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Clinical Research

Prevalence and Evolution of Right Ventricular Dysfunction Among Different Genetic Backgrounds in Dilated Cardiomyopathy

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See editorial by Lim et al., pages 1699–1701 of this issue.

ABSTRACT

Background: Titin (*TTN*)–related dilated cardiomyopathy (DCM) has a higher likelihood of left ventricular reverse remodelling compared with other genetic etiologies. No data regarding the evolution of right ventricular dysfunction (RVD) according to genetic background are available.

Methods: Consecutive 104 DCM patients with confirmed pathogenic genetic variants (51 *TTN*-related DCM; 53 other genetic DCM) and a control group of 139 patients with negative genetic testing and available follow-up data at 12-24 months were analysed. RVD was defined as a right ventricular fractional area change (RVFAC) < 35%. The main study end point was the comparison of the evolution of RVD and the change of RVFAC throughout the follow-up according to etiology. A

RÉSUMÉ

Contexte : La cardiomyopathie dilatée (CMD) liée à la titine (TTN) présente une probabilité plus élevée de remodelage inverse du ventricule gauche par rapport aux autres étiologies d'ordre génétique. Il n'existe pas de données concernant l'évolution de la dysfonction ventriculaire droite (DVD) en fonction du contexte génétique.

Méthodes : Cent quatre patients successifs atteints de CMD avec des variants génétiques pathogènes confirmés (51 CMD liées à la TTN; 53 autres CMD génétiques) et un groupe témoin de 139 patients avec un test génétique négatif et des données de suivi disponibles à 12-24 mois ont été analysés. La DVD était définie comme une modification de la fraction de raccourcissement en surface du ventricule droit (FRSVD) < 35 %. Le principal critère d'évaluation de l'étude était la

Dilated cardiomyopathy (DCM) is a primary heart muscle disease defined by left- or biventricular systolic dysfunction in the absence of abnormal loading conditions or significant coronary artery disease.[1,2] A specific genetic background is identified in up to 40% of patients with DCM, with 40 to 60 causative genes involved in determining the clinical phenotype.[3,4] Among these, truncating variants in the titin gene (*TTN*) represent the most prevalent etiology, accounting for 11% to 25% of genetically determined DCM.[4]

Recently, considerable efforts have been devoted to characterize the clinical phenotype of *TTN*-related DCM. Evidence suggests that *TTN*-truncating variants are associated with milder forms of DCM and a higher likelihood of left ventricular reverse remodelling (LVRR) with guideline-directed medical treatment (GMT).[5-7]

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composite of all-cause mortality and heart transplantation was included as outcome measure.

Results: At enrollment, RVD was present in 29.1% of genetically positive DCM without differences between genetic cohorts. At 14 months follow-up, 5.9% of *TTN*-related DCM patients vs 35.8% of other genetic DCM patients had residual RVD after treatment ($P < 0.001$). Accordingly, RVFAC significantly improved in the *TTN*-related DCM cohort and remained stably impaired in other genetic DCM patients. However, the evolution of RVD was similar between *TTN*-related DCM and patients without a genetic mutation. After adjusting for RVD at follow-up, no differences in the outcome measure were seen in the study cohorts.

Conclusions: The evolution of RVD in DCM is heterogeneous in different genetic backgrounds. *TTN*-related DCM is associated with a higher chance of RVD recovery compared with other genetic etiologies.

comparaison de l'évolution de la DVD et de la variation de la FRSVD tout au long du suivi, en fonction de l'étiologie. Un composite de mortalité toutes causes confondues et de transplantation cardiaque a été inclus comme indice de mesure du résultat.

Résultats : Lors de l'inclusion, la DVD était présente dans 29,1 % des DCM avec prédisposition génétique sans différences entre les cohortes avec étiologies d'ordre génétique. Après 14 mois de suivi, 5,9 % des patients atteints de CMD liée à la TTN contre 35,8 % des autres patients atteints de DCM génétique présentaient une DVD résiduelle après traitement ($P < 0,001$). Par conséquent, la FRSVD s'est améliorée de manière significative dans la cohorte de patients atteints de DCM liée à la TTN et est restée stable chez les autres patients atteints de DCM génétique. Cependant, l'évolution de la DVD était similaire entre la DCM liée à la TTN et les patients sans mutation génétique. Après ajustement de la DVD au cours du suivi, aucune différence dans l'indice de mesure des résultats n'a été observée parmi les cohortes étudiées.

