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The prevalence of left and right bundle branch block morphology ventricular tachycardia amongst patients with arrhythmogenic cardiomyopathy and sustained ventricular tachycardia: insights from the European Survey on Arrhythmogenic Cardiomyopathy

Bernard Belhassen [1,2]*, Mikael Laredo [3], Rob W. Roudijk[4], Giovanni Peretto[5], Guy Zahavi[2,6], Srijita Sen-Chowdhry[7], Nicolas Badenco[3], Anneline S.J.M. Te Riele[4,8], Simone Sala [5], Guillaume Duthoit[3], J. Peter van Tintelen [4,9], Gabriele Paglino[5], Jean-Marc Sellal[10], Alessio Gasperetti [11], Elena Arbelo[12], Antoine Andorin[13], Sandro Ninni[14], Anne Rollin[15], Petr Peichl [16], Xavier Waintraub[3], Laurens P. Bosman[4,8], Bertrand Pierre[17], Eyal Nof [2,18], Chris Miles[19], Jacob Tfelt-Hansen[20,21], Alexandros Protonotarios[22,23], Carla Giustetto[24], Frederic Sacher[25], Jean-Sylvain Hermida[26], Stepan Havranek[27], Leonardo Calo[28], Ruben Casado-Arroyo[29], Giulio Conte [30], Konstantinos P. Letsas[31], Esther Zorio[32,33], Francisco J. Bermúdez-Jiménez[34], Elijah R. Behr[19], Roy Beinart [2,18], Laurent Fauchier [17,35], Josef Kautzner[16], Philippe Maury [15], Dominique Lacroix[14], Vincent Probst[13], Josep Brugada[36], Firat Duru [11], Christian de Chillou[10], Paolo Della Bella[5], Estelle Gandjbakhch[3], Richard Hauer [4,8], and Anat Milman [2,18]

[1]Heart Institute, Hadassah University Hospital, Kalman Ya'Akov Man Street, 9112001, Jerusalem, Israel; [2]Sackler School of Medicine, Tel Aviv University, P.O. Box 39040, Tel Aviv 6997801, Israel; [3]Sorbonne Université, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Institut de Cardiologie, 47-83 Boulevard de l'Hôpital, 75013 Paris, France; [4]Netherlands Heart Institute, Moreelsepark 1 3511 EP Utrecht, The Netherlands; [5]IRCCS San Raffaele Scientific Institute, Via Olgettina, 60, 20132 Milano, Italy; [6]Department of Anesthesiology, Sheba Medical Center, Tel Hashomer, 5265601, Israel; [7]Institute of Cardiovascular Science University College London, 62 Huntley St, London WC1E 6DD, UK; [8]Department of Cardiology, University Medical Center, 62 Huntley St, London WC1E 6DD, The Netherlands; [9]Department of Genetics, University Medical Center, Moreelsepark 1 3511 EP Utrecht, The Netherlands; [10]Département de Cardiologie, Centre Hospitalier Universitaire de Nancy, Vandœuvre lès-Nancy, Rue du Morvan, 54500 France; [11]Department of Cardiology, University Heart Center Zurich, Hottingerstrasse 14 CH-8032 Zürich, Switzerland; [12]Cardiovascular Institute, Hospital Clinic and IDIBAPS, Calle Villarroel, 170 08036 Barcelona, Catalonia, Spain; [13]Service de Cardiologie, CHU de Nantes, Bd Jacques Monod – 44800 Saint-Herblain, Nantes, France; [14]Université de Lille et Institut Cœur-Poumon, CHRU, Boulevard du Professeur Jules Leclercq, 59000 Lille, France; [15]Cardiology, University Hospital Rangueil, 1 Avenue du Professeur Jean Poulhès, 31400 Toulouse, France; [16]Department of Cardiology, Institute for Clinical and Experimental Medicine (IKEM), Vídeňská 1958, 140 21 Praha 4, Prague, Czech Republic; [17]Service de Cardiologie, Centre Hospitalier Universitaire Trousseau, 2 Boulevard Tonnellé, 37000 Tours, France; [18]Leviev Heart Institute, Sheba Medical Center, 5265601 Tel Hashomer, Israel; [19]Cardiovascular Sciences and Cardiology Clinical Academic Group St. George's University Hospitals NHS Foundation Trust, Cranmer Terrace London SW17 0RE, UK; [20]The Department of Cardiology, The Heart Centre, Copenhagen University Hospital, Rigshospitalet, Copenhagen 2100, Denmark; [21]Department of Forensic Medicine, Faculty of Medical Sciences, University of Copenhagen, Blegdamsvej 3B, 2200, Copenhagen, Denmark; [22]Nikos Protonotarios Medical Centre, Περιφερειακός, 843 00, Naxos, Greece; [23]UCL Institute of Cardiovascular Science, 62 Huntley St, London WC1E 6DD, UK; [24]Division of Cardiology, Department of Medical Sciences, University of Torino, Città della Salute e della Scienza Hospital, Corso Bramante, 88, 10126 Torino TO, Italy; [25]Hôpital Cardiologique du Haut-Lévêque & Université Bordeaux, LIRYC Institute, Avenue du Haut Lévêque, 33600 Pessac, Bordeaux, France; [26]Centre Hospitalier Universitaire d'Amiens-Picardie, 2 Place Victor Pauchet, 80080 Amiens, France; [27]Second Department of Medicine-Department of Cardiovascular Medicine, First Faculty of Medicine, Charles University and General University Hospital in Prague, Kateřinská 1660/32, 121 08 Nové Město, Prague, Czech Republic; [28]Division of Cardiology, Policlinico Casilino, Via Casilina, 1049, 00169 Roma RM, Italy; [29]Department of Cardiology, Erasme University Hospital, Université Libre de Bruxelles, Route de Lennik 808, 1070 Bruxelles, Belgium; [30]Electrophysiology Unit, Department of Cardiology, Fondazione Cardiocentro Ticino, Via Tesserete 48, 6900 Lugano, Switzerland; [31]Arrhythmia Unit, Second Department of Cardiology, "Evangelismos" General Hospital of Athens, Ipsilantou 45-47, Athina

*Corresponding author. Tel: +972 52 4 266 856; fax: +972 153 52 4266856. E-mail address: bblhass@gmail.com; bblhass@hadassah.org.il

106 76, Athens, Greece; [32]Cardiology Department at Hospital Universitario y Politecnico La Fe and Research Group on Inherited Heart Diseases, Sudden Death and Mechanisms of Disease (CaFaMuSMe) from the Instituto de Investigación Sanitaria (IIS) La Fe, Avenida Fernando Abril Martorell, Torre 106 A 7planta, Valencia, Spain; [33]Center for Biomedical Network Research on Cardiovascular Diseases (CIBERCV), Av. Monforte de Lemos, 3-5. Pabellón 11. Planta 0 28029, Madrid, Spain; [34]Cardiology Department, Hospital Universitario Virgen de las Nieves, Av. de las Fuerzas Armadas, 2, 18014 Granada, Spain; [35]Université François Rabelais, 60 rue du Plat D'Etain 37020 Tours cedex 1, France; and [36]Cardiovascular Institute, Hospital Clínic Pediatric Arrhythmia Unit, Hospital Sant Joan de Déu University of Barcelona, Passeig de Sant Joan de Déu, 2, 08950 Esplugues de Llobregat, Barcelona, Spain

