

Heart Failure with Preserved Ejection Fraction and Diabetes Mellitus

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Abstract

Heart failure with preserved ejection fraction (HFpEF) constitutes approximately 50% of heart failure patients. The prevalence of diabetes mellitus in HFpEF is high at 30-40%. The paper provides a systematic review of the pathophysiological features underlying HFpEF in diabetes mellitus. The importance of mechanisms other than left ventricular diastolic dysfunction underlying this important condition is emphasised. Thus, ventricular-arterial coupling & vascular dysfunction together with chronotropic incompetence & cardiovascular reserve dysfunction play an important role. The various morphologic and molecular features occurring in the myocardium and vasculature in diabetes secondary to hyperglycaemia and other metabolic disturbances are also discussed. These include microangiopathy, myocardial fibrosis, increased oxidative stress, impaired calcium homeostasis, activation of the cardiac renin-angiotensin system, autonomic neuropathy, endothelial dysfunction, re-expression of foetal gene response as well as stem cell involvement. Nonetheless, a lot is still unknown and further studies are needed to establish the underlying pathophysiological mechanisms with the hope that novel pharmacotherapies targeting this disease will be developed. In the meantime, cardiometabolic factors, including hyperglycaemia, hypertension and dyslipidaemia should be targeted and aggressively treated.

Background

In the past decade, there has been increasing interest in patients with signs and symptoms of heart failure (HF) despite a normal or near-normal left ventricular (LV) systolic function, for which the term “heart failure with preserved ejection fraction” (HFpEF) has been introduced. HFpEF constitutes approximately 50% of HF patients [1]. The Cardiovascular Health Study [2] suggests that it may be even commoner amongst patients with heart failure in the community and in women.

In the past, HFpEF was referred to as “diastolic heart failure” as opposed to “systolic heart failure” which relates to HF with reduced ejection fraction (HFrEF). However, there is now increasing emphasis on abandoning the terms diastolic/systolic HF since mechanisms other than diastolic dysfunction may contribute to HFpEF and an element of diastolic dysfunction exists in most cases of HFrEF [3]. The term ‘heart failure with preserved systolic function’ has also been used by some authors but the term HFpEF is preferable since parameters of systolic function other than EF may be abnormal. The problem with the present terminology and diagnostic criteria is that HFpEF cannot be diagnosed in subjects with low EF, even if diastolic dysfunction contributes significantly to their symptoms and prognosis. This problem can only be resolved if the diagnosis of HFpEF be based on only positive criteria or if the diagnosis is allowed in subjects in whom clinical or biochemical manifestations of heart failure are disproportionate to the degree of reduction in EF.

The differentiation between HFpEF from HFrEF is not only of academic interest but is also useful in clinical practice since medications used in the treatment of HFrEF have been disappointing in HFpEF. This observation also suggests that HFpEF is a separate pathophysiological entity [4]. Nonetheless, others argue that HFpEF and HFrEF are not separate entities but rather form part of one HF spectrum [5].

The prevalence of diabetes mellitus (DM), especially type 2 DM, is steadily increasing [6]. Although DM is a well-known risk factor for atherosclerosis and for coronary artery disease (CAD), its role in development of HF is less established. Nevertheless, the prevalence of DM in HF is approximately 20-35% [7] and is somewhat higher in patients with HFpEF, at 30-40% [8]. HFpEF and type 2 DM commonly coexist. Both conditions are associated with hypertension, obesity and old age [1], all of which promote the occurrence of HF. However, irrespective of underlying cardiovascular disease, DM has a crucial role in HFpEF as demonstrated in the CHARM study whereby the relative risk of cardiovascular death or HF hospitalization conferred by DM was significantly greater in patients with HFpEF compared with those with HFrEF [9]. The prevalence of HFpEF may be high even in asymptomatic and well-controlled diabetic subjects [10,11]. Despite the increased prevalence and poor outcome, pathophysiological features underlying HFpEF in DM remain uncertain, and will therefore be addressed hereunder.

Methods

A systematic review of the published literature was performed using Medline and Embase as computerized databases. The search included all published papers up to 21st May, 2011. The terms “heart failure with preserved ejection fraction”, “heart failure with normal ejection

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fraction" and "diastolic dysfunction" in association with "diabetes mellitus", were utilised in the search strategy.

1. Physiological Abnormalities associated with HFpEF in Diabetes

Four sets of guidelines have been published for the diagnosis of HFpEF [5,12-14]. They all require the simultaneous and obligatory presence of signs and/or symptoms of HF, normal LV ejection fraction, and evidence of diastolic LV dysfunction or of surrogate markers of the latter, e.g. LV hypertrophy, left atrial enlargement, atrial fibrillation, or elevated plasma natriuretic peptide levels. Although evidence of diastolic dysfunction forms an integral part in the diagnostic algorithms of HFpEF, this does not mean that it represents the sole contributor to disease pathophysiology. It is being increasingly recognized that other mechanisms play important roles, mainly resting and exercise-exacerbated systolic dysfunction [14-19], impaired ventricular-vascular coupling [17,18,20,21], abnormal exercise-induced and flow-mediated vasodilation [15-17,22], chronotropic incompetence [15,17,18,23], and pulmonary arterial hypertension [24,25]. The risk factors for progression to HFpEF are variable according to the underlying diseases [26]. However, many of the mechanisms above-mentioned are thought to play a role in the pathophysiology of HFpEF in DM.

1A. Left Ventricular Diastolic Dysfunction

LV diastolic dysfunction has been suggested as the first manifestation of diabetic heart disease in both type 1 and type 2 DM patients [27,28] (Figure 1). In the Strong Heart Study [30], which investigated the effect of DM on LV filling pattern in normotensive and hypertensive individuals, type 2 DM was associated with an impaired relaxation pattern independently of age, blood pressure (BP), LV mass and LV systolic function. The combination of DM and hypertension resulted in more severe abnormal LV relaxation than groups with either condition alone, suggesting a synergistic deleterious effect when both conditions were present. Moreover, abnormal relaxation in DM subjects was associated with higher fasting glucose and glycated haemoglobin (HbA1c) levels. The impact of poor glycaemic control on development of HF was also demonstrated in a registry of 49,000 DM individuals whereby each 1% increase in HbA1c was associated with an 8% increased risk of HF [31].

