Acta Scientific MEDICAL SCIENCES (ISSN: 2582-0931)

Volume 9 Issue 1 January 2025

Review Article

Diastolic Dysfunction and Cardiac Energy Deficit: Understanding Progressive Heart Failure in the Light of SGLT2 Inhibitors

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DOI: 10.31080/ASMS.2025.09.1994

Received: November 06, 2024

Published: December 16, 2024

Abstract

Heart Failure and its subtype Heart Failure with Preserved Ejection Fraction (HFPEF) represent a vexing pathophysiological conundrum. Till date the exact mechanism of heart failure progression and HFPEF has not been clearly defined. However recent research into cardiac energetics and the suprising success of drugs like SGLT2 Inhibitors show us that our understanding of heart failure pathophysiology needs to be redefined in terms of metabolic rather than structural abnormality. We seek to propose a novel cyclical model explaining Diastolic Dysfunction in terms of energy deficit and its relation with coronary microcirculation insufficiency to explain progressive HFPEF and likely mechanism of action of SGLT2 Inhibitors to interrupt it.

Keywords: Heart Failure; Calcium

Abbreviations

ACC: American College of Cardiology; ADP: Adenosine Di Phosphate; AHA: American Heart Association; AMI: Acute Myocardial Infarction; ARNI: Angiotensin Receptor Neprilysin Inhibitor; ATP: Adenosine Tri Phosphate; Ca: Calcium; CAD: Coronary Artery Disease; CFR: Coronary Flow Reserve; CMR: Cardiac Magnetic Resonance; CPT: Carnitine Palmitoyl Transferase; ECG: Electrocardiogram; FA: Fatty Acid; HCM: Hypertrophic Cardiomyopathy; HF: Heart Failure; HFHS: High Fat High Sucrose; HFPEF: Heart Failure with Preserved Ejection Fraction; HFREF: Heart Failure with Reduced Ejection Fraction; HOCM: Hypertrophic Obstructive Cardiomyopathy; LCAD: Long Chain Acyl-CoA Dehydrogenase; LVH: Left Ventricular Hypertrophy; LVOT: Left Ventricular Outflow Tract; MACE: Major Adverse Cardiovascular Events; MHD: Metabolic Heart Disease; MINOCA: Myocardial Infarction with Non Obstructive Coronary Arteries; MRA: Mineralocorticoid Receptor Antagonist; NAD: Nicotinamide Adenine Dinucleotide; PCr: Phospho-Creatine; PET: Positron Emission Tomography; PKA: Protein Kinase A; SCFA: Short Chain Fatty Acid; SERCA: Sarcoplasmic/Endoplasmic Reticulum Calcium ATPase; SGLT: Sodium Glucose co-Transporter; SGLTi: Sodium Glucose co-Transporter Inhibitor; TnC: Troponin C; VLCAD: Very Long Chain Acyl-CoA Dehydrogenase

Introduction

Heart Failure (HF) is defined as a complex clinical syndrome with symptoms and signs that result from any structural or

functional impairment of ventricular filling or ejection of blood (ACC) [1].

Myocardial energy deficiency and subsequent altered metabolic pathways are increasingly being recognized as an essential part of the heart failure jigsaw [2,3].

Up to half of the cases [4-7] with heart failure suffer from Heart Failure with Preserved Ejection Fraction (HFPEF). It has been shown that progressive worsening of diastolic dysfunction is associated with increased incidence of heart failure [8]. However, the pathophysiology behind this progressive worsening has not been clearly understood.

The discovery of SGLT2 Inhibitors has recently upended the successful management of HFREF as well as HFPEF. The exact mechanism of action of SGLT2I on cardiac physiology is unknown.

Hence we seek to examine a novel pathophysiological model by reconciling the seemingly disparate processes of diastolic dysfunction and energy deficiency into a single unified cycle incorporating the effects of myocardial circulatory insufficiency acting as a binding force via which the two feed off each other causing progressive heart failure also thus explaining the metabolic effect of SGLT2I.

