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Review

Interventional and surgical therapeutic strategies for pulmonary arterial hypertension: Beyond palliative treatments

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ABSTRACT

Despite significant advances in pharmacological treatments, pulmonary arterial hypertension remains an incurable disease with an unreasonably high morbidity and mortality. Although specific pharmacotherapies have shifted the survival curves of patients and improved exercise endurance as well as quality of life, it is also true that these pharmacological interventions are not always accessible (particularly in developing countries) and, perhaps most importantly, not all patients respond similarly to these drugs. Furthermore, many patients will continue to deteriorate and will eventually require an additional, non-pharmacological, intervention. In this review we analyze the role of atrial septostomy and Potts anastomosis in the management of patients with pulmonary arterial hypertension, we summarize the current worldwide clinical experience (case reports and case series), and discuss why these interventional/surgical strategies might have a therapeutic role beyond that of a "bridge" to transplantation.

Contents

Introduction

Idiopathic pulmonary arterial hypertension (IPAH) is characterized by a progressive elevation of pulmonary artery pressure (PAP), right heart dysfunction/failure, and untimely death [1,2]. It has long been recognized that the survival of patients with IPAH (formerly called primary pulmonary hypertension or PPH) clearly

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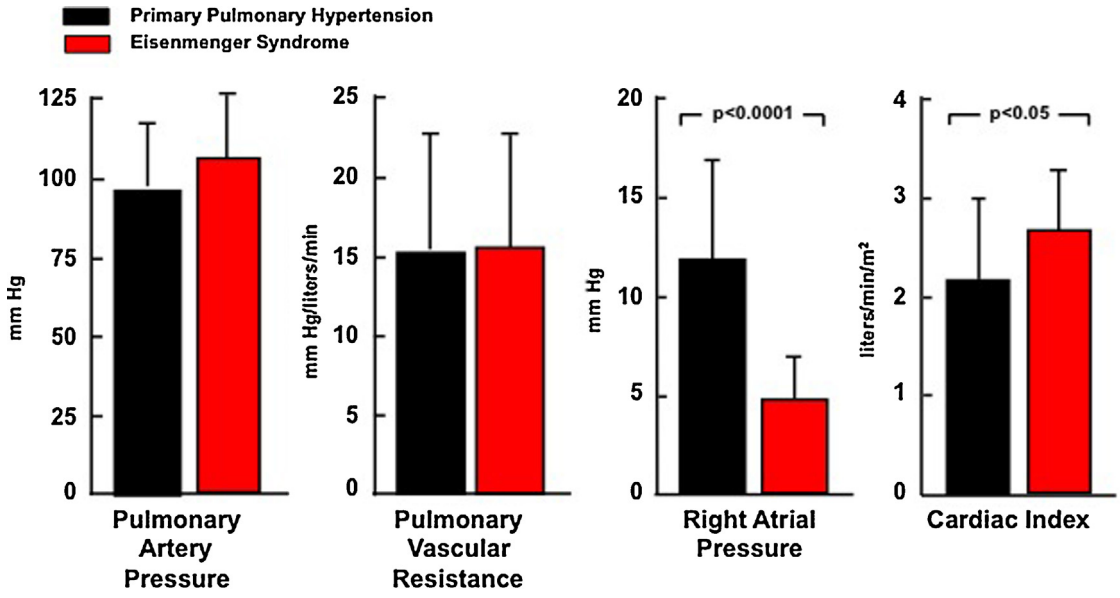

Fig. 1. Despite similar levels of pulmonary artery pressures and pulmonary vascular resistances, patients with Eisenmenger syndrome show lower right atrial pressure and higher cardiac index than those with primary pulmonary hypertension suggesting a better performance of the right heart in Eisenmenger syndrome. Adapted from Hopkins et al. [9].

depends on the adaptation of the right ventricle (RV) to increased pressure-overload as many studies have demonstrated that the variables assessing right ventricular function (or dysfunction) such as right atrial pressure and cardiac index are the most powerful predictors of mortality [1,2]. Indeed, the classic study by D'Alonzo et al. reporting the results of the first registry of the National Institutes of Health of the USA demonstrated that PPH patients with a cardiac index (CI) lower than 2.0 L min m^2, or patients with a mean right atrial pressure (mRAP) higher than 20 mmHg had a dismal prognosis [1]. These findings have been validated by contemporary [2] and modern studies and underscore the importance of understanding RV biomechanics and cellular physiology, in order to design integral treatment strategies for patients with PAH.

There is no question that the advent of PAH-specific pharmacotherapies has shifted the survival curves of PAH patients. New-generation therapies have been shown to improve exercise endurance, quality of life, and survival [3]. However, it is also true that these pharmacological interventions are not always accessible (particularly in developing countries) and, perhaps most importantly, not all patients respond similarly to these drugs [3,4]. In fact, many treated patients will continue to clinically deteriorate and will require interventional and/or surgical alternatives such as atrial septostomy (AS), Potts shunt, and lung transplantation [3–6]. In the present review we analyze the role of AS and Potts anastomosis in the management of PAH, we summarize the current worldwide clinical experience, and discuss why these interventional/surgical strategies might have a therapeutic role beyond that of a "bridge" to transplantation.

Atrial septostomy

Historical development and rationale

For some time now there has been clinical as well as experimental evidence suggesting that in the setting of PAH an inter-atrial right-to-left shunt may be of benefit. From the clinical point of view, we know that PAH patients with a patent foramen ovale live longer than those without shunting [7]. We also know that Eisenmenger patients with a comparable degree of pulmonary hypertension live longer and do not develop severe RV dysfunction when compared to patients with PAH [8,9]. Interestingly, Hopkins et al. [9] have shown that despite having similar degrees of pulmonary hypertension, patients with Eisenmenger syndrome have a lower RAP and better CI than patients with PAH, reflecting better RV performance (Fig. 1) [9]. It could be said that the idea behind the creation of a right-to-left shunt at inter-atrial level (AS) in patients with PAH was partly derived from the studies of patients with Eisenmenger syndrome.

From the experimental point of view, the first study supporting the role of interatrial shunts was published by Austen et al. over 50 years ago [10]. This particular study is extraordinary not only because it was the first to show that an inter-atrial shunt in PPH was beneficial but also because they described most of the knowledge we have about the physiological changes caused by AS. In their original publication they described the results obtained in 20 dogs with chronic RV pressure-overload, a model created in a 3-month period by progressive constriction of the pulmonary artery with a band placed via thoracotomy as the first intervention. Through a second thoracotomy, the heart was exposed and cannulated, connecting the superior vena cava with the left atria, forming a right-to-left shunt. This shunt could be manipulated by clamping. When the shunt was opened there was a significant decrease in RV and in right atrial (RA) pressures along with an increase in cardiac output and systemic pressure. As expected, there was also a decrease in arterial oxygen saturation (SaO_2%). All of these changes were reversed when the shunt was closed (Fig. 2A).

A second set of experiments, performed in a separate group of dogs, consisted of the surgical creation of an atrial septal defect through a second operation in 50% of the dogs with the other 50% serving as the control group (sham group). Hemodynamic measurements were performed 10 days after surgery and were performed at rest and during mild and severe exercise as defined by running on a lead for 200 and 400 yards, respectively. These dogs were previously trained to perform the exercises. Fig. 2B, constructed with the data presented by the author, summarizes the results of this experiment. Dogs with an atrial septal defect were able to significantly increase their cardiac output during both mild and severe exercise at the expense of only a modest increase in right ventricular end-diastolic pressure (RVEDP). On the other hand, dogs in the control group not only did not increase cardiac