Right Heart Morphology and Its Association With Excessive and Deficient Cardiac Visceral Adipose Tissue

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ABSTRACT: Visceral adipose tissue is an independent risk factor for the development of atherosclerotic coronary disease, arterial hypertension, diabetes and metabolic syndrome. Right heart morphology often involves the presence of adipose tissue, which can be quantified by non-invasive imaging methods. The last decade brought a wealth of new insights into the function and morphology of adipose tissue, with great emphasis on its role in the pathogenesis of heart disease. Cardiac adipose tissue is involved in thermogenesis, mechanical protection of the heart and energy storage. However, it can also be an endocrine organ that synthesises numerous pro-inflammatory and anti-inflammatory cytokines, the effect of which is accomplished by paracrine and vasocrine mechanisms. Visceral adipose tissue has several compartments that differ in their embryological origin and vascularisation. Deficiency of cardiac adipose tissue, often due to chronic pathological conditions such as oncological diseases or chronic infectious diseases, predicts increased mortality and morbidity. To date, knowledge about the influence of visceral adipose tissue on cardiac morphology is limited, especially the effect on the morphology of the right heart in a state of excess or deficient visceral adipose tissue.

KEYWORDS: Cachexia, epicardial adipose tissue, histology, imaging, right heart morphology

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Introduction

Depots of visceral adipose tissue (VAT) are associated with the development of atherosclerotic disease and contribute to an increased cardiovascular risk significantly more than subcutaneous adipose tissue.[1,2] Adipocytes in cardiac visceral adipose tissue (CVAT) are metabolically active cells that secrete pro-inflammatory and anti-inflammatory cytokines. The former, such as leptin, resistin, IL-1β, IL-6, TNF-alpha and monocyte chemotactic protein-1, affect the development and destabilisation of atherosclerotic plaque through paracrine and vasocrine action.[3-5] In the scientific literature, there is still some terminology confusion regarding the different fat compartments that make up CVAT, especially with the term 'pericardial fat'. Nevertheless, according to the latest research, CVAT can be divided into 2 main compartments separated by a parietal sheet of pericardium: intrapericardial and extrapericardial adipose tissue. Intrapericardial fat tissue refers to (a) epicardial (or subepicardial) adipose tissue (EAT) located between the myocardium and visceral pericardium, which is in direct contact with the coronary arteries, (b) perivascular adipose tissue surrounding the coronary arteries (continuation of EAT) and their branches (arteries and arterioles) and (c) adipose tissue located within the pericardial sac (sometimes referred to only as a pericardial adipose tissue [PAT] plus paracardial fat).[6] Conversely, extrapericardial adipose tissue (paracardial, mediastinal or intrathoracic fat) is the tissue located on the external surface of the parietal pericardium.[7-9] EAT has no fascias to separate it from the myocardium, and it can be found mostly around the atrioventricular and interventricular grooves and more predominantly around the free wall of the right ventricle (RV) than around the right atrium (RA).[10] More commonly present in the RV, ectopic adipose tissue accumulations can be found in healthy individuals as a common finding during routine computed tomography (CT) imaging, with a prevalence of 16% to 43%, or during autopsies and endocardial biopsies.[11-13]

According to available data, routine imaging methods can detect the different compartments of CVAT. However, due to insufficient information on the role of fatty cells in the pathophysiology of right heart diseases, finding adipose tissue is not described in routine clinical practice. This scientific review aims to systematically analyse known information about and the possibilities for the imaging of cardiac visceral fat depots,

the frequency of their occurrence and their effects in excessive and deficient states on the pathophysiology and morphology of the right heart.

Right Heart Morphology in Different Body Composition Statuses

Based on previous knowledge, CVAT in surplus or deficiency may be the cause of certain pathological conditions or their consequences.

