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The Pan African Pulmonary Hypertension Cohort (PAPUCO): implementing a contemporary registry on pulmonary hypertension in Africa

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THE PAN AFRICAN PULMONARY HYPERTENSION COHORT (PAPUCO): IMPLEMENTING A CONTEMPORARY REGISTRY ON PULMONARY HYPERTENSION IN AFRICA

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ABSTRACT

Introduction

Pulmonary Hypertension (PH) is a devastating, progressive disease, with increasingly debilitating symptoms and, usually, shortened overall life expectancy due to narrowing of the pulmonary vasculature and consecutive right heart failure. Little is known about PH in Africa, but limited reports suggest that PH is more prevalent in Africa compared to developed countries due to the high prevalence of risk factors in the region.

Methods and Analysis

A multinational multicentre registry-type cohort study was established and tailored to resource-constraint settings to describe disease presentation, disease severity and aetiologies of PH, comorbidities, the diagnostic and therapeutic management, and natural course of PH in Africa. PH will be diagnosed by specialist cardiologists using Echocardiography (RVSP>35 mmHg, absence of pulmonary stenosis and acute right heart failure) usually accompanied by shortness of breath, fatigue, peripheral oedema, and other cardiovascular symptoms, electrocardiogram and chest x-ray changes in keeping with PH as per guidelines. Additional investigations such as CT-scan, ventilation/perfusion scan or right heart catheterisation will be performed at the discretion of the treating physician. Functional tests include 6-minute walk test and Karnofsky Performance Score. The WHO classification system for PH will be applied to describe the different aetiologies of PH. Several sub-studies have been implemented within the registry to investigate specific types of PH and their outcome at up to 24 months. Data will be analysed by an independent institution following a data analyse plan.

Ethics and Dissemination

All local Ethics Committees of the participating centres approved the protocol. The data will be disseminated through peer-reviewed journals, at national and international conferences and public events at local care providers.

ARTICLE SUMMARY

Article focus

- In this manuscript we aim to provide an overview of pulmonary hypertension in Africa and the epidemiology of risk factors prevalent in the region.
- We aim to answer the question why Africa needs a registry for pulmonary hypertension.
- We describe how we implemented the registry in scarce resources settings.

Key messages

- Risk factors for pulmonary hypertension are highly endemic in Africa.
- The incidence of pulmonary hypertension is expected to be higher in Africa compared to developed countries.
- A diagnostic algorithm to diagnose pulmonary hypertension in resource-constraint settings without access to right heart catheterisation has been developed.
- 12 centres are participating in the Pan African Pulmonary hypertension Cohort (PAPUCO) study and more than 250 patients have been recruited so far.

Strengths and limitations of this study

- The PAPUCO study is the first multinational registry on pulmonary hypertension in Africa.
- PAPUCO centres have different levels of medical infrastructure and not all patients underwent the same rigorous work-up.

INTRODUCTION

Pulmonary Hypertension (PH) is a devastating, progressive disease, with increasingly debilitating symptoms and, usually, shortened overall life expectancy due to narrowing of the pulmonary vasculature and consecutive right heart failure (RHF).[1] The epidemiology of PH in Africa and the distribution of its multitude of aetiologies has not yet been described, but limited reports suggest that the incidence of PH in Africa is higher than that reported from developed countries, owing to the pattern of diseases prevalent in the region.[2-5] Many known risk factors for PH are hyperendemic in this part of the world, including human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), rheumatic heart disease (RHD), hereditary haemoglobinopathies, schistosomiasis and other parasitic infections, and chronic hepatitis B and C infection. On the other hand, a high prevalence of tuberculosis (TB), poorly treated asthma, high levels of pollution in urban areas and exposure to mining, may subsequently lead to various forms of pulmonary disease, PH and, often, to RHF with premature death. Also a lack of specialist paediatric services to diagnose and manage congenital heart disease (CHD) potentially also leads to PH.[6] Furthermore, the high prevalence of RHD and endomyocardial fibrosis, the latter possibly also due to the high burden of parasitic infections, may contribute to secondary PH.[6-8] However, Africa is in epidemiological transition with increased prevalence of non-communicable forms of heart disease such as hypertensive and ischemic heart disease. Left heart disease is the most common cause of heart failure in Africa and most likely a major contributor to PH and consecutive RHF.[4,9] Thus, within the registry we expect the entire spectrum of aetiologies of PH. In this manuscript, we aim to provide an overview of PH in Africa and the epidemiology of risk factors prevalent in the region, and answer the question why Africa needs a registry for PH just as much as most other parts of the world and how we implemented it in the setting of scarce resources.

Preliminary evidence of a significant burden of pulmonary hypertension and its risk factors in Africa

In recent years, there has been increasing awareness of the clinical significance of PH and cor pulmonale in Africa. This applies equally to the recognition of the importance of PH and RHF as both a primary diagnosis and as a poor prognostic marker for those primarily affected by left-sided heart failure. Data on the precursors and risk factors of those conditions are limited to few reports. The largest study on PH/RHF in Africa has been conduction within *the Heart of Soweto Study in* South Africa; 2505 patients presented with *de novo* heart failure between 2006-2008.[5] Of those 697 (28%) were diagnosed with PH/RHF. PH/RHF was the primary diagnosis in 50% of those patients. The majority presented with dyspnoea and a mean right ventricular systolic pressure (RVSP) above 50 mmHg. Left heart disease (31%), chronic lung disease due to Chronic Obstructive Pulmonary Disease (COPD) and tuberculosis (26%), and PH (20%) due to HIV (HIV-PH), CHD, or idiopathic PH were the most common causes of PH. Sani et al. described the prevalence of PH in patients with RHD at a tertiary centre in Nigeria.[10] Of 1312 Echocardiography (ECHO) studies 10% had evidence of RHD; secondary PH was present in 80% of patients with RHD. The same centre reported on 53 patients with PH on ECHO among 80 patients admitted with heart failure with hypertensive heart disease (25%), peripartum cardiomyopathy (25%), dilated cardiomyopathy (17%), and RHD (13%) being the most common causes of PH.[11] A study from Uganda showed a prevalence of PH in patients with newly diagnosed RHD (n=309) of 33%.[12] A smaller survey from Lagos, Nigeria investigated the prevalence of cardiovascular disease in an HIV-positive cohort and found one patient of 100 patients to have HIV-PH.[13] An ECHO study on 102 HIV-patients presenting with cardiac symptoms in Tanzania revealed PH in 13%.[14] PH with a RVSP>30 mmHg was present in 4% of long-term

survivors in a Zimbabwe cohort of vertically acquired HIV infection.[15] Haemolytic anaemia is a known risk factor for PH; a screening study of patients with sickle-cell disease (SCD) in Nigeria showed a PH prevalence of 25%;[16] a study from Egypt indicates that patients with β-Thalassaemia are at risk of PH.[17] Another study from Egypt found a PH prevalence of 9% in patients seropositive for schistosomal antibodies. Ahmed et al. from Sudan described 14 consecutive cases of PH with previously treated pulmonary TB and conclude that PH can even occur after resolution of TB, most like due to persistent lung destruction.[18] This data suggests that left heart disease, chronic lung disease, RHD, HIV, schistosomiasis and SCD might be the most common underlying diseases to cause PH within the spectrum of aetiologies of PH that we will find within the Pan African Pulmonary hypertension Cohort (PAPUCO)

RATIONAL AND OBJECTIVES

Worldwide, PH has received great increase in awareness at the beginning of the 21st century (Figure 1), but less than one per cent (0.7%) of the publications are from Africa. It is expected that PH is more prevalent in Africa compared to developed countries, but little information is available about African patients with PH. Exposure to risk factors, human genetic variation, different socio-economic backgrounds, lifestyles, co-morbidities, nutrition and disparities in access to health services makes the African population unique, but heterogeneous at the same time. Therefore, most research data and clinical guidelines from high-income countries cannot be translated into the African context. It is within the context described above that the Pan African Pulmonary hypertension Cohort (PAPUCO), a Pan Africa registry-type cohort study, was established (Figure 2).

Scientific and clinical research has been fundamental in improving human health.[19] In fact, research has demonstrated to be an excellent vehicle to implement new technologies and to

facilitate training for its use, and to develop new systems and establish the services around it - jointly leading to technical improvement, sharpening of skills and capacity development. Besides the main objectives of the PAPUCO registry to define and understand PH in Africa (Box 1), this multinational and multicentre research project therefore aims to also develop sustainable clinical and research capacity across the African continent as well as raising awareness for PH and its risk factors.

Box 1: PAPUCO objectives
Primary objective • To describe disease presentation, disease severity and aetiologies of PH, comorbidities, the diagnostic and therapeutic management, and natural course of PH in Africa *Secondary objectives* • To describe the overall 6-month survival rate • To describe the 24-month survival rate in patients with HIV-PH • To compare 6-month survival rates between different groups of PH • To determine the predictors of mortality access the different groups.
Abbreviations: PH, pulmonary hypertension; HIV, human immunodeficiency virus

The prevalence of PH in Africa varies geographically, according to underlying risk factors and diseases and the diagnosis of PH is most likely often missed, not only during early stages due to the subtle nature of presentation of PH, but also at more advanced stage of disease due to lack of awareness by primary care doctors and low index of suspicion, limited access to ECHO services and tertiary care. However, it is crucial to diagnose PH in Africa early and reliably to ensure better care for these patients (Box 2).

Box 2: The significance of PH in Africa: Why we need to diagnose?
• The right to know • Prognostic implications

• Access to tertiary care: heart failure management, anticoagulation, home oxygen, COPD management, access to PH-specific drugs (Sildenafil) • Access to cardiothoracic surgery: valve repair/replacement, correction of congenital heart disease, heart transplantation • Access to social and disability grants • To raise awareness of PH and its risk factors
Abbreviations: PH, pulmonary hypertension; COPD, chronic obstructive pulmonary disease

METHODS AND ANALYSIS

Study design and setting

The Pan African Pulmonary hypertension Cohort (PAPUCO) research group was established in 2011 with the aim to implement a registry-type cohort study on pulmonary hypertension in Africa according to STROBE guidelines. The registry aims to recruit consecutive patients 1) with newly diagnosed PH based clinical and ECHO criteria, 2) are able or likely to return for 6-month follow-up, 3) are at least 18 years old (except for paediatric centres in Mozambique and Nigeria), and 4) consented in writing to participate in the registry. Centre eligibility include 1) availability of ECHO and training in assessing right heart function, 2) experience in diagnosing PH according to WHO classification, 3) experience in clinical management of patients with right heart failure, and 4) resources to review patients at 6-month follow-up. Participating centres will be invited to join the registry at African cardiac meetings and conferences.

Definition of pulmonary hypertension, diagnostic algorithm and data points

As shown in Box 3, PH is defined as documented elevated RVSP>35 mmHg on trans-thoracic ECHO in the absence of pulmonary stenosis and acute right heart failure; usually accompanied by shortness of breath, fatigue, peripheral oedema, and other cardiovascular symptoms, and possibly electrocardiogram (ECG) and chest x-ray (CXR) changes in keeping with PH as per guidelines.[20] Right heart catheterisation is optional. The WHO

classification system for PH will be applied to describe the different aetiologies of PH. Once definitive assessment and treatment has been applied, the following specific data will be documented for each individual: a) all major cardiovascular diagnoses according ICD 10 coding, and b) up to five non-cardiovascular diagnoses according ICD 10 coding.[21] Figure 3 shows the diagnostic algorithm to diagnose PH in resource-constraint settings without access to right heart catheterisation that has been developed following the guidelines for the diagnosis of PH of the European Society of Cardiology and European Respiratory Society.[20] Key information collected will include information on demographic profile, socio-economic background, medical history, co-morbidities, cardiac risk factors, and environmental exposures. The clinical aspects of the assessment include symptoms scoring, a full clinical examination, physical and clinical status; functional tests include WHO functional class (WHO FC), 6-minute walk test (6MWT) and Karnofsky Performance Score. Technical procedures include ECHO, CXR, and 12-lead ECG. Further investigations are at the discretion of the treating physician and typically include lung function tests, ventilation/perfusion lung scans, and high resolution computed tomography and computed tomography pulmonary angiography, and right heart catheterization, if available (Figure 3). Data on heart failure treatment and co-medication, hospitalization and death, and 6-month outcome will also be collected.

Box 3: Evidence to diagnose PH in resource-constraint settings
• Symptoms: SOB, fatigue, cough, chest pain, palpitations • Clinical exam: raised JVP, peripheral oedema, ascites, loud p2, systolic murmur, central cyanosis • ECG: sinus tachycardia, p-pulmonale, right axis deviation, right bundle branch block, RVH • CXR: cardiomegaly, pleural effusion, prominent pulmonary arteries • ECHO: dilated right atrium and ventricle, interventricular septal flattening, RVSP>35 mmHg, TAPSE<15 mm
Abbreviations: SOB, shortness of breath; JVP, jugular vein pressure; ECG, electrocardiogram; RVH, right ventricular hypertrophy; CXR, chest X-ray; ECHO, Echocardiography; RVSP, right ventricular

systolic pressure; TAPSE, tricuspid annular plane systolic excursion

Echocardiography

Echocardiography in adults

ECHO modalities applied included M-mode, two dimensional (2D) and Doppler studies. ECHO will be done with 3 to 5 MHz sector transducer. Complete 2D ECHO examination will be performed according to the recommendations of the American Society of ECHO (ASE).[22] M-mode ECHO will be derived from 2D images. The M-mode cursor on the 2D scan will move to specific areas of the heart to obtain measurements according to the recommendation of the committee on M-mode standardization of the ASE. Doppler indices of left ventricular (LV) diastolic filling will be obtained. Complete Doppler study will be done according to the recommendations of the ASE. From the M-mode measurements, indices of LV function will be derived. These include shortening fraction, ejection fraction (EF), and LV mass, cardiac output and relative wall thickness. ECHO examinations include (a) valvular assessment, (b) left atrial size, (c) left ventricular size and function, (d) a semi quantitative estimate of the severity of valvular regurgitation, (e) size and function of the right atrium and ventricle and (f) evidence of pulmonary hypertension. Doppler will be used to examine the valves on suspicion of any valvular lesion. ECHO findings associated with PH includes dilated pulmonary artery and dilation and hypertrophy of the right ventricle (RV), diastolic flattening of the interventricular septum and Doppler evidence of PH.[23] Doppler ECHO estimates pulmonary artery systolic pressure (PASP). By measuring the maximum velocity of the tricuspid regurgitant jet (v), the transtricuspid pressure gradient will be calculated using the modified Bernoulli equation ($4v^2$).[24] The PASP is approximated by adding the transtricuspid gradient to the right atrial pressure (RAP) as applied in the formula [$PASP=4v^2+RAP$]. The PASP is equivalent to RVSP in the absence of pulmonary outflow obstruction. In our study, the systolic regurgitant tricuspid flow will be assessed in the

parasternal right ventricular inflow, parasternal short-axis, and apical four-chamber views to determine the highest velocity, which reflects PASP/RVSP.[25] PH is defined as *mild* if RVSP was 36-50 mmHg, *moderate* if RVSP was 51-60 mmHg and *severe* if RVSP was >60 mmHg.[26] In addition, we further assessed right ventricular function by measuring the systolic displacement of the lateral portion of the tricuspid annular plane excursion (TAPSE) on the M-mode tracing under the 2D-echo guidance.[27] Peak mitral early diastolic velocity (E in m/s), the E-wave deceleration time (DCT in ms) and the velocity at atrial contraction (A in m/s) are measured using pulsed-wave Doppler. Left ventricular filling pressure classes were defined in accordance with the ASE 2009 guidelines.[28] In patients with heart failure and reduced ejection fraction (HFrEF) raised LV filling pressure is defined as E/A ≥2 if in sinus rhythm or DCT <150 ms if in atrial fibrillation (AF); normal LV filling pressure is defined as E/A <1 in patients in sinus rhythm or DCT ≥200 ms for those in AF; patients between these limits will be classified as undetermined. In heart failure and preserved ejection fraction (HFpEF), LV filling pressure is classified as follows: raised LV filling pressure if left atrium is dilated and normal LV filling pressure if left atrium has normal size.

