Obesity has traditionally been considered an independent risk factor for heart failure whose pathophysiology is generally believed to be associated with the consequence of myocyte hypertrophy, myocardial fibrosis, and abnormalities of intracellular calcium handling. Obesity-related comorbidities like chronic inflammation, coronary artery disease, diabetes, and hypertension play some causative roles in the development of heart failure. Currently, cardiac apoptosis and cardiac fibrosis are found in obesity and leptin-deficient animal models. Leptin pretreatment exerts antiapoptotic effects in cardiomyocytes. In obese rat hearts, key components of Fas-dependent apoptosis (Fas ligand, tumor necrosis factor-alpha, Fas death receptors, Fas-associated death domain, activated caspase 8, and activated caspase 3) as well as those of mitochondria-dependent apoptosis (Bad, Bax, Bax-to-Bcl2 ratio, cytosolic cytochrome c, activated caspase 9, and activated caspase 3) manifestly increased compared with lean controls. Obesity will activate cardiac Fas- and mitochondria-dependent apoptotic pathways while increasing cardiac fibrosis, which may provide one of the possible mechanisms for developing heart failure in obesity.

1. Introduction

Heart failure, in pathophysiologic terms, can be defined as the inability of the heart to deliver blood and, hence, oxygen at a rate necessary for adequate tissue metabolism. Obesity or abdominal obesity is traditionally viewed as an independent risk factor for heart failure [1,2]. Obesity was considered as a major risk factor for the development of heart failure in relative risk ranging from 1.8 to 5.6, depending on degree of obesity, even with other known risk factors excluded [3,4]. Elevated body mass index was associated with an increased risk of heart failure, even in less obese people [5]. Severe
obesity in humans has long been recognized as causing various cardiac abnormalities characterized by markedly higher rates of chronic volume overload, development of heart failure, hypertension, and left ventricular hypertrophy [3,4,6,7]. Various types of heart failure-associated abnormalities like biventricular failure and left ventricular dysfunction were found in morbidly obese patients [8,9]. However, the relationship between heart failure and obesity is complex and not completely understood.

2. Possible pathophysiology of heart failure in obesity

The pathophysiology of heart failure with diastolic function abnormality is generally believed to be associated with a consequence of myocyte hypertrophy, myocardial fibrosis, and abnormality of intracellular calcium handling [10]. Hypertension, diabetes, and coronary artery disease play causative roles in developing heart failure in obesity [10]. Past years have seen conventional risk factors like hypertension, type 2 diabetes, and dyslipidemia implicated in heart failure; several study highlights a pivotal role of obesity as an independent risk factor [1,2,11]. Chronic inflammation was also considered as a novel metabolic risk factor [12,13]. Vious and complicated obesity predisposes patients to heart failure due to the presence of many comorbidities and intrinsic pathophysiologic mechanisms. Hence, it is difficult to indentify the pathophysiology of heart failure in obesity independent of obesity-related comorbidities.

3. Cardiomyopathic changes in obesity

Obesity is often associated with hemodynamic overload, ventricular remodeling, and higher cardiac output due to augmented stroke volume and an increase in heart rate [6,14]. Obesity cardiomyopathy typically occurs in severe and long-standing obesity, which may progressively develop cardiac abnormalities like dilated heart, congestive heart failure, and sudden cardiac death [6]. In our prior study, 5- to 6-month-old genetic obese Zucker rats appeared to increase their relative cardiomyopathic changes, such as myocardial disarray and minor cardiac fibrosis. We speculate that obese rats progressively develop deleterious cardiomyopathic changes at an earlier age than 5–6 months. In obese Zucker rats, the cardiac hypertrophic effect will be underestimated if we only use the ratio of whole heart weight to whole body weight, traditionally regarded as an index of cardiac hypertrophy. Potential inducers of cardiac hypertrophy and cardiac apoptosis include hypertension [15], volume overload, hypoxia [16,17], and oxidative stress [18,19]. However, it is difficult to identify pathophysiology of cardiomyopathic changes in obesity independent of obesity-related intrinsic abnormalities or comorbidities. Specific factors or comorbidities like hypertension, diabetes, lipotoxic, volume overload, nocturnal hypoxemia, oxidative stress, or other unclear factors may potentially cause these cardiomyopathic changes.

