

Factors Associated With Isolated Right Heart Failure in Women[☆]

A Pilot Study From Western Kenya

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ABSTRACT

Background: Small observational studies have found that isolated right heart failure (IRHF) is prevalent among women of sub-Saharan Africa. Further, several risk factors for the development of IRHF have been identified. However, no similar studies have been conducted in Kenya.

Objective: We hypothesized that specific environmental exposures and comorbidities were associated with IRHF in women of western Kenya.

Methods: We conducted a case-control study at a referral hospital in western Kenya. Cases were defined as women at least 35 years old with IRHF. Control subjects were similarly aged volunteers without IRHF. Exclusion criteria in both groups included history of tobacco use, tuberculosis, or thromboembolic disease. Participants underwent echocardiography, spirometry, 6-min walk test, rest/exercise oximetry, respiratory health interviews, and human immunodeficiency virus (HIV) testing. Home visits were performed to evaluate kitchen ventilation, fuel use, and cook smoke exposure time, all surrogate measures of indoor air pollution (IAP). A total of 31 cases and 65 control subjects were enrolled. Surrogate measures of indoor air pollution were not associated with IRHF. However, lower forced expiratory volume at 1 s percent predicted (adjusted odds ratio [AOR]: 2.02, 95% confidence interval [CI]: 1.27 to 3.20; $p = 0.004$), HIV positivity (AOR: 40.4, 95% CI: 3.7 to 441; $p < 0.01$), and self-report of exposure to occupational dust (AOR: 3.9, 95% CI: 1.14 to 14.2; $p = 0.04$) were associated with IRHF. In an analysis of subgroups of participants with and without these factors, lower kitchen ventilation was significantly associated with IRHF among participants without airflow limitation (AOR: 2.63 per 0.10 unit lower ventilation, 95% CI: 1.06 to 6.49; $p = 0.04$), without HIV (AOR: 2.55, 95% CI: 1.21 to 5.37; $p = 0.02$), and without occupational dust exposure (AOR: 2.37, 95% CI: 1.01 to 5.56; $p = 0.05$).

Conclusions: In this pilot study among women of western Kenya, lower kitchen ventilation, airflow limitation, HIV, and occupational dust exposure were associated with IRHF, overall or in participant subgroups. Direct or indirect causality requires further study.

Several studies have shown that isolated right heart failure (IRHF), defined as right heart failure in the absence of both left ventricular heart failure and valvular disease, is more prominent in African women than in those living in high-income nations [1,2]. Stewart et al. [1] in their prospective study of 844 patients admitted to the Baragwaneth Hospital, South Africa, with de novo presentations of cardiac disease found 121 individuals (14%) with IRHF, a majority of whom were women. This is in contrast to the EuroHeart Failure Survey II, which reported a prevalence of only 3.2% for right heart failure either in isolation or in combination with left heart failure [3]. In high-income countries, IRHF is often associated with a shortened life expectancy and diminished quality of life [4]. These outcome measures may be much worse for African women given their general lack of access to health care.

Risk factors for the development of IRHF in Africa have been identified [5] and include the following: chronic obstructive lung disease (COPD) [6]; pneumoconiosis [7,8]; human immunodeficiency virus (HIV) [9–13]; hemoglobinopathies [14,15]; schistosomiasis [16–18]; healed tuberculosis infection [19]; living at high altitude [20]; and thromboembolic disease [21]. In addition, indoor air pollution (IAP) has been directly and indirectly linked to IRHF [22]. However, it remains to be determined which factors are most important in women living in western Kenya.

This pilot study aimed to look at the association of surrogate measures of IAP, airflow limitation, HIV, and occupational dust exposure and IRHF in women living in western Kenya. These factors were chosen as they were common in the study community, easily measured, and

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were previously identified as risk factors in other studies in sub-Saharan Africa.

STUDY DESIGN

Study population

From November 1, 2010 to February 29, 2012, all female patients 35 years and older undergoing echocardiographic evaluation at the Moi Teaching and Referral Hospital in Eldoret, Kenya, were screened for eligibility to participate. Cases were defined as women at least 35 years of age with IRHF. Control subjects were similarly aged volunteers without IRHF who were recruited from a population of women accompanying family members to the general medical wards as caregivers. Control subjects were not related biologically to the cases, but they shared similar sociodemographics and cultural perspectives.

Study setting

All subjects were living in the Uasin Gishu district, an area that is predominantly rural with few small towns serving as trading centers. The district is basically agricultural and hence most of the industries are agro-based. The high population growth rate has led to increased unemployment, high demand for basic services, and increased environmental degradation. The people of the region are generally poor. Overall poverty was estimated at 41.9% and 53.3% in rural and urban areas, respectively [23]. In the area, women often cook on 3-rock stoves using wood fuel and located indoors in poorly ventilated kitchens.