Uniqueness of cardiac metabolism

Fatty acid (FA) oxidation serves as a major source of energy (60-90%) for the myocytes while carbohydrates and multiple other substrates can also be potentially used depending on the metabolic conditions. The myocardium also has very limited anaerobic capacity [9,10]. The net energy yield of long-chain FA oxidation is much higher (105 ATP per molecule of Palmitic acid) compared to glucose (31 ATP) and anaerobic metabolism (2 ATP). The fetal heart utilizes glucose and lactate as its main energy sources, however after birth this gradually transitions towards FA oxidation which becomes the predominant energy source thereafter [11]. Thus, this metabolic switch provides a major energy boost but effective FA oxidation is only guaranteed under an abundant supply of oxygen [12,13].

Cardiac metabolism in heart failure

Heart failure has been shown to diminish the mitochondrial capacity to oxidize FA and ATP production becomes inefficient [14].

Similarly, it has been shown in conditions such as those leading to cardiac hypertrophy and in heart failure that there occurs a reverse switch to a fetal type energy metabolism [15]. This is accompanied by re-expression of several isoforms of enzymes, of transcription factors, and of structural and other proteins normally expressed in the fetal heart [16]. This switch is considered to enable cardiomyocytes to maintain ATP production with lesser oxygen and is also seen in chronic hypoxia due to several pathological conditions [17].

A decrease in palmitate utilization [18,19] has been demonstrated in rats with cardiac hypertrophy from pressure overload and in myocardial infarction as has a reduction in oleate oxidation in pacing induced heart failure in dogs [20]. Similar findings have been noted in human studies involving patients with nondiabetic dilated cardiomyopathy and patients with idiopathic cardiomyopathy [21,22]. Rodent heart failure models also show downregulation of CPT 1 and 2, which are important components of the carnitine shuttle [18,23].

Reduced levels of the enzymes responsible for beta oxidation of very-long chain and long-chain FA, VLCAD, and LCAD has also been noted and is thought to be responsible for a “backlog” in fatty acid metabolism, resulting in accumulation of toxic lipid intermediates in the heart, further aggravating the metabolic derangements in heart failure [23-25].

In summary, the cumulative data from multiple animal and human studies demonstrates increased dependence on inefficient metabolic pathways like glycolysis, causing progressive energy deficit [18,26] in the failing heart.

Regulation of active relaxation by [ADP]

Calcium dissociation from TnC (Troponin C) and detachment of actin-myosin crossbridge have been proposed as possible rate limiting steps in myocardial relaxation [27]. It is important to identify that apart from being the energy supply for the power stroke, ATP supply is also important for the detachment of the myosin head from the actin filament and other active processes in diastole. Increase in [ADP] can adversely affect cross bridge cycling and SERCA2a pump activity by reducing the activity of their ATPase reactions. During cross bridge cycling if some myosin heads remain attached to the actin molecule as an intact crossbridge, the myocyte

remains in a partially contracted state with increased resting tone during diastole [28]. Similarly, decreased activity of the SERCA2a pump leads to residual cytosolic Ca2+ which does not return to the baseline and slows cross bridge cycling by keeping the binding sites exposed due to its continual attachment to the Troponin complex [28]. This phenomenon has been observed in many studies and given several different names in the past like "diastolic contracture" [27,29], "diastolic stiffness" [30], "resting tension" [30], "decreased LV chamber volume" "decreased LV cavity size" [31], but they essentially indicate Diastolic Dysfunction. It also shares similarities with the state of rigor mortis in skeletal muscles post mortem causing contractures after depletion of [ATP] [32] . Thus, as per available evidence, rising [ADP] due to progressive energy (ATP) deficit culminates into diastolic dysfunction [33-35].

Coronary blood flow

The human heart has the highest per gram oxygen consumption of any organ, extracting up to ~70% to 80% of delivered oxygen even under resting conditions [36-38]. This means that any further enhancements to oxygen extraction are rather limited [40] and maintenance of coronary perfusion is vital to sustain the production of high energy phosphates.

