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"Treat-to-close": Non-repairable ASD-PAH in the adult☆ Results from the North American ASD-PAH (NAAP) Multicenter Registry

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ABSTRACT

Background: Adults presenting with an unrepaired atrial septal defect and pulmonary arterial hypertension (ASD-PAH) are typically classified as "correctable" or "non-correctable". The use of directed PAH medical therapy in non-correctable ASD-PAH leading to favorable closure candidacy, repair status and long-term follow-up is not well studied. We therefore sought to characterize response to PAH targeted therapy in 'non-correctable' ASD-PAH.

Methods and results: Nine North American tertiary care centers submitted retrospective data from adults with unrepaired ASD-PAH that did not meet recommendations for repair at initial presentation (1996–2017). Sixty-nine patients (women 51(74%), 40 ± 15 years, mean pulmonary artery pressure (mPA) 51 ± 13 mm Hg, pulmonary vascular resistance (PVR) 8.7 ± 4.9 Wood units, Qp:Qs 1.6 ± 0.4) were enrolled. All patients were prescribed PAH targeted therapy and late shunt repair occurred in 19(28%) (Women 15(29%) vs. Men 4(22%), $p = 0.6$). At late follow-up (4.4 ± 2.9 years) 6-minute walk test distance (6MWTD) was significantly better in the group that underwent repair (486 ± 89 m vs. 375 ± 139 m, $p < 0.05$). Transthoracic echo showed significant improvement in right ventricular (RV) function (severe dysfunction in repaired 8(40%) vs. unrepaired groups 35(69%), $p < 0.05$). Divergent survival curves suggest that with larger studies and more follow-up, differences in survival between repaired and unrepaired groups may be important. (repaired: 17(94%) vs. unrepaired: 32(81%), $p = 0.18$).

Conclusions: This is the first and largest multicenter study evaluating the "treat-to-close" approach in non-correctable ASD-PAH. Our new data supports further study of this strategy in patients who have reversibility of PAH in response to targeted therapy. We demonstrate that in the carefully selected patient with non-correctable ASD-PAH, successful shunt repair is possible if post-therapy PVR is ≤6.5 Wood units. Patients who underwent repair had improved RV function following PAH targeted therapy. Divergent survival curves suggest that with further study, defect repair may affect medium-term to late survival.

1. Introduction

Scientific understanding and treatment of pulmonary arterial hypertension (PAH) in the 21st century has rapidly evolved with recent advances in disease-targeted therapies including: phosphodiesterase type 5 inhibitors (PDE5i), endothelin receptor antagonists (ERA), soluble guanylate cyclase inhibitors (sGC) and/or prostacyclins (PC). Studies have found that these therapies improve exercise capacity and quality of life in unrepaired congenital heart disease (CHD) patients (CHD-PAH). Medical therapy has also been associated with improved CHD-PAH survival in observational studies; however, their role in patients failing to meet criteria for repair is unknown.

Pulmonary arterial hypertension, due to pulmonary vascular histopathologic changes, has been reported in 6–35% of patients with an unrepaired ASD [1–4] and has been associated with increased mortality, atrial tachyarrhythmia and functional limitations [5]. Preoperative PAH

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is also a predictor of worse outcome following repair, with increased mortality, arrhythmia and heart failure [3,6,7]. In patients with an unrepaired ASD, previous studies have demonstrated that transcatheter or surgical repair/closure for patients with PAH may be safe and effective only if PAH is mild or appears reversible on hemodynamic catheterization before repair [8,9]. However, an appropriate and consensus guided therapeutic strategy in patients with ASD-PAH remains controversial, particularly in patients requiring PAH-specific medications. Both the United States [10,11] and European guidelines [12] utilize a diagnostic classification in which ASD-PAH patients are classified as "correctable" or "non-correctable" shunts (synonymous with "non-repairable"). The "non-correctable" cohort (so-called Type 2 CHD-PAH; PAH with prevalent systemic-to-pulmonary shunts [12]), characterized by a sizeable ASD and significantly elevated pulmonary vascular resistance (PVR) without Eisenmenger syndrome (ES) is of increasing interest, and has led to controversy regarding treatment strategies. Specifically, the use of PAH targeted therapy to achieve operability criteria in Type 2 CHD-PAH patients with an ASD, allowing for surgical or percutaneous repair, known as the 'treat-to-close' model, is not well studied. Moreover, medium and long-term outcome data are lacking in ASD-PAH patients who receive PAH-targeted therapy and undergo late defect repair.

