The impact of morbid obesity on cardiac structure and function in pregnancy

by

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SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In fulfilment of the requirements for the degree:

Master of Medicine in Anaesthesiology

Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN

Date of Submission: 11 December 2017

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DECLARATION

I, *Dr Nicole Lucy Fernandes*, 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

Bigna Buddeberg, for the opportunity to work with and learn from you in the field of echocardiography. You have become a mentor and a friend.

Professor Robert Dyer, without your support, guidance and encouragement this work would not have been possible.

Adri Vorster, Blanche Cupido, Carl Lombard, Justiaan Swanevelder and Thierry Girard, for their valued contributions as co-investigators and tireless work to bring this project to fruition.

The maternity centre staff of Mowbray Maternity and Groote Schuur Hospitals, for welcoming us into your units and supporting our efforts to make a difference to the women we, as a team, treat.

Estiaan, my husband, your unwavering faith in my ability to climb this mountain is the greatest gift I could ever ask for.

List of Abbreviations

BMI	Body mass index
BSA	Body surface area
CI	Cardiac index
CI	Confidence interval
CO	Cardiac output
CS	Caesarean section
CW	Cardiac work
DT	Deceleration time
FAC	Fractional area change
FS	Fractional shortening
HR	Heart rate
IVRT	Isovolumetric relaxation time
IVSd	Interventricular septum in diastole
IQR	Interquartile range
LA	Left atrium
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVEDD	Left ventricular end-diastolic diameter
LVH	Left ventricular hypertrophy
LVIDd	Left ventricular internal diameter in diastole
LVM	Left ventricular mass
LVMI	Left ventricular mass index
LVOT	Left ventricular outflow tract
LVPWd	Left ventricular posterial wall thickness in diastole

MAP	Mean arterial pressure
OSA	Obstructive sleep apnoea
PLAX	Parasternal long axis
PWd	Posterior wall thickness in diastole
PWT	Posterior wall thickness
RV	Right ventricle
RWT	Relative wall thickness
SV	Stroke volume
SVI	Stroke volume index
SVR	Systemic vascular resistance
TAPSE	Tricuspid annular plane systolic excursion
TTE	Transthoracic echocardiography
TVR	Total vascular resistance
TVRI	Total vascular resistance index
VTI	Velocity time integral
WHO	World Health Organization

Chapter 1: Review of the Literature

1. Objectives

The aim of the following narrative review is to examine the current evidence for cardiovascular changes in pregnancy, and for the differences between cardiac function in morbidly obese and non-obese non-pregnant individuals. Echocardiographic findings in the hearts of non-pregnant obese subjects are discussed in depth, exploring advances in functional measurement techniques. The utility of echocardiography in the clinical management of the parturient is also briefly outlined, including the limited data available on the obese parturient.

2. Literature Search Strategy

All publications relevant to the subject were obtained online, from the University of Cape Town Health Science Library search facility. This includes resources from 17 medical digital archive databases worldwide. Literature published up to- and including the year 2017 was included. In total, 51 relevant papers were identified. Literature not published in the English language was excluded.

3. Quality Criteria

Keywords and phrases used in the search, in various combinations, included: obesity, pregnancy, cardiac function, diastolic dysfunction, transthoracic echocardiography and tissue Doppler.

4. Summary of the Literature

a. Introduction

Obesity is an ever-increasing global health issue. Previously predominantly a disease of the developed world, lower- and middle-income countries have displayed alarming increases in the proportion of overweight and obese people in recent years. The World Health Organisation (WHO) classifies

weight status according to body mass index (BMI) as follows:

- Underweight: BMI $\leq$ 18.5 kg/m^2,
- Normal weight: BMI 18.5 - 24.9 kg/m^2,
- Overweight: BMI 25.0 - 29.9 kg/m^2, and
- Obesity: BMI $\geq$ 30 kg/m^2.

Obesity is subdivided into class I (30.0 - 34.9 kg/m^2), class II (35.0 - 39.9 kg/m^2), and class III ($\geq$40 kg/m^2), with any BMI above 35 equating to morbid obesity.[1] In 2013, South Africa was ranked the country with the third highest incidence of obesity, behind only the United States of America and Mexico. The prevalence of overweight and obesity, as defined above, in South African women more than 20 years old is 69.3%, while 26.3% of women below 20 years fall into the same categories. Forty two percent of women above the age of 20 years and 9.6% of below 20 years are considered obese.[2]

