A not-so-rare form of heart failure in urban black Africans: pathways to right heart failure in the Heart of Soweto Study cohort

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Received 19 April 2011; revised 28 June 2011; accepted 1 July 2011

Aims
Preliminary data suggest that right heart failure (RHF) may be more common in urban Africans than first suspected. We examine the characteristics and pathways to RHF in the Heart of Soweto cohort.

Methods and results
A clinical registry captured data from 5328 de novo presentations of heart disease to the Cardiology Unit, Chris Hani Baragwanath Hospital in Soweto, South Africa during 2006–08. Of 2505 cases of HF (47% of total cohort), 697 (28%) were diagnosed with RHF (50% primary diagnosis). Despite more females than males (379 vs. 318 cases), proportionately more men presented with RHF [15 vs. 12% of cases; odds ratios (OR) 1.27, 95% confidence intervals (CI) 1.08–1.49] and Africans predominated overall (n = 642, 92%). Apart from concurrent left-sided heart disease (213 cases, 31%) there were many pathways to RHF including chronic lung disease (179 cases, 26% including COPD and tuberculosis) and 141 cases (20%) of pulmonary arterial hypertension (PAH). On an adjusted basis, women were almost two-fold more likely to present with PAH (OR 1.72, 95% CI 1.17–2.55; P = 0.006) while those with low levels of education (OR 0.69, 95% CI 0.47–1.01; P = 0.054) and originating from Soweto (OR 0.64, 95% CI 0.42–0.96; P = 0.029) were less likely to present with PAH compared with the rest of the cohort.

Conclusion
These data suggest cases of RHF and related PAH are relatively common among urban Africans presenting with de novo heart disease.

Keywords
Right heart failure • Pulmonary arterial hypertension • Africa

Introduction
In contrast to the findings of the European Heart Failure Survey II, whereby only 3.2% of a cohort of patients registered with the syndrome heart failure (HF) had a component of right heart failure (RHF), we have previously noted surprisingly high levels of RHF in the Heart of Soweto Study cohort. In the first year of capturing data on all presentations of heart disease (pre-established and de novo) to the Chris Hani Baragwanath Hospital, we found that one in five of all cases of HF involved a component of RHF. Potential reasons for high levels of RHF in Soweto are many and varied, and may mirror those found in other populations in economic transition such as post-war Northern England. As reported from the international BOLD Study, South Africa has a particularly high prevalence of COPD that develops across all ages in towns such as Soweto for a range of reasons. This includes exposure to pulmonary irritants from at-risk occupations such as mining, direct and passive smoking, urban pollution, and indoor pollution from domestic (solid fuel) heaters. It also includes endemic levels of a broad range of antecedent diseases, most notably tuberculosis and human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) that remain poorly detected and controlled. In children, lack of adequate paediatric services to deal with congenital heart disease that lead to
Right heart failure in Soweto

Right heart failure in Soweto (RHF) is commonly seen\(^7\) and there is also a high incidence of aggressive forms of rheumatic heart disease (RHD) which includes a strong component of RHF.\(^8,9\) High altitude (Johannesburg is \(\approx 1000\) m above sea level) may also be a contributory factor. Greater levels of PAH, when compared with reports from high-income countries,\(^10,11\) are less easy to explain.

Using 3-year data from the Heart of Soweto Study cohort documenting the characteristics of de novo presentations of heart disease to a tertiary hospital in the predominantly African community of Soweto, South Africa, we specifically examined the nature of RHF presentations in this cohort.

**Methods**

**Study setting and design**

Descriptions of the purpose and methods of the Heart of Soweto Study, the largest and most comprehensive study of emergent heart disease in sub-Saharan Africa, have been described in detail in previous reports.\(^2\) Data derived from this study cohort represent an important (but not exclusive) barometer of heart disease in urban communities in sub-Saharan Africa. The data described in this report are derived from the 3500-bed Chris Hani Baragwanath Hospital (case load of \(>125,000\) in-patients) servicing the tertiary care needs of Soweto (population of 1.1 million) and surrounding communities. All cases of suspected heart disease were referred to the hospital’s Cardiology Unit for advanced diagnostic testing and gold-standard treatments. A prospective clinical registry of all de novo presentations of the same collected data was implemented during the period 2006–08.