As a result of the tremendous compressive forces of the myocardium in systole around 80% of antegrade blood flow to the left ventricle occurs during diastole [36,37]. Thus compared to other non-compressible tissues, where the arterial to venous pressure difference determines tissue perfusion, myocardial blood flow is determined by the gradient between diastolic blood pressure and intramyocardial tissue pressure [39-42]. Hence, it may be inferred that inability of the myocardium to adequately relax viz diastolic dysfunction is detrimental to its own perfusion.

Diastolic dysfunction cycle

We seek to propose a model explaining progressive heart failure as a cyclic interplay between diastolic dysfunction and energy deficiency due to impaired intramyocardial perfusion (Figure 1).

Individual links between diastolic dysfunction cycle

Current understanding of the pathophysiology of heart failure considers components of this cycle in isolation or in binary form.

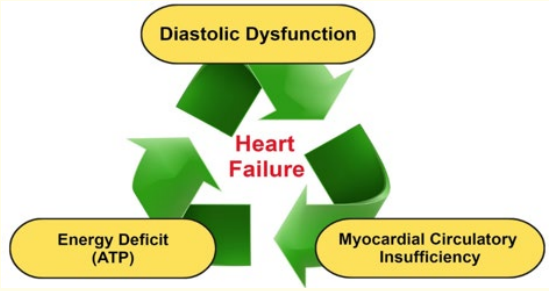

Figure 1: Diastolic Dysfunction Cycle (ATP – Adenosine Tri-phosphate).

The associations between individual components of the diastolic dysfunction cycle have been established over the last few decades (Figure 2).

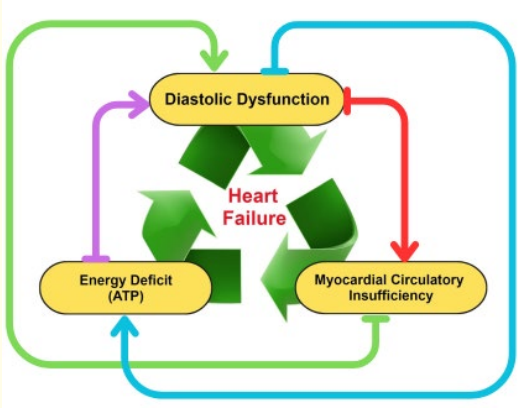

Figure 2: Links between components of Diastolic Dysfunction Cycle Red Arrow [43-46] Green Arrow [47-50] Purple Arrow [33,53] Blue Arrow [52].

Diastolic dysfunction has been implicated as a determinant of myocardial circulation even in the absence of coronary artery disease in studies based on CFR [43-46]. Conversely, several studies have shown that myocardial circulatory insufficiency produces diastolic dysfunction in acute conditions like AMI (Acute Myocardial Infarction) as well as in chronic CAD (Coronary Artery Disease) [47-50]. Similarly, diastolic dysfunction associated with energy deficit has been documented in multiple animal studies [35,51]. Recent studies involving animal models fed with HFHS (High Fat High Sucrose) diet also seem to provide useful insights into this relationship [53].

Toersten Doesn't., *et al*. studied the effect of pressure overload on Sprague-Dawley rats and concluded that decreased rates of substrate oxidation with activation of compensatory metabolic pathways predicts development of HFPeF and subsequently HFReF [52].

In the light of this growing body of evidence, we believe progressive Heart Failure needs to be considered as a result of a cyclic relationship between Diastolic Dysfunction, Energy Deficit and Myocardial Circulatory Insufficiency to explain the progression of heart failure from an asymptomatic to advanced state.

How SGLT2 inhibitors may improve cardiac energy metabolism and diastolic dysfunction

Historically the management of Diabetes Mellitus consisted of mainly insulin secretagogues and direct insulin injections. The boosted insulin levels essentially increase the glucose uptake by the tissues for metabolism reducing circulating sugar levels.

