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INTRODUCTION

Arterial hypertension affects an estimated 25% of the Worldwide adult population(1). Different patterns of hypertensive heart disease are recognized. Both the original echocardiographic classification(2) of left ventricular (LV) remodeling and hypertrophy in hypertension, and the more recent cardiac magnetic resonance (CMR) revision to this classification(3) describe symmetrical patterns of hypertensive heart disease only. Asymmetric patterns of hypertensive heart disease have been described with 2D echocardiography(4). CMR offers precise measurements of left ventricular mass, volume and wall-thickness(5) and is the current non-invasive gold-standard investigation for assessing these parameters and LV systolic function(6). The prevalence and asymmetric LV phenotypes as defined by CMR gold-standard has previously been described in the context of aortic stenosis(7). However, no such comprehensive CMR data currently exists for arterial hypertension, which is the most common disease state of increased afterload.

CMR is gaining an increasing role as a useful imaging technique in certain subjects with arterial hypertension and has been recognized in the recent European Society of Hypertension/Cardiology hypertension guidelines particularly due to its tissue characterization properties(8). As such, understanding the prevalence of asymmetric hypertensive heart disease is important as an increasing number of patients with hypertension and/or suspected HCM are being referred for CMR to attempt to distinguish between the two pathologies and the number is set to increase with the increased availability of CMR.

Consequently, the aims of this study were to describe the prevalence and predictors of asymmetric hypertensive heart disease.

MATERIALS AND METHODS

Study population

Patients with hypertension were recruited from the Bristol Heart Institute tertiary hypertension clinic between February 2012 and April 2015. The local research ethics committee confirmed that the study conformed to the governance arrangements for research ethics committees. Subjects provided written consent. Baseline demographic and clinical characteristics were recorded, including review of baseline 12-lead electrocardiograph for the presence of LVH by Sokolow-Lyon voltage criteria(9) and for ECG-strain pattern, defined as ≥1mm concave down-sloping ST-segment depression and asymmetrical T-wave inversion in the lateral leads(10), by an experienced clinician blinded to the CMR data. In order to investigate asymmetric hypertensive heart disease only, the study cohort was carefully selected to exclude patients with any concomitant myocardial pathology that may confound the remodeling pattern and/or the hypertrophic response. Exclusion criteria therefore consisted of: any evidence of moderate-severe valvular heart disease, acquired or inherited cardiomyopathy and suspected athlete's heart. Aortic valve pathology was excluded by radial cine of the aortic valve and phase contrast magnetic resonance angiography images in the aortic root. Mitral valve disease was excluded by visual assessment on the 4-chamber, 3-chamber, 2-chamber and short-axis cines. In particular, HCM was excluded on the basis of clinical data, family history and electrocardiographic features supportive of this diagnosis. A severely decreased

estimated glomerular filtration rate (eGFR) <30ml/min/1.73m^2 was also an exclusion criterion.

Average office systolic (SBP) and diastolic blood pressures (DBP) were acquired in all subjects after seated rest from both arms, assessed using standard automated sphygmomanometry with an appropriately-sized cuff(11). Patients were stratified by hypertension severity on the basis of their office blood pressure level in accordance to the 2013 ESH/ESC hypertension guidelines(8). In a subgroup of hypertensive subjects (n=85), standard 24-hour ambulatory blood pressure monitoring (ABPM) was also performed(12).

CMR protocol

All CMRs was performed at 1.5T (Avanto, Siemens, Erlangen, Germany). Steady state free precession (SSFP) short axis whole LV cines (8mm slice thickness, no slice gap, temporal resolution 38.1ms, echo time 1.07ms, representative field of view in-plane pixel size 1.5 x 0.8mm) were used for the estimation LV mass (LVM) and volumes, which then indexed to body surface area (BSA), as previously described(13). Previously validated(14) threshold-detection software (CMR42, Circle Cardiovascular Imaging Inc., Calgary, Canada) was used to include papillary muscles and LV trabeculation to be included in LVM estimation in accordance with the latest Society of Cardiovascular Magnetic Resonance imaging guidelines(15). Papillary muscles and trabeculations were then included in the blood pool volume for assessment of end-diastolic volume (EDV), end-systolic volume (ESV) and stroke volume (SV) as described previously(13). LV hypertrophy was defined as indexed LV mass > upper