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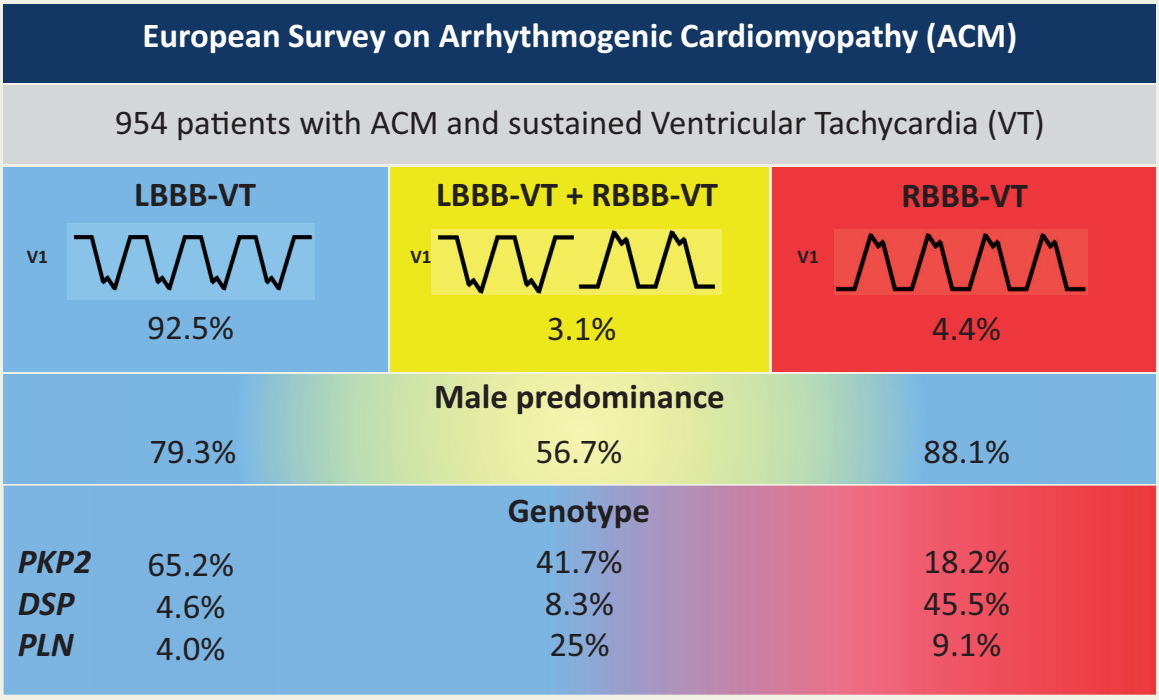
Aims In arrhythmogenic cardiomyopathy (ACM), sustained ventricular tachycardia (VT) typically displays a left bundle branch block (LBBB) morphology while a right bundle branch block (RBBB) morphology is rare. The present study assesses the VT morphology in ACM patients with sustained VT and their clinical and genetic characteristics.

Methods and results Twenty-six centres from 11 European countries provided information on 954 ACM patients who had ≥1 episode of sustained VT spontaneously documented during patients' clinical course. Arrhythmogenic cardiomyopathy was defined according to the 2010 Task Force Criteria, and VT morphology according to the QRS pattern in V1. Overall, 882 (92.5%) patients displayed LBBB-VT alone and 72 (7.5%) RBBB-VT [alone in 42 (4.4%) or in combination with LBBB-VT in 30 (3.1%)]. Male sex prevalence was 79.3%, 88.1%, and 56.7% in the LBBB-VT, RBBB-VT, and LBBB + RBBB-VT groups, respectively ($P = 0.007$). First RBBB-VT occurred 5 years after the first LBBB-VT (46.5 ± 14.4 vs 41.1 ± 15.8 years, $P = 0.011$). An implanted cardioverter-defibrillator was more frequently implanted in the RBBB-VT (92.9%) and the LBBB + RBBB-VT groups (90%) than in the LBBB-VT group (68.1%) ($P < 0.001$). Mutations in *PKP2* predominated in the LBBB-VT (65.2%) and the LBBB + RBBB-VT (41.7%) groups while *DSP* mutations predominated in the RBBB-VT group (45.5%). By multivariable analysis, female sex was associated with LBBB + RBBB-VT ($P = 0.011$) while *DSP* mutations were associated with RBBB-VT ($P < 0.001$). After a median follow-up of 103 (51–185) months, death occurred in 106 (11.1%) patients with no intergroup difference ($P = 0.176$).

Conclusion RBBB-VT accounts for a significant proportion of sustained VTs in ACM. Sex and type of pathogenic mutations were associated with VT type, female sex with LBBB + RBBB-VT, and *DSP* mutation with RBBB-VT.

Graphical Abstract



Keywords Arrhythmogenic cardiomyopathy • Arrhythmogenic right ventricular cardiomyopathy/dysplasia • Arrhythmogenic left ventricular cardiomyopathy • Ventricular tachycardia • Genetics • European survey

What's new?

- Of 954 patients with spontaneous sustained monomorphic ventricular tachycardia (VT) recorded during the course of arrhythmogenic cardiomyopathy, 882 (92.5%) displayed left bundle branch block (LBBB)-VT alone and 72 (7.5%) right bundle branch block (RBBB)-VT [alone in 42 (4.4%) or in combination with LBBB-VT in 30 (3.1%)]
- Male prevalence was significantly lower in the LBBB + RBBB-VT group than in the LBBB-VT or RBBB-VT groups.
- First RBBB-VT occurs ~5 years after the first LBBB-VT.
- Female sex is associated with LBBB + RBBB-VT.
- DSP mutation is associated with RBBB-VT.

Introduction

Four decades ago, Marcus *et al.*[1] described a pathologic condition in which sustained ventricular tachycardia (VT) of left bundle branch block (LBBB) morphology was associated with fibro-fatty replacement of the right ventricular (RV) musculature and named it 'arrhythmogenic RV dysplasia' (ARVD). The same disease was later considered to be a cardiomyopathy and also referred to as 'arrhythmogenic RV cardiomyopathy' (ARVC). Frequent left ventricular (LV) involvement was demonstrated in ARVC/D that led to use the broader term of arrhythmogenic cardiomyopathy (ACM).[2] About one decade ago, a new classification of ACM into three types was proposed:[3] (i) the *classic form*, with isolated RV disease or LV involvement in association with predominant RV impairment (ARVC/D); (ii) the *left-dominant form*, with early and prominent LV involvement and relatively mild right-sided disease[4] (left-dominant ACM), which has to be distinguished from LV diverticulum; and (iii) the *biventricular form*, in which both ventricles are affected to a similar extent throughout the disease course.