In 2010, 44% of parturients attending an antenatal clinic in South Africa were classified as obese or morbidly obese.[3] These patients were found to be at significantly increased risk of urinary tract infections and gestational diabetes mellitus, and more often needed induction of labour and longitudinal skin incision at caesarean section (CS).[3] The adverse effects of obesity in pregnancy are well documented in numerous studies and include, but are not limited to, increased rates of CS[4] and difficult neuraxial anaesthesia[5]. This is of particular relevance to anaesthesia practice. Obese women are also at higher risk of early pregnancy losses,[6] postpartum haemorrhage, surgical site infections and venous thromboembolic disease.[7]

Whilst many studies have suggested an increased association with gestational hypertension, preeclampsia and cardiovascular disease in obese pregnant women,[4] little is known about the long-term sequelae. A large cohort study published in 2015 followed up more than 18 000 women who were admitted with a major cardiovascular event, up to 50 years post-delivery of their first child. The authors concluded that maternal overweight and obesity were strongly associated with premature death from cardiovascular disease.[8]

b. Cardiovascular and haemodynamic changes in uncomplicated pregnancy

The maternal cardiovascular adaptations to pregnancy are numerous and well documented. From as early as 5 weeks' gestation, systemic vascular resistance (SVR) decreases, with a compensatory increase in maternal heart rate.[9,10] The increase in heart rate is initially responsible for the observed increase in cardiac output (CO) during pregnancy. Further CO increases are attributable to a greater stroke volume (SV) as pregnancy progresses.[9] Systolic, mean and diastolic blood pressure all decrease during pregnancy, with the lowest values recorded in the second trimester. Thereafter there is an increase in blood pressure to pre-pregnancy levels at term.[9,10] The total blood volume increases from the 6th week of gestation to 40% above pre-conception levels by term, which in turn leads to an increase in preload.[9,11-13] An increase in the compliance of the arterial and venous systems allows for accommodation of the increased plasma volume.[11]

The structural changes which occur in response to the above-mentioned volume-loaded state have been studied by echocardiography since as early as 1979.[13] There is consensus in the literature that the left atrium (LA) displays a gradual and continuous, significant increase in size in response to the physiological state of volume overload.[12-14] The changes of the left ventricle (LV) are less consistent, with some authors reporting a definite increase in left ventricular end-diastolic dimensions, whilst others reported no observed change.[11,12,14] A study by Simmons et al[15] demonstrated echocardiographic evidence of left ventricular hypertrophy (LVH), which was directly related to the increased work-load imposed on the heart during pregnancy. The mean increase in LV wall thickness of 11% was in keeping with numbers reported in other studies.[11,15,16] The increase in left ventricular mass (LVM) was noted in some studies to be in excess of the increase in body size[11,15] indicating a true hypertrophic response. When indexed to the ventricular diastolic volume in a study by Tso and colleagues[13], the LVM showed no significant increase

between the second and third trimesters. The authors suggested that an eccentric rather than concentric pattern of hypertrophy was present in the ventricle.

The reported changes in LV systolic function, measured as LV ejection fraction (LVEF) and fractional shortening (FS), are varied across the literature. The variability in results may be due to the measurement methods used in older studies. Where LV ejection fraction is calculated using the Teicholz formula, measurements cannot be assumed to be accurate.[16] This formula presumes certain geometric norms which are no longer present in pregnancy, due to the changes in left ventricular wall thickness and shape which have been described previously. Studies using the Teicholz formula and M-mode imaging modalities for the quantification of ejection fraction tended to report an initial increase in LV systolic function up to the end of the second trimester, and a subsequent decrease in ejection fraction toward term. Despite the observed decrease, CO still remained higher than pre-pregnancy levels.[16,17] Data from newer studies, employing more modern echocardiography techniques, have produced results which contradict the notion that CO decreases at term. Simmons et al found that both fractional shortening and rate-adjusted mean velocity of circumferential fibre thickening were increased up to- and including the third trimester. When corrected for the abnormal loading conditions of pregnancy, load-adjusted indices of myocardial contractility were still normal, suggesting that contractility is unaffected.[15]

Diastolic function has not been shown to change significantly in normal pregnancy.[13-15] The increase in plasma volume, and subsequently preload, leads to an expectedly high trans-mitral inflow velocity (E), but no change in the conventional measurement for diastolic dysfunction (E/A ratio) was noted.[13]

Although the physiological changes associated with pregnancy have been thoroughly studied, quantifying these changes in a meaningful way with echocardiography has proved challenging due to the heterogeneity of the literature available.

c. Cardiac structure and function in the non-pregnant obese population

The changes in cardiac structure and function caused by obesity have been extensively studied and documented.[18-20] There is good evidence that obesity is associated with the development of hypertension, hyperlipidaemia and diabetes, as well being an independent risk factor for the development of congestive cardiac failure.[21,22]

