Clinical and prognostic relationships of pulmonary artery to aorta diameter ratio in patients with heart failure: a cardiac magnetic resonance imaging study

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Abstract

Background:

The pulmonary artery (PA) distends as pressure increases.

Hypothesis:

The ratio of PA to aortic (Ao) diameter may be an indicator of pulmonary hyper- tension and consequently carry prognostic information in patients with chronic heart failure (HF).

Methods:

Patients with chronic HF and control subjects undergoing cardiac magnetic resonance imaging were evaluated. The main PA diameter and the transverse axial Ao diameter at the level of bifurcation of the main PA were measured. The maximum diameter of both vessels was measured throughout the cardiac cycle and the PA/Ao ratio was calculated.

Results:

A total of 384 patients (mean age, 69 years; mean left ventricular ejection fraction, 40%; median NT-proBNP, 1010 ng/L [interquartile range, 448–2262 ng/L]) and 38 controls were included. Controls and patients with chronic HF had similar maximum Ao and PA diameters and PA/Ao ratio. During a median follow-up of 1759 days (interquartile range, 998–2269 days), 181 patients with HF were hospitalized for HF or died. Neither PA diameter nor PA/Ao ratio predicted outcome in univariable analysis. In a multivariable model, only age and NT-proBNP were independent predictors of adverse events.

Conclusions:

The PA/Ao ratio is not a useful method to stratify prognosis in patients with HF.

1. INTRODUCTION

For patients with chronic heart failure (HF), pulmonary hypertension, right ventricular (RV) dysfunction, and increased venous pressure and congestion are associated with a poor prognosis whether or not left ventricular ejection fraction (LVEF) is reduced.[1-8]

An enlarged main pulmonary artery (PA) and an increased pulmonary artery/aorta (PA/Ao) diameter ratio are indirect signs of pulmonary hypertension.[9-11] Their clinical and predictive value has been mainly studied in patients with respiratory diseases, including chronic obstructive pulmonary disease (COPD)[12–14] and pulmonary arterial hypertension.[11,15] Previous studies suggest that the PA/Ao ratio, as assessed on computed tomography (CT), may be a useful measure of pulmonary hypertension, especially in patients age < 50 years.[16] A PA/Ao ratio > 1 detected by CT is also a powerful predictor of severe COPD exacerbations.[12] However, the clinical and prognostic utility of this measure in patients with chronic HF is unknown.

We therefore studied the association between PA/Ao diameter ratio and both clinical characteristics and outcome in patients with HF using cardiac magnetic resonance imaging (cMRI).

2. METHODS

2.1. Study population

This is a single-center, prospective, observational study. Between June 2005 and November 2011, ambulatory patients referred with suspected HF to a community HF clinic who had

undergone cMRI as part of their investigation were enrolled. The analysis plan was designed post hoc; the scans were not performed specifically to determine PA/Ao diameter ratio. Patients were followed up until June 1, 2015. Physical examination, routine laboratory tests (including N-terminal pro B-type natriuretic peptide [NT-proBNP]), and electro- cardiogram were performed on the same day. HF was defined as LVEF <50% on cMRI or plasma concentration of NT-proBNP>220 pg/mL, consistent with the 2007 European Society of Cardiology (ESC) consensus statement for diagnosis of HF with preserved ejection fraction.[17]

A congestion score was used based on lung auscultation (normal, basal, mid zone, or diffuse crepitations), jugular venous pressure (not raised, raised 1–4 cm, up to the earlobe), peripheral edema (none, ankles, below or above knees), and liver (not palpable, palpable), with 1 point attributed for each degree of severity. Patients with a score ≥ 3 were defined as being congested.[18]

Data regarding deaths and hospitalizations were collected from the hospital's electronic systems, supplemented by information from patients, discharge letters, and their family doctors. Our hospital is the only one in the region offering acute medical services. We have access to both primary and secondary care records. Outcome was censored at the point of last medical contact in primary or secondary care. The vital status of all patients who had no local medical contact in the previous 6 months was ascertained from national records. The primary outcome was a composite of hospitalization for HF and all- cause mortality. Hospitalizations were considered to be HF related if the diagnosis was included in the death or discharge documentation and if the discharge letter supported HF as a key reason for admission.

The study conformed to the principles outlined in the Declaration of Helsinki and was

approved by relevant ethical bodies. Written informed consent was obtained from each patient.

