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Review

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An Overview of the Mechanism behind Excessive Volume of Pericardial Fat in Heart Failure

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Heart failure (HF) is a clinical syndrome characterized by myocardial dysfunction leading to inefficient blood filling or ejection. Regardless of the etiology, various mechanisms, including adipokine hypersecretion, proinflammatory cytokines, stem cell proliferation, oxidative stress, hyperglycemic toxicity, and autonomic nervous system dysregulation in the pericardial fat (PCF), contribute to the development of HF. PCF has been directly associated with cardiovascular disease, and an increased PCF volume is associated with HF. The PCF acts as neuroendocrine tissue that is closely linked to myocardial function and acts as an energy reservoir. This review aims to summarize each mechanism associated with PCF in HF.

Key words: Heart disease, Heart failure, Fat

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INTRODUCTION

The heart is predominantly surrounded by pericardial fat (PCF), including epicardial adipose tissue (EAT),[1-3] and PCF has metabolic roles such as lipid storage, secretion of endocrine factors, and release of fatty acids.[4,5] Under physiological conditions, EAT provides mechanical, biochemical, and thermogenic cardioprotective effects; under pathological conditions, EAT can locally secrete proinflammatory cytokines through paracrine pathways and can impact cardiovascular disease.[6] In addition, EAT, also a metabolically active endocrine organ, can modulate cardiac structure and produce numerous harmful effects like atherosclerosis, activation of proinflammatory cytokines, atherogenic changes in monocytes and endothelial cells, cardiomyopathy, and modulation of intrinsic autonomic nerve activity.[7] PCF has been directly associated with cardiovascular outcomes and risk factors due to its direct effects on the myocardium, and an increased PCF volume is associated with myocardial dysfunction in heart failure (HF).[8-11] PCF has attracted the attention of physicians in relation to cardiovascular disease because it covers the heart's surface and surrounds the adventitia of the coronary arteries. Therefore, a positive correlation exists between PCF volume and severity of cardiovascular disease.[12] This review summarizes the basic science of the association of HF with PCF (Fig. 1).

ADIPOKINES

Adipokines, including specific cytokines, play a role in obesity and its associated co-morbidities. The PCF (including EAT) secretes hormones, cytokines, growth factors, vasodilators, and other substances that function as important signaling molecules.[13,14]

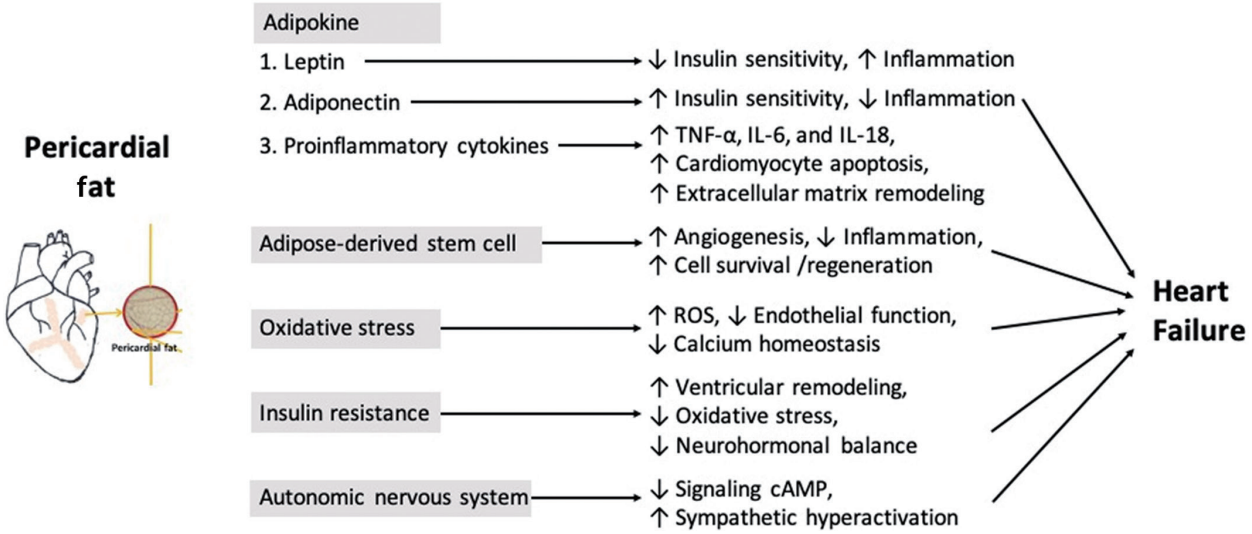

Figure 1. A basic perspective of heart failure associated with pericardial fat. TNF-α, tumor necrosis factor α; IL, interleukin; ROS, reactive oxygen species; cAMP, cyclic 3′,5′-adenosine monophosphate.

