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Prevalence of Spontaneous Sustained Ventricular Tachycardia of Left or Right Bundle Branch Block Morphology in Patients with Arrhythmogenic Cardiomyopathy. Data from the European Survey on Arrhythmogenic Cardiomyopathy.

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ABSTRACT

Aims. In arrhythmogenic cardiomyopathy (AC), sustained ventricular tachycardia (VT) typically displays left bundle branch block (LBBB) morphology. While left ventricular involvement is frequent, sustained VT with right bundle branch block (RBBB) morphology has been scarcely reported. The present study assesses the BBB-VT morphology of AC patients with sustained VT and their clinical and genetic characteristics.

Methods and results. Twenty six centres across 11 European countries provided information on 954 AC patients with ≥1 episode of sustained VT. Overall, 882 (92.5%) patients had LBBB-VT and 72 (7.5%) RBBB-VT [alone in 42 (4.4%) or in combination with LBBB-VT in 30 (3.1%) patients]. Male-sex prevalence was 90.5%, 79.3% and 56.7% in the RBBB-VT, LBBB-VT and LBBB+RBBB-VT groups, respectively (P=0.003). First RBBB-VT occurred 5 years after first LBBB-VT (46.3±14.5 vs. 41.1±15.8 years, P=0.015). An ICD 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). *PKP2* mutations predominated in the LBBB-VT (62.3%) and the LBBB-VT+RBBB-VT (40%) groups and *DSP* mutations in the RBBB-VT group (42.3%). By multivariate analysis, female-sex was associated with LBBB+RBBB-VT (P=0.033) while *DSP* mutation was a predictor of RBBB-VT (P<0.001). After a median time of 161 (75-234) months, death occurred in 106 (11.1%) patients with no intergroup difference (P=0.46).

Conclusion. RBBB-VT accounts for a non-negligible proportion of VTs in AC. Genotype and sex are significant predictors of VT types which may correlate with the anatomic type of AC. The first documented RBBB-VT occurred approximately 5 years after the first documented LBBB-VT.

Keywords: Arrhythmogenic cardiomyopathy; Arrhythmogenic right ventricular cardiomyopathy/dysplasia; Arrhythmogenic left ventricular cardiomyopathy; Ventricular tachycardia; Genetics

Introduction

Four decades ago, Marcus, Fontaine and coworkers 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).[1] 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 (AC).[2,3] About one decade ago, a new classification of AC into 3 types was proposed by Sen-Chowdhry *et al*.[4]: (a) the *classic form*, with isolated RV disease or LV involvement in association with predominant RV impairment (ARVC/D); (b) the *left dominant form*, with early and prominent LV manifestations and relatively mild right-sided disease[5] (ALVC); and (c) the *biventricular form*, characterized by parallel involvement of both ventricles.

Despite the frequent LV involvement in all these AC variants, the large majority of sustained monomorphic VT related to AC exhibit an LBBB morphology,[1,2,6,7] and originate from the RV.[8] To our best knowledge, only 15 case-reports on sustained VT with a right bundle branch block (RBBB) morphology have been published.[9]

The present study has 2 main objectives: 1) to assess the prevalence of spontaneous sustained VT with LBBB, RBBB or both morphologic types in a large cohort of AC patients with sustained VT; 2) to compare their clinical and genetic characteristics.

Methods

The study was approved by the Sheba Medical Centre Institutional Review Board committee.

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 AC patients with VT.

Study inclusion and exclusion criteria

Patients were eligible if they were diagnosed with AC according to the 2010 modified Task Force criteria (TFC)[10] for ARVC/D diagnosis, together with at least one episode of sustained (lasting ≥30sec) VT documented on 12-lead ECG during their disease's course. VT was classified as either an LBBB morphology (dominant S wave in V1) or RBBB morphology (dominant R wave in V1).[11]

Study exclusion criteria included: a) patients with ventricular flutter or non-sustained VT (<30sec); b) patients with electrophysiological-induced (not spontaneous) VT; c) 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, accepted to participate in the survey. Twenty-three (88.5%) centres provided data from their single centre, whereas the remaining 3 (11.5%) provided data from multiple institutions in their countries (**Supplemental Table 1)**.

Data acquisition

Participating centres were asked to provide anonymised patient information regarding: 1) gender; 2) age at first documented VT as well as its QRS morphology (LBBB or RBBB) ; 3) morphology (LBBB or RBBB) of any further documented sustained VT during clinical course ; 4) level of diagnosis certitude of the disease diagnosis according to the 2010 TFC[10] ; 5) patient management [implantation of an automatic cardioverter-defibrillator (ICD) or VT ablation] and outcome (death); 6) 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*)]. Genetic variants associated with AC were reviewed by specialists of cardiac genetics at each center and their pathogenicity classified using the ACMG criteria: pathogenic, likely pathogenic, variants of unknown significance (VUS) or benign. The latter were assimilated to negative genetic results.

