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

Word count: Abstract 196, Text 1917.

Pierpaolo Pellicori[1#] MD, FESC, Alessia Urbinati[1,2#] MD, Jufen Zhang PhD[1], Anil C Joseph[1], Pierluigi Costanzo[1] MD, FESC, Elena Lukaschuk[1], Alessandro Capucci[2], John GF Cleland[1,3] MD, FRCP, FESC, FACC, Andrew L Clark[1] MA, MD, FRCP

[#] First author equal contribution
[1]Department of Cardiology, Castle Hill Hospital, Hull York Medical School (at University of Hull), Kingston upon Hull, HU16 5JQ, UK

[2] Cardiology and Arrhythmology Clinic, Marche Polytechnic University, University Hospital "Ospedali Riuniti", Via Conca, 71, 60126 Ancona, Italy

[3]National Heart & Lung Institute and National Institute of Health Research Cardiovascular Biomedical Research Unit, Royal Brompton & Harefield Hospitals, Imperial College, London.

Corresponding author:

Dr Pierpaolo Pellicori

Address for correspondence

Department of Cardiology, Hull York Medical School

Hull and East Yorkshire Medical Research and Teaching Centre

Castle Hill Hospital, Cottingham, Kingston upon Hull, HU16 5JQ, UK

Tel: + 44 1482 461811; Fax: +44 1482 461779;

Email: p.pel@libero.it

pierpaolo.pellicori@hey.nhs.uk

Conflict of interest: none declared.

Key words: pulmonary artery, aortic diameter, PA/Ao ratio, heart failure, cardiac MRI, prognosis.

Abstract

Background: The pulmonary artery (PA) distends as pressure increases. The ratio of PA to aortic (Ao) diameter may be an indicator of pulmonary hypertension and consequently carry prognostic information in patients with chronic heart failure (CHF).

Methods: Patients with CHF and control subjects undergoing cardiac magnetic resonance imaging (CMRI) were evaluated. The main PA diameter and the transverse axial Ao diameter at the level of bifurcation of the main pulmonary artery were measured. The maximum diameter of both vessels was measured throughout the cardiac cycle and the PA/Ao ratio was calculated.

Results: 384 patients (mean age 69 years, mean left ventricular ejection fraction 40%, median amino terminal pro-brain natriuretic peptide (NTproBNP) 1,010 (IQR: 448-2,262) ng/l) and 38 controls were included. Controls and patients with CHF had similar maximum Ao and PA diameters, and PA/Ao ratio.

During a median follow up of 1,759 days (998-2,269), 181 patients with HF were hospitalised 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 heart failure.

Introduction

For patients with chronic heart failure (CHF), pulmonary hypertension (PHT), 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/aorta (PA/Ao) diameter ratio are indirect signs of pulmonary hypertension (PHT) [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 younger than 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 CHF 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).

Methods

Study population

This is a single-centre 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 1st June 2015. Physical examination, routine laboratory tests (including NTproBNP), and

electrocardiogram (ECG) were performed on the same day. Heart failure was defined as LVEF <50% on CMRI or plasma concentration of amino-terminal pro-B-type natriuretic peptide (NTproBNP) >220 pg/ml, consistent with the 2007 ESC consensus statement for diagnosis of heart failure with preserved ejection fraction [17].

A congestion score 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 oedema (none, ankles, below or above knees), and liver (not palpable, palpable) with one point attributed for each degree of severity was used. Patients with a score ≥3 were defined as being congested [18].

Data regarding deaths and hospitalisations 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. Hospitalisations 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.

Cardiac magnetic resonance imaging measurements

Cardiac magnetic resonance images were acquired using a 1.5 T scanner (either Sigma CV/I, GE Medical Systems or Achieva, Philips Medical Systems) equipped with a phased-array coil placed over the praecordium. ECG-gated cine acquisitions were performed during breath-hold (in expiration), using a steady state free precession pulse sequences in two standard long axes 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 analysed offline using QMass MR software (MEDIS, Leiden, The Netherlands). The multi-slice, short-axis cine data-sets were analysed to calculate left ventricular (LV) and right ventricular (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 (EDV) and end-systolic (ESV) volumes were calculated using summation of area × [slice thickness + interslice gap] for each slice (Simpson's 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. RV volumes, mass and EF were calculated in a similar fashion. Left atrium (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 inter-variability data for CMRI measurements in our department have been reported [19].

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

Statistical analysis

Categorical data are presented as number and percentages; normally distributed continuous data as mean ±SD; non-normally distributed variables as median and interquartile range (IQR). Independent samples t-tests, one-way ANOVA and Kruskal-Wallis tests were used to compare continuous variables between groups, and chi-squared tests were used for categorical variables.