We sought to identify adults in North America that presented with an unrepaired ASD and PAH who were deemed "non-correctable" at presentation. The primary goal of the registry was to evaluate the cohort's response to PAH-targeted therapy, and repair if applicable (i.e. "treat-to-close" strategy).

2. Methods

2.1. Study design and data collection

Nine North American tertiary care centers submitted retrospective cases (1996–2017). Patients ≥18 years of age with an unrepaired ASD and PAH were rigorously screened and included in the dataset if they met inclusion criteria: (PAH initiated on medical therapy, unrepaired ASD, available echo/walk test/hemodynamic cath data at baseline and at ≥6 months after initiation of PAH-therapy) (Supplementary material online, *Table S1*). All patients were evaluated locally including assessment of functional class, echocardiography and invasive hemodynamic right heart catheterization. Patients with significant PAH that were deemed "non-correctable" according to the most reasonable published data at the time of presentation [11–13], and initiated on PAH-targeted therapy were included. In general, the data available that spanned the study timeframe suggests that a PVR >4.6–7 Wood units would be considered high-risk and therefore, a "non-correctable" defect. The decision about correctability based upon PVR at presentation varied throughout the study and was made individually at each center by institutional experts (On average PVR was <6.4 Wood units for the repair group in this cohort, consistent with evidence-based recommendations during the study timespan) (Supplementary material online, *Table S2*) [11,13,14]. Data was collected at 4 time points: i) *Baseline*, ii) *Time point 1*, iii) *Time point 2* and iv) *Final follow-up*, which was conducted in the last year of data collection (2017) and included only survival status (alive, dead, and lost to follow-up) (Fig. 1).

Determination of repair candidacy was made individually at each site based upon clinical presentation and evaluation. In all centers, the institutional experts on PAH were involved in the coordinated care of patients including decisions regarding initiation and type of PAH-targeted therapy offered. Assessment and care followed current guideline recommendations to stratify the subtype of CHD and PAH, identifying those in with Type-2 CHD-PAH which require classification as "Correctable" or "Non-correctable" [11,14,15]. The study was in compliance with the Declaration of Helsinki, and ethical implications were reviewed and approved by the institutional review board at each participating site.

2.2. Statistical methods

Results are expressed as mean ± SD or frequency (%) as appropriate. Descriptive data and characteristics were generated. Subjects who went on to have late ASD repair were compared to those that remained unrepaired. Shapiro-Wilks criteria were used to examine data for normality; non-normally distributed data was log-transformed before statistical analyses were performed. Differences between subjects that had repair and those that remained unrepaired were analyzed using the Student *t*-test for continuous normally distributed variables, and the Wilcoxon rank sum test was used for continuous non-normally distributed variables. Categorical variables were analyzed with Chi-square or Fisher's exact test. For survival analysis, the date of presentation was considered to be the date of diagnosis and the cutoff follow-up date was December 2017. The Kaplan-Meier method was used to estimate survival and curve comparisons were made using the Wilcoxon logrank test (censoring in treatment groups was the same). For all parameters analyzed, significance was defined at an α-level of <0.05. The data were analyzed using JMP® Pro, Version 12.2.0. SAS Institute Inc., Cary, NC, 2015.

3. Results

3.1. Baseline characteristics, defect subtype and medical therapy

There were 69 patients (8 ± 5 per center) enrolled in the study (Women 51(74%), 40 ± 15 years, mPA 51 ± 13 mm Hg, PVR 8.7 ± 4.9, Qp:Qs 1.6 ± 0.4). Secundum ASD was the most common subtype in 53(76%) patients followed by superior sinus venosus in 15(22%) and an ostium primum defect in 1(2%). Partial anomalous pulmonary venous return (PAPVR) was present in 16(24%) patients. After treatment with PAH specific medical therapy, 19(28%) patients underwent late ASD repair (secundum 13(25%), superior sinus venosus 5(33%), ostium primum 1(100%) (Supplementary material online, *Fig. S1*). Both men and women underwent similar rates of ASD repair (women 15(29%) vs. men 4(22%), $p = 0.56$). Baseline characteristics of all patients are reported in Table 1. Nearly all patients received PAH specific medical therapy 67(99%); one patient was prescribed, but refused therapy (Supplementary material online, *Fig. S2A*). The majority of patients received a 2-drug PAH treatment regimen: (1-drug 17(25%), 2-drug 34 (51%), 3-drug 16(23%)). Of patients whom received a 2-drug regimen, there was no difference in late repair rate (late repair: 11(61%) vs. unrepaired: 23(48%), χ^2 0.91, $p = 0.34$) (Supplementary material online, *Fig. S2B,C*). In the repaired group, 18 of 19 patients (95%) continued to receive medical therapy post-repair for an average of 7 ± 3 years, with 15(79%) on at least 1 medication at most recent follow-up.

