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# Management and Closure Strategies for Atrial Septal Defect with Bidirectional Shunt and Pulmonary Arterial Hypertension: A Comprehensive Review of the Paradigm Shift Toward Reverse Remodelling

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**ABSTRACT**

Atrial septal defect (ASD) complicated by severe pulmonary arterial hypertension (PAH) and bidirectional shunting represents a critical clinical challenge in adult congenital heart disease[1]. Traditionally, these patients were often deemed inoperable due to the perceived irreversibility of pulmonary vascular disease and the high risk of acute right heart failure following defect closure[2]. However, recent advances in pharmacological therapy and interventional techniques have catalyzed a significant paradigm shift from "Treat and Repair" to "Repair and Treat," emphasizing the biological potential for reverse remodeling of the pulmonary vasculature[11]. This comprehensive review examines the physiological mechanisms of reverse remodeling, diagnostic challenges including invasive hemodynamic assessment, and the strategic use of fenestrated closure devices [6]. By synthesizing contemporary clinical data and longitudinal outcomes, we provide a robust framework for optimizing survival and functional outcomes in this high-risk population[13].

**INTISARI**

Defek septum atrium (ASD) yang disertai dengan hipertensi pulmonal (PAH) berat dan pirau bidireksional merupakan tantangan klinis yang kritis pada penyakit jantung bawaan dewasa[1]. Secara tradisional, pasien-pasien ini sering dianggap tidak dapat dioperasi karena persepsi ireversibilitas penyakit vaskular paru dan risiko tinggi gagal jantung kanan akut pasca penutupan defek[2]. Namun, kemajuan terbaru dalam terapi farmakologis dan teknik intervensi telah memicu perubahan paradigma yang signifikan dari "Treat and Repair" menjadi "Repair and Treat," yang menekankan potensi biologis untuk remodeling terbalik (reverse remodelling) pada vaskular pulmonal[11]. Tinjauan komprehensif ini membahas mekanisme fisiologis reverse remodelling, tantangan diagnostik termasuk penilaian hemodinamik invasif, dan penggunaan strategis perangkat penutup berventilasi (fenestrated)[6]. Dengan menyintesis data klinis kontemporer dan hasil jangka panjang, kami menyediakan kerangka kerja yang kuat untuk mengoptimalkan kelangsungan hidup dan hasil fungsional pada populasi berisiko tinggi ini[13].

## INTRODUCTION

Atrial septal defect (ASD) is the second most common congenital heart lesion diagnosed in adults[1]. While many ASDs follow a benign course in childhood, the chronic left-to-right shunt leads to progressive pulmonary over-circulation, which can eventually trigger the development of pulmonary arterial hypertension (PAH)[2]. Approximately 6% to 15% of adults with unrepaired ASDs develop significant PAH, a condition that markedly increases morbidity and mortality[1].

The hemodynamic spectrum of ASD-associated PAH is broad[2]. The most challenging group includes patients with severe PAH and bidirectional shunting, where the pulmonary vascular resistance (PVR) is significantly elevated [11]. In these individuals, the interatrial shunt acts as a critical "pop-off" valve to maintain systemic cardiac output during periods of increased pulmonary pressure[9]. Historically, management was conservative, focused on symptom relief and palliative medical therapy. However, the introduction of potent pulmonary vasodilators and the development of fenestrated closure devices have redefined the boundaries of operability[10]. The concept of reverse

remodeling, the regression of pathological vascular and cardiac changes, is now the central focus of modern therapeutic strategies[4, 5]. This review provides an in-depth analysis of the pathophysiology, diagnostic challenges, and evolving management paradigms for ASD with bidirectional shunts.

## DISCUSSION

### Pathophysiology of Pulmonary Vascular Remodelling and Reverse Remodelling

Chronic shear stress and circumferential stretch on the pulmonary vascular endothelium initiate a cascade of molecular and cellular events[3]. These include endothelial dysfunction, characterized by reduced production of nitric oxide (NO) and prostacyclin (PGI2), and medial hypertrophy of the small pulmonary arteries due to proliferation of smooth muscle cells[4]. In advanced stages, intimal fibrosis and plexiform lesions occur, signifying often irreversible damage[3, 4].

