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Medical Preconditioning in Infants and Young Children with Secundum Atrial Septal Defect: Effects of Preload and Afterload Reduction on Defect Size and Right Ventricular Remodeling

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Medical Preconditioning in Infants and Young Children with Secundum Atrial Septal Defect: Effects of Preload and Afterload Reduction on Defect Size and Right Ventricular Remodeling

Abstract

Objectives:

To evaluate the effects of preload reduction using furosemide and combined preload–afterload reduction therapy using furosemide plus captopril on atrial septal defect (ASD) secundum size, right ventricular (RV) dimensions, and cardiac remodeling in infants and young children over a one-year follow-up period.

Patients & Methods:

This prospective, non-randomized controlled study included 90 infants and young children with isolated secundum ASD. Patients were allocated into three equal groups: Group I receivedf urosemide, Group II received furosemide plus captopril, and Group III served as untreated controls. Clinical, anthropometric, and echocardiographic assessments were performed at baseline, 6 months, and 12 months. Primary outcomes were changes in ASD diameter and RV size. Secondary outcomes included left ventricular ejection fraction (EF), fractional shortening (FS), tricuspid annular plane systolic excursion (TAPSE), TAPSE Z-score, and TAPSE/ESPAP ratio. Statistical analysis included ANOVA, Kruskal–Wallis, paired tests, and post hoc comparisons

Results:

Baseline characteristics were comparable among the three groups. After 12 months, ASD size differed significantly between groups ($P < 0.001$). The mean reduction in ASD size from baseline to one year was greatest in Group II (3.4 ± 5.5 mm), followed by Group I (1.31 ± 4.3 mm), whereas Group III showed minimal change (0.32 ± 2.5 mm; $P = 0.004$). Post hoc analysis demonstrated significant differences between Group II and Group III ($P = 0.001$) and between Group I and Group III, while the difference between Groups I and II showed a trend toward significance ($P = 0.05$). RV diameter decreased significantly in both treated groups at 6 and 12 months ($P < 0.001$) but remained persistently dilated in untreated controls. EF showed a mild but statistically significant improvement in treated groups compared with controls. TAPSE and

TAPSE Z-scores improved significantly over time in all groups, with no significant intergroup differences.

Conclusion:. The use of furosemide, alone or with captopril, significantly were associated with ASD size reduction and favorable right ventricular remodeling in infants and young children with secundum ASD, providing effective medical bridging strategy to transcatheter closure.

Keywords:

Atrial septal defect; Right ventricular remodeling; Furosemide; Captopril; Medical preconditioning.

Introduction : Atrial septal defect (ASD) represents one of the most common congenital heart diseases in infants and children, arising from incomplete closure of the interatrial septum and resulting in abnormal left-to-right shunting [1]. ASD, along with Patent foramen ovale (PFO), ventricular septal defect (VSD), and patent ductus arteriosus (PDA), accounts for the largest proportion of congenital heart disease (CHD) worldwide [2]. Secundum ASD constitutes approximately 75% of all cases, followed by ostium primum and sinus venosus defects; coronary sinus ASD is rare and usually associated with venous anomalies [3]. The natural history of moderate and large secundum ASDs is characterized by chronic right-sided volume overload due to persistent left-to-right shunting. This leads to progressive dilation of the right atrium and right ventricle, increased pulmonary blood flow, recurrent respiratory infections, impaired growth, atrial arrhythmias, pulmonary hypertension, and, in untreated adults, premature mortality[4]. Echocardiography remains the cornerstone for diagnosis, allowing precise visualization of ASD morphology, assessment of surrounding rims, evaluation of RV dilation, and measurement of shunt impact [4]. Treatment strategies for ASD in children are well established. Multiple studies have shown trans-catheter ASD closures to be equally as safe and efficacious with similar outcomes when compared with surgical ASD closures[5]. Closure may be postponed in infants with low body weight, large defects, or deficient rims where procedural risk is higher. During this period, medical therapy is frequently used to stabilize symptoms related to pulmonary over-circulation. Diuretics such as Furosemide reduce preload, improve respiratory symptoms, and help control heart failure manifestations in infants with significant shunt [1]. Angiotensin enzyme (ACE) inhibitors, particularly captopril, reduce afterload and influence intra-cardiac pressure gradients, potentially modifying shunt dynamics. Recent reports suggest that ACE

inhibitors may facilitate conditions favorable for spontaneous reduction in ASD size or at least limit its progression, especially in moderate-sized defects [1, 6]**.** Although medical therapy does not close the defect, preload and afterload reduction may indirectly improve hemodynamics by decreasing pulmonary venous return, reducing RV volume load, and optimizing ventricular performance [1]. Improvements in RV remodeling and reduction in shunt volume may theoretically enhance suitability for future device closure, particularly in infants with borderline anatomy [7, 8]. Nevertheless, evidence supporting a structural benefit of medical therapy in ASD remains limited, and few studies have prospectively evaluated whether Furosemide alone or combined furosemide–captopril therapy influences ASD size or RV dimensions over time [5]**.** To our knowledge, few prospective studies have directly compared the effects of preload reduction alone versus combined preload–afterload reduction on ASD size progression and right ventricular remodeling in infants. Given these gaps in knowledge, the present study aimed to prospectively evaluate the effects of preload reduction (furosemide) and combined preload–afterload reduction therapy (furosemide plus captopril) on ASD size progression and right ventricular remodeling over a 12-month period in infants with secundum ASD. By comparing treated groups with an untreated control group, this study provides novel insight into whether medical preconditioning may play a role beyond symptomatic management and potentially alter the structural course of ASD during early childhood.

