Non-Invasive Identification of Left Ventricular Hypertrophy (LVH)/ Cardiomegaly in US Firefighters

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ABSTRACT

Background: Cardiovascular disease (CVD) causes 45% of firefighters' on-duty deaths, but the risk of these events is limited to susceptible individuals. Left ventricular hypertrophy (LVH)/cardiomegaly increases arrhythmia, myocardial infarction, stroke and death risks, and is a condition which renders firefighters susceptible to CVD events. Autopsies demonstrate LVH/cardiomegaly in most firefighter CVD fatalities. If recognized beforehand, however, effective treatments are available. In this work we i) describe the state of the art knowledge on the definition of cardiac enlargement across imaging modalities, normalization techniques (indices) and reference ranges; ii) estimate the current prevalence of cardiac enlargement among the US firefighters; and iii) identify the significant predictors of LV mass (LVM).

Methods: We conducted a literature review to compare measurements for heart size and mass by cardiac MRI (CMR), Echocardiograms (ECHO) and autopsies in healthy and diseased hearts in the general population (Chapter 1). We selected 400 participants by an enriched randomization sampling strategy from a population of active firefighters. All participants received a screening ECHO, followed by CMR. Prevalence estimates for LVH were derived among the active firefighters based on ECHO and CMR. Separate estimates were made by examining autopsies of other firefighters who suffered a noncardiac on-duty fatality (Chapter 2). Risk factors were evaluated as predictors for LVM normalized for height (Chapter 3).

Results: The findings from Chapter 1 demonstrated a wide variance in LVH definitions and reference ranges; ECHO remains the most widely used diagnostic tool; and few direct comparisons exist between imaging and autopsies studies at this time. Chapter 2 showed a wide range of prevalence estimates of cardiac enlargement and body mass index (BMI) to be a major driver of heart weight. Chapter 3 identified BMI as the most significant and only consistent independent predictor of LVM indices.

Conclusions: Standardization of cardiac enlargement definitions is needed. However, BMI drives LVM, heart weight and LV wall thickness. Therefore, reducing obesity will decrease the prevalence of LVH/cardiac enlargement in the fire service, which should in turn reduce CVD events.

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Introduction

Cardiovascular disease (CVD) is the leading cause of on-duty death among US firefighters and an important and costly cause of morbidity. CVD causes 45% of firefighters' on-duty deaths. As in the general population, these cardiovascular events are largely due to coronary heart disease (CHD). [1-4] There is also an increasing recognition in the role of Left Ventricular Hypertrophy (LVH)/cardiomegaly in the risk of Sudden Cardiac Death (SCD) independent of the presence of CHD, although it has long been recognized that individuals dying of CHD tend to have heavier hearts than those dying of non-cardiac causes.[5-7] For every fatal on-duty CVD event, there are an estimated 25 nonfatal, line-of-duty CVD events in the US fire service. [8,9] The extent of this problem in the U.S. fire service has not changed significantly in the last two decades, despite major advances in cardiovascular medicine.[1 4,10,11] In addition, firefighting combines situations that are both physically demanding (intense work, heavy tools & personal protective gear) and psychologically stressful (alarm response, danger) that together with environmental hazards (heat stress, noise, dehydration, particulate and gaseous exposures in smoke) can easily trigger a CVD event in a susceptible individual. [1,12]

LVH/cardiomegaly is considered a structural abnormality of the heart[13,14] and appears to be a key pen-ultimate and predisposing step on the causal pathway that makes a firefighter susceptible to CVD events[1,15,16]. LVH/cardiomegaly has been widely recognized to increase the risk of lethal ventricular arrhythmias, myocardial infarction and stroke; and it is a proven predictor of CVD and overall mortality in the general population but have not been adequately researched in the fire service.[17-21] Current evidence from autopsy-based case series of SCD indicates that LVH is common among US firefighters, often co-morbid with CHD and plays a major role in CVD

events and SCD risk in the fire service. In fact, the majority of CVD death victims suffered from LVH/cardiomegaly, which was usually unrecognized before death. [22,23]

Beyond its role in CVD and the fact that it is likely common, in order to justify screening for LVH/cardiomegaly, we also need to recognize that it can be treated and reversed at an early stage. The detection of LVH by imaging should rarely, if ever, be a career-ending event for a firefighter. In fact, there are several proven effective treatments for LVH based on its underlying risk factors. In the presence of hypertension, anti-hypertensive drugs and particularly, angiotensin converting enzyme (ACE) inhibitors can produce echocardiographically-confirmed regression of LVH.[21] Furthermore, in patients with Obstructive Sleep Apnea (OSA), continuous positive airway pressure (CPAP) can produce reductions in LVH.[24] Finally, weight loss through both diet and exercise in overweight and obese subjects is beneficial because it can improve OSA, blood pressure control and can reverse obesity-related effects on LV mass (LVM).[25]

Despite the critical prognostic significance of LVH/cardiomegaly for CVD and SCD events, its definition demonstrates wide variability among measurement techniques, imaging modalities, normalization processes, technicians and institutions. [26,27] Evidence suggests an increasing prognostic value, when LVH is based on the accurate assessment of LVM, with LVM being an independent predictor for cardiovascular risk. [26,28] However, the role of LVM in clinical practice and desicion-making has not been firmly established due to a number of controversies that surround its assessment[28,29]. LVM values present a wide distribution among healthy individuals, with distinct differences observed by sex and ethnicity,creating the need to account for body size in order to be able to make reasonable inferences. Indexing LVM, using different methods with

different body size parameters, such as height, weight, body mass index or body surface area, has been the most common normalization process to date. However, there is no agreed upon consensus regarding cut-off values on LVM indices, creating further challenges in the definition of LVH.[27,29-31]

Echocardiography (ECHO) and cardiac magnetic resonance (CMR), the two most frequently used imaging modalities for LVM assessment, use different algorithms and measurement techniques, providing different average values along with different degrees of accuracy. [26,27] In addition, LVM can also be physiologically increased by healthy behaviors such as endurance physical training, an observation that should be accounted for while establsihing LVM reference values.[28,32,33]

There is no consensus on the measurement of LVM, the calculation of LVM indexing, the classification of LVH/cardiomegaly based on firm cut-off values. To date most studies in firefighters have relied on autopsy data. Forensic studies, however, rarely assess LVM, and instead, they measure routinely total cardiac mass as an indicator of potential cardiomegaly, creating challenges on direct comparisons between the mass of the left ventricle and the total cardiac mass, in order to establish a firm relationship between the two.

By combining the use of CMR with ECHO along with other comprehensive clinical data, we can most accurately estimate the prevalence of LVH/cardiomegaly in career firefighters. Moreover, by identifying the significant predictors of LVM there will be a tremendous effect in clinical practice and therapeutic decision-making, allowing for identification of LVH/cardiomegaly in a

timely fashion, thus enabling clinical interventions to decrease firefighters' morbidity and mortality.

Dissertation Goal

The specific aims of this dissertation are: 1) to conduct a systematic literature review so as to describe heart size and mass ranges in normal and diseased hearts in the general population, with specific goals: i) to compare measurements for heart size and mass by CMR, ECHO, and autopsies in healthy and diseased hearts; and ii) to assess the relationship between LVM and total heart weight (see Chapter 1); 2) to estimate the prevalence of cardiac enlargement (including LVH) in active career US Firefighters and present how the prevalence estimates vary according to the method of assessment; by autopsies, ECHO and CMR (see Chapter 2); and 3) to identify the most important predictors of LVM in male firefighters in the United States that could further contribute to more accurate medical screening and wellness programs for firefighters (see Chapter 3) .

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CHAPTER 1: A Review of Heart Size and Mass Ranges by cardiac MRI, ECHO, and Autopsies in Normal and Diseased Hearts

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Abstract

Left ventricular hypertrophy (LVH) is widely recognized as an independent and significant predictor of cardiovascular disease (CVD) and sudden cardiac death (SCD) risk. It is also assumed that the predictive value of LVH is increased by its accurate assessment based on LV mass (LVM). However, LVH definition along with LVM reference values, demonstrate wide variability among imaging modalities, technicians, indexing methods and institutions. In addition, currently autopsy studies measure total heart weight rather than LVM, which makes them difficult to correlate with imaging data. Therefore, we conducted a systematic literature review for existing data on methods used and reference values for both normal and diseased hearts. Echocardiography remains the most widely used diagnostic tool for the evaluation of LVH, with the optimal body-size indexing formula remaining controversial and in urgent need of more standardization. Future forensic studies are needed to directly compare total cardiac mass to left ventricular mass and in order to update reference values considering significant changes in the population's height and weight.

Keywords: heart weight, left ventricle, hypertrophy, autopsies, echocardiography, cardiac magnetic resonance

Background

Cardiomegaly is a general term used to describe increased heart size whereas left ventricular hypertrophy (LVH) describes both increased wall thickness and mass, due to a thickening of the heart muscle surrounding the left ventricle. Both cardiomegaly and LVH are considered structural abnormalities of the heart. [1,2] Cardiomegaly and LVH are strongly associated with cardiovascular morbidity and mortality,[1,3-5] all cause mortality,[6,7] and, in particular, sudden cardiac death (SCD).[8]Cardiomegaly/LVH are known to increase the risk of lethal ventricular arrhythmias, myocardial infarction, and stroke.[3,9-12] For example, the risk of SCD is approximately six times greater for men with electrocardiographically detected LVH than men without LVH.[13] Although it has long been recognized that individuals dying of Coronary Heart Disease (CHD) tend to have heavier hearts than those dying of non-cardiac causes, [14] the prevalence and relevance of cardiomegaly/LVH have received far less attention than has the presence of coronary atherosclerosis and stenosis. Significantly, a recent study that retrospectively studied the cardiac findings of adults who died of SCD and attributed the deaths to cardiomegaly/LVH, CHD, or both found that cardiomegaly/LVH is a frequent cause of SCD in the general public and is highly associated with obesity and death at a younger age than CHD.[15] Hypertensive individuals with LVH present a 2-to 5-fold increase in fatal and non-fatal cardiovascular events when compared to those with hypertension alone;[16] hence, LVH is currently recognized as target-organ damage that influences prognosis in hypertensive populations.[17-19]

There is a consensus that the presence of LVH is best determined by estimating the Left Ventricular mass (LVM). The accurate evaluation of LVM is fundamental, not only for the determination of the degree of hypertrophy but also for the assessment of its regression.[20-22] Over the last two decades, along with the recognition of the critical prognostic value of LVM in

cardiovascular risk algorithms, [10,23] substantial progress has been made in educating both clinicians and epidemiologists on the role of LVM.[24] However, despite this increasing recognition of the importance of LVM, the best way to incorporate it's measurement into clinical practice has not been firmly established due to a number of controversies that surround its quantitative assessment.[23,25,26]

LVM values present a wide distribution among healthy individuals, with distinct differences observed by sex and ethnicity, as well as the frequency of athletic training. Hence, anthropometric parameters should be taken into account to make meaningful comparisons among individuals. Indexing LVM, using different methods with regards to height, weight, body mass index or body surface area, has been the most common normalization process to date. The LVM indexing method has a critical role in the definition of LVH and its performance as a cardiovascular risk predictor.[17,18,23,25,27-29] And yet, there is currently no agreed upon convention for normalizing LVM. This lack of consensus on normalization complicates efforts to identify the most appropriate cut-off values for defining LVH or initiating treatment.

Not only is there inconsistency in the normalization of LVH values, there are also different modalities for assessing LVM. The two most frequently used imaging modalities for the assessment of LVM, and thus non-invasive identification of LVH, have been echocardiography (ECHO) and cardiac magnetic resonance (CMR).[30] ECHO and CMR rely on different technologies and use different algorithms for the assessment of LVM, providing different average values along with different degrees of accuracy.[23,31,32] The differences between these methods can make the distinctions between disease states and normality harder to make.[33]

Heart weight is routinely assessed during autopsies. Such information holds promise to better

describe the normal distribution of heart size and mass as well as to improve the understanding of cardiac pathology. The accurate assessment of the heart weight at autopsies and the ability to conduct comparisons with updated reference values are key considerations in determining the presence of structural heart disease among deceased individuals.[34] However, directly comparing heart weight at autopsy with clinical data during life is hampered by different assessment techniques and a lack of comparative data. So far, limited information exists, thus not allowing direct comparisons between heart mass in autopsies and clinical imaging. Imaging modalities focus on the determination of cardiomegaly/LVH via LVM assessment, while autopsies focus on total cardiac mass and left ventricular wall thickness for establishing cardiomegaly/LVH. In addition, little is known regarding the relationship of LVM to the total cardiac mass, a feature that could facilitate extrapolations or comparisons between imaging modalities and autopsies.

The main aim of this review is to describe heart size and mass ranges in normal and diseased hearts in the general population. The specific goals are: 1) to compare measurements for heart size and mass by CMR, ECHO, and autopsies in healthy and diseased hearts; and 2) to assess the relationship between LVM and total cardiac mass.