Study design

Following the consent process, participants underwent the following tests: 1) physiology testing (rest and exercise pulse oximetry, 6-min walk test with a Borg dyspnea score [24]); 2) spirometry (using a portable EasyOne spirometry [Ind Medical Technologies, Inc., Andover, MA, USA] following American Thoracic Society guidelines [25]); 3) radiographic testing (posterior to anterior and lateral chest radiograph); 4) HIV testing; and 5) a health questionnaire to assess environmental exposure and respiratory symptoms (modified version of the American Thoracic Society and the Division of Lung Disease Adult Questionnaire [ATS-DLD-78A] [26] appropriate for use in Kenya and translated into Kiswahili). Occupational dust exposure was assessed by the ATS-DLD-78A question: "Have you ever worked for a year or more in any dusty job?" [26]. Radiologic studies were not performed if a woman was known to be pregnant or both premenopausal and amenorrheal for at least 3 months. In addition, we conducted home visits within 2 weeks of enrollment to assess surrogates of IAP, including kitchen construction, window-to-floor surface area ratio (surrogate for kitchen ventilation), hours typically spent cooking, stove type, and fuel type, amount used and cost (in Kenyan shillings).

Exclusion criteria included the following: previous tuberculosis treatment or abnormal findings on chest x-ray

consistent with tuberculosis ($n = 19$); history of known thromboembolic disease ($n = 1$); self-report of current or former tobacco use ($n = 16$); inability to undergo physiologic testing (spirometry, 6-min walk test) due to physical or mental disability ($n = 23$); inability to give informed consent ($n = 5$); or refusal to participate ($n = 32$).

Definitions

In concert with several published guidelines [27–29], IRHF was defined as the absence of left ventricular heart failure, valvular disease, or pericardial diseases in conjunction with the presence of all 3 of the following: 1) symptoms of dyspnea or venous congestion; 2) enlarged right ventricular dimensions; and 3) evidence of pulmonary hypertension (measurable tricuspid regurgitation velocity with estimated right ventricular systolic pressure >25 mm Hg by echocardiogram). In the absence of right ventricular outflow tract obstruction, right ventricular pressure approximates systolic pulmonary arterial pressure [29]. Systolic pulmonary arterial pressure was measured by adding the estimate of the right atrial pressure to the peak pressure gradient across the tricuspid valve using the modified Bernoulli [29].

We are unaware of sensitivity and specificity measures for echocardiography in diagnosing IRHF. However, on the basis of a large systematic review and quantitative meta-analysis of systolic pulmonary artery pressure estimated from echocardiography versus measured by right heart catheterization, the sensitivity and specificity of echocardiography for diagnosing pulmonary hypertension was found to be 83% (95% confidence interval [CI]: 73 to 90) and 72% (95% CI: 53 to 85), respectively [30].

Airflow limitation was defined as the ratio of forced expiratory volume at 1 s (FEV1)/forced vital capacity (FVC) $< 70\%$ [31].

Statistical methodology

The clinical measurements, selected questionnaire responses, and measures of IAP from the home visit were summarized for cases and control subjects. Logistic regression was used to estimate the association between surrogate measures of IAP, airflow limitation, HIV, and exposure to occupational dust and the relative risk of prevalent IRHF in terms of odds ratios (OR) and associated 95% CI. Because we measured several risks for IRHF, the associations between IAP and lung function measures with IRHF were examined using multiple logistic regression analyses after adjusting for HIV status, occupational dust exposure, and age (linear and squared terms). The association between HIV status and exposure to occupational dust with IRHF were examined in a multiple logistic regression model that included both terms and adjusted for age (linear and squared terms). Finally, as a secondary analysis, we explored the association between kitchen ventilation and prevalent IRHF within subgroups of participants defined by other risks, airflow limitation status, HIV status, or dust exposure, using multiple logistic

regression, adjusted for age (linear and squared terms) and HIV status. Goodness of fit of the logistic regression models was assessed using the Hosmer-Lemeshow goodness-of-fit test.

Published statement of informed consent

Informed consent was obtained from each study subject. Furthermore, the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Specifically, this study was approved by the Institutional Human Research Committees of: Moi University School of Medicine (IREC/2010/70), Lifespan (Brown University) (CMTT#2092-10), Duke University (Pro00025887), and National Heart, Lung, and Blood Institute (NIH) (07COE-RAO1).

