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Circulating biomarkers of left ventricular diastolic function and dysfunction: filling the research gap under high pressure

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Left ventricular diastolic function is the ability of the left ventricle to relax and then fill under normal chamber pressures, which is an important part of a normal cardiac cycle. When left ventricular diastolic function is altered, usually by impaired left ventricular relaxation and increased left ventricular chamber stiffness, left ventricular filling develops under high pressures and left ventricular diastolic dysfunction (LVDD) is established.[1]

In the general population, asymptomatic LVDD has a prevalence above 25%, rising up to 64% in high-risk subjects.[2,3] Furthermore, even in preclinical stages, LVDD is associated with an increased risk of incident heart failure and both fatal and non-fatal cardiovascular events.[2,4] Thus because of its high prevalence and adverse-related outcomes, LVDD is an important public health problem and prevention target.

Echocardiographic assessment of left ventricular function is an important tool for clinical evaluation that is performed through several parameters because no variable alone is diagnostic of LVDD. Among common parameters are: early transmitral flow velocity (E), late transmitral flow velocity (A), early mitral annulus velocity (e′), tricuspid regurgitation systolic jet velocity (TR) and left atrial maximum volume index, among others. According to current recommendations, LVDD is present if more than half of the suggested variables (E/e′, e′, TR and left atrial volume index) meet the cut-off values.[1] However, echocardiographic definitions and cut-off values have some particular concerns in subclinical LVDD: many individuals are classified as having 'indeterminate' left ventricular diastolic function and there is a lower LVDD prevalence in population studies,[3,5] criteria based largely on expert consensus reports[1] and technical limitations (e.g. high operator dependence) among others.

Biomarkers of left ventricular diastolic function and dysfunction

The natural history and pathophysiology of LVDD has attributed a potential role for biomarkers in the prevention, diagnosis and management of LVDD in its early stages.[2,6] Although a large amount of evidence is available about biomarkers in heart failure with preserved and reduced ejection fraction, there is a large unfilled research gap in LVDD, especially in the early or asymptomatic phases. The FLEMENGHO study – a landmark family-based population study from Belgium – has helped to fill this research gap by relating different biomarkers with echocardiographic parameters of high diastolic pressure.

Over the past decade FLEMENGHO's researchers have reported different blood and urinary biomarkers of left ventricular diastolic function and LVDD, which are summarised in Table 1. The FLEMENGHO study has associated left ventricular function (assessed mainly as E, A, e′ and E/e′) and LVDD with genetic polymorphism, urinary proteomics, circulating markers of collagen turnover, markers of cardiomyocyte injury, cytokines and circulating metabolites related to energy substrate utilisation and oxidative stress protection. A few other studies have identified different biomarkers of LVDD: natriuretic peptides, long non-coding RNAs, markers of collagen turnover, pentaxine-3, thiol, fatty acid-binding protein 4 (FAB4), inflammatory markers and peroxisome proliferator-activated receptor polymorphisms (see Table 1).

Natriuretic peptides (such as brain natriuretic peptide (BNP) and NT-proBNP) have been researched mostly for the diagnosis of heart failure with preserved ejection fraction,[6] conditions in which LVDD is usually present. However, some studies have researched

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Table 1. Biomarkers of left ventricular function researched in population studies.