LVM in healthy & diseased hearts

LVM has been shown to be a strong predictor of cardiovascular events among individuals without[3,35,36] and with prior coronary heart disease[37,38] and those with heart failure[1,39]. An increase in LVM is associated with a higher incidence of cardiovascular events, including death, while a decrease is a marker of lower risk for cardiovascular events, especially among patients on anti-hypertensive treatment.[20,22] Therefore, the correct assessment of LVM using non-controversial reference ranges is vital to accurately determine prognosis. [23]

The evaluation of LVM can be performed by a number of imaging modalities, with the ECHO and the CMR being the most studied so far.[40] For both techniques, scientific societies have developed guidelines regarding technical procedures, validation, and clinical indications.[31,32,41] However, these guidelines are not standardized, allowing for a great variation in the measurement of LVM and thus the classification of LVH, which can differ from study to study, from institution to institution, and from laboratory to laboratory. The primary method of LVM determination is based on calculating the shell volume which is obtained as the difference of epicardial and endocardial volumes. The shell volume is subsequently converted to mass by multiplying it by the specific density of myocardial tissue, which is usually assumed to be 1.05g/ml.[31,42]

Electrocardiography (EKG), though widely used, lacks sufficient sensitivity as an LVH screening tool and does not provide anatomic measurements of size or weight.[12] Moreover, because EKG LVH criteria rely on voltage,[43,44] the EKG is even less sensitive in obese individuals due to the attenuation of voltage signals by increased distance and tissues between the heart and the EKG leads.[45]

Assessment of LVM by imaging modalities

Assessment of LVM by ECHO

Motion-mode (M-mode), 2-dimensional (2D) echocardiography and 3-dimensional (3D) echocardiography are the cornerstones of LVM echocardiographic assessment in modern cardiology practice and research.[42] M-mode was the first non-invasive imaging technique developed in 1950s, at that time producing only one-dimensional information.[46]

Its use is reasonable for normally shaped ventricles, as well as for abnormally shaped ventricles if real time images are used.[31,42] Currently, 2D guided M-mode and 2D ECHO can be used routinely in each echocardiographic examination and remain the recommended method for the assessment of LVM and thus the determination of LVH.[31,41,47] In the future, 3D ECHO, will be the next step in the LVM evaluation, but it is still currently experimental.[42]

The echocardiographic determination of LVM has several limitations that need to be understood and sufficiently addressed to enable informed clinical decision-making and for interpreting and generalizing the corresponding findings. First, the need to calculate myocardial volume by cubing linear dimensions based on geometric assumptions limits the accuracy and reproducibility of this method.[48-51] Moreover, due to the use of cubing values, the LVM algorithm may magnify measurement errors. In addition, ECHO measurements are dependent on the ability to obtain an adequate acoustic window and this may be complicated by body habitus, respiratory conditions, etc. The technical adequacy of ECHO measurements is also dependent on operator skill and experience.[31]

The most recent reference values for ECHO chamber quantification were developed jointly by the American Society of ECHO (ASE)and the European Association of ECHO (EAE) in 2005[31]; revised recommendations with unchanged reference ranges have recently been published.[41,43] These values were derived from a population of normal-weight, normotensive, and non-diabetic, White, African American, and American Indian adults without recognized cardiovascular disease. Table 1.1 presents the reference values of LVM for both men and women as suggested by these guidelines.[31,41] It is crucial to note that the reference limits for LVM, as presented by Lang et al.,[31,41,43] are lower than other limits that have been published in previous ECHO studies, but are identical to those based on cut-off values used in clinical trials.[22,31,45,52,53] However, we should consider that reference ranges that are derived based on healthy individuals only, can result in low cut-off values that may not be clinically realistic when applied to the diverse "real world" heterogeneous population.[31] Moreover, the Echocardiographic Normal Ranges Meta-Analysis of the Left Heart (EchoNoRMAL) Collaboration derived ethnic-specific normative reference ranges for echocardiographic LVM, using population-based datasets of echocardiographic measurements from adults with no clinically evident cardiovascular disease or risk factors. The specifics of these ethnic-specific ranges is beyond the scope of the current paper, but are available elsewhere.[54]

Table 1.1: Reference limits of Left Ventricular Mass and geometry by Echocardiography and Definition of Left Ventricular Hypertrophy, according to the Left Ventricular Mass index (LVMi) Cutoff Value by both Echocardiography and CMR.

ECHO	Women			Men		
	Reference Ranges	**Abnormal**	**Severely Abnormal**	**Reference Ranges**	**Abnormal**	**Severely Abnormal**
M-Mode/Linear Method						
LVM (g)	67-162	163-210	≥211	88-224	225-292	≥293
LVM/BSA, (g/m^2)	43-95	96-121	≥122	49-115	116-148	≥149
LVM/height, (g/m)	41-99	100-128	≥129	52-126	127-162	≥163
LVM/$height^{2.7}$ ($g/m^{2.7}$)	18-44	45-58	≥59	20-48	49-63	≥64
Relative wall thickness (cm)	0.22-0.42	0.43-0.52	≥0.53	0.24-0.42	0.43-0.51	≥0.52
Septal thickness (cm)	0.6-0.9	1.0-1.5	≥1.6	0.6-1.0	1.1-1.6	≥1.7
Posterior wall thickness (cm)	0.6-0.9	1.0-1.5	≥1.6	0.6-1.0	1.1-1.6	≥1.7
2D Method						
LVM (g)	66-150	151-182	≥193	96-200	201-254	≥255
LVM/BSA, (g/m^2)	44-88	89-112	≥113	50-102	103-130	≥131

LVMi Cutoff Values

		Women	Men
ECHO	**BSA**	>95 (g/m^2)[31]	>115 (g/m^2) [31]
	$Height^{1.7}$	>60 ($g/m^{1.7}$)[27]	>81 ($g/m^{1.7}$)[27]
	$Height^{2.7}$	>47 ($g/m^{2.7}$)[25]	>50 ($g/m^{2.7}$)[25]
CMR	**BSA**	>84.6 (g/m^2)[55]	>106.2 (g/m^2)[55]
	$Height^{1.7}$	>60 ($g/m^{1.7}$)[27]	>80 ($g/m^{1.7}$)[27]
	$Height^{2.7}$	>38 ($g/m^{2.}$)[55]	>45.1 ($g/m^{2.7}$)[55]

CMR, cardiac magnetic resonance; ECHO, echocardiography; BSA, body surface area; LVM, left ventricular mass; LV, left ventricular; 2D, 2-dimensional LVMi, left ventricular mass index.

Table adapted from Armstrong et al. [30] and Lang et al. [31]

Assessment of LVM by CMR

LVM determination by CMR allows for a 3D high-resolution modeling of the left ventricle. It offers the advantages of being free of cardiac geometric assumptions, contrast infusion, acoustic window dependency, or ionizing radiation.[42] In CMR, LVM is derived again as the product of the myocardial volume and the density of the myocardium. Assessment of myocardial volume is done at end-diastole by convention. Nonetheless, measurement techniques still crucially influence LVM estimation.[56-59] For instance, some controversy exists regarding the inclusion of papillary muscles in the calculation of the myocardial mass. The results from Multi-Ethnic Study of Atherosclerosis (MESA), which had the largest population for CMR assessment, show better reproducibility when the papillary muscles are excluded.[60] However, Farber et al. in a more recent study of 58 explanted cardiomyopathy hearts suggests that the exclusion of papillary muscles should be reconsidered.[61] Moreover, evidence suggests that CMR estimates of LVM show increased susceptibility to inter-observer segmentation variation among healthy subjects, which should be taken under consideration in the case of multi-center or longitudinal studies. [62]

Important limitations to the widespread clinical use of CMR include the high operational cost, the time to acquire and analyze the imaging (cine) data, the hazards associated with ferromagnetic metal devices, as well as issues related to claustrophobia in susceptible patients.[30,40,59]

Although ECHO and CMR derived LVM estimates show high correlation, their absolute values differ, with CMR consistently yielding lower average values for the same subjects.[49,50] The

difference between the estimates suggests that the two methods cannot be used interchangeably in the assessment of LVM. Farber et al. suggest that CMR, following the steady-state free precession process, is truly the gold standard for the non-invasive calculation of both the left and right ventricular mass, based on strong correlations between the imaging derived mass and the respective autopsy mass ($r=0.99$, $p<0.001$ and $r=0.95$, $p<0.001$ for total cardiac mass and LVM respectively) .[61]

Despite the fact that CMR is considered the gold-standard for assessing LVM, ECHO is a well validated, non-invasive, and the widely used method in clinical practice.[63] Table 1.2 presents the major comparative differences between the two modalities.

Table 1.2: Comparative Assessment between Echocardiographic and Cardiac Magnetic Resonance's assessment of Left Ventricular Mass.

Features/Attributes	Best Performing Imaging Modality
Non-Invasive Modality	**ECHO, CMR**[40]
Cost	**ECHO**[40]
Fast	**ECHO**[42]
Acceptability/Availability	**ECHO**[31,40,42]
Inter-Study Reproducibility (Relevant to normal, dilated & hypertrophic hearts)	**CMR**[11]
Acoustic Window Dependency	**CMR**[31,42]
Operator's Experience Dependency	**CMR**[31]
Free of cardiac geometric Assumptions	**CMR**[40,64]
Accuracy & Precision	**CMR**[40,63]
Lower Measurement Error	**CMR**[23]
Standardization of Measurements	**CMR**[23,31]
Hazards associated with metal devices	**ECHO**[40,59]
Claustrophobia	**ECHO**[40,59]

CMR, cardiac magnetic resonance; ECHO, echocardiography.

Assessment of LVM by indexing methods

LVM and heart size increase in proportion to the overall body size and thus differ by gender, with higher values seen in men.[55,33] Anthropometric parameters should be considered to normalize myocardial mass, minimizing the effect of body size in the population distribution.[30] An LVM "index" is derived by dividing LVM with height, or by body surface area (BSA), or by comparing it to a reference group of healthy subjects. Due to the fact that relationships between body size and organ dimensions are often non-linear, allometric approaches are necessary, in which LVM is divided by a body size variable raised to a scalar exponent intended to describe the unique relationship between the variable and LVM.[27,52,65] The normal range of the LVM index can subsequently be derived from a reference sample of individuals believed to be free of risk factors that could otherwise cause LV enlargement.[55] It is also important to consider that in order to be clinically useful an indexed LVM should be more predictive of a cardiovascular event than non-indexed LVM.[55]

No optimal method to account for body size has been firmly established and the issue remains controversial.[23,31,33,55] Indexing to BSA was the first normalization process used, but it underestimates the prevalence of LVH in obese and in overweight hypertensive patients.[66] On the other hand, when height is used for indexing and weight is not accounted for, as expected, the prevalence of LVH is higher in the obese subjects.[55] Indexing by height to the allometric power of 2.7 ($height^{2.7}$) appears to best account for the relationship between height and LVM in hypertensive and obese individuals, while it also appears to be less variable among normal

subjects, providing a more sensitive cutoff for LVH.[52,67,68] Indexing to height$^{2.7}$ also appears to be the method best suited to detect LVH in the presence of acromegaly, particularly among those subjects who are also overweight.[69]

De Simone et al. conducted two studies comparing different indexing methods of echocardiographic LVM assessment. In the first study, they used a population of hypertensive individuals with a low prevalence of obesity (22%, with only 3% and 0.1% in class II and class III obesity, respectively).[66] After adjusting for age and sex, indexing by height, height$^{2.7}$, or height$^{2.13}$ performed as well as BSA as outcome predictors. In a second study, the same authors followed prospectively an American Indian population free of prevalent CVD at a baseline examination, but with a high prevalence of obesity.[70] In this study, LVM normalization by height to allometric powers performed better than LVM normalization by BSA, as outcome predictors, allowing the detection of obesity-related LVH with a worse prognosis that was unidentified using BSA and being associated with a higher proportion of incident CVD cases attributable to LVH. In addition, the results of this study suggest that the indexation of height to allometric powers should be preferable for the identification of high risk LVH individuals in populations with high prevalence of obesity, generally mild hypertension and good control of blood pressure .[70]

As far as CMR assessment of LVH, two studies have been conducted, both using participants from MESA, to compare different indexing methods with regards to their prognostic performance.[27,55,71] Chirinos et al.[27] analyzed CMR data from the MESA study and ECHO data

from the Asklepios Study[72] to assess different metric relationships between LVM and body size, and compared the ability of different normalization methods to predict cardiovascular events. The authors concluded that the allometric exponent, which adequately described the LVM - body height relationship was 1.7 in both studies; this is different from both the unity and the 2.7 exponents suggested previously. In addition, they found that LVM/height$^{2.7}$ systematically misclassified subjects in regards to the presence of LVH, whereas the LVM-BSA relationship seemed to be approximately linear. More specifically, LVM/height$^{2.7}$ grossly overestimated the prevalence of LVH in individuals with shorter body height across genders, while it underestimated its prevalence in those with greater body height. Finally, the authors demonstrated that LVH defined by LVM/height$^{1.7}$ was more sensitive than LVM/BSA in the identification of obesity-related LVH, and was most consistently associated with cardiovascular events and all-cause death. However, only White and Chinese MESA participants and White European participants from the Asklepios study were included in the analyses.[27] In the second study, Brumback et al used MESA participants to develop allometric indices for LVM measured by CMR and compared prevalence estimates and LVH predictive values as defined by their new indices and the previously defined ones in the MESA study.[55] Namely, the authors investigated indexation by BSA, height^2, height$^{2.7}$, percent-predicted LVM based on height and sex, and percent-predicted LVM based on height, weight, and sex. The authors reported that no significant differences were observed in relation to the predictive ability of the indices, while LVH prevalence was higher for those indices that did not account for weight.[55]

Table 1.1, adapted from Armstrong et al.[30] and Lang et al.[31], summarizes different indexing methods within and between imaging modalities for LVH classification.

