Mechanisms of heart failure with preserved ejection fraction in the presence of diabetes mellitus


Published in:
Translational Metabolic Syndrome Research

Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

Publisher rights
Copyright 2020 the authors.
This is an open access article published under a Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution and reproduction in any medium, provided the author and source are cited.

General rights
Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.
Mechanisms of heart failure with preserved ejection fraction in the presence of diabetes mellitus

Sargon Lazar, Benjamin Rayner, Guillermo Lopez Campos, Kristine McGrath, Lana McClements

PII: S2588-9303(20)30002-5
DOI: https://doi.org/10.1016/j.tmsr.2020.04.002
Reference: TMSR 12

To appear in: Translational Metabolic Syndrome Research

Received Date: 9 February 2020
Revised Date: 1 April 2020
Accepted Date: 1 April 2020


This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© [Copyright year] The Authors. Production and hosting by Elsevier B.V. on behalf of KeAi Communication Co., Ltd.
Credit Author Statement

**Sargon Lazar**: data/information curation, writing original draft preparation

**Benjamin Rayner**: writing-reviewing-editing, supervision

**Guillermo Lopez Campos**: methodology, software, writing

**Kristine McGrath**: writing-reviewing-editing, supervision

**Lana McClements**: conceptualization, writing-reviewing-editing, supervision
Title: Mechanisms of heart failure with preserved ejection fraction in the presence of diabetes mellitus

Sargon Lazar¹, Benjamin Rayner², Guillermo Lopez Campos³, Kristine McGrath¹, Lana McClements¹

¹ School of Life Sciences, Faculty of Science, University of Technology Sydney, NSW, Australia
² Heart Research Institute, Sydney Medical School, University of Sydney, NSW, Australia
³ The Wellcome-Woolfson Institute for Experimental Medicine, School of Medicine, Dentistry and Biomedical Sciences, Queen’s University Belfast, Northern Ireland, United Kingdom

Abstract

Cardiovascular disease (CVD) is the leading cause of death globally. People living with type 2 diabetes mellitus (T2DM) have a three times higher risk of developing CVD, particularly heart failure with preserved ejection fraction (HFpEF), for which there is no treatment. The need for tangible interventions has led to investigations into a number of biomarkers associated with metabolic and vascular dysfunction that could be utilised for diagnostic and treatment purposes. This review discusses the importance and mechanisms of inflammatory and angiogenic biomarkers, which have shown the most potential in the pathogenesis and diagnosis of HFpEF in the presence of diabetes. In depth “in silico” analysis was also carried out to identify pathogenic pathways associated with HFpEF, both in the presence and absence of diabetes. The results identified mostly inflammatory pathways associated with HFpEF in the presence of diabetes, and a number of pathways related to angiogenesis, remodelling and metabolism. In addition, the results also identified inflammation, in the absence of diabetes. The shared and unique pathways identified in HFpEF in the presence and absence of diabetes, should be explored further in order to improve management and outcomes of people living with HFpEF.
Introduction

Diabetes and cardiovascular disease

Over the past 40 years there has been a four-fold increase in the incidence of type 2 diabetes mellitus (T2DM) globally. According to the World Health Organisation (WHO), the number of people living with diabetes reached 422 million in 2014, where the world population had climbed to 7.2 billion. Over the last 20-30 years, sedentary lifestyle choices and the influence of the Western diet, have led to a global increase in obesity and subsequent co-morbidities, such as, CVD. Worldwide, CVD is the biggest killer, claiming ~18 million lives annually, equating to 31% of total deaths, with the incidence of CVD up to three-fold higher in people with diabetes.

Heart failure as a diabetic comorbidity in Australia

Hyperglycaemia, as the major hallmark of diabetes, has been linked to both micro- and macrovascular complications, including coronary artery disease and stroke. Poor glycaemic management, therefore, can lead to the development of co-morbidities, such as heart failure (HF), which is associated with high morbidity and poor prognosis. Currently, HF is classified as either heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF). It is estimated that approximately 480,000 Australians, 66% of whom are male, are affected by HFrEF, accounting for ~2% of the total population, or 6.3% of people aged 45 years and over. Comparatively, HFpEF is estimated to affect a similar amount of people, although predominating within the female population.
While HFrEF has been more closely studied and pharmacologically well managed [14], HFpEF is still poorly understood and lacking effective treatment strategies. HFrEF is defined as a left ventricular ejection fraction (LVEF) measurement of less than 50%, with or without signs of clinical heart failure. In contrast, defining HFpEF has proven to be much more complicated, as the main marker of cardiac abnormality (LVEF) is, by definition, preserved. As such, the definition of HFpEF (with or without clinical signs of heart disease) is constantly changing and, currently the diagnosis includes a LVEF of at least 50%, with other evidence such as structural heart disease or diastolic dysfunction [15]. HFpEF is associated with high morbidity, a shortened life expectancy, and a 5-year mortality of newly diagnosed patients that is as high as 50%. This is likely due to the lack of effective interventions and diagnostics for the HFpEF form of the syndrome and a paucity in knowledge in relation to the pathogenesis leading to HFpEF in both people with and without diabetes [16][17]. Reliable blood-based biomarkers reflective of the cardiac pathology could be beneficial in predicting the risk of HFpEF occurrence and also be utilised in the development of novel therapeutic agents [18]. In this review, we give a detailed outline of angiogenic and inflammatory mechanisms in HFpEF, particularly in the presence of diabetes, and carry out “in silico” analysis of pathogenic pathways implicated in HFpEF in the presence or absence of diabetes. These identified mechanisms could be investigated and validated in the future studies as biomarkers or targets for prevention or treatment of HFpEF in people with diabetes.

