Hemodynamic Assessment to Evaluate Pulmonary Hypertension in Patients with Aortic Stenosis

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***Abstract*—Pulmonary hypertension (PHT) is highly prevalent in patients with Aortic Stenosis (AS) and significantly increases mortality. Correlation between echocardiogram derived right ventricular pressure and measured pulmonary artery systolic pressure (PASP) by right heart catheterization (RHC) have been reported to be poor. Retrospective data of 56 patients with AS who underwent coronary angiography and RHC from June 1999 to 2008 were reviewed. 20 patients (35.1%) had severe PHT with PASP > 55 mmHg on RHC. PASP did correlate with the body weight (r = 0.473, p<0.01). There was a significant correlation between PASP on RHC and RVSP on echo (r = 0.344 p<0.01) but a Bland-Altman plot showed poor association. In patients with PVR < 3, there was correlation between the PASP and LVEDP on RHC (r = 0.655, p<0.001). 34 patients had an estimated RVSP <40 mm Hg on echo and 9 (25.7%) of these patients had severe PHT on RHC. Using a RVSP cutoff of 40 mmHg, echo had 46.8% sensitivity. There was higher mortality at 3 years in patients with severe PHT (44% vs. 10.7%, p <0.01) Conclusions: Severe PHT was found in up to 35% of patients with AS and had higher mortality. Obese patients with AS had a higher likelihood of severe PHT. Echocardiography underestimates PHT in patients with AS. PHT is related to diastolic dysfunction in these patients. RHC should be considered in select patients with aortic stenosis in order to risk stratify and assess for early aortic valve replacement, in patients in whom a reliable TR jet velocity is unobtainable by echo Doppler.**

***Index Terms*—Aortic Stenosis, Pulmonary Hypertension, Invasive Hemodynamics**

I. Background

SEVERE pulmonary hypertension is prevalent as high as 29% in patient with severe aortic stenosis and significantly increases morbidity and mortality in these patients. Early Aortic Valve Replacement (AVR) for this high-risk subset of patients with Aortic Stenosis (AS) has been recommended (1).The etiology of Pulmonary Hypertension (PHT) in severe AS remains unclear however left ventricular (LV) dysfunction may be of one important etiology (2). Prior to AVR all patients undergo coronary angiography but hemodynamic cardiac catheterization is performed in minority of patients, consistent with current practices (3). Transthoracic echocardiography (TTE) is relied upon to measure the pulmonary artery systolic pressure using the modified Bernoulli equation. However, this may not accurately assess the right ventricular systolic pressure in some cases due to suboptimal tracing of the regurgitation jet, decreased tricuspid jet velocity due to high right atrial pressure or poor estimation of right atrial pressures, and generally poor technique for several reasons (4). Correlations between echo-derived right ventricular pressure and measured pulmonary artery systolic pressure (PASP) by right heart catheterization (RHC) have been reported to be poor when assessed in patients with pulmonary disease (5, 6). No studies have compared echocardiographic assessment of PHT in AS with invasively obtained pulmonary artery pressure using RHC. The reliability of echocardiographic detection and degree of PHT in patients with AS is unknown. The gold standard for diagnosing PHT has been RHC. At our center, we perform hemodynamic measurements on all patients with aortic stenosis planning to undergo valve replacement. We report the unreliability of echocardiographic measurements when assessing for degree of stenosis and PHT.

II. Materials and Methods

Approval was obtained from the Institutional Review Board at Indiana University, Indianapolis, Indiana for this retrospective study. Cardiac Catheterization Lab database from an inner city tertiary care center was used to retrieve patients with AS. At our center, all patients with AS undergo