95th confidence interval of established age- and gender-specific CMR reference ranges respectively(13). The LV mass/volume ratio (M/V), CMR equivalent of the echocardiogram-derived relative wall thickness measurement, was derived by dividing LVM by EDV(16). Maximal wall thickness was defined as the end-diastolic wall thickness (EDWT) measured in the middle of the thickest segment according to the American Heart Association 17-segment model(17) from the LV short-axis cines, excluding left and right ventricular trabeculations. Asymmetric wall thickness was defined as a regional wall thickness ≥15mm in ≥1 myocardial segments, In accordance with European guidelines on the diagnosis of HCM(18), and segmental EDWT >1.5-fold the opposing segment, as previously described(**Figure 1**)(7). Such measurements from short axis cine CMR images have been previously demonstrated to result in good inter and intra-observer variability(19). Global longitudinal strain was measured with voxel-tracking post-processing software (TissueTracking, CVI42, Circle Cardiovascular Imaging Inc, Calgary) using 4-chamber and 2-chamber cines. All measurements were performed by an experienced CMR reader, blinded to clinical data.

Myocardial replacement fibrosis was assessed by late gadolinium enhancement (LGE)(20). An inversion-recovery fast gradient echo sequence performed in two phase-encoding directions were performed approximately 10-15 minutes after intravenous administration of 0.1mmol/kg gadobutrol (Gadovist, Bayer Pharma AG, Germany). Tailored inversion times were used in each patient to null the myocardium. The presence LGE was quantified by visual analysis by two

independent experienced CMR readers blinded to the clinical and remodeling/hypertrophy data. Any discrepancies were resolved by consensus.

Aortic distensibility

As previously described(21), ascending aortic distensibility was estimated as follows: distensibility = $\Delta A / (A_{diast} \times \Delta P)$, measured from cine image perpendicular to the vessel at the level of the right pulmonary artery, where A_{diast} is the ascending aortic area at end-diastole and ΔP (in mmHg) is the pulse pressure estimated from SBP – DBP. Excellent interobserver agreement and reproducibility of this measure has previously been reported(22). Aortic distensibility measurements were performed by an experienced CMR reader, blinded to all other CMR and clinical data.

The aortoseptal angle was measured from the 3-chamber CMR cine with a previously described and reproducible method(23) which is a modification of the original echocardiographic technique(24). The aortoseptal angle was defined as the angle between a line drawn along the border of the right and left interventricular septum (parallel to the proximal right ventricular endocardial border), and a line drawn through the long axis of the aortic root, where a value of 180^{o} would be a straight line from septum to aorta and reducing values representing increased angulation **Figure 2**). Aortoseptal angle measurements were performed by an experienced CMR reader, blinded to all other CMR and clinical data.

Statistical analysis

Statistical analysis was performed using SPSS Version 21 (Armonk, NY, USA: IBM Corp). Normally distributed continuous variables were expressed as mean ± standard deviation and compared using unpaired Student's T test, with post-hoc correction for multiple T tests, or one-way analysis of variance with least significant difference post-hoc correction as appropriate. Categorical variables were expressed as percentages and analysed using the Fisher's exact test. R-values quoted are for Pearson's correlation coefficient. Univariate and multivariate logistic regression analysis was performed to identify predictors of asymmetric hypertensive heart disease with morphological overlap with HCM. Statistical significant was set at two-sided $P<0.05$.

RESULTS

Study population

One hundred and fifty hypertensive patients underwent CMR. Twenty-one patients were excluded(**Figure 1**), including 9 subjects with subendocardial LGE consistent with previous MI, resulting in a final study size of 129 patients (age: 50.8±15.2 years, 49.6% male, SBP: 170.4±30.0mmHg, DBP: 97.3±15.5mmHg). There was no difference in the prevalence of diabetes mellitus and history of ischaemic heart disease between the cohorts. ECG evidence of LVH was significantly more common in subjects with CMR defined LVH but no asymmetry and ECG-strain pattern was significantly more common in subjects with asymmetric wall thickening but the overall prevalence of these ECG features was low(**Table 1**).

