Increased Pulse Pressure Causes Vascular Injury in Pulmonary and Systemic Arteries. Decreasing the Pulsatility with Banding and Vasodilators Can Stabilize Pulmonary Hypertension

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Abstract

In congenital heart disease with large shunts at the ventricular or arterial level the mean pulmonary artery pressure is increased to systemic levels. In addition, these shunts also increase the pulse pressure (PP) in the pulmonary arteries; the increased pulsatility, acts apart from mean pressure. Increased PP injures the arterial wall from exaggerated distension with each heart beat, producing medial hypertrophy that narrows the lumen, increasing pulmonary vascular resistance—a positive feedback. Thus, pulmonary arterial hypertension (PAH) is progressive and surgical intervention was considered dangerous. However we have observed adults with PAH who are stable and asymptomatic; they had central PAH but the pressure was reduced in the distal pulmonary arteries by valvular or bilateral distal stenosis. We present briefly two adults: one illustrates the stabilizing effect of damping pulsatility in the pulmonary arteries, and the second illustrates the catastrophic effects of excessive pulsatility from a shunt.

Recently, surgical advances have demonstrated that stabilization of patients with a large ventricular septal defect by short term surgical banding can be achieved with modest mortality, adding pre- and post-operative pharmacologic vasodilators, such as calcium channel blockers, nitric oxide, acetylcholine, endothelin receptor antagonists, and prostacyclin.

Excess PP has also been recognized to cause vascular injury in the systemic circulation predicting adverse cardiovascular outcomes, unaffected by current antihypertensive therapy. Perhaps increased PP in the systemic circulation might respond to pharmacologic measures that have been successful with PAH.

Keywords: Pulmonary hypertension; Pulsatility; Vascular injury

Introduction

Pulmonary arterial hypertension (PAH) is normally present in the first few days after birth, and positive remodeling occurs rapidly so that after 3 days the pulmonary artery pressure is less than one-fifth of the systemic. However, large ventricular septal defects (VSD) and arterial ducts transmit systemic pressure to the right ventricle from birth, creating pulmonary hypertension (PAH) with increased pulsatility. If the VSD is not closed, the PAH will lead eventually to Eisenmenger syndrome, characterized by obstructive lesions in the pulmonary arteries with a marked increase in pulmonary vascular resistance. Most patients with obstructive pulmonary hypertension follow a downhill course with limited life expectancy [1-3]. However we have observed a few patients with a large VSD and mean PAH who have done much better; they had dampening of PP in the pulmonary arteries from mild pulmonic stenosis. (Severe stenosis would result in a tetrad physiology with mean pulmonary artery pressures below normal.) We have also observed an adult tetrad of Fallot who received an overly large shunt to the pulmonary circuit resulting in an acute Eisenmenger syndrome.

Until recently, patients with marked PAH have not been offered surgical correction because of the high risk based on earlier surgical experience. That has changed with new surgical approaches, assisted by new pharmacologic treatment, with substantial reduction of the PAH. There have also been recent reports that abnormal pulsatility in the systemic circulation causes vascular injury that does not respond to ordinary antihypertensive medications.

To illustrate the clinical effects of pulsatility, a review is presented of the pathophysiology of two patients, one with effective damping relative to PAH and one with catastrophic progressive PAH following an excessively large surgical shunt. A review of publications follows, assessing the role of pulsatility injury in both pulmonary and systemic vasculature, and the stabilizing effect on the pulmonary artery pressure after surgical banding and repair.

