ORIGINAL ARTICLE

CrossMark

Prognostic significance of anterior mitral valve leaflet length in individuals with a hypertrophic cardiomyopathy gene mutation without hypertrophic changes

Hannah G. van Velzen[1] · Arend F. L. Schinkel[1] · Myrthe E. Menting[1] · Annemien E. van den Bosch[1] · Michelle Michels[1]

Abstract

Purpose Previous studies suggest that anterior mitral valve leaflet (AMVL) elongation is a primary phenotypic feature in hypertrophic cardiomyopathy (HCM). Our aim was to assess AMVL length in individuals with HCM gene mutations and in healthy controls and to identify predictors of the development of HCM during follow-up.

Methods A total of 133 HCM mutation carriers and 135 controls underwent cardiac examination including electro- and echocardiography. AMVL length was measured in the parasternal long axis and apical three chamber view during diastole. Univariate and multivariable cox proportional hazard regression analyses were performed to identify predictors of HCM.

Results There were no significant differences between HCM mutation carriers and controls regarding age and sex. In the parasternal long axis view, AMVL length was similar in mutation carriers and controls (24 ± 4 vs 24 ± 4 mm, $p = 0.8$). In the apical three chamber view, AMVL were shorter in mutation carriers (29 ± 4 vs 30 ± 4 mm, $p = 0.02$). When averaged for both views, AMVL length was similar in mutation carriers and controls (27 ± 3 vs 27 ± 3 mm, $p = 0.2$). During 5.8 ± 3.0 years follow-up, 13 (14%) HCM mutation carriers developed HCM. Pathological Q wave (hazard ratio 9.89, $p = 0.004$), E/e′ ratio (hazard ratio 2.52, $p = 0.001$), and maximal wall thickness (hazard ratio 2.15, $p = 0.001$) were independent predictors of HCM. AMVL length was not predictive of the development of HCM.

Conclusions AMVL length is similar in HCM mutation carriers and controls. AMVL length is not predictive of the development of HCM, in contrast to pathological Q wave, E/e′ ratio, and maximal wall thickness.

SOMMARIO

Obiettivi Studi precedenti suggeriscono che l'allungamento della cuspide anteriore della valvola mitrale (LAVM) è una caratteristica fenotipica primaria nella cardiomiopatia ipertrofica (HCM). Il nostro obiettivo era quello di valutare la lunghezza del LAVM in individui con mutazioni del gene HCM e nei controlli sani e di identificare i predittori dello sviluppo di HCM durante il follow-up.

Metodi Un totale di 133 portatori di mutazione HCM e 135 controlli sono stati sottoposti ad un esame cardiologico che comprendeva un elettrocardiogramma ed ecocardiografia. La lunghezza del LAVM è stata misurata durante la fase diastolica in proiezione parasternale asse longitudinale ed in proiezione 3 camere apicali. Le analisi di regressione del rischio proporzionale coassiale univariata e multivariata sono state eseguite per identificare I predittori di HCM.

Risultati Non sono risultate differenze significative tra portatori di mutazione HCM e controlli per quanto riguarda età e sesso. Nella proiezione parasternale asse lungo, la lunghezza del LAVM era simile nei portatori di mutazione e controlli (24 ± 4 vs 24 ± 4 mm, $p = 0.8$). Nella proiezione 3 camere apicale, i valori del LAVM erano minori nei portatori di mutazione (29 ± 4 vs 30 ± 4 mm, $p = 0.02$). Eseguendo la media dei valori per entrambe le proiezioni, la lunghezza del LAVM era simile nei portatori di mutazione e nei controlli (27 ± 3 vs 27 ± 3 mm, $p = 0.2$). Durante un periodo di follow-up di 5.8 ± 3.0 anni, 13 (14%) dei portatori della mutazione HCM hanno sviluppato HCM. L'onda Q patologica (hazard ratio 9.89, $p = 0,004$), il

---

Extended author information available on the last page of the article

rapporto E/e′ (hazard ratio 2.52, $p = 0.001$) e lo spessore massimale della parete (hazard ratio 2.15, $p = 0.001$) sono risultati predittori indipendenti di HCM. La lunghezza del LAVM non era predittiva di sviluppo di HCM.