Total Heart Weight (total cardiac mass) in healthy & diseased hearts

Significance & Challenges of Assessment

Accurate measurements of total heart weight at autopsies used together with appropriate reference ranges are considered crucial for pathologists to determine the presence of cardiomyopathies.[34,73] An elevated heart weight can be suggestive of conditions such as hypertensive and valvular heart disease, hypertrophic cardiomyopathy, ischemic heart disease, pulmonary hypertension, and cardiac failure due to various causes.[34] Thus, it is of critical importance to be able to judge correctly whether an increased weight represents a pathological condition or not.

However, defining cutoffs for cardiomegaly and establishing a firm definition of cardiomegaly by consensus, based on the measurement of heart weight, presents a great challenge. The scientific evidence available relies largely on older autopsy studies (1970-1990's) for total cardiac mass when the population was shorter and leaner than at present.[73-77] In light of the increased life expectancy and the undeniable "obesity epidemic" that is a growing global health problem, the effects of age and body weight on heart weight need, to be re-addressed.[41,74,78,79] Another challenge in the calculation of correct reference ranges for heart weight arises from the fact that some studies have not excluded hearts with pathologic changes, confounding normative data with those from abnormal hearts.[73,80] In addition, establishing ethnicity-specific reference

standards for heart weight is also important.[73,76,81] Overall, it is understood that the reference values provided for heart weight can only be valid for a limited period of time and should be regularly updated.[34,73]

It would be ideal to identify a parameter that correlates well with heart weight, so as to be able to use it as a surrogate. Results from older studies suggested that body weight and body height were the best predictors of heart weight.[34,74,76] On the other hand, recent studies argue that the most predictive factor for normal hearts is BSA, while for diseased hearts it is height[1.7].[34,53,73] However, the majority of new studies lack statistical significance to prove superior correlations of these parameters with heart weight, and thus, body weight is still considered as the best surrogate of heart weight;[53,73,82] Data from a review of 300 autopsies in a population of older patients with multiple comorbidities, suggest that, in males, heart weight is increased only in association with BMI and not age, while increasing age and not BMI is associated with LVH.[41]

Reference Ranges for Total Heart Weight

As indicated above, it is evident that the current reference ranges provided are based on older studies and should be updated. The heart weight reference values most cited are based on papers from 1942 and 1988, including some data taken from populations more than a century ago.[34,74] Grandmaison et al. in 2001 provided updated reference values for organ weights, including the heart, based on a population of French Caucasian individuals with a mean age of 45 years, with measures between 1987 and 1991.[73] All the adults in the study died from external causes and showed no pathological changes. The authors reported mean total cardiac mass for both genders

365 (71) g and 312 (78) g for men and women, respectively.[73] In a more recent study, Mandal et al. aimed to illustrate the effect of obesity on heart weight and thus they provided mean heart weight per BMI category. They reviewed 300 full or "no-brain" autopsies between September 2007 and April 2010, based on a population of older patients with multiple comorbidities, White and African Americans, 40% of whom were obese and 29% overweight. For the normal BMI category of 18.5-24.9 kg/m^2 the mean heart weight was 477±130g and 384±101g, for men and women, respectively. In addition, the mean total heart weight was 547±158g and 465±172g for men and women, respectively.[41] Obviously then, the data from Mandal et al. are likely to be confounded by persons with dabnormal hearts and obesity, which is also a disease state.

Vanhaebost et al. provided a user-friendly internet application, which computes the predicted normal heart weight as a function of body weight.[34] In the majority of the studies, the mean heart weight was found to be 30-40% greater in men than in women with a similar body weight.[34,41,73]

Total heart weight has also been expressed as a percentage of body weight, facilitating extrapolations from one to the other and allowing the best use of existing data. In most of the relatively recent studies, heart weight represents 0.51% of body weight in both genders,[53] indicating slight differences from previous studies, probably due to the fact that older studies may have failed to exclude those participants with hypertension.[74,78,79]

Relationship of LVM to Total Heart Weight

Autopsies vary considerably based on the different forms and protocols utilized across various jurisdictions. Most autopsies do not report individual ventricular weight, but rather they report the total heart weight. Total Heart Weight (THW) consists of many different components, such as the epicardial fat, the ventricular weight, and the atrial weight. Thus, having only THW makes it challenging to reach any firm conclusions about the proportional contribution of the LV mass to it.[81,83] In addition, the specific measurement technique used by pathologists may add challenges in the estimation of the LV weight through the THW, thus producing further discrepancies among different pathologists and/or different laboratories.[40,73,81,83]

Given the significance of the LVM, we tried to understand better the relationship between LVM and THW, based on current data available. Therefore, we made an effort to estimate the contribution of the weight of the left ventricle to THW. First, we used the mean values of the THW and LVM both by CMR and through pathologists' measurements from Farber et al., where the authors used 55 explanted cardiomyopathy hearts. Autopsy based data suggest that LVM contributes 70.3% of the THW while CMR based data suggest that the contribution of the LVM to the THW is 66.9% in this population of diseased hearts.[61] On the other hand, population-based CMR data[31] and forensic autopsy cases[73] from normal hearts, suggest that LVM contributes only around 42% of the THW in men and around 35.5% in women. Unfortunately, very little data is currently available to study the relationship between the mass of the left ventricle and the total heart weight, suggesting an area urgently in need of future research.

The Phenomenon of "Athlete's Heart"

An additional controversy surrounding the assessment of LVM relates to adaptive rather than pathological hypertrophy which can occur because of healthy behaviors, such as physical training and exercise.[23] LVM in some elite athletes can reach twice that of sedentary, but otherwise healthy individuals[54,84]. Athletes may undergo routine medical examinations with suspicious electrocardiographic changes, especially for LVH and an increased LVM that could be extremely important for maintaining optimal cardiac performance during training and competition. [85]Apart from the clinical examination, ECHO remains the principal way of differentiating between adaptive and maladaptive cardiac hypertrophy; the athlete's heart typically shows an eccentric biventricular hypertrophy with wall thickness under 15mm and a moderately dilated left ventricle, with left ventricular end diastolic diameters up to 58mm.[54,86]

A second area of controversy in athletes is whether these adaptive changes are always non-pathologic. Rowland has raised provocative questions about the arrhythmogenic nature of LVH that accompanies athletic training.[87] In the absence of definitive pathological stigmata this creates further challenges to the definition of normal LVM and thus LVH.[88] For instance, if trained athletes are included inadvertently in a normal control population, it is more likely that the range for LVM and wall thickness will be higher, leading to a decreased sensitivity in actually detecting true cardiac abnormalities.[85]

The idea that the cardiovascular system of trained athletes differs both structurally and functionally from that of untrained, normal individuals due to physiologic adaptation is more than 100 years old.[54,89-92] Thus, it is apparent, based on the literature, that exercise induces

functional and structural changes in the cardiovascular system with the type of training (endurance versus strength training) to be of particular importance.[54,85,86,93,94] Evidence suggests that strength training alone almost never causes physiologic hypertrophy of the heart and thus, if hypertrophy is evident, it is highly likely that structural heart disease is present.[86]

A heart with moderately increased mass and a high working capacity triggered by the repetitive additional cardiac workload which is induced by regular exercise training (longer than 5-6 hours a week) and without any serious valvular or other functional disorders is called an "athlete's heart".[86,95,96] In addition, the upper limit for physiological hypertrophy is set between 160-170g/m^2, measured echocardiographically with the Devereux formula.[97,98] However, it is important to consider that two-dimensional echocardiography is more likely to significantly overestimate LVM in untrained as well as highly trained individuals compared with the CMR.[97] Absolute cardiac dimensions are considered to fall outside clinically accepted partition values when left ventricular wall thickness is more than 12 mm, with somewhat lower cutoffs for female and adolescent athletes.[99,100] A maximum left ventricular wall thickness of 15mm in young trained athletes represents the upper limit of physiologic LVH.[101] However, a significant number of patients with hypertrophic cardiomyopathy show no or only mild wall thickening in a gray zone of 13 to 15 mm, which overlaps with that found in elite athletes, and thus absolute values of wall thickness may not be adequate for differential diagnosis.[101,102] Moreover, in physiologic hypertrophy of athletes, even though the anterior ventricular septum is usually the segment of the LV wall that is maximally thickened, the overall pattern is both symmetric and

homogeneous, with a difference of 2mm or less between all portions of the LV.[101]

CMR's role in the differential diagnosis of pathologic hypertrophy from physiologic LV remodeling in trained athletes has been receiving a great deal of attention lately. It is often superior to ECHO, particularly when increased wall thickness is completely or predominantly limited to focal areas of the anterior free wall, posterior septum, and apex.[103,104] However, in trained athletes with physiologic cardiac remodeling, and in the absence of any localized wall thickening, CMR findings indicate right ventricular and left ventricular cavity enlargement of normal shape.[96] Prakken et al. [80] conducted a study primarily among Dutch Caucasians to determine both reference values for endurance athletes based on CMR and the upper limits for a physiological adaption to exercise training. The authors concluded that endurance athletes (either regular or elite) showed an increase in ventricular volumes, diameters, wall mass, and wall thickness, when compared to a healthy population with recreational sports activities. Interestingly, regular athletes showed a mean LVM closer to the elite athletes (difference:14 g) than to non-athletes (difference: 44g), even though training hours per week of regular athletes were half compared to elite ones. Prakken et al. also suggested that a high number of hours per week of training and male gender could result in an overlap with standard thresholds for cardiomyopathy and recommended the use of the 95th percentile reference values for the standard upper limits for the general population.[80]

Conclusions

LVH is recognized as a significant clinical and epidemiologic marker of cardiovascular disease. Its objective assessment by measuring LVM is considered to improve prognostic accuracy. In clinical practice, 2D-guided M-Mode ECHO and 2D ECHO remain the most widely used and most accessible imaging modalities for the assessment of LVM, while CMR represents the gold standard. Despite many years of research and practice, LVH definitions using LVM cut-off reference ranges for LVH assessment demonstrate wide variability among technicians, laboratories, and institutions, with a need of greater standardization. In addition, there are only a few direct comparisons of ECHO and CMR, and the methods used are currently not cross-standardized. For both ECHO and CMR, the optimal method of indexing for body size remains a controversial issue, affecting the definition of pathological hypertrophy. Another area that warrants more research is the overlap of LVM in "athletes'" hearts with abnormal ranges, and whether all changes associated with "athletes'" hearts are truly benign.

Notwithstanding the known significance of LVM as a marker of LVH and CVD risk, forensic studies rarely assess LVM, and instead, they measure routinely total cardiac mass as an indicator of potential cardiomegaly. Autopsy investigations clearly support cardiomegaly as a marker of CVD and SCD risk. However, very little autopsy data exist to facilitate direct comparisons between the mass of the left ventricle and the total cardiac mass, in order to establish a firm relationship between the two. The limited data available suggest that LVM accounts for a much greater proportion of total cardiac mass in diseased hearts as compared to normal hearts. Another important area for future research is the updating of reference ranges for total heart weight in light of the contemporary population's changes in height and weight.

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CHAPTER 2: Cardiac Enlargement in US Firefighters: Prevalence estimates by Echocardiography, Cardiac Magnetic Resonance and Autopsies

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Abstract

Background: Cardiovascular disease (CVD) accounts for 45% of on-duty deaths in US fire service; cardiac enlargement is common among US firefighters; and plays a major role in firefighter sudden cardiac death (SCD).

Aims: To estimate the prevalence of cardiac enlargement in US Firefighters by autopsies, echocardiography (ECHO) and cardiac magnetic resonance (CMR).

Methods: In the present cross-sectional study, the prevalence of left ventricular hypertrophy (LVH)/cardiomegaly was a) estimated non-invasively among active career firefighters and b) examined by reviewing autopsies of firefighters who suffered a non-cardiac, on-duty fatality. LVM among active career firefighters was assessed by ECHO and CMR, and normalized (indexed) for body surface area (BSA) and height. Autopsy estimates were based on cardiac weights and other forensic parameters.

Results: LVH prevalence estimates among active career firefighters presented a range from 3.3% to 32.8% among ECHO and 0.0% to 5.3% among CMR criteria. LVH was present in 17.5% and 0.4% of the active firefighters as defined by LVM indexed to height$^{1.7}$ (by ECHO and CMR, respectively). LVM indexed to BSA as measured by CMR indicated zero prevalence of LVH. Among non-cardiac traumatic autopsies, prevalence estimates of cardiomegaly and LVH were 39.5% (95%CI 33.7–45.3) and 45.4% (95%CI 39.5–51.4) respectively, even after adjustment for age and bmi.

Conclusions: The prevalence of cardiac enlargement varied widely depending on the imaging assessment, the cutoffs and the normalization techniques. For autopsy data, BMI was a major determinant of heart weight. Future CVD-outcome based studies are needed to provide evidence for the most accurate cutoffs, while standardization of autopsies is needed across protocols and jurisdictions.

Keywords: cardiomegaly, hypertrophy, echocardiography, cardiac magnetic resonance, autopsies, fire service

Introduction

Firefighting is widely recognized as an inherently dangerous occupation, and more than 1 million Americans are involved in this critical public service.[1] Intuitively, one may think that most on-duty deaths result from burns or smoke inhalation, however, cardiovascular disease (CVD) is the leading cause of duty related fatalities among firefighters (45% of on-duty fatalities).[2-5]Moreover, for every fatal on-duty CVD event, there are an estimated 25 additional nonfatal CVD events[6,7]. Therefore, CVD events are a problem of paramount importance in the US fire service.