Our patients

The first patient is a 48-year-old male whose original diagnosis was tetrad of Fallot with hemitruncus; the left pulmonary artery originated unobstructed from the ascending aorta. A right Blalock-Taussig shunt was performed at 14 years of age because of severe cyanosis (the mother would not agree to an attempt at total repair). At 22 he requested surgical intervention. Dr. Paul Ebert, then at San Francisco, closed the VSD, patched open the right ventricular outflow tract, and connected the left pulmonary artery to the main pulmonary artery, creating moderate stenosis at the anastomosis to reduce the systemic pressure present preoperatively in the left lung. In the past 25 years this patient has had several echocardiograms that showed...
a pressure in the right ventricle and main pulmonary artery of 90 mmHg, but a drop of 50 mmHg into the left branch of the pulmonary artery. There was no apparent stenosis of the right pulmonary artery by Doppler echocardiograms. He has remained asymptomatic (Class I NYHA). He recently married and has two children. He was concerned about his prognosis, considering the PAH. An MRI revealed a stenosis in the right pulmonary artery, produced by an upward tenting at the site of the old Blalock-Taussig connection to the right pulmonary artery that had been ligated by Dr. Ebert. Based on close follow-up for over 25 years, this patient’s PAH has not progressed because of reduction of the pulmonary PP by the bilateral stenoses.

The second patient was a 47-year-old woman with pulmonary atresia and large collateral vessels. She had two normal pregnancies that produced normal children, indicating that she did not have pulmonary hypertension for most of her life [1]. At 39 years of age, because of increasing dyspnea and fatigue she was referred for consultation elsewhere and unifocalization of both pulmonary branches was planned. This was accomplished for the right pulmonary artery, but unifocalization on the left could not be safely accomplished with the exposure of that thoracotomy. The right pulmonary artery at surgery had low pressure, and a short but wide systemic collateral artery was anastomosed end-to-side into it. She initially improved in relation to cyanosis and exercise tolerance, but over the course of the next two or three years she became progressively symptomatic, and returned to the outside hospital for possible unifocalization on the left. Cardiac catheterization revealed marked PAH. She declined further surgery, and returned to our hospital for treatment with bosentan, an endothelial receptor antagonist. She enjoyed some improvement but is still NYHA Class III-IV.

Pathogenesis of PAH from the medical literature

There have been relatively few studies of the physiology of PAH recently compared to more numerous studies involving endothelial dysfunction, platelet function, and possible immune dysfunction [4]. Similarly, there have been dramatic advances involving the genetics of primary pulmonary hypertension [5]. Some etiological clues have been derived from the clinical response to various interventions such as oxygen inhalation, calcium channel blockers, nitric oxide, acetylcholine, endothelin receptor antagonists, and prostacyclin [6].

Some form of injury has been inferred from tissue pathology observed from autopsies, lung biopsies, and animal experiments. Rabinovitch’s 1989 hypothesis [4] on the “mechanism of PAH in congenital heart disease with chronic high flow states” is shown in her Figure 42.24. However, the accompanying text identifies the stimulus as “high pulse pressure.” (Patients with an atrial septal defect, the most common congenital defect with high pulmonary flow, rarely develop PAH during childhood.) The second phase of development of vascular pathology is described as a release of elastase in the subendothelium; this is described as encouraging hypertrophy of mature smooth muscle cells that migrate into the subendothelium. The results are encroachment on the lumen, thereby increasing the resistance to flow.

In 2009, Hassoun et al. [7], including Rabinovitch, described “inflammatory processes” in the pathogenesis of PAH, and compared them to connective tissue diseases. Specifically they described the presence of “macrophages, lymphocytes, and dendritic cells in the vascular lesions, as well as circulating chemokines and cytokines.” They did not address whether the changes could be a response to injury rather than a ‘primary inflammatory diseases.’

An important effect of PAH was demonstrated by Mahapatra et al. [8], namely increased stiffness of all of the pulmonary arteries that they deduced caused increased mortality in PAH. This stiffness increases the afterload of the right ventricle by eliminating the windkessel function of the main pulmonary artery that absorbs some of the ejection energy and releases it as diastolic flow. This also causes an earlier reflected wave, further increasing the resistance to forward flow through the lung. All of these effects of stiffening ultimately increase the likelihood of failure of the right ventricle and death.