The commonly encountered changes are:

i. Left ventricular remodelling:

The left ventricular mass has been shown to be significantly increased in obese subjects.[18,19,23-26] The clinically accepted method to measure LVM by echocardiography is the formula suggested by Devereux, which states that LVM = 0.8{1.04[([LVEDD + IVSd + PWd]^3 – LVEDD^3)]} + 0.6, where LVEDD is the left ventricular end-diastolic diameter, IVSd is the thickness of the interventricular septum in diastole and PWd is the posterior wall thickness in diastole.[27] Indexing of LVM in obesity is a controversial issue in the literature. The DuBois formula for calculating body surface area has been shown to be inaccurate in patients with a weight greater than 150 kilograms[27] and the increase in body surface area (BSA) in these patients is greater than the increase in LVM, often leading to a falsely normal or low measurement of left ventricular mass index (LVMI). Normalisation of LVM to height or to height to the power of 2.7 has been shown to be a more appropriate method of indexing in this population. One study identified significantly higher values of LVM indexed to height$^{2.7}$ in their obese study population than in normal weight controls, a finding which was absent when indexing was to BSA in the same persons.[23] Elevated BMI is a robust predictor of LVH and increases in LVM, confirming a definite causal relationship between obesity and hypertrophy, even in normotensive subjects.[24,25,28] Interestingly, females seem to have a greater increase in LVM in response to obesity than men of similar age, degree and duration of obesity.[23]

There is no consensus in the literature as to the pattern of hypertrophy noted in obese subjects. This is likely due to the differences in age, gender, co-morbidities and exclusion criteria between studies. The majority of authors have reported findings of an eccentric pattern of hypertrophy,[23,24,28] whilst some others have found the changes to be more in keeping with concentric hypertrophy.[25,29] Concentric hypertrophy is present when there are increases in LVM, LVMI, LV wall thickness and relative wall thickness (RWT) but the LV chamber size remains unchanged. Peterson et al[28] studied a group of healthy young obese women with no other co-morbidities. It is of concern that this group displayed concentric remodelling, as this has previously been associated with increased cardiovascular morbidity and mortality.[30] The changes in LV geometry are, however, not permanent and can be reversed with weight loss, even if some degree of obesity persists.[31]

ii. Right ventricular size

There is little work published on the changes in right ventricular size as a result of obesity. Wong et al found the right ventricle (RV) to be increased in diameter and noted an increase in right ventricular wall thickness.[32] It has previously been suggested that right heart changes in obesity develop as a consequence of obstructive sleep apnoea (OSA) and sleep disordered breathing.[33] This was not found in Wong's study, where the changes were unrelated to the presence or severity of OSA, but did appear to be related to the degree of obesity.[32]

iii. Left atrial size

Left atrial diameter has been found to be consistently enlarged.[18,31] This is likely due to the increased plasma volume in obesity leading to a state of volume overload. Diastolic filling abnormalities, which are addressed in detail later in this review, may also contribute to the noted increase.

iv. Left ventricular systolic function

The increased tissue mass associated with obesity leads to an increase in total

blood volume and oxygen demand, with a subsequent increase in CO.[26] Both preload and afterload have been shown to be increased in obese subjects when compared with persons of normal weight.[33] Cardiac systolic function in obesity has been widely studied, by different methods. There has been controversy in the literature since 1981, with a cardiac catheterisation study describing impaired systolic function[26], whilst others have suggested that contractile function is preserved.[34] Echocardiography now allows non-invasive quantification of LV function by a number of different methods. The LVEF and FS as measured by two-dimensional echocardiography, have been shown to be preserved, and sometimes augmented, even in severe obesity.[35,36] LVEF and FS are, however, insensitive methods of determining systolic function. They are known to be load-dependent variables, which are unreliable in the face of the abnormal physiological loading state in obesity. Subclinical changes in systolic function have been detected in young, otherwise healthy, obese women using newer echocardiography modalities.[28] Tissue Doppler Imaging (TDI) measures the velocity of the movement of individual walls of the myocardium[37] and has been shown to demonstrate subtle dysfunction in obese persons, even in the face of a preserved LVEF.[19,24,25] A limitation of TDI is that it is unable to distinguish myocardial movement due to contraction, from passive movement of the myocardium.[37] Strain rate imaging, which is less affected by passive movement of the myocardium, has also demonstrated a global decrease in left ventricular contractility in obesity.[24,38]