Cardiac visceral adipose tissue and the state of chronic inflammation

The surplus of PAT and EAT is correlated with the development of heart failure, atherosclerosis and atrial fibrillation (AF).[14-16]

In some pathological conditions, such as obesity and metabolic syndrome, there is a reduced bioavailability of protective adipokines and an increased expression of pro-inflammatory genes (EAT and pericoronary adipose tissue) with the consequent development of adipocyte hypertrophy, tissue hypoxia, inflammation and oxidative stress.[17,18] Conversely, in the state of positive energy balance and overflow of the free fatty acids in the body, β-oxidation leads to the excessive expression of reactive oxygen species (ROS), which are the earliest predicators of insulin resistance and diastolic dysfunction.[19,20] The fact that EAT is more than just a fat depot stems from its secretory activity and its being a source of numerous cytokines, adipokines and chemokines.[21] Adipose tissue expansion, hypertrophy and death of adipocytes due to hypoperfusion, release of pro-inflammatory adipokines and recruitment of macrophages occur in obesity.[22,23] Tissue macrophages then recruit circulating monocytes, which mature and interfere with adipocytes, leading to the stimulation of pro-inflammatory and the suppression of anti-inflammatory adipokine production.[24] The interaction between adipocytes and macrophages eventually leads to a chronic state of low-grade inflammation. The development of insulin resistance, type 2 diabetes and CVD are considered to be due to chronic adipose tissue inflammation.[25]

The importance of such an active metabolic tissue and its role in the pathogenesis of CVD are unquestionable. In physiological terms, EAT weighs around 50 g and makes up to 20% of the ventricular total weight. Nevertheless, its effect on the heart's morphology is still unclear.[26] The difficulty in understanding the altered morphology of the right heart in relation to the presence of visceral adipose tissue stems from the fact that there are still no exact criteria for the degree of normal amount of EAT. Some reasons are the different results of echocardiographic studies based on measuring the thickness of adipose tissue, poor spatial resolution of ultrasound, the inability to measure the volume of adipose tissue and the unavailability of CT and magnetic resonance (MR) imaging during routine cardiac examination.

Right heart intramyocardial adipose tissue contains small or large clusters of adipocytes in the myocardial wall itself, sometimes accompanied by fibrotic changes. Although adipocytes can be found in a healthy heart, they can also be found in various pathological conditions. The role of infiltrated adipocytes in the myocardial wall has not been fully elucidated but has been associated with ischaemic and non-ischaemic heart disease and with arrhythmogenic potential.[8,9,11]

Deficiency of cardiac visceral adipose tissue

Available insights into altered cardiac morphology under the condition of deficient cardiac adipose tissue are scarce. Chronic diseases (eg, malignant, chronic infectious and metabolic diseases) and certain hereditary diseases (eg, congenital generalised lipodystrophy [CGL]) can be manifested by cardiac atrophy and decreased EAT. In 1950, Hellerstein and Santiago-Stevenson[27] performed a post-mortem study based on the analysis of 85 cases of atrophic heart of different pathogenesis. The causes of atrophy were usually neoplasms (predominantly malignant), followed by chronic infectious diseases. A decrease in the total mass of the atrophic heart was observed in relation to the set limit values. Furthermore, reduced or completely absent subepicardial adipose tissue was found in 52% of atrophic hearts, which, according to today's knowledge and nomenclature, would belong to EAT. Fat infiltration was reported in 14% of atrophic hearts. As shown in the microscopic analysis, the fat cells were small and partially collapsed with the described vacuolated spaces at the peripheral boundaries. In addition, an increased number of hyperchromatic nuclei per visual field and hypercellularity were reported, and this was explained by a sparse lymphoid cell exudate and an increased prominence of the underlying stroma. Autopsy findings in patients with CGL, in addition to normal or slightly hypertrophic myocytes, showed a reduction of perivascular and subepicardial adipose tissue.[28] Using MR and localised photon spectroscopy, patients with CGL were found to have a threefold increase in lipid content within the myocardium.[29]

