**Obesity and Sudden Cardiac Death in the Young. Clinical and Pathological Insights from a Large National Registry**

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Keywords: sudden death, obesity

Word count: 2785

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**Abstract**

**Aims:** Obesity is a rising public health problem and widely known risk factor for cardiovascular diseases. The aim of the study was to determine the main features and aetiologies in a large cohort of sudden cardiac deaths (SCD) occurred in obese subjects

**Methods:** Between 1994 and 2014, 3684 consecutive cases of unexpected SCD were referred to our cardiac pathology centre. This study was confined to young individuals (age ≤ 35 years) where information about body mass index (BMI) was available and comprised of 1033 cases.

**Results:** Four hundred ninety-one patients (25%) were obese. In obese SCD victims the main post-mortem findings were: normal heart (sudden arrhythmic death syndrome, SADS) (n=192, 39%), unexplained left ventricular hypertrophy (LVH) (n=88, 18%) and critical coronary artery disease (CAD) (n=57, 12%). Less common were hypertrophic cardiomyopathy (HCM) (n=24, 4%) and arrhythmogenic right ventricular cardiomyopathy (ARVC) (n=22, 4%). When compared with non-obese SCD victims, SADS was less common (39 vs 51%, p<0.001) whereas LVH and critical CAD were more frequent (18 vs 3%, p<0.001 and 12 vs 6%, p<0.001 respectively). The prevalence of critical and non-critical CAD was significantly higher in obese individuals (23 vs 10% in non-obese, p<0.001).

**Conclusions:** Various conditions underlie SCD in obesity, with a prevalence of SADS, LVH and CAD. The degree of LVH measured by heart weight is excessive even after correction for body size. Almost one in four young obese sudden death victims show some degree of CAD, underscoring the need for primary prevention in this particular subgroup.

**Introduction**

Obesity is a growing public health concern and an established risk factor for cardiovascular disease1. Although progressive heart failure is the most common cause of death in obese patients, an increased risk of sudden cardiac death (SCD) is also reported in these patients2. The relationship between obesity and SCD is unclear and based on small cohort studies and there is a lack of knowledge on the prevalence of specific aetiologies underlying SCD in obese individuals.

Various mechanisms underlying fatal arrhythmias in obese individuals have been proposed. An association between QT interval and BMI has been observed3,4 especially in individuals exhibiting abdominal obesity. Similarly, increased late potentials have been linked to increase risk of SCD and the signal average ECG is often significantly abnormal in marked obesity5.The role of obesity as independent risk factor for SCD is unclear. Recently Adabag et al.2 showed that the association between BMI and SCD appeared to be largely mediated by cardiovascular risk factors in a cohort of 14,491 men and women aged 45-64 years. The burden of SCD in young (< 35 years of age) obese individuals and the aetiologies of SCD are not well understood.

The aim of this study was to determine the main pathological substrates in a large cohort of young obese individuals who died suddenly.

**Methods**

**Study setting**

The Cardiac Risk in the Young (CRY) centre for cardiac pathology was established at the Royal Brompton Hospital and subsequently transferred at St. George’s University of London. The center is led by MNS who provides a specialist cardiac pathology service for cases of SCD across the United Kingdom (UK) and is funded by CRY. The centre receives over 500 cases of SCD annually. General pathologists are likely to refer when the clinical history is suggestive of inherited cardiac disease, especially when the death affects a young individual or when the cause of death is uncertain after the initial autopsy.

**Study cohort**

Between 1994 and 2014, 3684 consecutive cases of unexpected SCD were referred to our cardiac pathology centre and included in the Cardiac Risk in the Young SCD database. SCD was defined as death within 12 hours of apparent wellbeing. The study was confined to young individuals (age ≤ 35 years) where information about body mass index (BMI) was available and comprised of 1033 cases (71% male; mean age 24±8 years). Obesity was defined as a BMI ≥ 30. Clinical information was obtained from referring coroners who were asked to complete a questionnaire inquiring about the demographics of the deceased, past medical history, family history, cardiac symptoms and circumstances of death.

