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## **Phenotype/genotype relationship in left ventricular non-compaction. Ion channel gene mutations are associated with preserved left ventricular systolic function and biventricular non compaction**

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Gilbert Habib and Philippe Charron are equal last authors.**

### **Short title**

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### **Journal Subject Terms**

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## Abstract.

**Background:** Few data exist concerning genotype-phenotype relationships in left ventricular non-compaction (LVNC).

**Methods and Results:** From a multicenter French Registry, we report the genetic and clinical spectrum of 95 patients with LVNC, and their genotype/phenotype relationship.

Among the 95 LVNC, 45 had at least one mutation, including 14 cases of mutation in ion channel genes (ICG).

In a complementary analysis including 16 additional patients with ICG mutations, giving a total of 30 patients with ICG mutation, we found that those patients had higher median LV ejection fraction (60% vs 40%,  $p < 0.001$ ) and more biventricular non compaction (53.1% vs 18.5%,  $p < 0.001$ ) than the 81 other patients with LVNC.

Among them, both the 19 patients with *HCN4* mutation and the 11 patients with *RYR2* mutation presented with higher LVEF and more frequent biventricular non-compaction than the 81 patients with LVNC but with no mutation in ICG, but only patients with *HCN4* mutation presented with a lower heart rate.

**Conclusions:** ICG mutations should be systematically searched in patients with LVNC associated with either bradycardia or biventricular non-compaction, particularly when LV systolic function is preserved. Identifying causative mutations is of utmost importance for genetic counselling of at-risk relatives of patients affected by LVNC.

Key-words: left ventricular non-compaction, phenotype, genotype, echocardiography, registry

## **Introduction**

Left ventricular non compaction (LVNC) is a rare cardiomyopathy characterized by clinical and genetic heterogeneity (1). Recent studies reported that mutations in the *HCN4* gene could lead to sinus bradycardia and myocardial non compaction (2-4), but little is known about genotype-phenotype relationships and large prospective studies of LVNC are lacking.

A multicenter French Registry enrolled patient newly diagnosed with LVNC between 2012 and 2013. This study was conducted as part of the French Programme Hospitalier de Recherche Clinique (PHRC Ref: 2011-A - 00987-34) aiming at comparing the prognosis of a new prospective cohort of LVNC with matched patients with dilated cardiomyopathy. The main clinical results of this study are currently being analyzed. The genetic defects carried by those patients were recently published (5). We took the opportunity of this registry to report the comparison between the genetic and echocardiographic characteristics of unrelated patients affected with LVNC. Since there is a relatively strong evidence that ion-channel mutations may be associated with LVNC (2, 4), we particularly focused on patients with those mutations, i.e. *HCN4*, *SCN5A*, and *RYR2*. In addition, after completion of this registry, 16 additional cases of ion channel genes mutations were identified and compared with patients carrying other mutations

## **Material and methods**

### **Patients**

From 2012 to 2013, 95 patients newly diagnosed with LVNC were included. This study complies with the Declaration of Helsinki and was approved by our institutional review board. Written informed consent was obtained from all patients. Since the end of the inclusion period (2013), 16 additional new cases of ion channel genes mutations were identified, giving a total of 111 patients with LVNC. Finally, the echocardiographic characteristics of 30 patients with channel gene mutations were compared to those of other forms of LVNC.

## **Echocardiography**

All patients underwent a comprehensive clinical and echocardiographic study with core lab analysis as well as genetic analysis. Heart rate was measured on rest electrocardiogram in all patients. In addition to standard measurements, echocardiographic studies focused on trabeculations quantification, extent, and localization. Trabeculated segments were defined after calculation of their non compacted (NC) and compacted (C) layer thicknesses. The diagnosis of LVNC was based on the NC/C ratio in end-systole following Jenni's criteria (1). Left ventricular ejection fraction was calculated using Simpson's biplane method and right ventricular non compaction was qualitatively assessed by visual estimation. Both evaluations were blinded to the genotype status of patients.

**Genetic analysis.** The genetic analysis was performed as previously reported (5) and included all coding exons and  $\pm$  50 base pairs of flanking intronic regions of 107 genes known to be involved in cardiomyopathies (77 genes) and arrhythmias (30 genes). Only "pathogenic" and "likely pathogenic" (class 5 and class 4 according to current ACMG guidelines (5)) variants were retained after bioinformatics filtering and analyzed for the phenotype-genotype correlation study.