**Study cohort**

We captured data on 5328 cases of de novo heart disease being managed by the Cardiology Unit during the 3-year study period. The majority of cases were either current inpatients at the Baragwanath Hospital (\(n = 1992, 37.4\%) or referred by another outpatient department (\(n = 2568, 48.2\%) including a respiratory clinic for patients diagnosed with chronic lung disease (where respiratory diagnoses were made). The study was approved by the University of the Witwatersrand Ethics Committee and conforms to the principles outlined in the Declaration of Helsinki.

**Study data**

A complete list of study data captured by the registry, comprising basic socio-demographic (including years of education and determining if a person was born in Soweto) and advanced clinical profiling, has been described previously.\(^2\) Echocardiography (according to gold-standard criteria\(^12\)) and 12-lead electrocardiogram (ECG) (blinded classification to Minnesota criteria\(^13\)) were performed in all cases. Wherever possible, we have adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for this type of study.\(^14\)

**Right heart failure and pulmonary hypertension**

All study data were independently reviewed and adjudicated (using a consensus approach) by K.S. and S.S. Classification of complex cases with valve dysfunction was based on criteria used in a recent report on valve disease in this cohort.\(^9\) For the purpose of this report focusing on RHF, we prospectively classified all cases using recent guidelines published by the European Society of Cardiology (relating to HF\(^15\)) and American Heart Association (relating to PAH\(^16\)) to create the study definitions shown in the text box below.

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**Text box. Study definitions**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical features</th>
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<tbody>
<tr>
<td><strong>Right heart failure (RHF)</strong></td>
<td>HF secondary to right-sided pathology with increased jugular venous pressure and liver size, tricuspid regurgitation and/or elevated right ventricular systolic pressure (RVSP) (&gt;35) mmHg; Usually accompanied by peripheral oedema as unique or concomitant to left HF. Isolated RHF excludes significant left ventricular and valvular involvement (e.g. RHD) and pulmonary disease.</td>
</tr>
<tr>
<td><strong>Pulmonary arterial hypertension (PAH)</strong></td>
<td>Documented elevated RVSP ((&gt;35) mmHg) on echocardiography; usually accompanied by shortness of breath and possibly ECG and chest X-ray changes. Confirmation by right heart catheterization was obtained in selected cases to confirm the diagnosis or where treatment with a phosphodiesterase-5 inhibitor on a trial basis was planned. Idiopathic PAH: no identifiable causal factor for elevated pulmonary arterial pressure. HIV-related PAH: PAH associated with a confirmed diagnosis of HIV infection and/or treatment with highly active anti-retro viral therapy. Connective tissue disorder-related PAH: PAH associated with a prior diagnosis of connective tissue disorder (e.g. scleroderma). Congenital PAH: PAH associated with a congenital disorder (e.g. Eisenmenger’s syndrome).</td>
</tr>
<tr>
<td><strong>Left-sided heart disease</strong></td>
<td>Evidence of left-sided pathology with a documented left ventricular ejection fraction (LVEF) (&lt;45%) and/or mitral valve disease (other than that associated with RHD). This includes idiopathic dilated cardiomyopathy (CMO) requiring additional left ventricular dimension in diastole (&gt;55) mm of indeterminate origin (coronary artery disease excluded by coronary angiography).</td>
</tr>
<tr>
<td><strong>Rheumatic heart disease (RHD)</strong></td>
<td>Medical history of acute rheumatic fever, clinical examination and according to standard echocardiographic criteria.</td>
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<tr>
<td><strong>Chronic lung disease</strong></td>
<td>Documented chronic lung condition including chronic bronchitis, asthma, COPD, and pulmonary tuberculosis supported by clinical investigations (including pulmonary function tests).</td>
</tr>
<tr>
<td><strong>Thrombo-embolic disease</strong></td>
<td>Evidence of thrombo-embolic disease (typically in the pulmonary vasculature).</td>
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</table>
Statistical analyses