It is crucial to note, that the risk of on-duty CVD events is not evenly distributed among all firefighters, but is highly concentrated among the most susceptible individuals. [2,8] On-duty CVD events and heart disease retirements occur primarily in firefighters with underlying disease (known or subclinical) or excess cardiovascular risk factors. [9-11] Thus, considering that firefighting is very strenuous and can trigger a CVD event in a susceptible individual [2,12], and many hazards cannot be fully avoided or mitigated by engineering/ administrative controls.[12] Much attention has focused on the key prevention question of what can make an individual firefighter susceptible. Increasingly, evidence is pointing to a major role of left ventricular hypertrophy (LVH)/cardiomegaly in the risk of sudden cardiac death (SCD) independent of the presence of Coronary Heart Disease (CHD).[13-15]

Left ventricular hypertrophy (LVH)/cardiomegaly is a structural abnormality of the heart[16,17] and appears to be a key pen-ultimate and predisposing step on the causal pathway that makes a firefighter susceptible to CVD events [2,11,18]. Cardiomegaly is a general term used to describe increased heart size, whereas LVH describes both increased wall thickness and mass, due to a thickening of the heart muscle that surrounds the left ventricle. LVH/cardiomegaly has been

widely recognized to increase the risk of fatal ventricular arrhythmias, myocardial infarction and stroke; and it is a proven predictor of CVD and overall mortality in the general population. [19-23] Moreover, evidence from studies based on autopsy reports from active career firefighters, indicates that LVH/cardiomegaly is common among US firefighters and plays a major role in CVD events and SCD risk in the fire service. [9,24]

Notwithstanding, the known significance of LVH/cardiomegaly as a clinical and epidemiologic marker of CVD and SCD, its definition demonstrates wide variability among imaging modalities, technicians, normalization processes and algorithms. [25-27] Evidence suggests an increasing prognostic value, when LVH is based on the accurate assessment of LV mass (LVM). The two most frequently used imaging modalities for the non-invasive identification of LVH are echocardiography (ECHO) and cardiac magnetic resonance (CMR), with CMR considered the gold standard.[28] ECHO and CMR use different algorithms for the assessment of LVM, providing different average values along with different degrees of accuracy. [25,28] In addition, indexing to body size parameters has been the most common normalization process to account for anthropometric variation, although the optimal method remains controversial. [27,29] Overall, it is important to note that the variability between the imaging techniques, the reference ranges, the body size indexing and other adjustments could critically affect the distinctions between disease states and normality. In contrast to clinical studies, forensic autopsies rarely assess LVM, and instead they routinely measure total heart weight as an indicator of cardiomegaly. With regard to LVH, pathologists may measure wall thickness and comment on the appearance of the ventricle.

The aim of this paper is to estimate the prevalence of cardiac enlargement (including LVH) in US firefighters and determine how these prevalence estimates vary according to different methods of assessment; namely by autopsies, ECHO and CMR; as well as by the criteria used to

define enlargement/hypertrophy.

Methods

In the current study we present prevalence estimates of LVH among active career firefighters by two imaging techniques (ECHO and CMR). We also compare these with prevalence estimates observed by direct measures of heart weight and LV wall thickness at autopsy among formerly active firefighters who suffered a non-cardiac fatality while on-duty.

Study Population (Imaging assessment)

Male career firefighters, aged 18 years and older were recruited from the Indianapolis Fire Department (IFD). Eligible firefighters had no restrictions on duty and had a recorded fire department-sponsored medical exam in the last two years that included a submaximal exercise tolerance test.

From those eligible (n=1059), we selected a total of 400 participants, utilizing an "enriched" randomization strategy based on age at randomization, obesity, hypertension (HTN) and cardio-respiratory fitness (CRF) status at last examination, so that a larger number of higher risk participants would be selected. Thus, we randomly selected: 100 participants from the entire eligible population; 75 low-risk participants (age <40, non-obese, free of HTN and high CRF) and 225 higher risk participants (at least 2 of the following: age >/=40, obese, HTN or low CRF) for further LVH/cardiomegaly screening and imaging tests. Obesity was defined by standard criteria (BMI >/=30 kg/m^2). Hypertension was considered present if resting blood pressure is >/=140/90 mm Hg. Low CRF was defined as the bottom tertile, as measured by the recorded treadmill time and the estimated maximal VO_2 during the last exercise test. Those selected were included in the study if they had no contraindication to CMR and signed informed consent to

participate. Out of the 400 active career firefighters, we excluded 7 participants with missing measurements of LVM, as assessed by CMR.

Definitions of Cardiac Enlargement by Imaging Assessment

LVM was assessed by both ECHO and CMR imaging. First, a transthoracic cardiac echocardiogram was done as a simple two-dimensional (2-D) study with limited m-mode recordings. An abbreviated cardiac MRI (CMR) was performed as "function only" immediately after the ECHO. Images were obtained using a retrospectively EKG-gated steady-state free precession cine sequence. In this fashion, a contiguous short axis stack of 8 mm slices was obtained parallel to the atrioventricular groove to cover the entire length of the LV. Then, manual tracing of end-diastolic epicardial and endocardial borders was performed. Standard long axis views were also obtained including horizontal long axis, vertical long axis, and 3-chamber views, facilitating the interpretation of ventricular function. Board certified specialists performed the clinical interpretation of imaging.

LVM indices were derived by dividing LVM in kilograms with either body surface area (in meters^2) or height to the allometric powers of 1.7 and 2.7 (in meters$^{1.7}$ and meters$^{2.7}$, respectively). Body surface area was estimated with the Mosteller formula. LVH/cardiomegaly was defined based on the cutoff values presented in Table 2.1, for posterior and septal wall thickness, LVM and LVM indices.

Table 2.1: Definition of Cardiomegaly/Left Ventricular Hypertrophy, by both Imaging Modalities (echocardiography and cardiac magnetic resonance) and Autopsies.

Cutoff Values for Cardiomegaly/Left Ventricular Hypertrophy		
ECHO/CMR	Posterior wall thickness (cm)	≥1.2
	Septal thickness (cm)	≥1.2
ECHO	LVMi _BSA (g/m^2)	>115
	LVMi _Height$^{1.7}$ ($g/m^{1.7}$)	>81
	LVMi _Height$^{2.7}$ ($g/m^{2.7}$)	>50
	LVM (g)	>225
CMR	LVMi _BSA (g/m^2)	>106.2
	LVMi _Height$^{1.7}$ ($g/m^{1.7}$)	>80
	LVMi _Height$^{2.7}$ ($g/m^{2.7}$)	>45.1
	LVM (g)	>203.5
	Quantitative Definitions	
	Heart Weight (g)	≥ 450
	LV wall thickness (cm)	≥1.2
	Qualitative Definitions	
Autopsy Reports	Heart size abnormality noted	YES
	Increased Wall Thickness noted	YES
	Comprehensive definitions	
	Cardiomegaly	≥ 450 and/or YES
	Left Ventricular Hypertrophy	≥1.2 and/or YES

LVMi, Left Ventricular Mass index; LVM, left ventricular mass; ECHO, echocardiography; CMR, cardiac magnetic resonance.

Assessment of Cardiovascular Risk Factors

Height was measured in the standing position with a clinical stadiometer. Body weight was measured with bare feet and in light clothes on a calibrated scale. BMI was calculated as the weight in kilograms divided by the square of height in meters. Blood pressure was measured using an appropriately sized cuff with the subject in the seated position. Heart rate and blood pressure were obtained in a resting state from the physical examination (and were not measured prior to the exercise test). Medical exam data were further supplemented by a pre-imaging questionnaire, which collected comprehensive information on smoking status, personal history of heart rhythm problems, family history of cardiac problems, self-reported HTN and moderate to vigorous physical activity level in minutes per week. High Obstructive Sleep Apnea (OSA) risk was assessed using the widely used and validated Berlin Questionnaire.[30]

Direct measures of Heart weight and wall thickness based on autopsy reports

Non-cardiac traumatic fatalities (deaths due to blunt trauma, burns, or asphyxiation) were identified for 2006 to 2012 from a firefighter autopsy research data bank maintained by the National Fallen Firefighters Foundation. The inclusion criteria for the non-cardiac trauma controls were (1) age ≤ 65 years, (2) duty-related death, and (3) cause of death determined by autopsy to be due to blunt trauma, burns, or asphyxiation and not related to any cardiovascular pathologic entity. For the purpose of this study, we used only male autopsy reports from those eligible.

Definitions of Cardiac Enlargement based on autopsy reports

We defined LVH and cardiomegaly from autopsy data, based on both qualitative and quantitative criteria. (Table 2.1) Qualitative definitions were based on the conclusions documented in the autopsy report. Qualitatively, we considered cardiomegaly present if the autopsy report indicated a heart size abnormality, and LVH present if the autopsy reported an increased wall thickness. Quantitative definitions were based on the reported values of LV wall thickness and heart weight. Quantitatively, we defined cardiomegaly as a heart weight ≥ 450 g and LVH as a LV wall thickness ≥ 1.2 cm. The cutoff values of 1.4cm and 1.7cm were also used in analyses for LV wall thickness. In the absence of qualitative or quantitative information on LV wall thickness and/or heart weight, we classified the deceased individuals as not affected by LVH or cardiomegaly. The qualitative and quantitative definitions for LVH and cardiomegaly were not mutually exclusive and therefore we created a comprehensive definition as well; more specifically, all subjects who met the criteria for the qualitative and/or the quantitative definitions were classified as affected by LVH or cardiomegaly under the comprehensive definition.

Data from 353 autopsy reports were available. We conducted our main analysis with data from 293 autopsy records, excluding those with missing information on BMI. We also performed a series of sensitivity analyses with data from all 353 autopsy records, where the prevalence rates of LVH and cardiomegaly were estimated assuming a BMI of 25 kg/m^2 and then 27 kg/m^2 for all records with missing information. Under the assumption based on that the pathologists would have reported the weight in the autopsies if this was in the obesity range, we set the values of BMI for sensitivity analyses to fall either in the normal/ overweight range.

Statistical Analysis

We performed a weighted analysis regarding the imaging data so as to account for our enriched randomization sampling strategy. Weights were calculated based on the total number of risk factors per subject with the technique of inverse probability weighting (Appendix table 2.1). Baseline characteristics were described using the mean (SD) for quantitative variables and the frequency (%) for categorical variables. Prevalence estimates for LVH based on ECHO and CMR assessments were presented as percentages (95% CI). Comparisons of prevalence estimates between paired data were performed with the McNemar's test.

Prevalence estimates of LVH and cardiomegaly based on autopsy records were adjusted for age and BMI according to the age and BMI distributions of the active career firefighter population using the method of direct standardization. Age was classified in 10-years classes (26-35, 36-45, 46-55, 56-65) while BMI was categorized as normal (BMI<25 kg/m^2), overweight (25<BMI <29 kg/m^2), obesity class I (30<BMI<34 kg/m^2), obesity class II/III (BMI≥35 kg/m^2). Agreement between the qualitative and the quantitative definitions applied to detect cardiomegaly and LVH among autopsy records was evaluated using the Cohen's kappa. The significance of the trend across ordered groups of ages or BMI was evaluated with the use of the score test under a linear trend of odds.

Analyses were performed using SPSS, version 21.0 (IBM, Armonk, New York) and Stata, version 14.0 (StataCorp, College Station, Texas). A p-value < 0.05 was considered statistically significant and all tests performed were two-sided.

Results

The baseline characteristics are summarized in Table 2.2. After adjusting for the weighted sampling strategy, the mean age of active career firefighters was 45.3 years (SD 8.1) and their mean BMI was 30.3 kg/m^2 (SD 4.5). There were 41.3% with family history of cardiac problems, 44.8% were obese, 31.6% had high risk of OSA based on the Berlin Questionnaire and 34.3% had low CRF. The mean LVM measured was 186.9 grams (SD 36.6) by ECHO, and 137.6 grams (SD 23.4) by CMR. Among autopsy data, the mean age at death was 42.7 years (SD 10.3) and the mean BMI at death was 31.2 kg/m^2 (SD 6.9). The mean heart weight at death was 438 grams (SD 99) while the average LV wall thickness (LVWT) was 0.9 cm (SD 0.4cm).

The prevalence estimates of LVH by both ECHO and CMR assessment based on different criteria are summarized in Table 2.3. Great variability was observed within ECHO based on different definitions/indices applied. Across ECHO assessment, 14.1% of active career firefighters demonstrated LVH based on LVM, 13.1% based on posterior wall thickness and 32.8% based on septal wall thickness. Considering the CMR measurements, 5.3% of the career firefighters studied were identified as having LVH, as defined by posterior wall thickness. When considering definitions based on LVM normalized to height to the power of 1.7, LVH was present in 17.5% and 0.4% of the active career firefighters (ECHO and CMR, respectively). Normalization by BSA using CMR measurements was the only criterion to deliver zero prevalence of cardiac enlargement. Overall, higher values of LVM and therefore, LVH prevalence were observed among ECHO measurements compared to CMR.

All comparisons of LVH prevalence estimates obtained by ECHO were significantly different ($p<0.05$) based on varying definitions, while within CMR measurements the estimates showed

similarity ($p=0.125$), only when definitions were based on the height indices ($height^{1.7}$ vs. $height^{2.7}$). Comparisons of LVH prevalence between ECHO and CRM were significantly different ($p<0.001$) for estimates based on LVM, PWT and indexing to $height^{1.7}$.

