“Treat and repair” strategy for shunt lesions: a critical review

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Abstract
The issue of operability in patients with shunt lesions and raised pulmonary vascular resistance is contentious. Several reports suggest that patients traditionally considered inoperable may be operated after treatment with targeted drug therapy for pulmonary arterial hypertension. We reviewed all the published literature of “treat and repair” approach to gain more insights into the utility of this approach. A critical appraisal of the published literature suggests that this approach is less established for patients with post tricuspid shunts, and for patients with pre-tricuspid shunts with modestly elevated indexed pulmonary vascular resistance (possibly greater than 11 WU.m²). Targeted drug therapy may be able to extend the therapeutic window in carefully selected patients, but its use as a routine in this setting seems unwarranted.

Keywords
Pulmonary artery hypertension, congenital heart disease, Eisenmenger syndrome, operability

Introduction
It is well established now that patients with large left to right shunt lesions may be cured if operated early in life. It is also recognised that closing the defect beyond a certain elevation of pulmonary vascular resistance (PVR) is detrimental, although the decision is not simply based on a numerical value of PVR.1,2 Several recommendations are available to guide decision making for operability in patients with left to right shunt lesions.3-5 Most of these recommendations favour a conservative strategy and consider operating patients with indexed pulmonary vascular resistance (PVRI) lesser than 4-6 Wood units.m² (WU.m²) as safe.4,6 However, in real world, and more so in the low- and middle-income countries, a large number of patients with shunt lesions present with raised PVRI at an older age. Decision to repair the defect in such patients is contentious, since the clinical course of such patients is adversely affected if they are operated, while the pulmonary vasculature has developed irreversible remodelling.7-10 Lack of well-defined clinical cut-offs to identify this “point” or “zone” of irreversibility further complicates the decision making. Thus, identifying that patient who has modifiable or reversible elevation of PVRI remains a major challenge to the cardiologist. The advent of targeted drug therapy (TDT) for pulmonary arterial hypertension (PAH) has added a new dimension to this pre-existing dilemma. These drugs include phosphodiesterase 5 inhibitors (PDE5i), endothelin receptor antagonists (ERA) and prostanoids. Experimental studies have demonstrated anti-proliferative effect of these drugs on vascular endothelial and smooth muscle cells.11,12 It was naturally hypothesised that these drugs could reverse the remodelling process in patients who have not developed advanced or irreversible pulmonary vascular changes and may allow successful surgical correction in those patients with marginally elevated PVRI. This formed the basis of the so-called “treat and repair” approach. Numerous questions regarding the utility of this approach remain, including patient selection, type of the drug or drug combinations, duration and efficacy of the therapy. In this article, we review the published literature regarding “treat and repair” approach to gain insight into the appropriateness of this strategy.
We performed a comprehensive literature search using the PubMed and EMBASE database with the following search terms: “pulmonary hypertension”, “congenital heart disease”, “Eisenmenger syndrome”, “Treat and repair”, “borderline operability”, “Sildenafil”, “Tadalafil”, “Bosentan”, “Macitentan”, “Ambrisentan”, “Prostanoids”. We included publications which reported outcomes of treat and repair strategy and analysed them based on the type of lesion and degree of elevation of PVR values. In addition we analysed large studies which reported hemodynamic data of patients before and after administration of TDT (Table 1).

Magnitude of change in PVRI with TDT

Although the change in PVRI brought about by TDT would vary due to numerous factors, it may be relevant to scrutinise the available experience with these therapeutic agents. Most large studies that have reported the change in PVRI pertain to patients with idiopathic pulmonary arterial hypertension (IPAH) and the situation in patients with shunt lesions may be different. The duration of follow-up, baseline tension (IPAH) and the situation in patients with shunt lesions may be different. The duration of follow-up, baseline PVRI and various patient characteristics are not standardized among these studies. However, an approximation of the quantitative change in PVRI with the use of TDT can be obtained from these reports, although the individual patient response may vary. Nevertheless, it is noteworthy that the reduction in PVRI in these studies range between 2 and 5 WU.m⁻². Although the change in PVRI with TDT appears similar with all drugs, there is a larger clinical experience with intravenous prostanoids and these drugs may be more efficacious, but are also more difficult to use. Further, whether the fall in PVRI is maintained with long-term use or tachyphylaxis to the drug effect would occur has not been well studied. The need for increasing dosages of prostanoids, PDE5i and ERA with time is well recognized. A small study suggested the possibility of decreasing effect over time, whereas few other studies have reported persistent salutary effects with long-term use. This issue warrants further studies.

