

The clinical associations with cardiomegaly in patients undergoing evaluation for pulmonary hypertension

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ABSTRACT

Background

Chest radiographs can identify important abnormalities in patients undergoing diagnostic evaluation for cardiovascular diseases. Cardiomegaly often reflects cardiac chamber dilation, or cardiac muscle hypertrophy, or both conditions. The clinical implications of cardiomegaly depend on the underlying clinical disorder. Does cardiomegaly have any clinical, laboratory, echocardiographic, and right heart catheterization associations in patients undergoing evaluation for pulmonary hypertension?

Methods

Patients referred to a pulmonary vascular disease clinic for possible pulmonary hypertension underwent a comprehensive evaluation that included right heart catheterization. These patients also had chest radiographs, laboratory studies, and echocardiograms. The patients were divided into two groups based on the presence or absence of cardiomegaly.

Results

This study included 102 patients (63.7% female) with a mean age of 62.3 ± 15.0 years. Patients with cardiomegaly ($n = 64$) had elevated BNP, BUN, and creatinine levels. They had elevated right atrial pressures, right ventricular pressures, and pulmonary artery pressures and reduced cardiac indices and reduced mixed venous oxygen saturations. There were no differences in echocardiographic parameters between the two groups.

Conclusions

This study demonstrates that the presence of cardiomegaly on chest radiographs has important clinical implications, including increased BNP levels and increased right heart pressures, in patients undergoing evaluation for pulmonary hypertension. Consequently, the presence of cardiomegaly supports the need for additional evaluation, including right heart catheterization, and provides useful information for primary care physicians and specialists.

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Abbreviation

:BNP- brain natriuretic peptide; BUN- blood urea nitrogen

1. Background

Routine chest radiographs can provide important information about the cardiovascular system, and important observations include cardiomegaly, pulmonary congestion/edema, and pleural effusions. Cardiomegaly can reflect chamber dilation, ventricular wall hypertrophy, and/ or pericardial effusion. In most patients, cardiomegaly represents the end result of an important clinical disorder, such as hypertension, ischemic heart disease, valvular heart disease, cardiomyopathy, or pulmonary hypertension [1–3]. Cardiomegaly may have important clinical implications and potentially predicts abnormal laboratory results, abnormal echocardiographic parameters, and abnormal hemodynamics. In addition, cardiomegaly has important effects on lung function [4,5].

2. Purpose

This study evaluates the associations between cardiomegaly on plain chest x-rays with clinical, laboratory, echocardiographic, and hemodynamic tests in patients undergoing evaluation for possible pulmonary hypertension [6,7].

3. Methods

Information was collected from electronic medical records on patients referred to the Pulmonary Vascular Disease Clinic in the Department of Internal Medicine at Texas Tech University Health Sciences Center in Lubbock, Texas, who underwent right heart catheterization at University Medical Center in Lubbock between 1 January 2019 and 20 May 2020. This retrospective study included all patients undergoing right heart catheterization during this time interval. There were no exclusions. Demographics, clinical information, laboratory results, chest x-rays, echocardiograms, and right heart catheterization hemodynamic parameters were recorded. Cardiomegaly was defined radiographically as a heart size that exceeded 50% of the internal diameter of the thorax on the posterior-anterior film; these calculations were made by the senior author (KN, a pulmonary physician with more than 40 years of experience in clinical medicine). A hemodynamic composite score based on a recent publication was calculated using right heart catheterization data (Table 1) [8]. All cardiac catheterizations were done by one author (VT, a pulmonary physician with 21 years of experience in performing and interpreting right heart catheterizations).

4. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics. Results were summarized using means,

Table 1. Hemodynamic summary score classification.

Hemodynamic Parameter	Value Range	Assigned Score (1–3)
Right Atrial Pressure (mm Hg)	< 8	1
	8–14	2
	> 14	3
Cardiac Index (L/min/m ²)	≥ 2.5	1
	2.0–2.4	2
	< 2.0	3
Mixed Venous Oxygen Saturation (%)	> 65	1
	60–65	2
	< 60	3
Composite scores		
Low score group	3,4,5	
Mid score group	6,7	
High score group	8,9	

Modified from reference⁸

standard deviations, and numbers with percentages. Numerical values were compared between participants with and without cardiomegaly using independent samples t-tests. Levene's test was used to determine the equality of the variances. If $p < 0.05$ for Levene's test, equal variance was not assumed. BNP levels and echocardiographic parameters did not have a normal distribution; these values were converted to log 10 and did have a normal distribution for statistical analysis. Some numerical variables were divided into high and low groups based on the median to compare to cardiomegaly using Chi-Square test and odds ratio. Statistical significance was set at $p < 0.05$.

