Electrocardiographic and Echocardiographic Abnormalities in Patients with Risk Factors for Atrial Fibrillation

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Disclosure statement

The authors have nothing to disclose.

Key Words

Atrial fibrillation; 12-lead electrocardiogram; Echocardiogram; Risk Factors

Key Points

- The electrocardiogram and various echocardiography modalities are important risk markers for atrial fibrillation (AF)
- Electrocardiographic criteria of left atrial enlargement (LAE), advanced interatrial block (IAB), and PR interval prolongation are atrial risk markers for AF
- Transthoracic Echocardiography is elementary for risk stratification of AF.
- Transesophageal echocardiography is a valuable tool to detect cardiac sources of embolism if early cardioversion is necessary
- Intracardiac echocardiography is a real-time tool for guidance of percutaneous interventions, including radiofrequency ablation and left atrial appendage (LAA) closure in patients with AF

Introduction

Atrial fibrillation (AF) is the most common sustained irregular cardiac arrhythmia. The prevalence of AF is 0.12%–0.16% in <49-year-old, 3.7%–4.2% in those between 60–70 years, and 10%–17% of≥80-year-old individuals. Male to female ratio is 1.2:1. The incidence of AF ranges between 0.21 and 0.41 per 1,000 person-years. AF is permanent in ≈ 50% of patients, while the prevalence is 25% in both paroxysmal and persistent AF. AF may present without comorbidities or it may be associated with hypertension, hyperthyroidism, coronary or valvular heart disease, cardiomyopathies, heart failure, obesity, obstructive sleep apnea, etc.[1] AF is associated with a two- to three-fold increased risk of cardiovascular mortality and sudden cardiac death,[2] a fivefold increased risk of stroke,[3] and a threefold increased risk of heart failure.[4]

Electrocardiographic markers for AF

I) Prolonged P-wave duration

Prolonged P-wave duration (PWD) is an ECG risk factor marker for AF that reflects atrial dromotropic disturbance. It is defined by manual annotation of the earliest onset and latest offset of the P-wave in the 12-lead ECG. Prolonged PWD is indicative of underlying atrial disease with hemodynamic changes leading to elevated intra-atrial pressure, atrial wall stress, atrial fibrosis, and abnormal electrical coupling between atrial cardiomyocytes through gap junctions Cx40 and Cx43,[5] causing dromotropic disturbance.[6] The vulnerability to arrhythmias is determined by the combined presence of an arrhythmogenic substrate and initiating triggers, which most frequently originate from firing foci in the pulmonary veins and/or superior vena cava. Triggers for AF include sleep deprivation, physical illness, strong emotions, recent surgery, premature menopause, exhaustive exercise, nasal decongestants, cocaine, recreational

drug and alcohol, excess caffeine intake, low carbohydrate diets, caffeinated drinks and dehydration, etc.

Congenital short QT syndrome (SQTS) is a genetic example of a very short effective refractory period with high AF tendency (Figure 1).

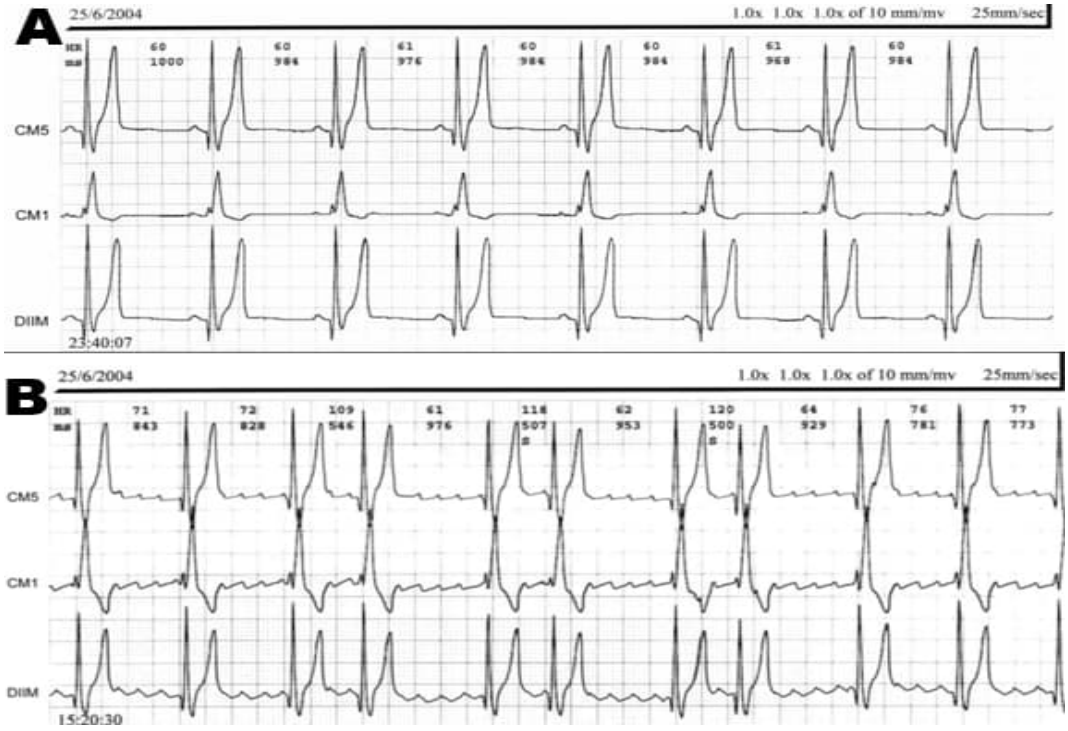

Figure 1. ECG in a patient with congenital Short QT Syndrome (SQTS)

(A) Holter monitoring strip: Sinus rhythm, tall/peaked, narrow-based T waves and very short QT interval:

(B) Eight hours later, the patient had a transient paroxysmal atrial fibrillation (AF).

