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Peripheral vascular structure and function in hypertrophic cardiomyopathy

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ABSTRACT

Background Hypertrophic cardiomyopathy (HCM) is characterised by idiopathic cardiac enlargement and represents the most frequent cause of sudden cardiac death in athletes under the age of 35 years. Differentiation between physiological (ie, exercise-related) and pathological (ie, HCM-related) cardiac remodelling is challenging. In line with cardiac remodelling, vascular structure and function are altered following training, but little is known about peripheral vascular adaptations in HCM. We hypothesised that, while HCM patients and athletes would exhibit similar cardiac characteristics, differences would be apparent in their brachial and carotid arteries.

Methods In age-matched groups of HCM patients (n=18, 39±15 years), highly competitive athletes (n=18, 38±12 years) and recreational controls (n=10, 37±14 years), we used high-resolution ultrasound to assess the diameter and wall thickness of the carotid and brachial arteries, with flow-mediated dilator function (FMD) of the brachial arteries also assessed.

Results A significant difference between athletes and HCM was evident in arterial wall thickness (carotid 519±60 vs 586±102 µm, p<0.05; brachial 345±80 vs 456±76 µm, p<0.05) and the brachial artery peak blood flow response following forearm ischaemia, an index of resistance artery remodelling (998±515 vs 725±248 ml/min, p<0.05). Similar differences were noted between athletes and controls, while controls and HCM did not differ. Brachial FMD% was not different between groups.

Conclusions Athletes and HCM subjects, who can be difficult to differentiate on the basis of cardiac measures, exhibit differences in indices of arterial structure. While this may be a disease-related effect, we cannot discount a generic impact of physical activity on arterial structure, as the athlete's arteries were also different to untrained control subjects. Future studies should assess artery function and structure in athletic HCM subjects.

INTRODUCTION

The cardiovascular system adapts and remodels in response to physical activity and disease. The response of the heart to chronic physical exercise has been extensively studied, reviewed and meta-analysed in echocardiographic and more latterly cardiac MRI studies, involving large athlete cohorts.^{1–5} These studies have provided insights into the nature and magnitude of cardiac adaptation in response to different quantities and types of physical training. The observed cardiac enlargement in response to physical training, together with adaptations in mechanical and electrical function, has been termed as 'Athletes Heart'.^{6,7}

These studies have led to the establishment of upper limits of cardiac structural adaptation, providing clinically relevant information for differentiation between pathological and physiological left ventricular hypertrophy. Nonetheless, differentiation between Athlete's heart and hypertrophic cardiomyopathy (HCM), which is the most frequent cause of sudden cardiac death in young physically fit individuals under the age of 35 years,^{8–10} remains a diagnostic conundrum and approaches such as detraining,¹¹ cardiopulmonary exercise testing,¹² a detailed family history and genetic markers⁸ may not be acceptable to an athlete (detraining) or robust enough to establish definitive diagnostic differentiation (genetics).

Abnormal vascular responses have previously been reported in HCM. For example, exercise hypotension has been reported in HCM patients, along with inappropriate and exaggerated decreases in systemic vascular resistance at high workloads.¹³ Haemodynamic instability in patients with HCM has been reported in another study in association with abnormal vascular responses.¹⁴ This is supported by the findings of Imaizumi *et al* who reported that the maximal vasodilator capacity of resistance vessels is limited in patients with HCM, compared with age-matched control subjects.¹⁵ These findings suggest that abnormalities in peripheral arteries may exist in HCM.

To date, limited and conflicting evidence exists pertaining to the function and structure of peripheral conduit arteries in HCM patients.^{15–18} Flow-mediated dilation (FMD) of conduit arteries has been reported to be similar between HCM patients and controls, although HCM had lower blood flow values.¹⁷ Conversely, recent studies observed impaired endothelium-dependent vascular responses in the brachial artery of HCM patients,¹⁸ or increased plasma biomarkers of endothelial dysfunction.^{19,20} Evidence pertaining to differences in peripheral conduit artery structure in HCM is scant, but autopsy studies have suggested that coronary walls may be thickened with luminal narrowing^{21–23} and attenuated pressure-induced myogenic activation has been documented in small coronaries of mice with induced HCM.²⁴ The aim of this study was to examine brachial and carotid vascular structure and brachial function in HCM patients, compared with age-matched athletes and controls. We hypothesised that differences would exist between athletes and HCM subjects and that HCM subjects would also differ from healthy controls.