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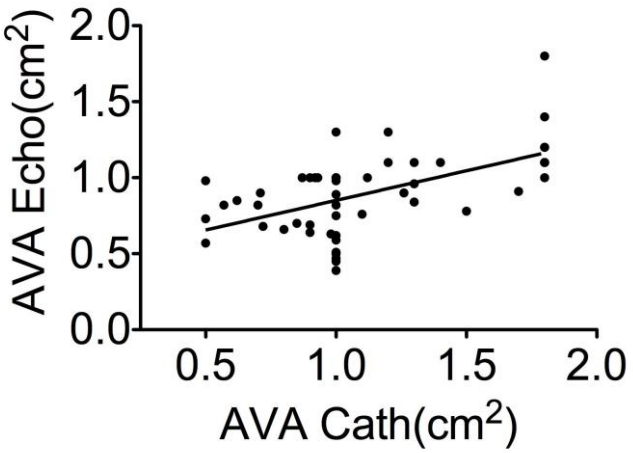

Fig. 1A. Correlation between aortic valve area as reported by catherization versus echocardiogram R^2=0.308 p<0.0001

hemodynamic measurements with coronary angiography. Data from June 1999 to June 2008 was obtained. Patients with aortic stenosis felt to be significant by 2-D echocardiography or clinically symptomatic, had been referred for LHC and RHC. Our study population included all patients with AS undergoing both LHC and RHC. Only patients who underwent hemodynamic studies within 1 month from the time of echocardiography were included in the study. Severe AS was defined as AVA of <1 cm^2 on cardiac catheterization. PHT was defined as PASP of >35 mm Hg and severe PHT was defined as PASP of > 55 mm Hg. Clinical parameters retrieved included age, race, gender, severity of aortic stenosis and hemodynamic parameters. Echocardiographic parameters were obtained from reports that were retrieved from an electronic database. Echo reports were read by attending physicians from the division of cardiology. All echocardiograms were reviewed by the author to reconfirm the RVSP using the modified Bernoulli equation (4 x TR Velocity^2+ right atrial pressure). Data was analyzed using SPSS version 16. Linear regression analysis and Pearson correlation analysis was used to assess relationship between linear parameters. Bland-Altman curves were plotted using Graph Pad Prism 5. Chi-square testing was used to assess significance between groups.

III. Results

From June 1999 to June 2008, 56 patients with aortic stenosis underwent LHC and RHC. Patients with AVA of >1 cm^2 on echocardiography had LHC and RHC if they were having symptoms of angina, syncope or worsening dyspnea on exertion. Patient demographics and severity of AS are shown inTable1. 52 out of 56 patients had pulmonary hypertension with PASP > 30 mm Hg. (92.8%). 20 out of 56 patients had severe pulmonary hypertension with PASP > 55 mm Hg (35.1%). 34.2 % if PVR <3 excluded. If patients with disease conditions that could cause PHT were excluded, the prevalence of severe PHT was 31.8 %. Hemodynamic measurements are illustrated in Table 2. RVSP on Echocardiography ranged from 20 to 80 mm Hg (mean =32.3). ECHO was unable to assess the RVSP in 5 patients due to poor TR velocity tracing. 18 patients (31.5 %) had RVSP > 40 mm Hg. Among patients with ECHO RVSP >40 mm Hg, only 1 patient had normal pulmonary pressures on RHC hemodynamic measurement. 34 patients had ECHO RVSP <40 mm Hg. 9 out of 34 (25.7%) of these patients had severe PHT on RHC. Using a RVSP cutoff of 40 mm Hg, echocardiography had

Patient Demographics	**Range (Mean)**
TOTAL PATIENTS	56 patients
WITH AS	41 – 84 (61.8) years
AGE	
GENDER	43 % (24 patients)
Male	57 % (32 patients)
Female	
RACE	55.4% (31 patients)
Caucasian	30.4% (17 patients)
Blacks	12.5% (7 patients)
Hispanic	0.02 % (1 patient)
Oriental	126 – 314 lbs (190.45 ± 46.8)
WEIGHT	
AS SEVERITY (Aortic Valve Area on Cath)	18% (10 patients)
Mild (1.5-1.8)	20% (11 patients)
Moderate (1.0 to 1.5)	55% (31 patients)
Severe (<1.0)	7% (4 patients)
Unknown	36% (20 patients)
CAD	
OSA	5.3 % (3 patients)
COPD	3.5 % (2 patients)
OTHER VALVULAR DISEASE	11 % (6 patients)
Severe MR, TR or AR	21% (12 patients)
Moderate	

