European Journal of Heart Failure (2015) **17**, 1210–1212
doi:10.1002/ejhf.439

EDITORIAL COMMENT

Latent ischaemia as a trigger for a *circulus vitiosus* of inflammation, fibrosis, and stiffness in HFPEF

Carsten Tschöpe[1,2,3]* and Heiner Post[1]

[1]Department of Cardiology, Charité–Universitätsmedizin Berlin, Campus Virchow Klinikum, Berlin, Germany; [2]Berlin-Brandenburg Center for Regenerative Therapies, Charité–Universitätsmedizin Berlin, Campus Virchow Klinikum, Berlin, Germany; and; and [3]German Centre for Cardiovascular Research (DZHK), Charite, Berlin, Germany

This article refers to 'Association of impaired left ventricular twisting–untwisting with vascular dysfunction, neurohumoral activation, and impaired exercise capacity in hypertensive heart disease'[†], by I. Ikonomidis *et al.*, published in this issue on pages 1249–1260.

Heart failure (HF) is defined as the inability of the left ventricle to generate an adequate cardiac output at physiological filling pressures. When HF starts from myocardial damage and loss of cardiomyocytes, the left ventricle will undergo dilatative remodelling with a progressive reduction of EF (HFREF) and subsequent systemic neurohumoral activation. However, almost 50% of clinical HF cases present with a preserved LVEF (HFPEF). HFPEF is understood to evolve not from a single trigger, but from the accumulation of cardiovascular risk factors over time, such as ageing, hypertension, obesity, diabetes, renal dysfunction, and physical inactivity.[1] Via mechanisms that are still not completely understood, a specific LV remodelling process is induced that ultimately leads to a loss of LV compliance and increased LV filling pressures, i.e. a leftward shift of the LV end-diastolic pressure–volume relationship (EDPVR). Such a shift of the EDPVR is a hallmark of LV dysfunction in HFPEF patients[2] and predicts clinical outcome.[3]

Decreased LV end-diastolic distensibility can result from slowed LV relaxation, in particular at higher heart rates when early diastolic suction by LV untwisting becomes essential for timely LV filling, and/or increased passive LV stiffness. Upstream of the left ventricle, chronotropic incompetence, atrial dysfunction, and AF may contribute to decreased cardiac output.[4] In more severe cases, cardiac dysfunction extends to the right ventricle via elevated pulmonary vascular resistance and pressures. Also, pulmonary hypertension *per se* can limit LV filling by right ventricular enlargement.[5] Distal to the left ventricle, stiffening of the arterial vascular bed can impair ventriculo-arterial coupling, and finally skeletal muscle abnormalities may also be causally involved in the exercise intolerance of HFPEF patients. Given this heterogeneity in terms of aetiology, pathophysiology, and co-morbidities, it is not surprising that HFPEF represents a clinical entity with an obvious lack of evidence-based pathophysiological concepts, universal diagnostic algorithms, and guideline therapies. Consequently, most pharmacological studies did not demonstrate a benefit in HFPEF.

In this issue of the journal, Ikonomidis *et al.*[6] report on a comprehensive, non-invasive diagnostic study in newly diagnosed, drug-naive hypertensive subjects ($n = 320$) compared with normotensive controls ($n = 160$). Although patients did not present with HF, they demonstrated an apparently low maximum oxygen uptake (<25 mL/min/kg), concentric LV hypertrophy with normal LVEF, left atrial enlargement, and elevated BNP levels. As further cardiovascular risk factors and disease such as diabetes, renal insufficiency, or CAD were excluded, this well-defined cohort with hypertensive heart disease at a fairly young age (mean 50 years) may thus be seen at high risk for the transition into HFPEF driven by the risk factor hypertension over time. The authors assessed LV dimensions, LV three-dimensional function, and coronary flow reserve by echocardiography, natriuretic peptide levels, blood pressures, arterial stiffness by pulse wave velocity, serum markers of matrix and collagen turnover, and exercise capacity (in a subset of patients). Not unexpectedly, LV concentric hypertrophy was already accompanied by reduced longitudinal shortening and prolonged untwisting. The strength of the study is that it demonstrates that this alteration of LV function is correlated to reduced coronary flow reserve, increased pulse wave velocity, and elevated NT-proBNP levels, and serum markers of collagen turnover and matrix remodelling. In particular, prolonged LV untwisting was predicted by elevated serum markers of fibrosis just as well as by NT-proBNP. In the subset of patients undergoing exercise testing, decreased maximum workload was related to prolonged LV untwisting and reduced coronary flow reserve.

The opinions expressed in this article are not necessarily those of the Editors of the *European Journal of Heart Failure* or of the European Society of Cardiology.

[†]DOI: 10.1002/ejhf.403

*Corresponding author. Department of Cardiology Charité–University of Medicine Berlin, Campus Virchow Klinikum, Augustenburgerplatz 1, D- 13353 Berlin, Germany. Tel: +49 30 450553712, Fax: +49 30 4507553712, Email: Carsten.Tschoepe@charite.de

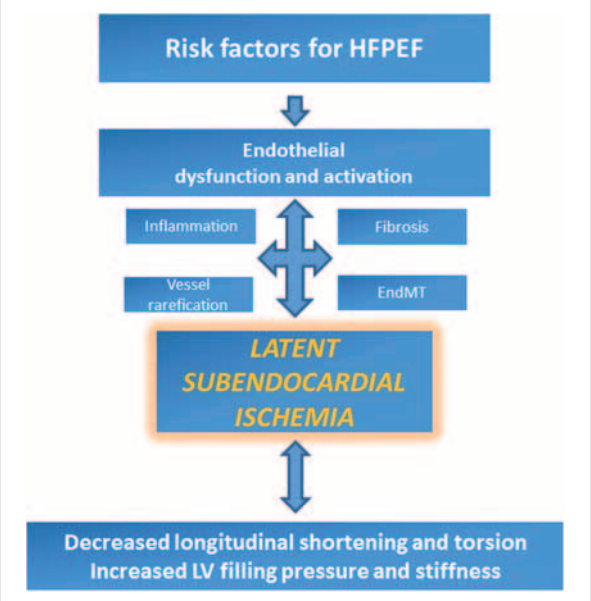

Figure 1 Proposed role of latent ischaemia, inflammation, fibrosis, and LV stiffness in HFPEF. Risk factors for HFPEF such as obesity, hypertension, diabetes mellitus, and hyperlipidaemia induce a systemic inflammatory state leading to an endothelial activation and dysfunction, promoting subendocardial ischaemia in a hypertrophied left ventricle. Mechanisms involved include endothelial-to-mesenchymal transition (EndMT), a process by which endothelial cells transdifferentiate into (myo)fibroblasts and give rise to aggregate fibrosis and vessel rarefication. Thereby, myofibroblasts act as collagen accumulator and inflammatory supporter cells increasing both inflammation/oxidative stress and fibrosis. Cardiac fibrosis and cardiomyocyte stiffness contribute to impaired diastolic and systolic deformation, leading to increased LV stiffness and filling pressures, which can trigger as a *circulus vitiosus* subendocardial ischaemia, endothelial activation, and dysfunction.

The study by Ikonomidis *et al.*, due to the high number of individuals studied, does not provide direct evidence of increased peripheral vascular or myocardial fibrosis and cannot establish cause–effect relationships. Nevertheless, the connection between arterial stiffening, reduced coronary flow reserve, and LV functional impairment in hypertensive patients at risk for HFPEF is intriguing. Coronary blood flow can increase up to five-fold to meet myocardial energy demand during strenuous exercise, and LV relaxation—at the cardiomyocyte level relying on the energy-dependent process of calcium resequestration into the sarcoplasmatic reticulum—is highly sensitive to an imbalance of myocardial oxygen demand–supply. It has been recognized that LV functional alterations in HFPEF are aggravated substantially during an exercise challenge. LV rotational dysfunction can be mild at rest, but becomes most prominent already during a mild exercise challenge.[7] In addition, the leftward shift of the LV EDPVR in HFPEF patients is not static, but is further pronounced during exercise.[8,9] Coronary microvascular dysfunction[10] and rarefication,[11] leading to subendocardial ischaemia not at rest, but during exercise, would be a very plausible explanation for LV dysfunction during exercise, in particular as primarily subendocardial muscle fibres mediate LV longitudinal shortening and LV untwisting.

Potential mechanisms are still to be established. Endothelial dysfunction/activation may contribute to cardiac fibrosis by different means. In addition to latent ischaemia being able to induce fibrosis over time, we demonstrated that endothelial activation/dysfunction triggers a low gradient inflammatory state that via transforming growth factor-β (TGF-β) induces a transition of fibroblasts to myofibroblasts.[12] Myofibroblasts release chemokines that aggravate inflammation, oxidative stress, endothelial activation, and fibrosis, and thereby contribute to an increase in LV stiffness. In addition, endothelial activation induces endothelial-to-mesenchymal transition (EndMT) by inflammation [TGF-β1 and tumour necrosis factor-α (TNF-α)], oxidative stress, oxidized LDL, diabetes mellitus, hypertension, and age, all parameters/co-morbidities which are associated with HFPEF.[13] Thereby endothelial cells are converted to a mesenchymal cell type, which can give rise to fibroblasts and contribute to microvascular rarefaction and subsequent chronic ischaemia in the injured heart, ultimately leading to cardiac fibrosis.[14] Ischaemia, inflammation, and oxidative stress potentiate each other and impact on endothelial function and matrix turnover, as well as on cardiomyocyte function (*Figure 1*).[15]

Such pathophysiological mechanisms correspond to the clinical findings of Ikonomidis *et al.* The authors suggest that systemic profibrotic processes may be the common denominator of LV and vascular remodelling in hypertension and represent a therapeutical target to prevent the transition of hypertensive heart disease into HF, i.e. HFPEF. However, whether the described processes are an epiphenomenon or a therapeutic target in HFPEF remains to be tested in further studies, since it is not likely that these processes are purely hypertension and HFPEF specific. In addition, the HFPEF population is heterogeneous and may need subgroup-specific diagnostic and treatment approaches.[16]

Conflct of interest: none declared.

