European Journal of Heart Failure (2017) **19**, 1466–1467
doi:10.1002/ejhf.968

EDITORIAL COMMENT

The complex interplay between systolic and diastolic function at rest and during exercise in heart failure: the case of cardiac amyloidosis

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This article refers to 'Inotropic myocardial reserve deficiency is the predominant feature of exercise haemodynamics in cardiac amyloidosis' by T.S. Clemmensen *et al.*, published in this issue on pages 1457–1465.

Cardiac amyloidosis (CA) has been traditionally considered a restrictive cardiomyopathy and a typical cause of diastolic heart failure or, better, of 'heart failure with preserved ejection fraction' (HFpEF).[1] In recent years, however, various observations have challenged this paradigm:

- Left ventricular (LV) ejection fraction (EF) in CA varies quite widely and is <50% in more than 40% of cases.[2,3]
- Left ventricular longitudinal function is impaired from a relatively early phase of the disease, even in cases with normal circumferential function (normal EF).[3]
- Left ventricular torsion and strain rate are often abnormal.[3,4]
- Myocardial infiltration is not the only pathogenetic mechanism responsible for cardiac dysfunction. A direct toxic effect of circulating precursor proteins on cardiomyocytes has been demonstrated in primary light chain related (AL) disease.[5,6]

The work of Clemmensen *et al.*[7] published in this issue of the Journal offers a further insight into the complex pathophysiology of CA. The principal merit of the study is the direct evaluation of central haemodynamics both at rest and during exercise in a group of patients with CA due to various aetiologies: AL, wild-type, or mutant transthyretin CA. Although it is well known[1,8] that many patients with so-called diastolic dysfunction have a normal or mildly elevated LV filling pressure at rest and that symptoms will develop with physical activity because of rising filling pressures—needed to maintain an adequate stroke volume—this is the first study to provide such an in-depth evaluation of cardiac performance in CA.

Although LV EF at rest was preserved in all the cases and pulmonary capillary wedge pressure was abnormal in only 50% of patients, exercise unmasked an abnormal haemodynamic response in the vast majority of patients, characterised by increased left- and right-sided filling pressures (more pronounced in the right heart), impaired inotropic reserve, and reduced pulmonary arterial compliance. This exercise-induced haemodynamic derangement was significantly related to the reduced exercise capacity of the patients. In detail, despite an adequate increase in LV filling pressure, CA patients were unable to increase stroke volume during exercise and this was accompanied by reduced myocardial efficiency. The authors interpret this finding as an expression of reduced inotropic reserve. This is probably true and exercise-induced myocardial ischaemia secondary to amyloidotic infiltration of coronary arteries at the microvascular level could be one of the mechanisms involved (not explored in this study design). Unfortunately, LV volumes were not measured in this study and no direct information on volumes and EF during exercise is provided. It is, however, highly probable that LV filling during exercise is also limited, since the increase in filling pressure is not sufficient to induce an adequate stretching of the ventricular wall. Therefore, it could be hypothesized that a combination of absence of increase in end-diastolic volume and a limited or absent decrease in end-systolic volume is responsible for the observed absent or limited increase in stroke volume.

Notably, the limited increase in heart rate during exercise (1.6 times among CA patients vs. 2.5 in normal controls) could partly explain the limited increase in cardiac output during exercise.

The demonstration of a significant reduction in pulmonary arterial compliance during exercise is another key finding of the study of Clemmensen *et al.*[7] The Authors intriguingly argue that this could be a consequence of pulmonary vascular amyloidotic infiltration and not merely due to excessive pulmonary arterial vasoconstriction. It is known that right ventricular function is an independent determinant of prognosis in CA and other conditions with HFpEF.[9,10] Since the right ventricle—infiltrated by amyloidosis as the left ventricle—is very dependent on loading conditions,

The opinion 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.899

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Table 1 Pathogenesis of amyloidotic cardiomyopathy

Main pathophysiological mechanisms
• Infiltration of myocardium leading to reduced deformability
• Infiltration of atrioventricular valves, coronary and pulmonary circulation
• Direct toxic effect of precursor proteins on myocardial cells
• Reduced cardiac sympathetic innervation
Other cardiovascular effects
• Reduced pulmonary compliance
• Reduced atrial passive function
• Reduced atrial active function
• Atrial fibrillation/flutter
• Bradyarrhythmia and chronotropic incompetence
• Atrioventricular valve regurgitation
• Microvascular myocardial ischaemia
Effects on left and right ventricular function
• Reduced longitudinal function
• Reduced circumferential function
• Reduced torsion
• Reduced ventricular filling
• Reduced inotropic and preload reserve
Effects on the most used indexes of cardiac function at rest
• Restrictive filling pattern at echo Doppler
• Increased filling pressures
• Reduced S wave
• Reduced e' wave
• Increased E/e'
• Reduced global longitudinal strain (with apical sparing)
• Reduced ejection fraction
• Reduced stroke volume/cardiac output
• Reduced myocardial contraction fraction
Effects on the most used indexes of cardiovascular function during exercise
• Reduced exercise tolerance (oxygen consumption; 6-minute walk test)
• Further increase in filling pressures
• Inadequate increase in cardiac output

reduced pulmonary arterial compliance has major consequences for right ventricular function and increases the risk for late right ventricular failure.

Considering these findings alongside other recent studies on cardiac function in CA,[2–6,8–12] a complex and intriguing scenario emerges. To better understand this interplay, we need to focus separately on the intimate mechanisms of this condition, as well as their effects on the different components of cardiac pathophysiology and on the various indexes of cardiac function both at rest and during exertion. *Table 1* summarizes these three different—albeit interrelated—levels.

In conclusion, despite the fact that exercise testing is not often used and requires a greater effort from both the patient and the physician, in CA it does not only lead to greater pathophysiological comprehension, but also to a more comprehensive assessment of the patient and can aid decision-making.

Conflict of interest: none declared.

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