Prevalence of asymmetric hypertensive heart disease

In our cohort consisting exclusively of patients with hypertension, asymmetric EDWT ≥15mm in ≥1 myocardial segment(s) and >1.5-fold the opposing segment(s) occurred in 21% (n = 27) (**Table 2**). Subjects with asymmetric EDWT were significantly older than both subjects with concentric and subjects with normal indexed LV mass (57±13 vs 48±14 vs 49±16 years, P<0.05 respectively) and there was a significantly higher proportion of male subjects (74% vs 48% vs 43%, P<0.05 respectively). Despite similar left ventricular ejection fraction, subjects with asymmetric wall thickness had the lowest global longitudinal strain(**Table 2**).

Location and magnitude of the asymmetric hypertrophic response

Patients with asymmetric hypertensive heart disease had significantly higher maximal EDWT compared to patients with concentric LVH (18±2 vs 13±1mm, P<0.05)(**Table 2**). Furthermore, indexed LV mass was significantly higher in subjects with asymmetric hypertensive heart disease compared to subjects with LVH but no wall asymmetry (109±27 vs 96±10g/m^2, P<0.05). In asymmetric hypertensive heart disease, the maximal EDWT was exclusively located in the basal to mid septum. The segmental distribution and magnitude of asymmetrical EDWT is demonstrated in **Figure 4**.

Myocardial replacement fibrosis

The anatomical location of replacement fibrosis is demonstrated in **Figure 5**. Mid-wall myocardial replacement fibrosis was significantly more common in subjects with asymmetric EDWT (15% vs 0% vs 1%, P<0.05 respectively). However, the overall prevalence of mid-wall LGE was low in our patient population at 4% (n=5). The

prevalence of RV insertion point LGE was significantly higher in subjects with asymmetric wall thickness compared to subjects without LVH (41% vs 9%, P<0.05) but not significantly different to those subjects with concentric LVH (41% vs 22%, P=0.07).

Aortic function

The aortoseptal angle in subjects with asymmetric hypertensive heart disease was significantly lower (implying a more acute angle between the anatomical structures) than in subjects with concentric LVH and in subjects without LVH (114±10^{o} vs 125±9^{o} vs 123±12^{o}, P<0.05 respectively)(**Table 2**). Aortic distensibility was significantly reduced in subjects with asymmetric EDWT compared to those without wall asymmetry and without LVH (1.01±0.60 vs 1.83±1.65mm^{2}/mmHg x10^{3}, P<0.05). Increasing EDWT correlated with significant reduction in aortic distensibility (R=0.302, P<0.001) and significant reduction in aortoseptal angulation (R=-0.414, P<0.0001).

Predictors of asymmetric hypertensive heart disease

In univariate analysis, increasing age, male gender, increasing body mass index, increasing indexed LV mass, lower aortic distensibility and lower aortoseptal angle were all significant predictors of the presence of asymmetric hypertensive heart disease (**Supplementary data**). However, only increasing age (odds ratio [95th confidence interval]: 1.10[1.02–1.18], P<0.05) and increasing indexed LV mass (1.09[1.04–1.14], P<0.05) remained significant predictors in the multivariate logistic regression statistical model.

DISCUSSION

To our knowledge, this is the first study to define the prevalence of asymmetric hypertensive heart disease with CMR. Asymmetric EDWT ≥15mm and >1.5-fold the opposing myocardial segment in ≥1 segments occurred in 21% of our purely hypertensive cohort. Our results demonstrate how frequently hypertensive heart disease can morphologically overlap with HCM according to the EDWT threshold of 15mm advocated by European HCM guidelines(18).

We also show that advanced hypertrophic response and increasing age are independent predictors of the asymmetric hypertensive phenotype. Multivariate logistic regression analysis confirms that the higher prevalence of male gender and higher BMI in the asymmetric cohort, which may be potential confounding factors of the hypertrophic process(25), do not exert significant independent effects.