These compounds contribute to the development of metabolic syndromes, including cardiovascular diseases. Leptin, which was discovered in 1994, was the first identified adipokine.[15] Adiponectin, another member of the adipokine family, has a role in glucose regulation and fatty acid oxidation.[16,17] Proinflammatory cytokines inhibit lipoprotein lipase in adipocytes, leading to insulin resistance and secretion of circulating free fatty acids.[18] Insulin resistance is also associated with oxidative stress, hyperglycemia, hyperlipidemia, dysregulated secretion of adipokines, and inappropriate activation of the renin-angiotensin II-aldosterone system and the sympathetic nervous system. Insulin resistance is a major factor in the development of HF.[19]

Leptin

Leptin is an important hormone in weight regulation and energy homeostasis.[20] It acts on the central nervous system to regulate appetite and directly or indirectly affects cardiovascular functions.[21,22] Leptin is primarily produced by adipose tissue, but it is also secreted by other tissues, such as the skeletal muscles, placenta, gastric mucosa, and heart.[23,24] Its main role is regulating energy balance and cell metabolism and controlling inflammatory and immune responses. Leptin is secreted from the PCF and is crucial in maintaining homeostasis in the cardiovascular system.[25] The signaling of leptin involves various pathways, including Janus kinase, signal transducers and activators of transcription, insulin receptor substrate, phosphatidylinositol 3 kinase, mitogen-activated protein kinase, and extracellular signal-regulated protein kinase.[20] Elevated leptin often is found in obese individuals, and this increase can be associated with leptin resistance, which can lead to cardiac dysfunction and HF.[25] Studies have shown that elevated leptin level is associated with an increased risk of HF in men without preexisting coronary heart disease independent of body mass index and other potential mediators.[26]

Adiponectin

Adiponectin is an adipokine protein and hormone that exerts various effects on metabolic processes; it is mainly known for its insulin-sensitizing and anti-inflammatory effects.[17,27] Although the PCF is the primary site of production, adiponectin is also secreted by cardiomyocytes and connective tissue cells within the heart. Adiponectin is crucial in several metabolic processes, including promoting fatty acid oxidation, inhibiting glucose production in the liver, increasing insulin release from the pancreas, and promoting fat storage in subcutaneous fat pads.[17] In humans, the plasma concentration of adiponectin typically ranges from 5 to 30 μg/mL.[2,28] The adiponectin concentration tends to increase gradually with increasing severity of cardiovascular diseases, including HF.[29] Kistorp et al.[30] reported that high plasma level of adiponectin could serve as an independent predictor of mortality in HF, and adiponectin may have implications for the prognosis and outcome of HF (Fig. 2).