Of the many studies, BREATHE-5 and MAESTRO exclusively included patients with Eisenmenger syndrome (ES). The mean change in PVRI brought about by TDT in these studies appears to be similar to other pulmonary hypertension studies. The increase in PVRI in the placebo arm over the study period of 16 weeks ranged from 0.98 (±0.75) WU.m⁻² in the MAESTRO study to 1.93 (±1.67) WU.m⁻² in the BREATHE-5 study. The progressive elevation of PVRI with time is expected in patients with pulmonary hypertension, and as such, the quantum of benefit with TDT may vary with the age of the patient also.

| Study     | Intervention    | Duration of therapy | Number of patients | Mean baseline PVRI (WU.m⁻²) | Mean change in PVRI (WU.m⁻²) |
|-----------|-----------------|---------------------|--------------------|-----------------------------|------------------------------|
| SUPER¹³   | Sildenafil 20 mg | 12 weeks            | 65                 | NA                          | −1.52 (−2.71 to −0.33)       |
|           | Sildenafil 40 mg |                     | 63                 | −1.78 (−2.72 to −0.86)       |
|           | Sildenafil 80 mg |                     | 65                 | −3.26 (−4.56 to −1.96)       |
|           | Placebo         |                     | 65                 | 0.61 (−0.67 to 1.91)         |
| PHIRST¹⁴  | Tadalafil 20 mg  | 12 weeks            | 17                 | −3.1 (−4.85 to −1.5)         |
|           | Tadalafil 40 mg  |                     | 18                 | −2.61 (−5.07 to −0.16)       |
| BREATHE-5⁵| Bosentan         | 16 weeks            | 37                 | 42.81 (±17.62)               |
|           | Placebo         |                     | 17                 | 35.87 (±15.11)               |
| ARIES- E¹⁶| Ambrisentan 5 mg| 60 weeks            | 35                 | 10.1 (±5.4)                  |
|           | Ambrisentan 10 mg|                    | 30                 | 11.65 (±6.6)                 |
| SERAPHIN¹⁷| Macitentan 3 mg | 6 months            | 47                 | 11.67 (±7.05)                |
|           | Macitentan 10 mg|                     | 57                 | 11.55 (±6.63)                |
|           | Placebo         |                     | 68                 | 11.25 (±6.95)                |
| MAESTRO¹⁸ | Macitentan 10 mg| 16 weeks            | 19                 | 35.26 (±16.51)               |
|           | Placebo         |                     | 17                 | 34.7 (±18.18)                |
|           | Placebo         |                     | 236                | 25 (±1)                      |
| Simonneau G et al¹⁹ | Treprostenil | 12 weeks            | 233                | 26 (±1)                     |
|           | Placebo         |                     | 236                | 25 (±1)                      |
| Rubin²⁰  | Epoprostenol    | 8 weeks             | 10                 | 21.6 (−13.1 to −2.2)         |
|           | Conventional therapy |          | 9                  | 20.6                         |

Bold values are expressed as Mean (95% confidence interval). Other values are expressed as Mean (± Standard Deviation).

PVRI: indexed pulmonary vascular resistance; WU.m⁻²: Wood units. m⁻².

⁵PVRI values mentioned in place of PVRI.