5. Ethical considerations

This study (L20-174) was approved by the Institutional Review Board at Texas Tech University Health Sciences Center in Lubbock, Texas, and had administrative approval from University Medical Center in Lubbock, Texas.

6. Results

This study included 102 patients presenting for evaluation for possible pulmonary hypertension who underwent comprehensive evaluations, including right heart catheterization. The mean age was 62.3 ± 15.0 years, 63.7% of patients were female, and 24.5% were Hispanic. Sixty-four patients (62.7%) had cardiomegaly based on chest radiographs. There were no statistically significant differences in age, gender, or ethnicity between patients with or without cardiomegaly. Ninety-one patients (89.2%) presented with shortness of breath. There was no statistically significant difference between the frequency of shortness of breath in patients with cardiomegaly compared to those without cardiomegaly. Forty-eight patients (47.1%) presented with edema peripheral edema during their initial evaluation. There was no statistically significant difference

Table 2. Laboratory value association with cardiomegaly.

Laboratory Value	Cardiomegaly	No Cardiomegaly	p Value
Log BNP	3.12 ± 0.80*	2.40 ± 0.71	0.00003**
Na ⁺ (mmol/L)	139.1 ± 3.8	140.3 ± 2.9	0.092
K ⁺ (mmol/L)	4.14 ± 0.54	4.18 ± 0.47	0.065
Cl ⁻ (mmol/L)	99.8 ± 5.7	102.6 ± 3.5	0.003
CO ₂ (mm Hg)	26.7 ± 5.7	25.5 ± 2.7	0.133
BUN (mg/dL)	24.1 ± 13.6	17.2 ± 10.4	0.005
Creatinine (mg/dL)	1.34 ± 1.05	0.89 ± 0.29	0.002

* All numbers represent the mean ± 1 SD; **bold numbers represent p values less than 0.05.
BNP- brain natriuretic peptide; BUN-blood urea nitrogen.

in the frequency of edema in patients with cardiomegaly compared to those without cardiomegaly. Common comorbidities included hypertension (73.5%), diabetes (38.2%), and obstructive sleep apnea (38.2%). There was no statistically significant association between cardiomegaly and any comorbidity. There were no statistically significant differences in systolic or diastolic blood pressures in these two groups.

Patients with cardiomegaly had significant differences in some laboratory tests compared to patients without cardiomegaly; these included significantly higher log brain natriuretic peptide (BNP), significantly higher blood urea nitrogen (BUN) and creatinine levels, and significantly lower chloride levels (Table 2). There were no significant differences in right atrial indices, right ventricular indices, left atrial indices, or left ventricular indices measured by echocardiography in patients with or without cardiomegaly (Table 3). There were no significant differences in left ventricular global strain, left ventricular free wall strain, septal strain, or right ventricular free wall strain on echocardiography between patients with or without cardiomegaly (Table 3). Patients with cardiomegaly had significantly higher cardiovascular pressures on right heart catheterization than patients without cardiomegaly; these included right atrial pressures, right ventricular systolic pressures, and pulmonary artery pressures (Table 4).

Cardiac catheterization results were analyzed by grouping patients based on a hemodynamics score that includes right atrial pressure, cardiac index, and mixed venous O₂ saturation (Table 1). Patients with cardiomegaly had significantly higher right atrial pressures ($p = 0.0002$) and were 4.23 times more likely to have high right atrial pressure ($p = 0.001$) than patients without cardiomegaly. Patients with cardiomegaly had significantly lower mixed venous O₂ saturations ($p = 0.01$) and were 3.22 times more likely to have low mixed venous oxygen saturation ($p = 0.007$). Based on criteria in Table 1, patients with cardiomegaly had higher hemodynamic summary scores with a mean hemodynamic summary score of 5.75 ± 1.65 ; in comparison patients without cardiomegaly had a mean score of 4.79 ± 1.55 ($p = 0.004$) (Figure 1). Patients with cardiomegaly were 3.47

Table 3. Echocardiographic parameters in cardiomegaly.

y	Cardiomegaly	No Cardiomegaly	p Value
Log Right Atrial Index [log (ml/m ²)]	1.59 ± 0.21*	1.45 ± 0.30	0.064
Log Right Ventricular Index [log(ml/m ²)]	1.70 ± 0.20	1.63 ± 0.23	0.235
Log Left Atrial Index [log(ml/m ²)]	1.46 ± 0.21	1.37 ± 0.27	0.161
Log Left Ventricular Index [log(ml/m ²)]	1.72 ± 0.20	1.66 ± 0.17	0.379
Log Global Volume Index [log (ml/m ²)]	2.25 ± 0.14	2.17 ± 0.18	0.080
Left Ventricular Global Strain (%)	-13.1 ± 4.5	-12.7 ± 3.4	0.765
Left Ventricular Free Wall Strain (%)	-13.4 ± 5.5	-14.2 ± 4.2	0.601
Septal Strain (%)	-16.7 ± 4.9	-17.4 ± 6.0	0.659
Right Ventricular Free Wall Strain (%)	-18.0 ± 5.4	-18.5 ± 4.8	0.739

* All numbers represent the mean ± 1 SD.

