

**QUANTIFICATION OF CARDIAC STRUCTURE AND FUNCTION
USING TRANSTHORACIC ECHOCARDIOGRAPHY
IN TERM WOMEN WITH HIV**

By

Matthew Winton Gibbs

Submitted in partial fulfilment for the degree

MMed (Anaesthesia)

Faculty of Health Sciences, UNIVERSITY OF CAPE TOWN

Date of Submission: 3 March 2016

Supervisors:

Prof AT Dennis *Royal Women's Hospital, University of Melbourne, Australia,*

Prof RA Dyer *Groote Schuur Hospital & the University of Cape Town South Africa*

The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.

Table of Contents

<i>Declaration</i>	3
<i>Glossary</i>	4
<i>Abstract</i>	6
<i>Study Protocol</i>	9
<i>Literature review</i>	18
<i>References</i>	34
<i>Print Ready Article IJOA (International Journal of Obstetric Anesthesia)</i>	38
<i>Title Page</i>	38
<i>Abstract</i>	39
<i>Introduction</i>	41
<i>Aims</i>	42
<i>Methods</i>	42
<i>Results</i>	46
<i>Discussion</i>	48
<i>Acknowledgements</i>	53
<i>References</i>	53
<i>Figure 1</i>	55
<i>Figure 2</i>	56
<i>Table 1 Demographic and obstetric data</i>	57
<i>Table 2 Haemodynamic and left ventricular systolic data</i>	58
<i>Table 3 Left ventricular diastolic and structural data</i>	60
<i>Table 4 Right ventricular functional data</i>	62
<i>Appendix 1 Consent Form</i>	63
<i>Appendix 2 Ethics Approval</i>	68
<i>Appendix 3 IJOA Author Pack</i>	70

DECLARATION

I, *Matthew Winton Gibbs*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signed by candidate

Signature: Signature Removed

Date: 14/02/2016

Glossary

A4C - Apical 4 Chamber View

A5C - Apical 5 Chamber View

AIDS - Acquired Immunodeficiency Syndrome

ARV - Anti-Retroviral (drugs)

AV - Aortic Valve

BMI - Body Mass Index

BSA - Body Surface Area

CD4 - Cluster of Deviation 4 cells

CS - Caesar Section

DNA - Deoxyribose Nucleic Acid

ED - End-diastolic

EF - Ejection Fraction

ES - End-systolic

FS - Fractional Shortening

FAC - Fractional Area Change

HAART - Highly Active Anti-Retroviral Therapy

HIV - Human Immunodeficiency Virus

IV - Isovolumetric

LA - Left Atrium

LV - Left Ventricle

LVEDD - Left Ventricular End Diastolic Diameter

IVCT - Isovolumetric Contraction Time

IVRT - Isovolumetric Relaxation Time

MV- Mitral Valve

PLAX - Parasternal Long Axis View

PPCM - Peripartum Cardiomyopathy

PSAX - Parasternal Short Axis View

RA - Right Atrium

RV - Right Ventricle

SD - Standard Deviation

TOE - Transoesophageal Echocardiography

TTE - Transthoracic Echocardiography

QUANTIFICATION OF CARDIAC STRUCTURE AND FUNCTION USING TRANSTHORACIC ECHOCARDIOGRAPHY IN TERM WOMEN WITH HIV

M Gibbs¹, A Dennis², R Dyer¹, L Nel¹, J Castro², J Swanevelder¹ ¹*Groote Schuur Hospital & The University of Cape Town, South Africa;* ²*Royal Women's Hospital, St Vincent's Hospital Melbourne, & University of Melbourne, Australia*

Abstract

Introduction: In South Africa, up to 30% of pregnant women are human immunodeficiency virus (HIV) positive and morbidity and mortality is high in this group. HIV positive men and women may have multiple cardiovascular comorbidities, which include systolic dysfunction that may progress to heart failure secondary to dilated cardiomyopathy. However the concurrent effect of pregnancy and HIV infection on haemodynamics has not been extensively researched. The aims of this study were to quantify haemodynamics using transthoracic echocardiography (TTE) in term pregnant women with HIV on antiretroviral (ARV) treatment and compare the data with term healthy women in the same population.

Method: After ethics approval and written consent, 30 consecutive term HIV positive women and 40 healthy term pregnant women were recruited. HIV positive women had a CD4 count greater than 200 and were either on Highly Active Anti-Retroviral Therapy (HAART) or single drug management.

Results: Haemodynamic assessment was possible in all patients and women in the two groups were similar in age, and body mass index. Mean CD4 count was 452 ± 187.8 and duration of therapy was 15.9 ± 22.4 months. Compared

with healthy pregnant women, women with HIV have systolic changes exhibited by reductions in left ventricle (LV) septal and right ventricle (RV) systolic myocardial velocities as well as increased LV end-diastolic (ED) areas and diastolic changes of increased RV isovolumetric (IV) relaxation and reduced RV e' diastolic myocardial velocities. These changes occur in the presence of a reduced LV mass. Pericardial effusions occurred more frequently and are of a larger size in women with HIV.

These findings suggest subclinical impairment of systolic function in the LV as well as subclinical impairment of both systolic and diastolic function in the RV.

Discussion: Transthoracic echocardiography can quantify cardiac function in healthy pregnant women and in pregnant women with HIV and is acceptable to the patients. HIV positive pregnant women at term on anti-retroviral therapy have hearts that have subclinical systolic dysfunction in the presence of decreased LV mass and increased end-diastolic areas. This may represent a failure to compensate for the increased haemodynamic demands of pregnancy and may be as a result of the direct effects of HIV itself or due to anti-retroviral drugs.

- Preliminary results of this work were presented as an oral presentation and a published abstract at The Obstetric Anaesthetists Association meeting Dublin, United Kingdom May 2014: Dennis AT, Dyer RA, Gibbs M, Nel L, Castro JM, Swanevelder JL. Cardiac function and structure using transthoracic echocardiography in term HIV positive women. *International Journal of Obstetric Anesthesia* 2014; 23(S1): S7
 - Best trainee presentation at The Obstetric Anaesthetists Association meeting Dublin, United Kingdom May 2014

Subsequent to finalising the transcript of this paper for the *International Journal of Obstetric Anesthesia*, it was decided to include this work and publish it in *Anaesthesia* as part of the larger 'Transthoracic

Echocardiography in Pregnant Women' study, HREC 442/2013, hence some of the similarities highlighted in the attached Turnitin report.

Dennis, A. T., Dyer, R. A., **Gibbs, M.**, Nel, L., Castro, J. M. and Swanevelder, J. L. (2015), Transthoracic echocardiographic assessment of haemodynamics in severe pre-eclampsia and HIV in South Africa. *Anaesthesia*, 70: 1028–1038. doi:10.1111/anae.13038

Study Protocol

Quantification of cardiac structure and function using transthoracic echocardiography in term women with HIV

An observational study of healthy term pregnant women and pregnant women with human immunodeficiency virus.

Matthew Gibbs, Anaesthesia Registrar, Department of Anaesthesia,
University of Cape Town

Introduction

The identification of cardiac disease in pregnancy is made difficult by the physiological changes of pregnancy, which result in increasing dyspnoea and diagnostic challenges associated with the gravid uterus. Recent developments in transthoracic echocardiography (TTE), a noninvasive technique involving the placement of an external probe on the woman's chest wall, have led to elucidation of cardiac physiology and pathophysiology of pregnancy.¹ TTE not only enables better definition of cardiac dysfunction, but also contributes to point of care management.² TTE has been shown to be acceptable and applicable in pregnant women with no known side effects.

Human immunodeficiency virus (HIV) positive women have many cardiovascular comorbidities, which include an as yet undefined incidence of systolic dysfunction, which may progress to heart failure due to dilated cardiomyopathy. Research in Rwanda has shown that HIV-associated dilated cardiomyopathy may occur in up to 17% of untreated HIV positive patients.³ In another prospective cohort trial, the incidence of systolic dysfunction was up to 34% and diastolic dysfunction of 48% in asymptomatic HIV positive patients on HAART.⁴ The effect of pregnancy and HIV infection on

haemodynamics has not been extensively researched. A recent limited study in Uganda suggests that HIV infection in patients on HAART is not necessarily a risk factor for the echocardiographic signs of cardiomyopathy or pulmonary hypertension.⁵ In South Africa, up to 30% of parturients presenting for delivery at State Hospitals are HIV positive.⁶ TTE could help identify cardiac dysfunction, guide treatment, and reduce risk in these patients. As a convenience sample, thirty patients will be studied, due to the lack of studies performed in this population.

A group of forty gestationally matched healthy pregnant women will be studied as a basis for comparison.

Overall, the use of TTE in the patients recruited to this study can only be of benefit, both as an aid to diagnosis of cardiac pathology in the individual case, and how HIV and pregnancy affect cardiac structure and function.

Hypotheses

That term pregnant women with HIV infection have reduced systolic function with or without preservation of diastolic function

Aims

To determine the differences, if any, between the haemodynamics, cardiac function and structure of term HIV pregnant women and healthy term pregnant women using transthoracic echocardiography.

Method

This study will be conducted with Institutional Ethics Committee approval. Participant recruitment will take place on the day of the study.

Experimental design and location

This will be a prospective observational study performed at Mowbray Maternity and Groote Schuur Hospitals, Cape Town, South Africa.

Study group

The study will involve two groups of pregnant women:

1. Healthy term women (40 women)
2. Term HIV positive women (30 women)

Inclusion criteria

Healthy pregnant women (term and preterm)

Healthy pregnant women will be gestationally matched with women with HIV. Healthy pregnant women are defined as American Society of Anesthesiologists (ASA) Classification I or II, with no significant medical or surgical illness, singleton pregnancy, with no uterine abnormalities and normally defined placentation. They will not be receiving any vasoactive medication including salbutamol or thyroid replacement hormones. Healthy pregnant women will be recruited from a variety of settings throughout the hospital.

Term women with HIV

Thirty HIV positive women who are ≥ 37 weeks gestation will be recruited. The most recent CD4 count must be greater than 200, and all patients must be

on treatment: either Highly Active Antiretroviral Therapy (HAART) or single drug therapy.

Exclusion criteria

Healthy pregnant women

Exclusion criteria include current administration of vasoactive drugs including salbutamol and thyroxine, pre-existing or gestational diabetes, known cardiac disease including pre-existing or gestational hypertension, multiple pregnancy, a known uterine abnormality or abnormal placentation, any woman in labour, inability to consent to the study.

Women with HIV

Multiple pregnancies, women in labour, inability to consent to the study.

Experimental procedure

All participants will rest in the left lateral flat position for a minimum of five minutes before the measurements. Baseline systolic and diastolic blood pressure will be obtained non-invasively using a calibrated sphygmomanometer on the left arm recording the diastolic value as Korotkoff V according to the American Heart Association.⁷ An electrocardiograph (ECG) will be attached to each woman. All TTE studies will be performed by either the investigator AD or LN, according to published guidelines by the American Society of Echocardiography (ASE).⁸⁻¹² The parasternal long axis (PLAX), parasternal short axis (PSAX), apical 2-, 4- and 5- chamber (A2C, A4C, A5C) views will be obtained, including 2-dimensional imaging and continuous, pulse wave, colour flow and tissue Doppler will be performed.

Images will be converted to digital images and communications in medicine (DICOM) format and analysed off-line using ProSolv® software. Two investigators will independently review and measure the stored images in random order (Professor AT Dennis and Dr. Julian Castro). Each investigator will record an average of three consecutive beats. Inter- and intraobserver variability will be calculated.

Participant baseline demographic, obstetric, biochemical and urinary data will be collected. Haemodynamic and systolic cardiac data as well as diastolic and structural cardiac data will be obtained.

Management of abnormalities findings

Abnormalities detected by TTE will be immediately notified to the treating clinician.

Rationale for the sample size

The sample size of 40 pregnant women in the term healthy groups is based on data from previous published work.¹³

The sample size of 30 women with HIV and term pregnancy is a convenience sample. This will enable the range of haemodynamics in this group to be determined thereby facilitating the design and estimation of the sample size for a larger study.

Statistical and mathematical methods

Demographic and obstetric data will be displayed as mean and standard deviation, median with interquartile ranges, or number and percentage as appropriate. Analysis of recorded TTE variables and heart rate and blood

pressure will be made using analysis of variance (ANOVA) and a General Linear Model with significant p value defined as < 0.05 after performing F tests on the collected data. Pearson's correlation will be used to assess the strength of the linear relationship between variables. All the haemodynamic measurements from one participant will be assumed to be a family of measurements, therefore a Ryan-Holm stepdown Bonferroni procedure will be applied to the outcomes of the ANOVA in order to reduce the risk of a Type 1 error.¹⁴⁻¹⁶ The null hypothesis will be rejected if critical $p < 0.05$ for each of the variables.

Ethical considerations and consent

Echocardiography will be performed at the time of recruitment. Most patients will be recruited from the Antenatal clinic at Mowbray Maternity Hospital, with additional recruitment taking place in MK ward, Groote Schuur Hospital. Hospital-wide awareness of the study and immediate notification of the investigators will be an important factor in the success of the study. Patient demographic, haemodynamic and echocardiographic data will be examined without any related identifiers. Prospective written informed consent will be obtained in patients recruited to the study. No treatment delay or affect on patient flow is expected. All information regarding the study will be available for the patients' records.

Feasibility

Participant recruitment and scanning will take place over an intensive two-week period. Two investigators including the scanning investigator will be exclusively available for most of this time period to recruit and scan eligible pregnant women. Each TTE scan will take approximately 15-20 minutes to perform with all measurements being performed offline. It is estimated that

approximately 15-20 women will be able to be recruited to this study each day.

Anticipated outcomes of this study

1. Increased understanding of the range of haemodynamics and cardiac structure in women who are pregnant at term and HIV positive
2. Increased understanding of the haemodynamics and cardiac structure in healthy pregnant women
3. A better understanding of the role of TTE in pregnant women in two South African hospitals

It is anticipated that this work will be published in peer-reviewed journals and that the de-identified TTE data obtained in this study will be used for teaching and educational purposes.

References

1. Dennis AT. Transthoracic echocardiography in obstetric anaesthesia and obstetric critical illness. *Int J Obstet Anesth* 2011;20:160-8.
2. Dennis A, Stenson A. The use of transthoracic echocardiography in postpartum hypotension. *Anesth Analg* 2012;115:1033-7.
3. Twagirumukiza M, Nkeramihigo E, Seminega B, Gasakure E, Boccara F, Barbaro G. Prevalence of dilated cardiomyopathy in HIV-infected African

patients not receiving HAART: a multicenter, observational, prospective, cohort study in Rwanda. *Curr HIV Res* 2007;5:129–37.

