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Prevalence of undocumented cardiovascular disease in male and female cadaveric donors

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Abstract
Current mortality statistics reveal that cardiovascular disease (CVD) is the leading cause of death worldwide, contributing to 1 out of every 3 deaths. Most diagnoses are based on medical history, but autopsy is the gold standard in identifying the precise cause of death and contributing factors. However, in the USA, the current autopsy rate is only 8%, suggesting that many individuals thought to be unaffected by CVD may possess cardiovascular risk factors contributing to their cause of death. Medical record examination of 41 cadaveric donors revealed that 49% possessed at least one form of CVD. In contrast, gross examination revealed mild to severe CVD in 98% of donors, with a higher prevalence of undocumented CVD detected in female donors. These results suggest that an abundance of CVD remains undetected in the absence of conventional autopsy, indicating that the prevalence of CVD may be much higher than what is commonly accepted.

Keywords: cardiovascular disease, autopsy, cadaver, hypertrophic cardiomyopathy, dilated cardiomyopathy

1. Introduction
Cardiovascular disease (CVD) encompasses a variety of conditions including myocardial infarction, stroke, hypertension, heart disease, and others. According to the American Heart Association (AHA), nearly half of all adults in the US are affected by some form of CVD [1]. These conditions can be identified as the underlying cause of death in approximately 1 out of every 3 cases, amounting to 836,546 deaths per year in the US and 17.8 million deaths per year globally, making CVD the leading cause of death both in the US and worldwide [2-3]. These numbers alone are compelling, but research suggests that there may be a population of individuals possessing undiagnosed CVD which remains unknown even after death. Current statistics for CVD as an underlying cause of death or significant health condition are based on medical history and diagnosed cases; however, autopsy is considered the gold standard for determining the exact cause of death through confirmation of pre-mortem diagnoses or identification of undiagnosed conditions [4-6]. Current autopsy rates have progressively declined over the past several decades, dropping from one in every five deaths receiving an autopsy in the 1970s to a mere 8% in 2007 [6,7]. Advanced diagnostic tools allowing for more accurate pre-mortem diagnoses are thought to be the cause of this drastic decline [4,8], but current research has demonstrated that these pre-mortem evaluations may prove insufficient for a precise diagnosis of an individual's cause of death [9]. While medical imaging allows for some level of diagnosis and detection, these techniques cannot provide the same depth and specificity obtained through postmortem gross and histologic examination. Previous studies have suggested that many risk factors for CVD go undetected in the absence of a conventional autopsy, indicating that the prevalence of CVD as an underlying cause of death (COD) or significant medical condition may be much higher than what is commonly accepted. Since only 8% of all deaths receive an autopsy [6], there remains 92% of the population whose stated cause of death may be inaccurate or incomplete. Two-thirds of these people are presumed to be unaffected by CVD [2], but in the absence of an autopsy, this can neither be confirmed nor denied. Therefore, these individuals may possess unknown CVD risk factors contributing to their cause of death which are never revealed due to the absence of a conventional autopsy. The possibility of undiagnosed CVD in these individuals is significant since many forms of CVD are familial in nature and therefore were likely passed on to future generations unaware of their risk for developing CVD [10, 11]. Hypertrophic and dilated cardiomyopathies are two forms of familial CVD which are inherited in an autosomal dominant manner and are associated with many genetic variants affecting various cytoskeletal and sarcomeric proteins [12-15]. Without knowledge of their predisposition towards CVD, individuals may remain ignorant of these diseases in their early stages when preventative measures would be most effective [16]. In order to facilitate methods of early diagnosis and treatment, individuals must be aware of the genetic predispositions they possess; ignorance may contribute to increased incidence of CVD-related death and disease.

2. Materials and methods
This study examined hearts from 18 male and 23 female adult human cadavers routinely utilized in gross anatomy dissection courses in the Department of Biology and Chemistry at Liberty University in Lynchburg, VA, USA. The hearts were removed from the mediastinum by removing the pericardial sac and cutting through the ascending aorta, pulmonary trunk, superior vena cava, inferior vena cava, and pulmonary veins [17]. A longitudinal incision was then made through the entire heart to reveal all four chambers. Gross morphology was observed to reveal any abnormalities. The left ventricular wall thickness was measured 1.5cm below the mitral valve hinge line, as described by Ho *et al* [18]. Hearts were classified as normal if they possessed a left ventricular thickness of 12-15mm, with values greater than 15mm classified as hypertrophic and values less than 12mm classified as dilated. Measurements

of right ventricular wall thickness were taken in the upper one-third of the distance between the tricuspid valve annulus and the right ventricular apex, as described by Ho *et al* [19]. Hearts with a right ventricular thickness of 3-5mm were classified as normal, with values greater than 5mm classified as hypertrophic and values less than 3mm classified as dilated, excluding trabeculations [19] (Table 1). These classification standards were utilized for all heart sample measurements; however, it was noted that for 4 samples, these standard measurements for right-side cardiomyopathy designated them as hypertrophic or normal, while gross observation displayed severe dilation, suggesting that revision of right-sided cardiomyopathy classification methods may be advisable for more accurate identification.

