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Review Article

Structural and Metabolic Effects of Obesity on the Myocardium and the Aorta

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Obesity · Cardiovascular diseases · Cardiac imaging techniques

Abstract
Obesity per se is a recognized risk factor for cardiovascular disease exerting independent adverse effects on the cardiovascular system. Despite this well documented link, the mechanisms by which obesity modulates cardiovascular risk are not well understood. Obesity is linked to a wide variety of cardiac changes, from subclinical diastolic dysfunction to end stage systolic heart failure. In addition, obesity causes changes in cardiac metabolism that make ATP production and utilization less efficient producing functional consequences that are linked to the increased rate of heart failure in this population. This review focuses on the cardiovascular structural and metabolic remodelling that occurs in obesity with and without co-morbidities and the potential links to increased mortality in this population.

Introduction

Obesity is associated with an increased cardiovascular mortality rate, and even greater risk is associated when the BMI exceeds 35 kg/m^2 [1]. Structural and functional changes to the cardiovascular system in obesity include ventricular hypertrophy, diastolic dysfunction and aortic stiffness [2, 3]. Whilst left ventricular hypertrophy [4, 5] and diastolic dysfunction [6] are associated with all-cause mortality, impaired aortic elastic function is associated with cardiovascular events in healthy and diseased populations [7]. It is therefore likely that adverse cardiovascular outcomes in obesity occur, at least in part, as a result of the long-term cardiovascular sequelae of increased body weight.

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This review will focus on the adverse effects of obesity and excess adiposity on the cardiovascular system [2, 8]. These include a spectrum of changes ranging from a hyperdynamic circulation and subclinical changes in cardiac structure [9] to overt heart failure [10].

Left Ventricular Geometric Remodelling in Obesity

Both cardiac output and total blood volume are elevated in obesity, leading to chronic volume overload. Although early studies reported an association with eccentric left ventricular (LV) remodelling [2, 8], it is now evident that both LV cavity size and wall thickness are increased in obesity. In the traditional model, the hypertrophic response of the ventricle is secondary to increased wall stress from cavity dilatation and elevated filling pressures [11, 12]. Although this accounts for the eccentric hypertrophic pattern, recent studies have reported concentric hypertrophy in obesity without co-morbidities [13, 14], contradicting earlier studies. Advances in the understanding of the cardiovascular effects of adipokines have suggested an alternative scenario, whereby the hypertrophic response occurs independently from the dilatory response.

The disproportionate degree of concentric LV remodelling in obesity [15, 16] may relate to elevated leptin levels [17]. Leptin receptor isoforms are expressed in the myocardium [18], and leptin induces hypertrophy in cardiomyocyte culture [19–21]. This effect occurs even in the absence of wall stress, suggesting a direct molecular mechanism [22]. The hypertrophic effects of leptin involve several signalling cascades including JAK/STAT, MAPK, protein kinase C and Rho/ROCK-dependent kinases [23–25] whilst hyperleptinaemia has also been linked to LV hypertrophy in severe obesity in humans [26]. Hyperinsulinaemia, as a result of insulin resistance, is another potential candidate for the ventricular hypertrophic response seen in the obese population, and hyperinsulinaemia itself has been linked to ventricular hypertrophy in obesity directly via the binding of insulin to myocardial insulin-like growth factor 1 receptors which are found in abundance in the myocardium [27].

One explanation for the different patterns of reported LV hypertrophy may be that multiple imaging modalities have been used. Most early studies used 2D echocardiography, in which image quality in obesity may be limited by poor acoustic windows. Echocardiography is also limited by the need for geometric assumptions to infer 3D parameters (i.e. LV mass and LV end-diastolic volume) from a 2D dataset. These limitations are overcome by cardiovascular magnetic resonance (CMR) imaging [15, 16]. All CMR studies in obesity to date report both a concentric and eccentric element of hypertrophy in line with a mixed haemodynamic (chronic volume overload) and metabolic (adipokine) mediated response.