Conclusions : L'évolution de la DVD dans la CMD est hétérogène selon différents contextes génétiques. La CMD liée à la TTN est associée à une plus grande chance de récupération de la DVD par rapport aux autres étiologies génétiques.

So far, no data are available about the prevalence and evolution of right ventricular (RV) involvement in patients affected by *TTN*-related DCM. Right ventricular dysfunction (RVD) is identifiable in approximately 30% of DCM patients at the initial clinical presentation,[8,9] with a high rate of RVD recovery after 6 to 12 months of GMT.[10] However, differences in the prevalence and progression of RVD according to genetic background have not been explored.

The aim of the present study was to assess the prevalence and evolution of RVD in patients with *TTN*-related DCM compared with other pathogenic genetic variants and with DCM patients with no genetic determinants.

Methods

Inclusion and exclusion criteria

All consecutive patients enrolled in the Trieste Heart Muscle Disease Registry, Italy,[11] from January 1995 to December 2017 were screened for inclusion. Patients with an available genetic test documenting a pathogenic or likely pathogenic mutation and available follow-up data at 12-24 months were eligible. A control group of genetically tested DCM patients enrolled in the same time frame, in which genetic testing was either negative or demonstrated a variant of uncertain significance, was also included. The enrollment was considered to be the first evaluation in our centre.

DCM was defined as left ventricular ejection fraction (LVEF) $< 50\%$ in the absence of a history of significant hypertension, $> 50\%$ stenosis of a major epicardial artery, excessive alcohol intake, chemotherapy, advanced systemic disease affecting short-term prognosis, pericardial diseases, congenital heart diseases, cor pulmonale, persistent supraventricular tachyarrhythmias, or active myocarditis.[1,2] Furthermore, as previously reported,[12] all patients fulfilling criteria for "definite," "probable," or "possible" arrhythmogenic right ventricular cardiomyopathy (with the exception of desmosomal mutation carrier status) were also excluded.[13]

The presence of coronary artery disease was ruled out by means of coronary artery angiography or computed tomography. Endomyocardial biopsy was performed in patients with suspected active myocarditis.

All patients were on GMT, unless contraindicated or not tolerated,[14] and received implanted cardioverter defibrillators (ICDs) and/or cardiac resynchronisation therapy (CRT) according to international guidelines.[15]

Echocardiographic analysis

Left ventricular and RV dimensions and function were assessed according to international guidelines.[16] Left ventricular volumes and diameters were indexed according to patients' body surface areas. LVEF was calculated by the Simpson biplane method.

RVD was considered to be RV fractional area change (RVFAC) ([end-diastolic area − end-systolic area]/end-diastolic area × 100) $< 35\%$. Changes in RV function from baseline to follow-up were assessed.

LVRR was defined by an absolute increase in LVEF $\geq 10\%$ (or absolute LVEF at follow-up $\geq 50\%$), associated with a relative reduction in indexed left ventricular end-diastolic diameter $\geq 10\%$ (or absolute value at follow-up ≤ 33 mm/m^2).[17]

Mitral regurgitation (MR) was considered to be significant only if moderate to severe (grade 2-4).

Genetic analysis and cluster classification

With the use of next-generation sequencing (NGS), patients' blood samples were tested for cardiomyopathy-related genes. The genetic testing covered more than 95% of known DCM-related genes, as previously reported.[12] All patients were sequenced; see Supplemental Appendix S1 for more details on the genetic panel used. All variants were validated with bidirectional Sanger sequencing and were classified according to current guidelines.[18] The minor allele frequency was verified in the gnomAD database (https://gnomad.broadinstitute.org/variant/22-46449891-G-A) and crosschecked with the

ClinVar (http://www.ncbi.nlm.nih.gov/clinvar) and Cardio Classifier (https://www.cardioclassifier.org) databases.

Patients with rare variants in genes belonging to the same subcellular compartment or with similar functions were clustered in different groups, as previously described.[7]

Based on the genetic test results, patients were divided into 2 groups: *TTN*-related DCM and other genetic DCM.

Study end point and outcome measure

The primary end point was the change throughout of RVFAC and the different prevalence of RVD from baseline to follow-up revaluation between patients with *TTN*-related DCM and those with other genetic DCM. A subsequent analysis conducted in the genetically tested negative DCM patients was also included and compared with the 2 main cohorts.