v. Left ventricular diastolic function

Diastolic function can be quantified during echocardiography by measuring mitral inflow patterns. The ratio between mitral early (E) and atrial (A) velocities is a marker of LV relaxation and filling. The mitral E-wave velocity describes filling during early diastole, while the A-wave velocity describes the atrial component to LV filling. The E-wave deceleration time (DT) and isovolumetric relaxation time (IVRT) are also frequently used as surrogates for diastolic function.[39,40] The changes to mitral inflow velocities noted in obesity are consistent in the literature; however, being load-dependent indices, their interpretation is difficult in this population. The observed decrease in E/A ratio

and increase in E-wave deceleration suggest impaired early ventricular filling, whilst IVRT, a marker of impaired relaxation, has consistently been found to be prolonged in obese subjects.[19,27,35,41] These changes have been detected in obese children and adolescents who are otherwise healthy, which could indicate that diastolic dysfunction occurs very early in obesity and is not related to the expected age-related changes in myocardial relaxation.[41]

TDI, again, is not influenced by the abnormal loading conditions in obesity, and gives a true reflection of diastolic function. Measurements are made at the septal and lateral insertion sites of the mitral leaflets, which allows one to quantify the velocity and amplitude of excursion of the mitral annulus.[39] Various studies have demonstrated diastolic dysfunction in obese persons using TDI.[19,28,41] The study populations were, once again, adolescents[41] and young healthy women[28], suggesting that diastolic changes are the first sign of cardiac dysfunction in obesity.

vi. Right ventricular function

The overlap between obesity and sleep-disordered breathing makes quantification of alterations in right ventricular function difficult to interpret. OSA has been shown to lead to RV hypertrophy and reduced RV systolic function in previous studies.[33,43,44] A study by Wong et al[32] compared RV function in obese and non-obese subjects, all of whom had confirmed OSA diagnosed by polysomnography. The authors showed that the systolic and diastolic dysfunction correlated positively with the degree of obesity, but was not related to the presence of sleep-disordered breathing. These findings were confirmed by another group who used TDI to quantify diastolic and systolic RV function.[38]

All of the above-mentioned changes in cardiac structure and function appear to be positively correlated with the duration of obesity. Alpert et al[45] showed significant associations between duration of obesity and increased markers of preload and afterload on echocardiography. These alterations in LV loading in turn lead to the increased LVMI and impairment of diastolic function described above. Post weight-loss studies in obese populations undergoing bariatric

surgery have shown that all abnormalities reported show some improvement with a decrease in BMI.[42,45]

d. Haemodynamics in the obese parturient

Whilst the issues of haemodynamic adaptations to both pregnancy and obesity have been well documented, the changes brought about by the two in combination are not as well understood. Three studies have interrogated the issue, studying various echocardiographic parameters in obese pregnant women. Their study populations are, however, small and definite conclusions cannot be firmly drawn.[46–48]

Mean arterial pressure (MAP) has been shown to be significantly higher in obese pregnant subjects when compared with their non-obese counterparts.[10,47] Veille et al.[48] found that obese parturients had increased septal and posterior wall thickness and LVM, but no significant changes in left ventricular dimension, FS and cardiac index (CI). Dennis et al[47] reported a significantly elevated LVM in their obese subjects, but found no differences in the degree of systolic or diastolic function measured by TDI. This is in contrast with another study which showed that SV and contractility, measured by strain indices which eliminated the effects of abnormal loading conditions, decreased during the third trimester. The concern in such individuals is that they may not be able to mount an adequate cardiovascular response to the haemodynamic demands of pregnancy. Load-dependent indices of myocardial function failed to detect any differences between obese and non-obese pregnant women, suggesting again that these methods are inadequate to assess cardiac function in the group of interest.[46] Serial transthoracic echocardiography (TTE) studies performed on each of the women in the study group showed that myocardial performance improved in obese pregnant women post-partum.[46]

e. Transthoracic echocardiography as an assessment tool

TTE is an attractive assessment tool in parturients. It is non-invasive, and ultrasound as a modality of evaluation is acceptable to pregnant women as a routine aspect of their care. TTE is increasingly becoming an essential component of the anaesthetist's armamentarium. A variety of medical

subspecialties are relying on echocardiography for diagnosis and management, especially in the perioperative period.[49,50] The diagnosis of cardiac disease in pregnancy is challenging as peripheral oedema and breathlessness are often seen in this population, even when significant underlying disease is absent. Obesity compounds this diagnostic dilemma. Dennis and her co-authors were able to obtain acceptable echocardiographic images in all of the patients enrolled in their study, even those classified as being morbidly obese.[47] The parasternal and apical views are easily obtained in pregnancy, however performing subcostal views is not recommended in this group.[47,51] Echocardiography is both feasible and acceptable in the assessment of pregnant women.

