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Von Willebrand factor is associated with atrial fibrillation development in ischaemic patients after cardiac surgery

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Aims Atrial fibrillation (AF) is associated with an increased morbidity and mortality after cardiac surgery. Von Willebrand factor (vWF) has been proposed as a biomarker of endothelial damage/dysfunction. We hypothesized that vWF levels could be used as valuable biomarker for AF occurrence after cardiac surgery. Moreover, we explored the potential association between vWF and tissue remodelling as possible implication in post-surgical AF.

Methods and results We prospectively recruited 100 consecutive patients who undergoing programmed cardiac surgery with cardiopulmonary bypass and with no previous history of AF. Plasma vWF levels were determined from citrated plasma samples. Right atrial appendage tissue was obtained during cardiac surgery, and vWF expression as well as interstitial fibrosis was analysed by immunostaining and Masson's trichrome, respectively. We found raised vWF plasma levels in ischaemic vs. valvular patients (200.2 $\pm$ 66.3 vs. 157.2 $\pm$ 84.3 IU/dL; $P = 0.015$). Fibrosis degree was associated with plasma vWF levels. Plasma vWF was an independent prognostic marker for AF development in ischaemic patients [odds ratio, OR 6.44 (95% confidence interval, CI 1.40–36.57), $P = 0.035$].

Conclusion Plasma vWF levels are associated with tissue fibrosis in patients undergoing cardiac surgery and with post-surgical AF development in ischaemic patients. These findings suggest an association among vWF levels, atrial remodelling, and AF development. It is supported by higher vWF expression in right atrial tissue in ischaemic patients, who developed post-surgical AF.

Keywords Atrial fibrillation • Coronary artery bypass grafts • CABG • Aortic valve replacement • Endothelium • Fibrosis

Introduction

Atrial fibrillation (AF) is associated with an increased morbidity and mortality after cardiac surgery and a higher hospital length of stay.[1] Changes in atrial function and structure are known as atrial remodelling and participate in its development.[2] It has been hypothesized that remodelling in the atria tissue as a result of hypertension, diabetes, or ischaemic heart disease can lead to AF.[3] Moreover, there are emerging data supporting a significant association between fibrosis, inflammation, oxidative stress and the development, and recurrence and perpetuation of AF.[4]

Atrial fibrillation after cardiac surgery occurs in ~20–50% of patients undergoing cardiac surgery.[5] Numerous predisposing factors such as advanced age, hypertension, diabetes, left atrial enlargement, left ventricular hypertrophy, or intra-operative and post-operative factors such as atrial injury or ischaemia have been associated with the development of post-operative AF.[6] There is also an association with an inflammatory state, as well as the presence of cardiac fibrosis, oxidative stress, and myocyte apoptosis.[7,8]

Von Willebrand factor (vWF) is a well-established index of endothelial damage/dysfunction,[9] and it has been previously found increased in AF patients.[10] Increased plasma levels have been found

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What's new?

- We found raised von Willebrand factor (vWF) plasma levels in ischaemic vs. valvular patients, all of them undergoing cardiac surgery.
- Fibrosis degree in right atrial tissue was associated with plasma vWF levels.
- We propose plasma vWF as an independent prognostic marker for atrial fibrillation (AF) development in ischaemic patients, since an association among vWF levels, atrial remodelling, and AF development has been found.

in inflammatory and atherosclerotic vascular diseases in which the endothelium is likely to be damaged.[11] In a previous study of our group, we found that high plasma vWF levels were an independent risk factor for adverse events in anticoagulated permanent AF patients.[12] We hypothesized that atrial remodelling is a pre-existing process in patients developing AF after cardiac surgery. In these patients, surgery acts as a trigger that accelerates AF appearance in preconditioned patients. Von Willebrand factor levels could be raised in these patients due to atrial remodelling and can be used as a valuable biomarker of AF occurrence after cardiac surgery. We also studied whether vWF is associated with myocardial tissue fibrosis and the possible implication of this endothelial marker when evaluated within the tissue in the AF pathophysiology. We tested this hypothesis in a consecutive cohort of patients undergoing cardiac surgery.

