Obesity, metabolic dysfunction, and cardiac fibrosis: pathophysiological pathways, molecular mechanisms, and therapeutic opportunities

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Cardiac fibrosis is strongly associated with obesity and metabolic dysfunction and may contribute to the increased incidence of heart failure, atrial arrhythmias, and sudden cardiac death in obese subjects. This review discusses the evidence linking obesity and myocardial fibrosis in animal models and human patients, focusing on the fundamental pathophysiological alterations that may trigger fibrogenic signaling, the cellular effectors of fibrosis, and the molecular signals that may regulate the fibrotic response. Obesity is associated with a wide range of pathophysiological alterations (such as pressure and volume overload, metabolic dysregulation, neurohumoral activation, and systemic inflammation); their relative role in mediating cardiac fibrosis is poorly defined. Activation of fibroblasts likely plays a major role in obesity-associated fibrosis; however, inflammatory cells, cardiomyocytes, and vascular cells may also contribute to fibrogenic signaling. Several molecular processes have been implicated in regulation of the fibrotic response in obesity. Activation of the renin-angiotensin-aldosterone system, induction of transforming growth factor β, oxidative stress, advanced glycation end-products, endothelin 1, Rho-kinase signaling, leptin-mediated actions, and upregulation of matricellular proteins (such as thrombospondin 1) may play a role in the development of fibrosis in models of obesity and metabolic dysfunction. Moreover, experimental evidence suggests that obesity and insulin resistance profoundly affect the fibrotic and remodeling response after cardiac injury. Understanding the pathways implicated in obesity-associated fibrosis may lead to the development of novel therapies to prevent heart failure and attenuate postinfarction cardiac remodeling in patients with obesity. (Translational Research 2014;164:323–335)

Abbreviations: α-SMA = α-smooth muscle actin; ACE = Angiotensin converting enzyme; AGEs = Advanced glycation end-products; AT1 = Angiotensin type 1; BMI = Body-mass index; EndMT = Endothelial-mesenchymal transition; ET-1 = Endothelin-1; MMP = Matrix metalloproteinase; (PAI)-1 = Plasminogen activator inhibitor-1; (PPAR)-α = Peroxisome proliferator-activated receptor-α; RAAS = Renin-angiotensin-aldosterone system; RAGEs = Receptor for advanced glycation end-products; RhoA = Ras homolog gene family member A; ROCK = Rho-kinase; ROS = Reactive oxygen species; (TGF)-β1 = Transforming Growth Factor-β1; (TSP)-1 = Thrombospondin-1; WT = Wildtype

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INTRODUCTION

The strong association between obesity and cardiovascular disease is not only because of the well-established links between obesity and the traditional coronary risk factors, but also involves direct effects on the heart, independent of the atherosclerotic process.[1] A growing body of evidence suggests that obese individuals are at a higher risk for development of heart failure.[2] Moreover, overweight subjects and individuals with increased abdominal adiposity also exhibit an increased risk of heart failure.[3] Echocardiographic examinations in healthy men and women participating in the Framingham Heart Study documented that body mass index (BMI) was associated with increased left ventricular hypertrophy, particularly in subjects with a BMI exceeding 30.0; this association was independent of age and systemic blood pressure levels.[4] The effects of obesity and its associated metabolic perturbations are not limited to effects on cardiomyocytes, but also involve the cardiac interstitium. The development of cardiac fibrosis has been extensively documented in patients with obesity. In 1847, William Harvey reported for the first time autopsy findings of a severely obese man, describing the heart as "large, thick and fibrous."[5] Fibrotic cardiac remodeling of the ventricle associated with evidence of diastolic dysfunction is often observed in normotensive subjects with abdominal obesity,[6] highlighting the effects of increased adiposity on the cardiac matrix. Fibrosis is also a dominant pathologic alteration in animal models of obesity[7] and may increase myocardial stiffness resulting in the development of diastolic dysfunction.

Although the link between obesity and cardiac fibrosis is well established, the pathophysiological basis for fibrotic interstitial remodeling in the hearts of obese subjects remains poorly understood. Whether the observed cardiac alterations represent direct effects of increased adiposity or reflect consequences of the many pathophysiological "companions" of obesity (such as hypertension, volume overload, insulin resistance, etc.) remains unknown. This review article presents the evidence documenting interstitial myocardial changes in obese subjects and discusses the cellular effectors and molecular pathways responsible for the development of fibrosis in obesity.

THE CARDIAC INTERSTITIUM IN THE NORMAL HEART

Preservation of cardiac architecture and transmission of contractile force are dependent on an intricate network of extracellular matrix comprising fibrillar collagen.[8] In addition to collagen I (that forms thick fibers and confers tensile strength) and collagen III (that typically forms thin fibers and maintains elasticity),[9,10] the interstitial cardiac extracellular matrix also contains glycosaminoglycans, glycoproteins, and proteoglycans. Large amounts of proteases and growth factors are bound to the cardiac extracellular matrix; their activation after injury plays an important role in cardiac remodeling. Cardiomyocytes and interstitial cells (including fibroblasts, vascular cells, and immune cells) are enmeshed into the collagen-based matrix and continuously interact with the matrix, thus sensing alterations in their microenvironment. Cardiac fibroblasts are the most abundant interstitial cells in the adult mammalian myocardium and are responsible for formation and preservation of the matrix network.[11] During the neonatal period, as the heart transitions from the fetal to the neonatal circulation, elevation of left ventricular pressures results in marked expansion of the cardiac fibroblast population.[12] In young adult hearts, cardiac fibroblasts appear to maintain quiescence, exhibiting limited inflammatory or proliferative activity. In aging hearts, cardiomyocyte loss is associated with expansion of the interstitium and increased collagen content.[13-15] Extensive evidence, derived from animal models and human studies, suggests that obesity is associated with acceleration and accentuation of fibrotic myocardial changes.

CARDIAC FIBROSIS IN ANIMAL MODELS OF OBESITY

The development of cardiac fibrosis has been documented in most experimental models of obesity and is often associated with diastolic dysfunction. The severity of cardiac fibrosis is dependent on the species, strain, and age of the animals, the underlying mechanism of obesity, and on the presence and severity of concomitant pathophysiological conditions (such as hypertension and metabolic dysfunction). db/db mice harbor a mutation resulting in the expression of a nonfunctional truncated long-form of the leptin receptor. These animals have hypothalamic resistance to leptin, and develop a voracious appetite, marked obesity, and overt diabetes at a young age. Cardiac interstitial fibrosis has been consistently documented in db/db animals using both histologic and biochemical techniques at the age of 4–6 months[7,16]; fibrotic changes in db/db mice are associated with diastolic dysfunction.[17] Much like db/db mice, leptin-deficient ob/ob animals develop severe obesity, insulin resistance, and cardiac hypertrophy at a young age[18]; however, evidence documenting cardiac fibrosis in ob/ob mice is less consistent. Zaman et al[19] showed that ob/ob mice exhibit significant perivascular cardiac fibrosis associated with elevated expression of transforming growth factor (TGF)-β1 and plasminogen activator inhibitor (PAI)-1, suggesting activation of matrix-preserving pathways. In contrast, Van den Bergh