A composite of all-cause mortality and heart transplantation (HT) was also included as an outcome measure. Outcome data were obtained directly from the patient, their general physician, or from the registries of death of the municipalities of residence.

The study was approved by the Ethics Committee of Trieste, in accordance to the national Ministry of Health (approval 43/2009) and performed according to the Helsinki declaration. All patients gave written informed consent.

Statistical analysis

Clinical and laboratory variables were expressed as mean ± SD, median (interquartile range [IQR]), or n (%) as appropriate. Cross-sectional comparisons between groups were made by means of the analysis of variance test on continuous variables, with the use of the Brown-Forsythe statistic when the assumption of equal variances did not hold or the nonparametric median test when necessary. Chi-square or Fisher exact test was calculated for categoric variables. For binary variables, the McNemar test was calculated. Paired-sample *t* tests were performed to assess the evolution of RVFAC in the different cohorts. Univariable logistic regression was performed to assess the baseline parameters associated with the maintenance or incidence of RV dysfunction at follow-up. A multivariable model including the variables with P value < 0.1 at the univariable analysis[19] was performed. Because of the low number of events, 2 other multivariable models were built and the areas under the receiver operating characteristic curves of the models were compared. A Kaplan-Meier curve for all-cause mortality and HT was used to compare patients according to their genetic background. Cox regression analysis was performed to assess the role of genetic background and RVD at follow-up in determining the outcome measure. In the main analysis, familial cases were included. A sensitivity analysis considering only probands was performed. Interobserver and intraobserver variabilities in RVFAC measurement were ascertained by randomly selecting a sample of 40 patients with DCM. Two different operators (P.M. and V.N.) performed a double evaluation to achieve 90% power and, thus, to detect an intraclass correlation (ICC) of 0.8 under the null hypothesis of ICC = 0.6, by using an F test with a significance level of 0.05. The kappa agreement was also computed for both RVFAC and RVD as binary parameters. IBM SPSS software version 24 (IBM, Armonk, NY, USA) and R statistical software (library "cmprisk") were used for the analysis.

Results

Study population

We identified 139 patients with a genetically determined DCM. Of these, 32 patients with missing echocardiographic data in the follow-up period, or where RVFAC could not be estimated owing to poor echocardiographic windows, were excluded. Moreover, 3 patients (1 in the *TTN*-related DCM group and 2 in the other genetic DCM group) died before the follow-up evaluation. A final cohort of 104 patients (51 [49%] affected by *TTN*-related DCM and 53 [51%] with another genetic etiology) constituted the study population (Supplemental Table S1 and Supplemental Fig. S1).

The baseline characteristics of the study population are presented in Table 1. Patients were predominantly males, and those affected by *TTN*-related DCM were older than those with other genetic DCM (47 ± 14 vs 37 ± 15 years old, respectively; $P = 0.002$). Generally, patients had recent onset of heart failure (HF) (1 [IQR 0-8] months), without differences between the groups, and severely depressed LVEF. After a median follow-up of 14 [IQR 10-18] months, significantly more patients in the *TTN*-related DCM group achieved LVRR compared with the other genetic DCM group (37.2% vs 18.9%; $P = 0.049$) (Table 2 and Supplemental Table S2).

Prevalence and evolution of RVD according to genetic background

At baseline, RVFAC was significantly higher among *TTN*-related DCM patients (42 ± 11% vs 35 ± 11%; $P = 0.011$), despite a nonsignificant difference in the prevalence of RVD in the two groups (21.6% vs 35.8%; $P = 0.132$) (Table 1).

At follow-up, RVFAC significantly improved in the *TTN*-related DCM group (from 42 ± 11% to 46 ± 7%; $P = 0.023$), while it remained almost unchanged in the other genetic DCM group (from 35 ± 11% to 36 ± 10%; $P = 0.340$). Moreover, the prevalence of RVD at follow-up significantly differed in the study groups (5.9% vs 35.8% in *TTN*-related DCM vs other genetic DCM, respectively; $P < 0.001$), with a clear reduction of RVD prevalence in the *TTN*-related DCM group (from 21.6% to 5.9%) and no differences between baseline and follow-up in the other genetic DCM group (from 35.8% to 35.8%) (Table 2 and Fig. 1).