Methods

We prospectively recruited consecutive patients admitted to the Cardiovascular Surgery Department, from November 2010 until February 2012, undergoing programmed cardiac surgery with cardiopulmonary bypass. We excluded patients with previous AF (paroxysmal or permanent), with unstable angina, hepatic or renal failure (creatinine clearance <50 mL/min), and chronic inflammatory or neoplastic diseases. Patients undergoing urgent surgery, those with previous history of pacemakers and infectious endocarditis, and those undergoing AF-related surgery were also excluded.

We documented AF during the post-operative period in the intensive care unit by continuous 3-derivation telemetry and by a Holter device once the patient was in the hospitalization cardiac surgery unit. Holter monitoring was extended until a maximum of 10 days after surgery. In addition, a 12-derivation electrocardiogram was performed in symptomatic patients and daily during the hospitalization. Atrial fibrillation development was defined as an episode of AF lasting for >2 min in any of ECG registry.

All echocardiographic measurements were performed off-line by the same accredited cardiologist who was unaware of clinical and laboratory data.[13] Left atrial volume was calculated according to the ellipsoid model that assumes that the left atrium can be adequately represented as a prolate ellipsoid with a volume of 4p/3(L/2)(D1/2)(D2/2), where L is the long-axis (ellipsoid) and D1 and D2 are orthogonal short-axis dimensions.[14] Left atrial volume calculations were indexed to body surface area calculated according to Gehan and George.[15]

The study was carried out according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee in our hospital. All the included patients gave informed consent to participation.

Blood samples and laboratory assays

Venipuncture was performed the morning of cardiac surgery with the patient fasting for >12 h. We collected samples immediately before cardiac surgery. Plasma fractions were obtained by centrifugation for 15 min at 3500 *g*. Aliquots were stored at -40°C to allow batch analysis in a blinded fashion.

Plasma vWF levels were determined in an automated coagulometer ACL Top 3 G, HemosIL von Willebrand factor (Instrumentation Laboratory, Lexington, MA, USA). The inter-assay and intra-assay coefficients of variation were 1.4 and 9%, respectively, and the lower limit of detection was 2.2 IU/dL.

Right atrial appendage tissue obtaining and staining

Atrial appendage tissue was obtained during surgery, when cannulation for the extracorporeal circulation. This cannulation was performed directly into the right atria with non-absorbable suture in a 'tobacco bag' shape. To provide adequate cannula apposition, the bag is opened and cut. The remaining appendage tissue is collected for the tissue study objectives.

All recruited subjects gave their informed consent to participate in the study. All surgical procedures were performed under cardiopulmonary bypass, with mild hypothermia (30°C), cardioplegic arrest of the heart, and left ventricular (LV) venting through the right superior pulmonary vein. We used anterograde and retrograde cold intermittent blood cardioplegia (Cardi-Braun®; B-Braun, Inc., Barcelona, Spain) for myocardial protection.

The tissue samples were processed, paraffin embedded, and cut at 2–3 μm sections. For histochemical evaluation of connective tissue infiltration within myocardial tissues, a Masson's trichrome staining was performed on sections from affected specimens by an automatized staining system (Dako Artisan, Dako, Carpinteria, CA, USA), following the manufacturer's recommendations. The degree of connective tissue infiltration was measured by a qualitative scaling from 0 to 3 (0 negative, 1 mild, 2 medium, and 3 high infiltration) attending at the location within the tissue (perivascular or interstitial fibrosis). All assessments were blinded and performed twice to ensure the repeatability of the results. The analysis was made by using an Axio Scope A1 transmitted-light microscope (Carl Zeiss, Jena, Germany).

We also evaluated vWF immunostaining in the right atrial appendage tissue according to previous studies.[7] Polyclonal antibody ref. IR727 (without further dilution) from Dako (Glostrup, Denmark) was used for von Willebrand Factor. Three-micrometre sections of paraffin-embedded tissue samples were stained in a Dako Autostainer Link 48 using the Dako EnVision Flex kit. Diaminobenzidine was used as chromogen. Immunostainings used for comparative purposes were processed simultaneously. Immunostaining intensity was graded by evaluating endocardium immunoreaction (Grade 0, no staining; Grade 1, weak focal staining; Grade 2, multifocal staining; and Grade 3, diffuse strong staining). When a dichotomical variable was used, Grade 3 was assumed as high vWF staining vs. Grade 0–2.