3.2. Functional parameters

At *baseline* there was no difference in subjective exercise tolerance, objective functional capacity or resting and nadir oxygen saturation during the 6-minute walk test (6MWT) (Fig. 2). At *Time point 1* (1.8 ± 2.1 years) patients who ultimately underwent ASD repair demonstrated statistically insignificant increased distance achieved on 6MWT (437 ± 98 m vs. 371 ± 117 m, $p = 0.15$) (Fig. 2A). However, to better understand whether post-PAH therapy walk test distance may be associated, and potentially predictive of repair candidacy after therapy, we identified patients that achieved a walk distance ≥300 m, given that this value has previously been felt to identify those with a poor prognosis [12,16]. Using a pairwise comparison we found that 100% of patients that underwent late repair had a 6MWTD > 300 m at *Timepoint 1*, vs. 74% who walked >300 m in the unrepaired group at *Timepoint 1* ($p = 0.05$) (Fig. 2,B). At *Time point 2* (4.4 ± 2.9 years) 6MWT distance continued to improve and was significantly better in the group that underwent repair (486 ± 89 m vs. 375 ± 139 m, $p < 0.05$). Resting oxygen saturation was significantly better at both *Time point 1* and *Time point 2* in patients who underwent ASD repair and nadir oxygenation was higher in the repaired group at *Time point 2* (Fig. 2B,C).

3.3. Imaging and hemodynamic data

Transthoracic echocardiogram (TTE) was used to evaluate heart structure and function, with no significant differences at baseline between the group that underwent late repair and those that remained unrepaired (Supplementary material online, *Table S3*). There were 51 patients with a TTE at *Time point 1* (1.8 ± 1.5 years) and 53 with a TTE at *Time point 2* (5.0 ± 3.3 years). There was no significant difference in atrial volume, RVSP, or PA diameter at *Time point 1*, however there was a trend toward RV systolic dysfunction in the unrepaired group (≥Moderate RV dysfunction 32(72%) vs. 8(50%), $p = 0.13$) (Supplementary material online, *Table S3*, Fig. 3F). At *Time point 2* there was significant improvement in RV size and function in patients who underwent repair (Fig. 3E,F). Right atrial size and RVSP also

