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Original article

Clinical symptoms of right ventricular failure in experimental chronic pressure load are associated with progressive diastolic dysfunction

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ABSTRACT

Background: Right ventricular failure (RVF) due to pressure load is a major cause of death in congenital heart diseases and pulmonary hypertension. The mechanisms of RVF are unknown. We used an experimental approach based upon clinical signs of RVF to delineate functional and biological processes associated with RVF.
Methods and results: Wistar rats were subjected to a pulmonary artery banding (PAB n = 12) or sham surgery (CON, n = 7). After 52 ± 5 days, 5/12 PAB rats developed clinical symptoms of RVF (inactivity, ruffled fur, dyspnea, ascites) necessitating termination (PAB + CF). We compared these to PAB rats with RVF without clinical symptoms (PAB−). PAB resulted in reduced cardiac output, RV stroke volume, TAPSE, and increased end diastolic pressure (all $p < 0.05$ vs. CON) in all rats, but PAB + CF rats were significantly more affected than PAB−, despite similar pressure load (p = ns). Pressure–volume analysis showed enhanced contractility (end systolic elastance) in PAB− and PAB + CF, but diastolic function (end diastolic elastance, end diastolic pressure) deteriorated especially in PAB + CF. In PAB + CF capillary density was lower than in PAB−. Gene-array analysis revealed down-regulation of both fatty acid oxidation and carbohydrate metabolism in PAB + CF.
Conclusion: Chronic PAB led to different degrees of RVF, with half of the rats developing severe clinical symptoms of RVF, associated with progressive deterioration of diastolic function, hypoxia-prone myocardium, increased response to oxidative stress and suppressed myocardial metabolism. This model represents clinical RVF and allows for unraveling of mechanisms involved in the progression from RV adaptation to RV failure and the effect of intervention on these mechanisms.

1. Introduction

Right ventricular failure (RVF) due to increased pressure load is a primary risk factor for morbidity and mortality in patients with congenital heart diseases as well as in patients with pulmonary hypertension (PH) [27,37]. Moreover, RV dysfunction has also been demonstrated to be an important prognostic determinant in left ventricular failure [25].

Unfortunately, the pathophysiology of RV failure is yet insufficiently understood [4], which precludes the development of RV specific treatments. Research into these mechanisms is hampered by the lack of a model reflecting clinical RVF. It is in this perspective that a National Heart, Lung and Blood Institute working group on cellular and molecular mechanisms of right heart failure stated that 'researchers must develop reliable, reproducible and relevant animal models of RV failure' [38].

Since RV function is a critical prognostic determinant in PH [37], RV dysfunction has often been studied in animal models of PH, such as the monocrotaline rat model [10]. Although these models have proven to be valuable, they have two important disadvantages: direct therapeutic effects on the RV cannot be distinguished from (afterload-reducing) effects on the pulmonary vasculature and the used 'hits' necessary to induce PH may affect the RV [19]. The use of a pulmonary artery banding (PAB) to inflict chronic pressure load on the RV circumvents these limitations. However, it has been debated whether the phenotype of the chronic PAB model represents compensated adaptation instead of RV failure [7,14,32]. Heart failure is defined as the inability to meet the metabolic requirements of the tissues of the body. Heart failure is not an entity as such but a continuum of disease severity, graded according to the NYHA class. RV failure is defined similarly, but the clinical signs and symptoms differ from those in LV failure. The cardinal clinical characteristics of RV failure are fluid retention (presenting as peripheral

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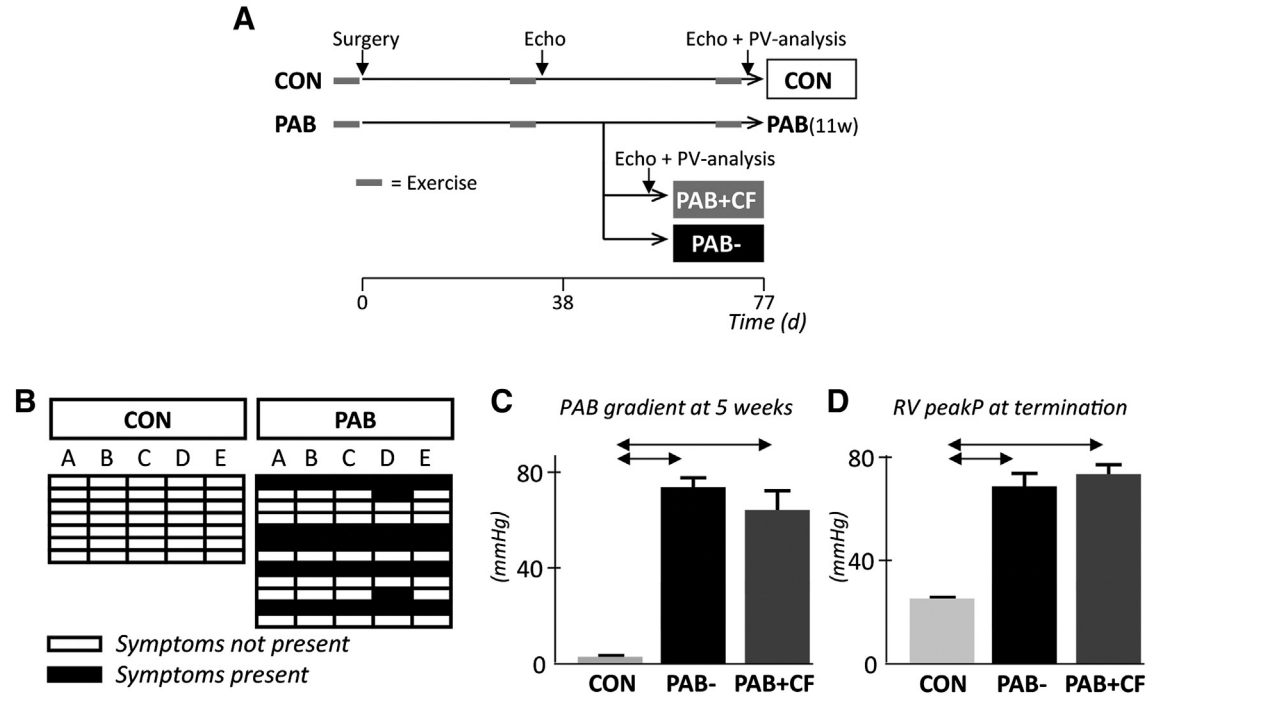

