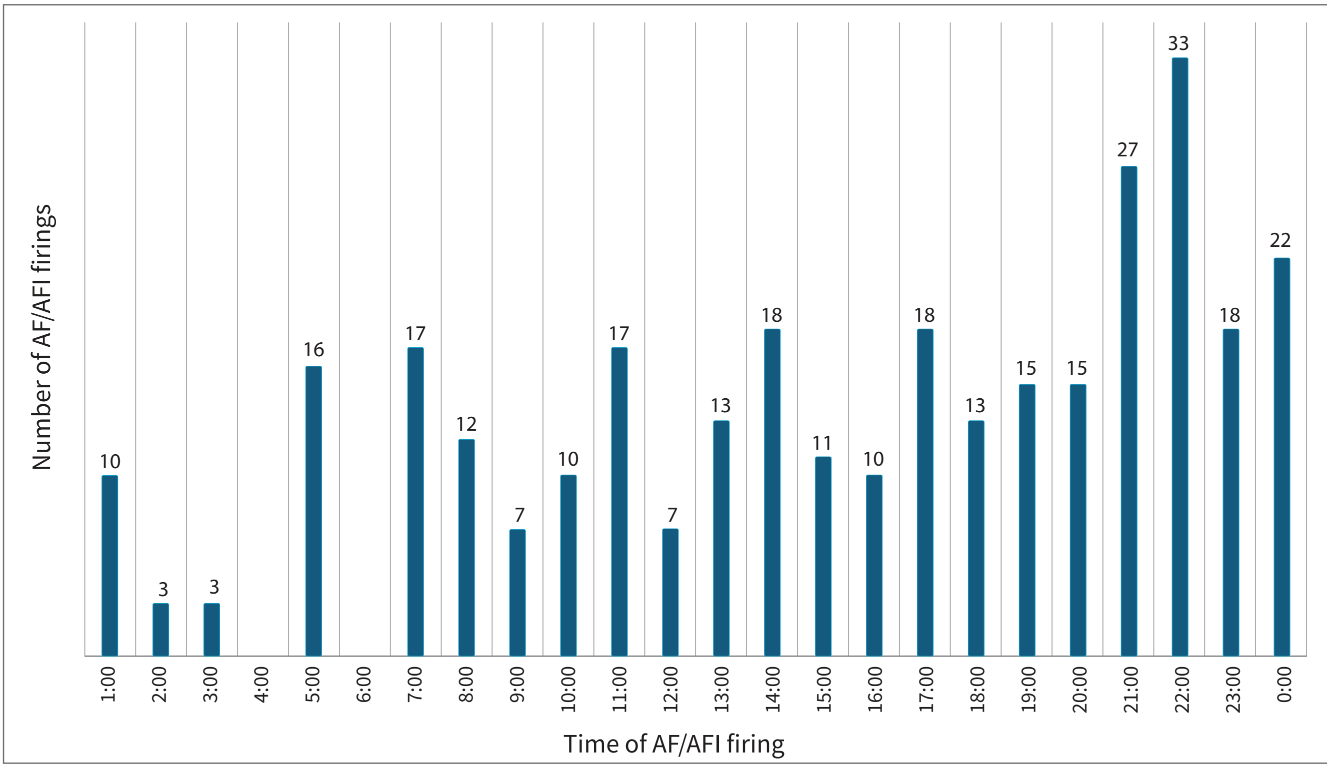

Figure 4: The majority of atrial fibrillation or flutter (AF/AFl) events started in the evening and rarely in the night between 1 and 6 o'clock. Most events recorded between 4 and 5 o'clock (n = 16) occurred in a single patient. The adrenergic drive seems more important than cholinergic as the autonomic modulator of AF/AFl induction in our patient.

atrial repolarisation time in patients with a complete AV-block. The average P-Ta duration was 449–512 ± 55–60 ms (mean ± SD), which is in agreement with our data. In addition, in 58% of AF-group patients, AF/AFl induction correlated with a distinct pattern of outbursts of early AEBs and AEB runs. This "electrical storm" activity, however, predicted AF/AFl events in the time frame of minutes to hours (not shown). It seems however, that long-term prediction of AF/AFl events could also be feasible (e.g., for weeks or even months in two of our patients) but should be proven in a larger group of patients. However, we suspect that diagnostic sensitivity for 24-hour recordings might be low since a high and low burden of early AEBs and AF/AFl events had been encountered in a single patient (not shown). Nevertheless, high burden of early AEBs may be considered a manifestation of an arrhythmogenic state.