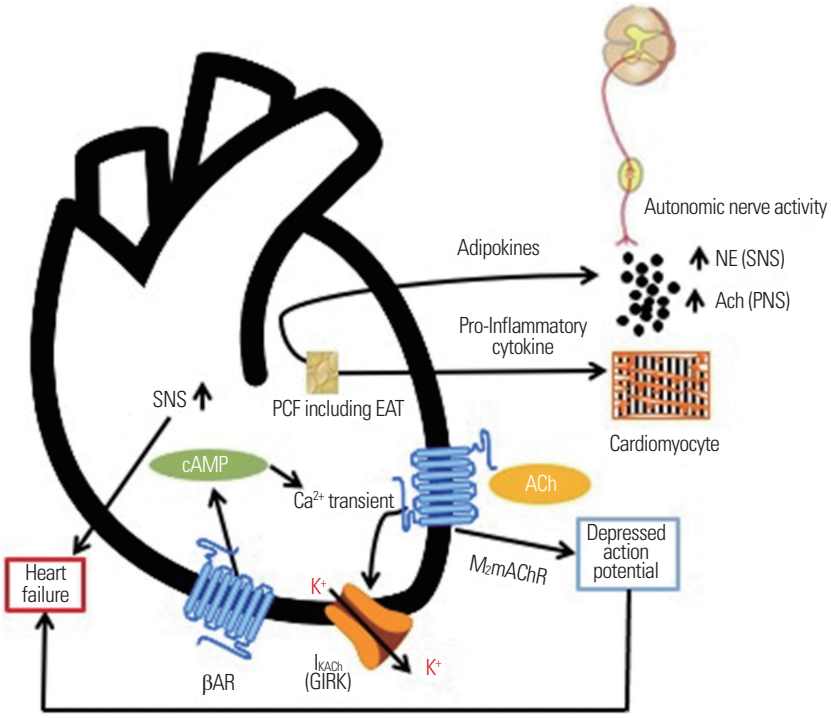

Figure 2. Various biological mechanisms that present as excessive volume of pericardial fat (including epicardial fat) that may lead to heart failure. NE, norepinephrine; SNS, sympathetic nervous system; Ach, acetylcholine; PNS, peripheral nervous system; PCF, pericardial fat; EAT, epicardial fat; cAMP, cyclic 3′,5′-adenosine monophosphate; βAR, β-adrenergic receptor; I_{KACh}, cholinergic potassium hyperpolarizing current; GIRK, G protein-gated K^+ channel; M_2mAChR, muscarinic acetylcholine receptor.

Overall, leptin and adiponectin play a significant role in metabolic regulation, insulin sensitivity, and inflammation. Their involvement in cardiovascular disease, particularly HF, suggests their potential as biomarkers and therapeutic targets for cardiovascular conditions.

Proinflammatory cytokines

Proinflammatory cytokines are low-molecular-weight proteins that have a crucial role in immune and inflammatory reactions. They are involved in various physiological and pathological processes, including recruiting immune cells to inflammatory sites and stimulating cell division, proliferation, and differentiation.[31] In HF, proinflammatory cytokines, such as tumor necrosis factor α, interleukin (IL)-6, and IL-18, are activated and released into the surrounding tissue as part of the inflammatory response. These cytokines can directly affect the structure and function of cardiomyocytes.[32] Circulating and intracardiac levels of proinflammatory cytokines have been reported to be elevated in HF.[33,34] The presence of these cytokines is associated with the progression of HF. The mechanisms by which proinflammatory cytokines contribute to the progression of HF include cardiac myocyte hypertrophy, contractile dysfunction, cardiac myocyte apoptosis, and extracellular matrix remodeling.[32] These effects of proinflammatory cytokines on cardiomyocytes and cardiac tissue contribute to the development and progression of HF (Fig. 2).

ADIPOSE-DERIVED STEM CELLS

Adipose-derived stem cells (ADSCs) were first discovered by Zuk et al.[35] in 2001 and are a type of mesenchymal stem cell. These cells can differentiate into various cell types found in the cardiovascular system, including cardiomyocytes, endothelial cells, and vascular smooth muscle cells.[36] One of the significant characteristics of ADSCs is their secretion of various protective factors and signaling molecules. These compounds include vascular endothelial growth factor, hepatocyte growth factor, insulin-like growth factor-1, various types of mRNAs, and cytokines. These factors have multiple functions, such as promoting angiogenesis, reducing inflammation, and supporting cell survival and regeneration. This type of stem cell can secrete these factors to modulate signaling pathways in

neighboring cells and to contribute to tissue repair and regeneration[36] and has the unique property of being able to replace, repair, and regenerate dead or damaged cells in various tissue. They can integrate into the existing tissue and differentiate into specific cell types to restore functionality. However, an excessive volume of PCF can have detrimental effects on various signaling pathways, including those generating reactive oxygen species (ROS). The generation of ROS can induce apoptosis in ADSCs, potentially limiting their regenerative capability. Managing oxidative stress and maintaining proper mitochondrial function are essential for the survival and functionality of ADSCs.[37]

OXIDATIVE STRESS

Oxidative stress refers to an imbalance between the production of ROS and the antioxidant defense mechanism. ROS are generated within the cellular environment through various sources, including mitochondria during oxidative phosphorylation, nicotinamide-adenine dinucleotide phosphate (NADPH), xanthine oxidase (XO), and uncoupled nitric oxide (NO) synthase.[38] ROS are highly reactive oxygenated biochemical species that include superoxides (O_2^-), hydroxyl radicals, and nonradicals capable of generating free radicals like hydrogen peroxide. Excessive generation of ROS can lead to cellular dysfunction, lipid and protein peroxidation, DNA damage, irreversible cell damage, and cell death. These processes contribute to the development of various pathological cardiovascular conditions.[38]

NO is an essential biochemical molecule involved in normal cardiovascular homeostasis. It has a role in cardiac function, coronary vasodilatation, modulation of cardiac contractile function, and inhibition of platelet and neutrophil adhesion and activation.[39] NO also acts as an antioxidant by inhibiting the activity of the enzymes XO and NADPH oxidase, and it helps maintain the homeostatic balance between O_2^- and NO in the body.[39] However, increased level of peroxynitrite, a reaction product of NO and O_2^-, can compromise the physiological functions and bioavailability of NO. ROS directly influence contractile function in the heart by modifying proteins involved in calcium handling. For example, ROS can modify critical –SH groups on the ryanodine receptor to increase the probability of calcium release from intracellular stores. ROS can also suppress the L-type calcium channel current and interact with Ca^{2+} ATPase, inhibiting calcium uptake into intracellular stores. These interactions disrupt calcium homeostasis, which is crucial for proper cardiac function.[40-42] Numerous scientists and clinicians have reported that HF is associated with excessive generation of ROS.[43-45] Landmesser and Drexler[46] also reported that oxidative stress could cause endothelial dysfunction in HF, contributing to impaired vascular function.