Most of the available studies on the association between cardiac atrophy and cardiac morphology are based on the microscopic and macroscopic changes in the animal model of malignant diseases, and they include findings such as reduction of myofibrils, collagen and soluble proteins; a higher degree of fibrosis; and an increase in endoplasmic reticulum volume and the degree of cardiac steatosis.[30-32] Similarly, the animal model must be taken with caution because of the different physiological representations of adipose tissue between humans and different animal species.[21] However, a full understanding of altered right heart morphology in CVAT-reduced conditions requires new studies on morphological and physiological characteristics, which should ultimately lead to a better comprehension of the relationship between altered morphology and heart physiology. As there has been little research in this area,

and some studies are somewhat outdated, deficiency of cardiac visceral adipose tissue is a promising area of heart research that may considerably influence our understanding of heart tissue physiology and pathology.

Influence of cardiac cachexia on right ventricular morphology and function

Cardiac cachexia (CC) is a multifactorial condition associated with chronic heart failure (CHF) and is defined by loss of at least 5% of body weight over the past 12 months (oedema free), or a body mass index (BMI) $<20\,kg/m^2$, and the presence of at least 3 of the following clinical and laboratory findings: decreased muscle strength, anorexia, fatigue, low fat-free mass index and laboratory elevated inflammatory markers (CRP, IL-6).[33] CC has no pathognomonic clinical or laboratory findings. Obesity is known to be an independent risk factor for the development of heart failure and CVD, but paradoxically, the same factor may have a protective effect on obese patients with CHF ('obesity paradox') compared with patients with normal or reduced BMI ('lean paradox').[34-36] The factors contributing to the development of CC include an imbalance between anabolic and catabolic processes, dysfunction of the gastrointestinal system (malnutrition and malabsorption), neurohumoral and immune activation and decreased food intake. Unlike anorexia and malnutrition, which are conditions that can be corrected by proper nutrition, CC poses a significant challenge in treatment and prevention. As there are still no generally accepted recommendations for the treatment of CC, therapeutic non-pharmacological measures are aimed at nutritional support and maintenance of aerobic physical activity.[37]

Right heart dysfunction in patients with CHF, regardless of the degree of pulmonary hypertension, is associated with a poorer disease outcome.[38,39] Melenovsky et al[40] were the first to describe how the coexistence of CHF and RV dysfunction leads to a change in body composition or loss of total adipose tissue (sum of skin folds converted to total body fat and fat mass index obtained by indexing the square of body height), which ultimately contributes to a poorer disease outcome. In the same study, moderate to severe RV dysfunction was present in 51% of patients, often accompanied by decreased systemic blood pressure, severe tricuspid regurgitation and increased RV filling pressure, and these patients were more likely to meet the clinical and laboratory criteria for cachexia. Furthermore, in patients who had RV dysfunction and met the criteria for cachexia, a higher degree of RV dilatation, a more severe degree of dysfunction and a higher incidence of adverse outcomes were reported. Therefore, total adipose tissue loss in patients with CHF and RV dysfunction predicts an increased incidence of adverse outcomes. This suggests that the loss of adipose tissue reduces its cardioprotective properties, thus supporting the obesity paradox, in the context of heart failure and is a sign of increased catabolism (imbalance of anabolic and catabolic processes in CC). Other studies have found that morphological changes in the heart begin to present only after several months of CC diagnosis, depending on imaging technique but primarily based on altered left ventricle (LV) morphology.[41,42]

Diagnostic Tools for Right Cardiac Visceral Adipose Tissue Assessment

To visualise and quantify the amount of CVAT, several imaging methods are available, including transthoracic echocardiography (TTE), CT and MR, which all differ in spatial resolution. However, the question remains when and how to quantify CVAT, within which set values should normal be considered and how to implement the obtained results in clinical practice.

