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Arrhythmia and impaired myocardial function in heritable thoracic aortic disease: An international retrospective cohort study

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A B S T R A C T

Background: Heritable thoracic aortic diseases (HTAD), typically entailing aortic complications, can be caused by pathogenic variants or likely pathogenic variants (PV/LPVs) in several genes, including fibrillin1 (*FBN1),* Actin Alpha2 (*ACTA2*) and genes encoding components of the transforming growth factor (TGF)-β signaling pathway. In addition to aortic complications, non-aortic cardiac disease such as impaired myocardial function and/or arrhythmia have been increasingly reported, mainly in Marfan syndrome with underlying *FBN1* PV/LPVs and are acknowledged as additional causes of morbidity and mortality. The prevalence of these manifestations in the various HTAD entities is largely unknown.

Methods: This international multicentre retrospective study collected data on patients with HTAD presenting non-aortic cardiac disease. A total of 9 centers from 7 different countries participated. Patients 12 years or older carrying a PV/LPV in one of the following genes: *FBN1*, *TGFBR1*, *TGFBR2*, *TGFB2*, *TGFB3*, *SMAD3* and *ACTA2* were screened. Non-aortic cardiac disease included impaired myocardial function and/or arrhythmia. Impaired myocardial function was defined as (a) symptomatic reduced ejection fraction (EF<50%). Arrhythmias included atrial fibrillation (AF), atrial flutter (AFL), ventricular tachycardia (VT), ventricular fibrillation (VF) and (aborted) sudden cardiac death (presumed arrhythmogenic) (SCD).

Results: Medical records of 3219 patients with HTAD were screened (2761, 385 and 73 carrying a PV/LPV in *FBN1*, in a TGF-β signaling gene and in *ACTA2* respectively). Non-aortic cardiac disease was reported 142 times in 101 patients (3.1%) (age 37 [range 12–77] years, 39% female): 88 patients carrying an *FBN1* PV/LPV and 13 carrying a PV/LPV in one of the TGF-β signaling genes. Neither impaired myocardial function nor arrhythmia was reported in screened patients carrying a PV/LPV in *ACTA2*. Among the 142 reported non-aortic cardiac diseases, 68 (48%) were impaired myocardial function, 47 (33%) were AF/AFL and 27 (19%) were VT/VF/SCD. Among the patients with non-aortic cardiac disease, prior cardiac surgery was noted in 80% and severe valvular disease (valvular surgery or severe valvular regurgitation) in 58%, while 18% of the patients developed non-aortic cardiac disease in the absence of any of the latter.

Conclusions: In patients with HTAD, arrhythmia and impaired myocardial function was reported in patients with PV/LPVs in *FBN1* and in the TGF-β signaling genes and not in patients harboring PV/LPVs in *ACTA2*. Though infrequent, non-aortic cardiac disease should be acknowledged as potentially severe, also occurring in young patients with no underlying significant valvular or aortic disease.

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1. Introduction

Heritable Thoracic Aortic Disease (HTAD) refers to a heterogeneous group of syndromic and non-syndromic disorders characterized by aortic dilatation, aneurysm formation and dissection or rupture(Pyeritz, 2014). Syndromic HTAD entities include Marfan syndrome (MFS, ORPHA:558, OMIM #154700), Loeys-Dietz syndrome (LDS, ORPHA:60030, OMIM #609192, 610168, 614816, 615582) and Aneurysm Osteoarthritis syndrome (ORPHA:284984, OMIM #613795). In patients with HTAD, the aortic root is most notably affected, but aneurysms and dissection can occur in all segments of the vessel. For obvious reasons, preventing life-threatening aortic complications has been the main focus in follow-up and treatment of patients with HTAD(Groth et al., 2018). However, other cardiovascular manifestations can occur, the most notable of which is mitral valve disease in patients with MFS and LDS. In addition, thorough cardiac surveillance in larger patient groups, has led to the observation of additional cardiac features such as arrhythmia and impaired myocardial function(Alpendurada et al., 2010; Audenaert et al., 2015; Hetzer et al., 2016; Hoffmann et al., 2013; Muiño-Mosquera et al., 2020; Yetman et al., 2003). Several publications describe patients with Marfan syndrome developing impaired myocardial function, ranging from subclinical reduced ejection fraction (EF) (Alpendurada et al., 2010; Meijboom et al., 2005) to end-stage heart failure necessitating heart transplantation(Audenaert et al., 2015; Kesler et al., 1994; Rao et al., 2018). Likewise, arrhythmia and sudden cardiac death (attributed to malignant arrhythmia) have been increasingly reported in patients with MFS(Muiño-Mosquera et al., 2020; Yetman et al., 2003). A recent Danish registry study showed that impaired myocardial function, (supra)ventricular tachycardia and sudden cardiac death were exceedingly prevalent in patients with MFS compared to an age and sex-matched control population(Andersen et al., 2021). These features often result from underlying valvular disease or occur after surgery. Nonetheless, primary (bi)ventricular myocardial involvement in the absence of valvular disease or cardiac surgery has also been demonstrated(Alpendurada et al., 2010; Rybczynski et al., 2010).