Reference	Biomarker	Study type	*n*	Findings and comments
FLEMENGHO population study				
J Hypertens 2008; 26: 1229–1236	Adducin polymorphisms	Cross-sectional	473	LVDF is modulated by genetic variation in ADD1 and ADD3
Am J Hypertens 2012; 25: 986–993	Steroid biosynthesis genes	Cross-sectional	532	3β-hydroxysteroid-dehydrogenase GCC haplotype is associated with lower LVDF
Eur Heart J 2012; 33: 2342–2350	Urinary proteome	Case-control	38	Only hypertensive patients; 85 urinary peptides were different between control subjects and those with LVDD
Int J Cardiol 2014; 176: 158–165	Urinary proteome	Cross-sectional	745	Two urinary proteomic classifiers (HF1 and HF2) were associated with LVDF and HF1 with LVDD
BMC Med Genet 2014; 15: 121	SNP of the ATP12A gene	Cross-sectional	1166	Carriers of rs10507337 C allele had better LVDF
Int J Cardiol 2015; 185: 177–185	hs-cardiac troponin T	Cross-sectional	727	hs-cardiac troponin correlated with LVDF and biomarkers of collagen I turnover; hs-troponin also increased the risk of LVDD
Int J Cardiol 2015; 185: 177–185	NT-proBNP	Cross-sectional	727	NT-proBNP correlated with LVDF, biomarkers of collagen I turnover and predicted LVDD
PLoS One 2015; 10: e0141394.	CXCR3 ligands	Case-control	67	MIG, IP10 and I-TAC increased the risk of LVDD. Groups were divided by hypertension status and symptoms
J Am Soc Hypertens 2015; 9: 975–984.e3	Cytokines	Nested case-control	110	IL-18, HGF and MIG were significantly different between hypertensives with and without left ventridular remodelling, hypertrophy or LVDD
J Am Heart Assoc 2016; 5: e002681	Circulating metabolites	Cross-sectional	711	Circulating metabolites indicative of energy substrate utilisation and protection against oxidative stress were associated with LVDF and LVDD
Int J Cardiol 2016; 214: 180–188	Blood mitochondrial DNA	Longitudinal	701	Higher mitochondrial DNA content was associated with better LVDF at baseline, but not at follow-up
PLoS One 2016; 11: e0167582	Urinary and serum collagen biomarkers	Cross-sectional	782	LVDF correlated with urinary collagen I and III and serum markers of collagen I deposition. LVDF was associated with higher levels of TIMP-1
J Am Soc Hypertens 2018; 12: 438–447.e4	Urinary peptidomic marker (HF1)	Longitudinal	645	HF1 was associated with LVDF at baseline and increased the risk of LVDD at 5-year follow-up
PLoS One 2018; 13: e0193967	Matrix Gla protein (MGP)	Cross-sectional	1054	Higher levels of inactive desphospho-uncarboxylated MGP correlated with worse LVDF and LVDD
Other selected studies with asymptomatic individuals				
Diabetes Care 2012; 35: 2510–2514	BNP	Longitudinal	300	General population. Higher BNP was associated with LVDF at 8-year follow-up. The effect was stronger in type 2 diabetes
J Cardiac Fail 2009; 15: 377–384	NT-proBNP	Cross-sectional	1012	Asymptomatic patients at high risk of heart failure. High NT-proBNP increased the risk of LVDD
Sci Rep 2016; 6: 37354	Circulating long non-coding RNAs	Case-control	60	Well-controlled diabetics. Long intergenic non-coding RNAs predicting cardiac remodeling were inversely associated with LVDF and directly associated with LVDD

(continued)

Table 1. Continued

Reference	Biomarker	Study type	*n*	Findings and comments
Eur J Heart Fail 2011; 13: 1087–1095	Markers of collagen turnover	Cross-sectional	275	Stable hypertensive patients. Serum levels of MMP9 and TIMP1 identified risk of LVDD
J Am Coll Cardiol 2011; 57: 861–869	Pentraxin 3	Cross-sectional	323	In 171 patients without heart failure, pentraxin 3 correlated with the presence of LVDD
Scand J Clin Lab Invest 2015; 75: 667–673	Thiol (antioxidant)	Cross-sectional	138	Newly diagnosed hypertensive patients. Plasma thiol was an independent predictor for the presence of LVDD
Cardiovasc Diabetol 2014; 13: 126	Fatty acid-binding protein 4 (FAB4)	Cross-sectional	190	General population. Serum FABP4 concentration was independently correlated with LVDF
J Hum Hypertens 2014; 28: 557–563	PPARGC1A Gly482Ser polymorphism	Cross-sectional	205	Well-controlled hypertensives. The presence of the Ser–Ser allele was independently associated with LVDF
J Hum Hypertens 2013; 27: 13–17	Inflammatory markers	Cross-sectional	1016	A population of elderly people. 1-Selectin and high-sensitive CRP were related to LVDF