All study data were documented on standardized case report forms and entered into a dedicated database (Microsoft Access) at the Soweto Cardiovascular Research Unit, at the Chris Hani Baragwanath Hospital. Data were then verified and transferred to SPSS Statistics 17.0 for all analyses by an independent team at Baker IDI (Australia). Normally distributed continuous data are presented as mean ± standard deviation and non-Gaussian distributed variables as median plus interquartile range. Categorical data are presented as percentages with 95% confidence intervals (CI) where appropriate. For patient group comparisons, we initially used χ² analysis with calculation of odds ratios (OR) and 95% CI (where appropriate) for discrete variables and Student’s t-test and analysis of variance for normally distributed continuous variables. Multiple logistic regression analyses (entry model) were performed on age, sex, and baseline risk factors to derive adjusted ORs for the risk of presenting with RHF overall, chronic lung disease, and PAH within the entire Heart of Soweto cohort. Significance was accepted at the two-sided level of 0.05.

Results

Right heart failure in 5328 de novo cases of heart disease

During the period 2006–08, a total of 2505 of all 5328 de novo cases of heart disease (47%) were diagnosed with any form of HF. Of these HF cases, 697 (28%) were diagnosed with RHF. Right heart failure was the primary diagnosis in 345 cases (50%). There were more women than men diagnosed with RHF (379 vs. 318 cases) but proportionately more men were affected (15 vs. 12% of all 5328 cases, OR 1.27, 1.08–1.49; P = 0.003). There were also more patients of African descent diagnosed with RHF than any other ethnic group (642 vs. 55 other ethnic cases). On an adjusted basis, compared with the remainder of the Heart of Soweto cohort (n = 4631), RHF cases were more likely to be African (adjusted OR 2.33, 95% CI 1.59–3.41), and have a history of smoking (OR 1.72, 95% CI 1.42–2.10). Alternatively they had a lower body mass index (OR 0.96, 95% CI 0.94–0.97 per kg/m²) and were less likely to have a family history of heart disease (OR 0.79, 95% CI 0.64–0.96).

Overall pattern of right heart failure (n = 697)

Table 1 compares the clinical and demographic characteristics of all 697 cases of RHF according to gender. Overall, 57% of patients were current or ex-smokers with more men than women reporting this major risk factor (77 vs. 40%), while women had a higher mean body mass index and total cholesterol levels. From a clinical perspective, there were marked differences in left and right ventricular parameters reflective of differences in the predominant form of RHF seen in men and women (see below). Contributory causes of RHF were many and varied in the study cohort. Figure 1 shows the spectrum of diagnoses associated with RHF according to sex. In women (n = 379, 54% of RHF cases) the main concurrent diagnoses were left-sided heart disease (29%; including 34 cases of idiopathic dilated CMO), PAH (28%), RHD (18%), and pulmonary disease (17%). Isolated right ventricular failure with no obvious causality occurred in 28 cases (7%). Similarly, Figure 1 shows that the main diagnoses associated with concurrent RHF in men (n = 318) were similar in nature but proportionately different. Right heart failure in men was most commonly associated with concurrent pulmonary disease (36%), mainly comprising COPD (50%) and tuberculosis (23%). Other common diagnoses were left-sided heart disease (32% including 42 cases of idiopathic CMO) and PAH (15%).