Echocardiography in infants and children

Translating the definitions of PH in adults to children, especially to infants, is controversial. Within the paediatric cardiology community experts suggest that the ratio of the PASP to the systemic systolic blood pressure >0.4 should be the diagnostic criterion.[29] The fact that the threshold of pulmonary vascular resistance (PVR) increase has not been included in the abovementioned definition is another limitation to its use in children or infants, since paediatric PH is mainly caused by left-to-right shunt congenital heart disease; and if PVR shows no significant increase in such cases, the patient may be considered only as a dynamic PH case led by increased pulmonary blood flow, rather than pulmonary vascular disease.

Paediatric guidelines suggest that PAP >25 mmHg and PVR>3 Wood units remain in the definition of PH.[30] In our cohort of children with congenital heart malformations we not only used tricuspid and pulmonary regurgitation envelops, but also the flow across the ventricular septal defect or persistent ducts arteriosus to measure the gradient between the two circulations and therefore estimate the pulmonary pressure. Indirect signs of PH such as dilatation of the RV, RV-hypertrophy and dilatation of the main pulmonary artery were added to Doppler data to confirm the diagnosis.

Accuracy of Echocardiography in the diagnosis of PH

Diagnosing PH is challenging when relying on bedside tests. RHC is the gold standard to diagnose and confirm PH, but performing RHC on all patients with dyspnoea would bear excessive risks and be impractical in any cost-constrained environment. Also RHC is only available at very few centres in Africa. A viable device to diagnose PH in Africa needs to be widely available, accurate, safe, and cost-effective. ECHO has become increasingly available in Africa and reliably allows the measurements to describe functional and morphologic features of PH and to indirectly measure the pressures in the pulmonary artery; hence, to diagnose PH. Nonetheless, the exact measurements of the mean and systolic pulmonary artery are not possible, the PASP remains estimate, and the use of ECHO to diagnose PH questionable.[31,32] A number of possible explanations for this “inaccuracy” merit attention: 1) conditions for a reproducible calculation of PAPS/RVSP include the presence of sufficient TR to produce a Doppler envelope and appropriate gain adjustments. An “undergained” spectral signal will tend to result in underestimated PAPS whereas an “overgained” spectral signal might overestimate the measurements; 2) careful adjustment of the transducer position and the use of colour flow Doppler are critical in order to reduce the Doppler angle and to obtain the maximal regurgitant flow velocity and severe TR will cause a laminar flow which

invalidates the Bernoulli equation; 3) volume status and systemic blood pressure are other factors that potentially influence the measurement of PAPS; and 4) the highest value of RAP in the ASE guidelines is 15 mmHg, but RAP measured by RHC can exceed 15 mmHg. In spite of all these shortcomings, several studies have been published in the literature demonstrating good sensitivity and specificity of ECHO versus RHC.[33-35] In the REVEAL registry, there was a good correlation in PASP between ECHO and RHC at baseline, even if repeated ECHO measurements alone were not sufficient to monitor changes in PASP or progression of PH.[36] In the first systematic review and meta-analysis addressing the diagnostic accuracy of ECHO in PH by Janda and colleagues, the authors concluded that the correlation of PASP by ECHO compared to PASP by RHC was good with a summary correlation coefficient of 0.70 (95% CI 0.67 to 0.73).[37] Also, the authors showed that the diagnostic accuracy of ECHO in PH was also acceptable with a summary sensitivity and specificity of 83% (95% CI 73 to 90) and 72% (95% CI 53 to 85), respectively. Additional, Damy and colleagues demonstrated in their recent work that PAPS when measured in "good ECHO hands" is a strong predictor of mortality.[38] Last but not the least, easily obtainable ECHO parameters like E/A ratio, DCT, LA size can reliably distinguish between PH due to lung disease and PH due to left heart disease, allowing for rapid triage of patients with need for RHC. In summary, ECHO is far beyond a good modality to confirm both the presence and aetiology of PH in the majority of suspected cases when performed and interpreted by the requisite expertise under incorporation of all information obtained during a detailed ECHO assessment. ECHO will always provide incremental information in PH that cannot be obtained using RHC, whether in developed or developing countries.

Data cleaning process and statistical analysis

All study data will be collected on electronic case report forms and stored on a dedicated secure central database. Cases will be reviewed by at least two investigators (FT, AD, KS, AOM) for completeness and data validated. Query reports will be sent to the sites and resolved by the site investigators. If consensus on the WHO classification of PH cannot be reached, a third investigator's opinion will be requested. Data will then be verified and transferred to SPSS Statistics 17.0 for all analyses by an independent team at Preventative Health, Baker IDI Heart and Diabetes Institute, Melbourne, Australia. Normally distributed continuous data will be presented as mean ± standard deviation and non-Gaussian distributed variables as median plus interquartile range. Categorical data will be presented as percentages with 95% confidence intervals (CI) where appropriate. For patient group comparisons, we will use Chi Square (χ^2) analysis with calculation of odds ratios (OR) and 95% CI (where appropriate) for discrete variables and Students t-test and analysis of variance for normally distributed continuous variables. Multiple logistic regression analyses (entry model) will be performed on age, sex and baseline risk factors to derive adjusted ORs for the risk of presenting with PH/RHF overall, chronic lung disease and PH WHO Group 1. Significance will be accepted at the two-sided level of 0.05. ECG analysis will be will be subject to blinded coding according to published Minnesota criteria to determine any pathological abnormalities.[39]

PAPUCO sub-studies

Several sub-studies have been established within the PAPUCO registry. The ECHO sub-study aims to describe in detail the ECHO characteristics of right ventricular function in PH. The HIV-PH sub-study aims to describe the phenotype of HIV-PH in Africa. The congenital heart disease and rheumatic heart disease sub-studies aim to describe the contribution of congenital heard disease and rheumatic heart disease to PH in Africa. In addition, serum will

be collected at selected centres for studies on biomarker profile. The HIV.INFLAME sub-study aims to examine the role of inflammatory markers and oxidative stress on the development of HIV-PH. We hypothesizing that HIV-positive patients with PH have a pro-inflammatory state and raised markers of oxidative stress compared to healthy HIV-positive controls and that increased markers of inflammation and oxidative stress and decreased antioxidant capacity are predictors of outcome and indicators of disease severity.

Ethics and dissemination

All PAPUCO centres require ethical approval from their local ethics committee review board. Written inform consent must be obtain from every patient participating in the registry.

Study results will be disseminated in peer-reviewed journals. The first publication will include baseline and 6-month follow-up data from all centres. Sub-study publications on the HIV-cohort with 24-month follow-up and the cohort of patients with PH due to left heart disease will be published after recruitment and follow-up has been completed. Laboratory-based research will be published after work is completed.

The online data collection platform

A tailor-made databases has developed by *integerafrica research and development* to fulfil the study requirements. Open-source technology was used to develop the web-based system that allows investigators to collect, store, analyse, report on and exports clinical research data. The interface is simple and user friendly and leads the user through the data entry process. It anonymises personal patient data: data is stored as electronic case report forms on a secure, encrypted and backed-up server. It provides hierarchic permissions and validation at the point of data entry. Multimedia data formats, i.e. scans of ECGs, CXRs, and ECHO images can be uploaded on the platform, allowing storage of complete clinical records and data together.

Tools for education, training, and communication are installed within the web-portal. Frequently Asked Questions serve as a guide on how to the use of the platform. After secure login, documents such as paper case report forms, informed consent forms, study information sheets and patient education sheets on PH are available for download. All data can be exported in various formats for further analysis. The platform has been developed to cater for mobile Internet connectivity available in most parts of Africa and a unique research platform far beyond a simple web-based database.

Recruitment process

Twelve centres have received ethics approval and are currently actively recruiting; additional six countries are showing interest in joining the registry (Figure 2). All centres are government-run public health care institutions with different medical infrastructure profiles and all but one are cardiac centres within tertiary care hospitals (Table 1); one centre is an infectious diseases referral clinic in South Africa. At total of 254 patients have been recruited until December 2013 (Figure 5).

Table 1: Medical infrastructure at PAPUCO centres - diagnostic equipment and medical services

Centre	ECG	CXR	ECHO	RHC	CS	HRCT	CTPA	LFT	V/Q	Lab
CM01	X[1]	X[1]	X[1]			X[1]	X[1]	X[1]		X[1]
CM02	X[1]	X[1]	X[1]	X[1]	X[1]					X[1]
CM03	X[1]	X[1]	X[1]							X[1]
MZ01	X	X	X							X
MZ02	X	X	X			X		X		X
NG01	X[1]	X[1]	X[1]			X[1]		X[1]		X[1]
NG02	X[1]	X[1]	X[1]			X[1]	X[1]	X[1]		X[1]
NG03	X[1]	X[1]	X[1]			X[1]	X[1]	X[1]		X[1]

NG04	X[1]	X[1]	X[1]							X[1]
NG05	X[1]	X[1]	X[1]			X[1]	X[1]	X[1]		X[1]
SA01	X	X	X	X	X	X	X	X	X	X
SA02	X	X	X			X	X			X

Abbreviations: CM01, Douala General Hospital, Douala, Cameroon; CM02, Cardiac Centre, Shisong Hospital, Kumbo, Cameroon; CM03, Douala Cardiovascular Centre, Douala, Cameroon; MZ01, Instituto Nacional de Saúde, Maputo, Mozambique; MZ02, Division of Cardiology, Maputo Central Hospital, Maputo, Mozambique; NG01, Department of Medicine, Federal Medical Centre, Abeokuta, Nigeria; NG02, Department of Medicine, Bayero University and Aminu Kano Teaching Hospital, Kano, Nigeria; NG03, Department of Medicine, College of Medicine, Lagos, Nigeria; NG04, Department of Medicine, University of Uyo Teaching Hospital, Uyo, Nigeria; NG05, Federal Medical Centre, Umuahia, Nigeria; SA01, Division of Cardiology, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa; SA02, Infectious Diseases Referral Clinic, GF Jooste Hospital, Mannenberg, South Africa and Rapid Assessment Unit, Khayelitsha District Hospital, Khayelitsha, South Africa. ECG, electrocardiogram; CXR, chest X-ray; ECHO, Echocardiography; RHC, right heart catheterisation; CS, cardiac surgery; HRCT, high resolution computed tomography; CTPA, computed tomography pulmonary angiography; LFT, lung function tests; V/Q, ventilation/perfusion lung scan; Lab, laboratory facility for haematology, chemistry, and microbiology; X, equipment/service available at the centre and free-of-charge for the patients; X[1], patients have to cover the costs for the service (out of pocket payments).

LIMITATIONS

The PAPUCO registry is an example of a functioning registry in low-resource settings. Limited resources should therefore not be seen as a limitation, but rather as a development opportunity. PAPUCO centres have different levels of medical infrastructure and not all patients will undergo the same rigorous work-up in all centres - especially when compared to developed countries. Therefore, the clinical skills of the treating physician are often more important (and valuable!) than an additional diagnostic test in order to pin down the aetiology of PH in a patient. Moreover, patients often have to pay out of their pocket for diagnostic tests and therefore accessibility to tests is limited due to the financial means of the patient. Although we aim for consecutive patient enrolment at each centre, we understand that this is often not feasible due to high patient volume and workload of doctors.

SUMMARY

PAPUCO is a contemporary registry on PH in Africa using high international standards to diagnose PH. It will provide new insight on PH in Africa and ultimately improve diagnosis and care of patients. PAPUCO is already a showcase for registry activities in Africa and a vehicle to capacity generation and sustainable development in the health care sector. It interconnects health centres far beyond pulmonary hypertension.

LEGENDS OF FIGURES

Figure 1: Number of publications on pulmonary hypertension per annum since 1970 (grey bars) with moving average (blue line). Title search terms in PubMed were "pulmonary hypertension", "pulmonary arterial hypertension" or "pulmonary venous hypertension"; results are displayed annually between 1970 and 2013.

Figure 2: The PAPUCO map displays countries currently participating in the PAPUCO registry (number of centres per country in brackets).

Figure 3: Diagnostic algorithm to diagnose pulmonary hypertension in resource-constraint settings. Abbreviations: PH, pulmonary hypertension; ECG, electrocardiogram; TB, tuberculosis; PCP, pneumocystis pneumonia; COPD, chronic obstructive pulmonary disease; LHD, left heart disease; ECHO, Echocardiography; HIV, human immunodeficiency virus; US, ultrasound; LFT, liver function tests; HRCT, HRCT, high resolution computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiography; V/Q, ventilation/perfusion lung scan

Figure 4: Diagnosing pulmonary hypertension using transthoracic 2D-Doppler Echocardiography. A: 4-chamber view showing grossly enlarged RV and RA; with right

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Figure 5: PAPUCO registry - monthly enrolment until December 2013. Number of patients recruited per month since the launch of the registry in May 2011.

