

## ORIGINAL ARTICLE

# Masked hypertension in young patients after successful aortic coarctation repair: impact on left ventricular geometry and function

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Life expectancy is still reduced in aortic coarctation (AoC) patients despite a successful repair because of late arterial hypertension and atherosclerosis. Masked hypertension (MH) consists of an elevated daytime or awake ambulatory blood pressure (BP) in the presence of a normal BP on conventional measurement at the office. To assess the prevalence of MH among AoC normotensive young patients successfully treated and to evaluate the impact of MH on left ventricular (LV) geometry and function. We studied 76 AoC patients (mean age  $14.5 \pm 5.7$  years, male 64%). According to 24 h ambulatory BP monitoring (ABPM) our sample was divided in real normotensive patients (Group RN,  $n = 40$ ) and MH patients (Group MH,  $n = 36$ ). There was an

increased pressure gradient in the aortic arch ( $15 \text{ mm Hg} \pm 4$  vs  $13 \text{ mm Hg} \pm 4.7$ ,  $P < 0.05$ ), increased LV mass ( $51 \text{ g m}^{-2.7} \pm 13$  vs  $46 \text{ g m}^{-2.7} \pm 12$ ,  $P < 0.05$ ), in MH AoC patients. Regional longitudinal deformation properties of the basal septal segment ( $-15\% \pm 2.4$  vs  $-20\% \pm 5$ ,  $P < 0.01$ ) and LV twist values ( $14^\circ \pm 1.6$  vs  $12^\circ \pm 1.9$ ,  $P < 0.0001$ ) were reduced in the MH group. There is a high prevalence of MH in young patients with repaired AoC, which is associated with abnormal LV structure and function. Clinicians should consider 24 h ABPM measurements in apparently normotensive patients followed up for AoC repair.

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**Keywords:** aortic coarctation; ventricular function; 24 h ambulatory blood pressure

## Introduction

Despite a successful repair the long-term follow-up data of aortic coarctation (AoC) show that life expectancy remains reduced in AoC patients.<sup>1–4</sup> The main determinants of cardiovascular events are late arterial hypertension and atherosclerosis.<sup>1–4</sup> Many cardiovascular complications in adults often find their roots in risk factors already present early in life.<sup>5</sup> Masked hypertension (MH) is an elevated daytime or awake ambulatory blood pressure (BP) in the presence of a normal BP on conventional measurement at the office.<sup>5–8</sup> Previous studies demonstrated that MH in adults is associated with left ventricular (LV) hypertrophy<sup>5,7,8</sup> and a worse cardiovascular prognosis.<sup>5,7–9</sup> Successful repair of AoC is not always associated with normalisation

of the BP profile,<sup>1,3,10</sup> even when these patients are identified as normotensive by office BP measurement.

To the best of our knowledge, no previous study addressed the prevalence and impact on cardiac morphology and function of MH in young patients after successful AoC repair.

Thus, our aims were to assess the prevalence of MH among AoC normotensive young patients, > 12 months after successful de-coarctation, and to evaluate the impact of MH on LV geometry and function in such patients.

## Methods

### Study population

We studied consecutive young patients (age range 6–20 years) with repaired AoCs regularly followed at our out-patient clinic. Each patient performed all the investigations on the same day. The studied patients were enrolled from June 2003 to January 2010.

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We included AoC patients without major associated cardiovascular abnormalities, such as ventricular septal defect and aortic and mitral valve functional abnormalities (more than mild), without evidence of re-coarctation ( $>20$  mmHg pressure gradient at continuous Doppler in the aortic arch and the presence of a diastolic tail),<sup>11,12</sup> and no evidence of aortic aneurysm at the last outpatient visit.

Patients with clinical history of hypertension or with office systolic BP or diastolic BP (DBP)  $\geq 90^\circ$  percentile at the last clinical visit were excluded from the study. Patients under medical treatment for hypertension were excluded from the study.