4. Reinsch N, Kahlert P, Esser S, Sundermeyer A, Neuhaus K, Brockmeyer N, Potthoff A, Erbel R, Buck T, Neumann T. Echocardiographic findings and abnormalities in HIV-infected patients: results from a large, prospective, multicenter HIV-heart study. *Am J Cardiovasc Dis* 2011;1:176–84.
5. Longenecker CT, Mondo C, Le V, Jensen TP, Foster E. HIV infection is not associated with echocardiographic signs of cardiomyopathy or pulmonary hypertension among pregnant Ugandan women. *Int J Cardiol* 2011;147:300–2.
6. Moodley J, Pattinson RC. *Saving Mothers 2008-2010 : Fifth report on the Confidential Enquiries into Maternal Deaths in South Africa Saving Mothers 2008-2010*. 2010.
7. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Roccella EJ. Recommendations for blood pressure measurement in humans and experimental animals. Part 1: Blood pressure measurement in humans: A statement for professionals from the subcommittee of professional and public education of the American Heart Association. *Hypertension* 2005;45:142–61.
8. Reichek N, Sahn D, Schnittger I. Recommendations for Quantitation of the Left Ventricle by Two-Dimensional Echocardiography. *J Am Soc Echocardiogr* 1989;2:358–67.
9. Quiñones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 2002;15:167–84.
10. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MSJ, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group,

developed in conjunction with the European Association of Echocardiograph. J Am Soc Echocardiogr 2005;18:1440–63.

11. Gottdiener JS, Bednarz J, Devereux R, Gardin J, Klein A, Manning WJ, Morehead A, Kitzman D, Oh J, Quinones M, Schiller NB, Stein JH, Weissman NJ. American Society of Echocardiography recommendations for use of echocardiography in clinical trials. J Am Soc Echocardiogr 2004;17:1086–119.

12. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth O a, Waggoner AD, Flachskampf F a, Pellikka P a, Evangelista A, Evangelisa A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr 2009;22:107–33.

13. Dennis A, Arhanghelschi I, Simmons S, Royse C. Prospective observational study of serial cardiac output by transthoracic echocardiography in healthy pregnant women undergoing elective caesarean delivery. Int J Obstet Anesth 2010;19:142–8.

14. Ludbrook J. Multiple comparison procedures updated. Clin Exp Pharmacol Physiol 1998;25:1032–7.

15. Ludbrook J. Statistical techniques for comparing measurers and methods of measurement: A critical review. Clin Exp Pharmacol Physiol 2002;29:527–36.

16. Ludbrook J. Comparing methods of measurements. Clin Exp Pharmacol Physiol 1997;24:193–203.

Literature review

A search of the Pubmed, SCOPUS and Google Scholar databases was performed, using the keywords: "HIV", "cardiomyopathy", "echocardiography", and "pregnancy". Pertinent articles were reviewed and further references were extracted from the relevant papers.

Introduction

Human Immunodeficiency Virus (HIV) infection has reached pandemic proportions with an estimated global population of 35 million infected people.¹ In Sub-Saharan Africa, the prevalence is 4.7% as compared to a worldwide prevalence of 0.8%. South Africa is disproportionately affected with a prevalence of 10%, approaching thirty percent in pregnant women, significantly effecting morbidity and mortality. 53% of maternal deaths are due to non-pregnancy related infections and, of those, ninety percent are HIV positive.²

Cardiovascular effects of pregnancy

Pregnancy causes a swathe of changes in a woman's body, the cardiovascular system being notably affected by momentous hormonal fluctuations. Such changes include an increase in blood volume of 35%, plasma volume by 45%, cardiac output by 40% and falls in systolic and diastolic blood pressure as well as peripheral resistance and pulmonary resistance.³ Hormonal changes are also encountered including elevated oestrogen and human placental lactogen levels. As cardiac output increases over the course of pregnancy, it is to be expected that cardiac remodeling and changes in contractility might occur.

Transthoracic echocardiography is a non-invasive measure of haemodynamics and cardiac structures using ultrasound. Despite the obvious difficulty of obtaining images with a gravid uterus, particularly the subcostal four-chamber view, pregnancy has certain advantages as regards to finding ideal acoustic windows for echocardiography. As partial left tilt is necessary to reduce the aortocaval compression induced by the gravid uterus, this, along with an elevated diaphragm, results in anterior and left displacement of the heart, bringing structures closer to the transducer.⁴ Because of their exposure to ultrasound early in pregnancy, and the low risk involved, echocardiography is well accepted by pregnant patients.⁵ Echocardiography has the advantage of not only quantifying cardiac function but also visualizing cardiac structures in 2- and 3-D, and, as it can be performed at the bedside, can benefit point-of-care management.⁶

Various longitudinal studies on the haemodynamics of pregnancy have been performed using echocardiography in the healthy pregnant population, validating this technique in this population. Desai and Moodley in 2004 performed 160 echocardiographic studies on 35 healthy pregnant patients from early second trimester until term and until 6-12 weeks after delivery.⁷ They showed a gradual increase in cardiac output over second trimester with peak values being reached in early to mid third trimester. This cardiac output was maintained until term and left ventricular function was not affected. Cardiac output increased by 46-51% from base values, contributed to by an increase in stroke volume of 24% and heart rate of 15%. Structural changes included an increase in left atrial size and left atrial/aorta size ratio and increases in LV mass and LV mass index (compensating for Body Mass Index). Values returned to normal by 6-8 weeks post partum.

An earlier study using echocardiography but with only 18 patients was also performed in the USA.⁸ Studies were performed in the first trimester and then regularly until 6 to 12 weeks postpartum. The investigators found similar results, with an increase in stroke volume of 18% and heart rate 29%, with a concomitant increase in LV mass and wall thickness. Peak cardiac output was at 36-39 weeks.

Simmons et al examined 44 normotensive women during the course of their pregnancy using echocardiography and found an increase in cardiac index of 25% between the first and third trimesters.⁹ Due to a concern that a pregnancy induced rise in cardiac index could result in LV hypertrophy and a decrease in contractility, the investigators examined load independent variables of systolic function including end-systolic stress (ESS) and rate-corrected velocity of circumferential fiber shortening (V_{CFC}). The LV wall thickened on average by eleven percent, resolving in the postpartum phase, and LV mass index increased from 66 to 76 g/m², on average. Although there was a decrease in ESS and a small increase in V_{CFC} , there was no significant change in the relationship between ESS and V_{CFC} during the course of pregnancy. This demonstrated that women with a normal blood pressure during pregnancy did not have any changes in contractility. Left ventricular function also remained preserved, and demonstrated the ability of the heart of the normal pregnant woman to adequately compensate for the increased intravascular volume of pregnancy.

These findings show significant cardiac changes during normal pregnancy with peak effects occurring at or near term. They also show how echocardiography can be used to investigate the haemodynamics of pregnancy in a repeatable fashion, to an international standard.

Transthoracic echocardiography in obstetric critical illness

Echocardiography has also proved to be useful in the emergent setting in obstetrics. Papers by Dennis et al demonstrate the feasibility of transthoracic echocardiography as a point-of-care device to help illicit information that helps guide management of critically ill patients.⁴ Point-of-care echocardiography can be useful in divergent conditions, such as hypotension and maternal collapse,⁶ breathlessness¹⁰ and preeclampsia.¹¹

Echocardiography is able to provide information on regional wall motion abnormalities, the presence of shunting, global ventricular function, chamber size, the presence of emboli (whether amniotic, thrombotic or air) and pericardial effusions.

The ROSE examination (Rapid Obstetric Screening Echocardiography) is a protocol developed by Dennis,⁴ which has the following elements:

- It is acceptable and applicable
- It is a bedside test performed in the left lateral position
- It is a comfortable and concise examination, primarily focused on the parasternal short and long axis as well as the apical 4 chamber view
- It is focused on the diagnosis and response to any therapy instituted – in particular, assessment of contractility and volume status
- A rapid scan for any embolism present may be performed (e.g. air/amniotic fluid/thrombus) by imaging right heart function and relative size
- The exam also allows fetal heart rate assessment to be made.

A ROSE is indicated whenever obstetric critical illness is encountered: major obstetric haemorrhage, cardiac failure, sepsis, preeclampsia, aortic dissection, trauma and even in respiratory emergencies such as asthma.

HIV Molecular Biology

Human Immunodeficiency Virus is a ribonucleic acid (RNA) retrovirus, identified in 1983, that produces deoxyribonucleic acid (DNA) from RNA via reverse transcriptase, a common target for drug therapy.¹² Two other important targets for drug therapy include integrase, which is responsible for the integration of the HIV DNA produced into the cell DNA, and protease, which cleaves the protein precursors produced by the modified cell DNA into the final proteins required in the infectious virion. The virus also expresses three important proteins: GP120 (on the surface membrane), GP41 (through the cell membrane) and p24 (inside the body of the virus, on the nucleocapsid). Once inside the CD4+ cell, the GP120 and GP41 remain as GP160, which is used later for forming new viral membranes. The HI virus targets mainly CD4 positive T lymphocytes (recognized by the GP120 molecule, and a co-receptor like CCR5 or CXCR4) and CD4+ cells of monocytes lineage, but can infect any CD4 expressing cell.¹³ Therefore, cells in the liver, lung and heart can all be affected. After replication of the viral DNA, protein synthesis and new virion formation, CD4 death results from cell lysis or by cell exhaustion from the excess protein production required.

Cardiovascular effects of HIV

Even in the pre-HAART era, it was clear that HIV infected men and non-pregnant women had a high incidence of cardiovascular diseases. Cohen first linked HIV to a dilated cardiomyopathy in 1986, in a case series of three patients with AIDS.¹⁴ Other cardiac manifestations in HIV positive patients include systolic dysfunction, diastolic dysfunction, pericardial effusions, coronary artery disease, dilated cardiomyopathy or pulmonary hypertension.

Pathogenesis includes direct myocardial invasion by the HI virus, opportunistic infections, abnormalities of the autonomic nervous system, autoimmune disorders, endothelial dysfunction, HIV related malignancies (e.g. Kaposi sarcoma) and dyslipidemia.¹⁵ The exact mechanism is, however unknown.

Proposed mechanisms

HIV requires a CD4 receptor and a co-receptor (either CCR5 or CXCR4) to bind cell wall proteins thereby entering the cell. Because some cardiac myocytes lack a CD4 receptor, HIV cannot bind and enter these cells. However, HIV can enter and infect myocardial interstitial cells. The gp120 subunit of the HIV envelope glycoprotein has been implicated in HIV-associated cardiomyopathy. P38 mitogen-activated protein (MAP) kinase is part of a group of intracellular enzymes that phosphorylate proteins in response to inflammatory mediators (like cytokines) and stress (ischaemia). The HIV gp120 subunit has been associated with prolonged MAP kinase pathway activation that may lead to delayed negative inotropy, ischaemia and chronic heart failure as well as mitochondrial damage.¹³

Myocarditis is also commonly found in HIV positive patients with cardiomyopathy. In one case series of patients with HIV and dilated cardiomyopathy who underwent endomyocardial biopsy, 63 out of 76 patients had a histological diagnosis of myocarditis.¹⁶ Common causative organisms included Coxsackie virus B3, Epstein-Barr virus and *Toxoplasma Gondii*. Even in patients without diagnosed cardiomyopathy, myocarditis was diagnosed in 28% of patients at necropsy in a Brazilian case series.¹⁷

HIV may also cause chronic immune activation via the production of interleukin-1 (IL1) and Tumour Necrosis Factor-alpha (TNF-alpha).¹⁸

Inducible nitrous oxide synthase (iNOS) levels are also higher in HIV associated cardiomyopathy when compared to idiopathic dilated cardiomyopathy (IDCM) and healthy controls.¹⁹ This again suggests a role for cytokine activation in the development of HIV-associated cardiomyopathy.

Besides the effects of the virus itself, the treatment used may also cause cardiovascular complications. HAART can cause cardiac pathology via either direct toxic means or via changes to metabolism resulting in dyslipidaemia. Particular drug classes implicated are the Nucleoside Reverse Transcriptase Inhibitors (NRTIs) such as Zidovudine (AZT) and the Protease Inhibitors (PIs) like Ritonavir. The NRTIs were one of the first drugs to be used to treat HIV infection, and when initially administered in high doses and as a single drug, it caused dilated cardiomyopathy and cardiac failure in a significant portion of patients.²⁰ NRTIs prevent the reverse transcriptase process whereby the virus is incorporated into cell DNA. They also inhibit Pol- γ , an enzyme involved in the replication of mitochondrial DNA. This results in mitochondrial dysfunction and therefore problems may arise in cells that rely on mitochondria for energy production like cardiac myocytes.¹⁸

Protease inhibitors, on the other hand, produce dyslipidaemia by a number of mechanisms. Although protease inhibitors are very specific in their effects on HIV protease, resulting in immature virions being released, they are similar in size and shape to cellular protease substrates. This results in inhibition of cellular enzymes involved in lipid metabolism and in the regulation of adipocytes. This, in turn, leads to metabolic dysfunction and lipodystrophy.^{21,22} They also inhibit GLUT-4 in adipocytes, resulting in defective glucose uptake, insulin resistance and type 2 diabetes.²³ Accelerated atherosclerotic disease is also a concern.²⁴ A 2002 study of 5672 HIV positive patients from the HOPS (HIV Outpatient Study) showed that the use of

protease inhibitors was strongly associated with the likelihood of having a myocardial infarction. Logistic regression models, controlling for factors such as diabetes and hypertension, still showed a strong association of myocardial infarction with the use of protease inhibitors.²⁵

Prevalence of HIV-associated cardiac dysfunction

HIV associated cardiac dysfunction is more common than once thought. Clinical manifestations, including breathlessness and chest pain, are common, however it is dysfunction at the subclinical level that raises the need for increased vigilance. In a prospective cross sectional cohort study of HIV positive patients without symptoms of heart failure, Reinsch and colleagues found that 32% of patients had mild systolic dysfunction as indicated by LV ejection fraction of between 45% and 54%.²⁶ Up to 48% had diastolic dysfunction as evidenced by impaired mitral annular plane excursion and 38.7% of patients had an E/A ratio less than 1. This was in a first world environment in patients who were mostly on HAART with an average CD4 count of 509/mm³. Investigating a cohort of treatment-naïve New York Heart Association (NYHA) Class 1 HIV positive patients with a CD4 greater than 600, Barbaro et al showed that there was a mean reduction in ejection fraction by 19.7%, E/A ratio by 34.6% and an increase in isovolumetric relaxation time of 19.7% as compared with healthy controls, again implying subclinical systolic and diastolic dysfunction.²⁷

Twagirumukiza et al prospectively recruited 416 HIV-infected African patients who did not have documented cardiovascular disease. In a third world environment and an ARV-naïve population in Rwanda, they found 71 patients (17.7%) had dilated cardiomyopathy, defined by LV ejection fraction

less than 45% and LV dilatation (LV end-diastolic volume index $>80\text{ml}/\text{m}^2$).²⁸ These patients had a lower mean CD4 count and higher mean HIV-1 plasma viral load than patients without cardiomyopathy. Cardiomyopathy also correlated with duration of HIV infection, increased viral load, WHO clinical staging, low socio-economic status and low plasma selenium levels.

