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Balloon Dilation Atrial Septostomy for Advanced Pulmonary Hypertension in Patients on Prostanoid Therapy

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***Background*: Prostanoid therapy improves quality of life and may increase survival in patients with advanced pulmonary hypertension (PH). Balloon dilated atrial septostomy (BDAS) can palliate or bridge to transplantation for patients resistant to medical therapy. The safety and efficacy of BDAS in the prostanoid era has not previously been reported. *Methods*: All patients had progressive symptoms despite prostanoid therapy at the time of their first BDAS. Sixteen patients who underwent a total of 23 septostomies between 2004 and 2014 were included in this retrospective case series. *Results*: Patients were aged 47.6 years ± 11.3 with 12/16 women. Etiologies included idiopathic (7), methamphetamine (6), scleroderma (1), and anorexigen (2). One patient died within 24 hr post-procedure. Thirty-day and 1-year survival were 75% and 64%, respectively. Six of the septostomies were revisions, including two which were ultimately stented. Three subjects were successfully bridged to transplant. Pulmonary capillary wedge pressure (PCWP) increased from a mean of 13 to 17 mm Hg, cardiac index increased from 2.1 to 2.4 L/min/m^2, and arterial saturation decreased from 90.7 ± 4.3 to 82.5 ± 5.6%. All non-survivors at 30 days were male and had higher baseline serum creatinine, mean RAP, right ventricular end diastolic pressure (RVEDP), and left ventricle (LV) filling pressures, and lower right ventricle (RV) ejection fraction. Mortality was associated with unchanged post-septostomy cardiac output despite an increase in left ventricular end diastolic pressure (LVEDP). *Conclusions*: BDAS may be an alternate therapy for select PH patients who have symptomatic progression despite prostanoid therapy. Survival is comparable to prior reports of BDAS in the pre-prostanoid era.**

Key words: intracardiac echo; right ventricle; transeptal cath

INTRODUCTION

Pulmonary hypertension (PH) is a progressive disease culminating in right heart failure, syncope, obstructive shock, and death [1,2]. Based on observational data showing improved survival in PH patients with patent foramen ovale, balloon dilated atrial septostomy (BDAS) was first performed in 1983 by Rich and Lam to create an iatrogenic right to left shunt that would both unload the strained right heart and improve left ventricular filling pressures [3–6]. While right to left shunting decreases arterial oxygen saturation, numerous

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series have reported improved cardiac output and increased systemic oxygen transport in properly selected patients [7,8]. Widespread use of BDAS has been limited by relatively high procedural and periprocedural mortality rates of 5% and 16%, respectively [9,10]. Experience in the past decades has shown mortality is highest in patients with severe disease (mean right atrial pressure >20 mm Hg, pulmonary vascular resistance index >4400 dynes sec cm^{-5}/m^2), baseline hypoxia (arterial oxygen saturation <90% on room air), and higher baseline left heart filling pressures (left ventricular end diastolic pressure >18 mm Hg) [10,11]. Indications for BDAS in the United States have therefore been limited to bridging to transplantation, palliative therapy, and intractable right heart failure symptoms despite medical therapy [6,12].

Medical treatment of PH has advanced significantly in recent years, most noticeably with the addition of prostanoids. Prostanoids increase local levels of prostacyclin I_2, a potent vasodilator. The most commonly used and best studied prostacyclin, epoprostenol, has been shown to improve hemodynamic parameters, functional capacity, and survival in patients with idiopathic pulmonary arterial hypertension [12–15]. With the majority of data on outcomes of BDAS published before the addition of prostanoids to PH therapy, the utility of BDAS with concurrent prostanoid therapy has not been previously reported.

MATERIALS AND METHODS

Demographics

Between March 2004 and May 2014, 23 BDAS were performed on 16 patients with continued PH despite prostanoid therapy at University of California, Davis Medical Center. All patients were referred from our PH clinic for septostomy due to repeated episodes of right heart failure symptoms refractory to aggressive medical therapy (diuretics, anticoagulation, and pulmonary vasodilators) including prostanoids. The majority of patients (14/16) had WHO functional Class IV symptoms at the time of their first BDAS. The other two patients had WHO class III symptoms with limited alternative medical or surgical options. In addition, five patients had syncope and five patients had presyncope. A specialist with experience in advanced therapies for PH referred all patients. Hemodynamic, echocardiographic, and baseline demographic data were retrospectively collected and independently confirmed. Cardiac index was calculated using thermodilution for the vast majority of patients. A high proportion was on supplementary oxygen prior to the procedure, therefore Fick cardiac outputs were not used for calculations in this study. As our catheterization lab does not routinely assess oxygen consumption during the procedure, oxygen consumption was assumed stable. All echocardiograms and hemodynamics were collected from the chart and individually confirmed by a single cardiologist. Right ventricular ejection fractions were calculated using Simpsons rule. The internal review board at UC Davis Medical Center approved this study, protocol no. 201018634-1.