RESULTS

Demographics, environmental measurements, and pulmonary physiologic assessments of the study participants and unadjusted OR are shown in Table 1. There were 31 cases and 65 control subjects enrolled. Home visits were successfully conducted for 29 of 31 cases (93.5%) and 63 of 65 control subjects (96.9%). Cases were older than control subjects, with the median age of cases 64 years (range: 36 to 87) and control subjects 48 years (range: 35 to 87). Kitchen ventilation, measured as the ratio of window-to-floor surface area, was lower among cases than control subjects (0.14 vs. 0.20), but it was not significantly associated with IRHF in unadjusted analysis. Cases spent less time cooking (4 vs. 5 h per day) and less money on fuel (743 vs. 1,000 Kenyan shillings per month) than control subjects did; these variables were not significantly associated with IRHF.

Several measures of lung function were significantly associated with IRHF in unadjusted analyses. Median FEV1% predicted was lower for cases than for control subjects (35.5 vs. 86.5) as was median FEV1/FVC (61 vs. 75). Meters walked in 6 min were lower for cases than for control subjects (290 vs. 408). Additionally, cases had lower resting oximetry than control subjects did (82 vs. 97) and lower oxygen saturation after walking (75 vs. 97). Among cases, 84% underwent HIV testing compared with 92% of control subjects; cases had a higher seropositive rate than control subjects did (13% vs. 3%), but this difference did not reach statistical significance. A larger proportion of cases reported exposure to occupational dust (65% of cases vs. 31% of control subjects); dust exposure was significantly associated with IRHF in unadjusted analyses.

Table 2 shows the adjusted OR and 95% CI for IRHF for surrogate measures of IAP, pulmonary function measurements, HIV, and occupational dust. Overall, the surrogate measures of IAP (kitchen ventilation, hours spent cooking, and money spent on cooking fuel) were not significant predictors of IRHF. Pulmonary function assessment tests (FEV1% predicted, 6-min walk, and resting and

TABLE 1. Description of women with IRHF with suitably selected control subjects

	IRHF (n = 31)	Control Subjects (n = 65)	Unadjusted OR (95% CI)
Age, yrs	65 (36, 87)	48 (35, 75)	2.32 (1.52, 3.53)*
Ventilation [†]	0.14 (0.03, 0.68)	0.20 (0.02, 0.78)	1.27 (0.92, 1.76) [‡]
Hours spent cooking per day	4 (1, 12)	5 (1, 12)	0.84 (0.69, 1.05)
Cost of fuel for cooking, monthly	743 (200, 3,100)	1000 (120, 6,000)	0.97 (0.90, 1.05) [§]
FEV1% predicted	35.5 (16, 95)	86.5 (15, 120)	2.03 (1.53, 2.7)
FEV1/FVC	61 (17, 96)	75 (29, 95)	1.34 (1.07, 1.68)
Distance in 6-min walk test, m	290 (100, 477)	408 (312, 502)	1.49 (1.23, 1.81) [¶]
Resting oximetry	82 (64, 96)	97 (91, 99)	2.33 (1.5, 3.6) [#]
Post-exercise oximetry	75 (60, 95)	97 (87, 99)	1.94 (1.35, 2.79) [#]
Post-exercise minus resting oximetry	-5 (-20, 1)	0 (-8, 5)	2.12 (1.54, 2.92) [#]
HIV status			
Negative	22 (71)	56 (88)	Reference
Positive	4 (13)	2 (3)	5.09 (0.87, 29.8)
Test not done	5 (16)	7 (9)	2.12 (0.59, 7.67)
Occupational dust exposure	20 (65)	20 (31)	4.09 (1.66, 10.11)

Categorical measures are presented as n (%), and continuous measures as median (range). CI, confidence interval; FEV1, forced volume expiratory volume at 1 s; FVC, forced vital capacity; HIV, human immunodeficiency virus; IRHF, isolated right heart failure; OR, odds ratio.

*Per 10 years older.
[†]Ratio of window-to-floor surface area in the cook hut.
[‡]Per 0.1 lower.
[§]Per 100 Kenyan shilling higher.
^{||}Per 10 units lower.
[¶]Per 10 m shorter.
[#]Per 1 unit lower.

post-exercise oximetry) were predictive of IRHF. Adjusting for age, exposure to dust, and HIV status differences, lower FEV1% predicted was significantly associated with IRHF (adjusted odds ratio [AOR]: 2.02 per 10 units lower; 95% CI: 1.27 to 3.20; $p = 0.004$). Adjusting for age and HIV status, the self-report of exposure to occupational dust was a significant risk for IRHF (AOR: 4.6; 95% CI: 1.36 to 15.6; $p = 0.014$).

