

## COMMENTARY

# Right and left ventricles: as inseparable as the twin brothers ‘Castor and Pollux’

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Studies on the functional and structural abnormalities that develop as a consequence of cardiovascular risk factors have primarily focused on the left ventricle. Less attention has been paid to the right ventricle, despite evidence showing its extensive involvement.

Left-sided heart disease may be associated with the development of pulmonary hypertension in patients with systemic hypertension and ischemic heart disease; in these conditions, pulmonary hypertension develops as a consequence of impaired left ventricular relaxation. The elevation in pulmonary capillary pressure due to a chronic increase in left-sided filling pressure leads to lung capillary injury and right ventricular overload and failure through a cascade of anatomical and functional effects.<sup>1</sup>

The increase in blood pressure often associated with metabolic syndrome or type 2 diabetes mellitus may alter cardiac structure and function. The impact of systemic hemodynamic overload on the pulmonary circulation and the right ventricle was highlighted several years ago by Olivari *et al.*<sup>2</sup> Biventricular dysfunction was documented in a small group of hypertensive patients with left ventricular hypertrophy or strain. Systemic hypertension was associated with elevated pulmonary artery pressure and pulmonary arteriole resistance. Additionally, coinciding with the development of ECG signs of left ventricular strain, the performance of both ventricles was shown to deteriorate. Since these studies, the involvement of the left and right ventricles in hypertensive patients has been a subject of great interest.<sup>3</sup>

Elevated systemic pressure is associated with right ventricular thickening, and right ventricular remodeling develops in parallel with left ventricular remodeling, likely as a result of ventricular interdependence. Increased pulmonary afterload and the influence of trophic factors targeting both ventricles may impair the right ventricular filling rate, which accompanies a similar phenomenon in the left ventricle.

This process is at least partly independent of the structural remodeling of both ventricles. In fact, in addition to the hemodynamic stimuli, non-hemodynamic factors may favor the development of inflammation and fibrosis. An increase in sympathetic tone, an impairment in the balance between vasoconstrictors and vasodilators and an increase in growth factors, such as aldosterone, angiotensin II, insulin-like growth factors, endothelin and proto-oncogenes, acting on both sides of the circulation may contribute to abnormal vasoconstriction of the pulmonary circulation and alter cardiac function. A role has been proposed for impaired insulin sensitivity leading to increased pulmonary resistance,<sup>4</sup> and ventricular systolic and diastolic dysfunction were observed in patients with other phenotypes of the insulin resistance syndrome, such as non-alcoholic fatty liver disease.<sup>5</sup> Recently, in the MESA study, overweight and obesity were independently associated with differences in right ventricular morphology, as evaluated by magnetic resonance, even after adjusting for the respective left ventricular measurements. Increased right ventricular afterload, increased blood volume, hormonal effects or direct obesity-related myocardial effects could explain this association.<sup>6</sup> Diabetes seems to affect right ventricular glucose metabolism and systolic function similar to the left ventricular, which

could be due to ventricular interdependence and the uniform effect of diabetes on the heart.<sup>7</sup>

The study by Paneni *et al.*<sup>8</sup> provides new information regarding the involvement of the systolic and diastolic function of both ventricles and identifies the most important determinants of biventricular dysfunction. The authors analyzed the degree of both left and ventricular dysfunction by a tissue Doppler evaluation of the myocardial performance index (MPI) in 345 hypertensive patients, and found that there was a progressive impairment in systolic and diastolic function parameters in the left and right ventricles of patients with metabolic syndrome or diabetes alone or both diabetes mellitus and metabolic syndrome.

The MPI is a parameter that can be derived from conventional measurements and by tissue Doppler imaging (TDI) measurements, and is conceptually attractive as a global measure of cardiac function.<sup>9,10</sup> The TDI-derived MPI offers the advantage of recording systolic and diastolic tissue velocity simultaneously in the same cardiac cycle. TDI-derived MPI has been shown to be more sensitive than conventional Doppler in detecting preclinical abnormalities in cardiac function, as confirmed by Paneni *et al.*, showing a weaker correlations between conventional MPI and metabolic parameters compared with a TDI-derived MPI.

The findings by Paneni *et al.*<sup>8</sup> further strengthen the conclusion that a TDI-derived MPI is reproducible and may allow for a better estimation of preclinical abnormalities in cardiac function and a more accurate prediction of cardiovascular risk.<sup>11,12</sup> The authors were also able to define the MPI ‘normal values’ according to the value distribution in the large group of normal subjects who were studied, whereas other

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studies have defined MPI cutoff values based on prognostic significance, which has been demonstrated in some but not all studies.

At first sight, the results of this study appear to confirm previous findings that metabolic syndrome and diabetes mellitus are associated with increased left ventricular mass, a more concentric geometry, diastolic filling abnormalities and a slightly reduced systolic fiber shortening in the endocardium.<sup>13,14</sup>

However, these results are stimulating from at least two perspectives. First, in this group of patients, there is a significant influence of metabolic abnormalities but not pressure load on biventricular function. A possible explanation is that most of the hypertensive patients were receiving antihypertensive treatment and had only slightly elevated BP values, which might also explain the absence of elevated filling pressures in the right and left ventricles, as indicated by the  $E/E'$  ratios. In addition, this study measured the peripheral arterial pressure, while differences in central blood pressure might represent a stronger determinant of myocardial hypertrophy and fibrosis.

The second interesting conclusion is the effect of inflammation on cardiac function, as indicated by the independent association with plasma CRP (C-reactive protein). A pro-inflammatory state is a common characteristic of obesity, dyslipidemia, diabetes and metabolic syndrome and has been associated with left ventricular dysfunction and increased risk of heart failure. Among the markers of inflammation, CRP has been most extensively studied, has been proven to be associated with left ventricular hypertrophy (LVH) and concentric remodeling and is an independent predictor of heart failure. CRP could have direct myocardial effects because CRP can cause intimal hypertrophy both *in vitro* and in animal studies or could act indirectly by affecting perivascular fibrosis, leading to functional diastolic and systolic abnormalities.

In this study, CRP was mostly increased in patients with both diabetes and metabolic syndrome, in whom LVH and relative wall thickness were more severely increased and functional abnormalities were more extensive.

Despite the above-mentioned results, the study by Paneni *et al.*<sup>8</sup> also has some limitations, which the authors have partially acknowledged. Estimating the glomerular filtration rate would have added value to the manuscript and could have provided new data on the relationship between early right ventricular dysfunction and changes in kidney function.<sup>15–17</sup>

In conclusion, the study by Paneni *et al.*<sup>8</sup> provides a valuable contribution to ongoing research on the early impairment of cardiac function on both sides in the presence of cardiovascular risk factors.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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