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Effect of Atrial Septostomy on the Survival of Patients with Severe Pulmonary Arterial Hypertension

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ABSTRACT

Objective: Atrial septostomy (AS) is a palliative treatment for right ventricular failure from severe pulmonary arterial hypertension (PAH). We sought to investigate the effect of AS, alone or combined with PAH-specific pharmacotherapy, on the survival of patients with PAH.

Methods: We performed a retrospective analysis of the functional and hemodynamic changes in patients with PAH following AS and of long-term survival characteristics for the whole group and separately for the subgroup who received post-procedural pharmacotherapy.

Results: Fifty procedures performed in 34 patients (age: 35 ± 10 years) resulted in hemodynamic and symptomatic improvement in most. Only one procedure-related death occurred (2%). Due to spontaneous closure of the defect, AS was repeated in 10 patients. In 21 patients, AS was the only form of treatment while eleven received additional pharmacotherapy after AS. During follow-up (mean 58.5 ± 38 months) 21 patients died; median survival of the group was 60 months (95%CI, 43 to 77). Median survival for patients on pharmacotherapy additional to AS was 83 months (95%CI, 57 to 109) which is better than that for patients with AS alone [53 months (95%CI, 39 to 67); log-rank, 6.52; p=0.010].

Conclusions: In selected patients with PAH, AS is a safe and effective intervention that exerts a beneficial impact on long-term survival. The survival appears to be improved when AS is combined with PAH-specific pharmacotherapy.

Key words: atrial septostomy, pulmonary hypertension, survival

INTRODUCTION

Atrial septostomy (AS) represents an additional strategy for the treatment of right ventricular failure (RVF) from severe pulmonary arterial hypertension (PAH) [1]. Several reasons still justify its use: 1) the deleterious impact of RVF on patient survival [2, 3], 2) the unpredictable response to medical treatment, 3) the disparity in the availability of these treatments throughout the world, and the limited access to lung transplantation [4].

Little information exists regarding the long-term impact of AS on the survival of PAH patients [5-7]. In most of the reported series [5, 7-11], the procedure was performed *after* all available medical therapy failed, late in the course of the disease, when the risk of procedural death is increased and the impact of the intervention on long-term survival is minimized. We describe the effect of AS on the survival of a group of patients with PAH in whom the procedure was performed either as an isolated treatment intervention or *prior* to the use of PAH-specific pharmacologic therapy.

METHODS

Patient population. Between January 1995 and November 2006 we performed fifty AS procedures in 34 patients with PAH, including fifteen previously reported [12]. All patients underwent thorough diagnostic workup that included: history and physical exam; hematology, chemistry, and coagulation studies; pulmonary and liver function tests; chest X-ray and CT scan evaluation; echocardiography, and right heart catheterization. The diagnosis of PAH was established by exclusion of secondary causes of pulmonary hypertension and demonstration of a mean pulmonary artery pressure (PAP) > 25 mmHg at rest, and a pulmonary capillary wedge pressure (PCWP) < 15 mmHg [13].

Procedure. Atrial septostomy for the treatment of PAH has been approved by our institutional ethics committee. Written consent is obtained after an unbiased presentation of the palliative nature of the procedure, its risks, and expected outcome is presented to each patient.

Our technique for balloon dilation AS has been reported elsewhere [12, 14]. Briefly, baseline right and left heart pressures are simultaneously recorded and cardiac output is calculated (Fick method). Following trans-septal puncture using standard technique, the septostomy orifice is balloon-dilated in a carefully graded step-by-step approach, beginning at a diameter of 4 mm and followed by 8, 12, and 16 mm. dilatations. Between each step, and after a 3 minute waiting period allowed for stability, left ventricular end-diastolic pressure (LVEDP) recordings and arterial oxygen saturation (SaO_2%) determinations are obtained. The final size of the defect is individualized in each patient and corresponds to when any of the following first occurs: (1) an LVEDP rise > 18 mmHg, (2) a SaO_2 % reduction near to 80% or (3) a 10 percent SaO_2% drop from baseline.