II) Left atrial enlargement

Electrocardiographic criteria for LAE are: duration of the negative (terminal) portion of the P-wave in lead V_1 >40 ms, depth of the negative (terminal) portion of the P-wave in lead $V_1 \geq 1$ mm, total P-wave duration in lead II >110 ms, and bimodal P-wave in lead II with inter-peak notch duration >40 ms. (Figure 2).

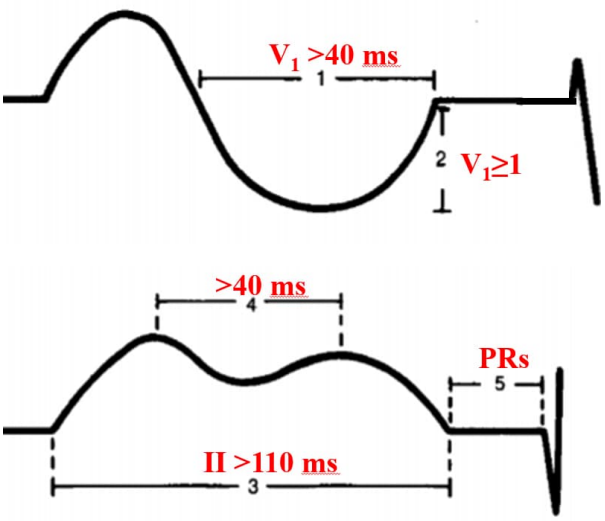

Figure 2. Schematic representation of ECG criteria for LAE: (duration of negative portion of P-wave in lead V1 > 40 ms (1) ; depth of negative portion of P-wave in lead V1 ≥1 mm; P-terminal force (1 x2) ≥ , Negative P-terminal force in lead V1 ≥0.04 mm/s (Morris index).[7] ; total PWD in lead II (3) >110 ms; bimodal P-wave in lead II with interpeak notch duration (4) > 40 ms; and total PWD (3): PRs =PR segment (5).

Macruz, et al. proposed a simple formula for electrocardiographic recognition of right, left, and biatrial atrial enlargement. It is based on the measurement of the PR interval, PWD, and PR segment. According to these authors, the normal ratio of the PWD to the PR segment ($^{PWD}/_{PRs}$) as measured in standard lead II is between 1.0 and 1.6, with an average value of 1.2. In cases of RAE, there is no significant prolongation of the PWD, but the PR interval increases, and therefore, the PR segment ratio falls below the normal range. LAE, on the other hand, does not affect the PR interval, but the P wave lengthens at the expense of the PR segment. The result is a ratio above the normal upper limit of 1.6. In biatrial enlargement, both the PR interval and P wave are prolonged, and the PWD to PR segment ratio is normal.[8]

III) The concept of interatrial block and its association with AF

Interatrial block (IAB) is a conduction delay between the RA and LA with higher prevalence in the elderly and in patients with structural heart disease (Figure 3)

Partial interatrial block **Advanced interatrial block**

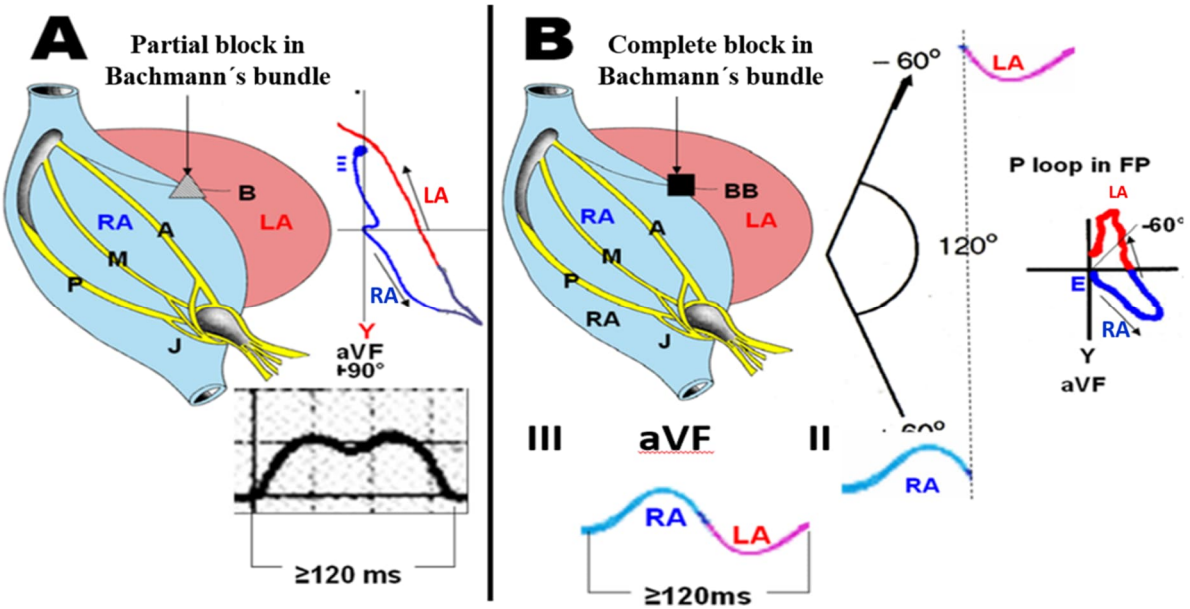

Figure 3A. Partial interatrial block: PWD ≥120 ms. **3B.** Advanced IAB: PWD ≥120 ms and biphasic positive/negative P-wave in the inferior leads. LA activation occurs retrogradely (caudo-cephalic). FP = frontal plane; LA = left atrium.

IV) Prolonged PR interval

The PR interval is measured from the beginning of the P wave to the beginning of the QRS complex, and it reflects the time it takes for the electrical impulse to travel from the sinus node through the atrio-ventricular (AV) node to the ventricles (Figure 4).