Simple and multiple linear regression models were used to identify 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 NTproBNP 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 (v22) and Stata software, a two-sided P-value of 0.05 was considered statistically significant.

Results

Patient characteristics

Of 422 patients enrolled, 384 met the criteria for heart failure. The other 38 subjects were taken to be controls. Compared to controls, patients with HF were older, and were more likely to have ischaemic heart disease (IHD) and atrial fibrillation (AF). 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. Amongst patients with HF, those in the highest tercile of PA/Ao ratio (greater PA/Ao ratio) were younger, had more severe symptoms and overall more congestion than the other two terciles.

Those in the highest PA/Ao tercile 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 MRI 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, whilst in patients with LVEF > 40%, decreasing age and creatinine levels were associated with increasing PA/Ao ratio.

PA/Ao ratio was similar in men and women and in patients with or without COPD. Patients with more severe symptoms and congestion, and those with a clinically higher JVP had a greater PA/Ao ratio (Supplementary Table 1).

PA/Ao ratio and outcome

During a median follow-up of 1,759 days (IQR: 998-2,269) days (censored at time of first event) the primary outcome (hospitalization for HF and all-cause mortality) was reached by 47% (n=181) of patients with CHF 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 (BSA; BSA 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 multivariable model, including CMRI variables, only increasing age and NT-pro BNP were independent predictors of an adverse outcome (table 3).

There was no difference in outcome between patients who had PA/Ao >1 compared to ≤1 (HR: 1.07, 95% CI: 0.74-1.60, p=0.67) or between patients who had PA/Ao ≥0.9 versus <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 >1versus ≤1 (HR: 1.05, 95% CI: 0.71-1.56, p=0.80); PA/Ao ≥0.9 versus <0.9 (HR: 0.97, 95% CI: 0.71-1.30, p=0.82). There was no difference in the primary outcome amongst the three PA/Ao terciles (figure 2).

During the study 147 patients died; neither minimum nor maximum PA (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.

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 left atrial and right ventricular volumes, it was not an important predictor of an adverse outcome.

Nakanishi and colleagues studied 1,326 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 a smaller aorta, but Nakanishi found that an elevated PA/Ao ratio (≥ 0.9) was an independent predictor of mortality. However, there were few death (58 compared to 147 in our

study) with only 15 deaths in patients with a PA/Ao ≥0.9. They excluded patients with a dilated aorta (>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 3,176 patients from the Framingham Heart Study which showed that the PA/Ao was lower in older participants [25].

Limitations

This was a single centre 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 heart failure population. Older patients with many co-morbidities and more advanced heart failure who might have a more dilated pulmonary artery are less likely to be referred for a CMRI, due to frailty, or contra-indications to a CMRI, such as an implanted pacemaker. Some authors might not accept an NTproBNP >220 pg/ml as diagnostic for heart failure with preserved ejection fraction, although it is consistent with ESC consensus statement available when the study was conceived [17].

Some might also argue that a control group consisting of symptomatic individuals with comorbidities which might cause heart failure 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 heart failure, 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 over-

estimations of the main artery diameters.

Invasive or non-invasive echocardiographic evaluation of PA pressure was not done at the time of the CMRI, so we do not know how many patients had PHT in this study.

Conclusions

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

References

[1] Pellicori P, Kallvikbacka-Bennett A, Khaleva O, et al.Global longitudinal strain in patients with suspected heart failure and a normal ejection fraction: does it improve diagnosis and risk stratification?. Int J Cardiovasc Imaging. 2014;30:69-79.

[2] Bursi F, McNallan SM, Redfield MM, et al. Pulmonary pressures and death in heart failure: a community study. J Am Coll Cardiol. 2012;59:222-31.

[3] Ghio S, Gavazzi A, Campana C, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure . J Am Coll Cardiol. 2001:37:183-188.

[4] Lam CS, Roger VL, Rodeheffer RJ, et al. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am Coll Cardiol. 2009;53:1119-26.

[5] Pellicori P, Kallvikbacka-Bennett A, Zhang J, et al. Revisiting a classical clinical sign: jugular venous ultrasound. Int J Cardiol. 2014;170:364-70.

[6] Pellicori P, Kallvikbacka-Bennett A, Dierckx R, et al. Prognostic significance of ultrasound-assessed jugular vein distensibility in heart failure. Heart. 2015;101:1149-58.

[7] Pellicori P, Carubelli V, Zhang J, et al. IVC diameter in patients with chronic heart failure: relationships and prognostic significance. JACC Cardiovasc Imaging. 2013;6:16-28.

