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Title page

Full title: Characterisation of Hypertensive Heart Disease: Pathological insights from a sudden cardiac death cohort to inform clinical practice

Running head: Hypertensive Heart Disease: A pathological study

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Abstract and Key Words

Hypertensive heart disease refers to changes in the myocardium that result from hypertension. The relationship between hypertensive heart disease and sudden cardiac death is well established but there are few pathological studies. We examined the clinical and pathological features of hypertensive heart disease in sudden cardiac death victims from a national cardiovascular pathology registry.

We investigated 5239 cases of sudden cardiac death between 1994 and 2018. Hearts were examined by two expert cardiac pathologists. Diagnostic criteria included history of hypertension, increased heart weight and left ventricular wall thickness in the absence of other causes. Collagen was quantified using Picrosirius red staining and imaging software.

Of 75 sudden cardiac death cases due to hypertensive heart disease (age at death: 54±16years; 56% male), 56 (75%) reported no prior cardiac symptoms. Thirty-four (45%) recorded a BMI≥30. Only two (2.7%) had hypertensive heart disease diagnosed antemortem. Four (5%) were diagnosed clinically with hypertrophic cardiomyopathy, but lacked myocyte disarray at autopsy. All hearts showed concentric left ventricular hypertrophy and myocyte hypertrophy. Fibrosis was identified microscopically in 59 cases (81%). The posterior left ventricular wall showed the greatest increase in percentage of collagen in hypertensive diseased hearts compared to controls (25.2% vs 17.9%, p=0.034).

Most sudden deaths due to hypertensive heart disease occur without prior cardiac symptoms thus clinical risk stratification is challenging. Hypertensive heart disease can be misdiagnosed in life as hypertrophic cardiomyopathy which has major implications for relatives. Pathologists require a history of hypertension and histology for a definitive diagnosis of hypertensive heart disease.

Keywords:

Hypertensive Heart Disease

Sudden Cardiac Death

Hypertension

Hypertrophic cardiomyopathy

Text

Introduction

Hypertension is one of the leading risk factors for cardiovascular disease and represents a significant cause of morbidity and mortality. In 2010, hypertension was thought to affect 1.39 billion persons worldwide with an estimated prevalence of 31.1% [1]. In 2017, the AHA/ACC defined hypertension as a systolic blood pressure (BP) greater or equal to 130mmHg, or a diastolic BP of 80mmHg or greater [2]. It is well established that hypertension may result in end-organ damage within the circulatory system, including hypertensive heart disease (HHD).

HHD is characterised by left ventricular hypertrophy (LVH) in the absence of other causes. LVH may be subcategorised as concentric or eccentric. Concentric hypertrophy is defined as an increase in left ventricular (LV) wall thickness without a corresponding increase in LV chamber radius whilst eccentric hypertrophy is defined as an increase in LV wall thickness and radius [3]. Hypertension leads to breakdown of the existing extracellular matrix resulting in the accumulation of collagen type 1 and type 3 with fibrosis [4,5]. Adverse cardiac remodelling predisposes to atrial fibrillation (AF), ventricular arrhythmias, and heart failure. Both hypertension and LVH have been strongly and independently associated with sudden cardiac death (SCD) [6,7].

Between 2013-2019, 29,526 deaths in UK were attributed to HHD [8]. Despite this, there are few autopsy studies on HHD, published in the 1970s and 1980s [9,10]. Many pathologists label enlarged hearts as HHD when there is no coronary artery disease or valvular disease, even in the absence of a clinical history of hypertension. This can be erroneous as cardiomyopathies, especially hypertrophic cardiomyopathy (HCM), may mimic HHD macroscopically. Furthermore, idiopathic left ventricular hypertrophy is a separate entity. It is therefore essential to examine the heart and take histology when a heart is enlarged at autopsy. We present the first detailed pathological study on SCD in HHD in the absence of coronary artery disease or valvular disease.