‘Inflammation’ in the systemic arteries

Atherosclerosis that results in stiffening of the systemic arteries was described by Tabas in 2010 [9], as ‘defective inflammation resolution’. He postulates that this disease process is normally prevented by a process that involves the suppression of inflammatory cell influx, effective clearance of apoptotic cells, and clearance of inflammatory cells, similar to the cytochemical inflammatory processes described by Rabinovitch for the pulmonary vessels in PAH. A major difference is that atherosclerosis does not increase the systemic vascular resistance, but can generate localized plaques that can trigger sudden occlusions of coronary arteries by thrombus formation, unlike the gradual narrowing of the lumen of the pulmonary vasculature from within, producing PAH.

In both the pulmonary and systemic arterial disease process it is not obvious why inflammation is blamed in stead of simply a response to injury. Neither publication advocates treatment with anti-inflammatory drugs.

Excess pulsatility in the systemic circulation

Increased PP in the systemic circulation is associated with increased mortality in elderly subjects. In 2000, Glynn et al. [10], as part of the National Institute on Aging studies of subjects 65 to 102 years, compared death rates adjusted for sex, age, medical history and disabilities according to combinations of systolic and diastolic pressures. Both low diastolic BP and high systolic BP were independent predictors of mortality, but increased PP from the combination was the best single predictor of mortality. They found that usual antihypertensive treatment did not affect this relationship of increased PP and cardiovascular mortality.

In 2008, Gazes et al. [11] studied the risk factors for increased brachial artery PP and found that they were the same as the risk factors for coronary heart disease, namely increased body mass index, diabetes, hypercholesterolemia, and age. The increased PP was an effect of the atherosclerotic disease, not a cause, although Glynn [10] suggested that the increased PP contributed to the formation, progression and rupture of plaques.

Stability and reversibility of PAH relative to banding the pulmonary artery

PAH has generally been regarded as progressive [12]. In the early days of open heart surgery a consensus developed that surgical intervention was associated with an unacceptably high risk of death in the presence of substantial PAH. But at that time, using cardiopulmonary bypass during infancy was somewhat hazardous. For these reasons, surgical banding of the pulmonary artery was introduced. Surgical banding was initially suggested primarily as palliation for seriously ill infants with large VSDs, and in 1952, Muller and Dammann [13] showed that experimental banding of the pulmonary artery could successfully lower the pulmonary artery...
pressure and flow in the presence of a large ventricular septal defect. Stark and colleagues [14] reported the results of banding in 146 children from 1957 to 1966: banding reduced the distal pulmonary artery pressure to normal or near-normal levels, with an overall mortality of 7%. In 1971, Hunt and co-workers [15] reported the banding of 111 infants and children, most of whom had a VSD. In follow-up, they found that patients under 2 years of age had shown a fall in pulmonary vascular resistance toward normal, and none showed progression of pulmonary vascular disease.

**Outcomes from surgical closure of VSD**

In 1977, Hallidie-Smith et al. [16] reported on 27 survivors after closure of a VSD at ages 3 to 12 years. Six to 16 years after closure of the VSD, all led normal lives with satisfactory exercise tolerance. Although with exercise their pulmonary artery pressures rose, there was no progression of their PAH, indicating that stability of the pulmonary vasculature was possible after reduction of the high PP. Meijboom et al. [17] in The Netherlands in 1994 reported long-term follow-up of infants and children operated on between 1968 and 1980. They examined 119 patients after a mean of 14.5 years; all were in good or very good condition, 84% had normal exercise capacity. By echocardiography they found “no signs of pulmonary hypertension.”

In 1998, Novick et al. [18] published their initial experience with double-patch closure of VSDs in 18 patients from Third World countries that lacked the resources for cardiopulmonary bypass surgery. The average age of their patients was 5.7 years and they had an average pulmonary vascular resistance of 11.4 Woods units. A patch placed over the defect contained a relatively small opening that reduces the pressure transmitted from the left ventricle thereby reducing the right ventricular pressure by providing a ‘stenosis’ between the two ventricles. A tethered flap permitted decompression of the right ventricle in the event of postoperative crises of PAH. All 18 children survived although 1 death occurred 9 months later. Postoperatively, there was a drop in pulmonary artery pressure to a mean of 42 mmHg, from a preoperative mean of 105 (p<0.001).