Despite the frequent LV involvement in all these ACM variants, the great majority of sustained monomorphic VT spontaneously documented in patients with ACM exhibit an LBBB morphology,[1,5,6] and originate from the RV.[7] Clinical right bundle branch block (RBBB)-VT is scarcely reported.[8]

The present study has two main objectives: (i) to assess the prevalence of spontaneous sustained VT with LBBB, RBBB, or both morphologic types in a large cohort of ACM patients with sustained VT and (ii) to compare their clinical and genetic characteristics.

Methods

The Sheba Medical Center Institutional Review Board committee approved the study. All centres complied by local IRB registry protocols.

Data source and centre selection

A Medline search using the terms 'arrhythmogenic right or left ventricular dysplasia or cardiomyopathy and ventricular tachycardia' was performed to select European centres with experience in the diagnosis and management of ACM patients with VT.

Study inclusion and exclusion criteria

Patients were eligible if they fulfilled both conditions: (i) they were diagnosed with definite, probable, or borderline ACM according to the revised 2010 Task Force Criteria (TFC)[9] for ARVC/D diagnosis and (ii) they exhibited at least one *spontaneous* episode of sustained (≥30 s) VT documented on 12-lead electrocardiogram (ECG) during their disease's course. Ventricular tachycardia was classified as either an LBBB morphology (QS, rS or qrS in V1) or RBBB morphology (mono-, bi, or triphasic R waves in V1, Rs, or qR in V1).

Study exclusion criteria included: (i) patients with ventricular flutter (rate ≥ 250/min) or non-sustained VT (<30 s); (ii) patients with only electrophysiologically induced VT; and (iii) patients in whom VT could be related to a different cardiac pathology.

Centre recruitment

Twenty-six (67%) of the 39 initially contacted centres, belonging to 11 European countries, agreed to participate in the survey. Twenty-three (88.5%) centres provided data from their single centre, whereas the remaining three (11.5%) provided data from multiple institutions in their countries (*Table 1*).

Data acquisition

Participating centres were requested to provide anonymized patient information regarding (i) patient sex; (ii) age at first documented VT; (iii) QRS morphology (LBBB or RBBB) of first documented VT; (iv) morphology (LBBB or RBBB) of any further documented sustained VT during clinical course; (v) level of certitude of the disease diagnosis according to the 2010 TFC;[9] (vi) patient management [implantation of an automatic cardioverter-defibrillator (ICD) or VT ablation] and outcome (death); and (vii) results of molecular-genetic testing when available.

In patients who underwent genetic testing, all genetic assays sequenced at least five desmosomal genes [plakophilin-2 (*PKP2*), desmoplakin (*DSP*), desmoglein-2 (*DSG2*), desmocollin-2 (*DSC2*), and plakoglobin (*JUP*)]. Specialists of cardiac genetics at each centre reviewed genetic variants associated with ACM and their pathogenicity classified using the ACMG criteria: pathogenic, likely pathogenic, variants of unknown significance or benign. The benign variants were assimilated to negative genetic results. Only pathogenic and likely pathogenic variants were taken into account in regression analyses.

A local committee (B.B. and A.M.) reviewed the data provided by each participating centre. ECG tracings were reviewed by referring cardiologists as well as three of the senior study co-authors (B.B., A.M., and M.L.).

Patients were categorized into three groups according to the morphology of the spontaneous sustained VT documented during clinical course: LBBB-VT only, RBBB-VT only, or both LBBB + RBBB-VT.

The cases of four patients included in this survey were previously reported.[8]

Statistical analysis

The data are presented as mean (standard deviation), median (interquartile range), or count (percent). Non-parametric statistical tests were systematically used for comparisons because of imbalanced group sizes. Fisher's exact test, Mann–Whitney *U* test, and Kruskal–Wallis test were used as appropriate. *Post hoc* tests were done with the Fisher's exact test and a Bonferroni correction of the *P*-values. Multinomial logistic regression was used for VT morphology prediction. Predictors with *P*-value <0.05 in univariable models were included in a multivariable model. Missing data about genetic testing and the results of specific gene mutations were considered as 'No'. Otherwise, missing data were reported as 'Unknown' and was not included in univariable statistical comparisons.

All statistical analyses were done with *R* version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

The study population included 954 patients (78.9% males) with ACM and at least 1 episode of spontaneous sustained monomorphic VT documented during clinical course (*Table 2*).

The diagnosis of ACM, based on the revised 2010 TFC, was definite, borderline, or possible in 89.9%, 6.3%, and 3.8% of patients, respectively.

In the entire cohort, age at first documented sustained VT of any morphology ranged from 7 to 87 (mean 41.5 ± 15.8) years (*Figure 1A*). The first documented VT predominated in the 46–55 years age group for females and the 36–45 years age group for males; however, the mean ages at first VT were not significantly different between males and females

(41.3 ± 15.9 vs 42.1 ± 15.2 years, respectively, $P = 0.488$) (Supplementary material online, *Figure S1*). The male-to-female ratio was 3.8 for the whole cohort, with the lowest (2) and highest (11) ratios observed in the paediatric and elderly age groups, respectively (*Figure 1B*).

Ablation of VT was performed in 550 (57.7%) patients. Median duration of follow-up after first VT was 103 (51–185) months. Death occurred in 106 (11.1%) patients at a median time of 143 (75–228) months after first VT.

Prevalence of left bundle branch block and right bundle branch block-ventricular tachycardia

During the clinical course of the 954 study patients, 882 (92.5%) exhibited LBBB-VT, 42 (4.4%) RBBB-VT, and 30 (3.1%) both LBBB and RBBB-VT (*Figures 2A and B and 3A and B*). The total prevalence of RBBB-VT morphology amongst the survey patients was 7.5% (*Tables 1* and *2*).

Clinical characteristics

The demographic and clinical characteristics of the study patients according to VT group are compared in *Table 2*.

A definitive diagnosis of ACM was more common amongst patients with LBBB-VT than in those with RBBB-VT (91.4% vs 66.7%, respectively, $P < 0.001$).

Table 1 Countries and number of centres participating in the survey with RBBB-VT distribution

Country	Number of centres	Total number of patients (%)	All RBBB-VT (%)
France	8	417 (43.7)	20 (4.8)
Netherlands	1	133 (13.9)	10 (7.5)
Italy	3	132 (13.8)	14 (10.6)
Spain	3	53 (5.6)	10 (18.9)
Switzerland	2	52 (5.5)	5 (9.6)
Czech Republic	2	49 (5.1)	6 (12.2)
Greece	2	31 (3.2)	0 0
Israel	2	28 (2.9)	2 (7.1)
UK	1	26 (2.7)	2 (7.7)
Denmark	1	24 (2.5)	1 (4.2)
Belgium	1	9 (0.9)	2 (22.2)
Total	26	954	72 (7.5)

RBBB, right bundle branch block; VT, ventricular tachycardia.