Table 1: Demographics

46.8 % sensitivity (95% CI 0.29-0.64) and 100 % specificity (95% CI 0.74-1) to detect pulmonary hypertension in patients with aortic stenosis. (Table 4). Correlations between hemodynamic parameters are shown in Table3. There was significant correlation between AVA as measured by LHC vs. ECHO, however there was tendency for TTE to overestimate the AVA (Fig 1A) and the two methods showed little agreement per the Bland-Altman plot. There was positive correlation between measured PASP by RHC and patient's bodyweight (Fig 2). There was significant correlation between

PASP and RVSP measured by ECHO (Fig 3A) but a Bland-Altman plot shows poor agreement between the two methods (Fig 3B). There was a significant correlation between PASP and LVEDP (Fig 4). When patients with PVR >3 were excluded, there was stronger correlation between PASP and LVEDP with R=0.655 p=0.0001. There was still no correlation between degree of AVA and PASP (R= - 0.023 p=0.892). The presence of aortic, mitral regurgitation, OSA or COPD did not correlate with the degree of PASP. (R=0.013 p=0.939). Correlation between PASP and RVSP on ECHO was significant (R=0.326 p=0.046). There was no significant correlation between PASP and Ejection Fraction. (R=-0.295 p=0.136).

All cause mortality within 3 years was 44% (8/18) in patients with PASP >55 mm Hg. Patients with PASP <55 had a mortality of 10.7% (3/28). There was statistically significant higher mortality in patients with severe PHT on Chi Square Testing (p <0.01, 95% CI). Mean PASP in the group with mortality within 3 years was 65.6 mm Hg compared to 48.3 mm Hg to the group that was alive at 3 years.

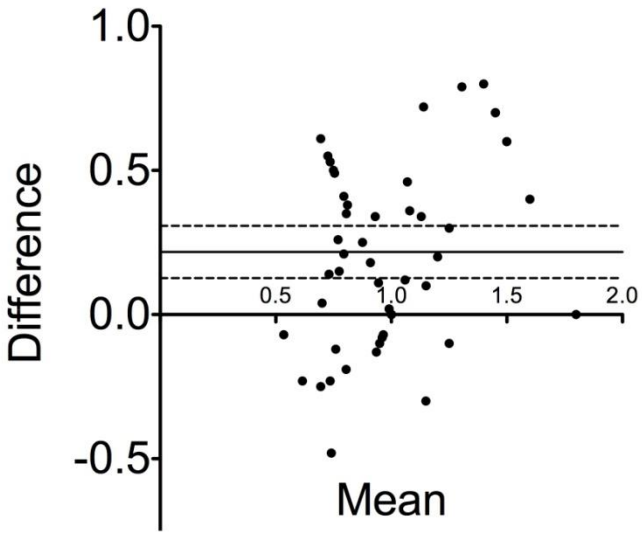

Fig 1B. Bland-Altman plot of aortic valve area as calculated by echocardiogram versus cardiac catheterization.

IV. Discussion

Coronary angiography is routinely performed in patients with aortic stenosis with symptoms of angina to identify concomitant coronary artery disease. Some centers choose to obtain a hemodynamic assessment during the cardiac catheterization study however this is not routinely done. Connelly et al showed a gradual decrease in hemodynamic cardiac catheterization since 1990 at the Mayo Clinic with less than 15% of patients undergoing hemodynamic cardiac catheterization in 1998 and 1999 for assessment of valvular hemodynamics (3). This decrease is mostly due to the diagnostic certainty of hemodynamics, thought to be provided by echocardiography. TTE may reliably assess the severity of aortic stenosis as compared to left heart catheterization hemodynamics (10). However, no prior studies have compared right heart catheterization hemodynamics with TTE in aortic stenosis.

Arcasoy et al (11) and Swanson et al (12) showed that in patients with advanced lung disease, right ventricular systolic pressure obtained with Doppler echocardiography is not reliably accurate in assessment of pulmonary hypertension. To our knowledge, our study is the first to compare the ability of echo Doppler to reliably assess for pulmonary hypertension comparing it to the gold standard of invasive hemodynamic measurements.