However as we have pointed above this excessive insulin action is counter productive to cardiac metabolism as glucose is not the preferred energy substrate for the human heart which mainly uses fatty acids for its energy requirements as fatty acids are more energy dense providing higher ATP's per molecule.

The newer anti diabetic drugs viz SGLT2I however have a different mechanism of actions. Instead of producing high spikes of endogenous or exogenous insulin SGLT2I essentially throw out the excess sugars via the kidneys instead of forcing metabolic tissues like the heart to utilize the sugars. In addition by promoting lipolysis due to decreased circulating carbohydrates SGLT2I restore the natural and substrate balance for the heart allowing to revert to preferentially use more fatty acids. This restoration of energy supply from energy dense fatty acids then contributes to resolving diastolic dysfunction explaining the beneficial effects of SGLT2I in heart failure.

A similar mechanism of action can be used to explain the cardio-beneficial effects of other newer drugs like GLP1 Analogues.

Conclusion

The uniqueness of the myocardial metabolism and its blood flow mechanisms along with a continuous unrelenting workload makes for an insatiable energy appetite which can mainly be satisfied during the diastolic phase of the cardiac cycle.

Decades of research trying to improve systolic function of the failing heart led to development and use of various inotropic drugs, yet none have been found to significantly improve survival.

We believe, in the light of new research and results from trials of newer drugs like SGLT2I, that a new model of heart failure progression should be considered which explains the cyclic interplay between diastolic dysfunction and energy deficit myocardial metabolism.

Using this new model we can observe that newer drugs like SGLT 2 inhibitors are likely altering cardiac substrate metabolism and correcting a possible energy deficit. Unlike insulin or insulin secretagogue's like sulphonylurea's, SGLT2i do not force the heart to utilize more glucose by potentiating insulin levels but instead allow the heart to switch back to a predominant Fatty Acid metabolism restoring its energy deficit and thus improving Diastolic function.

Recognising this altered cardiac metabolism based on glucose, the resulting ATP deficit and abnormal diastolic function as a key driver of progressive heart failure may hold the key towards opening new avenues of research for understanding and prevention of progressive heart failure.

Bibliography

1. Heidenreich PA., *et al*. "2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines". *Circulation* (2022).

2. Palm CL., *et al*. "Short-Chain Fatty Acids in the Metabolism of Heart Failure – Rethinking the Fat Stigma". *Frontiers in Cardiovascular Medicine* (2022).

3. Kolwicz SC Jr., *et al*. "Cardiac Metabolism and its Interactions With Contraction, Growth, and Survival of Cardiomyocytes". *Circulation Research* (2013): 603-616.

4. van R., *et al*. "Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion". *European Journal of Heart Failure* 16.7 (2014): 772-777.

5. Ceia F., *et al*. "Prevalence of chronic heart failure in Southwestern Europe: the EPICA study". *European Journal of Heart Failure* 4.4 (2002): 531-539.

6. Bleumink G., *et al*. "Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study". *European Heart Journal* 25.18 (2004): 1614-1619.

7. Koh A., *et al*. "A comprehensive population-based characterization of heart failure with mid-range ejection fraction". *European Journal of Heart Failure* 19.12 (2017): 1624-1634.

8. Kane G., *et al*. "Progression of left ventricular diastolic dysfunction and risk of heart failure". *JAMA* 306.8 (2011): 856-863.

9. BALLINGER W., *et al*. "Anaerobic metabolism of heart". *Circulation Research* 11 (1962): 681-685.

10. Opie L. "Metabolism of the heart in health and disease. I". *American Heart Journal* 76.5 (1968): 685-698.

11. Rowe GC., *et al*. "PGC-1 Coactivators in Cardiac Development and Disease". Kelly DP, ed. *Circulation Research* (2010): 825-838.

12. Ventura-Clapier R., *et al*. "Energy metabolism in heart failure". *The Journal of Physiology* (2004): 1-13.

13. Lopaschuk GD., *et al*. "Myocardial Fatty Acid Metabolism in Health and Disease". *Physiological Reviews* (2010): 207-258.