Male sex predominance was significantly lower in the LBBB + RBBB-VT group (56.7%) than in the RBBB-VT group (88.1%) or the LBBB-VT group (79.3%) ($P = 0.007$).

Patients' age at time of first documented VT did not significantly differ amongst the three VT groups ($P = 0.126$).

In the LBBB + RBBB VT group, 12 patients exhibited LBBB-VT first while 18 patients exhibited RBBB-VT first. The age at first RBBB-VT was significantly greater than the age at first LBBB-VT in that patient group (47.6 ± 12.2 vs 35.1 ± 11.5 years, $P < 0.01$). When comparing the age of the 894 patients who displayed first or only LBBB-VT with that of the 60 patients who displayed first or only RBBB-VT, the difference was statistically significant (41.1 ± 15.8 vs 46.5 ± 14.4 years, respectively, $P = 0.011$).

Higher rates of ICD implantation were observed in the LBBB + RBBB-VT and the RBBB-VT groups than in the LBBB-VT group ($P < 0.001$). Higher rates of VT ablation were also noted in the LBBB + RBBB-VT group as compared to the other two groups ($P = 0.016$). Death rates did not differ significantly amongst the three VT groups ($P = 0.176$). The estimated survival time after the first VT was similar in all three VT group patients ($P = 0.43$, log-rank test) (Supplementary material online, *Figure S2*).

Genetic results

Out of the 954 survey patients, 538 (56.4%) underwent genetic testing, comprising a higher proportion of patients with LBBB + RBBB-VT and RBBB-VT ($P = 0.018$) (*Table 3*). Gene variants were discovered in 359 (66.7%) patients including single pathogenic/likely pathogenic mutations in desmosomal and *PLN* genes in 293 and 18 patients, respectively. *PKP2* mutations predominated in the LBBB-VT and the LBBB + RBBB-VT groups (65.2% and 41.7%, respectively, $P < 0.001$) while *DSP* mutations predominated in the RBBB-VT group (45.5%, $P < 0.001$). *PLN* mutations were more commonly observed in the LBBB + RBBB-VT group (25%) than in the other VT groups ($P = 0.047$).

Table 2 Main clinical characteristics of the 954 survey patients according to their VT group

		All	LBBB-VT	LBBB-VT + RBBB-VT	RBBB-VT	*P*-value
Number of patients (%)		954	882 (92.5)	30 (3.1)	42 (4.4)	
2010 TFC						
	Definite	858 (89.9)	806 (91.4)	24 (80.0)	28 (66.7)	**<0.001**
	Borderline	60 (6.3)	48 (5.4)	4 (13.3)	8 (19.0)	
	Possible	36 (3.8)	28 (3.2)	2 (6.7)	6 (14.3)	
Male (%)		753 (78.9)	699 (79.3)	17 (56.7)	37 (88.1)	**0.007**
Age at first VT (years)						
	Range	7–87	7–87	12–67	16–77	
	Mean ± SD	41.5 ± 15.8	41.2 ± 15.8	42.6 ± 13.3	46.0 ± 15.4	0.126
ICD implantation						
	Yes	667 (69.9)	601 (68.1)	27 (90.0)	39 (92.9)	**<0.001**
	Unknown	25 (2.6)	24 (2.7)	1 (3.3)	0 (0.0)	
VT ablation						
	Yes	550 (57.7)	500 (56.7)	25 (83.3)	26 (61.9)	**0.016**
	Unknown	9 (0.9)	8 (0.9)	1 (3.3)	0 (0.0)	
Death during F/U						
	Yes	106 (11.1)	97 (11.0)	6 (20.0)	3 (7.1)	0.176
	Unknown	28 (2.9)	25 (2.8)	3 (10.0)	0 (0.0)	
F/U after first VT (months)	Median	103 (51–185)	105 (53–188)	110 (58–170)	63 (27–136)	**0.036**

ICD, implanted cardioverter-defibrillator; F/U, follow-up; LBBB, left bundle branch block; RBBB, right bundle branch block; SD, standard deviation; TFC, Task Force Criteria; VT, ventricular tachycardia. The bold was included in order to emphasize the fact these results were statistically significant.

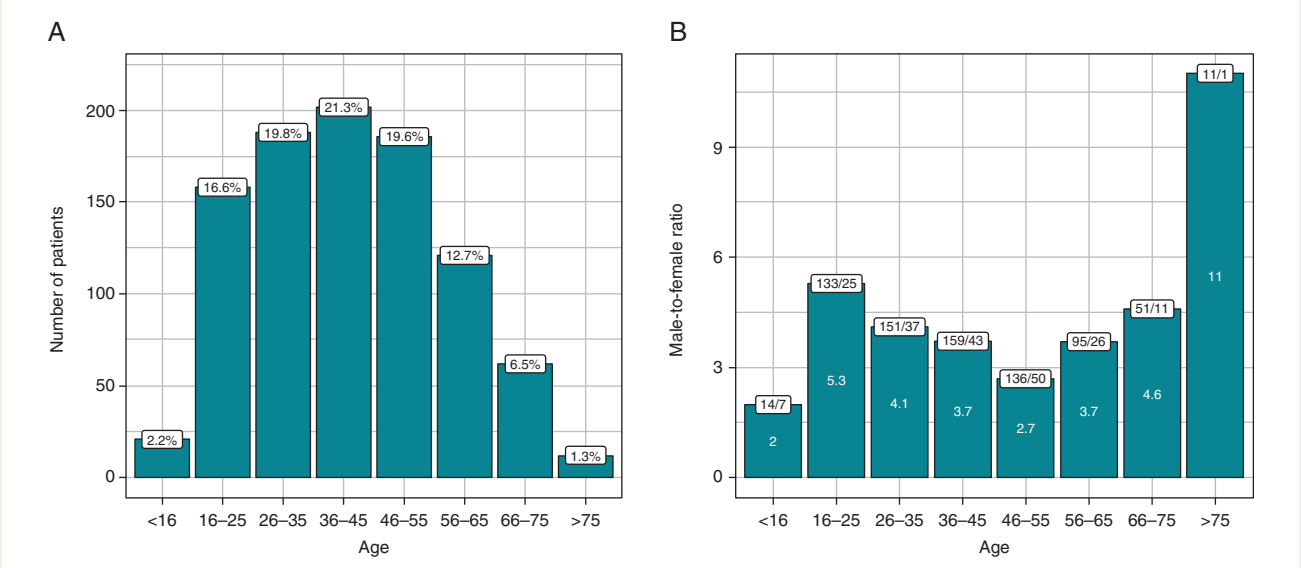


Figure 1 (*A*) Age distribution in the entire population cohort. (*B*) Male-to-female ratio of the entire population cohort in various age groups.

