pagepress

**GLOBAL CARDIOLOGY**
*Global Cardiology* 2024; **4**
Published online 30 December 2024 | **DOI**: 10.4081/cardio.2024.53

ARTICLE

# The association of iron deficiency with right ventricular dysfunction in Africans with heart failure

Adeseye A. Akintunde,[1,2,3] Sope T. Orugun[3]

[1]Department of Medicine, Faculty of Clinical Sciences, Bowen University, Iwo; [2]Department of Medicine, Faculty of Clinical Sciences, Ladoke Akintola University of Technology, Ogbomoso; [3]Cardiology Units, Department of Medicine, Bowen University Teaching Hospital, Ogbomoso and LAUTECH Teaching Hospital, Ogbomoso, Nigeria

## Abstract

**Background**: Iron deficiency (ID) is one of the common comorbidities in heart failure (HF) and is associated with poor morbidity and mortality, especially in Africans. It occurs along the full spectrum of HF phenotypes and is significantly related to left ventricular systolic function. Right ventricular dysfunction (RVD) is often associated with poorer prognosis and mortality. The association of ID and RVD in Africans with HF has not been well explored. We aimed to describe the relationship, if any between iron status and related parameters with right ventricular dysfunction in Africans with HF.
**Methods**: 140 subjects with HF were recruited consecutively from LAUTECH and Bowen Universities Teaching Hospitals, Ogbomoso, Nigeria. Full iron parameters were done for all participants. SPSS 25.0 was used for statistical analysis. ID was defined according to standardized criteria. RVD was determined using the tricuspid annular systolic pulmonary excursion (TAPSE) <20 mm. A p-value<0.05 was taken as statistically significant.
**Results**: The mean age of the study participants is 63.0±16.3 years. The mean body mass index was 24.7±6.5 kg/m$^{2,}$ while 42.9% were males. Anaemia was present in 106 (75.7%) of the study. RVD was present in 76 (54.3%) of the study participants, and it was commoner among those with ID (69.0%) compared to those with normal iron status (32.1%), p<0.001. Mean TAPSE was significantly lower among HF with ID compared with those without ID, 14.4±3.8 *vs* 16.6±4.52 mm, respectively; p<0.05. Pulmonary hypertension was commoner among HF with ID compared to those with normal iron parameters (33.3% *vs* 25.9%, respectively; p=0.048). In logistic regression analysis, serum ferritin, transferrin, and left atrial dimension were the major determinants of RVD in the study population.
**Conclusions**: ID is associated with RVD among Africans with HF. The prognostic implication and the potential reversibility of iron replacement therapy need further scrutiny. Identifying those with ID is congruent with increased risk of RVD in HF. Routine iron studies may be essential for future cardiovascular screening in Africans with heart failure and prevention of right ventricular dysfunction.

**Key words:** iron deficiency, right ventricular dysfunction/abnormalities, heart failure, Nigeria.

*Received: 16 October 2024; Accepted: 26 November 2024.*
**Correspondence to: Prof. Adeseye A. Akintunde, P.O. Box 3238, Osogbo, Nigeria. E-mail: aaakintunde@lautech.edu.ng*

## Introduction

Heart failure (HF) is a growing burden in Africa. This is due to the increasing prevalence of cardiovascular risk factors, increased life expectancy, and the availability of newer therapies for its management.[1] Right ventricular dysfunction (RVD) may occur in many cardiovascular diseases including hypertension and HF.[1-4] Several comorbidities exist alongside HF which can affect its prognosis and outcomes among which include hypertension, ischaemic heart disease, dyslipidaemia, diabetes mellitus, chronic kidney disease, atrial fibrillation, iron deficiency (ID), obstructive sleep apnoea, anaemia, *etc*.[2-4] Initial reports from our centre have revealed that iron homeostasis is severely deranged among HF patients in Nigeria irrespective of the presence or absence of anemia.[5,6] ID is associated with poor quality of life, poor functional status, and worse clinical outcomes. Evidence suggests that ID results in impairment in mitochondrial function and cardiomyocyte contractility.[7-8] It is one of the most common comorbidities in HF and is highly prevalent in HF patients, especially in Africa. In many cardiovascular diseases including HF, the right ventricle is in a similar way exposed to pressure, volume, and chemical changes with subsequent subcellular damage and oxidative processes eventually leading to HF.[9-10] These adaptations ultimately involve

the right ventricle due to a similar endogenous mechanism and via the interphase in the interventricular septum.[11] Markers such as tricuspid annular plane systolic or diastolic excursion (TAPSE), RV ejection fraction (EF), RV index of myocardial performance (Tei index), right atrial size, and RV dilatation among others are useful in assessing for RVD.[12] There is little information on whether iron deficiency is associated with RVD in HF subjects. Therefore, this study aimed to describe the association, if any, of ID with RVD in chronic HF subjects in Nigeria. It also aimed to describe the determinants of RVD concerning iron parameters among these HF subjects.