Procedure

Right heart catheterization was performed with a Swan Ganz catheter after obtaining access in the right internal jugular vein or right femoral vein. Left heart catheterization was performed with a 5 or 6 Fr pigtail catheter placed in the left ventricle for left ventricular end diastolic pressure (LVEDP) monitoring. An 8-Fr Mullins sheath was placed via the right femoral vein. A Brockenbrough needle (Medtronic) was advanced through the sheath, and transseptal puncture was performed under direct intracardiac echocardiography (ICE) guidance (AcuNav™, BiosenseWebster). In 16 patients, the ICE catheter was placed in the ipsilateral right femoral vein with the pulmonary artery catheter. In three patients, the ICE catheter was placed in the contralateral left femoral vein. Two patients in 2004 were done without ultrasound guidance, with another case employing transesophageal ultrasound. The Mullins sheath (Medtronic) was then carefully advanced into the left atrium. The Brockenbrough needle was then removed and LA pressures were measured. A 7-Fr multipurpose catheter was inserted in the Mullins sheath into the left atrium. A soft J-wire was advanced into the left upper pulmonary vein for anchoring. The multipurpose catheter was then switched for a Powerflex™ (Cordis) or a Maxi LD™ (Cordis) balloon to perform the septostomy. Serial balloon dilations of the septostomy were then performed measuring 4 mm and ranging as high as 20 mm. With each dilation, angiographic, clinical, and echocardiographic data were collected with specific attention paid to arterial oxygen saturation, LVEDP, and cardiac index. The size of the septostomy was titrated to maximize left sided filling pressures (with an LVEDP no greater than 16 mm Hg) and cardiac index, while maintaining arterial oxygen saturation greater than 80%. Echocardiographic images were repeated to assess the size of the septostomy and flow with the balloon deflated (Fig. 1). In six patients later in our series, interatrial stenting was performed (Fig. 2). After transseptal puncture in a relatively thicker portion of the interatrial septum as determined by ICE, a 0.014″ extra support wire was place in the left upper pulmonary vein. A 6-Fr multipurpose guide catheter was advanced over the wire, through the Mullins sheath, and into the left atrium. A

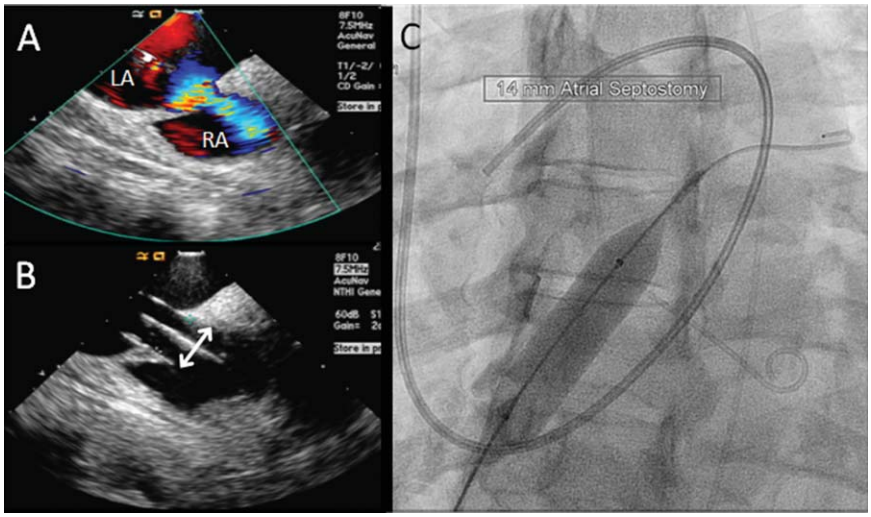

Fig. 1. ICE and fluoroscopy of BDAS. A: Doppler image with right to left flow across the interatrial septum after successful balloon atrial septostomy. The right atrium is at the top of the image, the left atrium at the bottom. B: Balloon dilation of the interatrial septum over a guidewire. Arrow indicates diameter of balloon dilated over the guidewire. C: Fluoroscopy of BDAS. Clockwise from the top: right heart catheter, pigtail catheter in LV, transseptal catheter with inflated 14 mm balloon, and ICE catheter. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