Table 2.2: Baseline descriptive characteristics.

Variables	Imaging Study Sample (N= 393)	Imaging Study Sample Unweighted	Autopsy Data (N=293)
Age years †	46.5 ± 8.2	45.3 ± 8.1	42.7 ± 10.3
Height inches †	70.3 ± 2.5	70.3 ± 2.6	70.1 ± 3.9
Heart Rate bpm †	80.5 ± 13.4	79.5 ± 13.0	NA
Resting SBP mmHg †	126.3 ± 9.7	125.2 ± 9.4	NA
Resting DBP mmHg †	81.8 ± 8.1	81.3 ± 7.4	NA
Self-reported HTN *	95 (24.7)	225 (21.6)	NA
High Risk of OSA *	112 (38.1)	254 (31.6)	NA
Body Mass Index kg/m^2 †	31.1 ± 4.6	30.3 ± 4.5	31.2 ± 6.9
Smoking *	50 (13.0)	135 (12.9)	NA
Personal History of Heart Rhythm Problems *	60 (15.7)	153 (14.7)	NA
Family History of cardiac problems*	153 (40.2)	426 (41.3)	NA
Age >= 40 years *	301 (78.2)	770 (72.7)	172 (58.7)
BMI>= 30 kg/m^2 *	260 (56.1)	474 (44.8)	142 (48.5)
Low CRF *	178 (46.7)	363 (34.3)	NA
MVPA Physical Activity min/week †	177.4 ± 117.3	187.3 ± 117.7	NA
Cardiac Measures			
LVM_ECHO g †	189.0 ± 38.1	186.9 ± 36.6	NA
LVM_CMR g †	139.2 ± 24.0	137.6 ± 23.4	NA
Heart weight g †	NA	NA	438 ±99 ‡
LVM_ECHO indexed to height$^{1.7}$ g/m$^{1.7}$ †	70.4 ± 13.3	69.7± 12.9	NA
LVM_ECHO indexed to height$^{2.7}$ g/m$^{2.7}$ †	39.5 ± 7.6	39.1 ± 7.4	NA
LVM_ECHO indexed to BSA g/m^2 †	85.3 ± 14.5	85.4 ± 14.5	NA
LVM_CMR indexed to height$^{1.7}$ g/m$^{1.7}$ †	52.0 ± 8.3	51.4 ± 8.1	NA
LVM_CMR indexed to height$^{2.7}$ g/m$^{2.7}$ †	29.2 ± 4.7	28.8 ± 4.6	NA
LVM_CMR indexed to BSA g/m^2 †	62.6 ± 8.7	62.8 ± 8.7	NA
Posterior wall Thickness_ECHO cm †	1.03 ± 0.1	1.02 ± 0.1	NA
Posterior wall Thickness_CMR cm †	0.93 ± 0.2	0.92 ± 0.2	0.9 (0.4) §
Septal wall Thickness_ECHO cm †	1.12 ± 0.1	1.11 ± 0.1	NA

SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; OSA, obstructive sleep apnea; BMI, body mass index; CRF, cardiorespiratory fitness; MVPA, Moderate to Vigorous Physical Activity; LVM, left ventricular mass; ECHO, echocardiography; CMR, cardiac magnetic resonance. † Mean (SD) for continuous variables; * n (%) for categorical variables. Low CRF was defined as the lowest tertile, as measured by the recorded treadmill time and the estimated maximal VO_2 during the last exercise test. ‡Information available in 251 (85.7%) autopsy records. §Information available in 139 (47.4%) autopsy records, a value of 0.9 was imputed for missing data.

Table 2.3: Prevalence estimates of left ventricular hypertrophy (LVH) by echocardiography and cardiac magnetic resonance.

		LVH (n,%)	
		Study Sample (N=393)	**Study Sample Unweighted**
ECHO	LVM	58 (15.3)	146 (14.1)
	Posterior Wall Thickness	61 (16.0)	136 (13.1)
	Septal Wall Thickness	140 (36.7)	341 (32.8)
	LVM/BSA	13 (3.4)	34 (3.3)
	LVM/Height$^{1.7}$	70 (18.7)	181 (17.5)
	LVM/Height$^{2.7}$	34 (9.1)	90 (8.7)
CMR	LVM	4 (1.1)	9 (1.0)
	Posterior Wall Thickness	21 (6.0)	50 (5.3)
	BSA	0 (0.0)	0 (0.0)
	Height$^{1.7}$	2 (0.6)	3 (0.4)
	Height$^{2.7}$	1 (0.3)	2 (0.2)

LVM, left ventricular mass; BSA, body surface area; ECHO, echocardiography; CMR, cardiac magnetic resonance.

LVH and cardiomegaly distributions by age and BMI categories and based on quantitative definitions among the non-cardiac traumatic autopsies are presented in table 2.4. Prevalence rates steadily increased with increasing age and BMI.

Unadjusted prevalence estimates (based on comprehensive definitions) showed cardiomegaly to be present in 41.3% (n=121) of non-cardiac traumatic fatalities and LVH in 45.5% (n=135). The agreement between the unadjusted qualitative and quantitative definitions was low for both cardiomegaly and LVH (Cohen's kappa 0.35 and 0.18, respectively), while 28.3% of the autopsies reported both LVH and cardiomegaly, based on the comprehensive definitions (Appendix table 2.2). An age- and BMI-adjusted prevalence estimate of cardiomegaly (comprehensive definition) as high as 39.5% (95%CI 33.7–45.3) was documented among the non-cardiac traumatic firefighter fatalities (Appendix table 2.3), while the age- and BMI-adjusted prevalence estimate of LVH (comprehensive definition) was 45.4% (95%CI 39.5–51.4) (Appendix table 2. 4). The prevalence estimates of cardiomegaly and LVH did not change considerably in either of the sensitivity analyses conducted (results shown for BMI=27 in appendix tables 2.5 and 2.6).

Table 2.4: Distribution of LVH and cardiomegaly by age and body mass index by autopsy reports.

	Heart weight ≥ 450g				LV wall thickness ≥ 1.2 cm				LV wall thickness ≥ 1.4 cm				LV wall thickness ≥ 1.7 cm			
	No	(%)	Yes	(%)	No	(%)	Yes	(%)	No	(%)	Yes	(%)	No	(%)	Yes	(%)
Age (years)																
26–35	56	(73)	21	(27)	49	(64)	28	(36)	56	(73)	21	(27)	69	(90)	8	(10)
36–45	75	(76)	27	(24)	68	(67)	34	(33)	78	(76)	24	(24)	94	(92)	8	(8)
46–55	42	(56)	33	(44)	35	(47)	40	(53)	42	(56)	33	(44)	60	(80)	15	(20)
56–65	17	(44)	22	(56)	20	(51)	19	(49)	2	(56)	17	(44)	32	(82)	7	(18)
P trend[a]				<0.001				0.026				0.007				0.051
Body mass index																
Normal	45	(94)	3	(6)	36	(75)	12	(25)	39	(81)	9	(19)	47	(98)	1	(2)
Overweight	80	(78)	23	(22)	66	(66)	37	(36)	73	(71)	30	(29)	91	(88)	12	(12)
Obesity, class I	37	(52)	34	(48)	39	(55)	32	(45)	46	(65)	25	(35)	65	(92)	6	(8)
Obesity, class II/III	28	(39)	43	(61)	31	(44)	40	(56)	40	(56)	31	(44)	52	(73)	19	(27)
P trend[a]				<0.001				<0.001				0.003				<0.001

[a] Score test for linear trend of odds

Discussion

The results from the present study in US firefighters demonstrate great variability of the prevalence estimates of LVH within and between ECHO and CMR, according to the different criteria utilized. Considerable variance was also observed using direct measures at autopsy, again, depending on the criteria used. Additionally, autopsy findings clearly indicated that BMI was a major determinant of heart weight. Prevalence estimates of LVH were significant, though realistic when based on LVM indices and assessed by ECHO. Although CMR is considered to be the gold standard among imaging techniques, the prevalence estimates of cardiac enlargement observed in the present study seemed unrealistically low, especially when compared to direct measures at autopsy in a similar firefighter population. Given the great variance in LVM and LVH estimates, surprisingly, the average LV wall thickness was similar across both imaging techniques and at autopsies.

Taken together, our results reflect the lack of standardization among definitions of cardiac enlargement, and therefore, prevalence estimates were highly variable depending critically on the choice of the normalization technique, the imaging modality and the cutoff values. Among the non-cardiac traumatic fatalities, the comprehensive estimates for prevalence of cardiomegaly and LVH were quite high, even after adjustment for age and BMI (39.5% and 45.5%, respectively). To the best of our knowledge, our study is the first to evaluate the prevalence of cardiac enlargement among active career firefighters by both ECHO and CMR measurements based on different criteria, as well as the first to compare these estimates to those derived from non-cardiac traumatic fatalities.

We previously found the prevalence of cardiomegaly to be 22% in a smaller sample of non-cardiac, traumatic firefighter fatalities limited to those under the age of 45 years of age.[31] Our estimates for these age groups were similar, 27% and 24% for those under the age of 35 and 45 years of age respectively.

Prevalence estimates of LVH were substantially higher when ECHO measurements were considered as compared to CMR. Nonetheless, great variability was still observed among ECHO prevalence estimates. This could be explained by the fact that the measurement of LVM, which was the main and single variant component of calculating LVM indices was on average 49.3 grams higher by ECHO than by CMR. Our findings are in general agreement with previously published literature regarding the controversies surrounding the LVM assessment and thus the definition of LVH based on imaging.[28,29] Along the same lines, current evidence suggests that CMR consistently yields lower average values compared to ECHO for the same subjects.[32,33]

Taken together this wide range of prevalence estimates of cardiac enlargement that was observed among the same subjects, could be explained in large by the fact that the cut off values used by each criterion are very close between the ECHO and the CMR measurements, indicating the urgent need of adjustments that should be made in these cutoffs. Given the large differences in mean LVM consistently observed between ECHO and CMR, it is puzzling that suggested LVH cutoff values are so close for the two different imaging techniques.

Considering all the different values of the prevalence estimates based on imaging assessments, taken together with the high prevalence of obesity and CVD risk factors among active career firefighters and autopsy-derived direct measures, we believe that our results suggest that the estimates provided based on CMR are likely to be unrealistically low, while those provided by LVM indexed to height and based on ECHO seem to be more realistic.

Our results are in line with current evidence from previous studies. First when cardiac enlargement is assessed by imaging, normalization to anthropometric parameters should be in place, so as to minimize the influence of body size in the estimates provided and provide more accurate estimates. [27,28,34] Second, evidence suggests that height to an allometric power best accounts for the relationship between height and LVM, being less variant among subjects with normal BMI and more accurate among those overweight or obese. Therefore, indexing to height is a more optimal method than BSA as a means to index for body size. Third, evidence based on both ECHO and CMR assessments suggests height to the allometric power of 1.7 to be the preferred indexing coefficient for both imaging modalities.[27,29] This suggestion is supported by our autopsy results. Considering that autopsies are providing a direct measure of assessment and are the gold standard criterion, in this study we have found that the prevalence estimates of LVH

among obese non-cardiac fatalities to be around 40% (Appendix Table 2.4). Therefore, we would not expect prevalence much lower than that in an active group of firefighters with high prevalence of obesity, OSA and HTN. The only index that showed closer prevalence estimates to the ones provided by autopsies was the one based to height $^{1.7}$ (17.5%). Our results also suggest that normalization by BSA is less likely to be appropriate for an obese population like firefighters, since it is considered that including BSA in the index in a way we account for body weight and thus indexing to BSA leads to a gross underestimation of cardiac enlargement among obese and overweight individuals.[27,34] This is also supported by our results, where the prevalence estimates provided by indexing to BSA were null, which is difficult, if not impossible to believe given the population's risk profile.

Among traumatic deaths, where any possible contribution of cardiac pathology to the death was reasonably excluded, around 40% demonstrated cardiomegaly while approximately 50% presented LVH. This can be explained in large by the high prevalence of obesity that was documented among those noncardiac traumatic controls, while in addition our results suggested the prevalence of cardiac enlargement to be steadily increasing as a function of BMI. Our findings are consistent with the literature, which finds obesity to be a significant risk factor for LVH and increased cardiac mass.[2,24] Furthermore, one could hypothesize that traumatic fatalities occur more frequently in obese firefighters as they could be more inclined to be physically trapped during a fire secondary to their body size and relative physical immobility. [31] In fact, the average BMI of the non-cardiac fatalities was higher than that of the active firefighter study base population (31.2 vs. 30.3) and that previously reported for representative, population-based firefighter samples (28.6 for career firefighters).[35]

One limitation of the data and therefore, of the current study is the fact that we were not able to conduct direct comparisons between heart mass or LVM in autopsies and clinical imaging, with imaging modalities focusing on the determination of cardiac enlargement via LVM assessment, and autopsies using total heart weight. None of the autopsies reviewed in the present study reported individual ventricular weights, but rather only the total heart weight. However, total heart weight consists of many different components, such as the epicardial fat, the ventricular weight, and the atrial weight, and therefore, having only measurements for total heart weight makes it challenging to reach any firm conclusions about the proportional contribution of the LV mass.[36,37]

Another limitation of our study is the low correlation between the quantitative, qualitative and comprehensive definitions of LVH and cardiomegaly among autopsy reports, due to the fact that autopsies vary considerably based on different forms and protocols utilized across various jurisdictions. It seems from current data that values on LV wall thickness and heart weight were more likely to be reported if they were relatively high, while sometimes instead of the value itself the medical examiner/coroner only reported qualitatively for the presence of hypertrophy and/or enlargement without giving an actual value. Considering that heart weight and LV wall thickness are valuable criteria, it is really important to ensure that actual values would be reported through standardization of the forms of the autopsy reports, in order to be able to be used for current and future comparisons.