Of the initial 194 AoC patients, 114 were excluded from the study for the following reasons: (a) evidence of  $>20$  mmHg pressure gradient at continuous Doppler in the aortic arch and/or the presence of a diastolic tail ( $n=40$ ); (b) office systolic BP or DBP  $\geq 90^\circ$  percentile or medical treatment for hypertension ( $n=80$ ); (c) ventricular septal defect ( $n=11$ ); (d) aortic valve functional abnormalities more than mild ( $n=18$ ); (e) mitral valve functional abnormalities more than mild ( $n=15$ ); (f) Obesity ( $n=13$ ) defined when body mass index, calculated as weight in kilograms divided by the square of height in metres, exceeded the 97th percentile for sex and age according to reference values;<sup>13</sup> (g) patients with increased daytime BP at a single 24-h ABPM ( $n=4$ ) were excluded. None was excluded for suboptimal image quality.

The remaining 76 AoC patients (mean age  $14.5 \pm 5.7$  years) were included in the study. The median duration of follow-up was 100 months (range 36 to 252 months).

#### *Clinical assessment*

Resting BP was measured three times at right arm by an automatic oscillometric cuff device (Dinamap, Critikon Inc., Tampa, FL, USA). On monitoring day, the study nurses used a standard mercury sphygmomanometer to measure the office BP three times consecutively, after the subjects had rested in the sitting position for at least 5 min. DBP was determined at Korotkoff phase 4 in children younger than 13 years and at phase 5 in older adolescents. Hypertension was defined when office BP was  $>90^\circ$  percentile for age, sex and height.<sup>14</sup>

All the patients included in the study were normotensive as assessed by office BP measurement.

#### *24 h ambulatory BP monitoring (24-h ABPM) study*

We initiated the ambulatory recordings on regular school days between 0830 and 0900 hours. On monitoring days, the participants did not engage in vigorous exercise. We programmed oscillometric SpaceLabs 90207 monitors (SpaceLabs Inc, Redmond, WA, USA) to obtain BP readings at 20-minute intervals from 0600 hour until midnight and at

30-minute intervals from midnight until 0600 hour.<sup>5</sup> During the day, an acoustic signal warned the subjects to keep their arm relaxed during inflation and deflation of the cuff. Measurements were automatically repeated when readings were outside the ranges of 70–220 mmHg systolic or 40–140 mmHg diastolic.<sup>5</sup> We did not otherwise edit the ambulatory recordings, from which we calculated time-weighted BP means for the whole day, daytime (1000 to 2000 hours) and night time (midnight to 0600 hour). These short fixed clock-time intervals closely corresponded to the awake and asleep parts of the day in all subjects and excluded the transition periods in the morning and evening, during which the BP rapidly changed.<sup>5</sup> On monitoring days, the study nurses used a standard mercury sphygmomanometer to measure the office BP three times consecutively, after the subjects had rested in the sitting position for at least 5 min. DBP was determined at Korotkoff phase 4 in children younger than 13 years and at phase 5 in older adolescents. Published diagnostic thresholds for the conventional<sup>14</sup> and daytime ambulatory<sup>15</sup> BP delineated two conditions. In 'real normotensive' (RN) patients, both the conventional ( $<90^\circ$  percentile for age, sex and height) and the daytime ambulatory BPs ( $<95^\circ$  percentile for age, sex and height) were consistently normal.

MH was an increased daytime BP ( $>95^\circ$  percentile for age, sex and height) in the presence of a normal office BP. In patients with increased daytime BP, 24-h ABPM was repeated. Only patients with persistent MH, defined as MH on at least two consecutive examinations, including that of last contact, were enrolled in the study.

One experienced paediatric cardiologist, blinded with regard to the BP of the study participants, used a System Seven echocardiograph (GE, Horten, Norway) with a 3.5 MHz transducer to perform the echocardiographic evaluation.

#### *Standard echocardiographic evaluation*

The ascending aorta and the aortic arch were visualised by means of high, long-axis view and suprasternal view. LV measurements were taken from two-dimensional guided M-mode tracings.

Parameters measured by echocardiography were pressure gradient throughout the former coarctation region and the LV and aortic morphology. LV mass indexed for height<sup>2,7</sup> (LVMI) was calculated using the Devereux-modified American Society of echocardiography cube equation.<sup>16</sup>

Relative wall thickness (RWT) was calculated at end-diastole as the ratio of the posterior wall thickness plus septal thickness over the LV internal dimension. The RWT was normalised for age (RWTa) by the following equation:  $RWTa = RWT - 0.005 \times (\text{age} - 10)$ .<sup>17</sup>

Using pulsed-wave Doppler, mitral inflow velocities, peak early diastolic velocity (E), peak late

diastolic velocity (A), E/A ratio and E wave deceleration time were measured. Myocardial velocities were obtained from the apical acoustic window to minimise the effect of cardiac translation. The peak velocities at the lateral annulus (Em) during early diastole were measured. The ratio of peak transmitral E velocity to early diastolic mitral annular velocity (E/Em) was calculated.