Patients were classified into 3 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 4 patients included in this survey were previously reported.[9,12-14]

Statistical analysis

The data are presented as mean (SD), median [interquartile range (IQR)] or count (percent). Non-parametric statistical tests were systematically used for comparisons because of imbalanced group sizes. Fisher's exact test, Mann-Whitney U and Kruskal-Wallis test were used as appropriate. Post hoc tests were done with Fisher's exact test and a Bernoulli correction of the P-values. Multinomial logistic regression was used for VT morphology prediction. Predictors with $p<0.10$ in univariate models were included in a multivariate model. All statistical analyses were done with *R* version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) **(Supplementary material).**

Results

Study population

The study population included 954 patients (79% males) with AC and at least 1 episode of sustained monomorphic VT documented during clinical course **(Table 1).** The AC diagnosis according to 2010 modified TFC was definite in 89.9% of patients. 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 36-45 years age-group for males and in the 46-55 years age-group for females; however, the mean ages at first VT were not significantly different between the 2 genders (41.3±15.9 years vs.42.1±15.3 years, respectively, P=0.530) **(Supplemental Figure 1).** The male-to-female ratio was 3.8 for the whole cohort, with the lowest (2) and highest (11) ratios observed in the pediatric and elderly age-groups, respectively **(Figure 1B).**

Ablation of VT was performed in 551 (57.8%) patients. Death occurred in 11.1% at a median time of 161[75-234] months after first VT.

Prevalence of LBBB and RBBB-VT

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 2 and 3). The total prevalence of RBBB-VT morphology amongst the survey patients was 7.5% (Supplemental Table 1).

Clinical characteristics

The demographic and clinical characteristics of the study patients according to VT group are compared in Table 1.

Patients with LBBB-VT received a definite diagnosis of AC more easily than those with RBBB-VT (91.4% vs. 66.7%, respectively, P<0.001).

Male-sex predominance was significantly lower in the LBBB+RBBB-VT group (56.7%) than the RBBB-VT group (90.5%) or the LBBB-VT group (79.3%) (P=0.003).

Patients' age at time of first documented VT did not significantly differ among the 3 VT groups (P=0.157).

In the LBBB+RBBB VT group, 13 patients exhibited LBBB-VT first while 17 patients exhibited RBBB-VT first. When comparing the age of the 895 patients who displayed first or only LBBB-VT with that of those 59 patients who displayed first or only RBBB-VT, the difference was statistically significant (41.1±15.8 vs. 46.3±14.5 years, respectively, P=0.015).

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 2 groups (P=0.004). Death rates did not differ amongst the 3 VT groups (P=0.461).

The estimated survival time after the first VT was similar in all 3 VT group patients (P=0.7, log-rank test) (Supplemental Figure 2).

Genetic results

Out of the 954 survey patients, 537 (56.3%) underwent genetic testing, comprising a higher proportion of patients with LBBB+RBBB-VT and RBBB-VT (P=0.017) (Table 2). Gene mutations were discovered in 391 (72.8%) patients with single mutations in desmosomal and

PLN genes in 343 (63.9%). In the latter group, pathogenic mutations, likely pathogenic mutations and VUS were observed in 75.6%, 13.8% and 9.4% of patients, respectively. Single mutations in desmosomal genes were found in 83.7%, 66.7% and 84.6% in patients with LBBB-VT, LBBB+RBBB-VT and RBBB-VT, respectively (P=0.242). *PKP2* mutations predominated in the LBBB-VT and the LBBB+RBBB-VT groups (62.3% and 40%, respectively) and *DSP* mutations in the RBBB-VT group (42.3%). *PLN* mutations were more commonly observed in the LBBB+RBBB-VT group (20%) than in the 2 other VT groups..

Prediction of VT morphology

Multinomial logistic regression was used for VT morphology prediction among patients who underwent genetic testing (n=537) (**Table 3).** In univariate models, female sex and *PLN* mutation were positive predictors of LBBB+RBBB-VT, *DSP* mutation was a predictor for both LBBB+RBBB-VT and RBBB-VT, and *PKP2* was associated with LBBB-VT. A multivariate model demonstrated similar trends of association, although *PKP2* and *PLN* did not reach statistical significance.