Conclusion

Obesity is an ever increasing public health issue and especially affects clinicians in the South African context.[1–3] Obese parturients are considered to be high-risk patients at risk of multiple peri-partum complications.[3–7] The physiologic changes of the cardiovascular system during pregnancy are well understood and documented.[9,10] Echocardiography has been used as a measure to quantify the adaptation of the heart to these changes in terms of morphology and function. Healthy pregnant women frequently display changes on echocardiography, including larger left sided chambers and increased LVM; however measures of cardiac function have shown varied results.[11–16]

The additional demands placed on the cardiovascular system by obesity result in changes in cardiac structure and function. The combined effect of pregnancy and obesity has not been studied in large cohorts, with only three groups publishing small studies describing the echocardiography parameters in such individuals.[46–48] Echocardiography has been shown to be feasible in obese pregnant women[47], but this review identifies a need for a larger cohort study, to more clearly define structural and functional differences between morbidly obese and non-obese parturients.

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Chapter 2: Manuscript

Title Page

The impact of morbid obesity on cardiac structure and function in pregnancy

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Conflicts of interest:

The authors have no conflicts of interest to declare.

Number of words in Abstract: 351

Number of words in Introduction: 434

Number of words in Discussion: 514

Abbreviated Title (running head): Obesity and cardiac function in pregnancy

Abstract

Background

The increasing prevalence of obesity worldwide is a major threat to global health. Structural and functional changes in the heart are well documented for obesity as well as for pregnancy, but there is limited literature on the impact of obesity on cardiac function in pregnancy. We hypothesized that cardiac maladaptation to pregnancy occurs more frequently in otherwise healthy morbidly obese pregnant women than in pregnant women of normal body mass index (BMI).

Methods

This prospective cohort study was performed in two referral maternity units in Cape Town, South Africa, over a 3-month period. Forty morbidly obese pregnant women (BMI ≥40 $kg.m^{-2}$) (Group O) were compared to 40 pregnant women of BMI ≤30 $kg.m^{-2}$ (Group N). Cardiac structure and function were assessed by transthoracic echocardiography, according to the recommendations of the British Society of Echocardiography.

Results

Acceptable echocardiographic images were obtained in all obese women. Statistical significance was defined as $P< .005$ after applying the Bonferroni correction for multiple comparisons. Mean [SD] mean arterial pressure was higher in Group O (91 [8.42] vs 84 [9.49] mmHg, $P<0.001$). There were no between-group differences in heart rate, cardiac output, or cardiac index (84 [12] vs 79 [13] $beats.min^{-1}$, $P=0.103$; 5447 [1048] vs 4740 [1183] $mL.min^{-1}$, $P=0.006$; 2551 [474] vs 2729 [623] $mL.min^{-1}.m^{-2}$, $P=0.156$, respectively). Stroke volume index was lower, and left ventricular mass higher in Group O

(30.14 [4.51] vs 34.25 [7.00] mL.m^{-2}, *P*=0.003; 152 [24] vs 115 [29] g, *P*<0.001). Isovolumetric relaxation time was significantly prolonged in Group O (73 [15] vs 61 [15] milliseconds, *P*<0.001). The septal tissue Doppler index E' sept was lower in Group O (9.08 [1.69] vs 11.28 [3.18], *P*<0.001). There were no between- group differences in E' average (10.7 [2.3] vs 12.0 [2.7], *P*=0.018), or E/E' average (7.85 [1.77] vs 7.27 [1.68]).

Conclusion

Obese pregnant women had a similar cardiac output and cardiac index to those with normal BMI. Their increased left ventricular mass and lower stroke volume index could indicate a limited adaptive reserve. Obese women had minor decreases in septal left ventricular tissue Doppler velocity, but the E/E' average values did not suggest clinically significant diastolic dysfunction.

Introduction

The worldwide epidemic of obesity is a major threat to global health. In 2014, the World Health Organisation (WHO) estimated that 39% of the population aged ≥18 years were overweight, defined by a body mass index (BMI) of ≥25 $kg.m^{-2}$. Thirteen percent had a BMI of ≥30 $kg.m^{-2}$ and were therefore classified as obese.[1,2] In the United States, 58.5% of women of childbearing age (20-39 years) are overweight and 31.8% are obese.[3] Numbers in other high and middle income countries are comparable.[2] The deleterious health effects of obesity are well documented, with most deaths in this population attributable to cardiovascular disease.[4,5] Structural and functional changes in the heart caused by obesity, such as left ventricular hypertrophy, left atrial enlargement and subclinical impairment of systolic and diastolic function, are well studied in the general population.[6] Much less is known about the impact of obesity on cardiovascular adaptation to pregnancy.