Prior studies have mostly used echocardiography to assess the degree of pulmonary hypertension. Johnson et al (13) and Faggiono et al (9) used invasive hemodynamics to assess degree of pulmonary hypertension in aortic stenosis and found the prevalence to be as high as 50% and 65 % respectively. Our study showed 93 % of patients with symptomatic aortic stenosis had PHT. Severe PHT was found in 35%. We report the highest prevalence of PHT in our population of patients with aortic stenosis. Even if patients with other medical conditions such as chronic obstructive lung disease, obstructive sleep apnea, and mitral or aortic insufficiency were excluded, prevalence of severe PHT was up to 30 %. Prior studies showed severe PHT to be 15-16% (9, 13). There was a positive correlation between weight and PASP obtained by catheterization, which is consistent with Weyman et al assessment of PASP obtained by echocardiography of normal subjects (18). The degree of obesity in our study population was a likely contributing factor to such a high prevalence of PHT. Obese patients are more likely to have poor quality studies, making it difficult to estimate the TR velocity (14). Regardless of the cause of PHT, these patients are at higher

HEMODYNAMIC MEASUREMENT	RANGE (MEAN)
LVEDP	7 – 41 (23.5) mm Hg
LVEF	15 – 75 % (50%)
PASP	22 - 118 (52.5)
PCWP	7 – 40 (20) mm Hg
PVR	1.21 – 7.6 (3.1)
ECHO-RVSP	20-80 (32.3) mm Hg

Table 2 : Legend: PASP – Pulmonary Artery Systolic Pressure, LVEDP – Left Ventricular End Diastolic Pressure, PVR – Pulmonary Vascular Resistant, LVEF – Left Ventricular Ejection Fraction PCWP – Pulmonary Capillary Wedge Pressure

risk of morbidity and mortality. The presence of pulmonary hypertension was also independent of underlying medical problems such as COPD, OSA or valvular regurgitation. Pulmonary hypertension may develop even in patients with mild aortic stenosis. It is unclear why certain patients with aortic stenosis develop severe PHT. Recently E/E' ratio on echo has been shown to be of prognostic value which points to diastolic dysfunction as a likely etiology (17). Our study also suggests that elevated LVEDP obtained by hemodynamics, correlates well with the severity of pulmonary HTN. However Siegel et al, showed no prognostic significance of PASP, based on echo-doppler. Prior studies showed that severe pulmonary hypertension is an independent predictor of perioperative mortality and early AVR has been recommended for this sub-group even when asymptomatic (7). Reversibility of PHT after AVR in patients with AS has been shown (8). This suggests relieving the aortic obstruction improves the LVEDP and subsequently, lowers the pulmonary pressure. The etiology of pulmonary hypertension in aortic stenosis remains unclear. Severity of pulmonary hypertension was independent of severity of aortic stenosis. This is consistent with the findings of Faggiano et al that PASP showed no relation to aortic valve area in patients with PHT and isolated AS (9). We found a weak albeit significant correlation between PASP measured by right heart hemodynamics and LVEDP measured by left heart catherization which is also consistent with prior studies (9, 13). A PVR > 3 suggests intrinsic pulmonary cause of pulmonary hypertension. In patients with PVR < 3, there was a stronger correlation between LVEDP and PASP suggesting diastolic dysfunction may be the initial insult in aortic stenosis leading to pulmonary hypertension. There was a higher 3- year

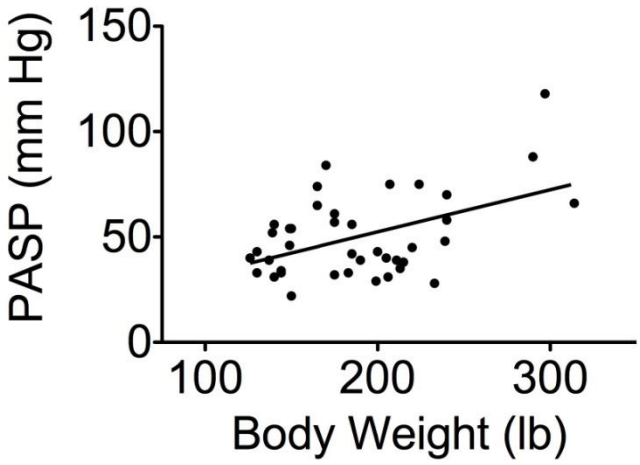

Fig. 2 There was a significant correlation betweens patients body weight and PASP obtained on cardiac catheterization. (R^2= 0.224 P=0.002)