**Post-mortem examination**

Cases of SCD underwent a full post-mortem evaluation by the local pathologist. Following the exclusion of extra-cardiac causes, the heart was referred to our centre after written consent from the coroner and the family of the deceased. A thorough toxicology screen was conducted in all cases in accordance with the usual investigation of sudden and unexpected deaths in the UK. All subjects underwent detailed autopsy evaluation including histological analysis by an expert cardiac pathologist in accordance with the Association for European Cardiovascular Pathology guidelines6.

A minimum of 10 blocks of tissue were taken for histological analysis as reported previously7,8. Sections of myocardium were fixed in formalin, embedded in paraffin and stained with haematoxylin and eosin as well as elastic Van Gieson stain to highlight myocardial fibrosis.

Criteria for defining specific cardiac pathologies, as sudden arrhythmic death syndrome (SADS), cardiomyopathies, left ventricular hypertrophy (LVH) and critical coronary artery disease (CAD) are summarized in Table 1 6,9,10. Critical CAD was defined by the presence of at least one coronary artery stenosis of > 75%. Mild and moderate coronary artery stenosis were defined as non-critical CAD10. The diagnosis of unexplained LVH required demonstration of left ventricular wall thickness of > 15 mm and heart weight >500 g in males and > 400 g in females in the absence of myocyte disarray or secondary causes as hypertension or valvular heart disease9,11. SADS was a diagnosis of exclusion in the presence of a normal heart at the post-mortem and normal toxicology.

**Ethical approval**

Ethical and research governance approval have been granted for this study (10/H0724/38). The next of kin consented to material retention for anonymised research

**Statistical analysis**

Statistical analysis was performed using the PASW software (PASW 18.0 Inc, Chicago, IL). Results are expressed as mean ± standard deviation (SD) for continuous variables or as number of cases and percentage for categorical variables. Comparison of groups was performed using Student’s T-test for continuous variables with correction for unequal variance when necessary and Chi-square test or Fisher Exact Test, as appropriate for categorical variables.

**Results**

The main demographic and clinical features of our cohort are summarized in Table 2. 212 (20%) of SCD victims were obese. Obese individuals were younger than non-obese individuals (mean age 23±8 vs 27±6, p<0.001). Family history of sudden death was reported in a similar proportion of obese and non-obese individuals (21; 9% vs 70; 8%).

Only a minority of obese individuals (n=25, 12%) were diagnosed with a cardiac condition during life, including 7 with cardiomyopathy (6 dilated cardiomyopathy and 1 hypertrophic cardiomyopathy) and 6 with congenital heart disease including 2 patients who underwent surgery for mitral valve replacement and atrial septal defect closure. Of the 187 obese individuals without a pre-mortem diagnosis, 24 (13%) were assessed for cardiac symptoms, including syncope in 5, chest pain in 9, palpitations/arrhythmias in 7, dyspnoea in 3, but the majority (n=163; 87%) were asymptomatic.

Obese individuals had a higher heart weight compared with non-obese individuals (450±141g vs 361±129g); p<0.001 and 50 (23%) hearts in obese individuals exceeded 500g compared with 83 (10%) in non-obese; p<0.001 (Figure 1). LV fibrosis was found in 42 (20%) obese and in 131 (16%) non obese individuals; p=0.19. Among obese individuals the main post-mortem findings were SADS (n=108; 50%), LVH (n=25; 12%) critical CAD (n=25; 12%) (Figure 2A). SADS was the commonest post-mortem finding in obese and non-obese individuals but was more common in non-obese victims (n=108; 50% v n=498; 60%; p=0.01). LVH in the absence of a diagnosis of hypertension or valvular heart disease was more prevalent in obese patients (n=25, 12% vs n=16, 2%; p<0.001) as was CAD (50 (23%) vs 82 (10%); p<0.001 (Figure 2B). Obese individuals also had a higher prevalence of critical CAD (n=25, 12% vs n=21, 3%; p <0.001).

**Discussion**

Obesity affects 20% of the population under 35 in the UK. In our cohort of young unexpected SCDs, 20% of individuals were obese. SADS was the most common post-mortem finding inyoungobese individuals, followed by a relatively high burden of unexplained LVH and CAD.