Conclusioni La lunghezza del LAVM è simile nei portatori della mutazione HCM e nei controlli. La lunghezza del LAVM non è risultata predittiva dello sviluppo di HCM, a differenza dell'onda Q patologica, del rapporto E/e', e dello spessore massimale della parete.

Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disease with an estimated prevalence of 1:500–1:200 [1–3]. The diagnosis is based on the presence of a maximal wall thickness ≥ 15 mm in index patients and ≥ 13 mm in relatives, that is not solely explained by abnormal loading conditions [2]. A pathogenic HCM mutation is identified in 40–60% of patients with HCM [2, 4]. Presymptomatic genetic testing of relatives has led to the identification of HCM gene mutation carriers who do not fulfill the echocardiographic criterion of HCM [5]. HCM mutation carriers are at risk of developing HCM [5]. Conflicting data exists on whether the anterior mitral valve leaflets (AMVL) are elongated in mutation carriers and whether AMVL elongation is a predictor of the development of HCM during follow-up [6–11]. The aim of this study was to assess AMVL length in HCM mutation carriers and healthy controls and to determine the prognostic significance of AMVL length in HCM mutation carriers for the development of HCM during follow-up.

Methods

Study design and population

This single-center retrospective case–control and cohort study included 133 HCM mutation carriers without clinical expression of HCM who were clinically evaluated at our cardio-genetic outpatient clinic between the years 2004–2017. Genetic assessment and the family screening strategy at our center have been described previously [12, 13]. For comparison, 135 healthy controls underwent cardiac evaluation [14]. Controls were recruited via an advertisement. Inclusion criteria were normal physical examination, normal electrocardiography (ECG), and left ventricular (LV) ejection fraction > 51%; exclusion criteria were prior cardiovascular disease or risk factors consisting of hypertension, diabetes mellitus, and hypercholesterolemia, systemic disease, medication known to influence cardiac function including thyroid medication (with the exception of asthma inhalers), professional athletes, body mass index > 40 and women with

breast implants [14]. The study conforms to the principles of the Declaration of Helsinki. All patients gave informed consent for inclusion in the registry and local institutional review board approval was obtained.

Clinical evaluation

Clinical evaluation included medical history, physical examination, ECG, and transthoracic echocardiography. Standard 12-lead ECG was performed in the supine position during quiet respiration. LV hypertrophy was evaluated with the Romhilt–Estes criteria. Pathological Q waves were defined as duration > 40 ms or depth > 30% R wave in ≥ 2 leads. T wave inversion was defined as ≥ 3 mm in ≥ 2 leads. Echocardiographic studies were analyzed according to the guidelines [15, 16]. Maximal wall thickness, left atrial size, leaflet and chordal systolic anterior motion of the mitral valve, and resting LV outflow tract peak velocity were assessed. LV outflow tract gradient was calculated with the Bernoulli equation. LV systolic function was categorized as: good (LV ejection fraction > 51%), mildly reduced (LV ejection fraction 41–51%), moderately reduced (LV ejection fraction 30–40%), and poor (LV ejection fraction < 30%) [16]. LV diastolic function was defined as normal, abnormal relaxation, pseudonormal or restrictive filling, based on Doppler mitral inflow pattern parameters including early (E) and late (A) LV filling velocities, E/A ratio, and tissue Doppler imaging-derived septal early diastolic velocities (e′) [17]. HCM during follow-up was defined as a maximal wall thickness ≥ 13 mm according to the guidelines [2].