The mechanical processes of diastole can be divided into active relaxation and passive compliance, both of which can be affected. In the absence of endocardial/pericardial disease, diastolic dysfunction results from increased myocardial stiffness that is determined by the extracellular matrix and the cardiomyocytes. In addition, both compartments influence each other via matricellular proteins. The actual contribution of LV relaxation and compliance to the development of HFpEF in DM is still unclear. In a study by Takeda *et al* [26] on 544 Japanese DM patients with ejection fraction (EF) $\geq 50\%$, female sex, high body mass index, low haemoglobin, and low diastolic wall strain (DWS) were independently associated with the prevalence of HFpEF. A low DWS indicates impairment of LV compliance [32]. On the other hand, the decrease in E velocity, an index of LV relaxation, was not

independently associated with HFpEF. This was a cross-sectional one and thus subject to various limitations, including survival bias and inability to assess cause and effect. Nonetheless, the impaired LV compliance noted is known to be associated with increased collagen accumulation and enhanced collagen cross-linking [33]. In DM, there is increased myocardial deposition of collagen and advanced glycation end-products (AGEs) which promote cross-linking [34]. Willemsen *et al* [35] have shown that DM HF patients had higher tissue AGEs and poorer exercise capacity than those without DM. Also, tissue AGEs correlate with mean E' in DM, suggesting a close relationship between tissue AGEs, diastolic function, and exercise capacity independent of EF.

The findings of Takeda *et al* [26] contrast with those of van Heerebeek *et al* [36]. The latter used LV endomyocardial biopsy samples from 64 patients (26 diabetic), to compare myocardial fibrosis, AGE deposition, and cardiomyocyte resting tension (F_{passive}) of isolated cardiomyocytes between DM and non-DM HFpEF patients and between DM and non-DM HFrEF patients. All patients had been hospitalized for worsening HF and none had CAD. It was shown that DM HFpEF patients had increased LV myocardial stiffness (assessed by radial LV stiffness modulus) in comparison to non-DM patients with HFpEF. Furthermore, the increased diastolic LV stiffness was related more to cardiomyocyte F_{passive} and less to AGE deposition. On the other hand, in DM HFrEF patients, the higher diastolic LV stiffness was related to both AGE deposition and interstitial fibrosis. The authors suggest that the high cardiomyocyte F_{passive} is probably secondary to a phosphorylation deficit of myofibrillar or cytoskeletal proteins [37,38]. High F_{passive} was accompanied by Z-line widening, suggesting that Z-line widening results from altered elastic properties of cytoskeletal proteins that pull at and open up adjacent Z lines. Also, F_{passive} rose progressively from HFrEF to HFpEF in non-DM to HFpEF in DM, and this rise was paralleled by an increase in cardiomyocyte diameter and a shift from eccentric to concentric LV remodeling. All of the HFpEF DM patients had type 2 DM and fasting hyperinsulinaemia. They thus suggest that the excess cardiomyocyte hypertrophy in DM HFpEF is probably secondary to insulin resistance since hyperinsulinaemia is known to stimulate prohypertrophic signaling in insulin-responsive tissues e.g. the myocardium [39].

The population studied by van Heerebeek *et al* showed different clinical characteristics to those observed in epidemiological studies. Thus, as suggested by Connelly *et al* [40], one should not conclude that fibrosis does not contribute to HFpEF in DM. Animal studies suggest that fibrosis contributes to this syndrome [41], while human studies have shown that collagen volume fraction is increased approximately 2-fold in both DM and non-DM subjects with HFpEF [42]. It seems that both fibrosis and cardiomyocyte F_{passive} are linked attributes to HFpEF in DM though the relative contribution of each remains under debate. Undoubtedly, research into new treatment strategies should include both antifibrotic and antihypertrophic strategies [40].