Echocardiographic assessment

TTE is a non-invasive, safe, inexpensive and time-efficient method that is standardly used in cardiovascular assessment. As early as 2003, Iacobellis et al[43] developed an echocardiographic model for the detection and quantification of right ventricular EAT (site with the greatest EAT thickness) in a standard 2D display guided by the M-mode in the long and short parasternal axis views. The examination was based on the measurement of the thickness of EAT at the end of the systole (due to possible adipose tissue compression in the diastole and obtaining underestimated values), visualising adipose tissue as an echo-free area between the myocardium and pericardial visceral sheet and taking measurements of 3 cardiac cycles to obtain the mean thickness. The obtained results were comparable with the values obtained by MR ($r=0.91$, $P=.001$) and without significant interobserver variability. While measuring EAT thickness, some studies took the values obtained by the end-diastolic measurement to better align with the results obtained by CT and MR.[44-46] According to the original research of Iacobellis et al[43] the mean EAT thickness was 7.30 cm (±3.42) in men and 6.84 cm (±2.76) in women, with no statistically significant difference. A significant correlation of EAT thickness was found in subjects with a predominant visceral fat accumulation in relation to subjects with a predominant peripheral fat distribution at 9.97 cm (±2.88) vs 4.34 cm (±1.98) in men and 7.19 cm (±2.74) vs 3.43 cm (±1.64) in women. Additionally, a good correlation was found between EAT thickness and waist circumference, and it could serve as a predictor of visceral obesity. Using an end-diastolic measurement, Nelson et al[47] reported a mean EAT thickness of 4.7 ± 1.5 mm in asymptomatic individuals and a significantly higher prevalence of carotid plaque in individuals with an EAT thickness ≥ 5.0 mm. Jeong et al[45] and Ahn et al[46] found a relevant correlation between EAT thickness and severity of coronary heart diseases; that is, thicker EAT was observed in participants with a more severe form of coronary atherosclerosis. Bertaso et al[48] suggested a cut-off value (>5 mm) for defining increased EAT thickness for patients with low cardiovascular risk. Due to the focal accumulation of EAT and the variability of the obtained results, Wang et al[49] suggested the interventricular groove in the parasternal short axis view as a new site for determining EAT thickness. The obtained values

showed a better correlation with EAT volume, the values of which were obtained using dual-source computer tomography, than when measured in the long parasternal axis view. As expected, an increased level of EAT was found in obese subjects compared with subjects with a normal body weight, and this was associated with an increased diameter of RV at the end of the diastole.[50] The use of TTE for measuring EAT thickness proved to be a helpful tool for predicting the occurrence of recurrent AF in patients after catheter ablation. In a small sample of 227 paroxysmal and 56 non-paroxysmal AF patients, the EAT thickness limit was defined as 6 mm for patients with paroxysmal AF and 6.9 mm for patients with non-paroxysmal AF.[51]

Despite the current knowledge on the correlation between EAT thickness, metabolic syndrome and the development of CVD, the routine evaluation of EAT during TTE is not performed because of undefined reference values, measuring modality and lack of research on a larger number of subjects.[52-56] Once the cut-off values are defined, the measurement of EAT during TTE examination is to be expected to become a part of the standard cardiovascular risk assessment. However, ultrasound is not suitable for detecting intramyocardial fat clusters because of its low spatial resolution.

Computed tomography assessment

Computed tomography (CT) is an inevitable imaging method for assessing the morphology and relationship of intrathoracic organs. Most of the available research based on the description and quantification of EAT has been conducted using CT because of its excellent spatial and temporal resolution. The combination of CT and angiography with volumetric acquisition provides the best spatial resolution for quantifying epicardial adipose tissue volume (EAV), with a cut-off value for cardiovascular disease of >100 ml.[57-60] The relevant advantage of CT compared with TTE is that it allows the quantification of EAT in the form of EAV more precisely, as the distribution of EAT in the heart is uneven.[61-63] The possibility of using EAV as a predicting factor for metabolic syndrome was demonstrated by Kim et al[64] using non-ECG-gated low-dose CT (LDCT), but a wider application of this method would require research on a larger sample of patients. Apart from the non-pathological presence of EAT, there is a series of pathological states with typical clusters of adipose tissue and altered RV morphology as a consequence.[12] Studies using CT have shown that obese patients have higher EAT values and that there is a proportional relationship between EAT amount, body weight and waist circumference.[65-67] An additional option of CT is the assessment of quality or metabolic activity of EAT. A lower attenuation obtained by CT (negative Hounsfield units) indicates an increased presence of lipid content within the heart and possibly a higher metabolic risk for developing insulin resistance and metabolic syndrome.[68,69]