mortality in patients with severe PHT, which is consistent with prior studies. There was a significant correlation between AVA measured by left heart catherization and echocardiography. However, echocardiography overestimates the severity of aortic stenosis and is unreliable when using AVA obtained by catheterization as a gold standard. Echocariographic measurements underestimate the number and severity of patients with pulmonary hypertension in aortic stenosis. By echocardiography alone, 31.5 % patients with aortic stenosis had PHT, which is consistent with prior studies (1). But if echocardiography were used alone, 25% of patients with severe PHT would be missed. Echocardiography testing that was unable to detect right heart pressures or detected normal pressures were considered missed diagnoses. Some patients in this group had such severe pulmonary hypertension that surgery would be contra-indicated.

PARAMETERS	r	p Value
AVA-ECHO and AVA-Cardiac Cath	0.555	<0.0001
PASP and ECHO-RVSP	0.344	0.009
PASP and LVEDP	0.348	0.024
PASP and LVEDP *	0.655	
PASP and AVA-Cardiac Cath	- 0.105	<0.0001
AVA-Cardiac Cath and LVEDP	-0.141	0.24
PASP and LVEF-Cardiac Cath	-0.296	0.419
PASP and Weight	0.473	0.136
		0.002

Table 3

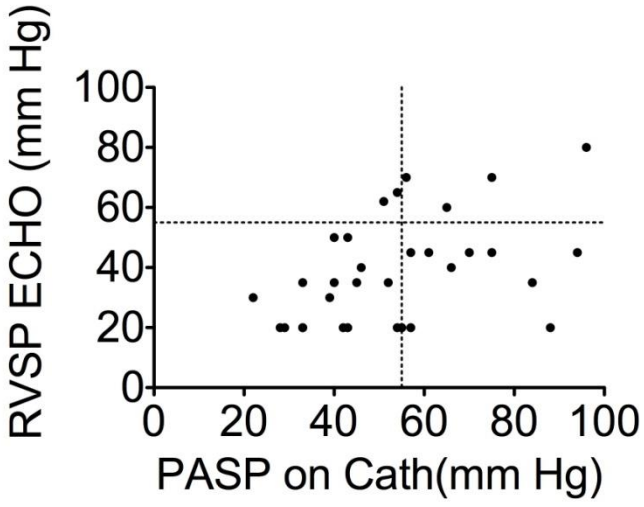

Fig. 3A Correlation between PASP obtained by hemodynamic measurement with catheterization vs. RVSP obtained on echocardiogram. There was correlation (R^2=0.208 p<0.01) however , using a cutoff of 55 mm Hg as moderate pulmonary HTN , there was a high number of false positives when echocardiogram is used to assess severity of pulmonary HTN.

Echocardiography had a sensitivity of 46.8% and a specificity of 100% for detecting pulmonary hypertension. This low sensitivity is consistent with studies that compared

echocardiography with RHC in other disease conditions that cause PHT (5, 15, and 16). Despite such a high specificity, due to such a low sensitivity of echocardiography in detecting PHT, RHC should be considered in patients with aortic stenosis when there is a concern for PHT.