In 2005, Novick with an expanded group of surgeons [19] operating in several institutions including third world institutions, published their results with the double-patch closure in 56 children with a large, isolated VSD. The early mortality was 3.6%. No long term results have been published, to my knowledge.

Schulze-Neick and colleagues [20] showed in 2002 that postoperative elevations of pulmonary vascular resistance responded to endothelin-A blockade, improving survival in patients with PAH. Other types of type of pharmacologic intervention are now widely used, with a variety of vasodilators, and in some cases, preoperative preparation with these drugs [21].

A novel surgical approach to late banding was published in 2004 that employed an adjustable band [22] (FloWatch; Lausanne, Switzerland—no longer produced). Placement of the band required thoracotomy but post-operatively the degree of stenosis could be adjusted at the bedside. In 2 to 3 months, surgical closure of the VSD was accomplished and the band easily removed. There were no early or late deaths or device-related complication.

Obviously, preparation with a few weeks of targeted anti-PAH therapy, if successful, would be preferable to an extra operation.

**PAH stabilization with medical treatment**

Duffels’ group [23] reported disease stabilization with medical treatment in older patients with PAH associated with congenital heart disease. There were 15 patients with a median age of 53 (28 to 74) who received one or more of prostacyclin, endothelin receptor antagonist, or phosphodiesterase-5-inhibitors.

After a mean of 23 months of treatment, there was a significant improvement in the younger patients; the others improved but not significantly, and no one deteriorated.

**Discussion**

PAH is normal during fetal life but the pulmonary vasculature remodels positively within three days after birth allowing pressures less than a fifth of systemic, offering grounds for optimism concerning PAH after surgical correction of congenital heart disease.

As to pathogenesis of PAH, injury to the endothelium had been suggested by Rabinovitch [4] as the initial change for high pulmonary artery pressure or flow with congenital heart disease. But high flow without high pressure, as with atrial septal defects, does not typically produce PAH for many years, if then. In contrast, large shunts at the ventricular or ductal level equalize pressure in the two ventricles from birth, increasing the mean pressure and the PP in the pulmonary vessels. The muscular pulmonary arteries do not undergo the usual remodeling after birth, and the increased PP associated with the shunt produces injury to the pulmonary arteries, presumably due to exaggerated distension of the arterial wall with each heart beat. With high pressure shunts the first step is probably an increase in the smooth muscle cells in the muscular pulmonary arteries, followed by endothelial changes, apoptosis of smooth muscle cells, and resorption of the extracellular matrix, including elastin.

The first of my two patients presented is an example of long term health with stable high mean pulmonary artery pressure, with dampened PP by virtue of bilateral pulmonary artery stenosis of moderate degree.

The second of the two patients presents evidence of the early effects of increased PP following an excessively large systemic to pulmonary shunt, namely an acute Eisenmenger’s syndrome. This patient had previously had the physiology of a tetrad of Fallot with lower than normal pressure in the pulmonary circuit. Obviously, excessively large or short systemic artery shunts to the pulmonary artery should be avoided when palliating for inadequate pulmonary blood flow for cyanotic congenital heart disease.

For younger patients with congenital heart disease PAH is reversible after surgical intervention demonstrated years ago [14-17]. Even for older patients, the usual case is one of stability after closure of the ventricular septal defect [23]. The risk of surgical intervention with patients that have PAH is now much less with new surgical techniques involving prior banding and treatment with pulmonary vasodilators [18-22].

There is increasing evidence that the systemic vasculature also demonstrates injury with increased PP [10], although the PP is secondary to atherosclerosis. Although this progression has not been altered with conventional antihypertensive treatment, trials with a vasodilator such as nifedipine, or elastase inhibitors have not been reported.

Finally, it is clear that PAH is not inevitably progressive. Pulsatility resulting from a large ventricular septal defect or arterial duct is a major factor for initiation and progression. Stabilization by congenital pulmonic stenosis, surgical banding, or closure of a large systemic-pulmonic shunt is compatible with a normal life and good survival.
References


