Right ventricular systolic function in Nigerians with heart failure secondary to hypertensive heart disease

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Abstract

Background: Right ventricular (RV) dysfunction has been shown to be a major contributor to the adverse outcomes in subjects with heart failure. Few studies evaluating the right ventricle in heart failure subjects have been carried out in Sub-Saharan Africa. This study was therefore designed to evaluate the right ventricular systolic function in subjects with heart failure secondary to hypertensive heart disease presenting to the University College Hospital, Ibadan Nigeria.

Methodology: Seventy-six subjects with heart failure secondary to hypertension and 92 normal controls underwent clinical, electrocardiographic and echocardiographic evaluation. Indices of right ventricular systolic function that were measured include tricuspid annular plane systolic excursion (TAPSE), tissue Doppler derived tricuspid peak systolic lateral annulus velocity (S’) and right ventricular fractional area change (RVFAC).

Results: Sixty-two (81.6%) heart failure subjects had right ventricular systolic dysfunction, 31 (40.8%) had abnormal TAPSE, 42 (55.5%) had abnormal S’ while 49 (64.5%) had abnormal RVFAC. Elevated pulmonary artery systolic pressure was found in 25 (32.9%) of the subjects. There was no relationship between the indices of right ventricular systolic function and the estimated systolic pulmonary artery pressures. The independent predictor of right ventricular systolic dysfunction was the right atrial size.

Conclusion: Right ventricular systolic function is impaired in patients with heart failure secondary to hypertensive heart disease. There is no relationship between the indices of right ventricular systolic function and systolic pulmonary artery pressure. Further studies are needed to assess right ventricular systolic function in Nigerians.

Keywords: Hypertension, Heart Failure, Right ventricular dysfunction, Nigeria, Sub-Saharan Africa.

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Introduction

Heart failure (HF) is a major and growing public health problem around the world with a prevalence of more than 23 million worldwide.1 Despite the advances in the prevention and management of cardiovascular diseases, mortality in heart failure is still high. Therefore, the identification of the predictors of mortality in heart failure has been an area of extensive research. A number of studies have provided evidence that right ventricular systolic function is an independent prognostic factor in moderate to severe heart failure.2-4 Pulmonary hypertension is considered an important contributor to exercise intolerance in heart failure.5,6 and several studies have reported an inverse relationship between right ventricular systolic function and pulmonary hypertension.7 Although there are newer and more advanced methods of assessing right ventricular systolic function, echocardiography has been reported to be equally clinically useful8,9 and still remains an attractive tool because of its obvious advantages of non-invasiveness, low cost and easy reproducibility.

Amongst the various indices of RV systolic function that can be evaluated using echocardiography, more studies have demonstrated the clinical utility and value of TAPSE, 2D RV FAC, and S' of the tricuspid annulus.10-13 RV FAC has been shown to correlate with RVEF by magnetic resonance imaging (MRI).11,14 TAPSE has been shown to correlate strongly with right ventricular systolic function obtained by radionuclide angiography.15

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Most of the studies on right ventricular systolic function in heart failure were carried out in Caucasians with very few studies on indigenous Africans. Heart failure in Africa is mostly attributed to non-ischaemic factors such as hypertension, valve disorders, idiopathic cardiomyopathy in contrast to western countries where ischaemic heart disease is a major contributor to the aetiology of heart failure. Studies across sub-Saharan Africa have documented hypertension as the commonest aetiology of heart failure in Africans. Local studies done in Nigeria have also reported hypertension as the commonest aetiology of heart failure in Nigerians.

This study therefore aimed to evaluate the right ventricular systolic function in subjects with heart failure secondary to hypertensive heart disease and to determine the relationship between right ventricular systolic function and estimated systolic pulmonary artery pressure.

Methodology
This study was carried out at the University College Hospital, Ibadan, Nigeria. The study protocol was approved by the ethics committee of the hospital and each participant signed an informed consent form in accordance with the Declaration of Helsinki. The study was cross-sectional in design. The study was powered at 90% to detect a mean difference of 2.5 mm in the tricuspid annular plane systolic excursion between subjects with heart failure and normal controls.