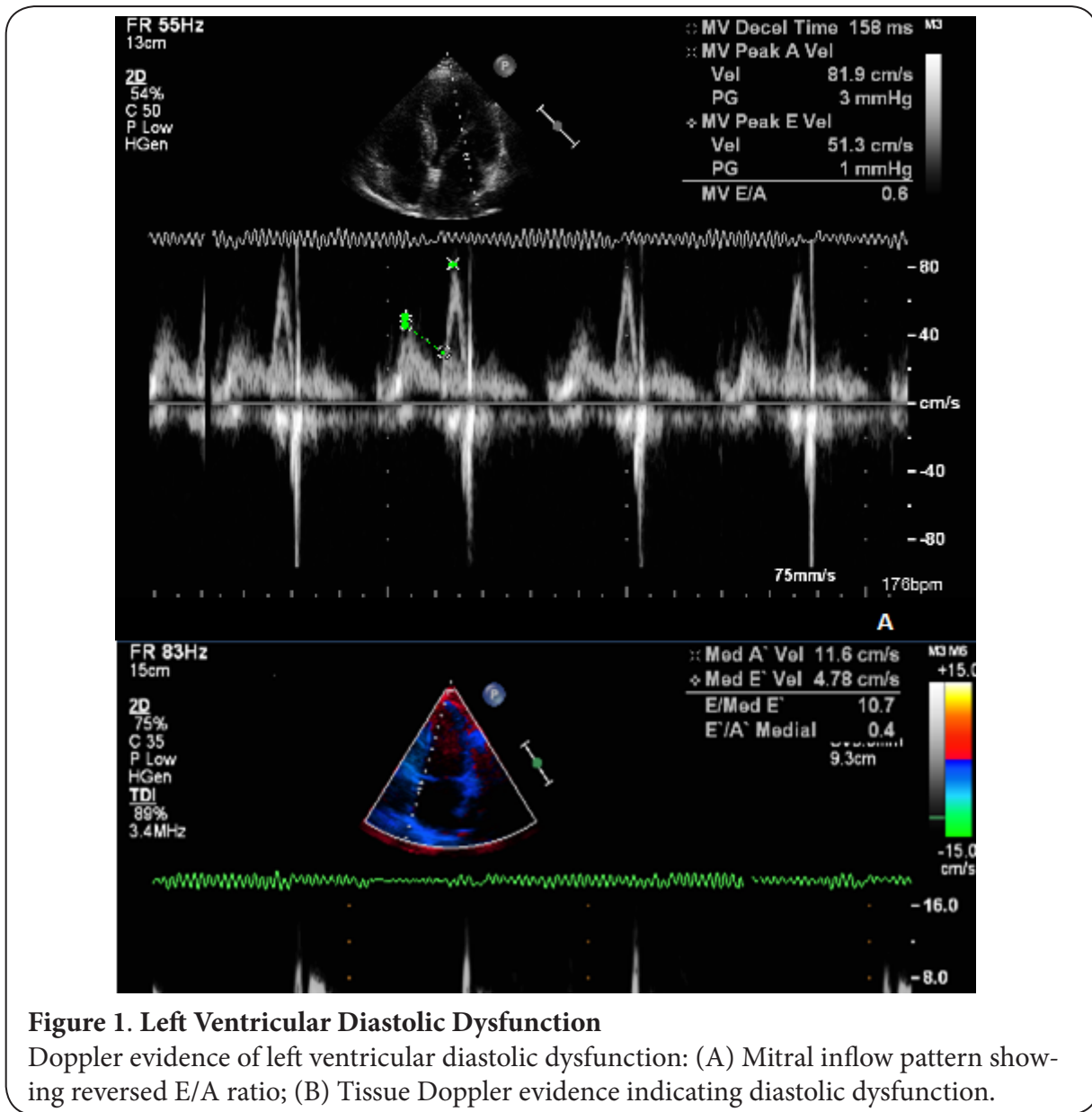


Figure 1. Left Ventricular Diastolic Dysfunction

Doppler evidence of left ventricular diastolic dysfunction: (A) Mitral inflow pattern showing reversed E/A ratio; (B) Tissue Doppler evidence indicating diastolic dysfunction.

1B. Ventricular-arterial Coupling & Vascular Dysfunction

EF is preserved in HFpEF, but EF is more accurately regarded as a measure of ventricular-arterial coupling than contractility alone [41]. Ventricular-arterial coupling can be expressed as the ratio of arterial elastance to end-systolic elastance [43]. Elastance is a measure of stiffness. Arterial elastance is determined by peripheral vascular resistance, total arterial compliance, impedance, and systolic and diastolic time intervals [44] and therefore represents the arterial afterload on the LV. In healthy subjects, ventricular-arterial coupling maintains this ratio within narrow limits, so as to optimise the energy efficiency of the myocardium.

However, ageing, hypertension, and DM lead to ventricular and vascular stiffening, with consequent HFpEF [8,45], the latter leading to greater BP lability with amplified BP changes for any alteration in preload/afterload [46]. Thus, although ventricular-arterial coupling appears beneficial in maintaining optimal cardiovascular performance [47,48], ultimately it results in adverse cardiovascular effects, including increased sensitivity to volume shifts and decreased exercise capacity [49]. Ventricular-arterial coupling may be particularly relevant in DM. The brachial-ankle pulse wave velocity (baPWV), an indirect surrogate of vascular compliance, is increased in DM subjects as compared with normal subjects [50].

Similarly, in the Digitalis Investigation Group (DIG) ancillary study, a higher pulse pressure was noted in HFpEF patients with DM compared to non-DM patients [51]. Increased arterial stiffness in DM is probably secondary to AGEs; this could have contributed to the increased risk of adverse cardiovascular outcomes in DM HFpEF patients [51].

Nonetheless, the role of ventricular-arterial coupling in DM patients with HFpEF is still controversial. In the study by Takeda *et al* [26], there was no difference in baPWV between DM subjects without HF and DM subjects with HF while Poulsen *et al* [52] have shown that valvulo-arterial impedance ($p=0.027$) and summed stress score, an indicator of myocardial ischaemia ($p<0.001$), are independent predictors of grade 2 diastolic dysfunction in type 2 DM, though only summed stress score ($p<0.001$) was a predictor of left atrial dilation. Taken together, these results suggest that ventricular-arterial coupling might play a role in the development of HFpEF in DM.

Systemic vasorelaxation with exercise is attenuated in HFpEF [15-17], promoting impaired delivery of blood flow to skeletal muscle. Vascular dysfunction in HFpEF may be partly secondary to endothelial dysfunction, as suggested by Borlaug *et al* [17] whereby impaired flow-mediated vasodilation was noted in HFpEF compared with healthy age-matched controls. Endothelial dysfunction is a common finding in DM, as discussed below.

1C. Chronotropic Incompetence & Cardiovascular Reserve Dysfunction

Various studies have highlighted the importance of abnormalities in cardiovascular reserve function with exercise stress in HFpEF [15-20,23], explaining why most patients with HFpEF complain of symptoms only on exertion. Normal exercise reserve function is determined by diastolic reserve, systolic reserve and chronotropic reserve. Abnormalities in each of these components have been identified in HFpEF, including subjects with DM.

Diastolic reserve is reduced in HFpEF such that patients display blunted increases in preload volume with exertion, despite marked elevations in filling pressure. In a comprehensive study using upright bicycle exercise testing with simultaneous right heart catheterization and serial radionuclide ventriculography [53], cardiac index, stroke volume index, and LV end-diastolic volume (LVEDV) at rest did not differ between HFpEF patients, some of whom were diabetic, and control subjects but were lower in patients with HFpEF at peak exercise. This resulted in markedly lower peak oxygen consumption. The authors suggest that this is secondary to impaired LV filling and failure to use the Frank-Starling mechanism properly [48]. An impaired chronotropic response was also reported. This is probably related to downstream deficits in β -adrenergic stimulation since there is a similar increase in plasma catecholamines with exercise in HFpEF and healthy controls [15]. This is possibly secondary to autonomic dysfunction, a common co-morbidity in DM, since baroreflex sensitivity is reduced and heart rate recovery impaired in HFpEF [15,54].

In a study by Borlaug *et al* [15], HFpEF patients, most of whom were diabetic, showed a lower increase in heart rate, lower decrease in systemic vascular resistance index, and lower increase in cardiac index during exercise when compared with controls while LVEDV increased similarly in both groups. These findings suggest that in HFpEF both the chronotropic and vasodilatory reserves are diminished [15]. The latter would result in reduced diastolic reserve. In another study by Westermann *et al* [55], a decrease in LVEDV and stroke volume were noted in HFpEF patients (17% diabetic) during pacing at 120 beats/min; this was interpreted as manifestation of increased LV stiffness. However, during handgrip, a more physiologic form of exercise, there was no change in LVEDV. In view of these contradictory results, further studies are needed to understand the haemodynamic response to exercise in HFpEF.

With respect to systolic reserve, blunted increases occur in EF, contractility, and longitudinal systolic shortening velocities during exercise [15-19]. It has been suggested that myocardial ischaemia (epicardial/microvascular coronary disease or vascular rarefaction), impaired β -adrenergic signalling [56], myocardial energetics [18,57], and abnormal calcium handling [58] play a role in systolic and diastolic reserve dysfunction in HFpEF. These pathological changes have been noted in DM (discussed below).