Unlike in those with pathological conditions such as lipomatous metaplasia (LM), a certain amount of intramyocardial adipose tissue is relatively common in healthy individuals, predominantly in the free wall of the RV, and in up to 85% of patients who died from non-CVD, according to autopsy findings.[70] In CT scans, it is most often manifested by patchy or linear accumulations of adipose tissue located subepicardial, around the apical and anterolateral segments of the RV free wall and around the outflow tract of the right heart, without affecting myocardial thickness.[71] Sometimes fatty infiltration may be more pronounced with transmural wall involvement and with an increase in myocardial thickness.[72]

Magnetic resonance assessment

Magnetic resonance assessment, as well as CT, allows the 3D assessment of EAT but without radiation exposure. Unlike CT, MR is limited by a lower spatial resolution, a more difficult performance in obese patients and a higher cost.[73,74] Among its additional features, MR provides the ability to assess cardiac function and the presence of intramyocardial adipose and connective tissue.[75-77] The Multi-Ethnic Study of Atherosclerosis was conducted in 2017 on 3988 participants with no proven CVD. The results showed that larger volumes of heart adipose tissue (epicardial and paracardial) are connected to the lower RV mass and lower end-systolic and end-diastolic RV volume (ie, lower stroke volume of the right heart).[78] Chahal et al[79] investigated the effect of excessive body mass on the morphology and function of RV. They proved that overweight and obese patients have an enlarged RV mass (by 6% and 9%), an increased end-diastolic volume (by 8% and 18%), increased stroke volume (by 7% and 16%), and a decreased RV ejection fraction (by ⩾1%). The study was conducted without considering the percentage of adipose tissue within the total mass of the heart.

Histological assessment

The histopathological analysis of the cardiac tissue is usually done on post-mortem tissue samples and after heart surgery or catheterisation and biopsy. It is valuable for the examination of the morphological changes in cardiac tissue under pathological conditions. However, this method always involves an invasive approach for tissue harvesting.

Histological assessment can reveal different microscopic changes in the heart tissue (eg, changes in myocyte morphology, fibrosis, metaplasia, necrosis, inflammation, etc.) under different pathological conditions (eg, myocardial infarction, tumours, myocarditis, sudden death). Routine histological stains for light microscopy may be supplemented by special staining techniques, immunohistochemistry and electron microscopy.[80,81] Basic and advanced morphometric studies can be performed on histological sections of cardiac tissue with the help of different software for image analysis.[13]

Histologically, lipid accumulation in the myocardium can be seen as intracellular lipid accumulation in myocytes (myocardial steatosis and lipotoxic cardiomyopathy) or as clusters of adipocytes (intramyocardial adipose tissue). Intracellular

accumulations of triglycerides in cardiomyocytes can make up to 1% of cardiac mass, and they usually present in healthy individuals but are 2 to 4 times more common in patients with metabolic syndrome.[82,83]

In physiological terms, intramyocardial adipose tissue is the most prominent in the lateral RV wall and apex and is rarely found in the LV. In the LV, it is more often of a pathological nature and usually represents scar tissue, individually or in combination with connective tissue, in the form of LM.[12,13]

Histological studies also show that adipocytes in cardiac visceral adipose tissue are smaller than those in peritoneal and subcutaneous adipose tissue, usually with stromal and inflammatory cells present and individual clusters of nervous and nodal tissue.[84,85]

