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ORIGINAL ARTICLE

Thromboembolic complications in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy

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Aims Incidence and clinical presentation of thromboembolic complications in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) were analysed. In reports on ARVD/C, thromboembolism is rarely mentioned. The possible risk factors are: right ventricle (RV) dilatation, aneurysms, and wall motion abnormalities.
Methods and results A group of 126 patients (89 male, 37 female, aged 43.6 $\pm$ 14.3) with ARVD/C was retrospectively analysed for the presence of thromboembolic complications. The mean follow-up period was 99 $\pm$ 64 months. Thromboembolic complications, i.e. pulmonary embolism ($n = 2$), RV outflow tract thrombosis with severe RV failure ($n = 1$), and cerebrovascular accident associated with atrial fibrillation ($n = 2$) were observed in 4% of the patients. Spontaneous echogenic contrast was observed in seven patients with severe damage to RV. In four of them supraventricular arrhythmias resulting in heart failure were reported. Annual incidence of thromboembolic complications was 0.5/100 patients.
Conclusions (i) ARVD/C may be complicated by thrombosis. Annual incidence of such complications is significantly lower than reported for left ventricle failure. (ii) Anticoagulation should be used in ARVD/C patients with large, hypokinetic RV and slow blood flow. (iii) Patients with severe forms of ARVD/C, thrombus formation in the RV and/or spontaneous echocardiographic contrast are at higher risk of a poor outcome.

Introduction

Patients with congestive heart failure are known to be at risk of thromboembolic complications, with an annual incidence of 1.9/100 patients. The risk seems to be even higher in severe cases of heart failure and in patients with presence of mural thrombi. Left ventricular thrombi are more frequently reported in patients with segmental wall motion abnormalities and slow flow through the left ventricle.[1,2]

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is a disease characterized by dilatation of the right ventricle (RV) and global or focal wall motion abnormalities, including aneurysms.[3] All these features are supposed to increase the risk of thrombus formation. However, the reports of right ventricular thrombosis in ARVD/C are surprisingly rare. The aim of our study was to analyse the incidence and clinical significance of thromboembolic complications in 126 patients with ARVD/C.

Patients

We analysed retrospectively the clinical outcome of 126 patients with ARVD/C. Diagnosis was based on ESC and ISFC criteria published in 1994.[4] The study group consisted of 89 men and 37 women; the mean age was 43.6 $\pm$ 14.3 years, ranging from 14 to 67 years. The mean follow-up period was 99 ($\pm$64) months, ranging from 2 to 240 months. Enlargement of RV and focal or/and global wall motion abnormalities were present in all patients. Severe dilatation of RV with global hypokinesis was seen in 25 patients. There were 16 patients with persistent and/or paroxysmal atrial fibrillation or flutter; all of them were treated with oral anticoagulants except for one patient, who was not aware of this arrhythmia [atrial fibrillation was revealed only after a cerebrovascular accident (CVA)].

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Methods

History, 2D-echocardiography (Echo), as well as spin and gradient echo MRI were carefully analysed in all patients. Chest X-ray was performed in patients with suspicion of pulmonary embolism. Complete transthoracic echocardiography was performed in every patient. Cross-sectional measurements of the right ventricular outflow and inflow tract were performed. The global and focal wall motion abnormalities, diastolic bulging, and changes in the morphology of right and left ventricle myocardium were carefully sought. Pulse tissue Doppler techniques were used for flow assessments.

Results

Thromboembolic complications were observed in five patients (4%), with annual incidence of 0.5/100 patients. Two of them developed pulmonary embolism. One patient, with evidence of thrombus in the right ventricular outflow tract, presented symptoms of severe right ventricular failure. Two patients with atrial fibrillation had CVAs. In seven patients with severe damage to the RV, spontaneous echogenic contrast was recorded (*Figure 1*). In five of them, atrial fibrillation or atrial tachycardia with atrioventricular block appeared, resulting in a serious heart failure.