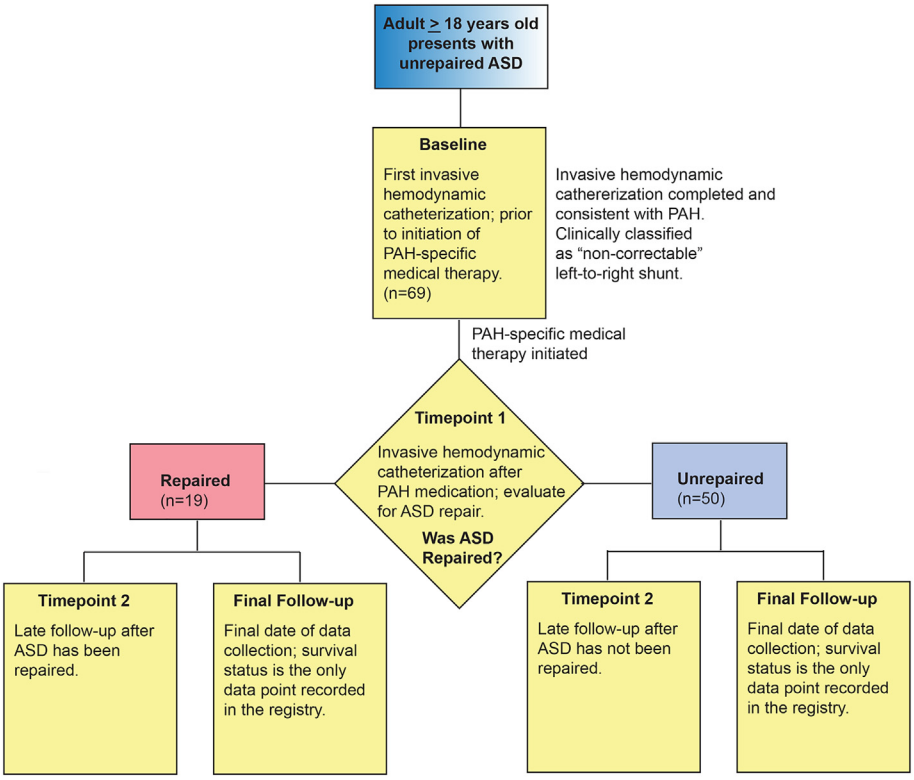

Fig. 1. Study design. Subjects enrolled were assessed at 4 time intervals: *Baseline* - at time of presentation when they underwent first hemodynamic catheterization diagnosing PAH, *Time point 1* - the first follow-up after initiation of medical therapy, which included repeat hemodynamic catheterization while the patient was on PAH medications and repairable shunts were not yet closed; if appropriate shunt was closed at this time, *Time point 2* - late follow-up after repairable defects were closed and non-repairable defects remained unrepaired, and at *Final follow-up*, during the final year of registry collection (2017).

regressed in the repair group, and at *Time point 2* none of these patients had severe TR (versus unrepaired group 7(18%), $p = 0.08$) (Supplementary material online, *Table S3*).

Baseline hemodynamic data was also not different between patients with unrepaired ASD-PAH and those that underwent repair, except a greater net left-to-right shunt at baseline (Qp:Qs 2.2 ± 1.5 vs. 1.3 ± 0.4, $p < 0.05$) in the late repair group. At *Time point 1* (2.0 ± 2.6 years) patients who ultimately underwent late repair had a trend suggesting lower PVR (6.4 ± 5.0 vs. 8.2 ± 4.4 Wood Units, p = 0.08), however there were no significant differences in mPA pressures or cardiac output at *Time point 1* or *Time point 2* (Fig. 3 and Supplementary online material Fig. S3).

Table 1
Baseline characteristics.

Characteristic (mean ± SD, or frequency (%))	Total population (n = 69)	Treat ➔ close (n = 19)	Treat ➔ unrepaired (n = 50)	p Value
Age (years)	40 ± 15	37 + 23	41 + 23	0.17
Female (n, %)	51(74)	15(79)	36(72)	0.76
BMI (kg/m^2)	26.3 ± 7.4	25.2 ± 6.4	26.4 ± 7.6	0.90
Baseline hemoglobin (g/dL)	14.8 ± 2.45	14.2 ± 1.7	15.1 ± 2.7	0.21
Tobacco use, current or past	30(43)	9(47)	21(42)	0.93
Atrial arrhythmia	16(23)	4(21)	12(25)	0.99
Diabetes	6(9)	1(5)	5(10)	0.99
CAD	6(9)	1(5)	5(10)	0.99
HTN	18(26)	5(26)	13(26)	0.99
NYHA functional class 3 or 4	38(55)	10(53)	28(50)	0.96
6MWT distance (meters)	354 ± 125	366 ± 137	348 ± 122	0.69
6MWT 02 Nadir	85 ± 8	86 ± 7	85 ± 9	0.93
RVSP (via TR velocity) (mm Hg)	74 ± 19	77 ± 19	74 ± 19	0.70
PA diameter (mm)	36 ± 8	35 ± 11	36 ± 6	0.18
Mean PA pressure (mm Hg)	51 ± 13	48 ± 13	52 ± 13	0.46
PCWP (mm Hg)	10 ± 6	8 ± 5	11 ± 6	0.15
PVR (Wood units)	8.7 ± 4.9	7.5 ± 4.3	9.3 ± 5.0	0.19
Qp:Qs	1.6 ± 0.4	2.2 ± 1.5	1.3 ± 0.4	<0.01

BMI: body mass index, CAD: coronary artery disease, HTN: hypertension, NYHA: New York Heart Association, PA: pulmonary artery, PCWP: pulmonary capillary wedge pressure, PVR: pulmonary vascular resistance, Qp:Qs: Flow pulmonary to flow systemic, RV: right ventricle, RVSP: right ventricular systolic pressure, SD: standard deviation, TAPSE: tricuspid annular plane systolic excursion, 6MWT: 6-minute walk test.