Gender-Specific Effects of Obesity on LV Remodelling

Obesity-related cardiovascular mortality in females is elevated to a lesser degree than in males, even when adjusted for confounding factors [28, 29]. This implies an apparent paradox, as obese males have less fat mass than obese females and yet have higher mortality [30], suggesting that gender-specific cardiac adaptations predispose males to excess cardiovascular risk. One explanation may be that, in the absence of traditional cardiovascular risk factors, obese males exhibit a greater concentric hypertrophic response than do females, where a mixed eccentric and hypertrophic response occurs [31]. Concentric hypertrophy is more strongly predictive of cardiovascular mortality than eccentric hypertrophy [32–34], providing a possible explanation for gender-specific mortality differences in obesity.

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Left Ventricular Function

Systolic Function

Although there is a clear relationship between obesity and heart failure on a population level [10], the majority of smaller cohort studies report that obesity has little or no effect on global measures of systolic function such as LV ejection fraction [35]. This suggests that although some individuals are susceptible to developing obesity cardiomyopathy and heart failure, it is not a universal phenomenon. Whilst obesity-related cardiac changes, such as LV hypertrophy, left atrial (LA) enlargement [36] and subclinical impairment of LV systolic and diastolic function [37], may precede the development of overt systolic failure, human studies, which have relied on cross-sectional data and not longitudinal follow-up studies, have not established a causal link. However, it is generally accepted that a longer duration of obesity is linked to the development of manifest LV systolic dysfunction [38].

The Obesity Paradox

Although a major risk factor for the development of congestive heart failure, obesity is associated with better survival in patients with established cardiac failure [39, 40]. The mechanisms for this phenomenon, termed the obesity paradox, are not well understood. However, there is now some evidence that subjects with congestive cardiac failure have reduced epicardial fat mass when compared to normal BMI-matched controls [41], and as obesity is linked to increased epicardial fat mass, there may be some 'protective' adaptations that occur in obesity to explain the paradox.

Diastolic Function

Asymptomatic diastolic dysfunction is associated with the development of heart failure [42, 43]. Obesity, both with and without additional co-morbidities, has been linked to diastolic dysfunction using a wide range of non-invasive imaging modalities [44–46]. Despite this, the mechanisms behind diastolic dysfunction in obesity are only partially understood [47]. Myocardial relaxation is determined by a combination of both active processes (including calcium homeostasis and myocardial energetics) [48] and passive processes related to the physical properties of the left ventricle (intrinsic mechanical stiffness as determined by wall thickness and chamber geometry) [49]. It is likely that diastolic dysfunction in obesity is a result of both passive and active mechanisms including LV hypertrophy and impairment in myocardial high-phosphate energetics [50–53]. The association between reduced myocardial energetics and diastolic dysfunction has been shown in multiple studies [48, 54]. This is consistent with the concept that an impairment in high-energy phosphate metabolism initially affects the ability of the sarcoplasmic reticular Ca^{2+} ATPase (SERCA), the energetically most demanding of all enzymes involved in contractile function [55], to lower cytosolic Ca^{2+} and thus impairs diastolic function.

The most likely mechanism for impaired energetics at rest in obesity is depletion of the total creatine pool, in proportion to the loss of phosphocreatine, as occurs in many other forms of hypertrophy [56]. Elevated free fatty acid levels increase mitochondrial uncoupling via promotion of myocardial uncoupling protein 3 (UCP3) expression [57]. This suggests that reduced high-energy phosphate levels, caused by increased mitochondrial uncoupling as a result of elevated free fatty acid levels, may lead to diastolic dysfunction.

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Cardiac Energy Metabolism in Obesity

ATP is the heart's only immediate source of energy for mechanical function and, as both systole and diastole are active processes [58, 59], cardiac ATP demand is very high. In order to sustain this demand for continuous and efficient contraction and relaxation, the heart needs to produce around 20 times its own weight in ATP per day [56]. Any detraction in ATP production, transfer or utilization can impair cardiac function [60]. Cardiac metabolism and ATP production are abnormal in obesity and are candidate mechanisms to explain the increased incidence in heart failure in this population [10].