METHODS

A group of highly trained (national standard) athletes ($n=18$, all male) were recruited from a range of sports (endurance runners $n=8$; endurance triathletes $n=5$; endurance cyclists $n=1$; canoeists $n=4$) along with age-matched recreationally active (<3 h per week of organised physical activity) healthy controls ($n=10$, all male) (table 1). Age-matched HCM patients ($n=18$, 16 male and 2 female) with clinical diagnosis based on phenotypical presentation and family history were recruited from patient registries at St. George's Hospital, London and The Countess of Chester NHS Hospital, Chester. The study procedures were approved by national (NHS National Research Ethics Service) and local (Liverpool John Moores University) research ethics committees. Written informed consent was gained from all participants prior to the experimental procedures.

Experimental design

Participants reported on one occasion to the testing laboratory after fasting for 6 h, abstaining from alcohol and beverages containing caffeine (ie, coffee, tea and energy drinks) for 12 h and refraining from any intense physical exercise for 24 h. After familiarisation and completion of a brief training/exercise history questionnaire, subjects rested for at least 20 min in the supine position. Baseline ultrasound scans of the right carotid and dominant arm brachial arteries were then collected for the assessment of resting diameter and wall thickness (WT) using high-resolution ultrasound. Following another >20 min rest period cardiac structural characteristics were assessed by echocardiography. Brachial artery FMD of the dominant arm was assessed followed by another 20 min supine rest before the ischaemic handgrip (iEx) test was completed.

Experimental measurements

Anthropometrics and body composition

Height (SECA, Hamburg, Germany) and body mass (SECA) were measured and used to calculate body mass index ($\text{BMI}=\text{weight in kilograms}/\text{height in square meters}$). Resting heart rate (HR) and systolic and diastolic blood pressures were

Table 1 Anthropometric characteristics of elite athletes, recreationally active controls and HCM patients

	Athletes ($n=18$)	Controls ($n=10$)	HCM ($n=18$)	p Value
Age (year)	38 ± 12	37 ± 14	39 ± 15	0.860
Systolic blood pressure (mm Hg)	127 ± 13	$124\pm 12^{\dagger}$	139 ± 15	0.018
Diastolic blood pressure (mm Hg)	$71\pm 9^{\dagger}$	$70\pm 7^{\dagger}$	87 ± 9	<0.001
Height (cm)	$180\pm 6^{\dagger}$	175 ± 10	173 ± 10	0.055
Weight (kg)	77 ± 9	83 ± 18	81 ± 19	0.572
Heart rate (beats/min)	$48\pm 10^{* \dagger}$	63 ± 15	70 ± 10	<0.001
Current symptoms	10/18			
SAM	3/18			
LVOT	2/18			
Medications	11/18			

Data are mean $\pm$ SD for continuous variables.

Current symptoms, palpitation, chest pain, breathlessness, pre-syncope, syncope; HCM, hypertrophic cardiomyopathy; SAM, systolic anterior motion; LVOT, left ventricular outflow tract obstruction; medications, β blockers, ACE inhibitors, calcium channel blockers, antiarrhythmic agents.

Significantly different when post hoc tests are applied * compared to controls, † compared to HCM, $p<0.05$.

determined twice using an automated sphygmomanometer (Dinamap; GE Pro 300V2, Tampa, Florida, USA).

Echocardiography

Quantitative assessments allow for morphological and functional information to be gathered throughout this project. Two experienced sonographers were used for all image collections using an echo ultrasound machine (Vivid I, GE Medical Systems, Horten, Norway) and a 1.6–4 MHz phased array transducer. Prior to every echocardiographic assessment the individual rested quietly in the supine position for 5 min. Then they were asked to lie in the left lateral decubitus position. Each image collected was recorded during apnoea over a minimum of three cardiac cycles and stored in a DICOM format to CD/DVD archive. Image analysis was performed on an offline system by the same individual on an Echo-pac software (Echo-pac, GE Medical Systems). Three cardiac cycles were measured with the average taken.