7 mm × 18 mm peripheral stent was advanced over the wire and positioned so that the distal half of the stent was in the left atrium, and the proximal half in the right atrium, with the right atrial side still positioned within the guide. Positioning was done under ICE guidance and also with contrast injections through the guide which allowed visualization of the interatrial septum. The stent was then inflated slowly with the left atrial side of the stent expanded first. After contrast injection and ICE confirmed positioning, the guide was withdrawn and the right atrial side of the stent was inflated. After balloon deflation and removal, hemodynamic measurements were taken and the stent was either left as is, or expanded sequentially with a larger 8 or 9 mm balloon.

Statistics

Descriptive variables are presented as means with standard deviations. Due to the small number of patients in this study, statistical comparisons between groups were not performed.

RESULTS

Demographics

The average age of patients at time of their first procedure was 47.6 years of age, of which 12 were women (75%). Seven of the 16 patients had idiopathic primary PH (43.8%), 6 were presumed secondary to methamphetamine use (37.5%), 1 secondary to scleroderma (6.3%), and 2 secondary to anorexigen use (12.5%). The baseline creatinine was 1.69 ± 1.0 with 9 patients having an estimated glomerular filtration rate less than 60. Fifteen of the patients were on treprostinil (3 subcutaneous, 5 oral, and 7 intravenous), along with one patient on intravenous epoprostenol. Other PH treatments concomitantly used were phosphodiesterase-5 inhibitors (7/16), endothelin receptor antagoists (9/16), and dipyridamole (4/16). Four of the procedures were performed on a semi-urgent basis with three of the patients requiring vasopressor/inotropic support. See Table I for further details of the demographics.

Hemodynamics

Pre- and post-procedure hemodynamic parameters are presented in Table II. All patients had hemodynamic and echocardiographic evidence of severe right ventricular systolic dysfunction. Post-procedure, the mean right atrial pressure did not change acutely, but LVEDP increased from a mean of 9.7 to 15.1 mm Hg, and cardiac index increased from 2.1 to 2.4 L/min/m^2. When compared to patients who survived greater than 30 days, patients with mortality in the first month had higher baseline right atrial pressures (18.9 vs. 13.3 mm Hg) and worse right ventricle (RV) systolic dysfunction (right ventricular ejection fraction (RVEF) 22 vs. 16%). Post-procedure, patients who died in the first month had higher pulmonary capillary wedge pressures (22 vs. 14 mm Hg), LVEDP (17 vs. 8 mm Hg), direct left atrial pressures (13 vs. 8 mm Hg), with no significant improvement in cardiac index (2.15 vs. 1.94 L/min).