⁵Total pulmonary resistance mentioned in place of PVRI.

dyn-sec/cm⁻⁵ were converted to wood units by dividing by 80.
Table 2. Reports of patients with post tricuspid shunts who underwent “treat and repair” strategy.

| Author                      | Year | Age (years) | Sex | CHD       | Mean PA pressure (mm Hg) | Mean PVR (WU.m²) | Qp/Qs ratio | Mean PVR/SV ratio | Whether vasoreactivity testing performed? | Drugs                                      | Duration of treatment (years) | PVR Post closure (WU.m²) | Whether medication continued after closure | Duration of follow-up after repair |
|-----------------------------|------|-------------|-----|-----------|--------------------------|------------------|-------------|-------------------|-------------------------------------------|------------------------------------------|-------------------------------|------------------------------|--------------------------------------|-------------------------------|
| Mitropoulos et al.³³        | 2007 | 39F         |     | PDA       | 75                       | 9.5             | 2.8         | 0.3               | Yes                                       | Bosentan                                  | 2.5                           | 5.3             | Yes                                   | 9 months                      |
| Ussia et al.²⁴              | 2007 | 63M         |     | PDA       | 65                       | –               | –           | –                 | Yes                                       | Bosentan                                  | 3 months                      | –               | Yes                                   | 8 months                      |
| Hu et al.²⁰                 | 2014 | 10F         |     | VSD       | 55                       | 18.8            | 0.8         | 1.32              | Yes                                       | Bosentan                                  | 3 months                      | –               | Yes                                   | 1 month                       |
| Akagi et al.³⁷              | 2018 | 49F         |     | VSD       | 76                       | 15.8            | 1.68        | 0.4               | Yes                                       | Ambrisentan + Sildenafil + Epoprostenol | 1 year                        | 11.5            | Yes                                   | 10 months                     |
| Akagi et al.³⁷              | 2018 | 20M         |     | VSD       | 71                       | 9.0             | 2.34        | 0.33              | Yes                                       | Tadalafil + Ambrisentan + Beraprost   | 1 year                        | 9.1             | Yes                                   | 3 years                      |
| Thomaz et al.³⁹             | 2019 | 9.7 (6.9–16.8) months |     | Post tricuspid shunt | 44 (40–57)         | 4.5 (3.5–6.9)  | 2.4 (1.6–3.0) | 0.29 (0.22–0.43) | Yes                                       | Sildenafil                                  | 27 days                       | –               | Yes                                   | –                            |

CHD: congenital heart defect, n: number, PA: pulmonary artery, PDA: patent ductus arteriosus, PVR: pulmonary vascular resistance, PVRI: indexed pulmonary vascular resistance, Qp/Qs: pulmonary to systemic blood flow, VSD: ventricular septal defect, WU.m²: Wood units.m²

*PVR values mentioned in place of PVRI.

Numerical variables are expressed as mean (+/- standard deviation)

Numerical variables are expressed as Median (interquartile range)
Published reports of “treat and repair”

We critically analysed the clinical and hemodynamic variables of reported patients who were treated with TDT and then underwent closure of their shunt lesion. The details of individual studies are shown in Tables 2 and 3. Most of the studies include case reports or series of few cases. There is significant heterogeneity across all studies with respect to the baseline characteristics of patients, criteria adopted to decide operability and representation of hemodynamic data. Successful repair has been demonstrated after treatment with almost all drugs including prostanoids,28–30 PDE5i31 ERAs32–34 and various drug combinations.35–37 Few authors report PVR, whereas others report PVRI. Operability is decided based on the baseline hemodynamic data by some authors, whereas others perform acute vasodilator testing before deciding operability. The number of patients in whom this strategy might have been tried but failed largely remains unknown. As seen with any new strategy, a “publication bias” for reporting only the successful outcomes cannot be excluded.

Reports of post-tricuspid shunt lesions

We identified seven studies reporting results of “treat and repair” in patients with post tricuspid shunts, the details of which are shown in Table 2. The published reports are not convincing that the long-term effects of treat and repair strategy would be better than the natural history of ES in most of the circumstances. For example, in a retrospective case series from China, the outcome of 41 adults with non-restrictive VSD, who were subjected to “treat and repair,” was reported.38 These patients were treated with Sildenafil or Bosentan for a mean duration of 7.6 ± 3.0 months. This group showed significant decrease in PVR from 17.1 ± 3.9 WU to 12.8 ± 2.7 WU. Despite all patients undergoing a flap valve VSD closure (which is considered to be a safer strategy in patients with borderline hemodynamics), this cohort had unacceptable mortality and morbidity. Two patients (4.9%) died in the immediate postoperative period and five patients (13.8%) continued to have severe PAH (mean pulmonary artery pressure > 50 mm Hg) at mean follow-up of 33.2 ± 6.7 months. Eight patients with a baseline pulmonary to systemic blood flow (Qp/Qs) ratio of ≤ 1 were treated with TDT and subsequently operated. Amongst them, five patients continued to have severe PAH during follow-up. Three of these patients could not afford to continue the drug therapy postoperatively and showed right to left shunt through the flap valve at last follow-up. Although treat and repair strategy did benefit some of these patients, the long-term outcome remains unknown.

