Review Article

Pre-eclampsia: does cardiac function differ in HIV-positive and -negative women?

Raeesa Bhorat, Ismail Bhorat, Olive P Khaliq, Jagidesa Moodley

Abstract

This review aimed to establish the impact of pre-eclampsia and HIV infection on cardiac function. Cardiovascular diseases have been reported to affect pregnancies complicated by both HIV and pre-eclampsia. Pre-eclampsia has been found to be associated with both systolic and diastolic dysfunction. Currently it has been found that there may be a dual, bidirectional pathophysiology, where placenta-mediated factors can influence cardiac function, or pre-existing cardiovascular disease can predispose to pre-eclampsia. Cardiovascular disease, HIV and pre-eclampsia are major health challenges individually and are interrelated with regard to pathophysiology. It has been found that both pre-eclampsia and HIV contribute to cardiac dysfunction as does the impact of antiretroviral therapy. Further research is needed to investigate the link between these diseases for the development of novel therapeutic interventions.

Keywords: pre-eclampsia, HIV, ART, cardiovascular disease

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Maternal health is often a representation of the adequacy and efficacy of a healthcare system. The success of modern medicine has been measured by its positive impact on maternal mortality in recent times. However, even though progress is evident, statistics reverberate that shortcomings persist despite global initiatives to improve maternal healthcare.

Human immunodeficiency virus (HIV), cardiovascular disease and hypertensive disorders in pregnancy (HDP) are some of the leading causes of maternal mortality, particularly in poorly resourced settings. There has been a decline in maternal deaths from HIV infection over the period 2008–2016, however, there has been no significant change in mortality rate related to HDP.[1,2]

Both HIV and cardiovascular diseases contribute largely to the disease burden in South Africa and are interwoven in terms of pathogenesis, leading to augmentation and perpetuation of disease. This review serves to illustrate the link between the disease entities, provide pathophysiological insights to better understand disease manifestations, and allow for early recognition, ultimately leading to the development of therapeutic interventions to alleviate suffering and contribute positively to decreasing maternal mortality in South Africa (SA).

Epidemiology of HDP

HDP are the commonest direct causes of maternal mortality and account for 18% of all maternal deaths in SA.[3] HDP have a prevalence of approximately 5% in high-income countries, however, the prevalence is higher in low-income countries.[1,4] The incidence of pre-eclampsia (PE), a pregnancy-specific category of HDP, was noted to be 12% in primigravidae in a large regional hospital in SA.[3] The World Health Organisation (WHO) reported that PE accounts for 1.8–16.7% of maternal deaths in countries such as SA, Egypt, Tanzania and Ethiopia.[1]

Prevalence of HIV in SA

HIV infection is a global health challenge. Sub-Saharan Africa accounts for 56% of the HIV-infected population and in 2017, women accounted for 59% of new adult infections.[1,5] In SA, 13% of the population is HIV positive and 20% involve women of childbearing age (15–49 years).[1]

Epidemiology of cardiovascular disease in SA

The global mortality and morbidity rate related to cardiac diseases in pregnancy has been reported to vary between 0.1 and 4%.[6] In the UK, the confidential enquiries into maternal deaths found that the overall rate of mortality from cardiac diseases had increased from 7.3 per million (1982–1984) to 22.7 per million births (2003–2005).[6]

Department of Cardiology, School of Clinical Medicine, University of KwaZulu-Natal, Durban, South Africa
Raeesa Bhorat, MB ChB, FCP SA, MMED, raeesabhorat.1@gmail.com

Foetal Medicine, Department of Obstetrics and Gynecology, University of KwaZulu-Natal, Durban, South Africa
Ismail Bhorat, MB ChB, FCOG

Department of Paediatrics and Child Health, University of the Free State, Bloemfontein, South Africa
Olive P Khaliq, PhD

Department of Obstetrics and Gynaecology and Women's Health and HIV Research Group, University of KwaZulu-Natal, Durban, South Africa
Jagidesa Moodley, MB ChB, MD

Heart failure is pervasive globally and is associated with a high mortality rate; it is estimated that 37.7 million globally are afflicted by the condition.[7] There is a paucity of published data describing the epidemiology of heart failure in SA.[7] Almost all studies are hospital based. The largest recent study of confirmed cases of heart failure in SA, the Heart of Soweto study (n = 4 162), included 1 593 newly diagnosed and 2 569 previously diagnosed cases who attended the cardiology unit at a tertiary hospital in Soweto, SA. It was noted that 59% of those affected were women, with females being slightly younger than males (mean age 53 vs 55 years, respectively); 25% of those studied were less than 40 years old and 85% were of African ancestry.[7]

Heart failure

Heart failure is defined as three subtypes: heart failure with preserved ejection fraction (HFpEF: left ventricular ejection fraction of ≥ 50%), heart failure with reduced ejection (HFrEF: left ventricular ejection fraction ≤ 40%) and heart failure with mid-range ejection fraction (HFmrEF: left ventricular ejection fraction 40–49%).[7]

Pathophysiology of heart failure

Heart failure is the clinical end-point of cardiac maladaptation; the structural and functional abnormalities leading either to HFrEF: decreased left ventricular (LV) contractility and LV dilation; or HFpEF: impaired myocardial relaxation and decreased LV compliance. However, even though ejection function is normal in HFpEF, contractility is abnormal: longitudinal fibre contractility is impaired as well as abnormal contractile reserve.[8]

Neuro-hormonal factors and altered fluid balance results in LV modelling, macroscopically seen as a change in LV geometry, volume and mass. In HFrEF, activation of the renin–angiotensin–aldosterone system (RAAS), increased sympathetic innervation and systemic vasoconstriction, lead to cellular and molecular aberrations within the myocardium. Microscopically, there is slippage and increased apoptosis of cardiac myocytes, disruption of ion channels, downregulation of receptors, altered cardiac metabolism and calcium homeostasis, electromechanical uncoupling, ischaemia, increased extracellular matrix deposition and myocardial fibrosis.