Reverse remodelling is the process by which these structural changes regress following the removal of the initiating stimulus[11]. The removal of the high-flow stimulus through ASD closure triggers apoptosis in hyperplastic smooth muscle cells and allows for vascular re-lumenization[4]. Restoring normal flow patterns allows the endothelium to regain its regulatory function, further promoting a vasodilatory state[11]. The potential for reverse remodelling is a key determinant of operability; if the vascular bed can regress its structural changes, the PAH is considered "reversible"[6].

#### Right Ventricular Adaptation and Recovery

Chronic PAH leads to RV pressure overload, resulting in hypertrophy and dilatation[5]. This dilatation causes the interventricular septum to shift toward the left ventricle (LV), impairing LV filling and reducing systemic cardiac output, a phenomenon known as ventricular interdependence[14]. Reverse remodelling post-closure results in decreased RV volumes, normalization of the septal position, and improved LV diastolic function[5, 11]. This recovery is a critical component of the overall clinical improvement observed in these patients [11].

### Diagnostic Challenges and Operability Assessment

Determining reversibility is the most critical step in management[6]. While non-invasive imaging like echocardiography and Cardiac Magnetic Resonance (CMR) provides valuable data on RV size and function, cardiac catheterization remains the gold standard for assessment [7, 13]. Key parameters include mean pulmonary artery pressure (mPAP), PVR, and the Qp:Qs ratio[13].

Table 1. International Guideline Recommendations for ASD Closure in PAH

| Parameter | ESC 2020 Guidelines [13] | AHA/ACC 2018 Guidelines [8] |
|---|---|---|
| Operable (Class I) | PVR < 3 Wood Units (WU) | Qp:Qs ≥ 1.5; PA pressure < 50% systemic; PVR < 1/3 SVR |
| Borderline (Class IIa/b) | PVR 3-5 WU (IIa); > 5 WU if responsive (IIb) | Qp:Qs ≥ 1.5; PA pressure > 50% systemic (IIb) |
| Inoperable (Class III) | PVR > 5 WU (unresponsive); Eisenmenger | Net Right-to-Left Shunt; PVR > 2/3 SVR |

For patients with bidirectional shunts, temporary balloon occlusion of the ASD is mandatory [7]. By closing the defect with a balloon during catheterization, clinicians can monitor the acute response: a rise in left atrial pressure (>10 mmHg) or a drop in systemic cardiac output suggests that total closure is unsafe, indicating the need for a fenestrated device[6,8].

The Paradigm Shift: From "Treat and Repair" to "Repair and Treat"

The traditional "Treat and Repair" strategy involves treating patients with PAH-specific medical therapies (e.g., endothelin receptor antagonists, PDE5 inhibitors) for 6–12 months before re-evaluating operability [9]. While effective for some, this approach can delay the elimination of the primary driver of vascular damage[10].

In contrast, the emerging "Repair and Treat" strategy advocates for earlier intervention using fenestrated devices[10,11]. This approach eliminates the shunt trigger immediately, with post-procedural medical therapy continued to support the ongoing biological process of reverse remodelling[11]. Recent data suggest that earlier closure can lead to better long-term RV recovery and survival compared to prolonged medical therapy alone[10].