14. Lopaschuk GD., *et al*. "Cardiac Energy Metabolism in Heart Failure". *Circulation Research* (2021): 1487-1513.

15. Breckenridge RA., *et al*. "Hypoxic Regulation of Hand1 Controls the Fetal-Neonatal Switch in Cardiac Metabolism". Tian R, ed. *PLoS Biology* (2013): e1001666.

16. Taegtmeyer H., *et al*. "Return to the fetal gene program: a suggested metabolic link to gene expression in the heart". *Annals of the New York Academy of Sciences* 1188 (2010): 191-198.

17. Su Z., *et al*. "Adaptive Cardiac Metabolism Under Chronic Hypoxia: Mechanism and Clinical Implications". *Frontiers in Cell and Developmental Biology* 9 (2021): 625524.

18. Sorokina N., *et al*. "Recruitment of Compensatory Pathways to Sustain Oxidative Flux With Reduced Carnitine Palmitoyltransferase I Activity Characterizes Inefficiency in Energy Metabolism in Hypertrophied Hearts". *Circulation* (2007): 2033-2041.

19. HEATHER L., *et al*. "Fatty acid transporter levels and palmitate oxidation rate correlate with ejection fraction in the infarcted rat heart". *Cardiovascular Research* (2006): 430-437.

20. Osorio JC., *et al*. "Impaired Myocardial Fatty Acid Oxidation and Reduced Protein Expression of Retinoid X Receptor-α in Pacing-Induced Heart Failure". *Circulation* (2002): 606-612.

21. Bedi KC Jr., *et al*. "Evidence for Intramyocardial Disruption of Lipid Metabolism and Increased Myocardial Ketone Utilization in Advanced Human Heart Failure". *Circulation* (2016): 706-716.

22. Dávila-Román VG., *et al*. "Altered myocardial fatty acid and glucose metabolism in idiopathic dilated cardiomyopathy". *Journal of the American College of Cardiology* (2002): 271-277.

23. Lai L., *et al*. "Energy Metabolic Reprogramming in the Hypertrophied and Early Stage Failing Heart". *Circulation: Heart Failure* (2014): 1022-1031.

24. Karwi QG., *et al*. "Loss of Metabolic Flexibility in the Failing Heart". *Frontiers in Cardiovascular Medicine* (2018).

25. He L., *et al*. "Carnitine Palmitoyltransferase-1b Deficiency Aggravates Pressure Overload–Induced Cardiac Hypertrophy Caused by Lipotoxicity". *Circulation* (2012): 1705-1716.

26. Kalsi KK., *et al*. "Energetics and function of the failing human heart with dilated or hypertrophic cardiomyopathy". *European Journal of Clinical Investigation* (1999): 469-477.

27. Little S., *et al*. "The rates of Ca2+ dissociation and cross-bridge detachment from ventricular myofibrils as reported by a fluorescent cardiac troponin C". *Journal of Biological Chemistry* 287.33 (2012): 27930-27940.

28. Selby D., *et al*. "Tachycardia-induced diastolic dysfunction and resting tone in myocardium from patients with a normal ejection fraction". *Journal of the American College of Cardiology* 58.2 (2011): 147-154.

29. Pouleur H., *et al*. "Focus on diastolic dysfunction: a new approach to heart failure therapy". *British Journal of Clinical Pharmacology* 28 (1989): 41S-52S.

30. van H., *et al*. "Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation end products, and myocyte resting tension". *Circulation* 117.1 (2008): 43-51.

31. Meyer M., *et al*. "Relationship of exercise capacity and left ventricular dimensions in patients with a normal ejection fraction. An exploratory study". *PLoS One* 10.3 (2015): e0119432.

32. BATE-SMITH E and BENDALL J. "Factors determining the time course of rigor mortis". *Journal of Physiology* 110.1-2 (1949): 47-65.