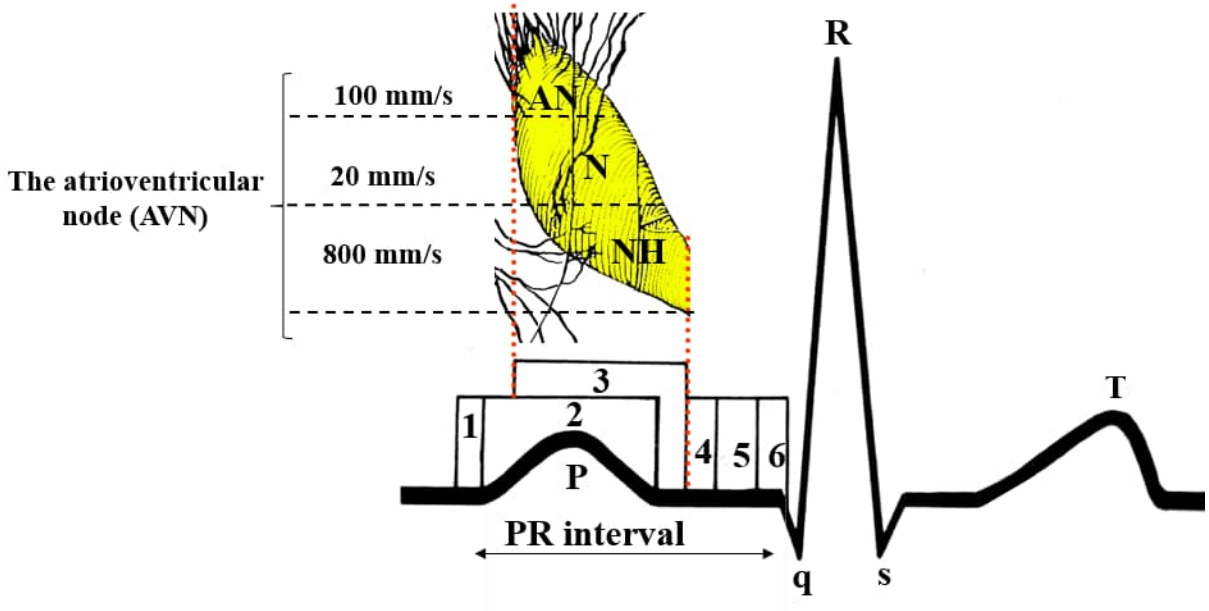

Figure 4. PR interval components. 1. sinoatrial (SA) Node;[9] 2. Atria; 3. Atrioventricular Node; 4. His Bundle Branch ; 5. Right and left bundle branch and their fascicles; 6. Purkinje fibers. AN: Atrionodal portion of AV node; N: Nodal portion of AV node; NHN: Nodo-Hissian portion of the AV node.

Association between PR-Interval prolongation and the Risk of AF

PR interval prolongation is associated with an increased risk for AF. Schumacher et al. studied the association between PR interval prolongation and LA remodeling measured as low voltage areas during catheter ablation of AF. Besides persistent AF and LA size, PR interval prolongation might be useful for the prediction of electro-anatomical substrate in AF patients.[10] The Framingham Heart Study (FHS) and the Atherosclerosis Risk in Communities (ARIC) Study investigated the association between PR-interval prolongation and the risk of AF.[11, 12] In the FHS, the risk of AF was found to be significantly higher in subjects with a PR-interval >200 ms compared with subjects without first-degree AV-block. In addition, each 1-standard deviation (20 ms) increment in PR-interval duration was associated with a hazard ratio (HR) of 1.11 (95% CI; 1.02-1.22; P = 0.02) for AF.[11]

As in the FHS, PR-interval duration was examined as both a continuous linear and a categorical variable (first-degree AV-block vs. no AV-block) in the ARIC study. The former was significantly associated with a risk of incident AF, while the latter did not reach statistical significance. Both in the FHS and the ARIC study, the reported associations were adjusted for a number of potential confounders, including age, gender, hypertension, body mass index, diabetes, and smoking status.

The Health ABC study demonstrated a linear increase in the risk of AF with longer PR-intervals.[13]

In a Finnish cohort study comprising more than 10,000 individuals and 30 years of follow-up, there was not even a trend towards an increased risk of AF for individuals with PR-interval >200ms compared with individuals with a normal PR-interval.[14]

In the Copenhagen ECG study, almost 300,000 individuals were followed for a median of approximately six years, and during this period, more than 11,000 subjects developed AF. The relatively strong statistical power in this study allowed for a more flexible and non-linear approach for investigating the association between PR-interval duration and AF. It was found that both women with a short PR-interval and women with a long PR-interval have an increased risk of AF compared with the reference group (a PR-interval of 148-157 ms). Regarding men, a long PR-interval was statistically significantly associated with an increased risk of AF, whereas the association between shorter PR-intervals and AF did not reach statistical significance.[15] Results from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)-AF Consortium (which included data from the ARIC, CHS, and FHS cohorts) are in line with the results from the Copenhagen ECG Study, and point to an increased risk of AF for short PR-intervals. In this study, PR-intervals <120ms conferred an increased risk of AF compared with PR-intervals in the range 120-199 ms. The authors did not find a statistically significant association for PR-intervals >199 ms.[16]

