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Characterization of a rat model of right-sided heart failure induced by pulmonary trunk banding

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Abstract

Animal models of disease are essential for cardiovascular research. However, animal models of right-sided heart failure are few and remain poorly characterized. The aim with this study was to establish a rat model of right-sided heart failure (HF) using pulmonary trunk banding (PTB) and subsequently to characterize the systemic and cardiac changes in this model, including protein expression of SERCA2 and α-sarcomeric actin. Rats underwent banding or sham operation. To evaluate the development of HF over time three groups were included in this study. They were killed 2–3, 5–7 or 16–17 weeks after operation, respectively. PTB rats showed marked hypertrophy of the right ventricle (RV). Catheterization of the RV showed a three- to four-fold increase in right ventricular systolic and diastolic pressures as well as increased dP/dT max and dP/dT min. Plasma analyses revealed increased liver enzymes in most PTB groups and post mortem examination revealed congestion of the liver as well as formation of ascites and hydrothorax in many PTB rats. Immunoblotting of the RV revealed no changes in SERCA2 or α-sarcomeric actin. In conclusion, PTB was an effective method to

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induce right-sided HF. The presence of HF was confirmed by severe signs of backward failure in conjunction with markedly elevated RV pressures and reduced RV ejection fraction (EF).

Keywords: Right-sided heart failure; Hypertrophy; Animal models; Pulmonary hypertension; Echocardiography; Pulmonary trunk banding; Actin; SERCA2

Introduction

The role of the right ventricle (RV) in cardiac function and disease has often been neglected as most attention is given to the function of the left ventricle (LV). However, it is well recognized that there is a relationship between the functioning of the two ventricles. Thus, impairment of the RV may influence LV function (or vice versa) (Clyne et al., 1989; Dittrich et al., 1989; Hill and Singal, 1997; Mizushige et al., 1989; Yu et al., 1996). In a state of right ventricular pressure overload this ventricular interdependence may be ascribed to pathologic septal motion, decreased LV preload or other unknown factors (Dittrich et al., 1989; Mizushige et al., 1989; Yu et al., 1996). RV function is an independent predictor of mortality and the development of heart failure (HF) in patients with known LV dysfunction (Zornoff et al., 2002) and right ventricular involvement during acute inferior myocardial infarction is a strong, independent predictor of major complications and in-hospital mortality (Zehender et al., 1993). Finally, 5–10% of patients with advanced chronic obstructive pulmonary disease (COPD) may suffer from severe pulmonary hypertension and present with a progressively downhill clinical course because of right heart failure added to the ventilatory handicap (Naeije, 2005).

In this context there is a need for a well-established animal model of right-sided HF for further investigation of RV function and pathology. Few animal models exist that are able to induce HF (whereas several models have been employed to induce RV hypertrophy, including monocrotaline (MCT) treatment (Jones et al., 2002; Jones et al., 2004; Kato et al., 2003), hypoxia (Bonnet et al., 2004; Pozeg et al., 2003), infarction (Nahrendorf et al., 2003) and also mild pulmonary trunk banding (PTB) (Adachi et al., 1995; Bar et al., 2003; Braun et al., 2003; Ikeda et al., 1999; Kuroha et al., 1991; Olivetti et al., 1988; Zierhut et al., 1990)). MCT treatment has been used to induce pulmonary hypertension resulting in RV hypertrophy and eventually HF (Chen et al., 2001; Doggrell and Brown, 1998). However, there are disadvantages to MCT in the form of disease manifestations not usually associated with human heart failure (hepatic cirrhosis and megalocytosis, venoocclusive disease and thrombocytopenia (Doggrell and Brown, 1998), and changes in hormones such as endothelin (Miyauchi et al., 1993)). PTB does not have the side-effects of MCT treatment and is a promising method for inducing symptomatic right-sided HF. Until now, the PTB HF model has not been characterized. The objective of this study was therefore to establish a rat model of right-sided heart failure using PTB and subsequently to characterize the systemic and cardiac changes in this model.