Variables associated with ventricular tachycardia morphology groups

Univariable and multivariable multinomial logistic regression models for VT morphology prediction are described in *Table 4*. *DSP* mutations were significantly associated with RBBB-VT alone in univariable [odds ratio (OR) 13, 95% confidence interval (CI) 5.32–31.76, $P < 0.001$] and multivariable (OR 11.42, 95% CI 4.4–29.65, $P < 0.001$) analyses but were not predictive of LBBB + RBBB-VT. In addition, RBBB-VT was significantly less likely amongst carriers of *PKP2* mutations, both in univariable (OR 0.19, 95% CI 0.06–0.54, $P = 0.002$) and

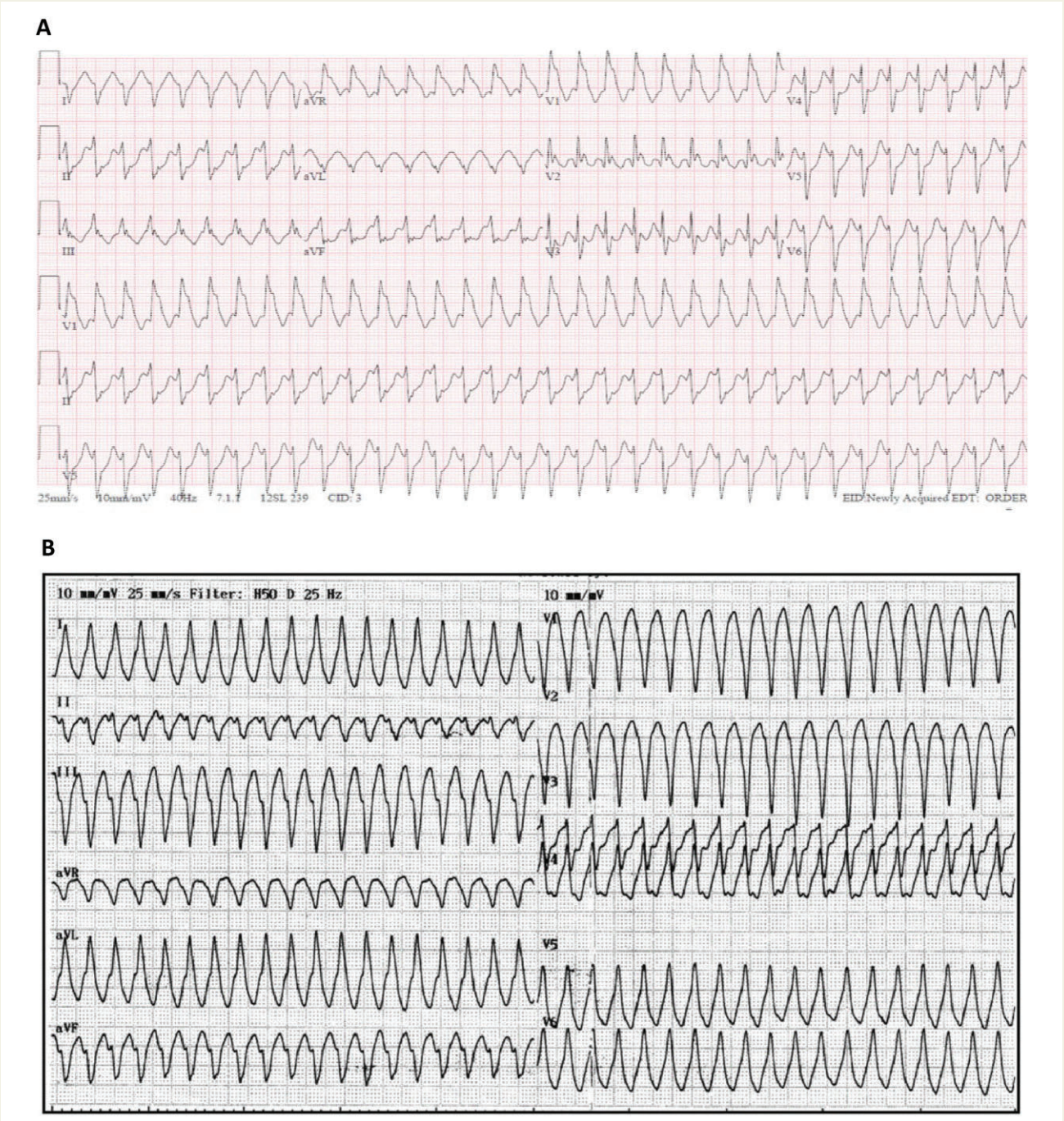


Figure 2 Familial ACM associated with *PKP2* mutation. (*A*) First spontaneous RBBB-VT recorded in a 68-year-old man. Reproduced from Rabey *et al.* (*Circulation.* 2018; 138:642–5) with permission of the publisher. (*B*) First spontaneous LBBB-VT recorded at hospital admission 7 years before, in his older brother, at age 78 years old. Reproduced from Belhassen *et al.* (*Isr Med Assoc J.* 2014; 16:385–7) with permission of the publisher.

multivariable (OR 0.28, 95% CI 0.09–0.84, $P = 0.023$) analyses. Comparable results were obtained when considering RBBB-VT as patients with RBBB-VT with or without LBBB-VT (Supplementary material online, *Table S1*). Female sex and *PLN* mutations were significantly associated with LBBB + RBBB-VT in univariable analyses (OR 3.42, 95% CI 1.44–8.10, $P = 0.005$ and OR 5.74, 95% CI 1.51–21.86, $P = 0.010$, respectively) but only female sex was independently associated with LBBB + RBBB-VT in multivariable analyses (OR 3.2, 95% CI 1.31–7.78, $P = 0.011$).

Survey results according to countries

These results are reported in Supplementary material online, *Tables S2A and B*. The prevalence of RBBB-VT (alone or in combination with LBBB-VT) according to country is summarized in *Table 1*.