Methods

The study was performed at the Cardiac Risk in the Young Cardiovascular Pathology Laboratory based at St George’s University of London. The centre receives cases of SCD from around the United Kingdom. Cases were identified from a cohort of 5239 referrals between 1994 and 2018 (see figure 1). SCD was defined as death that occurs within one hour of onset of symptoms in witnessed cases and within 24 hours of last being seen alive when unwitnessed [11]. Primary care correspondence, clinical notes, coroner’s history sheets, post mortem reports and family questionnaires were reviewed to obtain circumstances of death, past medical history and other pathological findings.

Cases were included based on a cause of death being attributed to HHD with an established diagnosis of hypertension pre-mortem. Hypertension was diagnosed by general practitioners and documented on medical records. Cases with a clinical history of cardiac failure (LV ejection fraction < 40%), positive toxicology or in which other causes of death were found such as pulmonary embolism or stroke were excluded.

During examination of the weighed heart, the coronary arteries are sliced at 2-3mm interval to look for evidence of significant coronary artery disease. The heart itself is sliced transversely from the apex to mid ventricle at 5mm intervals. Both ventricles are measured at mid-ventricular level (figure 2). The presence or absence of fibrosis, infarction, or fat in the myocardium is commented on. All four valves are examined and measured. Blocks are taken for histology routinely from the anterior, lateral and posterior right ventricle, the right ventricular outflow tract, the anterior, lateral and posterior LV as well as the interventricular septum (IVS). Sections of coronary artery, atria and conduction tissue are also sampled routinely. Normally, 10 sections are examined though more blocks will be taken if specific pathology is found. Following processing of the blocks, the slides are stained with both hematoxylin and eosin and a trichrome which highlights fibrosis (figure 2).

Pathological diagnostic criteria for HHD include increased heart weight above 500 grams in males and above 400 grams in females and a LV thickness of greater than 15mm (figure 2). Microscopic criteria included myocyte hypertrophy with/without fine interstitial fibrosis in the LV wall particularly in the subendocardium (figure 2). Cases with significant coronary artery disease (a lumen of less than 2mm2), ischaemic changes or valvular disease were excluded. HCM was diagnosed on the basis of the presence of 20% myocyte disarray in two LV and/or IVS tissue blocks. Myocyte disarray at the septal-free wall junctions and in the subendocardium around trabeculae is disregarded as this is a normal finding. In cases where there is a suspicion of HCM not meeting this diagnostic criterion, further blocks are taken. Hearts were examined macroscopically and microscopically by two expert cardiac pathologists (JDW and MNS).

Quantification of collagen

Quantification of collagenous tissue across regions of the heart was performed using image analysis software. HHD SCD cases where cardiac tissue was retained with consent for research (n=10) were age and sex matched to ten controls with morphologically normal hearts with a cause of death given as sudden adult death syndrome [12]. Cases were included based upon statements in the coroner’s report, the general practitioner notes and/or the family questionnaire confirming the absence of hypertension or any medical conditions as well as the absence of possible anti-hypertensive medication. Sections were stained with Picrosirius red, a marker of collagen, using a standard protocol. Slides were scanned at X20 magnification using a high-resolution Hamamatsu Nanozoomer 2.0RS slide scanner. Visiopharm (Visiopharm, Copenhagen, Denmark) software was utilized to select the region of interest and quantify the percentage of collagen with respect to total tissue area. Stereological techniques involving colour thresholds and shape analysis were employed, as previously reported [13].

Statistics

This is an exploratory study. All the variables have been explored and summarized according to their statistical type; categorical and binary data as frequencies and percentages and continuous data as means, standard deviations, medians, first and third quartiles and ranges.

Two-sided T-test was used to compare normally distributed continuous variables across two in/dependent groups. Chi-square test was used to assess independency between two categorical variables with Fisher’s exact test when cross tabulations exhibited numbers smaller than 5. Kruskal-Wallis test has been uses to assess non-normally distributed or ordinal variables across independent groups. Linear regression was used to explore potential associations between a continuous outcome and potential explanatory variables of interest. The statistical software package SPSS package 25 was utilised to perform these tests.

The study was approved by the London-Stanmore Research Ethics Committee (10/H0724/38).