Others had long ago demonstrated the importance of early AEBs in triggering AF/AFl events (19). It has been reported recently that in patients with cryptogenic stroke, 7 or more non-conducted early AEBs in 24-hour Holter-ECG predict AF (with a sensitivity of 62.5% and a specificity of 97.7%) (20). The minimum prematurity index of the AEBs (48% or less) at 12 months after catheter ablation of AF was shown to be an independent predictor of AF recurrence (21). On the other side, our observations suggest that late AEBs are related to slower repetitive atrial ectopic activity, such as we see with abnormal focal automaticity, which has, in our opinion, a low proarrhythmic or predictive potential for AF/AFl events.

The number of early AEBs in this study was probably underestimated since conduction from PVs to atria may be delayed in some cases (e.g., in patients with prolonged P-wave duration (Figure 5)) and ectopic atrial activity may not be visible behind QRS complex or in some leads. Therefore, we considered a longer cut-off value for early AEBs (coupling interval 530 ms) in patients with prolonged P-wave duration. For clinical practice, an alerting ECG sign of early, arrhythmogenic AEBs are non-conducted and aberrantly conducted AEBs. However, isolated AV-conduction abnormalities must first be excluded (e.g., a prolonged PQ interval or an incomplete bundle-branch block).

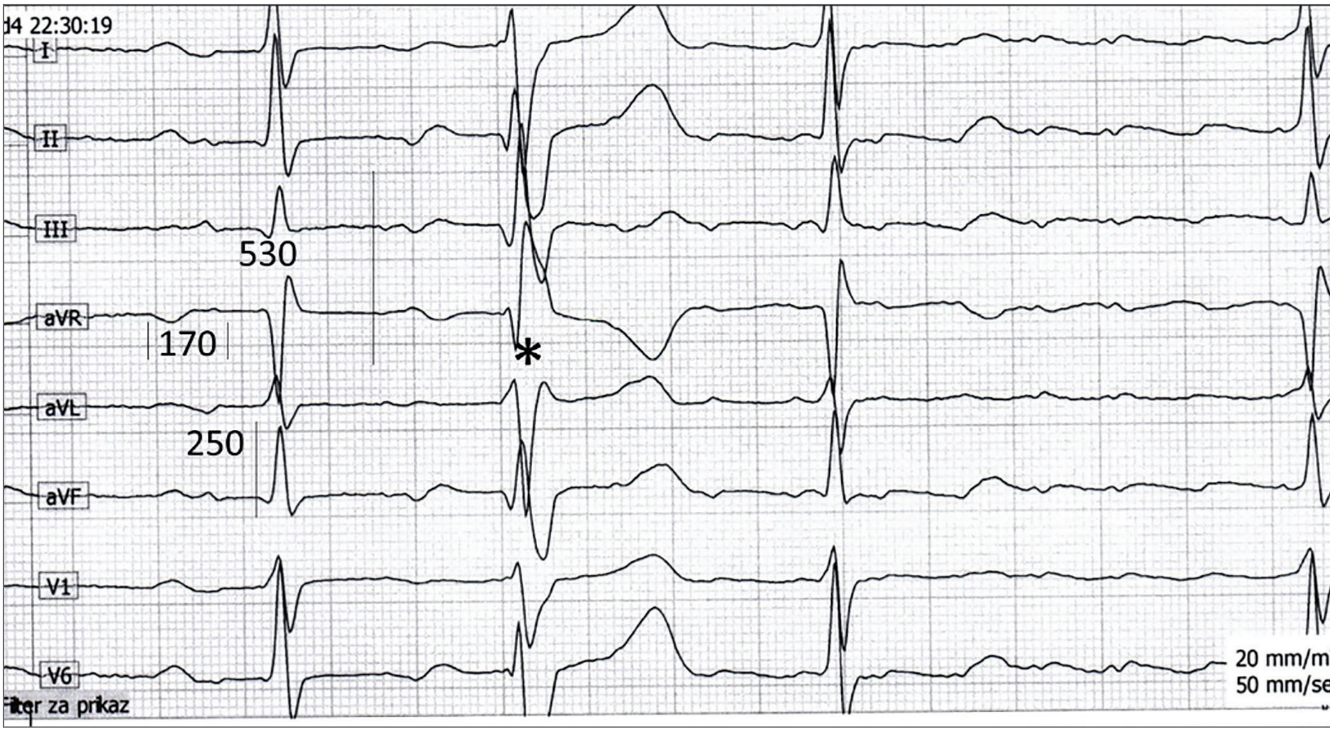

Figure 5: The sinus beat on the left shows a prolonged P wave (170 ms) and PQ interval (250 ms) due to slow atrial and AV-conduction. However, the coupling interval of early atrial ectopic beat is at the cut-off value of 530 ms which is still aberrantly conducted (*). More regular atrial fibrillation/flutter activity is induced on the background of atrial structural disease in this patien.
Source: archive of the Department of Cardiology, University Medical Centre Ljubljana.

4.2 Atrial conduction delay