## Materials and Methods

This prospective study was done in the cardiology clinics of Ladoke Akintola University of Technology (LAUTECH) Teaching Hospital, Ogbomoso, and Bowen University Teaching Hospital, Ogbomoso, Nigeria. The study population consists of one hundred and forty consecutive subjects with HF who have been on follow-up for at least six months. Recruitment was done between July to December 2018. Subjects were included if they fulfilled the inclusion criteria which include the diagnosis of HF using Framingham's criteria, they were >18 years of age as of their last birthday, they were willing to give written informed consent to participate in the study and had at least a minimum life expectancy >2 years. Exclusion criteria include those with a previous history of recent blood transfusion, established chronic kidney diseases, pregnant patients, history of chronic illness including malignancies, mental illness, chronic inflammatory disorders, stroke, Parkinson's disease, acute coronary syndrome and patients who were admitted for any reason in the previous month.

Patients' information including sociodemographic, clinical, and other relevant information were obtained using a data form. Some of the clinical and demographic variables taken include name, age, gender, occupation, marital status, address, and tribe. Previous history of diagnosis of hypertension, diabetes mellitus, smoking, alcohol intake, and family history of hypertension/diabetes were also obtained. All study participants had full clinical and systemic examinations. 10 mls. of venous blood was taken into EDTA and plain bottles, centrifuged at the plasma stored at -80 degrees for laboratory analysis. Full blood counts including packed cell volume, haemoglobin, total white cell count, platelet count, and blood film appearance were done. Mean corpuscular volume, mean corpuscular haemoglobin, and mean corpuscular haemoglobin concentration were also done. Serum transferrin was done by the immunoturbidimetric method using the kits from Fortress Diagnostics (Product Code BXC 0741). Serum ferritin was done using the Enzyme-linked Immunosorbent Assay (ELISA) kits produced by CALBIOTECH (catalogue No FR248T) with relevant colour colorimetry. Total serum Iron, unsaturated, and total iron binding capacity were measured using the colorimetric kits from Fortress Diagnostics (Product code BXC0234) using appropriate iron buffer, reductant, chromogen, UIBC buffer, and ferrous reagent. Iron deficiency was defined as Transferrin saturation (TSAT) <20% because it is a better marker of iron status than ferritin. This is because ferritin overestimates iron stores in proinflammatory conditions. Transferrin saturation (TSAT) = 100 x serum iron/Total iron binding capacity.

Other investigations done for the participants included 12-lead resting electrocardiography, trans-thoracic echocardiography, electrolytes, urea and creatinine, urinalysis, and fasting blood sugar. Weight was taken to the nearest kg while height was taken using a stadiometer. Body mass index was determined and categorized as normal BMI, overweight (BMI 25.0-29.9 kg/m$^2$), mild obesity (BMI 30-34.9kg/m$^2$), moderate obesity (BMI 35.0-39.9 kg/m$^2$), and severe obesity (BMI >40 kg/m$^2$). Functional classification was defined according to the New York Heart Association Classification as class I-IV.[13] The 12-lead resting electrocardiography was done using AT-2 Schiller ECG machine. Interpretation of the ECG was done independently by the cardiologist who was blinded to the patient data at the time of the interpretation. Echocardiography was done according to the American Society of Echocardiography guidelines with the patient in the appropriate position.[14] Parameters that were taken include left ventricular internal dimension in diastole (LVIDD), left ventricular end-systolic dimension (LVSD), posterior wall thickness dimension in diastole, interventricular septal thickness in diastole (IVSd), right ventricular dimension, left atrial dimension, aortic root dimension, and aortic cusp separation. Left ventricular mass, left ventricular mass index, and aortic root index were determined. The ejection fraction and the fractional shortening were determined using the Teicholz formula. RVD was defined by as TAPSE <20 mm.[15] Moderate-severe RVD was defined as TAPSE <15 mm. Right ventricular systolic and diastolic parameters and chamber dimensions were also compared between the groups. The study was based on the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Ladoke Akintola University of Technology Teaching Hospital, Ogbomoso, Nigeria. All participants gave written informed consent.