Patients and Methods : Study Design and Population: This prospective non-randomized controlled study was conducted on infants and young children diagnosed with isolated secundum atrial septal defect (ASD) who presented to the pediatric cardiology outpatient clinic of Specialized Pediatric Hospital, Cairo University and Al-Azhar University Hospitals. A total of 90 infants were enrolled and followed for 12 months. Group allocation was based on treating physician preference and clinical judgment; therefore, the study was non-randomized. Patients were consecutively recruited based on predefined inclusion and exclusion criteria and were allocated into three equal groups (n = 30 each). **Group I:** received preload reduction therapy using furosemide, **Group II:** received combined preload and afterload reduction therapy (furosemide plus captopril) and **Group III:** untreated control group receiving no medical therapy. **Inclusion Criteria;** Infants and children aged 1–48 months, isolated secundum ASD confirmed by two-dimensional and Doppler echocardiography, presence of right ventricular

volume overload or symptoms suggestive of increased pulmonary blood flow (e.g., recurrent respiratory tract infection, dyspnea) and no indication for immediate surgical or transcatheter closure. **Exclusion Criteria:** Ostium primum, sinus venosus, or coronary sinus defects, associated congenital cardiac anomalies (e.g., VSD, PDA, AV canal defect), pulmonary hypertension not attributable to ASD, significant valvular disease, renal dysfunction or contraindications to ACE inhibitors (in the combined therapy group) and Previous cardiac intervention. **Intervention Protocol: Group I (furosemide):** Patients received oral furosemide at standardized dosing regimens (dose is 1 mg /Kg /day) ،aiming for preload reduction and symptomatic improvement. **Group II (furosemide + captopril):** Patients received the same Furosemide protocol in addition to oral captopril at age-appropriate dosing. Captopril starting dose 0.1 mg/kg/day, titrated up to 1 mg/kg/day as tolerated. **Group III (untreated Controls):** Patients did not receive any cardiac-specific medical therapy but were followed clinically and by echocardiography at the same intervals. All medications were administered for the entire 12-months follow-up unless intolerance occurred. Furosemide can cause volume depletion, electrolyte abnormalities, and renal dysfunction. Captopril can cause hypotension, renal-function changes, and hyperkalemia. The adverse events, blood pressure monitoring, renal function, electrolytes, adherence, and treatment discontinuation were reported. **Clinical and Anthropometric Assessment:** At baseline and at 6-month intervals, all infants and young children underwent complete clinical evaluation, including history (assessment of symptoms, cardiac and respiratory history) and examination including growth parameters (body weight, length, body weight Z-score, length Z-score, and body surface area). Anthropometric Z-scores were calculated using WHO growth standards , vital data (heart rate ,respiratory rate &blood pressure) as well as general and local cardiac examination. **Transthoracic Echocardiographic Assessment**: Comprehensive echocardiographic studies were performed at baseline, 6 months, and 12 months using standard pediatric imaging protocols using 2D, M-mode and color flow Doppler from all standard echocardiographic views applying the segmental analysis, the following parameters were measured: ASD diameter in the subcostal and apical views, right ventricular (RV) diameter, left ventricular ejection fraction (EF) (Simpson method when applicable), Fractional shortening (FS), Tricuspid annular plane systolic excursion (TAPSE), TAPSE Z-score corrected for body surface area, TAPSE/ESPAP ratio. RV diameters in apical four chamber view. All measurements were averaged over three cardiac cycles and performed by

an experienced pediatric cardiologist blinded to group allocation. ASD diameter was measured by transthoracic echocardiography in the specified views and that spontaneous closure refers to complete echocardiographic closure without an intervention intended to close the defect. Regression and enlargement will be defined on any change in measured diameter at initial examination.

Study Outcomes: Primary Outcomes: Change in ASD size and RV diameter from baseline to 12 months. **Secondary Outcomes**: Changes in EF and FS, changes in TAPSE, TAPSE Z-score, and TAPSE/ESPAP ratio and changes in anthropometric parameters

Ethical Considerations

Removed

Statistical Analysis

Data were analyzed using SPSS software (version 26) Quantitative variables were expressed as mean ± standard deviation for parametric data or median (IQR) for non-parametric data as appropriate. For Between-group comparisons: One-way ANOVA for normally distributed variables and Kruskal–Wallis test for non-parametric variables, Post-hoc analysis included LSD (for parametric ANOVA) and Dunn's test (for non-parametric outcomes). For Within-group comparisons: Paired t-test was used for normally distributed variables and Wilcoxon signed-rank test for non-parametric variables. Categorical variables were compared using Chi-square or Fisher's exact test. A P-value < 0.05 was considered statistically significant.