It is well documented that atrial conduction delay represents a marker and electro-anatomical substrate for the development of AEBs and AF/AFl events; it was also named the "Bayes' syndrome" (13,14,22). The P-wave duration of >120 ms was predictive of AF in a large group of patients who were followed for 5.3 years (Perez 2013) (23). Our data confirm that a prolonged P-wave duration is associated with AF/AFl events (Table 1, Figure 5). Therefore, P-wave duration combined with early AEBs burden might be a useful Holter-ECG predictor of the near-future AF/AFl events. Nevertheless, the P-wave duration in our patients revealed an appropriate cut-off value at about 130 ms, similar to Holmquist's measurements (18).

4.3 Atrioventricular conduction

The study by Nilsen, et al. (2013) showed that long and also short PQ-intervals (< 130 ms) predict a new onset of AF (24). We saw a short PQ interval in only one patient from the AF group. In the majority, we demonstrated prolonged PQ intervals; however, the difference was not statistically significant, possibly due to a small patient sample and a high data variability. As mentioned above, there were some patients with normal or even short PQ intervals. In patients with a short PQ interval, it is obvious that aberrant conduction of early AEBs is less evident.

4.4 Source of atrial fibrillation firing

It has long been known that pulmonary veins are the major source of AF firing (PVs) (25). Therefore, it is highly probable that the majority of early AEBs originate from PVs, as we also observed in our patients during catheter ablation (Figure 6). It is interesting that localised reentry activity at this location may be an important triggering mechanism for AF/AFl onset. The coronary sinus (and vein of Marshall) with its diverse muscle fiber coating and the terminal crest with complex pectinate muscle anatomy are among other potential sources of AF/AFl triggering in about 10% of patients (26). An example of AF onset triggered from the terminal crest is shown in Figure 7.