In a recently published series from Brazil, 33 patients with pre-defined high-risk features (presence of at least three of the five following criteria: absence of clinical features of pulmonary overcirculation, bidirectional shunt across the defect, sustained or intermittent systemic desaturation <90%, Down syndrome, age >18 months) were administered sildenafil for a mean duration of just 27 days before undergoing surgery.39 The median age of the population was only 9.7 months, and median baseline PVRI was 4.5 WU.m². Although the authors concluded that the mid-term postoperative outcomes are predictable to an extent in patients receiving sildenafil pre- and post-surgery, the young age, very short duration of therapy, mildly elevated PVRI and high prevalence of Down syndrome in the study population make this conclusion less generalizable.

In the report by Akagi et al., three patients with large VSD and severe PAH underwent VSD closure after combination therapy consisting of PDE5i, ERA and prostanoids for one year.37 In two patients, the postoperative PVRI were 11.5 WU.m² and 9.1 WU.m² and both required continuous treatment with TDT. The third patient’s PVRI was reduced to 4 WU.m² six months after surgery. However, this patient had undergone unilateral pulmonary artery (PA) band previously which may have protected the pulmonary vasculature and made the surgical repair feasible. In another report, Hu et al. described successful outcome after VSD closure in a 10-year-old girl with a baseline PVRI of 18.84 WU.m².40 The patient’s Qp/Qs ratio changed from 0.80 to 1.42 after 12 weeks of Bosentan therapy. The patient stopped the therapy after one month of surgery and her PA pressure was estimated to be 40 mm Hg by tricuspid regurgitation jet velocity at one-year follow-up. Such a response in a patient with ES is a rarity where nearly four months of TDT with Bosentan has “cured” the patient.

We found two patients with patent ductus arteriosus (PDA), who were reported to undergo closure after TDT. The first patient had a baseline Qp/Qs ratio of 2.8 and no evidence of right to left shunt, suggesting operable hemodynamics.33 Similarly, in the other patient, wide pulse pressure and fall in PA pressures after PDA occlusion at baseline suggests hyperkinetic PAH and likely the patient was operable even without the therapy. The management decisions of patients with calculated PVRI beyond the operable range but with a significant left to right shunt are difficult. Although the evidence base is not large, most clinicians would possibly close such defects even without a trial of TDT. In patients with PDA, balloon occlusion may be useful in the decision regarding operability.41

Reports of pre-tricuspid shunt lesions

We identified 25 patients with atrial septal defect (ASD) who were shown to undergo closure after treatment with pulmonary vasodilators. The details of these studies are shown in Table 3.

In the patient reported by Kim et al., two years of sildenafil therapy reduced the PVRI from 25 WU.m² to 12.1 WU.m². However, the hemodynamic data revealed subnormal right and left atrial pressures (1 mmHg), which could have overestimated the baseline PVRI. The PVRI was
Table 3. Studies reporting patients with atrial septal defect who underwent “treat and repair” strategy.