Survey results according to countries

These results are reported in **Supplemental Tables 2A and 2B.** The prevalence of RBBB-VT (alone or in combination with LBBB-VT) according to country is summarised in **Supplemental Table 1.**

Discussion

The present study includes the largest cohort of patients with AC and sustained VT ever reported. Although sustained LBBB-VT represented by far the most frequent type of VT encountered in AC, RBBB-VT was documented in a non-negligible proportion of AC patients (7.5%) either alone or in association with an LBBB-VT. The study also revealed that genotype and sex were significant predictors of the VT types and that the first documented RBBB-VT occurred approximately 5 years later than the first documented LBBB-VT.

Morphology of sustained VT in AC patients

The first series of patients with ARVD published before the 1994 TFC[15] almost exclusively comprised LBBB-VT.[1,2] In the first multicentre series of ARVD as defined by the original

1994 criteria[15], Marcus *et al.*[6] 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 AC defined according to 2010 TFC[10], Cox *et al.*[7] reported that 117 (98.3%) patients displayed an LBBB morphology. The present survey confirms the marked prevalence of LBBB-VT (95.6%) [92.5% alone and 3.1% in association with RBBB-VT]. This high prevalence was comparable in all 11 countries participating in the study, ranging from 83.3% to 100%.

Contrasting with the well-known documentation of frequent ventricular ectopic activity of RBBB morphology in AC patients and especially left-dominant AC,[4,5] sustained VT of RBBB morphology was previously reported only as case reports[5,9,12-14,16-25] (**Supplemental Table 3**). In 3 of these 15 cases, both RBBB and LBBB morphologies were documented during patients' clinical course.[9,16,25] In our study we noticed that 72 (7.5%) of our 954 AC patients displayed RBBB-VT alone or in combination with LBBB-VT. It is noteworthy that the prevalence of RBBB-VT markedly varied from 0% (Greece) to 20.4% (Spain).

ECG-genetic correlations

In the setting of AC, LBBB-VT invariably originates in the RV[8,26] while limited data from invasive electro-anatomical mapping have shown that most RBBB-VT originate in the LV.[26] Therefore, we can assume that in the majority of AC patients, an LBBB-VT and an RBBB-VT indicate an RV and LV origin, respectively. The fact that the genetic profile of our study patients markedly differs according to the LBBB or RBBB-VT pattern makes tempting to speculate that these 3 VT groups correspond to the 3 types of AC described by Sen-Chowdhry *et al.*[4] Mutations in desmosomal genes (*PKP2, DSP, DSG2, DSC2 and JUP*) have been identified in 33% to 66% of probands with right, left and biventricular forms of AC[27]. *PKP2* mutations account for the vast majority of AC leading to the classical ARVC/D phenotype.[27] This is in agreement with our results: 62.2% of the LBBB-VT group patients had a single *PKP2* mutation and *PKP2* mutation was significantly associated with LBBB-VT. In contrast, *DSP* mutations, well-known to predominate in left-dominant AC[5,27] were more frequently observed in the RBBB-VT group (42.3%) and were associated with RBBB-VT,

with or without accompanied LBBB-VT. The proportion of patients who harbored *PLN* and other non-desmosomal mutations known to be associated with biventricular involvement,[28] was the highest in the LBBB+RBBB-VT group; also *PLN* mutations were associated with LBBB+RBBB-VT. Interestingly, the highest percentage of *DSP* mutations (20.8%) was found in Spain, the same country that showed the highest prevalence of RBBB-VT.

Gender distribution in AC

Because AC is transmitted as an autosomal pattern of inheritance, one would expect a similar prevalence in both genders. However, a male predominance has been universally demonstrated in cohorts of AC index patients with ventricular tachyarrhythmias.[7] Miles et al. reported that 82% of 202 cases of sudden cardiac death attributed to AC after post-mortem examinations were males.[29]. Males also predominated (67%) in the first 2 largest series of sustained VT occurring in ARVD patients.[1,2] In contrast, females predominated in asymptomatic AC patients.[7] In our study, the marked male predominance observed in the RBBB-VT group (90.5%) and the LBBB-VT group (79.2%) is in agreement with the above reported results. However, there was a lower male predominance in the LBBB+RBBB-VT group (56.7%) and female-sex was significantly associated with RBBB-VT+LBBB-VT, independently of underlying genotype. A possible explanation could be that an important proportion of males with biventricular AC may die suddenly before presenting with a documented sustained VT.[29] In contrast, females with a similar phenotype have been found to exhibit more heart failure-related death[30] and thus could be more prone to display both LBBB and RBBB-VT during their clinical course. However, we do not have any data showing an increased proportion of patients with ventricular dysfunction in this group that would support this speculation. Finally, our results also show for the first time a similar age at first documented VT in AC in both genders. However, the marked difference in the male-to-female ratio in the young vs. the elderly group is striking and confirms the observations made by others.[31, 32]