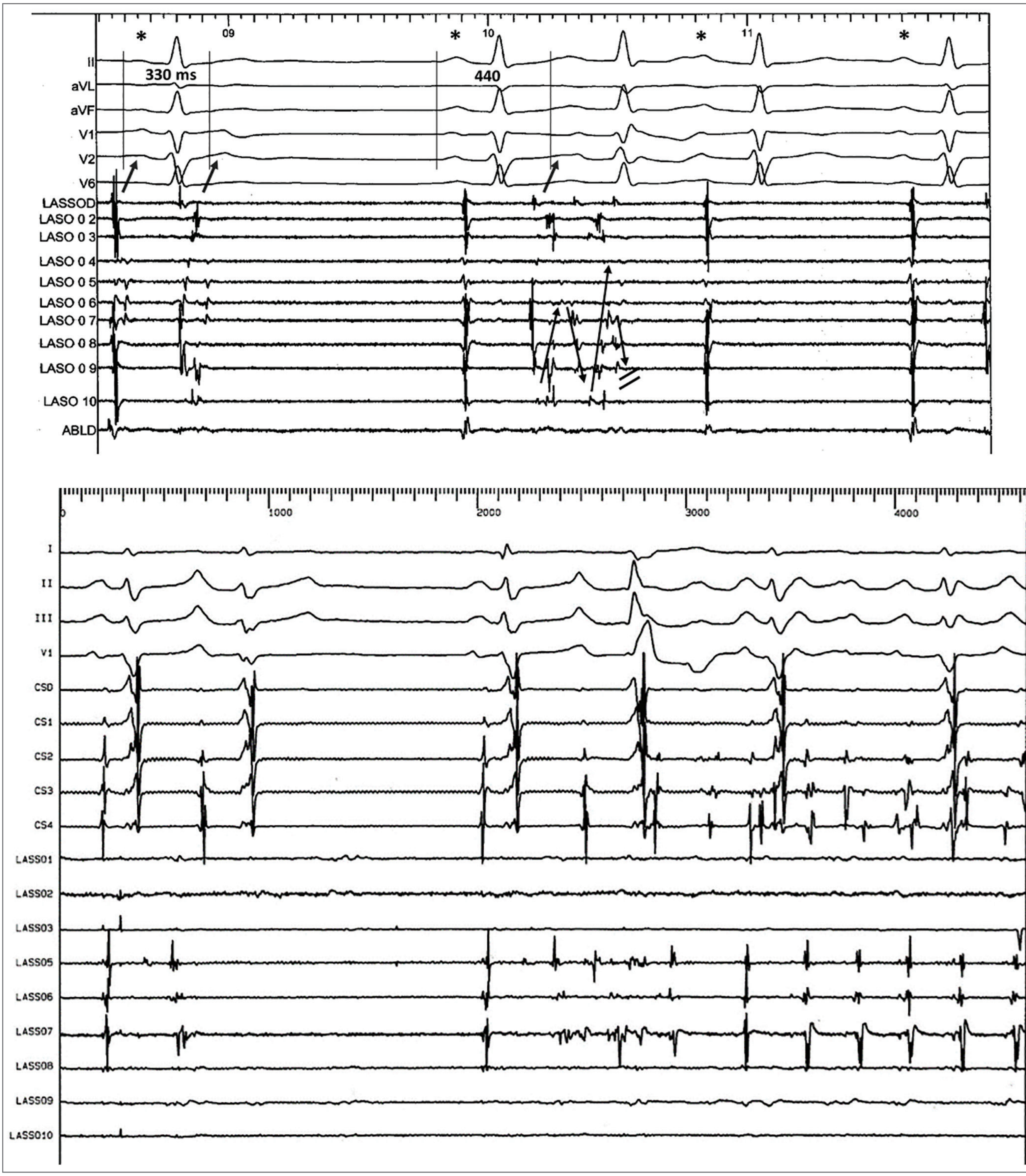

Figure 6: Two examples of triggered and reentry activity from the left pulmonary vein (PV) antrum. In this location, bipolar electrograms from the circular diagnostic catheter are marked by "LASO/LASSO". The first sinus beat (*) on the left upper tracing is fused with the ectopic beat (arrow). The second ectopic beat is not conducted to the ventricle, and the third is conducted aberrantly. After the third ectopic beat, a short reentry antral activity terminated spontaneously (arrows). Below, in another patient, a similar sequence of events induced atrial fibrillation, which is less regular in CS than in the left PV antrum.

Legend: ABLD – electrogram from ablation catheter; CS – bipolar electrograms from the coronary sinus.

Source: archive of the Department of Cardiology, University Medical Centre Ljubljana.