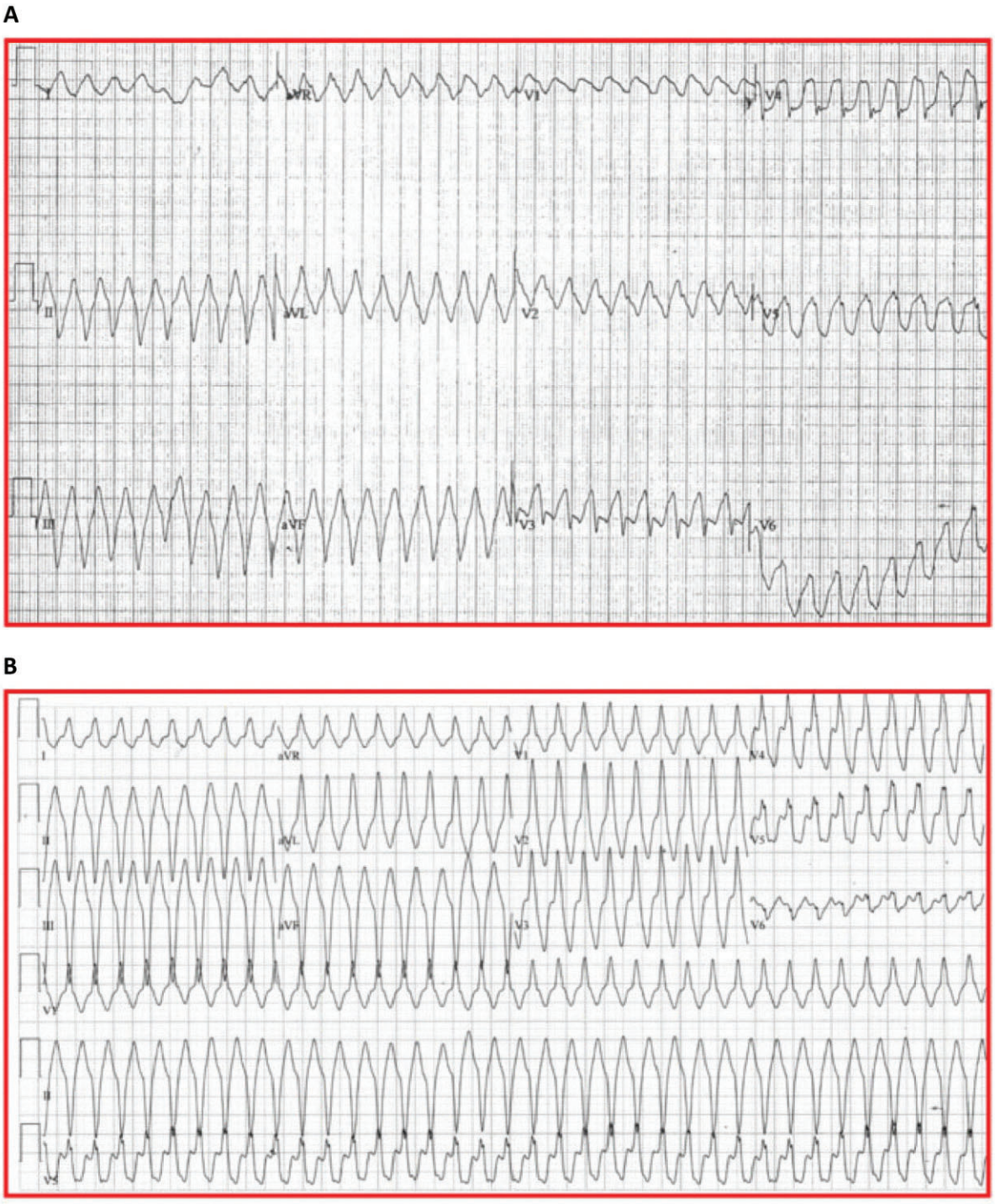


Figure 3 Documentation of LBBB- and RBBB-VT in a non-mutation carrier ACM patient. Reproduced from Belhassen *et al.* (*Eur Heart J Case Rep*. 2020; 4:1–7) with permission of the publisher. (*A*) First exercise-induced LBBB-VT (220/min) documented when the patient was 56-year-old. (*B*) First spontaneous RBBB-VT (220/min) recorded 8 years later.

Discussion

The present study includes the largest cohort of patients with ACM and sustained VT ever reported. Although sustained LBBB-VT represented by far the most frequent type of VT encountered, RBBB-VT was documented in a significant proportion of ACM patients (7.5%) either alone or in addition to an LBBB-VT. The study also revealed that sex and genotype were significant predictors of the

Table 3 Results of genetic testing amongst the study patients according to the VT group

	All VT groups	LBBB-VT	LBBB + RBBB-VT	RBBB-VT	*P*-value[a]
Number of patients	954	882	30	42	
Genetic test performed	538 (56.4)	486 (55.1)	22 (73.3)	30 (71.4)	**0.018**
No variant identified	121 (22.5)	113 (23.3)	5 (22.7)	3 (10.0)	
'Familial unknown'	45 (8.4)	44 (9.1)	0 (0.0)	1 (3.3)	
Variant identified	359 (66.7)	325 (66.9)	12 (54.5)	22 (73.3)	0.359
Plakophylin-2 (*PKP2*)	221 (61.6)	212 (65.2)	5 (41.7)	4 (18.2)	**<0.001**
Desmoglein-2 (*DSG2*)	26 (7.2)	23 (7.1)	1 (8.3)	2 (9.1)	1.000
Desmoplakin (*DSP*)	26 (7.2)	15 (4.6)	1 (8.3)	10 (45.5)	**<0.001**
Plakoglobin (*JUP*)	11 (3.1)	10 (3.1)	0 (0.0)	1 (4.5)	
Desmocollin-2 (*DSC2*)	9 (2.5)	8 (2.5)	0 (0.0)	1 (4.5)	
Multiple variants[b]	9 (2.5)	9 (2.8)	0 (0.0)	0 (0.0)	
Phospholamban (*PLN*)	18 (5.0)	13 (4.0)	3 (25.0)	2 (9.1)	**0.047**
Miscellaneous[c]	39 (10.9)	35 (10.8)	2 (16.7)	2 (9.1)	1.000
Variant of unknown significance[d]	32 (5.9)	26 (5.3)	3 (13.6)	3 (10.0)	
Unknown results	26 (4.8)	22 (4.5)	2 (9.1)	2 (6.7)	

LBBB, left bundle branch block; RBBB, right bundle branch block; VT, ventricular tachycardia. The bold was included in order to emphasize the fact these results were statistically significant.
[a]Adjusted *P*-value for single gene comparisons.
[b]Including 8 patients with PKP2 mutations (associated with another desmosomal mutation in 6).
[c]Including TMEM43 ($n = 5$); RYR2 ($n = 4$); FLNC ($n = 2$); TGFβ3 ($n = 1$); MYH7 ($n = 1$); KCNE1 ($n = 1$); CTNNA3 ($n = 1$); NKX2.5 ($n = 1$).
[d]Variant of unknown significance refers to the following desmosomal variants with their respective VT type:
PKP2 ($n = 8$): LBBB-VT ($n = 7$); RBBB-VT ($n = 1$).
DSG2 ($n = 10$): all in LBBB-VT patients.
DSP ($n = 8$): LBBB-VT ($n = 4$); LBBB + RBBB-VT ($n = 3$); RBBB-VT ($n = 1$).
JUP ($n = 2$): both in LBBB-VT patients.
DSC2 ($n = 4$): LBBB-VT ($n = 3$) and RBBB-VT ($n = 1$).

VT types and that the first documented RBBB-VT occurred ~5 years after the first documented LBBB-VT.