## Statistical analysis

Statistical analysis was done using the Statistical Package for Social Sciences SPSS version 25.0 (Chicago, IL, USA). Quantitative variables were summarized as means ± SD while qualitative variables were summarized as frequencies (percentages). Student's *t*-test, analysis of variance (ANOVA), and Chi-square were used to determine the statistical significance of differences between groups with continuous and nominal variables respectively. Pearson correlation statistics was also used to determine univariate correlation between continuous data. Logistic regression was also done to determine the determinants of right ventricular dysfunction and its relationship with iron parameters among chronic heart failure subjects. P-value <0.05 was taken as statistically significant.

## Results

The demographic characteristics of the study participants are shown in Table 1. The mean age of the study participants is 63.0±16.3 years. The mean body mass index was 24.7±6.5 kg/m$^2$ while 42.9% of them were males. Anaemia was present in 106 (75.7%) of the study participants while 44.3% were on digoxin and 36.4% were on one type of cardio-selective beta-blockers or the other. All the participants were on diuretics and anticoagulants/antiplatelets therapy. The correlation analysis of the measure of right ventricular systolic function in this study (TAPSE) with markers of iron status is shown in Table 2. Variables such as heart rate, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration and serum transferrin are significantly well correlated to TAPSE. Table 3 highlights the right ventricular functional parameters between HF participants with ID compared to those without ID. Right ventricular dysfunction as measured by TAPSE was significantly commoner among HF with ID compared to those with normal iron parameters (69.0% *vs* 32.1%, respectively, p<0.001). Similarly, mean peak pulmonary systolic pressure, tricuspid E wave velocity, TAPSE, and the ratio of TE/TA were significantly different between HF with ID compared to those with normal iron parameters. Pulmonary hypertension was commoner among HF with ID compared to those with normal iron parameters (33.3% *vs* 25.9%, respectively, p=0.048). The mean right ventricular dimension and the late tricuspid A wave velocity were not significantly different between the two groups. This is shown in Table 3. The clinical, demographic, and markers of iron status between HF with right ventricular dysfunction compared with those with normal right ventricular systolic function are as shown in Table 4. Both groups were similar in mean age, diastolic blood pressure, left atrial dimension, packed cell volume, haemoglobin concentration, mean corpuscular haemoglobin concentration, serum ferritin, total iron, transferrin saturation, and estimated glomerular filtration rate. HF subjects with right ventricular systolic dysfunction had significantly higher heart rate (96.9±24.4 *vs* 86.6±11.7/min, respec-

**Table 1.** Sociodemographic characteristics of study participants.

| Variables | Values |
|---|---|
| Age (years) | 63.0±16.3 |
| SBP (mmHg) | 125.1±22.5 |
| DBP (mmHg) | 78.2±14.0 |
| BMI (kg/m2) | 24.7±6.5 |
| Drugs - Digoxin | 62 (44.3%) |
| Beta blockers (n) | 51 (36.4%) |
| Gender (M/F) (n/%) | 60/80 (42.9/57.1%) |
| Anaemia (n) | 106 (75.7%) |
| Grade III DD | 19 (13.6%) |

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; M, male, F, female; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.

**Table 2.** Correlation analysis of tricuspid annular systolic excursion to haemogram and iron profile participants.

| Variable | Correlation | p-value |
|---|---|---|
| Heart rate (b/min) | -0.333 | 0.000** |
| Packed cell volume (%) | -0.030 | 0.754 |
| MCV (fl) | 0.155 | 0.102 |
| MCH (pg/c) | 0.246 | 0.009** |
| MCHC (g/dL) | 0.198 | 0.035* |
| Serum ferritin (ng/ml) | 0.045 | 0.636 |
| Atrial natriuretic peptide (pg/ml) | -0.080 | 0.398 |
| Transferrin (mcg/dl) | -0.213 | 0.023* |
| Total iron (mcg/dl) | 0.092 | 0.330 |
| Transferrin saturation (%) | -0.034 | 0.722 |
| Total white cell count (/mm3) | -0.047 | 0.625 |
| Tricuspid E/A ratio | 0.096 | 0.469 |

MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration.