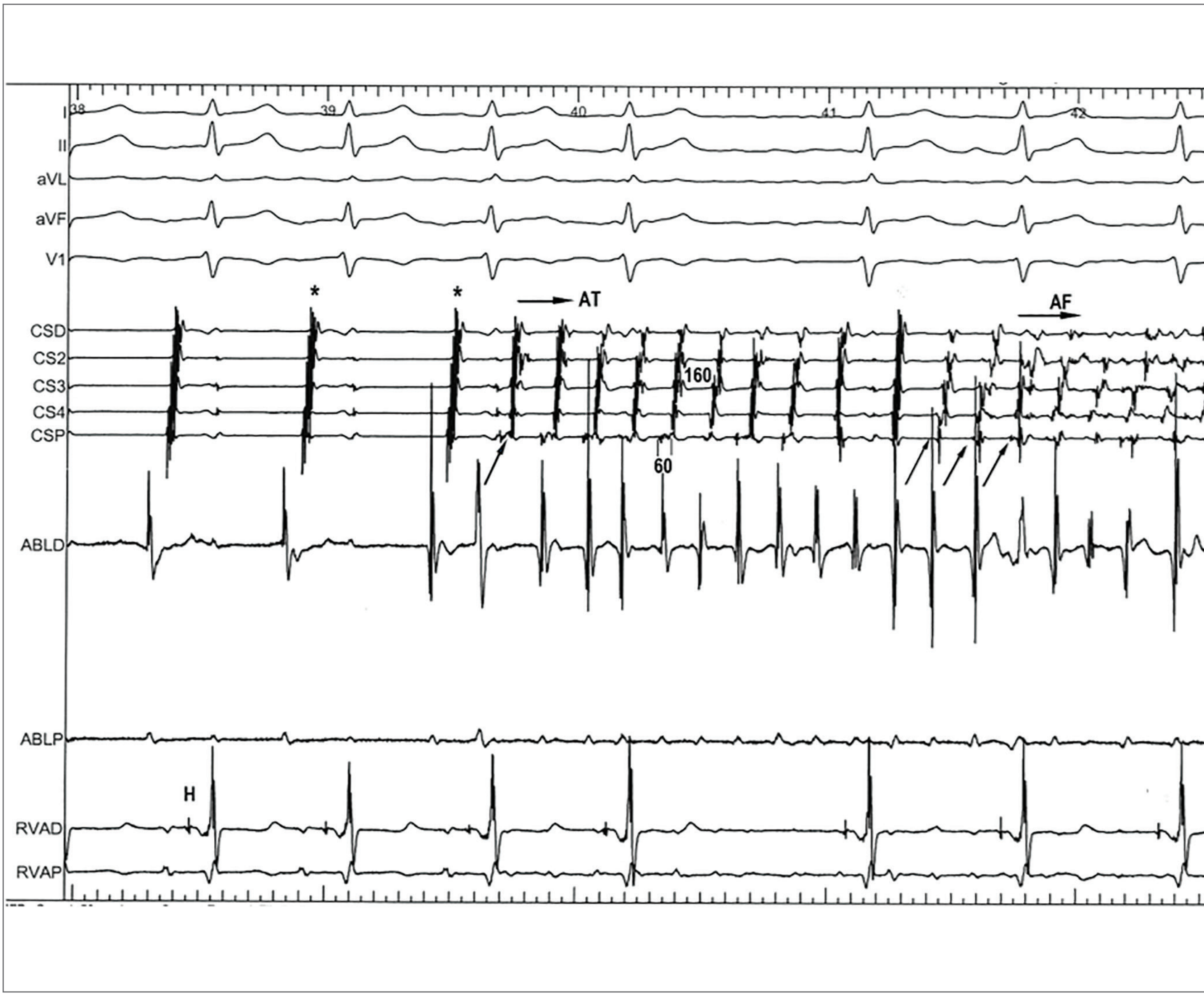

Figure 7: Early atrial ectopic beat from terminal crest (the first arrow on the left) is followed by fast regular atrial activity (AT) with fragmentation (cycle up to 160 ms), which converts to atrial fibrillation (AF) as first seen on the 10-polar catheter in the coronary sinus (CS). AF is most likely induced in CS or the left atrium. Sinus beats are marked with stars (*).
Legend: ABLD, ABLP – bipolar electrograms from ablation catheter positioned on the upper terminal crest of the right atrium; RVAD, RVAP – bipolar electrograms with His and right bundle electrograms (H).
Source: archive of the Department of Cardiology, University Medical Centre Ljubljana.

4.5 Mechanisms of atrial fibrillation triggering

The electrophysiological basis of AEBs is triggered activity, either by early afterdepolarisation in the case of prolongation of the action potential or by delayed afterdepolarisation in the case of increased heart rate (27). The reported leading mechanisms of AF induction were: a) triggered activity, which includes Ca^{2+} handling abnormalities, mainly by delayed after-depolarisations; b) reentry activity in structurally remodeled atria; and c) inflammatory signaling in some conditions (28). In addition, atria are highly innervated by the autonomic nervous system via the ganglionated plexi (29). Both the sympathetic and parasympathetic systems are involved in the occurrence of AEBs and AF by increasing the calcium transient and heterogeneous shortening of action potentials (30,31,32). The prevailing daytime firing of AF/AFl in our patients suggests the important role of sympathetic predominance before induction. Early AEBs seem to be related to fast repetitive activity from PVs as the main source, with triggered activity (and localized reentry) as the main mechanism of AF/AFl induction (Figure 6). The AF induction was also associated with long nocturnal