| Author            | Year | Baseline hemodynamic parameters | Hemodynamic parameters at follow-up | Change in WHO functional class | Remarks                                                                 |
|-------------------|------|---------------------------------|-------------------------------------|--------------------------------|-------------------------------------------------------------------------|
| Kijima et al.42   | 2016 | 103/40/64†                      | (40 ± 9) + RAP‡,c                    | 12.5 months                   | III --> II; Average reduction in PVRI of 9.0 WU.m² with medical therapy alone over a mean duration of 2.9 ± 3.4 years |
| Taniguchi et al.35| 2014 | 87/30/57                        | 29/15/22                           | 6 months                      | III --> I; 15 mm ASD, mild PAH on FU                                     |
| Tahara et al.32    | 2012 | 96/35/58                        | 43/18/33                           | 2.5 years                     | III --> I; 39 years old. Moderate PAH on FU                             |
| Oka et al.45       | 2019 | 59/–/50                         | 31/–/18                            | 2.5 years                     | III --> I; 66 years old. Doubtful reliability of baseline PVRI         |
| Jung et al.43      | 2013 | 76/36/48                        | 36 + RAP‡                        | 1 year                        | III --> II; 20 years old. Mild PAH on continued bosentan therapy       |
| Hirabayashi et al.30| 2009 | 106/32/58                       | 57/23/39                           | 1 year                        | III --> I; 31 years old. Persistent moderate PAH on epoprostenol       |
| Bradley et al.44   | 2013 | 121/38/66†                      | 42 + RAP‡                         | 2 months                      | III --> II; 29 years old. Short duration of therapy (4 months) and follow-up (2 months) |
| Schwerzmann et al.29| 2006 | 84/35/53                        | 54 + RAP‡                         | 1.5 years                     | III --> I; 38 years old. Lung biopsy – Heath Edwards Grade iv/vi, Persistent moderate PAH on bosentan |
| Nazrin et al.36    | 2013 | 121/38/66†                      | 42 + RAP‡                         | 2 months                      | III --> II; 29 years old. Short duration of therapy (4 months) and follow-up (2 months) |

(continued)
Table 3. Continued

| Author            | Year | Baseline hemodynamic parameters | Hemodynamic parameters at follow-up | Duration of last follow-up after repair | Change in WHO functional class | Remarks |
|-------------------|------|---------------------------------|-------------------------------------|----------------------------------------|--------------------------------|---------|
|                   |      | PA pressures (S/D/M) mm Hg | PVRI (WU.m²) | PA pressures (S/D/M) mm Hg | PVRI (WU.m²) |                        |                      |
| Frost et al.      | 2005 | 86/35/50                       | –                        | 45 + RAPc                  | –                        | 8 years     | III -> II            |
|                   |      |                                 |                         |                                 |                          | 29 years old. Incomplete hemodynamic data with no PVR, SVR, Qp/Qs. Received epoprostenol for six months then amlopidine from six months to eight years after ASD closure |
| Kim et al.        | 2010 | 87/20/55                       | 25.0                    | 58 + RAPc                  | –                        | 4 years     | III -> I            |
|                   |      |                                 |                         |                                 |                          | 41 years old. Lung biopsy – Heath Edwards Grade iv–v/vi. Spurious baseline hemodynamic data |
| Hoetzenecker et al.| 2009 | –/–/54                         | 3.9b                    | –/–/35                     | 4.2b                     | 8 months    | IV -> II            |
|                   |      |                                 |                         |                                 |                          | 71 years old, mean LAP 17mm Hg. PA pressure, calculated PVR raised possibly due to LV diastolic dysfunction. Incomplete hemodynamic data with no PVR, SVR, Qp/Qs |
| Suzuki et al.     | 2017 | 78/42/56                       | 8b                      | 29/12/20                   | 3.1b                     | 4.5 years   | II -> I            |
|                   |      |                                 |                         |                                 |                          | 13 years old. 11 mm ASD and BMPR2 mutation. Most likely a case of heritable PAH which responded to vasodilators |

ASD: atrial septal defect, FU: follow-up, LAP: left atrial pressure, LV: left ventricle, n: number, PA: pulmonary artery, PAH: pulmonary artery hypertension, PVR: pulmonary vascular resistance, PVRI: indexed pulmonary vascular resistance, RAP: right atrial pressure, Qp/Qs: pulmonary to systemic blood flow, (S/D/M): (Systolic/Diastolic/Mean), SVR: systemic vascular resistance, WHO: world health organization, WU.m²: Wood units.m²