A major strength of our study was the fact that we had access not only to data from active career firefighters, but also to autopsy reports from non-cardiac traumatic fatalities. In addition, our autopsy findings result rely mostly on quantitative data, with heart weight measurement reported in almost 90% of the non-cardiac autopsy reports examined. Taken together, we were able to evaluate the status of cardiac enlargement in the US fire service via many different assessments and get a more holistic picture of the current estimates.

Second, we were then able to make direct comparisons of prevalence estimates based on the same definitions within and between ECHO and CMR. This was important since there are only a few direct comparisons of ECHO and CMR prevalence estimates of cardiac enlargement, and the methods used are currently not cross-standardized. Another strength of our study is our age- and BMI- adjustment for the prevalence based on autopsies. Since, the use of non-cardiac trauma deaths for the purpose of this study was intended to find firefighters whose hearts reflect those of the whole population and in fact, our "control" population seemed to still be biased towards obesity, adjusting for age and BMI distributions for an actual working firefighter population should balance any introduced bias, providing realistic estimates. In addition we used the definition of 1.2 cm for defining LVH based on LV wall thickness, considering a more conservative approach to avoid any overall with physiologically enlarged hearts due to athletic training.

The present results, taken together reveal the huge potential impact of the choices of the clinicians/ researchers on defining cardiac enlargement, affecting greatly estimates of cardiac enlargement in the US fire service, and creating great challenges on which decisions are the most

accurate and appropriate in clinical practice. Irrespectively of the variability in prevalence estimates, our study clearly revealed BMI as a major driver of heart weight. In addition, LVM is considered as a more global assessment of the size of the left ventricle as opposed to wall thickness that could be considered a snapshot, and overall our results suggest the great need for CVD-outcomes' based studies that will provide definite evidence about the most accurate normalization indices and cutoffs; while another important area for future research could be the updating of reference ranges for total heart weight in light of the contemporary population's changes in height and weight. Furthermore, ECHO screening could be considered to evaluate possible cardiac enlargement, based on clinical judgment and the prevalence of CVD risk factors, such as stage 1 and 2 HTN, obesity, risk of OSA and age, as a relatively simple and inexpensive screening tool and based primarily on LVM indexed to height as most supported by the literature.

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Appendix

Table 2.1: Distribution of Risk Factors and calculation of weights based on Inverse Probability Weighting.

Number of Risk Factors	Study sample N (%)	Study base N (%)
0	48 (12.6)	161 (15.20)
1	82 (21.5)	367 (34.66)
2	122 (32.0)	298 (28.14)
3	103 (27.0)	172 (16.24)
4	26(6.8)	61 (5.76)
Weights per number of Risk Factors		
	Sampling Fractions	**Weights (Probability)**
0	48/161	161/48 (3.354)
1	82/367	367/82 (4.475)
2	122/298	298/122 (2.443)
3	103/172	172/103 (1.670)
4	26/61	61/26 (2.346)

Table 2.2: Agreement between the qualitative and the quantitative definitions of cardiomegaly and left ventricular hypertrophy.

Cardiomegaly **Quantitative definition**			
Qualitative definition	Negative	Positive	*Total*
Negative	172 (58.7%)	61 (20.8%)	233 (79.5%)
Positive	18 (6.1%)	42 (14.3%)	60 (20.5%)
Total	190 (64.8%)	103 (35.2%)	293 (100%)
Cohen's kappa: 0.35 (95%CI 0.24–0.46)			
Left ventricular hypertrophy **Quantitative definition**			
Qualitative definition	Negative	Positive	*Total*
Negative	158 (53.9%)	91 (31.1%)	249 (85.0%)
Positive	14 (4.8%)	30 (10.2%)	44 (15.0%)
Total	172 (58.7%)	121 (41.3%)	293 (100%)
Cohen's kappa: 0.18 (95%CI 0.09–0.28)			
Cardiomegaly and/or left ventricular hypertrophy **Left ventricular hypertrophy** **(comprehensive definition)**			
Cardiomegaly (comprehensive definition)	Negative	Positive	*Total*
Negative	120 (41.0%)	52 (17.7%)	172 (58.7%)
Positive	38 (13.0%)	83 (28.3%)	121 (41.3%)
Total	158 (53.9%)	135 (46.1%)	293 (100%)
Cohen's kappa: 0.38 (95%CI 0.27–0.48)			

*Data from 293 autopsies records.

Table 2.3: Stratum specific prevalence rates of cardiomegaly by autopsy reports.

		Autopsy Findings									
				Cardiomegaly, qualitative definition		Cardiomegaly, quantitative definition		Cardiomegaly, comprehensive definition		Indiana firefighters cohort	
Age (years)	Body mass index	N	(%)	Cases	Prevalence rate %	Cases	Prevalence rate %	Cases	Prevalence rate %	N	(%)
26/35	Normal	18	(6.1)	2	11.1	1	5.6	3	16.7	24	(2.3)
	Overweight	25	(8.5)	2	8.0	4	16.0	6	24.0	79	(7.5)
	Obesity, class I	12	(4.1)	2	16.7	7	58.3	7	58.3	45	(4.3)
	Obesity, class II/III	22	(7.5)	5	22.7	9	40.9	10	45.4	23	(2.2)
36/45	Normal	11	(3.8)	1	9.1	0	0.0	1	9.1	49	(4.6)
	Overweight	43	(14.7)	4	9.3	6	13.9	9	20.9	189	(17.9)
	Obesity, class I	31	(10.6)	3	9.7	12	38.7	12	38.7	119	(11.3)
	Obesity, class II/III	17	(5.8)	6	35.3	9	52.9	10	58.8	42	(4.0)
46/55	Normal	11	(3.8)	1	9.1	0	0.0	1	9.1	32	(3.0)
	Overweight	26	(8.9)	6	23.1	9	34.6	10	38.5	165	(15.7)
	Obesity, class I	18	(6.1)	6	33.3	9	50.0	10	55.6	121	(11.5)
	Obesity, class II/III	20	(6.8)	6	30.0	15	75.0	16	80.0	36	(3.4)
56/65	Normal	8	(2.7)	2	25.0	2	25.0	3	37.5	21	(2.0)
	Overweight	9	(3.1)	2	22.2	4	44.4	4	44.4	50	(4.7)
	Obesity, class I	10	(3.4)	4	40.0	6	60.0	8	80.0	41	(3.9)
	Obesity, class II/III	12	(4.1)	8	66.7	10	83.3	11	91.7	18	(1.7)
Total		293	(100)	60	20.5	103	35.1	121	41.3	1054	(100)
Standardized prevalence rate					19.6		33.8		39.5		

Table 2.4: Stratum specific prevalence rates of LVH by autopsy reports.

		Autopsies' data									
				LVH Qualitative definition		LVH Quantitative definition (1.2cm)		LVH Comprehensive definition		Indiana firefighters cohort	
Age (years)	Body mass index	N	(%)	Cases	Prevalence rate %	Cases	Prevalence rate %	Cases	Prevalence rate %	N	(%)
26/35	Normal	18	(6.1)	0	0.0	7	38.9	7	38.9	24	(2.3)
	Overweight	25	(8.5)	2	8.0	8	32.0	8	32.0	79	(7.5)
	Obesity, class I	12	(4.1)	0	0.0	5	41.7	5	41.7	45	(4.3)
	Obesity, class II/III	22	(7.5)	4	18.2	8	36.4	10	45.5	23	(2.2)
36/45	Normal	11	(3.8)	0	0.0	2	18.2	2	18.2	49	(4.6)
	Overweight	43	(14.7)	5	11.6	10	23.3	11	25.6	189	(17.9)
	Obesity, class I	31	(10.6)	2	6.4	12	38.7	13	41.9	119	(11.3)
	Obesity, class II/III	17	(5.8)	3	17.6	10	58.8	11	64.7	42	(4.0)
46/55	Normal	11	(3.8)	0	0.0	1	9.1	1	9.1	32	(3.0)
	Overweight	26	(8.9)	5	19.2	14	53.8	16	61.5	165	(15.7)
	Obesity, class I	18	(6.1)	3	16.7	11	61.1	11	61.1	121	(11.5)
	Obesity, class II/III	20	(6.8)	10	50.0	14	70.0	17	85.0	36	(3.4)
56/65	Normal	8	(2.7)	2	25.0	2	25.0	4	50.0	21	(2.0)
	Overweight	9	(3.1)	1	11.1	5	55.6	5	55.6	50	(4.7)
	Obesity, class I	10	(3.4)	2	20.0	4	40.0	5	50.0	41	(3.9)
	Obesity, class II/III	12	(4.1)	5	41.7	8	66.7	9	75.0	18	(1.7)
Total		293	(100)	44	15.0	121	41.3	135	46.1	1054	(100)
Standardized prevalence rate					13.7		41.5		45.5		

Table 2.5: Stratum specific prevalence rates of cardiomegaly by autopsy reports with a sensitivity analysis assuming a BMI=27 kg/m^2 for records with missing information.

		Autopsy Findings									
				Cardiomegaly qualitative definition		Cardiomegaly quantitative definition		Cardiomegaly comprehensive definition		Indiana firefighters cohort	
Age (years)	Body mass index	N	(%)	Cases	Prevalence rate %	Cases	Prevalence rate %	Cases	Prevalence rate %	N	(%)
26/35	Normal	18	5.1	2	11.1	1	5.6	3	16.7	24	(2.3)
	Overweight	44	12.5	3	6.8	6	13.6	8	18.2	79	(7.5)
	Obesity, class I	12	3.4	2	16.7	7	58.3	7	58.3	45	(4.3)
	Obesity, class II/III	22	6.2	5	22.7	9	40.9	10	45.4	23	(2.2)
36/45	Normal	11	3.1	1	9.1	0	0.0	1	9.1	49	(4.6)
	Overweight	62	17.6	5	8.1	8	12.9	12	19.3	189	(17.9)
	Obesity, class I	31	8.8	3	9.7	12	38.7	12	38.7	119	(11.3)
	Obesity, class II/III	17	4.8	6	35.3	9	52.9	10	58.8	42	(4.0)
46/55	Normal	11	3.1	1	9.1	0	0.0	1	9.1	32	(3.0)
	Overweight	44	12.5	8	18.2	12	27.3	14	31.8	165	(15.7)
	Obesity, class I	18	5.1	6	33.3	9	50.0	10	55.6	121	(11.5)
	Obesity, class II/III	20	5.7	6	30.0	15	75.0	16	80.0	36	(3.4)
56/65	Normal	8	2.3	2	25.0	2	25.0	3	37.5	21	(2.0)
	Overweight	13	3.7	5	38.5	7	53.8	8	61.5	50	(4.7)
	Obesity, class I	10	2.8	4	40.0	6	60.0	8	80.0	41	(3.9)
	Obesity, class II/III	12	3.4	8	66.7	10	83.3	11	91.7	18	(1.7)
Total		353	(100)	67	19.0	113	32.0	134	38.0	1054	(100)
Standardized prevalence rate					19.3		32.7		38.5		

Table 2.6: Stratum specific prevalence rates of LVH by autopsy reports with a sensitivity analysis assuming a BMI=27 kg/m^2 for records with missing information.

		Autopsy data									
				LVH Qualitative definition		LVH Quantitative definition (1.2cm)		LVH Comprehensive definition		Indiana firefighters cohort	
Age (years)	Body mass index	N	(%)	Cases	Prevalence rate %	Cases	Prevalence rate %	Cases	Prevalence rate %	N	(%)
26/35	Normal	18	5.1	0	0.0	7	38.9	7	38.9	24	(2.3)
	Overweight	44	12.5	3	6.8	9	20.5	10	22.7	79	(7.5)
	Obesity, class I	12	3.4	0	0.0	5	41.7	5	41.7	45	(4.3)
	Obesity, class II/III	22	6.2	4	18.2	8	36.4	10	45.4	23	(2.2)
36/45	Normal	11	3.1	0	0.0	2	18.2	2	18.2	49	(4.6)
	Overweight	62	17.6	7	11.3	14	22.6	15	24.2	189	(17.9)
	Obesity, class I	31	8.8	2	6.4	12	38.7	13	41.9	119	(11.3)
	Obesity, class II/III	17	4.8	3	17.6	10	58.8	11	64.7	42	(4.0)
46/55	Normal	11	3.1	0	0.0	1	9.1	1	9.1	32	(3.0)
	Overweight	44	12.5	6	13.6	17	38.6	20	45.4	165	(15.7)
	Obesity, class I	18	5.1	3	16.7	11	61.1	11	61.1	121	(11.5)
	Obesity, class II/III	20	5.7	10	50.0	14	70.0	17	85.0	36	(3.4)
56/65	Normal	8	2.3	2	25.0	2	25.0	4	50.0	21	(2.0)
	Overweight	13	3.7	2	15.4	9	69.2	9	69.2	50	(4.7)
	Obesity, class I	10	2.8	2	20.0	4	40.0	5	50.0	41	(3.9)
	Obesity, class II/III	12	3.4	5	41.7	8	66.7	9	75.0	18	(1.7)
Total		353	(100)	49	13.9	133	37.7	149	42.2	1054	(100)
Standardized prevalence rate					12.8		38.8		42.7		

CHAPTER 3: Body Mass Index predicts Left Ventricular Mass in Career Male Firefighters

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Abstract

Objective: Left ventricular mass (LVM) is a strong predictor of cardiovascular disease (CVD) events; increased LVM is common among US firefighters; and plays a major role in firefighter sudden cardiac death (SCD). We aim to identify significant predictors of LVM among firefighters.