The aetiology of HFpEF is heterogeneous and characterised by a pro-inflammatory phenotype, endothelial dysfunction, microvascular ischaemia and interstitial fibrosis. Studies have illustrated the role of macrophages in promotion and resolution of inflammation within the myocardium.[7,8]

Echocardiographic parameters and biomarkers

Both PE and HIV affect the cardiovascular system and manifest as systolic or diastolic dysfunction. Echocardiographically, patients who present with HFrEF have LVEF < 40%. In HFmrEF, patients have a LVEF of 40–49% and at least one additional criterion on echo: relevant structural heart disease [left ventricular hypertrophy (LVH) and/or left atrial enlargement (LAE)] or diastolic dysfunction. Patients with HFpEF have a LVEF > 50% as well as structural cardiac changes, as mentioned above, or diastolic dysfunction. In the latter case, these patients have elevated levels of natriuretic peptide (NT-proBNP > 125 pg/ml or BNP > 35 pg/ml).[7]

Definition of PE

PE is defined as new-onset, repeatedly high blood pressure levels (systolic ≥ 140 mmHg and/or diastolic ≥ 90 mmHg) accompanied by proteinuria or evidence of organ dysfunction occurring after 20 weeks of gestation with involvement of one or more organ systems.[9] Proteinuria is not mandatory for the diagnosis of PE. Severe PE is defined as systolic blood pressure ≥ 160 mmHg and diastolic pressure ≥ 100 mmHg. PE is divided into early- and late-onset types, early onset presenting prior to 33 weeks plus five days and late onset occurring after 34 weeks and zero days. The early-onset type is much more likely to have underlying cardiac dysfunction.

Pathogenesis of PE

The pathophysiology of PE is hypothesised to be a two-stage disease process that is placenta mediated. The first stage is hypothesised to involve impaired trophoblastic invasion of the uterine spiral arterioles and abnormal vascular remodelling.[10,11] These changes are measured objectively in early pregnancy as persistence of high resistance in uterine artery Doppler indices.[12,13] The abnormal vascular transformation results in the second stage: a hypoxic, inflammatory milieu that leads to an imbalance of pro- and anti-angiogenic factors and subsequent endothelial dysfunction: increased generation of reactive oxygen species (ROS), apoptosis, microvascular rarefaction, molecular alterations in gene expression that influence cellular interactions and cell migration.[10,12,14] The exact aetiology of PE is an area of ongoing research, however, angiogenic, cell-free foetal DNA, vasoactive mediators, immunological synapses as well as synctiotrophoblast microparticles play a role in the pathogenesis of the disease.[10,15]

The anti-angiogenic factors involved in the pathogenesis of PE include soluble fms-like tyrosine kinase 1 (sFlt1) and soluble endoglin. Soluble Flt1 is a spliced variant of the vascular endothelial growth factor receptor 1 and lacks the cytoplasmic binding domains of membrane-bound Flt1 and antagonises the effects of vascular endothelial growth factor and placental growth factor, thereby inhibiting normal angiogenesis.[16,17] Maynard showed in 2003 that sFlt1 levels were substantially higher in patients with established PE, and the decline in levels following delivery correlated with improvement in clinical symptoms.[18]

A study by Govender *et al*. (2013) noted that syncytial knots of the synctiotrophoblast contain large amounts of sFlt1. Syncytial knots separate from placental villi through fission, leading to multinucleated syncytial aggregates loaded with sFlt1 and able to synthesise additional sFlt1 from intrinsic mRNA.[16] Endoglin is a co-receptor for the transformation growth receptor family (TGF), which influences vascular transformation. Transformation growth factor stimulation activates the nitric oxide synthase pathway and induces cellular proliferation, migration and vascular remodelling.[16,17] However, soluble endoglin, a truncated variant of endoglin, antagonises the binding of TGF beta (TGF-β), preventing the downstream vasodilatory effect.[16,19] The interaction between the immune system and angiogenic factors is significant in PE. Toll-like receptor 9 (TLR9) inhibits angiogenesis and stimulates tumour necrosis factor alpha (TNF-α) expression, which increases the release of sFlt1.[16,20]

Recent studies have elucidated the role of synctiotrophoblast microparticles (STBM) as factors in the pathogenesis of PE: immune regulation, angiogenesis, hypercoagulability and

endothelial dysfunction.[10,21] STBM particles contain vesicles ranging from 20 to 3 000 nm in size, which are secreted from the placenta into the maternal circulation.[10,22] Exosomes are the main components of STBM. They are formed as part of the lysosomal pathway, contain myriad signalling molecules, growth factors, as well as miRNA and mRNA involved in immunity.[10,23,24] Exosomes play a role in maintaining immune tolerance at the foeto–maternal interface and they regulate cell function, proliferation, metabolism and apoptosis.[10,25,26] In addition, exosomes may cluster with matrix metalloprotease 14 (MMP14), resulting in increased release of soluble endoglin (sEng) from the placenta, the upregulation of which impairs normal vasculogenesis in PE.[16,27] Ultimately, exosomes may contribute to endothelial dysfunction.[27] Endothelial dysfunction in PE may be extrapolated to involve the maternal vasculature and cardiac function, and is postulated to predispose to cardiovascular disease.