Case 1

A 25-year-old man with ARVD/C was admitted in 1987 because of recurrent non-sustained ventricular tachycardia of left bundle branch block (LBBB) morphology resistant to antiarrhythmic drugs and multiple episodes of sinus bradycardia with syncope. Coronary angiography performed 2 years earlier was normal. Diagnosis of ARVD/C was established with non-invasive tests. The 12-lead ECG showed sinus bradycardia, QRS prolongation to 140 ms, epsilon wave in V1 and inverted T waves in leads V1–V5. The 2D-Echo revealed enlargement of the RV, global hypokinesis (ejection fraction evaluated by radionuclide angiography was 28%), significant tricuspid regurgitation, and dyskinetic apex with the evidence of mobile pedunculated thrombus (*Figure 2A*).

Urgent surgery, including right ventriculotomy, tricuspid valve replacement, and pacemaker implantation was performed. No clot was found during the operation; however, in the early post-operative period, there was clinical and radiological evidence of pulmonary embolism (*Figure 2B*). Oral anticoagulation was introduced because of both tricuspid valve replacement and thromboembolic complications. In 7 years of follow-up, thrombus formation was not observed. The patient died in 1994 of intracranial haemorrhage after thrombolytic therapy that was given because of tricuspid artificial valve thrombosis.

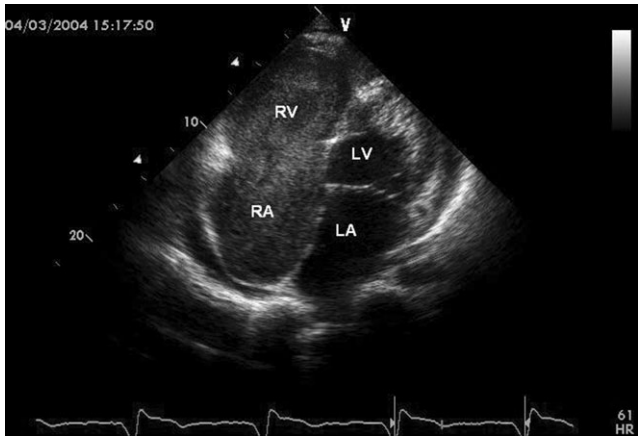

Figure 1 Spontaneous echogenic contrast in the patient with severe damage to the RV.

Case 2

A 47-year-old man was admitted to our hospital in 1984 because of chest pain and ventricular arrhythmias, namely: single premature beats, couplets, and episodes of non-sustained ventricular tachycardia. Echocardiography, ventriculography, and endomyocardial biopsy were typical for ARVD/C. Coronary angiogram was normal and the arrhythmia was effectively suppressed by amiodarone. No symptoms of heart failure were observed. In July 1997, the patient was admitted to a district hospital because of sudden orthopnoea and right ventricular failure. Pulmonary infarction was found. The diagnosis was made on typical chest X-ray signs. There were no clinical symptoms of venous thrombosis. Owing to poor general condition, he was given heparin i.v. which resulted in substantial improvement, thus further diagnostic procedures were abandoned. Serial echocardiographic follow-up did not reveal any intracardiac thrombus; nevertheless, oral anticoagulation was initiated. Echocardiography performed in 2004 did not show any new feature.

Case 3

A 45-year-old man was referred to our hospital in 1995 because of several episodes of syncope and non-sustained ventricular tachycardia of LBBB pattern. Left ventriculography and coronary angiography performed in a regional centre were normal. Non-invasive tests were typical for a severe form of ARVD/C: sinus rhythm with right bundle branch block morphology, QRS duration 150 ms in lead V1 and multiple late potentials were recorded on ECG. Severe dilatation of RV and global hypokinesis were detected on Echo and MRI. RV diastolic dimension measured on Echo was 6.5 cm and the radionuclide ejection fraction was 10%. Ventricular tachycardia was suppressed by amiodarone.

The same patient was re-admitted in August 1996 because of dyspnoea and fatigue. The 2D-Echo and MRI revealed a severely hypokinetic, enlarged RV with mural thrombus in the right ventricular outflow tract. (*Figure 3A*).The patient was treated for 6 weeks with heparin i.v. and oral anticoagulants. Echocardiography performed at 2 weeks showed significant decrease in thrombus dimensions (*Figure 3B*). The patient was discharged with the recommendation to continue oral anticoagulation. In the serial follow-up, no evidence of thrombus enlargement was recorded up to 2002. Finally, the patient died because of heart failure. He was disqualified for heart transplantation because of severe complications after brain surgery.