Results : The cohort of ninety infants and young children diagnosed with isolated secundum ASD was included and equally distributed among the three studied groups. Baseline demographic and clinical characteristics were comparable across groups. No significant differences were observed with respect to age ($P = 0.07$) or sex distribution ($P = 0.17$). The various clinical presentations including the rates of asymptomatic status, dyspnea, and recurrent lower respiratory tract infections which did not differ significantly among groups (all $P > 0.05$). CXR findings, including mild cardiomegaly and increased pulmonary vascular markings, also demonstrated no statistically significant variations between the three groups ($P = 0.61$) **(Table 1)**. Growth parameters showed overall improvement over the 12-month follow-up period in all groups. Body weight and length increased significantly from baseline to 6 months within each group (all $P < 0.001$). However, no significant differences were found between groups in baseline or follow-up measurements of body weight and its Z-score, length and its Z-score, or

body surface area (all P > 0.05). Additionally, within-group analyses revealed no significant changes in Z-scores over time (all P > 0.05) **(Table 2)**. Baseline left ventricular systolic function, assessed by ejection fraction (EF) and fractional shortening (FS), was comparable among the three groups (P = 0.06 and P = 0.46, respectively). At 6 and 12 months, EF was modestly but significantly higher in treated groups compared with controls at both follow-up points (P = 0.02). Post-hoc analysis revealed significantly higher EF values in both the furosemide and the combined-therapy groups compared with untreated controls, while no difference was found between the two treated groups. Within-group analyses showed no significant changes in EF over time. Fractional shortening did not differ significantly between groups at baseline or throughout follow-up (all P > 0.05), and no significant changes were observed within groups. Left ventricular ejection fraction (EF) showed a **statistically significant difference between groups after 6 and 12 months**, favoring treatment groups **(Table 3)**. At baseline, TAPSE values and TAPSE Z-scores were similar among the three groups (P = 0.17 and P = 0.62, respectively). TAPSE increased significantly over the follow-up period within each group (all P < 0.001), However, no significant between-group differences were observed at 6 or 12 months (P > 0.05). TAPSE Z-scores showed significant within-group improvement in Groups I and III (P < 0.001) and a modest improvement in Group II (P = 0.02), with no significant variation between groups at any time point. The TAPSE/ESPAP ratio also remained comparable between groups, although a significant within-group increase was noted only in the combined-therapy group (P < 0.001). TAPSE values significantly increased over time within all groups. No statistically significant differences were detected between groups at any time point **(Table 4)**. A significant increase in right ventricular (RV) size was observed over time in all groups, but much less compared to the control group. Post hoc analysis revealed significantly larger RV dimensions in the control group compared with treatment groups at 6 months and 1 year **(Table 5)**. ASD diameters at baseline were comparable across groups (P = 0.06). At 6 months, significant intergroup differences emerged (P = 0.02), with both treated groups showing reductions in ASD size relative to controls. At 12 months, these differences became more pronounced (P < 0.001), with Group II exhibiting the greatest reduction, followed by Group I, on the other hand untreated control group showed progression of the ASD size. The mean change in ASD size from baseline to 12 months also differed significantly (P = 0.004). Group II showed the largest mean reduction (3.4 ± 5.5 mm), followed by Group I (1.31 ± 4.3 mm), whereas Group III demonstrated a slight

change in the defect size (0.32 ± 2.5 mm). Post-hoc comparisons indicated a statistically significant difference between Group II and Group III (P = 0.001) and between Group I and Group III, while the comparison between Groups I and II showed a trend toward significance (P = 0.05). Categorical analysis of ASD outcomes revealed significant variation (P = 0.05). Spontaneous closed ASD was observed most frequently in Group II (26.7%), followed by controls (13.3%) then Group I (10%). The progression of the defect size was evident in 80% of untreated controls followed by Group I (60%) and the least was among Group II (50%). These findings highlight the beneficial impact of combined preload and afterload reduction therapy for limiting ASD size progression and promoting more favorable RV remodeling . A significant reduction in ASD size was observed in both treatment groups compared with controls. Spontaneous closure occurred more frequently in the combined therapy group. The control group showed a higher rate of increase of ASD size (**Table 6 and Figure 1 & Figure 2)**

Table (1): Baseline characteristics of the studied groups

Variables		**Group I (Furosemide) (n=30)**	**Group II (Furosemide +Captopril) (n=30)**	**Group III (Controls) (n=30)**	**P value**
Age (Months)	Median IQR	12 1-36	11 1-36	15.5 1 – 36	0.07
Sex	Male Female	10 (33.3%) 20 (66.7%)	17 (56.7%) 13 (43.3%)	12 (40%) 18 (60%)	0.17
Clinical History:	Asymptomatic Dyspnea Recurrent LRTI	14 (46.7%) 14 (46.7%) 14 (46.7%)	10 (33.3%) 11 (36.7%) 15 (50%)	12 (40%) 18 (60%) 16 (53.3%)	0.57 0.19 0.88
Chest& Heart-X ray	Normal Mild cardiomegaly EBVM EBVM+ mild cardiomegaly	14 (46.7%) 8 (26.7%) 5 (16.7%) 3 (10%)	15 (50%) 9 (30%) 4 (13.3%) 2 (6.7%)	13 (43.3%) 13 (43.3%) 4 (13.3%) 0 (0%)	0.61