Most of the non-aortic cardiac disease has been described in MFS, which is caused by pathogenic variants or likely pathogenic variants (PV/LPVs) (class 5 and 4) in the fibrillin 1 (*FBN1*) gene. Several other genes have been identified that associate with both syndromic and non-syndromic HTAD, the most frequent of which include *TGFBR1*, *TGFBR2*, *TGFB2*, *TGFB3*, *SMAD3* and *ACTA2*(De Backer and Renard, 2015). PV/LPVs in these genes result in alterations of the extracellular matrix configuration (*FBN1*), the transforming growth factor (TGF)-β signaling pathway (*TGFBR1*, *TGFBR2*, *TGFB2*, *TGFB3*, *SMAD3)* or the vascular smooth muscle cell contractile apparatus (*ACTA2*)(Zentner et al., 2020). Sporadic cases of heart failure and arrhythmia have also been reported in patients with PV/LPVs in the TGF-β signaling genes, but data from registries are lacking(De Backer and Braverman, 2018; Extramiana et al., 2018; Van Der Van Der Linde et al., 2012). Currently existing limitations to the reported studies include small population sizes, short follow-up times and an almost exclusive focus on MFS. With this study, we aimed to provide better insight into the prevalence of these features and obtain more detailed clinical characteristics of affected patients.

2. Methods

2.1. Study design

We conducted a retrospective, multicenter study including 9 centers from 7 different countries. Patients aged 12 years or older carrying a PV/LPV (class 5 and 4, according to the ACMG/AMP criteria(Richards et al., 2015)) in *FBN1*, *TGFBR1*, *TGFBR2*, *TGFB2*, *TGFB3*, *SMAD3* and *ACTA2* were screened. Detection and interpretation of the genetic variants was done according to the method applicable at the time of diagnosis in each participating center. Screening was performed based on electronic databases available at the respective centers and at the discretion of the local investigators. Patients with non-aortic cardiac disease were identified. Non-aortic cardiac disease included sustained ventricular tachycardia or -fibrillation (VT/VF), (aborted) sudden cardiac death (presumed arrhythmogenic) (SCD), atrial fibrillation or flutter (AF/AFL) or impaired myocardial function. Sustained VT was defined as a documented wide complex (QRS duration >120 ms) tachycardia at a rate of >100 beats per minute, lasting >30 s or accompanied by hemodynamic instability within 30 s(Priori et al., 2015). SCD was defined as a witnessed cardiac arrest or death within 1 h after the onset of acute symptoms, or an unexpected death in a patient known to have been well within the last 24 h. SCD was considered arrhythmogenic if autopsy showed no signs of dissection or if other potential causes were deemed highly unlikely based on findings and the timing of the last visit. Impaired myocardial function was defined as (a)symptomatic reduced ejection fraction (EF<50%). Calculation of ejection fraction was performed in accordance with the local echocardiographic follow-up protocols(Lang et al., 2015). Patients with arrhythmia or impaired myocardial function were seen at least once in the last 2 years before the non-aortic cardiac disease occurred. To estimate the prevalence of non-aortic cardiac disease in HTAD patients, the numerator consisted of any patient with a PV/LPV in a gene of interest and a medical record of non-aortic cardiac disease ever seen in each center, while the denominator denotes the total number of patients currently under follow-up (i.e. seen at least once in the last 3 years to exclude patients that were lost to follow-up). All respective Ethical Committees approved the study and granted waiver for the requirement of obtaining written informed consent.

2.2. Data collection

Clinical data obtained at the time of the non-aortic cardiac disease and from the last patient visit were extracted from the medical records. If available, data on family history, medical history, follow-up duration, medication, type of treatment and outcomes was collected. Surgical history involving the aorta and/or the heart valves was recorded. Severe valvular disease was defined as a history of valvular surgery (aortic or mitral) or presence of severe aortic or mitral valve regurgitation at the time of non-aortic cardiac disease. Aortic events were defined as aortic dissection (Stanford type A or B) or any type of prophylactic aortic surgery. Mitral valve surgery included any mitral valve surgery (isolated or in combination with aortic surgery) or mitral valve procedure (MitraClip). Echocardiographic data at the time of the non-aortic cardiac disease or the last available data before the occurrence, were recorded. Data on left and right ventricular dimensions, left systolic and diastolic function, valvular function, valvular prolapse and measurement of aortic diameters were analyzed. Echocardiographic images were assessed retrospectively looking for the presence of mitral annular disjunction (MAD) prior to any non-aortic cardiac disease. In case of mitral valve surgery, images taken prior to the surgery were used for assessment. MAD was defined as the presence of a visible separation (at least 1 mm) between the left atrial wall-mitral valve junction and the base of the LV wall. MAD distance was measured during end-systole in parasternal long-axis views from the left atrial wall-mitral valve leaflet junction to the base of the LV posterolateral wall(Dejgaard et al., 2018).

2.3. Statistics

Categorical data were reported as proportions or percentages and comparisons between groups were performed using Chi-squared test or Fisher's exact test. Continuous data are reported as means (±SD) or medians [interquartile range (IQR)]. The Shapiro–Wilk test was used to test for normality. Comparisons between groups were performed using either Student's t-test or Mann–Whitney *U* test. Statistical tests were two tailed, and a P value < 0.05 was considered statistically significant. Analyses were conducted using SPSS v27.0 (IBM Corp., Armonk, NY, USA).