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CONTRIBUTORS

KS, AOM, FT were responsible for the initial idea, literature review, and study design and planning. All authors have contributed to the setup of the PAPUCO registry and have contributed to various aspects of the study design with input relating to their specific expertise in the field. FT, AD, AOM, LB, MUS, KMK, OSO, AM, PU, ASI, AD, KS have developed the study protocol, FT and KS wrote the study protocol, FT developed the database, FT, AD, AOM, KS cleaned the database, LB trained the doctors in Echocardiography of the heart and developed the Echo protocol, AD trained doctors in Cameroon, OSO trained doctors in Nigeria, SS developed the statistical analysis plan. FT,

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COMPETING INTEREST

We declare no competing interest.

ETHICS APPROVAL

All centres received ethics approval fro their local ethic committees.

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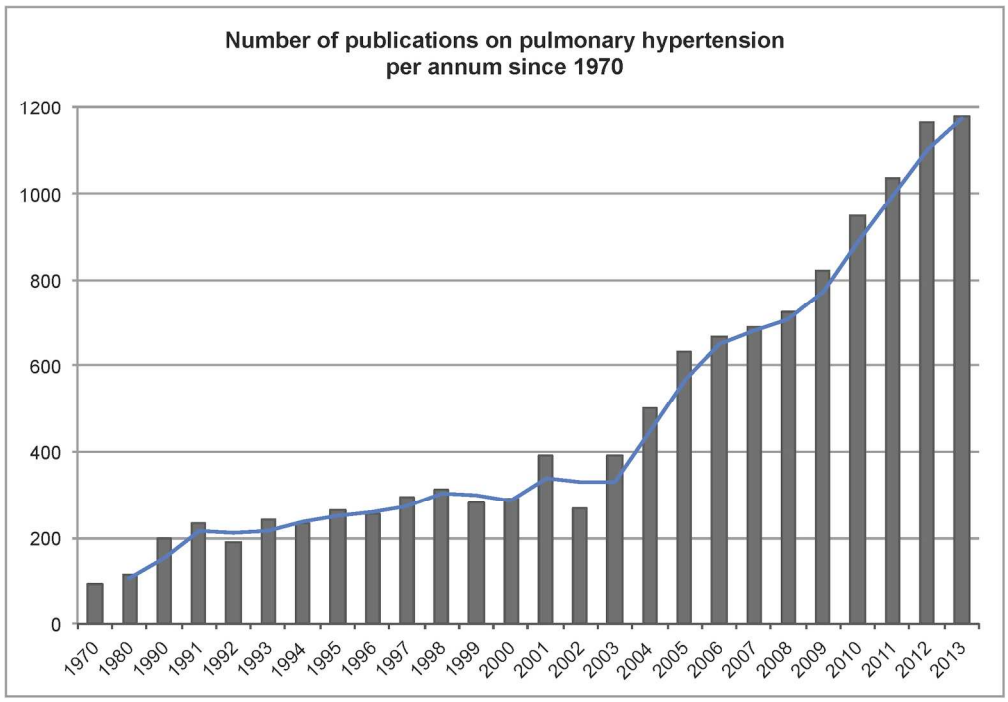

Number of publications on pulmonary hypertension per annum since 1970 (grey bars) with moving average (blue line). Title search terms in PubMed were "pulmonary hypertension", "pulmonary arterial hypertension" or "pulmonary venous hypertension"; results are displayed annually between 1970 and 2013.
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The PAPUCO map displays countries currently participating in the PAPUCO registry (number of centres per country in brackets).
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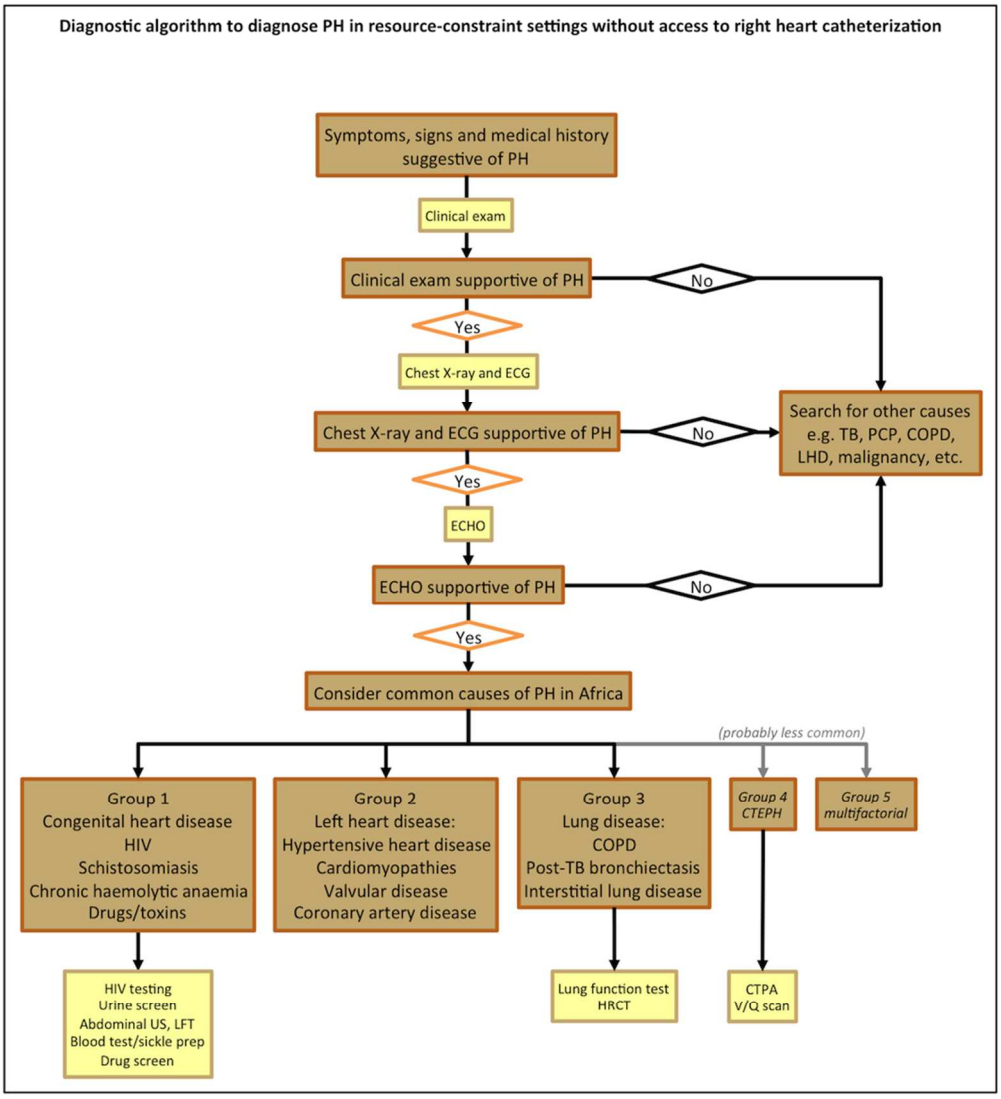

Diagnostic algorithm to diagnose pulmonary hypertension in resource-constraint settings. Abbreviations: PH, pulmonary hypertension; ECG, electrocardiogram; TB, tuberculosis; PCP, pneumocystis pneumonia; COPD, chronic obstructive pulmonary disease; LHD, left heart disease; ECHO, Echocardiography; HIV, human immunodeficiency virus; US, ultrasound; LFT, liver function tests; HRCT, HRCT, high resolution computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiography; V/Q, ventilation/perfusion lung scan
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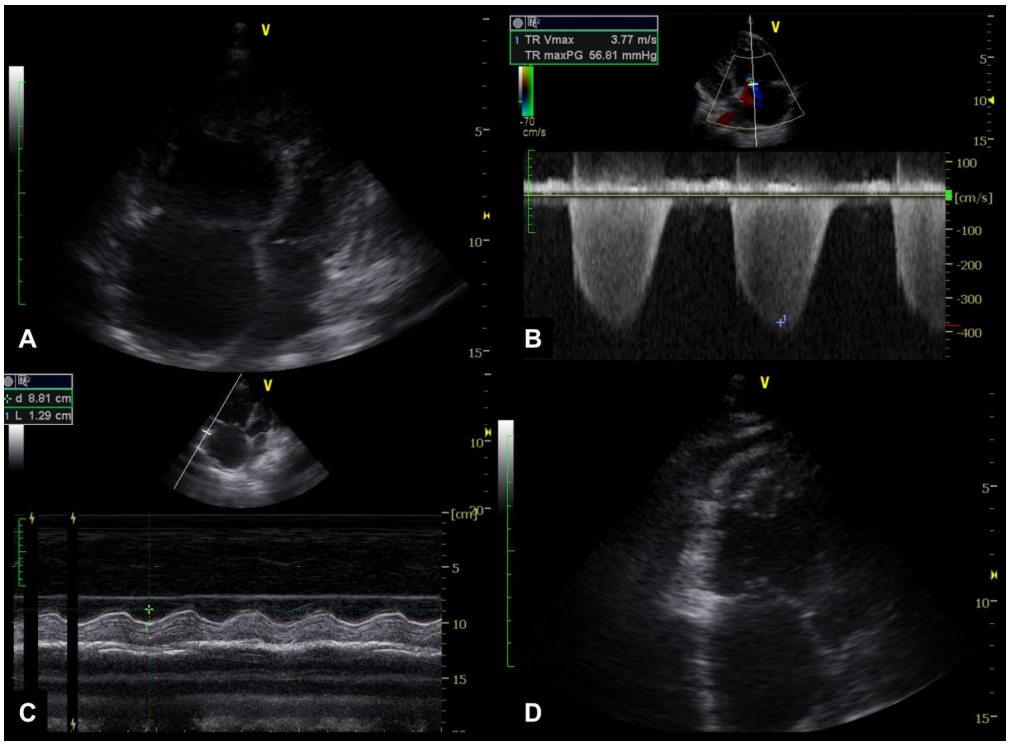

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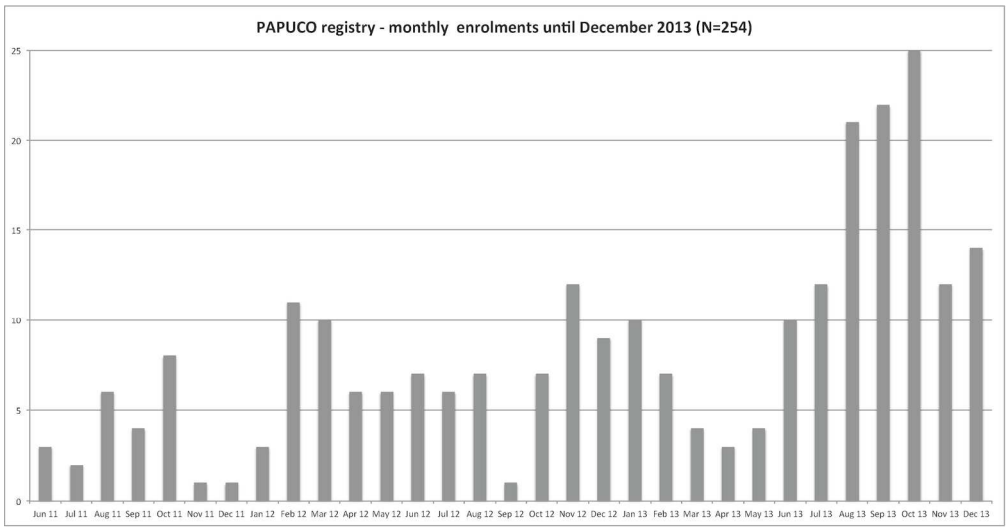

PAPUCO registry - monthly enrolment until December 2013. Number of patients recruited per month since the launch of the registry in May 2011.
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RATIONALE AND DESIGN OF THE PAN AFRICAN PULMONARY HYPERTENSION COHORT (PAPUCO) STUDY: IMPLEMENTING A CONTEMPORARY REGISTRY ON PULMONARY HYPERTENSION IN AFRICA

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RATIONALE AND DESIGN OF THE PAN AFRICAN PULMONARY HYPERTENSION COHORT (PAPUCO) STUDY: IMPLEMENTING A CONTEMPORARY REGISTRY ON PULMONARY HYPERTENSION IN AFRICA

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Running Title

The Pan African Pulmonary Hypertension Cohort (PAPUCO)

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ABSTRACT

Introduction

Pulmonary Hypertension (PH) is a devastating, progressive disease, with increasingly debilitating symptoms and, usually, shortened overall life expectancy due to narrowing of the pulmonary vasculature and consecutive right heart failure. Little is known about PH in Africa, but limited reports suggest that PH is more prevalent in Africa compared to developed countries due to the high prevalence of risk factors in the region.

Methods and Analysis

A multinational multicentre registry-type cohort study was established and tailored to resource-constraint settings to describe disease presentation, disease severity and aetiologies of PH, comorbidities, the diagnostic and therapeutic management, and natural course of PH in Africa. PH will be diagnosed by specialist cardiologists using Echocardiography (RVSP>35 mmHg, absence of pulmonary stenosis and acute right heart failure) usually accompanied by shortness of breath, fatigue, peripheral oedema, and other cardiovascular symptoms, electrocardiogram and chest x-ray changes in keeping with PH as per guidelines (ESC/ERS guidelines). Additional investigations such as CT-scan, ventilation/perfusion scan or right heart catheterisation will be performed at the discretion of the treating physician. Functional tests include 6-minute walk test and Karnofsky Performance Score. The WHO classification system for PH will be applied to describe the different aetiologies of PH. Several sub-studies have been implemented within the registry to investigate specific types of PH and their outcome at up to 24 months. Data will be analysed by an independent institution following a data analyse plan.

Ethics and Dissemination

All local Ethics Committees of the participating centres approved the protocol. The data will be disseminated through peer-reviewed journals, at national and international conferences and public events at local care providers.

ARTICLE SUMMARY

Article focus

- In this manuscript we aim to provide an overview of pulmonary hypertension in Africa and the epidemiology of risk factors prevalent in the region.
- We aim to answer the question why Africa needs a registry for pulmonary hypertension.
- We describe how we implemented the registry in scarce resources settings.