3. Results & Discussion

Many studies have demonstrated that the cause of death (COD) included on an individual's death certificate is often inaccurate or significantly incomplete, lacking pertinent medical information which likely played a significant role in the individual's cause of death. Ravakhah *et al.* compared death certificates with autopsy reports in 223 cases and revealed that cardiovascular disease was frequently underreported and misdiagnosed [4]. More recently, Mieno *et al* analyzed 562 autopsy reports and discovered that 115 disagreed completely with the stated cause of death. This study further demonstrated that within patients confirmed through autopsy to possess heart disease as their cause of death, only 60% had been correctly identified on their death certificate as having died of heart disease, while the remaining 40% had been assigned an inaccurate or incomplete diagnosis [20]. These studies suggest that postmortem diagnoses assigned in the absence of an autopsy may be unreliable or incomplete, and that CVD may affect a larger percentage of the population than currently supposed. Our examination of 41 cadaveric donor hearts revealed similar results. Examination of donor medical records revealed that 20 donors possessed CVD either as their primary cause of death or as a secondary medical condition (Table 2). However, autopsy examination of all 41 donors revealed the presence of mild to severe CVD in 40 individuals, confirming the presence of CVD in the 20 diagnosed individuals and revealing the presence of undocumented CVD in 20 of the remaining donors. Therefore, whereas the prevalence of CVD in these donors according to death certificate information was only 49%, autopsy examination revealed that this value may be as high as 98%, supporting the concern that many forms of CVD remain undiagnosed in the absence of autopsy examination. Previous studies have also revealed that cardiomyopathies are consistently underreported. None of the death certificates examined by Ravakhah *et al* indicated cardiomyopathy as the cause of death**,** but autopsy examination revealed that 5% of those patients had died as a result of cardiomyopathies [4]. In our study, further evaluation of donor health records revealed that of the donors possessing documented CVD, 11 had been diagnosed specifically with heart disease, either as a cause of death or as an underlying health condition. In contrast, gross examination revealed features characteristic of various heart disease forms such as hypertrophic and dilated cardiomyopathy (Figure 1) in 39 donors. This suggests a 95% prevalence of heart disease in cadaveric donors as opposed to the 27% possessing heart disease according to medical records (Table 2). Of the 39 donors observed to possess ventricular measurements consistent with cardiomyopathy, 8 displayed strictly left-sided cardiomyopathy, 6 displayed right-sided cardiomyopathy, and 25 donors possessed cardiomyopathies affecting the entire heart (Table 3). These findings confirm previous studies suggesting that heart disease is frequently under-diagnosed, making it likely that many individuals may possess undiagnosed cardiomyopathies. Assessment of CVD in male donors compared with female donors revealed that female donors were more likely to possess undocumented CVD (Table 4). 61% of male donors possessed CVD as a primary or secondary health condition according to documented health records, but only 39% of female donors possessed documented CVD. However, autopsy examination revealed a similar prevalence of CVD in both male and female donors, with 100% of male donors and 96% of female donors possessing mild to severe forms of CVD. Therefore, whereas only 39% of male donors possessed undocumented CVD, 57% of female donors displayed undocumented CVD, suggesting that while CVD is more commonly diagnosed in male patients before death, CVD may be equally prevalent in female patients but significantly underdiagnosed.

4. Tables and Figures

Table 1: Mean and Standard Error for Right and Left Ventricular Thickness in Normal and Diseased Hearts from Cadaveric Donors

Ventricular Thickness Mean (mm) ± SE	Normal	Dilated	Hypertrophic
Left	13.09 (± 0.31)	8.33 (± 0.43)	17.85 (± 0.91)
Right	4.18 (± 0.15)	2.67 (± 0.06)	8.68 (± 0.47)

Table 2: Prevalence of CVD and Heart-specific CVD in cadaveric donors according to documented records and autopsy examination

Pathology	Documented Records	Autopsy Examination
Total CVD	20	40
Heart-specific CVD	11	39

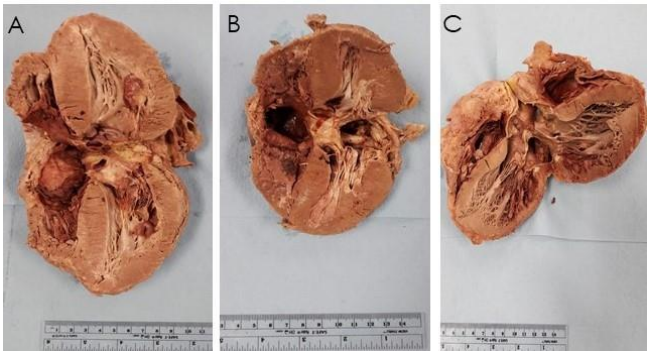

Fig 1: A normal cadaveric heart (A) compared with hypertrophic (B) and dilated (C) cardiomyopathy

Table 3: Number of cadaveric donors possessing left-sided, right-sided, or whole heart cardiomyopathies according to autopsy examination

Cardiomyopathy	Donors
Total	39
Left-sided	8
Right-sided	6
Left and Right-sided	25

Table 4: Presence of CVD in male and female donors according to documented records compared with results based on autopsy examination

	Males	Females
Possessing Documented CVD	11/18	9/23
Possessing Undocumented CVD	7/18	13/23
Total # of Donors Possessing CVD	18/18	22/23

5. Conclusions

These findings indicate that in the absence of an autopsy, many forms of CVD remain undiagnosed. While only 1 in every 3 individuals is thought to possess CVD as an underlying cause of death [2-3] and around 48% of the population is believed to be affected by CVD [1], many individuals in the remaining portion of the population may unknowingly possess advanced forms of CVD. These undiagnosed conditions may contribute to the individual's cause of death and due to the genetic nature of many types of CVD such as heart disease, these individuals may also unknowingly pass genetic predispositions on to future generations. Therefore, it is important that these genetic conditions be identified and documented in order to facilitate early intervention and treatment in affected individuals.

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