		PASP (mm Hg)		
		<40	>40	Total
ECHO RVSP (mm Hg)	<40	15	17	32
	>40	0	15	15
	Total	15	32	47

Table 4 Sensitivity – TP/TP+FN = 0.46875 (95% CI 0.29 – 0.64) Specificity – TN/FP + TN = 1 (95% CI 0.74 – 1)

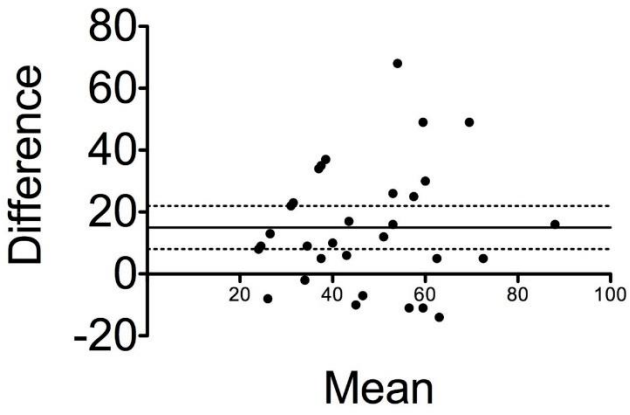

Fig. 3B. Bland-Altman plot of PASP determined by catheterization versus echocardiogram

V. Limitations

Our study did not compare aortic stenosis patients with and without pulmonary hypertension. There were a very small number of patients with no pulmonary hypertension. Surgical outcomes were not evaluated. It is not known if the presence of pulmonary hypertension across all severities of aortic stenosis concurs a poor prognosis. The duration of symptoms in our patients was not evaluated .The degree of pulmonary hypertension may vary with duration of symptoms. Our data base was limited to those patients with aortic stenosis who underwent cardiac catherization. Patients who were found to have mild aortic stenosis on echocardiography may not have been referred for hemodynamic studies. Also, pulmonary function tests and sleep studies were not available in all patients. We relied on previously documented disease or clinical symptoms .Some of our patients may have had an undiagnosed condition causing the pulmonary hypertension.

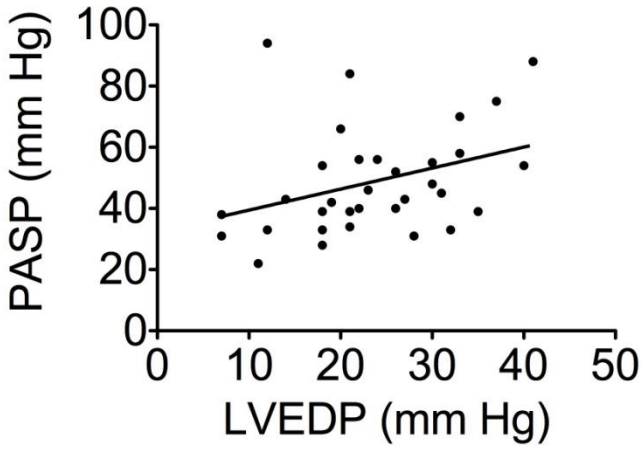

Fig. 4 – Correlation between LVEDP and PASP obtained on cardiac catheterization. (R^2=0.121 $p<0.05$)

VI. Conclusion

Pulmonary hypertension is highly prevalent in patients with all degrees of severity of aortic stenosis. Severe pulmonary hypertension was found in up to 35% of patients with aortic stenosis even after excluding patients with conditions that could potentially cause pulmonary hypertension. Echocardiographic assessment of RVSP correlates with PASP assessed by right heart hemodynamics however echocardiography underestimates pulmonary hypertension in patients with aortic stenosis, possessing a sensitivity of only 48%. RHC provides a more accurate assessment of PASP. PASP correlates with LVEDP, suggesting that diastolic dysfunction of the left heart (elevated LVEDP) and of the right heart (elevated RVEDP) may be at least in part be contributing to the elevated pulmonary pressures. Elevated left atrial pressure with backward transmission to the pulmonary veins and the pulmonary capillaries may also be responsible.

References

[1]. Silver K, Aurigemma G, Krendel S, Barry N, Ockene I, Alpert J. Pulmonary artery hypertension in severe aortic stenosis: incidence and mechanism. *Am Heart J* 1993; 125:146–50.