Key messages

- Risk factors for pulmonary hypertension are highly endemic in Africa.
- The incidence of pulmonary hypertension is expected to be higher in Africa compared to developed countries.
- A diagnostic algorithm to diagnose pulmonary hypertension in resource-constraint settings without access to right heart catheterisation has been developed.
- 12 centres are participating in the Pan African Pulmonary hypertension Cohort (PAPUCO) study and more than 250 patients have been recruited so far.

Strengths and limitations of this study

- The PAPUCO study is the first multinational registry on pulmonary hypertension in Africa.
- PAPUCO centres have different levels of medical infrastructure and not all patients underwent the same rigorous work-up.

INTRODUCTION

Pulmonary Hypertension (PH) is a devastating, progressive disease, with increasingly debilitating symptoms and, usually, shortened overall life expectancy due to narrowing of the pulmonary vasculature and consecutive right heart failure (RHF).[1] The epidemiology of PH in Africa and the distribution of its multitude of aetiologies has not yet been described, but limited reports suggest that the incidence of PH in Africa is higher than that reported from developed countries, owing to the pattern of diseases prevalent in the region.[2-5] Many known risk factors for PH are hyperendemic in this part of the world, including human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), rheumatic heart disease (RHD), hereditary haemoglobinopathies, schistosomiasis and other parasitic infections, and chronic hepatitis B and C infection. On the other hand, a high prevalence of tuberculosis (TB), poorly treated asthma, high levels of pollution in urban areas and exposure to mining, may subsequently lead to various forms of pulmonary disease, PH and, often, to RHF with premature death. Also a lack of specialist paediatric services to diagnose and manage congenital heart disease (CHD) potentially also leads to PH.[6] Furthermore, the high prevalence of RHD and endomyocardial fibrosis, the latter possibly also due to the high burden of parasitic infections, may contribute to secondary PH.[6-8] However, Africa is in epidemiological transition with increased prevalence of non-communicable forms of heart disease such as hypertensive and ischemic heart disease. Left heart disease is the most common cause of heart failure in Africa and most likely a major contributor to PH and consecutive RHF.[4,9] Thus, within the registry we expect the entire spectrum of aetiologies of PH. In this manuscript, we aim to provide an overview of PH in Africa and the epidemiology of risk factors prevalent in the region, and answer the question why Africa needs a registry for PH just as much as most other parts of the world and how we implemented it in the setting of scarce resources.

Preliminary evidence of a significant burden of pulmonary hypertension and its risk factors in Africa

In recent years, there has been increasing awareness of the clinical significance of PH and cor pulmonale in Africa. This applies equally to the recognition of the importance of PH and RHF as both a primary diagnosis and as a poor prognostic marker for those primarily affected by left-sided heart failure. Data on the precursors and risk factors of those conditions are limited to few reports. The largest study on PH/RHF in Africa has been conduction within *the Heart of Soweto Study in* South Africa; 2505 patients presented with *de novo* heart failure between 2006-2008.[5] Of those 697 (28%) were diagnosed with PH/RHF. PH/RHF was the primary diagnosis in 50% of those patients. The majority presented with dyspnoea and a mean right ventricular systolic pressure (RVSP) above 50 mmHg. Left heart disease (31%), chronic lung disease due to Chronic Obstructive Pulmonary Disease (COPD) and tuberculosis (26%), and pulmonary arterial hypertension (PAH) (20%) due to HIV (HIV-PAH), CHD, or idiopathic PAH were the most common causes of PH. Sani et al. described the prevalence of PH in patients with RHD at a tertiary centre in Nigeria.[10] Of 1312 Echocardiography (ECHO) studies 10% had evidence of RHD; secondary PH was present in 80% of patients with RHD. The same centre reported on 53 patients with PH on ECHO among 80 patients admitted with heart failure with hypertensive heart disease (25%), peripartum cardiomyopathy (25%), dilated cardiomyopathy (17%), and RHD (13%) being the most common causes of PH.[11] A study from Uganda showed a prevalence of PH in patients with newly diagnosed RHD (n=309) of 33%.[12] A smaller survey from Lagos, Nigeria investigated the prevalence of cardiovascular disease in an HIV-positive cohort and found one patient of 100 patients to have HIV-PAH.[13] An ECHO study on 102 HIV-patients presenting with cardiac symptoms in Tanzania revealed PH in 13%.[14] PH with a

RVSP>30 mmHg was present in 4% of long-term survivors in a Zimbabwe cohort of vertically acquired HIV infection.[15] Haemolytic anaemia is a known risk factor for PH; a screening study of patients with sickle-cell disease (SCD) in Nigeria showed a PH prevalence of 25%;[16] a study from Egypt indicates that patients with β-Thalassaemia are at risk of PH.[17] Another study from Egypt found a PH prevalence of 9% in patients seropositive for schistosomal antibodies. Ahmed et al. from Sudan described 14 consecutive cases of PH with previously treated pulmonary TB and conclude that PH can even occur after resolution of TB, most like due to persistent lung destruction.[18] This data suggests that left heart disease, chronic lung disease, RHD, HIV, schistosomiasis and SCD might be the most common underlying diseases to cause PH within the spectrum of aetiologies of PH that we will find within the Pan African Pulmonary hypertension Cohort (PAPUCO)

RATIONALE AND OBJECTIVES

Worldwide, PH has received great increase in awareness at the beginning of the 21st century, but less than one per cent of the publications are from Africa (Figure 1). It is expected that PH is more prevalent in Africa compared to developed countries, but little information is available about African patients with PH. Exposure to risk factors, human genetic variation, different socio-economic backgrounds, lifestyles, co-morbidities, nutrition and disparities in access to health services makes the African population unique, but heterogeneous at the same time. Therefore, most research data and clinical guidelines from high-income countries cannot be translated into the African context. It is within the context described above that the Pan African Pulmonary hypertension Cohort (PAPUCO), a Pan Africa registry-type cohort study, was established (Figure 2).

Scientific and clinical research has been fundamental in improving human health.[19] In fact, research has demonstrated to be an excellent vehicle to implement new technologies and to

facilitate training for its use, and to develop new systems and establish the services around it - jointly leading to technical improvement, sharpening of skills and capacity development[20,21]. Besides the main objectives of the PAPUCO registry to define and understand PH in Africa (Box 1), this multinational and multicentre research project therefore aims to also develop sustainable clinical and research capacity across the African continent as well as raising awareness for PH and its risk factors.

Box 1: PAPUCO objectives
Primary objective • To describe disease presentation, disease severity and aetiologies of PH, comorbidities, the diagnostic and therapeutic management, and natural course of PH in Africa *Secondary objectives* • To describe the overall 6-month survival rate • To describe the 24-month survival rate in patients with HIV-PAH • To compare 6-month survival rates between different groups of PH • To determine the predictors of mortality access the different groups.
Abbreviations: PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; HIV, human immunodeficiency virus

The prevalence of PH in Africa varies geographically, according to underlying risk factors and diseases and the diagnosis of PH is most likely often missed, not only during early stages due to the subtle nature of presentation of PH, but also at more advanced stage of disease due to lack of awareness by primary care doctors and low index of suspicion, limited access to ECHO services and tertiary care. However, it is crucial to diagnose PH in Africa early and reliably to ensure better care for these patients (Box 2).

Box 2: The significance of PH in Africa: Why we need to diagnose?
• The right to know

• Prognostic implications • Access to tertiary care: heart failure management, anticoagulation, home oxygen, COPD management, access to PH-specific drugs (Sildenafil) • Access to cardiothoracic surgery: valve repair/replacement, correction of congenital heart disease, heart transplantation • Access to social and disability grants • To raise awareness of PH and its risk factors
Abbreviations: PH, pulmonary hypertension; COPD, chronic obstructive pulmonary disease

METHODS AND ANALYSIS

Study design and setting

The Pan African Pulmonary hypertension Cohort (PAPUCO) research group was established in 2011 with the aim to implement a registry-type cohort study on pulmonary hypertension in Africa. The registry aims to recruit consecutive patients 1) with newly diagnosed PH based clinical and ECHO criteria, 2) are able or likely to return for 6-month follow-up, 3) are at least 18 years old (except for paediatric centres in Mozambique and Nigeria), and 4) consented in writing to participate in the registry. Centre eligibility include 1) availability of ECHO and training in assessing right heart function, 2) experience in diagnosing PH according to WHO classification, 3) experience in clinical management of patients with right heart failure, and 4) resources to review patients at 6-month follow-up. Participating centres will be invited to join the registry at African cardiac meetings and conferences.

Definition of pulmonary hypertension, diagnostic algorithm and data points

As shown in Box 3, PH is defined as documented elevated RVSP>35 mmHg on trans-thoracic ECHO in the absence of pulmonary stenosis and acute right heart failure; usually accompanied by shortness of breath, fatigue, peripheral oedema, and other cardiovascular symptoms, and possibly electrocardiogram (ECG) and chest x-ray (CXR) changes in keeping with PH as per European Society of Cardiology and European Respiratory Society

(ESC/ERS) guidelines on pulmonary hypertension.[5,22] Right heart catheterisation is optional. The updated WHO classification system for PH (Dana Point 2008) will be applied to describe the different aetiologies of PH[22,23]. Once definitive assessment and treatment has been applied, the following specific data will be documented for each individual: a) all major cardiovascular diagnoses according ICD 10 coding, and b) up to five non-cardiovascular diagnoses according ICD 10 coding.[24] Figure 3 shows the diagnostic algorithm to diagnose PH in resource-constraint settings without access to right heart catheterisation that has been developed following the ESC/ERS guidelines for the diagnosis of PH.[22] Key information collected will include information on demographic profile, socio-economic background, medical history, co-morbidities, cardiac risk factors, and environmental exposures. The clinical aspects of the assessment include symptoms scoring, a full clinical examination, physical and clinical status; functional tests include WHO functional class (WHO FC), 6-minute walk test (6MWT) and Karnofsky Performance Score. Technical procedures include ECHO, CXR, and 12-lead ECG. Further investigations are at the discretion of the treating physician and typically include lung function tests, ventilation/perfusion lung scans, and high resolution computed tomography and computed tomography pulmonary angiography, and right heart catheterization, if available (Figure 3). Data on heart failure treatment and co-medication, hospitalization and death, and 6-month outcome will also be collected.

Box 3: Evidence to diagnose PH in resource-constraint settings
• Symptoms: SOB, fatigue, cough, chest pain, palpitations • Clinical exam: raised JVP, peripheral oedema, ascites, loud p2, systolic murmur, central cyanosis • ECG: sinus tachycardia, p-pulmonale, right axis deviation, right bundle branch block, RVH • CXR: cardiomegaly, pleural effusion, prominent pulmonary arteries • ECHO: dilated right atrium and ventricle, interventricular septal flattening, RVSP>35 mmHg, TAPSE<15 mm

Abbreviations: SOB, shortness of breath; JVP, jugular vein pressure; ECG, electrocardiogram; RVH, right ventricular hypertrophy; CXR, chest X-ray; ECHO, Echocardiography; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion

Echocardiography

Echocardiography in adults

ECHO modalities applied included M-mode, two dimensional (2D) and Doppler studies. ECHO will be done with 3 to 5 MHz sector transducer. Complete 2D ECHO examination will be performed according to the recommendations of the American Society of ECHO (ASE).[25] M-mode ECHO will be derived from 2D images. The M-mode cursor on the 2D scan will move to specific areas of the heart to obtain measurements according to the recommendation of the committee on M-mode standardization of the ASE. Doppler indices of left ventricular (LV) diastolic filling will be obtained. Complete Doppler study will be done according to the recommendations of the ASE. From the M-mode measurements, indices of LV function will be derived. These include shortening fraction, ejection fraction (EF), and LV mass, cardiac output and relative wall thickness. ECHO examinations include (a) valvular assessment, (b) left atrial size, (c) left ventricular size and function, (d) a semi quantitative estimate of the severity of valvular regurgitation, (e) size and function of the right atrium and ventricle and (f) evidence of pulmonary hypertension. Doppler will be used to examine the valves on suspicion of any valvular lesion. ECHO findings associated with PH includes dilated pulmonary artery and dilation and hypertrophy of the right ventricle (RV), diastolic flattening of the interventricular septum and Doppler evidence of PH.[26] Doppler ECHO estimates pulmonary artery systolic pressure (PASP). By measuring the maximum velocity of the tricuspid regurgitant jet (v), the transtricuspid pressure gradient will be calculated using the modified Bernoulli equation ($4v^2$).[27] The PASP is approximated by adding the transtricuspid gradient to the right atrial pressure (RAP) as applied in the formula [$PASP=4v^2+RAP$]. The PASP is equivalent to RVSP in the absence of pulmonary outflow

obstruction. The RAP is estimated by the respiratory variation size of the vena cava inferior in M-mode.[28] In our study, the systolic regurgitant tricuspid flow will be assessed in the parasternal right ventricular inflow, parasternal short-axis, and apical four-chamber views to determine the highest velocity, which reflects PASP/RVSP.[29] PH is defined as *mild* if RVSP was 36-50 mmHg, *moderate* if RVSP was 51-60 mmHg and *severe* if RVSP was >60 mmHg.[30] In addition, we further assessed right ventricular function by measuring the systolic displacement of the lateral portion of the tricuspid annular plane excursion (TAPSE) on the M-mode tracing under the 2D-echo guidance.[31] Peak mitral early diastolic velocity (E in m/s), the E-wave deceleration time (DCT in ms) and the velocity at atrial contraction (A in m/s) are measured using pulsed-wave Doppler. Left ventricular filling pressure classes were defined in accordance with the ASE 2009 guidelines.[32] In patients with heart failure and reduced ejection fraction (HFrEF) raised LV filling pressure is defined as E/A ≥2 if in sinus rhythm or DCT <150 ms if in atrial fibrillation (AF); normal LV filling pressure is defined as E/A <1 in patients in sinus rhythm or DCT ≥200 ms for those in AF; patients between these limits will be classified as undetermined. In heart failure and preserved ejection fraction (HFpEF), LV filling pressure is classified as follows: raised LV filling pressure if left atrium is dilated and normal LV filling pressure if left atrium has normal size.