Standard two-dimensional and M-mode echocardiography

Two-dimensional (2D) and M-mode echocardiography were performed using harmonic imaging and images optimised to maximise spatial and temporal resolution. This involved adjustment of various ultrasound parameters including gain, dynamic range, depth, angle width, frame rate and frequency. 2D images were obtained in accordance with the American Society of Echocardiography²⁵ and a systematic approach was adopted. Initially, a 2D parasternal long-axis orientation was acquired. From this image an M-mode is taken of the left ventricular base to acquire offline measurements of systolic and diastolic septal and posterior WTs, cavity dimensions and the estimation of left ventricular mass (LVM).²⁶ Left ventricular end-diastolic (LVEDV) and systolic volumes were determined from 2-chamber and 4-chamber Apical views using the modified Simpsons biplane method. LV ejection fraction (EF%) and stroke volume were calculated from volume data. The LVEDV:LVM ratio was determined to assess the degree of concentric remodelling.

Standard Doppler echocardiography

LV diastolic filling assessment used pulsed-wave Doppler traces across the mitral valve following guidance from the Canadian Consensus on Diastolic Dysfunction.²⁷ An apical four-chamber window was used to place a sample volume at the tips of the mitral valve in diastole, parallel to the mitral inflow. To maximise the signal-to-noise ratio Doppler gain, pulse repetitive frequency, the baseline and high-pass filter were adjusted accordingly. Mitral inflow signals allowed measurements of peak flow velocities (cm s^{-1}) in early diastole (E) and late diastole following contraction (A) with the E:A ratio being calculated.

Conduit artery WT

Three standardised probe angles (posterior, lateral and antero-lateral) were used to determine resting WT and the diameter of the right carotid artery using a 10 MHz multi-frequency linear array probe attached to a high-resolution ultrasound machine (T3000, Terason, Burlington, Massachusetts, USA). The sonographer obtained a longitudinal B-mode image of the carotid artery 2 cm proximal to the carotid bifurcation. Recording was performed over a 10 s period. Settings were adjusted to focus on the far-wall of the arterial lumen interface and the media-adventitia. WT data were then collected from the brachial artery using the same procedures described above. For

practical reasons, two planes of assessment were used for the peripheral artery.

Endothelium-dependent FMD

Brachial artery dilation after a 5 min ischaemic stimulus was assessed to determine endothelium-dependent, largely nitric oxide (NO)-mediated, functional dilation.^{28 29} FMD was examined by one experienced sonographer. The dominant arm was extended and positioned at an angle of $\sim 80^\circ$ from the torso on a foam pillow. A rapid inflation and deflation pneumatic cuff (D.E. Hokanson, Bellevue, Washington, USA) was positioned around the forearm immediately distal to the olecranon process. A 10 MHz multifrequency linear array probe (T3000, Terason, Burlington, Massachusetts, USA) was used to image the brachial artery in the distal one-third of the upper arm. Ultrasound parameters were set to optimise the longitudinal, B-mode images of lumen-arterial wall interface and were then held stable for a 1 min baseline recording of the image and Doppler velocity. Continuous Doppler velocity assessment was collected using a 60° angle, which did not vary during each study. The occlusion cuffs were inflated to >200 mm Hg to completely block the arterial inflow for 5 min. Diameter and flow recordings resumed 30 s prior to cuff deflation and continued for 3 min thereafter, according to a recently published guidelines.^{28 30}

Hyperaemic peak blood flow response to iEx

Cuffs inflation with the addition of ischaemic exercise induces a near maximal blood flow responses, which are used as a surrogate measure of resistance artery remodelling. Cuffs were positioned proximally around the upper arm above the imaged artery. The ultrasound image was then optimised and recording began for 1 min prior to the cuff being inflated to >200 mm Hg for 5 min. During the middle 3 min, rhythmic ischaemic handgrip exercise was performed using a 3 kg weight at 30 contractions/min with the rhythm set by a metronome. Diameter and velocity recordings resumed 30 s prior to cuff deflation and continued for 3 min thereafter. The peak hyperaemic forearm blood flow response to this stimulus in humans provides a valid and accepted index of collective resistance artery size or remodelling.³¹