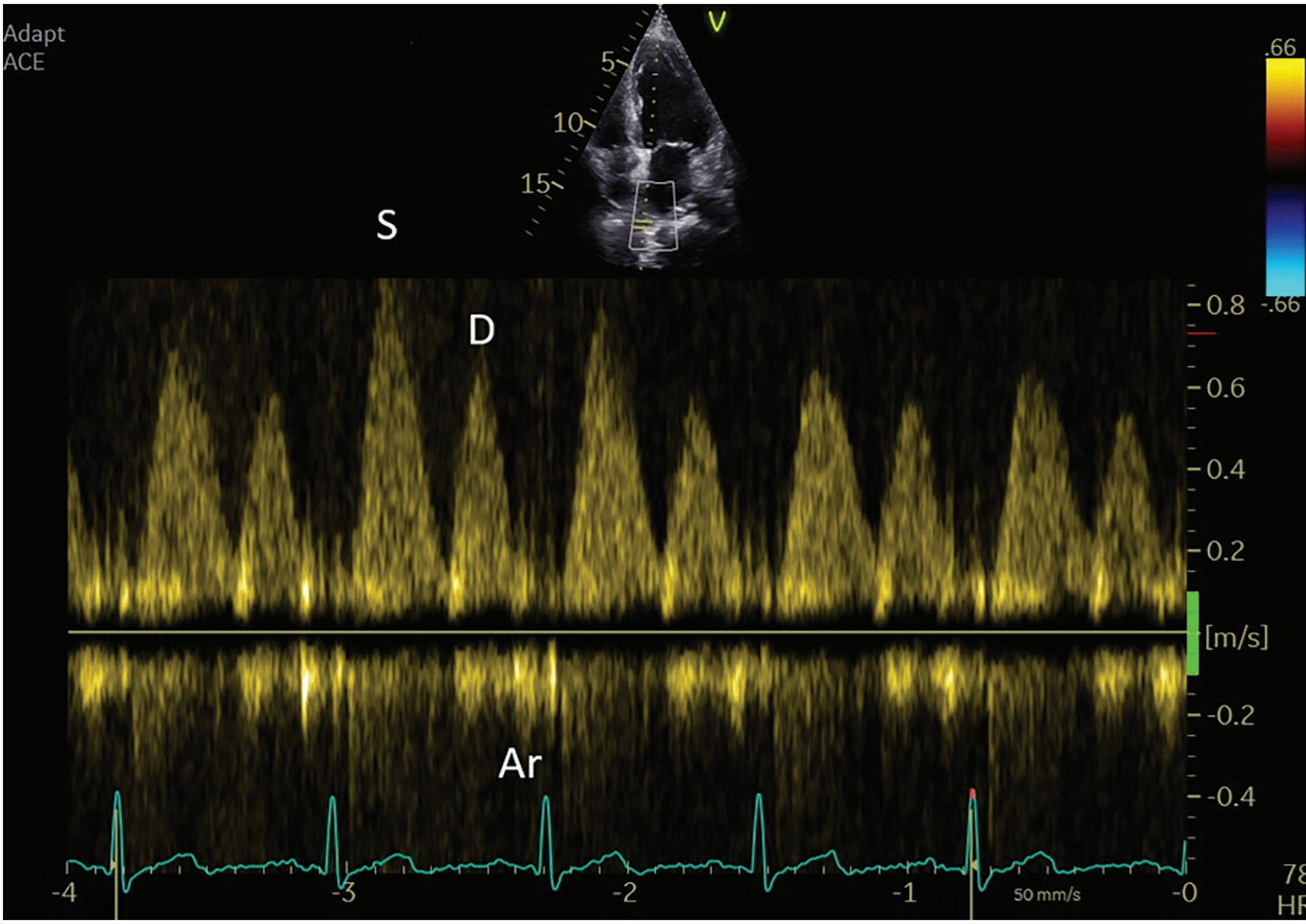

Figure 8: Pulsed-wave Doppler tracings (in yellow) of the right upper pulmonary venous flow with simultaneous ECG tracings. Reversal of blood flow with atrial contraction (Ar) at the end of ventricular diastole is followed by fast inflow during ventricular systole (S), the time of early atrial ectopic beats firing.
Legend: D – diastolic wave.
Source: archive of the Department of Cardiology, University Medical Centre Ljubljana.