Myocardial Fat as a Part of Cardiovascular Pathology

A pronounced accumulation of intracellular triglycerides occurs because of excessive intake of free fatty acids that exceeds the ability of mitochondrial β-oxidation, which leads to the increased formation of ROS, accumulation of ceramides, mitochondrial dysfunction, endoplasmic reticulum stress or lipotoxic activity.[8,86,87] In ischaemic heart disease, the preferred source of energy in the heart is glucose, which causes triglycerides to remain unused and unoxygenated, resulting in remodelling and cardiac steatosis.[88,89] Research conducted on rats fed a high fat diet (fat content 35%) has shown that there is a development of lipotoxic events due to the increased intracellular presence of lipids (triglyceride and cardiolipin), which then leads to the reduced usability of glucose in mitochondria, hypertrophy and myocardial fibrosis. These events did not occur in the control group of rats that were fed a standard diet (fat content 3.5%) or in the group that received an antioxidant.[90,91] These results point to a possible lipotoxic effect related to microRNA modulation and the consequent development of cardiac dysfunction.

Myocardial fat tissue can be presented as part of some genetic and acquired CVD, such as arrhythmogenic right ventricular dysplasia (ARVD), scar after myocardial infarction, neuromuscular dystrophy, cardiac tumour or lipomatous hypertrophy of interatrial septum (LHIAS). Some of these diseases carry increased arrhythmogenic potential.[9,92,93]

ARVD is a hereditary disease manifested by the infiltration of adipose tissue into the RV myocardium (from the epicardial layer). Therefore, all intramyocardial changes occur independent of metabolic syndrome and obesity. The area of infiltration, also called 'the triangle of dysplasia', is located between the RV inflow tract and the outflow tract and apex.[94] In terms of examination methods, CT has the advantage over MR because CT has a better visualisation of heart morphology in patients with ICD, which negatively affects images on MR. Adipose tissue infiltration in patients with ARVD most commonly affects the free wall of the RV, sparing the subendocardial layer. RV wall thickness in ARVD is manifested by areas with a markedly thinned wall of up to ⩽2 mm, whereas wall thickness in non-pathological infiltration is intact or enlarged.[95-97] Histological changes similar to those in RV can also be found in RA, which can explain the increased incidence of atrial tachyarrhythmias in patients with ARVD.[98,99]

Primary or idiopathic dilated cardiomyopathy is characterised by the dilatation of both ventricles or LV exclusively, with a global reduction of contractile function (in the absence of coronary heart disease) and a share of hereditary form (autosomal dominant inheritance pattern) of around 25%.[100] The main histological features of this most common cardiomyopathy are linear intramyocardial fat cell accumulation with interstitial fibrosis, lymphocyte clusters and degeneratively altered myocytes.[101,102]

About 15% to 89% of patients who survived myocardial infarction (MI), depending on the severity of myocardial ischaemia, necrosis and modality of measurement, exhibited LM or a remodelling process characterised by the replacement of collagen at the site of scarring by interstitial fat cells.[103-105] LM usually does not represent a transmural change, usually involving <75% of myocardial wall thickness, with progression from the subendocardial layer.[95] The LM process is more commonly seen in the LV because of its higher myocardial mass, higher complexity of coronary artery network, higher frequency of MI in the left heart and less prominent collateral network compared with the RV.[106,107] The degree of LM development in the postinfarction period is time dependent and is present in 9.1% of cases in the first year, 20.7% of cases between the second and third year and in 37% of cases between the fourth and seventh year.[105] LM is manifested in CT findings by typical changes, such as hypodense areas with negative attenuation in the subendocardial layer, thinned ventricular wall and calcification findings.[106] The application of MR allows LM to be detected in 78% of patients who have survived MI. LM in individuals with MI has a histological finding similar to ARVD.[108] Admittedly, most histological analyses of LM were based on LV analysis because of the more frequent left heart involvement with acute coronary events. Similar changes are seen in the most commonly inherited neuromuscular disease with heart involvement, myotonic dystrophy, in which hypertrophic myocytes can also be found aside from fatty and fibrous infiltration.[109,110]