Seventy-six patients with heart failure secondary to hypertensive heart disease and ninety-two apparently healthy controls were recruited consecutively. The exclusion criteria among subjects with heart failure included those with heart failure due to aetiology other than hypertension even if co-existing with hypertension, co-morbidities such as ischaemic heart disease/myocardial infarction, diabetes mellitus, thyroid disease, chronic kidney disease, anaemia, asthma and chronic obstructive pulmonary disease (COPD). Other exclusion criteria among subjects and controls included pregnancy, current smokers, significant alcohol use of more than 14 units per week for women and 21 units per week for men, gout, poor echocardiographic window and refusal to give consent.

Echo-cardiographic Studies
Trans-thoracic echocardiography was performed using a Toshiba Xario™ cardiac ultrasound system on all subjects and controls in the left lateral decubitus position and measurements were taken according to the recommendations of the American Society of Echocardiography. Measures of right ventricular systolic function evaluated included tricuspid annular plane systolic excursion (TAPSE) which was acquired by placing an M-mode cursor through the tricuspid annulus, in the apical four-chamber view, and measuring the amount of longitudinal excursion of the annulus at peak systole; tissue Doppler derived tricuspid peak systolic lateral annulus velocity (S’) was obtained from apical 4-chamber window with the pulsed Doppler sample volume placed on the lateral tricuspid annulus.

Systolic pulmonary artery pressure (SPAP) was estimated by measuring the maximum velocity of the tricuspid regurgitant jet. In the absence of a gradient across the pulmonary valve, SPAP is equal to the right ventricular systolic pressure (RVSP). RVSP was derived from the tricuspid valve regurgitant jet velocity, using the simplified Bernoulli equation and combining this value with an estimate of the right atrial (RA) pressure: RVSP = 4(V)² + RA pressure. Where V is the peak velocity (in meters per second) of the tricuspid valve regurgitant jet, and RA pressure was estimated from IVC diameter and respiratory changes. Inferior Vena Cava (IVC) diameter less than or equal to 2.1 cm that collapses greater than 50% with a sniff suggests a normal RA pressure of 3 mm Hg (range, 0-5 mm Hg), whereas an IVC diameter greater than 2.1 cm that collapses less than 50% with a sniff suggests a high RA pressure of 15 mm Hg (range, 10-20 mmHg). Normal resting values for SPAP values are usually defined as a peak TR gradient of 2.8 to 2.9 m/s or a peak systolic pressure of 35 or 36 mm Hg, assuming an RA pressure of 3 to 5 mm Hg.

Data management and analysis
Data was analysed using R statistical software version 3.3.2. For quantitative data, the mean ± standard deviation or the median ± median absolute deviation – for non-normally distributed data were reported for descriptive purposes while frequencies (percentages) were reported for qualitative data. The Shappiro-Wilk’s test was used to test for normality. Student’s ‘t’ test, or the Mann Whitney’s test (non-parametric testing for non-normal data) were used to test for the differences in the continuous variables between the two groups while chi-squared analysis was used to test for the differences in the categorical variables between the groups. Pearson’s correlation was used to evaluate the bivariate relationship between the
parameters of RV systolic function and some clinical and echocardiographic indices. A stepwise logistic regression model was used to determine the independent correlates of RV systolic dysfunction. A two-tailed p-value of < 0.05 was considered significant.

Results
A total of 168 subjects (76 patients with heart failure and 92 controls) were recruited consecutively for the study over a 6 month period. Table 1 compares the baseline characteristics of the subjects with heart failure and the controls. The subjects with heart failure were older and had higher pulse rate when compared with the controls. Table 2 shows the echocardiographic parameters and frequencies of abnormal RV parameters in the subjects.

Table 1: Baseline characteristics of the subjects

| Variable                  | Subjects n=76 | Control n=92 | P-value† |
|---------------------------|---------------|--------------|----------|
| Age (years)               | 55.0±13.00    | 49.0±11.6    | 0.0017   |
| Body Mass Index (kg.m⁻²)† | 24.9±4.768    | 25.3±4.44    | 0.2327   |
| Pulse (/min)              | 88.2±12.97    | 70.5±10.1    | 0.0000*  |
| Systolic Blood Pressure (mmHg)† | 116.0±20.76  | 120.0±14.8   | 0.5063   |
| Diastolic Blood Pressure (mmHg)† | 79.0±13.34   | 80.0±6.67    | 0.3146   |
| Pulse Pressure (mmHg)†    | 40.0±14.83    | 40.0±10.4    | 0.0528   |
| Mean Arterial Pressure (mmHg)† | 90.0±14.83   | 91.0±8.40    | 0.7424   |