AMVL measurements

AMVL length was measured in the parasternal long axis (PLAX) view and in the apical three chamber (A3C) view, during diastole and with the leaflet maximally extended. In the PLAX view, leaflet length was defined as the distance from the tip of the leaflet to the junction between the anterior leaflet and the posterior aortic wall (hinge point), according to Klues et al. [18]. In the A3C view, leaflet length was defined as the distance from the tip of the leaflet to the insertion of the noncoronary aortic leaflet, according to Alhaj et al. [19]. Examples of AMVL measurements in both views are shown in Fig. 1. All AMVL measurements were
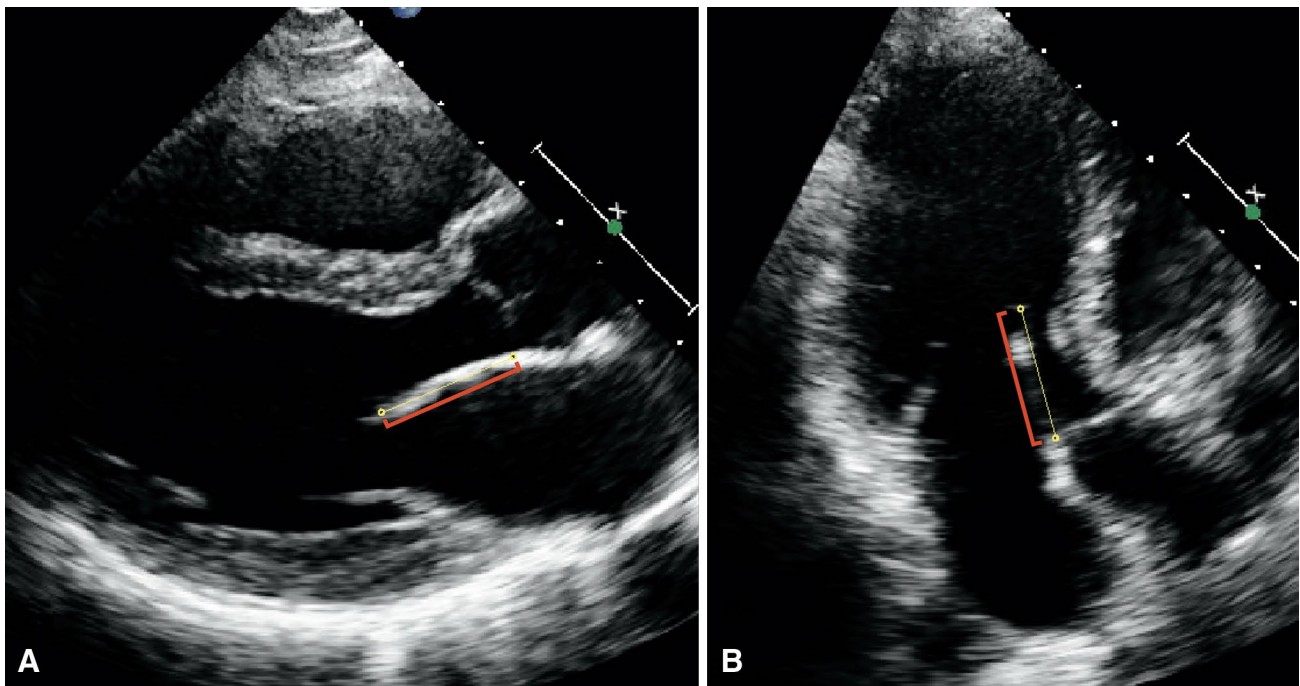
Fig. 1 Example of anterior mitral valve leaflet length (AMVL) measurements in a hypertrophic cardiomyopathy gene mutation carrier without hypertrophic changes. In the parasternal long-axis view, **a** the AMVL measured 26 mm, and in the apical three chamber view, **b** the AMVL measured 26 mm

performed by one reader. For intraobserver variability, one reader independently measured 40 AMVLs in the PLAX view and 40 AMVLs in the A3C view in an identical fashion on two occasions. For interobserver variability, two readers independently measured 20 AMVLs in the PLAX view and 20 AMVLs in the A3C view.