2.2. cMRI measurements

The cMRI images were acquired using a 1.5-T scanner (either SIGNA CV/i, GE Medical Systems, Waukesha, WI; or Achieva, Philips Medical Systems, Best, The Netherlands) equipped with a phased-array coil placed over the precordium. Electrocardiogram-gated cine acquisitions were performed during breathhold (in expiration), using a steady-state free precession pulse sequences in 2 standard long-axis and multiple short-axis slices, with slice thickness of 8 mm and inter- slice distance of 2 mm from the base to the apex of the heart.

Images were analyzed offline using QMass MR software (Medis, Leiden, The Netherlands). The multislice, short-axis cine datasets were analyzed to calculate left ventricular (LV) and RV volumes and masses. Endocardial and epicardial borders were traced manually by an experienced observer using end-diastolic and end-systolic frames in contiguous short-axis slices. LV end-diastolic and end-systolic volumes (LVEDV, LVESV) were calculated using summation of area × (slice thickness + interslice gap) for each slice (Simpson method), which were then used to calculate LVEF and LV mass. Papillary muscles were excluded from LV volume measurements and included in mass calculations. The interventricular septum was considered to be part of the LV. Right ventricular volumes, mass, and ejection fraction were calculated in a similar fashion. Left atrial (LA) maximum volume was measured at the frame just before mitral valve opening in the 4- chamber long-axis view. Mitral and tricuspid regurgitation volume was visually graded as none or trivial (0), mild (1), or moderate or worse (2). Intra- and intervariability data for cMRI measurements in our department have been reported.[19]

The transverse axial diameter of the main PA and the ascending Ao at the level of the bifurcation of the main PA were measured by a single research fellow (A.U.) specializing in cardiovascular imaging. The PA/Ao ratio was calculated as the ratio of their maximum diameters during the cardiac cycle (Figure 1).

2.3. Statistical analysis

Categorical data are presented as numbers and percentages, normally distributed continuous data as mean ± SD, and non–normally distributed variables as median and interquartile range. Independent samples t tests, 1-way ANOVA, and Kruskal-Wallis tests were used to compare continuous variables between groups, and $\chi 2$ tests were used for categorical variables.

Simple and multiple linear regression models were used to iden- tify variables associated with PA/Ao ratio. Only the variables associated with PA/Ao in univariable analysis were entered into the multivariable analysis. Log transformation of NT-proBNP and urea were used to satisfy the model assumptions. Associations between variables and prognosis were assessed using Cox proportional hazards models. Only variables associated with outcome ($P < 0.1$) in univariable analysis were entered into multivariable models. Treatment variables were not included in the model, as these are confounded by indication (patients who are sicker may be more likely to receive some treatments and less likely to tolerate others) and vary over time. Kaplan–Meier curves with the log-rank statistic were used to illustrate outcome. Analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY) and Stata software (StataCorp LP, College Station, TX). A 2-sided P value of 0.05 was considered statistically significant.

3. RESULTS

3.1. Patient characteristics

Of the 422 patients enrolled, 384 met the criteria for heart failure (HF). The other 38 subjects were taken to be controls. Compared with controls, patients with HF were older and more likely to have ischemic heart disease and atrial fibrillation. Their demographic and clinical characteristics are shown in Table 1.

PA and Ao diameters, and their ratio, were similar in patients with HF and controls. Among patients with HF, those in the highest tertile of PA/Ao ratio (greater PA/Ao ratio) were younger, had more severe symptoms, and overall had more congestion than the patients in the other 2 tertiles.

Those in the highest PA/Ao tertile had both larger PA diameter and smaller Ao diameters on average. They also had larger LA and RV end-diastolic volumes (Table 1).

Of the cMRI variables, increasing RVEDV was most strongly associated with increasing PA/Ao ratio. Only decreasing age and increasing LA and RV volumes were independently associated with increasing PA/Ao ratio (Table 2). In patients with LVEF ≤40%, only decreasing age independently predicted a greater PA/Ao ratio; whereas in patients with LVEF >40%, decreasing age and creatinine levels were associated with increasing PA/Ao ratio.

PA/Ao ratio was similar in males and females and in patients with or without COPD.

Patients with more severe symptoms and congestion, and those with a clinically higher jugular venous pressure, had a greater PA/Ao ratio (see Supporting Information, Table, in the online version of this article).

