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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

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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.

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Short title: Bundle Branch Block Morphology during Sustained Ventricular Tachycardia in Patients with Arrhythmogenic Cardiomyopathy

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1   **ABSTRACT**

2   **Aims.** In arrhythmogenic cardiomyopathy (ACM), sustained ventricular tachycardia (VT)

3   typically displays a left bundle branch block (LBBB) morphology while a right bundle

4   branch block (RBBB) morphology is rare. The present study assesses the VT morphology in

5   ACM patients with sustained VT and their clinical and genetic characteristics.

6   **Methods and results.** Twenty-six centres from 11 European countries provided information

7   on 954 ACM patients who had $\geq$1 episode of sustained VT spontaneously documented during

8   patients' clinical course. ACM was defined according to the 2010 Task Force criteria, and

9   VT morphology according to the QRS pattern in V1. Overall, 882 (92.5%) patients displayed

10   LBBB-VT alone and 72 (7.5%) RBBB-VT [alone in 42 (4.4%) or in combination with

11   LBBB-VT in 30 (3.1%)]. Male-sex prevalence was 79.3%, 88.1% and 56.7% in the LBBB-

12   VT, RBBB-VT and LBBB+RBBB-VT groups, respectively (P=0.007). First RBBB-VT

13   occurred 5 years after the first LBBB-VT (46.5$\pm$14.4 vs. 41.1$\pm$15.8 years, P=0.011). An ICD

14   was more frequently implanted in the RBBB-VT (92.9%) and the LBBB+RBBB-VT groups

15   (90%) than in the LBBB-VT group (68.1%) (P<0.001). Mutations in *PKP2* predominated in

16   the LBBB-VT (65.2%) and the LBBB+RBBB-VT (41.7%) groups while *DSP* mutations

17   predominated in the RBBB-VT group (45.5%). By multivariable analysis, female-sex was

18   associated with LBBB+RBBB-VT (P=0.011) while *DSP* mutations were associated with

19   RBBB-VT (P<0.001). After a median follow-up of 103 (51-185) months, death occurred in

20   106 (11.1%) patients with no intergroup difference (P=0.176).

21   **Conclusion.** RBBB-VT accounts for a significant proportion of sustained VTs in ACM. Sex

22   and type of pathogenic mutations were associated with VT type, female sex with

23   LBBB+RBBB-VT and *DSP* mutation with RBBB-VT.

24

What's New?

- Of 954 patients with spontaneous sustained monomorphic ventricular tachycardia (VT) recorded during the course of arrhythmogenic cardiomyopathy (ACM), 882 (92.5%) 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 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.

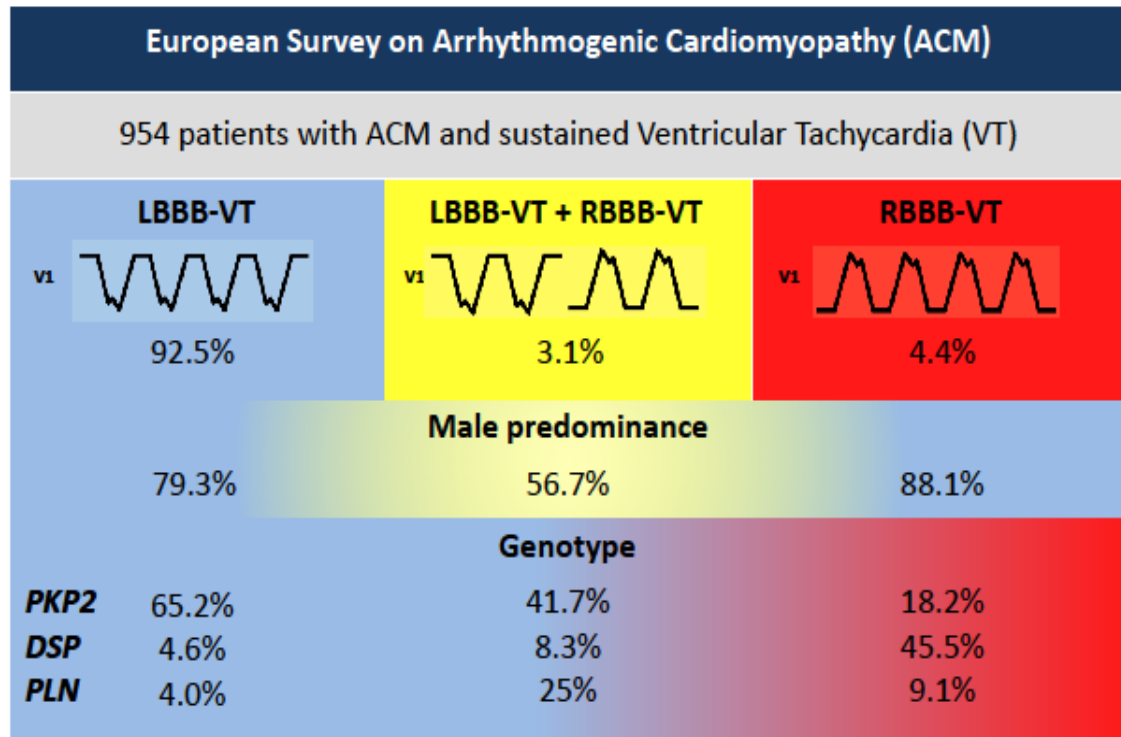- Female sex is associated with LBBB+RBBB-VT.