IQR: Interquartile Range**, LRTI: Lower respiratory tract infection, EBVM: Exaggerated bronchovascular marking,**

Table (2): Anthropometric measurements at baseline and after 6 months of follow-up

Variables	**Group I (Furosemide) (n=30)**	**Group II (Furosemide +Captopril)**	**Group III (Controls) (n=30)**	**Test**	**P**

			(n=30)			
Body Weight Baseline (kg)	Mean ± SD	8.22±2.7	8.55±2.87	9.77±2.36	2.85^	0.06 NS
Body Weight After 6 months (kg)	Mean ± SD	10.14±1.85	10.28±1.9	10.88±1.72	1.37^	0.26 NS
P!		**<0.001****	**<0.001****	**<0.001****		
Body Weight Z score Baseline	Median IQR	-0.70 -3.2-0.15	-0.59 -3.3-0.67	-0.68 -3.3 – 0.03	4.95$	0.08 NS
Body Weight Z score After 6 months	Median IQR	-0.47 -2.5 – 0.41	-0.60 -2.4-0.67	-0.85 -2.7 – -0.07	0.85$	0.40 NS
P¶		0.43 NS	0.49 NS	0.88 NS		
Length Baseline (cm)	Mean ± SD	70.3±10.36	71.25±11.18	73.78±9.76	0.89^	0.41 NS
Length After 6 months (cm)	Mean ± SD	77.87±7.42	78.03±8	79.21±7.95	0.27^	0.77 NS
P!		**<0.001****	**<0.001****	**<0.001****		
Length Z score Baseline	Median Range	-1 -2.3-0.11	-0.96 -2.3- -0.33	-0.92 -2.3 - -0.24	0.02$	0.99 NS
Length Z score After 6 months	Median Range	-0.90 -2.2 – 1	-1.29 -2.42 – 1	-1.47 -2.2 - -0.13	4.93$	0.09 NS
P¶		0.08 NS	0.06 NS	0.10 NS		
BSA Baseline (m^2)	Mean ± SD	0.39±0.09	0.39±0.10	0.41±0.07	0.83^	0.44 NS
BSA After 6 months (m^2)	Mean ± SD	0.46±0.07	0.45±0.07	0.45±0.09	0.01^	0.99 NS
P!		**<0.001****	**<0.001****	**<0.001****		

BSA: Body Surface Area, SD: Standard deviation, ^: One way ANOVA test, $:Kruskal Wallis test, !:Paired t test, ¶: Paired Wilcoxon test, NS: Non significant (P>0.05), *: Significant (P<0.05), **: Highly significant (P<0.001)

Table (3): Left ventricular systolic function during follow-up

Variables		**Group I (Furosemide) (n=30)**	**Group II (Furosemide +Captopril) (n=30)**	**Group III (Controls) (n=30)**	**Test**	**P**	**Post hoc**
EF(%) Baseline	Mean ± SD	75.7±5.58	78.1±4.18	73.4±11.09	2.9^	0.06 NS	----
EF (%) After 6 months	Mean ± SD	77.73±3.86	78.17±2.28	75.33±5.68	**4.00**^	**0.02 ***	0.69 NS[1] **0.01**[*2] **0.03**[*3]
EF (%) After 12 months	Mean ± SD	77.73±3.86	78.17±2.28	75.33±5.68	**4.00**^	**0.02**	0.69 NS[1] **0.01**[*2]

						*	**0.03**[*3]
P!		0.052 NS	0.93 NS	0.34 NS			
FS (%) Baseline	Mean ± SD	39.3±4.08	40.58±4.07	39.84±3.71	0.79^	0.46 NS	----
FS (%)After 6 months	Mean ± SD	39.72±3.5	40.5±2.5	40.0±4.5	0.30^	0.71 NS	----
FS (%) After 12 months	Mean ± SD	39.82±3.49	40.45±2.34	40.27±4.24	0.27^	0.76 NS	----
P!		0.56 NS	0.87 NS	0.36 NS			

EF: Ejection Fraction, FS: Fractional Shortening, SD: Standard deviation, ^: One way ANOVA test,!:Paired t test, £: McNemar test, NS: Non significant (P>0.05), *: Significant (P<0.05), **: Highly significant (P<0.001), LSD post hoc test, P1: Group I versus Group II, P2: Group I versus Group III, P3: Group II versus Group III