Table 4. Cardiovascular pressure association with cardiomegaly.

	Cardiomegaly	No Cardiomegaly	p Value
Right Atrial Pressure (mm Hg)	13.5 ± 6.9*	8.5 ± 5.0	0.0002**
Right Ventricular Systolic Pressure (mm Hg)	67.6 ± 24.4	50.8 ± 19.8	0.001
Right Ventricular Diastolic Pressure (mm Hg)	3.6 ± 4.8	2.5 ± 3.7	0.221
Pulmonary Artery Systolic Pressure (mm Hg)	68.7 ± 22.7	50.3 ± 20.2	0.00008
Pulmonary Artery Diastolic Pressure (mm Hg)	25.2 ± 9.2	18.1 ± 6.9	0.00009
Mean Pulmonary Artery Pressure (mm Hg)	41.6 ± 13.0	30.7 ± 11.1	0.00004
Wedge Pressure (mm Hg)	18.4 ± 15.4	13.6 ± 5.7	0.066

* All number represent the mean ± 1 SD; bold numbers represent values less than 0.05.

times more likely to be in the intermediate or high hemodynamic score group than the low score group ($p = 0.004$).

7. Discussion

This study demonstrates that the presence of cardiomegaly in patients undergoing comprehensive evaluations for possible pulmonary hypertension has important clinical implications. Patients with cardiomegaly had significantly higher cardiovascular pressures, including right atrial pressures, right ventricular pressures, pulmonary artery systolic and diastolic pressures, and mean pulmonary artery pressures. In our patients, BUN was increased from 17.2 ± 10.4 mg/dL in patients without cardiomegaly to 24.1 ± 13.6 mg/dL in patients with cardiomegaly. Kirtane et al. found an elevated BUN was independently associated with higher mortality and additional comorbidities, such as vascular disease in patients presenting with acute coronary syndromes [9]. A BUN between 20 and 25 mg/dL corresponded

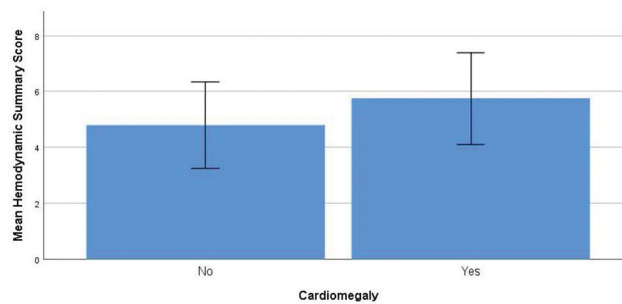


Figure 1. Hemodynamic summary score comparison based on cardiomegaly.

Bars represent ± 1 standard deviation.

to a hazard ratio of 1.9 for mortality, suggesting a link between BUN and mortality in patients with acute ischemic heart disease [9]. Log BNP, a marker of volume overload and heart failure, was also increased in patients with cardiomegaly. Cardiomegaly status was an important indicator of hemodynamic stress, and patients with cardiomegaly were 3.47 times more likely to be in the intermediate or high hemodynamic score group (Tables 1 and Table 4). Echocardiographic indices for chamber volumes tended to be higher in patients with cardiomegaly but did not reach statistical significance. Therefore, the presence of cardiomegaly on routine chest radiographs in patients undergoing evaluation for pulmonary hypertension supports an indication for additional evaluation, including right heart catheterization.

Cardiomegaly has important associations in autopsy studies, exercise studies, and outcomes studies. The cardiothoracic ratio measured by plain radiography and computed tomography in postmortem studies is correlated with heart weight. Michiue et al. used plain radiography of open chests in postmortem studies to determine the cardiothoracic ratio and its correlation with heart size [10]. There was a significant correlation between this ratio and heart weight in patients who had significant heart disease at the time of death ($N = 50$, $r = 0.63$, $p < 0.0001$). Winklhofer and colleagues used postmortem computed tomography to evaluate cardiothoracic ratio in 170 deceased adults [11]. Depending on the criterion used for normal heart weights, 57% to 67% of the adults in this autopsy study had enlarged hearts. The mean cardiothoracic ratio was 0.513 ± 0.07 with a range of 0.28–0.69, and a cardiothoracic ratio of 0.5 had a sensitivity of 78% and a specificity of 71% for detecting increased heart weights. These two studies suggest that increased cardiothoracic ratios in patients should correlate with a heavier heart provided that significant chamber dilatation and pericardial effusion are excluded.