Asymmetric LV responses have been recognized in health and disease. Goor et al. first coined the term ‘sigmoid septum’, describing variations in the septal contour in 50 ex-vivo humans hearts of varying ages(26). More recently, in a CMR study of young healthy army recruits, the prevalence of LV asymmetry, as defined as EDWT ≥13mm and >1.5-fold the opposing myocardial segment, was 2.2% at baseline, increasing to 10% following a period of intensive physical training(27). In the context of hypertension, Wicker et al. have previously documented a prevalence of 5% of asymmetric septal hypertrophy in a 2D echocardiographic study(28). Their definition of LV asymmetry consisted of >1.3 times the free LV wall, and did not have an

absolute EDWT threshold. In contrast, we observed a higher prevalence of hypertensive LV asymmetry with CMR. A putative explanation for this relates to the better whole heart 3D coverage with contiguous short axis cines and better tissue contrast of CMR, facilitating the identification of endocardial contours, relative to 2D echocardiography, which is a well-recognised phenomenon(29).

In our cohort, asymmetric wall thickness was exclusively located in the basal to mid septum. Asymmetric septal thickness has been described in echocardiographic(4) and CMR(7) studies of LVH secondary to aortic stenosis, the latter reported a prevalence of 27%, where a definition of asymmetry of ≥13mm and >1.5-fold the opposing myocardial segment was employed. Interestingly, those subjects with aortic stenosis and asymmetric septal thickness in both the aforementioned studies had high prevalence of concomitant hypertension. Our results, in a cohort with strict exclusion of valvular heart disease and other potential hypertrophic confounding pathologies, raise the question of the relative important of the type of afterload (aortic stenosis or arterial hypertension or a combination thereof) in the development of the asymmetric phenotype.

The reason why some patients develop asymmetric thickening is unclear. The fact that the basal septum is a site of increased wall stress may be implicated(30) and may explain the common appearance in both aortic stenosis and systemic hypertension, which both have increased afterload. Puntmann et al. demonstrated that impaired deformation follows the areas of increased wall stress in hypertensive heart disease(31). Our data show more acute aortoseptal angulation and less aortic

distensibility in hypertensives with basal to mid septal myocardial asymmetrical thickening. This may result in increased LV wall stress in this region of myocardium, driving asymmetric wall thickening. Our findings are consistent with those of Goor et al. who found increased aortic root angulation was associated with increasing septal prominence in their study of 50 ex-vivo human hearts(26). We are unable to determine a cause and effect relationship between aortic function and asymmetric LVH in our observation study. Age-related changes in aortic configuration and function and/or duration of hypertension may be important factors in this observed relationship. Increasing septal thickness with age is consistent with previous work(26).

Equally, the denser sympathetic innervation of the interventricular septum relative to the lateral wall has been postulated as a pathophysiological explanation for the asymmetric phenotype(32). Certainly, sympathetic activation is recognized in some, but not all, patients with essential hypertension, which may account for the heterogeneity of this appearance within hypertensive subjects(33). A further putative mechanism relates the angiotensin II receptor subtype, AT1, which has been shown to mediate protein synthesis and hypertrophy in rat models(34). Furthermore, AT1 receptor up-regulation has been demonstrated in spontaneously hypertensive and reno-vascular hypertensive rats with LVH(35). Differences in location and expression of AT1 could, theoretically, account for asymmetric LV wall thickening.

The exclusive location of asymmetry occurring in the basal to mid septal myocardial segments and the absolute mean wall thickness of 18 ± 2mm in our cohort may have clinical implications. The European Society of Cardiology guidelines advocate that a diagnosis of HCM be considered if regional wall thickness is ≥15mm in one or more LV myocardial segments or ≥13mm in a first degree relative of someone with HCM, measured by any imaging technique(18). The guidelines concede that the diagnosis should only be made in the absence of any abnormal loading conditions but do not provide a description of the predictable LV appearances in hypertension, a state of abnormal afterload. The hypertensive asymmetric phenotype in our cohort highlights that in approximately 1 in 5 subjects with hypertension morphologically overlap with the conventional HCM EDWT criterion. These results highlight that the diagnosis of HCM on the basis of wall thickness alone should be made with caution in the context of concomitant hypertension. However, the low prevalence of LGE in our cohort may be a useful discriminator, which is consistent with other studies of hypertensive heart disease(36), as LGE has been described in up to 72% of patients with HCM(37). LGE is a marker of focal replacement fibrosis. Future study may involve assessment of the extent and distribution of diffuse myocardial fibrosis, which can now be reliably measured with native and post-contrast CMR T1-mapping techniques.