**Statistical analysis.** Clinical, biological, and echocardiographic data were described and compared in the 95 LVNC cohort between patients with and patients without identified mutation. In addition, after completion of this registry, 16 additional cases of ion channel genes mutations were identified, giving a total of 30 patients carrying an ion channel gene mutation. This group was compared with the 81 remaining cases of LVNC without such mutation. Similar comparison was made between the different types of mutations among the most frequent ones. Quantitative parameters were described by their mean value (and standard deviation) or medians and interquartile ranges for normally and non-normally distributed data. In the initial cohort, quantitative data were compared using Student's t-test or Mann-Whitney test. Qualitative parameters were described by their numbers (and percentages), and compared using Chi-2 test when valid, or by Fisher's test otherwise. In the cohort with the 16 additional cases, family relatedness was taken into account: statistical tests were adapted (analysis of variance and

Cochran-Mantel-Haenszel test). Linear regression analysis was performed to verify that the association between LVEF and gene mutation persisted after adjustment to age, sex and family relatedness. Before performing the regression, assumptions, multicollinearity, and presence of outliers were verified. All tests were performed bilaterally, and for all analyses a p-value less than 0.05 was considered statistically significant. All the analyses were carried out under R 3.3.1 and SAS 9.4 software.

## RESULTS

### 1 – analysis of the data from the registry (*supplementary table 1*)

Characteristics at diagnosis of the 95 unrelated patients with LVNC are presented in *supplementary table 1*. Mean age at diagnosis was  $47.0 \pm 15.4$  years, and 54 (56.8%) patients were male. Median left ventricular ejection fraction (LVEF) was 41 % (32-57), 32 patients (34%) had a LVEF  $\geq 50\%$  and 19 patients (20%) had a LVEF  $<30\%$ . Median number of non-compacted segments was 5 (4-6) and mean NC/C ratio in end-systole was  $2.2 \pm 0.3$ . The most frequent localization was the apical and lateral walls. Biventricular non compaction was observed in 19 (20%) patients.

Mutations were identified in 45 (47%) patients, including sarcomeric mutations in 22 (48.9%) [9 *TTN*, 3 *MYH6*, 3 *MYH7*, 2 *MYBPC3*, 3 *ACTC1*, and 2 other sarcomeric genes], and ion channel mutations in 14 (31% of mutated patients) [7 patients with mutations in *HCN4*, 7 in *RYR2*]. No pathogenic mutation in *SCN5A* were found. The remaining 9 patients presented with diverse mutations (1 *LMNA*, 1 *TMEM43*, 1 *HEY2*, 1 *RBM20*, 1 *PDLIM3*, 1 *LDB3*, 1 *ANK2*, 1 *FLNC*, 1 *KCNA5*). Nine patients carried mutations in various genes involved in cardiomyopathies or arrhythmias, including desmosome and structure genes, as already discussed in our previous report of the LVNC French cohort (5). In the cohort, 10 patients (10.5%) showed a complex genotype with the presence of more than one pathogenic variant (*supplementary table 2*).

Patients with (n=45) and without (n=50) mutation presented with similar clinical and echocardiographic characteristics except a tendency to have more extensive trabeculations in patients with mutation 6 (4-7) segments) vs 5 (4-6) segments in patients without mutation (p=0.09).

Among the 95 patients, patients with mutation in sarcomeric genes (n=22, 23.2%) did not differ from other patients with LVNC (n=73, 76.8%), but patients with mutation in ion channel genes (n=14) had higher median LV ejection fraction (55% vs 40%, p=0.01) and more biventricular non compaction (7/14 patients (50.0%) vs 12/81 patients (14.8%), p=0.006) than the 81 other patients with LVNC (*supplementary table 1*). Patients with mutation in ion channel genes (n=14) also presented with higher median LV ejection fraction (55% vs 41%, p<0.01), and a trend to more biventricular non compaction (50% vs 27%), p=0.17) than the 22 patients with a sarcomeric mutation (*supplementary table 1*). No significant difference was observed between patients with sarcomeric mutations and other mutations.