There is growing evidence to suggest that impaired placentation may be the consequence of pre-existing cardiovascular disease and altered maternal haemodynamics, thereby inferring a duality in causality: pre-existing abnormal maternal vasculature can lead to poor placentation and clinical manifestations of PE.[12]

PE and cardiovascular disease

There may be additional factors other than trophoblast invasion that determine normal transformation of uterine spiral arterioles.[12,28] This is demonstrated in a case report that demonstrated a low uterine artery resistance index in an extra-uterine pregnancy (advanced abdominal pregnancy): indices found in a normal pregnancy despite lack of adequate trophoblastic invasion.

Further evidence is described by Binder *et al*. (2018) in a study describing a longitudinal uterine Doppler assessment into the third trimester of pregnancy. It was discovered that one-third of patients, who were shown to have had normal indices previously, developed a high resistance artery Doppler in the third trimester. These patients had a 30% higher prevalence of PE.[12,29] This finding of dynamic changes is counter-intuitive as it in essence implies reversal of initial spiral artery transformation. This therefore challenges the accepted hypothesis of impaired trophoblastic invasion being the key contributing factor in the maelstrom of abnormal vasculogenesis, and rather suggests a significant impact of inherent maternal cardiovascular function.[12,30,31]

Systematic reviews have found concordance in resistance artery indices of vessels of the systemic vasculature. Doppler assessment of radial and ophthalmic arteries has shown a corresponding decrease in resistance with progress in gestation as well as persistently high resistance in first-trimester pregnancies of patients at high risk for PE.[12,32,33] This measured uniformity demonstrates a common origin of disease and supports the understanding that abnormal placentation can be a result of pre-existing systemic disease. In corroboration, a prospective study that assessed pre-pregnancy haemodynamics in 530 women found that patients who had developed PE had lower cardiac output and higher systemic vascular resistance indices before placentation.[12,34]

To investigate for evidence of pre-pregnancy cardiovascular dysfunction, Foo *et al*. (2018) conducted a longitudinal assessment of cardiovascular function in 356 spontaneously conceived pregnancies in healthy women before conception.[34] It was noted that 15 (4.2%) women who developed PE had lower cardiac output and higher total peripheral resistance pre-conceptually compared to uncomplicated pregnancies.[12,34]

In a Scottish data-linkage cohort study, the risk of ischaemic heart disease was highest among women who had PE with an infant both preterm and small for gestational age.[35,36] In Norway, among 3 225 women who underwent a metabolic screening of blood pressure, serum lipids and body mass index pre and post pregnancy, the association between PE and postpartum cardiovascular risk was partly related to pre-existing risk factors.[35,37] These findings suggest that similar risk factors that predispose to placental vascular disease predispose to cardiovascular disease and its premature development.[35,38] This provides further evidence that the relationship between PE and cardiovascular disease is complex and interrelated. It is a clinical problem where causality is bidirectional, multifactorial, dynamic with temporal evolution, and the clinical manifestations are perpetuated by this auto-amplification loop.

PE and pathogenesis of cardiovascular disease

Pregnancy represents a fluid clinical paradigm, which exquisitely maintains functionality at a new physiological equilibrium in order to support both foetal development and maternal health. In order to achieve this balance, natural changes to the cardiovascular system occur.[39] Blood flow increases to accommodate an increase in metabolic demand.[39,40] Blood volume increases about 45% above pre-pregnancy levels. Stoke volume, heart rate and end-diastolic volume increase, leading to an increase in cardiac output, which rises to about 50% above pre-pregnancy levels at approximately 16–20 weeks' gestation.[28,41,42] Systolic and diastolic blood pressures decrease in the first and second trimesters, however blood pressures rise in the third trimester, returning to baseline at the end of gestation.[28,43]

The heart undergoes physiological changes in order to adapt to alterations in fluid volume and cardiac preload.[39,40] Physiological pregnancy-induced cardiac hypertrophy involves the proportional increase in cardiomyocyte size, resultant increase in LV wall thickness and normal myocardial capillary density.[39,44] It is not associated with increased oxidative stress, metabolic dysfunction, fibrosis, apoptosis, myocardial fibre disarray or genomic foetal reprogramming characteristic of pathological hypertrophy.[39,44] Importantly, the structural cardiac changes reverse postpartum.[39,45] The underlying molecular mechanisms that determine the divergent phenotypic pathways require further elucidation.

Animal models have demonstrated that pregnancy is associated with a decrease in cardiac glucose metabolism and increased utilisation of fatty acids, which contrasts with heart failure where there is a switch from myocardial fatty acid oxidation, glucose metabolism and oxidative phosphorylation.[39,46-48] However, a decrease in cardiac fatty oxidation has been reported as well.[39,49]

Insulin signalling and mitochondrial bio-energenetics are preserved in pregnancy but are depressed in pathological hypertrophy and cardiac failure.[39,46,50] Intracellular signalling and miRNA-omics determine the cardioprotective phenotype of pregnancy-induced hypertrophy. The pathways include the phosphoinositide-3-kinase/protein kinase B/glycogen synthase kinase 3-beta signalling, mitogen-activated protein kinase

(MAPK) signalling, calcineurin pathway and signal transducer and activator of transcription 3 (STAT 3) signalling. These pathways lead to gene expression that determines cellular proliferation, hypertrophy, apoptosis differentiation and angiogenesis.[51-53]

Cardiovascular complications occur as a consequence of cardiac maladaptation during pregnancy.[39,54,55] These complications manifest clinically as metabolic changes that occur in gestational diabetes, PE and gestational hypertension and functional changes that occur in peripartum cardiomyopathy.[39,56] These conditions lead to cardiac dysfunction and promote the development of heart failure.[39,57] This review focuses on cardiac maladaptation associated with PE.

