VIEWPOINT

Detailing Peripheral Arterial Tonometry in Heart Failure. An Endothelial Function Evaluation

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Introduction

Endothelium regulates cardiac function and vasomotor tone, adjusts vascular permeability, preserves blood fluidity, playing an important role in cardiovascular homeostasis.[1,2] In adults with heart failure (HF), endothelial dysfunction severity is related to diastolic dysfunction,[1,2] increase in cardiovascular risk,[1-10] heart failure,[11,12] exercise incapacity,[13] severity of cardiovascular symptoms,[6,7,10,14,15] cardiovascular events,[16] cardiac transplant and death.[17,18]

Although endothelium is at the interface between circulating cardiovascular factors and underlying organ tissues, cardiovascular and endothelial peripheral dysfunctions are not totally linked so far.[18-20] Evaluation of endothelial function appears as a tempting adjunct for cardiovascular risk stratification,[16] and understanding this matter may help having a faster approach and better screening in the cardiomyopathy field in everyday clinical practice, which brings the importance of this paper.

The objective of this study was to perform an interpretation of endothelial function development in HF patients.

Methods

Different databases (PubMed e Medline) were searched to identify the characteristics about endothelial function evaluation in both coronary and peripheral circulation, as a way to better explain the interface between endothelial dysfunction and heart failure.

Keywords

Endothelium / physiopathology; Heart Failure; Stroke Volume; Nitric Oxide.

Results

Heart failure represents the heart incapacity of performing sufficient cardiac output to satisfy all body demands[3, 20,11] either with preserved ejection fraction or not.[8,16]

There are several potential mechanisms by which endothelial dysfunction may contribute to disease progression in patients with heart failure (HF). Adult patients with HF, in New York Heart Association (NYHA) functional class II–III and more severe endothelial dysfunction would have a higher incidence of hospitalization due to decompensation of HF, cardiac transplantation, or cardiac-causing death in a 1-year follow-up than those with relatively preserved endothelium-dependent relaxation.[17]

Nonetheless, it may be a cycle dysfunction and it is not known whether endothelial dysfunction is the cause or the consequence of heart failure (Figure 1).[7-44]

Impaired availability of endothelium-derived nitric oxide (NO) contributes to this abnormal vasodilator response to physiological stimuli[7,17,20] in heart failure, both in the coronary and peripheral circulation.[13,14,23-28]

Regarding this, it is interesting to note also that a common polymorphism of endothelial NO-synthase (eNOS) shows increased vasoconstrictive response,[14,24,29] which may be associated with decreased NO-synthase (NOS) activity. This polymorphism is associated with poorer event-free survival and clinical endpoints reflecting progression of the disease in patients with heart failure.[30-32]