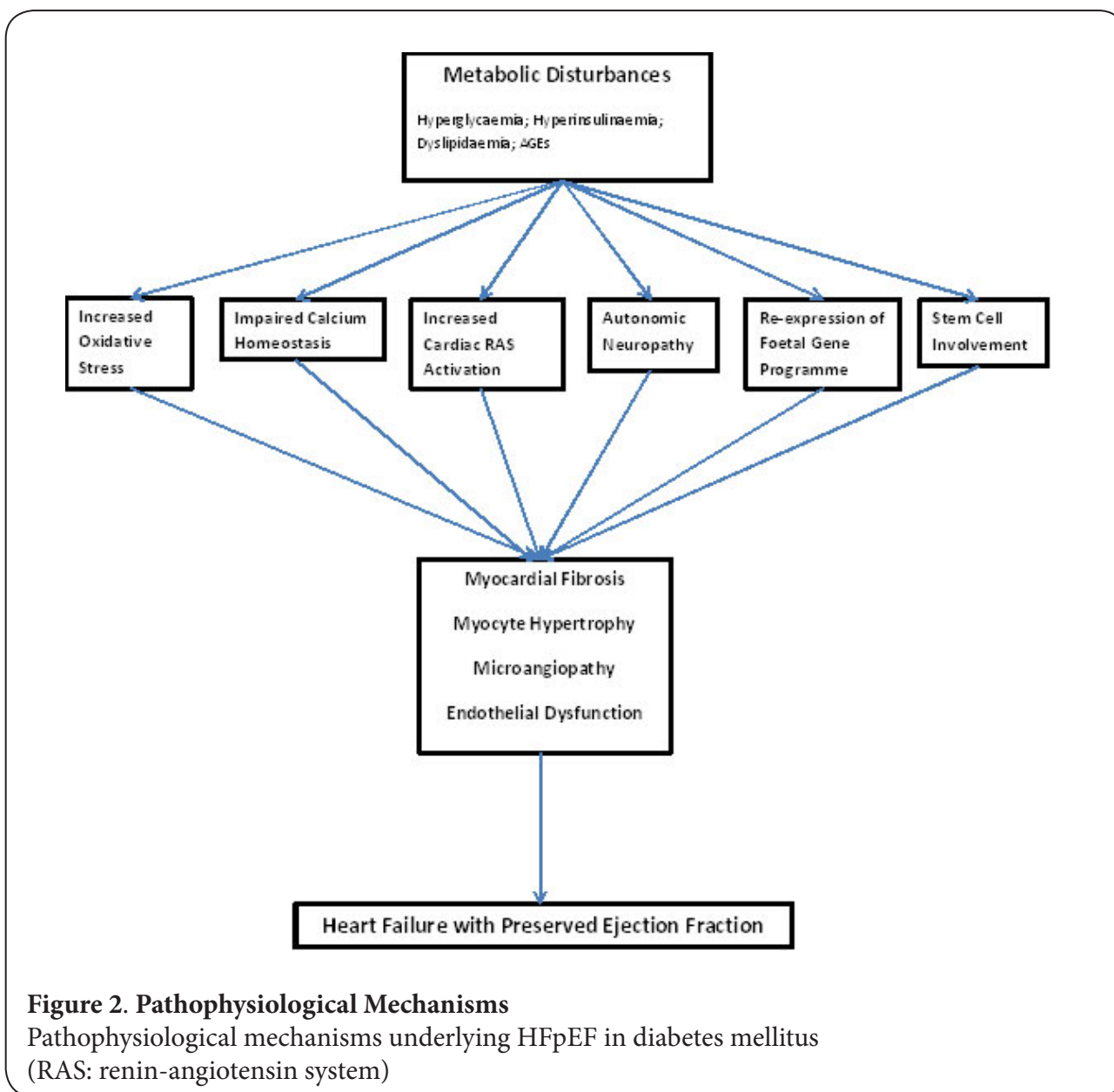
2. Pathophysiological Mechanisms underlying HFpEF in Diabetes

Various morphologic changes occur in the diabetic heart leading to the abnormal physiological findings described above. These include increased extracellular collagen deposition, interstitial fibrosis, myocyte hypertrophy and intramyocardial microangiopathy. These changes are probably secondary to altered myocardial glucose and free fatty acid metabolism (FFA) in DM as outlined below and in Figure 2.

2A. Hyperglycaemia

The hallmark of type 2 DM is insulin resistance with impaired myocardial glucose use and increased turnover of FFAs, leading to myocardial lipotoxicity, uncoupling of mitochondrial oxidative phosphorylation and disturbed contraction/relaxation coupling [59]. In type 1 DM, even though no hyperinsulinaemia is usually present, hyperglycaemia secondary to β -cell failure leads to numerous adverse cellular effects including down-regulation of sarcoplasmic reticulum calcium ATPase (SERCA) expression and activity, decreased Na^+/K^+ -ATPase function and decreased myocardial flow reserve, leading to both LV systolic and diastolic dysfunction [60]. Furthermore, diminished C-peptide levels in type 1 DM may adversely affect cardiac endothelial function [61,62], probably through diminished nitric oxide release [63].

Glycaemic control has been reported to improve diastolic dysfunction [64] and to reduce LV mass [65] over a 6-12 month period. It is important to note that good glycaemic control may also be a marker of improved metabolic control including free fatty acid concentration.



2B. Lipotoxicity

Diabetic subjects exhibit increased myocardial fat [66] and this is associated with diastolic dysfunction [67]. In both type 1 and type 2 diabetes, the myocardium is increasingly dependent on fatty acid rather than glucose metabolism for its energy requirements [68]. Since fatty acid metabolism requires more oxygen for energy production, it may lead to relative hypoxia. This may predispose to diastolic dysfunction [68] as ventricular relaxation is an energy-dependent process. Furthermore, intermediates of fat metabolism, such as ceramide might be toxic, inducing cell apoptosis [69].

2C. Hyperinsulinaemia

HFpEF is not only associated with diabetes but also with the metabolic syndrome [70] and with impaired glucose tolerance [71], suggesting that insulin resistance and/or hyperinsulinaemia might be implicated. Nichols *et al* [72] reported that insulin use was associated with both prevalent and incident HF. In the Uppsala Longitudinal Study of Adult Men, baseline fasting proinsulin and insulin resistance predicted future HF [73].

Cardiomyocyte-selective insulin receptor knockout mice show reduced cardiac and cardiomyocyte size [74]. In humans, insulin levels have been associated with LV relative wall thickness [75].