In pregnancy, obesity is associated with an increased risk for venous thromboembolism, hypertensive disorders, gestational diabetes, caesarean section, postpartum haemorrhage and adverse neonatal outcome.[7-10] Data from both the United Kingdom and the United States demonstrate that obesity is associated with an increased risk of death during pregnancy.[11-14] A large cohort study from Scotland published in 2015 found that maternal obesity during pregnancy is associated with major cardiovascular events later in life, and a shorter lifespan.[15]

Echocardiography has been used extensively to study cardiovascular changes in pregnancy.[16-19] However, to our knowledge there have only been two small studies assessing haemodynamic changes in obese parturients with echocardiography published to date. Dennis et al. studied 15 obese pregnant women with a mean BMI of 35 kg/m^2, comparing them with 40 pregnant women of normal weight. A significantly higher mean arterial pressure and left ventricular mass were found in the obese parturients.[20] Veille et al. compared 8 morbidly obese pregnant women with 36 parturients of normal weight and found an increase in left atrial size, left ventricular wall thickness and left ventricular mass in the obese group.[21]

As anesthesiologists, we are closely involved in the peripartum care of pregnant women. A thorough understanding of the cardiovascular changes of pregnancy and how these may be altered in the obese parturient, is crucial to deliver optimum care. Transthoracic echocardiography is a valuable non-invasive tool to study the cardiovascular system. The aim of our research was to study structural and functional changes in morbidly obese parturients (BMI ≥40 kg.m^{-2}) compared to pregnant women of normal body mass (BMI ≤30 kg.m^{-2}) at term, using transthoracic echocardiography. We hypothesized that there are both cardiac structural and functional differences between term healthy and morbidly obese parturients.

Methods

Patient Population

This prospective cohort study was conducted at the two referral maternity units affiliated to the University of Cape Town, Cape Town, South Africa: Mowbray Maternity- and Groote Schuur Hospital. Data collection took place from 1st January to 31st March 2016. Due to the limited availability of previous data on haemodynamic changes in morbidly obese pregnant women, a sample size calculation was not performed. We aimed to recruit at least 40 morbidly obese pregnant women (Group O) and 40 pregnant women of normal weight as controls (Group N), a sample size used in previous similar work.[19,22] The data was reported according to the principles of the STROBE guidelines. The study protocol was approved by the Human Research Ethics Committee of the University of Cape Town (HREC 021/2016). All participants provided written, informed consent. Obese and control parturients were recruited consecutively from the antenatal clinic and the antenatal wards at both hospitals. The exclusion criteria were: age below 18 years, inability to give informed consent, refusal to participate in the study, pre-existing cardiac co-morbidities, essential or gestational hypertension, a positive HIV status (previous work showed that HIV infection influences cardiac structure and function[22]) and active labour. For both groups, only women with singleton pregnancies who had reached at least 36 weeks of gestation were recruited. Recruitment to Group O required a BMI of at least 40 $kg.m^{-2}$ at the time of recruitment while for Group N, parturients had a BMI ≤30 $kg.m^{-2}$.

After enrolment, the following demographic and biological data were recorded: age, gravidity, parity, gestational age, ethnicity, height, weight, and haemoglobin level. Baseline blood pressure was measured in the sitting position after a period of rest. An automated oscillometric blood pressure device (Dinamap Carescape, General Electric Corporation, Boston, Massachusetts), with an appropriately sized cuff for the respective study participant, was used. The heart rate was obtained from a three lead electrocardiograph recorded during echocardiography.

Echocardiography Protocol

After a 5-minute rest period in the left lateral position, echocardiographic examination was performed according to international guidelines using 2-dimensional color flow-, continuous wave-, pulsed wave- and tissue Doppler imaging.[23-25] All echocardiographic examinations were conducted by the same certified investigator (BSB) using either a Vivid S or a Vivid Q echocardiography machine with a 1.5 – 3.6 MHz transducer (General Electric Corporation, Boston, Massachusetts). Structural and haemodynamic measurements were performed according to standard recommendations.[23-25]

Structural parameters [septal (IVSd) and posterior wall thickness (LVPWd) in diastole, left ventricular internal diameter in diastole (LVIDd)] and their derived parameters [left ventricular mass (LVM) and relative wall thickness (RWT)] were obtained from a 2-dimensional parasternal long axis view (PLAX). Controversy exists regarding appropriate indexing of left ventricular mass in the presence of morbid obesity. The ratio of LV mass to body

surface area (BSA) is often normal or even reduced, since BSA increases in excess of left ventricular mass in obese individuals. Several authors therefore prefer to index left ventricular mass either to height alone, or to height raised to the power of 2.7.[6] Therefore we performed 3 calculations, indexing to body surface area, height, and height$^{2.7}$.