Chronic lung disease (n = 179)

Patients presenting with a chronic lung condition or disease were on average 3 years older than the rest of the cohort (54.2 ± 17.6 vs. 51.2 ± 17.9 years; P = 0.054). In total, there were 64 female cases of chronic lung disease including COPD (31 cases, 48%) and pulmonary tuberculosis (19 cases, 30%). There were more equivalent male cases in men (n = 115, 64%) that also mainly comprised those with COPD (67 cases, 58%) or pulmonary tuberculosis (26 cases, 23%). On an adjusted basis, men and those with a history of smoking were two-fold more likely to present with concurrent lung disease when compared with women (OR 1.99, 95% CI 2.26–3.16; P = 0.003) and non-smokers (OR 2.07, 95% 1.27–3.34; P = 0.003).

Pulmonary arterial hypertension (n = 141)

Figure 2 shows the spectrum of PAH-related cases according to sex with nearly double the number of female (66%) than male cases overall. In women, the three most common forms of PAH were idiopathic PAH (34%—with no known cause established), PAH related to concurrent HIV infection (33%) and PAH related to connective tissue disorders (27%); the latter comprising 17 cases of scleroderma. In men, the dominant form of PAH was idiopathic PAH (60% of cases) with another 11 cases (23%) of HIV-related PAH. Overall, therefore, similar numbers of both sexes were affected by idiopathic PAH whereas significantly more women were affected by HIV and connective tissue related PAH. Consistent with the wider cohort, the majority of cases were of African descent and originated from somewhere other than Soweto. Compared with the rest of the Heart of Soweto cohort (n = 5187), on an adjusted basis, women were almost two-fold more likely to present with PAH (adjusted OR 1.72, 95% CI 1.17–2.55; P = 0.006) while those with low levels of education and originating from Soweto were less likely to present with PAH compared with those with higher levels of education (OR 0.69, 95% CI 0.47–1.01; P = 0.054) and migrants (OR 0.64, 95% CI 0.42–0.96; P = 0.029).

On average, those with any form of PAH were 7 years younger than the rest of the RHF cohort (46.5 ± 16.9 vs. 53.4 ± 17.8 years; P < 0.0001), largely due to the fact that affected women were significantly younger than their male counterparts (43.6 ± 16.6 vs. 52.0 ± 16.3 years; P < 0.01). Women also presented with slightly higher RVSP levels than men (56.5 ± 17.8 vs. 50.5 ± 18.8 mmHg; P = 0.153). However, Table 2 shows that within the various subgroups of PAH, there were important differences in demographic and clinical profiles.
Overall, 272 patients (46%) had an ECG abnormality indicative of right-sided pathology (including right axis deviation, right bundle branch block, p-pulmonale and right strain pattern indicative of right ventricular hypertrophy). Although there was no difference between the sexes in the presence of an ECG abnormality, women were more likely to present in first- or second-degree heart block [23 (7.1%) vs. 7 (2.6%) cases; OR 2.77 95% CI 1.21–6.36], while 33 (5.5%) cases presented in atrial fibrillation. Patients with ECG evidence of right-sided pathology were more likely to have left-sided disease (60%), RHD (56%), idiopathic PAH (54%), and right ventricular failure of unknown origin (50%).

### Discussion

In recent years, there has been increasing awareness around the underlying prevalence and clinical significance of cor pulmonale/RHF and more specific cases of PAH. This applies equally to recognition of the importance of RHF as both a primary diagnosis and as a poor prognostic marker for those primarily affected by left-sided HF. It is within this context that we present the largest and most comprehensive description of RHF in sub-Saharan Africa. In the majority of studies describing HF in the region (amounting to >100 papers reflecting increasing interest in an increasingly common syndrome), a component of cor pulmonale/RHF is reported; the historical proportion of affected HF patients typically ranges from <1% to up to 10% in most regions of Africa.
An important delineation between the Heart of Soweto Study and the majority of previous studies, however, is the size of the cohort investigated (>6000 cases), the focus on de novo presentations only, and the use of systematic screening with echocardiography to identify underlying HF. In the Heart of Soweto Study cohort, RHF was diagnosed in almost 700 cases (representing 28% of all HF cases). Numerically, there were more women than men but proportionately more men than women were diagnosed within the entire cohort. As expected, underlying causes of RHF were many and varied including the...
dilated cardiomyopathies, chronic lung disease, RHD and various forms of PAH. Those most likely to present with RHF were of African descent (greater than two-fold risk compared with other ethnic groups) and many had a history of smoking.