[2]. Nikhil Kapoor, Padmini Varadarajan, and Ramdas G. Pai. Echocardiographic predictors of pulmonary hypertension in patients with severe aortic stenosis. *European Journal of Echocardiography* (2008) 9, 31-33

[3]. Connolly HM, Ballman KV, Roger VL, Tajik AJ, Aosrtic stenosis: no more hemodynamic cardiac catherization (letter). *Mayo Clin Proc* 2001; 76:961

[4]. C.M. Schannwell, S. Steiner, B-E. Strauer, Diagnostics in Pulmonary Hypertension, *Journal of Physiology and*

Pharmacology 2008, 58, Suppl 5, 591-602

[5]. Homma A, Anzueto A, Peters JI et al., Pulmonary artery systolic pressures estimated by echocardiogram vs cardiac catherization in patients awaiting lung transplantation, *J Heart Lung Transplant*, 2001; 20: 833-39

[6]. Torbicki A, Skwarski K, Hawrylkiewics I et al Attempts at measuring pulmonary arterial pressure by means of Doppler echocardiography in patients with chronic lung disease.,*Eur Respir J*, 1989; 2: 856-60

[7]. Joseph F. Malouf, Maurice Enriquez-Sarano, Patricia Pellikka et al., Severe Pulmonary Hypertension in Patients With Severe Aortic Valve Stenosis: Clinical Profile and Prognostic Implications, *Journal of the American College of Cardiology*, 2002. Vol.40, No.4; 789-95

[8]. G.P. Tracy, M.S. Proctor and C.S. Hizny Reversibility of pulmonary artery hypertension in aortic stenosis after aortic valve replacement. *Ann Thorac Surg* , 1990 , Vol.50 , 89-93

[9]. Pompilio Faggiono , Francesco Antionin-Canterin, Falvio Ribichini et al., Pulmonary Artery Hypertension in Adult Patients With Symptomatic Valvular Aortic Stenosis**,** *Am J Cardiol* 2000;85:204-208

[10]. Leborgne L.; Tribouilloy C.; Otmani A; Peltier M.; Rey J. et al., Comparative value of Doppler echocardiography and cardiac catherization in the decision to operate on patients with aortic stenosis,
International Journal of Cardiology, 1998 , Vol. 65 , No.2 , 163-168

[11]. Arcasoy SM, Christie JD, Ferrari VA et al Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Clinical risk factors for primary graft failure following lung transplantation., *Am J Respir Crit Care Med* , 2003, 167:735-40

[12]. Karen L. Swanson , James P. Utz , Michael J. Krowka et al., Doppler echocardiography – right heart catherization relationships in patients with idiopathic pulmonary fibrosis and suspected pulmonary hypertension, *Med Sci Monit* , 2008; 14(4): CR177-182

[13]. LW Johnson, MB Hapanowicz, C Buonanno, MA Browser et al, Pulmonary hypertension in isolated aortic stenosis. Hemodynamic correlations and follow-up, *The Journal of Thoracic and Cardiovascular Su*rgery 1988, Vol 95 , 603-607

[14]. 14 Robert S. Finkelhor , Moayyed Moallem , and Robert C. Bahler, Characteristc and Impact of Obesity on the Outpatient Echocardiographic Laboratory *J Cardiol* 2006;97 :1082 – 1084)

[15]. 15 Wylie BJ , Epps KC , Gaddipati S , Waksmonski CA Correlation of transthoracic echocardiography and right heart catherization in pregnancy, *J Perinat Med*. 2007; 35(6):497-502

[16]. 16 Vivien M. HSU , Abel E. Moreyra, Alan C. Wilson et al., Assessment of Pulmonary Arterial Hypertension in Patients with Systemic Sclerosis: Comparison of Noninvasive Testing with Reults of Right-Heart Catherization, *J Rheumatol* 2008;35:458-65

[17]. 17 Biner S, Rafique AM, Goykhman P, Morrissey RP, Naghi J, Siegel RJ., Prognostic Value of E/E' Ratio in Patients With Unoperated Severe Aortic Stenosis *JACC Cardiovasc Imaging*. 2010 Sep;3 (9):899-90

[18]. 18. McQuillan BM, Picard MH, Leavitt M, Weyman AE., Clinical Correlates and Reference Intervals for Pulmonary Artery Systolic Pressure Among Echocardiographically Normal Subjects**,** *Circulation*. 2001 Dec 4;104 (23):2797-802

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