**Table 3.** Right ventricular functional parameters between HF patients with and without iron deficiency.

| Variables | Iron deficiency (84) | No iron deficiency (56) | p-value |
|---|---|---|---|
| RVD (n) | 58 (69.0%) | 18 (32.1%) | 0.000 ** |
| RV dimension | 29.9±4.9 | 30.3±5.1 | 0.278 |
| PPSV | 0.95±0.15 | 1.1±0.4 | 0.045* |
| TE | 0.60±0.38 | 0.37±0.37 | 0.003** |
| TA | 0.39±0.35 | 0.40 ±0.38 | 0.934 |
| TAPSE | 14.4± 3.8 | 16.6±4.52 | 0.002** |
| TE/TA | 1.05±0.58 | 0.76±0.73 | 0.0138* |
| Pulmonary hypertension | 28 (33.3% | 14 (25.9%) | 0.048* |

RVD, right ventricular dysfunction; RV, right ventricle; PPSV, peak pulmonary systolic velocity, TE, tricuspid E velocity, TA, tricuspid A wave velocity; TAPSE, tricuspid annular systolic pulmonary excursion.

tively, p<0.05), left ventricular internal dimension in diastole (56.6 ±10.1 *vs* 55.4±11.2 mm, respectively, p <0.05), transferrin (207.2 ±39.9 vs. 193.8 ± 21.3 respectively, p<0.05), and left ventricular mass (337.6±125.1 *vs* 291.9±122.6g/$m^{2,}$ respectively, p<0.05) compared to HF subjects with normal right ventricular systolic function as shown in Table 4. Mean systolic blood pressure (122.6±19.6 *vs* 130.7±23.4 mmHg, respectively, p<0.05), mean corpuscular volume (84.8±10.4 *vs* 90.7±8.2 fl., respectively, p<0.05), mean corpuscular haemoglobin (27.9±4.3 *vs* 30.9±3.0 pg/c, respectively, p<0.05) and ejection fraction (38.6±6.7 *vs* 43.2±10.3%, respectively, p<0.05) were significantly lower among HF subjects with RVD compared to Hf with normal right ventricular systolic function in the study cohort. The frequency of occurrence of different heart failure phenotypes based on left ventricular ejection fraction was not significantly different between those with and those without right ventricular dysfunction in this study, as shown in Table 4. Iron deficiency was also significantly higher among those with right ventricular dysfunction than those without right ventricular dysfunction. This is also shown in Table 4.

The logistic regression analysis of determinants of right ventricular systolic function especially iron markers is shown in Table 5. The major determinants were left atrial dimension, heart rate, serum ferritin, and transferrin. The pattern of

**Table 4.** Iron and haematological parameters between HF patients with and without RVD.

| Variables | HF with RVD (76) | HF without RVD (64) | All | p-value |
|---|---|---|---|---|
| Age (years) | 60.4±17.5 | 63.4±16.1 | 63.0±16.3 | 0.269 |
| Cigarette smoking (n) | 1.8±0.4 | 2.0±0.2 | 1.9±0.3 | 0.011* |
| Heart rate (b/min) | 96.9±24.4 | 86.6±11.7 | 90.2±18.8 | 0.007* |
| SBP (mmHg) | 122.6±19.6 | 130.7±23.4 | 125.1±22.5 | 0.013* |
| DBP (mmHg) | 76.7±15.6 | 79.9±12.9 | 78.2±14.0 | 0.444 |
| LVDD (mm) | 56.6±10.1 | 55.4±11.2 | 56.6±11.3 | 0.005* |
| LAD (mm) | 50.4± 10.8 | 45.4±12.0 | 47.4±11.6 | 0.080 |
| EF (%) | 38.6± 6.7 | 43.2±10.3 | 40.7±9.4 | 0.000** |
| PCV (%) | 31.5± 7.7 | 32.5±6.0 | 32.3 ±6.4 | 0.514 |
| HB (g) | 10.2± 2.9 | 10.8±2.0 | 10.7±2.6 | 0.455 |
| MCV (fl) | 84.8± 10.4 | 90.7±8.2 | 88.6±9.1 | 0.001* |
| MCH (pg/c) | 27.9± 4.3 | 30.9±3.0 | 29.8±3.7 | 0.000* |
| MCHC (g/dL) | 32.9± 3.4 | 34.2±2.7 | 33.6±2.8 | 0.062 |
| Ferritin (ng/mL) | 236.7± 183.4 | 228.4±156.2 | 227.2±163.0 | 0.739 |
| ANP (pg/mL) | 167.0±51.4 | 154.9±57.9 | 161.0±56.9 | 0.494 |
| Transferrin (mcg/dL) | 207.±39.9 | 193.8±21.3 | 200.03 ±29.6 | 0.049* |
| Total iron (mcg/dL) | 35.2± 9.2 | 40.0±21.6 | 39.3±20.7 | 0.110 |
| Transferrin saturation (%) | 17.4±5.4 | 21.0±12.3 | 19.9± 10.7 | 0.098 |
| LVM (g/$m^2$) | 337.6±125.1 | 291.9±122.6 | 317.8 ±125.5 | 0.017* |
| eGFR (mls/min) | 44.9±20.5 | 61.8±49.4 | 53.6±39.9 | 0.248 |
| ID (n) | 58 (76.3%) | 26 (40.6%) | 84 (60.0%) | 0.000 |
| HFpEF/HFmrEF/HFrEF (n) | 12/25/39 | 12/22/30 | 24/47/69 | 0.399 |