Insulin is a growth factor to many cells types, including the cardiomyocyte. The signaling pathways mediating the metabolic and growth factor properties of insulin are different. Crucially, insulin resistance seems to affect only the metabolic, but not the growth factor, effects of insulin. Therefore hyperinsulinaemia in subjects with type 2 DM or the metabolic syndrome exposes them to exaggerated growth factor-like effects.

2D. Advanced glycation endproducts (AGEs)

Chronic hyperglycemia leads to non-enzymatic glycation of matrix proteins in the vascular wall and myocardium, producing AGEs. AGEs stimulate collagen production and cross-linkage, leading to increasing LV diastolic stiffness and diminished compliance of the blood vessels [76]. AGEs increase oxidative stress and pro-inflammatory cytokine release while AGE receptor activation induces pro-fibrotic signaling and impairs calcium homeostasis [77,78]. Increased serum AGEs are associated with LV diastolic stiffness, endothelial dysfunction, impaired vascular compliance and reduced NO bioavailability, in both type 1 and 2 DM patients [77,78].

2E. Impaired calcium homeostasis

Calcium handling by the cardiomyocyte is important in both systole and diastole. Membrane depolarization results in the release of calcium from the sarcoplasmic reticulum (SR) into the cytosol (through ryanodine receptors), where it binds troponin C to start the contractile process. During diastole, calcium is taken up by the SR through activation of the SR calcium⁺ pump (SERCA2a), the sarcolemmal Na⁺-Ca²⁺ exchanger, and the sarcolemmal Ca²⁺ ATPase.

In both type 1 and 2 DM, disturbed cardiomyocyte calcium handling results from reduced activity of calcium handling proteins, such as SERCA2a, ryanodine receptor, Na²⁺/⁻Ca²⁺ exchanger and sarcolemmal Ca²⁺ ATPase. This leads to impaired excitation-contraction coupling and LV systolic and diastolic dysfunction [59,79].

2F. Myocardial Oxidative Stress

Hyperglycaemia induces oxidative stress via several mechanisms, mainly glucose auto-oxidation, formation of AGEs, activation of the polyol pathway and increased levels of FFAs and leptin [80]. Cardiovascular sources of reactive oxygen species (ROS) production include xanthine oxidoreductase, nicotinamide adenine dinucleotide 3-phosphate (NAD(P)H) oxidase, mitochondrial oxidases and uncoupled nitric oxide (NO) synthases [80,81]. Increased generation of ROS leads to cardiac injury and endothelial dysfunction, by direct oxidative cellular damage and by diminished NO bioavailability [81].

2G. Myocardial Fibrosis

Increased collagen deposition occurs in the diabetic myocardium, as evidenced by abnormal increased backscatter on echocardiography [82]. Hyperglycaemia, oxidative stress and elevated aldosterone and angiotensin II levels lead to increased expression

of collagen type I and downregulation of collagen-degrading matrix metalloproteinases [82].

2H. Left Ventricular Hypertrophy

LV hypertrophy is commoner in diabetic subjects, independently of BP and other factors [83,84]. This can be mediated through hyperinsulinaemia and/or insulin resistance (see above). Various adipokines may also be implicated. These include resistin [85] (a cytokine released by adipose tissue macrophages) and leptin [86] (a marker of fat mass), both of which are increased in type 2 diabetes and the metabolic syndrome.

2I. Endothelial dysfunction

Altered insulin signaling, glyco- and lipotoxicity, and AGEs accumulation, all factors that occur in DM, lead to endothelial dysfunction [87]. This results in dysregulation of vascular permeability, inflammatory responses, vascular remodelling and atherosclerosis, with consequent increased arterial stiffness, BP and pulse pressure [88,89]. The increase in afterload results in increased resting myocardial oxygen requirements and in myocardial hypertrophy which ultimately leads to LV diastolic dysfunction [90].

2J. Microangiopathy

Diabetic patients exhibit microangiopathy that is characterized by abnormal capillary permeability, microaneurysm formation, subendothelial matrix deposition, and fibrosis surrounding arterioles [91]. This impairs oxygen delivery to myocardial cells. Interestingly, coronary blood flow reserve is reduced in DM even in the absence of obstructive CAD [92,93]. Thus, myocardial ischaemia may play a role in diastolic dysfunction in DM in the absence of significant CAD since myocardial relaxation is an energy-dependent process. This can be further exacerbated by dependence on fatty acids as an energy substrate, mitochondrial uncoupling (see above) and LV hypertrophy that increases the diffusion distance between blood in the microcirculation and parts of the myocardium.

2K. Neurohormonal Regulation

Hyperglycaemia and hyperinsulinaemia activate the cardiac renin-angiotensin system (RAS) by increasing the expression of angiotensinogen, angiotensin II, and angiotensin II type 1 receptor. This contributes to diastolic dysfunction via hypertension and impaired myocardial relaxation [94-96]. Myocardial RAS activation has been demonstrated in streptozocin-induced diabetic rats [97].

2L. Autonomic Neuropathy

Diabetic autonomic neuropathy affects both the sympathetic and parasympathetic nervous system; this has been associated with impaired systolic and diastolic function [98]. In transgenic mice, an increased expression of the β 1-receptor results in enhanced apoptosis, fibrosis, hypertrophy, and impaired myocardial function [99].

2M. The Foetal Gene Programme

This entails the expression of genes normally expressed in foetal/early neonatal life. Re-expression of the foetal gene programme might be an adaptive response in the failing heart. It leads to upregulation of the β -myosin heavy chain (β -MyHC) gene and down-regulation of the fast contracting isoform, α -MyHC [100]. These changes may be adaptive: β -MHC would allow cardiac muscle to work more efficiently when chronically overloaded because it contracts and relaxes more slowly than α -MHC [101]. However, it may predispose to diastolic dysfunction as demonstrated in alloxan-induced diabetic rats [102].

2N. Stem Cell involvement

LV dysfunction in DM might be a stem cell disease. Rota *et al* [103] have shown that enhanced oxidative stress in DM can affect cardiac progenitor cell function leading to defective myocyte formation, premature myocardial aging and HF. It has been suggested that the p66shc gene is responsible for promoting the senescent phenotype [103].