Table 2 Cardiac structure and function parameters of elite athletes, recreationally active controls and HCM patients

	Athletes (n=17)	Controls (n=9)	HCM (n=18)	p Value
Cardiac				
LVIDd (mm)	52 $\pm$ 6 [†]	52 $\pm$ 5 [†]	46 $\pm$ 5	0.003
LVEDV (ml)	132 $\pm$ 31 [†]	126 $\pm$ 25 [†]	96 $\pm$ 26	0.002
PWT (mm)	12 $\pm$ 1	10 $\pm$ 2	12 $\pm$ 4	0.113
ST (mm)	13 $\pm$ 2	11 $\pm$ 1 [†]	15 $\pm$ 4	0.002
LVM (g)	263 $\pm$ 36	208 $\pm$ 33	257 $\pm$ 95	0.112
LVEDV/LVM	0.50 $\pm$ 0.09	0.60 $\pm$ 0.10 [†]	0.41 $\pm$ 0.16	0.002
% EF	62 $\pm$ 7	58 $\pm$ 8	68 $\pm$ 12	0.056
SV (ml)	83 $\pm$ 27	71 $\pm$ 18	71 $\pm$ 17	0.328
E/A	1.84 $\pm$ 0.50 [†]	2.02 $\pm$ 0.56 [†]	1.39 $\pm$ 0.45	0.011

Data are mean $\pm$ SD.

E/A, ratio of peak early to atrial left ventricular filling velocities; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; LVEDV, left ventricular end-diastolic; LVIDd; LVM, left ventricular mass; PWT, posterior wall thickness; ST, septal wall thickness; SV, stroke volume.

Significantly different when post hoc tests are applied to *compared to controls

[†]compared to HCM, $p<0.05$.

Data analysis

Cardiac analysis

All images were analysed by the same sonographer offline using specialised software (Echo-pac, GE Medical Systems). Three cardiac cycles were measured with the average taken.

Arterial edge detection, wall tracking and WT analysis

Post-test analysis of brachial artery diameter and velocity was performed using custom-designed edge-detection and wall-tracking software which is largely independent of investigator bias. Settings were recorded and maintained to establish consistency.^{32–34} The software is written in the icon-based graphical programming language (LabVIEW V7.0) and uses an IMAQ vision tool kit for image handling and analysis routines with arterial analysis using edge detection methods. Analysis of carotid and brachial artery WT was also performed using a DICOM-based software package, which has proven to be observer-independent and has been validated against phantoms.^{32–34}

Arterial functional analysis

All arterial FMD% and peak blood flow was analysed using an offline specific software package (DICOM Encoder&FMD/ Blood flow analysis, V3.0.5 Labview V7.0, National Instruments Corporation). Identification of the region of interest on the artery diameter and blood flow uses edge detection and wall tracking analysis throughout the recorded scan via a Rake routine. This measures 30 points a second throughout the analysis. Ultimately, from this synchronised diameter and velocity data, blood flow (the product of lumen cross-sectional area and Doppler velocity (v) and shear rate (four times velocity divided by diameter) were calculated at 30 Hz. Peak blood flow was taken over the initial first peak post cuff deflation over a 10 s continuous period. FMD was calculated as the percentage rise of this peak diameter from the preceding baseline diameter and in accordance with recent findings shear rate stimulus responsible for endothelium-dependent FMD.²⁸

Statistics

Statistical analyses were performed using SPSS V17.0 (SPSS, Chicago, Illinois, USA) software. All data are reported as mean ($\pm$ SD) unless stated otherwise, while statistical significance was assumed at $p<0.05$. A one-way analysis of variance (ANOVA) was used to examine differences between groups. Post hoc LSD test to correct for multiple comparisons were used to identify differences groups when the ANOVA revealed a significant effect.