3.4. Late follow-up and survival

Final follow-up (7.2 ± 3.7 years) data was available in 66 patients (Unrepaired $n = 48$, Closed $n = 18$). The longest follow-up in the closed group was 17 years and in the unrepaired group was 18 years. At this *final follow-up* there was no statistical difference in survival (17(94%) vs. 32(81%), $p = 0.18$), however the survival curves appear to diverge, suggesting that with increased enrollment, ASD repair may be associated with improved survival. (Fig. 3H).

4. Discussion

In the last decade there have been several case reports and small studies describing outcomes and late shunt repair in 'non-correctable' ASD-PAH patients treated with targeted PAH therapy. This data suggests that PAH therapies may permit safe repair in patients not meeting traditional criteria [17]. This begs the question we tried to answer with this study: "Are some of these patients' reasonable candidates for repair after PAH specific therapy, and if so, does repair make a difference in long-term prognosis and/or survival?". Unfortunately, this is an extremely difficult population to study for several reasons: 1) relative numbers at individual centers are small, 2) regionally the clinical approach is heterogenous and 3) prospective studies would take too long to achieve actionable results that would apply to patients who need decisions made in real-time. For these and other reasons, large-scale studies evaluating a "treat-to-close" approach and medium to long-term follow-up has not been available, and guidelines support

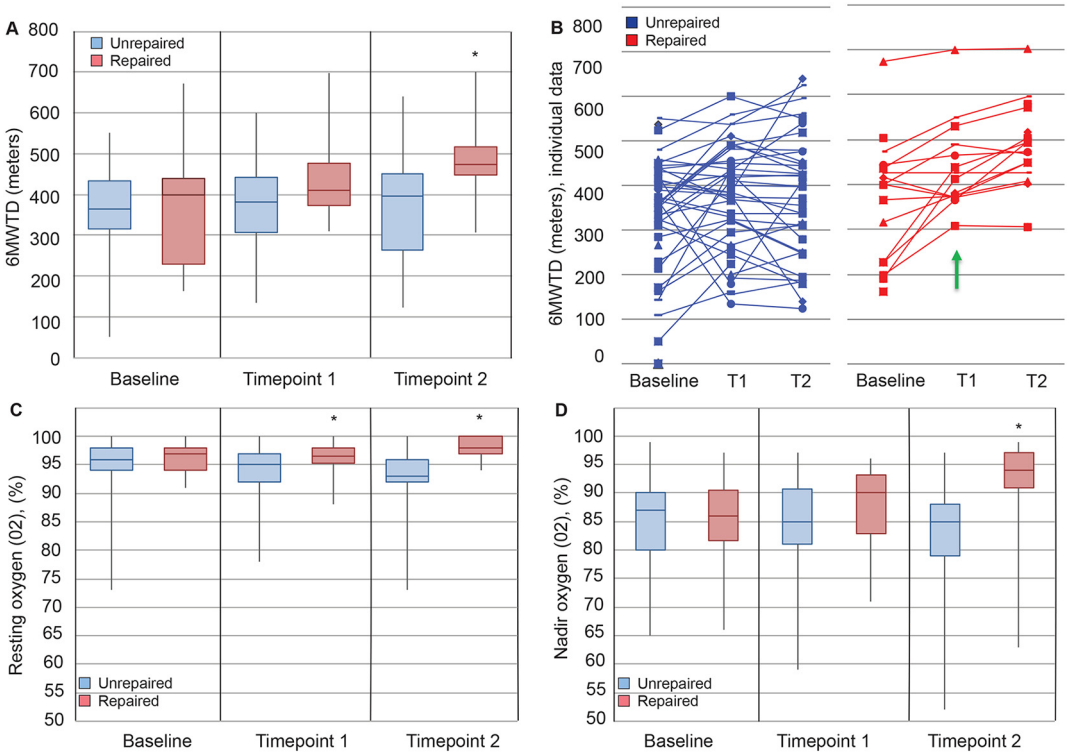

Fig. 2. Functional assessment. 6-minute walk test results including walk distance (A). Individual patient walk test distance at the first reassessment (*Time point 1*) after PAH medical therapy was initiated (but before ASD repair) shows that patients who later underwent ASD repair were all able to walk ≥300 m (B). Oxygen saturation/nadir (C,D) are shown with exercise at *Baseline*, after PAH medical therapy when assessing (prior to) ASD repair candidacy if appropriate (*Timepoint 1*) and at most recent follow-up (*Timepoint 2*). Insignificant trend in nadir oxygenation at *Time point 1* (C, $p = 0.18$). Walk distance and nadir oxygen saturation were both improved at *Time point 2* (C,D, $p < 0.05$).