Predictors of RVD at follow-up

After adjusting the model for the most relevant clinical variables with an *a priori* selection (ie, *TTN*-related DCM vs other genetic DCM, baseline LVEF, and RVD), genetic background different from *TTN* variants (odds ratio [OR] 16.458, 95% confidence interval [CI] 3.095-87.513; $P = 0.001$) and the presence of baseline RVD (OR 6.776, 95% C.I. 1.976-23.239; $P = 0.002$) independently predicted the persistence of RVD (Table 3). As a sensitivity analysis, 2 other models were built. Model 2 considered left atrial end-systolic area instead of LVEF, and model 3 was mildly overfitted and included all of the significant clinical variables at univariable

Table 1. Baseline characteristics of the study population

	Genetically positive cohort (n = 104)	*TTN*-related DCM (n = 51; 49%)	Other genetic DCM (n = 53; 51%)	*P* value
Age, years (0)	42 ± 15	47 ± 14	37 ± 15	0.002*
Male sex (0)	78 (75%)	40 (78%)	38 (71%)	0.500
Time since HF diagnosis, mo (6)	1 (0-8)	1 (0-8)	1 (0-7)	0.82
Hypertension (0)	22 (21.2%)	12 (23.5%)	10 (18.8%)	0.635
SBP, mm Hg (10)	119 ± 16	119 ± 18	120 ± 16	0.712
NYHA III-IV (0)	13 (12.5%)	6 (11.8%)	7 (13.2%)	1.000
β-blockers (0)	86 (82.7%)	46 (95.8%)	40 (83.3%)	0.091
ACEI/ARB/ARNI (0)	95 (89.4%)	47 (92.2%)	46 (86.8%)	0.527
Loop diuretics (0)	52 (50%)	23 (45.3%)	29 (54.7%)	0.220
CRT (during follow-up) (0)	10 (9.6%)	5 (9.8%)	5 (9.4%)	1.000
ICD (during follow-up) (0)	44 (42.3%)	25 (49%)	19 (35.8%)	0.234
HR, beats/min (12)	76 ± 17	78 ± 19	73 ± 18	0.053
QRS length, ms (31)	102 ± 24	103 ± 19	101 ± 28	0.734
LBBB (0)	10 (9.6%)	6 (11.7%)	4 (7.5%)	0.740
Echocardiography				
LVEF, % (2)	33 ± 10	33 ± 11	34 ± 10	0.400
LVEDDi, mm/m^2 (5)	34 ± 6	34 ± 6	35 ± 5	0.059
LVEDVi, mL/m^2 (6)	94 ± 32	93 ± 33	94 ± 34	0.295
LAESA, cm^2 (12)	25 ± 8	26 ± 8	24 ± 8	0.240
RVFAC, % (0)	39 ± 11	42 ± 11	35 ± 11	0.011*
RVD (0)	30 (28.8%)	11 (21.6%)	19 (35.8%)	0.132
Moderate-severe MR (0)	34 (32.7%)	19 (37.3%)	15 (28.3%)	0.404

P values refer to the comparison between *TTN*-related DCM and other genetic DCM. In the first column, the numbers in parentheses are the numbers of genetically tested positive patients missing the data.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CRT, cardiac resynchronisation therapy; DCM, dilated cardiomyopathy; HR, heart rate; HF, heart failure; ICD, implantable cardiac defibrillator; LBBB, left bundle branch block; LAESA, left atrial end-systolic area; LVEDDi, indexed left ventricular end-diastolic diameter; LVEDVi, indexed left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association functional class; RVD, right ventricular dysfunction; RVFAC, right ventricular fractional area change; SBP, systolic blood pressure; TTN, titin.

* Significant (ie, $P < 0.05$).

analysis (Supplemental Table S3). In both models, both baseline RVD and the genetic background remained independently associated with RVD at follow-up (Supplemental Table S4). There were no significant differences in the areas under the receiver operating characteristic curves of any of the models (Supplemental Fig. S2).

Outcome measure

At a median follow-up of 97 (IQR 48-160) months, 3 of the 51 patients of the *TTN* group (5.9%) and 16 of the 53 patients of the other genetic group (30.2%) reached the composite outcome of all-cause mortality/HT ($P = 0.022$) (Fig. 2). However, adjusting for the presence of RVD at follow-up abolished the observed difference ($P = 0.245$) (Fig. 2 and Supplemental Table S5).