Discussion

There are very few reports available on thromboembolic complications in patients with ARVD/C (*Table 1*). Most of them describe atrial thrombi in patients with extensive

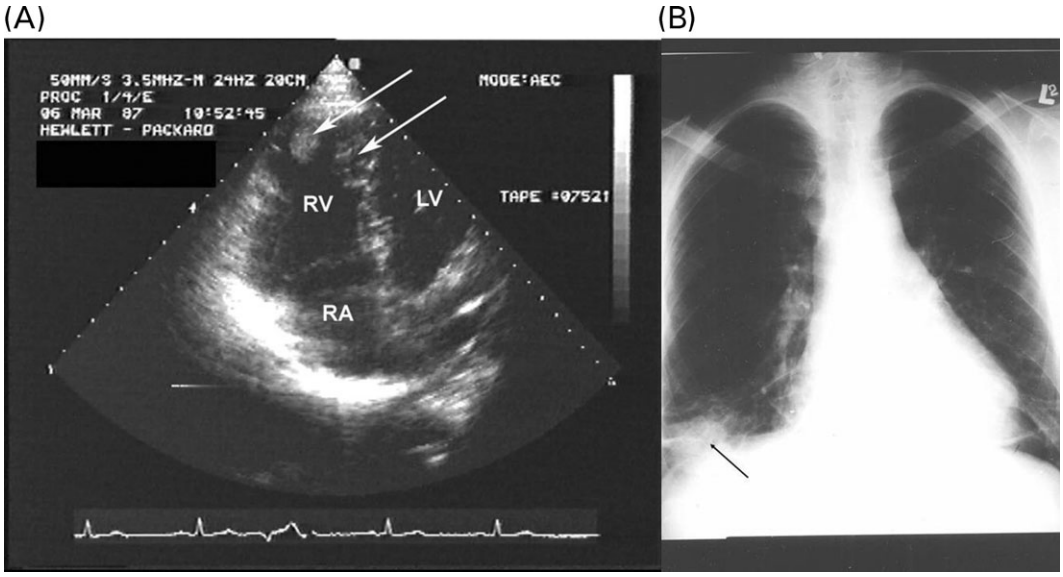

Figure 2 Case 1. (*A*) Echocardiographic display of a mobile thrombus in the apex of the RV. (*B*) Chest X-ray performed on the third day after urgent surgery showed evidence of pulmonary embolism.

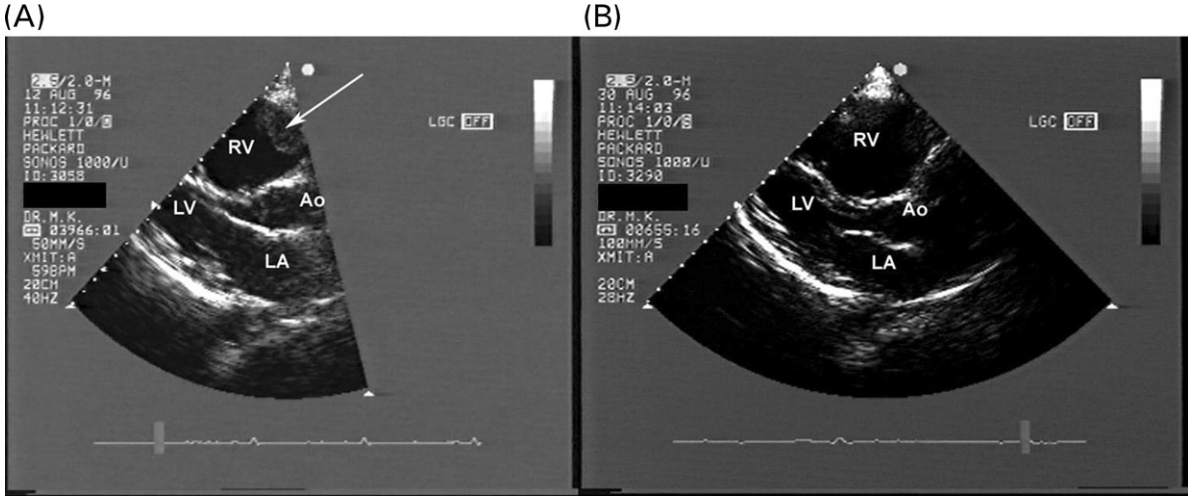

Figure 3 Case 3. (*A*) Echocardiographic evidence of a thrombus in the RV. 12 August 1996. (*B*) Thrombus dimensions significantly decreased. 30 August 1996.