3. Results

A total of 3219 patients with HTAD were under follow-up during the study at the different participating centers (2761 patients carrying a PV/LPV in *FBN1*, 385 patients carrying a PV/LPV in the TGF-β signaling genes and 73 patients carrying a PV/LPV in *ACTA2*). A total of 142 non-aortic cardiac diseases were reported in 101 patients (3.1%) of whom 88 (87%) carried a PV/LPV in *FBN1* and 13 (13%) carried a PV/LPV in one of the TGF-β signaling genes. Fig. 1 illustrates the reported non-aortic cardiac diseases for each group. None of the studied features were reported in the screened patients with a PV/LPV in *ACTA2*. The prevalence of impaired myocardial function and VT/VF/SCD was similar between patients carrying a PV/LPV in *FBN1* and patients carrying a PV/LPV in the TGF-β signaling genes (2.2% vs. 1.8%, p = 0.621 and 0.8% vs. 1.6%, p = 0.132 respectively). Among patients carrying PV/LPVs in the TGF-β signaling genes, the prevalence of VT/VF/SCD and of myocardial impairment was highest in patients carrying PV/LPVs in the *TGFBR2* gene (Supplemental Fig. 1). Atrial arrhythmia (AF/AFL) was more often reported in patients with PV/LPVs in *FBN1* compared to patients with PV/LPVs in the TGF-β signaling genes (1.7% vs. 0.3%, p = 0.033). In fact, within the group of patients with PV/LPVs in the TGF-β signaling genes, only one patient carrying a variant in the TGFB2 gene experienced AF/AFL.

3.1. Distribution of non-aortic cardiac disease

Among the 142 reported non-aortic cardiac diseases, 68 (48%) were impaired myocardial function, 47 (33%) were AF/AFL and 27 (19%) were VT/VF/SCD. The distribution of non-aortic cardiac diseases among patients carrying a PV/LPV in *FBN1* and in the TGF-β signaling genes are presented in Fig. 2 and corresponding patient characteristics can be found in Table 1. Of the 68 patients with impaired myocardial function, 37 had symptomatic reduced EF (median EF 35% [IQR 26–45]) whereas 31 had asymptomatic reduced EF (median EF 47% [IQR 43–48]). Heart transplantation (n = 8) was reported only in patients with PV/LPVs in

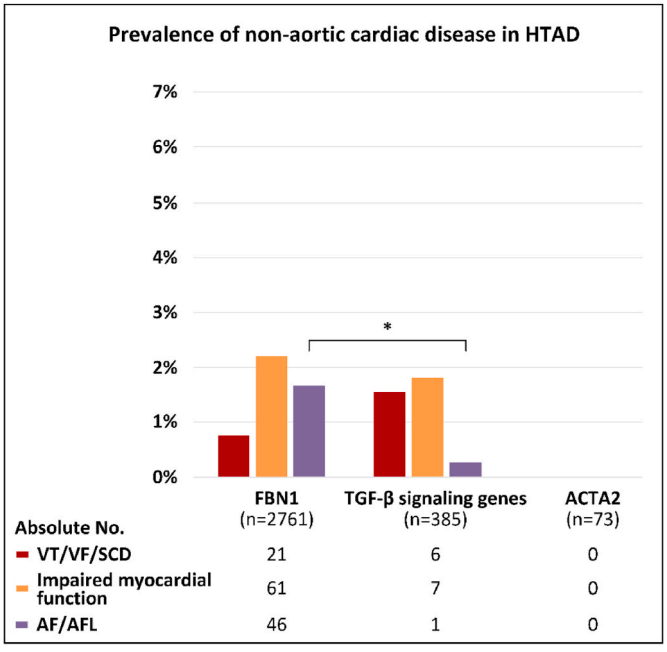

Fig. 1. Prevalence of non-aortic cardiac disease in HTAD
Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; HTAD, heritable thoracic aortic disease; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.
Figure legend: Bar chart illustrating the prevalence of non-aortic cardiac disease among patients with heritable thoracic aortic disease.

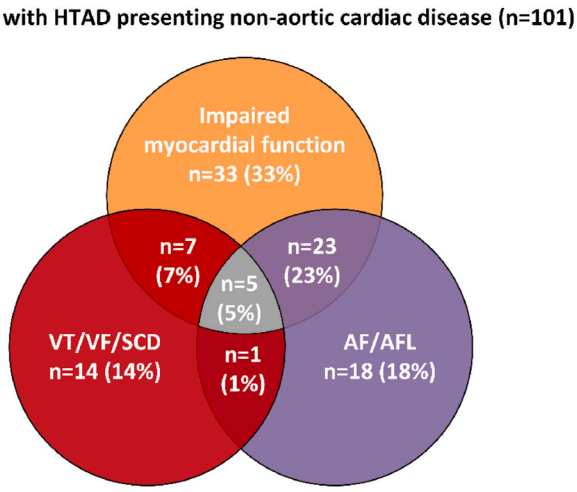

Fig. 2. Non-aortic cardiac disease among patients with HTAD
Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; HTAD, heritable thoracic aortic disease; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.
Figure legend: Venn diagram displaying the overlap in non-aortic cardiac disease among patients with heritable thoracic aortic disease.

FBN1. Patients with impaired myocardial function were often male (69%). Of the 27 patients presenting VT/VF/SCD, 21 had documented VT/VF (of which 5 also had SCD). Another 6 patients were reported with SCD without documentation of malignant arrhythmia.