4. Cardiac apoptosis in obesity

Cardiomyocyte apoptosis is a component of cardiac remodeling that contributes to heart failure in obesity [20]. Apoptosis, a physiologic program of cellular death, may contribute to many cardiac disorders [15,18]; its occurrence has been reported to contribute to the loss of cardiomyocytes in cardiomyopathies and is recognized as a predictor of adverse outcomes in patients with cardiac diseases or heart failure [21]. One study showed myocardial DNA laddering in obese rat hearts reaching 20 times the normal lean level, hinting that cardiac dysfunction in obesity is caused by liposapopsis and is prevented by reducing cardiac lipids [22]. In our previous study [23], increased body weight, increased whole heart weight, increased left ventricular weight, increased ratio of whole heart weight to tibia length, abnormal myocardial architecture, increased myocardial disarray, increased terminal deoxy-nucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL)-positive apoptotic cardiac cells and increased minor cardiac fibrosis were observed in genetic obese rat models. High levels of metabolic products are previously proposed to cause common complications of obesity like insulin resistance and cardiovascular disease, ultimately promoting programmed cell death [24]. Leptin-deficient and -resistant mice exhibit increased apoptosis, DNA damage, and mortality compared with wild type mice, suggesting that obesity or impaired leptin signaling enhances excess age-associated DNA damage and premature mortality [25]. By contrast, leptin pretreatment in hypoxia/reoxygenation H9c2 cells attenuated hypoxia/reoxygenation increased DNA fragmentation, TUNEL staining and caspase-3 activity, suggesting that leptin exerts anti-apoptotic effects in cardiomyocyte cells [20]. Acute leptin pretreatment mediates antiapoptotic effects on H2O2-induced apoptosis in H9c2 rat cardiomyocytes [26]. Both studies imply leptin as a promising target in preventing heart failure in obesity. High-calorie “Western” diet—induced obesity CAN also cause cardiac dysfunction [27]. Diet-induced oxidative stress was reflected in reduced transcript levels of manganese superoxide dismutase, glutathione peroxidase 1, and higher protein levels of mitochondrial transcription factor A, suggesting compensatory mitochondrial biogenesis in the face of increased mitochondrial damage [27]. Besides, “Western” diet-induced obesity enhance cardiac apoptosis, as evidenced by TUNEL positivity, elevated mRNA transcript levels and activity of caspase 3 [27]. Cardiac apoptosis is a potential mechanism of myocardial dysfunction and early mortality in obesity.

5. Cardiac Fas receptor-dependent poptotic pathway in obesity

The ‘extrinsic’ Fas receptor-dependent (type I) apoptotic pathway is believed to be one major pathway directly triggering cardiac apoptosis [18,19]. This pathway is initiated by binding the Fas ligand and receptor, which causes receptors to cluster and initiates an extrinsic pathway [19]. Fas-ligand binding followed by Fas-receptor oligomerisation is known to spawn the formation of death-inducing signal complex, starting with
recruitment of the Fas-associated death domain (FADD) of the adaptor protein [19]. Fas-receptor oligomerization recruits FADD and procaspase 8 to the complex, thus activating caspase 8, which cleaves procaspase 3 and undergoes autocatalysis to form active caspase 3, a principle effector caspase of apoptosis [28,29]. Additionally, activated caspase 8 can cleave Bcl-2 homology domain 3 (BH3)-interfering death agonist (Bid), and cleaved Bid to t-Bid then causes release of mitochondrial cytochrome c, leading to activation of procaspase 9, which then activates procaspase 3 [19, 30]. The t-Bid is a key component involved in intracellular molecule signaling from Fas-dependent apoptotic to the mitochondria-dependent apoptotic pathway [19,30]. The Fas-receptor dependent apoptotic pathway was more active in obese rat hearts, which can be characterized by increases in cardiac Fas ligands, Fas death receptors, FADDs, and activated caspase-8 and -3 levels in the obese group relative to the lean group [23]. Our previous study suggests that cardiac Fas receptor-dependent apoptotic pathway was more active in obesity [23].