- DSP mutation is associated with RBBB-VT.

Representative figure. Prevalence of LBBB-VT, RBBB-VT and LBBB-VT+RBBB-VT in 954 patients with arrhythmogenic cardiomyopathy and sustained monomorphic ventricular tachycardia, with corresponding male-sex proportion and most common genetic alterations.

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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 (ACM).[2] About one decade ago, a new classification of ACM into 3 types was proposed[3]: (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 involvement and relatively mild right-sided disease[4] (left-dominant ACM), which have to be distinguished from LV diverticulum; and (c) 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: 1) 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; 2) to compare their clinical and genetic characteristics.

Methods

1   The Sheba Medical Center Institutional Review Board committee approved the study. All

2   centers complied by local IRB registry protocols. The data that support the findings of this

3   study are available from the corresponding author upon reasonable request.

4   **Data source and center selection**

5   A Medline search using the terms "arrhythmogenic right or left ventricular dysplasia or

6   cardiomyopathy and ventricular tachycardia" was performed to select European centers with

7   experience in the diagnosis and management of ACM patients with VT.

8   **Study inclusion and exclusion criteria**

9   Patients were eligible if they fulfilled both conditions: a) they were diagnosed with definite,

10   probable or borderline ACM according to the revised 2010 Task Force criteria (TFC)[9] for

11   ARVC/D diagnosis; b) they exhibited at least one *spontaneous* episode of sustained ($\geq$30sec)

12   VT documented on 12-lead ECG during their disease's course. VT was classified as either an

13   LBBB morphology (QS, rS or qrS in V1) or RBBB morphology (mono-, bi or triphasic R

14   waves in V1, Rs, or qR in V1).

15   Study exclusion criteria included: a) patients with ventricular flutter (rate $\geq$ 250/min)

16   or non-sustained VT (<30sec); b) patients with only electrophysiologically-induced VT; c)

17   patients in whom VT could be related to a different cardiac pathology.

18   **Centre recruitment**

19   Twenty-six (67%) of the 39 initially contacted centers, belonging to 11 European countries,

20   agreed to participate in the survey. Twenty-three (88.5%) centers provided data from their

21   single centre, whereas the remaining 3 (11.5%) provided data from multiple institutions in

22   their countries (**Table 1**).

23   **Data acquisition**

24   Participating centers were requested to provide anonymised patient information regarding: 1)

25   patient sex; 2) age at first documented VT; 3) QRS morphology (LBBB or RBBB) of first

documented VT; 4) morphology (LBBB or RBBB) of any further documented sustained VT

during clinical course; 5) level of certitude of the disease diagnosis according to the 2010

TFC[9]; 6) patient management [implantation of an automatic cardioverter-defibrillator (ICD)

or VT ablation] and outcome (death); 7) 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 center

reviewed genetic variants associated with ACM and their pathogenicity classified using the

ACMG criteria: pathogenic, likely pathogenic, variants of unknown significance (VUS) 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 (BB, AM) reviewed the data provided by each participating center. ECG

tracings were reviewed by referring cardiologists as well as three of the senior study co-

authors (BB, AM, ML).

Patients were categorised 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 (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 Bonferroni

correction of the P-values. Multinomial logistic regression was used for VT morphology

prediction. Predictors with p<0.05 in univariable models were included in a multivariable

1 model. Missing data about genetic testing and the results of specific gene mutations was

2 considered as "No". Otherwise, missing data was reported as "Unknown" and was not

3 included in univariable statistical comparisons.

4 All statistical analyses were done with *R* version 3.6.1 (R Foundation for Statistical

5 Computing, Vienna, Austria).

6

7 **Results**

8 **Study population**

9 The study population included 954 patients (78.9% males) with ACM and at least 1 episode

10 of spontaneous sustained monomorphic VT documented during clinical course (**Table 2**)**.**

11 The diagnosis of ACM, based on the revised 2010 TFC, was definite, borderline or possible

12 in 89.9%, 6.3% and 3.8% of patients, respectively.