Table (4): TAPSE and right ventricular systolic function during follow-up

Variable		Group I (Furosemide) (n=30)	Group II (Furosemide +Captopril) (n=30)	Group III (Controls) (n=30)	Test	P
TAPSE Baseline	Mean ± SD	14.47±2.74	14.83±2.28	15.63±2.17	1.84^	0.17 NS
After 6 months	Mean ± SD	17.03±1.65	16.83±1.6	17.53±1.53	1.54^	0.22 NS
After 12 months	Mean ± SD	18.0±1.65	17.53±1.6	18.33±1.53	1.4^	0.25 NS
P!		**<0.001****	**<0.001****	**<0.001****		
TAPSE Z score Baseline	Median Range	0.35 -1.01 – 1.25	0.38 -0.28-1.25	0.38 -1.53 – 1.8	0.95$	0.62 NS
After 6 months	Median Range	0.8 -0.26-2.45	0.6 -0.84 – 1.91	0.54 -1.85 – 1.87	0.58$	0.70 NS
After 12 months	Median Range	1 -0.26-2.45	0.83 -0.84 – 1.91	0.74 -1.85 – 1.87	0.51$	0.77 NS
P¶		**<0.001****	**0.02***	**<0.001****		
TAPSE/ESPAP (Baseline)	Mean ± SD	0.63±0.13	0.60±0.08	0.63±0.13	0.54^	0.59 NS
(After 6 months)	Mean ± SD	0.68±0.14	0.67±0.13	0.63±0.12	2.15^	0.15 NS
(After 12 months)	Mean ± SD	0.69±0.14	0.68±0.13	0.63±0.12	2.22^	0.12 NS
P!		0.06 NS	**<0.001****	0.68 NS		

TAPSE: Tricuspid Annular Plane Systolic Excursion, ESPAP: Estimated Systolic Pulmonary Artery Pressure, SD: Standard deviation, ^: One way ANOVA test, $: Kruskal Wallis test, !: paired t test, ¶: Paired Wilcoxon test, NS: Non significant (P>0.05), *: Significant (P<0.05), **: Highly significant (P<0.001).

Table (5): Right ventricular size during follow-up

Variable		Group I (Furosemide) (n=30)	Group II (Furosemide +Captopril) (n=30)	Group III (Controls) (n=30)	Test	P	Post hoc
RV (mm) baseline	Mean ± SD	13.46±2.19	13.77±2.2	14.68±1.9	2.7^	0.07 NS	----
RV (mm) After 6 months	Mean ± SD	15.08±1.77	14.98±1.8	17.66±2.8	**14.34**^	**<0.001****	0.86 NS[1] **<0.001**[**2] **<0.001**[**3]
RV (mm) after 1 year	Mean ± SD	16.38±1.54	15.84±2.0	18.41±2.5	**12.64**^	**<0.001****	0.32 NS[1] **<0.001**[**2] **<0.001**[**3]
Difference	Median Range	3 1 - 5	2 0.8-3.8	4 1 – 8	**7.02**$	**0.03***	0.75 NS[1] **0.03**[*2] **0.02**[*3]
P!		<0.001*	0.001*	<0.001*			

RV: Right Ventricle, SD: Standard deviation, #: Chi square test, ^: ANOVA test, $: Kruskal Wallis test, NS: Non significant (P>0.05) NS: Non significant (P>0.05), *: Significant (P<0.05), **: Highly significant (P<0.001), LSD & Dunn's post hoc test, P1: Group I versus Group II, P2: Group I versus Group III, P3: Group II versus Group III

Table (6): Atrial septal defect (ASD) size and final outcomes among studied groups

Variables		Group I (Furosemide) (n=30)	Group II (Furosemide +Captopril) (n=30)	Group III (Controls) (n=30)	Test	P	Post hoc
ASD size base line (mm)	Mean ± SD	10.01±1.21	10.98±2.54	11.15±1.92	2.92^	0.06 NS	------
ASD size After 6 months (mm)	Mean ± SD	9.36±3.03	9.67±4.73	11.94±3.77	**3.9**^	**0.02***	0.75 NS[1] **0.01**[*2] **0.03**[*3]
ASD size after 1 year (mm)	Mean ± SD	8.7 ±4.2	7.5±6.1	12.1±5.05	**15.68**^	**<0.001***	0.07 NS[1] **<0.001**[**2] **0.05**[*3]
ASD fate	Spontaneous closed Decrease in size Increase in size	3 (10%) 9 (30%) 18 (60%)	8 (26.7%) 7 (23.3%) 15 (50%)	4 (13.3%) 2 (6.7%) 24 (80%)	**9.34**#	**0.05***	0.25 NS[1] **0.05**[*2] **0.04**[*3]

Mean difference at the end of study (baseline-end)	Mean ± SD Range	1.31±4.3 12.4 to -3.3	3.4±5.5 15.2 to -2.5	-0.32±2.5 8.5 to -2.5	**5.8**^	**0.004***	**0.05*** 0.14 NS **0.001***
P!		**0.04***	**0.009***	0.08 NS			

SD: Standard deviation, #: Chi square test, ^: ANOVA test,, NS: Non significant (P>0.05) NS: Non significant (P>0.05), *: Significant (P<0.05), **: Highly significant (P<0.001), LSD , P1: Group I versus Group II, P2: Group I versus Group III, P3: Group II versus Group III