6. Cardiac mitochondria-dependent apoptotic pathway in obesity

The ‘intrinsic’ mitochondria-dependent (type II) apoptotic pathway is mediated by internal factors, especially in mitochondria [19]. The mitochondria is the main site of action for members of the apoptosis-regulating protein family exemplified by Bcl-2 family, e.g., Bcl-2 and Bax [19]. Commitment to apoptosis is typically governed by opposing factions of this family, including pro- versus antiapoptotic family members [31]. These Bcl2 family members can homo- or heterodimerize to each other, and they appear to interact with and neutralize each other; relative balance of these effectors strongly influences cytochrome c release and cell fate [32]. Bcl-2, an anti-apoptotic protein, prevents cytochrome c release, whereas Bax and proapoptotic proteins, enhance cytochrome c release from mitochondria [19]. When cytochrome c is released from mitochondria into cytosol, it is responsible for caspase 9 activation, which further activates caspase 3 and executes the apoptotic program [33]. In the obese animal model compared with the lean rat heart, proapoptotic Bcl2 family members, BNIP3 and Bad levels, significantly rose, while the antiapoptotic Bcl2 family member Bcl2 level dropped significantly [34]. Cytosolic cytochrome c indicating cytochrome c release from mitochondria was significantly increased in the obese rat heart. Upstream pro-caspase-9 and -3 also significantly decreased, while activated caspase-9 and activated caspase-3 significantly increased in obese versus lean rat hearts, implying proforms of caspase-9 and -3 cleaved into active-forms caspase-9 and -3 [34]. Our previous study [34] suggested cardiac mitochondrial-dependent apoptotic pathways more active in obese Zucker rats, which is one possible apoptotic mechanism for heart failure in obesity. “Western” diet-induced obesity starkly reduces antiapoptotic Bcl2 [27], indicating diet-induced obesity may activate mitochondrial-dependent pathway. Leptin reduced hypoxia/reoxygenation-induced translocation of the Bax pro-apoptotic protein to the mitochondrial membrane, which provides a mechanism to explain protective effects of the intrinsic apoptosis pathway of in rat H9c2 cells [20]. This indirectly implies that leptin exerts an antiapoptotic effect on the mitochondrial-dependent apoptotic pathway in obesity.

7. Cardiac fibrosis in obesity

There is an association between turnover of collagens and remodeling of the rat ventricles [21,35], which progresses immediately after myocardial damage with an increased level of collagenases [36]. Collagens synthesized by fibroblasts invade and replace apoptotic myocytes [21,35,37,38]; myocardial interstitial changes resulting from increased collagen deposition lead to cardiac stiffness and cardiac dysfunction [37]. Accordingly, accumulated collagens will further contribute to the development of ventricular fibrosis and heart failure [38]. In our previous findings, abnormal myocardial architecture, increased interstitial space, and minor cardiac fibrosis in obese rat hearts suggest the development of cardiomyocyte death characterized by a distortion in the myocardium architecture and minor cardiac fibrosis in obesity [34]. A high-fat diet fed to normal female rats can elicit hypertensive response and induce perivascular fibrosis before the onset of overt obesity [39]. One study demonstrates that nutritional overfeeding and changes early in postnatal development with long-lasting effects on body weight and adiposity, along with cardiac fibrosis and heart structural, changes during adulthood [40]. This postnatal development of cardiac fibrosis may imply that cardiac fibrosis may be not easily
reversible. After integrating previous findings into hypothesized pathophysiology, we hypothesize that cardiac Fas- and mitochondrial-dependent apoptotic pathways are more active in obesity. Apoptotic cardiomyocyte and accumulated collagens can also contribute to the development of cardiac fibrosis and heart failure (Fig. 1).

REFERENCES