By highlighting the many pathways to RHF in Africans living in the urban enclave of Soweto, South Africa, these data raise a number of important clinical and public health issues. For example, in recent years, it has been increasingly recognized that the prevalence of PAH in its various forms is far higher than first imagined.10,11 It was often reported that one in a million (predominantly young women) are affected by this disabling and deadly condition with most cases diagnosed late when undiscovered PAH has led to advanced RHF (often with increasing dyspnoea of ‘unknown’ origin). Certainly, there has been increased focus on screening for PAH in high-risk patients. In South Africa, this includes both connective tissue disorders and those with HIV/AIDS, with the number of detected cases (via the systematic screening of cardiac cases at Baragwanath Hospital) suggesting an incidence rate of at least 10–15 cases per annum for each form of PAH in Soweto. The other most common form, idiopathic PAH, occurred in even greater numbers with an indicative rate of 20 cases per annum. These data are consistent with contemporary reports in even greater numbers with an indicative rate of 20 cases per annum. The other most common form, idiopathic PAH, occurred in even greater numbers with an indicative rate of 20 cases per annum. Beyond low-to-middle-income countries, these data suggest a higher incidence of all forms of pulmonary hypertension and specifically, PAH (particularly the three most common forms found in this cohort) than first thought. Consistent with these European data, women were more likely to present with PAH, but were younger than their male counterparts (who were not only older, but tended to have a more consistent age profile across the different forms of PAH). If as prevalent in other urban African communities, these data highlight the need for not only community-based screening programmes for RHF (and its precursor PAH) in South Africa (see below), but hospital-based programmes for high-risk patient sub-groups with the capacity to perform right heart catheterization for definitive diagnosis. The availability of relatively cheap but effective oral agents (e.g. endothelin receptor antagonists and phosphodiesterase-5 inhibitors)16 is also highly desirable in this context.

The fact that this study focused on the adult population explains the low number of PAH related to congenital heart disease. However, the importance of preventing or at least providing early effective treatments for PAH and RHF in young Africans cannot be overlooked. The lack of open-heart surgery, specialist paediatric cardiovascular services and poor parental awareness has led to the accumulation of patients with RHF as a consequence of untreated congenital heart disease, right heart valve disease, HIV/AIDS, endomyocardial fibrosis, pulmonary tuberculosis, schistosomiasis, and sickle cell disease.7 All are endemic in the paediatric population in Africa. For instance, RHD, the most common form of acquired cardiovascular disease in children and adolescents in Africa,22 presents in the most virulent forms usually associated with RHF, due to late presentation of patients with mitral and/or aortic valve disease.9

Given the high level of antecedents that could potentially contribute to a high prevalence of RHF in the region, in ideal circumstances there would be a strong argument for undertaking wide-scale screening programmes to determine its exact prevalence and antecedents; the focus of any longitudinal health study. With limited health care resources, a more pragmatic approach may involve the establishment of ‘breathlessness’ clinics in primary care facilities (remembering that 85% of cases presented with dyspnoea) in Soweto with the capacity to undertake point-of-care assessment of brain natriuretic peptide levels (for evidence of right or left atrial stretch), lung function tests and a 12-lead ECG to determine the need for more definitive evaluation (i.e. echocardiography and right heart catheterization). The cost effectiveness of such an approach is yet to be established. However, results from the Heart of Soweto Primary Care Registry of >1000 cases presenting with a broad spectrum of conditions24 highlights the potential benefit. Certainly, the results of the BOLD Study5 with respect to chronic lung disease (irrespective of cardiac involvement) in South Africa support the need for dedicated programmes targeting individuals with pulmonary pathology. Any improvement in the early detection of RHF cases will require a parallel investment in potentially costly treatments including open-heart surgery for congenital cases and pharmacological therapy for cases of PAH. Beyond low-to-middle-income countries, these data are a reminder that RHF may be more prevalent in high-income countries than data from the European Heart Failure Survey II (where possible bias towards describing those with left-sixed heart disease occurred) might suggest.1 Certainly, it reinforces the potential benefits of identifying primary and secondary diagnoses of RHF in high-risk individuals to improve health outcomes.17,18