Table 3 presents an analysis of the effect of kitchen ventilation on IRHF risk in those with and without airflow limitation, HIV, and occupational exposure to dust, adjusting for the measured confounders. Lower kitchen ventilation was found to be significantly associated with IRHF in those without airflow limitation (AOR: 2.63 per 0.10 unit lower ventilation, 95% CI: 1.06 to 6.49; $p = 0.039$), without HIV (AOR: 2.55 per 0.10 unit lower ventilation, 95% CI: 1.21 to 5.37; $p = 0.02$), and those not reporting occupational dust exposure (AOR: 2.37 per 0.10 unit lower ventilation, 95% CI: 1.01 to 5.56; $p = 0.05$).

DISCUSSION

In this pilot study of factors associated with IRHF in women of western Kenya, we found that a 10-unit decrease

TABLE 2. Evaluation of the odds of IRHF in women compared with healthy control subjects for several environmental and pulmonary factors, HIV, and exposure to occupational dust

Exposure	OR	95% CI	p Value
Correlates of IAP exposure*			
Lower kitchen ventilation, per 0.10 decrease	1.44	(0.9–2.29)	0.129
Hours spent cooking per day	0.77	(0.56–1.06)	0.112
Money spent on cooking fuel, in hundreds	0.99	(0.91–1.09)	0.892
Measurements of lung function*			
Lower FEV1% predicted, per 10 units	2.02	(1.27–3.20)	0.004
Lower FEV1/FVC, per 10 units	1.12	(0.82–1.54)	0.476
Shorter 6-min walk, per 10 m	1.60	(1.36–1.89)	<0.001
Lower resting oximetry, per 1 unit	4.31	(1.96–9.46)	<0.001
Lower post-exercise oximetry, per 1 unit	3.30	(2.16–5.03)	<0.001
HIV status			
Negative	Reference		
Positive	40.4	(3.7–441)	0.003
Unknown	9.8	(1.8–54)	0.010
Occupational dust[†]			
Self-reported exposure to occupational dust	3.87	(1.06–14.2)	0.04

IAP, indoor air pollution; other abbreviations as in Table 1.
*Adjusted for age, exposure to occupational dust, and HIV status.
[†]Adjusted for age and HIV status.

in kitchen ventilation was associated with a 44% increase (95% CI: –10% to 129%) in the odds of IRHF, a result that did not reach statistical significance. We also found that airflow limitation, HIV, and self-reported occupational dust exposure were significantly associated with IRHF. Among participants without these risk factors, a 10-unit decrease in kitchen ventilation was associated with a statistically significant higher odds of IRHF of about 150% (range of OR was 2.37 to 2.63).

These findings are in agreement with those of other studies from Africa [5]. COPD [6], pneumoconiosis [7,8], sickle cell disease [14,15], sequelae of pulmonary tuberculosis [19], living at high altitude [20], and chronic pulmonary thromboembolism [21] have all been identified as

TABLE 3. Effect of kitchen ventilation (window-to-floor surface area ratio) on IRHF within subgroups of individuals

Subgroup	Cases, n	Control Subjects, n	OR (per 0.10 decrease)	95% CI	p Value
Without airflow limitation	11	39	2.63	(1.06–6.49)	0.039
With airflow limitation	20	25	1.14	(0.68–1.93)	0.624
HIV negative	22	56	2.55	(1.21–5.37)	0.016
HIV positive	4	2	2.83	(0.43–18.67)	0.282
HIV unknown	5	6	0.62	(0.25–1.54)	0.310
No exposure to occupational dust	11	45	2.37	(1.01–5.56)	0.050
Exposure to occupational dust	20	20	0.99	(0.61–1.62)	0.974

Abbreviations as in Table 1.

causes of IRHF in African adults. In addition, infectious diseases such as acquired immunodeficiency syndrome [9–13] and schistosomiasis [16–18] have also been associated with IRHF.

Overall in our study, the surrogate measures of IAP (kitchen ventilation, hours spent cooking, and money spent on cooking fuel) were not significantly associated with IRHF. However, lower kitchen ventilation was positively (but not statistically significantly) associated with higher IRHF risk in the overall population. Moreover, as shown in Table 3, this association was even more pronounced and reached statistical significance in subgroups of participants without airflow limitation, those reporting no exposure to occupational dust, and those found to be HIV negative. Taken together, these results provide some evidence suggesting that long-term exposure to IAP may increase the risk of IRHF, supporting earlier biologic plausibility studies [32,33].