The pathogenesis of HFpEF in diabetes

HFpEF is classified as a diastolic dysfunction affecting the left ventricle (LV), manifesting as either an impairment of left ventricular relaxation or increased diastolic stiffness, which can be attributed to myocardial hypertrophy, progressive myocardial fibrosis and increased...
cardiomyocyte stiffness\textsuperscript{[19][20][21]}. The evident slowed relaxation is due to a loss in flexibility that impacts mid to late diastole, also resulting in elevated blood pressure \textsuperscript{[22]}. The loss of flexibility is due to the re-characterisation of a large sarcomeric protein called titin, which is responsible for recoil, remaining in a compressed state during systole \textsuperscript{[23]}. This occurs through transcriptional and post-translation modifications\textsuperscript{[24][25]} that results in extracellular matrix accumulation and fibrosis (i.e. an imbalance between depressed collagen degradation and exaggerated collagen synthesis), manifesting in disturbed LV filling\textsuperscript{[26]} and detrimental structural modifications\textsuperscript{[19][20][21]}. Furthermore, when stretching of the heart occurs, cardiomyocytes within the ventricles secrete a B-type natriuretic peptide (BNP) that may be used as a biomarker for the onset of HFpEF\textsuperscript{[27]}.

The presence of HFpEF is more common in diabetes, likely due to the accumulation of adipose tissue and lipid within non-adipose tissue that can lead to the development of insulin resistance within myocytes, hepatocytes and adipocytes \textsuperscript{[28]}. T2DM causes endothelial cell dysfunction and hence aberrant angiogenesis\textsuperscript{[29][30]}, elevating levels of fibrinogen\textsuperscript{[31][32]}, thrombin\textsuperscript{[33]}, coagulation factors VII\textsuperscript{[34]} & VIII\textsuperscript{[35]}, inflammatory mediators\textsuperscript{[36][37]} and Plasminogen-Activator Inhibitor Type 1\textsuperscript{[38]}. These factors induce a pro-thrombotic environment within the vasculature by accelerating atherosclerotic plaque formation through chronic inflammation and injury to arterial walls \textsuperscript{[39]}.

**Inflammation in HFpEF**

As far back as the 1990s, links between increased inflammatory profiles and LV dysfunction have been identified in a number of rat models\textsuperscript{[41]}, suggesting a cause and effect relationship between inflammation and the development of fibrosis. However, the element of time and the inflammatory cascade varies between species, as does the reliance of identifying specific biomarkers at specific time points in disease progression that may be relevant to overall heart
condition. Pentraxin-3 (PTX3) is one such biomarker that has a well-established association with vascular inflammation and, only recently Zlibut et al. highlighted a role for PTX3 in decreasing nitric oxide (NO) synthesis within endothelial cells, altering their function and inhibiting cell proliferation \(^{[42]}\). Furthermore, correlation between upregulation of the pro-inflammatory cytokine interleukin-6 (IL-6) and PTX3 have also been found in HFP EF\(^{[43]}\), with studies showing that IL-6 forms a cluster with periostin (involved in vasculature remodelling) and C-reactive protein (CRP), but only within a diabetic environment\(^{[44]}\). This pro-inflammatory state underlying the pathophysiology of HFP EF allows a contrast to be made when compared to the pathophysiology pathway of HFrEF, which has been more closely associated with NT-proBNP (as a result of oxidative stress and cardiac stretch) than HFP EF\(^{[45][46][47][48][49][50][51][52][53][54]}\).

Angiogenesis in HFP EF

Aberrant angiogenesis caused by a T2DM-induced prothrombotic environment arising from adipose tissue and lipid accumulation, resulting in insulin resistance, also plays an important role in the pathogenesis of diastolic dysfunction and HFP EF. Barroso et al. recently identified the endogenous angiogenesis inhibitor, endostatin, as a possible biomarker of HFP EF, due to its correlation to the presence and severity of HFP EF, with the evident deterioration of diastolic function correlated with increased endostatin levels \(^{[41]}\). Other angiogenesis biomarkers that have delivered predictive results particular to HFP EF and not in HFrEF are the vascular endothelial growth factor co-receptor neuropilin and the remodelling marker osteopontin \(^{[43]}\). Similarly, C-type natriuretic peptide (CNP)-guided therapy as studied by Lok et al. showed promise in predictive endpoints of patient re-hospitalizations as a result of HFP EF but not for patients with HFrEF, observing higher concentrations of NT-proCNP in HFP EF that increased at every rehospitalisation and enhanced the accuracy of the predictive outcome for each patient\(^{[55]}\). Furthermore, in the presence of diabetes, there is a direct
association between CNP and HFpEF, which is promising, especially considering its predominant localisation in the endothelium and the detrimental impact diabetes has on inducing endothelial damage\textsuperscript{[55]}.