Echocardiography in infants and children

Translating the definitions of PH in adults to children, especially to infants, is controversial. Within the paediatric cardiology community experts suggest that the ratio of the PASP to the systemic systolic blood pressure >0.4 should be the diagnostic criterion.[33] The fact that the threshold of pulmonary vascular resistance (PVR) increase has not been included in the abovementioned definition is another limitation to its use in children or infants, since paediatric PH is mainly caused by left-to-right shunt congenital heart disease; and if PVR

shows no significant increase in such cases, the patient may be considered only as a dynamic PH case led by increased pulmonary blood flow, rather than pulmonary vascular disease. Paediatric guidelines suggest that mPAP >25 mmHg and PVR>3 Wood units remain in the definition of PAH.[34] In our cohort of children with congenital heart malformations we not only used tricuspid and pulmonary regurgitation envelopes, but also the flow across the ventricular septal defect or persistent ducts arteriosus to measure the gradient between the two circulations and therefore estimate the pulmonary pressure. Indirect signs of PH such as dilatation of the RV, RV-hypertrophy and dilatation of the main pulmonary artery were added to Doppler data to confirm the diagnosis.

Accuracy of Echocardiography in the diagnosis of PH

Diagnosing PH is challenging when relying on bedside tests. RHC is the gold standard to diagnose and confirm PH, but performing RHC on all patients with dyspnoea would bear excessive risks and be impractical in any cost-constrained environment. Also RHC is only available at very few centres in Africa. A viable device to diagnose PH in Africa needs to be widely available, accurate, safe, and cost-effective. ECHO has become increasingly available in Africa and reliably allows the measurements to describe functional and morphologic features of PH and to indirectly measure the pressures in the pulmonary artery; hence, to diagnose PH. Nonetheless, the exact measurements of the mean and systolic pulmonary artery are not possible, the PASP remains estimate, and the use of ECHO to diagnose PH questionable.[35,36] A number of possible explanations for this “inaccuracy” merit attention: 1) conditions for a reproducible calculation of PASP/RVSP include the presence of sufficient TR to produce a Doppler envelope and appropriate gain adjustments. An “undergained” spectral signal will tend to result in underestimated PASP whereas an “overgained” spectral signal might overestimate the measurements; 2) careful adjustment of the transducer position

and the use of colour flow Doppler are critical in order to reduce the Doppler angle and to obtain the maximal regurgitant flow velocity and severe TR will cause a laminar flow which invalidates the Bernoulli equation; 3) volume status and systemic blood pressure are other factors that potentially influence the measurement of PASP; and 4) the highest value of RAP in the ASE guidelines is 15 mmHg, but RAP measured by RHC can exceed 15 mmHg. In spite of all these shortcomings, several studies have been published in the literature demonstrating good sensitivity and specificity of ECHO versus RHC.[37-39] In the REVEAL registry, there was a good correlation in PASP between ECHO and RHC at baseline, even if repeated ECHO measurements alone were not sufficient to monitor changes in PASP or progression of PH.[40] In the first systematic review and meta-analysis addressing the diagnostic accuracy of ECHO in PH by Janda and colleagues, the authors concluded that the correlation of PASP by ECHO compared to PASP by RHC was good with a summary correlation coefficient of 0.70 (95% CI 0.67 to 0.73).[41] Also, the authors showed that the diagnostic accuracy of ECHO in PH was also acceptable with a summary sensitivity and specificity of 83% (95% CI 73 to 90) and 72% (95% CI 53 to 85), respectively. Additional, Damy and colleagues demonstrated in their recent work that PASP when measured in "good ECHO hands" is a strong predictor of mortality.[42] Last but not the least, easily obtainable ECHO parameters like E/A ratio, DCT, LA size can reliably distinguish between PH due to lung disease and PH due to left heart disease, allowing for rapid triage of patients with need for RHC. In summary, ECHO is far beyond a good modality to confirm both the presence and aetiology of PH in the majority of suspected cases when performed and interpreted by the requisite expertise under incorporation of all information obtained during a detailed ECHO assessment. ECHO will always provide incremental information in PH that cannot be obtained using RHC, whether in developed or developing countries.

Data cleaning process and statistical analysis

All study data will be collected on electronic case report forms and stored on a dedicated secure central database. Cases will be reviewed by at least two investigators (FT, AD, KS, AOM) for completeness and data validated. Query reports will be sent to the sites and resolved by the site investigators. If consensus on the WHO classification of PH cannot be reached, a third investigator's opinion will be requested. Data will then be verified and transferred to SPSS Statistics 17.0 for all analyses by an independent team at Preventative Health, Baker IDI Heart and Diabetes Institute, Melbourne, Australia. Normally distributed continuous data will be presented as mean ± standard deviation and non-Gaussian distributed variables as median plus interquartile range. Categorical data will be presented as percentages with 95% confidence intervals (CI) where appropriate. For patient group comparisons, we will use Chi Square (χ^2) analysis with calculation of odds ratios (OR) and 95% CI (where appropriate) for discrete variables and Students t-test and analysis of variance for normally distributed continuous variables. Multiple logistic regression analyses (entry model) will be performed on age, sex and baseline risk factors to derive adjusted ORs for the risk of presenting with PH/RHF overall, chronic lung disease and PH WHO Group 1. Significance will be accepted at the two-sided level of 0.05. ECG analysis will be will be subject to blinded coding according to published Minnesota criteria to determine any pathological abnormalities.[43] We aim to adhere to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for this type of study wherever possible.[44]

PAPUCO sub-studies

Several sub-studies have been established within the PAPUCO registry. The ECHO sub-study aims to describe in detail the ECHO characteristics of right ventricular function in PH.

The HIV-PAH sub-study aims to describe the phenotype of HIV-PAH in Africa. The congenital heart disease and rheumatic heart disease sub-studies aim to describe the contribution of congenital heard disease and rheumatic heart disease to PH in Africa. In addition, serum will be collected at selected centres for studies on biomarker profile. The HIV.INFLAME sub-study aims to examine the role of inflammatory markers and oxidative stress on the development of HIV-PAH. We hypothesizing that HIV-positive patients with PH have a pro-inflammatory state and raised markers of oxidative stress compared to healthy HIV-positive controls and that increased markers of inflammation and oxidative stress and decreased antioxidant capacity are predictors of outcome and indicators of disease severity.

Ethics and dissemination

All PAPUCO centres require ethical approval from their local ethics committee review board. Written informed consent must be obtain from every patient participating in the registry. Study results will be disseminated in peer-reviewed journals. The first publication will include baseline and 6-month follow-up data from all centres. Sub-study publications on the HIV-cohort with 24-month follow-up and the cohort of patients with PH due to left heart disease will be published after recruitment and follow-up has been completed. Laboratory-based research will be published after work is completed.

The online data collection platform

A tailor-made databases has developed by *integerafrica research and development* to fulfil the study requirements. Open-source technology was used to develop the web-based system that allows investigators to collect, store, analyse, report on and exports clinical research data. The interface is simple and user friendly and leads the user through the data entry process. It anonymises personal patient data: data is stored as electronic case report forms on a secure,

encrypted and backed-up server. It provides hierarchic permissions and validation at the point of data entry. Multimedia data formats, i.e. scans of ECGs, CXRs, and ECHO images can be uploaded on the platform, allowing storage of complete clinical records and data together. Tools for education, training, and communication are installed within the web-portal. Frequently Asked Questions serve as a guide on how to the use of the platform. After secure login, documents such as paper case report forms, informed consent forms, study information sheets and patient education sheets on PH are available for download. All data can be exported in various formats for further analysis. The platform has been developed to cater for mobile Internet connectivity available in most parts of Africa and a unique research platform far beyond a simple web-based database.

Recruitment process

Twelve centres have received ethics approval and are currently actively recruiting; additional six countries are showing interest in joining the registry (Figure 2). All centres are government-run public health care institutions with different medical infrastructure profiles and all but one are cardiac centres within tertiary care hospitals (Table 1); one centre is an infectious diseases referral clinic in South Africa. At total of 254 patients have been recruited until December 2013 (Figure 5).

Table 1: Medical infrastructure at PAPUCO centres - diagnostic equipment and medical services

Centre	ECG	CXR	ECHO	RHC	CS	HRCT	CTPA	LFT	V/Q	Lab
CM01	X[1]	X[1]	X[1]			X[1]	X[1]	X[1]		X[1]
CM02	X[1]	X[1]	X[1]	X[1]	X[1]					X[1]
CM03	X[1]	X[1]	X[1]							X[1]
MZ01	X	X	X							X
MZ02	X	X	X			X		X		X

NG01	X[1]	X[1]	X[1]			X[1]		X[1]		X[1]
NG02	X[1]	X[1]	X[1]			X[1]	X[1]	X[1]		X[1]
NG03	X[1]	X[1]	X[1]			X[1]	X[1]	X[1]		X[1]
NG04	X[1]	X[1]	X[1]							X[1]
NG05	X[1]	X[1]	X[1]			X[1]	X[1]	X[1]		X[1]
SA01	X	X	X	X	X	X	X	X	X	X
SA02	X	X	X			X	X			X

Abbreviations: CM01, Douala General Hospital, Douala, Cameroon; CM02, Cardiac Centre, Shisong Hospital, Kumbo, Cameroon; CM03, Douala Cardiovascular Centre, Douala, Cameroon; MZ01, Instituto Nacional de Saúde, Maputo, Mozambique; MZ02, Division of Cardiology, Maputo Central Hospital, Maputo, Mozambique; NG01, Department of Medicine, Federal Medical Centre, Abeokuta, Nigeria; NG02, Department of Medicine, Bayero University and Aminu Kano Teaching Hospital, Kano, Nigeria; NG03, Department of Medicine, College of Medicine, Lagos, Nigeria; NG04, Department of Medicine, University of Uyo Teaching Hospital, Uyo, Nigeria; NG05, Federal Medical Centre, Umuahia, Nigeria; SA01, Division of Cardiology, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa; SA02, Infectious Diseases Referral Clinic, GF Jooste Hospital, Mannenberg, South Africa and Rapid Assessment Unit, Khayelitsha District Hospital, Khayelitsha, South Africa. ECG, electrocardiogram; CXR, chest X-ray; ECHO, Echocardiography; RHC, right heart catheterisation; CS, cardiac surgery; HRCT, high resolution computed tomography; CTPA, computed tomography pulmonary angiography; LFT, lung function tests; V/Q, ventilation/perfusion lung scan; Lab, laboratory facility for haematology, chemistry, and microbiology; X, equipment/service available at the centre and free-of-charge for the patients; X[1], patients have to cover the costs for the service (out of pocket payments).

LIMITATIONS

The PAPUCO registry is an example of a functioning registry in low-resource settings. Limited resources should therefore not be seen as a limitation, but rather as a development opportunity. PAPUCO centres have different levels of medical infrastructure and not all patients will undergo the same rigorous work-up in all centres - especially when compared to developed countries. Therefore, the clinical skills of the treating physician are often more important (and valuable!) than an additional diagnostic test in order to pin down the aetiology of PH in a patient. Moreover, patients often have to pay out of their pocket for diagnostic tests and therefore accessibility to tests is limited due to the financial means of the patient. Although we aim for consecutive patient enrolment at each centre, we understand that this is often not feasible due to high patient volume and workload of doctors.

SUMMARY

PAPUCO is a contemporary registry on PH in Africa using high international standards to diagnose PH. It will provide new insight on PH in Africa and ultimately improve diagnosis and care of patients. PAPUCO is already a showcase for registry activities in Africa and a vehicle to capacity generation and sustainable development in the health care sector. It interconnects health centres far beyond pulmonary hypertension.

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CONTRIBUTORS

KS, AOM, FT were responsible for the initial idea, literature review, and study design and planning. All authors have contributed to the setup of the PAPUCO registry and have contributed to various aspects of the study design with input relating to their specific expertise in the field. FT, AD, AOM, LB, MUS, KMK, OSO, AM, PU, ASI, AD, KS have developed the study protocol, FT and KS wrote the study protocol, FT developed the database, FT, AD, AOM, KS cleaned the database, LB trained the doctors in Echocardiography of the heart and developed the Echo protocol, AD trained doctors in Cameroon, OSO trained doctors in Nigeria, SS developed the statistical analysis plan. FT, AD, AOM, MUS, KMK, OSO, IM, AM, PU, KT, RB, AD, KS were substantially involved in data acquisition. All authors read and approved the final manuscript.

COMPETING INTEREST

We declare no competing interest.

ETHICS APPROVAL

All centres received ethics approval fro their local ethic committees.

FUNDING

Funding was received from PVRI, Bayer Health Care, and the University of Cape Town.

LEGENDS OF FIGURES

Figure 1: Number of publications on pulmonary hypertension per annum since 1970 (grey bars) with moving average (blue line). Less than one per cent (0.7%) of the publications were from Africa (not displayed). Title search terms in PubMed were "pulmonary hypertension", "pulmonary arterial hypertension" or "pulmonary venous hypertension" and Africa and African country names; results are displayed annually between 1970 and 2013.

Figure 2: The PAPUCO map displays countries currently participating in the PAPUCO registry (number of centres per country in brackets).

Figure 3: Diagnostic algorithm to diagnose pulmonary hypertension in resource-constraint settings. Abbreviations: PH, pulmonary hypertension; ECG, electrocardiogram; TB, tuberculosis; PCP, pneumocystis pneumonia; COPD, chronic obstructive pulmonary disease; LHD, left heart disease; ECHO, Echocardiography; HIV, human immunodeficiency virus; US, ultrasound; LFT, liver function tests; HRCT, HRCT, high resolution computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiography; V/Q, ventilation/perfusion lung scan

Figure 4: Diagnosing pulmonary hypertension using transthoracic 2D-Doppler Echocardiography. A: 4-chamber view showing grossly enlarged RV and RA; with right ventricularisation of the LV, and bulging of the RA into the LA; B: Color- and continuous-

wave Doppler across the TV in the 4-chamber view showing severe TR, despite the deceivingly less impressive color-flow jet seen across the valve; C: M-Mode measurement of TAPSE depicting right ventricular systolic dysfunction; D: Long-axis view of right ventricular apical thrombus. Abbreviations: RA, right atrium; RV: right ventricle; LA: left atrium; TV: tricuspid valve; TR: tricuspid regurgitation.

Figure 5: PAPUCO registry - monthly enrolment until December 2013. Number of patients recruited per month since the launch of the registry in May 2011.