Sensitivity analyses

Considering only the probands in cases of familial clusters, 94 patients were identified (46 [49%] affected by *TTN*-related DCM and 48 [51%] with other genetic etiology) (Supplemental Table S1). The baseline characteristics of this cohort are reported in Supplemental Table S6. The results in this cohort were consistent with the main analysis. In particular, *TTN*-related DCM was associated with significant improvement of RV function during follow-up, while persistent RVD was observed in the other genetic DCM group (Supplemental Table S6 and Supplemental Fig. S3).

Genetically tested negative DCM cohort

A cohort of 139 genetically tested negative DCM patients with available follow-up data and adequate echocardiographic

Table 2. Evolution of RVD and rates of LVRR of the study population at follow-up

	TTN-related DCM (n = 51; 49%)	Other genetic DCM (n = 53; 51%)	*P* value
LVRR (%)	19/51 (37.2%)	10/53 (18.8%)	0.049*
RVFAC (%) (0)	46 ± 7	36 ± 10	< 0.001*
RVD (%) (0)	3 (5.9%)	19 (35.8%)	< 0.001*
Persistent RVD (%) (0)	2/11 (18.1%)	13/19 (68.4%)	0.004*
Incident RVD (%) (0)	1/40 (2.5%)	6/34 (17.6%)	0.09

In the first column, the numbers in parentheses represent the numbers of genetically tested positive patients missing the data. Persistent RVD: patients who presented RVD at both baseline and follow-up; incident RVD: patients with a normal RV function at baseline who developed RVD subsequently at follow-up. See Supplemental Table S2 for complete characteristics at follow-up of the study population.

DCM, dilated cardiomyopathy; LVRR, left ventricular reverse remodelling; RVD, right ventricular dysfunction; RVFAC, right ventricular fractional area change; TTN, titin.

* Significant *P* values.