In addition, the absence of SAM may also be a useful discriminator. Critoph et al. looked at aortoseptal angulation and SAM in 160 subjects with hypertrophic cardiomyopathy(23). The found that an aortoseptal angulation of $\leq 100^{o}$ had 91% specificity for predicting provocable left ventricular outflow tract obstruction. This

degree of angulation is even more acute than our cohort of hypertensive subjects with asymmetric wall thickening. However, studies directly comparing appropriately matched subjects with asymmetric HHD and HCM are required to confirm these findings.

Limitations

There are several important limitations of this study. The influence of duration of hypertension was unable to be directly ascertained due to the prolonged subclinical course of systemic hypertension. In addition, myocardial ischaemia was not formally excluded with anatomical or functional testing. As a result, this could confound the patterns of hypertensive heart disease observed. However, hypertension is a risk factor for coronary atheroma and hypertensive LVH itself is associated with myocardial ischaemia(38) so we feel that exclusion of such patients would not have been appropriate.

We have been unable to determine the prognostic implications of asymmetric hypertensive heart disease due to relatively low annual event rates and only short-term follow-up of the cohort to date. Asymmetric LVH has been demonstrated to be an important marker of adverse prognosis in aortic stenosis(39). Longitudinal outcome studies, or even retrospective re-analysis of previous CMR studies of hypertensive heart disease that did not account for asymmetry(3), are required to confirm or refute whether asymmetric hypertensive heart disease carries similar significant prognostic importance.

Conclusions

Asymmetric hypertensive heart disease, with morphological overlap with hypertrophic cardiomyopathy, is common and occurs exclusively in the basal-mid septum. Our results highlight that the diagnosis of HCM on the basis of wall thickness alone should be made with caution in the content of concomitant hypertension. More acute aortoseptal angulation and reduced aortic distensibility were observed in subjects with asymmetric hypertensive heart disease. However, increasing age and indexed LV mass were the only independent, significant predictors of an asymmetric response in hypertension. Consequently, our results suggest that significant asymmetry in young hypertensive subjects is less likely to be related to their arterial hypertension.

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Conflict of interest: None.

Figure legends

Figure 1. A) Normal, B) Concentric left ventricular hypertrophy and C) Asymmetric left ventricular hypertrophy forms of hypertensive heart disease.

Figure 2. Aortoseptal angle (A) from 3-chamber steady state free precession cine at end-systole.

Figure 3. Study flow chart. *Image artifact from implantable loop recorder device precluding volumetric assessment from LV short axis stack. CMR = cardiac magnetic resonance, MI = myocardial infarction (defined as subendocardial late gadolinium enhancement on CMR), HCM = hypertrophic cardiomyopathy, LVNC = left ventricular non-compaction cardiomyopathy, DCM = idiopathic dilated cardiomyopathy, Mod AR = moderate aortic regurgitation, AVR = aortic valve replacement.

Figure 4. 16-segment American Heart Association bull's eye plots demonstrating: A) location of maximal wall thickness and B) magnitude (mean±SD) of maximal wall thickness in ventricles with asymmetric wall thickness.

Figure 5. 16-segment American Heart Association bull's eye plot demonstrating distribution of replacement fibrosis.