PE has been associated with a decrease in cardiac output that corresponds to an increase in systemic vascular resistance.[58] The perturbation in haemodynamics is attributed to increased sympathetic innervation, enhanced response to angiotensin II, increased catecholamine release, an imbalance of pro- and anti-angiogenic factors, endothelial dysfunction leading to vasoconstriction, increased systemic vascular resistance and increased left ventricular afterload.[58,59] This afterload mismatch in turn results in increased stroke work and myocardial ischaemia, impaired myocardial relaxation and diastolic filling.[58]

There is a phenotypic heterogeneity of PE: severity of cardiac disease, progression to heart failure and pulmonary oedema, which are determined by genetics, epigenetics and pre-existing cardiovascular dysfunction.[58] Systematic reviews of genetic risk factors showed that plasminogen activator inhibitor-1 (PAI-I) and FMS-related tyrosine kinase were associated with PE and are known to be associated with risks of coronary artery disease and heart failure.[12] There is also a role of exosomes causing endothelial dysfunction and contributing to cardiovascular disease.

Interestingly, there is a plethora of data underscoring the role of altered microRNA expression in pregnancies complicated by cardiovascular disease.[39,60] MicroRNAs (miRNAs) are non-coding RNAs that influence gene expression through post-translational modification by binding to the 3′ untranslated region (3′ UTR) of the target mRNA, leading to premature degradation or prevention of translation.[39,61]

Upregulated miRNAs in PE

Several studies have shown elevated levels of both miR-210-3p and miR-210-5p in PE.[39,62] MiR-210, a hypoxia-activated miRNA, is upregulated in pathological cardiac hypertrophy and cardiac failure.[39,63] Interestingly, it seems to be cardioprotective; in cardiomyocytes, Akt signalling was found to increase miR-210 expression, leading to decreased oxidative stress and cell death, likely through the programmed cell death protein 4 (PDCD4) pathway.[39,64] In addition, miR-210 inhibits cell cycle inhibitor adenomatous polyposis coli (APC), and miR-210-expressing female mice demonstrated reduced cardiomyocyte apoptosis, increased angiogenesis and improvement in cardiac function following myocardial infarction (MI).[39,65] Similarly, in exosome-derived miR-210, which inhibits the angiogenesis modulator ephrin A3, cardiac angiogenesis was promoted following MI in male mice.[39,66]

MiR-29a is upregulated in mild PE compared to controls and was found to have a dual role in cardiac failure.[39,67,68] In patients with hypertrophic cardiomyopathy, plasma miR-29a was found to be increased and correlated positively with both cardiac hypertrophy and fibrosis.[39,69] However, miR-29a demonstrated protection against phenylephrine-induced cardiomyocyte hypertrophy through directly stimulating the pro-hypertrophic NFATc4.[39,70]

Levels of miRNA may vary depending on the severity of disease. MiR-21 and MiR-155 were found to be elevated five- to eight-fold in severe PE compared to mild PE.[39,62] Increased miRNA expression has been noted to cause cardiomyocyte hypertrophy. It inhibits sprout homolog 1 (Spry 1) in cardiac fibroblasts and enhances extracellular signal-regulated kinase (ERK) MAPK signalling, leading to cardiac fibrosis and cardiomyocyte hypertrophy.[39,71] MiR-21 also stimulates fibrosis following MI in male mice through targeting small mothers against decapentaplegic 7 (SMAD 7), a negative regulator of the TGF-β1 pathway.[39,72] However, cardioprotective effects have been demonstrated in a rat model: miR-21 prevented cardiomyocyte apoptosis by targeting PDCD4,[39,73] suggesting inherent pleiotropy of the signalling mechanisms of these pathways.[39,74,75]

Of significance, differences in miRNA expression before clinical onset may be predictive of the development of PE. Plasma miR-206 was upregulated in the early third trimester in asymptomatic patients who later developed PE, in contrast to healthy pregnant patients.[39,76] In male mice, miR-206 was demonstrated to stimulate cardiac hypertrophy by targeting tumour suppressor Forkhead box protein 1.[39,77] Whether or not miR-206 is expressed at the time of disease onset remains to be investigated.

Downregulated miRNAs in PE

Various studies have shown plasma and serum levels of miR-144 to be downregulated in PE patients compared to controls in different stages of disease.[39,62] Loss of miR-144 signalling in male mice was noted to lead to impaired extracellular matrix remodelling following an MI, resulting in cardiac dysfunction. MiR-144 targets zinc finger E box binding homeobox 1 (Zeb 1), a mediator of mesenchymal transition and a profibrotic response following an insult.[39,78] In addition, loss of miR-144 in male mice enhances injury following an MI by targeting Ras-related c3 botulinum toxin substrate 1 (Rac1), a major component of NADPH oxidase, leading to generation of ROS and oxidative damage.[39,79]

MiR-125b-5p and miR-195-5p were found to be downregulated in severe PE compared to controls. However, elevated levels of miR-195-5p have also been described and shown to correlate positively with sFlt-1 levels.[39,80] In male mice, miR-195-5P stimulates angiotensin II-induced cardiomyocyte hypertrophy through downstream signalling: it targets tumour suppressor FBXW7 and mitofusin 2 (MFN 2), which inhibit mitochondrial membrane depolarisation and generation of ROS.[39,81]

Differential expression of miRNA levels prior to clinical onset could be predictive of disease development. Serum levels of miR-126, miR-204 and miR-15b in early gestation were found to be decreased in patients who developed severe PE in the third trimester, in contrast to patients who developed a healthy pregnancy.[39,82] MiR-126 plays a role in endothelial cell integrity as it represses anti-angiogenic modulator sprouty related, EVH1 domain-containing protein 1 (Spred 1), resulting in abnormal

angiogenesis following MI in miR-126-deficient mice.[39,83] In addition, through upregulation of vascular endothelial growth factor (VEGF) and superoxide dismutase (SOD) expression through the PI3K/Akt pathway, it protects microvasculature against hypoxia and re-oxygenation injury.[39,84]

MiR-204 plays a role in regulation of autophagy. It may target cardiomyocyte microtubule-associated protein 1 light chain 3 (LC3-II) necessary for autophagosome formation in cardiac ischaemia–reperfusion injury in rats.[39,85] MiR-15b was shown to inhibit several steps of the TGF-β pathway in cardiomyocytes, including p38 MAPK and TGF-β receptor 1 (TGF-βR-1), with antagonism promoting cardiomyocyte hypertrophy and fibrosis in pressure-overloaded mice.[39,86]

Novel markers have provided further insight into the cardiac pathophysiology of PE. Cardiovascular biomarkers such as atrial natriuretic peptide-converting enzyme, known as corin, and transcription factor storkhead box 1 (STOX 1) have been shown to be increased in PE.[39,87] Corin is a serine protease of the trypsin superfamily, identified as an enzyme expressed mainly in the atrial and ventricular myocardium.[88,89] The enzyme converts atrial natriuretic peptide (ANP) precursor (pro-ANP) to mature ANP. ANP regulates natriuresis, diuresis and vascular tone, and inhibits the neurohormonal axis of the RAAS system.[88,90]

Attenuated corin and ANP production have been shown to influence vascular and renal homeostasis. Recent animal studies demonstrated that Corin is able to activate ANP, allow for spiral artery remodelling in the pregnant uterus and prevent pregnancy-induced hypertension.[87,88] Studies involving transgenic mouse models of corin and STOX1 have highlighted their role in cardiovascular complications related to PE.[39,91] Corin-deficient mice or aberrant expression of corin developed cardiac hypertrophy, which did not resolve postpartum.[39,92]

Recent studies have shown that maternal corin levels are higher in PE.[88,93] The source of increased corin levels in PE has yet to be investigated. The heart is the main source of corin, however, the placenta may secrete the enzyme into the maternal circulation as well; the expression of corin was found in synctiotrophoblasts.[88,94,95] Increased expression of A disintegrin and metalloproteinase domain-containing protein 10 (ADAM10), the main corin-shedding enzyme, was increased in synctiotrophoblasts in PE.[88,96]

The natriuretic peptide family has three types of transmembrane receptors: NPR-A, NPR-B and NPR-C that modulate activity of ANP. NPR-A and -B receptors are guanylyl cyclase receptors that convert GTP (guanylyl triphosphate) to cGMP (guanylyl monophosphate), which stimulates protein kinase G, leading to vasodilation. NPR-C is a non-guanylyl cyclase receptor and through inhibition of guanine nucleotide regulatory protein (Gi), it is coupled to adenylyl cyclase inhibition or phospholipase C activation.[88,97] NPR-C clears circulating ANP and is the most prolifically expressed ANP receptor found in various tissues.[88,98] NPR-C therefore likely influences cellular proliferation, migration and vascular remodelling.[88,99]

In the study by Gu *et al*. (2018), it was discovered that maternal pro ANP levels were also increased in patients who presented with severe PE.[88] In addition, their results showed that NPR-A expression was decreased and NPR-C expression increased in maternal vascular endothelium in PE compared to normotensive controls.[88] The mechanism describing the altered expression of ANP receptors remains to be elucidated, however as NPR-C is a clearance receptor for ANP, it can be extrapolated that increased NPR-C expression leads to increased clearance or degradation of circulating ANP and abnormal cardiovascular haemodynamics in PE.

The study by Gu *et al*. (2018) found that corin levels were increased in PE. It remains to be investigated if the increased levels are a compensatory mechanism for systemic vasoconstriction in PE, or if corin gene mutations, noted in cases of PE, decreased enzymatic activity necessary for the processing of pro ANP.[87,88,100] Interestingly, in the study, it was also noted that pro ANP, but not corin levels were increased in pregnancies complicated with chronic hypertension, in contrast to pregnancies complicated by PE.[77] Although the sample size was small and further studies are needed to investigate the relationship between corin and cardiovascular disease, the difference in corin expression highlights the divergent pathophysiological mechanisms that underlie chronic hypertension and PE.[77]

Even though corin activity was not measured in the study, the aberrant expression of ANP receptors and an alteration in the downstream signalling provide evidence for the contribution of the pro ANP, corin, NPR-C axis to cardiovascular dysfunction in PE.[77] As the source of corin may be both placenta and heart, the study further underscores the duality of disease: PE is likely a manifestation of a complex interplay between maternal cardiovascular function and placenta-mediated factors.

Echocardiographic parameters in PE

Several maternal echocardiographic studies conducted at the clinical onset of PE have shown abnormal structural cardiac changes and diastolic dysfunction.[12,101,102]

A study by Bhorat *et al*. (2016) showed that left ventricular hypertrophy is a frequent finding in patients presenting with severe PE, the prevalence increasing from 63% in patients without pulmonary oedema to 75% in patients with pulmonary oedema and preserved systolic function, in contrast to 6% in controls.[58,103] The study used tissue Doppler imaging to assess haemodynamic changes in PE, using the ratio of the early trans-mitral flow velocity (Em) to the early tissue velocity at the mitral annulus (Ea) as an index of left ventricular filling. It was found that tissue Doppler Em and Ea were elevated in PE compared to controls.[58,104]

This reflected earlier studies where it was shown that PE was associated with diastolic dysfunction, left ventricular hypertrophy, increased left ventricular end-systolic and end-diastolic volumes, reduced cardiac output and increased filling pressures.[58,105] A study by Dennis *et al*. in 2015 demonstrated that in patients with severe but stable PE, echocardiograms showed preserved systolic function and non-dilated ventricles, with evidence of diastolic dysfunction.[106]

HIV, angiogenesis and PE

The HIV infection is characterised by systemic inflammation, endothelial injury, thrombosis and atherosclerosis. Immune dysregulation and abnormal angiogenesis could link the pathophysiology between PE and HIV infection. In pregnant HIV-positive patients, there is an increase in events such as miscarriages, PE, diabetes and preterm labour.[1] However, various studies highlight the paradoxical and unpredictable

relationship between PE and HIV infection.[1] Drug interactions further complicate the synaptic interplay as antiretrovirals (ARVs) polarise the immune response as well as influence the haemodynamics.[1] The paragraphs below highlight the various factors and cellular interactions, underscoring the need for further investigation describing the link between HIV and PE.

Angiogenesis is the formation of new blood vessels and involves migration, differentiation and proliferation of endothelial cells through upregulation of pro-angiogenic factors.[1,107] These molecules increase vascular permeability and stimulate proteolysis of extracellular matrix proteins, leading to migration and maturation of endothelial cells.[1,108] Angiogenesis is dysregulated in HIV, however, interestingly, Wimalasundera *et al*. (2002) found a decreased rate of the development of PE in HIV patients who did not receive antiretroviral therapy compared to patients receiving treatment.[19,109] Possible reasons could include immune restoration and imbalance of angiogenic factors as well as the direct impact of ARVs on angiogenesis.[110]

The influence of HIV on the development of PE is contradictory as both sFlt and sEng are downregulated in HIV, in contrast to what occurs in PE. Immunosuppression of HIV and immune activation of PE may impact on the equilibrium between pro- and anti-angiogenic factors, leading to the progression of PE. HIV-infected cells release transactivator of transcription (Tat) protein, which, even though it stimulates angiogenesis, alters endothelial cell morphology. The Tat protein is an angiogenic factor because of similar sequences to VEGF (arginine- and lysine-rich sequences) and therefore stimulates endothelial cell adhesion through binding to Flk and KDR, and promotes endothelial cell adhesion through binding to integrins and VEGFR-2 and KDR via its basic domain.

In addition, the synergistic Tat, FGF2 effect is attributed to fibroblast growth factor 2 (FGF2), which induces the expression of integrins that aid in tat binding. In addition, HIV glycoprotein 120 (gp120) binds to heparin sulphate proteoglycans (HSPG), promoting viral infectivity and release of Tat. However, the Tat protein alters endothelial cell morphology and gene transcription through attenuation of intracellular signalling as it activates the mitogen activated protein kinase (MAPK) pathway. The Tat stimulates angiogenesis through utilisation of matrix protein p17 to activate the endothelin 1/endothelin B receptor axis, thereby activating protein kinase Akt and extracellular signal-regulated kinase (ERK) signalling pathways. Moreover, gp 120 induces apoptosis in endothelial cells.[16,19,111-113]

Angiogenesis and antiretroviral therapy

The pro-inflammatory milieu of HIV infection resembles the immune dysregulation of PE, which could explain the prevalence of PE in HIV-positive women. Interestingly, even though ARVs alleviate the inflammatory state of HIV, a recent study on ARVs showed that both angiogenesis and lymphangiogenesis were downregulated with nucleoside reverse transcriptase inhibitors (NRTIs) through two main mechanisms. First, HIV tat and matrix protein p17 counter the beneficial effects of ARVs through impaired angiogenesis.[1] Second, NRTIs cause mitochondrial dysfunction, leading to increased oxidative stress and altered intracellular signalling of endothelial cells.[1,114]

Protease inhibitors are anti-angiogenic. They suppress the action of fibroblast growth factor and induce functional impairment of transcription factors, namely, adaptor protein 1 (AP-1), specificity protein 1 (SP1) and nuclear factor kappa B (NF kappa B), leading to deceased expression of matrix metalloproteases (MMP) and VEGF, thereby disrupting angiogenesis.[1] In addition, metabolic dysregulation associated with ARV regimens have predisposed HIV-infected persons to cardiovascular disease.[1,115] Antiretroviral therapy has been shown to decrease nitric oxide, increase oxidative stress and induce endothelial dysfunction, mechanisms that resemble the underlying pathophysiology of PE.[1,116]

It has been shown that upon ARV administration, the incidence of PE increases, however there are conflicting reports.[1] A study done by Torrani *et al*. (2008) demonstrated improved endothelial function following commencement of ARVs.[117] Savvidou *et al*. (2011) demonstrated normal placental perfusion in uncomplicated pregnancies of HIV-infected women in both groups, those receiving and those not receiving ARVs.[118] Conversely, a study done by Sebitloane *et al*. (2017) illustrated the correlation between ARVs and HDP among all women with HIV and found a greater risk of mortality due to HDP among patients who received ARVs, as opposed to those who were not on ARVs.[119] Further studies are needed to illustrate the effect of ARVs on lymphangiogenesis and the duration of ARVs and risk of development of PE.

Immunity, HIV and PE

Natural killer (NK) cell function is altered in HIV infection as well as in PE.[120] In normal pregnancy, these cells promote immune tolerance and placental development. At the maternal–foetal interface, NK cell inhibitory receptors, attenuation of vascular cell interactions and secretion of hepatocyte growth factor allow for adequate trophoblastic invasion and normal placentation.[1] However, this process is disrupted in PE where there is a predominance of activating receptors of NK cells.[121]

In HIV infection, NK cells are downregulated, similar to in a normal pregnancy.[122] With administration of ARVs, NK cells inhibit HIV replication through secretion of CC chemokines, which inhibit HIV replication through non-cytolytic mechanisms.[123] Studies have shown conflicting results regarding the effect of ARVs on NK cells. A study by Valentin *et al.* (2002) reported higher frequency of NK after initiation of ARVs.[124] A study by Fria *et al*. (2015) showed low NK recovery following ARV exposure compared to T-cell recovery, suggesting that viral infection of NK cells is necessary for viral persistence.[123,125]

With regard to PE, NK cell activation may lead to impaired trophoblastic invasion, resulting in an exaggerated immune response characteristic of PE. This suggests that T-cell activation rather than NK cell recovery may explain the development of PE in HIV.

Normal pregnancy is associated with T helper 2 (Th2) polarisation of the adaptive immune system, however PE is associated with a T helper 1 (Th1) pro-inflammatory phenotype.[126,127] During the progression of HIV, there is polarisation towards a Th2 phenotype, however, a Th1 response is predominant in HIV-infected pregnant women on ARVs.[128] These patients are therefore at increased risk of developing PE.[129]

It has been reported that PE is associated with an upregulation of T helper 17 (Th17) cells.[130] In contrast, these cells are downregulated with the progression of HIV infection.[131] However, there is a paucity of data investigating the secretion of IL-17A

in concurrent cases of PE and HIV infection and concomitant initiation of ARVs.[1]

Pregnancy is usually associated with an upregulation of regulatory T cells (Treg) to maintain peripheral tolerance and promote normal placentation, however a downregulation of Treg cells was reported in PE.[132,133] HIV infection is associated with an increase of Treg cells, however, with administration of ARVs, there was a decrease in Treg cells to levels similar to that of HIV-negative individuals.[134,135] However, further studies are needed to investigate the Treg cell modulation in cases of concomitant HIV infection and PE.

HIV and cardiovascular disease

HIV has been clearly shown to be associated with cardiovascular disease. The correlation is determined by myriad molecular pathways and synergistic pathophysiological mechanisms involving an interaction between HIV itself, opportunistic infections and drug therapy, which lead to both systolic and diastolic dysfunction.[7]

Epidemiology

Erqou *et al*. (2019) performed a systematic review and meta-analysis of cardiac dysfunction in persons with HIV (PHIV) and selected 54 studies done in various regions between the years 1988 and 2017.[136,137] They analysed data from 125 382 PHIV, 82% men, and calculated a heart failure prevalence of 6.5%. This value was high considering the relatively low average age of the cohort (47 years). Among those studied, only 77% were on ARVs, and the majority were ARV naïve and had uncontrolled infection.[136,137]

Multiple studies across various regions demonstrate that heart failure outcomes are worse among PHIV versus non-HIV-infected individuals.[136] Analysis of data from the predominantly male US Veterans Cohort suggests that among PHIV with heart failure, five-year mortality rates approached 50%.[136,137] Through the Sub-Saharan Africa Survey of Heart Failure (THESUS HF) study, Sliwa *et al*. (2013) confirmed worse outcomes among PHIV with heart failure.[136,138,139] The prospective multi-centre study recruited 1 006 people with acute heart failure (51% women) from nine countries in sub-Saharan Africa between 2007 and 2010. Within this cohort, the prevalence of hypertension was 56% while HIV prevalence was 7%. Sliwa *et al*. demonstrated that in this group, HIV status was associated with an increased risk of mortality and 60-day hospital re-admission.[138-140]

Pathogenesis

HIV infection can cause a cardiomyopathy through various mechanisms: direct myocardial infiltration by HIV itself as well as infiltration and inflammation caused by opportunistic infections; immune dysregulation and an auto-immune response within the myocardium; HIV-related vasculopathy; and metabolic dysregulation secondary to HIV itself or the initiation of ARVs.[136]

HIV influences the metabolism through immune dysregulation, neurohormonal mechanisms and hormonal perturbations, leading to relative growth hormone deficiency.[136,141-143] Early ARVs were associated with overt lipodystrophy, however even though newer regimens are better tolerated, ARVs can be associated with weight gain, excess adiposity, ectopic fat deposition and endothelial dysfunction.[140,144,145] Inflammation and altered metabolomics lead to myocardial fibrosis and steatosis, respectively, resulting in diastolic dysfunction.

Even though ARVs can mitigate the inflammatory response partially, inflammation persists and contributes to cardiovascular disease.[146,147] Low-level viral replication, co-infection and microbial translocation create a pro-inflammatory state. Myocardial steatosis may lead to inflammation within the myocardial structural space. Inflammation leads to the generation of ROS, endothelial dysfunction, microvascular rarefaction, ischaemia and fibrosis (Harrison's). In addition, traditional cardiovascular risk factors play a role and may have a synergistic effect with HIV-activated mechanisms.[136]

HIV has also been associated with an increase in circulating microparticles, which lead to endothelial dysfunction and have been shown to stimulate a pro-atherogenic phenotype.[148,149] Microparticles are small (100–1 000 nm) membrane vesicles that are released by various cell types as a response to multiple stimuli that lead to cell activation, apoptosis.[148,150] Circulating concentrations of endothelial-, platelet-, monocyte- and leucocyte-derived microparticles were found to be elevated in HIV-positive men treated with ARVs. These microparticles induced inflammation, oxidative stress, senescence and apoptotic susceptibility compared to microparticles obtained from HIV-negative men.[148]

Recently, a North American study focused on women with HIV (WHIV) and demonstrated diffuse myocardial fibrosis related to systemic inflammation as well as myocardial steatosis secondary to metabolic dysregulation.[136,151] In this study, WHIV showed increased myocardial fibrosis [confirmed by magnetic resonance imaging (MRI)], and diastolic dysfunction, measured by the circumferential diastolic strain rate on MRI.[136,151] In addition, novel immune markers of HIV-associated myocardial fibrosis have been identified.

Increased levels of the monocyte activation marker sCD163 have been shown to correlate with myocardial fibrosis, and increased expression of the cell surface receptor CCR2 on inflammatory monocytes ($CD14^+$ and $CD16^+$) was found to correlate with both myocardial fibrosis and diastolic dysfunction.[140,151] The CCR2 receptor promotes transmigration into target tissues among PHIV.[140,152] This suggests that in WHIV, activated $CD14^+$ and $CD16^+$ monocytes transmigrate to the myocardium and stimulate fibrosis through the inflammatory response. Within the same cohort, Toribio *et al*. (2019) revealed that WHIV showed marked myocardial steatosis with a three-fold increase in intramyocardial lipid content.[136,140]

Echocardiographic parameters and imaging modalities of cardiac function in HIV

In the meta-analysis by Erqou *et al.* (2019) of cardiac dysfunction involving multiple studies at different locations and different times, there was found to be a lower prevalence of systolic dysfunction among PHIV in locations with increased accessibility to ARVs.[137] It was found that the overall prevalence of left ventricular systolic dysfunction (EF < 50% or fractional shortening < 26%) was 12.3%.[137,140] This meta-analysis suggests the population prevalence of diastolic dysfunction among PHIV was 29.3%.[137,140]

Interestingly, in the Heart of Soweto study, Sliwa *et al*. (2012) evaluated the presentation of 515 PHIV (62% women, average 39 years and 54% on ART). Of all cardiovascular disease presentations, a significant proportion was caused by dilated cardiomyopathy (38%) and pericarditis (25%), and no cases of HFpEF were noted.[140,153]

In contrast, studies of predominantly male cohorts of American PHIV with heart failure (US Veterans Cohort, US Mon Cohort) showed a near equal number of those diagnosed with HFrEF and HFpEF.[140,154,155] In addition, Janjua's analysis of American WHIV with heart failure (Partners Healthcare cohort) showed a significant number of patients with HFpEF.[140,156] Of significance, the average age in the US cohort as well as the numbers treated with ARVs were higher compared to the South African cohort.

Of note, a meta-analysis by Cerrato *et al*. (2013) of cardiac dysfunction among PHIV, which included 11 studies (one from North Africa, one from Asia, six from Europe and three from North America) and was published between 2004 and 2011, showed a prevalence of diastolic dysfunction of 43.38%; the prevalence of systolic dysfunction was 8.33%. This study included 2 242 PHIV with a median age of 42 years and 98% were on ARVs, 74% of whom had an undetectable viral load.[140,157]

These findings underscore the heterogeneity of cardiovascular manifestations in HIV and an evolution of disease depending on factors such as age, gender and treatment, and increased prevalence of usual cardiovascular risk factors in the population. The incidence of HFpEF is increasing and will soon be the predominant form of heart failure. These findings are interesting as they raise myriad questions as to why the changes occur depending on the metabolic and transcriptomic alterations associated with HIV. Do these changes translate to dynamic changes in systemic vasculature and PE? This brings forth new avenues for research to investigate the underlying molecular changes, which would enhance our understanding and may lead to the development of new therapies.

HIV, cardiovascular disease and PE

Dennis *et al*. (2015) found that patients with HIV at term on echocardiographic assessment showed reductions in cardiac index, left and right systolic myocardial velocities and increased left ventricular end-diastolic areas. This could be related to the disease itself or treatment of the disease, or the effects of pregnancy on the cardiovascular system.[106]

There is a paucity of data on cardiac function in PE patients with HIV infection, and whether cardiac dysfunction is amplified by dual pathology, whether or not severity of PE or CD4 count plays a role in severity of cardiac manifestations and whether or not treatment of HIV ameliorates or exacerbates the cardiovascular disease manifestations.

Conclusion

The entities of cardiovascular disease, HIV infection and PE represent major healthcare challenges individually. This review has shown that they are interconnected and can therefore amplify disease severity and increase disease burden. It is therefore imperative to recognise the link to further elucidate pathophysiological mechanisms, which would provide a substrate for the development of novel therapeutic interventions, and the generation of predictive models to evaluate progression and outcome, which is necessary for timeous treatment in order to prevent complications, improve quality of life and decrease mortality.

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