3.2. Clinical presentation of non-aortic cardiac disease

Non-aortic cardiac disease was reported across a wide age spectrum (age range: 12–77 years). In patients with PV/LPVs in the TGF-β signaling genes, non-aortic cardiac disease occurred at a shorter follow-up duration (4.7 [1.7–7.8] years vs. 7.7 [4.3–10.1] years, p = 0.024) and at a younger age compared to patients with PV/LPVs in *FBN1* (18 [17–40] years vs. 41 [28–55] years, p = 0.012). Patients carrying PV/LPVs in the TGF-β signaling genes with impaired myocardial function were younger (18 [17–36] years vs. 37 [28–52] years, p = 0.035), but those with VT/VF/SCD showed no age difference (22 [15–36] years vs. 30 [21–47] years, p = 0.289) compared to patients carrying PV/LPVs in *FBN1*. Seven patients presented with non-aortic cardiac disease below the age of 16 years, 6 carried a PV/LPV in *FBN1* and 1 carried a PV/LPV in *TGFBR2*. Among these 7 patients, 3 presented SCD (of which 2 had documented VT/VF), 1 had symptomatic reduced EF, 2 had asymptomatic reduced EF and another had both documented VT/VF and symptomatic reduced EF. Of the 27 patients with VT/VF/SCD, 19 patients (70%) presented this feature as a first event while 8 patients (30%) had a preceding diagnosis of impaired myocardial function. Patients presenting with VT/VF/SCD as first event were young (28 [16–46] years) and mitral annular disjunction (MAD) was identified in almost all of those with available echocardiographic images (16 out of 17 (94%)). Likewise, impaired myocardial function (n = 68) was initially identified in 64 patients (94%), while 4 patients (6%) were diagnosed after the occurrence of VT/VF/SCD. Except for age, no significant differences were found in demographics, medical history and echocardiographic data between patients with PV/LPVs in *FBN1* and those carrying PV/LPVs in genes of the TGF-β pathway. Of note, a subgroup of 18 patients (18%) presented non-aortic cardiac disease in the absence of severe valvular disease or cardiac surgery (Table 2). In these 18 patients, impaired myocardial function was mostly mild: 5 had asymptomatic reduced EF (median EF 47% [IQR 46–48]) and only 1 was diagnosed with symptomatic reduced EF (EF 35%). In 6 of the 11 SCD cases (55%), severe valvular disease or a history of cardiac surgery was absent. No other significant differences were found in clinical characteristics

Table 1
Characteristics of patients with non-aortic cardiac disease per gene (group).

Demographics	Patients, No./total No. (%)			
	Total N = 101	*FBN1* N = 88	TGF-β signaling genes N = 13	*P* value
Age at the time of non-aortic cardiac disease (yrs)	37 [26–53]	41 [28–55]	18 [17–40]	**0.012**
Age <16 yrs at the time of non-aortic cardiac disease	7 (7)	6 (7)	1 (8)	1.000
Follow-up duration (yrs)	7.3 [3.5–10]	7.7 [4.3–10.1]	4.7 [1.7–7.8]	**0.024**
Female	39 (39)	33 (38)	6 (46)	0.550
History of pregnancy	13 (33)	13 (39)	0 (0)	0.081
Proband	69 (68)	59 (67)	10 (77)	0.750
Medication				
Beta blocker	88 (87)	76 (86)	12 (92)	1.000
ARB	51 (51)	44 (50)	7 (54)	0.796
History of arterial hypertension	21 (21)	20 (23)	1 (8)	0.292
History of hyperlipidemia	16 (16)	16 (18)	0 (0)	0.122
Non-aortic cardiac disease				
AF/AFL	47 (47)	46 (52)	1 (8)	**0.003**
VT/VF/SCD	27 (27)	21 (24)	6 (46)	0.103
Documented VT/VF	21 (21)	18 (21)	3 (23)	0.730
SCD	11 (11)	7 (8)	4 (31)	**0.033**
Impaired myocardial function	68 (67)	61 (69)	7 (54)	0.344
Symptomatic reduced EF	37 (37)	32 (36)	5 (39)	1.000
Asymptomatic reduced EF	31 (31)	29 (33)	2 (15)	0.334
Heart transplantation	8 (8)	8 (9)	0 (0)	0.592
Medical history				
Aortic event	69 (68)	61 (69)	8 (62)	0.544
Prophylactic ARR	59 (58)	52 (59)	7 (54)	0.720
Aortic dissection[f]	19 (19)	17 (19)	2 (15)	1.000
Type A dissection	13 (13)	11 (13)	2 (15)	0.673
Type B dissection[g]	9 (9)	8 (9)	1 (8)	1.000
Cardiovascular surgery (ARR and/or valvular surgery)	81 (80)	72 (82)	9 (69)	0.282
Valvular surgery (aortic or mitral)	56 (55)	49 (56)	7 (54)	0.901
Aortic valve surgery	31 (31)	25 (28)	6 (46)	0.211
Mitral valve surgery[e]	33 (33)	30 (34)	3 (23)	0.538
Ablation (after event)	12 (12)	11 (13)	1 (8)	1.000
Atrial ablation	10 (10)	10 (11)	0 (0)	0.352
Ventricular ablation	3 (3)	2 (2)	1 (8)	0.342
Device (after event)	22 (22)	19 (22)	3 (23)	1.000
PM	8 (8)	7 (8)	1 (8)	1.000
ICD	17 (17)	15 (17)	2 (15)	1.000
CRT-D	4 (4)	4 (5)	0 (0)	1.000
Echocardiographic data at the time of non-aortic cardiac disease (or last available prior to onset)				
LVEF (%)	47 [40–58]	47 [40–58]	49 [40–61]	0.569
LVESDi (mm/m^2)	21 [18–27]	21 [18–27]	21 [18–25]	0.677
LVEDDi (mm/m^2)	30 [27–35]	30 [27–35]	32 [28–38]	0.333
LA volume (indexed – ml/m^2)[a]	36 [26–55]	35 [27–56]	47 [24–54]	1.000
MVP (all types)	60 (59)	52 (59)	8 (62)	0.867
MAD presence[b]	41 (50)	36 (49)	5 (56)	1.000
Severe valvular regurgitation (Grade III-IV)	22 (22)	21 (24)	1 (8)	0.288
Severe MR	20 (20)	19 (22)	1 (8)	0.455
Severe AR	3 (3)	3 (3)	0 (0)	1.000
Aortic root[c] (mm)	41 ± 5	40 ± 4	43 ± 7	0.277
Aortic root Z-score[c,d]	3.1 ± 1.5	2.9 ± 1.2	4 ± 2.5	0.381