#### *Speckle tracking imaging study (STI)*

An ultrasound system (Vivid 7, GE Medical Systems, Horten, Norway) with an M3S probe was used for STI. The second-harmonic B-mode images of apical 3-, 4- and 2-chamber views and parasternal short axis at the mitral valve and apical level were obtained and digitally stored in cine-loop format for offline analysis (EchoPAC PC 6.0.0, GE Medical Systems). The frame rate was  $75 \pm 16$  frame/s. The methodology for strain analysis has been previously extensively described.<sup>18</sup> For the analysis of the longitudinal function (longitudinal strain), the apical views were analysed.

#### *LV twist*

The methodology for the study of LV twist is detailed elsewhere.<sup>18</sup> LV twist value was defined as the sum of the absolute values of the mean rotation at mitral valve and apical level ( $|\text{mean mitral valve rotation}| + |\text{mean apical rotation}|$ ).

#### *Acceptance of diagnostic procedures*

A visual analogue scale with a 10 cm line ranging from 'very annoying' on the left to 'not annoying at all' on the right<sup>19</sup> was used to determine the acceptance of diagnostic procedures.

#### *Statistical analysis*

The Statview software (SAS Institute Inc. SAS Campus Drive, Cary, NC, USA) was used for statistical analyses to calculate the mean, standard deviation, distribution and normal plots of the variables studied. Univariate analysis of continuous variables was performed using unpaired Student's *t*-test, and the Mann–Whitney *U* test. Dichotomous variables were analysed using  $2 \times 2$  tables and the  $\chi^2$ -test (by the method of Cochran–Mantel–Haenszel).

The correlations were studied by linear regression analysis. In addition, to identify significant predictors of MH, a multivariate logistic regression model using a significance level of  $P < 0.10$  for entry and  $P > 0.20$  for removal was developed. The following variables were included into the analysis: LVMI, LV end-diastolic diameter, interventricular septal end-diastolic dimension, E/A, basal septal peak systolic strain and LV twist. These variables were selected according to the results of univariate analysis. The ability of predictors to detect patients with MH was assessed using the area under the receiver-operating

characteristic curve (c-index) with 95% confidence interval. A c-index equal to 0.5 indicates that the discrimination was no better than random, whereas a c-index equal to 1.0 indicates perfect discrimination. All comparisons were two tailed.

The null hypothesis was rejected for a *P*-value  $< 0.05$ .

Reproducibility was determined in 40 randomly selected patients. Inter- and intra-observer variability was examined using both Pearson's bivariate two-tailed correlations and Bland–Altman analysis. Relation coefficients, 95% confidence limits and percent errors were reported.

## Results

According to 24-h-ABPM, the overall incidence of MH in our sample ( $n = 80$ ) was 45%, divided in RN patients (Group RN,  $n = 40$ ) and MH patients (Group MH,  $n = 36$ ). In four patients (5%) there was an increased daytime BP at a single 24-h ABPM, not confirmed at the second examination. These patients were excluded from the analysis.

Thus, our study cohort consisted of 76 AoC patients (mean age  $14.5 \pm 5.7$  years and male sex 64%). Of them, 51 (64.1%) had a bicuspid aortic valve without functional abnormalities.

AoC repair had been performed at a median age of 24 months (range 0.1 to 156 months), with 61 subjects (80%) undergoing surgery within the first year of life. All were in the typical juxtaductal position. Repair was by patch angioplasty in 50 (66%) patients, by end-to-end anastomosis in 16 (21%), by primary percutaneous stent implantation in 8 (10%) and by subclavian flap in 2 (3%). In 20 patients, there was a restenosis treated with balloon angioplasty (12 cases), with stent implantation (six cases), and three patients underwent repeat surgery. None of the patients who underwent balloon aortoplasty developed paracoarctation aneurysms.