Computational analysis of the literature on HFpEF biomarkers in the presence and absence of diabetes

A number of “omics” approaches have been employed in biomarker discovery of CVD including genomics, transcriptomics, proteomics and metabolomics in order to understand molecular mechanisms of underlying pathogenesis. The wealth of scientific data available in public repositories can also be helpful to integrate relevant biomarkers in HFpEF and contextualise these into pathogenic biological pathways. Therefore, we carried out a computational analysis of biomarkers identified in the literature to further evaluate pathogenic pathways associated with HFpEF both in the presence and absence of diabetes. For this purpose, we combined a series of literature queries, public data repositories (Pubtator, Reactome and gProfiler) and in-house developed R scripts that allowed us to retrieve and analyse these biomarkers in the context of pathways / gene sets, similar to what we previously described\textsuperscript{[56]}. To retrieve the relevant literature we built two queries, one focused in the detection of publications related with biomarkers for HFpEF in the presence of diabetes (1) and another one that does not include diabetes (2):

1. (("HFpEF"[Title/abstract] OR "heart failure with preserved ejection fraction"[Title/abstract]) AND ("Diabetes Mellitus"[MeSH Terms] OR "diabetes"[Title/abstract])) AND ("Biomarker"[Title/abstract] OR "biomarkers"[MeSH Terms]) AND ("1900/01/01"[EDAT] : "2019/06/01"[EDAT])

2. (("HFpEF"[Title/abstract] OR "heart failure with preserved ejection fraction"[Title/abstract]) NOT ("Diabetes Mellitus"[MeSH Terms] OR...
Our computational analysis generated the total number of 1,776 pathways in relation to HFpEF in the absence of diabetes, and 437 pathways in the presence of diabetes; 1,326 pathways were identified in HFpEF as shared between diabetes and in the absence of diabetes (Figure 1). When these results were extrapolated into specific pathways using Reactome knowledgebase, a number of inflammatory biomarkers were identified including tumour necrosis factor (TNF), nuclear factor NFκB and interleukin (IL) signalling pathways (Figure 2) as key in HFpEF pathogenesis in the presence of diabetes. On the other hand, in the absence of diabetes, a number of additional pathways were identified including extracellular matrix degradation, hypoxia inducible factor, coagulation, fibrosis and metabolic/insulin signalling pathways (Figure 3). These biomarkers and pathways should be further explored and validated using appropriate clinical samples from people with HFpEF with and without diabetes as well as pre-clinical in vivo and in vitro models of diabetes- and hypertension-induced HFpEF. Although our search of the literature excluded the word “diabetes” from titles and abstracts as a MeSH term, it does not garantie exclusion of diabetes in cases where these types of patients were included, but not reported as having diabetes in the publications.

Conclusion
This review outlines the complexity of HFpEF pathogenesis and the need for further investigation into specific biomarkers that could be utilised as diagnostic or therapeutic targets, both in the presence and absence of diabetes. Using a bioinformatics approach, we identified some shared and some unique pathogenic pathways of HFpEF in the presence and absence of diabetes, identifying inflammation as a key process associated with HFpEF. These
pathways should be explored further for their role and mechanism of action in the pathogenesis of HFpEF in order to develop more effective predictive, diagnostic and treatment strategies.

Figure 1. Individual and overlapping pathways identified as aberrantly activated in HFpEF in the presence and absence of diabetes. Diab_1, diabetes; Non_diab_2, non-diabetes.
Figure 2. Pathogenic pathways identified using “in silico” analysis of publicly available datasets in relation to HFpEF in the presence of diabetes.

Figure 3. Pathogenic pathways identified using “in silico” analysis of publicly available datasets in relation to HFpEF in the absence of diabetes as per our search strategy depicted above.
Funding: This project was funded through the Honour’s student fund provided by the Faculty of Science, University of Technology Sydney.

Bibliography


Diabetes care, 16(2), pp. 434–44.


Editorial Board

*Translational Metabolic Syndrome Research*

*Re: “Mechanisms of heart failure with preserved ejection fraction in the presence of diabetes mellitus”*

Dear Editorial Board,

We would like to declare that none of the authors listed on this manuscript have any conflicts of interest.

Thank you for your consideration.

Yours sincerely,

Dr. Lana McClements
Lecturer in Biotechnology
School of Life Sciences
University of Technology Sydney