Risk Prediction of Atrial Fibrillation

In a clinical setting, an AF risk score can serve as a tool in determining an individual's risk of developing AF. AF risk models have been developed and validated.[16] In the FHS-derived risk model for AF, the predictive value of several clinical risk factors for the assessment of long-term AF was investigated. Known risk factors for AF were incorporated into the risk score if they improved model discrimination (estimated by c-statistics) and calibration ($\chi 2$ test) in a setting of internal cross validation. As a result of these computations, the PR-interval was incorporated into the risk model in the way that 0 points were given for a PR-interval < 160 ms, 1 point for 160-199 ms, and 2 points for a PR-interval ≥200 ms. Later, the FHS-derived risk algorithm was externally validated in two independent cohorts: the age, Gene/Environment Susceptibility-Reykjavik Study (AGES) and the Cardiovascular Health Study (CHS)-cohorts with a subdivision of the CHS-cohort based on ethnicity (CHS Whites; CHS African Americans). Although the FHS-derived AF risk score was still of value in risk prediction of AF, the score had a considerably lower discriminative value in the external validation cohorts compared with the FHS derivation cohort. Whereas the c-statistic decreased from 0.78 to 0.76 in the original FHS-cohort when internal cross-validation was applied (using bootstrapping with 1,000 replications of individuals sampled with replacement), the c-statistic decreased much further in the external cohorts, where values of 0.67, 0.68, and 0.66 were obtained in the AGES, CHS Whites, and CHS African Americans cohorts, respectively.[17] A statistically significant association between a linear increase in PR-interval and the risk of incident AF was found in the AGES, CHS Whites, and FHS cohorts. However, the association did not reach statistical significance in the CHS African American cohort.

Another AF risk score was developed based on the ARIC study cohort. Selection of prediction variables was based on Cox regression and the use of backward stepwise elimination, where

variables were eliminated in case of an association less than $p<0.10$. As a result of this, the PR-interval was not included in the final risk model. C-statistics for the final model was 0.76 when internal validation was not applied and 0.77 when interval validation was applied. In the same study, the investigators tested the FHS-derived risk score and found c-statistic of 0.68, which is in accordance with previous external validations of the FHS-derived AF risk score.[18]

Electrocardiographic characterization of AF

Absence of the P-wave, presence of small waves of high frequency, (between 350 to 700 bpm) with irregular voltage, variable morphology and duration, called "f" waves. The complete variability in shape and timing of the atrial complexes rules out flutter. Sometimes f waves are clearly discernible, but they may be completely absent, at least temporarily. F waves are best identified in leads V_1 or V_1 and V_2 because these leads are close to the atria and because the direction of the waves usually heads to the front and the right. The ventricular rhythm in AF is irregular except when associated with complete AV block without capture beats (Figure 5).

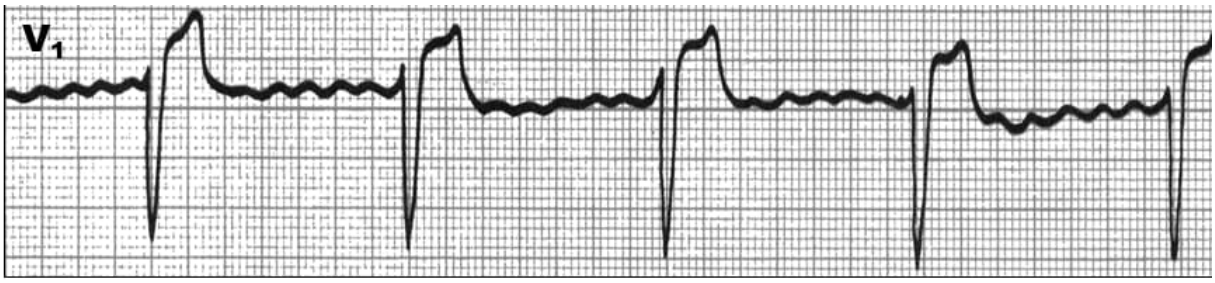

Figure 5. Coarse "f" waves, regular QRS complexes and very low heart rate in complete Atrio-Ventricular (AV) block.

Ashman phenomenon and AF

The Ashman phenomenon is an intraventricular conduction disorder that occurs in the His-Purkinje system, caused by a change in heart rate (HR). It is dependent on the effects of HR on the electrophysiological properties of the heart and may be modulated by metabolic, electrolytic

and drug-induced alterations, which alter the duration of the refractory period of the ventricular branches of the conduction system.[19] The Ashman phenomenon is commonly observed in AF, atrial tachycardia, and premature atrial contractions. Aberrant conduction occurs when a short cycle follows a long one (Figure 6).

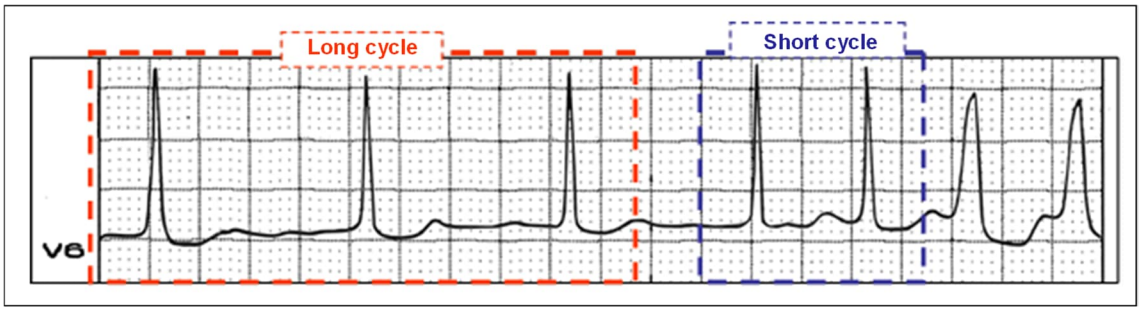

Figure 6. A long strip of V6 of a patient in atrial fibrillation (AF). Aberration occurs when a short cycle follows a long one. The two last QRS complexes are aberrant with a left bundle branch block pattern: Gouaux-Ashman or Ashman phenomenon.

Figure 7 illustrates the phenomenon of aberrant conduction and extrasystoles during atrial fibrillation (AF) with high ventricular rate.