Statistical analysis

Categorical variables are presented as counts (percentages), while continuous variable are presented as mean ± SD (standard deviation) or median (25th–75th percentiles), as appropriate. Kolmogorov–Smirnov test was used to check for normal distribution of continuous data.

Logistic regression analyses were performed to assess the association between AF development and different explored variables. The 75th percentile was considered as cut-off value (fourth quartile). This dichotomy for vWF levels was assessed into the logistic regression model to explore the overall predictive value of high vWF upon the AF development. Only those variables showing values with $P < 0.15$ in the univariate analysis were incorporated into the multivariate model.

Logistic regression analyses were performed to evaluate the association between vWF plasma level and atrial appendage fibrosis in tissues obtained by myectomy. We considered intensive fibrosis when the degree of connective tissue infiltration was 2 or 3 with Masson's trichrome stain. Chi-square test was performed for evaluation of vWF immunostaining in tissues depending on the patient type. Logistic regression analyses were performed to explore potential associations. Lineal regression analysis was carried out for the study of the association value of high vWF immunostaining degree. All *P*-values <0.05 were accepted as statistically significant. Statistical analysis was performed using SPSS 19.0 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

We included 100 patients undergoing cardiac surgery, 58 of them for CABG and 42 for aortic valve replacement. Seventy-seven patients were male, 47 presented diabetes mellitus, 70 patients had hypertension, and 65 had hypercholesterolaemia. After cardiac surgery, 20 patients developed AF. *Table 1* summarizes clinical and demographical variables in ischaemic and valvular cohorts.

Predictive value of plasma von Willebrand factor

We found higher levels of plasma vWF in CABG patients vs. valvular patients (200.2 ± 66.3 vs. 157.2 ± 84.3 IU/dL; $P = 0.015$). Von Willebrand factor levels were not predictive for AF development neither considering the whole cohort ($P = 0.264$), nor considering ischaemic ($P = 0.220$) and valvular ($P = 0.304$) patients separately. Only male sex showed significant association ($P = 0.002$) with AF (data not shown). Twelve of the 42 valvular patients (28.6%) developed AF, whereas 8 of the 58 ischaemic patients (13.8%) presented post-surgical AF. Importantly, an association of the patient type with AF development was found ($P = 0.034$). Thus, we decided to investigate the prognosis in the two cohorts separately.

We evaluated the association of different demographic, clinical, pharmacological, and perioperative variables with AF appearance (*Table 2*). We observed that vWF values above the 4th quartile (percentile 75th) were predictive of AF [odds ratio, OR 6.67 (95% confidence interval, CI 1.78–37.78), $P = 0.032$] in ischaemic patients. The same analysis was performed for the entire cohort and for valvular patients, and a lack of association was observed in both cases ($P = 0.271$ and 0.911, respectively). In a multivariate model adjusted by clinical and demographical data ($P < 0.15$ in univariate analysis), only vWF levels remained as independent predictor for AF [OR 6.442 (95% CI 1.40–36.57), $P = 0.035$] (*Table 2*). Valvular patients showed no significant association between vWF and AF development (data not shown).

Plasma von Willebrand factor is associated with right appendage fibrosis

When evaluating atrial appendage perivascular fibrosis by Masson's trichrome as indicated, 7 tissue samples showed low fibrosis (connective tissue infiltration Grade 1), 47 showed medium fibrosis (connective tissue infiltration Grade 2), and 37 showed high fibrosis (connective tissue infiltration Grade 3). Nine samples were not evaluable due to different technical reasons. Similarly, for interstitial fibrosis, 5 samples showed low fibrosis, 37 medium fibrosis, and 50

Table 1 Baseline characteristics of included patients ($n = 100$)

Clinical or demographic variable	Ischaemic ($N = 58$) [%, mean ± SD or median (IQR)]	Valvular ($N = 42$) [%, mean ± SD or median (IQR)]	*P*
Age (years)	63.0 ± 9.8	68.1 ± 8.5	0.008
Male	89.7	59.5	0.001
Smoking habit	29.3	14.3	0.095
Hypertension	72.4	66.7	0.659
Hypercholesterolaemia	70.7	57.1	0.161
Diabetes mellitus	48.3	45.2	0.840
DM insulin dependent	17.2	4.8	0.068
DM under oral treatment	37.9	38.1	0.987
Previous stroke	12.1	4.8	0.208
NYHA (I, II, III, IV)	29, 24, 5, 0	4, 26, 12, 0	<0.001
Left atrial diameter (mm)	40.00 ± 5.80	41.59 ± 5.71	0.225
Indexed left atrial volume (mL/m^2)	27.10 ± 8.61	26.95 ± 8.92	0.321
Cardiopulmonary bypass pump time (min)	97.34 ± 31.23	80.74 ± 21.85	0.002
Total hospitalization time (days)	9 (7–11)	14 (9–21)	0.088

I, Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs, etc; II, Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity; III, Marked limitation in activity due to symptoms, even during less than ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest; IV, Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.
NYHA, New York Heart association functional class.

Table 2 Logistic regression (conditional mode) for the prediction of AF occurrence in ischaemic patients undergoing cardiac surgery

Variable	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
Age	1.05	0.96–1.14	0.278			
Gender	3.83	0.57–25.60	0.165			
Diabetes mellitus	3.38	0.70–20.79	0.121	2.98	0.38–23.35	0.244
Hypercholesterolaemia	3.29	0.37–29.58	0.283			
Hypertension	3.00	0.94–26.56	0.323			
Ejection fraction	0.97	0.91–1.02	0.226			
TEC	1.01	0.98–1.03	0.692			
Clamping time	0.97	0.94–1.01	0.131	0.98	0.93–1.04	0.278
NAA	1.23	0.47–3.19	0.673			
NYHA	2.96	0.94–9.34	0.064	1.27	0.21–7.15	0.272
Previous stroke	1.05	0.11–10.06	0.968			
Previous treatment						
Aspirin	1.41	0.26–7.78	0.692			
Clopidogrel	2.50	0.54–11.65	0.243			
ARA II	1.06	0.18–5.94	0.951			
ACE inhibitor	2.72	0.58–12.70	0.263			
Statins	0.47	0.10–2.28	0.349			
Antiarrhythmic drugs	7.00	0.31–11.72	0.186			
vWF_{p75th}	6.67	1.18–37.78	0.032	6.44	1.4–36.57	0.035

vWF_{p75th}, plasma pre-operative vWF values above the fourth quartile; TEC, time of extracorporeal circulation; NYHA, New York Heart Association functional class; ARA II, angiotensin II receptor antagonists; ACE, angiotensin-converting enzyme inhibitor; NAA, number of affected arteries.

showed intensive interstitial fibrosis. Eight samples were not evaluable for interstitial fibrosis due to different technical reasons (*Figure 1A–D*).

We found an association between plasma vWF levels and high perivascular fibrosis [OR 1.01 95% CI (1.00–1.02), $P = 0.017$] or interstitial fibrosis [OR 1.01 (95% CI 1.00–1.03), $P = 0.042$] according to Masson's trichrome staining in the tissue (*Figure 2*).

Associative value of von Willebrand factor evaluated in atrial appendage tissue

Twenty-one patients showed Grade 1 staining, 25 Grade 2, 30 Grade 3, and 11 Grade 4 (*Figure 1E–H*). In addition, 11 tissue samples were not evaluable due to different technical reasons. We found a positive association between high vWF immunostaining and the type of patient. We found higher vWF immunostaining in ischaemic patients ($P = 0.039$).

When studying the prognostic value of vWF immunostaining, a significant association was obtained for vWF and the patient type as shown for plasma vWF ($P = 0.003$, *Figure 3*), indicating higher vWF immunostaining degree in tissue samples from ischaemic patients. We found no association with AF development for the whole population ($P = 0.177$). We found a clear association between the immunostaining degree and the patient type ($P = 0.001$); hence, we studied the prognosis in the two cohorts independently as performed for plasma vWF analysis.

In ischaemic patients, vWF immunostaining grade was at borderline significance, associated with AF development ($P = 0.053$). However we did not find any association in valvular patients ($P = 0.589$).