Clinical characteristics of the study groups are shown in Table 1. None of the studied patients were on medical therapy. The correlation between office and 24 h systolic BP values are presented in Figure 1. No correlation was found between office and 24 h DBP values.

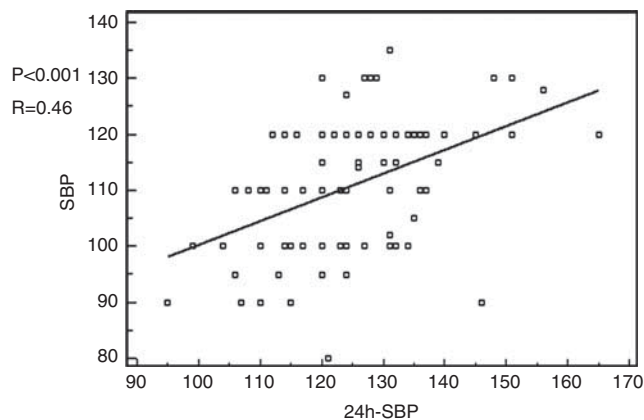
#### *Clinical characteristics of AoC patients with MH*

Sex ratio and mean age were similar between AoC patients with MH and the normotensive ones. There was not significant difference between groups for the age at correction ( $846 \pm 1491$  days vs  $670 \pm 1421$  days). Considering the AoC repair RN group counted 23 (57%) patch angioplasty, 9 (23%) end-to-end anastomosis, 6 (15%) primary percutaneous stent implantation and 2 (5%) subclavian flap, whereas MH group counted 24 (67%) patch angioplasty, 7 (19%) end-to-end anastomosis, 5 (5%) primary percutaneous stent implantation and 1 (3%)

**Table 1** General characteristics of the study groups, divided on the basis of 24-h ABPM

	RN (n = 40)	MH (n = 36)	P-value
Age (years)	14.6 ± 6.9	14.5 ± 3.9	0.9
Sex (M %)	57.5	72	0.3
Weight (kg)	52.2 ± 17.7	57.4 ± 17.8	0.2
Height (m)	1.56 ± 0.16	1.59 ± 0.17	0.8
Body mass index (kg m <sup>-2</sup> )	21 ± 3.6	22 ± 3.6	0.3
Office SBP (mm Hg)	111 ± 11	114 ± 12	0.3
Office DBP (mm Hg)	61 ± 8	64 ± 7	0.09
24 h SBP (mm Hg)	115 ± 8	134 ± 10	<0.0001
24 h DBP (mm Hg)	65 ± 5	73 ± 11	<0.0001
Daytime SBP (mm Hg)	114.24 ± 8.36	136 ± 9.76	<0.0001
Daytime DBP (mm Hg)	68.45 ± 4.82	78.16 ± 8.33	<0.0001
Nighttime SBP (mm Hg)	106.38 ± 8.56	121.65 ± 7.85	<0.0001
Nighttime DBP (mm Hg)	55.66 ± 5.4	64.74 ± 8.65	<0.0001
Heart rate (b.p.m.)	75 ± 11	79 ± 11	0.1
Age at correction (days)	845 ± 1491	604 ± 1357	0.5
Family history of hypertension (%)	3	11	0.3

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.



**Figure 1** Linear regression analysis between 24 h systolic blood pressure (mm Hg) and office systolic blood pressure (mm Hg).

subclavian flap; for the single types of correction no statistically significant differences were noted between the two groups.

**Echocardiographic evaluation of AoC patients with MH**  
Standard echocardiographic study (Table 2) demonstrated significantly increased pressure gradient in the aortic arch (15 mm Hg ± 4 vs 13 mm Hg ± 4.7,  $P < 0.05$ ), thicker walls (IVSd 9 mm ± 1.7 vs 8.2 mm ± 1.7,  $P < 0.05$ ), increased LVMI (51 g m<sup>-2.7</sup> ± 13.5 g m<sup>-2.7</sup> vs 43 g m<sup>-2.7</sup> ± 10 g m<sup>-2.7</sup>,  $P = 0.008$ ) and larger LV diameter (47.6 mm ± 6 vs 44.6 mm ± 3.1,  $P = 0.006$ ) in MH AoC patients compared with the RN patients. The MH group showed a reduced E/A when compared with RN group (E/A 1.6 ± 0.3 vs 1.83 ± 0.3,  $P < 0.01$ ). The study groups did not significantly differ each other when considering E/Em (MH = 8.4 ± 1.8 vs RN = 9.4 ± 3.2,  $P = 0.12$ ), bicuspid

aortic valve (MH = 66% vs RN = 67%,  $P = 0.8$ ) and gothic aortic arch morphology<sup>20</sup> (MH = 17% vs RN = 12%,  $P = 0.8$ ).