13 In the entire cohort, age at first documented sustained VT of any morphology ranged from 7

14 to 87 (mean 41.5±15.8) years (**Figure 1A**)**.** The first documented VT predominated in the 46-

15 55 years age group for females and the 36-45 years age group for males; however, the mean

16 ages at first VT were not significantly different between males and females

17 (41.3±15.9 years vs. 42.1±15.2 years, respectively, P=0.488) (**Supplemental Figure 1**)**.** The

18 male-to-female ratio was 3.8 for the whole cohort, with the lowest (2) and highest (11) ratios

19 observed in the pediatric and elderly age groups, respectively (**Figure 1B**)**.**

20 Ablation of VT was performed in 550 (57.7%) patients. Median duration of follow-up after

21 first VT was 103[51-185] months. Death occurred in 106 (11.1%) patients at a median time

22 of 143[75-228] months after first VT.

23 **Prevalence of LBBB and RBBB-VT**

24 During the clinical course of the 954 study patients, 882 (92.5 %) exhibited LBBB-VT, 42

25 (4.4%) RBBB-VT and 30 (3.1%) both LBBB and RBBB-VT (**Figures 2A+2B and 3A+3B**).

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).

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 among 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$\pm$12.2 vs. 35.1$\pm$11.5 years, P<0.01). When comparing the age of the 894 patients who displayed first or only LBBB-VT with that of the 60 patients who displayed first or only RBBB-VT, the difference was statistically significant (41.1$\pm$15.8 vs. 46.5$\pm$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) **(Supplemental Figure 2).**

Genetic results

1   Out of the 954 survey patients, 538 (56.4%) underwent genetic testing, comprising a higher

2   proportion of patients with LBBB+RBBB-VT and RBBB-VT (P=0.018) **(Table 3).** Gene

3   variants were discovered in 359 (66.7%) patients including single pathogenic/likely

4   pathogenic mutations in desmosomal and *PLN* genes in 293 and 18 patients, respectively.

5   *PKP2* mutations predominated in the LBBB-VT and the LBBB+RBBB-VT groups (65.2%

6   and 41.7%, respectively, P<0.001) while *DSP* mutations predominated in the RBBB-VT

7   group (45.5%, P<0.001). *PLN* mutations were more commonly observed in the

8   LBBB+RBBB-VT group (25%) than in the other VT groups (P=0.047).

9   **Variables associated with VT-morphology groups**

10   Univariable and multivariable multinomial logistic regression models for VT morphology

11   prediction are described in **Table 4.** *DSP* mutations were significantly associated with

12   RBBB-VT alone in univariable [odds-ratio (OR) 13, 95% confidence interval (CI) 5.32-

13   31.76, p<0.001] and multivariable (OR 11.42, 95% CI 4.4-29.65, p<0.001] analyses but were

14   not predictive of LBBB+RBBB-VT. In addition, RBBB-VT was significantly less likely

15   among carriers of *PKP2* mutations, both in univariable (OR 0.19, 95% CI 0.06-0.54,

16   p=0.002) and multivariable (OR 0.28, 95% CI 0.09-0.84, p=0.023) analyses. Comparable

17   results were obtained when considering RBBB-VT as patients with RBBB-VT with or

18   without LBBB-VT (**Supplemental Table 1**). Female-sex and *PLN* mutations were

19   significantly associated with LBBB+RBBB-VT in univariable analyses (OR 3.42, 95% CI

20   1.44-8.10, p=0.005 and OR 5.74, 95% CI 1.51-21.86, p=0.010, respectively) but only female-

21   sex was independently associated with LBBB+RBBB-VT in multivariable analyses (OR 3.2,

22   95% CI 1.31-7.78, p=0.011).

23   **Survey results according to countries**

24   These results are reported in **Supplemental Tables 2A and 2B.** The prevalence of RBBB-

25   VT (alone or in combination with LBBB-VT) according to country is summarised in **Table 1.**

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

Morphology of sustained VT in ACM patients

The first series of patients with ARVD published before the 1994 TFC[10] almost exclusively comprised LBBB-VT.[1] In the first multicenter 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] (**Supplemental Table 3**). 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.

VT 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% to 66% of probands with right-dominant, left-dominant, and biventricular

forms of ACM[15]. *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.[4,14]

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.