Lipomas are benign tumours and the second most common primary cardiac tumours after myxoma, with a prevalence of about 10%. They are mostly located in the RA, contain benign adipose tissue and are mostly asymptomatic.[111] The results obtained by CT show absorbent quality typical for adipose tissue.[95] A malignant and rare primary cardiac neoplasm, liposarcoma, usually originates from the right heart, more commonly in the RA. Primary liposarcoma or its metastases on CT scans are manifested as unencapsulated and inhomogeneous mass with a nodular appearance, usually septate with different patterns of attenuation characteristics for adipose tissue.[95,111] On MR images, lipomas are generally presented as a homogeneous nodular pattern on T1 images and are sometimes difficult to distinguish from liposarcomas. The thing that facilitates the

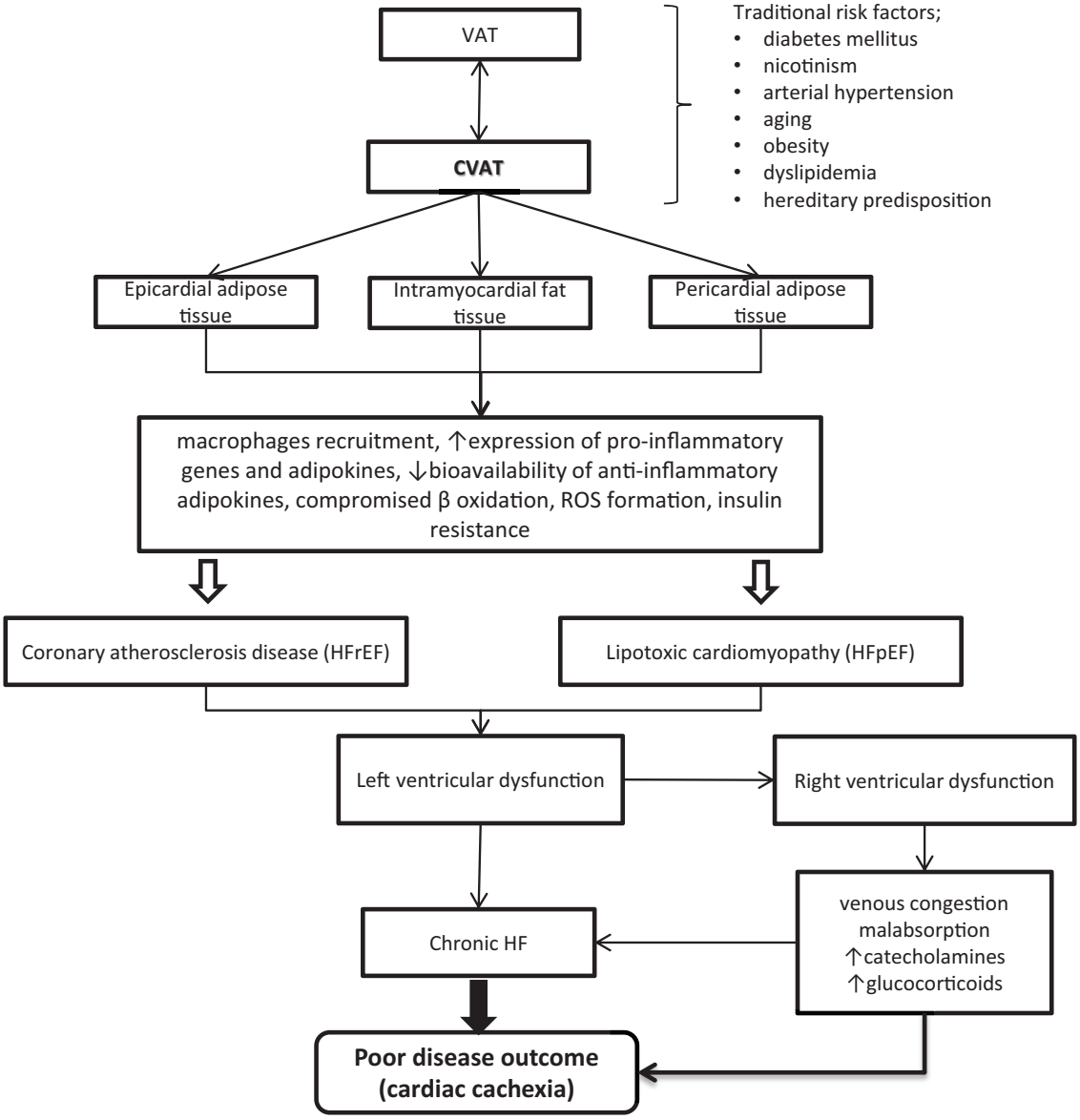

Figure 1. From cardiac obesity to cardiac cachexia.
Abbreviations: CVAT, cardiac visceral adipose tissue; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ROS, reactive oxygen species; VAT, visceral adipose tissue.
Pathophysiological role of cardiac visceral adipose tissue from the occurrence of cardiac obesity to the development of cardiac cachexia. The role of the RV obesity still remains unclear.
↑ – Increasing or upregulation.
↓ – Decreasing or downregulation.

distinction is the absence of a capsule in liposarcoma and the infiltration of the surrounding structures.[95,112,113]

LHIAS is a benign cardiac mass with an incidence rate of 1% to 8%, and it is caused by the accumulation of adipose tissue in the area of the interatrial septum (sparing the *fossae ovalis*) with a transverse diameter >2 cm. CT scans show a smooth, non-enhancing expansion of the interatrial septum in the transverse diameter, whereas the MR diagnosis is made by showing a thickening of the interatrial septum with homogeneous high signal intensity, similar to the intensity of subcutaneous adipose tissue. Histological findings show adipocyte hyperplasia and intramyocardial infiltration of the interatrial septum. The onset of LHIAS itself is mostly asymptomatic and rarely requires surgical treatment.[114,115]

Conclusion