Statistical methods

The statistical analysis was performed using SPSS 21 (IBM, Armonk, NY). Normally distributed continuous data are expressed as mean ± standard deviation and non-normally distributed data as median followed by interquartile range. For comparing categorical variables Pearson's Chi-square test was used. For comparing continuous variables *t* test was used, and Mann–Whitney U in case of non-normally distributed data. All analyses were two-sided; *p* values < 0.05 were considered significant. Inter-observer and intra-observer agreement was defined as the mean of the difference between two measurements ± standard deviation. Univariate and multivariable cox proportional hazard regression was performed to determine hazard ratios (HR) and 95% confidence intervals (CI). After screening for multicollinearity, the univariate significant variables with the highest HR were entered into the multivariable regression model. To calculate the allowed number of variables for inclusion in the multivariable analysis, the square root of the number of events was

used. This is an alternative method to determine the number of variables allowed for inclusion in the multivariable analysis [20].

Results

Clinical evaluation

HCM gene mutation carriers represented mutations in 10 different genes. The *MYBPC3* gene was most frequently affected (77%), followed by the *MYH7* gene (11%). Other genes affected were *TNNT2* (3%), *MYL2* (2%), *FHL1* (2%), *ALPK3* (2%) *MIB1* (0.75%), *TNNI3* (0.75%), *TPM1* (0.75%), and *MYL3* (0.75%). Clinical and echocardiographic characteristics in mutation carriers and controls are presented in Table 1. Mutation carriers and controls had similar age, gender, and body surface area. Compared to controls, more mutation carriers had pathological Q waves (4 vs 0%, $p = 0.02$), and mutation carriers had a higher E/e′ ratio (8.2 ± 1.9 vs 7.7 ± 1.9, $p = 0.03$), and a higher maximal wall thickness (8.9 ± 1.9 vs 8.0 ± 1.8 mm, $p = 0.001$).

AMVL measurements

Beeswarm plots of AMVL measurements in the PLAX and the A3C view are presented in Fig. 2. In the PLAX view,

**Table 1** Clinical and echocardiographic characteristics of the study population

Variable	Mutation carrier (n = 133)	Control (n = 135)	p value
Age (year)	41 ± 14	44 ± 14	0.11
Female gender n (%)	85 (64)	73 (54)	0.18
Body surface area (m^2)	1.9 ± 0.2	1.9 ± 0.2	0.86
Electrocardiography			
Romhilt–Estes ≥ 4 n (%)	10 (8)	4 (3)	0.09
T wave inversion n (%)	1 (1)	0 (0)	0.31
Pathological Q wave n (%)	5 (4)	0 (0)	0.02
Echocardiography			
Maximal wall thickness (mm)	8.9 ± 2.0	8.0 ± 1.8	<0.001
Left atrial size (mm)	34 ± 5	34 ± 4	0.24
LVOT gradient ≥ 30 mmHg[a] n (%)	0 (0)	0 (0)	0.50
AMVL, PLAX (mm)	24 ± 4	24 ± 4	0.85
AMVL, A3C (mm)	29 ± 4	30 ± 4	0.02
AMVL, averaged (mm)	27 ± 3	27 ± 3	0.17
Chordal systolic anterior motion n (%)	5 (4)	1 (1)	0.09
Leaflet systolic anterior motion n (%)	0 (0)	0 (0)	0.50
E/A ratio	1.4 ± 0.5	1.6 ± 0.7	0.03
E/e' ratio	8.2 ± 1.9	7.7 ± 1.9	0.03
Septal e' (cm/s)	9.5 ± 2.5	9.6 ± 2.6	0.61
Diastolic function			
Normal n (%)	105 (83)	111 (85)	0.66
Abnormal relaxation n (%)	10 (8)	7 (5)	0.39
Pseudonormal filling n (%)	11 (9)	13 (10)	0.76
Restrictive filling n (%)	0 (0)	0 (0)	0.50
Systolic function			
Good n (%)	132 (99)	135 (100)	0.31
Mildly reduced n (%)	1 (1)	0 (0)	0.31
Moderately reduced n (%)	0 (0)	0 (0)	0.50
Poor n (%)	0 (0)	0 (0)	0.50

Data are expressed as mean ± standard deviation or as absolute and (%)

AMVL anterior mitral valve leaflet, *A3C* apical three chamber view, *LVOT* left ventricular outflow tract, *PLAX* parasternal long-axis view