## 2 – analysis of patients with ion channel mutation (table 1)

In order to increase the number of patients in the group of those carrying ion channel gene mutations, we included in the cohort all the LVNC patients carrying mutations in *HCN4* and *RYR2* identified in our center. Since the end of the inclusion period (2013), 16 additional cases of ion channel genes mutations were identified, 13 of them being related with the patients from the original cohort, 3 patients representing new unrelated cases. These 16 patients included 12 new cases of *HCN4* and 4 *RYR2* giving a total of 30 patients carrying a ion channel genes mutation, i.e. 19 *HCN4* and 11 *RYR2*. *Table 1* presents the comparison between those 30 patients and the 81 patients from the registry with LVNC but without ion channel gene mutation.

The study of this larger population confirmed that patients with mutation in ion channel genes (n=30) had higher median LV ejection fraction (60% vs 40%, p<0.001), more frequent biventricular non compaction (53.1% vs 18.5%, p=0.001) and were slightly younger ( $41.2 \pm 18.5$  vs  $46.9 \pm 15.8$  years, p=0.23) than the 81 other patients with LVNC (*table 1*). The difference in LV ejection fraction persisted after adjustment for age, gender and family relatedness (difference in LVEF still p<0.001 between ion channel genes and other patients in an adjusted model on age, sex and family relatedness) (*supplementary table 3*).

Both the 19 patients with *HCN4* mutation and the 11 patients with a *RYR2* mutation presented with higher LVEF and more frequent biventricular non-compaction than the other patients with LVNC but

with no mutation in ion channel genes, but only patients with *HCN4* mutation presented with a lower heart rate than those 81 other LVNC patients (*table 1*). Comparison between the 19 *HCN4* and the 11 *RYR2* patients revealed similar frequency of biventricular noncompaction ( $p=1$ ), but lower heart rate ( $p<0.001$ ) in patients with *HCN4* mutation, as compared with the *RYR 2* patients.

Figure 1 shows an example of a patient presenting with *HCN4* mutation and both bi-ventricular noncompaction and sinus bradycardia.

## DISCUSSION

Left ventricular non compaction is a rare cardiomyopathy characterized by clinical and genetic heterogeneity. Recent studies reported that mutations in the *HCN4* gene could be associated with LVNC (2-4). However, the significance of such mutations has been debated (6-9) and if those patients present with a different phenotype than other patients with LVNC is unknown.

We recently reported our experience of Targeted panel sequencing in a prospective series of LVNC and found that LVNC was basically a genetic disease in most cases, with a large genetic heterogeneity (5). Although gene distribution resembled that observed in dilated cardiomyopathies, some specific genes such as *HCN4* were much more frequently observed in the LVNC population. The current study reports the largest published analysis of phenotype / genotype relationship in these patients with LVNC. The main results are:

- 1 - Patients with and without any mutation and patients with or without mutation in a sarcomeric gene present with similar echocardiographic characteristics.
- 2 - Patients with ion channel genes mutation are more likely to have preserved LV ejection fraction and biventricular non compaction than the other LVNC patients with no mutation in ion channel genes
- 3 – Only patients with *HCN4* mutation present with a lower heart rate than the other LVNC patients.

The first original feature of ion channel dysfunction-associated LVNC is the frequently observed biventricular noncompaction. The diagnosis of right ventricular noncompaction (RVNC) is always difficult since the right ventricle is already normally trabeculated. Although biventricular



noncompaction has already been reported by others (9), no strict criteria of RVNC exists yet, and biventricular noncompaction remains only a descriptive phenotype, characterized by a continuity between the right and left hypertrabeculation (figure 1). If biventricular noncompaction represents a different disease process is unknown.

Another interesting aspect of ion channel dysfunction is the association between morphologic (non-compaction) and rhythmic abnormalities in those patients (10). Some studies already reported such an association between *HCN4* mutation and both LVNC and bradycardia, sick sinus syndrome, or ventricular arrhythmias (4, 9-10). Other ion-channel genes dysfunction, such as *SCN5A*, have also been associated with both LVNC and rhythmic abnormalities, such as long QT and Brugada syndromes (11). Finally, *RYR2* mutations have similarly been involved in both LVNC and rhythmic abnormalities (12).