RVS, right ventricular dysfunction; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVDD, left ventricular internal dimension; LAD, left atrial dimension; EF, ejection fraction; PCV, packed cell volume; Hb, haemoglobin; MCV, mean corpuscular volume; MCH/H, mean corpuscular haemoglobin/concentration; ANP, atrial natriuretic peptides; LVM, left ventricular mass; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction, HFrEF, heart failure with reduced ejection fraction.

**Table 5.** Logistic regression analysis of iron parameters determinants of right ventricular dysfunction in HF subjects.

| Variables | B | Standard error | p-value |
|---|---|---|---|
| Heart rate | 0.035 | 0.018 | 0.049* |
| RVD | -0.079 | 0.091 | 0.381 |
| LAD | 0.110 | 0.040 | 0.006* |
| PCV | -0.037 | 0.057 | 0.514 |
| MCV | 0.152 | 0.271 | 0.576 |
| MCH | -0.755 | 0.770 | 0.326 |
| MCHC | 0.290 | 0.610 | 0.634 |
| Ferritin | 0.007 | 0.003 | 0.007** |
| Transferrin | 0.076 | 0.040 | 0.046* |
| Total iron | -0.171 | 0.145 | 0.236 |
| Transferrin saturation | 0.295 | 0.273 | 0.282 |
| K | -21.795 | 25.13 | 0.386 |

RVD, right ventricular dysfunction; LAD, left atrial dimension; PCV, packed cell volume; Hb, haemoglobin; MCV, mean corpuscular volume; MCH/H, mean corpuscular haemoglobin/concentration; ANP, atrial natriuretic peptides.

right ventricular systolic dysfunction among study participants is shown in Figure 1. Right ventricular systolic dysfunction predominates with the presence of ID among study participants than if subjects had normal iron parameters.

## Discussion

This study revealed that right ventricular systolic dysfunction is significantly associated with ID in chronic HF subjects in Nigeria. Right ventricular dysfunction is not unusual in patients with HF, and it is often associated with worse clinical outcomes and functional profile.[2-4,8] The correlation of the measure of right ventricular systolic function in this study (tricuspid annular systolic pulmonary excursion <20 mm) with markers of iron status such as mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration and serum transferrin lends credence to this. These variables are potential markers of iron homeostasis and their degree of impairment chronicles significant impairment in cellular metabolism and adaptation to various changes in cardiovascular haemodynamic of HF.[16,17] The inverse association with heart rate is also relevant as a higher heart rate has been related to significant morbidity and mortality in HF.[17] The relationship between ID and RVD has been sparsely demonstrated among Caucasians.[18] The prevalence of RVD as evaluated by TAPSE was significantly higher among HF subjects with ID compared to normal iron parameters. This is like what has been reported in other parts of the world.[18,19] Iron deficiency is prevalent in HF as a comorbidity with a prevalence of up to 60% in chronic HF in Nigeria.[5,6] Both anaemia and ID are of important prognostic potentials in HF. While the epidemiology and therapeutic importance of Iron replacement have been extensively studied in developed countries, data are still very scarce from Africa. Our group recently conducted a randomized controlled trial demonstrating the benefits of parenteral iron therapy in HF in terms of quality of life and functional outcomes among Africans with HF.[5,6] Despite the huge burden of anaemia with or without ID in Africa and the potential it offers by searching for it and correcting it as the signs and symptoms of HF will be overshadowed in HF, data and epidemiological data are scarce to recognize the significance of anaemia and ID in HF. From a clinical perspective, less attention is paid by clinicians to screening for anaemia and ID in HF, and in the same vein, as interventions are concerned.[20] Studies suggest that ID is associated with poor prognosis independent of other risk factors. The potential usefulness of oral iron supplementation has shown significant beneficial effects of haematological and physiological variables as the cost may limit the use of parenteral iron on a large scale in low and middle-income countries. This is in a bid to identify the optimal collaborative care/treatment regimen to treat ID in SSA.[21]