Follow-up of the patients is done in intensive care area for the first 48 hours where continuous supplementary oxygen is administrated. All patients are followed at our outpatient clinic with particular care to maintain correct oral anticoagulation and appropriate hemoglobin levels. PAH-specific pharmacologic treatment for some of the patients was dictated by the availability of these drugs at our center. Long-term follow up information was obtained during outpatient hospital visits or by telephone calls to the patients or their relatives. In case of death, all efforts were done to establish its cause.

Data analysis. We analyzed the clinical, functional, and hemodynamic variables before and after the procedure. We also analyzed the long-term survival characteristics for the whole group and separately in the subgroup of patients who received PAH-specific pharmacologic treatment *after* the procedure. The Kaplan-Meier method was used to

estimate overall survival distribution. The date of the first AS was used as the index from which to determine survival. Differences in survival curves for patients with and without concomitant pharmacologic treatment were tested by the log-rank procedure. Univariate analysis based on the Cox proportional hazards model was used to examine the relation between survival and selected demographic, medical history, laboratory, and hemodynamic variables. Results are expressed as hazard ratios with 95% confidence intervals (CIs). For all other analysis we used paired and unpaired t test. Results are expressed as mean value ± 1SD. A p value < 0.05 was considered as significant in all comparative analysis. Analyses were performed with the SPSS package for Windows 10.0.

RESULTS

Patients. Most patients are female (85%), with a mean age of 35 ± 10 years (range: 22 – 62). Etiologic diagnoses included idiopathic PAH in 29 (85%), distal (non-operable) chronic thromboembolic pulmonary hypertension in 3 (9%), PAH-associated to lupus in one case (3%), and PAH associated to previously corrected ventricular septal defect in another (3%). All patients had severe pulmonary hypertension, with a three-fold increase in mean PAP (70 ± 14 mmHg), a normal PCWP (8 ± 5 mmHg), and variable degrees of right heart failure (RHF) as reflected by a cardiac index of 2.32 ± 0.8 L min/m^2, and an increased right atrial pressure (RAP) of 12 ± 5.5 mmHg.

Most patients had severe functional limitation. World Health Organization (WHO) functional class of the group was 3.5 ± 0.6; 18 patients (53%) were in functional class IV; 14 (41%) were in class III, and 2 (6%) in class II. Exercise endurance, as assessed by the six-minute walk test (6MWT), was 100 ± 114 m (range = 0 – 380). During diagnostic right heart catheterization, none of these patients had responded to acute vasodilator challenge.

The symptomatic indications for AS were: syncope in 9 patients (26%), RHF in 14 (41%) and the coexistence of both in 11 patients (32%).

Immediate outcome. One of the patients (previously reported) died 48 hours after the procedure as a result of refractory hypoxemia. Most (88%), of the 33 surviving patients had clinical improvement after AS and 4 (12%) remained unchanged. The functional and hemodynamic results before and after AS are shown in Table 1. The mean final size of the balloon used for initial septostomy was 8.5 ± 2.5 mm (range: 6 – 16). After the procedure there was a moderate but significant decrease in right ventricular end-diastolic pressure (RVEDP), a significant increase in cardiac index, and, as expected, a significant decrease in SaO_2%. WHO functional class improved and the 6MWT reassessed at 2 weeks to one month after the procedure, increased significantly following AS. The change in cardiac index correlated with the change in 6MWT ($r = 0.66$; $p < 0.017$) and the 6MWT after septostomy correlated with survival ($r = 0.58$; $p < 0.016$).

Table 1. Hemodynamic and functional variables before and after atrial septostomy

Variable	Before AS	After AS	p value
RVEDP, mmHg	14.5 ± 6	10.7 ± 5.9	0.001
LVEDP, mmHg	6.4 ± 3.4	8.8 ± 2.7	0.001
Mean PAP, mmHg	66 ± 13	61 ± 16	0.002
Cardiac Index, L.min./m2	2.26 ± 0.43	2.97 ± 0.83	0.001
SaO2 %	91.7 ± 3.8	84 ± 6.3	0.001
6MWT meters	106 ± 115	214 ± 99	0.001
WHO Functional class	3.47 ± 0.62	2.19 ± 0.54	0.001

Abbreviations: AS: Atrial septostomy; RVEDP: right ventricular end-diastolic pressure; LVEDP: left ventricular end-diastolic pressure; PAP: pulmonary artery pressure; SaO2 %: arterial oxygen saturation; 6MWT: Six-minute walk test; WHO: World Health Organization.