This is in keeping with a study in Cameroon by Nzuobonatan and colleagues, who prospectively performed echocardiography on 75 patients referred for HIV testing.²⁹ Of 54 HIV positive patients, with a mean CD4+ of $119/\text{mm}^3$, 23.3% had a dilated cardiomyopathy, as defined by left ventricular fractional shortening $<28\%$ and left ventricular dilatation (LVEDD/BSA $>3.2\text{cm}/\text{m}^2$). A dilated cardiomyopathy was far more likely to be present with a CD4 count less than $100/\text{mm}^3$: 31.58% ($<100/\text{mm}^3$) vs. 6.06% ($>100/\text{mm}^3$). The striking aspect of these two studies was that most patients were clinically free from specific signs and symptoms of cardiovascular disease and suggests that cardiac abnormalities in African HIV-positive patients can be difficult to discern clinically.

Olusegun-Joseph et al performed echocardiography on 100 HIV positive male and non-pregnant female patients not on ARVs and matched them with 50 controls.³⁰ Significantly more abnormalities were found amongst the HIV positive patients, with 30% displaying signs of systolic dysfunction (reduced LV FS and EF) vs. 8% in controls and diastolic dysfunction (impaired E/A ratios or IVRT) in 32% vs. 8%. Again, pericardial effusions were appreciably higher in the HIV group with nearly half being affected with effusions of varying size, with none appearing in the control population. Only one patient with a pericardial effusion was symptomatic.

In the South African context, the Heart of Soweto Study prospectively studied all patients presenting to the cardiology unit at Chris Hani Baragwanath Hospital.³¹ Of 5328 cases of *de novo* heart disease, 9.7% were HIV positive. The most common diagnosis in these 518 patients was dilated cardiomyopathy (38% - LVEF <45% and LVEDD>55mm), with pericarditis/pericardial effusion (effusion > 0.5cm) being diagnosed in 25% of patients. HIV-associated pulmonary artery hypertension was found in 8.1% and coronary artery disease in only 2.4%.

Other cardiac manifestations of HIV

Pericardial Effusions

Pericardial effusions are the most common cardiac manifestation of HIV, with a prevalence of 20% and an incidence of 11% per year in the pre-HAART era.³² It is an independent predictor of mortality and does not necessarily correlate with CD4+ count. However, as HAART has become standard treatment, some studies have shown a decline in the prevalence of HIV-associated pericardial effusion.³³ As cytokine expression is enhanced in later stages of HIV, capillary leak increases resulting in serous fluid formation in the pleural and peritoneal surfaces. However, it is important to exclude other causes of a pericardial effusion, especially in areas where *Mycobacterium Tuberculosis (TB)* is endemic. GeneXpert studies may assist with in diagnosis.³⁴ In certain areas of Africa, TB is the causative organism in up to 86% of pericardial effusion in HIV positive patients.³⁵ Other organisms that can cause effusions include *Streptococcus* spp. *Staphylococcus* spp. and *Chlamydia*.

Pulmonary Arterial Hypertension

Patients with HIV are at increased risk for developing Pulmonary Artery Hypertension (PAH), probably due to a variety of viral factors that result in extensive remodeling of pulmonary vessels.³⁶ HIV has also been identified in alveolar macrophages on histology. These macrophages release TNF-alpha, oxide anions, and proteolytic enzymes in response to infection.³⁷ *Pneumocystis* pneumonia has also been implicated in the development of PAH, even after the disease has been fully treated. Signs and symptoms reflect the degree of disease and standard echocardiographic measures are used for diagnosis. It is unknown whether HAART affects the course of HIV-associated pulmonary hypertension.

Vasculitis

An assortment of vasculitides, including polyarteritis nodosa, has been associated with HIV infection, with an incidence of less than 1%. Large vessel vasculopathies including abdominal aortic aneurysms have been recognised in young African patients who have no other cause of vasculitis (e.g. syphilis) and present with slow-growing masses that may or may not be tender.³⁸

Endocarditis

Infective endocarditis is common in HIV, and the prevalence varies from 6.4% to 34%.³⁹ Although presentation is similar to HIV-negative patients, complication and mortality rates are higher in patients with advanced HIV.

Organisms include *Staphylococcus aureus* (75% of patients), *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Candida Albicans*.

Coronary artery disease (CAD) and metabolic syndrome

Initial reports have associated HIV with CAD since 1998, with accelerated atherosclerosis histologically distinct to HIV. Increase inflammatory markers may play a role and HIV-1 genomes have been found in coronary arteries of HIV positive patients dying of coronary arteritis and acute myocardial infarction.¹² Protease inhibitors are known to cause dyslipidaemia and are strongly associated an increased risk of myocardial infarction.²⁵ In Africa, CAD is relatively uncommon, but as socioeconomic changes occur, Western lifestyles and diet may have an impact on the burden of disease.^{31,38}

HIV and the anaesthetist

In South Africa, HIV is a common co-morbidity in those patients presenting for surgery. As pericardial effusions, myocarditis, reduced ejection fraction systolic dysfunction and impaired diastolic function are common cardiovascular manifestations of HIV, anaesthetists should have a high index of suspicion for these abnormalities, in both the pregnant and non-pregnant population. Patients with a CD4+ of less than 100 and not on HAART are particularly at risk of HIV-associated cardiomyopathy, so an ECG, chest x-ray and perioperative echocardiography may be warranted in such cases.

Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) occurs rarely but is a serious complication of pregnancy and can only be diagnosed in the absence of factors known to cause cardiomyopathy. It is characterized by new onset left ventricular failure between the last month of pregnancy and the first five months following delivery.⁴⁰ PPCM affects between 1:300 and 1:3000 pregnancies, depending on geographical areas. In South Africa, the incidence appears to be 1:1000.⁴¹

A 2009 review of the aetiology and risk factors for PPCM describes multiple conflicting causes including the pathogenetic role of viral myocarditis, abnormal immune response to pregnancy, abnormal response to the haemodynamic stress of pregnancy, accelerated myocyte apoptosis, cytokine-induced inflammation, malnutrition, genetic factors, excessive prolactin production, abnormal hormonal function, selenium deficiency, increased adrenergic tone and myocardial ischaemia.⁴² Important factors identified include vascular endothelial growth factor (VEGF), cathepsin D-cleaved 16kDA prolactin⁴³ and soluble fms-like tyrosine kinase-1 (sFlt-1) which disable proteins that promote new blood vessel development.⁴⁴

Other risk factors include advanced maternal age, high parity, high gravidity, prolonged lactation, twin pregnancy, the use of tocolytic therapy, African descent, non-Caucasian ethnicity and poverty. Other environmental factors may be at fault. In a high incidence area (one in a hundred live births) in Nigeria, young Hauta mothers lie on hot mud beds for up to forty days post-partum and are made to ingest large amounts of 'Kanwa' salt from nearby Lake Chad. This results in significant hypervolemia and fluid overload.⁴⁵

HIV and PPCM

Theories regarding the aetiology of PPCM are widely divergent.⁴² Viral infiltration has been found in a significant portion of myocardial biopsies in patients with PPCM, and given that HIV itself may invade the myocardium, the HIV positive pregnant women may be predisposed to develop a dilated cardiomyopathy.

A recent study by Sliwa et al did not show any worse outcomes in patients with PPCM infected with HIV as compared to a cohort without HIV.⁴⁶ Eighty consecutive PPCM patients were recruited at South African hospitals and followed up over 24 months. As expected, due to the high HIV prevalence in South Africa, a third (34%) of patients were HIV positive. There was no difference in demographics, body habitus and blood pressure between the HIV positive and negative groups and no difference was found between baseline echocardiographic measurements (both groups LV ejection fraction 30%). Even when compared at six-, twelve and 24-month intervals, there were no differences between the echocardiographic findings of the two groups. 26% of the HIV group had a CD4 less than 200/mm³ (World Health Organisation stage 4) but only two were initiated on ARVs. Despite this, over the study period, there was no significant difference in mortality between the two groups.

The only significant differences between the two groups were the lower hemoglobin levels (HIV+: 10.5 ± 2.1 g/dl vs. HIV-: 11.9 ± 1.7 g/dl) and a faster heart rate (110 ± 16 bpm vs. 97 ± 18 bpm). Pro-inflammatory cytokines, like TNF α , were equally elevated in both groups. These cytokines, in high enough concentrations, can themselves cause left ventricular dysfunction and cardiomyopathy.

HIV, pregnancy and cardiac dysfunction

There is very little data on what cardiac changes occur, if any, in HIV positive pregnant women. Anecdotes and case reports form the bulk of our knowledge. Mandal and Dattaray describe a case in which an HIV positive mother presented with signs of congestive cardiac failure for first time late in the third trimester.⁴⁷ Echocardiography showed a dilated cardiomyopathy in the absence of any other causes, with an ejection fraction (EF) of 35%, confirming the diagnosis of PPCM. Despite a reasonable CD4 count of 250, successful delivery of the fetus via caesarean section (CS) and appropriate anti-failure treatment, the patient succumbed to sustained ventricular tachycardia on the second day post-operatively. This well describes the increased risk during peri-partum care of patients with both diseases.

Longenecker and colleagues examined 41 HIV infected and 41 HIV negative pregnant women in Uganda.⁴⁸ Their study recruited HIV positive women at an average of 36 weeks gestation, at least 24 of whom were on ARVs, according to postnatal records. All patients were asymptomatic and underwent a standardized transthoracic echocardiogram according to American Society of Echocardiography guidelines. No echocardiographic evidence of peripartum cardiomyopathy or pulmonary hypertension was found – the seven measurements being left ventricular (LV) ejection fraction, LV end-diastolic volume index, LV mass index, left atrial (LA) volume index, mitral E/E' ratio, RV systolic pressure and cardiac output. The study was hampered by the lack of CD4 count, viral load, and that patients were not at term. Treatment length and type were also not fully documented.

Conclusion

Given the cardiovascular changes of pregnancy and the known potential for the development of systolic and diastolic dysfunction in HIV positive patients, it is not unreasonable to suppose that the heart of an HIV-infected patient may respond differently to the demands of pregnancy as compared to an HIV negative patient. As anaesthetists involved in the safe delivery of many of these patients, it is imperative that we know, firstly, if HIV causes cardiovascular changes in pregnancy, secondly, to what extent these changes occur and thirdly, how these changes effect our management of HIV positive pregnant patients. Lastly, we need to know whether any changes that occur revert to normal function in the post-partum period.

References

- 1 World Health Organisation. *World Health Statistics 2014*. 2014. http://apps.who.int/iris/bitstream/10665/112738/1/9789240692671_eng.pdf accessed 26_04_2015
- 2 Fawcus S, Pattinson R, Moodley J. *Tenth interim report on Confidential Enquiries into Maternal Deaths in South Africa*. 2012. http://indicators.hst.org.za/indicators/ChildHealth/Saving_Mothers_2012.pdf accessed 06_10_2014
- 3 Morgan GE, Mikhail MS, Murray MJ. *Clinical Anesthesiology*. 4th Edition. Lange Medical Books/McGraw-Hill; 2006:875
- 4 Dennis AT. Transthoracic echocardiography in obstetric anaesthesia and obstetric critical illness. *Int J Obstet Anesth* 2011;**20**(2):160–8. Doi: 10.1016/j.ijoa.2010.11.007.
- 5 Dennis A, Dyer RA. Cardiac output monitoring in obstetric anaesthesia. *Int J Obstet Anesth* 2014;**23**(1):1–3. Doi: 10.1016/j.ijoa.2013.11.001.
- 6 Dennis A, Stenson A. The use of transthoracic echocardiography in postpartum hypotension. *Anesth Analg* 2012;**115**(5):1033–7. Doi: 10.1213/ANE.0b013e31826cde5f.
- 7 Desai DK, Moodley J, Naidoo DP. Echocardiographic assessment of cardiovascular hemodynamics in normal pregnancy. *Obstet Gynecol* 2004;**104**(1):20–9. Doi: 10.1097/01.AOG.0000128170.15161.1d.
- 8 Mabie WC, DiSessa TG, Crocker LG, Sibai BM, Arheart KL. A longitudinal study of cardiac output in normal human pregnancy. *Am J Obstet Gynecol* 1994;**170**(3):849–56. Doi: 10.1016/S0002-9378(94)70297-7.
- 9 Simmons LA, Gillin AG, Jeremy RW. Structural and functional changes in left ventricle during normotensive and preeclamptic pregnancy. *Am J Physiol Hear Circ Physiol* 2002;**283**:H1627–33. Doi: 10.1152/ajpheart.00966.2001.
- 10 Vellin A, Antonini F, Muller L, et al. Lung Ultrasound Predicts Interstitial Syndrome and Hemodynamic Profile in Parturients with Severe Preeclampsia. *Anesthesiology* 2014;**120**:906–14.
- 11 Dennis AT. Management of pre-eclampsia: issues for anaesthetists. *Anaesthesia* 2012;**67**(9):1009–20. Doi: 10.1111/j.1365-2044.2012.07195.x.
- 12 Barbaro G, Lipshultz SE. Pathogenesis of HIV-Associated Cardiomyopathy. *Ann N Y Acad Sci* 2001;**946**:57–81. Doi: 10.1111/j.1749-6632.2001.tb03903.x.
- 13 Kan H, Xie Z, Finkel MS. p38 MAP kinase-mediated negative inotropic effect of HIV gp120 on cardiac myocytes. *Am J Physiol Cell Physiol* 2004;**286**(1):C1–7. Doi: 10.1152/ajpcell.00059.2003.

- 14 Cohen IS, Anderson DW, Virmani R, et al. Congestive Cardiomyopathy in Association with the Acquired Immunodeficiency Syndrome. *N Engl J Med* 1986;**315**:628–30.
- 15 Prendergast BD. HIV and cardiovascular medicine. *Heart* 2003;**89**:793–800.
- 16 Barbaro G, Lorenzo G Di, Grisorio B. Incidence of dilated cardiomyopathy and detection of HIV in myocardial cells of HIV-positive patients. *N Engl J Med* 1998;**339**(16):1093–9.
- 17 Pozzan G, Pagliari C, Tuon FF, et al. Diffuse-regressive alterations and apoptosis of myocytes: possible causes of myocardial dysfunction in HIV-related cardiomyopathy. *Int J Cardiol* 2009;**132**(1):90–5. Doi: 10.1016/j.ijcard.2007.10.057.
- 18 Garg H, Joshi A, Mukherjee D. Cardiovascular complications of HIV infection and treatment. *Cardiovasc Hematol Agents Med Chem* 2013;**11**(1):58–66.
- 19 Barbaro G, Lorenzo G Di, Soldini M, et al. Intensity of Myocardial Expression of Inducible Nitric Oxide Synthase Influences the Clinical Course of Human Immunodeficiency Virus-Associated Cardiomyopathy. *Circulation* 1999;(100):933–9.
- 20 Benbrik E, Chariot P, Bonavaud S, et al. Cellular and mitochondrial toxicity of zidovudine (AZT), didanosine (ddI) and zalcitabine (ddC) on cultured human muscle cells. *J Neurol Sci* 1997;**149**(1):19–25.
- 21 Reyskens KMSE, Essop MF. HIV protease inhibitors and onset of cardiovascular diseases: a central role for oxidative stress and dysregulation of the ubiquitin-proteasome system. *Biochim Biophys Acta* 2014;**1842**(2):256–68. Doi: 10.1016/j.bbadis.2013.11.019.
- 22 Murata H, Hruz PW, Mueckler M. Investigating the cellular targets of HIV protease inhibitors: implications for metabolic disorders and improvements in drug therapy. *Curr Drug Targets Infect Disord* 2002;**2**(1):1–8.
- 23 Koster JC, Remedi MS, Qiu H, Nichols CG, Hruz PW. HIV protease inhibitors acutely impair glucose-stimulated insulin release. *Diabetes* 2003;**52**(7):1695–700.
- 24 D'Ascenzo F, Cerrato E, Biondi-Zoccai G, et al. Acute coronary syndromes in human immunodeficiency virus patients: a meta-analysis investigating adverse event rates and the role of antiretroviral therapy. *Eur Heart J* 2012;**33**(7):875–80. Doi: 10.1093/eurheartj/ehr456.
- 25 Holmberg SD, Moorman AC, Williamson JM, et al. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. *Lancet (London, England)* 2002;**360**(9347):1747–8. Doi: 10.1016/S0140-6736(02)11672-2.
- 26 Reinsch N, Kahlert P, Esser S, et al. Echocardiographic findings and abnormalities in HIV-infected patients: results from a large, prospective, multicenter HIV-heart study. *Am J Cardiovasc Dis* 2011;**1**(2):176–84.