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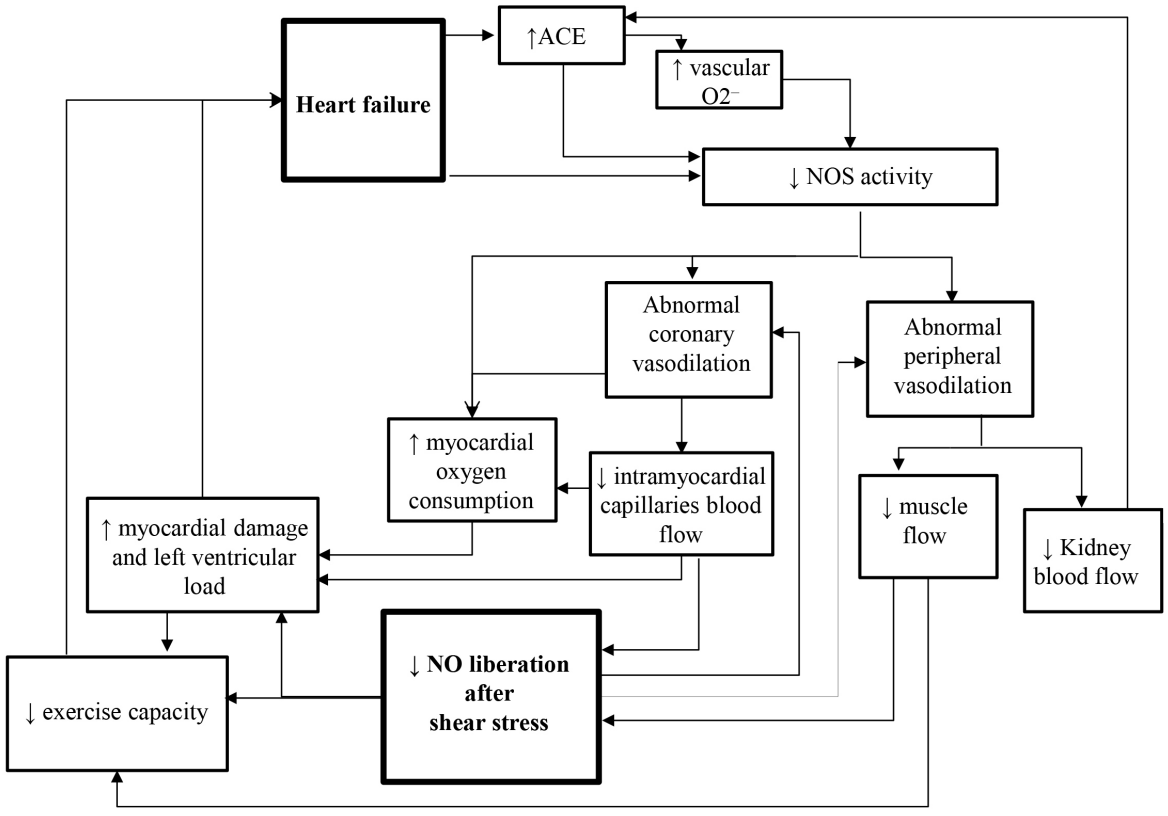

Figure 1 – *Cycle dysfunction representation between heart failure and endothelial dysfunction*
↑ increase; ↓ decrease; ACE: angiotensin converting enzyme; O2- O2-radical; NO: nitric oxide.

Therefore, endothelial dysfunction may contribute to the sympathetic tone systemically,[33-37] which contributes to exercise intolerance,[14,26,40] reduced capillary density in cardiac muscle,[28] impaired myocardial perfusion,[14,39] inhibited myocardial contractility,[30] impaired myocardial oxygen consumption,[40] impaired left ventricular relaxation in pressure-overload hypertrophy,[41] enhanced cardiac afterload,[14,22,25-27] left ventricular remodeling in HF,[14,29,31,42,43] and further increase in myocardial damage.[14,25,27,28,31,38,43,44]

Experimental and clinical studies have provided new data about the mechanisms of specific aspects of endothelial function, therefore a potential mechanism of endothelial dysfunction is alteration of the signaling mechanisms involved in eNOS activation.[45]

Some novel approaches in patients with polymorphisms or mutations of genes that might play a pathogenic role in endothelial dysfunction investigate the relationship between genetic factors associated with endothelial function and the development of cardiac alterations.[45-48]

The ecNOS gene a/b polymorphism and the β-Nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide phosphate (NADH/NADPH) oxidase $p22^{phox}$ gene C242T polymorphism are found to be significantly associated with the development of CAD.[45,46] Regarding this topic, the following reduce NO bioavailability: polymorphisms in the eNOS gene,[47] upregulation of matrix metalloproteinase-2,49 and elevated levels of dimethylarginine, which is a competitive antagonist of endothelial nitric oxide synthase (eNOS). Some studies also found microRNA 217 upregulation, an NAD-dependent deacetylase, as responsible for endothelial alteration and eNOS activity decrease.[46-50]

Other factors that may also worsen endothelial function, such as activation of the endoplasmic

reticulum(ER) stress response,[41] high pro-inflammatory status, inflammatory cytokines, such as E-selectin and P-selectin,[52-55] over expression of tumor necrosis factor α, interleukin, high levels of plasminogen-activator inhibitor 1 (PAI-1),[56] increased adipose tissue mass, lower adropin levels[4] and lower tissue 5-methyltetrahydrofolate (5- MTHF)[56-57] levels, are correlated with endothelium-dependent vasodilation impairment.

Therefore, endothelial cycle dysfunction is influenced by several correlated mechanisms, which promote better the understanding of the topic and also improve its contribution in the cardiovascular field (Figure 2).