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RATIONALE AND DESIGN OF THE PAN AFRICAN PULMONARY HYPERTENSION COHORT (PAPUCO) STUDY: IMPLEMENTING A CONTEMPORARY REGISTRY ON PULMONARY HYPERTENSION IN AFRICA

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ABSTRACT

Introduction

Pulmonary Hypertension (PH) is a devastating, progressive disease, with increasingly debilitating symptoms and, usually, shortened overall life expectancy due to narrowing of the pulmonary vasculature and consecutive right heart failure. Little is known about PH in Africa, but limited reports suggest that PH is more prevalent in Africa compared to developed countries due to the high prevalence of risk factors in the region.

Methods and Analysis

A multinational multicentre registry-type cohort study was established and tailored to resource-constraint settings to describe disease presentation, disease severity and aetiologies of PH, comorbidities, the diagnostic and therapeutic management, and natural course of PH in Africa. PH will be diagnosed by specialist cardiologists using Echocardiography (RVSP>35 mmHg, absence of pulmonary stenosis and acute right heart failure) usually accompanied by shortness of breath, fatigue, peripheral oedema, and other cardiovascular symptoms, electrocardiogram and chest x-ray changes in keeping with PH as per guidelines (ESC/ERS guidelines). Additional investigations such as CT-scan, ventilation/perfusion scan or right heart catheterisation will be performed at the discretion of the treating physician. Functional tests include 6-minute walk test and Karnofsky Performance Score. The WHO classification system for PH will be applied to describe the different aetiologies of PH. Several sub-studies have been implemented within the registry to investigate specific types of PH and their outcome at up to 24 months. Data will be analysed by an independent institution following a data analyse plan.

7 September 2014~~7 September 2014~~30 June 2014

Ethics and Dissemination

All local Ethics Committees of the participating centres approved the protocol. The data will be disseminated through peer-reviewed journals, at national and international conferences and public events at local care providers.

ARTICLE SUMMARY

Article focus

- In this manuscript we aim to provide an overview of pulmonary hypertension in Africa and the epidemiology of risk factors prevalent in the region.
- We aim to answer the question why Africa needs a registry for pulmonary hypertension.
- We describe how we implemented the registry in scarce resources settings.

Key messages

- Risk factors for pulmonary hypertension are highly endemic in Africa.
- The incidence of pulmonary hypertension is expected to be higher in Africa compared to developed countries.
- A diagnostic algorithm to diagnose pulmonary hypertension in resource-constraint settings without access to right heart catheterisation has been developed.
- 12 centres are participating in the Pan African Pulmonary hypertension Cohort (PAPUCO) study and more than 250 patients have been recruited so far.

Strengths and limitations of this study

- The PAPUCO study is the first multinational registry on pulmonary hypertension in Africa.
- PAPUCO centres have different levels of medical infrastructure and not all patients underwent the same rigorous work-up.

INTRODUCTION

Pulmonary Hypertension (PH) is a devastating, progressive disease, with increasingly debilitating symptoms and, usually, shortened overall life expectancy due to narrowing of the pulmonary vasculature and consecutive right heart failure (RHF).[1] The epidemiology of PH in Africa and the distribution of its multitude of aetiologies has not yet been described, but limited reports suggest that the incidence of PH in Africa is higher than that reported from developed countries, owing to the pattern of diseases prevalent in the region.[2-5] Many known risk factors for PH are hyperendemic in this part of the world, including human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), rheumatic heart disease (RHD), hereditary haemoglobinopathies, schistosomiasis and other parasitic infections, and chronic hepatitis B and C infection. On the other hand, a high prevalence of tuberculosis (TB), poorly treated asthma, high levels of pollution in urban areas and exposure to mining, may subsequently lead to various forms of pulmonary disease, PH and, often, to RHF with premature death. Also a lack of specialist paediatric services to diagnose and manage congenital heart disease (CHD) potentially also leads to PH.[6] Furthermore, the high prevalence of RHD and endomyocardial fibrosis, the latter possibly also due to the high burden of parasitic infections, may contribute to secondary PH.[6-8] However, Africa is in epidemiological transition with increased prevalence of non-communicable forms of heart disease such as hypertensive and ischemic heart disease. Left heart disease is the most common cause of heart failure in Africa and most likely a major contributor to PH and consecutive RHF.[4,9] Thus, within the registry we expect the entire spectrum of aetiologies of PH. In this manuscript, we aim to provide an overview of PH in Africa and the epidemiology of risk factors prevalent in the region, and answer the question why Africa needs a registry for PH just as much as most other parts of the world and how we implemented it in the setting of scarce resources.

Preliminary evidence of a significant burden of pulmonary hypertension and its risk factors in Africa

In recent years, there has been increasing awareness of the clinical significance of PH and cor pulmonale in Africa. This applies equally to the recognition of the importance of PH and RHF as both a primary diagnosis and as a poor prognostic marker for those primarily affected by left-sided heart failure. Data on the precursors and risk factors of those conditions are limited to few reports. The largest study on PH/RHF in Africa has been conduction within *the Heart of Soweto Study in* South Africa; 2505 patients presented with *de novo* heart failure between 2006-2008.[5] Of those 697 (28%) were diagnosed with PH/RHF. PH/RHF was the primary diagnosis in 50% of those patients. The majority presented with dyspnoea and a mean right ventricular systolic pressure (RVSP) above 50 mmHg. Left heart disease (31%), chronic lung disease due to Chronic Obstructive Pulmonary Disease (COPD) and tuberculosis (26%), and pulmonary arterial hypertension (PAH) (20%) due to HIV (HIV-PAH), CHD, or idiopathic PAH were the most common causes of PH. Sani et al. described the prevalence of PH in patients with RHD at a tertiary centre in Nigeria.[10] Of 1312 Echocardiography (ECHO) studies 10% had evidence of RHD; secondary PH was present in 80% of patients with RHD. The same centre reported on 53 patients with PH on ECHO among 80 patients admitted with heart failure with hypertensive heart disease (25%), peripartum cardiomyopathy (25%), dilated cardiomyopathy (17%), and RHD (13%) being the most common causes of PH.[11] A study from Uganda showed a prevalence of PH in patients with newly diagnosed RHD (n=309) of 33%.[12] A smaller survey from Lagos, Nigeria investigated the prevalence of cardiovascular disease in an HIV-positive cohort and found one patient of 100 patients to have HIV-PAH.[13] An ECHO study on 102 HIV-patients presenting with cardiac symptoms in Tanzania revealed PH in 13%.[14] PH with a

RVSP>30 mmHg was present in 4% of long-term survivors in a Zimbabwe cohort of vertically acquired HIV infection.[15] Haemolytic anaemia is a known risk factor for PH; a screening study of patients with sickle-cell disease (SCD) in Nigeria showed a PH prevalence of 25%;[16] a study from Egypt indicates that patients with β-Thalassaemia are at risk of PH.[17] Another study from Egypt found a PH prevalence of 9% in patients seropositive for schistosomal antibodies. Ahmed et al. from Sudan described 14 consecutive cases of PH with previously treated pulmonary TB and conclude that PH can even occur after resolution of TB, most like due to persistent lung destruction.[18] This data suggests that left heart disease, chronic lung disease, RHD, HIV, schistosomiasis and SCD might be the most common underlying diseases to cause PH within the spectrum of aetiologies of PH that we will find within the Pan African Pulmonary hypertension Cohort (PAPUCO)

RATIONAL AND OBJECTIVES

Worldwide, PH has received great increase in awareness at the beginning of the 21st century ~~(Figure 1)~~, but less than one per cent ~~(0.7%)~~ of the publications are from Africa (Figure 1). It is expected that PH is more prevalent in Africa compared to developed countries, but little information is available about African patients with PH. Exposure to risk factors, human genetic variation, different socio-economic backgrounds, lifestyles, co-morbidities, nutrition and disparities in access to health services makes the African population unique, but heterogeneous at the same time. Therefore, most research data and clinical guidelines from high-income countries cannot be translated into the African context. It is within the context described above that the Pan African Pulmonary hypertension Cohort (PAPUCO), a Pan Africa registry-type cohort study, was established (Figure 2).

Scientific and clinical research has been fundamental in improving human health.[19] In fact, research has demonstrated to be an excellent vehicle to implement new technologies and to

facilitate training for its use, and to develop new systems and establish the services around it - jointly leading to technical improvement, sharpening of skills and capacity development[20,21]. Besides the main objectives of the PAPUCO registry to define and understand PH in Africa (Box 1), this multinational and multicentre research project therefore aims to also develop sustainable clinical and research capacity across the African continent as well as raising awareness for PH and its risk factors.

Box 1: PAPUCO objectives
Primary objective • To describe disease presentation, disease severity and aetiologies of PH, comorbidities, the diagnostic and therapeutic management, and natural course of PH in Africa *Secondary objectives* • To describe the overall 6-month survival rate • To describe the 24-month survival rate in patients with HIV-PAH • To compare 6-month survival rates between different groups of PH • To determine the predictors of mortality access the different groups.
Abbreviations: PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; HIV, human immunodeficiency virus

The prevalence of PH in Africa varies geographically, according to underlying risk factors and diseases and the diagnosis of PH is most likely often missed, not only during early stages due to the subtle nature of presentation of PH, but also at more advanced stage of disease due to lack of awareness by primary care doctors and low index of suspicion, limited access to ECHO services and tertiary care. However, it is crucial to diagnose PH in Africa early and reliably to ensure better care for these patients (Box 2).

Box 2: The significance of PH in Africa: Why we need to diagnose?
• The right to know

• Prognostic implications • Access to tertiary care: heart failure management, anticoagulation, home oxygen, COPD management, access to PH-specific drugs (Sildenafil) • Access to cardiothoracic surgery: valve repair/replacement, correction of congenital heart disease, heart transplantation • Access to social and disability grants • To raise awareness of PH and its risk factors
Abbreviations: PH, pulmonary hypertension; COPD, chronic obstructive pulmonary disease

METHODS AND ANALYSIS

Study design and setting

The Pan African Pulmonary hypertension Cohort (PAPUCO) research group was established in 2011 with the aim to implement a registry-type cohort study on pulmonary hypertension in Africa ~~according to STROBE guidelines~~. The registry aims to recruit consecutive patients 1) with newly diagnosed PH based clinical and ECHO criteria, 2) are able or likely to return for 6-month follow-up, 3) are at least 18 years old (except for paediatric centres in Mozambique and Nigeria), and 4) consented in writing to participate in the registry. Centre eligibility include 1) availability of ECHO and training in assessing right heart function, 2) experience in diagnosing PH according to WHO classification, 3) experience in clinical management of patients with right heart failure, and 4) resources to review patients at 6-month follow-up. Participating centres will be invited to join the registry at African cardiac meetings and conferences.

Definition of pulmonary hypertension, diagnostic algorithm and data points

As shown in Box 3, PH is defined as documented elevated RVSP>35 mmHg on trans-thoracic ECHO in the absence of pulmonary stenosis and acute right heart failure; usually accompanied by shortness of breath, fatigue, peripheral oedema, and other cardiovascular symptoms, and possibly electrocardiogram (ECG) and chest x-ray (CXR) changes in keeping

with PH as per European Society of Cardiology and European Respiratory Society (ESC/ERS) guidelines on pulmonary hypertension.[5,22]~~[20]~~ Right heart catheterisation is optional. The updated WHO classification system for PH (Dana Point 2008) will be applied to describe the different aetiologies of PH[22,23]. Once definitive assessment and treatment has been applied, the following specific data will be documented for each individual: a) all major cardiovascular diagnoses according ICD 10 coding, and b) up to five non-cardiovascular diagnoses according ICD 10 coding.[24]~~[21]~~ Figure 3 shows the diagnostic algorithm to diagnose PH in resource-constraint settings without access to right heart catheterisation that has been developed following the ESC/ERS guidelines for the diagnosis of PH ~~of the European Society of Cardiology and European Respiratory Society~~.[22] Key information collected will include information on demographic profile, socio-economic background, medical history, co-morbidities, cardiac risk factors, and environmental exposures. The clinical aspects of the assessment include symptoms scoring, a full clinical examination, physical and clinical status; functional tests include WHO functional class (WHO FC), 6-minute walk test (6MWT) and Karnofsky Performance Score. Technical procedures include ECHO, CXR, and 12-lead ECG. Further investigations are at the discretion of the treating physician and typically include lung function tests, ventilation/perfusion lung scans, and high resolution computed tomography and computed tomography pulmonary angiography, and right heart catheterization, if available (Figure 3). Data on heart failure treatment and co-medication, hospitalization and death, and 6-month outcome will also be collected.