2O. Other Myocardial Changes in Diabetes

Other changes at the molecular level include altered protein kinase C metabolism resulting in endothelial dysfunction, increased leukocyte adhesion, increased albumin permeability, and impaired fibrinolysis [104,105]; impaired myocardial NO bioavailability resulting in increased LV diastolic stiffness [106]; and impaired myocardial cGMP synthesis leading to impaired protein kinase G (PKG) activity. PKG has anti-hypertrophic, anti-remodeling and anti-inflammatory actions [107]. Downregulation of NO-mediated cGMP-PKG signalling, probably induced by vascular inflammation and oxidative stress, could account for the high Fpassive of hypertrophied cardiomyocyte observed in DM HFpEF patients [108].

Conclusion

Although various studies have been performed to unravel the pathophysiology of HFpEF in diabetic patients, a lot is still unknown. The key issue is that diabetic individuals are at increased risk of HF, particularly HFpEF with associated poor prognosis. Therapeutic options for HFpEF are still controversial. Thus, currently, cardiometabolic prevention, focusing on dyslipidaemia, hypertension and hyperglycaemia, should form the cornerstone in the management of DM patients. Undoubtedly, further studies are needed to establish the pathophysiological mechanisms underlying HFpEF in DM with the hope that novel pharmacotherapies targeting this disease will be developed.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

All authors were involved in literature review, drafting the manuscript and revising it critically for important intellectual content. Furthermore, all have approved the final version to be published.

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References

1. Owan, T. E. *et al.* **Epidemiology of diastolic heart failure.** *Prog Cardiovasc Dis* **47**, 320-332
2. Kitzman, D. W. *et al.* **Importance of heart failure with preserved systolic function in patients \geq 65 years of age.** **CHS Research Group. Cardiovascular Health Study.** *Am J Cardiol* **87**, 413-419
3. Sanderson, J. E. **Heart failure with a normal ejection fraction.** *Heart* **93**, 155-158
4. Soma, J. **Heart failure with preserved left ventricular ejection fraction: concepts, misconceptions and future directions.** *Blood Press* **20**, 129-133
5. Paulus, W. J. *et al.* **How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology.** *Eur Heart J* **28**, 2539-2550
6. Wild, S. *et al.* **Global prevalence of diabetes: estimates for the year 2000 and projections for 2030.** *Diabetes Care* **27**, 1047-1053
7. Bertoni, A. G. *et al.* **Heart failure prevalence, incidence, and mortality in the elderly with diabetes.** *Diabetes Care* **27**, 699-703
8. Owan, T. E. *et al.* **Trends in prevalence and outcome of heart failure with preserved ejection fraction.** *N Engl J Med* **355**, 251-259
9. MacDonald, M. R. *et al.* **Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme.** *Eur Heart J* **29**, 1377-1385
10. Poirier, P. *et al.* **Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy.** *Diabetes Care* **24**, 5-10
11. Zabalgaitia, M. *et al.* **Prevalence of diastolic dysfunction in normotensive, asymptomatic patients with well-controlled type 2 diabetes mellitus.** *Am J Cardiol* **87**, 320-323
12. **How to diagnose diastolic heart failure. European Study Group on Diastolic Heart Failure.** *Eur Heart J* **19**, 990-1003
13. Vasan, R. S. *et al.* **Defining diastolic heart failure: a call for standardized diagnostic criteria.** *Circulation* **101**, 2118-2121
14. Yturralde, R. F. *et al.* **Diagnostic criteria for diastolic heart failure.** *Prog Cardiovasc Dis* **47**, 314-319
15. Borlaug, B. A. *et al.* **Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction.** *Circulation* **114**, 2138-2147
16. Ennezat, P. V. *et al.* **Left ventricular abnormal response during dynamic exercise in patients with heart failure and preserved left ventricular ejection fraction at rest.** *J Card Fail* **14**, 475-480
17. Borlaug, B. A. *et al.* **Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction.** *J Am Coll Cardiol* **56**, 845-854
18. Phan, T. T. *et al.* **Heart failure with preserved ejection fraction is characterized by dynamic impairment of active relaxation and contraction of the left ventricle on exercise and associated with myocardial energy deficiency.** *J Am Coll Cardiol* **54**, 402-409