References

1. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013;**62**:263–271.
2. Westermann D, Kasner M, Steendijk P, Spillmann F, Riad A, Weitmann K, Hoffmann W, Poller W, Pauschinger M, Schultheiss HP, Tschope C. Role of left ventricular stiffness in heart failure with normal ejection fraction. *Circulation* 2008;**117**:2051–2060.
3. Burke MA, Katz DH, Beussink L, Selvaraj S, Gupta DK, Fox J, Chakrabarti S, Sauer AJ, Rich JD, Freed BH, Shah SJ. Prognostic importance of pathophysiologic markers in patients with heart failure and preserved ejection fraction. *Circ Heart Fail* 2014;**7**:288–299.
4. Melenovsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. *Circ Heart Fail* 2015;**8**:295–303.
5. Kasner M, Westermann D, Steendijk P, Drose S, Poller W, Schultheiss HP, Tschope C. Left ventricular dysfunction induced by nonsevere idiopathic pulmonary arterial hypertension: a pressure–volume relationship study. *Am J Respir Crit Care Med.* 2012;**186**:181–189.
6. Ikonomidis I, Tzortzis S, Triantafyllidi H, Parissis J, Papadopoulos C, Venetsanou K, Trivilou P, Paraskevaidis I, Lekakis J. Association of impaired left ventricular twisting-untwisting with vascular dysfunction, neurohumoral activation and impaired exercise capacity in hypertensive heart disease. *Eur J Heart Fail* 2015;**17**:1249–1260.

7. Tan YT, Wenzelburger F, Lee E, Heatlie G, Leyva F, Patel K, Frenneaux M, Sanderson JE. 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* 2009;**54**:36–46.
8. Borlaug BA, Jaber WA, Ommen SR, Lam CS, Redfield MM, Nishimura RA. Diastolic relaxation and compliance reserve during dynamic exercise in heart failure with preserved ejection fraction. *Heart* 2011;**97**:964–969.
9. Kasner M SD, Lober J, Post H, Fraser AG, Pieske B, Burkhoff D, Tschöpe C. Heterogeneous responses of systolic and diastolic left ventricular function to exercise in patients with heart failure and preserved ejection fraction. *ESC Heart Fail* 2015;**2**:121–132
10. Tschope C, Bock CT, Kasner M, Noutsias M, Westermann D, Schwimmbeck PL, Pauschinger M, Poller WC, Kuhl U, Kandolf R, Schultheiss HP. High prevalence of cardiac parvovirus B19 infection in patients with isolated left ventricular diastolic dysfunction. *Circulation* 2005;**111**:879–886.
11. Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. *Circulation* 2015;**131**:550–559.
12. Lindner D, Zietsch C, Tank J, Sossalla S, Fluschnik N, Hinrichs S, Maier L, Poller W, Blankenberg S, Schultheiss HP, Tschope C, Westermann D. Cardiac fibroblasts support cardiac inflammation in heart failure. *Basic Res Cardiol* 2014; **109**:428.
13. Spillmann F, Miteva K, Pieske B, Tschope C, Van Linthout S. High-density lipoproteins reduce endothelial-to-mesenchymal transition. *Arterioscler Thromb Vasc Biol* 2015;**35**:1774–1777.
14. Tschope C, Van Linthout S. New insights in (inter)cellular mechanisms by heart failure with preserved ejection fraction. *Curr Heart Fail Rep* 2014;**11**: 436–444.
15. Hamdani N, Franssen C, Lourenco A, Falcao-Pires I, Fontoura D, Leite S, Plettig L, Lopez B, Ottenheijm CA, Becher PM, Gonzalez A, Tschope C, Diez J, Linke WA, Leite-Moreira AF, Paulus WJ. Myocardial titin hypophosphorylation importantly contributes to heart failure with preserved ejection fraction in a rat metabolic risk model. *Circ Heart Fail* 2013;**6**:1239–1249.
16. Shah SJ, Katz DH, Selvaraj S, Burke MA, Yancy CW, Gheorghiade M, Bonow RO, Huang CC, Deo RC. Phenomapping for novel classification of heart failure with preserved ejection fraction. *Circulation* 2015;**131**: 269–279.