For over 50 years, IAP has been associated with right-sided cardiac pathology in low- and middle-income countries [34]. Recently, biologic plausibility has been established for these effects via the production of reactive oxygen species and proinflammatory cytokines, and alteration in endothelin receptor expression, resulting in subsequent pulmonary vascular vasoconstriction [32,33].

Also in our study, airflow limitation was associated with IRHF. We assume that the airflow limitation found in these Kenyan women was an indicator of underlying asthma or COPD, possibly related to IAP. This too is well described. Globally, women exposed to indoor smoke are 2.3× more likely to develop COPD than those who cook and heat with electricity, gas, and other cleaner burning fuels [35]. Biomass fuels are used extensively throughout Africa, especially in the sub-Saharan area. Typical pollutants that result from the poor burning and ventilation of these fuels include particulate matter, aldehydes, carbon monoxide, hydrocarbons, volatile organic compounds, and oxides of nitrogen [36]. A study of rural South African women found an increased prevalence of COPD associated with the burning of cow dung in poorly ventilated houses [7]. In Kenya, high levels of IAP have been detected in homes where cooking was carried out on 3-rock stoves [37], placing these women at higher risk for the development of COPD.

We found that women with IRHF were more likely to be HIV positive than control subjects were, although this was not statistically significant. This result is in agreement with other studies that have shown an association between HIV and IRHF [38]. Although little is known about the potential mechanisms underlying this association, viral proteins and host factors (i.e., human leukocyte antigen, cytokines) may play an important role [39]. It is also possible that the hypercoagulable state associated with HIV could lead to thromboembolic disease and subsequent IRHF [40]. Previous work has demonstrated that the overlap of HIV and IRHF is significant in low-income countries such as Kenya. HIV may then represent a cofactor or an independent risk factor for the development of IRHF.

Interestingly, we also found that self-reported exposure to occupational dust was also associated with a higher risk of IRHF. If causal, it is possible that the link between occupational dust exposure and IRHF may, in part, be mediated through the development of airflow limitation and COPD. This finding deserves further scrutiny in the context of prospective studies where the timing of exposures, intermediates, and outcomes can be more fully assessed.

Study limitations. First, this was a pilot project to explore 2 issues we had noted locally: the marked prevalence of IRHF in women and their high exposure to IAP. As a result, our sample size was modest, possibly resulting in important associations being missed or lacking statistical significance. Next, our assessment of IRHF is likely to have been at least somewhat misclassified. A systematic review suggests that echocardiograms often underestimate pulmonary artery pressure [30], so our cases may represent those with more severe disease. It is also possible that we might have inappropriately excluded some women with apparent left heart disease. Right ventricular heart failure can precipitate left ventricular heart failure, and so excluding women who had concurrent right and left failure may have unnecessarily excluded some women with severe right-sided failure. Furthermore, we did not routinely exclude women with possible severe diastolic dysfunction and pulmonary hypertension; however, our exclusion criteria did include the more common left-sided heart diseases seen in the study community.

We were not able to establish the timing of IRHF onset or the duration of disease. Thus, it is possible that some of our results are due to reverse causation such that a participant's health status may affect their cooking behavior (e.g., hours spent cooking). In addition, due to limited resources and timing, we were not able to directly measure IAP exposure. Instead, we indirectly assessed IAP exposure through assessment of kitchen ventilation and questions regarding time spent cooking and amount of money spent on the purchase of biomass fuel. Although an inverse relationship between kitchen ventilation and IAP may exist [41], these surrogates of exposure to IAP will undoubtedly be lacking in comparison to direct measurement of IAP, likely biasing our findings toward the null hypothesis of no association. Direct measurement of indoor air pollutants is needed to better delineate true exposure and possible causal pathways in this population.

Furthermore, we did not perform bronchodilator challenge testing, precluding us from making a more definitive diagnosis of COPD in our study [42]. Exposure to occupational dust was self-reported and not assessed in more detail. Thus, this novel result needs to be replicated in future studies with more detailed exposure assessment.

Nonetheless, this study is significant due to the paucity of research on IAP health effects in low-income countries broadly, and in Kenya specifically. Moreover, the observed associations between self-reported occupational dust

exposure and IRHF is novel and worth further study. Future studies with greater number of subjects, incident cases of IRHF, and more detailed exposure assessment are needed in this population to confirm or refute these findings.

CONCLUSIONS

We have demonstrated an association between kitchen ventilation, airflow limitation, HIV, occupational dust exposure, and IRHF for women living in western Kenya. This is largely in agreement with other studies from Africa. Direct or indirect causality remains unclear but demands further study given the critical public health effect for those living in low-income countries.

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