[a] at rest

Fig. 2 Beeswarm plot of anterior mitral valve leaflet (AMVL) length measurements in hypertrophic cardiomyopathy gene mutation carriers without hypertrophic changes versus healthy controls, assessed with transthoracic echocardiography in the **a** parasternal long-axis view and **b** apical three chamber view
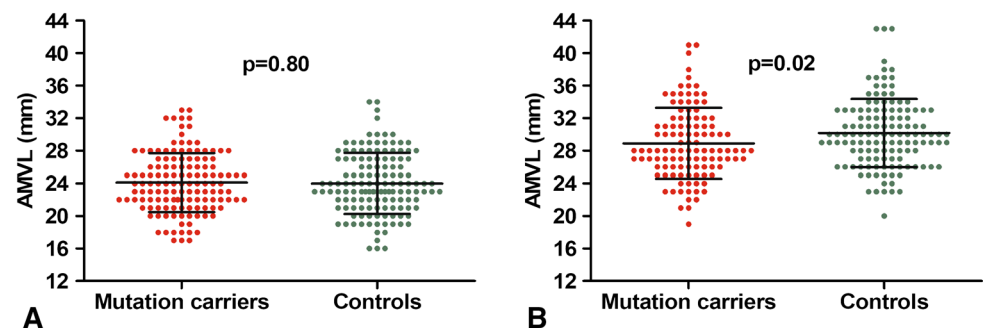
AMVL length did not differ between mutation carriers and controls (24 ± 4 vs 24 ± 4 mm, p = 0.8). In the A3C view, AMVL were shorter in the mutation carriers (29 ± 4 vs 30 ± 4 mm, p = 0.02). When averaged for both views, AMVL length was similar in mutation carriers and controls (27 ± 3 vs 27 ± 3 mm, p = 0.2). Overall, AMVL were significantly

longer in the A3C view than in the PLAX view (30 ± 4 vs 24 ± 4 mm, $p < 0.001$).

Intra-observer and inter-observer agreement

In the PLAX view, the inter-observer agreement was -2.7 ± 2.6 mm and the intra-observer agreement was -1.0 ± 3.5 mm. In the A3C view, the inter-observer agreement was 2.0 ± 2.5 mm and the intra-observer agreement was 0.5 ± 2.6 mm.

Follow-up

During 5.8 ± 3.0 years follow-up, 13 (14%) mutation carriers developed HCM. Mean age at HCM diagnosis was 52 ± 17 years. In these 13 mutation carriers, maximal wall thickness increased from a median 10 (interquartile range 8, 11) mm to 13 (interquartile range 13, 14) mm, with a mean rate of 0.7 ± 0.3 mm/year. Table 2 presents the baseline characteristics in those who developed HCM during follow-up and those who did not. Univariate significant predictors of the development of HCM were pathological Q wave (HR 9.74, 95% CI 2.53–37.46, $p = 0.001$), maximal wall thickness (HR 1.64, 95% CI 1.12–2.39, $p = 0.01$), E/e′ ratio (HR 1.63, 95% CI 1.20–2.23, $p = 0.002$), left atrial size (HR 1.16, 95% CI 1.03–1.31, $p = 0.01$), and age (HR 1.06, 95% CI 1.02–1.11, $p = 0.01$). AMVL length was not predictive

Table 2 Baseline characteristics of HCM gene mutation carriers who did and did not develop hypertrophic cardiomyopathy during follow-up

Variable	Developed HCM		
	Yes ($n = 13$)	No ($n = 77$)	p value
Age (years)	47 ± 19	39 ± 13	0.05
Male gender n (%)	8 (62)	25 (33)	0.04
Romhilt–Estes ≥ 4 n (%)	1 (8)	5 (7)	0.87
T wave inversion n (%)	1 (8)	0 (0)	0.01
Pathological Q n (%)	3 (23)	2 (3)	0.003
Left atrial size (mm)	39 ± 5	33 ± 5	<0.001
Maximal wall thickness (mm)	10 ± 2	9 ± 2	0.02
AMVL, PLAX (mm)	25 ± 5	24 ± 3	0.47
AMVL, A3C (mm)	29 ± 5	29 ± 4	0.90
Chordal systolic anterior motion n (%)	1 (8)	3 (4)	0.54
E/e' ratio	9.3 ± 1.8	8.1 ± 1.7	0.03
Septal e' (cm/s)	8.5 ± 2.7	9.5 ± 2.6	0.20
Abnormal diastolic function n (%)	4 (31)	11 (16)	0.21

