Pulmonary hypertension in developing countries: Limiting factors in time to diagnosis, specialised medications and contextualised recommendations

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Pulmonary hypertension (PH) is a fatal disease with no cure. Combination therapy that includes several specialised medications can improve survival and quality of life. However, there are many challenges, and these include a lack of effective screening tools, misdiagnosis and late diagnosis, a lack of awareness among clinicians and patients, expensive PH medication and the unavailability of these medications in many developing countries. Based on the literature, this paper provides helpful approaches and 'out of the box' ideas to try to surmount these challenges. We make the following recommendations: develop better (contextually fitting) screening tools, investigate novel therapeutics or novel drug targets, implement incentivised and accredited training for clinicians and implement awareness campaigns (by using traditional and social media and promoting awareness at healthcare or educational institutions). Other recommendations include greater advocacy that engages public and private funders, combine scarce skills and networks of social sciences and implementation sciences and invite non-profit organisations to the fight against PH in conjunction with researchers. Furthermore, the implementation of breathlessness clinics in rural areas can be helpful, as well as the investigation of the biomarker potential of genetic mutations or unique gene signatures of patients during research. We hope that healthcare professionals, researchers, scientists and regulatory authorities or research bodies, can use our recommendations in a practical setting, especially in developing countries where resources are limited and the healthcare burden is high.
Keywords. pulmonary hypertension; time to diagnosis; treatment options; specialised medications; developing countries; South Africa

Afr J Thoracic Crit Care Med 2022;28(1):28-32. https://doi.org/10.7196/AJTCCM.2022.v28i1.176

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure ≥25 mmHg, when measured with right-heart catheterisation.[1] Pathologic triggers (toxins, sheer stress, oxidative stress) cause cells in the pulmonary arterioles to undergo excessive proliferation, leading to the narrowing and obliteration of the vessel lumen, thereby increasing pulmonary artery pressure.[2] The global prevalence of PH is not known, but recent work has demonstrated that PH can no longer be considered a rare disease.[3] Global guidelines for PH promote right heart catheterisation as the gold standard for diagnosis,[4] while several studies, especially from developing countries, have shown that transthoracic echocardiography is also effective at diagnosing PH.[5,6] PH is managed with specialised therapies including endothelial receptor antagonists, nitric oxide stimulants, phosphodiesterase type-5 inhibitors and prostacyclin analogues.[7] In many countries, several of these drugs are combined for better clinical outcomes[8] and strong clinical evidence shows that combination therapy improves patients' quality of life and survival.[9,10]

However, there are several challenges pertaining to PH diagnosis and treatment in developing countries.[1] These include a lack of screening tools, delayed or misdiagnosis, lack of awareness among clinicians and patients, exorbitant costs of medication and the lack of specialised medication. These challenges complicate the fight against PH by preventing a qualitative and quantitative census of PH prevalence (per country)[11,12] and impedes the clinical management of the disease. Therefore, there remains a need for comprehensive clinical approaches and perhaps one needs to think 'out of the box' to overcome these challenges. To address these needs, this paper perused the literature using the search engines PubMed, LISTA (EBSCO), Web of Science Core and Google Scholar, for papers using the following terms: 'pulmonary hypertension challenges with diagnosis', 'pulmonary hypertension challenges with treatment', 'advances in pulmonary hypertension diagnostic tools', 'advances in pulmonary hypertension screening tools', 'advances in pulmonary hypertension biomarkers', and 'pulmonary hypertension patient experiences or responses'. Using this approach, we prioritised papers that were relevant to developing countries and extracted any recommendations or proposed strategies that may aid in overcoming these challenges. Where necessary, we provide recommendations based on clinical/scientific experience or evidence from studies conducted in fields adjacent to medical/biomedical research. The latter is important, as studies from other streams of medical research may often may have ideas or inventions[13-15] that are translatable to PH.