The association between cardiomegaly and exercise performance depends on the underlying cardiac pathophysiology and likely differs in patients who

have primarily left ventricular dysfunction in comparison to patients who have primarily right ventricular dysfunction secondary to pulmonary hypertension. Left ventricular anatomy and remodeling have direct association with exercise performance. For example, Lam et al. measured the effect of left ventricular geometry on exercise capacity based on treadmill performance [12]. This study demonstrated that patients with concentric remodeling (increased wall thickness and normal LV mass index) had better exercise performance than patients with eccentric hypertrophy (increased LV mass index and normal wall thickness) and concentric hypertrophy (increased LV mass index and increased wall thickness). The presence of pulmonary hypertension also has a direct effect on exercise performance. Butler et al. investigated pulmonary hypertension and hemodynamic parameters in patients presenting with heart failure, a condition often associated with cardiomegaly due to either systolic or diastolic dysfunction [13]. In this study, they grouped heart failure patients based on pulmonary vascular resistance into four groups: <1.5 Wood Units, 1.5–2.49 Wood Units, 2.5–3.49 Wood Units, and >3.5 Wood Units. Their analysis found that a higher pulmonary vascular resistance and, therefore, worse pulmonary hypertension was associated with lower resting and peak exercise cardiac outputs and lower peak exercise VO_2 s. Cardiomegaly can also affect lung volumes, which in turn influences exercise capacity and gas exchange. Olson et al. analyzed exercise capacity in 37 patients with heart failure [14]. Patients with increased cardiac volumes based on chest radiography had decreased forced vital capacities and decreased tidal volumes and increased respiratory rates at peak VO_2 .

Cardiomegaly is associated with increased mortality in community-based studies and in studies on some clinical disorders. Frishman and co-investigators prospectively studied the effect of cardiomegaly on mortality in a cohort of elderly subjects [15]. In this study, age, cardiomegaly, diabetes, and a prior myocardial infarction were independent predictors of mortality. After 10 years, 51% of the subjects with a cardiomegaly had died. Pocock et al.

determined the risk factors for morbidity and mortality in patients with chronic heart failure who were in a randomized control study of candesartan [16]. Multiple factors, including cardiomegaly, had an independent effect on outcomes. Centurion et al. summarized several studies evaluating cardiomegaly using cardiothoracic ratios on plain chest radiography and echocardiography and found a good correlation between these two modalities [17]. In addition, they reported that cardiomegaly in patients with some clinical disorders, such as chronic renal disease, had increased mortality. Increased right atrial pressures and decreased cardiac outputs are also associated with poor outcomes. Lai et al. concluded that patients with pulmonary hypertension with the highest risk of death are those with right heart failure with elevated right atrial pressures and decreased cardiac outputs [7]. Lam et al. further investigated this cardiovascular interaction and found that pulmonary hypertension based on a pulmonary artery systolic pressure >35 mmHg was present in 83% of their patients with diastolic heart failure [18]. Elevated pulmonary artery systolic pressure was a significant predictor of mortality and had a hazard ratio of 1.28 per 10 mmHg. Our study found that patients with cardiomegaly have very elevated right atrial pressure of 13.5 ± 6.9 compared to those without cardiomegaly who had a right atrial pressure of 8.5 ± 5.0 , indicating a higher risk of mortality. Hemodynamic group classification further allowed us to determine the correlation between specific parameters, such as right atrial pressure and cardiac index, to comprehensively assess cardiac status in these patients. BNP levels were elevated in the patients with higher hemodynamic scores and provide a simple index of disease severity.

Our study has several limitations. First, these patients were evaluated in a single pulmonary vascular disease clinic, and results may not be generalized to other clinics and hospitals. Second, these patients represent a select group of referred patients with possible right heart disease. These results may not apply to patients with predominantly left heart disease and cardiomegaly. Third, the study goals did not allow us to determine whether or not cardiomegaly predicts adverse outcomes. It does reflect the effect of the underlying disease on cardiac chambers and can have important effects on lung volumes and diffusion capacity. Consequently, cardiomegaly should have important associations with outcomes.

In summary, the presence of cardiomegaly on routine chest radiographs has important clinical implications. It helps validate patient's symptoms, predicts abnormal laboratory and hemodynamic parameters, and supports clinical decisions regarding the need for additional investigation. Primary care physicians can use this observation to support referral

decisions especially clinics, and specialist can use this observation during discussions with patients regarding diagnostic strategies.

Disclosure statement

The authors have no potential conflicts of interest to report related to this project in manuscript.

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