Data are expressed as mean $\pm$ standard deviation or as absolute and (%)

AMVL anterior mitral valve leaflet, *A3C* apical three chamber view, *HCM* hypertrophic cardiomyopathy, *PLAX* parasternal long axis view

of the development of HCM in the PLAX view (HR 1.03, 95% CI 0.87–1.22, $p = 0.72$) or in the A3C view (HR 0.99, 95% CI 0.86–1.15, $p = 0.92$). Multivariable cox regression analysis which included three variables demonstrates that pathological Q wave (adjusted HR 9.89, 95% CI 2.09–46.95, $p = 0.004$), E/e′ ratio (adjusted HR 2.52, 95% CI 1.48–4.29, $p = 0.001$), and maximal wall thickness (adjusted HR 2.15, 95% CI 1.36–3.42, $p = 0.001$) all were independent predictors of HCM during follow-up.

Discussion

During HCM family screening, individuals who carry a HCM gene mutation may not fulfil the echocardiographic diagnostic criterion of HCM [5]. Because of the age-related penetrance of HCM, long-term clinical follow-up including ECG and echocardiography is recommended [2, 3]. Currently, it is unclear which HCM mutation carriers will develop HCM [2, 11]. We aimed to assess AMVL length in mutation carriers and controls, and determine the prognostic value of AMVL length for the development of HCM during follow-up. Our main findings are: (1) AMVL length is similar in mutation carriers and controls, (2) AMVL length is not predictive of the development of HCM, and (3) pathological Q wave, E/e′ ratio, and maximal wall thickness are independent predictors of the development of HCM.

AMVL elongation is not a primary phenotypic feature of HCM

In patients with HCM, AMVL elongation has been demonstrated pathologically, on echocardiography, and on cardiovascular magnetic resonance imaging [10, 18, 21–23]. Among other factors, AMVL elongation contributes to systolic anterior motion of the mitral valve and LV outflow tract obstruction [23–25]. The etiology of AMVL elongation in patients with HCM is unclear. Both the pathological study of Klues et al. and the in vivo study of Kim et al. found that AMVL elongation is not secondary to LV outflow tract obstruction or systolic anterior motion of the mitral valve, since it also occurs in patients without LV outflow tract obstruction or systolic anterior motion [19, 21, 22]. Therefore, it was suggested that AMVL elongation is a primary phenotypic expression of HCM. Several studies have indeed reported AMVL elongation in mutation carriers as measured by magnetic resonance imaging [6, 7, 10], and echocardiography [9]. The current study contradicts these findings. In line with our findings, a recent magnetic resonance imaging study similarly reported no difference in AMVL length between mutation carriers and controls [8]. The discrepancy between the studies may be related to the small number of participants, different imaging modalities

2. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H (2014) ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 35(39):2733–2779

3. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW (2011) 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg 142(6):e153–e203

4. Ho CY, Charron P, Richard P, Girolami F, Van Spaendonck-Zwarts KY, Pinto Y (2015) Genetic advances in sarcomeric cardiomyopathies: state of the art. Cardiovasc Res 105(4):397–408

5. Olivotto I, Cecchi F, Poggesi C, Yacoub MH (2012) Patterns of disease progression in hypertrophic cardiomyopathy: an individualized approach to clinical staging. Circ Heart Fail 5(4):535–546

6. Maron MS, Olivotto I, Harrigan C, Appelbaum E, Gibson CM, Lesser JR, Haas TS, Udelson JE, Manning WJ, Maron BJ (2011) Mitral valve abnormalities identified by cardiovascular magnetic resonance represent a primary phenotypic expression of hypertrophic cardiomyopathy. Circulation 124(1):40–47