Results

Demographics, associated conditions, circumstances of death, symptoms and the use of anti-hypertensive medication are described in table 1. Of 5239 cases of SCD, 75 (1.4%) due to HHD were identified. The mean age of death was 54±16years (54, 44-68, 18-85); 42 males (56%) and 33 females (44%) (ratio 1.3:1) (figure 3 and table 2). There was no significant difference in the age of death between males and females succumbing to SCD due to HHD (p=0.37). The average BMI was 31±9 (30, 25-35, 16-65) with 45% of cases being obese (defined as a body mass index of greater than 30kg/m2).

Only 2 (2.7%) cases had a premortem diagnosis of hypertensive heart disease. Of the 6 (8.0%) cases labelled as cardiomyopathy, 4 (5.3%) had been labelled as HCM, despite the history of hypertension based upon echocardiography.

Mean weight of the heart was 601±140grams (597, 484-660, 401-975) (males 664±127grams, 644, 568-694, 510-975, females 509±105grams, 465, 438-573, 401-770). Mean maximal LV thickness was 17.5±3.5mm (17.0, 15.0-19.7, 10.0-30.0). All hearts showed concentric hypertrophy with hypertrophy of myocytes microscopically. LV fibrosis was identified on microscopic examination in 59 cases (81%) and was distributed throughout the intraventricular septum and left ventricular free wall (figure 2 and table 3). There was no evidence for associations between the presence of fibrosis and sex (p=0.31), BMI (p=0.17) or heart weight (p=0.48). There was no significant association between location of fibrosis and age or sex. Linear regression analysis of weight and heart weight showed a significant positive association (p=0.001) (figure 3).

Collagen quantification

There was no evidence to suggest differences between the clinical or pathological characteristics in 10 cases selected for collagen analysis and the other 65 cases. The posterior LV wall had the greatest increase in the percentage of collagen in HHD hearts compared to controls (25.2±9.1%, 21.7, 18.8-34.2, 15.0-40.1 vs 17.8±7.0%, 14.5, 12.6-23.0, 12.2-33.0 p=0.034). Based upon these results, the anterior LV wall (21.7±9.1%, 19.9, 16.5-25.0, 10.1-43.2 vs 17.9±6.1, 15.9, 13.3-19.9, 11.5-29.0) and intraventricular septum (20.2±8.4, 19.0, 15.5-22.4, 9.15-40.3 vs 15.1±6.9, 14.3, 8.9-19.0, 6.3-27.6) exhibited increases in the percentage of collagen in magnitude however these were not supported statistically (p>0.05). Our data were consistent with no significant difference between the right ventricle of HHD and control hearts (23.2±6.8, 21.7, 20.0-24.8, 14.3-39.5 vs 25.7±7.6, 25.3, 20.8-32.4, 12.3-37.6) (table 4 and figure 4). Based on these data, in HHD hearts, there was no evidence of differences between percentage of collagen in the different regions of the LV (p=0.50). There was no significant association between percentage of collagen and age (p=0.84), sex (p=0.73), or region of myocardium (p=0.22).

Discussion

There are no recent detailed autopsy studies on this subject despite nearly 30,000 deaths being attributed to HHD in the United Kingdom between 2013-2019 [8] and SCD occurring at a rate of 370 per 100,000 patient years in individuals with HHD in an Italian study [14].

Historical pathological studies have defined HHD as LVH in the absence of significant coronary artery disease or extra cardiac pathology [9,10]. They presumed that cardiomegaly developed solely from hypertension. However, the aetiology of LVH has now been shown to be more diverse. A number of different entities fulfil these criteria and occur in the absence of hypertension including HCM, metabolic disease including Fabry’s disease and more recently idiopathic LVH with/without fibrosis [15,16]. Here, we report the first cohort of SCD in clinically confirmed hypertension in the absence of coronary artery disease and valvular disease thus precisely defining HHD.

Our study showed that a number of those with HHD also had chronic kidney disease (12%). Hypertension and chronic kidney disease have a closely associated cause and effect relationship with BP rising with advancing kidney failure and hypertension hastening the progression of kidney disease [17].