Except for the conventional use of diuretics, digitalis, and anticoagulants which was common to all patients, in twenty-one of the surviving patients AS was as the only form of treatment. Eleven of the patients received PAH-specific pharmacologic treatment at different time intervals after AS (mean = 18 ± 13 months); most of them (82%) within the first two years. The medications included: subcutaneous treprostinil (n = 5), Bosentan (n = 3), Sitaxsentan (n = 1), Sildenafil (n = 1), and oral treprostinil (n = 1). In one of the patients, septostomy was performed after the failure of pharmacologic treatment with sq. treprostinil, which she had received for 6 years. For the purpose of the present study, this patient was excluded from the survival analysis.

Atrial septostomy had to be repeated in 10 patients (29.4%) at different intervals due to spontaneous closure of the defect. Two patients had four septostomies, two patients had three, and six had two. Redo procedures were equally distributed between the groups with and without concomitant pharmacologic treatment. In the group of patients with pharmacological treatment, no need for repeated procedures was necessary once the specific drug treatment was initiated.

Long-term survival. Over the whole follow-up period (mean 58.5 ± 38 months; range: 3 to 138), twenty one patients (66%) died; four patients were lost to follow up at 6, 15, 37, and 74 months, and seven patients are still alive. The mean time interval from procedure to death was 56 ± 30 months (range: 3 – 110). The identified causes of death were: progression of RHF (n = 16), cerebrovascular accident (n = 2), pneumonia (n = 2), and sudden death in one patient. No postmortem studies were performed.

Mortality associated factors (Table 2). In the exploratory analysis of the potential factors associated with survival after the procedure, mortality was not associated with age, hemodynamic variables, or septostomy size. A higher functional class after AS was associated with a significant risk of death, whereas higher arterial oxygen saturation,

exercise endurance, and the use of specific pharmacologic treatment after septostomy had a protective effect against such a risk.

Lifetime cumulative survival rates for patients with idiopathic PAH (n =27) are shown in figure 1A. The median survival of the group was 60 months [95% confidence interval (CI), 41.2 to 78.7 months]. As noted, survival after septostomy is better than the 1-, 2- and 3-year survival rates of 65.2%, 52.3%, and 42.8%, respectively, as predicted by the equation developed from the National Institutes of Health PPH registry data [2, 3].

Table 2. Univariate analysis relating survival time with selected variables at baseline and after atrial septostomy in the total group

Variable	Hazard Ratio (95% CI)	p value
Age, years	1.01 (0.97 – 1.06)	0.355
Female gender	1.68 (0.50 – 5.68)	0.397
Septostomy size	0.99 (0.83 – 1.18)	0.942
RVEDP before	1.04 (0.97 – 1.11)	0.257
RVEDP after	1.01 (0.95 – 1.08)	0.634
LVEDP before	1.08 (0.94 – 1.25)	0.255
LVEDP after	1.02 (0.86 – 1.20)	0.785
Mean PAP before	1.00 (0.97 – 1.03)	0.573
Mean PAP after	0.99 (0.97 – 1.02)	0.912
Cardiac Index before	0.38 (0.08 – 1.65)	0.200
Cardiac Index after	0.90 (0.48 – 1.66)	0.741
SaO2% before	0.94 (0.82 – 1.07)	0.407
SaO2% after	0.92 (0.85 – 0.98)	0.020
6MWT before	0.98 (0.97 – 0.99)	0.031
6MWT after	0.99 (0.98 – 0.99)	0.014
SaO2% after, < 85%	2.18 (0.87 – 5.4)	0.089

WHO functional class, before	1.75 (0.84 – 3.67)	0.133
WHO functional class, after	2.68 (1.08 – 6.66)	0.033
Pharmacological treatment after	0.31 (0.12 – 0.80)	0.015

Abbreviations as in Table 1

The eleven patients that received PAH-specific pharmacologic treatment after AS were comparable to those who only had septostomy in terms of age, septostomy size, and hemodynamic values before and after the procedure (Table 3)**.** Their survival, however, was better than that for patients with AS only [median 83 months (95% CI, 57 to 109) versus 53 months (95% CI, 39 to 67); chi-square log-rank, 6.52; p = 0.01, (Figure 1B)].