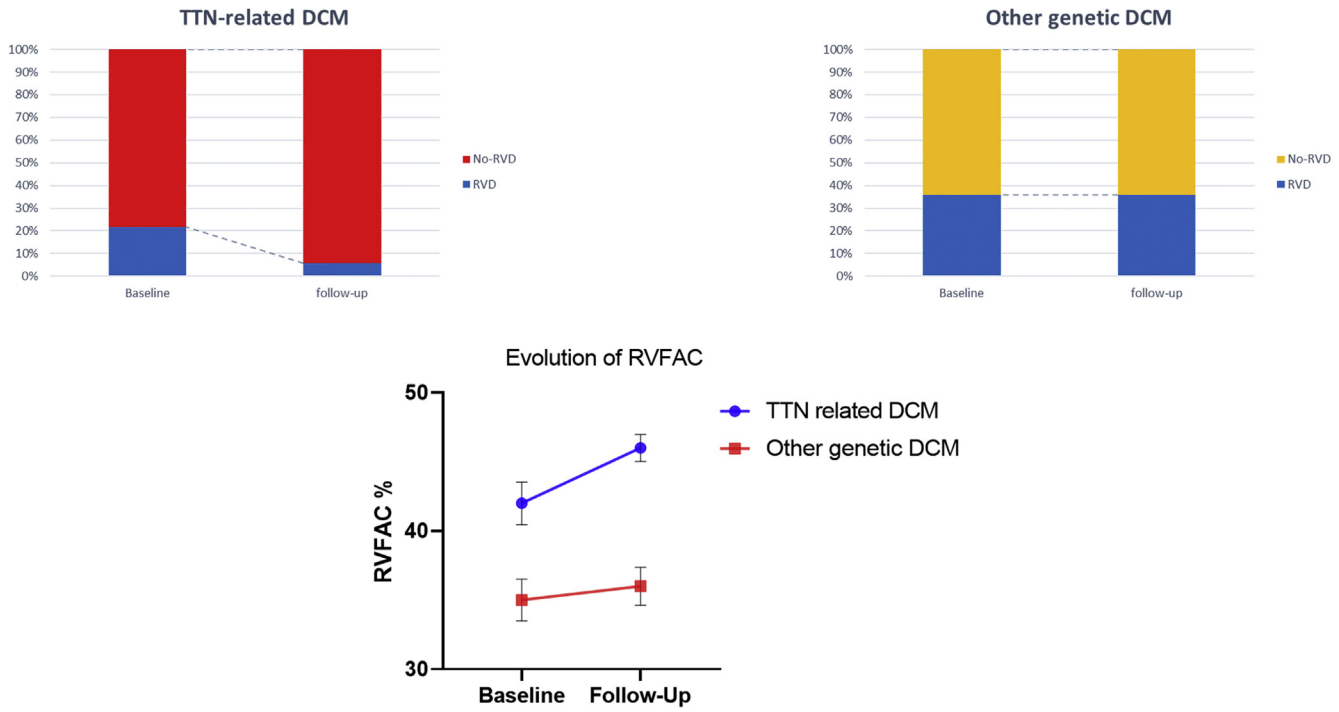

Figure 1. Evolution of RVFAC and prevalence of right ventricular dysfunction at baseline and follow-up in the two genetic cohorts. **Blue**: patients affected by *TTN*-related DCM; **red**: patients affected by other genetic DCM. Data are presented as mean ± SEM. DCM, dilated cardiomyopathy; RVFAC, right ventricular fractional area change; TTN, titin.

windows to calculate RVFAC were included as a control group. Compared with the genetically determined DCM cohort, genetically tested negative patients were older, more likely to suffer from associated hypertension, and had a higher prevalence of left bundle branch block and left atrial dilation. All the other clinical and echocardiographic characteristics were similar between the two groups (Supplemental Table S7). In particular, there were no significant difference in RVFAC (41 ± 12% vs 39 ± 11% in genetically negative vs genetically positive patients, respectively; $P = 0.304$), and the prevalence of RVD also was similar (28.6% vs 28.8%; $P = 1.000$).

At follow-up, genetically tested negative patients significantly improved their RVFAC (from 41 ± 12% to 44 ± 8%; $P < 0.001$) and the prevalence of RVD dropped from 28.8% to 7.8%.

Interestingly, at follow-up evaluation, both RVFAC and the prevalence of RVD were similar between genetically negative patients and those affected by *TTN*-related DCM (44 ± 8% vs 46 ± 7% [$P = 0.157$] and 7.8% vs 5.9% [$P = 0.764$], respectively). Conversely, when compared with other genetic etiologies, genetically negative patients had a significantly higher RVFAC (44 ± 8% vs 36 ± 10%; $P < 0.001$) and showed a lower prevalence of RVD (7.8% vs 35.8%; $P < 0.001$) (Table 4).

The unadjusted outcome measure was similar in genetically negative patients compared with those with pathogenic *TTN* mutations ($P = 0.390$), while it was significantly better than the in patients affected by other genetic etiologies ($P = 0.047$) (Supplementary Fig. S4).

Table 3. Multivariable analysis for persistence or incidence of RVD at follow-up

	OR	95% CI	*P* value
Other genetic DCM vs *TTN*-related DCM	16.458	3.095-87.513	0.001*
LVEF	0.962	0.902-1.025	0.231
RVD at baseline	6.776	1.976-23.239	0.002*

The univariable analysis is reported in Supplemental Table S3.

CI, confidence interval; DCM, dilated cardiomyopathy; OR, odds ratio; LVEF, left ventricular ejection fraction; RVD, right ventricular dysfunction; TTN, titin.

*Significant *P* values (ie, < 0.1).

Discussion

This analysis aimed to investigate the complex interplay between ventricles in DCM in one of the largest reported series of patients with available genetic testing and follow-up data. We report 3 important findings. First, the prevalence of RVD at clinical presentation is similar in different genetic DCM subgroups. Second, most patients with *TTN*-related DCM and genetically negative DCM improve their RV function with GMT and very rarely develop *de novo* RVD after their index presentation. In contrast, other genetic etiologies are less frequently associated with normalisation of RV function and, in a nonnegligible number of cases, show a late RV involvement during the natural progression of the disease. And third, the presence of RVD at initial presentation and a genetic background other than *TTN* are independently associated with the persistence RVD at follow-up.

