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Review Article

Pulmonary Hypertension Complicating Systemic Hypertension, Is Diastolic Dysfunction the Culprit?

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Abstract

Background: Elevation in PA pressures has been observed by 2D echo in some but not all hypertensive patients. The mechanism and hemodynamic impact of pulmonary hypertension in these patients remains unclear.

Methods: We reviewed echoes of all patients referred with systemic hypertension between 9/2006 to 5/2009 to identify those patients with left ventricular hypertrophy, normal systolic function, and evidence of PH (i.e., systolic PA pressure (sPAP) >35 mmHg by echo). Patients with primary pulmonary disease, renal disease requiring dialysis, systolic dysfunction, valvular heart disease, and infiltrative cardiac disease were excluded from analysis. Quantitative measures of cardiac chamber size, and right and left ventricular hemodynamics were assessed in these patients (n=185) using standard methods, including calculation of diastolic PA pressure (dPAP) and mean PA pressure ([mPAP). LV remodeling was assessed with relative wall thickness (RWT), and diastolic function using mitral annular tissue Doppler (E/E).

Results: Interestingly, sPAP correlated with left atrial area (R=0.18, p=0.03), while dPAP showed significant correlation to tissue Doppler septal E/E'(R=0.23, p<0.04). Right atrial area was associated with increases in mPAP (R=0.47, p<0.001), sPAP (R=0.19, p=0.02), and dPAP (R=0.25, p=004). In addition, mPAP was higher in patients with RWT ≥0.45 (37.37 mmHg vs 14.42, p=0.0013). Furthermore, a highly significant correlation was also observed between RWT and septal E/E' (R=0.33, p<0.0001).

Conclusions: In patients with systemic hypertension and evidence of PH, pulmonary pressure appears to be related to LV diastolic function as evidenced by both left atrial dilation and elevated diastolic filling pressure. This may be a consequence of the abnormal LV remodeling observed. These findings support a mechanism for development of PH in systemic hypertension. Moreover, the observed relation between pulmonary pressure and right atrial enlargement suggests important anatomic repercussions in this subset of patients.

ABBREVIATIONS

dPAP: diastolic Pulmonary Arterial Pressure; LA: Left Atrium; LV: Left Ventricle; LVH: Left Ventricular Hypertrophy; mPAP: mean Pulmonary Arterial Pressure; PA: Pulmonary Artery; RA: Right Atrium; RWT: Relative Wall Thickness; sPAP: systolic Pulmonary Arterial Pressure; TRV: Tricuspid Regurgitant Velocity

INTRODUCTION

Pulmonary hypertension (PH) has been observed in patients with systemic hypertension (HTN) and preserved left ventricular systolic function. However, the etiology and hemodynamic repercussions of pulmonary hypertension in this subset of hypertensive patients is not entirely clear. It is possible that the elevated pulmonary pressures may simply reflect transmitted elevations of systemic pressure, and that revert to normal when blood pressure is optimally controlled. Alternatively, PH may be related to impaired diastolic function due to left ventricular remodeling and associated with more important and potentially irreversible changes in right cardiac morphology and hemodynamics.

Invasive assessment of hypertensive patients with PH is limited. Olivari et al. performed invasive hemodynamic measurements in a small group of hypertensive patients and showed significant elevations in pulmonary pressures associated with elevation of systemic blood pressure. Although this analysis first described the relationship between pulmonary pressures and systemic pressure, the study did not offer insight into etiology, mechanisms or hemodynamic implications [1]. Subsequent studies have also identified the presence of PH in

patients with systemic HTN [2-4], but have largely been limited to observational reports regarding their coexistence. In the present study we proposed to clarify the determinants and repercussions of pulmonary hypertension in a large cohort of patients with systemic hypertension.