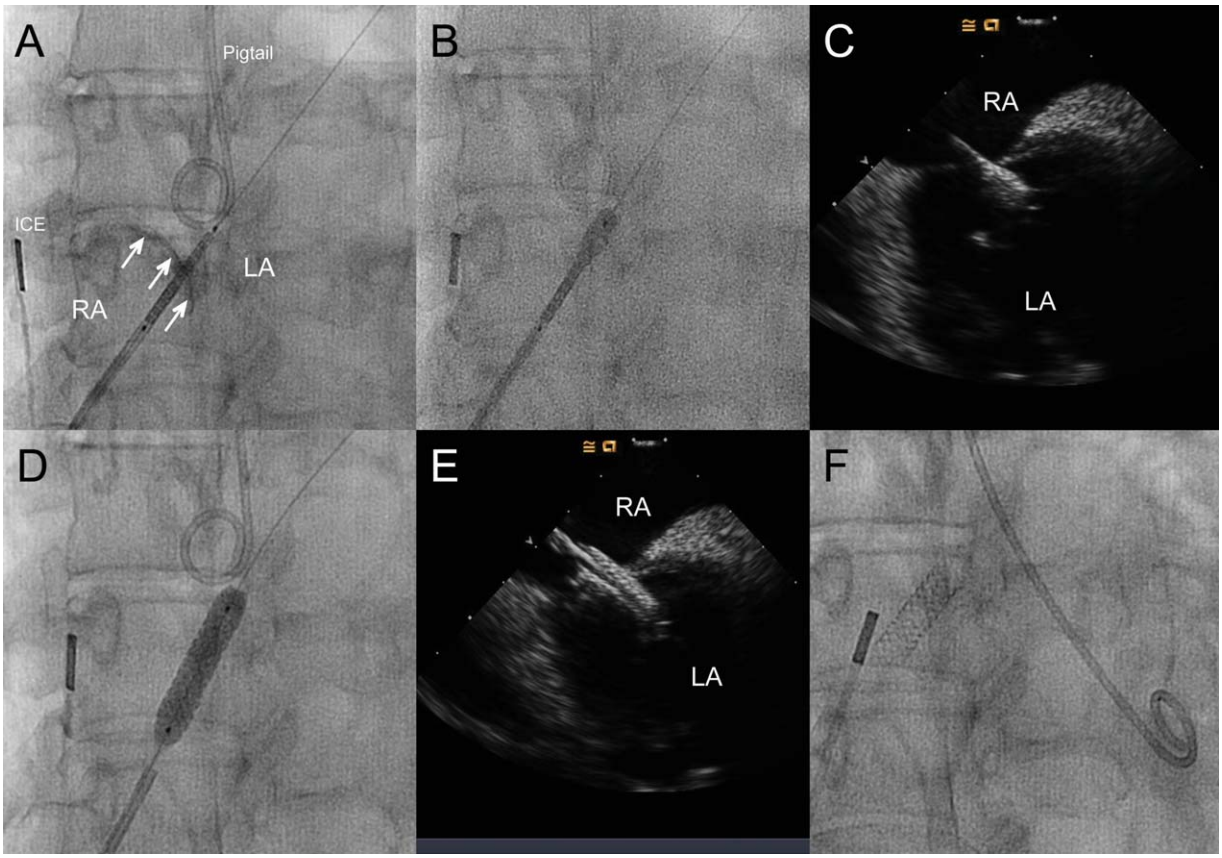

Fig. 2. Interatrial stent septostomy. A: Contrast injection showing outline of interatrial septum (white arrows). Pigtail catheter is in the aortic root and ICE catheter is in the right atrium (RA). Stent is seen spanning the septum with distal half in the LA (left atrium), RA aspect of stent is sheathed in 6 Fr multipurpose guide catheter. The left atrial side of the stent is deployed under fluoroscopy (B) and ICE (C). The guide is retracted and the stent is fully deployed under fluoroscopy (D) and ICE (E). Final fluoroscopic appearance of the stent (F). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE I. Baseline Patient Demographics

Age (years)	47.6 ± 11.3
Tobacco use (%)	3 (18.8)
Sex (% female)	12 (75)
Etiology	
Idoiopathic (%)	7 (43.8)
Methamphetamine (%)	6 (37.5)
Scleroderma (%)	1 (6.3)
Anorexigen (%)	2 (12.5)
Syncope (%)	5 (31.3)
RHF symptoms (%)	16 (100)
Hemoglobin (g/dL)	13.7 ± 1.6
Creatinine (mg/dL)	1.69 ± 1.0
BNP	687.5 ± 483.7
TAPSE	11.6 ± 2.8
Days to Follow-up	890.4 ± 955
Prostanoids (%)	16 (100)
Endothelin Rc antagonists (%)	9 (56.3)
PDE5 inhibitors (%)	7 (43.8)
Vasopressors (%)	3 (18.8)
WHO functional class IV (%)	14 (87.5)

One patient died within 24 hr of the procedure related to intractable shock, which predated procedure. No patients developed treatment resistant tachyarrhythmias after the procedure. One patient had worsening renal failure within one week of the septostomy, but was being treated for septic shock at the time of the renal failure. No other complications were noted directly associated with the procedure. The 30-day and 1-year survival rates were 75% and 62.5%, respectively. The mean time to follow-up was 890 days at the time of data collection (May 2014). For those who survived greater than 30 days, the mean time to follow-up was 1,184 days, with five of twelve patients currently alive.

Thirteen of 16 patients described functional improvement of at least one WHO functional class within one month of the procedure, during which there were no significant changes in medical therapy. The remaining three patients never left the intensive care unit. Four patients required a total of five repeat BDAS due to