Values are given as mean ± SD, median [IQR] or number (%).
Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; AR, aortic regurgitation; ARB, angiotensin receptor blocker; ARR, aortic root replacement; CRT, cardiac resynchronization therapy; ICD, Implantable cardioverter defibrillator; LA, left atrium; LVEDDi, left ventricular end-diastolic diameter indexed; LVEF, left ventricular ejection fraction; LVESDi, left ventricular end-systolic diameter indexed; MAD, mitral annular disjunction; MR, mitral regurgitation; MVP, mitral valve prolapse; PM, pacemaker.
[a] available data in 56 out of 101 patients.
[b] based on available echocardiographic images in 82 out of 101 patients.
[c] measured at the aortic sinus in patients without aortic root replacement.
[d] Z-score calculated according to Campens et al. (2014)
[e] Of whom 1 patient underwent MitraClip procedure.
[f] All patients with aortic dissection underwent aortic surgery.
[g] Of the 9 patients with type B dissection, 7 had prior aortic root replacement while 2 had aortic surgery for the type B aortic dissection.

between patients presenting non-aortic cardiac disease in the presence or absence of severe valvular disease or cardiac surgery (Table 2). A history of cardiovascular surgery (aortic surgery or any valvular surgery) was reported among 81 (80%) of the included patients and severe valvular disease was documented in 58% (Fig. 3). Among patients with impaired myocardial function (n = 68), severe valvular regurgitation (at the time of diagnosis) was noted in 27% and severe valvular disease (defined as severe valvular regurgitation or a history of valvular surgery) was present in 71%. A history of cardiovascular surgery was noted in 26 (84%) of the 31 patients with asymptomatic reduced EF and the median EF was 47% [IQR 43–48%]. Patients with symptomatic reduced EF more often had severe mitral valve regurgitation compared to patients with asymptomatic reduced EF (54% vs. 23%, p = 0.008). No significant differences were noted regarding severe aortic valve regurgitation (22% vs. 19%, p = 0.818) or cardiovascular surgery (97% vs. 84%, p = 0.085) respectively between patients with symptomatic reduced EF and those with asymptomatic reduced EF. In patients with AF/AFL (n = 47), median indexed left atrial volume was 44 ml/m^2 [IQR 30–76], severe valvular regurgitation (at the time of diagnosis) was noted in 15%, severe valvular disease (defined as severe valvular regurgitation or history of valvular surgery) in 64% and cardiovascular surgery in 85%.

4. Discussion

In this retrospective multicenter study, we present one of the largest analyses to date on non-aortic cardiac disease, including arrhythmia and/or impaired myocardial function in patients with HTAD with a confirmed underlying genetic cause. Medical records of 3219 patients were screened. Non-aortic cardiac disease was present in 3.1% and occurred across a wide age spectrum (age range 12–77 years). Though frequently associated with severe valvular disease (58%) and cardiac surgery (80%), we noted that 18% of the patients had non-aortic cardiac disease in the absence of any of the latter. Our study is the first to report on non-aortic cardiac disease in a large cohort of HTAD patients in whom the underlying genetic defect is known, allowing a better interpretation of the underlying gene-based pathophysiology.

When comparing the prevalence of non-aortic cardiac disease to the general population, demographic differences (i.e. age) among other factors should be considered in any made comparison. Though non-aortic cardiac disease was reported across a wide age spectrum, it can be noted that the median age of patients presenting non-aortic cardiac disease in our study (37 years) falls within the reported average age interval (ranging between 30 and 40 years) of FBN1, ACTA2 and TGF-β signaling gene cohorts described in other studies (Mühlstädt et al., 2019; Regalado et al., 2015). In our study, non-aortic cardiac disease was reported in 3.1% and the median age was 37 [26–53] years. Data from epidemiological studies and pooled population based cohorts (Ceia et al., 2002; Tromp et al., 2021) estimate a prevalence of HF of 1–1.4% in young patients (<55 years) compared to 2.1% of patients presenting with impaired myocardial function in our study. An increased occurrence of heart failure among patients with MFS compared to the general population has been suggested in several reports (on mostly non-genotyped populations) and was recently confirmed in a Danish registry study by Andersen et al.(Andersen et al., 2021; von Kodolitsch

Table 2
Comparison between patients having non-aortic cardiac disease with and without valvular disease or cardiovascular surgery.