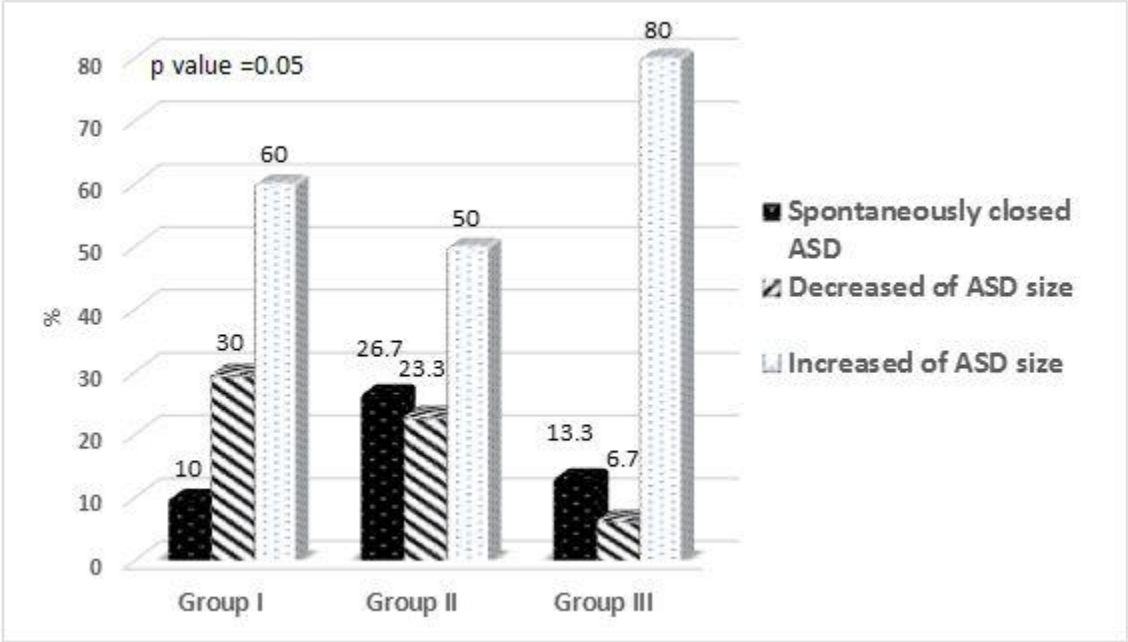


Figure 1: Distribution of atrial septal defect (ASD) outcomes after 1-year follow-up in the three studied groups.

Black bars represent spontaneously closed ASDs, striped bars represent decreased ASD size, and light gray bars represent increased ASD size. Group I: Furosemide, Group II: Furosemide + Captopril, Group III: untreated controls. The difference among groups was statistically significant (p = 0.05).