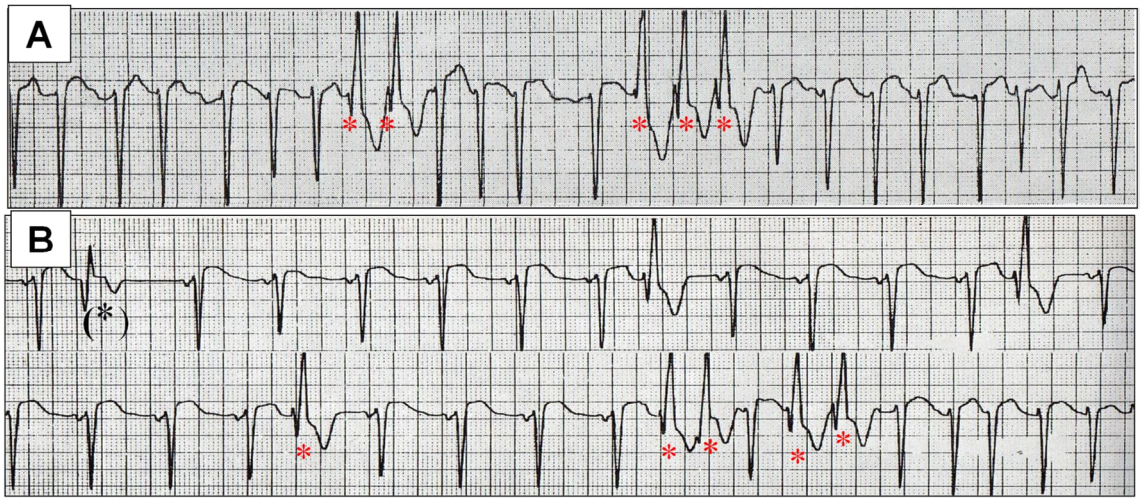

Figure 7. In the upper panel (A) the rhythm is atrial fibrillation (AF) with a high ventricular response rate. No atrial activity is observed, and QRS complexes are of irregular presentation with marked variation in timely occurrence. The QRS complexes indicated by asterisks* show

triphasic rsR' pattern of the right bundle branch block (RBBB) type, the first r deflection has the same direction as that of the predominant beats, and there is no compensatory pause. These 3 elements confirm the presence of aberrant conduction. Panel B shows the same tracing in sinus rhythm. The second beat (*) is a premature ventricular contraction (PVC) because the first deflection (Q) presents an opposite direction compared to the prevailing complexes (r) and because there is complete compensatory pause. Additionally, repolarization reveals an "injury current" and transmural ischemia with ST elevation. The beats indicated by red asterisks are supraventricular extrasystoles with aberrant conduction, because they have a triphasic RBBB pattern of variable width.

Figure 8 illustrates ECG aspects of atrial fibrillation (AF) in digitalis intoxication.

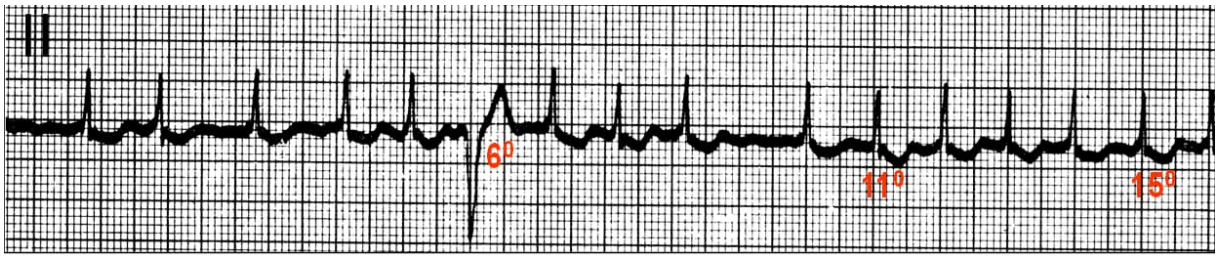

Figure 8. A patient with chronic obstructive pulmonary disease and regular digoxin medication. There is AF. The sixth beat is a PVC. Beats 11 to 15 have regular RR intervals, which in the presence of AF suggests digitalis intoxication.

Figure 9 shows atrial fibrillation (AF) in the context of pre-excitation.