Methods: Cross-sectional study of 400 career male firefighters selected by an enriched randomization strategy. Weighted analyses were performed based on the total number of risk factors per subject with inverse probability weighting. LVM was assessed by echocardiography (ECHO) and cardiac magnetic resonance (CMR), and normalized (indexed) for height. CVD risk parameters included resting vital signs, body mass index (BMI)-defined obesity, risk of obstructive sleep apnea (OSA), low cardiorespiratory fitness (CRF), self-reported hypertension (HTN) and physical activity. Linear regression models were performed.

Results: In multivariate analyses, BMI was the only consistent significant independent predictor of LVM indices (all, $p<0.001$). A 1-unit decrease in BMI was associated with 1 unit ($kg/m^{1.7}$) reduction of LVM/ height $^{1.7}$ after adjustment for age, HTN, OSA risk and cardiorespiratory fitness.

Conclusions: After height-indexing ECHO- and CMR-measured LVM, BMI was found to be a major driver of LVM among firefighters. Our findings taken together with previous research suggest that reducing obesity will improve CVD risk profiles and decrease on-duty CVD and SCD events in the fire service. Our results also support targeted noninvasive screening for LVH with ECHO among obese firefighters.

Keywords: firefighters, body mass index, left ventricular mass index, echocardiography, cardiac MRI

Background

Cardiovascular disease (CVD) is the leading cause of on-duty death among firefighters (45% of on-duty fatalities) and a major cause of morbidity. Moreover, 905 nonfatal on-duty CVD events were reported in 2014, such that for every fatal on-duty CVD event, there are an estimated 25 additional nonfatal events.[1,2] As in the general population, these cardiovascular events are largely due to coronary heart disease (CHD), [3-6] however, there is an increasing recognition of the role of left ventricular hypertrophy (LVH)/cardiomegaly in the risk of sudden cardiac death (SCD) independent of the presence of CHD.[7-10]

It is crucial to note though, that the risk of on-duty CVD events is not evenly distributed among all firefighters, but is highly concentrated among the most susceptible individuals. [3,11] On-duty CVD events and heart disease retirements occur primarily in firefighters with underlying disease (known or subclinical) or excess cardiovascular risk factors. [12-14] Thus, considering that firefighting is an inherently dangerous occupation and many of its hazards cannot be engineered out of the job[15], key prevention questions focus on what can make an individual firefighter susceptible as well as what is the prognostic value of the known CVD risk factors.

LVH/cardiomegaly is a structural abnormality of the heart[16,17] and appears to be a key pen-ultimate and predisposing step on the causal pathway that makes a firefighter susceptible to CVD events.[3,14,18] LVH/cardiomegaly has been widely recognized to increase the risk of lethal ventricular arrhythmias, myocardial infarction and stroke; and it is a proven predictor of CVD and overall mortality in the general population, but it has not been adequately researched in the fire service.[19-23] Current evidence from studies based on autopsies from active career firefighters indicates that LVH/cardiomegaly is common among US firefighters, often co-morbid with CHD

and plays a major role in CVD events and SCD risk in the fire service. [12,24]

Evidence suggests an improved prognostic value, when LVH is based on the accurate assessment of Left Ventricular Mass (LVM).[25] LVM has been also shown to be a strong predictor of cardiovascular events among individuals without[20,26,27] and with prior coronary heart disease[28,29] and those with heart failure[16,30]. An increase in LVM is associated with a higher incidence of cardiovascular events, including death, while a decrease is a marker of lower risk for cardiovascular events, especially among patients on anti-hypertensive treatment.[31,32]

Despite the critical prognostic significance of LVM, its measurement and role in clinical practice have yet to be established. [33] Echocardiography (ECHO) and cardiac magnetic resonance (CMR) are the two most commonly used imaging modalities for the assessment of LVM. Even though, CMR is considered the gold-standard for assessing LVM, ECHO is a well validated, non-invasive method that is more widely used in clinical practice.[34] In addition to considering different imaging modalities, disagreement exists as to the most appropriate method of indexing LVM to body size parameters. [25] Current evidence suggests indexing by height to the allometric powers of 1.7 and 2.7 are the most accurate normalization techniques. [33,35,36]

The aim of this paper is to identify the most important predictors of LVM after indexing for height among career male firefighters as assessed by both ECHO and CMR.

Methods

Study Population

Male career firefighters, aged 18 years and older were recruited from the Indianapolis Fire Department (IFD). Eligible firefighters had a recorded fire department-sponsored medical exam in the last two years that included a submaximal exercise tolerance test, and had no restrictions on duty.

From those eligible, we selected a total of 400 participants, utilizing an "enriched" randomization strategy based on age at randomization, obesity, hypertension (HTN) and cardio-respiratory fitness (CRF) status at last examination, where a larger number of higher risk participants could be selected. Thus, we randomly selected: 100 participants from the entire eligible population; 75 low-risk participants (age <40, non-obese, free of HTN and high CRF) and 225 higher risk participants (at least 2 of the following: age >/=40, obese, HTN or low CRF) for further LVH/cardiomegaly screening and imaging tests. Obesity was defined by standard criteria (BMI >/=30 kg/m^2). Hypertension was considered present if resting blood pressure is >/=140/90 mm Hg. Low CRF was defined as the bottom tertile, as measured by the recorded treadmill time and the estimated maximal VO_2 during the last exercise test. Those selected were included in the study if they had no contraindication to CMR and signed informed consent to participate.

Left Ventricular Mass

LVM was assessed by both ECHO and CMR imaging. First, a transthoracic cardiac echocardiogram was done as a simple two-dimensional (2-D) study with limited m-mode recordings. An abbreviated cardiac MRI (CMR) was performed as "function only" immediately

after the ECHO. Images were obtained using a retrospectively EKG gated steady-state free precession cine sequence. In this fashion, a contiguous short axis stack of 8 mm slices was obtained parallel to the atrioventricular groove to cover the entire length of the LV. Then, manual tracing of end-diastolic epicardial and endocardial borders was performed. Standard long axis views were also obtained including horizontal long axis, vertical long axis, and 3-chamber views, facilitating the interpretation of ventricular function. Board certified specialists performed clinical interpretation of imaging. LVM indices were derived by dividing LVM in kilograms with height to the allometric powers of 1.7 and 2.7 (in meters$^{1.7}$ and meters$^{2.7}$, respectively).

Assessment of Cardiovascular Risk Factors

Height was measured in the standing position with a clinic stadiometer. Body weight was measured with bare feet and in light clothes on a calibrated scale. BMI was calculated as the weight in kilograms divided by the square of height in meters. Blood pressure was measured using an appropriately sized cuff with the subject in the seated position. Heart rate and blood pressure were obtained in a resting state from the physical examination (and were not measured prior to the exercise test). Medical exam data were further supplemented by a pre-imaging questionnaire, which collected comprehensive information on smoking status, personal history of heart rhythm problems, family history of cardiac problems, self-reported HTN and moderate to vigorous physical activity level in minutes per week. High OSA risk was assessed using the widely used and validated Berlin Questionnaire.[37]

Statistical Analysis

We performed a weighted analysis so as to account for our enriched randomization sampling strategy. Weights were calculated based on the total number of risk factors per subject with the technique of inverse probability weighting (Appendix table 3.1). Baseline characteristics were described using the mean (SD) in the case of quantitative variables and the frequency (%) for categorical variables. The effects of the different independent variables on the LVM indices were assessed with the use of linear regression models. Any independent variables that were significant in the univariate regression models were included in the multivariate regression models. In the multivariate analysis, we followed the backward stepwise elimination process with a removal criterion of alpha=0.20. Then, considering the predictors that resulted from the backward elimination process and variables that we knew *a priori* to be important clinical predictors, we constructed the final multivariate regression models. The interaction effects between BMI with OSA and age were also assessed in these models. Collinearity was evaluated using the variance inflation factor. Analyses were performed using SPSS version 21.0 (IBM, Armonk, New York). A p-value of < 0.05 was considered statistically significant and all tests performed were two-sided.

Results

Out of the 400 firefighters, we excluded 7 participants with missing measurements of LVM, assessed by CMR. Baseline characteristics are summarized in Table 3.1. The mean age of the study subjects was 45.3 (8.1) years and their mean BMI was 30.3 (4.5) kg/m^2. There were 41.3% with a family history of cardiac problems, 44.8% were obese, 31.6% had high risk of OSA and 34.3% had low CRF. The mean LVM measured was 186.9 (36.6) grams by ECHO, and 137.6 (23.4) grams by CMR, respectively.

Table 3.1: Baseline descriptive characteristics.

Variables	Study Sample (N= 393)	Study Sample Weighted
Age years †	46.5 ± 8.2	45.3 ± 8.1
Height inches †	70.3 ± 2.5	70.3 ± 2.6
Heart Rate bpm †	80.5 ± 13.4	79.5 ± 13.0
Resting SBP mmHg †	126.3 ± 9.7	125.2 ± 9.4
Resting DBP mmHg †	81.8 ± 8.1	81.3 ± 7.4
Self-reported HTN *	95 (24.7)	225 (21.6)
High Risk of OSA *	112 (38.1)	254 (31.6)
Body Mass Index kg/m^2 †	31.1 ± 4.6	30.3 ± 4.5
Smoking *	50 (13.0)	135 (12.9)
Personal History of Heart Rhythm Problems *	60 (15.7)	153 (14.7)
Family History of cardiac problems*	153 (40.2)	426 (41.3)
Age >= 40 years *	301 (78.2)	770 (72.7)
BMI>= 30 kg/m^2 *	260 (56.1)	474 (44.8)
Low CRF *	178 (46.7)	363 (34.3)
MVPA Physical Activity min/week †	177.4 ± 117.3	187.3 ± 117.7
LVM_ECHO g †	189.0 ± 38.1	186.9 ± 36.6
LVM_CMR g †	139.2 ± 24.0	137.6 ± 23.4
LVM_ECHO indexed to $height^{1.7}$ g †	70.4 ± 13.3	69.7± 12.9
LVM_ECHO indexed to $height^{2.7}$ g †	39.5 ± 7.6	39.1 ± 7.4
LVM_CMR indexed to $height^{1.7}$ g †	52.0 ± 8.3	51.4 ± 8.1
LVM_CMR indexed to $height^{2.7}$ g †	29.2 ± 4.7	28.8 ± 4.6

SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; OSA, obstructive sleep apnea; BMI, body mass index; CRF, cardiorespiratory fitness; MVPA, Moderate to Vigorous Physical Activity; LVM, left ventricular mass; ECHO, echocardiography; CMR, cardiac magnetic resonance. † Mean (SD) for continuous variables; * n (%) for categorical variables. Low CRF was defined as the lowest tertile, as measured by the recorded treadmill time and the estimated maximal VO_2 during the last exercise test.

The univariate analyses revealed highly statistically significant associations between both LVM height indices, assessed by both ECHO and CMR, with resting SBP, HTN, high risk of OSA, low CRF and BMI (all $p<0.01$). Age, family history of cardiac problems and physical activity also showed a significant association with both LVM indices, when LVM was based on ECHO measurement (at least $p<0.01$).

In all 4 models evaluated, namely with LVM assessed by ECHO or CMR and normalized with height to either 1.7 or 2.7, only BMI was consistently associated with LVM in a statistically significant fashion ($p<0.001$) in all multivariate models. Family history of cardiac problems and smoking were also statistically significant predictors in the models, where LVM was assessed by ECHO or by CMR, respectively, following the backward stepwise elimination process.

Final multivariate regression models showing the associations between the statistically and clinically significant predictors of LVM are summarized in Table 3.3. The proportion of the variability in LVM normalized for height explained by our models ranged from 12.5% to 23.9%. In the final models, a 1-unit decrease in BMI was associated with 1 unit ($kg/m^{1.7}$) reduction of LVM/ height $^{1.7}$ after adjustment for age, HTN, OSA risk and cardiorespiratory fitness.

Table 3.2: Simple Linear Regression Models of Cardiovascular Risk factors and LVM assessed by ECHO and CMR and normalized for height to allometric powers of 1.7 and 2.7 as Continuous Variable.