19. Tan, Y. T. et al. **The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion.** *J Am Coll Cardiol* **54**, 36-46
20. Kawaguchi, M. et al. **Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations.** *Circulation* **107**, 714-720
21. Borlaug, B. A. et al. **Ventricular-vascular interaction in heart failure.** *Heart Fail Clin* **4**, 23-36
22. Borlaug, B. A. et al. **Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction.** *Circ Heart Fail* **3**, 588-595
23. Brubaker, P. H. et al. **Chronotropic incompetence and its contribution to exercise intolerance in older heart failure patients.** *J Cardiopulm Rehabil* **26**, 86-89
24. Kjaergaard, J. et al. **Prognostic importance of pulmonary hypertension in patients with heart failure.** *Am J Cardiol* **99**, 1146-1150
25. Lam, C. S. et al. **Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study.** *J Am Coll Cardiol* **53**, 1119-1126
26. Takeda, Y. et al. **Competing risks of heart failure with preserved ejection fraction in diabetic patients.** *Eur J Heart Fail* **13**, 664-669
27. Raev, D. C. **Which left ventricular function is impaired earlier in the evolution of diabetic cardiomyopathy? An echocardiographic study of young type I diabetic patients.** *Diabetes Care* **17**, 633-639
28. Seneviratne, B. I. **Diabetic cardiomyopathy: the preclinical phase.** *Br Med J* **1**, 1444-1446
29. Liu, J. E. et al. **The impact of diabetes on left ventricular filling pattern in normotensive and hypertensive adults: the Strong Heart Study.** *J Am Coll Cardiol* **37**, 1943-1949
30. Iribarren, C. et al. **Glycemic control and heart failure among adult patients with diabetes.** *Circulation* **103**, 2668-2673
31. Takeda, Y. et al. **Noninvasive assessment of wall distensibility with the evaluation of diastolic epicardial movement.** *J Card Fail* **15**, 68-77
32. Yamamoto, K. et al. **Myocardial stiffness is determined by ventricular fibrosis, but not by compensatory or excessive hypertrophy in hypertensive heart.** *Cardiovasc Res* **55**, 76-82
33. van Hoeven, K. H. et al. **A comparison of the pathological spectrum of hypertensive, diabetic, and hypertensive-diabetic heart disease.** *Circulation* **82**, 848-855
34. Willemsen, S. et al. **Tissue advanced glycation end products are associated with diastolic function and aerobic exercise capacity in diabetic heart failure patients.** *Eur J Heart Fail* **13**, 76-82
35. van Heerebeek, L. et al. **Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation end products, and myocyte resting tension.** *Circulation* **117**, 43-51
36. Borbely, A. et al. **Cardiomyocyte stiffness in diastolic heart failure.** *Circulation* **111**, 774-781
37. van Heerebeek, L. et al. **Myocardial structure and function differ in systolic and diastolic heart failure.** *Circulation* **113**, 1966-1973
38. Poornima, I. G. et al. **Diabetic cardiomyopathy: the search for a unifying hypothesis.** *Circ Res* **98**, 596-605
39. Connelly, K. A. et al. **Letter by Connelly et al regarding article, "Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation end products, and myocyte resting tension".** *Circulation* **117**, e483; author reply e484
40. Connelly, K. A. et al. **Functional, structural and molecular aspects of diastolic heart failure in the diabetic (mRen-2)27 rat.** *Cardiovasc Res* **76**, 280-291
41. van Heerebeek, L. et al. **Myocardial structure and function differ in systolic and diastolic heart failure.** *Circulation* **113**, 1966-1973
42. Borlaug, B. A. et al. **Contractility and ventricular systolic stiffening in hypertensive heart disease insights into the pathogenesis of heart failure with preserved ejection fraction.** *J Am Coll Cardiol* **54**, 410-418
43. Chantler, P. D. et al. **Arterial-ventricular coupling: mechanistic insights into cardiovascular performance at rest and during exercise.** *J Appl Physiol* **105**, 1342-1351
44. Sunagawa, K. et al. **Left ventricular interaction with arterial load studied in isolated canine ventricle.** *Am J Physiol* **245**, H773-780
45. Melenovsky, V. et al. **Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban Baltimore community: the role of atrial remodeling/dysfunction.** *J Am Coll Cardiol* **49**, 198-207
46. Borlaug, B. A. et al. **Ventricular-vascular interaction in heart failure.** *Heart Fail Clin* **4**, 23-36
47. Chantler, P. D. et al. **Arterial-ventricular coupling: mechanistic insights into cardiovascular performance at rest and during exercise.** *J Appl Physiol* **105**, 1342-1351
48. De Tombe, P. P. et al. **Ventricular stroke work and efficiency both remain nearly optimal despite altered vascular loading.** *Am J Physiol* **264**, H1817-1824
49. Kawaguchi, M. et al. **Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations.** *Circulation* **107**, 714-720
50. Ohnishi, H. et al. **Pulse wave velocity as an indicator of atherosclerosis in impaired fasting glucose: the Tanno and Sobetsu study.** *Diabetes Care* **26**, 437-440
51. Aguilar, D. et al. **Comparison of patients with heart failure and preserved left ventricular ejection fraction among those with versus without diabetes mellitus.** *Am J Cardiol* **105**, 373-377
52. Poulsen, M. K. et al. **Left ventricular diastolic function in type 2 diabetes mellitus: prevalence and association with myocardial and vascular disease.** *Circ Cardiovasc Imaging* **3**, 24-31
53. Kitzman, D. W. et al. **Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism.** *J Am Coll Cardiol* **17**, 1065-1072
54. Phan, T. T. et al. **Impaired heart rate recovery and chronotropic incompetence in patients with heart failure with preserved ejection fraction.** *Circ Heart Fail* **3**, 29-34
55. Westermann, D. et al. **Role of left ventricular stiffness in heart failure with normal ejection fraction.** *Circulation* **117**, 2051-2060
56. Chattopadhyay, S. et al. **Lack of diastolic reserve in patients with heart failure and normal ejection fraction.** *Circ Heart Fail* **3**, 35-43
57. Smith, C. S. et al. **Altered creatine kinase adenosine triphosphate kinetics in failing hypertrophied human myocardium.** *Circulation* **114**, 1151-1158
58. Liu, C. P. et al. **Diminished contractile response to increased heart rate in intact human left ventricular hypertrophy. Systolic versus diastolic determinants.** *Circulation* **88**, 1893-1906
59. Boudina, S. et al. **Diabetic cardiomyopathy revisited.** *Circulation* **115**, 3213-3223