**SCD in obesity**

Our study shows that in a cohort of SCD victims, where the post-mortem was performed at a single expert cardiac pathology centre, the prevalence of obesity was similar to that observed in the population under 35 in the UK12. These observational data suggest that at least in this young age subgroup, the burden of SCD is not higher in obese individuals compared with individuals with a normal body mass index. Further longitudinal prospective studies are required to validate this concept.

A diverse spectrum of diseases are implicated in SCD and the prevalence of specific diseases is generally dependent on the demographics of the victims and the circumstances of death9,13–15.

SADS was the most common cause of death in both obese and non-obese SCD victims. The association between obesity and electrical instability and prolonged QT interval has been described previously and it is possible that the QT prolongation is the mechanism underlying fatal arrhythmias in obese individuals with a structurally normal heart16. Unexplained LVH was more frequently observed in obese young SCD victims compared with non-obese individuals. Body weight is likely to affect the heart weight due to several reasons. Obesity is characterized by a hyperdynamic circulation due to the increased metabolic demand imposed by the expanded adipose tissue and increased blood volume. In addition to the increased preload, LV afterload is also elevated in obese individuals due to both increased peripheral resistance and greater arterial stiffness17. All these changes are likely contribute to the development of LVH. However previous studies have shown that the average weight for an adult male heart is 365 ± 71 g and the average for an adult female is 312 ± 78 g. These values are well below the current definition of idiopathic LVH (> 500 g in males and > 400 g in females)7,8,18,19. An autopsy study including obese individuals (BMI 25 to 34 kg/m2 with an average age of 42 in males and 49 in females) without any known comorbidities, showed an average heart weight of 400 ± 69 g in males and 362 ± 77 g in females18. Therefore, the average heart weight in obese individuals is lower than the proposed value of 500 g in males and 400 g in females for idiopathic LVH. Based on the current literature18, the degree of hypertrophy measured by heart weight in obese individuals was excessive even after correction for body size, therefore it is possible that in these individuals the disproportionate amount of LVH may have been a substrate for fatal arrhythmias. Since the nature of our study was observational, questions regarding the pathophysiological mechanisms leading to LVH and to arrhythmias in obese individuals remain unanswered.

Almost one in four young obese individuals showed CAD at post-mortem. 12% had critical CAD in at least one main epicardial vessel, which was the likely cause of SCD and 23% had mild to moderate coronary atherosclerosis which is a remarkable finding considering that obese individuals that died suddenly had an average age of 23 years old. CAD has been shown to be the most common cause of sports-related sudden cardiac death in the young in Switzerland20. Our findings underscore the need for primary prevention especially in obese individuals.

SCD in young obese individuals occurred frequently without antecedent symptoms or significant past medical history. Further studies are required to establish the possible role of cardiac screening in young otherwise healthy obese individuals for early detection of potentially fatal cardiac disease. Family screening of obese individuals who died suddenly with a post-mortem consistent with SADS or excessive LVH may provide important information regarding the heritability and genetic background of these conditions.

**Limitations**

The study may suffer from a referral bias, since local pathologists tend to refer cases were the diagnosis is uncertain. However, the St George’s cardiac pathology center evaluate a high volumes of cases annually (> 500) and given that SCD in the young is relatively rare, we believe that these data are a genuine representation of the type and frequency of cardiac diseases implicated in SCD in young individuals. As our study included cases examined more than 20 years ago, we could not explore the role of molecular autopsy in individuals dying from SADS.

**Conclusions**

Various cardiac disease underlie SCD in obesity, with a relatively high prevalence of SADS, idiopathic LVH and CAD. According to literature data18, the degree of hypertrophy measured by heart weight in some obese victims of SCD is excessive even after correction for body size. Almost one in four young obese SCD victims shows a certain degree of CAD, underscoring the need for primary prevention specifically on these individuals.