that "defect correction ('treat-to-close' concept) is not supported by available data" [12].

Our study provides new data that would support consideration of a treat-to-close strategy in select patients who have a sizeable left-to-right or bidirectional shunt with elevated PVR and significant improvement in hemodynamic parameters following PAH targeted therapy. More specifically, 6MWTD > 300 m and PVR <6.4 Wood units after PAH therapy at *Timepoint 1*, may be important markers of patients that are safe to consider for late repair. In the carefully selected patient undergoing ASD repair, we have shown improved RV function and divergent curves suggesting that in larger populations, survival benefit may be important. Patient selection for a potential 'treat-to-close' approach should, in part take into consideration several parameters after initiation of medical therapy including: 6MWT distance, oxygen saturation, invasive hemodynamics, RV size and RV function. We propose that ideal candidates for this approach should be reassessed after initiation of PAH targeted therapy, to see if they meet favorable repair criteria.

4.1. Mortality paradox and the right ventricle

Morbidity and mortality in the ASD patient are strongly linked to the presence and severity of PAH. However, there are no known predictors for the development of PAH in patients with an ASD if left unrepaired or following repair. Furthermore, there is a paucity of data that reliably describes the evolution of pulmonary pressures post-repair, either with or without upstream directed medical therapies for PAH. Specialists in CHD and/or pulmonary hypertension have long known that PAH in patients with atrial level shunt mimics IPAH and carries a prognosis worse than other shunt-related Eisenmenger's syndrome [18]. As a result, many clinicians have supported that ASD repair should not be performed if significant PAH persists despite medical therapy [19,20].

The so-called 'mortality paradox' in ASD-PAH (versus Eisenmenger's) is felt in part, to reflect the poor ability of the RV to compensate for high pulmonary pressures (i.e. retain normal function). In the CHD patient with PAH, even small reductions in RV systolic function are associated with adverse outcomes, yet in most cases therapy often only modestly improves RV function [21]. Right heart function is known to be highly associated with survival in PAH, and our results support this [22,23–25]. It should be clarified that these were volume overloaded RVs in the presence of significant left-to-right shunting on PAH therapy (mean Qp:Qs 2.2:1). Therefore, it is not surprising that removal of the volume overload by ASD repair results in positive RV remodeling and improvement in RV function.

Although the exact pathogenesis of PAH in patients with an ASD is not clearly defined, it has been postulated that increased pulmonary flow (Qp) leads to endothelial damage with resultant leukocyte activation and release of mediators, ultimately causing vasoconstriction and vascular hypertrophy [26]. This may lead to a maladaptive response of the RV in patients with unrepaired ASD-PAH that resembles IPAH, characterized by dilation and progressive RV systolic dysfunction [9,17]. In these patients, the increased pulmonary flow is determined by the size of the ASD and the difference in compliance between the right and left ventricles [17,27]. Therefore in patients with ASD-PAH, right ventricular enlargement and RV dysfunction can be expected, and use of PAH specific medical therapies to reduce PVR allowing potentially some degree of reverse remodeling and successful repair of the "non-correctable" patient, may lead to improved RV size and function by unloading RV volume. Therefore, a two-stage approach in which PVR is lowered first with resultant increase in Qp:Qs and increased RV volume, is followed by ASD repair with cessation of shunting and resolution of the RV volume overload. It is likely imperative to continue PAH targeted therapy given the presence of some degree of pulmonary vascular remodeling in this population.