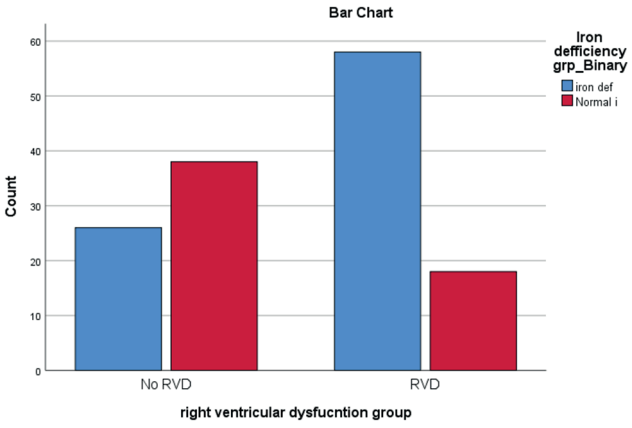


**Figure 1.** Prevalence of iron deficiency in HF patients with and without right ventricular dysfunction (RVD).

The synchronous pathologic sequelae of ID in HF may be similar in both the LV and the RV. Hence the association of ID with LV and RV markers. In a study to explore the pathophysiologic role of myocardial iron deficiency (MID) in HF, myocardial iron content in the left ventricle was lower in HF versus controls. It also shows that respiratory chain and Krebs cycle enzymatic activities were suppressed and strongly correlated with depleted iron stores in HF-MID hearts.[22,23] Other changes reported include impaired response to oxidative stress, worse adverse cardiac remodelling, and reduced iron uptake pathways including decreased translocation to the sarcolemma. The study further revealed that MID is highly prevalent in advanced human HF and exacerbates pathological remodelling in HF driven primarily by dysfunctional mitochondria and increased oxidative stress in the ventricle.[22-25] Similar events also take place in the right ventricle and may be responsible for the RV dysfunction associated with ID in HF.

Subclinical right ventricular dysfunction is often found in iron deficiency including decreased RV free wall global longitudinal strain even before other right ventricle systolic functional parameters commonly used on echocardiography such as right ventricular ejection fraction (RVEF), tissue doppler studies, right ventricular fractional area change (RV FAC in daily practice are deranged.[25] We, therefore, suggest that screening for ID in HF patients may facilitate early detection and treatment of ID which may ultimately prevent RV dysfunction in HF subjects.[26] The novelty in this study is the linkage between iron deficiency and right ventricular systolic and diastolic dysfunction among Africans as this appears to be the first set of information, especially among Africans. It also provides a platform for a theoretical possible reversal of the right ventricular dysfunction with iron replacement, a plausibility with further appropriate studies.

Structurally and hemodynamically, the relationship between ID and right ventricular systolic dysfunction may be explained by various theories: First, the severity of venous congestion by itself is an independent predictor of ID in HF and is greater in patients with RVD. The mechanism by which congestion worsens ID includes liver dysfunction, malabsorption syn-

drome, and subsequent abnormal ferritin and transferrin metabolism.[27-29] Secondly, hepcidin excess results from hepatic congestion and HF inhibits iron absorption from the intestine and iron release from macrophage stores although this remains controversial as other authors have reported low hepcidin levels.[30-32] What we may not know now is the trajectory of the iron biomarkers across the HF phenotypes and how they evolve. Evidence from animal models also suggests that ID directly and rapidly promotes vascular remodelling, pulmonary hypertension, and right ventricular hypertrophy.[33-34] The benefit of iron replacement in HF with left ventricular systolic dysfunction has been shown even in Nigerians but the effect in RVD should be a research focus for the future.