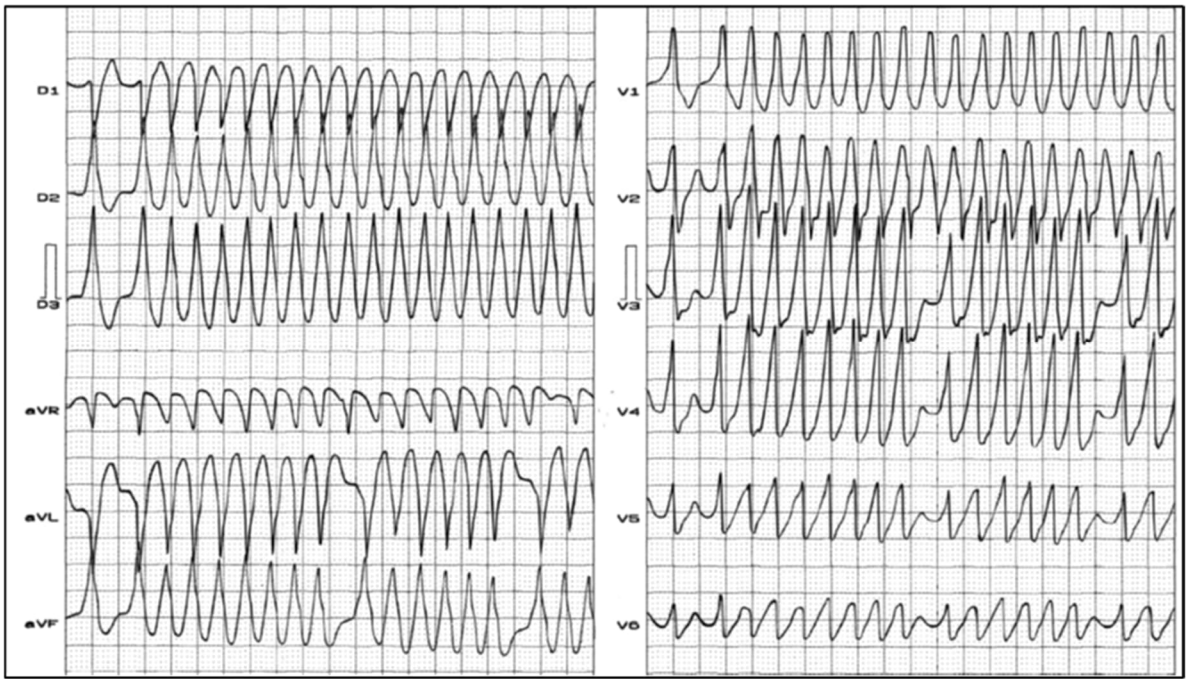

Figure 9. Atrial fibrillation (AF) in pre-excitation due to an accessory pathway with short refractory period: irregular RR intervals, QRS width with variable duration and fast ventricular rate (≈300 bpm).

Echocardiographic abnormalities in patients with atrial fibrillation

I) Transthoracic echocardiography

Transthoracic echocardiography (TTE), including two-dimensional imaging and Doppler assessment of the valves, is recommended for all subjects with AF.[20] TTE allows measurement of LA dimensions and volumes, left ventricular (LV) dimensions and volumes, LV ejection fraction, LV diastolic function, and valvular function. Harmonic imaging, alone or with micro-bubble contrast agents, allows enhanced endocardial border definition for assessment of LV volumes and function. Color M mode (CMM) and tissue Doppler imaging (TDI) allow more accurate assessment of the diastolic function and for the estimation of filling pressures. Assessment of systolic and diastolic LV function in AF may be challenging due to irregular RR interval and fast ventricular rate. TTE provides suboptimal visualization of the atrial

appendages and has inadequate sensitivity and specificity for diagnosing LAA thrombus[21] (Figure 10).

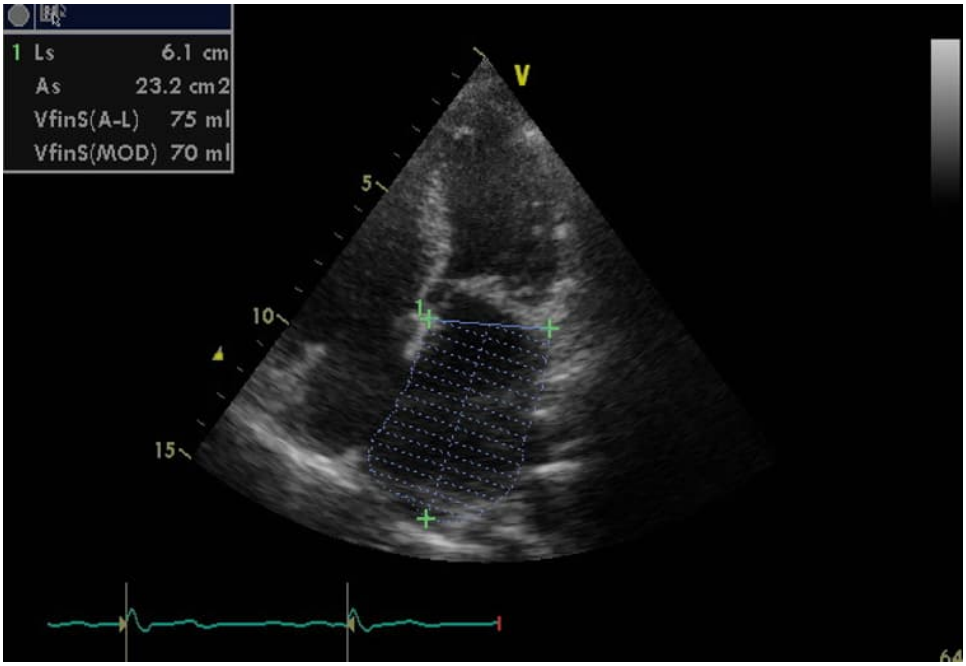

Figure 10. Mitral stenosis. Volume measurement of left atrium (LA) by Simpson method.

II) Transesophageal echocardiography

Transesophageal echocardiography (TEE) allows for high-resolution exploration of the posterior cardiac structures, including the atria, atrial septum, pulmonary veins and the atrial appendages for thrombus detection. More accurate evaluation of the is possible by TEE. Also, alternative thromboembolic sources can be identified, including complex atheroma's of the aorta. In AF, TEE is performed in patients at high risk of thromboembolism, those being considered for early cardioversion, or those with a secondary indication such as valvular disease.[20] Structures evaluated with TEE include: LA and Left Atrial Appendage (LAA): structure, function, spontaneous echo contrast and thrombus, right atrium (RA) and right atrial appendage (RAA) structure, function and thrombus, pulmonary vein anatomy/flow, atrial septum (patent foramen ovale, etc), ascending aorta and arch atheroma, valvular function (Figure 11).