Table 1. Demographics and clinical parameters

		No Asymmetric wall thickening			
	All patients (n=129)	**No LVH** (n=79)	**LVH** (n=23)	**Asymmetric wall thickening** (n=27)	**p-Value**
Demographics					
Age (years)	51±15	49±16	48±14	57±13	<0.05[†‡]
Male gender n(%)	65(50)	34(43)	11(48)	20(74)	<0.05[†‡]
Caucasian n(%)	108(84)	64(81)	22(96)	22(81)	=0.24
BMI (kg/m^2)	31±6	30±5	32±6	33±5	<0.05[†]
Heart rate (BPM)	72±14	74±14	68±14	68±13	<0.05[†]
Diabetes mellitus n(%)	15(12)	7(9)	2(9)	6(22)	=0.16
Ischaemic heart disease n(%)	17(13)	7 (9)	4 (17)	6 (22)	=0.17
ACEi/ARB n(%)	96(74)	55(70)	20(87)	21(78)	=0.23
ECG evidence of LVH n(%)	11(9)	2(3)	7(30)	2(7)	<0.05[‡§]
ECG-strain pattern n(%)	8(6)	2(3)	1(4)	5(19)	<0.05[†‡]
Office blood pressure					
SBP (mmHg)	170±30	166±28	176±33	178±31	=0.16
DBP (mmHg)	97±15	97±14	97±22	98±15	=0.90
Grade 1 n(%)	23(18)	20(25)	0(0)	3(11)	<0.05[§]
Grade 2 n(%)	27(21)	16(20)	4(17)	7(26)	=0.74
Grade 3 n(%)	52(40)	26(33)	13(57)	13(48)	=0.08
Ambulatory blood pressure*					
Overall SBP (mmHg)	152±21	149±17	156±27	163±24	=0.05[†]
Overall DBP (mmHg)	90±14	89±13	92±17	90±15	=0.75
Overall MAP (mmHg)	106±16	105±14	109±21	109±17	=0.57
Non-dipper n(%)	67(52)	36(46)	13(56)	19(69)	=0.28

(ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker).

* Ambulatory blood pressure data in n=85 (No asymmetric wall thickening and no LVH=52, No asymmetric wall thickening and LVH=17, Asymmetric wall thickening=16)

† Asymmetric wall thickening vs No asymmetric wall thickening and no LVH, P<0.05

‡ Asymmetric wall thickening vs No asymmetric wall thickening and LVH, P<0.05

§ No asymmetric wall thickening and LVH vs No asymmetric wall thickening and no LVH, P<0.05

Table 2. CMR parameters

		No Asymmetric wall thickening			
	All patients (n=129)	**No LVH** (n=79)	**LVH** (n=23)	**Asymmetric wall thickening** (n=27)	**p-Value**
CMR volumetrics and wall thickness					
Maximal EDWT (mm)	13±3	12±2	13±1	18±2	<0.0001†‡§
iLVM (g/m^2)	84±22	72±10	96±10	109±27	<0.0001†‡§
LVEF (%)	68±9	69±7	64±11	70±12	<0.05‡§
iEDV (ml/m^2)	77±17	72±12	91±15	79±24	<0.0001‡§
iESV (ml/m^2)	25±12	23±7	33±13	25±18	<0.001‡§
iSV (ml/m2)	52±8	50±7	55±8	52±9	<0.05§
M/V (g/ml)	1.12±0.28	1.02±0.21	1.08±0.18	1.44±0.28	<0.0001†‡
Cardiac output (l/min)	7.49±1.87	7.34±1.75	7.63±1.89	7.80±2.21	=0.67
Cardiac index (l/min/m^2)	3.67±0.77	3.71±0.77	3.69±0.70	3.56±0.85	=0.51
Myocardial strain					
Global longitudinal strain (%)	-16.6±4.0	-17.6±3.5	-15.8±4.6	-14.6±3.9	<0.05†§
Replacement fibrosis					
LGE present n(%)	27(21)	7(9)	6(26)	14(52)	<0.005†‡
Midwall LGE n(%)	5(4)	1(1)	0(0)	4(15)	<0.005†‡
RV insertion point LGE n(%)	23(18)	7(9)	5(22)	11(41)	<0.05†
Aortic function					
Aortic distensibility (mm^2/mmHg x10^3)	1.63±1.44	1.83±1.65	1.57±1.05	1.01±0.60	=0.07†
Aortoseptal angle (degrees)	122±11	123±12	125±9	114±10	<0.005†‡

† Asymmetric wall thickening vs No asymmetric wall thickening and no LVH, P<0.05

‡ Asymmetric wall thickening vs No asymmetric wall thickening and LVH, P<0.05

§ No asymmetric wall thickening and LVH vs No asymmetric wall thickening and no LVH, P<0.05

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