Table 3. Demographic, functional, and hemodynamic characteristics of AS patients with and without concomitant pharmacologic treatment

Variable	AS + drugs (n = 11)	AS only (n = 21)	p value
Gender, female	82 %	86%	0.782
Age, years	37 ± 9	33.5 ± 10	0.339
WHO functional class, before	3.27 ± 0.65	3.57 ± 0.60	0.201
WHO functional class, after	1.91 ± 0.30	2.33 ± 0.58	0.010
6MWT, meters; before	194 ± 153	60 ± 50	0.082
6MWT, meters; after	290 ± 95	174 ± 77	0.016
Septostomy size, mm	8.0 ± 1.5	9 ± 2.8	0.202
RVEDP, mmHg; before	18 ± 6	13 ± 4	0.067
RVEDP, mmHg; after	13 ± 7	9.0 ± 4.6	0.096
LVEDP, mmHg; before	6.6 ± 3	5.9 ± 4	0.534
LVEDP, mmHg; after	10 ± 3	8.0 ± 2.5	0.071
Mean PAP, mmHg; before	67 ± 16	66 ± 12	0.856
Mean PAP, mmHg; after	63 ± 21	59 ± 12	0.618
Cardiac index, L min/m2; before	2.53 ± 0.71	2.23 ± 0.82	0.764

Cardiac index, L min/m2; after	2.75 ± 0.41	3.1 ± 0.96	0.291
SaO2 %; before	92 ± 3	91 ± 4	0.596
SaO2 %; after	86 ± 4.5	83 ± 7	0.224

Abbreviations as in Table 1

DISCUSSION

In this relatively large series of patients with PAH, the combination of atrial septostomy with PAH-specific pharmacologic therapy appeared to exert a beneficial impact on long-term survival, which is superior to that provided by the atrial septostomy alone. One possible explanation for this finding is the timing of performance of AS. In most reported series [5, 7-11], AS has been performed only *after* the failure of different PAH-specific pharmacologic interventions. In the present study patients with concomitant pharmacologic treatment had the septostomy performed *before* pharmacologic treatment was initiated. Although not statistically significant, the prevalence of WHO class IV patients was lower (36%) in the group of septostomy plus PAH-specific pharmacologic therapy as compared to that in the group with atrial septostomy alone (62%)

Immediate outcome. AS produced immediate hemodynamic and functional improvement in most of our patients with results that are comparable to those described in similar series [5, 7-11,12,15-18]. The beneficial functional effects after septostomy appear to be related to the increase in cardiac index after septostomy [8]. In our study, the increase in 6MWT was significantly related to the increase in CI after AS.

The present study also demonstrates that safety in the performance of AS is an attainable goal. Our procedure-related mortality (death that occurs during or within one month after the procedure) was only 2% (1death out of 50 procedures). Operator experience and strict adherence to WHO safety recommendations [6, 19] certainly

account for this lower procedure-related fatality rate. In this regard, balloon dilation AS with graded step -by-step protocol, is used in most of the recent series which also report a procedural mortality that appears to be decreasing with this technical approach [20]. Other factors such as the timing of the procedure may also be important. In the analysis of the collective worldwide experience with AS [6,20], and that of other reports [7, 21], a mean RAP greater than 20 mmHg, as reflection of advanced disease, has been repeatedly identified as the most significant risk factor associated with procedure-related mortality. In a recent communication, Micheletti and coworkers [16] reported no fatalities associated with the procedure in 20 children with PAH. In their series, AS was performed at a relative early stage of the disease (mean RAP before the procedure was 9 ± 5 mmHg and syncope, rather than overt RHF, was the main indication for the procedure). Likewise, in our study, a significant proportion of patients (28%) had a RVEDP lower than 10 mmHg before the procedure. Accordingly, performing AS at earlier stages of the disease may reduce the risk of death during the procedure (16).