RVD in DCM

DCM represents the second most common HF etiology, with a higher prevalence of RV involvement compared with ischemic heart disease.[9] However, few large-scale studies have

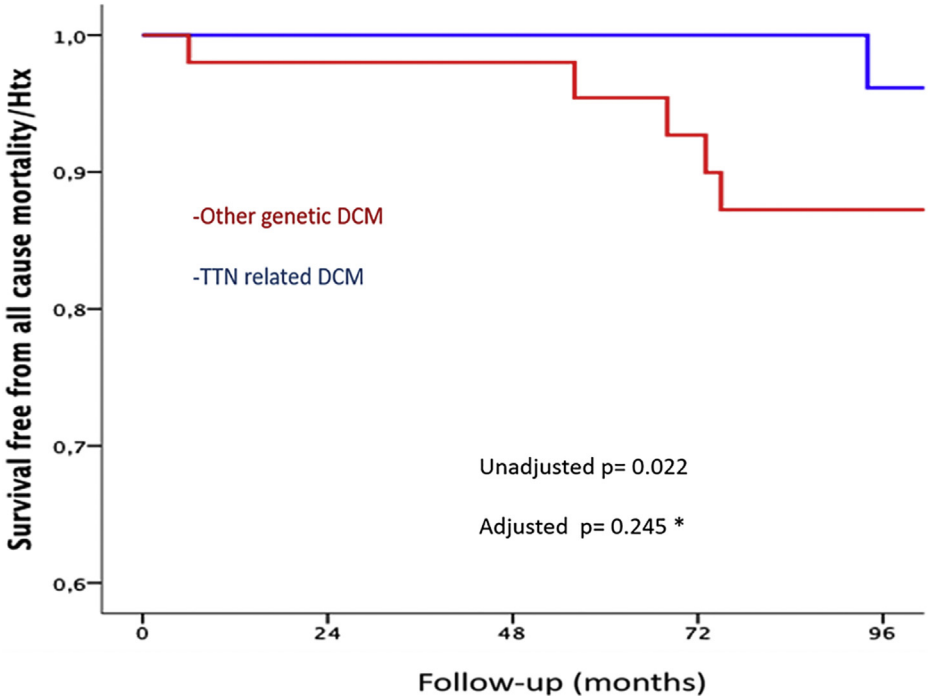

Figure 2. Kaplan-Maier survival curves for all-cause mortality/heart transplantation (HTx). The baseline was the evaluation at 14 (interquartile range 10-18) months. **Blue**: *TTN*-related DCM; **red**: other genetic DCM. *P value adjusted for right ventricular dysfunction at follow-up. DCM, dilated cardiomyopathy; TTN, titin.

previously described the prevalence and prognostic role of RVD in patients with DCM. Gulati et al. demonstrated, in a cohort of DCM patients investigated with the use of cardiac magnetic resonance (CMR), that up to one-third might present with RVD at the first clinical presentation.[8] Furthermore, after adjustment for other established prognostic factors, patients with baseline RVD had a 4-fold increase in cardiovascular mortality or HT.[8] Nevertheless, our group formerly documented that RVD is a dynamic process in the natural history of DCM and, although most patients normalise their RV function following GMT, persistent or late-onset RVD is strongly associated with poor prognosis.[10]

In the present analysis, we develop this understanding by describing, for the first time, differences according to genetic background. Approximately one-third of cases presented with RVD, regardless of genetic background. However, we describe a different evolution in *TTN*-related DCM patients compared with other genetic pathogenic variants. In fact, most patients in the *TTN*-related DCM group significantly improved their RV function over time and only ~ 5% of patients still had RVD at a median of 14 months after diagnosis. In contrast, patients with other genetic etiologies and RVD at first clinical presentation mostly maintained it during follow-up, and, in a nonnegligible number of cases (17.6%) (Table 2), a subsequent worsening of RV function in the successive 2 years after the initial presentation was documented. This was supported by the multivariable model, where a genetic background other than *TTN* was strongly and independently associated with the presence of RVD at follow-up ($P = 0.001$).

This finding is intriguing and suggests that *TTN*-related DCM is rarely a biventricular disease. Indeed, RVD at the first clinical presentation will normalise in the subsequent clinical course, likely representing hemodynamic impairment rather than structural disease or being more amenable to treatment. Therefore, appreciating the genetic background in patients presenting with DCM may be important to predict the dynamic evolution and the possible persistence of RVD,[20] which is associated with a poorer global outcome (Fig. 2).