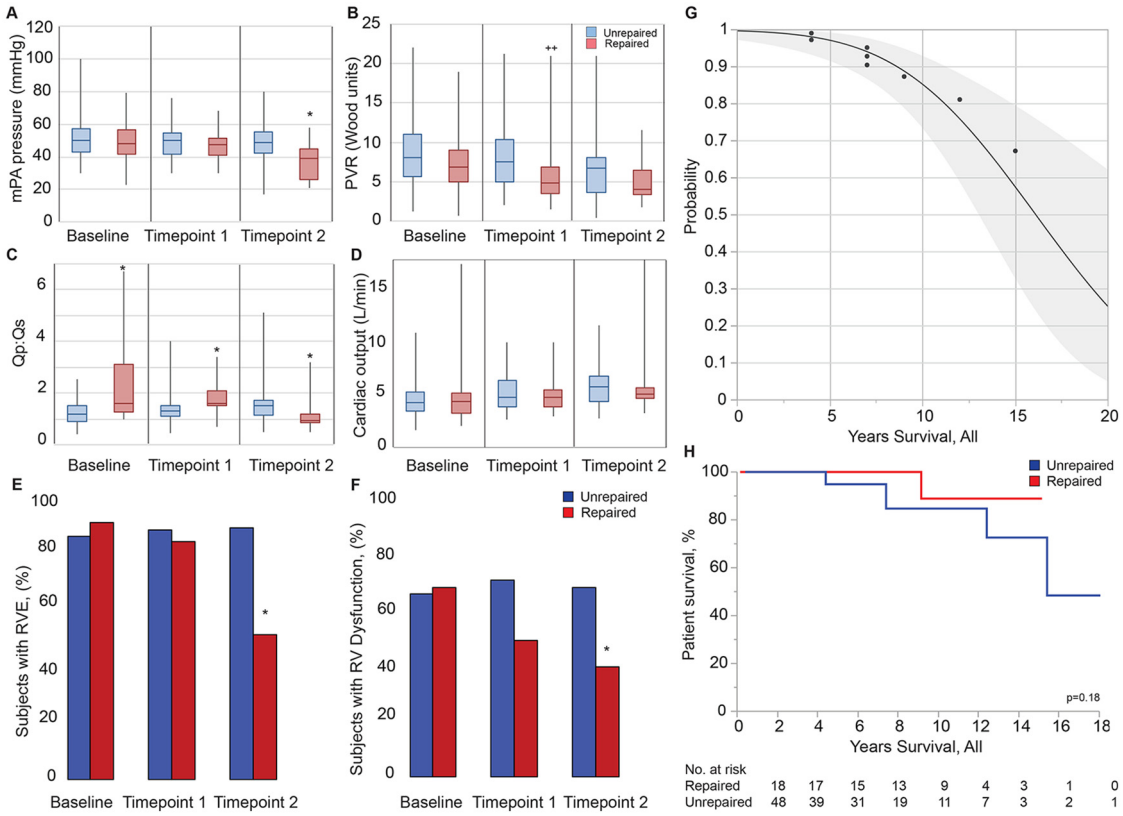

Fig. 3. Hemodynamics, Right heart size/function and survival in closed and unrepaired ASD-PAH. Hemodynamic cath was performed at *Baseline* ($n = 69$), *Time point 1* (n = 69) and *Time point 2* ($n = 50$). There was significant change in late (*Timepoint 2*) mPA pressure (A) and a trend toward reduced PVR at *Time point 1* ($p = 0.08$) in patients who ultimately underwent ASD closure after PAH therapy (B). Not surprisingly, Qp:Qs (B), was different at each timepoint reflecting that shunts which were eventually repaired tended to be in patients with increasing left-to-right direction (C). Right ventricular enlargement (RVE) was similar at baseline in both closed/unrepaired groups, however size regressed more in the late repair group (E). Reduction in RV size was seen only at late follow-up (*Timepoint 2*) in patients who underwent ASD repair (E). RV dysfunction was also improved at *Timepoint 2*, and although it did not reach statistical significance at *Timepoint 1*, it appears there may be important differences after medical therapy and before ASD repair ($p = 0.13$) (F). There was *Final follow-up* data for 63 of the 69 patients. On average this occurred 7.2 ± 3.4 years after presentation. Overall, adults presenting with ASD-PAH have impaired survival, with only half alive at 15 years of follow-up (G). However, divergent survival curves between repaired and unrepaired subjects suggest that perhaps survival is more favorable in ASD-PAH patients that undergo repair, however further studies with continued enrollment are required to determine if this is a statistically significant finding (H). (*p < 0.05, ǂp = 0.13, ++p = 0.08).