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 centers provided

10 of the 11 patients (91%) who harbored *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 3 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 ACM

Because ACM has as 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 among 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, among 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 our best

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 VT

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 approximately 5 years after the

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;[2] (2) 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

1 revised 2010 TFC were available when we designed the present study. Thus, we chose to

2 include not only those patients fulfilling definite diagnostic criteria but also those with

3 borderline or possible ARVC diagnosis. Our decision may be criticised because less

4 stringent criteria may facilitate unintentional inclusion of other disease entities and

5 phenocopies, such as dilated cardiomyopathy or cardiac sarcoidosis.[19,20] These limitations

6 prompted us to perform an additional analysis which included only those patients with

7 definite ARVC diagnosis (n=858). The results of this new analysis were generally in line

8 with those of the initial analysis (**Supplemental Tables 4-7).** However, we noted that first

9 VT in the RBBB-VT group occurred much later (8.8 years) than in the LBBB-VT group

10 (**Supplemental Table 5).** In addition, the overall number of patients with RBBB-VT (alone

11 or in combination with LBBB-VT) markedly decreased by 27.8% from 72 to 52 while the

12 prevalence of RBBB-VT dropped from 7.5% to 6.1%. Also, the mutations identified in 9 of

13 the 20 patients of the LBBB+RBBB-VT and RBBB-VT groups who had borderline/ possible

14 ARVC diagnosis **(Supplemental Table 8)**, were *DSP* (n=7), *PLN* (n=1) and *FLNC* (Filamin

15 C) (n=1), all known to be associated with non-classic (left-dominant and biventricular)

16 subtypes of ACM[4,15], but not with dilated cardiomyopathy. Thus, excluding patients with

17 borderline/possible ARVC diagnoses would result in exclusion of a significant proportion of

18 patients with left/biventricular ACM, and underestimation of RBBB-VT prevalence. Such

19 results support the inclusion of borderline or possible cases of ARVC in our survey.

20 **Study limitations**

21 First, this is a retrospective study dealing with a disease that has a low prevalence in most

22 countries. Therefore, the recruitment of patients spanned over long periods, especially at the

23 most experienced centers and it is likely that the first survey patients exhibited more

24 advanced ACM forms, underwent less modern diagnostic imaging techniques or modes of

25 treatment as well as less genetic testing. Conversely, the long duration of follow-up for some

1 of them as well as the fact that about a third of patients did not receive an ICD could have

2 enabled the recording of spontaneous VT episodes of multiple morphologies.

3 Second, we assumed that an LBBB-VT and an RBBB-VT indicated an RV and LV origin,

4 respectively. However, it is conceivable that a VT originating in a dilated RV spreading over

5 the LV might display an RBBB pattern and thus be successfully ablated from the RV rather

6 than from the LV. Marchlinski et al. [13] recently reported 19 ARVC patients who had 26

7 RBBB-VT induced during ablation procedures. They found that 11 (58%) of these 19 patients

8 had 16 RBBB-VTs that originated in the RV. A typical QRS morphology during VT (early

9 precordial transition in V2-V3 with a left QRS axis) was found to suggest a VT origin in the

10 RV. Applying the ECG criteria of presumed RV origin suggested by Marchlinski et al.[13] in

11 our 72 patients with RBBB-VT, showed that a RV origin of VT could be suspected in only a

12 small subset (10 of 72, 13.8%) of our patients. Importantly, this study only included patients

13 with a definite TFC diagnosis, thus potentially excluding patients with biventricular or LV

14 dominant ACM. Additionally, this study included an undisclosed proportion of induced

15 rather than clinical VT. These two points complicate the generalization of the study's finding

16 in a less selected ACM population. Nonetheless, the Marchlinski's study points out that the

17 exact site of origin of VT should be determined only after extensive endocardial and

18 epicardial biventricular mapping.

19 Third, the prevalence of RBBB-VT in ACM could be even higher than the one found in our

20 survey. The early policy adopted in some centers to implant an ICD after a first documented

21 sustained VT (usually an LBBB-VT) could hamper the 12-lead ECG recording of a

22 spontaneously occurring RBBB-VT after ICD implantation.

23 Fourth, decisions on genetic analysis, approaches to the evaluation of pathogenicity, and

24 adjudication and reporting of mutations were left to the discretion of participating centers.

25 Both the absence of a reference protocol and of central standardization may have led to

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 Table 9).** 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%) during

the clinical course of ACM patients, 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 a 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.

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Figure 1.

(A) Age distribution in the entire population cohort.

(B) Male-to-female ratio of the entire population cohort in various age groups.

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.

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.

Supplemental Figures legends

Supplemental Figure 1.

Age distribution by sex of the population cohort.

Supplemental Figure 2.

Estimated survival time after the first VT in the three VT groups.