Altered Myocardial Substrate Selection in Obesity

Cardiac substrate selection is a fundamental step in myocardial metabolism. In the normal heart in the resting, fasted state, the majority (60–90%) [61] of acetyl CoA that enters the Krebs cycle is derived from β-oxidation of free fatty acids [62], with the remaining 10–40% of acetyl CoA coming from the oxidation of pyruvate, in turn derived from either glycolysis or lactate oxidation [63]. The heart is highly flexible in its choice of substrate depending on the prevailing metabolic conditions [64, 65].

The heart is an extremely efficient scavenger of circulating non-esterified free fatty acids (up to 40% extraction fraction) [66], and the rate of uptake of fatty acids by the heart is primarily determined by their plasma concentration [67]. Obesity is associated with high circulating free fatty acid levels [68], and both human [69] and animal studies [51, 70] have shown increased oxidation of free fatty acids and a shift in substrate utilization towards free fatty acid metabolism.

The importance of the increase in fatty acid metabolism is that mitochondrial redox state, and therefore the free energy of hydrolysis of ATP, is affected by the substrate oxidized. Although fatty acid oxidation has high potential energy, this does not translate to greater mitochondrial redox power. The reasons for this lie in the architecture of fatty acid metabolism by β-oxidation, and the changes in mitochondrial membrane uncoupling proteins in response to persistently elevated free fatty acids. Only 50% of the reducing equivalents produced in the process of β-oxidation are able to donate electrons at complex I of the electron transport chain, whereas the remaining half are donated by $FADH_2$ at the flavoprotein site further 'downstream' at complex II [71]. This results in a reduced ATP yield and a loss of mitochondrial efficiency. The redox span of the respiratory chain is diminished during fat metabolism as the Q couple is reduced. This decreases the potential difference between matrix and inter-mitochondrial membrane space and therefore $\Delta G'_{ATP}$.

Elevated free fatty acids also increase the expression of uncoupling proteins [72], which decrease mitochondrial efficiency [73] by allowing the passage of protons into the matrix via non-ATP-generating pathways. Within the perfused heart, higher concentrations of free fatty acids increase the oxygen cost for the same work output by between 25% and 48% when compared to glucose and insulin infusion [74]. This loss of myocardial efficiency has been attributed to reductions in mitochondrial electron transport chain coupling and the increased stoichiometric oxygen requirement to oxidise fat [75]. As such, deleterious substrate selection may be a feature of obesity-related cardiomyopathy as it is in other myocardial diseases, intimately linking energetic performance and mortality [56, 75].

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The Role of Lipases in Lipotoxicity

Lipases appear to have many potential roles in the development of myocardial steatosis. Intracellular lipid accumulation (steatosis) and resultant lipotoxicity are key features of several cardiomyopathies. Under physiological conditions, lipoprotein lipase(LpL)-mediated lipolysis of triglyceride-rich particles represents a key route of fatty acid substrate delivery to the heart, and cardiomyocyte-restricted deletion of LpL results in impaired cardiac contractile function and perivascular fibrosis despite a compensatory increase in glucose oxidation [76]. In contrast, germline deletion of adipose tissue triglyceride lipase (a model with decreased myocardial lipid pool turnover, rather than uptake) resulted in dramatic cardiac lipid accumulation, contractile dysfunction and premature death [77]. Taken together, these studies support the hypothesis that increased myocardial lipid delivery, uptake or decreased turnover may impair cardiac contractile function and alter cardiac metabolism.

Mitochondrial Metabolism and Lipotoxicity in Obesity

Cardiac mitochondria contain a DNA genome that encodes some of the proteins required for electron transport complexes I, III, IV, and V [78]. In obesity, changes in both nuclear and mitochondrial transcription occur and are linked to changes in cardiac metabolism [50]. The peroxisome proliferator-activated receptors (PPARs) are key regulators of nuclear gene transcription for myocardial mitochondrial fatty acid oxidation. [79] PPARα is expressed in the myocardium [80] and is the primary transcriptional regulator of fat metabolism in tissues with the highest rates of fatty acid oxidation [81]. Cardiac PPARα activation increases the expression of several genes involved in fatty acid metabolism, including i) cardiac myocellular fatty acid uptake (FATP, FAT/CD36, FABP, ACS [82–84]) ii) mitochondrial fatty acid uptake via CPT I [85] and iii) mitochondrial and peroxisomal fatty acid β-oxidation via MCAD, LCAD, VLCAD and ACO [85].