Discussion

We hereby describe increased vWF plasma levels in ischaemic patients comparing with valvular patients in our cohort of patients undergoing cardiac surgery. This vWF is independently associated with AF occurrence in our subgroup of ischaemic patients after the surgery. In our cohort, 20% of patients showed clinical AF during their hospitalization stay after coronary surgery, consistent with previous data indicating the occurrence in ~20–50%.[5]

In the present study, ischaemic patients are found to increase vWF, indicating a higher endothelial dysfunction comparing with valvular patients. This apparent difference in the pathophysiological origin of the arrhythmia is also supported by the association between the degree of interstitial or perivascular fibrosis in the right atrial appendage and vWF plasma levels, suggesting a higher remodelling process in the atrial appendage tissue previous to the surgical intervention. Unfortunately, we did not find significant association between tissue fibrosis and AF development. In addition, we detected some differences in cardiovascular risk factors and other clinical and demographical variables that may also affect the elevation of vWF. In a previous study, we observed that pre-surgical hsTnT levels, an indicator of subclinical ongoing myocyte damage,[16] were associated with AF development in patients undergoing

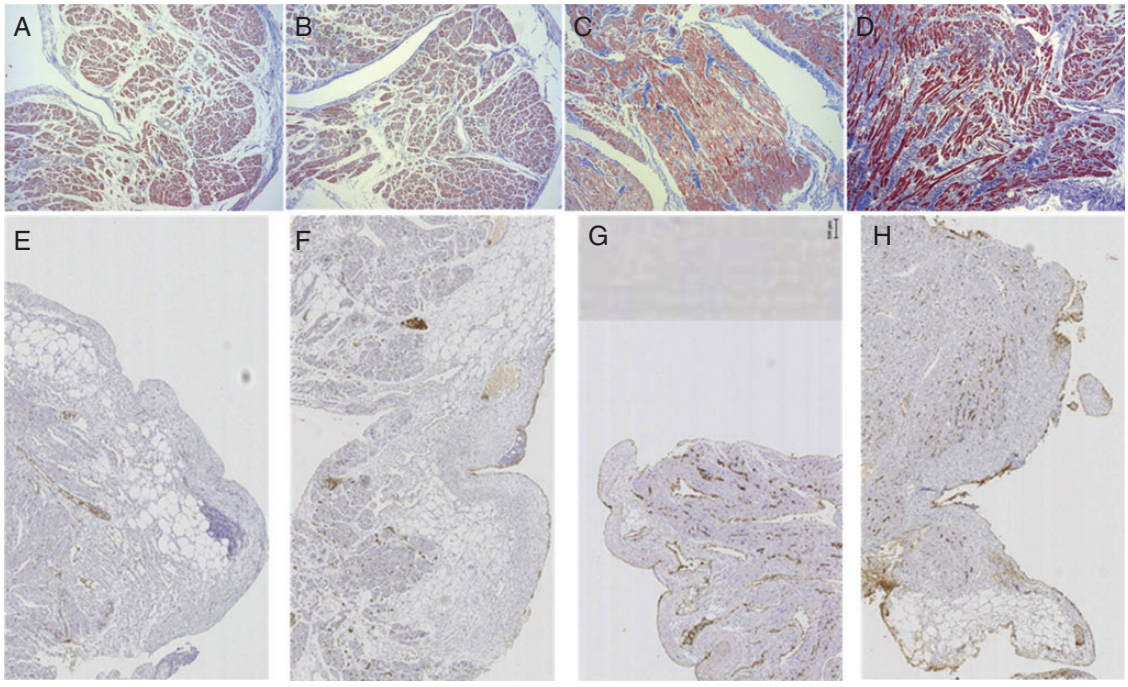

Figure 1 Classification of the myocardial fibrosis assessed by Masson's Trichrome staining infiltration grades: Grade 0 (*A*), 1 (*B*), 2 (*C*), and 3 (*D*). Von Willebrand factor classification by comparing endocardium and endothelial vessel in myocardium: Grade 1, only focal or little staining (*E*); Grade 2, diffuse, weaker staining (*F*); Grade 3, similar staining (*G*); and Grade 4, stronger staining (*H*). All micrographs at magnification ×100.