Demographics	Patients, No./total No. (%)			
	Total N = 101 (%)	Absence of cardiac surgery or severe valvular disease N = 18 (%)	Presence of cardiac surgery or severe valvular disease N = 83 (%)	*P* value
PV/LPV in *FBN1*	88 (87)	14 (78)	74 (89)	0.241
PV/LPV in the TGF-β signaling genes	13 (13)	4 (22)	9 (11)	0.241
Age at the time of non-aortic cardiac disease (yrs)	37 [26–53]	37 [16–51]	37 [28–53]	0.372
Age <16 yrs at the time of non-aortic cardiac disease	7 (7)	4 (22)	3 (4)	**0.018**
Follow-up duration (yrs)	7.3 [3.5–10]	4.4 [1.1–8.7]	7.4 [4.5–10]	**0.046**
Female	39 (39)	9 (50)	30 (36)	0.274
History of pregnancy	13 (33)	2 (22)	11 (37)	0.689
Proband	69 (68)	12 (67)	57 (69)	0.868
Medication				
Beta blocker	88 (87)	16 (89)	72 (87)	1.000
ARB	51 (51)	7 (39)	44 (53)	0.277
History of arterial hypertension	21 (21)	1 (6)	20 (24)	0.110
History of hyperlipidemia	16 (16)	3 (17)	13 (16)	1.000
Non-aortic cardiac disease				
AF/AFL	47 (47)	7 (39)	40 (48)	0.473
VT/VF/SCD	27 (27)	6 (33)	21 (25)	0.559
Documented VT/VF	21 (21)	2 (11)	19 (23)	0.350
SCD	11 (11)	6 (33)	5 (6)	**0.004**
Impaired myocardial function	68 (67)	6 (33)	62 (75)	**0.001**
Symptomatic reduced EF	37 (37)	1 (6)	36 (43)	**0.003**
Asymptomatic reduced EF	31 (31)	5 (28)	26 (31)	0.767
Heart transplantation	8 (8)	0 (0)	8 (10)	0.344
Medical history				
Ablation (after event)	12 (12)	1 (6)	11 (13)	0.688
Atrial ablation	10 (10)	1 (6)	9 (11)	0.686
Ventricular ablation	3 (3)	0 (0)	3 (4)	1.000
Device (after event)	22 (22)	2 (11)	20 (24)	0.347
PM	8 (8)	0 (0)	8 (10)	0.344
ICD	17 (17)	2 (11)	15 (18)	0.730
CRT-D	4 (4)	0 (0)	4 (5)	1.000
Echocardiographic data at the time of non-aortic cardiac disease (or last available prior to onset)				
LVEF (%)	47 [40–58]	60 [48–70]	46 [37–50]	**<0.001**
LVESDi (mm/m^2)	21 [18–27]	21 [17–24]	21 [18–27]	0.387
LVEDDi (mm/m^2)	30 [27–35]	31 [25–37]	30 [27–35]	0.800
LA volume (indexed – ml/m^2)[a]	36 [26–55]	30 [25–43]	36 [26–58]	0.326
MVP	60 (59)	9 (50)	51 (61)	0.370
MAD presence[b]	41 (50)	9 (60)	32 (48)	0.391
Aortic root[c] (mm)	41 ± 5	41 ± 5	41 ± 5	0.860
Aortic root Z-score[c,d]	3.1 ± 1.5	3.2 ± 1.7	3 ± 1.1	0.706

Values are given as mean ± SD, median [IQR] or number (%).
Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; AR, aortic regurgitation; ARB, angiotensin receptor blocker; ARR, aortic root replacement; CRT, cardiac resynchronization therapy; ICD, Implantable cardioverter defibrillator; LA, left atrium; LVEDDi, left ventricular end-diastolic diameter indexed; LVEF, left ventricular ejection fraction; LVESDi, left ventricular end-systolic diameter indexed; MAD, mitral annular disjunction; MR, mitral regurgitation; MVP, mitral valve prolapse; PM, pacemaker.
[a] available data in 56 out of 101 patients.
[b] based on available echocardiographic images in 82 out of 101 patients.
[c] measured at the aortic sinus in patients without aortic root replacement.
[d] Z-score calculated according to Campens et al. (2014)

et al., 2019) Estimates on the epidemiology of sudden cardiac death vary widely depending on data sources for case ascertainment, definitions used, and methods used for extrapolation of rates(Hayashi et al., 2015). Therefore, we refrained from comparing the prevalence of VT/VF/SCD in our cohort to other data sources. In addition, it would be of interest to compare the prevalence of non-aortic cardiac disease in patients with HTAD to other cohorts such as non-genetic aortic dissection/aneurysms in younger or older ages.

The overall prevalence of impaired myocardial function and VT/VF/SCD was similar in patients carrying PV/LPVs in *FBN1* as in patients carrying PV/LPVs in the TGF-β signaling genes, whereas atrial arrhythmia (AF/AFL) was mainly reported in patients with PV/LPVs in *FBN1*. PV/LPVs in *ACTA2* are reported in up to 14% of the non-syndromic HTAD patients(Guo et al., 2007). None of the 73 screened patients with a PV/LPV in *ACTA2* in this cohort were reported with non-aortic cardiac disease. In addition, to the best of our knowledge, current literature holds no case reports of arrhythmia or impaired myocardial function in patients with PV/LPVs in *ACTA2*. This suggests little to no involvement of *ACTA2* in the pathophysiology of impaired myocardial function or VT/VF/SCD. However, to correctly assess the true prevalence and allow for comparison with the other HTADs, a larger cohort of patients with PV/LPVs in ACTA2 is needed. In this context, gathering patients with PV/LPVs in genes associated with altered smooth muscle cell force generation (ACTA2, MYH11, MYLK and PRKG1) may address the paucity of patients to some extent.