* statistically significant, † median±median absolute deviation and Mann Whitney test †† Student ‘t’ test

Figure 1: Relationship between RV function parameters and number of abnormal RV function indices

TAPSE Tricuspid annular plane systolic excursion, S’ TDI Lateral Tricuspid Annular Systolic Velocity, RVFAC Right Ventricular Fractional Area Change, RVD Right Ventricular Internal Diameter

Figure 1: Relationship between RV function parameters and number of abnormal RV function indices
The limits of normal values for the indices of right ventricular systolic function were generated from the 2.5 percentile of the values obtained in the normal controls. The values generated were: TAPSE - 17.1 mm, S’ - 10.3 cm/s, RV FAC - 23.6%. Subjects were deemed to have right ventricular (RV) systolic dysfunction if they had values in any of the RV systolic function parameters below the generated cut-off points. The prevalence of right ventricular (RV) systolic dysfunction among the subjects with heart failure was 81.6%. TAPSE was abnormal in 31 (40.8%) of the subjects, S’ was abnormal in 42 (55.8%) of the subjects while RVFAC was abnormal in 49 (64.5%) of the subjects. Furthermore, 19 (25.0%), 26 (34.2%), and 17 (22.4%) of the subjects had one, two and three RV systolic function parameters abnormal respectively. Figure 1 shows the relationship between RV function parameters and the number of abnormal RV function indices among the subjects.

The estimated right ventricular systolic pressure (RVSP) and hence the systolic pulmonary artery pressure (SPAP) ranged from 10.2 mmHg to 84.7 mmHg. The mean value was 29 (14.6) mmHg. Using a cut-off value of 35 mmHg, 25 (32.9%) of the patients had pulmonary hypertension. Table 3 compares clinical and echocardiographic indices in the subject with hypertensive heart failure and pulmonary hypertension and those without pulmonary hypertension. The major difference between the two groups was the increased right atrial dimensions in the hypertensive heart failure subjects with pulmonary hypertension when compared with those without pulmonary hypertension.

| Variable† | Subjects (n=76) | Controls (n=92) | P-value |
|-----------|-----------------|-----------------|---------|
| Left Atrial Diameter (cm) | 4.65±0.667 | 3.21±0.44 | 0.0000* |
| Inter-ventricular Septal thickness – Diastole (cm) | 0.93±0.208 | 0.85±0.15 | 0.0011* |
| LV Posterior wall thickness – Diastole (cm) | 0.94±0.200 | 0.85±0.15 | 0.0000* |
| LV Internal Diameter – Diastole (cm) | 6.44±0.875 | 4.60±0.59 | 0.0000* |
| LV Internal Diameter – Systole (cm)‡ | 5.44±0.963 | 2.87±0.53 | 0.0000* |
| LV Fractional Shortening (%) | 15.2±6.598 | 35.9±6.40 | 0.0000* |
| LV Ejection Fraction (%) | 31.1±11.62 | 65.8±8.90 | 0.0000* |
| Right Atrial Diameter – major axis (cm) | 6.19±1.060 | 4.70±0.49 | 0.0000* |
| Right Atrial Diameter – minor axis (cm) | 4.70±0.652 | 3.71±0.43 | 0.0000* |
| Right Ventricular Internal Diameter (cm) | 3.08±0.645 | 2.30±0.30 | 0.0000* |
| Right Ventricular Fractional Area Change (%) ‡ | 21.2±8.041 | 35.2±5.58 | 0.0000* |
| Tricuspid Regurgitant Velocity (mm.s⁻¹) | 196.3±100.10 | 0.00±0.00 | 0.0000* |
| Right Ventricular Systolic Pressure (mmHg) | 25.0±15.17 | 0.00±0.00 | 0.0000* |
| Right ventricular outflow tract velocity (m.s⁻¹) | 0.58±0.141 | 0.67±0.15 | 0.0026* |
| Tricuspid Annular Plane Systolic Excursion (mm)‡ | 17.9±4.72 | 22.2±2.97 | 0.0000* |
| Lateral Tricuspid Annular Systolic Velocity (mm.s⁻¹)‡ | 10.1±1.82 | 13.1±1.93 | 0.0000* |

LV: Left Ventricle, *: statistical significance
†: values are median ± median absolute deviation and Mann-Whitney test except when stated
‡: means±sd and Student ‘t’ test, ††: X² analysis