4.2. Functional capacity

The 6MWT has been commonly used as a surrogate to exercise stress testing in PAH and therefore to assist in determining the effectiveness of PAH therapy on functional class and quality of life [28,29]. The 6WMT continues to be the basis for regulatory approval of all currently available medical therapies for PAH in the U.S. In our study, walk test distance was significantly higher in the group that ultimately underwent ASD repair, and we identified that a walk distance of 300 m may be an important cut-off in predicting which patients on PAH targeted therapy can safely move toward a treat-to-close management strategy and potentially achieve a better outcome. In prior studies, a walk distance of 380 m was found to be an important marker of survival, and therefore may be an important point to consider when determining treatment strategy, and ultimately survival [30].

4.3. Directed therapy in ASD-PAH

Survival into adulthood with CHD is no longer rare but expected, including patients with unrepaired intracardiac shunts including ASD-PAH [31]. As this population ages it is important to evaluate and treat sequelae such as PAH. There is a growing body of evidence supporting the use of PAH directed medical therapy in patients with Eisenmenger Syndrome [32]; however, there are less specific data on the "non-correctable" ASD-PAH patient. In our cohort we found no difference in the prescribing pattern of single, 2-drug, or 3-drug therapy regimens in this group of patients, more specifically related to late repair status. PDE5i and ERAs were the most common medications prescribed followed by prostacylins. Centers submitting early data to the registry were done at a time when there was only 1 medication approved for the treatment of PAH, making it difficult to determine whether or not multi-drug therapy regimens are more beneficial. However, there are numerous studies on combination therapy in other PAH populations, which generally favor this practice [33]. In the current era, where there are several PAH medication options, this cohort demonstrated no difference in therapy among those that were left unrepaired or those that were closed. This highlights that *any* PAH directed treatment, and not necessarily a specific PAH regimen, can favorably lower PVR for patients with Type 2 CHD-PAH due to an atrial level shunt. We identified 6MWT distance, oxygen saturations and RV size/function as potentially important clinical features that with further study may be markers of a patient that can safely undergo and benefit from repair after PAH therapy. Furthermore, our new data show that using PAH directed therapy in the 'non-correctable' ASD-PAH patient to achieve a hemodynamically safe repair of the shunt, is beneficial to the right heart and may contribute to improved survival. This is particularly true in patients that respond to PAH directed therapy with a reduction in PVR and increased left-to-right shunting.

4.4. Limitations

Our study is retrospective, and therefore subject to lack of uniform medical management, which could influence the evolution

of PAH, and outcomes in 'non-correctable' ASD-PAH patients. As with any multi-center study, the results are influenced by local practice including: time to initiation of therapy, follow-up testing, evaluation and reassessment time-points as well as therapy decisions. Given the span of time over which this study occurred with respect to the availability of PAH targeted therapy, it is reasonable to consider that immortal time bias may have affected when therapy was initiated, and therefore survival. Although the data were collected across 9 large North American tertiary care centers, the relative number of patients still remains small. Large registry data and collaboration are required to better determine the applicability of these findings in a prospective cohort.

5. Conclusions

This is the first multi-center study evaluating the "treat-to-close" approach in adults with 'non-correctable' ASD-PAH. The majority of patients received ≥1 PAH specific medication and approximately 1/3 went on to have successful late repair. Following ASD repair, patients had less subsequent RV enlargement and were less likely to have significant late RV systolic dysfunction. Objective markers of exercise tolerance, including the 6MWT and oxygen saturation were useful in determining the response to PAH medical therapy. This retrospective data is limited in that it cannot implicate that repaired status caused improvement in the right heart, however given that there was a trend toward improved survival in the closed ASD-PAH cohort, the data suggests that an association between the two exists. In the context of prior data linking right heart function to survival in PAH, we believe that further studies will show that ASD repair in appropriately selected 'non-correctable' ASD-PAH patient, can have an impact on long-term outcome. The decision to proceed with repair is often complex and should be individualized and made after a comprehensive multidisciplinary evaluation. We believe that our study provides new insight that would support, at minimum, consideration of a treat-to-close strategy in the carefully selected "non-correctable" ASD-PAH patient who has responded well to targeted PAH therapy. However, further large-scale prospective studies on this strategy are needed.

Disclosures

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Appendix A. Supplementary data

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