**Limitations:** This series represent a selection of patients recruited based on morphological criteria and cannot represent the full spectrum of LVNC. Particularly, some patients may have died from arrhythmia before the occurrence of cardiomyopathy and could not be included in this study. Similarly, only patients with echocardiographic features of LVNC were included in this study, and thus our results cannot represent all the clinical consequences of ion channel mutations. For instance, mutations in *HCN4* may also lead to sick sinus syndrome because of the pacemaker function of the *HCN4* ion channel gene, even in the absence of echocardiographic LVNC. Such patients were not analysed in our study. Another limitation is that 13/ 16 additional cases of ion channel genes mutations were related with the patients from the original cohort and cannot be considered as independent. However, since only clinical and echocardiographic parameters were studied, the comparison between groups still give clinically relevant information. We also acknowledge that the potential associations between genotype status and RV non-compaction should be interpreted with caution, given the difficulty in diagnosing RV non-compaction. Finally, the link between *HCN4* and *RYR2* mutations might be questioned since their prevalence is relatively high. However, the link between *HCN4* and LVNC was well established with segregation between genotype and phenotype in the studied families (9, 10). In addition, only “pathogenic” and “likely pathogenic” (class 5 and class 4 according to current ACMG guidelines (5) variants were retained in our study.

**CONCLUSION**

Ion channel mutations should be systematically searched in patients with LVNC associated with biventricular noncompaction, particularly when LV systolic function is preserved. HCN4 mutation should be particularly suspected in the presence of additional bradycardia. Identifying causative mutations is of utmost importance for genetic counselling in at-risk relatives of patients affected by LVNC.

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### **Data availability statement**

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

### **Figure legends:**

Figure 1: 40-year old lady presenting with *HCN4* mutation and both bi-ventricular noncompaction and sinus bradycardia with a continuum between left and right ventricle apical trabeculations (arrows)