One limitation of this study is that the study being a cross-sectional study cannot completely adduce the RVD to ID as other related factors may also be causally related. We also did not exclude other related causes of ID including intestinal parasitosis, acid-peptic diseases, and acute inflammation. We also limited our measurement of RVD measure to TAPSE, which could have underestimated RVSD in these cohorts.

## Conclusions

This study concludes that ID is associated with right ventricular systolic dysfunction in Nigerians with chronic HF and that it is correlated with some biomarkers of iron status some of which are the determinants of RVD in HF subjects. The prognostic significance of ID and RVD coexistence suggests poorer prognosis by other conventional markers such as left ventricular hypertrophy, ejection fraction and quality of life. We recommend further research work to highlight the therapeutic potential of reversing RVSD by parenteral iron replacement in Africans with chronic HF.

## Contributions

AAA, study concept, data collection and analysis, writing of the manuscript and final approval of the manuscript; STO, sample and data collection, review of the manuscript and final approval of the manuscript.

## Conflict of interest

The authors declare have no competing interests, and all authors confirm accuracy.

## Ethics approval and consent to participate

Ethical approval was obtained from the Research Ethics Committee of Ladoke Akintola University of Technology Teaching Hospital, Ogbomoso, Nigeria. Written informed consent was obtained from all study participants.

## Availability of data and materials

The data is available from the corresponding author on reasonable request and is also available on the LAUTECH RPSS repository (www.lautech.edu.ng).

## Funding

This study was partly sponsored by TETFund Nigeria through the Institutional Based Research Grant of 2017.

## Acknowledgments

The authors would like to acknowledge the Tertiary Education Fund (TETFUND) sponsorship for this study.

## References

1. Akintunde AA. Right ventricular function in patients with heart failure in a cardiac clinic in Southwest Nigeria. Niger Med J 2017;58:7-12.
2. Akintunde AA. The clinical value of the Tei index among Nigerians with hypertensive heart failure: Correlation with other conventional indices. Cardiovasc J Afr 2012;23:40-3.
3 . Akintunde AA, Akinwusi PO, Familoni OB, Opadijo OG. Effect of systemic hypertension on right ventricular morphology and function: An echocardiographic study. Cardiovasc J Afr 2010;21:252-6.
4. Akinwusi PO, Okunola OO, Opadijo OG, et al. Hypertensive heart failure in Osogbo South-Western Nigeria: Clinical presentation and outcome. Niger Med Pract 2009;56:53-6.
5. Akintunde AA, Akinlade MO, Aworanti OW. Disordered iron homeostasis among Nigerians with chronic heart failure: pattern, prevalence, and clinical correlates. J Am Coll Cardiol 2021;10:17-25.
6. Akintunde AA, Akinlade OM, Egbewale BE, Opadijo OG. Iron deficiency anemia in Nigerians with heart failure (IDAN-HF): Therapeutic efficacy of iron replacement: An interventional study. Niger J Clin Pract 2021;24:21-7.
7. Maeder MT, Khammy O, dos Remedios C, Kaye DM. Myocardial and systemic iron depletion in heart failure implications for anaemia accompanying heart failure. J Am Coll Cardiol 2011; 58:474–480.
8. Dong F, Zhang X, Culver B, et al. Dietary iron deficiency induces ventricular dilation, mitochondrial ultrastructural aberrations, and cytochrome c release: involvement of nitric oxide synthase and protein tyrosine nitration. Clin Sci (Lond) 2005;109: 277-86.
9. Karaye KM, Sai'du H, Shehu MN. Right ventricular dysfunction in a hypertensive population stratified by patterns of left ventricular geometry. Cardiovasc J Afr 2012;23:478-82.
10. Bogaard HJ, Abe K, Vonk Noordegraaf A, Voelkel NF. The right ventricle under pressure: Cellular and molecular mechanisms of right-heart failure in pulmonary hypertension. Chest 2009;135: 794-804.
11. Rako ZA, Kremer N, Yogeswaran A, et al. Adaptive versus maladaptive right ventricular remodelling. ESC Heart Fail 2023;10: 762-75.
12. Oketona OA, Balogun MO, Akintomide AO, et al. Right ventricular