METHODS

Study cohort

All echocardiograms performed at the George Washington University Hospital between September of 2006 and May of 2009 was reviewed to identify patients with systemic hypertension, as defined by blood pressure ≥ 140/90 or pharmacologic treatment, and LVH (defined as septal or posterior wall thickness ≥ 1.1 cm). Of the 2,444 patients identified, pulmonary hypertension (i.e., calculated sPAP ≥ 35mmHg on echo) was present in 394. Patients with primary pulmonary disease, renal failure requiring dialysis, LV systolic dysfunction, valvular heart disease, and infiltrative cardiac disease were excluded. The final study cohort included 185 patients with systemic hypertension and pulmonary hypertension without other secondary cause.

Transthoracic echocardiography and measurements

2D echocardiograms were performed using Philips IE-33 machines (Andover, Massachusetts) and analyzed on an Agfa Heartlab (Ridgefield Park, New Jersey) workstation. Quantitative measures of cardiac chambers size, right and left ventricular hemodynamics were assessed using standard methods. Echo data recorded for analysis included: LV septal and posterior wall thickness, RV mid 1/3 diameter, RA and LA areas, LV end diastolic and systolic diameters, pulmonic regurgitant peak and end velocities, tricuspid regurgitant velocity (TRV), mitral inflow E and A velocities and deceleration time, and annular tissue Doppler velocities (septal and lateral e').

Systolic pulmonary pressure was calculated from peak TRV using standard methods [5,6]. The calculation of diastolic and mean pulmonary pressures (dPAP, mPAP) was performed using Doppler velocity of the pulmonic regurgitant flow velocity [7,8]. Diastolic function of the left ventricle was assessed using the ratio of mitral inflow E velocity and tissue Doppler annular velocities (E/e'), as previously described for estimation of LV filling pressures [9]. Relative wall thickness was calculated using standard methods to categorize LV remodeling [10].

Statistical analysis

Demographic data is reported as a mean ± standard error. Pearson correlation coefficients with two-tailed p values were used to assess the relationship between sPAP and E/e' as well dPAP and LA size. Likewise, Pearson r was calculated for the correlation between sPAP, dPAP, and mPAP and RA size. T test was used to calculate the difference of mPAP in patients with RWT < 0.45 and those with RWT ≥ 0.45. Finally, Pearson correlation was calculated for the relationship between RWT and E/e'. Statistical calculations were performed using the MedCalc version 11.3 (Mariakerke, Belgium) software package.

RESULTS

Patient characterization

Patient demographics and pertinent medical history are summarized. Patients were older with a mean age over 70 years, and there was a slight male predominance (52%). Furthermore, more than one-third of the cohort were diabetic, and about one-fourth had prior admission or diagnosis of heart failure. Patients were taking a variety of antihypertensive medications; blood pressure at the time of echo was mildly elevated.

Echocardiographic findings

Echocardiographic findings are summarized. On average, patients demonstrated biatrial enlargement, as well as evidence of elevated LV filling pressure with the mean septal E/e' > 15. On average, pulmonary systolic pressure elevations were in the moderate range.

Correlates of pulmonary pressures

Pulmonary pressure correlated with markers of diastolic dysfunction. A statistically significant relationship was observed between sPAP and LA size, and between dPAP and septal E/e'.

Increasing pulmonary pressures (mPAP, dPAP and sPAP) were also associated with RA dilation, with the strongest correlation noted for mPAP.

Calculated Pearson correlations and p values are in summarized.

Pulmonary pressure and LV remodeling

mPAP was greater among hypertensive patients with concentric remodeling compared to those without evidence of remodeling (37.37 mmHg in patients with RWT ≥ 0.45 vs. 14.42 mmHg in the patients with RWT < 0.45 p = 0.0013). PVR was also greater in patients with LV remodeling (RWT ≥ 0.45) compared to patients with normal LV geometry, (2.38 vs. 1.16 woods units, p=0.028). A statistically significant correlation was observed between RWT and septal E/e', Pearson correlation was 0.33, p < 0.0001.