RESULTS

Anthropometric

The three groups recruited were of a similar age, height and body mass (table 1). Athletes had lower resting HRs than both HCM patients and control subjects. HCM patients had higher systolic and diastolic blood pressures compared with athletes and controls. While most HCM patients reported some current symptoms (palpitations, breathlessness, etc) and medication use (β blockers, etc) there was less evidence of systolic anterior motion or LV outflow obstruction.

Cardiac structure and function

The HCM patients had significantly smaller LVIDd and LVEDV compared to the athletes and controls (table 2). HCM patients

had similar septal WT compared to controls and athletes but greater posterior WT (PWT) than controls. The difference in PWT between HCM and athletes was not statistically significant. Consequently, IVM was similar in athletes and HCM patients. The LVEDV:IVM ratio was lower in HCM patients than controls. Global indices of LV systolic function were not different between groups. The E/A ratio, a marker of diastolic filling, was lower in HCM compared to athletes and controls.

Arterial structure and function

Athletes had significantly lower brachial artery WT and wall-to-lumen ratios compared with HCM patients and control participants (table 3 and figure 1). While athletes had lower carotid WT than controls or HCM patients the WT-to-lumen ratio was not different between groups. The highest brachial artery blood flow response to ischaemic handgrip exercises (iEx) occurred in athletes but was quite variable and not significant between groups (table 3 and figure 2). We observed no differences in brachial artery baseline diameter, maximal diameter, FMD% or shear rate responses between the three groups (table 3).

DISCUSSION

The novel findings from this study indicate that athletes and HCM patients, who exhibit similar cardiac morphological characteristics (eg, IVM), possess greater peripheral arterial WT and wall-to-lumen ratios but lower peak blood flow responses. These findings indicate that HCM and athletes can be differentiated on the basis of structural remodelling apparent in peripheral conduit and resistance arteries. However, differences in artery structure also existed between athletes and control subjects, and HCM and controls did not differ, suggesting that the differences we observed between athletes and HCM may reflect the well-established impact of intensive exercise training on peripheral arteries^{35–39} rather than an independent impact of HCM on peripheral arteries per se.

We recently published evidence that chronic exercise training modifies peripheral conduit artery lumen dimensions³⁹ and that this effect is likely mediated by localised factors associated

with repeated exercise bouts, such as episodic increases in endothelial shear stress.³⁸ In addition, we observed that athletes exhibit smaller arterial WT than non-athletes³⁸ and that this effect is more systemic in nature.^{38–39} These findings are generally supported by evidence that resistance arteries undergo remodelling in response to exercise training.^{40–42} Consequently, the impact of exercise on the arteries of athletes has recently been reviewed.³⁶ The findings in athletes in the present study are, therefore, consistent with those previously reported.

While previous studies have reported evidence of conduit artery dysfunction in HCM patients,¹⁸ data from this study demonstrate no differences between HCM patients and athletes or controls for brachial artery endothelium function (FMD). Our data are, however, consistent with another study in HCM patients, which suggested that conduit artery function was not impaired in HCM.^{17–19} An important limitation of previous studies is the use of limited time-point analysis of the FMD response, which does not reflect true peak dilation.³⁰ Importantly, future research related to conduit artery function in HCM should adopt similar assessment procedures as the current study that are based on recent consensus guidelines.^{28–43}

Our findings pertaining to brachial artery function are, at first glance, paradoxical. While no significant differences existed between the three groups studied, athletes had lower FMD than HCM and control subjects. However, this paradoxical decrease in FMD, often used as a measure of endothelial function and artery health, may relate to the larger artery lumen size in athletes, who also exhibit decreased WT.^{38–39} It is well established that both artery size^{44–45} and WT⁴⁶ impact upon functional

Table 3 Brachial, structure and function and carotid structure in athletes, recreationally active controls and HCM patients