Challenges

Symptom-related challenges: Identifying PH

Symptoms of PH include shortness of breath and the inability to perform actions, such as picking up items from the floor or walking upstairs.[16] Other symptoms are chest pain and a persistent cough.[16] Owing to the unspecific nature of these symptoms, they are often confused with those of other diseases. This strengthens the misconception that

a patient has a persistent cold or flu, only for doctors to realise too late that the patient had PH.[17] Thus, PH is often misdiagnosed,[18] leading to a delayed diagnosis.[17] The latter has long been recognised as a significant challenge in developing countries, where resources are limited.[1] A study conducted in the UK[19] found that almost half of 'patients did not receive a diagnosis until a year after first experiencing symptoms'. Armstrong *et al.*[19] demonstrated that in the first 12 months after patients first noticed symptoms, a definite PH diagnosis was received by 11% of patients who saw only one health professional, while 40% of patients saw four or more health professionals and 9% saw seven or more health professionals before receiving a diagnosis. Delayed diagnosis could be further complicated by the high burden on the healthcare system in developing countries, such as South Africa (SA).[20] Similar studies have been conducted in other developing countries on the African continent.[5,21,22] One could easily say that health education[23] among patients could mitigate a lack of awareness of PH. However, the study by Armstrong *et al.*[19] found that there was a lack of PH awareness among health professionals too. Moreover, patients indicated that healthcare professionals were reluctant to listen to them when seeking a diagnosis and some were 'dismissive' of their concerns.[19] Patients may be seen by a primary healthcare physician for months or years and still not receive the appropriate diagnosis.[1] This challenge is complex and requires intervention.[8]

Diagnosis-related challenges

It is now well-known that in developing countries, access to right heart catheterisation is not always feasible when trying to establish a diagnosis for PH.[22,24,25] To remedy this, transthoracic echocardiography has been suggested as a surrogate diagnostic tool in resource-limited settings.[5,6] It has become increasingly available in Africa and reliably describes the functional and morphological features of PH and indirectly measures the pressures in the pulmonary artery.[6] However, performing transthoracic echocardiography on all patients with dyspnoea could be impractical in resource-limited, high-burden settings.[6] Consequently, there is a need for contextually-fitting diagnostic tools as some countries may have to invent diagnostic tools unique to their conditions. An alternative to using right-heart catheterisation and transthoracic echocardiography for PH diagnosis, is biomarker assaying.[26] Several biomarkers have been identified over the years, such as circulatory or lung oxidative stress,[27] nitric oxide signalling,[27] cardiac troponin-I,[28] soluble ST-2,[29] and galectin-3.[30] However, although many of these biomarkers are good indicators of right ventricular functional or cardiac damage, they do not show potential to predict PH early enough.[26] Therefore, more research is needed to discover biomarkers that are better.

Challenges regarding treatment (wrong regimens, lack of advanced therapies, ethics)

PH is different to systemic hypertension.[17] The latter is mostly related to a lack of blood pressure regulation pathways and heightened vasoconstriction, while PH develops owing to a complex interplay between several molecular pathways.[16] These pathways lead to pulmonary vascular changes that are exclusively characteristic to PH[2] and result in increased proliferation of pulmonary artery smooth muscle cells and endothelial cells and resistance to apoptosis.[2] This has given PH what is known as the 'cancer-like' feature.[31] To a certain extent, these complex pathway interactions[32] make PH a much more complex disease. PH cannot be attenuated with only vasodilators, and therefore the most efficacious treatment regimens for PH comprise several specialised medications that target multiple molecular pathways. However, these specialised PH medications are lacking in many developing countries.[8] This can be ascribed to funding availability and legal agreements between countries and pharmaceutical companies. Some PH patients report that during the initial stages of their disease, they had visited their general practitioner multiple times and only received an asthma inhaler for shortness of breath.[19] This is concerning, as it means that many patients may have PH but are being treated for other diseases or symptoms and not the underlining disease. This may very well be due to doctors who find aesthetic value in giving a patient medication even if it does not provide symptomatic relief. The question remains, is it ethical to deprive patients in this way? How can this be addressed?

Patients have this fatal disease with no cure and reduced quality of life, yet medications that could improve this are either not available in certain developing countries, too expensive and in many cases not covered by medical aids, or combination therapy is not possible owing to the lack of several advanced medications (e.g. Sildenafil can be available but not Bosentan and Iloprost).[33] Could it be considered an ethical violation if patients are diagnosed late, which may lead to their death? Who can be held accountable in this case? It may not be an individual doctor who is held accountable, but if the system allows this injustice to occur, there is perhaps a collective liability. The seven principles of public healthcare ethics[34] include non-maleficence, beneficence, the maximisation of health, justice, efficiency, proportionality and respect for autonomy.[34] First, non-maleficence ensures that no one will be hurt or put at risk of being harmed.[34] If health professionals overlook new research regarding the identification of PH symptoms early on and better treatment approaches, these doctors may not test patients early enough and could be causing long-term harm. Moreover, delayed or misdiagnosis is disadvantageous to the patient, medically, financially, emotionally and mentally.[35] Delayed diagnosis can also cause excessive wastage of important health resources.[36,37] These are important ethical issues[38] that require urgent attention.