DISCUSSION

We identified a cohort of hypertensive patients with normal left ventricular systolic function and coexistent PH, in the absence of other underlying causes for elevated pulmonary pressure. Magnitude of pulmonary pressure elevation in these patients was associated with left ventricular diastolic dysfunction as evidenced by left atrial enlargement and calculated diastolic pressure by tissue Doppler imaging. Diastolic dysfunction and left atrial enlargement in systemic HTN have been reported by a number of investigators [2-4], and is believed to be an important marker of adverse remodeling that may contribute to the development of heart failure with preserved EF. [2].

The findings from the present study also suggest that left ventricular diastolic dysfunction also impacts importantly on the right-sided cardiac morphology and hemodynamics. In our study, this was apparent from the relationship between indices of diastolic dysfunction and right atrial size as well as magnitude of PH. Prior studies have shown that right atrial dilation was associated with increased in mortality in patients with primary PH [14,15]. Whether this increase in mortality extends to our cohort of hypertensive patients with evidence of elevated pulmonary pressures in the absence of other underlying cause is unclear.

Recent consensus statement has revised the classification of PH to better differentiate the etiology [11-13]. In this revised classification, clear distinction is made between pulmonary venous and pulmonary arterial hypertension. Pulmonary venous hypertension is caused by elevated left sided pressure [most commonly systemic hypertension] that is transmitted to the right sided circulation. Pulmonary venous hypertension is considered a reversible disorder; pressure can be decreased with afterload reduction and diuresis. On the other hand pulmonary arterial hypertension occurs as a consequence of increases in PVR and is often irreversible.

In our cohort of patients with systemic hypertension and coexistent pulmonary hypertension, pulmonary pressure did not correlate well with systemic pressures, although a single blood pressure recording may be of limited value in this regard. On the other hand, pulmonary pressure was significantly related to indices of left ventricular diastolic function, and importantly, pulmonary vascular resistance. These findings imply that the development of elevated pulmonary pressures in this cohort is multifactorial and not simply due to passive elevation of filling pressures. Lastly, left ventricular remodeling appeared to play a role in the development of PH in our hypertensive patients. Patients with remodeling and concentric LVH hypertrophy had substantially greater pulmonary pressures and higher PVR in comparison to patients with normal LV chamber sizes. This observation suggests that potentially irreversible changes in the pulmonary vascular may occur in these patients. We propose that patients with systemic hypertension develop varying degrees of diastolic dysfunction. In some patients, this diastolic dysfunction is associated with adverse remodeling and development of pulmonary hypertension.

Although optimal blood pressure management appears to be paramount in this subset of hypertensive patients, there may be a role for newer agents. Phosphodiesterase inhibitors, including sildenafil, have been an important therapeutic addition to the management of pulmonary arterial hypertension. These agents often reduce PVR and prevent progression of disease in patients with pulmonary arterial hypertension. In animal models of preserved systolic function heart failure treatment with sildenafil prevented the development of pulmonary hypertension in rats [16]. Furthermore, sildenafil improved functional class of patients with secondary pulmonary hypertension from left ventricular systolic dysfunction [17]. The role of phosphodiesterase inhibitors in patients with pulmonary venous hypertension in patients with preserved systolic function is under active clinical investigation [18].

LIMITATIONS

Our retrospective observational analysis has several limitations. We were unable to demonstrate a relationship between systemic blood pressure and pulmonary pressure. A single blood pressure was obtained proximate to the echocardiographic examination, may not reflect patients' mean pressure. Ambulatory monitoring would be more ideal as it would depict a more representative profile of blood pressure severity. Furthermore, patients were receiving a variety of antihypertensive medications, including calcium channel blockers that can affect pulmonary pressures.

Our analyses showed weak though statistically significant correlations among pulmonary pressures and diastolic function, as well as echocardiographic findings. This suggests that the development of elevated pulmonary artery pressure in systemic hypertension is multifactorial. Despite the weak correlations, the statistically significant relationships provide important data regarding a possible mechanism for development of pulmonary hypertension among certain hypertensive patients, and suggest important hemodynamic repercussions.