QT intervals in one-third of our patients. If we speculate that a long QT interval is also a marker of abnormal atrial repolarisation (due to localised autonomic nerve dysfunction), primary atrial repolarisation abnormality might be involved in AF/AFl induction in some of our patients. In the majority however, prolonged P-wave duration (and PQ interval) suggests that primary abnormality was an atrial conduction delay, possibly on the grounds of atrial cardiomyopathy with reentry as another important mechanism of AF/AFl induction and perpetuation (15). Furthermore, it seems that the location of AEBs firing may be clinically meaningful. In a swine model, AEBs originating from the lateral left atrium were associated with longer P-wave duration, greater echocardiographic atrial mechanical dyssynchrony, and longer induced AF duration than from the septal AEBs or after regular left atrial pacing at 130 beats/min (Higuchi 2024) (33).

Another mechanism for early AEB firing and AF induction has to be mentioned, i.e., the so-called "mechano-electrical feedback", proposed by Tse et al. (2001) (34). Early AEBs occur during atrial and ventricular contractions and atrial relaxation. The systolic traction on antral parts of PVs and changing blood flow directions might contribute to electrical triggering (Figure 8). This haemodynamic trigger of AF induction may play particular role in conditions with increased left ventricular filling pressures. An example is hypertensive cardiac disease, the most frequent comorbidity in patients with non-valvular AF (1,2).

4.6 The normal burden of atrial ectopic beats in Holter-ECG monitoring

There is currently no widely accepted consensus on reference ranges for 24-hour Holter-ECG AEB activity to guide interpretation. A threshold of 500 AEBs/24 h has been proposed in a consensus paper (35). However, a recent meta-analysis in a healthy adult population, although on limited available data, demonstrated that AEBs of >1000/24 hours increased with age, from 0 (95% CI 0–0%) in those aged 18–39 years to 6% (95% CI 0–17%) in those aged 60–79 years. Episodes of any AEB runs (minimum 3-5 beats) increased from 3% (95% CI 1–6%) in those aged 18–39 years to 28% (95% CI 9–52%) in those aged 60–79 years (6). In our patients, the median number of AEBs (in singles, pairs, and triplets) was below the suggested cut-off value of 500/24 hours (Table 1).

4.7 Limitations

Our pilot observational study has some limitations. The accuracy of readings and measurements of so many events and parameters over long time periods may be limited. Nevertheless, our results are reasonably accurate since we carefully checked the automatic analysis results many times. We assessed the burden of early AEBs in a semiquantitative way since it was almost impossible to count out correct numbers from thousands of events. Nevertheless, the separating value of more than 50% of early AEBs (of all AEBs in a 24-hour Holter-ECG recording) was evident (Figure 3). Also, in 4 out of 6 patients from the AF group who were taking antiarrhythmic drugs, P-wave duration was prolonged, and this effect may not be neglected. In addition, the selection of the control group of patients may be biased since some of them had had catheter ablation of focal sustained atrial tachycardia before. This arrhythmia, however, was not associated with AF/AFl events, thus confirming its different electrophysiological mechanism. Further, some patients from control group might have had a silent AF/AFl event before inclusion. Finally, the AF/AFl event would also be revealed in the control group if the duration of Holter-ECG recordings was similar to that of patients from the AF group. However, the difference between the groups would be even less evident in this case. Nevertheless, the diagnostic value of proposed Holter-ECG parameters for predicting AF/AFl events has to be re-evaluated in a larger group of patients.

5 Conclusions

The results of this pilot case-control observational study suggest that the increased burden of early AEBs over 50%, combined with prolonged P-wave duration beyond 130 ms, may be a useful Holter-ECG predictor for a near-future AF/AFl event.

Conflict of interest

None declared.

Acknowledgements

We express our sincere gratitude to Benjamin Jezernik, Ingrid Tušar and Matic Cesar for their thorough and pedantic work with data recording and collection.

This work was supported by the research grant No. 20210004, UMC Ljubljana.

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