[8]Bosch L, Lam CSP, Gong L, et al. Right ventricular dysfunction in left-sided heart failure with preserved versus reduced ejection fraction. Eur J Heart Fail. 2017 Jun 8. doi: 10.1002/ejhf.873. [Epub ahead of print]

[9] Haimovici JB, Trotman-Dickenson B, Halpern EF, et al. Relationship between pulmonary artery diameter at computed tomography and pulmonary artery pressures at right-sided heart catheterization. Massachusetts General Hospital Lung Transplantation Program. Acad Radiol. 1997;4:327-34.

[10] Sanal S, Aronow WS, Ravipati G, et al. Prediction of moderate or severe pulmonary hypertension by main pulmonary artery diameter and main pulmonary artery diameter/ascending aorta diameter in pulmonary embolism. Cardiol Rev. 2006;14:213-4.

[11] Alhamad EH, Al-Boukai AA, Al-Kassimi FA, et al. Prediction of pulmonary hypertension in patients with or without interstitial lung disease: reliability of CT findings. Radiology. 2011;260:875-83.

[12] Wells JM, Washko GR, Han MK, et al; COPDGene Investigators; ECLIPSE Study Investigators. Pulmonary arterial enlargement and acute exacerbations of COPD.N Engl J Med. 2012;367:913-21.

[13] Wells JM, Morrison JB, Bhatt SP, et al. Pulmonary artery enlargement is associated with cardiac injury during severe exacerbations of COPD. Chest. 2016;149:1197-204.

[14] Chung KS, Kim YS, Kim SK, et al; Korean Obstructive Lung Disease study group. Functional and Prognostic Implications of the Main Pulmonary Artery Diameter to Aorta Diameter Ratio from Chest Computed Tomography in Korean COPD Patients. PLoS One. 2016;11:e0154584

[15] Karakus G, Kammerlander AA, Aschauer S, et al. Pulmonary artery to aorta ratio for the detection of pulmonary hypertension: cardiovascular magnetic resonance and invasive hemodynamics in heart failure with preserved ejection fraction. J Cardiovasc Magn Reson. 2015;17:79.

[16] Ng CS, Wells AU, Padley SP. A CT sign of chronic pulmonary arterial hypertension: the ratio of main pulmonary artery to aortic diameter. J Thorac Imaging. 1999;14:270-8.

[17] Paulus WJ, Tschöpe C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J. 2007;28:2539-50.

[18] Pellicori P, Cleland JG, Zhang J, et al. Cardiac Dysfunction, Congestion and Loop Diuretics: their Relationship to Prognosis in Heart Failure. Cardiovasc Drugs Ther. 2016;30:599-609.

[19] Pellicori P, Joseph AC, Zhang J, et al. The relationship of QRS morphology with cardiac structure and function in patients with heart failure. Clin Res Cardiol. 2015;104:935-45.

[20] Futter JE, Cleland JG, Clark AL. Body mass indices and outcome in patients with chronic heart failure. Eur J Heart Fail. 2011;13:207-13.

[21] Terzikhan N, Bos D, Lahousse L, et al. Pulmonary artery to aorta ratio and risk of all-cause mortality in the general population: the Rotterdam Study. Eur Respir J. 2017;49(6).

[22] Nakanishi R, Rana JS, Shalev A, et al. Mortality risk as a function of the ratio of pulmonary trunk to ascending aorta diameter in patients with suspected coronary artery disease. Am J Cardiol. 2013;111:1259-63.

[23] Pearce WH, Slaughter MS, LeMaire S, et al. Aortic diameter as a function of age, gender, and body surface area. Surgery. 1993;114:691-7.

[24] Mohiaddin RH, Underwood SR, Bogren HG, et al. Regional aortic compliance studied by magnetic cardiac resonance imaging: the effects of age, training and coronary artery disease. Br Heart J. 1989;62:90-6.

[25] Truong QA, Massaro JM, Rogers IS, et al. Reference Values for Normal Pulmonary Artery Dimensions by Noncontrast Cardiac Computed Tomography The Framingham Heart Study. Circ Cardiovasc Imaging. 2012;5:147-154.

Legend to figures.

Figure 1: An axial cardiac magnetic resonance imaging (cMRI) image at the level of pulmonary artery (PA) bifurcation, where measurements of the diameter of the main PA (in blue) and the diameter of the aorta (Ao, in red) were obtained to calculate PA/Ao ratio.

Figure 2: Kaplan Meier curve for the primary outcome of death from all causes and heart failure hospitalizations. There was no difference in the primary outcome for patients among the three PA/Ao terciles.