Morphology of sustained ventricular tachycardia in arrhythmogenic cardiomyopathy patients

The first series of patients with ARVD published before the 1994 TFC[10] almost exclusively comprised LBBB-VT.[1] In the first multicentre series of ARVD as defined by the original 1994 criteria,[10] Marcus *et al.*[5] reported that 32 (84%) of their 38 patients with sustained VT had an LBBB morphology. In the Dutch registry of 119 patients with sustained VT who had ACM defined according to the 2010 TFC,[9] Cox *et al.*[6] reported that 117 (98.3%) patients displayed an LBBB morphology. Finally, Kimura *et al.*[11] reported that 88% of the 214 spontaneous VT documented in 90 ACM patients had an LBBB morphology. The present survey confirms the high prevalence of LBBB-VT (95.6%) (92.5% alone and 3.1% in association with RBBB-VT).

Opposed to the well-known frequent ventricular ectopic activity of RBBB morphology in ACM patients, especially those with left-dominant ACM,[4] sustained VT of RBBB morphology was previously reported only as case reports[8] (Supplementary material online, *Table S3*). In 3 of these 15 cases, LBBB-VT was also spontaneously documented during patients' clinical course.[8] In our study, we noticed that 72 (7.5%) of our 954 ACM patients displayed RBBB-VT alone or in combination with LBBB-VT.

Ventricular tachycardia morphology-genetic correlations

In the setting of ACM, LBBB-VT invariably originates in the RV[7,12] while, until recently,[13] limited data from invasive electro-anatomical mapping showed that most RBBB-VT originate in the LV.[12] Therefore, we assumed that in the majority of ACM patients, an LBBB-VT and an RBBB-VT suggested an RV and LV origin, respectively.

Mutations in desmosomal genes (*PKP2*, *DSP*, *DSG2*, *DSC2*, and *JUP*) have previously been identified in 33–66% of probands with right-dominant, left-dominant, and biventricular forms of ACM.[14] *PKP2* mutations account for the majority of cases with the classical ARVC/D phenotype,[14] whereas *DSP* mutations are associated with non-classic (left-dominant and biventricular) subtypes.[4,15]

The genetic profile of the present VT registry was similar. *PKP2* mutations predominated in the LBBB-VT group (65.2%, $P < 0.001$). Carriers of *PKP2* mutations were also significantly less likely to have any RBBB-VT on univariable binomial analysis or RBBB-VT only on multivariable multinomial analysis. In contrast, *DSP* mutations predominated in the RBBB-VT group (45.5%) and carriers of *DSP* mutations were significantly more likely to have RBBB-VT alone.

Table 4 Logistic regression analysis for prediction of VT morphology

VT morphology	LBBB + RBBB VT ($n = 22$)				RBBB VT ($n = 30$)			
	OR	95% CI	95% CI	*P*-value	OR	95% CI	95% CI	*P*-value
A. Univariable multinomial logistic regression models for VT morphology prediction (compared to LBBB-VT, $n = 486$)								
Female gender	3.42	1.44	8.1	0.005	0.68	0.26	1.83	0.448
Age at first VT	1	0.97	1.03	0.948	1.01	0.99	1.04	0.270
PKP2 mutation	0.36	0.13	0.98	0.045	0.19	0.06	0.54	0.002
DSG2 mutation	0.88	0.11	6.79	0.901	1.32	0.3	5.84	0.717
DSP mutation	1.24	0.16	9.72	0.839	13	5.32	31.76	<0.001
JUP mutation[a]	NA	NA	NA	NA	1.64	0.2	13.26	0.642
DSC2 mutation[a]	NA	NA	NA	NA	1.83	0.22	14.92	0.574
PLN mutation	5.74	1.51	21.86	0.010	2.6	0.56	12.08	0.223
VT morphology	**LBBB + RBBB VT ($n = 22$)**				**RBBB VT ($n = 30$)**			
	OR	**95% CI**	**95% CI**	***P*-value**	**OR**	**95% CI**	**95% CI**	***P*-value**
B. Multivariable multinomial logistic regression models (compared to LBBB-VT)								
Female gender	3.2	1.31	7.78	0.011	0.49	0.17	1.44	0.195
PKP2 mutation	0.39	0.14	1.11	0.078	0.28	0.09	0.84	0.023
DSP mutation	0.85	0.1	6.99	0.879	11.42	4.4	29.65	<0.001
PLN mutation	2.93	0.71	12.15	0.138	3	0.6	14.93	0.179

CI, confidence interval; LBBB, left bundle branch block; NA, Not Applicable; OR, odds ratio; RBBB, right bundle branch block; VT, ventricular tachycardia.
[a]Binomial logistic regression used since there were no mutations in the LBBB + RBBB VT group.

Interestingly, the LBBB + RBBB-VT group had the highest proportion of mutations in *PLN* (25%, $P = 0.047$), known to be associated with biventricular ACM.[15] *PLN* mutations were associated with increased odds of LBBB-VT + RBBB-VT (OR 5.74, 95% 1.51–21.86, $P = 0.01$) in univariable binomial analysis but significance was lost on multivariable analysis (*Table 4*).

Specific country-related observations

Our survey allowed interesting observations about specific ECG and genetic characteristics in some countries. The Netherlands registry provided 17 of the 18 patients with *PLN* mutations (94%, $P = 0.002$), which were first described in Dutch patients. Also, Greek centres provided 10 of the 11 patients (91%) who harboured *JUP* mutations, first described in Greek patients. More importantly, Spain, Italy, and the Czech Republic displayed the highest proportion of patients with RBBB-VT only (17%, 9.8%, and 8.2%, respectively) consistent with the fact these three countries exhibited the highest proportion of *DSP* mutations, well-known to be associated with left-dominant ACM (20%, 17.6%, and 28.6%, respectively).

Sex distribution in arrhythmogenic cardiomyopathy

Because ACM has an autosomal pattern of inheritance, one would expect a similar prevalence in both sexes. Nevertheless, a male predominance is typically demonstrated in cohorts of ARVD/C index cases with ventricular tachyarrhythmia, whereas females predominate amongst asymptomatic ARVD/C patients.[1,6] Reports on the sex distribution in non-classic disease cohorts vary from an equal sex ratio in the left-dominant subtype,[3,4] to a female predominance in biventricular disease[3] and in a recent study that did not distinguish between left-dominant ACM and biventricular disease.[16] In contrast, males accounted for 82% of in a series of 202 sudden cardiac death victims with a post-mortem diagnosis of ACM, of whom 87% had either isolated LV or biventricular involvement.[17] In our study, the male predominance observed in the LBBB-VT group (79.3%) is consistent with prior reports on classic right-dominant disease. The male predominance was significantly less, however, in the LBBB + RBBB-VT group (56.7%, $P = 0.007$). Furthermore, female sex was an independent predictor of LBBB + RBBB-VT in the multivariable multinomial model (OR 3.2, 95% CI 1.31–7.78, $P = 0.011$) (*Table 4*). The findings suggest that, amongst carriers of genetic mutations predisposing to non-classic disease (e.g. *DSP* and *PLN* mutations), women may have greater odds of presenting with the biventricular subtype, and men with the left-dominant subtype. One possible explanation is that sudden cardiac death may be the first manifestation of the disease in an important proportion of men with biventricular ACM, leading to their over-representation in post-mortem series and under-representation in clinical cohorts.[16,17] In contrast, females with a similar phenotype have been found to exhibit more heart failure-related death[11] and thus could be more prone to display both LBBB and RBBB-VT during their clinical course. However, we do not have data on ventricular dysfunction in this group that could support this speculation. Finally, to the best of our knowledge, our survey demonstrates for the first time similar ages at first documented VT in ACM

in both sexes (41.3 ± 15.9 years in males vs 42.1 ± 15.3 years in females). This result might suggest sex hormones have no significant role in time of onset of VT episodes in ACM.