#### STI study

STI data are shown in Table 2. Longitudinal myocardial deformation properties were similar between the two AoC groups (Mean Longitudinal Strain MH = -19.8 ± 2.6% vs RN = -19.4 ± 2.4%,  $P = \text{NS}$ ). Conversely, regional longitudinal deformation properties of the basal septal segment were significantly reduced in MH patients (MH = -15% ± 2.4 vs RN = -20.1% ± 5%,  $P < 0.0001$ ). LV twist values showed a significant reduction in the MH group (MH = 12° ± 1.9 vs RN = 14° ± 1.6,  $P < 0.0001$ ) and this reduction persisted after correction for heart rate (Group RN: 0.194 ± 0.0162 vs Group MH: 0.152 ± 0.0288,  $P = 0.003$ ).

Basal septal peak systolic strain and LV twist were significantly correlated with 24 h systolic BP.

At multivariate analysis performed including all the variables significantly different at the univariate analysis, the best predictors of MH were basal septal peak systolic strain and LV twist (Table 3).

The area under the receiver-operating characteristic curve, generated to assess the capability of basal septal strain and LV twist showed a better predictive value for basal septal strain (cut-off value ≤ -16.6%, sensitivity 83.3%, specificity 85% and an AUC of 0.85).

#### Acceptance

The diagnostic procedures were accepted by the whole population studied. The acceptance score ranged from 5 to 9.5 cm. ABPM had the lowest acceptance, whereas echocardiography reached the highest value.



**Table 2** Standard echocardiographic and speckle tracking imaging parameters of the study groups

	RN (n = 40)	MH (n = 36)	P-value
IVSd (mm)	8.2 ± 1.7	8.9 ± 1.8	<0.05
PWd (mm)	8.1 ± 1.7	8.4 ± 1.6	0.4
LVd (mm)	44.6 ± 3.1	47.6 ± 5.9	0.006
LVM (g)	147.7 ± 46.2	181.8 ± 72.8	0.015
LVMi (g m <sup>-2.7</sup> )	43 ± 10	51 ± 13	0.008
RWTa	0.33 ± 0.06	0.34 ± 0.07	0.5
LA (mm)	33 ± 6	34 ± 6	0.8
E/A	1.8 ± 0.3	1.6 ± 0.3	0.015
Deceleration time (msec)	189 ± 46	186 ± 42	0.7
E/Em	9.4 ± 3.2	8.4 ± 1.8	0.1
Pressure gradient in the aortic arch (mm Hg)	13 ± 5	15 ± 4	0.021
Bicuspid aortic valve (%)	67	66	0.9
Gothic arch morphology (%)	12	17	0.8
Mean longitudinal strain (%)	-19.4 ± 2.4	-19.8 ± 2.6	0.5
Basal septal longitudinal strain (%)	-20.1 ± 5	-15 ± 2.5	<0.001
LV twist (°)	14 ± 1.6	12 ± 1.9	<0.0001

Abbreviations: IVSd, interventricular septum end diastolic dimension; LA, left atrial width; LVd, left ventricle end diastolic dimension; LVMi, left ventricular mass corrected for height<sup>2.7</sup>; PWd, posterior wall end diastolic dimension.

**Table 3** Multivariate logistic regression analysis

Variable	Coefficient	Std. error	P
Basal septal peak systolic strain	0.3650	0.1413	0.0098
E/A	-1.5270	1.2678	0.2284
Aortic arch gradient	0.1200	0.08323	0.1493
LVMi	0.03365	0.03362	0.3168
LV twist	-0.6504	0.2410	0.0070
LVd	0.1579	0.09315	0.0900
IVSd	0.01809	0.2525	0.9429
Constant	6.9296		

Abbreviations: IVSd, interventricular septum end diastolic dimension; LV, left ventricle; LVd, left ventricle end diastolic dimension; LVMi, left ventricular mass corrected for height<sup>2.7</sup>.