7. Captur G, Lopes LR, Mohun TJ, Patel V, Li C, Bassett P, Finocchiaro G, Ferreira VM, Esteban MT, Muthurangu V, Sherrid MV, Day SM, Canter CE, McKenna WJ, Seidman CE, Bluemke DA, Elliott PM, Ho CY, Moon JC (2014) Prediction of sarcomere mutations in subclinical hypertrophic cardiomyopathy. Circ Cardiovasc Imaging 7(6):863–871

8. Tarkiainen M, Sipola P, Jalanko M, Helio T, Laine M, Jarvinen V, Hayrinen K, Lauerma K, Kuusisto J (2016) Cardiovascular magnetic resonance of mitral valve length in hypertrophic cardiomyopathy. J Cardiovasc Magn Reson 18(1):33

9. Peyrou J, Reant P, Reynaud A, Cornolle C, Dijos M, Rooryck-Thambo C, Landelle M, Montaudon M, Laurent F, Roudaut R, Lafitte S (2016) Morphological and functional abnormalities pattern in hypertrophy-free HCM mutation carriers detected with echocardiography. Int J Cardiovasc Imaging 32(9):1379–1389

10. Captur G, Lopes LR, Patel V, Li C, Bassett P, Syrris P, Sado DM, Maestrini V, Mohun TJ, McKenna WJ, Muthurangu V, Elliott PM, Moon JC (2014) Abnormal cardiac formation in hypertrophic cardiomyopathy: fractal analysis of trabeculae and preclinical gene expression. Circ Cardiovasc Genet 7(3):241–248

11. Cardim N (2017) Clinical detection of mutation carriers of hypertrophic cardiomyopathy in perspective: is cardiac imaging the crystal ball of the cardiologist? Eur Heart J Cardiovasc Imaging 18(4):390–391

12. van Velzen HG, Vriesendorp PA, Oldenburg RA, van Slegtenhorst MA, van der Velden J, Schinkel AF, Michels M (2016) Value of genetic testing for the prediction of long-term outcome in patients with hypertrophic cardiomyopathy. Am J Cardiol 118(6):881–887

13. Michels M, Hoedemaekers YM, Kofflard MJ, Frohn-Mulder I, Dooijes D, Majoor-Krakauer D, Ten Cate FJ (2007) Familial screening and genetic counselling in hypertrophic cardiomyopathy: the Rotterdam experience. Neth Heart J 15(5):184–190

14. Menting ME, McGhie JS, Koopman LP, Vletter WB, Helbing WA, van den Bosch AE, Roos-Hesselink JW (2016) Normal myocardial strain values using 2D speckle tracking echocardiography in healthy adults aged 20–72 years. Echocardiography 33(11):1665–1675

15. Nagueh SF, Bierig SM, Budoff MJ, Desai M, Dilsizian V, Eidem B, Goldstein SA, Hung J, Maron MS, Ommen SR, Woo A (2011) American society of echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with hypertrophic cardiomyopathy: endorsed by the American society of nuclear cardiology, society for cardiovascular magnetic resonance, and society of cardiovascular computed tomography. J Am Soc Echocardiogr 24(5):473–498

16. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging. Eur Heart J Cardiovasc Imaging 16(3):233–270

17. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelisa A (2009) Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr 10(2):165–193

18. Klues HG, Proschan MA, Dollar AL, Spirito P, Roberts WC, Maron BJ (1993) Echocardiographic assessment of mitral valve size in obstructive hypertrophic cardiomyopathy. Anatomic validation from mitral valve specimen. Circulation 88(2):548–555

19. Alhaj EK, Kim B, Cantales D, Uretsky S, Chaudhry FA, Sherrid MV (2013) Symptomatic exercise-induced left ventricular outflow tract obstruction without left ventricular hypertrophy. J Am Soc Echocardiogr 26(5):556–565

20. Altman DG (1990) Practical Statistics for Medical Research. Taylor & Francis Ltd, Milton Park

21. Klues HG, Maron BJ, Dollar AL, Roberts WC (1992) Diversity of structural mitral valve alterations in hypertrophic cardiomyopathy. Circulation 85(5):1651–1660

