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EDITORIAL

Diastolic heart failure: a misNOmer

Gerd Heusch

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Clearly, there are many patients with obvious heart failure symptoms, more women than men and more often with heart failure of hypertensive than ischemic origin, who have surprisingly little impairment of left ventricular ejection fraction [4, 5, 19, 20]. The increasing awareness that a relatively preserved ejection fraction does not exclude heart failure has led some, including Westermann et al. [16] in this issue, to propose the concept of "diastolic heart failure". Westermann et al. used the model of salt-induced hypertension in genetically susceptible rats with the subsequent development of left ventricular hypertrophy and ultimately heart failure and report the attenuation of the observed unfavorable alterations in left ventricular, notably diastolic function, morphology and signaling with concomitant pharmacological enhancement of endothelial nitric oxide (NO) synthase activity. The present opinionated editorial refutes the idea of "diastolic heart failure" as a genuine pathophysiological entity in its own standing and, accordingly, identifies the term "diastolic heart failure" as a misnomer. Why?

1. Heart failure is defined and its severity classified by clinical symptoms, i.e., dyspnea, edema, exercise intolerance, cachexia, etc. None of these symptoms can be attributed, not by the patient and not by his physician, to either systole or diastole.
2. Virtually, all studies on "diastolic heart failure" which looked at systolic ventricular function more carefully than just measuring ejection fraction, systolic ventricular function was in fact also impaired, notably in terms of regional left ventricular function and longitudinal ventricular shortening. Systolic left ventricular function impairment in "diastolic heart failure" is evident also in these authors' clinical and experimental data. In their recent excellent clinical study [15], left ventricular end-diastolic pressure in patients with "diastolic heart failure" was 16.1 mmHg on the average and thus half of them missed the definition of "diastolic heart failure" according to the ESC consensus document, i.e., left ventricular end-diastolic pressure >16 mmHg [12]; nevertheless, these patients had reduced stroke volume and cardiac output which just missed statistical significance. Also, in their present experimental study [16] in rats with salt-induced hypertension and consequent heart failure, not only left ventricular diastolic function but again stroke volume and cardiac output were significantly reduced.
3. Morphological and molecular findings in "diastolic heart failure" are non-specific, i.e., reflect heart failure, its temporal progression, and its underlying origin. With respect to the present experimental study [16], hypertrophy and fibrosis are typical consequences of long-standing hypertension and by no means characteristic of "diastolic heart failure"; the same is true for the activation of MAP kinases [11] and calcineurin. Systolic and simultaneously diastolic impairment of calcium transients in human heart failure is well established [1]. Apart from the underlying origin of heart failure, the temporal progression of all observed molecular, morphological and functional phenomena has to be taken into serious consideration; in this respect, "diastolic heart failure" may just be a relatively early stage in the progression to more severe heart failure.

G. Heusch (✉)
Direktor des Instituts für Pathophysiologie,
Universitätsklinikum Essen, Hufelandstraße 55,
45122 Essen, Germany
e-mail: gerd.heusch@uk-essen.de

4. "Diastolic heart failure" is not suited as a new drug target. In the CHARM-preserved trial [18] in patients with heart failure and preserved left ventricular ejection fraction, candesartan was not better than placebo with respect to the primary endpoint of cardiovascular death and hospital admission for heart failure. Likewise, in the I-PRESERVE trial [10], irbesartan was not better than placebo with respect to the primary endpoint of death from any cause and hospitalization for a cardiovascular cause. In the Hong Kong diastolic heart failure study [17], diuretics improved heart failure symptoms significantly, and neither irbesartan nor ramipiril provided additional benefit. Finally, in the ALLHAT trial, antihypertensive therapy with thiazide diuretics reduced the incidence of new onset heart failure with preserved ejection fraction more than lisinopril [3, 9]. Collectively, these studies reflect only modest activation of neurohumoral systems, and they are consistent with a relatively early stage of heart failure.

A beneficial effect of NO at low concentration on both systolic [14] and diastolic [13] left ventricular function in humans is well established, as is a dysbalance of NO in heart failure [2, 6]. Importantly, the origin of NO matters for myocardial function: NO derived from endothelial NO synthase optimizes contractile function for a given myocardial oxygen consumption [8]; whereas, NO derived from inducible NO synthase contributes to contractile dysfunction in experimental short-term hibernating myocardium [7]. For the present experimental study [16], however, it is entirely unclear to what extent the pharmacological enhancement of endothelial NO synthase attenuated the development of hypertension through a vascular action or had any independent effect on systolic and/or diastolic function of the failing heart. There is an obvious and understandable commercial interest of the pharmaceutical industry to create a new disease and in consequence identify a new target for their particular product. Again, "diastolic heart failure" is no new drug target.

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