In our series, “cardiomyopathy” was diagnosed in 6 cases, this was mainly due to LVH being detected and an incorrect clinical diagnosis of HCM being made. This highlights the potential pitfall of labelling a hypertensive individual with HCM, a genetic condition, which may lead to unnecessary familial cardiological screening. Furthermore, HCM may be aggravated by hypertension highlighting the importance of a detailed family history and clinical evaluation for diagnosis.

Three of the cohort were pregnant. Hypertensive disorders are the most common cause of maternal death. They are strongly associated with substandard care and can be prevented by improvements in treatment [18].

In contrast to SCD in the general population which occurs with an incidence rate ratio 2:1 in males (3.6 vs 1.8 per 100.000 person-years), SCD in HHD do not appear to be different between sexes [19]. This may be considered somewhat surprising given, in males, there is a higher prevalence (31% vs 26% in England in 2015 [Public Health England, 2017]), a lower awareness and an earlier incidence of hypertension [20]. Additionally, males have a significantly increased BP when compared to females. Numerous other studies have shown that females appear to be protected from hypertension pre-menopause. Possible mechanisms for this discrepancy between the sexes include the elevation of the BP by testosterone, decrease of BP by oestrogen, presence of two X chromosomes and age [21,22]. In our study, the age of death for males and females was similar although figure 3 shows a slight trend towards later occurrence in females.

Only 27 (36%) of our cohort had recorded symptoms prior to death. This is higher proportion than a previous UK study of autopsy negative sudden death (sudden arrhythmic death syndrome) which showed prior symptoms in 14% of individuals [12].

Almost half the cohort were obese, indicating that hypertension and obesity act synergistically to increase the risk of SCD. This may be explained through their direct causation of LVH [23]. Diabetes was present in 13% in keeping with the fact that it is an independent risk factor for SCD [24]. Diabetes has been shown to cause interstitial fibrosis independent of BP and coronary atherosclerosis [25].

Fibrosis was present in 80% of cases and was most frequently distributed throughout the LV affecting the posterior wall to the greatest degree. It appears to occur independently of sex, BMI and heart weight. Myocardial strain imaging with T1 mapping and quantification of fibrosis is becoming important in the management of hypertension and shows variable results for similar levels of hypertension [26]. The characterisation of collagen has been found to be important in prognosis. Ravassa et al showed that by measuring biomarkers for excess collagen type 1 cross linking and increased collagen type 1 deposition they could risk stratify patients [27]. Fibrosis was most markedly increased within the posterior wall and this is also commonly seen within those with severe aortic stenosis and in athletes suggesting that this area is most susceptible due to both systolic wall stress and reduced perfusion [28,29].

In the remaining 20% of cases no fibrosis was identified suggesting that the arrhythmogenic substrate may be hypertrophy in isolation. LVH is thought to increase the risk of arrhythmia through several mechanisms. It causes prolongation of repolarisation of the ventricular myocardium with a corresponding increase in QRS duration and QT interval. It may also cause QRS fractionation through non-uniform electrophysiological changes of the LV. At a molecular level, LVH causes a reduction in the density of sodium-potassium adenosine triphosphatase pumps which results in decreased intracellular potassium [30,31,32].

It has been postulated that aggressive anti-hypertensive control may lead to regression of LVH and thus lowers the risk of AF and SCD [30]. Whilst we only have pharmacological detail for 35% of cases, 25% were taking anti-hypertensive medication. Thus despite taking anti-hypertensives, individuals remain at risk of SCD. A large meta-analysis concluded that whilst anti-hypertensives reduce the incidence of myocardial infarction they do not reduce the incidence of sudden death [33].

In our cohort, SCD appears to occur in those with concentric hypertrophy rather than eccentric hypertrophy. This may be explained by the exclusion of those with a history of failure and our diagnostic criterion of a LV wall thickness of greater than 15mm. This highlights that hypertensive patients should be screened using an ECG to look for LVH which confers a greater risk of SCD and should continue to be monitored.

A major limitation of this study is the lack of medication history provided to pathologists at post mortem. We also acknowledge that as a tertiary centre for cardiac pathology, there is a referral bias. Selected cases are referred and the proportion of our cohort who experienced SCD in HHD will be an underestimation in the general population.

