Point-of-care ultrasound abnormalities in late onset severe preeclampsia: prevalence and association with serum albumin and brain natriuretic peptide

by

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Student Number: NTHELM001

Submitted to the University of Cape Town

In fulfilment of the requirements for the degree:

Master of Medicine in Anaesthesia

Faculty of Health Sciences

University of Cape Town

Date of submission: 19 February 2018

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DECLARATION

I, Elmari Neethling, hereby declare that the work on which this dissertation 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.

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Acknowledgements

I would like to sincerely thank Professor Robert A Dyer, he has been an incredible teacher and mentor to me. Without his encouragement, support, patience and believe in me this thesis would not have been possible. Thank you for opening my eyes to research.

Professor Justiaan Swanevelder, for showing me the incredible world of cardiothoracic anaesthesia, for setting my career path, and for teaching us by example. You are a great teacher and mentor.

Professor Clemens Ortner for giving me the opportunity to conduct this study with you, and for teaching me point of care ultrasound. You have not only become a mentor but also my friend.

Dr Margot Flint, for spending many late evenings with me at Mowbray Maternity Hospital to recruit patients. For always being enthusiastic no matter the time of day.

The staff of Mowbray Maternity Hospital, for welcoming us to your unit and for the incredible way you care for our patients.

The patients that are included in this study, thank you for willingness to be participate. We hope that our work will contribute to the care of women with preeclampsia in future.

I would also like to acknowledge my co-authors for the hard work that has gone into the research and preparation of the manuscript.

My husband Thinus, this work is dedicated to you, for being my constant source of support and for unconditionally loving me. Without you I would have never been able to overcome the challenges on this road.

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List of Abbreviations

AHA	American Heart Association
ASE	American Society of Echocardiography
BNP	Brain natriuretic peptide
CSF	Cerebrospinal fluid
CT	Computed tomography
CTG	Cardiotocograph
DBP	Diastolic blood pressure
ESC	European Society of Echocardiography
FAC	Fractional area change
FoCUS	Focused cardiac ultrasound
FS	Fractional shortening
ICP	Intracranial pressure
LV	Left ventricle
LVEDP	Left ventricular end-diastolic pressure
MRI	Magnetic resonance imaging
NT-pro BNP	N-terminal pro brain natriuretic peptide
ONSD	Optic nerve sheath diameter
PE	Preeclampsia
PIS	Pulmonary interstitial syndrome
POC	Point of care
PoCUS	Point of care ultrasound
ROSE	Rapid obstetric screening echocardiography
SBP	Systolic blood pressure
SD	Standard deviation
SVR	Systemic vascular resistance
TDI	Tissue Doppler index
TTE	Transthoracic echocardiography
US	Ultrasound

Chapter 1: Literature review

The diagnostic use of ultrasound and biomarkers in preeclampsia.

1 Objective

This narrative review aimed to summarise the literature on the use of point of care ultrasound (POCUS)-derived abnormalities in women with preeclampsia. The clinical utility of the biomarkers brain natriuretic peptide (BNP) and serum albumin is also discussed.

2 Research strategy

All publications used in this narrative review were obtained from the Pubmed database, and the literature includes studies published as recently as 2018. Keywords and terms used for the search included, but were not limited, "pregnancy", "preeclampsia", "echocardiography", "point of care ultrasound", "speckle tracking", "optic nerve sheath diameter", "brain natriuretic peptide", "lung ultrasound", "acid base disturbances" and "albumin". Literature included was limited to the English language, and included 59 publications.

3 Introduction

Point of care ultrasound (PoCUS) is a fast-growing clinical utility, and an essential clinical skill for all practitioners working with patients in the perioperative period. It has been adopted in multiple areas of medicine and is becoming the standard of care. This includes, but is not limited to anaesthesia, surgery, intensive care, gynaecology, general medicine, emergency medicine and paediatrics[1].

Bedside use of cardiac-, lung-, and optic nerve sheath diameter ultrasound imaging aids the rapid diagnosis of severe and life- threatening pathologies, and effective management. During the last decade the development of new digital technology, miniaturisation to handheld devices, affordability, and increased availability of equipment, has led to the introduction of this skill into everyday practice. In resource poor environments point of care ultrasound has been adopted as a screening tool before referral to larger centres[2].

4 Preeclampsia

Preeclampsia (PE) is a multisystem disorder of pregnancy, it is one of the leading causes of maternal and neonatal mortality and morbidity worldwide. It is estimated that 10-15% of maternal deaths worldwide are caused by this disease and its complications[3]. The life-threatening complications of preeclampsia and eclampsia are renal failure, cerebral haemorrhage, coagulopathy, cardiac failure, acute respiratory distress syndrome, and liver failure[3-6]. PE also has life-threatening consequences for the developing fetus - intrauterine growth restriction, oligohydramnios, preterm delivery, placental abruption, intrauterine death.

The features of PE are new onset hypertension and either the presence of end organ damage or significant proteinuria. Diagnostic criteria according to the American College of Obstetricians and Gynaecologists are the following [7]:

Hypertension defined as:

- New onset systolic blood pressure (SBP) after 20 weeks gestation ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg on two occasions at least 4 hours apart, in previously normotensive patients.
- If SBP is ≥ 160 mmHg or DBP ≥ 110 mmHg, treatment should be initiated within minutes.

AND

Proteinuria defined as:

- 24 hour urine collection ≥ 0.3 g

  or
- Protein:creatinine ratio ≥ 0.3
- Urine dipstick ≥ 1+ (when other methods of quantification are not available).

OR

If there is no proteinuria, preeclampsia can be defined as new onset hypertension in combination with new onset of any of the following features:

- Renal impairment.

    - Serum creatinine ≥ 97 umol/L, or more than twice baseline in the absence of previous renal disease.
- Thrombocytopenia.
    - Platelet count ≤ 100×10^9/L
- Liver dysfunction.
    - Transaminase level twice normal upper limit.
- Pulmonary oedema.
- Visual disturbance or cerebral impairment.

Preeclampsia with severe features is defined as:

- SBP ≥ 160 mmHg or DBP ≥ 110 mmHg on more than 2 occasions at least 4 hours apart, in a parturient on strict bed rest.
- New onset visual or cerebral disturbances.
- Pulmonary oedema.
- Platelet count ≤ 100×10^9/L.
- Worsening renal dysfunction defined as serum creatinine ≥ 97 umol/L or more than twice baseline in the absence of previous renal disease.
- Impaired liver dysfunction defined as transaminase level twice normal upper limit of local laboratory, severe and persistent epigastric or right upper quadrant pain non-responsive to conventional analgesics, and no other alternative diagnosis possible.

4.1 Pathophysiology of preeclampsia

Preeclampsia is caused by abnormal invasion of the spiral arteries by the interstitial and extravillous trophoblast[8]. This leads to decreased uteroplacental blood flow and therefore a relative hypoxic environment for the trophoblast[8]. This problem of hypoperfusion worsens as pregnancy progresses and the abnormal vasculature cannot accommodate the physiological rise in uteroplacental blood flow essential for fetal development. The hypoperfusion, subsequent ischaemia and hypoxia result in the development of preeclampsia. The ischaemic placenta releases factors that alter the maternal endothelial

function. This endothelial cellular dysfunction leads to the characteristic signs and symptoms of PE. The endothelial dysfunction results in vasospasm causing multi-organ hypoperfusion and systemic hypertension[9].

5 Cardiac ultrasound

Transthoracic echocardiography (TTE) is an easily accessible tool in the diagnosis of cardiac dysfunction in pregnancy; the parasternal and four-chamber views are easily identified even in the morbidly obese parturients[10]. Anatomical displacement of the heart anteriorly and towards the left further aids the performance of echocardiography in pregnant women[11].

TTE allows detailed assessment of cardiac structure, systolic and diastolic function. It is an essential tool in the guidance of anaesthesia and critical care management in pregnancy. It also aids in distinguishing between cardiogenic versus non-cardiogenic pulmonary oedema in preeclampsia. TTE can also be used to differentiate between pulmonary oedema in the setting of reduced or preserved ejection fraction[12]. Multiple echocardiographic techniques are employed for complete cardiac assessment, Motion Mode, Doppler, tissue Doppler Index (TDI), and recently the use of three dimensional imaging and myocardial strain assessment with speckle-tracking[12-14].

It is imperative to distinguish between a comprehensive TTE examination, focused cardiac ultrasound (FoCUS), and limited TTE. A comprehensive TTE examination involves the use of specific equipment, assists with diagnosing pathology, and requires a larger knowledge base with specialized training[15]. FoCUS as a screening modality is used to answer a specific clinical question, relating to chamber size, volume status, ventricular function, and pleural and pericardial effusion. This application does not require detailed cardiology knowledge, and a less intensive training period is needed[16]. However, interpretation of the images requires adequate training and is operator-dependent. FoCUS does not replace the requirement for a formal diagnostic echocardiography investigation. Each has a distinct role and clinical utility.

There are multiple guidelines for the use of echocardiography and point of care echocardiography[15,17-22]. Dennis et al described the Rapid Obstetric Screening Echocardiography (ROSE) protocol. It has been specifically developed in the obstetrics population[10] for haemodynamic and diagnostic assessment in the critically ill patient.

ROSE uses the basic parasternal and apical views (subcostal view is not feasible in this population) and follows the following main principles[10]:

- Are the views acceptable and applicable?
- The test is done at the bedside and on the left of the parturient.
- This an abbreviated examination.
- The aim is to diagnose a specific condition and monitor the response to initiated therapy (contractility and volume).
- Right heart function and assessment of size in relation to the left (detection of embolism-air, blood, amniotic fluid).
- Assessment of the fetal heart rate.

5.1 The cardiovascular pathophysiology of preeclampsia

TTE has been used extensively in research on preeclampsia, and has aided in identifying the underlying pathophysiology[13,23,24]. Studies have also identified the longer term cardiovascular complications of preeclampsia[13].

5.1.1 Pre clinical phase

In the early onset preeclampsia population, the impairment is more prominent than in the late onset group. Early onset preeclampsia has a more severe course than that of late onset disease. The initial findings during the course of the disease in the early onset group are low cardiac output, high peripheral vascular resistance, contracted intravascular volume and decreased venous capacity[25,26]. In the late onset group these changes are not as well delineated. Parturients that develop early or late onset preeclampsia also exhibit abnormal left ventricular (LV) remodelling[25,27]. Most commonly this can be identified as concentric remodelling and hypertrophy[25,27].

Women that will develop early onset preeclampsia have evidence of impaired myocardial relaxation and diastolic dysfunction[25,27]. This relaxation impairment is caused by the increased systemic vascular resistance (SVR) higher arterial blood pressure and subsequent LV remodelling. With the use of TDI and strain index, the assessment of systolic function shows preserved radial function and reduced longitudinal function[28]. This remodelling and dysfunction is similar to changes observed in early essential hypertension in non-pregnant patients[25,28]. These cardiovascular findings support our understanding that preeclampsia is not only related to placental abnormalities but also to maternal cardiovascular adaptation in response to placental hypoperfusion[25,28].

5.1.2 Clinical phase

Different disease patterns seen during this phase depend on the severity of the disease, treatment employed, pre-existing medical conditions, the presence or absence of labour, and fluid administration. LV remodelling patterns are characterised, most commonly by concentric hypertrophy[12,14,29], however Melchiorre et al also described asymmetrical hypertrophy (involving predominantly the anteroseptal portion, with the identification of a basal septal bulge). This occurred in patients with severe preeclampsia, who had global diastolic dysfunction[29]. There is a significant increase in LV mass compared to pregnant patients without preeclampsia[12,14,30].

Global systolic function is usually preserved in patients with preeclampsia as reported by Melchiorre et al and Tatapudi et al[24,29]. Dennis et al found that systolic function was increased in patients with PE compared to controls, which was attributed to increased inotropy[23]. The difference in findings in these studies can be attributed to the different parameters used for the assessment of systolic function. Speckle tracking, which is a relatively new echocardiographic method to assess subtle subclinical changes in myocardial strain, demonstrated decreased systolic and diastolic myocardial deformation in parturients with PE[31]. Cardiac magnetic resonance imaging has further demonstrated that composition of the myocardial wall in patients with PE differ from healthy controls, oedema was also identified in addition to hypertrophic changes[8].

Global diastolic dysfunction in PE occurs commonly, with left atrial (LA) enlargement, most likely due to increased LV filling pressure[25]. Dennis et al found that 43% of patients with untreated severe PE had grade 1 or 2 diastolic dysfunction[23]. In patients with treated severe preeclampsia this incidence was nearly 30%[30]. Significant pericardial effusion was also commonly identified in both treated and untreated patients with PE[23,30].

5.1.3 Long term cardiovascular outcome

Persistence of diastolic dysfunction, LV hypertrophy and development of essential hypertension occur more commonly in patients with early onset disease versus late onset disease[32]. In up to 60% of early onset disease these problems persist beyond the 1 year mark. There is a 15 fold increase in relative risk for the development of essential hypertension if these problems persist beyond 1 year[32]. Left ventricular remodelling improved significantly at 1 year, though 41 % still had concentric and eccentric hypertrophy with concentric remodelling[32]. This was most likely to occur in patients with early onset disease.

There was a significant increase in American Heart Association (AHA) stage B heart failure, this occurred most commonly amongst patients that had early onset disease. In the normal population above the age of 45 years the prevalence of stage B heart failure is 34 %; in previously early onset preeclamptics aged 31 years the prevalence is 70%[32].

6 Lung ultrasound and the assessment of pulmonary interstitial syndrome

The use of bedside lung ultrasound has now become standard of care in the critical care and emergency environments[33-37]. Powell et al demonstrated that a fluid bolus in healthy parturients prior to spinal anaesthesia lead to endothelial glycocalyx disruption[38]. Pulmonary interstitial syndrome (PIS), which may be a precursor of alveolar oedema, has been defined by the presence of multiple B-lines, defined as discrete laser-like vertical hyperechoic reverberation artifacts which arise from the pleural line to the bottom of the screen, moving as the pleural surfaces slide during respiration[39]. Three or more B-lines (any size and any distance apart) in a particular region, define a positive lung region. PIS

is diagnosed in the presence of two or more positive regions per side, which defined a "B-line pattern"[39]. In preeclampsia there is an alteration of the endothelial glycocalyx structure due to reduced mRNA transcription, and this may lead to an increase propensity to develop PIS[40]. Early identification of pulmonary interstitial oedema may avert the development of life-threatening pulmonary oedema, by timely intervention.

6.1 Lung ultrasound in preeclampsia

Data in this specific population is scarce, and only two studies could be identified. Ambrozic et al. included 21 patients with preeclampsia and 12 healthy controls in their study on lung and cardiac ultrasound for haemodynamic monitoring[40]. Fluid management was guided by the findings. Zieleskiewicz et al. included 20 patients with severe preeclampsia in their cohort study[41], and found that lung ultrasound predicted pulmonary interstitial oedema in 25 % of cases, and was associated with raised left ventricular end-diastolic pressure (LVEDP)[40,41]. Therefore lung ultrasound could be considered to guide the administration of fluid or diuretic therapy.

7 Optic nerve sheath diameter

7.1 Rationale for measurement

The optic nerve is covered by the optic nerve sheath. The sheath is an anatomical extension of the dura mater and is surrounded by the subarachnoid space. If pressure rises in the subarachnoid space the optic nerve sheath will increase in diameter and can therefore be used as a noninvasive bedside tool for the estimation of intracranial pressure (ICP)[42,43]. There is a linear correlation between optic nerve sheath diameter (ONSD) and intracranial pressure in patients with severe head injury[44]. The current gold standard for measurement of ICP remains invasive transcranial measurement with intraventricular or cerebral parenchymal catheters and probes[45]. This technique is associated with inherent risks.

7.2 Value of correlation

ONSD measurement during bedside ultrasonography has been directly correlated with magnetic resonance imaging (MRI) and computed tomography (CT) measurement for the assessment of raised intracranial pressure in children with hydrocephalus and adults with meningo-encephalitis[46-48]. The cost of advanced imaging modalities, availability in resource constraint environments, as well as exposure to radiation are all problems in evaluation of patients with possible raised intracranial pressure. This is further confounded by the fact that transport of these patients is often difficult and critical fetal monitoring may not possible during this period. Further the use of CT scan and MRI are not feasible for serial assessment of ICP. With the use of bedside ultrasonography the diagnosis of raised intracranial pressure can be expedited and complications prevented.

The normal optic nerve sheath diameter measured in different populations of normal non pregnant volunteers is 4.12 (4.09-4.15) mm[49]. Numerous publications have debated the ideal cut off value of ONSD that correlates with raised ICP (>20 mmHg). This value also differs in various ethnic groups, and an ideal value still needs to be established. A recent study by Jeon et al correlated bedside ultrasonography with direct intracranial pressure measurement during the placement of an extra ventricular drain catheter in neurosurgical patients[50]. The authors of this paper found that in the Korean population the optimal cut off value of ONSD was 5.6 mm with sensitivity 94% and specificity of 87%[50]. Direct correlations with invasive measurement of ICP showed a 95% risk for raised ICP with an ONSD measurement of 5.8 mm[51]. Direct measurement of intracranial pressure with opening pressure during lumbar puncture has further demonstrated that with withdrawal of cerebrospinal fluid (CSF) the optic nerve sheath decreases in diameter[52].

7.3 Optic nerve sheath diameter in preeclampsia and pregnancy

In the pregnant population data is limited. A small pilot study performed by Dubost et al found that in 25 healthy pregnant patients the average ONSD was 4.5 mm (4.3-4.8)[43]. In this study the ONSD of 26 patients with preeclampsia was evaluated. The mean ONSD in parturients with preeclampsia and severe features was 5.4 mm (4.7-5.9)[43]. Twenty percent

of patients with severe PE had an ONSD of >5.8 mm, which was compatible with raised ICP.

8 Biomarkers as predictors of disease severity

8.1 Brain natriuretic peptide

Brain natriuretic peptide (BNP) is secreted by the cardiac myocytes in response to atrial/ventricular wall stretching or ischemia. The serum measurement is used to diagnose and assess the severity of heart failure. It has been widely used as a predictor of cardiovascular events and mortality[53-55]. The inclusion of BNP as a predictor of cardiovascular risk has been incorporated in the assessment of cardiovascular risk for high risk individuals and as one of the mainstay methods of assessment in the recent guidelines published by the Canadian Cardiovascular Society[56]. Measurement of either 32 amino acid BNP (active form) or 76 amino acid N-terminal pro-BNP(NT-proBNP) can be made as both are cleaved from the prohormone proBNP. It is also now possible to measure BNP using a readily available and handheld POC device designed by Abbott in the form of i-STAT © cartilages.

A systematic review by Afshani et al found[57] that PE was associated with higher BNP levels compared with controls, these raised levels persisted for up to 6 months. In this review multiple studies found an association with diastolic dysfunction, raised SVR and decreased cardiac output. However the sensitivity and specificity did not allow the prediction of cardiovascular disease severity. The ideal cut-off value in this population still remains to be determined.

8.2 Albumin

Albumin is a major contributor to oncotic pressure, which opposes hydrostatic forces and prevents the development of oedema. Low albumin levels have been linked to the development of pulmonary oedema[58]. In a recent investigation performed by Ortner et al[59], a comprehensive physicochemical acid/base analysis was performed in pre-eclamptic women (AB-PreE-Trial), they identified the presence of simultaneous hypoalbuminaemic

alkalosis and hyperchloraemic acidosis. Overall base excess was similar to that in healthy patients. It was concluded that rather than the absolute value of the base excess, the magnitude of the offsetting contributors to base deficit could indicate disease severity. Hypoalbuminaemia may therefore be a widely available and inexpensive marker of pulmonary interstitial oedema in preeclampsia.

9 Conclusion

This narrative review showed that there is limited literature on POCUS-derived abnormalities in women with severe preeclampsia. We therefore aimed to establish the prevalence of PIS, cardiac dysfunction, and increased ONSD in late onset severe preeclampsia. Our primary aim was to examine the association between PIS/ONSD, and maternal serum albumin level. The secondary aims were to explore the association between PIS/ONSD and cardiac dysfunction and BNP level. The research thus attempted to establish the relative contribution of hypoalbuminaemia and cardiac dysfunction to the life-threatening complication of pulmonary oedema in PE. The association between POCUS-derived parameters with a suspicious or pathological cardiotocograph (CTG) was also analysed.

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Chapter 2: Publication ready manuscript

1 Abstract

Background:

Pilot studies using point-of-care ultrasound (POCUS) in preeclampsia suggest pulmonary interstitial- and cerebral edema, and cardiac dysfunction. In addition, laboratory markers of oncotic pressure (albumin) and cardiac dysfunction (brain natriuretic peptide [BNP]) may be abnormal, but the clinical application remains unclear. This study investigated the prevalence of pulmonary interstitial syndrome (PIS), cardiac dysfunction, and increased optic nerve sheath diameter (ONSD) in late onset severe preeclampsia. The primary aim was to examine the association between PIS/ONSD, and maternal serum albumin level. The secondary aims were to explore their association with cardiac dysfunction and BNP level, and the association between POCUS-derived parameters and the development of a suspicious or pathological cardiotocograph.

Methods:

Ninety-five women were enrolled in this prospective cohort study. At diagnosis, a POCUS examination of lungs, heart and ONSD was performed. PIS was defined as a bilateral B-line pattern on lung US, and diastolic dysfunction was measured following an algorithm defined by the American Society of Echocardiography. ONSD > 5.8 mm was interpreted as raised intracranial pressure (> 20 mmHg). Serum BNP and albumin levels were also measured.

Results:

PIS, diastolic-, systolic dysfunction, and raised left ventricular diastolic pressure (LVEDP) were present in 23 (24%,) 31 (33%), 9 (10%), and 20 (25%) women respectively. ONSD was increased in 27 (28%) women. Thirty-nine women (41%) had zero-, 34 (36%) had 1-, and 22 (23%) had ≥ 2 ultrasound abnormalities. No association was found between albumin levels and PIS ($p = 0.4$) or B-line score ($p = 0.7$). No association was found between serum albumin and PIS, ONSD, systolic dysfunction or increased LVEDP. PIS was associated with systolic- ($p < 0.03$) and diastolic dysfunction ($p = 0.02$), and raised LVEDP ($p = 0.009$). The BNP level was associated with PIS, systolic- and diastolic dysfunction ($p<0.001$), with low sensitivity and high specificity. On univariate analysis, there was no

association between ultrasound abnormalities and the development of a suspicious/pathological fetal heart tracing within 48 hours of diagnosis (p=0.07).

Conclusion:

Pulmonary interstitial syndrome, diastolic dysfunction and increased ONSD were found to be common in severe preeclampsia. Cardiac ultrasound abnormalities may be more useful than albumin levels in predicting PIS. The BNP level was associated with cardiac and lung ultrasound abnormalities, with high specificity.

Key Points Summary:

- Question:

  Since data on the prevalence of pulmonary interstitial edema (PIS), increased optic nerve sheath diameter (ONSD), and cardiac function as assessed by point of care ultrasound (POCUS) in severe late onset preeclampsia are limited, the prevalence of these abnormalities were studied, as well as the associations between PIS and ONSD and serum albumin level, cardiac dysfunction and serum brain natriuretic peptide (BNP).

- Findings:

  POCUS examination revealed a high prevalence of PIS, diastolic dysfunction, and increased ONSD, with no association between PIS or ONSD and serum albumin level, but a significant association between PIS and cardiac dysfunction and BNP level.

- Interpretation:

  In late onset severe preeclampsia, abnormalities of cardiac function may be more important than hypoalbuminemia in the generation of PIS, with BNP showing good specificity in predicting cardiopulmonary ultrasound abnormalities.

2 Manuscript

Point-of-care ultrasound abnormalities in late onset severe preeclampsia: prevalence and association with serum albumin and brain natriuretic peptide

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clinicaltrials.gov: NCT 02721771

Word count:
Abstract: 368
Introduction: 404
Discussion: 1105
Overall: 3714

Abbreviated Title: POCUS in late onset severe preeclampsia

Individual contributions to the manuscript:

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Introduction

Preeclampsia is a life-threatening hypertensive disorder involving the heart and vasculature and affecting 5-8% of pregnancies[1]. Predominant causes of maternal morbidity and mortality are cerebral complications and cardiorespiratory failure[2].

Point of care ultrasound (POCUS) is being used increasingly in preeclampsia for diagnostic purposes[3]. Using lung ultrasound, two recent pilot studies detected pulmonary interstitial syndrome (PIS) in 25% of women presenting with severe preeclampsia[4,5]. Such increases in pulmonary interstitial fluid may precede alveolar edema. In both studies, the authors concluded that women with PIS should be fluid restricted, but the precipitating factors, whether cardiac or non-cardiac, such as decreased oncotic pressure related to hypoalbuminemia, remain controversial[6].

Another POCUS application is to assess for increased optic nerve sheath diameter (ONSD), which has been shown in other clinical disciplines to be associated with raised intracranial pressure (ICP)[7]. In a pilot investigation, ONSD was found to be normal in healthy controls, but increased in 5/26 (19%) preeclamptic women[8]. The clinical application of this finding remains unclear. As in PIS, it has been hypothesized that reduced serum albumin level, an important determinant of oncotic pressure and biomarker of disease severity[9,10], might contribute to cerebral edema[11].

In a subset of preeclamptic women, signs of diastolic dysfunction and impaired myocardial contractility can be demonstrated with transthoracic echocardiography (TTE)[12]. Knowledge of cardiopulmonary function in the individual case is essential to the obstetric anesthetist for appropriate hemodynamic and fluid management. As the anesthesia provider does not have ready access to a comprehensive TTE study performed by a cardiologist, POCUS protocols have been developed and used successfully by non-cardiologists during recent years[13]. This implies a defined bedside ultrasound examination to identify critical pathophysiologic processes that remain undetected by clinical examination alone[13]. However, data on its application in preeclampsia are limited[3].

It is further well documented that the serum brain natriuretic peptide (BNP) level, a marker of cardiac dysfunction, is increased in preeclampsia[14,15]. However, there is insufficient data to confirm that elevated BNP levels identify those preeclamptic women at risk for cardiopulmonary abnormalities[16].

Therefore, this study was planned to describe the prevalence of POCUS-derived abnormalities in women with late onset severe preeclampsia on hospital admission. The primary aim was to examine the association between PIS or ONSD, and maternal serum albumin level. The secondary aims were to explore the association between PIS or ONSD, and cardiac dysfunction and BNP level. The association between POCUS-derived parameters with a suspicious or pathological cardiotocograph (CTG) was also analyzed.

Methods

After approval by the institutional Human Research Ethics Committee, and written informed consent, women presenting with late onset preeclampsia (>34 weeks gestation) with severe features, were enrolled in this prospective observational study. The investigation was conducted at the University of Cape Town (UCT), Cape Town, South Africa, (#IRB 864/2015), in collaboration with the Medical University of Vienna, Vienna, Austria, and the University of Washington, Seattle, USA, (#IRB HSD 50964), in accordance with the Declaration of Helsinki and Good Clinical Practice. This observational study was reported using the STROBE guidelines[17] and registered under ClinicalTrials.gov (NCT 02721771).

Subjects

Women diagnosed with late onset severe preeclampsia, admitted to Mowbray Maternity Hospital, a regional obstetrics state hospital facility in Cape Town, South Africa, were screened for enrollment by the study investigators (E.N. and M.F.) not providing clinical care.

Preeclampsia was defined according to the recommendations of the Royal College of Obstetricians and Gynaecologists[18], and regarded as severe if systolic blood pressure exceeded 160 mmHg and/or the diastolic blood pressure exceeded 110 mmHg on at least two separate occasions after admission, and proteinuria on urine dipstick was 3+ or more, or if there were other clinical features of severity (severe headaches or visual disturbances, renal impairment, impaired liver function tests, and/or thrombocytopenia). Late onset disease was defined as diagnosis after 34 weeks' gestation.

Following informed consent, maternal ultrasound examination was performed, after initiation of the established local treatment protocol of UCT. Seizure prophylaxis was administered, consisting of magnesium sulfate administered as a loading dose of 4 g intravenously, followed by 1 g hourly intravenously. Preeclamptic women were otherwise fluid restricted. Blood pressure was managed according to a standardized protocol, using alpha-methyldopa, nifedipine or dihydralazine, and the CTG was interpreted according to the guidelines of the Royal College of Obstetricians and Gynaecologists[19]. One non-

reassuring feature (early or variable decelerations, fetal basal heart rate 100-119 or 160-179 beats per minute [bpm], or variability less than 5 bpm for up to 40 minutes) and 2 normal/reassuring features on CTG defined a suspicious fetal heart tracing. Two or more non-reassuring features or 1 or more abnormal features on CTG (late or prolonged [>3min] decelerations, fetal basal heart rate < 100 or > 180 bpm, or variability less than 5 bpm for greater than 90 minutes) defined a pathological fetal heart tracing, which was considered to be an indication for cesarean delivery. The decision to proceed with cesarean delivery was made by the obstetrics team, independent of the investigators. Proceeding to caesarean section was not delayed by the performance of the ultrasound examination.

Women in labor or unable to understand the study procedure were not included in the study. Women with chronic pulmonary disease, collagen disorders, a history of lithium intoxication, chronic renal or hepatic disease, urinary tract infection, chorioamnionitis, intrauterine fetal death, a body mass index > 50 $kg.m^{-2}$, or acute asthma, were not considered eligible.

Ultrasound procedures

Ultrasound procedures were performed following recommendations of the Society for Critical Care Anesthesiologists on performing focused critical care basic ultrasound[20]. All ultrasound studies were performed by one of two trained echocardiography investigators (EN and CO) not involved in patient care. A Vivid S6 BT 12 machine with a M4S-RS 1.5-3.6 MHz cardiac transducer (General Electric Healthcare, Boston, Massachusetts) was used for lung and cardiac ultrasound, and a 12L-RS 6.0-13.0 MHz transducer for optic nerve ultrasound. Ultrasonography images were stored, converted to Digital Images and Communications in Medicine format, and analyzed off-line in a blinded manner. Approximately ten percent of the scans were randomly selected for re-evaluation, for calculation of intra- and inter-observer variability.

a) Lung Ultrasound

Lung ultrasound was performed using the validated Eight-region method[21], evaluating two anterior regions and two lateral regions in each hemithorax. Hyperechoic horizontal artifacts arising from the pleural line have been denoted A-lines[21] (online supplemental

Figure 1). PIS was assessed by the presence of multiple B-lines, defined as discrete laser-like vertical hyperechoic reverberation artifacts which arise from the pleural line to the bottom of the screen, moving as the pleural surfaces slide during respiration[21] (online supplemental Figure 1). Three or more B-lines (any size and any distance apart) in a particular region, defined a positive lung region. PIS was diagnosed in the presence of two or more positive regions per side, which defined a "B-line pattern"[21]. The total number of B-lines counted in all windows defined the B-line score. Less than two positive regions per side defined an "A-line pattern"[21].

b) Cardiac Ultrasound

Parturients rested in the left lateral position for at least 10 minutes before echocardiography. Left ventricular parameters were measured according to the recommendations of the American Society of Echocardiography[22], using parasternal and apical echocardiographic windows. Left ventricular systolic function was measured using the Quinones method[23], and systolic dysfunction was defined as fractional shortening (FS) < 25% (left ventricular internal diameter in diastole – left ventricular internal diameter in systole) / (left ventricular internal diameter in diastole). Systolic function was secondarily assessed by "eyeball" ejection fraction estimated from the apical four chamber view[24], and by measuring left ventricular fractional area change (FAC) in the parasternal short axis view[24].

Left ventricular diastolic function was assessed using pulsed-wave and tissue Doppler evaluation of the mitral valve apparatus. Left-ventricular early mitral peak flow velocity (E) was measured using pulsed-wave Doppler with sample volume at the tips of the opening mitral leaflets, and mitral annular tissue velocity (E´) was measured using the tissue Doppler function. Diastolic dysfunction and cardiac filling pressures were defined following recommendations available during patient recruitment and published by the European Society of Cardiology (ESC) and American Society of Echocardiography (ASE)[25,26]. Following the "Practical Approach to Grade Diastolic Dysfunction", diastolic dysfunction was defined as septal and lateral E´ below 8 and 10 cm/s, respectively[25]. Raised left ventricular end-diastolic pressure (LVEDP) was defined as average E/E´ >13

and/or septal and/or lateral E/E´ ratio above 15 and 12, respectively[25]. Normal LVEDP was defined as E/E´ ≤ 8. An average E/E´ ratio between 9 - 13 is considered non-diagnostic, and guidelines[25-27] recommend additional invasive or non-invasive testing. Following ESC-consensus statement[26], a concurrent serum BNP > 200 pg/ml is suggestive of increased cardiac filling pressures. Consequently, increased LVEDP was further defined by a mean E/E´ value of 9-13 in addition to a serum BNP level of > 200 pg/ml. A more detailed description of cardiac ultrasound methodology can be found as online supplemental material I.

c) Measurement of optic nerve sheath diameter (ONSD)

For the purpose of optic nerve sheath diameter measurement, the patient was positioned supine, with the head elevated 30 degrees. The entry of the optic nerve into the globe was observed by placing the linear transducer superior and lateral to the eye, on the upper eyelid. For each optic nerve two measurements were made, one in the transverse plane and the other in the sagittal plane. ONSD was calculated by taking the mean of the 4 values (2 per eye). Increased ICP was defined as a bilateral mean ONSD > 5.8 mm[8,28]. An illustrative example appears in the supplemental Figure 1.

d) Blood sampling

Venous blood samples were obtained from the extremity contralateral to the peripheral venous access. BNP was measured from one blood specimen immediately after sampling, with a designated BNP cartridge on an i-STAT® Analyzer (Abbott Laboratories, Abbott Park, IL, USA). Samples of separated plasma were sent to the central hospital laboratory services and analyzed for serum albumin, by a fully automated analyzer (Hitachi 917, Roche Diagnostics® GmbH, Mannheim, Germany).

Statistical analysis

Data was presented as mean and standard deviation for continuous variables, and frequency and percentage for categorical variables. For the a priori defined ultrasound outcomes of PIS, cardiac systolic dysfunction, diastolic dysfunction, raised left ventricular end diastolic pressure (LVEDP), and increased ONSD, the prevalence and 95% confidence intervals were calculated. The associations between ultrasound abnormalities and laboratory

markers, and between cardiac and pulmonary ultrasound abnormalities, were explored using the 2-sample t-test and the Chi-square test, for categorical and continuous variables respectively. The association between the presence of ultrasound abnormalities and a suspicious or pathological CTG, were explored using a univariate, binomial regression model with robust standard errors. For these exploratory analyses, no adjustment was made for multiple testing, and results were considered as hypothesis-generating. Intra-observer and inter-observer variabilities for lung- (using total B-line score), cardiac- (using left ventricular internal diameter in diastole), and optic nerve (using the left optic nerve sheath diameter) parameters were evaluated using the Bland-Altman method; results were expressed both graphically and quantitatively as mean difference (bias) and 95% limits of agreement.

Sample size calculation

Available data suggested that the incidences of PIS and increased ONSD detected by ultrasound in severe preeclampsia were 24 and 25% respectively[8,29]. Prior data in critically ill patients indicate a mean serum albumin level of 2.8 g/dL (SD 0.7) in patients with normal lung water, compared to 2.2 g/dL (SD 0.7) in patients with increased lung water[30]. With the biologically plausible assumption of a similar relationship in preeclampsia, where prior data suggests a mean serum albumin level ranging from 2.4 -2.9 g/dl in severe disease[10], and considering an alpha level of 0.05 and a power of 0.9, a sample size of 80 women was needed to show a difference of 0.6 g/dL (SD 0.7) in serum albumin level in patients with- and without PIS, or with- and without raised ONSD, assuming an unequal allocation ratio of 3. No formal sample size calculation was done for the secondary aims, and results were considered exploratory and hypothesis generating.

Results

Demographic, clinical, and laboratory features

Of the 201 patients initially screened, 95 patients were enrolled (pulsed wave Doppler measurements were incomplete in 15 cases, necessitating the recruitment of 15 additional patients to allow for a complete analysis in 80 patients, as per sample size calculation). Figure 1 shows the detailed flow diagram and numbers analyzed. Demographic and clinical characteristics of the patient cohort are shown in Table 1. In the entire cohort, 56 (59%) patients had at least one ultrasound abnormality. Patients with- and without ultrasound abnormalities were comparable with respect to demographic characteristics and had similar admission hemodynamic findings. With the exception of severe headaches or visual disturbances, which were more frequently present in women with ultrasound abnormalities (84% vs. 64%, $p = 0.03$), clinical features of disease severity were observed in similar proportion in women with- and without ultrasound abnormalities. Regarding admission laboratory findings, patients with ultrasound abnormalities had a higher mean BNP level (304.0 vs. 124.3 pg/ml, $p = 0.03$) and lower albumin level (31.6 vs. 33.4 g/l, $p = 0.03$) than those without ultrasound abnormalities.

Ultrasound findings

Table 2 describes the ultrasound findings in the cohort, and Figure 2 describes the prevalence of the major ultrasound abnormalities (diastolic and systolic dysfunction, PIS, raised LVEDP, and elevated ONSD). The mean lung ultrasound B-line score in the cohort was 12.2, with 24% of patients having evidence of PIS. The mean fractional shortening in the cohort was 32.5%, and 10% of patients had evidence of systolic dysfunction (FS < 25%). Thirty-three percent of patients had evidence of diastolic dysfunction, and 25% had increased LVEDP. The mean ± SD ONSD was 5.4 $\pm$0.5 mm in the overall cohort, with 28% of patients having ultrasonographic measurements compatible with an increased ICP (> 20 mmHg).

Association between ultrasound abnormalities and laboratory markers

Associations between ultrasound abnormalities and serum albumin level, and serum BNP are presented in Table 3. No association was found between serum albumin and PIS, ONSD, systolic dysfunction or increased LVEDP. Admission albumin level was associated with diastolic dysfunction ($p = 0.04$). Admission BNP levels were associated with an ultrasound diagnosis of systolic dysfunction ($p = 0.0009$), diastolic dysfunction ($p = 0.003$), increased LVEDP ($p = 0.007$) and total B-line score ($p = 0.002$).

Cardiopulmonary ultrasound relationships

Table 4 describes the relationship of PIS with cardiac function in the cohort. With respect to markers of systolic cardiac function, patients with PIS had a lower mean fractional shortening (29.7% vs. 33.4%, $p = 0.03$) and mean fractional area change (48.3% vs. 52.9%, $p = 0.02$), than patients without PIS. There was also a higher mean left-ventricular diameter in end-systole (3.2 cm vs. 2.9 cm, $p<0.001$) and higher mean left ventricular area in end-systole (10.4 cm^2 vs. 8.9 cm^2, $p = 0.01$) in patients with PIS, than in those without the syndrome. Patients with PIS had a higher prevalence of diastolic dysfunction (52% vs. 26%, $p = 0.02$), than those without the condition. The proportion of patients with a raised LVEDP was significantly different in those with and without PIS (55% versus 15 %, $p = 0.009$).

Association of ultrasound abnormalities with a suspicious or pathological CTG

The CTG was normal in 45-, suspicious in 27- and pathological in 21 women. In 2 women CTG was not performed prior delivery. There was no association between ultrasound abnormalities and the development of a suspicious or pathological CTG ($p=0.07$).

For lung, cardiac and optic nerve ultrasound measurements, intra-observer variability resulted in a mean difference (bias) of 0.3, -1.4 mm, and -0.2 mm, with respect to B-line score, left ventricular end-diastolic internal diameter, and ONSD, respectively. For the same lung, cardiac and optic nerve ultrasound measurements, inter-observer variability resulted in a bias of 0.6, -1.3 mm, and 0.3 mm respectively. The graphical depiction of the limits of agreement of intra- and inter-observer variabilities is presented in the supplementary online Figure 2.

Discussion

Employing several modalities of POCUS examination in women presenting with severe clinical features of preeclampsia at > 34 weeks of gestation, we found a high prevalence of PIS, diastolic dysfunction and raised ONSD, with acceptable inter- and intra-observer variability. The serum albumin level was lower in patients with ultrasound abnormalities, but there was no association with PIS or raised ONSD, or with echocardiographic markers of systolic dysfunction and raised LVEDP. PIS was associated with several echocardiographic abnormalities, including raised LVEDP. BNP was associated with PIS and echocardiographic abnormalities. There was no association between ultrasound- and CTG abnormalities.

Lung ultrasound has become a standard tool in the diagnosis of pulmonary disorders[21]. Zieleskiewicz et al.[29] detected PIS in 5/20 (25 %) women presenting with severe features of preeclampsia, and by applying a similar technique, we found a similar proportion of 24 % in a larger cohort of 95 preeclamptic women. Lung ultrasound is a highly sensitive tool to detect accumulation of extravascular fluid early in the course of lung injury[31], but it cannot differentiate between a cardiac or non-cardiac source of PIS[32]. Pulmonary-and cerebral edema in preeclampsia have several contributing factors. These include colloid osmotic pressure[33], capillary permeability (increased in the presence of a disrupted pulmonary endothelial glycocalyx), and capillary hydrostatic pressure (increased with excessive fluid administration and /or cardiac dysfunction, which is further evidenced by elevated BNP levels). Serum albumin, which is an important main determinant of colloid osmotic pressure, did not correlate with PIS or raised ONSD in our cohort. However, the mean serum albumin concentrations > 3.0 g/dl in our cohort are higher than those usually reported in early onset disease[9,10], where it has been described as a marker of disease severity, and may predict pulmonary edema, as well as the requirement for urgent delivery[9,10].

Using echocardiographic measures as surrogate markers for diastolic dysfunction, Zieleskiewicz et al.[29] found that a positive B-line pattern correlated with decreased lateral

E´ wave velocity and an increased E/E´ ratio. Performing a cardiac and lung ultrasound in 21 preeclamptic women and 12 healthy controls, Ambrozic et al.[5] measured higher mean E/E´ values in women with preeclampsia, but did not find a correlation between number of B-lines and raised E/E´ ratio. Using a comparable echocardiographic approach, we could confirm an association between diastolic dysfunction and the presence of PIS. In our cohort, there was a similar association between PIS and raised LVEDP on ultrasound, to that found by Zieleskiewicz et al.[29] Further exploratory analysis of our data showed that the absence of PIS had a specificity and negative predictive value of 85% for a raised LVEDP.

Based on measurements of FS and FAC, systolic function was preserved in most women in our cohort, and systolic dysfunction was present in a similar small subset as described in other comprehensive TTE investigations in preeclampsia[33,34]. We found a significant association between reduced FS, FAC, raised LVEDP and a B-pattern on lung ultrasound, indicating that reduced contractile function and cardiac reserve may increase the risk for the development of PIS.

An additional indication of validity of our cardiac ultrasound findings is the significant association found between raised BNP levels and echocardiographic markers of impaired systolic and diastolic function. The mean BNP level of 234 pg/ml in our study is comparable with the value of 254 pg/ml described in late onset disease by Hamad et al.[14] Post hoc analysis was performed, using a clinically relevant BNP threshold of 200 pg/ml, which is reported as the upper range during normal pregnancy and gestational hypertension[33,34]. This showed that elevated BNP was associated with systolic dysfunction (sensitivity and specificity 50% and 72%, respectively), diastolic dysfunction (sensitivity and specificity 54% and 84%), elevated left-ventricular end-diastolic pressure (sensitivity and specificity 57% and 82%), and PIS (sensitivity and specificity 58% and 79%). Overall, our results suggest that in late onset disease colloid osmotic pressure may be of lesser importance than cardiac dysfunction as a contributing factor to the development of PIS.

A reduced serum albumin level may also contribute to cerebral edema in critical illness and preeclampsia[11,35]. Assessing ONSD as a surrogate marker for cerebral edema[36], Dubost et al. found ONSD to be increased in 5/26 (19%) preeclamptic women[8], and measured a median ONSD of 5.4 mm in their preeclamptic cohort. Using similar methodology to measure ONSD and to define increased ICP, we found a similar mean ONSD of 5.4 mm and a prevalence of increased ICP of 28%. No association was observed between increased ONSD and any clinical symptom on admission, cardiopulmonary parameter on ultrasound, or laboratory biomarker.

Although there was no association between ultrasound- and CTG abnormalities in these patients with late onset disease, the clinical importance of POCUS in the identification of abnormalities in women with early onset disease (<34 weeks gestation), where expectant management is usually attempted, remains to be investigated.

There are some limitations to our study. Firstly, only patients with late onset disease were studied. Early onset disease seems to be associated with greater cardiac impairment[37], and in the setting of expectant management a POCUS examination could be of greater clinical importance in the prediction of the progression of disease severity. Secondly, we did not include healthy controls in our study. However, a recent lung ultrasound investigation in 150 healthy parturients at > 36 weeks gestation, found no B-patterns[38]. Furthermore, no B-patterns have been identified in previous investigations applying lung ultrasound in control cases in preeclampsia studies[5,29]. With regard to ONSD, Dubost et al. could not detect increased ONSD in any healthy control, and they reported a 95%CI of ONSD in healthy controls lying at 4.3 – 4.8 mm[8], which is significantly below the cut-off point of 5.8 mm used in both the study of Dubost and our own. The optimal ONSD cutoff value to define increased ICP remains controversial[39]. Lastly, beyond our pre-specified primary analysis, we conducted several additional analyses based on strong biologic plausibility, but without correction for multiple testing; thus, we consider the results of our secondary analyses to be exploratory and hypothesis-generating.

In conclusion, this study revealed a high prevalence of ultrasound abnormalities, with no association with serum albumin levels, in women presenting with severe features of late onset preeclampsia. Abnormalities of cardiac function were associated with PIS, and may be may be more important than hypoalbuminemia in the generation of PIS in late onset preeclampsia. BNP is associated with cardiopulmonary ultrasound abnormalities on admission. POCUS may serve as a useful adjunct to the clinical examination for the obstetric anesthesiologist caring for these complex patients. Further investigations are required in patients with early onset preeclampsia, to establish both the prevalence and predictive value of ultrasound abnormalities for maternal complications and delivery outcomes.

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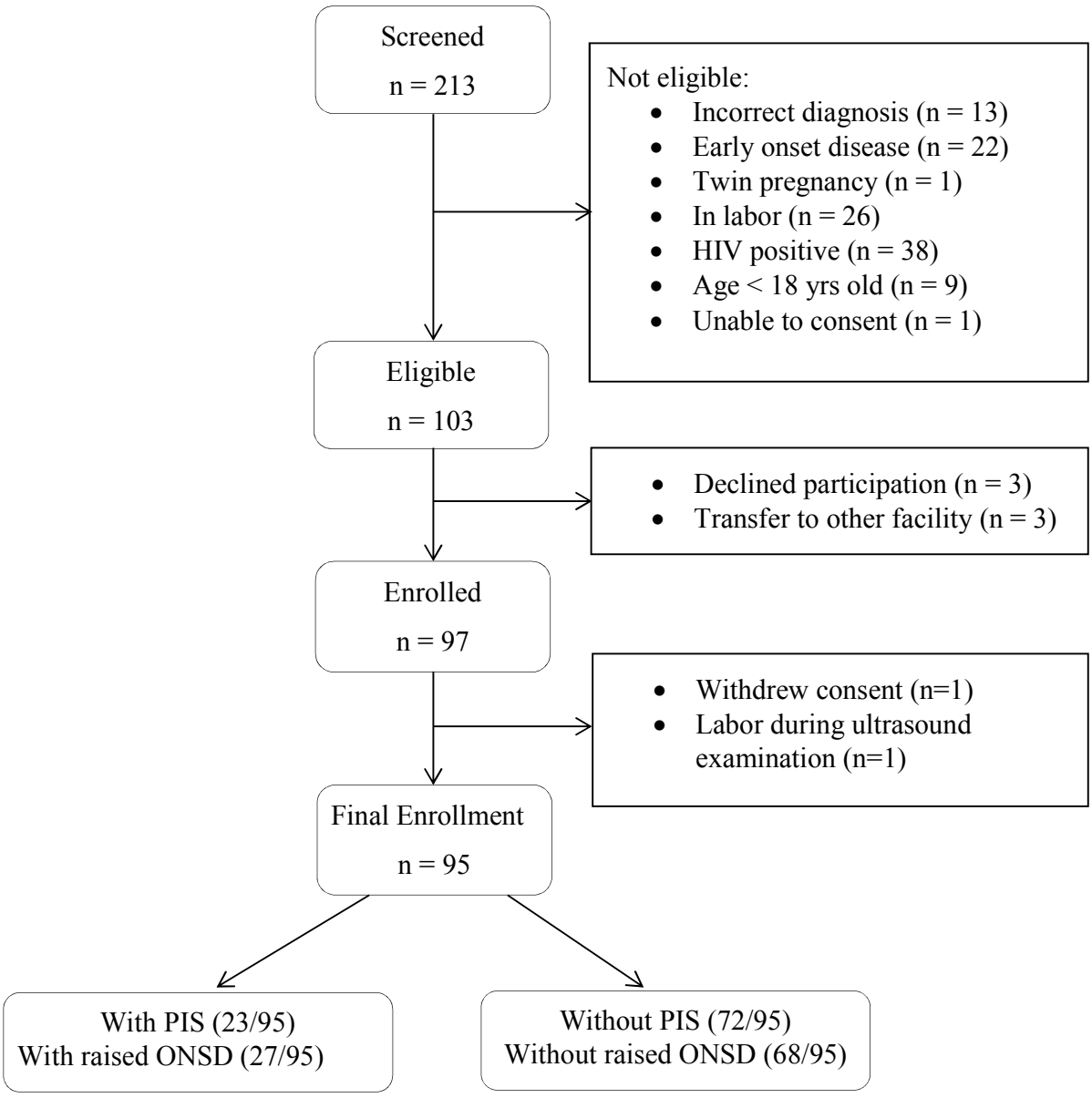
3 List of figures and tables for publication

Figure 1: Flow diagram of patient recruitment

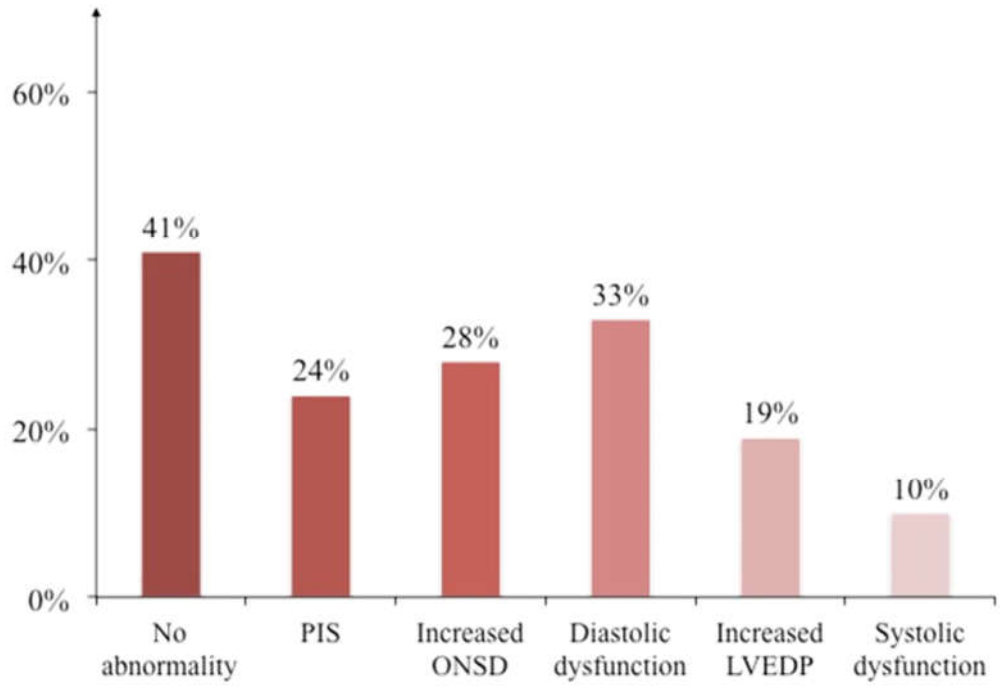
Enrollment date: March 2016 – July 2016



PIS: Pulmonary interstitial syndrome

ONSD: Optic nerve sheath diameter

Figure 2: Prevalence of ultrasound abnormalities in woman diagnosed with late onset preeclampsia and severe clinical features.



PIS: Pulmonary interstitial syndrome.

ONSD: Optic nerve sheath diameter.

LVEDP: Left ventricular end-diastolic pressure.

Table 1: Patient characteristics, clinical features and laboratory results.

Variable	All Patients (n=95)	No Ultrasound Abnormalities (n= 39)	≥ 1 Ultrasound Abnormalities** (n= 56)	p value
Clinical Characteristics				
Age (years)	27 ± 6	26 ± 6	27 ± 6	0.61
Gestation (weeks)	39 ± 2.5	39 ± 3	39 ± 2	0.99
Gravida	2 ± 1	2 ± 1	2 ± 1	0.78
Parity	1 ± 1	1 ± 1	1 ± 1	0.94
Weight (kg)	80 ± 18	78 ± 17	81 ± 18	0.23
Height (cm)	160 ± 6	160 ± 7	160 ± 6	0.73
Body mass index (kg/m^2)	31.3 ± 7.5	30.4 ± 7.1	32.0 ± 7.8	0.33
Systolic blood pressure (mmHg)	165 ± 18	163 ± 16	167 ± 19	0.35
Diastolic blood pressure (mmHg)	105 ± 12	103 ± 10	106 ± 14	0.37
Mean arterial blood pressure (mmHg)	125 ± 12	123 ± 10	126 ± 13	0.27
Heart rate	93 ± 17	91 ± 17	95 ± 17	0.29
Severe Features				
Hypertension	72 (76%)	30 (77%)	42 (75%)	0.83
Severe proteinuria	35 (37%)	12 (31%)	23 (41%)	0.31

Headache / visual disturbance	72 (76%)	25 (64%)	47 (84%)	**0.03**
Oliguria	2 (2%)	1 (3%)	1 (2%)	0.8
Impaired liver function	1 (1%)	0 (0%)	1 (2%)	0.4
Thrombocytopenia	2 (2%)	1 (3%)	1 (2%)	0.8
Number of Severe Features				0.13 (overall p)
1	23 (24%)	13 (33%)	10 (18%)	
2	56 (59%)	22 (56%)	34 (61%)	
> 2	16 (17%)	4 (10%)	12 (21%)	
Laboratory Results				
Hb (g/dl)	11.7 $\pm$ 1.8	11.9 $\pm$ 1.8	11.7 $\pm$ 1.9	0.63
Platelet count (x 10^9/l)	238 $\pm$ 79	222 $\pm$ 64	249 $\pm$ 88	0.1
Total protein (g/l)	61.8 $\pm$ 6.0	62.9 $\pm$ 6.6	61.0 $\pm$ 5.5	0.16
Creatinine (µmol/l)	55.0 $\pm$ 14.6	53.3 $\pm$ 11.8	56.1 $\pm$ 16.2	0.37
Albumin (g/l)	32.3 $\pm$ 4.1	33.4 $\pm$ 5.2	31.6 $\pm$ 2.9	**0.03**
Brain natriuretic peptide (pg/ml)	235 $\pm$ 346	124 $\pm$ 78	304 $\pm$ 425	**0.03**

Values are mean ($\pm$ SD) for continuous variables and frequencies (%) for categorical variables. Ultrasound abnormalities** include presence of increased optic nerve sheath diameter, pulmonary interstitial syndrome, or diastolic dysfunction.

Table 2: Ultrasound characteristics of patient cohort on hospital admission.

Variable	Preeclamptic Women (n = 95)
Optic Nerve Sheath Ultrasound:	
Optic nerve sheath diameter (mm)	5.4 ± 0.5
Raised intracranial pressure (ONSD > 5.8 mm)	27 (28 %) [95 % CI: 20 % - 39 %]
Lung Ultrasound:	
B-line score	12.2 ± 8.1
Pleural effusion	4 (4 %)
Pulmonary interstitial syndrome	23 (24 %) [95 % CI: 16 % - 34 %]
Cardiac Ultrasound:	
Left ventricular area end-diastole (cm^2)	19.1 ± 3.9
Left ventricular area end-diastolic area (cm^2)	9.3 ± 2.5
Fractional area change (%)	51.8 ± 8.3
Left ventricular internal diameter end-diastole (cm)	4.4 ± 0.9
Left ventricular internal diameter end-systole (cm)	3.0 ± 0.5
Fractional shortening (%)	32.5 ± 7.2
Systolic dysfunction	9 (10 %) [95 % CI: 4 % - 17 %]
Early mitral peak flow velocity ((E), cm/s)	92.4 ± 21.5
Atrial mitral peak flow velocity ((A), cm/s))	75.0 ± 18.1
E / A ratio	1.2 ± 0.35

Mitral inflow deceleration time (sec)	173.5 ± 40.4
Septal mitral annular tissue velocity (Septal-E′)	9.3 ± 2.2
Lateral mitral annular tissue velocity (Lateral-E′)	11.0 ± 2.8
Left atrial diameter (cm)	3.75 ± 0.55
Septal E / E′	10.3 ± 3.3
Lateral E / E′	8.9 ± 3.0
Diastolic dysfunction	31 (33 %) [95 % CI: 23 % - 43 %]
Raised LVEDP *(n = 80)*	20 (25 %) [95 % CI: 16 % - 36 %]

Values are mean ± standard deviation for continuous variables, and counts (percentage) for categorical variables.
Ultrasound abnormalities include raised intracranial pressures, pulmonary interstitial syndrome, systolic dysfunction, diastolic dysfunction and raised left ventricular end-diastolic pressure (LVEDP), and are presented as counts, percentage (%), and 95 % confidence intervals [95 % C.I.].
Incidence ratio of raised LVEDP is based on a denominator of 80 women with complete E / E′ measurements.

Table 3: Association of ultrasound abnormalities with serum albumin (g/L) and brain natriuretic peptide (BNP, pg/ml))

	Serum Albumin (g/L)	BNP (pg/ml)
Pulmonary interstitial Syndrome		
Positive (n=23)	31.8 (±3.3)	349 (±341)
Negative (n=72)	32.5 (±4.3)	197 (±342)
p-value	0.25	**0.047**
ONSD > 5.8 mm		
Positive (n=27)	32.1 (±2.5)	215 (±212)
Negative (n=68)	32.4 (±4.6)	242 (±385)
p-value	0.63	0.62
Systolic Dysfunction		
Positive (n=9)	31.3 (±3.4)	588 (±800)
Negative (n=86)	32.5 (±4.2)	192 (±222)
p-value	0.21	**0.0009**
Diastolic Dysfunction		
Positive (n=31)	31.2 (±3.2)	383 (±533)
Negative (n=64)	32.9 (±4.4)	156 (±137)
p-value	**0.04**	**0.003**
Increased LVEDP		
Positive (n=20)	32.2 (±7.3)	449 (±672)
Negative (n=60)	32.4 (±3.1)	170 (±183)
p-value	0.44	**0.007**

Values are presented as mean and standard deviation (±SD).
ONSD: optic nerve sheath diameter
LVEDP: Left ventricular end-diastolic pressure

Table 4: Association of Pulmonary Interstitial Syndrome (PIS) with Cardiac Ultrasound Parameters

Variable	No PIS (n=72)	PIS (n= 23)	p-value
Systolic Function			
Left ventricular area end-diastole (cm^2)	18.8 ± 3.9	20.2 ± 3.8	0.11
Left ventricular area end-systole (cm^2)	8.9 ± 2.4	10.4 ± 2.7	0.01
Fractional area change (%)	52.9 ± 7.4	48.3 ± 9.9	0.02
Left ventricular internal diameter end-diastole (cm)	4.3 ± 0.4	4.7 ± 1.8	0.09
Left ventricular internal diameter end-systole (cm)	2.9 ± 0.4	3.2 ± 0.4	< 0.001
Fractional shortening (%)	33.4 ± 7.2	29.7 ± 6.3	0.03
Systolic dysfunction	5 (7%)	4 (17%)	0.14
Diastolic Function			
Early mitral peak flow velocity (E) (cm/s)	92.1 ± 21.6	93.3 ± 21.8	0.83
Atrial mitral peak flow velocity (A) (cm/s)	74.2 ± 18.2	77.3 ± 10.0	0.52
E / A ratio	1.2 ± 0.3	1.26 ± 0.5	0.53
Mitral inflow deceleration time (sec)	174.2 ± 42.7	171.8 ± 34.3	0.82
Left atrial diameter (cm)	3.81 ± 0.51	3.78 ± 0.41	0.83

Septal mitral annular tissue velocity (Septal-E′)	9.3 ± 2.1	9.1 ± 2.5	0.74
Lateral mitral annular tissue velocity (Lateral-E′)	11.1 ± 2.7	11.0 ± 3.1	0.94
Septal E / E′	10.1 ± 3.1	10.9 ± 3.8	0.33
Lateral E / E′	8.7 ± 3.0	9.4 ± 3.0	0.4
Diastolic dysfunction	19 (26%)	12 (52%)	0.02
Raised LVEDP* (n=80)	9/60 (15%)	11/20 (55%)	0.009

Values are mean ± standard deviation for continuous variables, and counts (percentage) for categorical variables.
Pulmonary interstitial syndrome (PIS) was defined by bilateral B-line pattern in ≥ 2 lung regions on pulmonary ultrasound.
LVEDP ratios are based on a denominator of 80 women with completed E / E′ measurements on cardiac ultrasound.
* *Left ventricular end-diastolic pressure*

4 Supplementary material

Supplementary material 1: Cardiac Methodology

Point-of-care ultrasound abnormalities in late onset severe preeclampsia: prevalence and association with serum albumin and brain natriuretic peptide

Measurement of systolic function

Fractional shortening

Fractional shortening (FS) was assessed in the parasternal long axis view (PLAX) and measured at the level of the tips of the mitral valve [1,2]. Left ventricular end diastolic diameter (LVEDD) measurements were made at end-diastole, defined by the onset of QRS complex on ECG, from inner edge to inner edge of the endo-myocardial border just distal to the tips of the open mitral valve leaflets, between interventricular septum and posterior wall. The average of three measurements was calculated and taken as FS. Left ventricular end systolic (LVESD) measurements were made at the point marking the peak posterior deflection of the interventricular septum inner edge to inner edge. An average of three measurements was calculated and fractional shortening was estimated using the formula:
FS (%) = (LVEDD - LVESD) / LVEDD x 100
FS < 25 % was considered abnormal and defined systolic dysfunction[1,2].

Fractional area change

Fractional area change (FAC) was measured from the parasternal short axis image at the mid- papillary level. Left ventricular end-diastolic area (LVEDA [cm^2]) was calculated by freezing the largest image during the recorded cardiac cycle and by then manually tracing the endocardial surfaces, excluding papillary muscles[3,4]. The average of three measurements was calculated and defined LVEDA. Left ventricular end-systolic area (LVESA [cm^2]) was calculated by freezing the smallest image during the recorded cardiac cycle and by then tracing the endocardial surfaces and excluding the papillary muscles.

The average of three measurements was calculated and defined the LVESA.
Fractional area change was calculated using the following formula:
FAC (%) = (LVEDA – LVESA) / LVEDA x 100

Measurement of diastolic function

Tissue Doppler diastolic velocities

The tissue Doppler modality was used to measure the velocity of movement of the interventricular septum and lateral wall at the level of the mitral valve annulus during diastole. From the apical 4-chamber view (A4C), a 5 mm sample volume was positioned on the interventricular septum and lateral wall at the junction between the left ventricular wall and the fibrous mitral annulus. The septal and lateral E′ wave was the first downward (negative) waveform during diastole, of each beat. The peak velocity of the E′ waveform was measured during three consecutive beats, and the measurements were averaged. Septal or lateral E′ velocity < 8 $cm.s^{-1}$ or 10 $cm.s^{-1}$ respectively, are associated with diastolic dysfunction in the non-pregnant population, and were considered abnormal[5,6].

In non-pregnant individuals aged 21- 40 years, the normal mean ± SD (range) reference values for septal and lateral E′ velocity are 15.5 ± 2.7 (10.1 – 20.9) $cm.s^{-1}$ and 19.8 ± 2.9 (14 – 25.6) $cm.s^{-1}$, respectively[5].

Left atrial diameter

In the PLAX view, the cursor was directed perpendicular to the long axis of the aorta and through the aortic root at the level of the aortic valve cusps. Measurements were made when the left atrium was at its maximal size, immediately prior to the opening of the mitral valve, from the inner edge of the posterior wall of the aorta to the inner edge of the posterior wall of the left atrium, at the end of the T wave of the ECG. The average of three measurements was taken. The upper limit of normal was defined as ≤ 3.8 cm.

Estimation of left ventricular end-diastolic pressure

Early mitral peak flow velocity (E) was measured using pulsed-wave Doppler modality, with the sample volume at the tips of opening mitral leaflets. Increased left ventricular end-diastolic pressure (LVEDP) was defined by integrating recommendations from a consensus statement on the diagnosis of diastolic heart failure, published by the European Society of Cardiology[6] (ESC), and following recommendations on the evaluation of left ventricular diastolic function published by the American Society of Echocardiography (ASE)[5]. In accordance with both statements, an average E/E′ ratio ≤ 8 identifies patients with normal left ventricular filling pressures, whereas an average ratio of E/E′≥ 13, and/or septal E/E′ratio ≥ 12, and/or lateral E/E′ratio ≥ 15, respectively, indicates increased left ventricular pressures[5-7]. When average ratios are between 9 and 13, E/E′ ratios alone are non-diagnostic, and guidelines[5,6,8] recommend additional invasive or noninvasive testing. Following an ESC-consensus statement[6], a concurrent serum BNP > 200 pg/ml is suggestive of increased cardiac filling pressures. Consequently, increased LVEDP was further defined by average E/E′ of 9-13 with a concurrent serum BNP level of > 200 pg/ml (Supplemental online Figure 2).

References

1. Lang RM, Bierig M, Devereux RB, et al. 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 Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63.
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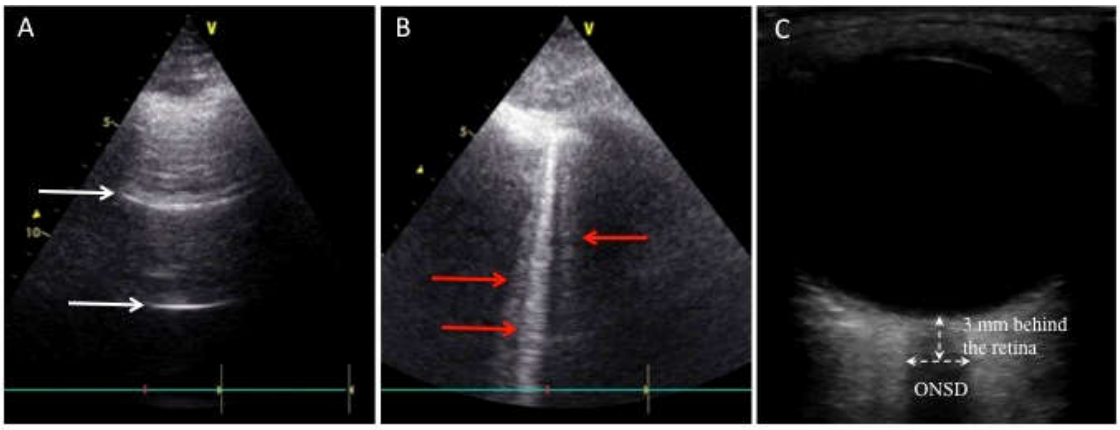
Supplemental Figure 1: Examples of lung and optic nerve ultrasound findings in a woman with severe preeclampsia.

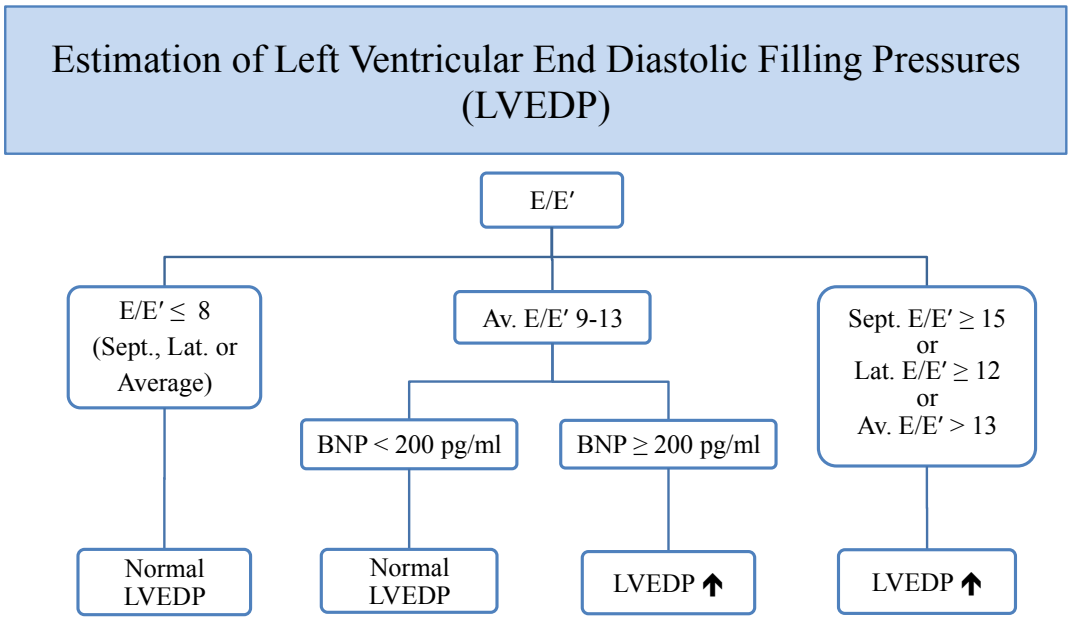


A: A-line pattern on lung ultrasound image indicating normal fluid content in lung interstitium.

B: Multiple B-lines on lung ultrasound image indicating increased fluid content in lung interstitium.

C: Measurement of optic nerve sheath diameter (ONSD) using ocular ultrasonography. In this patient ONSD was 5.2 mm, compatible with normal intracranial pressures.

Supplemental Figure 2: Diagnostic algorithm in the estimation of left ventricular end-diastolic pressure



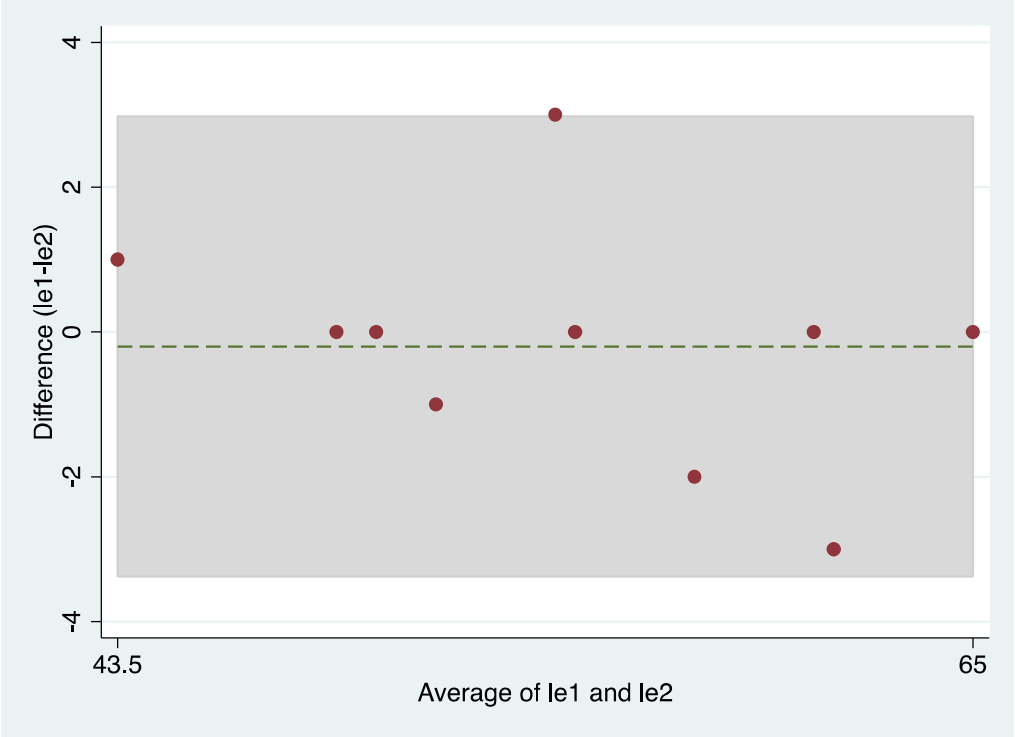
Diagnostic algorithm in the estimation of left ventricular end diastolic pressure (LVEDP) in patients with normal or reduced ejection fraction. Adapted from consensus statement on diagnosis of diastolic heart failure published by the European Society of Cardiology 2007.

Supplemental Figure 3: Intra-observer and inter-observer variabilities

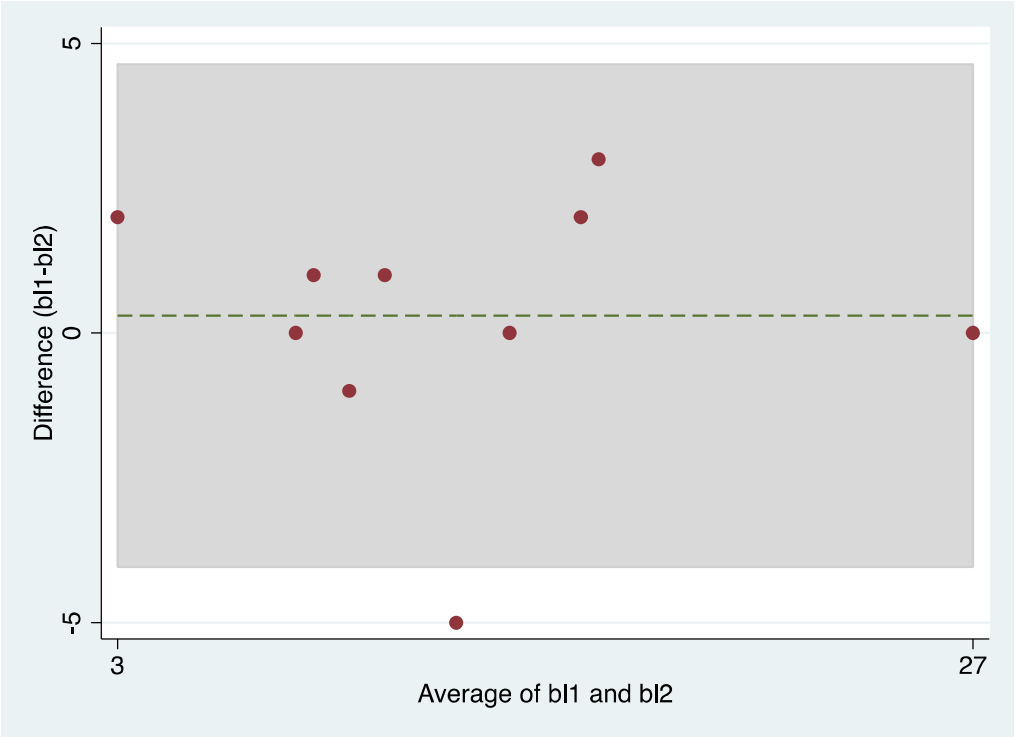
Intra-observer and inter-observer variabilities for lung- (using total B-line score), cardiac- (using left ventricular internal diameter in diastole), and optic nerve (using the left optic nerve sheath diameter) parameters evaluated using the Bland-Altman method; results are expressed as mean difference (bias) and 95% limits of agreement.

Intra-observer variability:

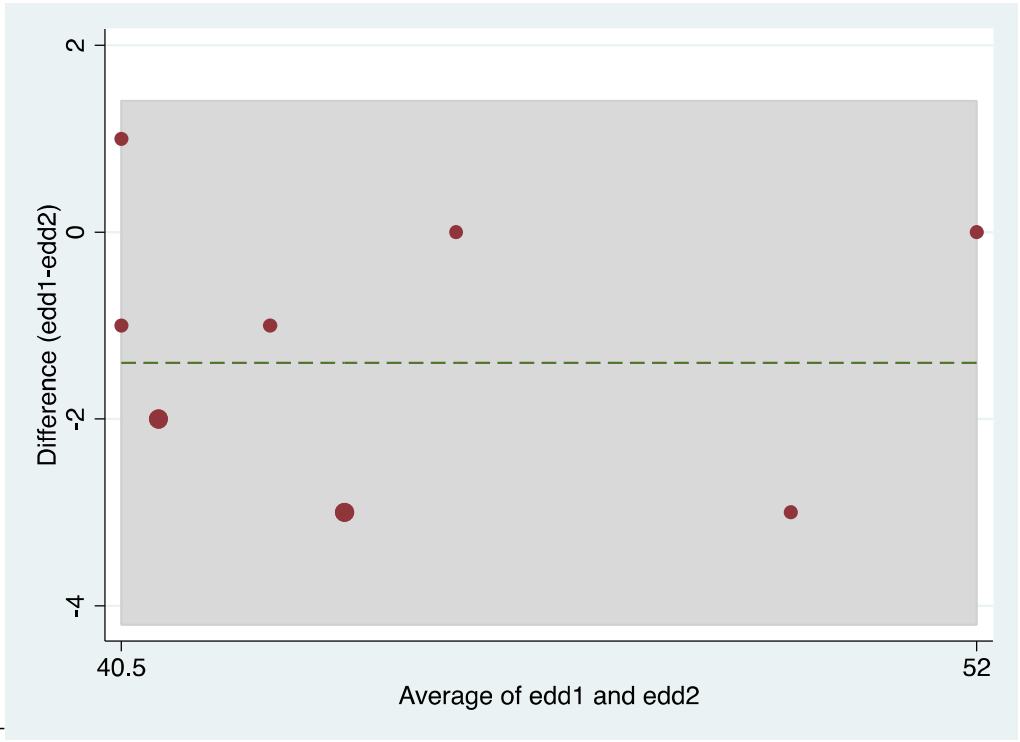
Optic nerve sheath diameter (ONSD):



Lung (total B-line score):

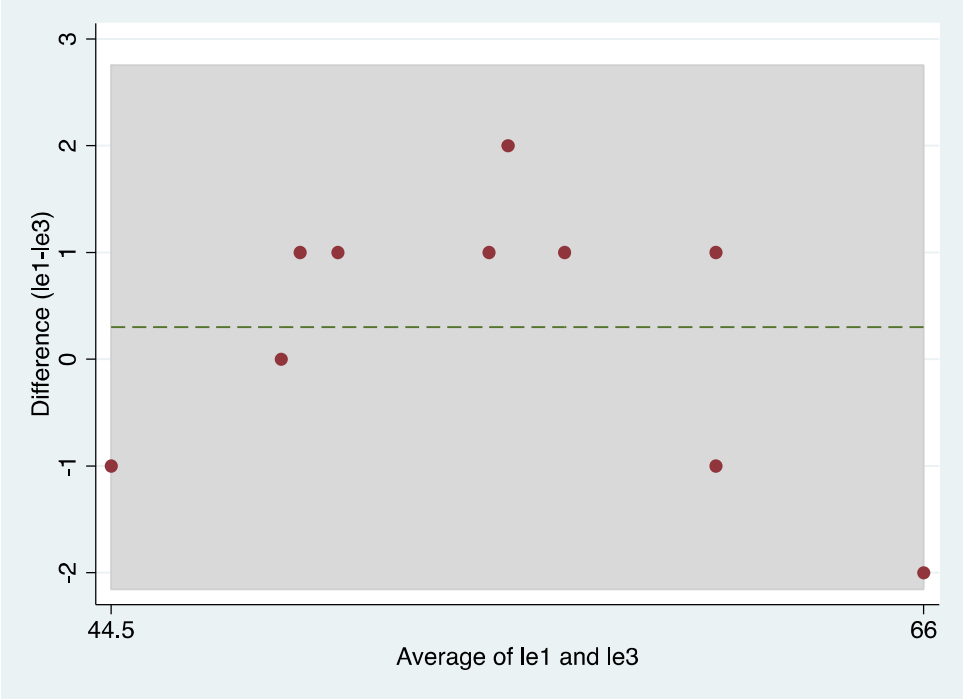


Cardiac (left ventricular internal diameter in diastole):

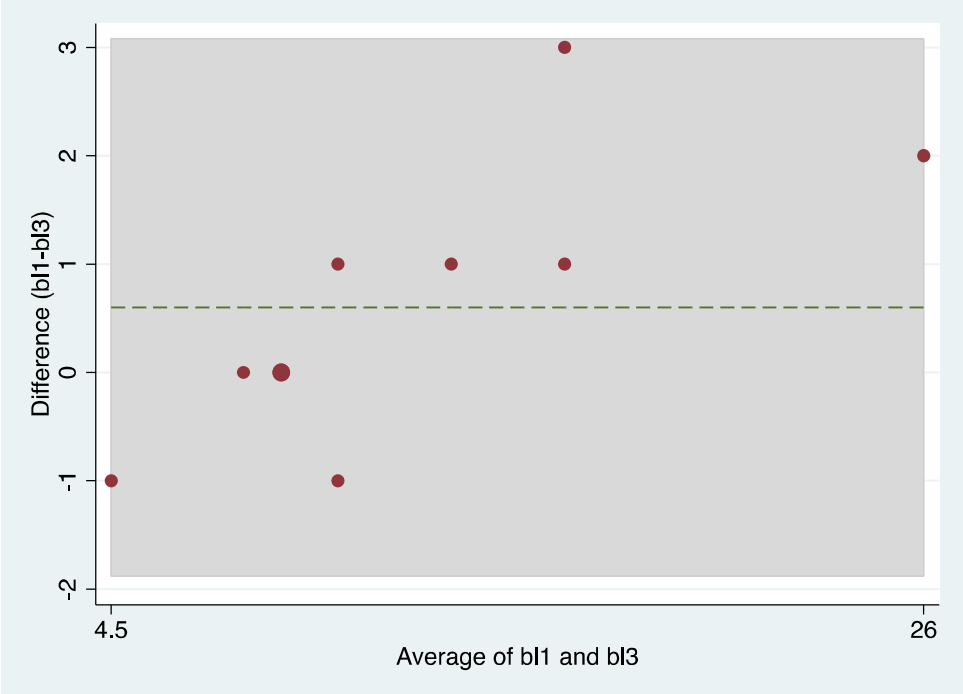


Inter-observer variability:

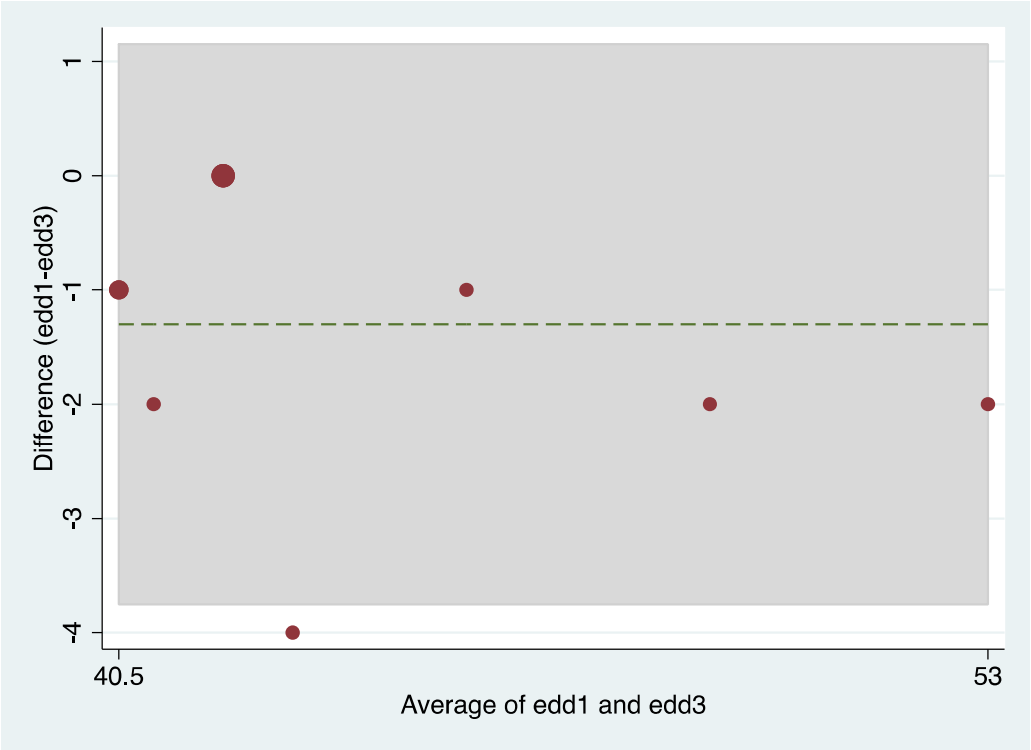
Optic nerve sheath diameter (ONSD):



Lung (total B-line score):



Cardiac (left ventricular internal diameter in diastole):



Chapter 3: Appendices

Appendix A: Human Research Ethics Committee Approval Letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
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Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
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02 March 2016

HREC REF: 864/2015

Prof R Dyer
Anaesthesia
D23, NGSH

Dear Prof Dyer

PROJECT TITLE: ACID-BASE DISTURBANCES AND ULTRASOUND MARKERS AS BIOLOGICAL PREDICTORS OF MATERNAL AND FETAL OUTCOMES IN SEVERE LATE ONSET PREECLAMPSIA

Thank you for your response to the Faculty of Health Sciences Human Research Ethics Committee dated 02 March 2016.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th March 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.

Appendix B: Consent form

Consent Form

Acid-base disturbances and ultrasound markers as biological predictors of maternal and fetal outcomes in severe late onset preeclampsia

Principal Investigators: Professor RA Dyer

Co-investigators:

Prof JL Swanevelder, Dr. E Neethling, M Flint, PhD, Prof CJ Lombard, Dr S Allie, Prof S Fawcus

International Collaborators:

Dr. C Ortner (Vienna Medical University, Vienna, Austria)

Dr V Krishnamoorthy (University of Washington, Seattle USA)

1. Purpose of the study

We are asking for you to be in this study because you are an otherwise healthy pregnant woman admitted to Mowbray Maternity Hospital labour and delivery unit, and you now have a diagnosis of "pre-eclampsia", a disease with high blood pressure in pregnancy. We want to see how results of a type of blood test and of ultrasound examinations of your chest and eyes compare to the outcome of your delivery. The blood test looks at so-called acid-base levels in the blood that may be off-balance in pre-eclamptic patients. The ultrasound examination is similar to examinations you might have had during your pregnancy, where pictures of your baby where taken with a device called ultrasound machine. An ultrasound machine makes sound that you or your baby do not hear or feel to make a picture. This "ultrasound" has also no known side effects. In a similar way, we are now making pictures of your heart, lung and eye. The pictures of the heart and lung will tell us if there is risk for too much water in your lungs. The picture of your eye will tell us if there is risk for brain swelling. This information is very important to the anaesthetist and eventually for the obstetrician. This information will also help us preventing these complications (lung water, brain swelling).

2. Study procedures

If you choose to be in this study, your participation in the study will take place during your stay in the hospital before delivery. The following research procedures will take place in addition to your standard clinical procedures:

Collection of blood from the vein:

We will collect a small amount of blood from you one time for this study. For standard clinical care, blood will also be collected from your vein. If possible, we will try to collect extra blood from the clinical draws. With the blood draw we will collect 2-3 teaspoons of blood, which will take less than 3 minutes to complete. This is necessary for research purposes, as some information cannot be obtained from the routine blood draw (detailed acid-base status).

Ultrasound examination of your heart, lung and eye nerve:

For the study purpose we will perform and ultrasound examination of your heart, lungs and eye within 24 hours of your admission. Ultrasound is a non-invasive method to make images of your heart, lung and eye nerve. The ultrasound examination of your eye can give us important information about the pressure behind your eye. For that purpose ultrasound gel will be applied on an ultrasound transducer that will be gently positioned on your chest and eye lids. The duration of the ultrasound examination on your chest will take 10-15 minutes, the examination of your eye will take 5 minutes. So in total the ultrasound examinations will take approximately 15-20 minutes.

Collection of data from the medical record: We will collect information about you and your newborn baby from the Mowbray Maternity Hospital record. We will collect information about your pregnancy, delivery, and medications from your health history until one-day post partum. We will collect information about your baby such as birth weight, APGAR score, and overall health.

3. What are the possible benefits?

There are no benefits associated with taking part in this study.

4. What are the possible risks?

The risk of the taking of a venous blood sample is very low. Besides some minor discomfort during ultrasound examination, the ultrasound examination is safe and there is no/minimum risk to you and your baby.
Main risk of the study would be a delay in your treatment. Our study procedures will only be performed after your admission has been completed and your clinical care has been initiated. Our study procedures will not intervene with your clinical care.

5. What if Something Goes Wrong?

This research study is covered by an insurance policy taken out by the University of Cape Town if you suffer a bodily injury because you are taking part in the study.

The insurer will pay for all reasonable medical costs required to treat your bodily injury, according to the SA Good Clinical Practice Guidelines 2006 (*or latest version*), which are based on the Association of the British Pharmaceutical Industry Guidelines. The insurer will pay without you having to prove that the research was responsible for your bodily injury. You may ask the study doctor for a copy of these guidelines.

The insurer will *not* pay for harm if, during the study, you:

- Use medicines or other substances that are not allowed
- Do not follow the study doctor's instructions
- Do not tell the study doctor that you have a bad side effect from the study medicine
- Do not take reasonable care of yourself and your study medicine

If you are harmed and the insurer pays for the necessary medical costs, usually you will be asked to accept that insurance payment as full settlement of the claim for medical costs. However, accepting this offer of insurance cover does not mean you give up your right to make a separate claim for other losses based on negligence, in a South African court.

It is important to follow the study doctor's instructions and to report straightaway if you have a side effect from the study medicine.

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?

We will record health information about you and your baby that will include your age, gender, weight, height, blood pressure, pulse rate and a history of existing disease. We will also record how far along your pregnancy is and if you've been pregnant before. We will further record how you deliver and the health status of your baby.

This is information that is usually routinely recorded as part of your pregnancy care.
You will receive a code number and all information will be stored anonymously in a secured area in the Department of Anaesthesia using only this code number.
The list that matches your name with the code number will be kept in a locked file in the Department of Anaesthesia.

On completion of this study the data will be presented for review by the University of Cape Town and also for possible publication in a medical journal. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared. Data will only be shared with the international collaborators as mentioned on this protocol (Dr. C Ortner, Dr V Krishanmoorthy) and only for the purpose of data analysis.
We will keep your participation in this research study confidential to the extent permitted by law. In accordance with regulatory guidelines, the information collected in this research project will be kept for at least 5 years.
However, it is possible that other people may become aware of your participation in this study. For example, the following people/groups may inspect and copy records pertaining to this research in order to ensure that the research complies with ethical and clinical requirements.

- Human Research Ethics Committee
  E 52, Room 24, Old Main Building, Groote Schuur Hospital, Observatory
  Telephone: 021 406 6338

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 Professor RA Dyer, (D23 Department of Anaesthesia, telephone 0214045142) if you would like to access your information or have further study related questions.

10. Can I withdraw from the study?

Participants may withdraw from the study at any time, without affecting their further management.

11. 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. If you want any information regarding your rights as a research participant, or complaints regarding this research study, you may contact Professor Marc Blockman at the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee which is an independent Committee established to help protect the rights of research participants on telephone number 021 4066492.

12. Consent

Your signature below means that you have received and understood the information regarding this study, have asked the questions you currently have about the research and those questions have been answered. You will receive a copy of the signed and dated form to keep for future reference.

By signing below, you indicate that you give permission to take part in this research.

_____ _____ _____ _____
Signature of Participant Date Printed Name

_____ _____ _____ _____
Signature of witness 1 Date Printed Name

Person Explaining the Research: Your signature below means that you have explained the research to the participant/participant representative and have answered any questions he/she has about the research.

_____ _____ _____
Signature of person who explained this research Date Printed Name

Interpreter (where applicable)

_____ _____ _____
Signature of interpreter Date Printed Name

Appendix C: STROBE Checklist

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

Please find below how and where in the manuscript each point of the Strobe Statement checklist is addressed by the authors in red and italics.

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract *This is mentioned in the abstract*
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found *Done*
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported *Background and rationale explained and reported in the introduction*
Objectives	3	State specific objectives, including any prespecified hypotheses *Objectives with primary and secondary aims are clearly stated in last paragraph of the Introduction*
Methods		
Study design	4	Present key elements of study design early in the paper *Stated in 1st paragraph Methods section*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection *Figure 1 (patient flow chart) and 2nd paragraph Methods section*
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *2nd paragraph Methods section (under Subjects)*
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed *not applicable*
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable *Diagnostic criteria: methods page 6, line 16-22* *Defined outcomes: statistical analysis section page 11, line 1-3*
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group

		Ultrasound procedures and laboratory measurements are explained in the methods section (page 8-10) and in the supplemental digital content submitted with the manuscript.
Bias	9	Describe any efforts to address potential sources of bias *In order to address measurement bias, intra- and inter-observer reliability were tested (methods page 11, line 11-15)* *Selection bias addressed through meticulous documentation of participant disposition presented in patient flow chart*
Study size	10	Explain how the study size was arrived at *Sample size calculation: page 11 final paragraph / page 12 1st paragraph*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. *Statistical analysis: page 11* If applicable, describe which groupings were chosen and why *not applicable .*
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding *Done, page 10-12*
		(*b*) Describe any methods used to examine subgroups and interactions *Inferential analysis was performed by t-test, Chi-squared test, and univariable binomial regression. No subgroup analysis was performed.*
		(*c*) Explain how missing data were addressed *Missing data was addressed by increasing number of subjects enrolled, to ensure 80 complete sets of data, as per sample size calculation*
		(*d*) If applicable, explain how loss to follow-up was addressed *No patient was lost to follow-up*
		(*e*) Describe any sensitivity analyses *No sensitivity analysis was performed.*
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed *Presented in Figure 1: patient flow chart*
		(b) Give reasons for non-participation at each stage *Presented in Figure 1: patient flow chart*
		(c) Consider use of a flow diagram *Done (Figure 1)*
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential

		confounders *Presented in Table 1 and Table 2*
		(b) Indicate number of participants with missing data for each variable of interest *In 15 patients, PW doppler imaging was incomplete; please see comment in the first paragraph of the Results section*
		(c) Summarise follow-up time (eg, average and total amount) *Participants were followed up until delivery (maximum 48 hrs post enrollment)*
Outcome data	15*	Report numbers of outcome events or summary measures over time *Presented in Table 1 -4*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included *For the a priori defined outcomes the prevalence and 95% confidence intervals were calculated. (Results)*
		(*b*) Report category boundaries when continuous variables were categorized *Done*
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period *not applicable*
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses *Intra-observer and inter-observer variabilities for ultrasound parameters were evaluated using the Bland-Altman method and expressed both graphically and quantitatively as mean difference (bias) and 95% limits of agreement (page 11)*
Discussion		
Key results	18	Summarise key results with reference to study objectives *Stated (1st paragraph of discussion section)*
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias *Limitations are discussed in detail in the penultimate paragraph of the discussion*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence *Done*
Generalisability	21	Discuss the generalisability (external validity) of the study results

		Done by, inter alia, comparing and confirming findings to those in comparable studies
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based *First author received institutional funding, as stated on title page.*

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Appendix D: Anesthesia & Analgesia- Instructions to authors

Available online from: http://edmgr.ovid.com/aa/accounts/ifauth.htm

We greatly appreciate your interest in submitting your manuscript to *Anesthesia & Analgesia* or *A&A Practice (formerly, A&A Case Reports)*. Our goal is to provide authors with a thorough yet timely review of their submissions. All decisions should be completed within 6 weeks, except for Review Articles and Special Articles, which may take up to 8 weeks. Authors will be updated as to the status of their manuscript and notified if delays occur.

Notice: The **Instructions for Authors** for *Anesthesia & Analgesia* and *A&A Practice (formerly, A&A Case Reports)* have been further revised. New submissions should be prepared according to the Instructions that follow. Failure to do so may result in your submission being returned without review.

This now current Version 1.3 of the Instructions for Authors replaces the earlier Version 1.2.

In an effort to further promote the existing expanded scope of A&A Case Reports—specifically, to publish content of practical appeal to a wide audience—the name of this journal will become A&A Practice starting in January 2018.

Additionally, as of January 1, 2018, all Echo Rounds and Echo Didactics articles will be published in A&A Practice.

A&A Practice will remain editorially aligned and operationally integrated yet distinct from Anesthesia & Analgesia.

Mission and Scope

Anesthesia & Analgesia exists for the benefit of patients under the care of health care professionals engaged in the disciplines broadly related to anesthesiology, perioperative medicine, critical care medicine, and pain medicine. The Journal furthers the care of these patients by reporting the fundamental advances in the science of these clinical disciplines and by documenting the clinical, laboratory, and administrative advances that guide therapy. *Anesthesia & Analgesia* seeks a balance between definitive clinical and management investigations and outstanding basic scientific reports. The Journal welcomes original manuscripts containing rigorous design and analysis, even if unusual in their approach.

Authors are encouraged to read this editorial, which describes some of the previous changes to the editorial philosophy of *Anesthesia & Analgesia*: Pittet JF, Vetter TR. Continuing the Terra Firma and Establishing a New EQUATOR for *Anesthesia & Analgesia*. Anesth Analg. 2016;123(1):8-9.

Authors are strongly encouraged to adhere to the fundamentals of English grammar, syntax, punctuation, and composition. If a paper is poorly written and thus difficult to understand, it will likely **not** receive as favorable a review, despite presenting strong science and/or novel information. If indicated, please consider using a Language Editing Service (see below) to address this issue **before** your initial submission.

***Anesthesia & Analgesia* and *A&A Practice* Instructions for Authors**

Anesthesia & Analgesia and *A&A Practice* have specific **Instructions for Authors** for submitting articles, which are found below. We strongly encourage all authors to read these instructions completely and carefully, and to prepare their manuscripts in accordance with these instructions.

Articles that are not submitted in accordance with our instructions may be returned for revision prior to peer-review or rejected outright.

Brevity is crucial for a well-written and effective scholarly article.
Particular attention should thus be paid to the listed word count, reference count, and table/figure limits for each article type, both for an initial submission and any subsequent revisions.

The word count, reference count, and table/figure limits will be strictly enforced, resulting in a manuscript being returned to the author(s) for revision prior to any initial or a subsequent peer-review.

Occasionally, authors will be asked by the Journal Editorial Board to resubmit their work as a different article type. If so, this subsequent manuscript will be handled as an entirely new submission, with a corresponding new assigned manuscript number.

Any changes (additions or deletions) of authors will need to be justified and clearly communicated. See below, **Section 8.A. Role of Authors and Contributors**.

Questions?

If you have a question specifically for the Editor-in-Chief, Dr. Jean-Francois Pittet, please email him at jpittet@iars.org, or contact the Deputy Editor-in-Chief, Dr. Thomas Vetter at thomas.vetter@austin.utexas.edu

If you have questions about these submission instructions, or the Journal peer review process in general, please contact the **Editorial Office** via editor@anesthesia-analgesia.org

Manuscripts may only be submitted via the Editorial Manager online submission system. Submit your manuscript here.

If you are new to our journal, our **Visual User Guide for Authors** will help you step-by-step to create an author account and to submit your new manuscript via Editorial Manager.

If you are submitting a revised manuscript, our **User Guide for Revisions** will help you step-by-step to submit your revised manuscript via Editorial Manager.

Download a PDF version of the full Instructions for Authors of *Anesthesia & Analgesia and A&A Practice*

INSTRUCTIONS FOR AUTHORS

Section 1A: *Anesthesia & Analgesia* Article Types

Section 1B: *A&A Practice* Article Topics

Except were specifically noted, instructions in the following Sections are the same for both *Anesthesia & Analgesia* and *A&A Practice*

Section 2: Articles at a Glance

Section 3: Standardized Study Reporting Requirements

Section 4: Standards for Statistical Methods and Statistical Reporting

Section 5: Digital Copyright Transfer Agreement

Section 6: Open Access Option for Publication

Section 7: Manuscript Preparation Requirements

Section 8: Editorial, Ethical and Legal Requirements

Section 9: Common Reasons Your Submission is Returned Without Review

SECTION 1A: *ANESTHESIA & ANALGESIA* ARTICLE TYPES (Back to Contents)

Original Clinical, Health Services or Education Research Report

Original Laboratory Research Report

Brief Report

Narrative Review Article

Systematic Review Articles

Meta-Analysis

Editorial

The Open Mind

Special Article

Echo Rounds

Echo Didactics

Letter to the Editor

Book and Multimedia Reviews

Meeting Report

SECTION 1B: *A&A PRACTICE* ARTICLE TOPICS (Back to Contents)

In an effort to further promote the existing expanded scope of A&A Case Reports—specifically, to publish content of practical appeal to a wide audience—the name of this journal will become A&A Practice starting in January 2018.

The scope and content of A&A Practice is intentionally broad. A&A Practice publishes short yet informative, peer-reviewed articles that simply **describe** (a) the unique clinical characteristics and/or perioperative, critical care, acute pain-related, or chronic pain-related clinical care of **one to three** patients; (b) an important teaching point or novel educational tool; or **especially** (c) an innovative solution to a perioperative, pain, patient safety, quality and performance improvement, or global health management issue.

Additionally, as of January 1, 2018, all Echo Rounds and Echo Didactics articles will be published in A&A Practice.

Data collection and analyses are neither expected nor encouraged for an **A&A Practice** submission.

Submissions to *A&A Practice* can form the basis for a subsequent, more extensive proof-of-concept study or formal research study that is submitted to *Anesthesia & Analgesia*.

A&A Practice will continue to be published only online but it will be indexed on PubMed.

Please note that the previous requirement for conventional written patient consent for case reports, as described in Nussmeier N, Saidman LJ, Shafer S. A & A Case Reports: A Progress Report and an Update on Requirements for Patient Consent. AA Case Rep. 2014 Dec 1;3(11):141, **has been eliminated for submissions from countries like the United States where conventional written patient consent is not required.**

Nevertheless, case reports for publication by *Anesthesia & Analgesia* originating from the United States **must** be prepared in accordance with the requirements of HIPAA privacy regulations (See below Section 7.D. ***A&A Practice*** **Compliance with HIPAA Privacy Regulations****).**

However, regulations outside the United States regarding case reports or case series, including a requirement to obtain written patient consent, must be followed.

A&A Practice

DESCRIPTIONS OF SPECIFIC ARTICLE TYPES

Anesthesia & Analgesia

Original Clinical, Health Services, or Educational Research Report (Back to Top)

- An Original Clinical, Health Services, or Educational Research Report describes an investigation that focuses on the clinical practice of anesthesiology, perioperative medicine, critical care medicine, or pain medicine.
- Original Clinical, Health Services, or Educational Research Reports span the spectrum of patient-reported outcomes, clinical effectiveness, quality and performance improvement, patient safety, health services delivery, dissemination and implementation science, health policy, healthcare economics, population health, and education.
- An Original Clinical, Health Services, or Education Research Report includes a Title Page and structured Abstract of no more than **400 words**.
- A "Key Points" summary is also provided, which describes the Question, Findings, and Meaning, each composed of **one sentence**.
- These Reports are divided into four sections: Introduction, Methods, Results, and Discussion.
- The Introduction section should be focused and contain no more than **400 words**. The Introduction succinctly describes, in a series of short paragraphs, the significance of the topic, pertinent background, rationale for the study, *a priori* study aims or objectives, and primary study hypothesis, and if appropriate, secondary study hypothesis.
- The Discussion section should also be focused and contain no more than **1,000 words**. The Discussion succinctly interprets the primary findings of the study and how they relate to previous published findings. The limitations of the present study are clearly stated. If applicable, future, related research opportunities are briefly proposed.

- An Original Clinical, Health Services, or Education Research Report ranges in total length from **1,500 to 4,000 words** (not counting the Abstract and references), with no more than **30-40 references** and **4-6 tables and/or figures**. Online supplemental material can be provided when appropriate.
- Study Reporting Requirement (EQUATOR)
- Instructions for Manuscript preparation
- Instructions for Figure preparation
- Instructions for Table preparation
- Instructions for Supplemental Material

Original Laboratory Research Report (Back to Top)

- An **Original Laboratory Research Report** describes an investigation that focuses on an aspect of basic science related to anesthesiology, perioperative medicine, critical care medicine, or pain medicine.
- Original Laboratory Research Reports span the spectrum of cell biology, immunology, neurobiology, biochemistry, pharmacology, microbiology, and genetics.
- An Original Laboratory Research Report includes a Title Page and structured Abstract of no more than **400 words**.
- A "Key Points" summary is also provided, which describes the Question, Findings, and Meaning, each composed of **one sentence**.
- These Reports are divided into four sections: Introduction, Methods, Results, and Discussion.
- The Introduction section should be focused and contain no more than **400 words**. The Introduction succinctly describes, in a series of short paragraphs, the significance of the topic, pertinent background, rationale for the study, *a priori* study aims or objectives, and primary study hypothesis, and if appropriate, secondary study hypothesis.
- The Discussion section should also be focused and contain no more than **1,000 words**. The Discussion succinctly interprets the primary findings of the study and how they relate to previous published findings. The limitations of the present study are clearly stated. If applicable, future, related research opportunities are briefly proposed.
- An Original Laboratory Research Report ranges in total length from **1,500 to 4,000 words** (not counting the Abstract and references), with no more than **30-40 references** and **4-6 tables and/or figures**. Online supplemental material can be provided when appropriate.
- Study Reporting Requirement (EQUATOR)
- Instructions for Manuscript preparation
- Instructions for Figure preparation
- Instructions for Table preparation
- Instructions for Supplemental Material

Brief Report (Back to Top)

- A **Brief Report** describes a clinical or laboratory investigation that does not require the breadth of experimentation or documentation expected of an Original Research Report.
- A Brief Report typically involves the analysis of either retrospective or preliminary data, thus forming the basis for a subsequent more extensive investigation.
- A Brief Report can also be technical in nature, describing the initial use of a new instrumentation or analytic technique.
- A Brief Report that presents data typically has a smaller sample size than an Original Research Report.
- A Brief Report includes a Title Page and an unstructured Abstract with no more than **100 words**. Brief Reports contain an Introduction, Methods, Results, and a very brief (no more than **1 paragraph** long) Discussion.
- A Brief Report contains no more than **1500 words** (not counting the Abstract and references), with no more than **15 references** and **1 table and/or 1 figure**.
- Study Reporting Requirement (EQUATOR)
- Instructions for Manuscript preparation
- Instructions for Figure preparation
- Instructions for Table preparation
- Instructions for Supplemental Material

Narrative and Systematic Review Articles (Back to Top)

- A **Narrative Review Article** or **Systematic Review Article** synthesizes previously published material into an integrated presentation of the current understanding of a topic.
- A Narrative Review can be either **focused** or **comprehensive**, based on its topic and scope.
- A Narrative Review Article should describe aspects of a topic about which scientific and evidence-based consensus exists, as well as aspects that remain controversial and are thus topics for ongoing and future research.
- A duly noted and entitled **Consensus Practice Guideline** is considered a specific type of a **focused Narrative Review**.
- A duly noted and entitled **Statistical Grand Rounds** is another specific type of a **focused Narrative Review** of the conventional or novel application of contemporary quantitative sciences (i.e., statistics, epidemiology, or database management) to issues of concern to anesthesia, critical care or pain researchers. Here the inclusion of programing code and/or illustrative datasets as online supplemental material is encouraged.
- For a Systematic Review, a formal strategy to search and to critically evaluate the medical literature should be applied and well-described. Such explicit methods are used in a Systematic Review to minimize bias in its content and findings.
- All Review Articles include a Title Page and an unstructured Abstract with no more than **400 words**.
- The Introduction section should be focused and contain no more than **400 words**.

- The Discussion section should also be focused and contain no more than **1,000 words**.
- A Review Article ranges in total length from **1,500 to 5,000 words** (not counting the Abstract and references), with up to **150 references** and **4-6 tables and/or figures**. Online supplemental material can be provided when appropriate.
- Exceptions to these word count, reference count, and table/figure limits may be granted at the discretion of the Journal Editorial Board for a **Consensus Practice Guideline** manuscript.
- Study Reporting Requirement (EQUATOR)
- Instructions for Manuscript preparation
- Instructions for Figure preparation
- Instructions for Table preparation
- Instructions for Supplemental Material

Meta-Analysis (Back to Top)

- A **Meta-Analysis** uses analytic techniques to combine the quantitative results from existing individual studies, which are initially identified via a **Systematic Review**, thereby (a) allowing for a more precise estimate of the magnitude of benefit or harm of an intervention and/or (b) increasing the applicability of the results to a broader range of patients.
- A Meta-Analysis should not be written and submitted as a Systematic Review Article but as a separate submission type.
- A Meta-Analysis includes a Title Page and structured Abstract of no more than **400 words**.
- A "Key Points" summary is also provided, which describes the Question, Findings, and Meaning, each composed of **one sentence**
- These manuscripts are divided into four sections: Introduction, Methods, Results, and Discussion.
- The Introduction section should be focused and contain no more than **400 words**.
- The Discussion section should also be focused and contain no more than **1,000 words**.
- A Meta-Analysis ranges in total length from **1,500 to 5,000 words** (not counting the Abstract and references), with no more than **150 references** and **4-6 tables and/or figures**. Online supplemental material can be provided when appropriate.
- Study Reporting Requirement (EQUATOR)
- Instructions for Manuscript preparation
- Instructions for Figure preparation
- Instructions for Table preparation
- Instructions for Supplemental Material

Editorial (Back to Top)

- Editorials are *solicited* by the Editorial Board

- An Editorial either (a) provides an editorial perspective on an article published in the Journal or (b) expresses the general policies or opinions of the Journal Editorial Board. If an Editorial is intended to provide an expert perspective on an article or topic published in the Journal, it is typically solicited from reviewer(s) who provided unusually thoughtful insight during the peer-review process, and which the Editors believe should be shared with the Journal readership.
- An Editorial includes a Title but not an Abstract.
- An Editorial contains no more than **2000 words** (not counting the references), with no more than **15 references** and occasionally **1 table and/or 1 figure**.
- Instructions for Manuscript preparation
- Instructions for Figure preparation
- Instructions for Table preparation
- Instructions for Supplemental Material

The Open Mind (Back to Top)

- The Open Mind is a unique forum for thoughtful, scholarly, and preferably well-referenced perspectives. The Open Mind is intended to stimulate lively yet civil discussion. It is a forum for (a) challenging myths or dogma and/or (b) proposing new approaches or solutions to an important issue facing the anesthesiology community.
- Submissions to The Open Mind include a Title Page but not an Abstract.
- An Open Mind article ranges in total length from **1,500 to 3,000 words** (not counting the references), with up to **20 references** and **2-3 tables and/or figures**.
- Instructions for Manuscript preparation
- Instructions for Figure preparation
- Instructions for Table preparation
- Instructions for Supplemental Material

Special Article (Back to Top)

- A Special Article is a manuscript that does not fit in any of the other article types. They are typically invited by the Editorial Board to examine a particular topic.
- Occasionally, authors produce a publishable scholarly text that does not fit one of the other article types. After first communicating directly with the Journal's Editor-in-Chief, these may be submitted as a Special Article.
- All Special Articles include a Title Page and an unstructured Abstract with no more than **400 words**.
- A Special Article ranges in total length from **1,000 to 5,000 words** (not counting the Abstract and references), with up to **150 references** and **4-6 tables and/or figures**.
- Instructions for Manuscript preparation

- Instructions for Figure preparation
- Instructions for Table preparation
- Instructions for Supplemental Material

Letter to the Editor (Back to Top)

- A Letter to the Editor can offer brief, objective, and constructive comments or criticism concerning previously published articles or provide other communication of general interest to the readership. Such correspondence submissions are not a venue for Case Reports, and authors must attest during the submission process, in their cover letter, that a case description is not included in their correspondence.
- A Letter to the Editor should be brief, with no more than **500 words**. Three or fewer references, a small table or a pertinent illustration may be provided.
- All Letters to the Editor should be submitted via the *Anesthesia & Analgesia* Online Submission and Review System and not via email or postal service.
- Letters are edited by the Correspondence Editor, sometimes extensively, to sharpen their focus. A Letter to the Editor may be sent for peer review, at the discretion of the Correspondence Editor.
- A Letter to the Editor that is written in response to a published paper must be submitted no later than 3 months after the first of day of the month of the original article's **print publication date**.
- Instructions for Manuscript preparation

Book and Multimedia Reviews (Back to Top)

- A Book and Multimedia Review reports on a current publication about anesthesiology, perioperative medicine, critical care medicine, or pain medicine.
- Publishers interested in having their book or multimedia material reviewed by the Journal should first contact our Media Reviews editor at: bookreviews@iars.org.
- A Book Reviews contains no more than **750 words**.
- Instructions for Manuscript preparation

Meeting Report (Back to Top)

- A Meeting Report is a scholarly outline of the program and content of a scientific meeting.
- A Meeting Report may be organized temporally (day by day) or thematically (topic by topic).
- Authors interested in submitting meeting reports should first contact our Media Reviews editor at bookreviews@iars.org to confirm that the meeting is of general interest to the readership.

- A Meeting report does not have an Abstract and contains no more than **1500 words**.
- Instructions for Manuscript preparation

A&A Practice (**Back to Top**)

Please note that when submitting a manuscript to *A&A Practice*, go to http://www.editorialmanager.com/aa/default.aspx and select "A&A Practice" as the submission type.

- An A&A Practice submission includes a Title Page and an unstructured Abstract with a maximum of 100 words.
- If applicable, the title for a case report should include the specific words "Case Report."
- An A&A Practice submission includes an Introduction; Description of the case, project, initiative, setting, or scenario; Discussion; and References.
- An A&A Practice submission contains no more than **1500 words** (not counting the references), with no more than **15 references**.
- Including pertinent figures, illustrations, tables, and/or supplementary digital and video and audio material that expands the reader's understanding of the case report is strongly encouraged.

    - Study Reporting Requirement (EQUATOR)
    - Instructions for Manuscript preparation
    - Instructions for Figure preparation
    - Instructions for Table preparation
    - Instructions for Supplemental Material

For more information about *A&A Practice* and to view examples of its published manuscripts, visit: http://journals.lww.com/aacr.

As of January 1, 2018, all Echo Rounds and Echo Didactics articles will be published in A&A Practice. Please adhere to the following, otherwise unchanged submission details for Echo Rounds and Echo Didactics submssions.

Echo Rounds (Back to Top)

- **Echo Rounds** provide a focused discussion of a unique or interesting perioperative clinical situation in which ultrasound was central to the clinical management. Submissions must provide succinct teaching points on echocardiographic/ultrasound views, techniques or calculations. Their teaching content must be supported by the current literature or standard reference texts of echocardiography, preferably those most accessible to the general reader.

- Authors are advised to examine previously published Echo Rounds (either via the Table of Contents or www.anesthesia-analgesia.org) to avoid submission of previously published topics.
- Echo Rounds should not be construed and presented as "mini Case Reports." Therefore, only the most relevant clinical details and specific echo findings should be succinctly presented in the first one-third of the manuscript. The specific echo findings and didactic discussion of the echo topic(s) should comprise the subsequent two-thirds of the manuscript.
- Echo Rounds include a Title Page but not an Abstract.
- Echo Rounds are short reports with no more than **800 words** (not counting the Abstract and references) and no more than **6 references.**
- Echo Rounds should be accompanied by **1-3 echocardiographic still images** and **1-3 video clips with legends.** The video clips will be available online. The still images usually, but not always, correspond to the respective video clip(s). Figures and clips should be appropriately labeled (e.g., arrows, abbreviations of anatomic structures, etc.). Authors may elect to consolidate consecutive time segments into a single clip, although adequate viewing time for each segment must be provided to clearly illustrate the primary findings being discussed in the text.
- One simple table is also allowed.
- Study Reporting Requirement (EQUATOR)
- Echo Rounds Submission Checklist
- Required HIPAA Waiver
- Instructions for Manuscript preparation
- Instructions for Figure preparation
- Instructions for Table preparation
- Instructions for Supplemental Material
- Instructions for Video Preparation

Echo Didactics (<u>Back to Top</u>)

- **Echo Didactics** are *solicited* submissions presenting a practical clinical *review* of a particular ultrasound topic (e.g., important measurements, specific anatomic or physiologic evaluation, and current or emerging technologies) related to transesophageal, surface/transthoracic, epicardial, epiaortic or intravascular echocardiography.
- Echo Didactics include a Title Page but not an Abstract. The author should instead provide 3 or 4 bulleted teaching points summarizing the most important teaching points.
- Echo Didactics submissions start with an index case, which is a 1-2 sentence clinical scenario to preface the content.
- The main focus of Echo Didactics should be a discussion of the most relevant background, the "nuts and bolts" of the assessment, measurement, or imaging, and new concepts.
- Echo Didactics contain no more than **1500 words** (not counting the bulleted teaching points and references) and no more than **10 references.**

- Echo Didactics should include 1 to 3 high-resolution figures and 1 to 3 video clips, which can be composite videos. Figures and clips should be appropriately labeled (e.g., arrows, abbreviations of anatomic structures, etc.). Authors may elect to consolidate consecutive time segments into a single clip, although adequate viewing time for each segment must be provided to clearly illustrate the primary findings being discussed in the text.
- **One** simple **table** is also allowed.
- Study Reporting Requirement (EQUATOR)
- Echo Didactics Checklist
- Instructions for Manuscript preparation
- Instructions for Figure preparation
- Instructions for Table preparation
- Instructions for Supplemental Material

SECTION 2: ARTICLES TYPES AT A GLANCE (<u>Back to Contents</u>)

Particular <u>attention</u> should be paid to the listed word count, reference count, and table/figure limits for each article type, both for an initial submission and any subsequent revisions.

These listed word count, reference count, and table/figure limits will be strictly enforced, resulting in a manuscript being returned to the author(s) for revision prior to any initial or a subsequent peer-review.

SECTION 3: STANDARDIZED STUDY REPORTING REQUIREMENTS (<u>Back to Contents</u>)

A. Enhancing the Quality of and Transparency of Health Research (EQUATOR) Network

The Enhancing the Quality of and Transparency of Health Research (EQUATOR) Network was created to monitor and to propagate the proper use of guidelines to improve the quality of scientific publications by promoting transparent and accurate reporting of human subjects, health services, and animal research.

As advocated by the EQUATOR Network, *Anesthesia & Analgesia* strongly encourages adherence to the applicable statement/guidelines and checklist for all submitted research-related manuscripts (see Table below). Manuscripts adhering to the applicable statement/guidelines and checklist will typically receive a more favorable review by the Journal.

Adhering to the applicable statement/guidelines and checklist promotes consistent study design and manuscript content, which are major advantages for the Journal's authors, reviewers, editors, and readers.

Authors should consult the EQUATOR Network webpage and/or the webpage URL or citation listed in the Table below for the most current version of the specific, applicable **statement or guideline and its checklist**.

- **The applicable study checklist should be completed and uploaded under the EQUATOR Checklist File category at the time of initial manuscript submission via Editorial Manager.**

Acronym	Full Title of Guideline	Webpage URL or Citation
CONSORT	Consolidated Standards of Reporting Trials (See footnote* below)	http://www.consort-statement.org/
TREND	Transparent Reporting of Evaluations with Nonrandomized Designs	http://www.cdc.gov/trendstatement/
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology	http://www.strobe-statement.org/
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses	http://www.prisma-statement.org/
SQUIRE	Standards for Quality Improvement Reporting Excellence	http://www.squire-statement.org/
SRQR or COREG	Standards for Reporting Qualitative Research Consolidated Criteria for Reporting Qualitative Research	PMID: 24979285 PMID: 17872937
CHEERS	Consolidated Health Economic Evaluation Reporting Standards	http://www.ispor.org/Health-Economic-Evaluation-Publication-CHEERS-Guidelines.asp
STARD or TRIPOD	Standards for Accurate Reporting of Diagnostic Tests *Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis*	http://www.stard-statement.org/ http://www.tripod-statement.org/
STREGA	Strengthening the Reporting of Genetic Associations	http://www.equator-network.org/reporting-guidelines/strobe-strega/
ARRIVE	Animal Research: Reporting of *In Vivo* Experiments	http://www.nc3rs.org.uk/arrive-guidelines
CARE	Case Reports	http://www.care-statement.org/

* The main CONSORT Statement is based on the "standard" two-group parallel design. However, there are several different types of randomized trials, some of which have

different designs (e.g., cluster, non-inferiority and equivalence, or pragmatic trials), interventions (e.g., herbal medicinal, non-pharmacological, or acupuncture) and data (e.g., harms), for which specific CONSORT Extensions exist.

B. SPECIFIC STUDY TYPE AND ASSOCIATED PUBLISHED GUIDELINE

1. Randomized Controlled Trials. Authors reporting the results of a **randomized controlled trial** must follow the CONSORT statement and provide a completed CONSORT checklist. Authors must also provide a CONSORT flow diagram as Figure 1 of the submitted manuscript.

Please note that there are CONSORT Extensions for several different types of randomized trials, and the most applicable Extension should be followed by authors.

2. Non-Randomized Controlled Trials. Authors reporting the results of a **non-randomized controlled trial** must follow the TREND statement and provide a completed TREND checklist.

3. Observational Studies. Authors reporting the results of a **cohort, case-cohort, nested case-control, case-control, or cross-sectional study (or any other type of observational study of human subjects)**, a case series of $\geq$ 4 patients, or a retrospective data collection study must follow the STROBE statement and provide a completed STROBE checklist.

Authors submitting the results of such a quantitative observational study should clearly indicate (a) whether the primary outcome(s) were defined and established *a priori*at initiation of the study design or were created post hoc during data exploration ("data mining") and accompanying statistical analysis and (b) whether subgroup or sensitivity analyses were identified and established *a priori* or *post hoc*. For studies evaluating a treatment effect, indicate whether and how a clinically meaningful effect size was defined, once again either *a priori* or *post hoc*.

For further insights and directions, see Eisenach JC, Kheterpal S, Houle TT. Reporting of Observational Research in ANESTHESIOLOGY: The Importance of the Analysis Plan. Anesthesiology. 2016;124(5):998-1000.

For a single case study or small case series of $\leq$ 3 patients, the STROBE statement is not applicable but instead the CARE statement (see below) should be followed.

4. Systematic Review or Meta-analysis. Authors reporting a **systematic review** or **meta-analysis of randomized trials or cohort studies** must follow the PRISMA (previously named QUOROM) Statement and provide a completed PRISMA checklist. Authors must also submit a PRISMA flow diagram as Figure 1 of the submitted manuscript.

5. Quality Improvement Research. Authors reporting the results of a **quality improvement study** must follow the SQUIRE 2.0 guidelines and provide a completed SQUIRE 2.0 checklist.

6. Qualitative Research. Authors reporting the results of a **qualitative study** (e.g., in-depth interviews and focus groups) must provide a completed SRQR checklist.

Alternatively, authors reporting the results of a **qualitative study** can provide a completed COREG checklist.

7. Mixed Methods Research. No definitive guidelines have been created for mixed (qualitative/quantitative) research. However, authors reporting the results of a mixed methods research study can reference the Good Reporting of A Mixed Methods Study (GRAMMS) framework.

See the following pertinent references:

Cameron RA, Trudy D, Scott R, Ezaz A, Aswini S. Lessons from the field: Applying the Good Reporting of A Mixed Methods Study (GRAMMS) framework'. Electronic Journal of Business Research Methods. 2013. https://works.bepress.com/roslyn_cameron/131/

O'Cathain A, Murphy E, Nicholl J. The quality of mixed methods studies in health services research. J Health Serv Res Policy. 2008;13(2):92-98.

O'Cathain A, Murphy E, Nicholl J. Three techniques for integrating data in mixed methods studies. BMJ. 2010 Sep 17;341:c4587.

8. Health Economic Evaluation Research. Authors reporting the results of a **health economic evaluation research study** must follow the CHEERS guidelines and provide a completed CHEERS checklist.

9. Diagnostic Accuracy. Authors reporting a **study of the accuracy of a diagnostic test** must follow the STARD statement and provide a completed STARD checklist. Authors must also provide a STARD flow diagram as Figure 1 of the submitted manuscript.

Alternatively, authors reporting studies of the accuracy of diagnostic tests can follow the TRIPOD Statement and provide a completed TRIPOD checklist.

10. Genetic Association Studies. Authors reporting a **genetic association study** must follow the STREGA guidelines and must submit a completed STREGA checklist.

11. Animal Studies. Authors reporting an **animal study** must follow the ARRIVE guidelines and must submit the ARRIVE checklist.

12. Echo Rounds and Echo Didactics Submission Checklist

- Authors must submit a completed checklist for an Echo Rounds submission Required Echo Rounds Submission Checklist
- Authors must submit a completed checklist for an Echo Didactics submission Required Echo Didactics Submission Checklist
- Echo Rounds or Echo Didactics for publication by *A&A Practice* must be prepared in accordance with the requirements of HIPAA privacy regulations (See Section 7.E. ***A&A* Echo Rounds and Echo Didactics Compliance with HIPAA Privacy Regulations**).

13. Case Reports. Authors reporting the details of a **case study** of a single patient or a **case series** of ≤3 patients must follow the CARE Guidelines and submit a completed CARE checklist.

Please note that in the CARE guidelines for Case Reports, item #13 states: "Informed Consent: The patient should provide informed consent for this case report."

However, per the CARE guidelines, for case reports originating from outside the United States written patient consent must be obtained.

Nevertheless, Case Reports for publication by Anesthesia & Analgesia from the United States must be prepared in accordance with the requirements of HIPAA privacy regulations (See Section 7.D. ***A&A Practice Compliance with HIPAA Privacy Regulations).***

In clinical case reports, authors should state whether they have reported serious adverse events to the manufacturer, United States Food and Drug Administration (FDA), or other governmental regulatory agency.

SECTION 4: STANDARDS FOR STATISTICAL METHODS AND STATISTICAL REPORTING (Back to Contents)

All authors who are presenting data and data analyses in their manuscripts submitted to the Journal are now required to attest via Editorial Manager that they have reviewed sections 4A, 4B, 4C and 4D located below and have implemented all of the relevant items.

This should be done preferably before implementing their study data collection but certainly as they undertook their statistical analyses and prepared their manuscript for initial submission and any requested revision(s).

While *Anesthesia & Analgesia* has elected not to implement a required formal statistical checklist to be completed and submitted by authors, adhering to the guidelines below will substantially improve chances of publication and avoid delays in the review process.

Authors may also find this editorial informative: Mascha EJ, Vetter TR. The Statistical Checklist and Statistical Review: Two Essential Yet Challenging Deliverables. Anesth Analg. 2017 Mar;124(3):719-721.

A. Statistical Analyses and Methods as Promulgated by the Statistical Analyses and Methods in the Published Literature (SAMPL) Guidelines

As advocated by the EQUATOR Network, *Anesthesia & Analgesia strongly* endorses adherence to the Statistical Analyses and Methods in the Published Literature (SAMPL) Guidelines.

Please see Lang TA, Altman DG. Basic statistical reporting for articles published in biomedical journals: The "Statistical Analyses and Methods in the Published Literature" or "The SAMPL Guidelines." Handbook, European Association of Science Editors. 2013:23-6.

The SAMPL Guidelines can be accessed at http://www.equator-network.org/reporting-guidelines/sampl/.

BASIC STATISTICAL METHODS AND REPORTING THAT SHOULD BE INCLUDED IN ALL QUANTITATIVE MANUSCRIPTS.

THESE ITEMS ARE COMMONLY MISSING OR DEFICIENT IN SUBMITTED MANUSCRIPTS, LEADING TO A LENGTHIER STATISTICAL REVIEW. AUTHORS ARE THUS STRONGLY ENCOURAGED TO PROACTIVELY ADDRESS ALL OF THESE ISSUES.

B. For All Studies That Include Data Analysis and/or Estimation:

1. **Primary and secondary outcomes**. Primary and secondary outcomes must be clearly identified and distinguished in the Abstract, Methods, Statistical Methods, Results, and Discussion. The designation as primary or secondary outcome should have been decided *a priori*. If true, this should be stated; if not, the reasons why should be explained. While it is acceptable to present findings not anticipated in the study design, these should be clearly identified as *post hoc* observations.
2. **Detailed statistical methods section**. The statistical methods section needs to closely follow the stated study hypotheses or aims (i.e., not a generic list of tests that could apply to most any study and its manuscript) and to be sufficiently detailed, including all conducted analyses.
3. **Assumptions**. Report how the key assumptions of the conducted statistical analyses were assessed and confirmed. For example: one-sided versus two-sided tests of statistical confidence.
4. **Type I error/multiple testing.** Explain how a Type I error is protected at the given level (e.g., 0.05), if there are multiple primary outcomes or multiple testing (e.g., Bonferroni correction or other method). Differentiate between overall

significance level and the significance criterion (P-value cut-point) that are applied to individual comparison tests.

Note: Authors are discouraged from using the argument that adjusting for multiple comparisons or multiple testing should not be done because it increases the risk of a Type II error (decreases power). While it is true that more stringent significance criterion decreases power, that is the price of multiple testing, and the sample size needs to be increased accordingly. Neglecting to adjust for Type I error can lead to extremely high chance of some or many of a study's statistically significant results being false positives. The goal should be to focus on key outcomes and exposures in the study design phase.

5. **Justify the sample size.** Whether the findings are positive or negative, authors should explain how the sample size was derived. Authors should also declare the planned (*a priori*) power or available (post-study) power to detect clinically important differences in the primary outcome. These are key features of the study design. This section should appear immediately after the statistical methods are detailed.
6. For post-study power (not calculated *a priori*), consider what difference would be clinically important, independent of the observed results. Post-study power should NOT be based on the observed differences, but rather on what the authors (and readers) would consider to be clinically important. For an estimation study with no statistical comparisons being made (e.g., estimating prevalence or diagnostic accuracy), report the planned or available width of the confidence interval for primary endpoint. A sample size calculation needs to have sufficient information to be reproducible by the reader.

   Note: Requiring authors to report on power to detect clinically important differences, as mentioned above, does not take away the importance of reporting confidence intervals and interpreting them well. Whereas power speaks to the design of the study, confidence intervals give important information on the available evidence from the observed data. Both are important and needed.

   For example, suppose in their design phase, authors had 80% power to detect a relative risk of 0.50 or stronger (low power). Then suppose the estimated risk ratio (RR) confidence interval from the study was 0.70 (0.30, 1.9). This study is not conclusively negative since clinically important effects are contained within the confidence limits. Reporting *a priori* low power to detect clinically important differences (independent of what was actually observed), in addition to the observed wide observed confidence interval limits, makes a negative conclusion even stronger.

7. **Results section should follow clearly from the statistical methods and study objectives.** Primary and then secondary aims should be addressed in sequence, with clear differentiation. No new statistical methods should be introduced in the Results, when they have not been provided and referenced earlier in the Methods.

8. **Report treatment effect estimates and variability** (standard error or confidence interval) of treatment effect estimate at least for the primary outcome(s). Confidence intervals and P-values must be reported in both the Abstract and Results sections. Also report confidence intervals for estimates of incidence, prevalence, when they are the primary outcome. Confidence intervals for the primary outcomes should be interpreted as the best evidence for where the treatment effect or association of interest may fall. Non-significant results should be given more weight as conclusively negative when the confidence interval does not include what authors or others would consider to be clinically important effects.
9. **Similar/equivalent**. When conducting tests for superiority, it is not appropriate to make claims of groups being "equivalent" or "similar." **Non-significant results from superiority tests should only make claims of no difference being found**. A specific design (equivalence study) and tailored analytic methods are required before one can make claims of equivalence or similarity.
10. **Baseline comparisons**. In a randomized trial, authors should not include P-values or related tests comparing randomized groups on baseline characteristics. Rather, simply discuss whether clinically important differences in the observed numbers are apparent or not. Since there is no hypothesis being tested at baseline, the P-values are not appropriate. Instead consider assessing balance using standardized difference (guidance is that absolute standardized difference greater than 0.10 is evidence of imbalance). In statistical methods, say what you had planned to do, if anything, if clinical imbalances were found at baseline (e.g., include those variables in a multivariable model when assessing association between exposure and outcome.).
11. On the other hand, for nonrandomized studies, comparing groups on baseline characteristics using statistical tests is important and highly recommended.
12. **Conclusions.** Conclusions should not go beyond what was tested or assessed in the study, and should focus on primary endpoint(s). In particular, observational studies—whether retrospective or prospective—can only identify association between a variable and an outcome. Do not use language that would imply a cause and effect relationship (see below).

C. Additional Elements for Non-Randomized Observational Studies Assessing an Association Between Exposure and Outcome. However, still Follow Part A and Part B above.

1. **Confounding**. Address potential confounding of the relationship of interest as thoroughly as possible using multivariable regression, propensity score methods, or other methods. Since the goal is typically to adjust for as much confounding as possible, it is usually neither desired nor ideal to use a so-called parsimonious model when considering which variables to adjust for. Adjustment should instead be more liberal. When limited adjustment is made, for whatever reason, list this as a strong limitation in the Discussion.

Example: In retrospective database studies, researchers may assess the association between an exposure of interest (such as receiving an intraoperative blood transfusion or not) and a major postoperative complication or event. Since the exposure groups are not randomized, they may differ on baseline variables (e.g., age, sex, BMI, comorbidities, ASA physical status), variables which themselves may be strongly associated with the outcome variable. Researchers will want either to control for such variables in a multivariable model when assessing the association of interest, or alternatively to use propensity score (PS) methods either to match exposed and non-exposed patients on the set of potentially confounding variables or alternatively to weight by or adjust for the PS. With each method, the goal is to reduce confounding.

2. **Causation versus association**. Avoid using language suggesting causation, such as the exposure "reduced" the outcome, or "effect" of the exposure on outcome. Also avoid referring to an independent variable as a "risk factor" in an observational study. Instead, state and discuss that an "association" was observed between exposure and outcome.
3. When discussing observational results, please be as conservative as possible. Many observational studies demonstrate—in essence—that sicker patients do worse; this is not a novel finding! Methodologic limitations, including the potential for unidentified confounding, should be transparently discussed. A statement such as “further research is needed” can be greatly enhanced with a further few sentences describing how prospective research should be conducted, and what the available power to detect a difference might be.

D. Additional Details for All Studies

1. **P-values**. Report all actual P values, not “NS.” P-values should usually be rounded to 2 or 3 decimal places.
2. Say “multivariable” instead of “multivariate” when there are multiple independent variables and a single outcome variable.
3. Tables should include the patient or unit denominator (sample size), and should reference the utilized statistical methods in the table footnotes.
4. Tables and figures should stand alone. Tables and figures, along with their legends and footnotes, should include enough information about what was done statistically to basically stand alone, independent of the statistical methods subsection of the manuscript.
5. **Trend**. Authors should not say that the nearly statistically significant result represents a trend in the data. Neither should authors say “there was an effect of X on Y” and then say that it was non-significant—instead, simply state that it was non-significant or that no association was found.

SECTION 5: DIGITAL COPYRIGHT TRANSFER AGREEMENT (Back to Contents)

An Electronic Copyright Transfer and Disclosure Questionnaire is completed by the corresponding author during submission.

Upon submission, the co-authors are emailed a hyperlink to verify their co-authorship and complete the electronic Copyright Transfer and Disclosure Form within Editorial Manager.

Questions About the Copyright Transfer and Disclosure Form?

Please contact our editorial office at editor@anesthesia-analgesia.org

SECTION 6: OPEN ACCESS OPTION FOR PUBLICATION (Back to Contents)

Authors of accepted peer-reviewed articles have the choice to pay a fee to allow perpetual unrestricted online access to their published article to readers globally, immediately upon publication. **The article processing charge for *Anesthesia & Analgesia* is $3,200 (for CCBY-NC-ND license, $4,000 for CCBY) and for *A&A Practice* is $600 (CCBY-NC-ND only)**. Please see the **Open Access page** for more details.

SECTION 7: *ANESTHESIA & ANALGESIA* AND *A&A Practice* MANUSCRIPT PREPARATION (Back to Contents)

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Statistical Analysis

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Manuscript Organization (Back to Top)

ALL articles should be arranged in the following order.

1. Manuscript, as a single file, consisting of Title Page, Abstract (not required for all article types – see Articles At A Glance), Body Text, References
2. Tables (each Table should be a separate .doc file or placed at the end of the manuscript file)
3. Figure Legends (placed consecutively, in numerical order, all on the same page)
4. Figures (each Figure should be uploaded as a separate file)
5. Appendices (each Appendix should be a separate file)

Title Page (Back to Top)

- Article Title
- First name, middle initial, and last name of each author, with their highest academic degree (M.D., Ph.D., *etc.*), and institutional affiliations.
- Name, mailing address, phone number, and e-mail address of the corresponding author.
- Disclosure of funding received for the work from National Institutes of Health (NIH), Wellcome Trust, Howard Hughes Medical Institute (HHMI), and all other financial support, including departmental or institutional funding. If no funding received, state Financial Disclosures: None
- Please list any conflicts of interest the authors have had within the 36 months of submission. If no conflicts, state Conflicts of interest: None
- Clinical trial number and registry URL, if applicable.

- **List the word count of the Abstract, Introduction, and Discussion. Also list the overall word count for the entire body of text (excluding Abstract and References).**
- Abbreviated Title (running head) that states the essence of the article (< 50 characters). This is not required for all article types (see above).
- List each author's individual contribution to the manuscript. For each author, please list the individual contribution using the following text: "Author Name: This author helped…"

Abstract (Back to Top)

Manuscript Type	Abstract Type	Number of words
Original Clinical Research Report	Structured	400
Original Laboratory Research Report	Structured	400
Brief Report	Unstructured	100
Narrative Review	Unstructured	400
Systematic Review	Unstructured	400
Meta-Analysis	Structured	400
Editorial	NA	NA
The Open Mind	NA	NA
Special Article	Unstructured	400
Echo Rounds	NA	NA
Echo Didactics	3 bulleted teaching points	NA
Letter to the Editor	NA	NA
Book and Multimedia Review	NA	NA
Meeting Report	NA	NA
Case Report	Unstructured	100

Key Points Summary (Back to Top)

For Original Clinical/Laboratory Research Reports and Meta-Analyses, a "Key Points" summary should be included directly underneath the structured abstract. The key points summary should describe the Question, Findings, and Meaning, each composed of one sentence. Please format the summary as three bullet points:

- Question: [One Sentence Text]
- Findings: [One Sentence Text]
- Meaning: [One Sentence Text]

Body (Back to Top)

The body of the manuscript should typically be divided into four parts (does not apply to all article types – See Article Types At A Glance):

- Textual material (body text, tables, figure legends etc.) should be submitted as a .doc or .docx word processing file
- 12 point Arial or Times New Roman font
- Introduction (new page). This should rarely exceed one page in length.
    - Should ideally contain only 4 to 5 short paragraphs: (1) significance, (2) background, (2) rationale, and (3) the study's aims or objectives and if applicable, (5) primary study hypothesis, and if appropriate, the secondary study hypothesis.

    - Avoid the temptation and frequent tendency to provide an extensive literature review in the Introduction.

- Methods (new page)

    - A subsection entitled "Statistical Analysis" should appear at the end of the Methods section when appropriateA statement that the study was approved by the appropriate IRB/Research Ethics Committee and written informed patient consent was obtained, or that the requirement for written informed consent was waived. (See section C Protection of Human Subjects).

    - If applicable, authors should include their clinical trial registration number, registry, principle investigator and date of registration. (See section G Registration of Clinical Trials)
    - A statement indicating the author has followed the appropriate EQUATOR guidelines should be included in the Methods section.
        - Example: "This manuscript adheres to the applicable CONSORT guidelines."
    - A subsection entitled "Statistical Analysis" should appear at the end of the Methods section when appropriate
- Results (new page)
- Discussion (new page). Focuses on the findings in the current work

Acknowledgements (Back to Top)

For acknowledgement of individuals or organizations, provide complete name, degrees, academic rank, department, institutional affiliation, city, state, and country. Add description of the contribution to the study.

References (Back to Top)

- *Anesthesia & Analgesia* and *A&A Practice* follow the American Medical Associate (AMA) citation style; Consult the American Medical Association Manual of Style, 10th ed., New York, Oxford University Press, 2007, for style.
- Number references (as superscripts) in the sequence they appear in the text.
- In text, tables, and legends, identify references with superscript Arabic numerals.
- If there are 6 or fewer authors/editors, list all 6; if there are more than 6, list the first 3 followed by "et al."
- Abbreviate names of journals according to the journals abbreviation list maintained by PubMed
- Manuscripts "In Press" – A "manuscript in press" is defined as an article that has been accepted for publication, but has not yet been published by the accepting journal, in print or online and is being cited as basis for the study being described in the submitted manuscript. Please submit an electronic copy (Word, PDF) of any "In Press" manuscript that is cited in the reference list, labeled as "In Press, Reference # ___."

Tables (<u>Back to Top</u>)

- *Anesthesia & Analgesia* and *A&A Practice* follow the American Medical Associate (AMA) table format.

- Tables should be uploaded as a separate Word file or presented in the main document word file, just after the references.
- Use a separate page for each table.
- Individual tables should not exceed two typed pages. If a table exceeds two typed pages, start a new table on the subsequent page.
- For any table that exceeds two typed pages and cannot be divided into a new table, the table should be submitted as a supplemental digital content file (see formatting requirements for Supplemental Digital Content files below).
- Double-space all table material.
- Do not submit tables as photographs or pasted images. Tables should be black and white only.
- Number the tables consecutively and cite them consecutively (on first instance) in the text.
- Do not create multi-part tables (e.g., Table 1A, Table 1B). Such tables should instead be cited as "Table 1," "Table 2," etc.
- Each table should have a brief title.
- Each column in a table should have a brief column header name.
- Use footnotes (not table titles or column headings) for explanatory matter and definitions of abbreviations. Abbreviations must be described with footnotes even if they are defined in the text or in other tables.
- For footnotes within a Table, use lower-case italicized letters in sequential alphabetical order.
- If you include a block of data, a table, or a figure from another source, whether published or unpublished, acknowledge the original source.

Appendices (Back to Top)

- Uploaded as a separate file
- Each appendix must be cited within the text, in consecutive order.
- Appendix content counts towards the table and/or figure limits. If the inclusion of an appendix exceeds the table and/or figure limit for the respective article type, submit the appendix as a supplemental digital content file.

Figure Legends (Back to Top)

- Supply a legend for each figure.
- Group Figure legends on a single page just after the references
- If a figure has multiple panels (e.g., left, right or A, B, C) please specify each panel in the legend.
- Repeat definitions of any abbreviations used in the legend

Figures (Back to Top)

- Figures should be uploaded as separate .tiff, .jpeg, .pdf or .pptx files. Figures will have to be uploaded at a resolution of 300 dpi or higher at acceptance.
- Figures with multiple panels should be condensed into a single file for each figure (for example, Figure 1A through 1F should be in one file, Figures 2a through 2F should be in a second file, etc.). Each individual panel should be labeled with a capital letter.
- *Anesthesia & Analgesia* and *A&A Practice* publish in full color, and encourage authors to use color to increase the clarity of figures.
- Standard colors should be used (black, red, green, blue, cyan, magenta, orange, and gray).
- Avoid colors that are difficult to see on the printed page (e.g., yellow) or are visually distracting (e.g., pink).
- Figure backgrounds and plot areas should be white, not grey.
- Axis lines and ticks should be black and thick enough to clearly frame the image.
- Axis labels should be large enough to be easily readable and printed in black.
- Number figures consecutively. Supply a brief title for each. Cite figures in the text in consecutive, numerical order on first instance.
- If a figure has already been published, acknowledge the original source. You must obtain and submit written permission from the copyright holder to reproduce the material when you submit the manuscript for review. Unpublished figures require permission of the author. Permission is required to reproduce any previously published material except for documents or figures in the public domain. See Permissions
- Define all abbreviations used in each figure. Repeat definitions of any abbreviations used in subsequent legends.

Video preparation for Echo Rounds or Echo Didactics (Back to Top)

The video clip(s) accompanying Echo Rounds or Echo Didactics submissions should conform to the following:

- Formatted in MPEG, QuickTime (MOV), Windows Media Video (WMV) or MP4.
- Play on *both* Windows and Macintosh platforms. The review process will be delayed if the Editorial Office cannot play your video clip.
- Individual size should not exceed 15 MB. Use video-compression software to reduce video size if necessary.
- Optimal video frame dimensions of 480 x 360 pixels and 640 x 480 pixels. Videos of 320 x 240 pixels have inadequate resolution for teaching.
- Duration of individual video clip should be less than 15-25 seconds.
- Combinations of clips: If you combine several video clips, for example several TEE echocardiographic loops, please provide adequate time for each segment, and leave a suitable gap between the videos. Use appropriate labeling to ensure that the viewer can understand the timing of the pathology and events. Labeling can be added with video editing programs such as Adobe Premiere or iMovie.
- Authors should complete a video checklist form for each video when submitting a revised manuscript. The video checklist form provides the information necessary to upload the video on the journal website's video gallery.

The figure(s) accompanying Echo Rounds or Echo Didactics submissions should conform to the following:

- Formatted in high-resolution JPEG or TIFF formats.
- Individual size should not exceed 500 KB (to permit adequate resolution for printing).

Supplemental Material (<u>Back to Top</u>)

- Authors may submit separate supplemental material to enhance their article's text and to be considered for online-only posting.
- Supplemental material may include the following types of content: text documents, graphs, tables, figures, audio, and video.
- Cite all supplemental digital content consecutively in the text.
- Citations should include the type of material submitted, should be clearly labeled, and should include a sequential number (Example "Supplemental Figure1", "Supplemental Table 1", "Supplemental Video 1").
- Supplemental Legends should be submitted at the end of the manuscript file and should provide a brief description of the supplemental content. For example: "Supplemental Table 1: Lists all medications used in this study."
- Each supplemental digital content file must be composed to standalone. For example, tables and figures must include titles, legends, and/or footnotes, following journal style, so the viewer can fully understand the supplemental content on its own. Production will not make any edits to the supplemental files; they will be presented as submitted.

- It is recommended to group multiple supplemental figures/tables into one supplemental digital content file when submitting. Each file will be given a permanent hyperlink when the Publisher prepares the supplemental digital content for posting. To avoid excessive hyperlinks in your publication, please group figures/tables.
- For audio and video files, enter the author name, videographer, participants, length (minutes), and size (MB) of file in Editorial Manager. Authors should mask patients' eyes and remove patients' names from supplemental digital content unless they obtain written consent from the patients and submit written consent with the manuscript. Copyright for video or audio supplemental digital content will be required upon acceptance.
- For a list of acceptable file types and size limits, please review LWW's requirements for submitting supplemental digital content: http://links.lww.com/A142

Additional Information (Back to Top)

1. Units of Measurement

   Use metric units. The units for pressures are mmHg or cmH2O. Diagonal slashes are acceptable for simple units, *e.g.*, mg/kg; when more than two items are present, negative exponents should be used, *i.e.*, $ml \cdot kg^{-1} \cdot min^{-1}$ instead of ml/kg/min.

2. Abbreviations

   Define all abbreviations except those approved by the International System of Units for length, mass, time, temperature, amount of substance, *etc.* Do not create new abbreviations for drugs, procedures, experimental groups, *etc.*

3. Drug Names and Equipment

   Use generic names. If a brand name must be used, insert it in parentheses after the generic name. Provide manufacturer's name, city, state, and country. Be careful about the use of trademarked terms (*e.g.*, Thrombelastography™, TEG™, *etc.*).

4. Statistical Analysis

   Detailed statistical methodology must be reported. Describe randomization procedures and the specific tests used to examine each part of the results; do not simply list a series of tests. Care should be taken with respect to a) parametric vs. nonparametric data, b) corrections for multiple comparisons, and c) rounding errors (summary statistics should not contain more significant digits than the original data). Median range (or percentiles) is preferred for nonparametric data.

5. Patient Identification

Do not use patients' names, initials, or hospital numbers. An individual (other than an author) must not be recognizable in photographs unless written consent of the subject has been obtained and is provided at the time of submission.

Permissions (Back to Top)

Authors must submit written permission from the copyright owner (usually the publisher) to use direct quotations, tables, or illustrations that have appeared in copyright form elsewhere, along with complete details about the source. Any permission fees that might be required by the copyright owner are the responsibility of the authors requesting use of the borrowed material, not the responsibility of Wolters Kluwer or the editorial office. To request permission and/or rights to use content from *Anesthesia & Analgesia*, access the Copyright Clearance Center) and enter *Anesthesia & Analgesia* in the 'Get Permissions' field in the upper-right corner. Please note: Permission will not be granted to adapt figures that have been previously published in *Anesthesia & Analgesia*. Contact the Editorial Office at editor@anesthesia-analgesia.org for further information.

Language Editing Services (Back to Top)

Articles submitted to the Journal must be written with a solid basis of English language. Awkward or non-intelligible English grammar and syntax can adversely affect the review process and this likelihood of acceptance of a manuscript. **Authors whose native language is not English should thus strongly consider having their manuscript copy-edited by a native English language medical/technical writer prior to initial submission.**

If you need assistance in preparing a manuscript for submission, our publisher, Wolters Kluwer, in partnership with Editage, offers a range of editorial services for a fee, including:

- Premium Editing: Intensive language and structural editing of academic papers to improve the clarity and impact of your manuscript.
- Advanced Editing: A complete language, grammar, and terminology check to give you a publication-ready manuscript.
- Translation with Editing: Write your paper in your native language and Wolters Kluwer Author Services will translate it into English, as well as edit it to ensure that it meets international publication standards.
- Plagiarism Check: Helps ensure that your manuscript contains no instances of unintentional plagiarism.
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in any way imply a guarantee, or even a likelihood, of acceptance of your manuscript in *Anesthesia & Analgesia* or *A&A Practice*.

Section 8: EDITORIAL, ETHICAL AND LEGAL REQUIREMENTS (Back to Contents)

Anesthesia & Analgesia and *A&A Practice* follow the International Committee of Medical Journal Editors (ICMJE) "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals"**.**

All authors submitting a manuscript to *Anesthesia & Analgesia* and *A&A Practice* are required to understand and to adhere to the material below.

A. Role of Authors and Contributors

Anesthesia & Analgesia and *A&A Practice* adhere to the ICMJE recommendations for defining the role of authors and non-author contributors

Anesthesia & Analgesia and *A&A Practice* therefore defines manuscript authorship as meeting the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

2. Drafting the work or revising it critically for important intellectual content; AND

3. Final approval of the version to be published; AND

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those individuals who do not meet all four criteria should be acknowledged as "**non-author contributors**" on the Title Page of the submission, which will be printed in an Acknowledgement section of the published paper.

Each manuscript must have a "Corresponding Author." The corresponding author serves as the primary contact during the submission and review process on behalf of all co-authors. Upon submission, the corresponding author is required to attest to the validity and legitimacy of the data and interpretation. The corresponding author is responsible for ensuring that all authors have reviewed the manuscript and have completed the conflict of interest disclosures. If the manuscript is accepted, the corresponding author is responsible for reviewing the proof.

If during the manuscript review process or with a complete resubmission, an initial author is deleted or another author is added, this change must be justified in the

revision cover letter. The deleted or added author must be formally notified in writing, with a copy of this co-author correspondence sent to the Journal Editorial Office.

Upon acceptance, the Editorial Office will also require a completed Authorship Change Verification form, finalizing the agreed upon authorship order for the accepted submission from each author listed, as well as, those who were added or removed.

B. Author Conflict of Interest

Anesthesia & Analgesia A&A Practice endorse the ICMJE recommendations for defining the role of authors' conflict of interest.

- *Anesthesia & Analgesia* A&A Practice holds that a conflict of interest exists when professional judgment concerning the primary interest, including patients' welfare or the validity of research, may be influenced by a secondary interest like financial gain. Perceptions of conflict of interest are as important as actual conflicts of interest.
- Authors therefore must define all funding sources supporting their work. This includes departmental, hospital, or institutional funds. The authors must disclose commercial associations that might pose a conflict of interest in connection with the work submitted. Financial relationships such as employment, consultancies, stock ownership or options, honoraria, patents, and paid expert testimony must also be reported.

C. Protection of Human Subjects

Research is a systematic investigation for the creation of generalizable knowledge. Any investigation submitted for publication demonstrates intent to create generalizable knowledge, and thus constitutes research.

The name of the institutional research ethical review and oversight committee varies with country and local custom. In the United States, this committee is called the Institutional Review Board (IRB). Other countries may use other terms (e.g., "Research Ethics Committee") for their research ethical review committee. "Institutional Review Board" is used here generically to refer to the local board that reviews the ethical treatment of human subjects and grants institutional approval for the study.

- Regardless of the country of origin, all clinical investigators undertaking human subjects research must abide by the "Ethical Principles for Medical Research Involving Human Subjects" outlined in the Declaration of Helsinki, and adopted in October 2000 by the World Medical Association.

Clinical studies not meeting the Declaration of Helsinki criteria will not be considered for publication. If published research is subsequently found to be noncompliant, it will be retracted.

- On the basis of the Declaration of Helsinki, *Anesthesia & Analgesia* requires that all manuscripts reporting clinical research state in the first paragraph of the Methods section that:

1. The study was approved by the appropriate Institutional Review Board (IRB), and

2. Written informed consent was obtained from all subjects, a legal surrogate, the parents or legal guardians for minor subjects, or that the requirement for written informed consent was waived by the Institutional Review Board (IRB).

The Editors of *Anesthesia & Analgesia* may question the authors about the details of the IRB review, informed consent forms, or the consent process. On occasion, the Editor-in-Chief may request a copy of the approved IRB application from the author. Lack of appropriate consent or its documentation will be grounds for rejection or subsequent retraction.

- Patients also have a right to privacy regarding their protected health information (PHI). Access to their protected health information (PHI) should not occur without their written authorization of use or disclosure of PHI for the explicit purposes of (a) research or (b) a case report (N = 1) or case series (N $\leq$ 3). Under certain circumstances, the requirement for patient written authorization may be waived by the Institutional Review Board (IRB).

D. *A&A Practice* Compliance with United States HIPAA Privacy Regulations

A patient's protected health information (PHI) can be viewed and used in a clinical setting by those who are assisting with or learning how to provide health care to patients. For example, a patient's PHI can be used internally for grand rounds or quality improvement and patient safety projects and related presentations.

However, the circumstances are different in the United States if the PHI is to be shared outside one's own HIPAA-covered entity's clinical education setting.

When making presentations outside one's HIPAA-covered entity's clinical education setting or when preparing a case report or case series (with an N $\leq$ 3) for publication, the researcher or educator must adhere to two requirements:

1. One must remove all PHI data elements from the patient information before using it. If all of the 18 PHI data elements, found at http://www.hhs.gov/hipaa/for-professionals/privacy/special-topics/de-identification/index.html#standard, are removed from the presentation or a case report or case series (with an N $\leq$ 3) for publication, then the information is de-identified data and contains no PHI.

Take special note that one these 18 PHI data elements includes: "Any other unique identifying number, characteristic, or code." This scenario includes a clinical case so unique that individuals with personal knowledge of the incident could identify the patient. In this situation, a written authorization must be obtained for disclosure of the PHI in a case report or case series (with an $N \leq 3$) for publication.

2. If a clinician, educator, or researcher must include any PHI data elements as part of the activity (including the above "other unique identifying characteristic"), then the second requirement also applies. The patient must authorize the use of their PHI by signing a written HIPAA-compliant authorization, which prescribes how their PHI will be used for a specific purpose. Examples of situations for which patient authorization is required include preparation of a case report or case series (with an $N \leq 3$) for publication, a lecture to national or international professional meeting, and presentation to a class or seminar outside the covered entity's clinical education setting.

A case report or retrospective chart review with three (3) or fewer patients ($N \leq 3$), which is not presented as a systematic investigation that is designed to contribute to generalizable knowledge, is not considered research. Such efforts do not require Institutional Review Board (IRB) approval, if originating from the United States.

A&A Practice therefore, for submissions originating from the United States, (a) does not require IRB approval but (b) does require that written HIPAA authorization (permission) is obtained from the patient (or deceased patient's relative) for submission of a Clinical Case Report or Case Series for potential publication. **Authors should use their own institutional HIPAA Authorization form for this purpose**.

This authorization must be obtained before submission of the manuscript, and the authors must state this authorization was obtained at the end of the introduction section. If photographs of the patient, in any form, are used, a specific signed permission from the patient must be obtained, and a copy of this signed permission be submitted with the manuscript. Failure to comply with these requirements will result in rejection of the manuscript.

As noted above, regulations outside the United States regarding case reports or case series, including a requirement to obtain IRB or Research Ethics Committee approval and written patient consent, must be followed.

E. *A&A Practice* Echo Rounds and Echo Didactics Compliance with HIPAA Privacy Regulations

A patient's protected health information (PHI) can be viewed and used in a clinical setting by those who are assisting with or learning how to provide health care to patients. For example, a patient's PHI can be used internally for grand rounds or quality improvement and patient safety projects and related presentations.

The circumstances are different if the PHI is to be shared outside one's own HIPAA-covered entity's clinical education setting.

When making presentations outside one's HIPAA-covered entity's clinical education setting or when preparing a case report (N = 1) (which includes an Anesthesia & Analgesia Echo Rounds) or case series (with an N < 3) for publication, the researcher or educator must adhere to two requirements:

1. One must remove all PHI data elements from the patient information before using it. If all of the 18 PHI data elements, found at http://www.hhs.gov/hipaa/for-professionals/privacy/special-topics/de-identification/index.html#standard, are removed from the presentation or a case report or case series (with an N ≤ 3) for publication, then the information is de-identified data and contains no PHI.

   Take special note that one these 18 PHI data elements includes: "Any other unique identifying number, characteristic, or code." This scenario includes a clinical case so unique that individuals with personal knowledge of the incident could identify the patient. In this situation, an authorization must be obtained for disclosure of the PHI in a case report or case series (with an N ≤ 3) for publication.

2. If a clinician, educator, or researcher must include any PHI data elements as part of the activity, then the second requirement applies. The patient must authorize the use of their PHI by signing a written HIPAA-compliant authorization, which prescribes how their PHI will be used for a specific purpose. Examples of situations for which patient authorization is required include preparation of a case report or case series (with an N ≤ 3) for publication, a lecture to national or international professional meeting, and presentation to a class or seminar outside the covered entity's clinical education setting.

A case report or retrospective chart review with three (3) or fewer patients (N < 3), which is not presented as a systematic investigation that is designed to contribute to generalizable knowledge, is not considered research. Such efforts do not require Institutional Review Board (IRB) approval.

As with Case Reports (see Section 7.D above), *Anesthesia & Analgesia* therefore (a) does not require IRB approval but (b) does require that a HIPAA-compliant written authorization of use or disclosure of PHI, for the explicit purposes of the Echo Rounds manuscript, is obtained from the patient (or a deceased patient's relative) for submission of an Echo Rounds for potential publication. This written authorization of use or disclosure of PHI must be obtained before submission of the manuscript. The author(s) must state they obtained this written authorization of use or disclosure of PHI in their submission cover letter. Failure to comply with these requirements will result in rejection of the manuscript.

F. Investigational Drugs

The Editorial Board of *Anesthesia & Analgesia* may exercise judgment about the ethics of a clinical trial involving investigational drugs that differs from the view of the investigators' Institutional Review Board. This situation most frequently occurs in studies involving neuraxial or perineural drug administration; drug studies in children; and nonconformity in dose, route, or indication ("off-label" use).

- Studies using drugs injected into the neuraxial (caudal, intrathecal, or epidural) or perineural space must meet at least one of three criteria:

1. The drug is approved for neuraxial or perineural administration by the United States (US) Food and Drug Administration (FDA) or the equivalent regulatory agency for the country in which the study took place.

2. The drug is not approved for neuraxial or perineural use, but it is widely used and accepted for neuraxial (e.g., fentanyl) or perineural administration. The publication of dosing guidelines in multiple textbooks represents a reasonable demonstration that a drug is widely used and accepted for neuraxial or perineural administration.

3. The study is performed under an Investigational New Drug (IND) or Biologics License Application (BLA) application approved by the US FDA or the equivalent agency in the investigator's country.

- *Anesthesia & Analgesia* is committed to expanding knowledge of the clinical pharmacology of drugs in children. However, studying drugs in children when there is no pediatric indication poses ethical concerns. Therefore, studies of drugs in children must meet at least one of three criteria:

1. The drug is approved for pediatric administration by the US FDA or an equivalent regulatory agency.

2. The drug is not approved for use in children but is widely used and accepted for pediatric administration. A reasonable demonstration that the drug is clinically accepted for use in children is when the administration in the study is consistent with the route, dose, and indication reported in multiple textbooks.

3. The study is done under an IND application approved by the US FDA or the equivalent agency in the investigator's country. Investigators in the United States are directed to the FDA website for further information on obtaining an investigator IND.

Anesthesia & Analgesia will not publish a paper describing a retrospective assessment involving pediatric drug administration, if the treatment would be considered inappropriate or unethical in a prospective trial.

- Drugs are commonly used off-label in clinical trials, and the practice is generally acceptable. However, the Editorial Board of *Anesthesia & Analgesia* reserves the right not to review a manuscript describing off-label administration of a drug if the Editorial Board believes the study posed unacceptable risk to subjects. To preclude such a determination, investigators are encouraged to obtain an Investigator IND from the US FDA or an equivalent agency in their country before initiating studies involving off-label drug administration.

G. Registration of Clinical Trials

All clinical trials involving assignment of patients to treatment groups must be registered prior to the start of the trial and any patient enrollment is undertaken.

The registry, registration number, principal investigator's name, and date of registration must be stated in the first paragraph of the Methods section of the manuscript.

Authors must state in the Methods section of their manuscript that registration of their clinical trial occurred prior to the start of the trial and any patient enrollment undertaken.

A number of registries have been approved by the International Committee of Medical Journal Editors (http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/), including http://www.clinicaltrials.gov (the most commonly used registry in the United States), http://isrctn.org, http://www.umin.ac.jp/ctr/index/htm, http://www.anzctr.org.au, and http://www.trialregister.nl. Submissions that have registered with the European Clinical Trials Database, EudraCT (https://eudract.ema.europa.eu/) meet this requirement.

H. Protection of Animal Subjects

Manuscripts describing investigations performed in vertebrate animals must explicitly state that the study was approved by the authors' Institutional Review Board for animal research (e.g., Institutional Animal Care and Use Committee, IACUC). The Journal expects humane and ethical treatment of all experimental animals, and requires that the study has been conducted in a manner that does not inflict unnecessary pain or discomfort upon the animals, as outlined by the United States Public Health Service Policy on Humane Care and Use of Laboratory Animals and the Guide for the Care and Use of Laboratory Animals (1996), prepared by the National Academy of Sciences' Institute for Laboratory Animal Research. A statement to this effect should appear at the beginning of the Methods section of the manuscript.

I. Plagiarism

Plagiarism is the use of previously published material without attribution. **The Editorial Office screens all submitted manuscripts for plagiarism, using a sophisticated software program, prior to peer review.** This software screening process identifies

passages of text that have been previously published and generates a qualitative/quantitative report. This report is reviewed by the Journal Editorial Board and its support staff.

Text copied from previously published work is interpreted using the following taxonomy:

- *Intellectual theft* is misrepresentation by an author that words and ideas previously published by another author represent the plagiarist's own scholarship. It is the most serious form of plagiarism. Intellectual theft identified during screening results in immediate rejection of the manuscript and a request for an explanation from the author.
- *Intellectual sloth* is the use of the words of another author to avoid the effort of writing new text. It commonly occurs when descriptions of research methodology are taken from prior publications. It is less serious than intellectual theft, because the text is generic and of no particular value. Submissions containing intellectual sloth are typically returned to the authors with a request that the copied text either correctly cite the original author or be rewritten in the authors' own words.
- *Plagiarism for scientific English* occurs when authors uncomfortable using scientific English compose their manuscripts as a patchwork of previously published sentences and paragraphs. Papers constructed in such a manner are rejected outright, primarily because patchwork plagiarism suggests that the authors may not understand the text they have submitted for publication.
- *Technical plagiarism* is the use of verbatim text not identified as taken verbatim, but simply referenced to the original source. The offense is a technical one, and authors are simply asked to correct it prior to peer review.
- "*Self-plagiarism"* occurs when an author uses his or her verbatim words from a previous manuscript in a new submission. Provided the authors are not engaged in duplicate publication, the Journal does not view "self-plagiarism" as misconduct. Authors are permitted to reuse their own words, and are encouraged to do so when describing identical research methods in multiple papers.

J. Duplicate Submission or Duplicate Publication

- *Duplicate submission* is concurrent submission of a nearly identical manuscript to two journals. It is improper for authors to submit a manuscript describing essentially the same research simultaneously to more than one peer-reviewed research journal. Authors should not submit the same manuscript, in the same or different languages, simultaneously to more than one journal. Duplicate submissions identified during peer review will be immediately rejected. Duplicate submissions that are discovered after publication in the Journal will be retracted.

- *Duplicate publication* is prior publication of a manuscript with considerable content overlap, particularly in the research results, by the same author or co-authors. Prior publication may be in the same language or it may be a translation (usually from the author's native language to English). Submitted manuscripts must not have been published elsewhere, in whole or in part, on paper or

electronically. This includes personal, departmental, educational, or other Internet sites. This does not apply to abstracts of scientific meetings or to lecture handouts (*e.g.*, IARS Annual Meeting, ASA Annual Meeting). *Anesthesia & Analgesia* requests that authors inform the Journal when results of a submitted manuscript have been previously presented or published in *any* venue. If a manuscript has been published previously, the submission to *Anesthesia & Analgesia* and *A&A Practice* will be rejected unless it has already been published by the Journal, in which case it will be retracted.

K. Scientific Misconduct

When *Anesthesia & Analgesia* has concerns or receives allegations of scientific misconduct, *Anesthesia & Analgesia* reserves the right to proceed according to the procedures described below.

Anesthesia & Analgesia recognize its responsibility to appropriately address concerns allegations of misconduct. Examples of misconduct include: fraud, data fabrication, data falsification, plagiarism, improper designations of authorship, duplicate publication, misappropriation of others' research, failure to disclose conflict(s) of interest, and failure to comply with applicable legislative or regulatory requirements. Misconduct also includes failure to comply with any rules, policies, or procedures implemented by *Anesthesia & Analgesia*.

In general, *Anesthesia & Analgesia* follows the recommendations of the Committee on Publication Ethics (COPE) when working to address allegations of misconduct. When a concern or allegation is raised involved parties generally will be contacted to provide an explanation of the situation. As needed, *Anesthesia & Analgesia* may also contact the institution at which the study was conducted and any other involved journals. *Anesthesia & Analgesia* will attempt to determine whether there was misconduct and the Editor-in-Chief will respond with an appropriate action. Examples of action include:

- Sending a letter of explanation only to the person(s) involved or against whom the allegation is made.
- Sending a letter of reprimand to the same person(s), warning of the consequences of future, similar instances.
- Sending a letter to the relevant head of the educational institution and/or financial sponsor of the person(s) involved, expressing the concerns and information collected.
- Publishing in *Anesthesia & Analgesia*a notice of duplicate publication, "salami" publishing, plagiarism, or other misconduct, if clearly documented. In cases of ghostwritten manuscripts, the notice may include the names of the responsible companies as well as the submitting author(s).
- Providing specific names to the media and/or government organizations, if contacted regarding the misconduct.
- Formally withdrawing or retracting the article from *Anesthesia & Analgesia*, and informing readers and indexing authorities

- Banning an author or authors from publishing any manuscript in Anesthesiology for a specified time period, with notice to the author(s) institution.

Section 9: Common Reasons Why a Submission is Returned Without Review (Back to Contents)

1. Incomplete Title Page - e.g., missing conflict of interest statement for each author or incomplete author information
2. Abstract is missing in the Word file or not properly structured.
3. Missing page numbers
4. Entire manuscript is not double-spaced
5. Methods section does not begin with an IRB approval and written patient consent statement.
6. Clinical Case Report does not specifically state at the end of the introduction section that or "a written HIPAA authorization to use/disclose existing protected health information" (required in the United States") or "written patent consent" (if required outside the United States) was obtained.
7. References do not adhere to AMA style (**see above**).
8. The above noted word count, reference count, and table/figure count limits are not followed for a specific article type.