### Reproducibility

Pearson's correlations—longitudinal peak systolic strain:  $r = 0.83$ ,  $P = 0.0001$ . Bland–Altman analysis—peak systolic strain (95% confidence interval + 3.1, percent error 2.8%).

LV twist:  $r = 0.83$ ,  $P = 0.0001$ ; Bland–Altman analysis—LV twist (95% confidence interval + 2.5, percent error 3.1%).

## Discussion

The main finding of our study was that, in a relatively large population, MH occurred in 45% of AoC children and adolescents successfully treated. Furthermore, in young AoC patients, despite successful repair, MH is associated with LV hypertrophy, diastolic abnormalities, reduced LV twist and reduced basal septal longitudinal myocardial deformation property.

As hypertension and LV hypertrophy are precursors of adverse cardiovascular outcomes later in life, MH in AoC young patients should be considered as a condition that needs further follow-up, life-style intervention, and therapy when this disorder persists.<sup>5</sup>

In this study, AoC patients with MH showed increased LVMi and a starting diastolic dysfunction. These features combined or alone are harbingers of increased cardiovascular risk and of development of sustained hypertension later in life.

Using for the first time, peak systolic STI, we demonstrated the presence of regional abnormal systolic function in AoC patients with MH compared with normotensive patients. STI is a new parameter recently proposed as a strong index of LV contractility.<sup>21</sup> In several studies the new ultrasonic-derived deformation indexes demonstrated a higher ability than standard echocardiography in unmask preclinical systolic abnormalities.<sup>21</sup> In hypertensive patients with apparently normal systolic function, and in presence of a normal diastolic function, the application of STI demonstrated the presence of preclinical LV systolic abnormalities.<sup>22</sup>

Of note, in our study, global longitudinal deformation properties were not altered, whereas abnormal systolic function was detected only in the basal septal region. These findings are probably explained by the increased regional stress on the basal subendocardial longitudinal fibres, which are the most sensitive to ischaemia and the main contributors to long axis shortening, produced by MH.

The basal septal region is peculiarly impaired in hypertensive heart disease.<sup>22</sup> The presence of this impairment in AoC patients with MH is a demonstration that MH is a dangerous condition, which can affect the cardiovascular system similarly to the classical hypertension.

### LV twist

Of interest in our study MH was associated also with a reduced LV twist. Torsional deformation of the LV or twist during systole results in potential energy storage during ejection. LV twist is significantly influenced by physiological variables such as

preload, after load and contractility.<sup>23,24</sup> As RN patients and MH patients showed similar age, end diastolic LV dimensions, LV EF (ejection fraction) and global longitudinal strain, we may postulate that preload and contractility are similar in both groups. This would suggest that the reduced LV twist in MH group could be explained by the increased after load.

#### Perspectives

If confirmed in larger prospective cohort, our findings have important implications for the diagnosis and treatment of hypertension in AoC children and adolescents. In young AoC patients with normotension, 24-h ABPM is mandatory, especially in presence increased LVMI, reduced LV twist or reduced basal septal strain. From a therapeutic point of view, MH in AoC young patients is an indication for further close follow-up and the institution of lifestyle measures. In presence of persistent MH, BP-lowering therapy should be considered strongly in young patients with LV hypertrophy.

#### Study limitations

This is a short-term study of a relatively small number of patients. Another limitation is the lack of longitudinal data that may help in understanding whether MH become more overt with time, its association with increasing progression of LV dysfunction, and the role of treatment. Cardiac magnetic resonance imaging currently is the gold standard for the assessment of aortic arch morphology and LV twist. However, it is not widely available and its analysis is tedious and time consuming. Thus, further prospective multicentre studies are necessary to confirm these results.

#### What is known about the topic

- Life expectancy is still reduced in aortic coarctation (AoC) patients despite a successful repair because of late arterial hypertension and atherosclerosis.
- No previous study addressed the prevalence of masked hypertension (MH), and its impact on cardiac morphology and function in young patients after successful AoC repair.

#### What this study adds

- MH occurred in 45% of AoC young patients successfully treated.
- In these patients, MH is associated with abnormal ventricular geometry and function.

#### Conflict of interest

The authors declare no conflict of interest.

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