INSULIN RESISTANCE

Insulin is a powerful hormone that exerts diverse effects depending on the cell type. Its primary metabolic functions include stimulating glucose uptake in skeletal muscles and adipocytes, promoting glycogen synthesis in skeletal muscles, suppressing hepatic glucose production, and inhibiting lipolysis in adipocytes.[47] Insulin resistance refers to a condition in which the biological effect of insulin is lower than expected, either clinically or experimentally. Impaired responsiveness to insulin occurs in insulin resistance, leading to increased lipid synthesis in hepatocytes and enhanced lipolysis in adipocytes, and results in elevated levels of circulating fatty acids and triglycerides.[48]

Insulin resistance is associated with alterations of the left ventricular structure and function.[49] Cardiac insulin resistance is directly related to systemic insulin resistance due to the metabolic and endocrine overload of insulin.[49] Factors such as oxidative stress, hyperglycemia, hyperlipidemia, dysregulated secretion of adipokines/cytokines, and inappropriate activation of the renin-angiotensin II-aldosterone axis contribute to the development of cardiac insulin resistance.[19] This condition leads to metabolic inflexibility, impaired calcium handling, mitochondrial dysfunction, dysregulated myocardial-endothelial interactions, energy deficiency, impaired diastolic dysfunction, myocardial cell death, and cardiac fibrosis.[19]

Insulin resistance severely affects cardiac function, including coronary heart disease, cardiorenal syndrome, hypertension, diabetic cardiomyopathy, and obesity cardiomyopathy.[50-52] The development of these conditions is associated with increased circulating levels of nutrients, oxidative stress, and alterations in the neurohumoral and cytokine balance, which have been considered a risk factor for HF.[19,53] Clinical studies have shown that insulin resistance

predicts the development of HF, indicating a strong association between insulin resistance and HF.[50]

AUTONOMIC NERVOUS SYSTEM

The cardiac autonomic nervous system contains the ganglion plexus located in the EAT pads of the PCF. These fat pads play a role in sympathetic and parasympathetic innervation in the heart.[54] In adjacent cardiac myocytes, the neurotransmitter acetylcholine activates a specific M2 subtype known as muscarinic acetylcholine receptors. Activation of these receptors leads to stimulation of G protein-gated K^+ channels, resulting in hyperpolarization of the cardiomyocytes through a cholinergic potassium hyperpolarizing current (IKACh). This process inhibits the synthesis and signaling of the second messenger cyclic 3′,5′-adenosine monophosphate. It counteracts the intracellular Ca^{2+} elevation produced by activation of β-adrenergic receptors during cardiac sympathetic hyperexcitation. Dysregulation of this balance between sympathetic and parasympathetic activity can contribute to development and progression of HF.[55] An increased PCF volume is closely associated with dysregulation of autonomic nervous activity, which can lead to increased risk of HF and mortality. Furthermore, EAT, which is located in the PCF, has 5.6-fold higher catecholamine level compared with subcutaneous adipose tissue. In HF, there is increased biosynthetic activity of catecholamines in the EAT, which is likely due to the increased volume of EAT that contains a large number of adipocytes that synthesize catecholamines.[56] Dysregulation of the autonomic nervous activity and the increased presence of catecholamines in the PCF contribute to the pathophysiology of HF and can further exacerbate the sympathetic hyperexcitation in HF and have implications for disease progression and outcomes. Understanding the role of PCF in cardiac autonomic regulation and the production of catecholamines provides insights into potential therapeutic targets for HF (Fig. 2).

CONCLUSION

Excessive deposition of PCF, particularly in the form of epicardial and pericardial adipocytes, can have detrimental effects on the heart and contribute to the development of HF. Managing body weight and reducing excess adipose tissue deposition,[57] including PCF, may be important for preventing or managing HF.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Study concept and design: KWK; acquisition of data: KWK; analysis and interpretation of data: SK and KKW; drafting of the manuscript: SK and KKW; critical revision of the manuscript: KWK; statistical analysis: KWK; obtained funding: KWK; administrative, technical, or material support: KWK; and study supervision: KWK.

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