| Table 2 Socio-demographic profile of pulmonary arterial hypertension cases (n = 141) |
|--------------------------------------|-----------------|--|--|--|--|--|
|                                     | Idiopathic PAH (n = 61) | HIV-related PAH (n = 42) | Connective tissue-related PAH (n = 28) |
|                                     | Men | Women | Men | Women | Men | Women |
| Mean age (years)                    | 50.5 ± 17.8 | 45.6 ± 18.4 | 50.5 ± 17.8 | 39.3 ± 14.4 | 53.8 ± 17.8 | 49.8 ± 15.0 |
| Women                               | –   | 32 (53%) | –   | 31 (74%) | –   | 25 (81%) |
| African descent                     | 25 (86%) | 31 (97%) | 9 (82%) | 31 (100%) | –   | 3 (100%) |
| <6 years education                  | 13 (45%) | 16 (50%) | 6 (35%) | 11 (36%) | 1 (33%) | 8 (32%) |
| Originally from Soweto              | 10 (35%) | 6 (19%)     | 3 (27%) | 13 (42%) | 1 (33%) | 6 (24%) |
There are a number of limitations that require comment. The diagnosis of RHF and PAH was, in the majority of the cases, based on the criteria outlined in the case definitions presented in the Methods using a combination of symptoms, signs, echocardiography, lung function tests, chest X-ray, and ECG changes. While only a minority had right heart catheterization (the gold-standard for diagnosing PAH) elevated RVSP levels have been shown to be a reliable marker of pulmonary arterial pressures and, in a resource-poor environment, we applied a pragmatic approach to classifying cases. Moreover, these data are yet to be confirmed in other communities. We also do not know the prognostic outcome for this cohort, although it is likely to be poor when considering PAH-specific reports and recent results from the Euro Heart Failure Survey II, suggesting 16.4% 1 year mortality in those presenting with de novo acute HF (rising to 22% in those with evidence of congestion/RHF as indicated by an elevated jugular venous pressure). With the support of the Pulmonary Vascular Research Institute Sub-Saharan Taskforce (led by K.S. and A.M.), a registry to describe the epidemiology of pulmonary hypertension among patients attending referral units for cardiovacular and pulmonary diseases in a number of sub-Saharan African countries is soon to be launched. This information will be crucial to the development of effective and resource-sensitive strategies to tackle this condition in the region.

In conclusion, we are unaware of any similar reports from sub-Saharan Africa specifically focusing on the nature of RHF and its key clinical components (including PAH) in such a large cohort and in such detail. Overall, these data suggest that RHF is a common, and to a large extent preventable, condition that is attributable to a range of causes among urban Africans presenting with de novo heart disease. If proven correct, the challenge now is to develop cost-effective screening and treatment programmes within a resource-poor environment being increasingly challenged by a combination of new- and old-forms heart disease.

Acknowledgements
We gratefully acknowledge the contribution of Louis Kuneka, Elsabeth Tshele, and Phuthuma Methusi in data collection, Geraldine Lee in coding all ECG traces and Ann Tandyo for managing study data. S.S. and M.J.C. are supported by the National Health and Medical Research Council of Australia.

Funding
The registry was broadly supported by the University of the Witwatersrand and unconditional research grants from Adcock-Ingram, the Medtronic Foundation, BHP Billiton and Servier.

Conflict of interest: none declared.

References