CONCLUSION

Pulmonary hypertension is not uncommon in patient with systemic hypertension. The mechanism for development of pulmonary hypertension may be related to LV geometry and remodeling, and consequent changes in diastolic function. Elevated pulmonary pressure in this subset of patients appears to be associated with changes in right atrial size, an important predictor of morbidity and mortality. Optimal blood pressure control would appear to be of particular importance in this subset of hypertensive patients. The role of agents, such as phosphodiesterase inhibitors in management of these patients is an area of active investigation.

REFERENCES

1. Olivari MT, Fiorentini C, Polese A, Guazzi MD. Pulmonary hemodynamics and right ventricular function in hypertension. Circulation. 1978; 57: 1185-1190.
2. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am Coll Cardiol. 2009; 53: 1119-1126.
3. Enriquez-Sarano M, Rossi A, Seward JB, Bailey KR, Tajik AJ. Determinants of pulmonary hypertension in left ventricular dysfunction. J Am Coll Cardiol. 1997; 29: 153-159.
4. Tumminello G, Lancellotti P, Lempereur M, D'Orio V, Pierard LA. Determinants of pulmonary artery hypertension at rest and during exercise in patients with heart failure. Eur Heart J. 2007; 28: 569-574.
5. Berger M, Haimowitz A, Van Tosh A, Berdoff RL, Goldberg E. Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound. J Am Coll Cardiol. 1985; 6: 359-365.
6. Bossone E, Bodini BD, Mazza A, Allegra L. Pulmonary arterial hypertension: the key role of echocardiography. Chest. 2005; 127: 1836-1843.
7. Lee RT, Lord CP, Plappert T, Sutton MS. Prospective Doppler echocardiographic evaluation of pulmonary artery diastolic pressure in the medical intensive care unit. Am J Cardiol. 1989; 64: 1366-1370.
8. Masuyama T, Kodama K, Kitabatake A, Sato H, Nanto S, Inoue M. Continuous-wave Doppler echocardiographic detection of pulmonary regurgitation and its application to noninvasive estimation of pulmonary artery pressure. Circulation. 1986; 74: 484-492.
9. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr. 2009; 22: 107-33.
10. Ganau A, Devereux RB, Roman MJ, de Simone G, Pickering TG, Saba PS, et al. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. J Am Coll Cardiol. 1992; 19: 1550-1558.
11. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology

Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol. 2009; 53: 1573-1619.

12. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2009; 54: S43-54.

13. Hoeper MM, Barberà JA, Channick RN, Hassoun PM, Lang IM, Manes A, et al. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. J Am Coll Cardiol. 2009; 54: S85-96.

14. Cioffi G, de Simone G, Mureddu G, Tarantini L, Stefenelli C. Right atrial size and function in patients with pulmonary hypertension associated with disorders of respiratory system or hypoxemia. Eur J Echocardiogr. 2007; 8: 322-331.

15. Bustamante-Labarta M, Perrone S, De La Fuente RL, Stutzbach P, De La Hoz RP, Torino A, et al. Right atrial size and tricuspid regurgitation severity predict mortality or transplantation in primary pulmonary hypertension. J Am Soc Echocardiogr. 2002; 15: 1160-1164.

16. Yin J, Kukucka M, Hoffmann J, Sterner-Kock A, Burhenne J, Haefeli WE, et al. Sildenafil preserves lung endothelial function and prevents pulmonary vascular remodeling in a rat model of diastolic heart failure. Circ Heart Fail. 2011; 4: 198-206.

17. Lewis GD, Shah R, Shahzad K, Camuso JM, Pappagianopoulos PP, Hung J, et al. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. Circulation. 2007; 116: 1555-1562.

18. Guazzi M, Vicenzi M, Arena R, Guazzi MD. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. Circulation. 2011; 124: 164-174.

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