a: transthoracic echocardiography

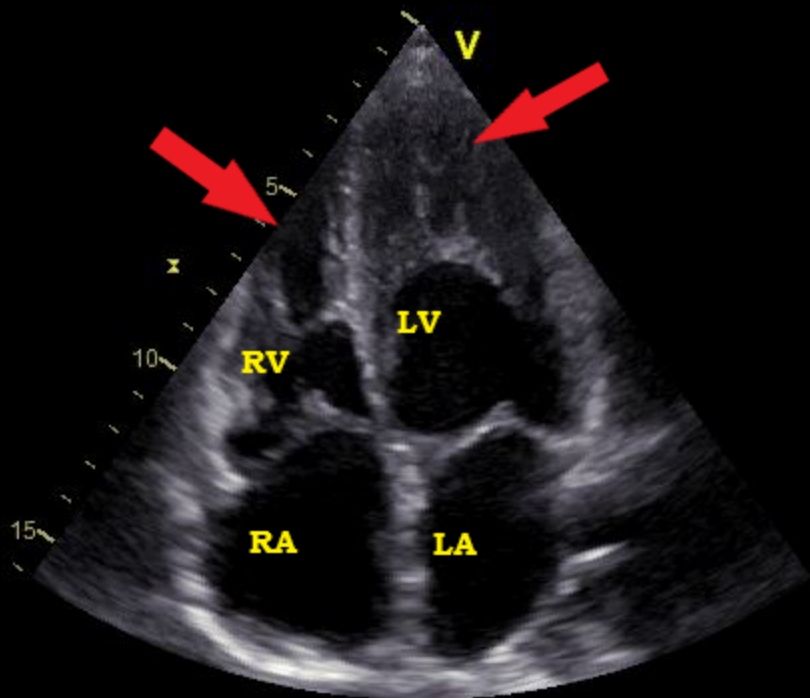
b: cardiac magnetic resonance imaging

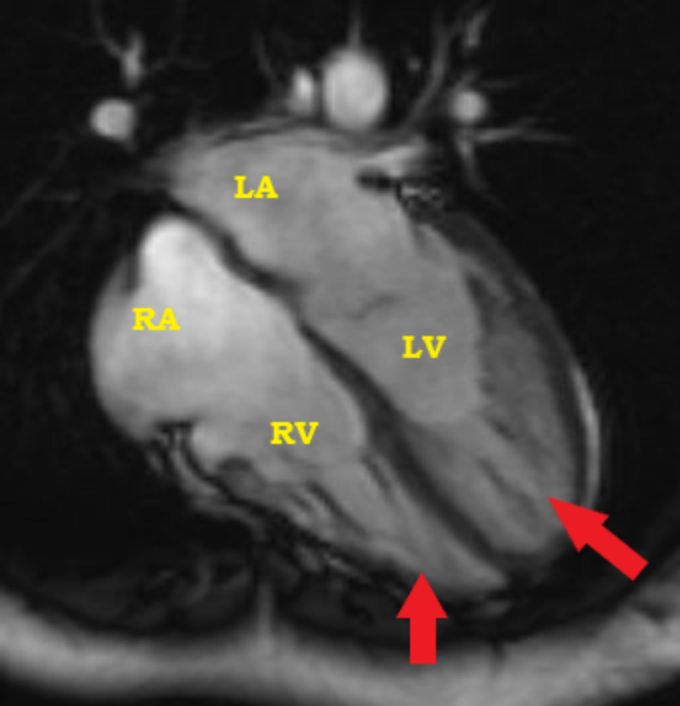
Abbreviations: LV: left ventricle, LA : left atrium, RV: right ventricle, RA : right atrium