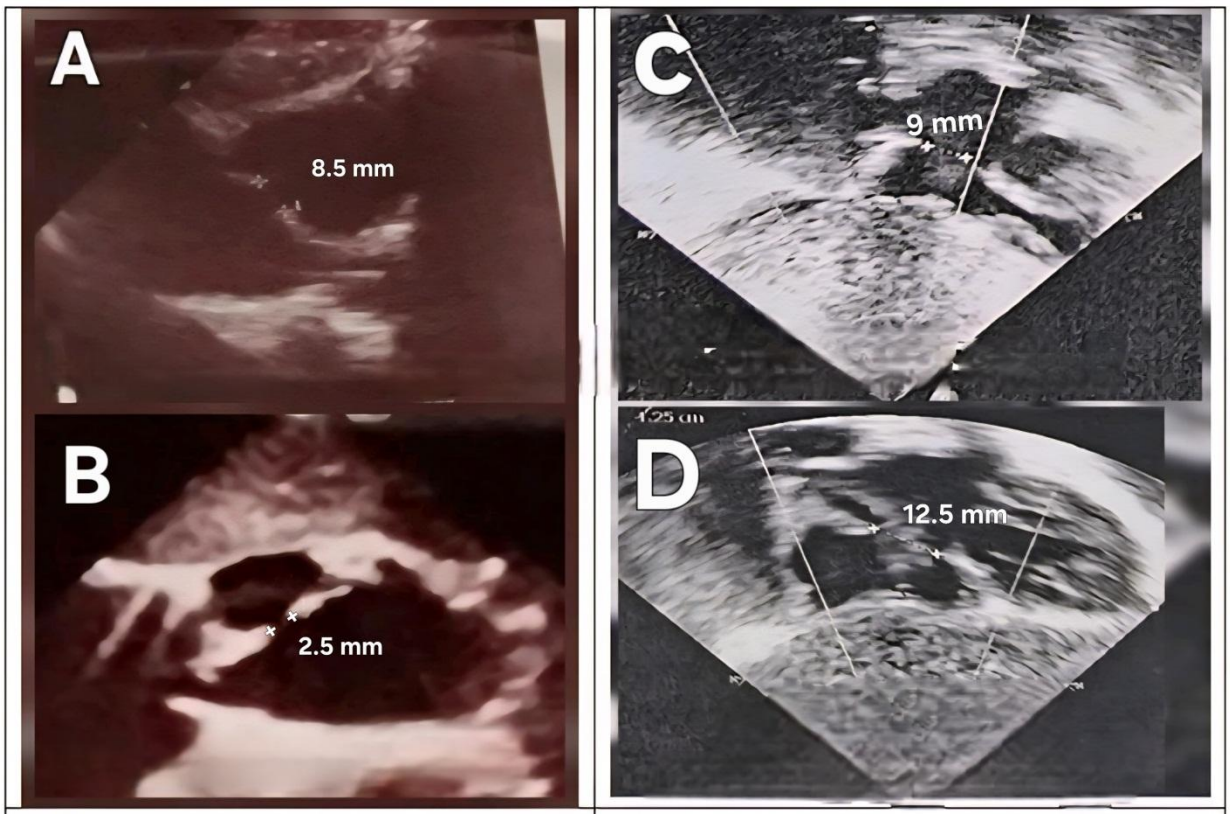


Figure 2: Subcostal 2-D transthoracic echocardiography illustrating treatment effects and natural progression of ASD secundum. **A:** Patient 5 (group II) before Furosemide and Captopril therapy, ASD measuring 8.5 mm. **B:** Same patient after treatment, showing a marked reduction to 2.5 mm. **C:** Patient 10 (untreated control, group III) at baseline, ASD measuring 9 mm. **D:** Same patient at 1-year follow-up, demonstrating natural enlargement of the defect to 12.5 mm.

Discussion ***:*** This study suggests that combined furosemide–captopril therapy prevented progression of ASD size in infants, effective and safe bridging strategy reducing the need for larger occluders. This medical therapy supports favorable cardiac remodeling in infants and children not yet suitable for transcatheter closure. The combined therapy appears more effective than diuretics alone and may allow future use of smaller and safer occluder devices. The treatment was associated with a greater reduction in measured ASD diameter. This approach is particularly valuable for underweight infants or those in whom early intervention is not feasible, offering a safe and practical bridging strategy. Atrial septal defect (ASD) is among the most common congenital heart lesions in children and is associated with right heart volume overload, pulmonary over-circulation, and growth impairment in moderate and large defects [9, 10]. Although current guidelines recommend closure in the presence of significant shunting or RV enlargement, the optimal timing in infants remains controversial. In many centers, medical therapy is used as a bridge to definitive closure in patients who are too small or not yet anatomically suitable for device implantation **[8, 11]**. In the present study, baseline demographic and clinical characteristics were well balanced among the three groups, with no significant

differences in age, sex, symptoms, or radiographic findings. The female predominance observed in our cohort is consistent with previous reports of secundum ASD [6, 11]. Early diagnosis in infancy reflects contemporary echocardiographic screening and is important because spontaneous closure is more likely in younger children with small defects, whereas large defects rarely close spontaneously [12-14]. The lack of significant baseline differences supports the validity of attributing subsequent changes in ASD size and RV dimensions to the medical interventions rather than pre-existing disparities. Anthropometric measures (weight, length, BSA) increased significantly within all groups over the follow-up period. Weight- and length-for-age Z-scores remained slightly below zero, reflecting persistent growth vulnerability common in CHD. This under-nutrition is well recognized in children with CHD due to increased metabolic demands, feeding difficulties, and recurrent respiratory infections [15-17]. Our findings suggest that growth improved over follow-up, but the effect of medical therapy on somatic growth compared with controls was not statistically significant. This is in accordance with previous observations that nutritional outcomes in CHD are multifactorial and not solely driven by pharmacologic therapy [11, 15]**.** Left ventricular ejection fraction (EF) showed a statistically significant difference between groups after 6 and 12 months favoring treatment groups. It is known that the pathophysiology of isolated secundum ASD, where the hemodynamic burden predominantly affects the right heart and pulmonary circulation, while LV systolic performance is usually preserved . Previous pediatric and adult studies reported normal EF and FS in unrepaired ASD despite marked right-sided dilation, with functional changes more evident in RV indices and strain parameters rather than LV systolic measures [4, 18, 19]. Our data therefore confirm that the studied medical regimens did not adversely affect LV function. Right ventricular systolic function, as measured by TAPSE and TAPSE Z-score, was preserved at baseline and improved significantly over time within all groups, reflecting both physiological maturation and remodeling. The observed improvement in TAPSE across all groups likely reflects physiological maturation, although combined therapy showed favorable trends in RV–pulmonary coupling [18, 20] . These findings suggest that medical therapy, particularly when incorporating afterload reduction, may favorably influence RV performance relative to pulmonary pressures, even if standard TAPSE values alone do not fully capture the degree of volume overload [18] Overall, however, RV functional indices remained globally preserved, in keeping with prior ASD cohorts. The most clinically relevant finding of this study relates to ASD size progression. At baseline, mean ASD diameters were comparable among the three groups. Over the one-year follow-up, both treated groups demonstrated significant reductions in ASD size, with the greatest decline observed in the furosemide plus captopril group, whereas the untreated control group showed persistence or slight enlargement of the defect. The overall mean change from baseline to one year differed significantly between groups, and categorical analysis confirmed a higher proportion of closure or decrease in the treated arms, versus a predominance of defect enlargement in controls. These results are in strong agreement with the study by Lee et al. (2021) [11], who reported that diuretic therapy in children with large secundum ASDs was associated with a reduction in defect size and a higher likelihood of transcatheter device closure, compared with non-diuretic cohorts. Our findings extend this concept by demonstrating that combined preload and afterload reduction may confer an even greater remodeling benefit than diuretics alone. The likely mechanism involves reduction of right atrial and RV volume load, limitation of rim stretching, and possible alterations in intracardiac pressure gradients that reduce the left-to-right shunt **[8, 21]**. Reductions in ASD diameter may permit the use of smaller occluder devices, potentially reducing procedural complications and improving long-term