	Athletes (n=18)	Controls (n=10)	HCM (n=18)	p Value
Vascular				
Brachial diameter (mm)	4.6±0.6	4.1±0.5	4.3±0.9	0.171
Brachial max diameter	5.2±0.8	4.6±0.7	4.8±0.7	0.114
iEx test (mm)				
Brachial WT (μm)	345±80*†	460±34	456±76	<0.001
Brachial W:L ratio	0.07±0.02*†	0.10±0.01	0.10±0.03	<0.001
Brachial FMD%	5.1±1.9	5.3±1.2	6.9±4.1	0.154
Brachial shear rate (s, 10 ³)	16615±8098	17440±5701	18154 ±10066	0.875
Brachial peak BF (ml/min)	998±515	592±148	725±248	0.041
Carotid diameter (mm)	6.8±0.5	6.9±0.7	6.9±0.7	0.724
Carotid WT (μm)	519±60*†	602±55	586±102	0.016
Carotid W:L ratio	0.08±0.01	0.09±0.01	0.09±0.02	0.097

Data are mean±SD.

BF, blood flow; FMD, flow-mediated dilator function; HCM, hypertrophic cardiomyopathy; iEx, ischaemic handgrip exercises; W:L, vessel wall to lumen ratio; WT, wall thickness.

Significantly different when post hoc tests are applied *compare to controls,

†compared to HCM p<0.05.

Figure 1 Arterial wall thickness averages and SD in (A) brachial and (B) carotid artery in athletes, hypertrophic cardiomyopathy and control groups. * Represents a significant difference between groups p<0.05 HCM, hypertrophic cardiomyopathy.

Figure 2 Peak blood flow of the brachial artery averages and SD of athletes, hypertrophic cardiomyopathy and control groups. * Represents a significant difference between groups $p < 0.05$. HCM, hypertrophic cardiomyopathy.

responses. This may, in subjects who differ in arterial structural characteristics a priori, complicate the interpretation of between subject differences in FMD.³⁶ In any event, FMD is clearly not useful in differentiating between athletes and HCM subjects and we believe that future studies, preferably involving athletes with HCM, should focus on structural or morphological impacts of HCM on the peripheral vasculature.

The principal limitation of this study is that we did not include a group of athletes with known HCM. Although limited in number as well as difficult to diagnose and identify, such a group would allow assessment of the impact of HCM, independent of athletic status, on peripheral artery structure in future. This would have a much more powerful impact in the real world of athlete screening if the athletes with HCM had low penetrance of the disease and thus existed within the grey-zone for differential diagnosis. We attempted to approach this issue in the current study by not assessing HCM patients with gross morphological LV phenotypes. Another limitation was the absence of endothelium-independent arterial dilation measures. We did not administer glyceryl trinitrate because it may exacerbate outflow gradients in HCM patients. Information regarding vascular smooth muscle in HCM is, therefore, currently unavailable. A secondary limitation is that we selected HCM patients with relatively mild LV phenotypes, as surrogates for not having access to a large number of active athletes with HCM. The lack of differences between HCM patients and athletes (or controls) for brachial artery FMD may be due to the mild HCM expression in our participants. This mild HCM may not result in modulation of arterial function similar to that has been reported in past studies of HCM patients where WT have been much larger than in the current study.¹⁸ Further the impact of individual variation in bloody pressure, which was moderately elevated in HCM patients, symptomology, medications (etc) cannot be determined but are worthy of further study.

In conclusion, HCM patients demonstrated greater WTs in the brachial and carotid artery and impaired peak blood flows in the brachial artery compared to athletes with a similar heart size. FMD% did not differ between groups; however, the FMD data must be interpreted with caution in groups which differ in artery structure. Future studies should assess peripheral vascular structure in athletes who have been diagnosed with HCM to distinguish if arterial WT is lower than non-athletic individuals with HCM.

What this study adds

- Findings from this study indicate that athletes and hypertrophic cardiomyopathy (HCM) patients, who exhibit similar cardiac morphological characteristics (eg, left ventricular mass), possess differences in peripheral arterial wall thickness' and arterial wall-to-lumen ratios.
- While athletes demonstrate higher peak brachial blood flow responses, flow-mediated vasodilatation of the brachial artery is not enhanced compared to controls or HCM patients.
- These data require verification and extension to athletic HCM patients but they provide some additional insight into the impact of HCM on the cardiovascular system that may be useful in differentiating from athletes.

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