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LA

RA

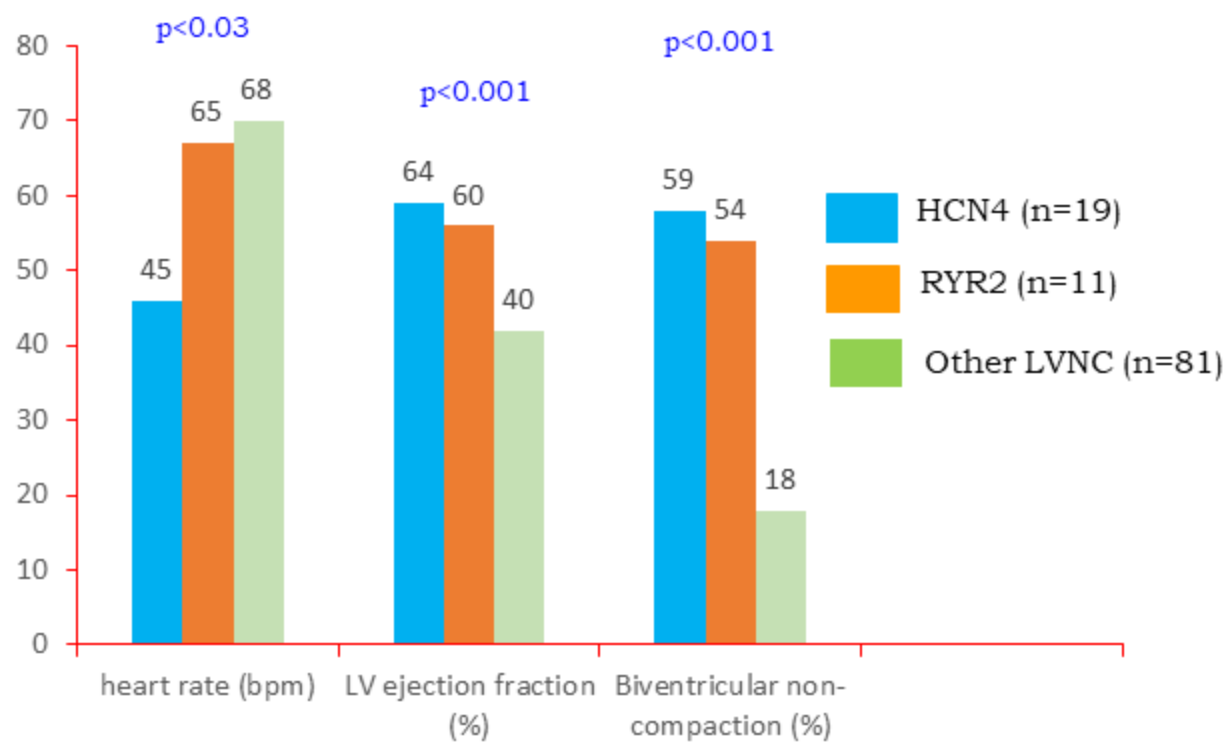
RV

LV

**Table 1** Comparison of patients with ion channel genes mutations with other patients with LVNC

	Ion channel genes mutations	Other patients	p	HCN4 mutated	Other patients	p	RYR2 mutated	Other patients	p
	<i>n = 30 (27%)</i>	<i>n = 81 (73%)</i>		<i>n = 19 (19%)</i>	<i>n = 81 (81%)</i>		<i>n = 11 (12%)</i>	<i>n = 81 (88%)</i>	
Male gender (%)	13 (43.3)	47 (58.0)	0.29	8 (42.1)	47 (58.0)	0.43	5 (45.5)	47 (58.0)	0.44
Age at diagnosis (years)	41.2 ± 18.5	46.9 ± 15.8	<b>0.23</b>	43.9 ± 19.5	46.9 ± 15.8	0.41	36.6 ± 16.5	46.9 ± 15.8	0.32
Heart rate (bpm)	51 (45-63)	68 (60-76)	0.22	45 (41-50)	68 (60-76)	<b>0.03</b>	65 (60-74)	68 (60-76)	0.78
Left ventricular ejection fraction (%)	60 (47-68)	40 (30-55)	<b>&lt;0.001</b>	64 (53-68)	40 (30-55)	<b>&lt;0.01</b>	60 (45-67)	40 (30-55)	<b>0.01</b>
Indexed telediastolic volume (mL/m <sup>2</sup> )	66 (58-75)	84 (58-112)	0.43	69 (59-82)	84 (58-112)	0.75	66 (58-71)	84 (58-112)	0.41
Indexed telesystolic volume (mL/m <sup>2</sup> )	25 (19-34)	48 (26-75)	<b>&lt;0.01</b>	23 (19-34)	48 (26-75)	<b>0.02</b>	27 (21-34)	48 (26-75)	<b>0.05</b>
NC/C diastole	2.3 (2.1-2.8)	2.3 (2.2-2.7)	0.97	2.6 (2.2--2.9)	2.3 (2.2-2.7)	0.17	2.2 (2.0-2.6)	2.3 (2.2-2.7)	0.37
NC/C systole	2.2 (2.0-2.3)	2.2 (2.0-2.4)	0.82	2.2 (2.0-2.3)	2.2 (2.0-2.4)	0.69	2.1 (2.0-2.5)	2.2 (2.0-2.4)	0.99
Number of non-compacted segments	5.5 (4-7)	5.0 (4-6)	0.69	6.0 (4-7)	5.0 (4-6)	0.68	4.0 (3-7)	5.0 (4-6)	0.82
Biventricular non-compaction (%)	17 (53.1)	15 (18.5)	<b>&lt;0.001</b>	11 (58.9)	15 (18.5)	<b>&lt;0.001</b>	6 (54.5)	15 (18.5)	<b>0.02</b>

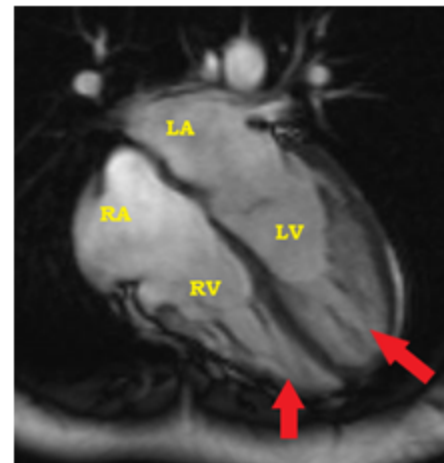
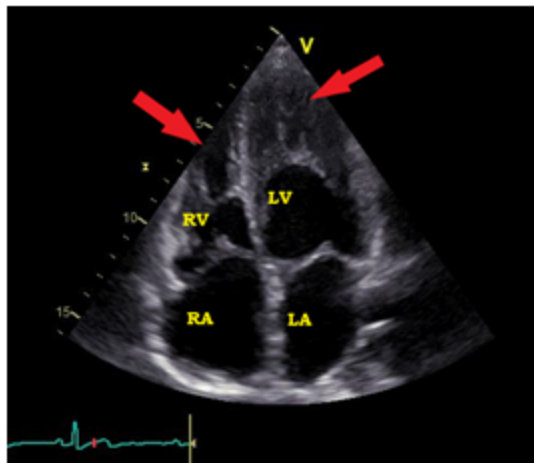
Quantitative data are expressed with mean ± SD (Student t test) or with median (Interquartile range) (Mann-Whitney test).



Comparison of patients with ion channel genes mutations with other patients with LVNC

**Ion channel gene mutation should be researched in patients with LVNC and:**

- Bradycardia
- Biventricular non-compaction
- Preserved left ventricular systolic function



Biventricular non-compaction (echocardiography and MRI)