CVAT, along with traditional risk factors, is an independent risk factor for the development of different CVDs. On one hand, its role is physiological (mechanical protection, thermogenesis, energy source), but on the other hand, adipose tissue surplus (EAT and intramyocardial adipose tissue) can be associated with pathological changes in the heart. The mechanisms underlying this phenomenon are still unclear and are probably multifactorial in nature. There is a high probability that cardiac fatty cells have an important role in the functional and morphological changes in the heart. This is proportional to lifespan, neurohormonal activity of the fatty cells and adjoint cardiovascular and metabolic conditions (Figure 1). To perform adequate studies on the role of fatty cells in cardiac health and

disease, it is important to know the possibilities of the available imaging techniques and to include them in regular clinical practice. TTE, which is the most available but also the most inaccurate one, provides a simple, non-invasive and inexpensive method of detection with an insufficiently defined performance algorithm and result interpretation. Methods such as MR and CT (including volumetric acquisition) give more accurate results. However, their application is still limited and not suitable for the routine examination of healthy individuals during cardiovascular risk assessment. Most of the currently available studies are based on morphological changes in the left heart. However, at the same time, special attention is given to the appearance of adipose tissue in the right heart and its influence on the development of arrhythmias. This calls for more research on right heart-associated fat.

To date, there are no clearly defined criteria for differentiating between the state when CVAT represents a physiological finding and that when it shows a pathological finding. Furthermore, the deficiency of CVAT is even a greater mystery in the context of evaluating the morphology and function of the heart. It is necessary to conduct more basic and clinical research to fully understand the role of CVAT in changing the heart morphology and pathophysiology. A better understanding of cardiac disease development from the molecular level to the clinical presentation can benefit diagnostic procedures, prevention and therapy in cardiology.

Author Contributions

D.V., N.B., and K.SR. carried out the study concept, design and drafting of the manuscript. All authors participated in the acquisition of the data. D.V., N.B., and K.SR. carried out analysis and interpretation of the data. E.R., J.R., B.D., T.B., and D.M. participated in the critical revision of the manuscript. K.SR. and N.B. carried out supervision of the study.

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