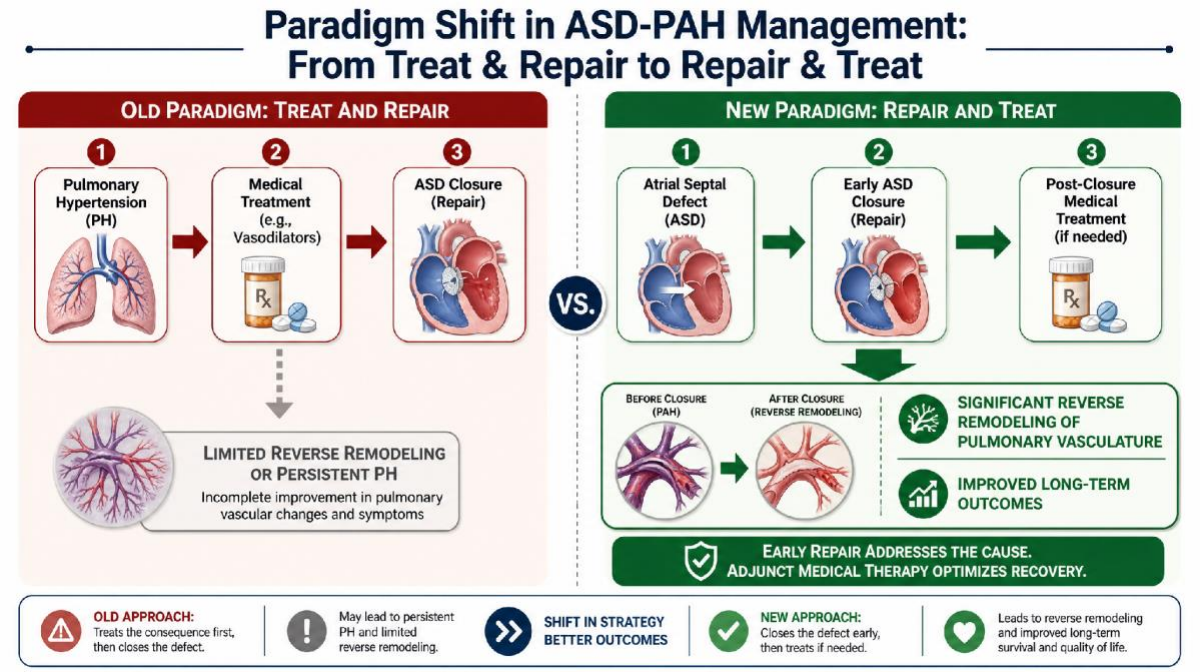


**Figure 1.** Comparison between the traditional 'Treat and Repair' and the proactive 'Repair and Treat' strategy.

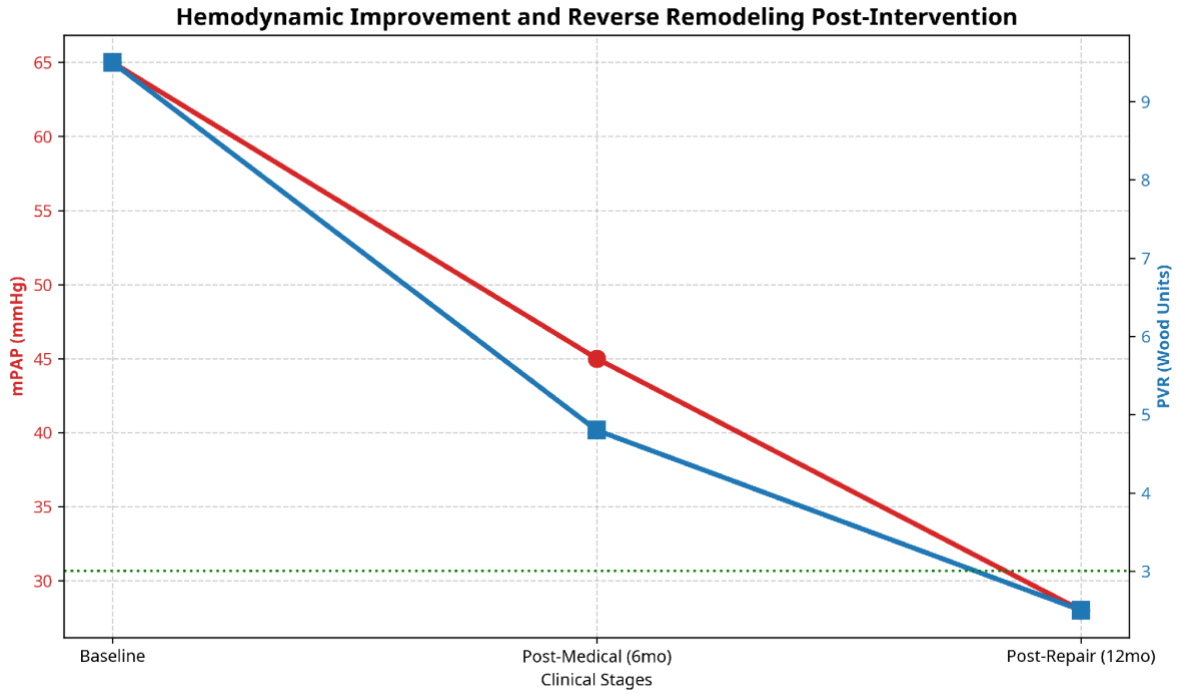


**Figure 2.** Trends in mean Pulmonary Artery Pressure (mPAP) and Pulmonary Vascular Resistance (PVR) post-intervention.

**Clinical Outcomes and Technical Nuances**

Fenestrated closure acts as a "pop-off valve," preventing acute RV failure during periods of increased pulmonary pressure while still reducing the overall left-to-right shunt and volume overload [9, 11]. Longitudinal data have shown that patients with severe PAH who undergo fenestrated closure combined with targeted therapy show a significant reduction in PVR over 12–24 months [11].

