World Heart Journal
Volume 13, Number 1

ISSN: 1556-4002

Circadian Variation in Metabolism and Inflammation: Role in Obesity-Induced Heart Failure with Preserved Ejection Fraction

Fadhel A. Alomar[1], Jaipaul Singh[2], Ram B. Singh[3,*], and Keshore R. Bidasee[4,5]

[1]Department of Pharmacology and Toxicology, College of Clinical Pharmacy, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia
[2]School of Natural Sciences, University of Central Lancashire, Preston, UK
[3]Medical Hospital and Research Centre, Centre of Nutrition & Heart Research, Moradabad, India
[4]Department of Pharmacology and Experimental Neuroscience; Department of Environment and Occupational Health, University of Nebraska Medical Center, Omaha, NE, Lincoln NE, USA
[5]Nebraska Redox Biology Center, Lincoln NE, USA

Introduction and Aim

Obesity has become a public global health problem. More than 13% of the world's 7.8 billion people (11% of men and 15% of women) are obese, defined as having a body mass index above 30 kg/m^2. In North America and several Middle Eastern Countries, more than 30% of adults are obese. The alarming problem is that children as young as twelve years of age are now becoming obese. Obesity with high-fat and high-sugar diets is a risk factor for type 2 diabetes mellitus (T2DM), hypertension and early-onset heart failure (HF) with preserved ejection fraction (HFpEF) that leads to frequent hospitalizations. It is possible that diet, inactivity and other modern lifestyle factors may have an important role in the development of heart failure, either with or without decrease in ejection fraction [1]. This mini review discusses whether circadian oscillations in metabolism and inflammation could be responsible for the time-of-day-dependence of adverse cardio-vascular events in patients with HFpEF by increasing production of cytotoxic a-dicarbonyl species methylglyoxal (MG) and by decreasing expression of the primary MG-degrading enzyme glyoxalase-1 (Glo1), respectively.

Review and Conclusion

There is much evidence in the literature that peri-conceptional, perinatal nutritional factors as well dietary fatty acids in later life after birth are important in the pathogenesis of cardiovascular diseases (CVDs) [2-5]. Increased consumption of saturated, monounsaturated or n-6 polyunsaturated fatty acids

* Correspondence: Dr. Jaipaul Singh.
Email: jSingh3@uclan.ac.uk

has also shown beneficial effects in rodent studies [2]. This effect is associated with decline in inflammation and improved resistance to mitochondrial permeability transition. The underlying mechanisms are complex and may be due to cardiac adaptation, in particular when diets rich in saturated fat are administered. A more thorough knowledge is necessary to comprehend the effects of various fatty acids on cardiac phospholipids, lipid metabolites and metabolic flux in the normal and failing heart. Increased intake of high-sugar and high-fat diet may cause obesity-induced expression of Glo1 under inflammatory conditions, which may blunt accumulation of MG with circadian clock dysfunction of the cardiomyocyte and fibroblast.

It is proposed that the presence of other nutrients such as flavonoids, coenzyme Q10 and ω-3 fatty acids decrease the lipotoxic effects of saturated fat and slow the progression of hypertrophy, resulting in HFpEF, rather than HFrEF. It is clear that alterations in dietary fat intake may have promise in the management of HF. The effects of diet on cardiac cells may depend on various biomarkers that are known to damage cardiomyocytes. Increase in ceramides due to high glucose or fast food diets, high levels of trimethylamine N-oxide (TAMO) due to increased intake of red meat and eggs (choline and lecithin) as well as increase in advanced glycation products due to high-fat diets are new biomarkers of cardiac hypertrophy. These markers should be prevented by new therapies, which can avoid the development of cardiac hypertrophy as well as HFpEF. Cohort studies and animal experiments are needed to determine the role of healthy diet in terms of saturated, monounsaturated and n-6 polyunsaturated fatty acids intake for this group of vulnerable population (see Figure 1).