Spontaneous closure of AS. As already described in most of the reported series, subsequent closure of the defect was a relatively frequent feature in our series. The reason for this remains unknown. In our study, there was no significant difference in age, hemodynamic profile, or septostomy size between patients with spontaneous closure and those in whom the septostomy remained open. In our study, septostomy size refers to the maximal size of the balloon used for septostomy. An echocardiography measurement of the inter-atrial orifice diameter was not obtained in all patients. Due to tissue elastic recoil, the true size of the defect should be smaller than the maximal balloon diameter used.

To solve the problem of closure, we elected to repeat septostomy as many times as necessary, and achieved this without complications. Recently, this problem has been

approached differently by other investigators. Micheletti [16] placed a custom-made fenestrated atrial septal device at the end of the procedure to maintain the septostomy open. By doing this in seven out of 20 children, the short-term spontaneous closure of the defect was successfully avoided. This approach has been followed by other investigators [22-27]. Both, a high long-term occlusion rate (25), as well as long-term patency of these devices has been reported (26, 27). At present, it is difficult to anticipate the long-term risk/ benefit of this approach.

Effect of atrial septostomy on long-term survival. Our study series provides the longest follow up of patients with atrial septostomy in the setting of PAH, and, as in other study series (5, 7, 27), AS significantly improved long-term survival in these patients. Atrial septostomy improves hemodynamic parameters that correlate with survival (cardiac index, and right ventricular filling pressures) and also improves 6MWT, another surrogate of survival in PAH, and this may explain the impact of the procedure on short-term survival. The decrease in survival after 3 to five years in our patients with septostomy alone (Figure 1B), confirms the palliative nature of this intervention [5].

To our knowledge, the present study is the first to suggest the potential benefit of combining strategies (interventional plus pharmacological) in the management of PAH. In effect, we found that the benefit of AS alone on survival was significantly increased by the concomitant addition of PAH-specific drug therapies. As shown in Figure 1B, the 3-, and 5-year survival of 100% and almost 90%, respectively for this combination, is impressive. It is important to stress, however, that we do not have a group with PAH-specific pharmacologic therapy alone for comparison and, thus, we do not know whether introduction of PAH targeted medical therapy alone would not result in identical outcome to that created by septostomy combined with pharmacotherapy.

Although the concomitant use of drugs and AS has been used in many of the previously reported series, the sequence of combining these strategies is different in our study. We did not wait until the failure of medical treatment was evident to perform AS, instead, the septostomy was performed first and then the specific drugs were added when they became available. In previous reports, AS septostomy has been used as the last or almost last resort in the management strategy, when the patients were most likely in an advanced stage of the disease [28]. The performance of septostomy at a relatively earlier stage of the disease in our study may probably account for the encouraging results.

Limitations

First, the study is a single centre and the numbers are limited, but this is related to the low incidence of the underlying pathology and the current availability of specific-PAH therapy. Second, although the data were collected from a accurate follow-up database, the study design remains retrospective. Finally, as discussed, an obvious limitation of the trial is that it does not provide an answer whether introduction of targeted therapy alone would not result in identical outcome to that created by septostomy combined with pharmacotherapy. The true benefit of an intervention can only be assessed in a randomized controlled study, however, the malignant nature of PAH and the availability of new specific drugs and transplantation would make it unethical to run a study with a true survival end-point.

Conclusions

In our experience, atrial septostomy is a safe and effective intervention. Operator experience and strict adherence to WHO recommendations account for our low fatality rate. Atrial septostomy improves hemodynamic parameters that correlate with functional improvement

and survival. The potential benefit of an early combination of AS and PAH-specific drug therapies suggested by the results of the present study is appealing and, in our opinion, worthwhile to be further evaluated.

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Figure Legends

Figure 1. Survival after atrial septostomy. A: Kaplan Meier survival estimates after atrial septostomy in the whole group of patients with pulmonary arterial hypertension. The median survival of the group was 60 ± (SEM) 8 months (95% confidence interval (CI), 43 to 77 months). A predicted survival curve (open circles) is plotted for comparison. 95% CI for both curves at each year of follow up are also plotted. B: The survival estimates for PAH patients with atrial septostomy plus PAH-specific pharmacologic treatment (continuous line) are better than those in patients with atrial septostomy alone (dotted line) [median survival 83 months (95% CI, 57 to 109) *versus* 53 months (95% CI, 39 to 67) respectively; chi-square log-rank, 6.52; p = 0.01].