	Assessed by ECHO				Assessed by CMR			
	Model 1[a]		Model 2[b]		Model 3[a]		Model 4[b]	
	β (SE)	P	β (SE)	p	β (SE)	p	β (SE)	p
Age, years	0.11 (0.1)	0.02*	0.10 (0.0)	<0.01*	0.01 (0.1)	0.8	0.03 (0.0)	0.18
Heart Rate, bmp	-0.01 (0.03)	0.78	-0.02 (0.0)	0.33	-0.02 (0.0)	0.34	-0.02 (0.0)	0.08
Resting SBP, mmHg	0.13 (0.04)	<0.01*	0.08 (0.0)	<0.01*	0.17 (0.0)	<0.01*	0.10 (0.0)	<0.01*
Resting DBP, mmHg	-0.002 (0.1)	0.97	0.002 (0.0)	0.96	0.14 (0.1)	<0.01*	0.08 (0.0)	<0.01*
Self-reported HTN, %	5.23 (0.97)	<0.01*	3.08 (0.6)	<0.01*	3.44 (0.6)	<0.01*	2.05 (0.4)	<0.01*
High risk of OSA, %	5.64 (0.99)	<0.01*	3.12 (0.6)	<0.01*	3.90 (0.6)	<0.01*	2.20 (0.3)	<0.01*
Body Mass Index, kg/m^2	0.95 (0.1)	<0.01*	0.51 (0.1)	<0.01*	0.86 (0.1)	<0.01*	0.46 (0.0)	<0.01*
Smoking, %	-2.62 (1.2)	0.03*	-1.3 (0.7)	0.05*	-1.11 (0.77)	0.15	-0.63 (0.4)	0.15
Personal History of Heart Rhythm Problems, %	-2.68 (1.2)	0.02*	-1.48 (0.6)	0.02*	-0.98 (0.75)	0.19	-0.57 (0.4)	0.19
Family History of cardiac problems, %	3.26 (0.8)	<0.01*	2.01 (0.5)	<0.01*	0.07 (0.6)	0.89	0.24 (0.5)	0.44
Low CRF, %	3.24 (0.8)	<0.01*	1.94 (0.5)	<0.01*	1.53 (0.6)	<0.01*	0.95 (0.3)	<0.01*
MVPA Physical Activity, min/week	-0.02 (0.0)	<0.01*	-0.01 (0.0)	<0.01*	-0.002(0.0)	0.46	-0.001 (0.0)	0.28

bpm: beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; OSA, obstructive sleep apnea; CRF, cardiorespiratory fitness; MVPA, Moderate to Vigorous Physical Activity. * statistically significant p-values.

a. LVM normalized for height to the allometric power of 1.7.

b. LVM normalized for height to the allometric power of 2.7

Table 3.3: Multivariate Linear Regression Models of Cardiovascular Risk factors and LVM assessed by ECHO and CMR and normalized for height to allometric powers of 1.7 and 2.7 as Continuous Variable.

	Assessed by ECHO				Assessed by CMR			
	Model 1[a]		Model 2[b]		Model 3[a]		Model 4[b]	
R^2	0.134		0.125		0.239		0.215	
	***β* (SE)**	**P**	***β* (SE)**	**p**	***β* (SE)**	**p**	***β* (SE)**	**p**
Age, years	0.04 (0.1)	0.52	0.07 (0.0)	0.07	0.02 (0.0)	0.56	0.04 (0.0)	0.05
Self-reported HTN	1.06 (1.2)	0.37	0.66 (0.7)	0.34	1.29 (0.7)	0.05	0.76 (0.4)	0.05
High risk of OSA	0.76 (1.1)	0.49	0.36 (0.6)	0.57	0.15 (0.6)	0.81	0.11 (0.4)	0.76
Body Mass Index, kg/m^2	1.01 (0.1)	<0.001*	0.55 (0.1)	<0.001*	0.83 (0.1)	<0.001*	0.45 (0.0)	<0.001*
Low CRF	-0.23 (1.0)	0.83	-0.34 (0.6)	0.57	-0.96 (0.6)	0.1	-0.70 (0.3)	0.05

a. LVM normalized for height to the allometric power of 1.7.

b. LVM normalized for height to the allometric power of 2.7

Discussion

The present cross-sectional study in US firefighters using ECHO and CMR measurements found BMI to be the strongest and most consistent independent predictor of LVM indexed by height to the allometric powers of 1.7 and 2.7. In simple linear regression models, apart from BMI, the associations were highly statistically significant for self-reported HTN, high risk of OSA, resting SBP and low CRF consistently in all four models ($p<0.01$). In multivariate models, however, while following the stepwise backward elimination process, except for BMI, other conventional CVD risk factors such as family history of cardiac problems and smoking, were significant predictors of LVM. However, in all 4 models, the effect of BMI was the only consistently significant predictor, even after adjustment for age, HTN, high risk of OSA and low cardiorespiratory fitness. Therefore, our study clearly supported BMI as a major determinant of LVM.

Given the epidemic level of obesity in the US fire service, it is not surprising that we found BMI to be the strongest predictor of LVM in this population. This is consistent with the literature, which finds obesity to be a risk factor for LVH and increased cardiac mass.[3,24] Additionally, given that obesity is associated with CVD risk factor clustering[38,39], it probably explains why other factors like blood pressure and OSA risk were weaker predictors in multivariate models because their association with LVM may be closely linked to their association or co-morbidity with obesity.[18] Given our previous findings that obesity-associated SCD among younger firefighters was largely driven by an increased cardiac mass in SCD victims compared to controls,[40] our results reinforce that decreasing obesity in the fire service will improve firefighters' cardiovascular risk profiles, including their risk of LVH and on-duty CVD events, particularly SCD. Even small reductions on BMI may produce significant beneficial effects on

metabolic syndrome and other CVD risk factors. [41,42] Our results suggest that a 1-unit decrease in BMI, will reduce the index of LVM with height to the allometric power of 1.7 by 1 unit ($kg/m^{1.7}$) even after adjustment for age, self-reported HTN, high risk of OSA and low cardiorespiratory fitness.

The results for the cohort's baseline characteristics, especially for BMI, OSA and CRF are concerning. Almost 32% of the cohort screened at high risk of OSA, and more than one third had low CRF. We attribute these findings to the fact that almost half of the study participants were obese. However, after adjusting for our weighted sampling, our prevalence estimates of obesity, high risk of OSA and low CRF remain high and in general agreement with results from previously published literature on the US Fire Service. [11,38,43]

LVM measurements by ECHO were on average 49.3 grams higher than those by CMR. This finding is in line with current evidence, which suggests that CMR consistently yields lower average values compared to ECHO values for the same subjects.[44,45] This suggests the urgent need for reference ranges adjustments for ECHO and CMR LVM estimates, respectively.

Based on the values of R^2 for our final multivariate regression models, we were able to explain 12.5% to 13.4% of the variability of LVM indexed by height to the allometric powers of 1.7 and 2.7 based on ECHO assessments and 21.5% to 23.9% based on CMR assessments. The models of the LVM when normalized with $height^{1.7}$ yielded the best prediction within each imaging technique. Our models' predictive ability is in line with the observed ranges for the explained variability of LVM. [46] We were in fact able to explain 10% more of the LVM variability with the CMR models as compared to ECHO ones, irrespective of the indexation technique. This is likely explained by the fact that CMR measurements are more standardized across techniques and

institutions, and less dependent on operator's skill and experience, acoustic window adequacy and LVM geometric assumptions.[25,47]

Our study has some modest limitations. Because of its cross-sectional design, we can only demonstrate associations and not causation, however, the findings are consistent with past studies[48] and are biologically plausible. Also, because of the very small number of participating women firefighters in our study, only male participants were included in the present study.

Our study also has a number of important strengths. We were able to collect comprehensive data on CVD risk factors from both medical examinations and a screening questionnaire. The BMI was measured during medical examinations, which avoided self-reporting biases towards lower weights and taller heights and any other random misclassification. In addition, risk of OSA was assessed by the widely used and validated Berlin Questionnaire, which has high sensitivity and specificity (86% and 77%, respectively), and demonstrates a high yield in public safety occupations.[11,37] Moreover, we used imaging results for LVM by both ECHO and CMR, which boosted the clinical significance and applicability of our results across cardiology laboratories. Another important strength of our study is that we normalized LVM by height to two different allometric powers, which allowed us to perform a more holistic assessment of its potential predictors, considering that height is the parameter suggested as the most accurate for normalization purposes. Furthermore, our results were consistent among the imaging modalities and the indexing methods, making our findings more robust. Finally, even though we used the enriched randomization sampling technique, our sample had similar anthropometric characteristics and CVD risk factors to those found in other epidemiologic studies of firefighters.[38,39,49] Therefore, we believe that our results could be generalized to most male career firefighters.

In conclusion, after normalizing ECHO- and CMR-measured LVM for height, BMI was the strongest independent determinant of LVM among male career firefighters. Previous research in the fire service has found that SCD among younger firefighters was largely driven by an increased cardiac mass in SCD victims as compared to controls, with 2/3 of SCD victims to be obese. Taken together with previous research our current findings suggest that reducing obesity will decrease the risk of LVH and therefore, reduce on-duty CVD and SCD events in the fire service. Our findings also support targeted noninvasive screening for LVH with ECHO among obese firefighters.

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Appendix

Table 3.1: Distribution of Risk Factors and calculation of weights based on Inverse Probability Weighting.

Number of Risk Factors	Study sample N (%)	Study base N (%)
0	48 (12.6)	161 (15.20)
1	82 (21.5)	367 (34.66)
2	122 (32.0)	298 (28.14)
3	103 (27.0)	172 (16.24)
4	26(6.8)	61 (5.76)
Weights per number of Risk Factors		
	Sampling Fractions	**Weights (Probability)**
0	48/161	161/48 (3.354)
1	82/367	367/82 (4.475)
2	122/298	298/122 (2.443)
3	103/172	172/103 (1.670)
4	26/61	61/26 (2.346)

Summary and Conclusions

The goals of this dissertation were: 1) to evaluate Left Ventricular Hypertrophy (LVH)/Cardiomegaly and assess how the different non-invasive screening as well as forensic methods and reference ranges can affect distinctions between disease states and normality; 2) to provide more definitive prevalence estimates of cardiac enlargement among US firefighters; and 3) to identify the most significant clinical predictors of Left Ventricular Mass (LVM) in this special occupational cohort. The findings of this work were extremely promising, suggesting LVM normalized by height to an allometric power to be the most appropriate method of assessing LVH among the US firefighters. In addition, considering their current CVD risk profiles, the work highlights body mass index (BMI) as an independent predictor that drives LVM, heart weight and LV wall thickness, and therefore, supports reducing obesity in the US fire service as a means to prevent on-duty CVD events.

The results of Chapter One indicated that even though LVH/Cardiomegaly is well-recognized as a significant clinical and epidemiologic marker of CVD, its assessment by measuring LVM demonstrates wide variability depending critically on the choice of the normalization technique, the imaging modality and the cutoff values, thus calling for an urgent need of standardization. In addition, Chapter One showed that echocardiography (ECHO) remains the most widely used diagnostic tool for the assessment of LVH, while it also emphasized that few direct comparisons between imaging and autopsies studies exist, with methods that are currently not cross-standardized; and the paucity of autopsy data that could further facilitate direct comparisons between the mass of the left ventricle

and the total cardiac mass. Overall, Chapter One highlighted the need for standardization of the definition of LVH/Cardiomegaly and for conducting forensic studies that will facilitate direct comparisons with imaging, as well as update the reference ranges for total heart weight in light of the contemporary population's changes in height and weight.

Chapter Two demonstrated a wide range of prevalence estimates of cardiac enlargement within and between imaging modalities according to the different criteria utilized, and indicated BMI as a major driver of heart weight. Therefore, the results from Chapter Two indicate that the choices of clinicians and researchers of imaging modalities, the normalization on indexing technique and the reference ranges, not only can critically affect the accurate determination of cardiac enlargement in the US fire service, but also create challenges in general clinical practice. The results from this study also suggest the need of outcomes' based research that will define the best cutoffs as well as the standardization of autopsy report forms across protocols and jurisdictions.

Chapter Three revealed BMI as the most significant and only consistent independent predictor of LVM normalized for height to the allometric powers of 1.7 and 2.7, by both ECHO and CMR measurements. In addition, a 1-unit decrease in BMI was associated with 1 unit reduction of the LVM indexed to height$^{1.7}$, even after adjustment for CVD risk factors. Previous research in the fire service has found that SCD among younger firefighters was largely driven by an increased cardiac mass in SCD victims compared to controls, with 2/3 of SCD victims to be obese. Results from Chapter Three indicate BMI as a major driver of LVM. Thus, decreasing obesity among firefighters will lead to a decrease in the risk of LVH and in turn reduce on-duty CVD and SCD events in the fire

service.

Taken together, the work in this dissertation suggests the urgent need of standardization of cardiac enlargement definitions that will further facilitate the establishment of its role in clinical practice and will in turn lead to an accurate determination of LVH/cardiomegaly in the US fire service. Given previous findings that obesity-associated SCD among firefighters was largely driven by an increased cardiac mass in SCD victims compared to controls, our results reinforce that decreasing obesity in the fire service will improve firefighters' cardiovascular risk profiles, including their risk of LVH and significantly reduce on-duty CVD events, particularly SCD. Moreover, results from chapter Three support BMI as a major driver of LVM, while results from Chapter Two suggest that BMI is driving heart weight and LV wall thickness. Chapter One suggests that LVM accounts for a greater proportion of total heart weight in diseased hearts compared to controls, and therefore, collectively our work suggests targeted noninvasive screening for LVH with ECHO among obese firefighters.

We believe that future studies are needed to validate the assessment of LVH/Cardiomegaly based on the LVM normalized by height to the allometric power of 1.7, and to identify the reference values that would be most appropriate for US firefighters considering the special CVD risk profiles of this occupational cohort. Moreover, future forensic studies are needed to directly compare total cardiac mass to left ventricular mas, in order to establish a firm relationship between the two. Finally, we suggest that future prospective studies of CVD events are needed to show that BMI is the most significant and useful prognostic indicator of LVM, and therefore, likely CVD

susceptibility within the US fire service. We hope that this work has contributed valuable information to the scientific community and will lead the way forward to improved health and employment outcomes among firefighters in the US.