A case study of a 42-year-old female with severe PAH (PVR 9.5 WU) demonstrated successful reverse remodelling [10]. After initial medical therapy and subsequent fenestrated closure, her PVR normalized to 2.5 WU, accompanied by

significant RV recovery and clinical improvement from NYHA Class III to Class I [10, 11].

Table 2. Longitudinal Hemodynamic Evolution in the Case Study

| Stage | mPAP (mmHg) | PVR (Wood Units) | Qp:Qs | Functional Class (NYHA) |
|---|---|---|---|---|
| Baseline | 65 | 9.5 | 1.2:1 | III |
| Post-Medical (6mo) | 45 | 4.8 | 1.8:1 | II |
| Post-Repair (12mo) | 28 | 2.5 | - | I |

Advanced Molecular Mechanisms of Reverse Remodelling

The biological basis of reverse remodelling extends beyond simple hemodynamic relief. It involves a complex interplay of signalling pathways, including the bone morphogenetic protein receptor type 2 (BMPR2) pathway, which is often downregulated in PAH [4]. Repairing the shunt may help restore BMPR2 signalling, which inhibits the proliferation of pulmonary artery smooth muscle cells (PASMCs) and promotes their apoptosis. Furthermore, the reduction in mechanical stretch leads to a decrease in the expression of pro-inflammatory cytokines and growth factors, such as vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGF-β), which are key drivers of vascular remodelling [3, 4].

**Management of Peri-procedural Challenges**

The closure of an ASD in the presence of severe PAH requires careful anaesthetic and peri-procedural management. Anaesthetic agents can significantly affect systemic vascular resistance (SVR) and PVR, potentially worsening a right-to-left shunt and leading to severe desaturation [15]. Maintaining SVR within normal or slightly elevated ranges is crucial to favour a left-to-right shunt during the procedure. Post-procedural care in an intensive care unit (ICU) is often necessary to monitor for signs of acute RV failure or pulmonary oedema. The use of inhaled nitric oxide or intravenous prostanoids in the immediate post-operative period can be a vital bridge until the pulmonary vasculature begins to adapt to the new hemodynamic state [6, 15].

**Long-Term Arrhythmia and Anticoagulation Management**

Patients with unrepaired ASDs are at high risk for atrial arrhythmias, particularly atrial fibrillation and flutter, due to chronic right atrial stretching [1]. These arrhythmias can persist even after successful closure and can significantly worsen the prognosis by reducing cardiac output and exacerbating PAH. Long-term monitoring with Holter or event recorders is often indicated. Furthermore, the choice of anticoagulation in these patients is complex, balancing the risk of paradoxical embolism (especially if a fenestration remains patent) with the risk of pulmonary haemorrhage in the setting of severe PAH [9, 12].

**Future Directions and Research Gaps**

Despite the success of the "Repair and Treat" strategy, several questions remain. The optimal size of the fenestration, the timing of its eventual closure (if ever), and the duration of post-procedural PAH therapy are still areas of active debate [9]. The development of bio-absorbable fenestrated devices that close spontaneously once reverse remodelling is complete represents a promising future direction. Additionally, identifying molecular biomarkers that can accurately predict the potential for reverse remodelling before intervention would represent a major step forward in personalized management [10, 13].

## CONCLUSION

The biological capacity for reverse remodelling provides the foundation for proactive intervention in ASD with bidirectional shunts [11]. Combining advanced diagnostics with fenestrated devices and potent PAH therapies offers a promising pathway for recovery in patients once considered inoperable [10, 13]. A multidisciplinary approach involving ACHD specialists, PH experts, interventionalists, and anaesthesiologists is essential for achieving optimal outcomes in this high-risk population.

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## DISCLOSURES AND ETHICS

The authors declare that there is no conflict of interest.

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