TABLE II. Hemodynamics

	Total (16)	>30 Day survivors (12)	<30 Day survivors (4)
mRAP (mm Hg)			
Pre	16.6 ± 6.7	15.1 ± 6.4	23.2 ± 1.4
Post	17.1 ± 5.8	17.1 ± 4.9	19.5.5 ± 3.5
mPAP (mm Hg)			
Pre	62.0 ± 13.2	60.9 ± 13.9	66.75 ± 9.6
Post	69.5 ± 10.8	56.7 ± 9.9	69.5 ± 9.5
PVRI (dynes sec cm^{-5}/m^2)			
Pre	2,392 ± 1,844	2,434 ± 1,986	2,126 ± 351
Post	1,518 ± 540	1,441 ± 457	1,920 ± 912
PCWP (mm Hg)			
Pre	13.0 ± 6.1	11.9 ± 4.6	17.8 ± 9.9
Post	16.8 ± 4.8	15.0 ± 1.9	21.7 ± 16
LVEDP (mm Hg)			
Pre	9.7 ± 5.5	8.2 ± 3.9	17 ± 6.5
Post	15.1±6.3	13.2±4.7	24.3±7.6
LAP (mm Hg)			
Pre	10.4 ± 6.2	8.7 ± 4.2	19 ± 8.7
Post	14.5 ± 7.0	12.8 ± 5.9	21.7 ± 7.6
CI ($L/min/m^2$)			
Pre	2.10 ± 0.6	2.11 ± 0.66	2.15 ± 0.45
Post	2.43 ± 0.6	2.40 ± 0.58	1.94 ± 0.29
SaO2 (%)			
Pre	90.7 ± 4.3	93.9 ± 6.1	89.0 ± 8.2
Post	82.5 ± 5.6	84.1 ± 5.1	80.1 ± 6.7
LVEF (%)			
Pre	64.4 ± 7.8	62.6 ± 8.2	70.1 ± 11.4
Post	61.1± 8.0	61.8 ± 6.7	58.3 ± 5.8
SOT (L_{O2}/min)			
Pre	650 ± 229	633 ± 214	758 ± 342
Post	664 ± 228	676 ± 234	641 ± 283
RVEF (%)			
Pre	20.7 ± 3.3	22.3 ± 2.3	16.0 ± 1.4

clinical and echocardiographic evidence of septostomy closure. At the time of the repeat procedure, arterial blood gas shunt studies were performed with 100% inhaled O_2 to confirm closure of the shunt. Three patients were successfully bridged to transplantation, all of which occurred without complication associated with the septostomy.

Three patients who subsequently died within 30 days were in the ICU prior to BDAS with evidence of decompensated right heart failure with evidence acute renal failure (Table III). The primary causes of death were septic shock, obstructive shock, and bowel obstruction. Mean follow-up to death was 501 days overall, increasing to 734 days when excluding those who died within 30 days. Functional improvement could not be assessed in the four patients who ultimately died, due to the severity of their disease. Mortality was associated with unchanged post-septostomy cardiac index despite an increase in LVEDP.

DISCUSSION

Early experience with BDAS was associated with high mortality rates, largely due to difficulty in controlling the size of the shunt, thereby leading to severe hypoxemia and acute left ventricular failure [16–18]. More recent series have shown decreased procedural and one-month mortality rates, due largely to improved patient selection and the advent of graded balloon septostomy [10–12]. Regardless, BDAS currently occupies a limited niche in PH treatment, serving as a bridge to transplantation, palliation, and for patients with symptoms despite aggressive medical therapy [11,12]. During this same time, mortality has improved in PH as a whole. Endothelin receptor antagonists (e.g., bosentan), phosphodiesterase inhibitors (e.g., sildenafil), and most importantly prostacyclins (e.g., epoprostenol) have been shown to improve mortality, functional status, and hemodynamics [13,14,19–21]. With the scope of PH treatment so drastically changed, the role of BDAS needs to be re-examined. Progressing despite aggressive medical treatment has new connotations, as this now connotes a patient more advanced in the natural course of PH; thanks to prostanoids. In addition, prostanoids specifically affect hemodynamics, potentially interplaying the role of BDAS [14]. Our study sought to evaluate the safety and efficacy of graded balloon atrial septostomy in a background setting of these important medications.

There were four early mortalities of sixteen patients in our series. All four were critically ill in the ICU at the time of the BDAS, three of which were on dopamine (Table III). Two of these patients had become acutely decompensated due to aggressive and necessary fluid resuscitation for septic shock. The other two had intractable hypotension despite maximal medical therapy. These patient died a negotiated death at approximately 24 hr and 22 days after no improvement after septostomy. All four patients who died soon after BDAS had no noted sequelae of the procedure directly leading to their death. Analysis of their hemodynamics illustrated higher baseline mean right atrial pressure (mRAP) as well as higher left sided filling pressures. While admittedly a small sample size, early mortality was associated with male gender, higher baseline creatinine, higher mRAP, higher right ventricular end diastolic pressure (RVEDP), lower RVEF, higher left ventricle (LV) filling pressures, and unchanged post septostomy cardiac output. These trends are consistent with previously identified risk factors associated with poor outcome [7,9,22].