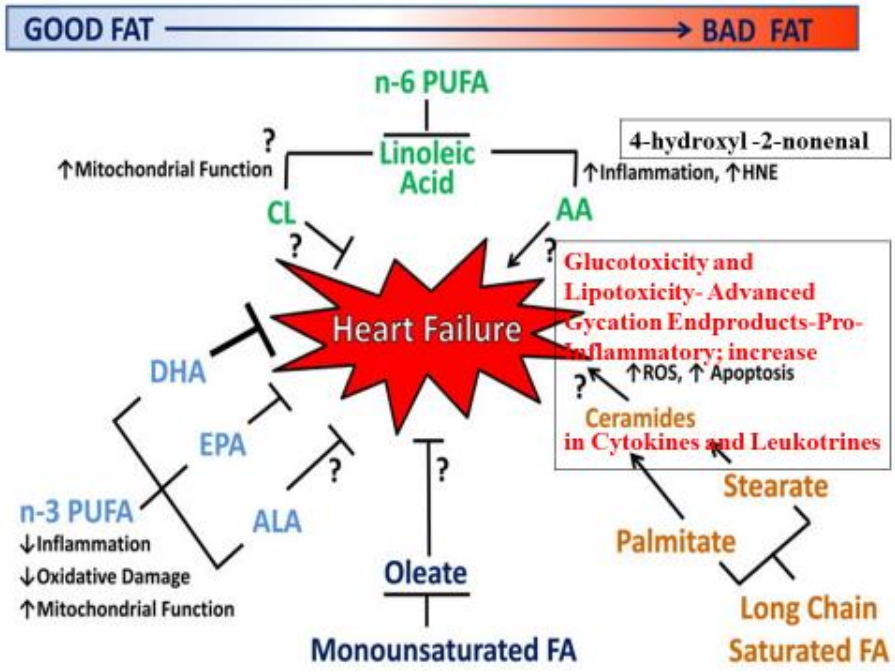

Figure 1. Modified flow diagram depicting the potential underlying mechanisms of how high-fat and high-glucose diets predispose to the development and progression of heart failure.

Specific pharmacologic agents to treat HFpEF are non-existent, in part because it is a diagnosis of exclusion, if speckle tracking echocardiography is not available. Recent advances in imaging have demonstrated that early cardiac dysfunction may be identified in a stage of pre-heart failure, which may be indicative of HFpEF. Clinical studies targeting the renin-angiotensin-aldosterone system (RAAS) to attenuate key co-morbidities associated with HFpEF, including endothelial cell dysfunction, vascular stiffening, impaired myocardial relaxation, fibrosis and improved vascular perfusion, have shown only

modest decreases in hospitalization rates and adverse clinical outcomes, suggesting that activation of RAAS may not be a primary cause. The severity of adverse cardiovascular events in patients with HFpEF exhibits a time-of-day-dependence. It is possible that circadian oscillations in metabolism and inflammation could be responsible for the time-of-day-dependence of adverse cardiovascular events in patients with HFpEF by increased circadian production of cytotoxic a-dicarbonyl species methylglyoxal (MG) and by decreasing expression of the primary MG-degrading enzyme glyoxalase-1 (Glo1), respectively. It is clear that any antioxidant agent such as higher intake of omega-3 and monounsaturated fatty acids and flavonoids administered as chronotherapy may enhance Glo1 release, leading to decline in MG and improvement in cardiac function.

In brief, it is possible that an increase in the expression of Glo1 under inflammatory conditions may blunt accumulation of MG and reset the circadian clock function of the cardiomyocyte and fibroblast, which could serve as a novel therapeutic strategy to attenuate the development of HFpEF [6].

Acknowledgements

The authors declare that they have no conflict of interest with this work. This work was supported in part by NIH.

References

[1] Cilia L, Saaed A, Ganga HV, Wu WC. Heart failure with preserved ejection fraction: prevention and management. *Am J. Lifestyle Med* 2019; 13(2): 182-189.

[2] Ng SF, Lin RC, Laybutt DR, Barres R, Owens JA, et al. Chronic high-fat diet in father's programs β-cell dysfunction in female rat offspring. *Nature* 2010; 467: 963-966.

[3] Schiattarella GG, Altamirano F, Tong D, et al. Nitrosative stress drives heart failure with preserved ejection fraction. *Nature* 2019; 568(7752): 351-356. doi: 10.1038/s41586-019-1100-z.

[4] Wang Z, Klipfell E, Bennett BJ, et al. Gut flora metabolism of phosphatidylcholine promotes cardio-vascular disease. *Nature* 2011; 472: 57–63.

[5] Stanley WC, Dabkowski ER, Ribeiro RF Jr, O'Connell KA. Dietary fat and heart failure: moving from lipotoxicity to lipoprotection. *Circ Res* 2012; 110(5): 764-776. doi:10.1161/CIRCRESAHA.111.253104.

[6] Alomar, F, Singh, J, Jang, H-S, Rozanski, G, Shao, C-H., Padanilam, B, Mayham, W., Bidasee, K. Smooth muscle- generated methylglyoxal impairs endothelial cell-mediated vasodilatation of cerebral micro-vessels in type 1 diabetic rats. *Brit J Pharmacol* 2016; 173(23): 3307-3326. doi.org/10.1111/bph.13617.