form of the disease and with concomitant atrial fibrillation.[4,8–10] We did not observe in our group any case of thrombus formation within the atria. However, two of our patients with persistent atrial fibrillation had CVAs. Patients with blood stasis were anticoagulated that probably explains why no thromboembolic complications were observed in this group, though two patients died and one underwent heart transplantation because of progressive heart failure.

Our results show that the frequency of thromboembolic complications in ARVD/C is significantly lower than in patients with left ventricle failure. Similar results were found in another study, with only one mural thrombus in 42 hearts diagnosed as having ARVD/C by morbid anatomical examination.[14] Despite this low incidence, thromboembolic complications should not be neglected, because their clinical presentation is usually very serious: three patients from our study group had severe pulmonary embolism with serious outcomes or severe heart failure symptoms because of the obstruction of the right ventricular outflow tract. In the literature, we found a case of lethal pulmonary thromboembolism as the first symptom of the disease.[9] One report describes extensive thrombus formation in the RV in a patient with ARVD/C and prothrombin gene mutation G20210A, associated with high plasma levels of prothrombin and increased risk of venous thrombosis.[6] In this case, thrombus formation was resistant to heparin and oral anticoagulation that resulted in its partial calcification. After successful heart transplantation, thromboembolic complications did not recur, confirming the significant role of acquired disturbances connected with congestion in the pathogenesis of thrombosis.

We agree with other authors that severe dilatation of the RV and significant wall motion abnormalities may lead to the process of thrombosis in the RV. It is worth mentioning that formation of thrombi in right ventricular aneurysms in

Table 1 Thromboembolic complications in patients with ARVD/C

Authors	Characteristic of patients	Heart rhythm	Thromboembolic findings in RV	Other thromboembolic complications	Additional features
Lui *et al.*[4]	A woman with peripartum ARVD/C	AF	—	Embolic stroke	Advanced atrio-ventricular block
Goldberg[5]	A patient with ARVD/C	SR	Thrombus	—	—
Attenhofer Jost *et al.*[6]	A 36-year-old woman with inherited coagulopathy and ARVD/C, developing end-stage biventricular heart failure	SR	A large (4 cm), partially calcified thrombus in dilated (9 cm), akinetic RV with extensive fibro-fatty tissue replacement. Thrombus appeared despite oral anti-coagulation and was resistant to combined treatment with heparin and aspirin.	(1) Thrombosis of right subclavian vein, right internal jugular vein and right axillary vein (2) Thrombus in LV found one month earlier and successfully treated with oral anticoagulation; (3) One episode of TIA after ICD implantation	This type of coagulo-pathy (prothrombin gene mutation) is associated with increased risk of deep vein thrombosis; after OHT, there were no episodes of thrombosis (due to normal systolic function)
Antonini-Canterin *et al.*[7]	A patient with ARVD/C	SR	Thrombus in a single apical aneurysm	—	Normal systolic function of RV
Bilge *et al.*[8]	A patient with ARVD/C	SR	—	Thrombus in right atrium	Blood stasis due to systolic dysfunction of RV
Kazimierczak *et al.*[9]	A patient with ARVD/C and atrial epicardial pacing with long stimulus to P wave interval	AAI	—	Two thrombi in right atrium	Leftward displacement of RV and sympto-matic bradycardia after treatment with sotalol
Kesoi *et al.*[10]	A patient with ARVD/C	SR	Thrombus	Multiple thrombi in right atrium	Thrombi formation concomitant with progressive heart failure
Schionning *et al.*[11]	A 57-year-old woman with ARVD/C (ident-ified by autopsy)	—	—	Pulmonary thromboembolism	No suspection of ARVD/C prior to sudden death
Basso *et al.*[12]			Mural thrombosis only in patients with biventricular heart failure	One case of cerebral thromboembolism	Constant presence of inflammatory infiltrates in biopsy
Calvo *et al.*[13]	A patient with ARVD/C		Huge thrombus occurring twice in the same patient (once despite oral anticoagulation)	—	Both times thrombus was resolved with standard heparin
Corrado *et al.*[14]	A patient with ARVD/C (identified by autopsy)		Thrombus	—	—