Table 2: Echocardiographic parameters in the subjects
Table 4 shows the correlation of the parameters of RV systolic function with some clinical and echocardiographic variables. TAPSE correlated with the LV ejection fraction and negatively correlated with right atrial diameter and RV internal diameter while S' had negative correlations with right atrial diameter and RV internal diameter. RV-FAC had positive correlation with LV ejection fraction and negative correlation with LV internal diameter.
A stepwise logistic model was evaluated to determine the independent correlates of RV systolic dysfunction among subjects with heart failure. The explanatory variables included in the model were the age and gender of the subjects, body mass index, DBP, left atrial diameter, left ventricular internal diameter, LV ejection fraction, RV internal diameter, right atrial major-axis diameter and RV outflow tract velocity. The only determinant of RV systolic function in this study is the right atrial dimension. (Table 5).

Table 5: Independent Relations of RV Systolic Dysfunction in the Subjects

| Variable                      | Odds Ratio | p-value | 95% Conf. Intervals |
|-------------------------------|------------|---------|---------------------|
| Right Ventricular Outflow Tract Velocity | 0.13       | 0.3942  | 0.001–0.698         |
| Right Atrial Diameter – major axis | 3.11       | 0.0060  | 1.477–7.663         |
| Left ventricular ejection fraction | 0.94       | 0.0715  | 0.867–1.003         |

p-value = 0.0045, Nalgelkerke R² = 0.486, *statistical significance
Discussion

In this study, about 80% of our subjects with heart failure secondary to hypertensive heart disease have impaired RV systolic function. Also, about one-third of subjects with hypertensive heart disease in this study had elevated pulmonary artery pressure which, however, had no significant association with RV systolic dysfunction in the study population. The LV ejection fraction, right atrial and RV dimensions are associated with parameters of RV systolic function while right atrial dimension is the only independent correlate of RV systolic dysfunction in this group of subjects with hypertensive heart failure.

The finding of high prevalence of RV systolic dysfunction in heart failure seen in this study supports findings from other studies that had documented varying prevalence of RV systolic dysfunction in subjects with heart failure. Puwanant and his colleagues studied right ventricular systolic function in subjects with heart failure using RV FAC, S' and TAPSE. However, the study group was heterogenous with respect to the aetiology of heart failure: 51% had coronary artery disease, 37% had diabetes and 32.5% had cardiomyopathies. The subjects were grouped into heart failure with preserved ejection fraction (HFPEF) and heart failure with reduced ejection fraction (HFREF). They reported a finding of a prevalence of 40%, 50%, 33% for TAPSE, S' and RV FAC respectively in those with HFPEF and 76%, 73%, 63% in those with HFREF. In comparison with this study in which 89.5% of the subjects with heart failure had HFREF, the study of Puwanant et al. had a much higher prevalence of abnormal TAPSE and S' for the subjects with HFREF. The prevalence of abnormal RV FAC was comparable in both studies. The marked difference in the prevalence of abnormal TAPSE and S' may be accounted for by the difference in the aetiology of heart failure between the subjects in the two studies. Coronary artery disease causes regional wall abnormalities which may affect indices of right ventricular systolic function like TAPSE and S' to a greater extent than RV FAC. Hypertension is likely to affect RV FAC more than TAPSE and S' because of ventricular interdependence. In actual fact, the prevalence of abnormal RV FAC was slightly higher in this study than in the study of Puwanant et al.

Ojji and his colleagues in a prospective study of 611 subjects with hypertensive heart failure found RV systolic dysfunction – by TAPSE – in 44.5% of his subjects. This is comparable with the prevalence of abnormal TAPSE of 40.8% obtained in our study despite a higher cut-off point – 17.1mm versus 15mm – used in our study. Abnormal RV systolic function has been shown to be a major adverse factor in the prognosis of heart failure. Thus, there is a need for increased emphasis on the evaluation of the right heart in heart failure and more efforts at investigation of therapies directed at the right heart.