'Out of the box' recommendations

Medicine is a constantly evolving profession that requires continuous learning and education.[39] In SA's ethical guidelines for good clinical practice, healthcare practitioners have a duty to 'to maintain and improve the standard of their performance by keeping their professional knowledge and skills up to date throughout their working life. They should regularly take part in educational activities that would enhance their provision of health services'.[40] This emphasises the importance of healthcare providers' involvement in regular educational activities. If PH awareness is not incorporated robustly in medical school curricula, doctors could be required to cover it during continued professional development (CPD). The lack of updated PH knowledge and awareness among clinicians, could be overcome by providing accredited training opportunities to practicing clinicians. This can be achieved by means of workshops, online courses, webinars or diploma specialisation courses and by providing incentives such as CPD points or accredited certificates. Also, awareness campaigns can

be implemented in two ways. First, by utilising the power of traditional or social media,[41] newspapers, magazines, television, YouTube, Facebook, Twitter and Instagram. Second, by raising awareness at educational[42] and health institutions, high schools, hospitals, libraries and clinics (Fig. 1).[43]

It is the norm that researchers approach the usual funders to support their research this is usually done via the respective institutions or universities. However, nothing stops researchers from approaching public and private funders[44] to pledge resources that can aid the improvement of PH diagnosis and clinical management. It is plausible that many private funders are not aware of PH and raising awareness among them could be of great value. It is perhaps time to think out of the box. The more funding provided for research that addresses PH challenges, the better. Using the skills, social networks and experience of non-profit organisations[45] can be a useful way to get stakeholders in civil society involved in the fight against PH. It is obvious that non-profit organisations work routinely in a certain sphere of society and have built strong networks with companies or organisations to whom clinicians or researchers may not be exposed. Moreover, collaboration with various stakeholders is important to ensure better access to expensive medication and investigations and more equitable distribution of resources. Regardless, involving nonprofit organisations in the fight against PH, could be extremely helpful.

Furthermore, it could be helpful to move away from the traditional clinical studies that only involve medical doctors. PH clinical studies should combine the efforts and skills of clinicians, basic scientists and investigators from the social sciences[46] and implementation sciences.[47] This type of collaborative approach could provide a better understanding of how PH progresses, who is at risk and in what ways we can address the identified challenges (Fig. 1). The skills of social scientists may help to understand what patients experience when doctors try to establish a diagnosis and this can be done via in-person interviews and thematic analysis of data. Implementation scientists could provide insights into the best approaches to implement new diagnostic inventions, awareness campaigns etc.

A good approach to diagnosing patients earlier is better screening tools.[48] An ideal screening tool or methodology would be easily available, non-invasive, inexpensive and producing reproducible results with high specificity and sensitivity.[48] The implementation of breathlessness clinics can make patients more aware of the clinical significance of symptoms like shortness of breath, and bring them into a space where an earlier diagnosis can be achieved.[49] This approach can be adjusted in a way that is contextually fitting as not all screening approaches would necessarily work across countries. In this case, countries could develop their own context-tailored approaches when, for example, using echocardiography for screening purposes (Fig. 1). Inevitably, there are cases where patients experience PH symptoms, but may be lost in the system for many years[19] and unfortunately some may even die before a diagnosis is made. This is often observed when patients return to their homes with persistent symptoms and prescribed medication that do not affect PH progression.[19] This challenge in diagnosis could be overcome by following-up these patients during home visits[50] to closely monitor and re-engage at-risk individuals.[51]