22. Kim DH, Handschumacher MD, Levine RA, Choi YS, Kim YJ, Yun SC, Song JM, Kang DH, Song JK (2010) In vivo measurement of mitral leaflet surface area and subvalvular geometry in patients with asymmetrical septal hypertrophy: insights into the mechanism of outflow tract obstruction. Circulation 122(13):1298–1307

23. Teo EP, Teoh JG, Hung J (2015) Mitral valve and papillary muscle abnormalities in hypertrophic obstructive cardiomyopathy. Curr Opin Cardiol 30(5):475–482

24. Sherrid MV, Balaram S, Kim B, Axel L, Swistel DG (2016) The Mitral Valve in Obstructive Hypertrophic Cardiomyopathy: a Test in Context. J Am Coll Cardiol 67(15):1846–1858

25. Levine RA, Hagege AA, Judge DP, Padala M, Dal-Bianco JP, Aikawa E, Beaudoin J, Bischoff J, Bouatia-Naji N, Bruneval P, Butcher JT, Carpentier A, Chaput M, Chester AH, Clusel C, Delling FN, Dietz HC, Dina C, Durst R, Fernandez-Friera L, Handschumacher MD, Jensen MO, Jeunemaitre XP, Le Marec H, Le Tourneau T, Markwald RR, Merot J, Messas E, Milan DP, Neri T, Norris RA, Peal D, Perrocheau M, Probst V, Puceat M, Rosenthal N, Solis J, Schott JJ, Schwammenthal E, Slaugenhaupt SA, Song JK, Yacoub MH, Leducq N (2015) Mitral transatlantic, mitral valve disease–morphology and mechanisms. Nat Rev Cardiol 12(12):689–710

26. Captur G, Ho CY, Schlossarek S, Kerwin J, Mirabel M, Wilson R, Rosmini S, Obianyo C, Reant P, Bassett P, Cook AC, Lindsay S, McKenna WJ, Mills K, Elliott PM, Mohun TJ, Carrier L, Moon JC (2016) The embryological basis of subclinical hypertrophic cardiomyopathy. Sci Rep 6:27714

27. Teare D (1958) Asymmetrical hypertrophy of the heart in young adults. Br Heart J 20(1):1–8

28. Ho CY, Cirino AL, Lakdawala NK, Groarke J, Valente AM, Semsarian C, Colan SD, Orav EJ (2016) Evolution of hypertrophic cardiomyopathy in sarcomere mutation carriers. Heart. https://doi.org/10.1136/heartjnl-2016-310015

29. Lakdawala NK, Thune JJ, Maron BJ, Cirino AL, Havndrup O, Bundgaard H, Christiansen M, Carlsen CM, Dorval JF, Kwong RY, Colan SD, Kober LV, Ho CY (2011) Electrocardiographic features of sarcomere mutation carriers with and without clinically overt hypertrophic cardiomyopathy. Am J Cardiol 108(11):1606–1613

30. Kauer F, van Dalen BM, Michels M, Soliman OI, Vletter WB, van Slegtenhorst M, ten Cate FJ, Geleijnse ML (2013) Diastolic abnormalities in normal phenotype hypertrophic cardiomyopathy gene carriers: a study using speckle tracking echocardiography. Echocardiography 30(5):558–563

31. Lin E, Alessio A (2009) What are the basic concepts of temporal, contrast, and spatial resolution in cardiac CT? J Cardiovasc Comput Tomogr 3(6):403–408

32. To AC, Flamm SD, Marwick TH, Klein AL (2011) Clinical utility of multimodality LA imaging: assessment of size, function, and structure. JACC Cardiovasc Imaging 4(7):788–798

Affiliations

Hannah G. van Velzen[1] ⦿ · **Arend F. L. Schinkel**[1] · **Myrthe E. Menting**[1] · **Annemien E. van den Bosch**[1] · **Michelle Michels**[1]

✉ Hannah G. van Velzen
   h.g.vanvelzen@erasmusmc.nl

[1] Department of Cardiology, Thorax-center, Erasmus Medical Center, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands