Abstract

Pulmonary hypertension is a syndrome of diverse etiology that can be defined on haemodynamic grounds by elevated pulmonary artery pressures. It portends high morbidity and mortality and has deserved increased recognition by the medical and scientific communities. Despite the latest therapeutic developments, such as endothelin-1 receptor antagonists, pulmonary vascular resistance still evolves and the right ventricle is unable to bare progressive increases in afterload. Right ventricular failure is an important cause of mortality and a fundamental prognosis determinant and therefore has been considered a research priority. Still, the myocardial actions of currently used lung vessel vasodilators are not well defined. In severe pulmonary hypertension patients also develop left ventricular dysfunction, but the underlying mechanisms are also incompletely understood. Though the majority of evidence points to a fundamental role of ventricular interaction, some reports suggest intrinsic left ventricular myocardial dysfunction. Moreover, with disease progression and inflammatory activation disturbances of myocardial metabolism and cardiac cachexia further aggravate the clinical condition. Cardiac cachexia complicates an important part of heart failure cases and substantially worsens its prognosis. In point of fact, heart failure patients with high body mass indices paradoxically show improved survival. Analogously, it would not be surprising that well established cardiovascular risk factors such as Western-type diet regimens could actually have entirely distinct effects in heart failure and cardiac cachexia. With the works carried out we aimed at (i) establishing whether the left ventricular myocardium is intrinsically dysfunctioning in pulmonary hypertension and what could be the responsible mechanisms, (ii) assessing an haemodynamic test based on evaluation of end-diastolic pressure elevation induced by acute afterload elevations as a tool to discriminate failing from healthy myocardium, (iii) evaluating the effects of a Western-type diet in pulmonary hypertension, heart failure and cardiac cachexia, and, finally, (iv) characterizing the myocardial and lung vessel actions of endothelin-1 antagonists. For these purposes we conducted studies in the rat model of monocrotaline-induced pulmonary hypertension, and a perioperative evaluation of patients undergoing coronary artery bypass grafting. We have documented (i) intrinsic left ventricular myocardial dysfunction and potential causal mechanisms, namely neuroendocrine and inflammatory activation, in pulmonary hypertension, (ii) the accuracy of diastolic tolerance to acute afterload elevation in discriminating myocardial dysfunction, and the close relationship between contraction and relaxation, (iii) attenuation of pulmonary hypertension, and improvements in myocardial function and cardiac cachexia with a Western-type diet, partly due to anti-inflammatory actions, according to the lipoprotein-endotoxin hypothesis, and partly to the increased energy intake and preservation of myocardial metabolism, and, lastly, (iv) that endothelin-1 antagonists not only attenuate pulmonary hypertension but also preserve myocardial function, due at least in part to an anti-inflammatory action and modulation of acute regulators of lung vessel tone and myocardial function. Our findings have contributed to a better understanding of left ventricular dysfunction in pulmonary hypertension and of the pharmacological actions of endothelin-1 antagonists, suggesting that intravenous acute blockade may be an effective replacement therapy in patients who cannot use the oral route, such as those undergoing surgery or admitted to intensive care. We have also provided *in vivo* experimental support for the “obesity paradox” and the lipoprotein-endotoxin

hypothesis, sanctioning clinical trials in cardiac cachexia patients. Finally we have demonstrated the close relationship between contractility and relaxation and clearly demonstrated that even baseline systemic arterial pressures can contribute to diastolic dysfunction in heart failure.