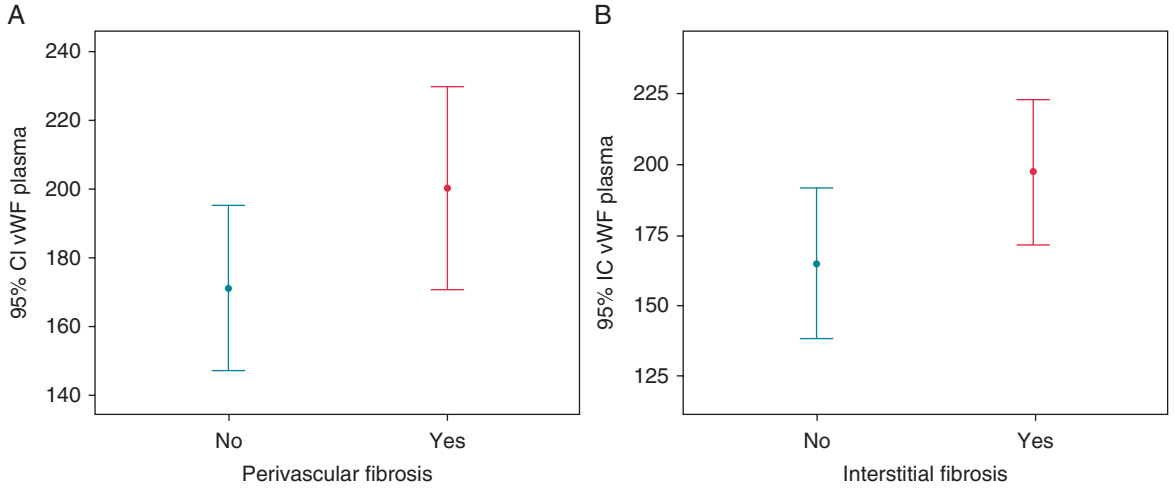

Figure 2 Association of the concentration of plasma vWF with perivascular (*A*; $P = 0.017$) or interstitial fibrosis (*B*; $P = 0.042$).

cardiac surgery. Indeed, structural remodelling has been proposed as the main arrhythmogenic substrate perpetuating AF.[17]

Furthermore, we evaluated endocardial vWF in the right atrial appendage, and we also found that vWF immunostaining was associated with the patient type, being higher in ischaemic patients, as observed for plasma vWF levels. This vWF immunostaining degree seems to be associated with for post-surgical AF development in ischaemic patients, but not in valvular patients. Similar results have been previously reported for non-valvular AF patients where increased endocardial expression of vWF was found in left atrial appendage.[16] In the same line, high vWF expression in the left atrial appendage has been described, especially in patients with an

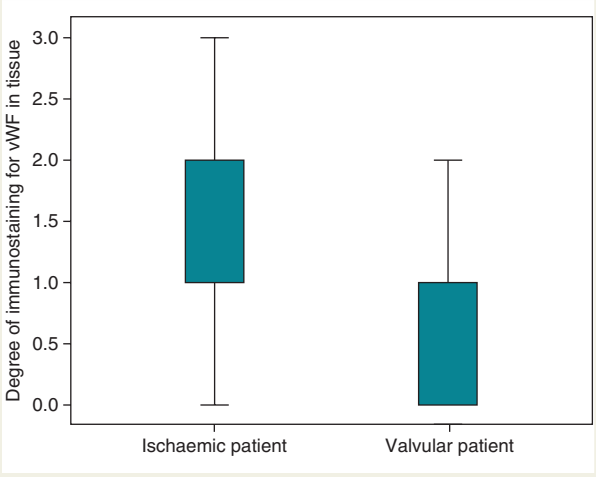

Figure 3 Association of the vWF immunostaining degree with the patient type (ischaemic vs. valvular patients, $P = 0.003$).

overloaded appendage that seems to correlate with the presence of adherent platelet thrombus.[18] In addition, left atrial appendage is the most common place of thrombosis in patients with AF,[19] and endothelial dysfunction has been reported to be involved in intracardial thrombosis development.[20] Hence, vWF expression in left atrial appendage can be biased in consequence. Our results, including vWF expression from right atrial appendage, suppose, to our knowledge, the biggest cohort of evaluated tissue samples. It is also the first study evaluating the utility of vWF in prognosis for post-surgical AF, as a model for the study of the involvement of the atrial remodelling process in AF development.