Fig. 1. A. Schematic overview of experimental set-up. B. Clinical symptoms of RV failure. Solid box = symptoms present. Open box = symptoms absent. Each row represents 1 rat. ABCDE refer to: A activity and appearance, B bodyweight, C cyanosis and/or hampered peripheral circulation, D dyspnea and/or tachypnea, E effusions: pleural or ascites (see Data supplement for details). C. PAB gradient measured by echocardiography at 5 weeks after surgery. D. Invasively measured RV peak pressure measured before termination. Mean ± SEM. Arrows indicate $p < 0.05$ between respective groups.

edema, effusion, ascites) and low cardiac output (evident in decreased exercise tolerance, fatigue, dyspnea and poor peripheral circulation) [3,20].

Previously described PAB models showed features of chronic adaptation and mild RV dysfunction, e.g. RV dilatation, reduced TAPSE and hypertrophy [1,7,14], but whether these represent the clinical phenotype of RV failure is unclear because the studies with hemodynamical analyses lack data on clinical symptoms of RVF [17,21] and conversely, the studies reporting on the clinical phenotype of RV failure lack (extensive) hemodynamical data [7,32].

The clinical phenotype of RV failure consists of signs and symptoms as dyspnea at rest, hepatomegaly, ascites, pleural effusion and mortality [20,38].

In the current study we aimed to characterize a phenotype of clinical RVF in rats with a tighter PAB (1.1 mm) than described before [7,8,14,31], using clinical symptoms in the rats (ABCDE-system), as reported

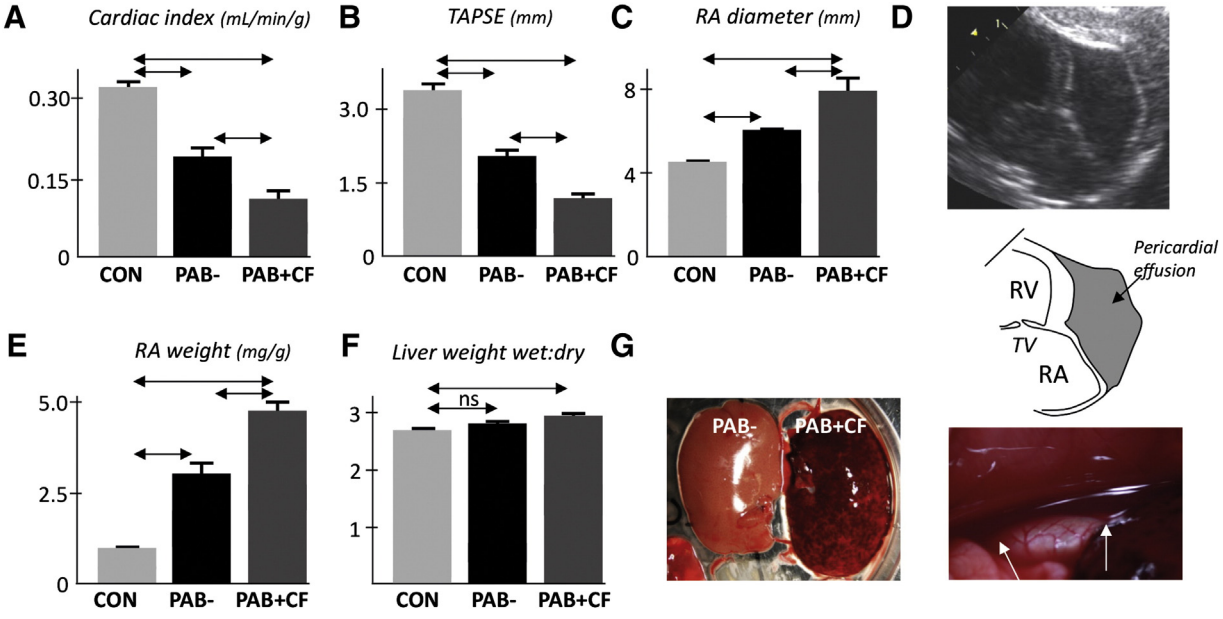

Fig. 2. Echocardiographic and pathological confirmation of clinical RVF. PAB + CF was distinct from PAB − with regard to cardiac index (A), TAPSE (B), RA diameter (C), presence of pericardial effusion (example echo-image in D), RA weight (E) and liver wet-to-dry ratio (F). Representative images of liver congestion (left-hand panel in G) and ascites (right-hand panel in G). Mean ± SEM. Arrows indicate $p < 0.05$ between respective groups. TAPSE = tricuspid annular plane systolic excursion, RA = right atrium, TV = tricuspid valve.