AAI, atrial stimulation; AF, atrial flutter; ICD, implantable cardioverter-defibrillator; LV, left ventricle; SR, sinus rhythm; TIA, transient ischaemic attack.

patients without global right ventricular dysfunction seems to be extremely rare: we found one case in the literature and none in our group of 126 patients.[7]

Conclusions

(1) ARVD/C may be complicated by thrombosis in the RV.
(2) Anticoagulant treatment should be considered in ARVD/C patients with large hypokinetic RV and slow blood flow within the RV on echocardiography.
(3) Patients with severe form of ARVD/C, thrombus formation in the RV and/or spontaneous echocardiographic contrast are at higher risk of a poor outcome.

References

1. Baker DW, Wright RF. Management of heart failure IV. Anticoagulation for patients with heart failure due to left ventricular systolic dysfunction. *JAMA* 1994;**272**:1614–8.
2. Cohn JN, Benedict CR, LeJemtel TH, Grover J, Shindler DM, Shelton B. Risk of thromboembolism in left ventricular dysfunction: SOLVD. *Circulation* 1992;**86**(Suppl. I): I-252.
3. McKenna WJ, Thiene G, Nava A, Fontaliran F, Blomström-Lundqvist C, Fontaine G *et al*. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Br Heart J* 1994;**71**:215–8.
4. Lui CY, Marcus FI, Sobonya RE. Arrhythmogenic right ventricular dysplasia masquerading as peripartum cardiomyopathy with atrial flutter, advanced atrioventricular block and embolic stroke. *Cardiology* 2002;**97**:49–50.

5. Goldberg L. Right ventricular thrombosis in arrhythmogenic right ventricular dysplasia. *Cardiovasc J S Afr.* 2000;**11**:95–6.
6. Attenhoffer Jost CH, Bombeli T, Schrimpf C, Oechlin E, Kiowski W, Jenni R. Extensive thrombus formation in the right ventricle due to a rare combination of arrhythmogenic right ventricular cardiomyopathy and heterozygous prothrombin gene mutation G20210 A. *Cardiology* 2000;**93**:127–30.
7. Antonini-Canterin F, Sandrini R, Pavan D, Zardo F, Nicolosi GL. Right ventricular thrombosis in arrhythmogenic cardiomyopathy. A case report. *Ital Heart J* 2000;**1**:415–8.
8. Bilge M, Eryonucu B, Guler N. A case of arrhythmogenic right ventricular cardiomyopathy in sinus rhythm associated with thrombus in the right atrium. *J Am Soc Echocardiogr* 2000;**13**:154–6.
9. Kazmierczak J, Kornacewicz-Jach Z, Wojtarowicz A. Atrial epicardial pacing with long stimulus to P wave interval in a patient with arrhythmogenic right ventricular dysplasia complicated by right atrial thrombosis. *Pacing Clin Electrophysiol* 1999;**22**:1111–3.
10. Kesoi I, Gojak I, Enyezdi J, Deak G. Arrhythmogenic right ventricular cardiomyopathy associated with multiple right atrial thrombi. *Orv Hetil* 1997;**138**:3185–8.
11. Schionning JD, Frederiksen P, Kristensen IB. Arrhythmogenic right ventricular dysplasia as a cause of sudden death. *Am J Forensic Med Pathol* 1997;**18**:345–8.
12. Basso C, Thiene G, Corrado D, Angelini A, Nava A, Valente M. Arrhythmogenic right ventricular cardiomyopathy. Dysplasia, dystrophy, or myocarditis? *Circulation* 1996;**94**:983–91.
13. Calvo JR, Duran RM, Vazques de Prada JA. Resolution of relapsing thrombus by heparin therapy in right ventricular dysplasia. *Int J Cardiol* 1990;**26**:238–9.
14. Corrado D, Basso C, Thiene G, McKenna WJ, Davies MJ, Fontaliran F *et al*. Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multicenter study. *J Am Coll Cardiol* 1997;**30**:1512–20.