Our study found no relationship between the indices of right ventricular systolic function and estimated pulmonary artery systolic pressure. There is conflicting data on the pulmonary vasculature haemodynamics in hypertension. Fiorentini and his colleagues had observed that pulmonary vascular resistance rises in parallel with peripheral vascular resistance due to the "concept that the vasomotility of the greater and lesser circulation in hypertension is disturbed by the same type of disorder". On the other hand, Fagard et al. reported that there was no association between systolic pulmonary artery pressure and TAPSE. Karaye and colleagues in their study on hypertensive subjects – without heart failure also observed that pulmonary artery systolic pressure (PASP) was a correlate of TAPSE while S' had no relationship with PASP. Ghio and colleagues, in their prognostic study of right ventricular systolic function and pulmonary artery pressure (PAP) in patients with chronic heart failure, found an inverse relationship between pulmonary artery pressure (PAP) and RV ejection fraction in heart failure. However, they also observed subjects with preserved RV function despite elevated PAP and other subjects with abnormal RV function and normal PAP. They reported that their data demonstrated that RV function may be preserved despite elevated PAP and that RV dysfunction may be observed even in patients with normal PAP. They also noted that the inverse relationship between PAP and RV dysfunction was seen in the patients with RV dysfunction resulting from RV after-load mismatch such as in dilated and ischaemic cardiomyopathy.

Since the mechanism of right ventricular dysfunction in hypertension results more from ventricular interdependence than changes in the pulmonary vasculature, this...
may explain why in this study, there was a failure to observe the inverse relationship between PASP and the indices of right ventricular systolic function, which has been documented in heart failure.

Another explanation for the failure of this study to demonstrate any relationship between PASP and RV systolic function is that over diuresis has been documented to reduce pulmonary artery systolic pressure\(^8\); some of the recruited patients had chronic heart failure and had been on long term diuretic therapy.

In univariate analyses, the relations of TAPSE found in our study were LV ejection fraction, right atrial diameter and RV internal diameter. This is similar to findings from other studies\(^4,31\) in which TAPSE was found to be significantly related to the LV ejection fraction. The effect of LV ejection fraction on right ventricular function had been attributed to the effects of ventricular interdependence.\(^25,34\) In our study, only the right atrial dimension was the independent correlate of RV systolic function our subjects. Ojji and colleagues\(^4\) had noted the significant associations of right atrial size and LV ejection fraction as independent correlates of TAPSE in their study. However in our study, LV ejection fraction had no independent relationship with RV systolic dysfunction. This could be due to our use of composite values of TAPSE, S’ and RVFAC as our measure of RV systolic dysfunction while Ojji and colleagues only used TAPSE to define RV systolic dysfunction. The contribution of right atrial function to heart failure was investigated by Ojji and colleagues\(^35\). They suggested that diminished right atrial function might play a critical role in the pathophysiological process of heart failure patients. Further studies on the role of the right atrium in the heart failure process are needed.

Several studies had attempted to validate echocardiographic parameters of RV function using cardiac magnetic resonance imaging (CMRI) as gold standard.\(^11,36,37\) These echocardiographic parameters correlated significantly with CMRI derived RV ejection fraction. The sensitivity and specificities of the parameters were TAPSE (83.4%, 70.0%), S’ (100%, 66%) and RV FAC (40%, 80%). The authors suggested that TAPSE and S’ provided better accuracy than RV FAC in subjects with pulmonary hypertension.\(^37\)

Our study generated the cut-off points for the parameters of right ventricular function from the values of the control subjects. These values are comparable to the limits of RV function parameters guidelines of the American Society of Echocardiography\(^13\) apart from the RVFAC. Our cut-off limits compared with the ASE guidelines are TAPSE – 17.1 mm versus 16 mm, S’ 10.3 cm/s versus 10 cm/s and RVFAC 23.6% versus 35%. The ASE limits were generated mostly from normal Caucasians. However, few normative studies have been carried out among African subjects. The marked difference in the cut-off points for RVFAC indicate that studies to define the limits of normal RV function parameters in indigenous Africans are needed.

Although our study subjects were heart failure patients secondary to hypertension with the exclusion of other causes of heart failure, the contribution of subclinical coronary artery disease to the heart failure could have been missed as coronary artery disease was excluded largely on clinical and electrocardiographic grounds alone without myocardial perfusion imaging and/or coronary angiography.

**Conclusion**

Right ventricular systolic dysfunction is present in about 80% of Nigerians with heart failure secondary to hypertensive heart disease. It is therefore important that the assessment of RV function should form part of the echocardiographic assessment of subjects with heart failure. Though pulmonary arterial hypertension is found in about a third of our subjects, it had no relationship with the degree of right ventricular dysfunction. The contribution of right atrial function to the pathophysiology and prognosis of heart failure is an area that needs further clarification.

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