Left ventricular systolic function was assessed by fractional shortening (FS) (derived from a 2-dimensional PLAX view), fractional area change (FAC) (measured during systole and diastole from the parasternal short axis image at mid-papillary level), and by the systolic tissue Doppler velocity (S'). The latter was obtained from an apical 4 chamber view. Stroke volume (SV) and cardiac output (CO) were calculated from left ventricular outflow tract (LVOT) diameter (measured in the PLAX view), the Doppler-derived velocity time integral of the left ventricular outflow tract (LVOT VTI) measured in the apical five chamber view, and the heart rate. Cardiac work (CW) and total vascular resistance (TVR) were calculated from mean arterial pressure (MAP) and cardiac output. Diastolic function was assessed by mitral valve inflow velocities E and A, mitral valve deceleration time (DT), isovolumetric relaxation time (IVRT) derived from septal tissue Doppler measurements, early diastolic tissue Doppler velocity E' (obtained in an apical four chamber view) and the ratio of early mitral flow peak velocity to early diastolic tissue Doppler velocity (E/E'). Right ventricular systolic function was assessed by tricuspid annular plane systolic excursion (TAPSE) and right ventricular systolic tissue Doppler velocity (RV S') from the right ventricular free wall (both obtained from an apical 4 chamber view). Right ventricular diastolic

function was assessed by early and late tissue Doppler velocities of the right ventricular free wall (RV E' and RV A', respectively).

Echocardiography images were stored and analysed off-line by BSB. The average value of three consecutive beats for each measurement were used for data analysis. A second certified investigator (BC) independently measured LVOT, LVOT VTI, FAC and LVIDd of every 5th participant to enable inter-observer variability to be calculated. These parameters reflect hemodynamics, function and anatomy.

Statistical Analysis

Descriptive statistics including frequency, mean, standard deviation, median and interquartile range were calculated for the two study groups. The two sample t-test with unequal variance was used for the comparison of the mean values between the groups. The mean difference between the groups, and 95% confidence interval (CI) was reported for the continuous variables. The range of BMI was by definition restricted, therefore values are reported as median (interquartile range [IQR]). After adjustment for multiple comparisons using the Bonferroni correction, $p < .005$ was considered statistically significant. The inter-observer bias was estimated by calculating the mean difference and 95% CI between readings recorded by two observers, of LVOT, LVOT VTI, FAC and LVIDd of every 5th participant.

Results

Forty morbidly obese pregnant women (BMI ≥40 $kg.m^{-2}$) and 45 pregnant women of normal weight (BMI ≤30 $kg.m^{-2}$) were recruited to the study. Data was analysed from all of the morbidly obese parturients recruited. None had pre-existing cardiac disease and all had acceptable echocardiographic image quality. Five subjects in the control group were excluded; three as a result of poor echocardiographic image quality, and two due to undiagnosed pre-existing cardiac conditions. In one woman hypertrophic obstructive cardiomyopathy was suspected, and the other had a severe tachyarrhythmia. Both women were referred for review by a cardiologist.

Demographic and obstetric characteristics of both groups are shown in Table 1. There were no significant between-group differences in age, gestational age, ethnicity, gravidity, parity and haemoglobin level. The median BMI of Group O was 42.9 $kg.m^{-2}$ (IQR: 41.3 to 47.1 $kg.m^{-2}$) versus 27.3 $kg.m^{-2}$ (IQR: 24.2 to 29.2 $kg.m^{-2}$) in Group N.

Table 2 summarises the haemodynamic findings. MAP was significantly higher in Group O (91 vs 84 mmHg). There were no significant between-group differences in heart rate (HR), stroke volume (SV) and cardiac output (CO). The stroke volume index was significantly lower in Group O (34.25 vs 30.14 $mL.m^{-2}$) The mean difference (95% CI) was 4.11 $mL.m^{-2}$ (-6.73 to -1.47).