Box 3: Evidence to diagnose PH in resource-constraint settings
• Symptoms: SOB, fatigue, cough, chest pain, palpitations • Clinical exam: raised JVP, peripheral oedema, ascites, loud p2, systolic murmur, central cyanosis • ECG: sinus tachycardia, p-pulmonale, right axis deviation, right bundle branch block, RVH

• CXR: cardiomegaly, pleural effusion, prominent pulmonary arteries • ECHO: dilated right atrium and ventricle, interventricular septal flattening, RVSP>35 mmHg, TAPSE<15 mm
Abbreviations: SOB, shortness of breath; JVP, jugular vein pressure; ECG, electrocardiogram; RVH, right ventricular hypertrophy; CXR, chest X-ray; ECHO, Echocardiography; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion

Echocardiography

Echocardiography in adults

ECHO modalities applied included M-mode, two dimensional (2D) and Doppler studies. ECHO will be done with 3 to 5 MHz sector transducer. Complete 2D ECHO examination will be performed according to the recommendations of the American Society of ECHO (ASE).[25][~~22~~] M-mode ECHO will be derived from 2D images. The M-mode cursor on the 2D scan will move to specific areas of the heart to obtain measurements according to the recommendation of the committee on M-mode standardization of the ASE. Doppler indices of left ventricular (LV) diastolic filling will be obtained. Complete Doppler study will be done according to the recommendations of the ASE. From the M-mode measurements, indices of LV function will be derived. These include shortening fraction, ejection fraction (EF), and LV mass, cardiac output and relative wall thickness. ECHO examinations include (a) valvular assessment, (b) left atrial size, (c) left ventricular size and function, (d) a semi quantitative estimate of the severity of valvular regurgitation, (e) size and function of the right atrium and ventricle and (f) evidence of pulmonary hypertension. Doppler will be used to examine the valves on suspicion of any valvular lesion. ECHO findings associated with PH includes dilated pulmonary artery and dilation and hypertrophy of the right ventricle (RV), diastolic flattening of the interventricular septum and Doppler evidence of PH.[26][~~23~~] Doppler ECHO estimates pulmonary artery systolic pressure (PASP). By measuring the maximum velocity of the tricuspid regurgitant jet (v), the transtricuspid pressure gradient will be calculated using the modified Bernoulli equation ($4v^2$).[27][~~24~~] The PASP is approximated

by adding the transtricuspid gradient to the right atrial pressure (RAP) as applied in the formula [PASP=4v^2+RAP]. The PASP is equivalent to RVSP in the absence of pulmonary outflow obstruction. The RAP is estimated by the respiratory variation size of the vena cava inferior in M-mode.[28] In our study, the systolic regurgitant tricuspid flow will be assessed in the parasternal right ventricular inflow, parasternal short-axis, and apical four-chamber views to determine the highest velocity, which reflects PASP/RVSP.[29]~~[25]~~ PH is defined as *mild* if RVSP was 36-50 mmHg, *moderate* if RVSP was 51-60 mmHg and *severe* if RVSP was >60 mmHg.[30]~~[26]~~ In addition, we further assessed right ventricular function by measuring the systolic displacement of the lateral portion of the tricuspid annular plane excursion (TAPSE) on the M-mode tracing under the 2D-echo guidance.[31]~~[27]~~ Peak mitral early diastolic velocity (E in m/s), the E-wave deceleration time (DCT in ms) and the velocity at atrial contraction (A in m/s) are measured using pulsed-wave Doppler. Left ventricular filling pressure classes were defined in accordance with the ASE 2009 guidelines.[32]~~[28]~~ In patients with heart failure and reduced ejection fraction (HFrEF) raised LV filling pressure is defined as E/A ≥2 if in sinus rhythm or DCT <150 ms if in atrial fibrillation (AF); normal LV filling pressure is defined as E/A <1 in patients in sinus rhythm or DCT ≥200 ms for those in AF; patients between these limits will be classified as undetermined. In heart failure and preserved ejection fraction (HFpEF), LV filling pressure is classified as follows: raised LV filling pressure if left atrium is dilated and normal LV filling pressure if left atrium has normal size.

Echocardiography in infants and children

Translating the definitions of PH in adults to children, especially to infants, is controversial. Within the paediatric cardiology community experts suggest that the ratio of the PASP to the systemic systolic blood pressure >0.4 should be the diagnostic criterion.[33]~~[29]~~ The fact that

the threshold of pulmonary vascular resistance (PVR) increase has not been included in the abovementioned definition is another limitation to its use in children or infants, since paediatric PH is mainly caused by left-to-right shunt congenital heart disease; and if PVR shows no significant increase in such cases, the patient may be considered only as a dynamic PH case led by increased pulmonary blood flow, rather than pulmonary vascular disease. Paediatric guidelines suggest that mPAP >25 mmHg and PVR>3 Wood units remain in the definition of PAH.[34][~~30~~] In our cohort of children with congenital heart malformations we not only used tricuspid and pulmonary regurgitation envelopes, but also the flow across the ventricular septal defect or persistent ducts arteriosus to measure the gradient between the two circulations and therefore estimate the pulmonary pressure. Indirect signs of PH such as dilatation of the RV, RV-hypertrophy and dilatation of the main pulmonary artery were added to Doppler data to confirm the diagnosis.

Accuracy of Echocardiography in the diagnosis of PH

Diagnosing PH is challenging when relying on bedside tests. RHC is the gold standard to diagnose and confirm PH, but performing RHC on all patients with dyspnoea would bear excessive risks and be impractical in any cost-constrained environment. Also RHC is only available at very few centres in Africa. A viable device to diagnose PH in Africa needs to be widely available, accurate, safe, and cost-effective. ECHO has become increasingly available in Africa and reliably allows the measurements to describe functional and morphologic features of PH and to indirectly measure the pressures in the pulmonary artery; hence, to diagnose PH. Nonetheless, the exact measurements of the mean and systolic pulmonary artery are not possible, the PASP remains estimate, and the use of ECHO to diagnose PH questionable.[35,36][~~31,32~~] A number of possible explanations for this “inaccuracy” merit attention: 1) conditions for a reproducible calculation of PASP~~PS~~/RVSP include the presence

of sufficient TR to produce a Doppler envelope and appropriate gain adjustments. An "undergained" spectral signal will tend to result in underestimated PASPPS whereas an "overgained" spectral signal might overestimate the measurements; 2) careful adjustment of the transducer position and the use of colour flow Doppler are critical in order to reduce the Doppler angle and to obtain the maximal regurgitant flow velocity and severe TR will cause a laminar flow which invalidates the Bernoulli equation; 3) volume status and systemic blood pressure are other factors that potentially influence the measurement of PASPPS; and 4) the highest value of RAP in the ASE guidelines is 15 mmHg, but RAP measured by RHC can exceed 15 mmHg. In spite of all these shortcomings, several studies have been published in the literature demonstrating good sensitivity and specificity of ECHO versus RHC.[37-39][33-35] In the REVEAL registry, there was a good correlation in PASP between ECHO and RHC at baseline, even if repeated ECHO measurements alone were not sufficient to monitor changes in PASP or progression of PH.[40][36] In the first systematic review and meta-analysis addressing the diagnostic accuracy of ECHO in PH by Janda and colleagues, the authors concluded that the correlation of PASP by ECHO compared to PASP by RHC was good with a summary correlation coefficient of 0.70 (95% CI 0.67 to 0.73).[41][37] Also, the authors showed that the diagnostic accuracy of ECHO in PH was also acceptable with a summary sensitivity and specificity of 83% (95% CI 73 to 90) and 72% (95% CI 53 to 85), respectively. Additional, Damy and colleagues demonstrated in their recent work that PASPPS when measured in "good ECHO hands" is a strong predictor of mortality.[42][38] Last but not the least, easily obtainable ECHO parameters like E/A ratio, DCT, LA size can reliably distinguish between PH due to lung disease and PH due to left heart disease, allowing for rapid triage of patients with need for RHC. In summary, ECHO is far beyond a good modality to confirm both the presence and aetiology of PH in the majority of suspected cases when performed and interpreted by the requisite expertise under incorporation of all

information obtained during a detailed ECHO assessment. ECHO will always provide incremental information in PH that cannot be obtained using RHC, whether in developed or developing countries.

Data cleaning process and statistical analysis

All study data will be collected on electronic case report forms and stored on a dedicated secure central database. Cases will be reviewed by at least two investigators (FT, AD, KS, AOM) for completeness and data validated. Query reports will be sent to the sites and resolved by the site investigators. If consensus on the WHO classification of PH cannot be reached, a third investigator's opinion will be requested. Data will then be verified and transferred to SPSS Statistics 17.0 for all analyses by an independent team at Preventative Health, Baker IDI Heart and Diabetes Institute, Melbourne, Australia. Normally distributed continuous data will be presented as mean ± standard deviation and non-Gaussian distributed variables as median plus interquartile range. Categorical data will be presented as percentages with 95% confidence intervals (CI) where appropriate. For patient group comparisons, we will use Chi Square (χ^2) analysis with calculation of odds ratios (OR) and 95% CI (where appropriate) for discrete variables and Students t-test and analysis of variance for normally distributed continuous variables. Multiple logistic regression analyses (entry model) will be performed on age, sex and baseline risk factors to derive adjusted ORs for the risk of presenting with PH/RHF overall, chronic lung disease and PH WHO Group 1. Significance will be accepted at the two-sided level of 0.05. ECG analysis will be will be subject to blinded coding according to published Minnesota criteria to determine any pathological abnormalities.[43]~~[39]~~ We aim to adhere to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for this type of study wherever possible.[44]

PAPUCO sub-studies

Several sub-studies have been established within the PAPUCO registry. The ECHO sub-study aims to describe in detail the ECHO characteristics of right ventricular function in PH. The HIV-PAH sub-study aims to describe the phenotype of HIV-PAH in Africa. The congenital heart disease and rheumatic heart disease sub-studies aim to describe the contribution of congenital heard disease and rheumatic heart disease to PH in Africa. In addition, serum will be collected at selected centres for studies on biomarker profile. The HIV.INFLAME sub-study aims to examine the role of inflammatory markers and oxidative stress on the development of HIV-PAH. We hypothesizing that HIV-positive patients with PH have a pro-inflammatory state and raised markers of oxidative stress compared to healthy HIV-positive controls and that increased markers of inflammation and oxidative stress and decreased antioxidant capacity are predictors of outcome and indicators of disease severity.

Ethics and dissemination

All PAPUCO centres require ethical approval from their local ethics committee review board. Written informed consent must be obtain from every patient participating in the registry. Study results will be disseminated in peer-reviewed journals. The first publication will include baseline and 6-month follow-up data from all centres. Sub-study publications on the HIV-cohort with 24-month follow-up and the cohort of patients with PH due to left heart disease will be published after recruitment and follow-up has been completed. Laboratory-based research will be published after work is completed.

The online data collection platform

A tailor-made databases has developed by *integerafrica research and development* to fulfil the study requirements. Open-source technology was used to develop the web-based system

that allows investigators to collect, store, analyse, report on and exports clinical research data. The interface is simple and user friendly and leads the user through the data entry process. It anonymises personal patient data: data is stored as electronic case report forms on a secure, encrypted and backed-up server. It provides hierarchic permissions and validation at the point of data entry. Multimedia data formats, i.e. scans of ECGs, CXRs, and ECHO images can be uploaded on the platform, allowing storage of complete clinical records and data together. Tools for education, training, and communication are installed within the web-portal. Frequently Asked Questions serve as a guide on how to the use of the platform. After secure login, documents such as paper case report forms, informed consent forms, study information sheets and patient education sheets on PH are available for download. All data can be exported in various formats for further analysis. The platform has been developed to cater for mobile Internet connectivity available in most parts of Africa and a unique research platform far beyond a simple web-based database.

Recruitment process

Twelve centres have received ethics approval and are currently actively recruiting; additional six countries are showing interest in joining the registry (Figure 2). All centres are government-run public health care institutions with different medical infrastructure profiles and all but one are cardiac centres within tertiary care hospitals (Table 1); one centre is an infectious diseases referral clinic in South Africa. At total of 254 patients have been recruited until December 2013 (Figure 5).

Table 1: Medical infrastructure at PAPUCO centres - diagnostic equipment and medical services

Centre	ECG	CXR	ECHO	RHC	CS	HRCT	CTPA	LFT	V/Q	Lab
CM01	X[1]	X[1]	X[1]			X[1]	X[1]	X[1]		X[1]

CM02	X[1]	X[1]	X[1]	X[1]	X[1]					X[1]
CM03	X[1]	X[1]	X[1]							X[1]
MZ01	X	X	X							X
MZ02	X	X	X			X		X		X
NG01	X[1]	X[1]	X[1]			X[1]		X[1]		X[1]
NG02	X[1]	X[1]	X[1]			X[1]	X[1]	X[1]		X[1]
NG03	X[1]	X[1]	X[1]			X[1]	X[1]	X[1]		X[1]
NG04	X[1]	X[1]	X[1]							X[1]
NG05	X[1]	X[1]	X[1]			X[1]	X[1]	X[1]		X[1]
SA01	X	X	X	X	X	X	X	X	X	X
SA02	X	X	X			X	X			X

Abbreviations: CM01, Douala General Hospital, Douala, Cameroon; CM02, Cardiac Centre, Shisong Hospital, Kumbo, Cameroon; CM03, Douala Cardiovascular Centre, Douala, Cameroon; MZ01, Instituto Nacional de Saúde, Maputo, Mozambique; MZ02, Division of Cardiology, Maputo Central Hospital, Maputo, Mozambique; NG01, Department of Medicine, Federal Medical Centre, Abeokuta, Nigeria; NG02, Department of Medicine, Bayero University and Aminu Kano Teaching Hospital, Kano, Nigeria; NG03, Department of Medicine, College of Medicine, Lagos, Nigeria; NG04, Department of Medicine, University of Uyo Teaching Hospital, Uyo, Nigeria; NG05, Federal Medical Centre, Umuahia, Nigeria; SA01, Division of Cardiology, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa; SA02, Infectious Diseases Referral Clinic, GF Jooste Hospital, Mannenberg, South Africa and Rapid Assessment Unit, Khayelitsha District Hospital, Khayelitsha, South Africa. ECG, electrocardiogram; CXR, chest X-ray; ECHO, Echocardiography; RHC, right heart catheterisation; CS, cardiac surgery; HRCT, high resolution computed tomography; CTPA, computed tomography pulmonary angiography; LFT, lung function tests; V/Q, ventilation/perfusion lung scan; Lab, laboratory facility for haematology, chemistry, and microbiology; X, equipment/service available at the centre and free-of-charge for the patients; X[1], patients have to cover the costs for the service (out of pocket payments).

LIMITATIONS

The PAPUCO registry is an example of a functioning registry in low-resource settings. Limited resources should therefore not be seen as a limitation, but rather as a development opportunity. PAPUCO centres have different levels of medical infrastructure and not all patients will undergo the same rigorous work-up in all centres - especially when compared to developed countries. Therefore, the clinical skills of the treating physician are often more important (and valuable!) than an additional diagnostic test in order to pin down the aetiology of PH in a patient. Moreover, patients often have to pay out of their pocket for diagnostic

tests and therefore accessibility to tests is limited due to the financial means of the patient. Although we aim for consecutive patient enrolment at each centre, we understand that this is often not feasible due to high patient volume and workload of doctors.

SUMMARY

PAPUCO is a contemporary registry on PH in Africa using high international standards to diagnose PH. It will provide new insight on PH in Africa and ultimately improve diagnosis and care of patients. PAPUCO is already a showcase for registry activities in Africa and a vehicle to capacity generation and sustainable development in the health care sector. It interconnects health centres far beyond pulmonary hypertension.

LEGENDS OF FIGURES

Figure 1: Number of publications on pulmonary hypertension per annum since 1970 (grey bars) with moving average (blue line). Less than one per cent (0.7%) of the publications where from Africa (not displayed). Title search terms in PubMed were "pulmonary hypertension", "pulmonary arterial hypertension" or "pulmonary venous hypertension" and Africa and African country names; results are displayed annually between 1970 and 2013.