- 27 Bárbaro G, Barbarini G, Di G. Early Impairment of Systolic and Diastolic Function in Asymptomatic HIV-Positive Patients : A Multicenter Echocardiographic and Echo-Doppler Study. *AIDS Res Hum Retroviruses* 1996;**12**(16):1559–63.
- 28 Twagirumukiza M, Nkeramihigo E, Seminega B, et al. Prevalence of dilated cardiomyopathy in HIV-infected African patients not receiving HAART: a multicenter, observational, prospective, cohort study in Rwanda. *Curr HIV Res* 2007;**5**(1):129–37.
- 29 Nzuobontane D, Blackett KN, Kuaban C. Cardiac involvement in HIV infected people in Yaounde, Cameroon. *Postgrad Med J* 2002;**78**(925):678–81.
- 30 Olusegun-Joseph DA, Ajuluchukwu JNA, Okany CC, et al. Echocardiographic patterns in treatment-naïve HIV-positive patients in Lagos, south-west Nigeria. *Cardiovasc J Afr* 2012;**23**(8):e1–6. Doi: 10.5830/CVJA-2012-048.
- 31 Sliwa K, Carrington MJ, Becker A, et al. Contribution of the human immunodeficiency virus/acquired immunodeficiency syndrome epidemic to de novo presentations of heart disease in the Heart of Soweto Study cohort. *Eur Heart J* 2012;**33**(7):866–74. Doi: 10.1093/eurheartj/ehr398.
- 32 Heidenreich PA, Eisenberg MJ, Kee LL, et al. Pericardial Effusion in AIDS : Incidence and Survival. *Circulation* 1995;**92**(11):3229–34. Doi: 10.1161/01.CIR.92.11.3229.
- 33 Lind A, Reinsch N, Neuhaus K, et al. Pericardial effusion of HIV-infected patients - Results of a prospective multicenter cohort study in the era of antiretroviral therapy. *Eur J Med Res* 2005;**16**:480–3.
- 34 Dhana AV, Howell P, Sanne I, Spencer D. Identification of Mycobacterium tuberculosis from pericardial fluid using the new Xpert MTB/RIF assay. *BMJ Case Rep* 2013;**2013**:1–3. Doi: 10.1136/bcr-2013-200615.
- 35 Ntsekhe M, Mayosi BM. Tuberculous pericarditis with and without HIV. *Heart Fail Rev* 2013;**18**(3):367–73. Doi: 10.1007/s10741-012-9310-6.
- 36 Syed FF, Sani MU. Recent advances in HIV-associated cardiovascular diseases in Africa. *Heart* 2013;**99**(16):1146–53. Doi: 10.1136/heartjnl-2012-303177.
- 37 Pellicelli, M. A, Barbaro, et al. Primary pulmonary hypertension in HIV patients: A systematic review. *Angiology* 2001;**52**(1):31–41.
- 38 Ntsekhe M, Hakim J. Impact of Human Immunodeficiency Virus Infection on Cardiovascular Disease in Africa. *Circulation* 2005;**112**:3602–7. Doi: 10.1161/CIRCULATIONAHA.105.549220.
- 39 Khunnawat C, Mukerji S, Havlichek D, Touma R, Abela GS. Cardiovascular manifestations in human immunodeficiency virus-infected patients. *Am J Cardiol* 2008;**102**(5):635–42. Doi: 10.1016/j.amjcard.2008.04.035.

- 40 Twomley KM, Wells GL. Peripartum cardiomyopathy: a current review. *J Pregnancy* 2010;**2010**:149127. Doi: 10.1155/2010/149127.
- 41 Sliwa K, Fett J, Elkayam U, Schweitzer HA. Peripartum cardiomyopathy. *Lancet* 2006;(368):687-93.
- 42 Ntusi NB a, Mayosi BM. Aetiology and risk factors of peripartum cardiomyopathy: a systematic review. *Int J Cardiol* 2009;**131**(2):168-79. Doi: 10.1016/j.ijcard.2008.06.054.
- 43 Hilfiker-Kleiner D, Kaminski K, Podewski E, et al. A cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. *Cell* 2007;**128**(3):589-600. Doi: 10.1016/j.cell.2006.12.036.
- 44 Patten IS, Rana S, Shahul S, et al. Cardiac angiogenic imbalance leads to peripartum cardiomyopathy. *Nature* 2012;**485**(7398):333-8. Doi: 10.1038/nature11040.
- 45 Okeke T, Ezenyeaku C, Ikeako L. Peripartum cardiomyopathy. *Ann Med Health Sci Res* 2013;**3**(3):313-9. Doi: 10.4103/2141-9248.117925.
- 46 Sliwa K, Forster O, Tibazarwa K, et al. Long-term outcome of peripartum cardiomyopathy in a population with high seropositivity for human immunodeficiency virus. *Int J Cardiol* 2011;**147**(2):202-8. Doi: 10.1016/j.ijcard.2009.08.022.
- 47 Mandal D, Dattaray C, Dutta M, Sarkar G, Sinha P. Peripartum cardiomyopathy coexistent with human immunodeficiency virus: a substantial obstetric jeopardy. *Heart Views* 2013;**14**(1):26-8. Doi: 10.4103/1995-705X.107117.
- 48 Longenecker CT, Mondo C, Le V, Jensen TP, Foster E. HIV infection is not associated with echocardiographic signs of cardiomyopathy or pulmonary hypertension among pregnant Ugandan women. *Int J Cardiol* 2011;**147**(2):300-2. Doi: 10.1016/j.ijcard.2010.12.047.HIV.

Print Ready Article (International Journal of Obstetric Anesthesia)

Title Page

QUANTIFICATION OF CARDIAC STRUCTURE AND FUNCTION USING TRANSTHORACIC ECHOCARDIOGRAPHY IN TERM WOMEN WITH HIV

M Gibbs¹, A Dennis², R Dyer¹, L Nel¹, J Castro², J Swanevelder¹ ¹*Groote Schuur Hospital & The University of Cape Town, South Africa;* ²*Royal Women's Hospital, St Vincent's Hospital Melbourne, & University of Melbourne, Australia*

Corresponding author: Dr. Matthew Gibbs (mattwintgibbs@gmail.com)

Phone: +27 73 148 2026

Address: D23 Anaesthesia Department, Groote Schuur Hospital, Anzio Road,
Observatory, 7935, Republic of South Africa

Abstract

Introduction: In South Africa, up to 30% of pregnant women are human immunodeficiency virus (HIV) positive and morbidity and mortality is high in this group. HIV positive men and women may have multiple cardiovascular comorbidities, which include systolic dysfunction that may progress to heart failure secondary to dilated cardiomyopathy. However the concurrent effect of pregnancy and HIV infection on haemodynamics has not been extensively researched. The aims of this study were to quantify haemodynamics using transthoracic echocardiography (TTE) in term pregnant women with HIV on Anti-Retroviral (ARV) treatment and compare the data with term healthy women in the same population.

Method: After ethics approval and written consent, 30 consecutive term HIV positive women and 40 healthy term pregnant women were recruited. HIV positive women had a CD4 count greater than 200 and were either on Highly Active Anti-Retroviral Therapy (HAART) or single drug management.

Results: Haemodynamic assessment was possible in all patients and women in the two groups were similar in age, and body mass index. Mean CD4 count was 452 ± 187.8 and duration of therapy was 15.9 ± 22.4 months. Compared with healthy pregnant women, women with HIV have systolic changes exhibited by reductions in LV septal and RV systolic myocardial velocities as well as increased LV ED areas and diastolic changes of increased RV IV relaxation and reduced RV e' diastolic myocardial velocities. These changes occur in the presence of a reduced LV mass. Pericardial effusions occur more frequently and are of a larger size in women with HIV.

These findings suggest subclinical impairment of systolic function in the LV as well as subclinical impairment of both systolic and diastolic function in the RV.

Discussion:

Transthoracic echocardiography can quantify cardiac function in healthy pregnant women and in pregnant women with HIV and is acceptable to the patients. HIV positive pregnant women at term on anti-retroviral therapy have hearts that have subtle systolic dysfunction in the presence of decreased LV mass and increased end-diastolic areas. This may represent a failure to compensate for the increased haemodynamic demands of pregnancy and may be as a result of the direct effects of the HI virus itself or due to anti-retroviral drugs.

Main Text

Introduction

South Africa has experienced an incredibly rapid rise in HIV infection, where prevalence in adults has increased from about 1% in 1990 to about 25% in 2000.¹ Despite the rollout by government of ARVs in 2005 and an overall rate now reduced to 17.9%, pregnant women remain disproportionately affected, with a prevalence up to 30% in 2010.² Mortality and morbidity is high in this group, as demonstrated by maternal deaths in South Africa due to non-pregnancy related infections representing 26% of all maternal deaths, of whom 90% were HIV positive.³

HIV positive men and women may have multiple cardiovascular comorbidities, which include systolic dysfunction that may progress to heart failure due to dilated cardiomyopathy. Research in Rwanda has shown that HIV-associated dilated cardiomyopathy may occur in up to 17% of untreated HIV positive patients.⁴ In another prospective cohort trial, the incidence of systolic dysfunction was up to 34% and diastolic dysfunction of 48% in asymptomatic HIV positive patients on HAART.⁵ A recent limited study in Uganda suggests that HIV infection in pregnant patients on HAART is not necessarily a risk factor for the echocardiographic signs of cardiomyopathy or pulmonary hypertension.⁶

However the effect of pregnancy and HIV infection on haemodynamics has not been extensively researched. Increasing dyspnea and haemodynamic changes associated with aortocaval compression caused by the normal physiological changes of pregnancy make the identification of cardiac disease problematic. Recent developments in transthoracic echocardiography (TTE) have led to an improved understanding of cardiac physiology and pathophysiology of pregnancy.⁷ TTE not only enables better definition of cardiac dysfunction, but also contributes to point of care management in pregnancy.⁸ TTE has been shown to be acceptable and applicable in pregnant

women with no known side effects. TTE could help identify cardiac dysfunction, guide treatment, and reduce risk in this population.

Aims

Our aims in this study were to recruit a group of otherwise healthy HIV positive pregnant women at term and compare cardiac structure and function using transthoracic echocardiography with a matched cohort of healthy pregnant patients. Transthoracic echocardiography is validated in pregnancy and is a well accepted and minimally invasive method of determining cardiac structure and function.⁹⁻¹¹

Methods

This multicentre, prospective observational study was performed in collaboration with the Royal Women's Hospital, Parkville and the University of Melbourne, Australia and Groote Schuur Hospital and Mowbray Maternity Hospital and The University of Cape Town, South Africa. This study formed part of the larger "Transthoracic echocardiography in pregnant women study", approved by the Human Research Ethics Committee University of Cape Town 442/2013, UTN U1111-1147-2431, and registered with the Australian Clinical Trial Registry: ACTRN12613000992707. After written informed consent, we recruited a convenience sample of 30 term HIV women and 40 healthy term women (based on previous work which required 40 healthy women for comparison haemodynamic data) from outpatient clinics from the two hospitals in South Africa.

Term HIV (CD4 count was greater than 200/mm³ and if they were on ARVs – either HAART or single drug therapy (zidovudine: AZT) and healthy women older than 18 years, were recruited electively at term ($\geq 37^0$ weeks gestation).

Exclusion criteria included inability to consent, refusal, pre-existing or gestational diabetes, known cardiac or hypertensive disease, multiple pregnancy, a known uterine abnormality or abnormal placentation or any woman in labour.

All ultrasound studies were performed by one of two trained echocardiography investigators (ATD, LN) using a Vivid Q or Vivid S6 with 7.5 MHz transducer (GE VINGMED ULTRASOUND A/S N-3191 Horten, Norway) using 2-dimensional, M-mode, colour-flow, continuous, pulsed wave and tissue Doppler imaging according to American Society of Echocardiography guidelines and following the methodology previously published.^{12,13}

Transthoracic echocardiography occurred in the left lateral position after five minutes rest. A three lead electrocardiograph was attached. A mercury sphygmomanometer was placed on the left arm and baseline systolic and diastolic blood pressures were obtained, recording the diastolic value as Korotkoff V according to the American Heart Association guidelines. The measurement was made to the closest two mmHg. The mean arterial pressure was calculated.

All echocardiography measurements were performed and analysed off-line. Each measurement was the average of three consecutive beats. Standard

views were obtained, including apical 2-, 4- and 5-chamber (A2C, A4C, A5C), and parasternal long and short axis (PLAX and PSAX) views. The exam included 2-dimensional imaging and continuous, pulse wave, colour flow and tissue Doppler. The stored images were reviewed and measured independently in random order by two investigators (AD/JC).

Haemodynamic measurements were performed according to standard recommendations. Stroke volume was calculated after calculating the product of the left ventricular outflow tract (LVOT) diameter (cross sectional area) obtained from the PLAX view, and the Doppler derived velocity time integral of the left ventricular outflow tract (LVOT VTI), obtained from the A4C. This in turn multiplied by the heart rate gives cardiac output.

Fractional shortening was measured using the M-mode recording at the tips of the mitral valve in the PLAX view. Fractional area change was measured during systole and diastole from the parasternal short axis image at the mid-papillary level. Systemic vascular resistance was calculated from mean arterial pressure and cardiac output. Diastolic function was measured using mitral valve inflow velocities E and A ($\text{cm}\cdot\text{s}^{-1}$), mitral valve deceleration time (ms), mitral valve A wave duration (ms), isovolumetric relaxation time (ms) and left atrial diameter (cm). Myocardial Tissue Doppler recorded the myocardial interventricular septum diastolic velocities of e' and a' and the systolic velocity of s' . Insonation angles were between 0-5 degrees. The left ventricular mass was calculated using measurements obtained from the PLAX M-mode image of the left ventricle during diastole. The Tei index, the measurement of overall myocardial performance was measured using tissue Doppler time intervals.

Haemodynamic data are presented as mean (standard deviation [SD]) or number (proportion) of women. Where appropriate, data were compared using unpaired two-tailed t-tests with Welch's correction, and proportions compared using Fisher's exact test. Interobserver and intraobserver variability was determined using Bland Altman methodology and expressed as bias (mean difference) and limits of agreement ($2 \times$ SD mean difference). A second observer (JMC) independently measured the LVOT diameter and LVOT VTI to enable interobserver variability to be calculated and the single observer (AD) performed one repeated measurement of the LVOT diameter and LVOT VTI four months apart to enable intraobserver variability to be calculated. P was considered significant at less than 0.05.

Results

From August 2013 through December 2013, we recruited 83 women (Figure 1). Six were excluded from the HIV group and seven from the healthy term group. There were no complications related to the study and no maternal deaths. No woman refused consent.

The demographics of the HIV positive and healthy term patients are shown in Table 1. Anaemia, defined as haemoglobin concentration of $<11.0 \text{ g.dl}^{-1}$, was common in both groups, with up to a third in the healthy group and 17% in the HIV positive group. Obesity, defined as a body mass index of $\geq 30 \text{ kg.m}^{-2}$, was present in 59% of the total cohort, with a mean of 32 in each group.

The 30 term HIV and 40 healthy pregnant women were well matched for all characteristics except for smoking status. In the term HIV group, CD4 counts were $452 \pm 187.8 \text{ cells/mm}^3$ and the duration of treatment was 15.9 ± 22.4 months (mean \pm SD).

Haemodynamics and left ventricular systolic data for the two groups of patients are shown in Table 2. HIV patients had significantly reduced cardiac indices and cardiac work indices, reduced septal s' tissue Doppler velocities and increased left ventricular end-diastolic and end-systolic areas compared with gestationally matched healthy pregnant women. Corrected flow time was also significantly decreased. Three (10%) of HIV positive patients had left ventricular end diastolic diameters (LVEDD) greater than 5.3 cm.

Ten per cent of asymptomatic healthy term pregnant women demonstrated reductions in fractional shortening and one healthy patient had a dilated ventricle with a left ventricular end diastolic diameter of > 5.3 cm.

Table 3 shows left ventricular diastolic and structural data for the two groups of patients. Although there was no significant LV diastolic differences between the two groups, approximately 40% of healthy pregnant patients and patients with HIV had mitral valve E/septal e' ratios greater than eight, with two women in each group having mitral valve E/A ratios less than one. Other structural changes seen in the HIV group included a decreased LV mass (mean of 140g vs. 170g) and a decreased interventricular septal and LV posterior wall thickness. Pericardial effusions, although present about half of healthy women, were more common in patients with HIV (83% vs. 53%) and were also of larger size (mean 0.52 cm vs. 0.3 cm) than in healthy pregnant women.

Right ventricular functional data are shown in table 4. Biphasic s' waves were common in all groups. Patients with HIV had reductions in right ventricular s' velocities, reductions in right ventricular e' velocities and increases in the right ventricular isovolumetric relaxation time but with similar tricuspid annular plane systolic excursion (TAPSE) values compared with healthy pregnant women. Right ventricular myocardial performance index (i.e. Tei index) was also increased.

Interobserver variability, using Bland-Altman methodology, for the LVOT diameter and LVOT VTI was determined for the total group. The mean \pm SD differences for the LVOT diameter and LVOT VTI between two observers ATD and JMC were 0.27 ± 1.1 mm and -0.71 ± 1.4 cm.s⁻¹. For the LVOT

diameter this equates to 95% of the interobserver measurements being within 2.2 mm (11 %) of the mean LVOT measurement for the 2 observers of 19.9 mm. For the LVOT VTI this equates to 95% of the interobserver measurements being within 2.7 cm.s⁻¹ (12 %) of the mean value for the two observers of 21.5 cm.s⁻¹.

Intraobserver variability, calculated using Bland-Altman methodology, for the LVOT diameter and LVOT VTI for the group, determined the mean \pm SD differences for the LVOT diameter and LVOT VTI between two observations for the single observer AD to be 0.0 ± 0.2 mm and 0.05 ± 0.6 cm.s⁻¹. For the LVOT diameter this equates to 95% of the intraobserver measurements being within 0.4 mm (2 %) of the mean LVOT measurement for the two observations of 19.9 mm. For the LVOT VTI this equates to 95% of the intraobserver measurements being within 1.1 cm.s⁻¹ (5 %) of the mean value for the two observations of 21.7 cm.s⁻¹.

Discussion

This study determined important haemodynamic and cardiac structural characteristics of HIV positive term pregnant women and healthy term women in the context of a high maternal mortality rate. In HIV positive term women, our data showed decreased systolic function in the left ventricle with significantly decreased cardiac index and decreased cardiac work index. Other findings consistent with this was a decreased LV septal s'. Diastolic changes in the LV included decreased lateral and septal a' velocities. In the right ventricle, both the isovolumetric relaxation time and isovolumetric contraction time were increased, as well as decreased s' and e' velocities, demonstrating subclinical systolic and diastolic dysfunction. Other key

findings in the HIV group include a decreased LV mass (140 g vs. 170 g), increased LV end-diastolic and end-systolic areas (17.2 cm² vs. 15.1 cm²; 7.6 cm² vs. 6.3 cm²) and increased number and size of pericardial effusions.

Anaemia was a common co-existing problem. Not only did 17% of the HIV group have a haemoglobin less than 11g.dl⁻¹, but so did 33% of the healthy women. This is however much lower than in a recent South African retrospective cohort study on anaemia in pregnancy in HIV positive women, with a prevalence of up to 64% with risk factors including a CD4 count less than 200 and increased gravidity.¹⁴ This discrepancy may be explained by our selection of patients with a CD4 count greater than 200. Anaemia in the healthy group may represent generalized socioeconomic conditions facing many South Africans, which in turn affect nutrition and other environmental factors. The potential affect of anaemia on cardiac output should be considered when interpreting findings.

Regarding our haemodynamic findings, the presence of systolic and diastolic dysfunction is consistent with both European and African data in HIV positive non-pregnant populations.^{4,5,15,16} There is a relative lack of data on structural and functional changes in HIV positive pregnant patients. In our study, the HIV positive group had a significantly decreased cardiac index (2.8 l.min⁻¹ vs. 3.1 l.min⁻¹. Longenecker et al studied HIV positive pregnant patients in Uganda, but certain important data are lacking.⁶ Of the 41 patients recruited in the HIV positive group, records for anti-retroviral treatment were only available for 24 patients, CD4 and viral load data are not available and the average gestational age at the time of the study was 36 weeks, compared to 39 and 40 weeks respectively in our HIV positive and healthy control groups. As antiretroviral therapy and the HI virus itself may all affect cardiac structures,¹⁷ it is difficult to make any concrete conclusions. Cardiac output in the Ugandan study was reported as not being significantly different (4.2 l.min⁻¹ vs. 4.3 l.min⁻¹, p=0.84) but no correction for BMI was made. It is

possible that our findings of a dilated left ventricle (in both systole and diastole) and a decreased LV mass in conjunction with decreased left and right ventricular systolic myocardial velocities are representative of early echocardiographic signs of dilated cardiomyopathy. Reinsch et al, however, found that in a prospective study of 803 HIV-positive non-pregnant patients that the interventricular septum and posterior wall thickness were increased in 18.0% and 11.1%⁵.

Pericardial effusions were common in both groups, with a prevalence of 83% in the HIV positive group. This is in keeping with other research which has shown that effusions are the most common manifestation of HIV associated cardiac changes.^{15,18} The overall prevalence is 20% in the non-pregnant population, which reaches 25% in the South African context.¹⁶ Pericardial effusions in HIV positive patients have been linked with an increased mortality rate, independent of CD4 count and are therefore an ominous sign.¹⁹ Figure 2 demonstrates the typical appearance of such a pericardial effusion.

All patients studied were on ARVs, yet we know that ARVs can cause cardiac dysfunction.¹⁷ The World Health Organisation guidelines state that all pregnant patients should be initiated on HAART lifelong as first line therapy. These guidelines have been implemented in the Western Cape. The regimen in the Western Cape is for a fixed dose combination tablet (FDC) consisting of emtricitabine, tenofovir (both NRTIs) and efavirenz (NNRTI) once daily, commencing on the day of diagnosis. If HAART cannot be started promptly, patients are initiated on AZT until such time as they can be counseled and initiated. AZT is well known for its effects on myocyte mitochondria, which can result in dilated cardiomyopathy if given as a single drug and in high doses.²⁰ The five women in our study on AZT were due to be initiated shortly, and therefore had limited exposure to the drug (less than six months). Nine women had been on ARVs for more than twelve months, and as such, were more likely to have myocardial changes due to their drug regimens. It is

unlikely however that the FDC combination would have significant cardiac effects.

In South Africa, HIV is a common co-morbidity in those patients presenting for surgery. As pericardial effusions, myocarditis, reduced ejection fraction, systolic dysfunction and impaired diastolic function are common cardiovascular manifestations of HIV, anaesthetists should have a high index of suspicion for these abnormalities, in both the pregnant and non-pregnant population. Patients with a CD4+ of less than 100 and not on HAART are particularly at risk of HIV-associated cardiomyopathy, so an ECG, chest x-ray and perioperative echocardiography may be warranted in such cases. The treating physician should therefore be cautious of diagnosing an HIV-positive patient presenting with signs and symptoms of a dilated cardiomyopathy with peripartum cardiomyopathy.

This study has some limitations. All patients were recruited from a small geographical area and the study numbers were limited by the availability of appropriate staff to perform TTE. We did not record ethnicity as part of our demographic data, however data exists that demonstrate that black African women have a higher incidence of PPCM than their American counterparts, with some areas of Africa having an incidence as high as 1 in a 100 live births (compared to 1 in 4000 in Caucasian women).²¹ AZT is well known to have effects on the myocardium via mitochondrial toxicity, causing systolic dysfunction. Those patients on monotherapy may have been affected by this, although high doses and prolonged use are usually necessary for this to occur.¹⁷ Our findings were based on single echocardiographic examinations at term, not a set of serial examinations, and we have not performed follow up studies in the post partum phase to determine if cardiac function returns to normal.

Future Research

There is a paucity of longitudinal data on changes in cardiac structure and function in HIV positive patients through the whole of pregnancy, and further studies need to be conducted to find whether the changes found in this study return to baseline. It is yet unclear how environmental and dietary factors affect cardiac function in our population in South Africa, and how concomitant HIV infection is related to cardiac dysfunction in the Western Cape context.

Conclusions

This is the first study to show subclinical changes in cardiac structure and function in normal HIV positive women at term. In this population, anaemia and obesity are a problem. Term women with HIV were associated with reduced left and right ventricular systolic function shown by decreased left ventricular cardiac index, and decreased right ventricular s' velocities. Structural changes were evidenced by pericardial effusions increased both in size and number as well as left ventricular dilatation and decreased left ventricular mass when compared with healthy pregnant women. Even in some healthy women, abnormal cardiac function was found to be present. We were able to establish echocardiographic reference ranges for healthy term women and term women with HIV. Point-of-care TTE was shown to be practical and acceptable to all pregnant patients in this study.

Acknowledgements

The investigators would like to acknowledge and thank all the women who participated in this study. The investigators would like to acknowledge the support provided by GE Healthcare in providing the transthoracic echocardiography machines for this study.

References

- 1 Dabis F, Ekpini ER. HIV-1/AIDS and maternal and child health in Africa. *Lancet (London, England)* 2002;**359**(9323):2097–104. Doi: 10.1016/S0140-6736(02)08909-2.
- 2 National Department of Health. *The National Antenatal Sentinel HIV and Syphilis Prevalence Survey, South Africa*. 2010. http://www.gov.za/sites/www.gov.za/files/hiv_aids_survey_0.pdf accessed 06_10_2014
- 3 Fawcus S, Pattinson R, Moodley J. *Tenth interim report on Confidential Enquiries into Maternal Deaths in South Africa*. 2012. http://indicators.hst.org.za/indicators/ChildHealth/Saving_Mothers_2012.pdf accessed 06_10_2014
- 4 Twagirumukiza M, Nkeramihigo E, Seminega B, et al. Prevalence of dilated cardiomyopathy in HIV-infected African patients not receiving HAART: a multicenter, observational, prospective, cohort study in Rwanda. *Curr HIV Res* 2007;**5**(1):129–37.
- 5 Reinsch N, Kahlert P, Esser S, et al. Echocardiographic findings and abnormalities in HIV-infected patients: results from a large, prospective, multicenter HIV-heart study. *Am J Cardiovasc Dis* 2011;**1**(2):176–84.
- 6 Longenecker CT, Mondo C, Le V, Jensen TP, Foster E. HIV infection is not associated with echocardiographic signs of cardiomyopathy or pulmonary hypertension among pregnant Ugandan women. *Int J Cardiol* 2011;**147**(2):300–2. Doi: 10.1016/j.ijcard.2010.12.047.HIV.
- 7 Dennis AT, Castro J, Carr C, et al. Haemodynamics in women with untreated pre-eclampsia. *Anaesthesia* 2012;**67**(10):1105–18. Doi: 10.1111/j.1365-2044.2012.07193.x.
- 8 Dennis AT. Transthoracic echocardiography in obstetric anaesthesia and obstetric critical illness. *Int J Obstet Anesth* 2011;**20**(2):160–8. Doi: 10.1016/j.ijoa.2010.11.007.
- 9 Ecimovic P, Loughrey JPR. Ultrasound in obstetric anaesthesia: a review of current applications. *Int J Obstet Anesth* 2010;**19**(3):320–6. Doi: 10.1016/j.ijoa.2010.03.006.

- 10 Dennis AT, Castro JM. Echocardiographic differences between preeclampsia and peripartum cardiomyopathy. *Int J Obstet Anesth* 2014;**23**(3):260–6. Doi: 10.1016/j.ijoa.2014.05.002.
- 11 Armstrong S, Fernando R, Columb M. Minimally- and non-invasive assessment of maternal cardiac output: go with the flow! *Int J Obstet Anesth* 2011;**20**(4):330–40. Doi: 10.1016/j.ijoa.2011.07.006.
- 12 Lawrence G Rudski MD FC, Wyman W Lai MD MPH, Jonathan Afilalo MD M, et al. Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report from the American Society of Echocardiography. *J Am Soc Echocardiogr* 2010;**23**:685–713. Doi: 10.1016/j.echo.2010.05.010.
- 13 Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009;**22**:107–33. Doi: 10.1016/j.echo.2008.11.023.
- 14 Nandlal V, Moodley D, Grobler A, et al. Anaemia in pregnancy is associated with advanced HIV disease. *PLoS One* 2014;**9**(9):e106103. Doi: 10.1371/journal.pone.0106103.
- 15 Ntsekhe M, Hakim J. Impact of Human Immunodeficiency Virus Infection on Cardiovascular Disease in Africa. *Circulation* 2005;**112**:3602–7. Doi: 10.1161/CIRCULATIONAHA.105.549220.
- 16 Sliwa K, Carrington MJ, Becker A, et al. Contribution of the human immunodeficiency virus/acquired immunodeficiency syndrome epidemic to de novo presentations of heart disease in the Heart of Soweto Study cohort. *Eur Heart J* 2012;**33**(7):866–74. Doi: 10.1093/eurheartj/ehr398.
- 17 Garg H, Joshi A, Mukherjee D. Cardiovascular complications of HIV infection and treatment. *Cardiovasc Hematol Agents Med Chem* 2013;**11**(1):58–66.
- 18 Khunnawat C, Mukerji S, Havlichek D, Touma R, Abela GS. Cardiovascular manifestations in human immunodeficiency virus-infected patients. *Am J Cardiol* 2008;**102**(5):635–42. Doi: 10.1016/j.amjcard.2008.04.035.
- 19 Heidenreich PA, Eisenberg MJ, Kee LL, et al. Pericardial Effusion in AIDS : Incidence and Survival. *Circulation* 1995;**92**(11):3229–34. Doi: 10.1161/01.CIR.92.11.3229.
- 20 Benbrik E, Chariot P, Bonavaud S, et al. Cellular and mitochondrial toxicity of zidovudine (AZT), didanosine (ddI) and zalcitabine (ddC) on cultured human muscle cells. *J Neurol Sci* 1997;**149**(1):19–25. Doi: 10.1016/S0022-510X(97)05376-8.
- 21 Ntusi NB a, Mayosi BM. Aetiology and risk factors of peripartum cardiomyopathy: a systematic review. *Int J Cardiol* 2009;**131**(2):168–79. Doi: 10.1016/j.ijcard.2008.06.054.

Figure 1

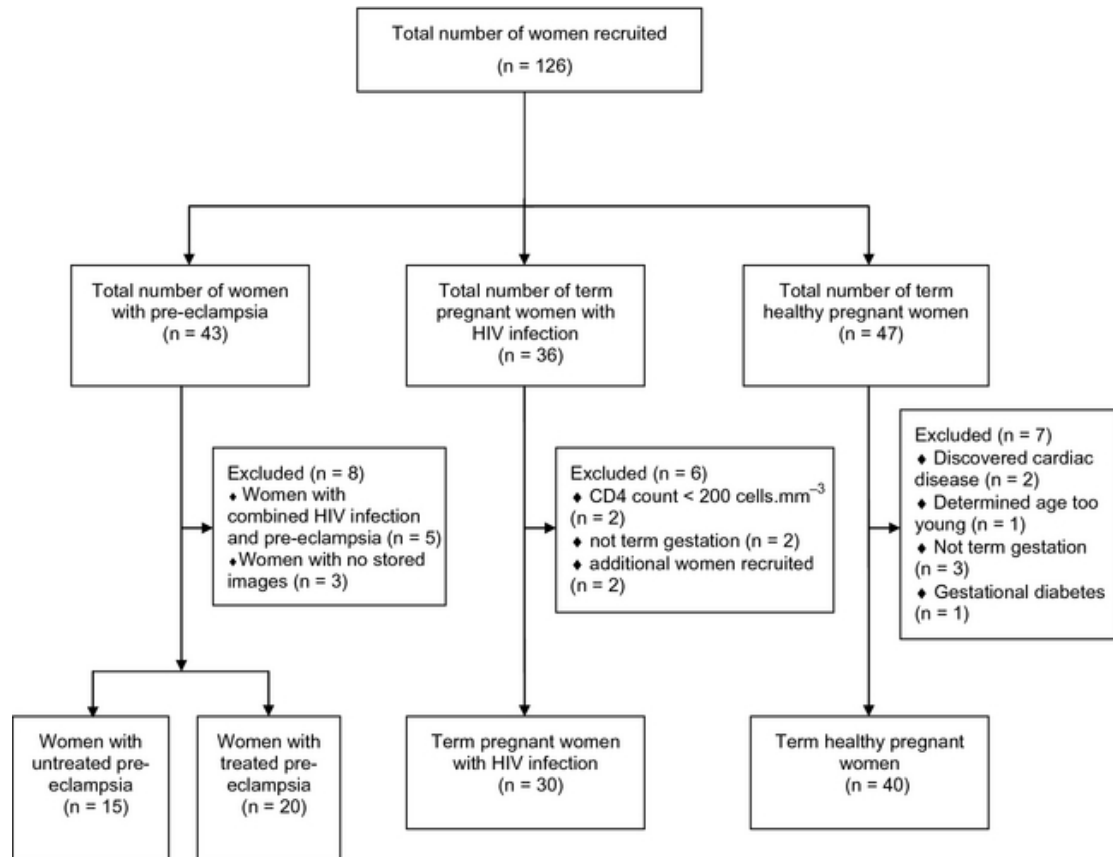


Figure 2

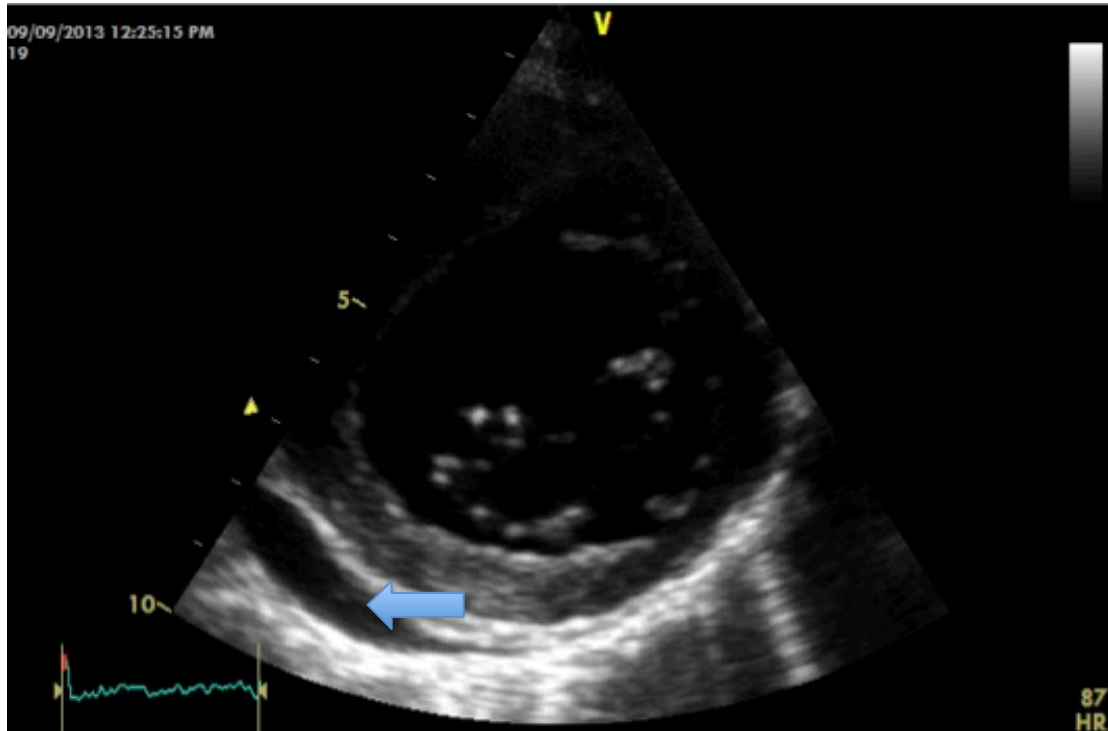


Figure 2: Parasternal short axis view of an HIV-positive pregnant patient at term. Note the haemodynamically insignificant pericardial effusion.

Table 1 Demographic and obstetric data

Characteristic	HIV	Healthy	P value
	Term	Term	HIV vs. Healthy
	n=30	n=40	
Age (years)	27.0 (4.8)	27 (6.3)	0.928
Gestation (weeks)	39 (1.6)	40 (1.8)	0.010
Height (m)	161 (7.2)	160 (6.9)	0.262
Weight (kg)	84 (18.1)	81 (17.4)	0.348
Body mass index (kg.m ⁻²)	32 (7.0)	32 (7.2)	0.646
Nulliparous	6 (20)	14 (35)	0.193
Haemoglobin (g.dl ⁻¹)	11.1 (1.4)	10.7 (1.42)	0.245
Haemoglobin < 11.0 g.dl ⁻¹	5 (17)	13 (33)	0.172
Current smoker	1 (3)	10 (25)	0.019

Data are mean (SD), number of women (percentage)

Table 2 Haemodynamic and left ventricular systolic data

Variable	HIV	Healthy	P value
	Term	Term	HIV vs.
	n=30	n=40	Healthy
Systolic blood pressure (mmHg)	110 (15.4)	114 (20.2)	0.329
Diastolic blood pressure (mmHg)	68 (13.2)	70 (14.0)	0.597
Mean arterial pressure (mmHg)	82 (13.1)	84 (15.2)	0.454
Cardiac index (ml.min ⁻¹ .m ⁻²)	2.8 (0.64)	3.1 (0.70)	0.029
Systemic vascular resistance (dyne.s.cm ⁻⁵)	1323 (343.9)	1237 (320.8)	0.290
Cardiac output (ml.min ⁻¹)	5198 (1283.2)	5699 (1281.1)	0.091
Stroke volume (ml)	64 (14.4)	65 (14.1)	0.625
Heart rate (BPM)	83 (15.7)	88 (13.1)	0.162
Left ventricular stroke work index (mmHg.ml.m ⁻²)	2756 (661.6)	3016 (778.4)	0.137
Left ventricular stroke work index (J.beat ⁻¹ .m ⁻²)	0.4 (0.09)	0.4 (0.10)	0.115
Cardiac work index (mmHg.l.m ⁻²)	226 (62.5)	265 (77.3)	0.025
Fractional shortening (parasternal long axis) (%)	42 (6.3)	40 (8.8)	0.154
Fractional shortening (parasternal long axis) < 28%	0 (0)	4 (10)	0.130
LV end diastolic area (cm ²)	17.2 (3.1)	15.1 (2.7)	0.004
LV end systolic area (cm ²)	7.6 (2.1)	6.3 (1.7)	0.005
Fractional area change (%)	55.7 (8.1)	58.2 (9.9)	0.259
Left ventricular end diastolic diameter (cm)	4.8 (0.49)	4.56 (0.44)	0.108
Left ventricular end diastolic diameter > 5.3 cm	3 (10)	1 (3)	0.307
Flow time (corrected) (ms)	358.7 (35.2)	395.4 (30.8)	<0.001
Left ventricular outflow tract maximal velocity(cm/s)	101.7 (15.6)	100.8 (18.5)	0.833
J wave (LVOT)	22 (73)	39 (98)	<0.001
Biphasic s' wave (septal)	9 (31)	6 (15)	0.148
Biphasic s' wave (lateral)	23 (77)	25 (63)	0.299
Septal isovolumetric contraction time (ms)	57.6 (9.9)	53.4 (10.7)	0.104
Septal s' duration (ms)	273.3 (33.8)	264.3(28.7)	0.260
Septal s' velocity (cm.s ⁻¹)	8.5 (1.5)	9.3 (1.7)	0.042
Lateral s' duration (ms)	275.1 (36.7)	270.2 (36.0)	0.576

Lateral s' velocity (cm.s ⁻¹)	9.4 (2.31)	9.6 (1.69)	0.691
Velocity circumferential fibre shortening - corrected	1.5 (0.23)	1.39 (0.42)	0.151
Strain (Apical 4 Chamber)	-	-	-

LV = left ventricle, RV = right ventricle, MV = mitral valve, BPM = beats per minute, LVOT = left ventricular outflow tract, Data are mean (SD), number of women (percentage)

Table 3 Left ventricular diastolic and structural data

Variable	HIV	Healthy	P value
	Term	Term	HIV vs.
	n=30	n=40	Healthy
E velocity (cm.s ⁻¹)	88.5 (21.9)	91.9 (18.4)	0.500
Deceleration time (ms)	158.2 (39.2)	145.3 (36.7)	0.167
A velocity (cm.s ⁻¹)	56.4 (19.2)	63.4 (35.7)	0.295
A duration (ms)	132.0 (30.8)	121.4 (20.6)	0.107
Total mitral valve E&A wave duration (ms)	375.1 (133.8)	354.3 (81.5)	0.454
MV E/A	1.7 (0.65)	1.6 (0.50)	0.463
MV E/A < 1	2 (7)	2 (5)	1.000
MV beat fusion	17 (57)	21 (53)	0.811
Left atrial diameter (cm)	3.6 (0.47)	3.6 (0.38)	0.759
Septal e' velocity (cm.s ⁻¹)	11.5 (2.4)	12.4 (2.5)	0.142
Septal a' velocity (cm.s ⁻¹)	7.4 (2.3)	8.5 (2.0)	0.041
Septal e'/a'	1.7 (0.7)	1.54 (0.49)	0.216
Septal e'/a' < 1	1 (3)	3 (8)	0.636
Septal isovolumetric relaxation time (ms)	62.5 (12.9)	63.9 (17.3)	0.699
Septal isovolumetric contraction time (ms)	57.6 (9.9)	53.4 (10.7)	0.104
Lateral e' velocity (cm.s ⁻¹)	13.4 (3.2)	14.4 (2.9)	0.175
Lateral a' velocity (cm.s ⁻¹)	6.6 (1.5)	8.1 (2.6)	0.003
Lateral e'/a'	2.1 (0.64)	1.94 (0.62)	0.220
Lateral e'/a' < 1	1 (4)	2 (5)	1.000
Lateral isovolumetric relaxation time (ms)	53.6 (13.1)	57.3 (13.4)	0.257
Lateral isovolumetric contraction time (ms)	61.3 (17.9)	59.5 (15.3)	0.660
MV E/Septal e'	7.7 (2.0)	7.73 (2.13)	0.893
MV E/Septal e' ≤ 8	17 (61)	24 (62)	1.000
MV E/Septal e' > 15	0	0	N/A

MV E/Lateral e'	7.0 (2.3)	6.54 (1.54)	0.364
MV E/Lateral e' ≤ 8	20 (67)	32 (80)	0.272
MV E/Lateral e' >15	0	0	N/A
(E/Septal e')/LVEDD	1.5 (0.67)	1.72 (0.53)	0.194
LVMPI	0.4 (0.08)	0.453 (0.117)	0.689
Interventricular septal thickness (cm)	0.8 (0.17)	0.99 (0.17)	<0.001
Posterior wall thickness (cm)	1.0 (0.23)	1.11 (0.27)	0.021
Left ventricular mass (g)	140 (38.8)	170(40.4)	0.003
Pericardial effusion	25 (83)	21 (53)	0.011
Size of effusion (cm)	0.52 (0.20)	0.3 (0.28)	<0.001

LV = left ventricle, RV = right ventricle, MV = mitral valve, EDD = end diastolic diameter, TDI = tissue Doppler indices, Data are mean ± SD, number of women (percentage), LVMPI = left ventricular myocardial performance index = Tei index (septal TDI)

Table 4 Right ventricular functional data

Variable	HIV	Healthy	P value
	n=30	n=40	HIV vs. Healthy
TAPSE (cm)	2.54 (0.43)	2.64 (0.39)	0.327
Biphasic s' wave (Right ventricle)	23 (77)	25 (63)	0.299
RV isovolumetric relaxation time (ms)	44.1 (10.4)	37.5 (12.8)	0.008
RV isovolumetric contraction time (ms)	63.3 (8.0)	50.5 (15.5)	<0.001
RV s' duration (ms)	257.1 (37.4)	264.3 (40.3)	0.759
RV s' velocity (cm.s ⁻¹)	14.7 (3.1)	17.0 (2.9)	0.001
RV e' velocity (cm.s ⁻¹)	16.3 (4.1)	18.7 (3.4)	0.013
RV a' velocity (cm.s ⁻¹)	14.9 (5.3)	15.2 (4.6)	0.806
RV e'/a'	1.17 (0.42)	1.32 (0.42)	0.226
RV e'/a' < 1	5 (18)	10 (26)	0.555
RVMPI	0.42 (0.08)	0.35 (0.12)	0.002

RV = right ventricle, TAPSE = Tricuspid annular plane excursion, RVMPI = right ventricular myocardial performance index, Data are mean (SD), number of women (percentage)

Appendix 1

Consent form

PARTICIPANT INFORMATION AND CONSENT FORM

Site: Mowbray Maternity and Groote Schuur Hospitals, Cape Town, South Africa

Full Project Title: Transthoracic echocardiography in pregnant women

Principal Researcher: RA Dyer

Associate Researchers: AT Dennis, M Gibbs, J Swanevelder

1. Introduction

You are invited to take part in this research project because you are receiving your care at either the Mowbray Maternity or the Groote Schuur Hospitals through which this research is being conducted.

This is because you are either a woman who has developed preeclampsia (high blood pressure and protein in the urine) during your pregnancy, or you have HIV infection or you have developed a heart problem during your pregnancy, or you are a healthy pregnant woman.

If you are a healthy pregnant women the results of your heart function test will be compared to sick pregnant women in order to help us understanding the differences between healthy women's heart function and sick women's heart function.

The research project aims to determine heart function in women with preeclampsia or HIV before. This can assist with our understanding of these diseases.

We also aim to examine the blood flow in your eye. This tells us about the blood flow in your brain. This may explain why some women get more sick than others, or may help predict which women will get more sick.

This Participant Information and Consent Form tells you about the research project. It explains what is involved to help you decide if you want to take part.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local health worker.

Participation in this research is voluntary. If you don't wish to take part, you don't have to.

If you decide you want to take part in the research project, you may be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read;
- Consent to take part in the research project;
- Consent to be involved in the procedures described;
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2. What is the purpose of this research project?

The aims of the project are to better understand heart function in women with preeclampsia, pregnant women with HIV, women who have heart problems in pregnancy and healthy pregnant women. This is important because there is very little information about how a woman's heart responds to the diseases of preeclampsia and HIV. Understanding the response may help us treat the disease better.

We also aim to better understand blood flow in the eyes in the same patients above.

230 women will be taking part in the project.

This project involves collaboration with researchers from The University of Melbourne and the Royal Women's Hospital, Melbourne Australia.

This research is supported by equipment supplied (GE Vivid Q transthoracic echocardiography machine) and software supplied by ProSolv software.

3. What does participation in this research project involve?

Procedures

Participation in this project will involve undergoing an ultrasound scan of your heart known as a transthoracic echocardiography (TTE) examination. The images of your heart will be recorded and stored for measurement after the scan is completed. This scan is exactly the same procedure as the ultrasound scan on your abdomen to examine your baby except that it is looking at your heart. It is a comfortable examination with no side effects. The TTE scan will take place with you lying comfortably on your left hand side on a bed, wearing your normal clothes or hospital gown. If you have preeclampsia after you have commenced medications another TTE scan may

be performed to examine the effect of the mediation on your heart. If you have a caesarean birth a TTE examination may be performed before, during and after the birth of your baby. This will not interfere with your birth experience or your ability to bond with your baby. The TTE images will not identify you. The TTE images will also be used for educational purposes to teach other health care professionals how to scan pregnant women's hearts and perform measurements on the images.

An ultrasound of your right or left eye will also be done. This is done by gently pressing a similar ultrasound probe to your closed eye and examining the blood flow in the main blood vessel that supplies the eye. The examination does not take long. There are no side effects or complications.

Reimbursement

You will not be paid for your participation in this research.

4. What are the possible benefits?

We cannot guarantee or promise that you will receive any benefits from this project.

There is the possibility that examination of your heart with the TTE may detect a previously undetected abnormality which could then be assessed and managed that would otherwise have gone undetected. It is possible that the findings of the TTE scan may assist with your management if the scan is performed when you are very sick.

One aim of this study is to increase our knowledge of the effects on the heart of preeclampsia and HIV in pregnant women so this may have benefits for future women and their babies.

5. What are the possible risks?

There are no known risks of ultrasound to either you or your baby.

6. Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you choose to not participate, this will not affect your treatment, care or relationship with this hospital. If you decide to take part and later change your mind, you are free to withdraw from the project at a later stage.

7. How will I be informed of the final results of this research project?

If you desire, you can be sent the results of this research in the form of a summary document or publication arising from the research.

8. What will happen to information about me?

Any information obtained in connection with this research project that can identify you will remain confidential and will only be used for the purpose of this research project. It will only be disclosed with your permission, except as required by law. In any publication and/or presentation, information will be provided in such a way that you cannot be identified,

9. Can I access research information kept about me?

In accordance with relevant laws, you have the right to access the information collected and stored by the researchers about you. Please contact one of the researchers named at the end of this document if you would like to access your information.

In addition, in accordance with regulatory guidelines, the information collected in this research project will be kept for at least 5 years.

10. Is this research project approved?

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of the University of Cape Town.

11. Consent

I have read, or have had this document read to me in a language that I understand, and I understand the purposes, procedures and risks of this research project as described within it.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project, as described.

I understand that I will be given a signed copy of this document to keep.

Participant's name (printed)

Signature

Date

Declaration by researcher: I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Researcher's name (printed)

Signature

Date

Note: All parties signing the consent section must date their own signature.

Whom can I contact in connection with the study results?

Professor RA Dyer, D23 Department of Anaesthesia, telephone 0214045142

Appendix 2

Ethics approval

Appendix Removed Due to Visible Signatures

Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix 3

Author guidelines IJOA

AUTHOR INFORMATION PACK 18 Dec 2013 www.elsevier.com/locate/ijoa 1

INTERNATIONAL JOURNAL OF OBSTETRIC ANESTHESIA

Official journal of the [Obstetric Anaesthetists' Association \(OAA\)](#) . Members of the OAA receive the journal as a benefit of their membership.

AUTHOR INFORMATION PACK

TABLE OF CONTENTS

ISSN: 0959-289X

DESCRIPTION

The International Journal of Obstetric Anesthesia is the only journal publishing original articles devoted exclusively to obstetric anesthesia and bringing together all three of its principal components; anesthesia care for operative delivery and the perioperative period, pain relief in labour and care of the critically ill obstetric patient.

- Original research (both clinical and laboratory), short reports and case reports will be considered.
- The journal also publishes invited review articles and debates on topical and controversial subjects in the area of obstetric anesthesia.
- Articles on related topics such as perinatal physiology and pharmacology and all subjects of importance to obstetric anaesthetists/anesthesiologists are also welcome. The journal is peer-reviewed by international experts. Scholarship is stressed to include the focus on discovery, application of knowledge across fields, and informing the medical community. Through the peer-review process, we hope to attest to the quality of scholarships and guide the Journal to extend and transform knowledge in this important and expanding area.

IMPACT FACTOR

2012: 1.799 © Thomson Reuters Journal Citation Reports 2013

ABSTRACTING AND INDEXING

EMBASE/Excerpta Medica

MEDLINE®

Science Citation Index

Scopus

Zentralblatt MATH

EDITORIAL BOARD

Editor-in-Chief:

R. Russell, Nuffield Dept.of Anaesthesia, John Radcliffe Hospital, Oxford, OX39DU, UK. Fax: +44 (0)1865 220027, Email: robin.russell@nda.ox.ac.uk

AUTHOR INFORMATION PACK 18 Dec 2013 www.elsevier.com/locate/ijoa 2

Editors:

J. Douglas, Vancouver, BC, Canada

W.D. Ngan Kee, Shatin, Hong Kong

P. Popham, Carlton, VIC, Australia

Statistical Advisor:

M. Columb, Manchester, UK

Editorial Advisory Board:

P. Angle, Toronto, ON, Canada

Y. Beilin, New York, NY, USA

D. Benhamou, Bicêtre, France

D. Bogod, Nottingham, UK

A Butwick, Stanford, CA, USA

B. Carvalho, Stanford, CA, USA

R. Collis, Cardiff, UK

R. D'Angelo, Winston-Salem, NC, USA

G. Dahlgren, Stockholm, Sweden
A. Dennis, Parkville, VIC, Australia
D. Dob, London, UK
R.A. Dyer, Cape Town, South Africa
R. Fernando, Greater London, UK
Y. Ginosar, Jerusalem, Israel
S. Halpern, Toronto, ON, Canada
P. Howell, London, UK
R. Landau, Seattle, WA, USA
N. Lucas, Greater London, UK
G. O'Sullivan, London, UK
M.J. Paech, Perth, WA, Australia
F. Plaat, London, UK
L. Polley, Ann Arbor, MI, USA
A.W. Ross, Heidelberg, VIC, Australia
I. Russell, East Yorkshire, UK
M. Scrutton, Bristol, UK
A. Sia, Singapore
R.M. Smiley, New York, NY, USA
G. Stocks, London, UK
H. Sumikura, Tokyo, Japan
L.C. Tsen, Boston, MA, USA
M. Van de Velde, Leuven, Belgium
M.J.A. Wilson, Birmingham, England, UK
C.A. Wong, Chicago, IL, USA

AUTHOR INFORMATION PACK 18 Dec 2013 www.elsevier.com/locate/ijoa 3

GUIDE FOR AUTHORS

INTRODUCTION

Types of article

Original research (both clinical and laboratory), case series, reports and correspondence will be considered. To be accepted for publication, individual case reports need to have important and novel learning points; a simple narrative of a complex or challenging patient(s) is insufficient. Case series dealing with important areas of practice with a thorough review of relevant literature will be considered. The journal also publishes invited review articles and debates on topical and controversial subjects in the area of obstetric anaesthesia. Reviews are usually commissioned, although authors may contact the Editor-in-Chief if they wish to discuss potential topics.

Contact details for submission

Authors may send queries concerning the submission process, manuscript status, or journal procedures to the Editorial Office at:

IJOA, Editorial Office, ELSEVIER.

E-mail: ijoa@elsevier.com

BEFORE YOU BEGIN

Ethics in publishing

For information on Ethics in publishing and Ethical guidelines for journal publication see <http://www.elsevier.com/publishingethics> and <http://www.elsevier.com/journal-authors/ethics>.

A paper that contains the results of human and/or animal studies will only be accepted for publication if it is made clear that a high standard of ethics was applied in carrying out the investigation. All clinical investigators must follow the Ethical Principles for Medical Research Involving Human Subjects outlined in the [Declaration of Helsinki](#). In the case of invasive studies of humans, the text should include a statement that the research protocol was approved by a local institutional review board or ethics committee and that written consent was obtained from all subjects. For case reports subjects must not be identifiable; however, the patient's written consent to publish should be given (see Patient Details). Please note that the patient's written consent to publication of the case MUST be given and included with the submission. Failure to provide written consent will result in the manuscript being rejected. Where there are difficulties obtaining written consent, the Editor-in-Chief should be contacted but publication will only be considered in exceptional circumstances.

Conflict of interest

All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of

beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. See also <http://www.elsevier.com/conflictsofinterest> . Further information and an example of a Conflict of Interest form can be found at:

http://help.elsevier.com/app/answers/detail/a_id/286/p/7923 .

Submission declaration and verification

Submission of an article implies that the work described has not been published previously (except in the form of an abstract or as part of a published lecture or academic thesis or as an electronic preprint, see <http://www.elsevier.com/postingpolicy>), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. To verify originality, your article may be checked by the originality detection service CrossCheck

<http://www.elsevier.com/editors/plagdetect> .

Changes to authorship

This policy concerns the addition, deletion, or rearrangement of author names in the authorship of accepted manuscripts: Before the accepted manuscript is published in an online issue :

Requests to add or remove an author, or to rearrange the author names, must be sent to the Journal Manager from the corresponding author of the accepted manuscript and must include:

(a) the reason the name should be added or removed, or the author names rearranged and (b) written confirmation (e-mail, fax, letter) from all authors that they agree with the addition, removal or rearrangement. In the case of addition or removal of authors, this includes confirmation from the author being added or removed. Requests that are not sent by

AUTHOR INFORMATION PACK 18 Dec 2013 www.elsevier.com/locate/ijoa 4

the corresponding author will be forwarded by the Journal Manager to the corresponding author, who must follow the procedure as described above. Note that: (1) Journal Managers will inform the Journal Editors of any such requests and (2) publication of the accepted manuscript in an online issue is suspended until authorship has been agreed.

After the accepted manuscript is published in an online issue : Any requests to add, delete, or rearrange author names in an article published in an online issue will follow the same policies as noted above and result in a corrigendum.

Reporting clinical trials

Researchers are recommended to pre-register their trials on a public registry at or before the time of first recruitment. Several web-based public registries are now available including <http://www.clinicaltrials.gov> . Nevertheless, IJOA does not currently regard pre-registration of a clinical trial as a compulsory pre-requisite to submission and possible publication, and does not favour those that have been pre-registered or discriminate against those that have not.

Copyright

Upon acceptance of an article, authors will be asked to complete a 'Journal Publishing Agreement' (for more information on this and copyright see <http://www.elsevier.com/copyright>). Acceptance of the agreement will ensure the widest possible dissemination of information. An e-mail will be sent to the corresponding author confirming receipt of the manuscript together with a 'Journal Publishing Agreement' form or a link to the online version of this agreement. Subscribers may reproduce tables of contents or prepare lists of articles including abstracts for internal circulation within their institutions. Permission of the Publisher is required for resale or distribution outside the institution and for all other derivative works, including compilations and translations (please consult <http://www.elsevier.com/permissions>). If excerpts from other copyrighted works are included, the author(s) must obtain written permission from the copyright owners and credit the source(s) in the article. Elsevier has preprinted forms for use by authors in these cases: please consult <http://www.elsevier.com/permissions> .

Retained author rights

As an author you (or your employer or institution) retain certain rights; for details you are referred to: <http://www.elsevier.com/authorsrights> .

Role of the funding source

You are requested to identify who provided financial support for the conduct of the research and/or preparation of the article and to briefly describe the role of the sponsor(s), if any, in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in

the decision to submit the article for publication. If the funding source(s) had no such involvement then this should be stated. Please see <http://www.elsevier.com/funding> .

Funding body agreements and policies

Elsevier has established agreements and developed policies to allow authors whose articles appear in journals published by Elsevier, to comply with potential manuscript archiving requirements as specified as conditions of their grant awards. To learn more about existing agreements and policies please visit <http://www.elsevier.com/fundingbodies> .

Open access

This journal offers authors a choice in publishing their research:

Open Access

- Articles are freely available to both subscribers and the wider public with permitted reuse
- An Open Access publication fee is payable by authors or their research funder

Subscription

- Articles are made available to subscribers as well as developing countries and patient groups through

our access programs (<http://www.elsevier.com/access>)

- No Open Access publication fee

All articles published Open Access will be immediately and permanently free for everyone to read and download. Permitted reuse is defined by your choice of one of the following Creative Commons user licenses:

AUTHOR INFORMATION PACK 18 Dec 2013 www.elsevier.com/locate/ijoa 5

Creative Commons Attribution-NonCommercial-ShareAlike (CC BY-NC-SA) : for noncommercial purposes, lets others distribute and copy the article, to create extracts, abstracts and other revised versions, adaptations or derivative works of or from an article (such as a translation), to include in a collective work (such as an anthology), to text and data mine the article, as long as they credit the author(s), do not represent the author as endorsing their adaptation of the article, do not modify the article in such a way as to damage the author's honor or reputation, and license their new adaptations or creations under identical terms (CC BY-NC-SA). Creative Commons Attribution-NonCommercial-NoDerivs (CC BY-NC-ND) : for noncommercial purposes, lets others distribute and copy the article, and to include in a collective work (such as an anthology), as long as they credit the author(s) and provided they do not alter or modify the article.

Elsevier has established agreements with funding bodies,

<http://www.elsevier.com/fundingbodies> . This ensures authors can comply with funding body Open Access requirements, including specific user licenses, such as CC BY. Some authors may also be reimbursed for associated publication fees. If you need to comply with your funding body policy, you can apply for the CC BY license after your manuscript is accepted for publication. To provide Open Access, this journal has a publication fee which needs to be met by the authors or their research funders for each article published Open Access.

Your publication choice will have no effect on the peer review process or acceptance of submitted articles.

The publication fee for this journal is \$2,500.00 , excluding taxes. Learn more about Elsevier's pricing policy: <http://www.elsevier.com/openaccesspricing>

Language (usage and editing services)

Please write your text in good English (American or British usage is accepted, but not a mixture of these). Authors who feel their English language manuscript may require editing to eliminate possible grammatical or spelling errors and to conform to correct scientific English may wish to use the English Language Editing service available from Elsevier's WebShop (<http://webshop.elsevier.com/languageediting/>) or visit our customer support site (<http://support.elsevier.com>) for more information.

Informed consent and patient details

Studies on patients or volunteers require ethics committee approval and informed consent, which should be documented in the paper. Appropriate consents, permissions and releases must be obtained where an author wishes to include case details or other personal information or images of patients and any other individuals in an Elsevier publication. Written consents must be retained by the author and copies of the consents or evidence that such consents have been obtained must be provided to Elsevier on request. For more information, please review the Elsevier Policy on the Use of Images or Personal Information of Patients or other Individuals , <http://www.elsevier.com/patient-consent-policy> . Unless you have written permission from the

patient (or, where applicable, the next of kin), the personal details of any patient included in any part of the article and in any supplementary materials (including all illustrations and videos) must be removed before submission. You can find an example of a generic patient consent form [here](#) which you may use if you do not have one available from your own research/clinic.

Submission

Submission to this journal proceeds totally online and you will be guided stepwise through the creation and uploading of your files. The system automatically converts source files to a single PDF file of the article, which is used in the peer-review process. Please note that even though manuscript source files are converted to PDF files at submission for the review process, these source files are needed for further processing after acceptance. All correspondence, including notification of the Editor's decision and requests for revision, takes place by e-mail removing the need for a paper trail. Submission of an article implies that the work described has not been published previously (except as an abstract or part of a published lecture or academic thesis), that it is not under consideration (in whole or in part) for publication elsewhere, that its publication is approved by all Authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, without the written consent from the International Journal of Obstetric Anesthesia, the copyright-holder.

AUTHOR INFORMATION PACK 18 Dec 2013 www.elsevier.com/locate/ijoa 6

Please submit your article via <http://ees.elsevier.com/ijoa>.

PREPARATION

Use of word processing software

It is important that the file be saved in the native format of the word processor used. The text should be in single-column format. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. In particular, do not use the word processor's options to justify text or to hyphenate words. However, do use bold face, italics, subscripts, superscripts etc. When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns.

The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier: <http://www.elsevier.com/guidepublication>).

Note that source files of figures, tables and text graphics will be required whether or not you embed your figures in the text. See also the section on Electronic artwork.

To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

Manuscripts should have 1.5 line spacing, including tables and references and lines should be numbered. Pages should be numbered consecutively. Authors are advised to study recent issues of the International Journal of Obstetric Anesthesia to assess the level of detail required for publication.

For guidance, original research articles should not exceed 3000 words, case reports 1500 words, reviews 5000 words, editorials 1500 words and correspondence 750 words (excluding references)

Article structure

Abstract. This should consist of not more than 250 words summarising the contents of the article and should contain no references or abbreviations. Where appropriate use a structured abstract with the headings: Background, Methods, Results, Conclusions - followed by Key Words.

Headings should be appropriate to the nature of the paper. In general those for experimental papers should follow the usual conventions. Introduction, Methods, Results, Discussion etc. do not need to be on separate sheets. Other papers can be subdivided as the author desires; the use of headings enhances readability. Do not insert compulsory line breaks within the text. When reporting randomized trials, authors are advised to refer to <http://www.consort-statement.org>. For observational studies authors should refer to <http://www.strobe-statement.org>.

Essential title page information

- Title. Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.
- Author names and affiliations. Where the family name may be ambiguous (e.g., a double name), please indicate this clearly. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of

each affiliation, including the country name and, if available, the e-mail address of each author.

- Corresponding author. Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. Ensure that phone numbers (with country and area code) are provided in addition to the e-mail address and the complete postal address. Contact details must be kept up to date by the corresponding author.

- Present/permanent address. If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

Abbreviations

Avoid abbreviations in the title and abstract. All unusual abbreviations should be fully explained at their first occurrence in the text. Avoid numerous invented abbreviations. All measurements should be expressed in metric units, SI units being preferred except in the case of fluid pressures. For more detailed recommendations, authors may consult the Royal Society of Medicine publication: Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors. Propriety names and drugs, instruments etc. if essential, should start with initial capital letters.

Electronic artwork

General points

AUTHOR INFORMATION PACK 18 Dec 2013 www.elsevier.com/locate/ijoa 7

- Make sure you use uniform lettering and sizing of your original artwork.
- Embed the used fonts if the application provides that option.
- Aim to use the following fonts in your illustrations: Arial, Courier, Times New Roman, Symbol, or use fonts that look similar.
- Number the illustrations according to their sequence in the text.
- Use a logical naming convention for your artwork files.
- Provide captions to illustrations separately.
- Size the illustrations close to the desired dimensions of the printed version.
- Submit each illustration as a separate file.

A detailed guide on electronic artwork is available on our website:

<http://www.elsevier.com/artworkinstructions>

You are urged to visit this site; some excerpts from the detailed information are given here.

Formats

If your electronic artwork is created in a Microsoft Office application (Word, PowerPoint, Excel) then please supply 'as is' in the native document format.

Regardless of the application used other than Microsoft Office, when your electronic artwork is finalized, please 'Save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):

EPS (or PDF): Vector drawings, embed all used fonts.

TIFF (or JPEG): Color or grayscale photographs (halftones), keep to a minimum of 300 dpi.

TIFF (or JPEG): Bitmapped (pure black & white pixels) line drawings, keep to a minimum of 1000 dpi.

TIFF (or JPEG): Combinations bitmapped line/half-tone (color or grayscale), keep to a minimum of 500 dpi.

Please do not:

- Supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG); these typically have a low number of pixels and limited set of colors;
- Supply files that are too low in resolution;
- Submit graphics that are disproportionately large for the content.

Color artwork

Please make sure that artwork files are in an acceptable format (TIFF (or JPEG), EPS (or PDF), or MS Office files) and with the correct resolution. If, together with your accepted article, you submit usable color figures then Elsevier will ensure, at no additional charge, that these figures will appear in color on the Web (e.g., ScienceDirect and other sites) regardless of whether or not these illustrations are reproduced in color in the printed version. For color reproduction in print, you will receive information regarding the costs from Elsevier after receipt of your accepted article. Please indicate your preference for color: in print or on the Web only. For further

information on the preparation of electronic artwork, please see <http://www.elsevier.com/artworkinstructions>.

Please note: Because of technical complications which can arise by converting color figures to 'gray scale' (for the printed version should you not opt for color in print) please submit in addition usable black and white versions of all the color illustrations.

Figure captions

Ensure that each illustration has a caption. Supply captions separately, not attached to the figure. A caption should comprise a brief title (not on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.

Tables

Number tables in the order in which they are cited in the text. Place footnotes to tables below the table body and indicate them with superscript lowercase letters. Avoid vertical rules. Ensure that the data presented in tables are not duplicated in the text.

Citation in text

Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication.

AUTHOR INFORMATION PACK 18 Dec 2013 www.elsevier.com/locate/ijoa 8

Reference style

The accuracy of references is the responsibility of the author. References should be entered consecutively by superscript Arabic numbers in the text after punctuation and not preceded by spaces. The references should be listed in numerical order. References to journals should include the author's name and initials (list all authors when six or fewer; when seven or more, list only the first three and add et al.), full title of the paper, journal title abbreviated using Index Medicus abbreviations, year of publication, volume number, first and last page numbers. If not in Index Medicus journal titles should be given in full.

For example: Scott DB, Tunstall ME. Serious complications associated with epidural/spinal blockade. *Int J Obstet Anesth* 1995; 4: 133-9.

References to books should be set out as follows: Eisenach JC. The pain of childbirth and its effect on the mother and fetus. In: Chestnut DH, ed. *Obstetric Anesthesia Principles and Practice*. 3rd ed. Philadelphia: Elsevier Mosby; 2004:3288-301.

Citing and listing of Web references. As a minimum, the title of the website or document, the full uniform resource locator (URL) and the accessed date should be given. Any further information, if known (DOI, author names, reference to a source publication, etc.), should also be given. Web references should be included in order of citation, in the reference list. Electronic material from a web site should be set out as follows: National Institutes of Health. NIH guidelines on the inclusion of women as subjects in clinical research. Available at:

<http://grants.nih.gov/grants/guide/not94-100.html>. Accessed September 30, 2009.

Journal abbreviations source

Journal names should be abbreviated according to the List of title word abbreviations:

<http://www.issn.org/2-22661-LTWA-online.php>.

Supplementary data

Elsevier accepts electronic supplementary material to support and enhance your scientific research. Supplementary files offer the author additional possibilities to publish supporting applications, high resolution images, background datasets, sound clips and more. Supplementary files supplied will be published online alongside the electronic version of your article in Elsevier Web products, including ScienceDirect: <http://www.sciencedirect.com>. In order to ensure that your submitted material is directly usable, please provide the data in one of our recommended file formats. Authors should submit the material in electronic format together with the article and supply a concise and descriptive caption for each file. For more detailed instructions please visit our artwork instruction pages at <http://www.elsevier.com/artworkinstructions>.

Submission checklist

The following list will be useful during the final checking of an article prior to sending it to the

journal for review. Please consult this Guide for Authors for further details of any item. Ensure that the following items are present:

One author has been designated as the corresponding author with contact details:

- E-mail address
- Full postal address
- Phone numbers

All necessary files have been uploaded, and contain:

- Keywords
- All figure captions
- All tables (including title, description, footnotes)

Further considerations

- Manuscript has been 'spell-checked' and 'grammar-checked'
- References are in the correct format for this journal
- All references mentioned in the Reference list are cited in the text, and vice versa
- Permission has been obtained for use of copyrighted material from other sources (including the Web)
- Color figures are clearly marked as being intended for color reproduction on the Web (free of charge) and in print, or to be reproduced in color on the Web (free of charge) and in black-and-white in print
- If only color on the Web is required, black-and-white versions of the figures are also supplied for printing purposes

For any further information please visit our customer support site at <http://support.elsevier.com>

AFTER ACCEPTANCE

AUTHOR INFORMATION PACK 18 Dec 2013 www.elsevier.com/locate/ijoa 9

Use of the Digital Object Identifier

The Digital Object Identifier (DOI) may be used to cite and link to electronic documents. The DOI consists of a unique alpha-numeric character string which is assigned to a document by the publisher upon the initial electronic publication. The assigned DOI never changes. Therefore, it is an ideal medium for citing a document, particularly 'Articles in press' because they have not yet received their full bibliographic information. Example of a correctly given DOI (in URL format; here an article in the journal Physics Letters B):

<http://dx.doi.org/10.1016/j.physletb.2010.09.059>

When you use a DOI to create links to documents on the web, the DOIs are guaranteed never to change.

Proofs

One set of page proofs (as PDF files) will be sent by e-mail to the corresponding author (if we do not have an e-mail address then paper proofs will be sent by post) or, a link will be provided in the e-mail so that authors can download the files themselves. Elsevier now provides authors with PDF proofs which can be annotated; for this you will need to download Adobe Reader version 7 (or higher) available free from <http://get.adobe.com/reader>. Instructions on how to annotate PDF files will accompany the proofs (also given online). The exact system requirements are given at the Adobe site: <http://www.adobe.com/products/reader/tech-specs.html>.

If you do not wish to use the PDF annotations function, you may list the corrections (including replies to the Query Form) and return them to Elsevier in an e-mail. Please list your corrections quoting line number. If, for any reason, this is not possible, then mark the corrections and any other comments (including replies to the Query Form) on a printout of your proof and return by fax, or scan the pages and e-mail, or by post. Please use this proof only for checking the typesetting, editing, completeness and correctness of the text, tables and figures. Significant changes to the article as accepted for publication will only be considered at this stage with permission from the Editor. We will do everything possible to get your article published quickly and accurately – please let us have all your corrections within 48 hours. It is important to ensure that all corrections are sent back to us in one communication: please check carefully before replying, as inclusion of any subsequent corrections cannot be guaranteed. Proofreading is solely your responsibility. Note that Elsevier may proceed with the publication of your article if no response is received.

Offprints

The corresponding author, at no cost, will be provided with a PDF file of the article via email (the PDF file is a watermarked version of the published article and includes a cover sheet

with the journal cover image and a disclaimer outlining the terms and conditions of use). For an extra charge, paper offprints can be ordered via the offprint order form which is sent once the article is accepted for publication. Both corresponding and co-authors may order offprints at any time via Elsevier's WebShop (<http://webshop.elsevier.com/myarticleservices/offprints>). Authors requiring printed copies of multiple articles may use Elsevier WebShop's 'Create Your Own Book' service to collate multiple articles within a single cover (<http://webshop.elsevier.com/myarticleservices/offprints/myarticlesservices/booklets>).

AUTHOR INQUIRIES

For inquiries relating to the submission of articles (including electronic submission) please visit this journal's homepage. For detailed instructions on the preparation of electronic artwork, please visit <http://www.elsevier.com/artworkinstructions> . Contact details for questions arising after acceptance of an article, especially those relating to proofs, will be provided by the publisher.

You can track accepted articles at <http://www.elsevier.com/trackarticle> . You can also check our Author FAQs at <http://www.elsevier.com/authorFAQ> and/or contact Customer Support via <http://support.elsevier.com> .

© Copyright 2012 Elsevier | <http://www.elsevier.com>