33. Tian R., *et al*. "Role of MgADP in the development of diastolic dysfunction in the intact beating rat heart". *Journal of Clinical Investigation* (1997): 745-751.

34. Bernard M., *et al*. "On the Relations among ATP Hydrolysis, Cation Accumulation, and Diastolic Dysfunction". In: Lorell BH, Grossman W, eds. Diastolic Relaxation of the Heart: The Biology of Diastole in Health and Disease. Springer US; (1994): 73-78.

35. Tian R., *et al*. "Failure to Maintain a Low ADP Concentration Impairs Diastolic Function in Hypertrophied Rat Hearts". *Circulation* (1997): 1313-1319.

36. Duncker D and Bache R. "Regulation of coronary blood flow during exercise". *Physiology Review* 88.3 (2008): 1009-1086.

37. Feigl E. "Coronary physiology". *Physiology Review* 63.1 (1983): 1-205.

38. Tune JD. "Coronary Circulation". *Colloquium Series on Integrated Systems Physiology: From Molecule to Function* (2014): 1-189.

39. Downey J. "Myocardial contractile force as a function of coronary blood flow". *American Journal of Physiology* 230.1 (1976): 1-6.

40. Downey J., *et al*. "Effects of myocardial strains on coronary blood flow". *Circulation Research* 34.3 (1974): 286-292.

41. Downey J and Kirk E. "Distribution of the coronary blood flow across the canine heart wall during systole". *Circulation Research* 34.2 (1974): 251-257.

42. Downey J and Kirk E. "Inhibition of coronary blood flow by a vascular waterfall mechanism". *Circulation Research* 36.6 (1975): 753-760.

43. Galderisi M., *et al*. "Impact of myocardial diastolic dysfunction on coronary flow reserve in hypertensive patients with left ventricular hypertrophy". *Italian Heart Journal* 2.9 (2001): 677-684.

44. Konerman M., *et al*. "Reduced Myocardial Flow Reserve Is Associated With Diastolic Dysfunction and Decreased Left Atrial Strain in Patients With Normal Ejection Fraction and Epicardial Perfusion". *Journal of Cardiac Failure* 24.2 (2018): 90-100.

45. Taqueti V., *et al*. "Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction". *European Heart Journal* 39.10 (2018): 840-849.

46. Hong D., *et al*. "Prognostic Impact of Cardiac Diastolic Function and Coronary Microvascular Function on Cardiovascular Death". *Journal of the American Heart Association* 12.3 (2023): e027690.

47. Ohara T and Little W. "Evolving focus on diastolic dysfunction in patients with coronary artery disease". *Current Opinion in Cardiology* 25.6 (2010): 613-621.

48. Prasad S., *et al*. "Determinants of Diastolic Dysfunction Following Myocardial Infarction: Evidence for Causation Beyond Infarct Size". *Heart Lung Circulation* 29.12 (2020): 1815-1822.

49. Maragiannis D., *et al*. "Association of Left Ventricular Diastolic Dysfunction with Subclinical Coronary Atherosclerotic Disease Burden Using Coronary Artery Calcium Scoring". *Journal of Atherosclerosis and Thrombosis* 22.12 (2015): 1278-1286.

50. Galderisi M., *et al*. "Independent association of coronary flow reserve with left ventricular relaxation and filling pressure in arterial hypertension". *American Journal of Hypertension* 21.9 (2008): 1040-1046.

51. Kagaya Y., *et al*. "Glycolytic inhibition: effects on diastolic relaxation and intracellular calcium handling in hypertrophied rat ventricular myocytes". *Journal of Clinical Investigation* 95.6 (1995): 2766-2776.

52. Doenst T., *et al*. "Decreased rates of substrate oxidation ex vivo predict the onset of heart failure and contractile dysfunction in rats with pressure overload". *Cardiovascular Research* 86.3 (2010): 461-470.

53. Luptak I., *et al*. "Decreased ATP production and myocardial contractile reserve in metabolic heart disease". *Journal of Molecular and Cellular Cardiology* 116 (2018): 106-114.