**Acknowledgements:** charity Cardiac Risk in the Young (CRY), Charles Wolfson Charitable Trust.

Contribution of each author:

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | StudyDesign | DataCollection | DataInterpretion | QualityControl | StatisticalAnalysis | ManuscriptPreparation | ManuscriptRevision |
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| Ms DC |  |  |  |  |  |  |  |
| DR ERB |  |  |  |  |  |  |  |
| Dr MT |  |  |  |  |  |  |  |
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All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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**Table 1.** Pathological macroscopic and microscopic criteria defining main underlying diseases.

|  |  |  |
| --- | --- | --- |
|  | **Macroscopic** | **Microscopic** |
| Hypertrophic cardiomyopathy | Left ventricular wall thickness >15 mm circumferentially or focally and/or heart weight >500 g\*∞ | Myocyte hypertrophy, myocyte disarray (> 20% of myocardial disarray in at least two tissue blocks of 4 cm2) and interstitial fibrosis |
| Idiopathic left ventricular hypertrophy | Left ventricular wall thickness >15 mm and heart weight >500 g\* | Myocyte hypertrophy +/-fibrosis in the absence of myocyte disarray |
| Idiopathic left ventricular fibrosis | Normal heart weight and wall thickness with/without scarring macroscopically | Fibrosis (> 20% in at least two tissue blocks of 4 cm2) with no myocyte disarray |
| Arrhythmogenic right ventricular cardiomyopathy | Right or left ventricular thinning, fatty replacement, fibrosis on the epicardial surface or outer wall | Fat and fibrosis (> 20% in at least two tissue blocks of 4 cm2) in the wall of the right and/or left ventricle, particularly in outer wall, with degenerative changes in the myocytes |
| Myocarditis | Normal or dilated ventricles | Inflammation (> 20% in at least two tissue blocks of 4 cm2) with myocyteNecrosis |
| Anomalous coronary artery | Anomalous origin of the coronary artery,coronary artery atresia, stenosis | Fibrosis/acute/chronic infarction in the leftVentricle |
| Coronary atherosclerosis | Atherosclerosis with estimated luminal narrowing >75% | Acute or chronic infarction inthe left ventricle |
| Dilated cardiomyopathy | Increase in heart weight (> 500 g in males, > 400 g in females) with dilated left ventricle (> 4cm) and thin wall (<10mm). Absence of coronary artery disease. | Diffuse interstitial and replacement fibrosis (> 20% in at least two tissue blocks of 4 cm2) in the left ventricle with degenerative changes in the myocytes |
| Mitral valve prolapse | Prolapse of mitral valve above the atrio-ventricular junction with ballooning between chordae in one or both leaflets | Myxoid degeneration with expansion in spongiosa of leaflets and destruction of fibrosa layer  |
| Bicuspid aortic valve | Fusion of two aortic cusps, with or without presence of a raphe often with significant valve stenosis |  |
| Morphologically normal heart | Normal | Normal |

**Table 2.** Demographic and clinical data of obese and non-obese SCD victims.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Obese (n=212)** | **Non-obese (n=821)** | **p** |
| **Age (years)** | 23±8 | 27±6 | <0.001 |
| **Males n (%)** | 137 (65) | 575 (70) | 0.19 |
| **Caucasian n (%)** | 194 (91) | 749 (91) | 0.89 |
| **BSA (m2)** | 2.3±0.3 | 1.8±0.4 | <0.001 |
| **Family history of SD\* n (%)** | 21 (9) | 70 (8) | 0.74 |
| **Heart weight (g)** | 450±141 | 361±129 | <0.001 |
| **LV fibrosis n (%)** | 42 (20) | 131 (16) | 0.19 |

**Legends:** BSA: body surface area; LV: left ventricular; SD: sudden death.

\*Sudden death in a family member of less than 50 years of age.

**Figure legends:**

**Figure 1.** Heart weight (g) in obese (A) and non-obese (B) SCD victims.

**Figure 2.** Causes of sudden cardiac death in obese and non-obese individuals (A); Prevalence of coronary artery disease in obese and non-obese individuals (B). **Abbreviations:** ARVC: arrhythmogenic right ventricular cardiomyopathy; CAD: coronary artery disease; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; LVH: left ventricular hypertrophy; IF: idiopathic fibrosis; SADS: sudden arrhythmic death syndrome.

**Figure 1.**



**Figure 2.**