The pathophysiology underlying arrhythmia and impaired myocardial function in patients with HTAD is incompletely understood and therefore remains speculative. However, it is not unthinkable that both genetic abnormalities as well as aortic or valvular complications may act in conjunction. In this context, the theory of altered mechanobiology (Humphrey et al., 2015) appears to be supported by our results. According to this concept, changes in mechanical forces (induced by valvular dysfunction or cardiac surgery) and abnormal interaction between cardiomyocytes and the ECM (due to underlying genetic abnormalities) may lead to altered responsive cellular adaptation and remodeling. Evidence supporting a secondary nature is provided by the high prevalence of valvular disease and cardiovascular surgery among patients presenting non-aortic cardiac disease, whereas the individual role of genetic abnormalities may be more overt in certain patients, since a subgroup of patients did not have any severe valvular disease or history of cardiovascular surgery at the time of presentation. In our study, we observed the presence of severe valvular regurgitation in 27% of the patients with impaired myocardial function. When adding the number of patients having incurred cardiac surgery for valvular heart disease, the proportion of patients with severe valvular disease rose to 70%, confirming the role of valvular function in this manifestation while also suggesting that the myocardial function may not fully recover after valvular surgery. The importance of valvular function is further supported by the finding that patients with PV/LPVs in *ACTA2* (typically less affected by valvular disease than patients with PV/LPVs in *FBN1* or in the TGF-β signaling genes) did not have impaired myocardial function. Cardiovascular surgery and the accompanying exerted stress on the myocardium have also been suggested as contributive factors(Hetzer et al., 2016). Our data may support this hypothesis, as we found that a history of cardiovascular surgery in a significant proportion of the patients (80%) with impaired myocardial function, but this can only be proven by comparing with a non-Marfan population. Myocardial dysfunction in these patients might however also be caused by a primary intrinsic problem of the myocardium due to an abnormal extracellular

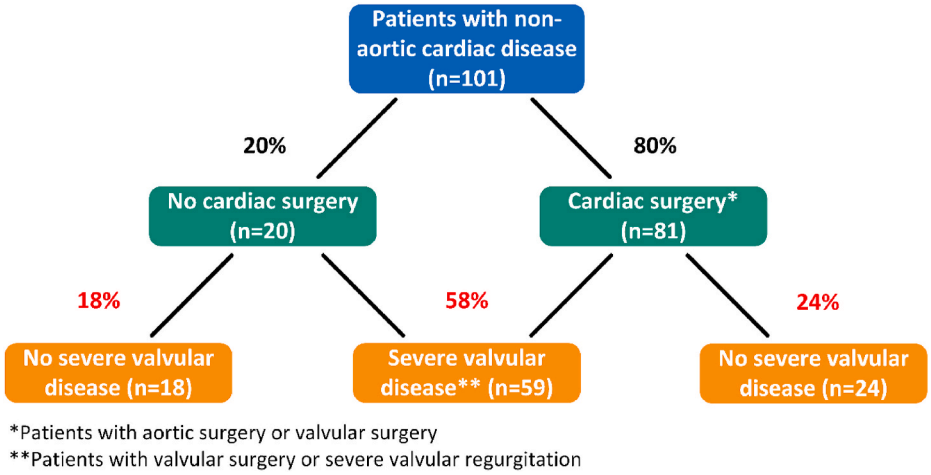

Fig. 3. Cardiac surgery and valvular disease among patients with non-aortic cardiac disease.
Figure legend: Presence of cardiac surgery and valvular disease among patients presenting with non-aortic cardiac disease.

matrix in some patients(Alpendurada et al., 2010; De Backer et al., 2006; Kiotsekoglou et al., 2011; Muiño-Mosquera et al., 2020). In our study, a subgroup of patients with non-aortic cardiac disease (18%) did not have any severe valvular disease or history of cardiovascular surgery at the time of presentation, suggesting that these features can indeed be a primary manifestation that may be aggravated by valvular disease or cardiovascular surgery. Of note, the impairment of myocardial function was mostly mild in these patients without severe valvular disease or history of cardiovascular surgery. At this point, it is unclear whether the role of cardiovascular surgery is causal or merely associative. Some patients with impaired myocardial function had a history of valvular surgery with no severe residual valvular regurgitation at the time of presentation, which could signify an incomplete resolution of LV dilatation after valvular surgery. Similar to the findings of Andersen et al. and other studies, patients with impaired myocardial function tended to be male(Alpendurada et al., 2010; Andersen et al., 2021; Kiotsekoglou et al., 2009). This could be in line with more aggressive aortic disease in male patients with MFS(Roman et al., 2017). A clear explanation for this sex difference is not available but deserves further research.