outcomes [21]**.** Taken together, our data support the concept of medical preconditioning in infants with hemodynamic significant ASD secundum who are not yet ideal candidates for device closure. Preload and afterload reduction did not compromise growth or LV function and were associated with favorable RV remodeling and significant attenuation of ASD progression compared with conservative observation alone. These effects may be particularly valuable in younger or underweight children, or in resource-limited settings where early intervention is not always feasible. However, medical therapy remains a bridge and adjunct, not a substitute, for definitive closure. Captopril inhibits angiotensin-converting enzyme and reduces angiotensin II formation, thereby lowering systemic vascular resistance and afterload. Furosemide promotes natriuresis and diuresis and can reduce intravascular volume and cardiac filling pressures. These are established pharmacological effects. However, neither mechanism establishes that treatment directly promotes anatomical regression of the interatrial septum.This study supports the use of furosemide, with or without captopril, as a safe and effective bridging strategy for infants with moderate-to-large ASD secundum who are not yet candidates for transcatheter closure. It may promote favorable cardiac remodeling in infants and children not yet suitable for device closure. Regular echocardiographic monitoring and nutritional assessment are recommended, and decisions regarding timing of closure should be individualized. Larger and longer-term studies are needed to confirm these findings. Future prospective, randomized, multi-center studies with longer follow-up are needed to confirm these findings, to refine patient selection, and to clarify the optimal duration and composition of medical therapy prior to intervention. **Study Limitations*:*** The study was limited by its single-center design, modest sample size, and one-year follow-up period. Advanced imaging and cardiac biomarker assessments were not included, and medication adherence was not objectively measured. The absence of randomization may introduce residual confounding despite comparable baseline characteristics. Larger multicenter studies with longer-term evaluation are needed to confirm these findings. Our study evaluated echocardiographic outcomes during follow-up and did not prospectively compare occluder sizes, procedural feasibility, device-related complications, or postprocedural outcomes. We therefore cannot conclude that medical treatment resulted in smaller devices or safer transcatheter closure.

Conclusion: Medical therapy with furosemide, either alone or in combination with captopril, was associated with significant reduction in ASD size over a one-year follow-up period compared with conservative observation alone. The greatest reduction in defect size was observed with combined preload and afterload reduction therapy. Right and left ventricular systolic functions remained preserved, and somatic growth improved similarly across all groups. These findings support the use of preload and afterload reduction as a safe and effective bridging strategy in infants who are not yet suitable candidates for transcatheter ASD closure.

List of abbreviation

- **ACEi** – Angiotensin-Converting Enzyme Inhibitor
- **ANOVA** – Analysis of Variance
- **ASD** – Atrial Septal Defect
- **BSA** – Body Surface Area
- **EF** – Ejection Fraction

- **ESPAP** – Estimated Systolic Pulmonary Artery Pressure
- **FS** – Fractional Shortening
- **IQR** – Interquartile Range
- **LRTI** – Lower Respiratory Tract Infection
- **LV** – Left Ventricle
- **P-value** – Probability Value
- **PDA**- Patent Ductus arteriosus
- **PFO**- Patent Foramen Ovale
- **SD** – Standard Deviation
- **TAPSE** – Tricuspid Annular Plane Systolic Excursion
- **TAPSE/ESPAP** – Tricuspid Annular Plane Systolic Excursion/ Estimated Systolic Pulmonary Artery Pressure
- **Z-score** – Standardized Score
- **VSD**- ventricular septal Defect

Declarations Ethics approval and consent to participate

Informed consent was obtained from the parents or legal guardians of all enrolled infants, including both patients and controls, before participation in the study. The research protocol was reviewed and approved by the Research Ethics Committee of the Pediatrics Department and the Faculty of Medicine, Al-Azhar University. The study aims, procedures, anticipated benefits, and potential risks were clearly explained to all caregivers prior to enrollment. Confidentiality of patient information was ensured throughout the study, and families were informed of their unrestricted right to withdraw at any stage without any consequences to their child's medical care.

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