aAverage S/D/M of 7 patients. 1 patient did not have baseline hemodynamic data.
bPVR values mentioned in place of PVRI.
cDoppler echocardiography derived right ventricular systolic pressures.
d5 Responders out of 12 who underwent ASD closure.
demonstrated to have halved despite an increase in mean PA pressure from 55 mmHg at baseline to 75 mmHg after 2 years of Sildenafil therapy. The patient was subsequently operated and shown to be asymptomatic at four years’ follow-up; however, the PA pressures are not known. Intraoperative lung biopsy in this patient revealed plexiform lesions with medial hypertrophy, which are considered “irreversible” form of hypertensive pulmonary arteriopathy. In about half of the reports of pre-tricuspid shunts, catheterisation was not repeated after surgery and authors relied on Doppler echocardiography alone for the estimation of PA pressure, thereby underestimating to an extent and also making it difficult to assess an average change in PVRI due to TDT in this population.

In the retrospective series by Bradley et al., 12 patients with ASD and severe PAH with PVR > 6 WU and PVR/SVR > 0.3 were treated with TDT for a duration of 6–12 months. Five of them responded with >30% reduction in PVR with final PVR < 6 WU and underwent ASD closure. Responders were younger and had a lower baseline PVR (7.2 ± 1.5 WU vs. 9.9 ± 1.7 WU) compared to non-responders. Such a cautious approach in the utility of “treat and repair” approach may possibly expand the operability window in patients with modest elevation of PVRI.

**Real success stories**

In contrast to the reports discussed above, there are a few patients with ASD and markedly elevated PVRI who have shown unequivocal benefits after TDT and successful clinical outcomes after closure. Kijima et al. showed successful application of “treat and repair” approach in their cohort of eight patients who received TDT for a median duration of 2.5 years (range 2 weeks to 10 years). The average PVRI reduced from 14.3 WU.m² at baseline to 5.3 WU.m² preoperatively. All the patients underwent transcatheter closure of shunt and had an estimated systolic PAP of 40 ± 9 mmHg at last follow-up which was significantly lower as compared to baseline PAP of 104 ± 27 mmHg. Long-term prostanoids were used in six out of eight patients, which could have resulted in favourable outcomes.

Whether these patients represent a different subgroup of ASD-PAH remains unknown. Whether the responders are genetically different remains to be studied. What proportion of ASD-PAH patients would follow such a course with TDT is also not known.

**Other issues**

Although “treat and repair” strategy might have reduced the perioperative mortality of patients with shunt and raised PVRI, the long-term outcome needs to be carefully investigated. Delayed rise in PVRI, even after 10 years of surgical closure of shunt lesions has been documented, further enforcing the need for long-term data. It is shown that some amount of vasoreactivity is preserved even in patients with ES. Therefore, TDT may reduce PVRI in some of these patients to an extent which may allow surgical repair with decreased perioperative mortality. But whether it would alter the natural history of ES is unclear. In the reported cases, almost all patients needed to continue TDT. The need for continued TDT after operation and its financial implications, especially in the low- and middle-income countries, needs to be taken into account since not ensuring drug supply may in fact be counterproductive. Further, other issues such as choice of the drug or drug combinations, optimal duration of drug therapy before assessing for response still remains.

The “treat and repair” approach, which could rather be paraphrased as “treat, repair and treat”, seems to have expanded the window of opportunity in selected patients with moderately raised PVRI. Based on our analysis of the magnitude of PVRI change brought about by TDT, we empirically suggest that patients with pre-tricuspid shunt with PVRI elevation up to 11 WU.m² may be treated with TDT for at least six months and should be reassessed. This approach is not likely to be useful at higher PVRI and in post-tricuspid shunts. Systematic and large volume prospective multicentre studies with longer duration follow-up are needed to ascertain the safety of the treat and repair approach. Considering the difficulties in designing such a study, multicentre systematic registry-based database should be initiated. The routine application of the “treat and repair” strategy may instead lead to “repair in haste and regret at leisure” outcome for many patients.

**Conclusion**

“Treat and repair” strategy may extend the window of operability in carefully selected patients with borderline hemodynamics. The published literature is insufficient to justify the overall enthusiasm regarding the utility of this approach. More systematic studies are warranted.

**Conflict of interest**

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