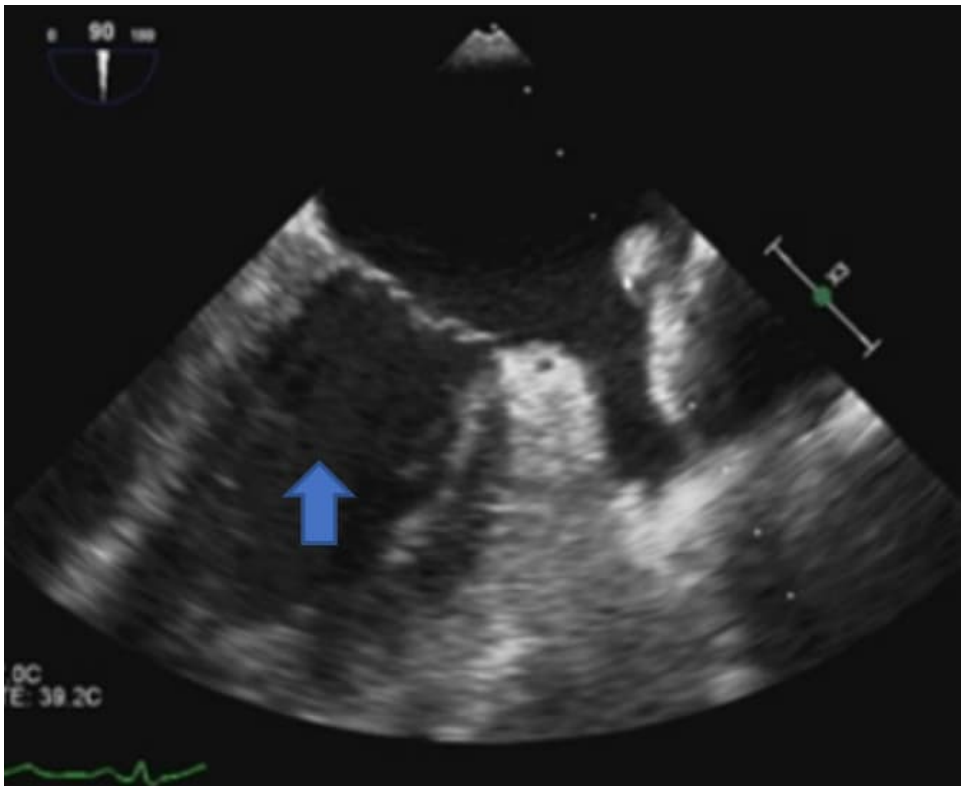

Figure 11. Transesophageal Echocardiogram (TEE) to 90º. Left Atrial Appendage (LAA) free of thrombi.

III) Intracardiac echocardiography

Intracardiac echocardiography (ICE) is performed with a transducer placed in the RA via a 6–10 French sheath in the femoral vein. Modified from intravascular ultrasound probes, these steerable monoplane transducers produce ultrasound waves mechanically or via phased array. The latter offer the same modalities as TEE, including color, pulsed wave, and continuous wave Doppler, to allow assessment of intracardiac flow in addition to 2D visualization of structures. ICE can play a key role in the guidance of cardiac interventions and is used for radiofrequency ablation procedures,[22] for percutaneous closure of patent foramen ovale or atrial septal defects. Structures evaluated include: LA/LAA structure and function, LA/LAA thrombus, atrial septum, pulmonary vein anatomy and flow.

IV) Speckle tracking bidimensional echocardiography

Through longitudinal atrial strain, reservoir, conduction and pump functions can be measured, which are inversely correlated with the degree of fibrosis estimated by late gadolinium enhancement. A low strain value guides us towards a fibrous atrium, not included and with decreased contractile capacity[23] (Figure 12). However, in the latest guidelines by the American Society of Echocardiography and the European Association of Cardiovascular Imaging for diastolic evaluation[24] and the quantification of chamber function and size, the estimation of atrial strain has not been included.