systolic function in hypertensive heart failure. Vasc Health Risk Manag 2017;13:353-60.
13. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599-726.
14. Cheitlin MD, Armstrong WF, Aurigemma GP, et al. ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). J Am Soc Echocardiogr 2003;16:1091-110.
15. Aloia E, Cameli M, D'Ascenzi F, et al. TAPSE: An old but useful tool in different diseases. Int J Cardiol 2016;225:177-83.
16. Tkaczyszyn M, Comín-Colet J, Voors AA, et al. Iron deficiency and red cell indices in patients with heart failure. Eur J Heart Fail 2018;20:114-22.
17. Chopra VK, Anker SD. Anaemia, iron deficiency and heart failure in 2020: facts and numbers. ESC Heart Fail 2020;7:2007-11.
18. Miñana G, Santas E, de la Espriella R, et al. Right ventricular function and iron deficiency in acute heart failure. Eur Heart J Acute Cardiovasc Care 2021;10:406-14.
19. Yu J, Yu L, Li Y, Hu F. Iron deficiency is a possible risk factor causing right heart failure in Tibetan children living in high altitude area. Medicine (Baltimore) 2020;99:e21133.
20. Amaechi UM, Chukwudum E, Aiwuyo HO, et al. Clinical and echocardiographic correlates of iron status in chronic heart failure patients: a cross-sectional descriptive study. Cureus 2023;15:e39998.
21. Makubi A, Lwakatare J, Ogah OS, et al. Anaemia and iron deficiency in heart failure: epidemiological gaps, diagnostic challenges and therapeutic barriers in sub-Saharan Africa. Cardiovasc J Afr 2017;28:331-7.
22. Makubi A, Roberts DJ. Investigation and treatment for iron deficiency in heart failure: the unmet need in Lower- and Middle-Income Countries. Br J Haematol 2017;177:896-904.
23. Zhang H, Jamieson KL, Grenier J, et al. Myocardial iron deficiency and mitochondrial dysfunction in advanced heart failure in humans. J Am Heart Assoc 2022;11:e022853.
24. Mousavi-Aghdas SA, Farashi E, Naderi N. Iron dyshomeostasis and mitochondrial function in the failing heart: a review of the literature. Am J Cardiovasc Drugs 2024;24:19-37.
25. Brown DA, Perry JB, Allen ME, et al. Mitochondrial function as a therapeutic target in heart failure. Nat Rev Cardiol 2017;14:238-50.
26. Nickel A, Löffler J, Maack C. Myocardial energetics in heart failure. Basic Res Cardiol 2013;108:358.
27. Engin K, Sinan UY, Arslan S, Kucukoglu MS. The effect of iron deficiency on RV function in acute decompensated heart failure patients. Eur Heart J 2023;44:ehad655.929.
28. van der Wal HH, Grote Beverborg N, Dickstein K, et al. Iron deficiency in worsening heart failure is associated with reduced estimated protein intake, fluid retention, inflammation, and antiplatelet use. Eur Heart J 2019;40:3616-25.
29. Ohno Y, Hanawa H, Jiao S, et al. Liver congestion in heart failure contributes to inappropriately increased serum hepcidin despite anemia. Tohoku J Exp Med 2015;235:69-79.
30. Grote Beverborg N, van der Wal HH, Klip IT, et al. Differences in clinical profile and outcomes of low iron storages vs defective iron utilization in patients with heart failure. JAMA Cardiol 2019;4:696-701.
31. Nemeth E, Valore EV, Territo M, et al. Hepcidin, a putative mediator of anemia of inflammation, is a type II acute-phase protein. Blood 2003;101:2461-3.
32. Ganz T. Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. Blood 2003;102:783-8.
33. Rhodes CJ, Howard LS, Busbridge M, et al. Iron deficiency and raised hepcidin in idiopathic pulmonary arterial hypertension: clinical prevalence, outcomes, and mechanistic insights. J Am Coll Cardiol 2011;58:300-309.
34. Anker SD, Kirwan B-A, van Veldhuisen DJ, et al. Effects of ferric carboxymaltose on hospitalizations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. Eur J Heart Fail 2018;20:125-33.