Table 4. Prevalence of RVD in genetically positive and genetically negative DCM at follow-up

	Genetically negative DCM (n = 139)	*TTN*-related DCM (n = 51)	Other genetic DCM (n = 53)	*P* value
RVFAC (%)	44 ± 8	46 ± 7	36 ± 10	< 0.001*,†
RVD (%)	11 (7.8%)	3 (5.9%)	19 (35.8%)	< 0.001*,†
Persistent RVD	7/40 (17.5%)	2/11 (18.1%)	13/19 (68.4%)	0.004†; < 0.001*
Incident RVD at follow-up	4/99 (4.1%)	1/40 (2.5%)	6/34 (17.6%)	0.01*

Only significant *P* values (ie, < 0.05) are reported.
DCM, dilated cardiomyopathy; RVD, right ventricular dysfunction; RVFAC, right ventricular fractional area change; TTN, titin.
* Genetically negative DCM vs other genetic DCM.
† *TTN*-related DCM vs other genetic DCM.

TTN-related DCM and cardiac reverse remodelling: a benign mutation?

TTN pathogenic mutations are the most frequent cause of genetically determined DCM, representing almost one-third of this cohort.[4] *TTN*-related DCM is thought to be associated with a milder phenotype of the disease and a particularly high rate of LVRR with GMT.[5-7]

Previous studies have reported that genetically determined DCM patients are less prone to favourable LVRR compared with their genetically negative counterparts.[5] Interestingly, this difference was not evident in patients with *TTN* mutations compared with genetically negative patients.[5]

In our analysis, we confirmed that *TTN*-related DCM has a higher incidence of LVRR compared with other genetic etiologies ($P = 0.049$). Furthermore, we also demonstrated that RVD recovery is also similar in *TTN*-related DCM and genetically negative DCM, reaching approximately 80% in both groups. The latter finding is totally new and assumes that pathogenic *TTN* mutations might lead to a milder form of genetically determined DCM, in which there is a higher likelihood of global cardiac reverse remodelling with GMT.

Outcomes in genetically determined DCM; a matter of RVD?

After adjusting for the presence or absence of RVD at follow-up, no differences in the composite end point of all-cause mortality and HT were evident (Fig. 2).

This reinforces the importance of genotyping DCM patients. Indeed, in presence of *TTN*-related DCM, RVD might represent a therapeutic target. Conversely, in other genetic etiologies, RVD is more likely the epiphenomenon of advanced disease.

These results are promising, but the low number of events in our population did not allow us to adjust the differences in clinical outcomes for other variables, representing an important limitation. Furthermore, a trend toward a worse outcome for patients with other genetic DCM was seen. Future studies should be designed in order to assess this important concept.

Study limitations

This study has the intrinsic limitation of all observational registry-based studies. Because patients were enrolled from a referral center for cardiomyopathies, the results might not be generalisable for all DCM patients.

The enrollment period was long, starting in 1995, and several important advances in GMT occurred in this time.

B-Type natriuretic peptide levels were not systematically available and could not be included in the preset analysis. Drug doses also were not available, but, importantly, we did not observe any baseline and follow-up differences in rates of prescription.

The multivariable model included only 3 variables owing to the low number of events, which limited the statistical power of our analysis. However, in 2 sensitivity models, both RVD and genetic background remained significant.

Tricuspid annular plane excursion was available in only a minority of patients, and RVD was defined by RVFAC only.

Two-dimensional echocardiography clearly manifests some limitations in the assessment of RV compared with CMR. However, we performed an interobserver and intraobserver variability analysis that indicated a good performance level (ICC 0.929, 95% CI 0.888-0.958; $P < 0.001$; kappa agreements 0.84 and 0.81 for intraobserver and interobserver analyses, respectively) and we previously reported good correlation between echocardiographic RVFAC and CMR RV ejection fraction in a series of 50 DCM patients.[10]

Unfortunately, the low number of patients for each single pathogenic mutation did not allow us to draw any conclusions regarding the possible prevalence of RV involvement in single specific mutations, and this should be pursued in the future.

Conclusion

RVD is present in almost one-third of DCM cases. However, while the majority of patients affected by *TTN*-related DCM and patients without a demonstrable pathogenic variant normalise their RVD during follow-up, other genetic backgrounds mostly maintain it, which is associated with worse outcome. These results suggest that the evolution of RVD is heterogeneous in genetically determined DCM and genotyping appears to be pivotal in this context. These findings should be confirmed in larger series.

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Disclosures

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2021.06.024.