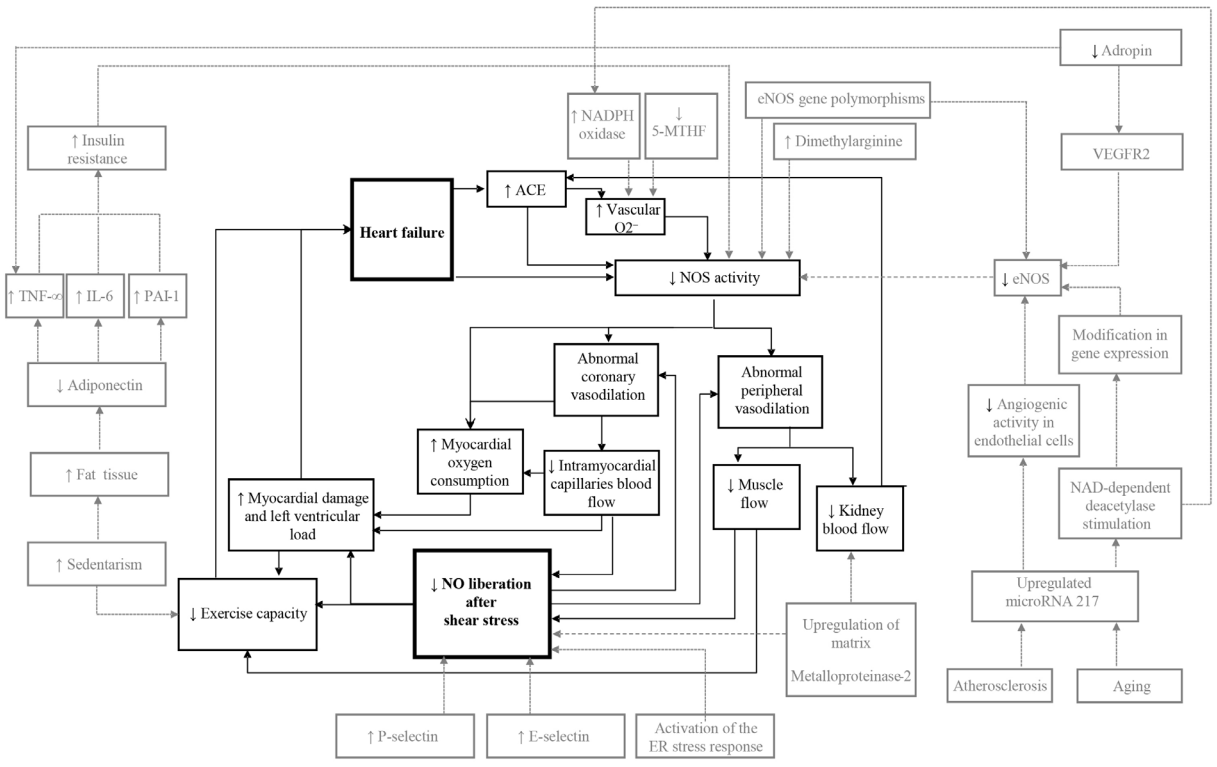

Figure 2 – *Representation of cycle dysfunction between heart failure and endothelial dysfunction with genetic and other influences*
↑ increase; ↓ decrease; 5- MTHF: 5-methyltetrahydrofolate; ACE: angiotensin converting enzyme; O2 - O2-radical; eNOS: endothelial nitric oxide synthase; ER: endoplasmic reticulum; IL-6: interleukin 6; NO: nitric oxide; PAI-1: plasminogen-activator inhibitor 1; TNF-∞: tumor necrosis factor α; VEGFR2: vascular endothelial growth factor receptor-2.

Conclusion

Low endothelial response to blood flow contributes to cardiac dysfunction. The other way around is also accurate, which involves cardiac dysfunction as a start for endothelial change. Therefore, a cycling dysfunction may be involved in both central and peripheral alterations.

Author contributions

Conception and design of the research: Tavares AC, Guimarães GV. Acquisition of data: Tavares AC, Guimarães GV. Analysis and interpretation of the data: Tavares AC, Bocchi EA. Writing of the manuscript: Tavares AC, Guimarães GV. Critical revision of the manuscript for intellectual content: Tavares AC, Bocchi EA, Guimarães GV. Making of Figures: Tavares AC.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

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