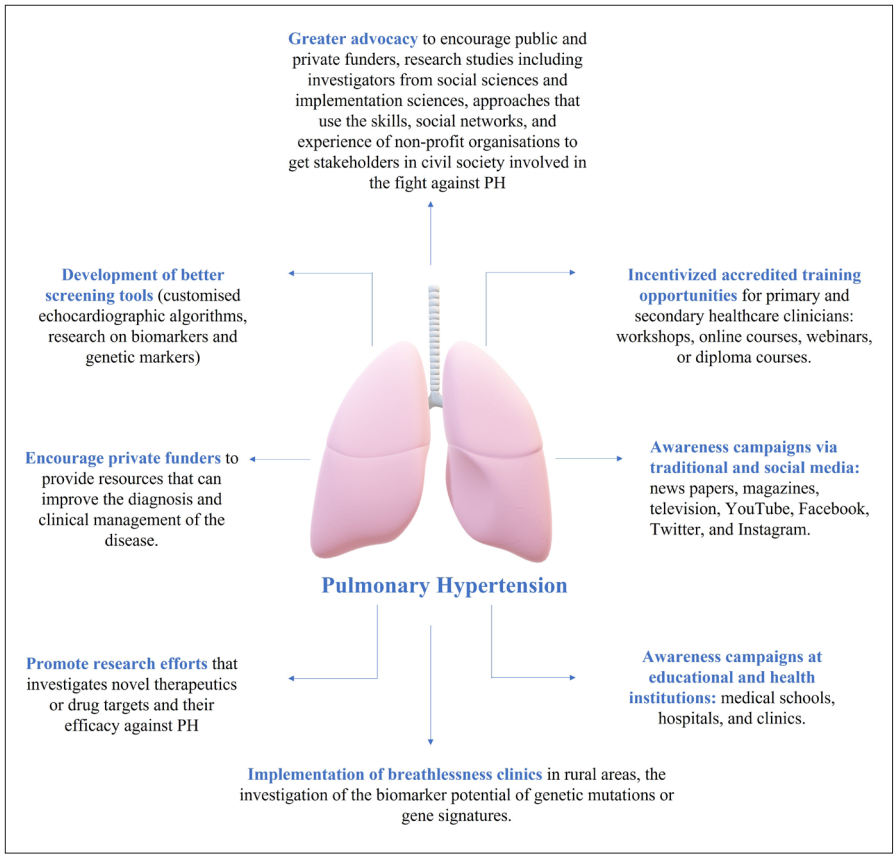

Fig. 1. An overview of several recommendations to aid in addressing the challenges related to PH (diagnosis, clinical management, and lack of awareness).

In addition, the challenge regarding biomarkers as a screening tool requires more research.[26] Nothing stops us from investigating the biomarker potential of genetic mutations[52] or unique gene signatures[53] or investing more funding into research that aims to discover new proteins[54,55] or novel genes involved in PH pathogenesis.[56,57] We should promote research efforts that investigate novel therapeutics or novel drug targets and their efficacy against PH. In cases where these studies have been conducted, rigorous follow-through from animal studies to phase one clinical trials should be assured, instead of a pile-up of papers from experimental studies that lie abandoned and unused. Novel experimental therapies that may counteract PH include melatonin[2,58,59] and other natural herbs and medicinal plants,[59] as well as novel (potential) drug targets such as metallothioneins (mitochondrial regulators).[60,61] Furthermore, during the COVID-19 pandemic, there was an outcry by clinicians around the world that regulating authorities should allow the repurposing of drugs to treat COVID-19.[62-64] This same type of approach could be useful in treating PH.

Recommendations

Several challenges impede the effective assessment of PH prevalence and its impactful clinical management. These include a lack of effective screening tools, misdiagnosis and delayed diagnosis, a lack of awareness among clinicians and patients, costs of PH medication and the unavailability of these medications in developing countries. This paper suggests the following recommendations to overcome these challenges: the development of better screening tools, engaging private funders, the investigation of novel therapeutics or drug targets, the implementation of incentivised accredited training opportunities for clinicians and the use of awareness campaigns (via media and healthcare or educational institutions). Other recommendations include greater advocacy to encourage public and private funders, research studies with combined efforts between clinicians, basic scientists, social scientists, and implementation scientists. Furthermore, there is a need to capitalise on the skills, social networks and experience of non-profit organisations to involve stakeholders in the fight against PH, and lastly, the implementation of breathlessness clinics in rural areas, and the investigation into the biomarker potential of genetic mutations or unique gene signatures. Although the greatest challenge of these recommendations will be implementation, it is nonetheless surmountable.

Declaration. None.

Acknowledgements. I would like to thank the Somersault18:24 team for providing the animations (https://www.somersault1824.com/resources/).

Author contributions. GM conceptualised the paper and wrote and revised the manuscript.

Funding. I would like to thank the following funders: the Faculty of Medicine and Health Sciences of Stellenbosch University, the South African Medical Research Council (SAMRC), the National Research Foundation of South Africa (NRF), and the Harry Crossley Foundation.

Conflicts of interest. None.

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Accepted 22 November 2021.