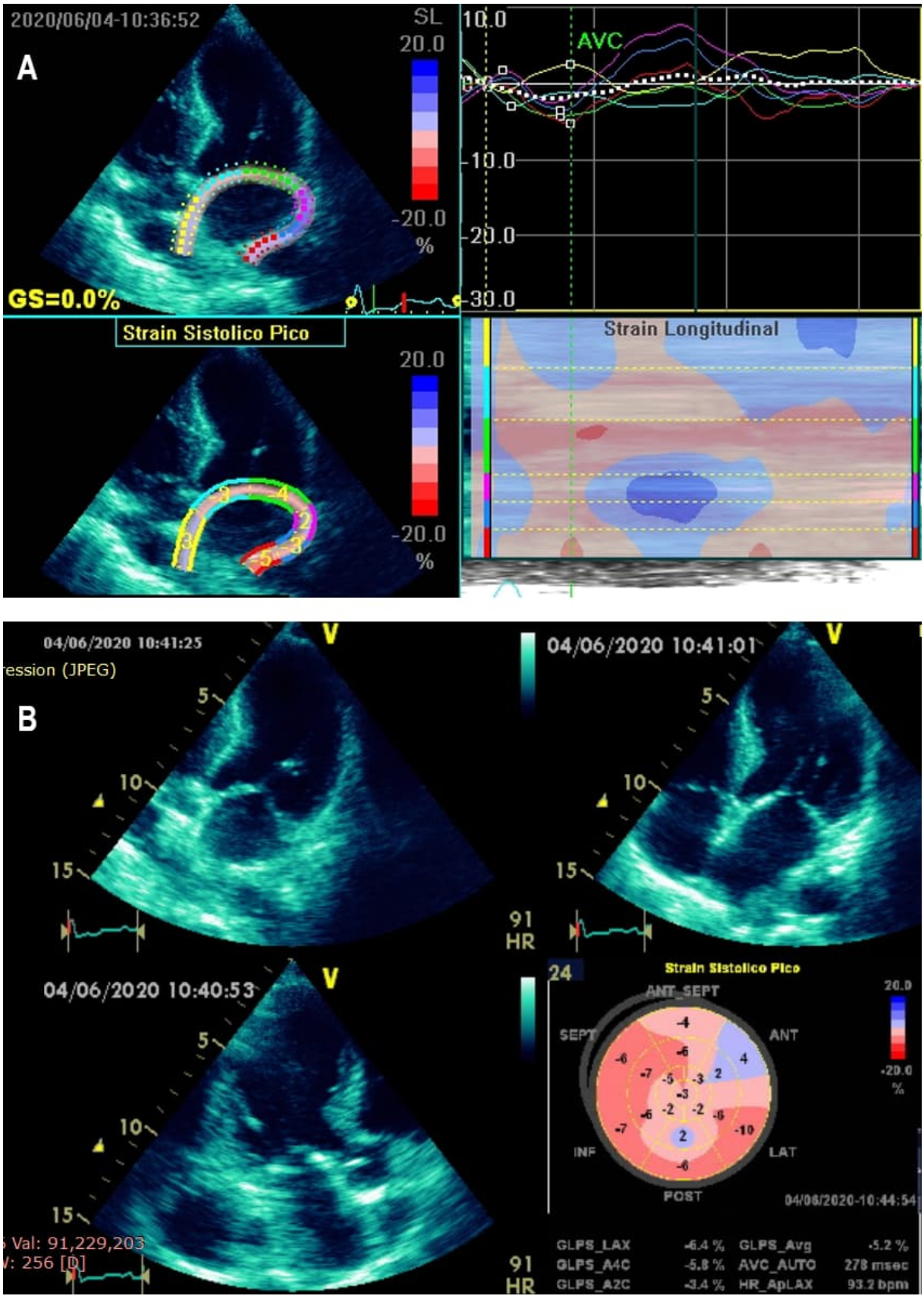

Figure 12. A) Strain of left atrium (LA). Severe contractile deficit that predicts short-term atrial fibrillation (AF) in a patient with acute myocardial infarction and severe decrease in left

ventricular systolic function. B) Longitudinal global strain of left ventricle in the same patient. Ejection Fraction by Simpson: 28%.

References

1. Zoni-Berisso M, Lercari F, Carazza T, *et al.* Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol. 2014;6:213-220.

2. Chen LY, Sotoodehnia N, Buzkova P, *et al.* Atrial fibrillation and the risk of sudden cardiac death: the atherosclerosis risk in communities study and cardiovascular health study. JAMA Intern Med. 2013;173:29-35.

3. Kannel WB, Wolf PA, Benjamin EJ, *et al.* Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol. 1998;82:2N-9N.

4. Wang TJ, Larson MG, Levy D, *et al.* Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation. 2003;107:2920-2925.

5. van Veen AA, van Rijen HV, Opthof T. Cardiac gap junction channels: modulation of expression and channel properties. Cardiovasc Res. 2001;51:217-229.

6. van der Velden HM, Jongsma HJ. Cardiac gap junctions and connexins: their role in atrial fibrillation and potential as therapeutic targets. Cardiovasc Res. 2002;54:270-279.

7. Morris JJ, Jr., Estes EH, Jr., Whalen RE, *et al.* P-Wave Analysis in Valvular Heart Disease. Circulation. 1964;29:242-252.

8. Macruz R, Perloff JK, Case RB. A method for the electrocardiographic recognition of atrial enlargement. Circulation. 1958;17:882-889.

9. de CA, de AD. Spread of activity through the atrioventricular node. Circ Res. 1960;8:801-809.

10. Schumacher K, Buttner P, Dagres N, *et al.* Association between PR interval prolongation and electro-anatomical substrate in patients with atrial fibrillation. PLoS One. 2018;13:e0206933.

11. Cheng S, Keyes MJ, Larson MG, *et al.* Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. JAMA. 2009;301:2571-2577.

12. Soliman EZ, Prineas RJ, Case LD, *et al.* Ethnic distribution of ECG predictors of atrial fibrillation and its impact on understanding the ethnic distribution of ischemic stroke in the Atherosclerosis Risk in Communities (ARIC) study. Stroke. 2009;40:1204-1211.

13. Magnani JW, Wang N, Nelson KP, *et al.* Electrocardiographic PR interval and adverse outcomes in older adults: the Health, Aging, and Body Composition study. Circ Arrhythm Electrophysiol. 2013;6:84-90.

14. Aro AL, Anttonen O, Kerola T, *et al.* Prognostic significance of prolonged PR interval in the general population. Eur Heart J. 2014;35:123-129.

15. Nielsen JB, Pietersen A, Graff C, *et al.* Risk of atrial fibrillation as a function of the electrocardiographic PR interval: results from the Copenhagen ECG Study. Heart Rhythm. 2013;10:1249-1256.

16. Alonso A, Krijthe BP, Aspelund T, *et al.* Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. J Am Heart Assoc. 2013;2:e000102.

17. Schnabel RB, Aspelund T, Li G, *et al.* Validation of an atrial fibrillation risk algorithm in whites and African Americans. Arch Intern Med. 2010;170:1909-1917.

18. Chamberlain AM, Agarwal SK, Folsom AR, *et al.* A clinical risk score for atrial fibrillation in a biracial prospective cohort (from the Atherosclerosis Risk in Communities [ARIC] study). Am J Cardiol. 2011;107:85-91.

19. Gouaux JL, Ashman R. Auricular fibrillation with aberration simulating ventricular paroxysmal tachycardia. Am Heart J. 1947;34:366-373.

20. January CT, Samuel Wann L, Calkins H., et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial

Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation. 2019;140:e125–e151

21. Omran H, Jung W, Rabahieh R, *et al.* Imaging of thrombi and assessment of left atrial appendage function: a prospective study comparing transthoracic and transoesophageal echocardiography. Heart. 1999;81:192-198.

22. Cooper JM, Epstein LM. Use of intracardiac echocardiography to guide ablation of atrial fibrillation. Circulation. 2001;104:3010-3013.

23. Olsen F, Bertelsen L, de Knegt M, Christensen T, Vejlstrup N, Svendsen J, et al. Multimodality cardiac imaging for the assessment of left atrial function and the association with atrial arrhythmias. Circ Cardiovasc Imaging. 2016; 9(10):1-17.

24. Badano L, Kolias T, Muraru D, Abraham T, Aurigemma G, Edvardsen T, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging. 2018; 19(6):591-600.