Aside from the aforementioned three mortalities due to non-procedure related causes, patients benefited hemodynamically and functionally. One year survival was 62.5%, which, while lower than the 91% predicted by the REVEAL trial calculator, is reasonable given the lack of alternative therapies for these patients [2]. As expected with successful BDAS, there were

TABLE III. Baseline Hemodynamics/Lab Values of Mortalities Within 30 Days

Mortality (patient no.)	Creatinine (mg/dL)	mRAP (mm Hg)	mPAP (mm Hg)	PCWP (mm Hg)	LVEDP (mm Hg)	PVRI (dynes sec/ cm^5/m^2)	CI ($L/min/m^2$)	Cause of death	Days post BDAS
1	1.6	27	68	14	17	2631	1.64	Bowel obstruction	13
2	3.4	25	75	16	14	2101	2.32	Septic shock	8
3	0.9	22	71	32	26	1786	2.51	Obstructive shock[a]	22
4	3.9	19	53	9	11	X[b]	X[b]	Obstructive shock[a]	1

[a]Negotiated death.
[b]Patient too unstable for cardiac output, oxygen content, and hence PVRI to be calculated.

significant increases in pulmonary capillary wedge pressure (PCWP), LVEDP, and cardiac index and a decrease in arterial oxygen saturation. Despite the patients' functional improvement, our series showed no significant improvement in either mRAP or systemic oxygen transport. These hemodynamic findings did not appear to correlate to the clinical response observed in patients or the increased cardiac index. Importantly, there were no immediate mortalities or complications associated with the procedure. This lower periprocedural mortality appears consistent with more recent data showing BDAS is a relatively safe procedure when performed in an experienced center on appropriately selected patients [12,23]. In our series, BDAS was performed by highly experienced operators typically under ICE guidance allowing greater control of shunt size and avoidance of atrial wall puncture. A high degree of transseptal experience and imaging guidance may help explain the low rate of periprocedural mortality and morbidity in our series.

Five of the 16 patients required repeat procedures due to shunt closure. This was more frequent than the previously described rate of closure between 6 and 17% [24]. Patients were chosen for revision based on clinical decline, echocardiographic evidence of a decrease in shunt, and decreased arterial oxygen saturation when performing an arterial blood gas on 100% inhaled oxygen (i.e., shunt study). Since risk is incurred with each repeat procedure, it is potentially beneficial to employ methods to prevent septostomy closure. Multiple institutions, including our own, are investigating the prospect of septostomy stenting or fenestrated septal occluders to maintain patency [25,26]. Six of our patients underwent transseptal stent placement with no periprocedural complications noted and, as of yet, no need for repeat procedures (Fig. 2).

CONCLUSION

While previous studies have included patients on prostanoid therapy, there is currently no literature specifically analyzing this expanding group of PH patients [9,24,27]. Our series shows BDAS appears to be a promising therapy for select PH patients who have symptomatic progression despite prostanoid therapy, offering symptomatic relief and a trend toward improved survival. As PH becomes more of a chronic illness, larger, prospective studies would be of benefit to readdress the role of BDAS in current treatment algorithms. As Allcock et al. described, randomized controlled trials pose a challenge, as it might be unethical to withhold transplantation to truly assess the mortality benefits of BDAS [27]. Given the documented trend toward improved mortality in properly selected patients and decreased periprocedural risk, BDAS may be of benefit earlier in the disease course [5,6,23,24]. While this case series is small and data are uncontrolled, it reminds us that despite advances in treating PH, septostomy in experienced hands is a viable treatment option in selected patients.

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AUTHOR CONTRIBUTIONS

Dr. Brooks Kuhn participated in study design, data collection, statistical analysis, and interpretation. Dr. Kuhn is a guarantor of the validity of this study. Dr. Usman Javed participated in study design, data collection, statistical analysis, and interpretation. Dr. Ehrin J. Armstrong

participated in study design, data collection, statistical analysis, and interpretation. Dr. Gagan D Singh participated in data collection, statistical analysis, and interpretation. Dr. Charles J. Whitcomb participated in study design and interpretation. Dr. Roblee P. Allen participated in study design and interpretation. Dr. Jason H. Rogers participated in study design, data collection, statistical analysis, and interpretation, as well as serving as primary investigator. Dr. Rogers is a guarantor of the validity of this study.

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