3.2. PA/Ao ratio and outcome

During a median follow-up of 1759 days (interquartile range, 998–2269 days [censored at time of first event]), the primary out- come (hospitalization for HF and all-cause mortality) was reached by 47% (n = 181) of patients with chronic HF and 29% (n = 11) of controls. Neither minimum nor maximum PA and Ao diameter, nor their ratio, were associated with adverse outcomes in univariable analysis, even when PA diameter was indexed for body surface area (body surface area is closely related to an adverse outcome in this, and in a larger, dataset).[20] The only cMRI predictors of adverse events were greater LA volume and lower LA and RV ejection fractions. In a multi- variable model, including cMRI variables, only increasing age and NT- proBNP were independent predictors of an adverse outcome (Table 3).

There was no difference in outcome between patients who had PA/Ao ratio > 1 compared with ≤1 (hazard ratio [HR]: 1.07, 95% confidence interval [CI]: 0.74-1.60, P = 0.67) or between patients who had PA/Ao ≥0.9 vs <0.9 (HR: 1.02, 95% CI: 0.76-1.37, P = 0.90). Even when patients with a dilated ascending Ao (>4 cm) were excluded (n = 25), results did not change substantially (PA/Ao >1 vs ≤1: HR: 1.05, 95% CI: 0.71-1.56, P = 0.80; PA/Ao≥0.9 vs <0.9: HR: 0.97, 95% CI: 0.71-1.30, P = 0.82). There was no difference in the primary outcome among the 3 PA/Ao tertiles (Figure 2).

During the study, 147 patients died; neither minimum nor maxi- mum PA diameter (HR: 0.99, 95% CI: 0.95-1.03, P = 0.55), maximum Ao diameter (HR: 0.99, 95% CI: 0.96-1.03, P = 0.75), nor their ratio (HR: 0.82, 95% CI: 0.24-2.78, P = 0.75) were associated with all-cause mortality.

4. DISCUSSION

Measurement of the PA/Ao ratio may be of prognostic value in patients with respiratory disease.[12,21] However, although we found that for patients with HF a higher PA/Ao ratio measured by cMRI was associated with more clinical evidence of congestion and larger LA and RV volumes, it was not an important predictor of an adverse outcome.

Nakanishi and colleagues studied 1326 patients undergoing coronary CT angiography for suspected coronary artery disease.[22] Consistent with our results, those with larger PA/Ao ratio were younger and had smaller aortas, but Nakanishi found that an elevated PA/Ao ratio (≥0.9) was an independent predictor of mortality. However, there were few deaths (58, compared with 147 in our study), with only 15 deaths in patients with a PA/Ao ≥0.9. They excluded patients with a dilated Ao (>4 cm), but excluding such patients did not improve prediction in our analysis.

There is a linear association between aortic size and increasing age,[23] and increasing aortic size is associated with decreased distensibility.[24] Our finding of an inverse correlation between PA/Ao ratio and age is consistent with a previous study of 3176 patients from the Framingham Heart Study, which showed that the PA/Ao ratio was lower in older participants.[25]

4.1. Study limitations

This was a single-center study and a retrospective analysis of data collected primarily for other purposes. Our findings should be prospectively tested before being considered definitive. The population enrolled in our study is not entirely representative of the HF population. Older patients with many comorbidities and more advanced HF who might have a more dilated PA are less likely to be referred for a cMRI, due to frailty or contraindications to cMRI such as an implanted pacemaker. Some authors might not accept an NT-proBNP>220 pg/mL as diagnostic for HF with preserved ejection fraction, although it is consistent with the ESC consensus statement available when the study was conceived.[17]

Some also might argue that a control group consisting of symptomatic individuals with comorbidities that might cause HF is not appropriate for the initial evaluation of a method to stratify prognosis. Others will argue that a control population comprising conditions closely associated with HF, such as ours, is more relevant. The reader should decide. A control group of perfectly healthy older people would certainly be of interest, but unfortunately it was not locally available.

PA and Ao diameters were measured from axial images, which in some cases were not planned exactly in line with the vessel orientation. This could have led to occasional under- or overestimations of the main artery diameters.

Invasive or noninvasive echocardiographic evaluation of PA pressure was not done at the time of the cMRI, so we do not know how many patients in this study had pulmonary

hypertension.

5. CONCLUSION

Our findings suggest that a higher PA/Ao ratio is not a useful indicator of a poorer prognosis in patients with chronic HF. Publication of results from other centers would be of interest to confirm or refute our findings.

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