Age at the time of first documented VT

In two early series including 23 and 15 AC patients, the first LBBB-VT occurred at mean

ages of 32 and 29 years, respectively.[1,2] In the Dutch AC registry, the mean age at VT onset of 147 patients, including 122 who presented with almost exclusive sustained LBBB-VT was 37 years.[7] Bhonsale *et al.* demonstrated that AC patients experienced their first sustained monomorphic VT at a median age of 36 years[33]. In an Italian study of 301 consecutive AC patients, Mazzanti *et al.* found that the first arrhythmic event (including sudden cardiac death, resuscitated arrhythmias or appropriate ICD interventions) occurred at a mean age of 39±15 years in 73 patients but did not provide information on the patients' age at the time of the sustained VT.[34] 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 approximately 5 years after first documented LBBB-VT. These results could be explained in two ways: (1) LV arrhythmogenic remodeling occurs later in the course of the disease in classical ARVC/D and in patients with presumed predominant LV involvement;[3] (2) As compared to the RV, the thicker LV wall may be less vulnerable to reentry given a similar amount of scar, and a higher scar burden 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 AC families when they approach adolescence.[34]

Diagnostic criteria

The 2010 revision improved the diagnostic performances of the TFC and consequently the management of ARVC/D as compared to the original 1994 criteria.[10,15] Nonetheless, TFC remain poorly efficient at identifying patients with left-dominant and bi-ventricular AC types before an advanced disease stage. Henceforth, the fact that the definition of AC in our survey was based on the 2010 modified TFC is consistent with the lower rate of AC diagnosis in patients with RBBB-VT as compared to those with LBBB-VT.

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 AC 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 VT episodes of multiple morphologies.

Second, the prevalence of RBBB-VT in AC could be even higher than the one found in our survey. The policy adopted in some centres to implant an ICD after a first documented sustained VT[35] (almost always an LBBB-VT) could hamper the 12-lead ECG recording of a spontaneously occurring RBBB-VT after ICD implantation.

Third, genetic testing was available in relatively small cohorts of patients with LBBB+RBBB-VT or RBBB-VT as compared to the LBBB-VT group. Nonetheless genetic data in AC patients presenting with *sustained* RBBB-VT in the literature are scarce.

Conclusions

Sustained RBBB-VT was documented in a non-negligible proportion (7.5%) of AC patients with VT, indicating that LBBB-VT can no longer be considered as the exclusive ventricular arrhythmia occurring in AC. Pathogenic mutations and gender were associated with VT type, with *DSP* being associated with RBBB-VT and female sex with LBBB+RBBB-VT. Further studies are needed to investigate the link between VT types and various AC anatomic forms. Inclusion of sustained RBBB-VT in future TFC revisions may improve their diagnostic performance especially with regard to AC forms with LV involvement.

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FIGURES LEGENDS.

Figure 1:

(A) Age distribution at time of first documented VT in all 954 survey patients.

(B) Male-to-female (M/F) ratio for the 954 survey patients.

Figure 2. Familial AC associated with *PKP2* mutation.

(A) First spontaneous RBBB-VT recorded in a 68-year-old man. Reproduced from Rabey et al. (Circulation. 2018;138:642-645) 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;16:385-387) with permission of the Publisher.

Figure 3. Documentation of LBBB- and RBBB-VT in a non-mutation carrier AC 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 documented when the patient was 56-year-old.

(C) First spontaneous RBBB-VT recorded 8 years later.

LEGENDS OF SUPPLEMENTAL FIGURES.

Supplemental Figure 1. Age distribution at time of first documented VT in all 954 survey patients according to gender.

Supplemental Figure 2. Time from the first VT to death estimated with Kaplan-Meier survival (time-to-event) functions.

LEGENDS OF TABLES.

Table 1. Comparison of the main demographic and clinical results in all survey patients in respect to their VT group.

Table 2. Comparison of the main genetic results in all survey patients in respect to their VT group.

LEGENDS OF SUPPLEMENTAL TABLES.

Supplemental Table 1. List of the 11 countries and 26 centres participating in the survey along with the distribution of the 954 survey patients according to their VT group.

Supplemental Table 2. List of published case reports of sustained RBBB-VT in the setting of AC. Adapted from Belhassen et al. (*Eur Heart J Case Report.* 2020;4:1-7) (with permission of the Publisher).

Supplemental Table 3. Main demographic, clinical and genetic results in all survey patients according to country of origin.