Age at the time of first documented ventricular tachycardia

In the first series including 23 ARVD patients, the first LBBB-VT occurred at a mean age of 32 years old.[1] In the Dutch ACM registry, the mean age at VT onset of 147 patients, including 122 who presented with almost exclusive sustained LBBB-VT was 37 years.[6] Our survey patients exhibited a mean age of 41.5 ± 15.8 years at first documented VT of any morphology while first documented RBBB-VT occurred ∼5 years after the first documented LBBB-VT. These results could be explained in two ways: (i) LV arrhythmogenic remodelling occurs later in the course of the disease in classical ARVC/D and in patients with presumed predominant LV involvement;[2] (ii) As compared to the RV, the thicker LV wall may be less vulnerable to fatty/fibrotic transformation and a longer evolution of the disease may be required for RBBB-VT to occur. Finally, we observed a marked time-dependent rise in VT incidence from 2.2% (age group <16 years) to 16.6% (age group 16–25 years) that supports the recommendation to screen children belonging to ACM families when they approach adolescence.

Diagnostic criteria

As compared to the original 1994 TFC, the 2010 TFC revision has improved the diagnostic accuracy and consequently the management of ARVC/D.[9,10] Nonetheless, TFC mainly focuses on RV abnormalities and remain poorly efficient at identifying patients with left-dominant or biventricular ACM types before an advanced disease stage.[18] However, only the revised 2010 TFC were available when we designed the present study. Thus, we chose to include not only those patients fulfilling definite diagnostic criteria but also those with borderline or possible ARVC diagnosis. Our decision may be criticized because less stringent criteria may facilitate unintentional inclusion of other disease entities and phenocopies, such as dilated cardiomyopathy or cardiac sarcoidosis.[19,20] These limitations prompted us to perform an additional analysis which included only those patients with definite ARVC diagnosis ($n = 858$). The results of this new analysis were generally in line with those of the initial analysis (Supplementary material online, *Tables S4–S7*). However, we noted that first VT in the RBBB-VT group occurred much later (8.8 years) than in the LBBB-VT group (Supplementary material online, *Table S5*). In addition, the overall number of patients with RBBB-VT (alone or in combination with LBBB-VT) markedly decreased by 27.8% from 72 to 52 while the prevalence of RBBB-VT dropped from 7.5% to 6.1%. Also, the mutations identified in 9 of the 20 patients of the LBBB + RBBB-VT and RBBB-VT groups who had borderline/possible ARVC diagnosis (Supplementary material online, *Table S8*), were *DSP* ($n = 7$), *PLN* ($n = 1$) and *FLNC* (Filamin C) ($n = 1$), all known to be associated with non-classic (left-dominant and biventricular) ACM subtypes[4,15] but not with dilated cardiomyopathy. Thus, excluding patients with borderline/possible ARVC diagnoses would result in exclusion of a significant proportion of patients with left/biventricular ACM, and underestimation of RBBB-VT prevalence. Such results support the inclusion of borderline or possible cases of ARVC in our survey.

Study limitations

First, this is a retrospective study dealing with a disease that has a low prevalence in most countries. Therefore, the recruitment of patients spanned over long periods, especially at the most experienced centres and it is likely that the first survey patients exhibited more advanced ACM forms, underwent less modern diagnostic imaging techniques or modes of treatment as well as less genetic testing. Conversely, the long duration of follow-up for some of them as well as the fact that about a third of patients did not receive an ICD could have enabled the recording of spontaneous VT episodes of multiple morphologies.

Second, we assumed that an LBBB-VT and an RBBB-VT indicated an RV and LV origin, respectively. However, it is conceivable that a VT originating in a dilated RV spreading over the LV might display an RBBB pattern and thus be successfully ablated from the RV rather than from the LV. Marchlinski *et al.*[13] recently reported 19 ARVC patients who had 26 RBBB-VT induced during ablation procedures. They found that 11 (58%) of these 19 patients had 16 RBBB-VTs that originated in the RV. A typical QRS morphology during VT (early precordial transition in V2–V3 with a left QRS axis) was found to suggest a VT origin in the RV. Applying the ECG criteria of presumed RV origin suggested by Marchlinski *et al.*[13] in our 72 patients with RBBB-VT, showed that an RV origin of VT could be suspected in only a small subset (10 of 72, 13.8%) of our patients. Importantly, this study only included patients with a definite TFC diagnosis, thus potentially excluding patients with biventricular or LV dominant ACM. Additionally, this study included an undisclosed proportion of induced rather than clinical VT. These two points complicate the generalization of the study's finding in a less selected ACM population. Nonetheless, the Marchlinski's study points out that the exact site of origin of VT should be determined only after extensive endocardial and epicardial biventricular mapping.

Third, the prevalence of RBBB-VT in ACM could be even higher than the one found in our survey. The early policy adopted in some centres to implant an ICD after a first documented sustained VT (usually an LBBB-VT) could hamper the 12-lead ECG recording of a spontaneously occurring RBBB-VT after ICD implantation.

Fourth, decisions on genetic analysis, approaches to the evaluation of pathogenicity, and adjudication and reporting of mutations were left to the discretion of participating centres. Both the absence of a reference protocol and of central standardization may have led to the skewing of genetic data. However, the paucity of data on the genetic profile of ACM cases with sustained RBBB-VT renders our Registry the largest source to date.

Finally, the sample of genotyped RBBB-VT cases remains limited, resulting in under-powering of many statistical analyses. In particular, the logistic regression models were powered at <70% and <40% for all predictors on univariable and multivariable analysis, respectively. The power achieved for the genetic predictors varied from 60% for *PKP2* to <20% for other genes in the univariable model, falling to consistently <30% in the multivariable model (Supplementary material online, *Table S9*). Under-powering likely accounts for the failure of certain predictors (e.g. *PLN*) to retain their significance on proceeding from univariable to multivariable analysis.

Conclusions

Spontaneous sustained RBBB-VT was documented in a significant proportion (7.5%) of patients during the clinical course of ACM, indicating that LBBB-VT can no longer be considered as the exclusive ventricular arrhythmia occurring in ACM. We propose the establishment of a more open ECG criterion accepting an RBBB pattern of VT as a relatively common finding in typical cases of ARVC and call for further studies to investigate the link between VT types and various ACM anatomic forms.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of interest: none declared.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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