60. Desai, A. et al. **Heart failure with preserved ejection fraction: hypertension, diabetes, obesity/sleep apnea, and hypertrophic and infiltrative cardiomyopathy.** *Heart Fail Clin* **4**, 87-97
61. Hansen, A. et al. **C-peptide exerts beneficial effects on myocardial blood flow and function in patients with type 1 diabetes.** *Diabetes* **51**, 3077-3082
62. Johansson, B. L. et al. **C-peptide improves adenosine-induced myocardial vasodilation in type 1 diabetes patients.** *Am J Physiol Endocrinol Metab* **286**, E14-19
63. Johansson, B. L. et al. **C-peptide increases forearm blood flow in patients with type 1 diabetes via a nitric oxide-dependent mechanism.** *Am J Physiol Endocrinol Metab* **285**, E864-870
64. Grandi, A. M. et al. **Effect of glycemic control on left ventricular diastolic function in type 1 diabetes mellitus.** *Am J Cardiol* **97**, 71-76
65. Aepfelbacher, F. C. et al. **Improved glycemic control induces regression of left ventricular mass in patients with type 1 diabetes mellitus.** *Int J Cardiol* **94**, 47-51
66. McGavock, J. M. et al. **Cardiac steatosis in diabetes mellitus: a 1H-magnetic resonance spectroscopy study.** *Circulation* **116**, 1170-1175
67. Rijzewijk, L. J. et al. **Myocardial steatosis is an independent predictor of diastolic dysfunction in type 2 diabetes mellitus.** *J Am Coll Cardiol* **52**, 1793-1799
68. Diamant, M. et al. **Diastolic dysfunction is associated with altered myocardial metabolism in asymptomatic normotensive patients with well-controlled type 2 diabetes mellitus.** *J Am Coll Cardiol* **42**, 328-335
69. Zhou, Y. T. et al. **Lipotoxic heart disease in obese rats: implications for human obesity.** *Proc Natl Acad Sci U S A* **97**, 1784-1789
70. von Bibra, H. et al. **Diastolic dysfunction in diabetes and the metabolic syndrome: promising potential for diagnosis and prognosis.** *Diabetologia* **53**, 1033-1045
71. Celentano, A. et al. **Early abnormalities of cardiac function in non-insulin-dependent diabetes mellitus and impaired glucose tolerance.** *Am J Cardiol* **76**, 1173-1176
72. Nichols, G. A. et al. **Congestive heart failure in type 2 diabetes: prevalence, incidence, and risk factors.** *Diabetes Care* **24**, 1614-1619
73. Ingelsson, E. et al. **Insulin resistance and risk of congestive heart failure.** *JAMA* **294**, 334-341
74. Belke, D. D. et al. **Insulin signaling coordinately regulates cardiac size, metabolism, and contractile protein isoform expression.** *J Clin Invest* **109**, 629-639
75. Karason, K. et al. **Impact of blood pressure and insulin on the relationship between body fat and left ventricular structure.** *Eur Heart J* **24**, 1500-1505
76. Ziemann, S. et al. **Advanced glycation end product cross-linking: pathophysiologic role and therapeutic target in cardiovascular disease.** *Congest Heart Fail* **10**, 144-149; quiz 150-141
77. Hartog, J. W. et al. **Advanced glycation end-products (AGEs) and heart failure: pathophysiology and clinical implications.** *Eur J Heart Fail* **9**, 1146-1155
78. Goldin, A. et al. **Advanced glycation end products: sparking the development of diabetic vascular injury.** *Circulation* **114**, 597-605
79. Cesario, D. A. et al. **Alterations in ion channel physiology in diabetic cardiomyopathy.** *Endocrinol Metab Clin North Am* **35**, 601-610, ix-x
80. Jay, D. et al. **Oxidative stress and diabetic vascular complications.** *Free Radic Biol Med* **40**, 183-192
81. Hare, J. M. et al. **NO/redox disequilibrium in the failing heart and cardiovascular system.** *J Clin Invest* **115**, 509-517
82. Asbun, J. et al. **The pathogenesis of myocardial fibrosis in the setting of diabetic cardiomyopathy.** *J Am Coll Cardiol* **47**, 693-700
83. Devereux, R. B. et al. **Impact of diabetes on cardiac structure and function: the strong heart study.** *Circulation* **101**, 2271-2276
84. Eguchi, K. et al. **Association between diabetes mellitus and left ventricular hypertrophy in a multiethnic population.** *Am J Cardiol* **101**, 1787-1791
85. Kim, M. et al. **Role of resistin in cardiac contractility and hypertrophy.** *J Mol Cell Cardiol* **45**, 270-280
86. Barouch, L. A. et al. **Disruption of leptin signaling contributes to cardiac hypertrophy independently of body weight in mice.** *Circulation* **108**, 754-759
87. Widlansky, M. E. et al. **The clinical implications of endothelial dysfunction.** *J Am Coll Cardiol* **42**, 1149-1160
88. Wilkinson, I. B. et al. **Nitric oxide and the regulation of large artery stiffness: from physiology to pharmacology.** *Hypertension* **44**, 112-116
89. Scuteri, A. et al. **Metabolic syndrome amplifies the age-associated increases in vascular thickness and stiffness.** *J Am Coll Cardiol* **43**, 1388-1395
90. Fang, Z. Y. et al. **Diabetic cardiomyopathy: evidence, mechanisms, and therapeutic implications.** *Endocr Rev* **25**, 543-567
91. Aneja, A. et al. **Diabetic cardiomyopathy: insights into pathogenesis, diagnostic challenges, and therapeutic options.** *Am J Med* **121**, 748-757
92. Pop-Busui, R. et al. **Sympathetic dysfunction in type 1 diabetes: association with impaired myocardial blood flow reserve and diastolic dysfunction.** *J Am Coll Cardiol* **44**, 2368-2374
93. Yokoyama, I. et al. **Coronary microangiopathy in type 2 diabetic patients: relation to glycemic control, sex, and microvascular angina rather than to coronary artery disease.** *J Nucl Med* **41**, 978-985
94. Friedrich, S. P. et al. **Intracardiac angiotensin-converting enzyme inhibition improves diastolic function in patients with left ventricular hypertrophy due to aortic stenosis.** *Circulation* **90**, 2761-2771
95. Schunkert, H. et al. **Distribution and functional significance of cardiac angiotensin converting enzyme in hypertrophied rat hearts.** *Circulation* **87**, 1328-1339
96. Flesch, M. et al. **Angiotensin receptor antagonism and angiotensin converting enzyme inhibition improve diastolic dysfunction and Ca(2+)-ATPase expression in the sarcoplasmic reticulum in hypertensive cardiomyopathy.** *J Hypertens* **15**, 1001-1009
97. Fiordaliso, F. et al. **Myocyte death in streptozotocin-induced diabetes in rats in angiotensin II-dependent.** *Lab Invest* **80**, 513-527
98. Zola, B. et al. **Abnormal cardiac function in diabetic patients with autonomic neuropathy in the absence of ischemic heart disease.** *J Clin Endocrinol Metab* **63**, 208-214
99. Bisognano, J. D. et al. **Myocardial-directed overexpression of the human beta(1)-adrenergic receptor in transgenic mice.** *J Mol Cell Cardiol* **32**, 817-830
100. Depre, C. et al. **Streptozotocin-induced changes in cardiac gene expression in the absence of severe contractile dysfunction.** *J Mol Cell Cardiol* **32**, 985-996
101. Izumo, S. et al. **Protooncogene induction and reprogramming of cardiac gene expression produced by pressure overload.** *Proc Natl Acad Sci U S A* **85**, 339-343
102. Golfman, L. et al. **Differential changes in cardiac myofibrillar and sarcoplasmic reticular gene expression in alloxan-induced diabetes.** *Mol Cell Biochem* **200**, 15-25

103. Rota, M. et al. **Diabetes promotes cardiac stem cell aging and heart failure, which are prevented by deletion of the p66shc gene.** *Circ Res* **99**, 42-52
 104. Tesfamariam, B. et al. **Contraction of diabetic rabbit aorta caused by endothelium-derived PGH2-TxA2.** *Am J Physiol* **257**, H1327-1333
 105. Tesfamariam, B. et al. **Elevated glucose impairs endothelium-dependent relaxation by activating protein kinase C.** *J Clin Invest* **87**, 1643-1648
 106. Paulus, W. J. et al. **Nitric oxide's role in the heart: control of beating or breathing?** *Am J Physiol Heart Circ Physiol* **287**, H8-13
 107. McKinsey, T. A. et al. **Small-molecule therapies for cardiac hypertrophy: moving beneath the cell surface.** *Nat Rev Drug Discov* **6**, 617-635
 108. van Heerebeek, L. et al. **The failing diabetic heart: focus on diastolic left ventricular dysfunction.** *Curr Diab Rep* **9**, 79-86
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