Blood pressure data was not available as this is a post mortem study, therefore a remote chance that the controls may be hypertensive however, this has been minimised through selection of a cases specifically stating absence of the condition/conditions on all documentation and exclusion of cases on anti-hypertensive related medication. These findings are derived from a pure sudden cardiac death cohort and therefore may not extrapolate to the wider HHD population. Further clinical confirmatory studies could address this.

Conclusions

This is a detailed pathological study of HHD with SCD. Despite therapy, a percentage of those with treated hypertension remain at risk of SCD.

The presence of LVH in all our cohort indicates that hypertensive patients should be screened for LVH using ECG. If present, further investigation with ECHO and MRI, to look for fibrosis, particularly within the posterior wall, may be warranted to enable better risk stratification and more aggressive treatment.

HHD should be excluded in those with LVH and hypertension prior to consideration of HCM. It is therefore essential to take histology in cases with a history of HCM at post mortem especially in concomitant hypertension.

Pathologists require a history of hypertension and histology for a definitive diagnosis of hypertensive heart disease.

Summary table

What is known about topic

• Hypertensive heart disease is characterised by left ventricular hypertrophy in the absence of other causes.

• The relationship between hypertensive heart disease and sudden cardiac death is well established but there are few pathological studies.

What this study adds

• Despite therapy, a percentage of those with treated hypertension remain at risk of sudden cardiac death.

• The presence of left ventricular hypertrophy in all our cohort indicates that hypertensive patients should be screened for hypertrophy using ECG.

• Hypertensive heart disease should be excluded in those with left ventricular hypertrophy and hypertension prior to consideration of hypertrophic cardiomyopathy.

Disclosure

We have no conflicts of interest to declare.

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Legends

Figure 1, A flowchart illustrating the selection of cases for inclusion into the study and for inclusion into collagen quantification. (SCD = Sudden Cardiac Death, HHD = Hypertensive Heart Disease)

Figure 2, The macroscopic and microscopic appearance of hypertensive heart disease. The top left panel shows a mid-ventricular slice through the normal heart whilst the right panel shows concentric left ventricular hypertrophy in keeping with hypertensive heart disease. Middle left, normal microscopic appearance (H&E, x40); middle right, myocyte hypertrophy and interstitial fibrosis (H&E, x40); bottom left, interstitial fibrosis (H&E, x20); bottom right, interstitial fibrosis (trichrome, x20).

Figure 3, Population pyramid and scatterplot of weight and heart weight. The left panel shows a population pyramid showing frequency of age at SCD by gender. The plot highlights a possible trend towards females dying suddenly from hypertensive heart disease at a greater age when compared to males. The right panel shows a Scatterplot and Linear Regression Analysis of Weight and Heart Weight. Linear regression analysis of weight and heart weight showed a significant but very weak effect size (R2 = 0.199, p=0.001).

Figure 4, Collagen percentage in the right ventricle (RV) and left ventricle (LV) for 10 hypertensive heart disease cases vs age and sex matched non-cardiac death controls as assessed by picrosirius red staining and semi-autonomous quantification using Visiopharm software. There is a significant increase in collagen percentage in the posterior left ventricular wall of hypertensive heart disease cases.

Table 1, Characteristics of the SCD in HHD cohort. Characteristics including demographics, premortem diagnosed medical conditions, circumstances of death, preceding symptoms and medication history.

Table 2, Comparison between male and female individuals with hypertensive heart disease. The table gives the number, age, BMI, heart weight and presence or absence of fibrosis on light microscopy. The lower half compares the collagen percentage for the different regions of the heart between males and females. (RVOT = right ventricular outflow tract, RV = right ventricle (free wall), LV = left ventricle).

Table 3, Pathological assessed heart parameters. The heart parameters for cohort including heart weight in grams, maximal left ventricular wall thickness in millimetres and the presence of left ventricular fibrosis identified on light microscopy of heart sections.

Table 4, The distribution of collagen. Percentage of collagen present in the intraventricular septum, anterior left ventricular wall and posterior left ventricular wall in HHD hearts vs controls.