In obesity and in insulin resistance, the heart initially adapts to increases in circulating fatty acid levels by increasing PPARα, resulting in a compensatory increase in myocardial fatty acid uptake and β-oxidation [86], which limits ectopic cardiac lipid accumulation. However, despite these initial adaptive/protective mechanisms, obesity is associated with cardiac lipotoxicity [87]. Fatty acid inhibition of myocardial glucose metabolism appears to be one important contributing factor [88, 89]. Exposure of the heart to high levels of fatty acids can cause accumulation of lipids within cardiomyocytes, which increases the intracellular pool of long-chain fatty acyl-CoA. This provides a fatty acid substrate for non-oxidative processes, including synthesis of triacylglycerol, diacylglycerol and ceramide, which in turn lead to cellular dysfunction, insulin resistance and apoptosis. The link between lipid accumulation and cardiomyopathy has been further established through transgenic mouse models in which either the rate of lipid uptake or esterification of fatty acids by the heart was increased or the mitochondrial capacity for oxidation of fatty acids was reduced [87, 90].

Although lipid accumulation can cause cardiac dysfunction, triglyceride accumulation may not be entirely maladaptive. There is now evidence to suggest that cardiac triglyceride accumulation limits ceramide and diacylglycerol synthesis, providing a protective mechanism against lipotoxicity [91]. Regardless of whether ectopic lipid deposition is a maladaptive or a protective process, there is strong evidence that myocardial steatosis promotes the development of insulin resistance, cardiac hypertrophy, impaired cardiac function, fatty acid-induced apoptosis and interstitial fibrosis [92].

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Obesity and the Aorta

In the absence of traditional cardiovascular risk factors, obesity is associated with increased aortic pulse wave velocity [93], which is a non-invasive clinical measure of aortic stiffness and independently predicts cardiovascular mortality. Obesity is associated with a predominantly distal pattern of aortic stiffness. The reasons for this are not known but changes in aortic distensibility in obesity have been attributed to factors that are not present in hypertension, including hyperleptinaemia [94], external physical compression from adipose tissue [95], elevated circulatory inflammatory cytokines [96] and increased free fatty acid levels [97, 98]. Obese individuals have excess abdominal visceral fat, which is a better predictor of cardiovascular and metabolic risk than total body fat alone and is also linked to altered vascular function [3].

The Effects of Weight Loss

Obesity is associated with mortality although a growing body of evidence suggests that weight loss reduces this risk [99]. There is, however, very little information on the cardiovascular effects of weight loss in obese individuals who have no other identifiable cardiovascular risk factors.

In principle there are two main methods of weight loss: dietary intervention and bariatric surgery. Weight loss induced by surgery leads to more effective weight management than dietary weight loss [100], and reduces long-term mortality [99]. The global utilization of bariatric surgery is rapidly increasing.

Irrespective of the method, weight loss has beneficial effects on cardiac geometry, with reduced ventricular mass and cavity size as early as 3 months following bariatric surgery [46, 101]. Multiple studies have shown improvements in diastolic function in adult and elderly populations [102–104]. Furthermore, weight loss improves aortic elastic function [93, 105] and high-energy phosphate metabolism [106].

Conclusion

Obesity per se, in the absence of traditional risk factors, is associated with circulatory, hormonal and sub-acute inflammatory changes which together produce a sequence of changes in the cardiovascular system manifesting as ventricular hypertrophy, cavity dilatation, diastolic dysfunction, reduced aortic elastic function, altered myocardial metabolism and reduced myocardial energetics, all of which are independent predictors of future cardiovascular events and mortality. Significant weight loss, irrespective of mode, is associated with partial resolution of these adaptive changes. It is likely that the structural and functional changes in the cardiovascular system are at least partially responsible for the reduced mortality seen with weight loss.

Disclosure Statement

Conflicts of Interest: None.

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