This study is limited by its observational design, and we could explore only associations and no causality is implied. The recruitment protocol did not guarantee the exclusion of patients with silent atrial fibrillation into the study. Although vWF level is an established marker for poor outcomes in cardiovascular diseases, we cannot ignore possible changes in vWF levels over time. Platelet contribution to vWF levels cannot be discarded; however, since all samples were processed in a similar manner for all patients minimizing platelet activation, we assumed that platelet activation due to sample management should be disregarded. In addition, the lack of association between antiplatelet treatment and AF development, or antiplatelet treatment and vWF levels (data not shown) indicated that platelet contribution may not be significant, in spite of that, whether or not platelet activation contributes to vWF and AF development is beyond the scope and aims of this study. Another limitation is based on the assumption that the observed features for atrial appendage are generalized for the entire atria. Finally, the size of our population is a potential limitation, since only a borderline signification could be reached when analysing vWF in the tissue of a sub-cohort of ischaemic patients.

Conclusion

As a conclusion, we can summarize that vWF levels are higher in ischaemic vs. valvular patients undergoing cardiac surgery. Plasma vWF levels are associated with tissue fibrosis and with post-surgical AF development in ischaemic patients, suggesting an implication of a previous remodelling process these patients. This involvement is supported by higher vWF expression in right atrial tissue in ischaemic patients developing post-surgical AF.

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Conflict of interest: none declared.

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Cystic tumour of the atrioventricular node: can an electrophysiological study predict sudden death?

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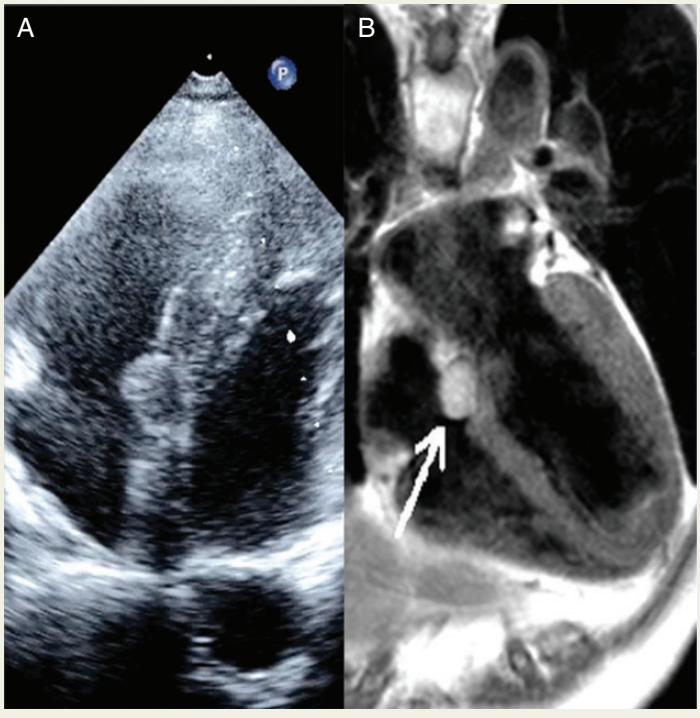

A 58-year-old woman presented with palpitation. A resting electrocardiogram revealed sinus rhythm and first-degree atrioventricular (AV) block. Transthoracic echocardiography showed a 15 mm × 17 mm round tumour in the lower interatrial septum (*Panel A*) that appeared as high signal intensity on T1-weighted magnetic resonance imaging (*Panel B*). We clinically diagnosed a cystic tumour of the AV node (CTAVN). An electrophysiology study (EPS) revealed that slight prolongation of the AV interval (275 ms) and effective refractory period of the AV node (330 ms) were observed, but both were normalized with atropine. Additionally, electrical stimulations from the right ventricular apex and right ventricular outflow tract induced neither sustained ventricular tachycardia nor ventricular fibrillation. The patient underwent surgical tumour resection. Pathological diagnosis was compatible with CTAVN. The patient was given a dual-chamber pacemaker post-operatively for persistent complete AV block.

Cystic tumour of the AV node is a rare congenital cardiac tumour with a predilection for women, and few cases diagnosed ante-mortem with successful excision have been reported. Cystic tumour of the AV node can cause various degrees of heart blockage and is considered the smallest tumour capable of causing sudden death, and surgical intervention is therefore indicated in all cases. To our knowledge, this is the first report of CTAVN in which an EPS was performed pre-operatively.

The full-length version of this report can be viewed at: http://www.escardio.org/Guidelines-&-Education/E-learning/Clinical-cases/Electrophysiology/EP-Case-Reports.