Figure 2: The PAPUCO map displays countries currently participating in the PAPUCO registry (number of centres per country in brackets).

Figure 3: Diagnostic algorithm to diagnose pulmonary hypertension in resource-constraint settings. Abbreviations: PH, pulmonary hypertension; ECG, electrocardiogram; TB, tuberculosis; PCP, pneumocystis pneumonia; COPD, chronic obstructive pulmonary disease; LHD, left heart disease; ECHO, Echocardiography; HIV, human immunodeficiency virus;

US, ultrasound; LFT, liver function tests; HRCT, HRCT, high resolution computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiography; V/Q, ventilation/perfusion lung scan

Figure 4: Diagnosing pulmonary hypertension using transthoracic 2D-Doppler Echocardiography. A: 4-chamber view showing grossly enlarged RV and RA; with right ventricularisation of the LV, and bulging of the RA into the LA; B: Color- and continuous-wave Doppler across the TV in the 4-chamber view showing severe TR, despite the deceivingly less impressive color-flow jet seen across the valve; C: M-Mode measurement of TAPSE depicting right ventricular systolic dysfunction; D: Long-axis view of right ventricular apical thrombus. Abbreviations: RA, right atrium; RV: right ventricle; LA: left atrium; TV: tricuspid valve; TR: tricuspid regurgitation.

Figure 5: PAPUCO registry - monthly enrolment until December 2013. Number of patients recruited per month since the launch of the registry in May 2011.

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CONTRIBUTORS

KS, AOM, FT were responsible for the initial idea, literature review, and study design and planning. All authors have contributed to the setup of the PAPUCO registry and have contributed to various aspects of the study design with input relating to their specific expertise in the field. FT, AD, AOM, LB, MUS, KMK, OSO, AM, PU, ASI, AD, KS have developed the study protocol, FT and KS wrote the study protocol, FT developed the database, FT, AD, AOM, KS cleaned the database, LB trained the doctors in Echocardiography of the heart and developed the Echo protocol, AD trained doctors in Cameroon, OSO trained doctors in Nigeria, SS developed the statistical analysis plan. FT, AD, AOM, MUS, KMK, OSO, IM, AM, PU, KT, RB, AD, KS were substantially involved in data acquisition. All authors read and approved the final manuscript.

COMPETING INTEREST

We declare no competing interest.

ETHICS APPROVAL

All centres received ethics approval fro their local ethic committees.

FUNDING

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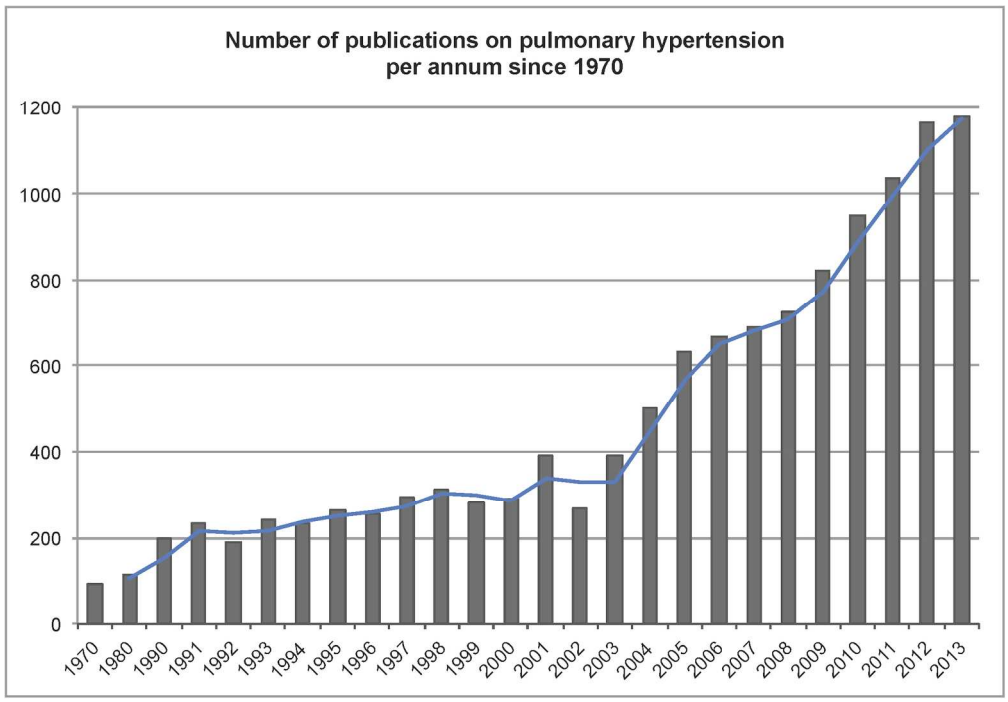
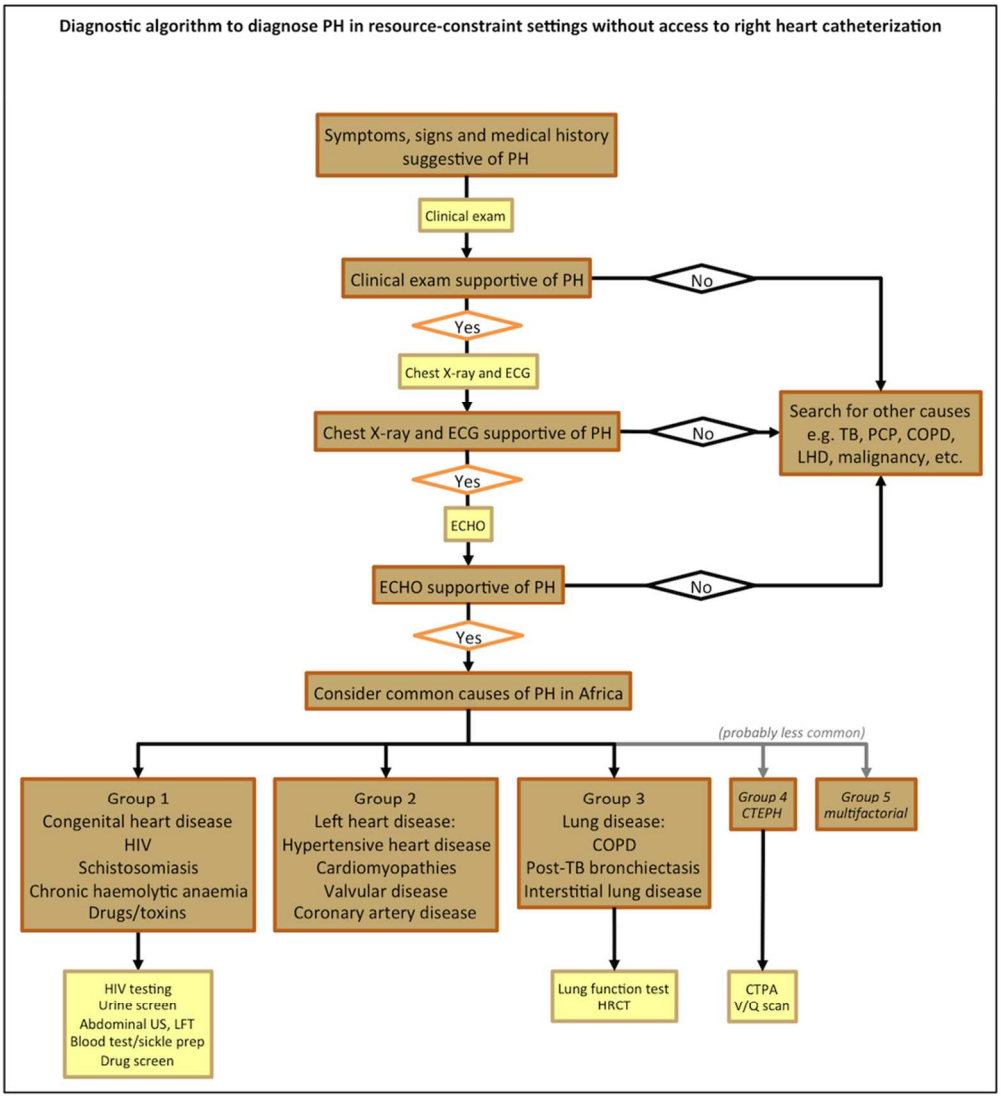
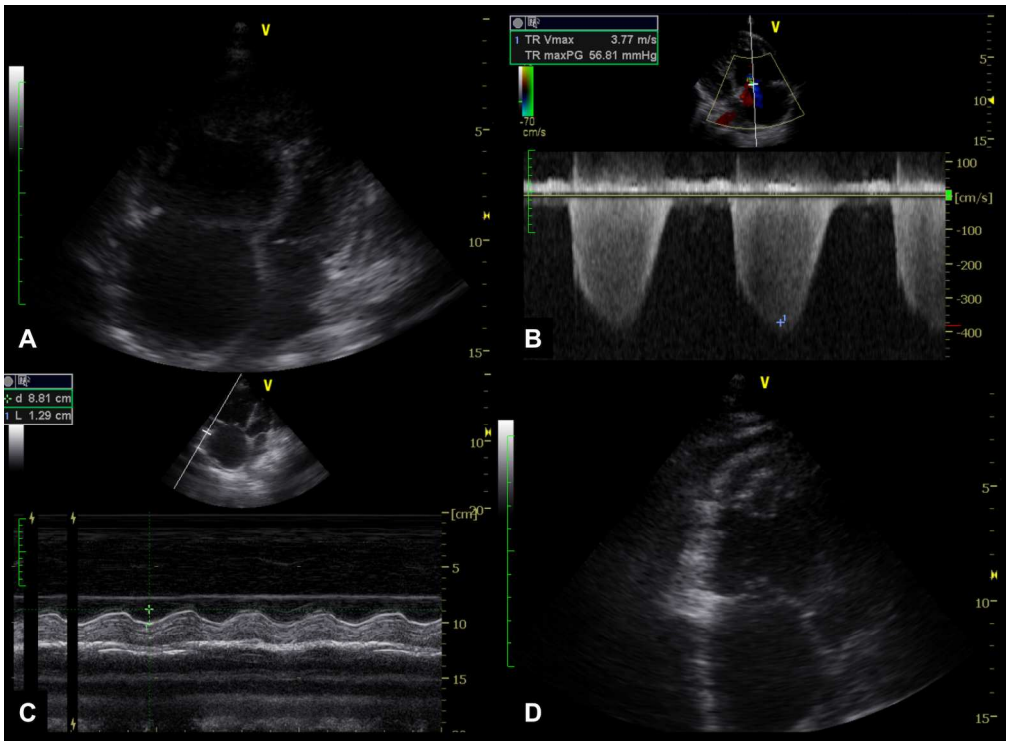


Number of publications on pulmonary hypertension per annum since 1970 (grey bars) with moving average (blue line). Less than one per cent (0.7%) of the publications were from Africa (not displayed). Title search terms in PubMed were "pulmonary hypertension", "pulmonary arterial hypertension" or "pulmonary venous hypertension" and Africa and African country names; results are displayed annually between 1970 and 2013.
180x124mm (300 x 300 DPI)

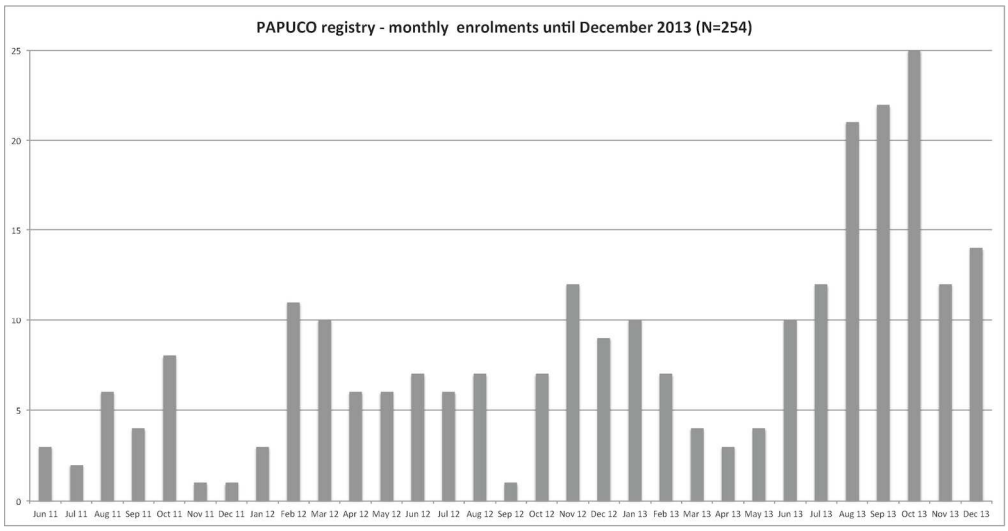
The PAPUCO map displays countries currently participating in the PAPUCO registry (number of centres per country in brackets).
90x99mm (300 x 300 DPI)



Diagnostic algorithm to diagnose pulmonary hypertension in resource-constraint settings. Abbreviations: PH, pulmonary hypertension; ECG, electrocardiogram; TB, tuberculosis; PCP, pneumocystis pneumonia; COPD, chronic obstructive pulmonary disease; LHD, left heart disease; ECHO, Echocardiography; HIV, human immunodeficiency virus; US, ultrasound; LFT, liver function tests; HRCT, HRCT, high resolution computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiography; V/Q, ventilation/perfusion lung scan
90x98mm (300 x 300 DPI)



Diagnosing pulmonary hypertension using transthoracic 2D-Doppler Echocardiography. A: 4-chamber view showing grossly enlarged RV and RA; with right ventricularisation of the LV, and bulging of the RA into the LA; B: Color- and continuous-wave Doppler across the TV in the 4-chamber view showing severe TR, despite the deceivingly less impressive color-flow jet seen across the valve; C: M-Mode measurement of TAPSE depicting right ventricular systolic dysfunction; D: Long-axis view of right ventricular apical thrombus. Abbreviations: RA, right atrium; RV: right ventricle; LA: left atrium; TV: tricuspid valve; TR: tricuspid regurgitation.
180x132mm (300 x 300 DPI)



PAPUCO registry - monthly enrolment until December 2013. Number of patients recruited per month since the launch of the registry in May 2011.
180x93mm (300 x 300 DPI)