LVDF: left ventricular diastolic function; LVDD: left ventricular diastolic dysfunction.

natriuretic peptides in asymptomatic LVDD (Table 1). In addition to FLEMENGHO, the Horn Study and other studies performed in the general population have reported higher BNP and proBNP levels in subjects with LVDD, and an inverse relationship with echocardiographic measures of left ventricular function, with a higher strength of association in diabetes, in which basal BNP levels also predict left ventricular diastolic function at follow-up.[7] Moreover, in individuals with cardiovascular risk factors, plasma levels of NT-proBNP and high-sensitivity cardiac troponin T could indicate subclinical organ damage and cognitive impairment.[8,9] Finally, the STOP-HF trial in high-risk patients proved that BNP-based screening and collaborative care reduce the prevalence of asymptomatic left ventricular dysfunction, with or without heart failure, but not the prevalence of asymptomatic LVDD alone after adjusting for baseline characteristics.[10] To our knowledge, no other biomarker has proved its utility regarding the treatment or prevention of LVDD.

Circulating metabolites as biomarkers of diastolic function

In the current issue of the *European Journal of Preventive Cardiology*, FLEMENGHO's researchers used a non-targeted metabolomic approach to associate circulating metabolites with left ventricular diastolic function and predict asymptomatic LVDD at a 5-year follow-up.[11] A total of 570 participants from the community were enrolled to asses left ventricular diastolic function by echocardiography (e′, E/e′ and E/A) and to measure 43 circulating metabolites by nuclear magnetic resonance spectroscopy. Cross-sectional analysis indicated that higher valine and glucose plus taurine values were associated with greater e′, while higher valine and 2-oxobutyrate values were inversely associated with E/e′. In a longitudinal analysis, higher pantoate at baseline was associated with lower e′, and higher valine and glucose plus taurine at baseline were associated with lower E/e′ at follow-up. After adjustment for baseline characteristics, the risk of LVDD or LVDD progression incidence at follow-up decreased with higher baseline glucose plus taurine. Through pathway analysis, the most important pathways associated with LVDD included branched chain amino acid metabolism and aminoacyl-tRNA.

The results described above are important to advance in filling the research gap regarding LVDD biomarkers. First of all, most of the community-based studies – including those about natriuretic peptides – are cross-sectional studies with known methodical limitations; however, the present study longitudinally relates circulating biomarkers with left ventricular diastolic function. And second, there is biological plausibility to propose branched chain amino acids as biomarkers, based on their catabolic pathway in LVDD. Thus a new potential circulating biomarker for early stages of LVDD is born.

Current limitations and high pressure need for research

Despite the strengths of the article of Zhang and collaborators,[11] some limitations need to be addressed by answering the following questions. What were the mean and standard deviation of the main metabolites that were studied? Do circulating metabolites have a considerable biological variability? What frequent conditions or comorbidities affect their values? Is the strength of

association different between normal individuals and those with LVDD at baseline (effect modification)? Is there also a 'dose–response' effect with LVDD grades? How do branched chain amino acids change during the period predicted for left ventricular diastolic function deterioration? Will it be possible to translate these population findings to a clinical setting?

Many of the limitations mentioned above for the analysis of circulating metabolites are common setbacks in the study of other biomarkers of LVDD. However, more issues need to be solved for most of them: validated normal range values, diagnostic performance, causes of false positive and negative values, usefulness of serial measurements, utility in therapy guidance, cost and availability and a standardised LVDD definition for population studies, among others.[6,12]

Conclusion

In summary, even though the presented article represents an important advance in the field of LVVD, many issues remain unsolved regarding the utility of circulating metabolic biomarkers of left ventricular diastolic function. However, the paper presents a new biomarker to address in research and also recalls the importance of filling the research gap under 'high pressure' for better cardiovascular health.

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