The present study also provides novel data on arrhythmia in patients with HTAD. Both VT/VF/SCD and impaired myocardial function can occur isolated or in conjunction. However, the pathophysiology remains puzzling and identification of predisposing factors is challenging. A predisposition for both supraventricular and ventricular arrhythmias has been demonstrated in MFS(Andersen et al., 2021; Aydin et al., 2013; Hoffmann et al., 2013; Muiño-Mosquera et al., 2020; Yetman et al., 2003). Our data show that atrial arrhythmia (AF/AFL) was mostly reported in patients with PV/LPVs in *FBN1*. The reason why atrial arrhythmia appears to be more frequent in patients harboring PV/LPVs in *FBN1* is unclear and could be related to the small sample size and younger age of included patients with PV/LPVs in the TGF-β signaling genes. Other potential reasons include a higher occurrence of valvular disease and left atrial enlargement in the *FBN1* cohort. Whether fibrillin-1 plays a specific role in the development of AF/AFL still needs to be elucidated. With regard to ventricular arrhythmia, no differences were found between patients with PV/LPVs in *FBN1* and patients carrying PV/LPVs in the TGF-β signaling genes. Ventricular arrhythmia has been frequently studied in patients with MFS, whereas only case series are available in patients with LDS(Aydin et al., 2013; Demolder et al., 2021; Extramiana et al., 2018; Hoffmann et al., 2013; Muiño-Mosquera et al., 2020; Yetman et al., 2003). Non-sustained ventricular tachycardia may be present in up to 10–20% of patients diagnosed with MFS according to the revised Ghent criteria and studies report life-threatening arrhythmias in 7–9% of their patients along with sudden cardiac death most likely due to arrhythmia occurring in up to 4%(Aydin et al., 2013; Hoffmann et al., 2013; Savolainen et al., 1997; Schaeffer et al., 2015; Yetman et al., 2003). In our study, we found lower percentages of VT/VF/SCD compared to current literature(Aydin et al., 2013; Hoffmann et al., 2013; Savolainen et al., 1997; Schaeffer et al., 2015; Yetman et al., 2003), which could be explained by center-dependent percentages in smaller population sizes. Several factors predisposing to ventricular arrhythmia have been suggested, but the pathophysiology is complex and still incompletely understood. Among patients with PV/LPVs in the TGF-β signaling genes included in this study, patients carrying a PV/LPV in *TGFBR2* appeared to have a higher tendency of VT/VF/SCD when compared to patients harboring PV/LPVs in the other TGF-β signaling genes. A study by Extramiana et al. reported that PV/LPVs in *TGFBR2* were associated with ventricular repolarization abnormalities including QT-prolongation(Extramiana et al., 2018), but other genes were not explored in their study. Despite the multicentric nature and a large total patient group in our study, only limited numbers of patients with PV/LPVs in *TGFB2* and *TGFB3* were included. Therefore, larger studies are definitely needed to confirm the possibility of gene-based differences. Recently, mitral annular disjunction (MAD) has been associated with ventricular arrhythmia in patients with MFS(Demolder et al., 2021). In line with this finding, MAD was identified in almost all patients (94%) with VT/VF/SCD as first manifestation (without prior diagnosis of impaired myocardial function) and in a significant proportion of the total number of patients presenting VT/VF/SCD (76%). Since MAD has been reported in up to one third of the patients with MFS (Chivulescu et al., 2020; Demolder et al., 2021), the involvement of other factors such as an arrhythmogenic substrate as a potential trigger of arrhythmia should be considered. It should be noted that patients with VT/VF/SCD had little to no symptoms before the onset of the event, implying the need for further research in predisposing factors of these sudden and unpredictable features.

5. Limitations

The current study has several limitations. First, evident limitations related to a retrospective study design can be expected. Due to the multicentric and retrospective nature of the study, differences in imaging modalities and methods for the assessment of ejection fraction cannot be excluded. However, since the information was retrieved from medical records, results presented in this paper are expected to reflect real-life clinical data. Second, the screening process relies on review of medical records and the study is therefore subject to incomplete or missing reports of non-aortic cardiac disease, which is especially relevant in the case of asymptomatic reduced EF. Data on certain factors (i.e. family history) were not available for all patients and should be

interpreted with caution. Third, we acknowledge the limitations associated with the small number of patients harboring PV/LPVs in the TGF-β signaling genes and in *ACTA2*. Data on the prevalence of non-aortic cardiac event in these patient groups should be interpreted within this context. Fourth, autopsy was rarely performed and therefore data on the exact cause of death in the SCD cases are limited. Lastly, some of the participating centers are specialized in pediatric patients while other are specialized in adult patients, which could result in an inaccurate estimation of the actual prevalence: non-aortic cardiac disease may establish during adulthood, though pediatric patients may also present a more severe phenotype when they are diagnosed as proband.

6. Conclusions

In patients with HTAD, arrhythmia and impaired myocardial function were found in patients harboring LP/PVs in the *FBN1* gene and the TGF-β signaling genes but not in patients carrying LP/PVs in the *ACTA2* gene. This indicates the usefulness of a gene-tailored approach for the management of HTAD patients. Cardiovascular surgery and valvular heart disease in addition to intrinsic ventricular factors may play an important role in the development of left ventricular dysfunction while MAD seems to be highly prevalent in patients presenting ventricular arrhythmias. Atrial arrhythmia (AF/AFL) was almost exclusively reported in patients with LP/PVs in the *FBN1* gene but might be related to the significantly older age of this patient group. Despite the low prevalence, these features should not be disregarded and screening with ambulatory ECG, echocardiography and (if indicated) cardiovascular magnetic resonance imaging may be warranted for early detection.

Author statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the *European Journal of Medical Genetics*.

Ethical committee approval

All respective Ethical Committees approved the study and granted waiver for the requirement of obtaining written informed consent.

Declaration of competing interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2022.104503.

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