Table 3 shows the results for left ventricular structural and functional parameters. IVSd and LVPWd were both significantly thicker in Group O

(0.82 vs 0.66 cm, and 1.07 vs 0.95 cm). The mean difference (95% CI) was 0.16 (0.11 to 0.22) and 0.12 (0.06 to 0.19) cm respectively. There was no significant between-group difference in the RWT and the LVIDd. LVM was significantly higher in Group O (152 vs 115g). with a mean difference (95% CI) of 37 (25 to 49) g. When indexed to body surface area (BSA), there was no significant difference in the left ventricular mass index (71 vs 66 $g.m^{-2}$). Indexing to height and $height^{2.7}$resulted in significantly higher values for Group O (95 vs 71 $g.m^{-1}$ and 43 vs 32 $g.m^{-2.7}$ respectively). The mean differences (95% CI) for these parameters were 24 (16 to 31) $g.m^{-1}$ and 11 (8 to 15) $g.m^{-2.7}$ respectively. Fractional shortening (FS), fractional area change (FAC) and both lateral and septal systolic tissue Doppler velocities were comparable between groups.

Diastolic measurements are summarised in Table 4. Global diastolic function was not significantly reduced in Group O. However, septal E' was significantly reduced (9.08 vs 11.28 $cm.s^{-1}$). The mean difference (95% CI) was -2.20 (-3.34 to -1.06) $cm.s^{-1}$. The isovolumetric relaxation time was significantly longer in Group O (73 vs 61 ms). The mean difference (95% CI) was 12 (6 to 19) ms.

Table 5 summarises the findings for the right ventricle. There was no between-group difference in right ventricular systolic function. RV E'/A' was not significantly different between groups.

Calculation of inter-observer variability showed the following results (mean difference [95% CI]): LVOT 0.05 cm [-0.02 to 0.12], LVOT VTI 0.64 cm/s [-0.26 to 1.54], LVIDd -0.14 cm [-0.27 to -0.2], FAC -2.03 % [-4.99 to 0.92].

Discussion

There are limited data available on cardiovascular structure and function as assessed by transthoracic echocardiography in morbidly obese pregnant women. To our knowledge this is the largest comparative study in this field. Previous work studied fewer women of lower BMI.[20,21] It is noteworthy that all obese patients in our study had acceptable image quality. We found differences in LV structure and function when comparing obese parturients with those with normal BMI. IVSd and LVPWd, LVM, and LVM indexed to height and height$^{2.7}$, were all significantly increased in the obese population. MAP was higher in Group O. Stroke volume index (SVI) was lower in Group O, with no significant differences in CO or cardiac index (CI). Fractional shortening and septal systolic tissue Doppler velocities were similar in the 2 Groups. With regard to diastolic parameters, there was a significant increase in the IVRT, and septal E' was significantly lower in Group O. There were no significant inter-observer differences in the reported measurements for LVOT, LVOT VTI, and FAC. The difference for LVIDd was statistically- but not clinically significantly different (1.4 mm). It was noted that for certain haemodynamic (MAP, but not TVRI), structural (LVM) and functional (IVRT) parameters, there appeared to be a correlation across the BMI range. Thus the reported differences were not only present at the extremes of the biological range represented by the study groups.

Dennis et al. found a similar increase in left ventricular mass and in the mean arterial pressure, but reported no changes in the isovolumetric relaxation time or the septal tissue Doppler velocities.[20] Veille et al. reported increased

IVSd, LVPWd and LVM in obese patients, but no significant changes in left ventricular dimension, fractional shortening and cardiac index.[21]

Echocardiographic studies of cardiovascular changes in obese non-pregnant subjects demonstrate similar changes to those we observed in the obese pregnant population. In isolated obesity LVM is increased.[26,27] Left ventricular ejection fraction has been reported as reduced, normal or supranormal.[6] Findings regarding diastolic function are conflicting. The most consistent finding is a prolongation of the IVRT.[28-30] Two studies reported altered right ventricular diastolic filling characteristics, one of which also reported reduced systolic tissue Doppler velocities for right-sided chambers. Right ventricular ejection fraction was not altered.[26,31]

A recently published study by Vinayagam et al. compared hemodynamics of 30 morbidly obese pregnant women with 32 pregnant women of normal weight, using the non-invasive cardiac output monitoring system USCOM®. They found a significantly reduced SVI and CI in obese patients, while the total vascular resistance index (TVRI) was significantly higher in these parturients.[32]

Confounding variables were carefully considered in the design phase of this study, and clear exclusion criteria were established, importantly hypertension and pre-existing cardiac disease. While the lack of any significant differences in the patient characteristics do not eliminate confounding variables; it is unlikely that there were clinically significant differences in these characteristics other than obesity. Ideally, both groups of patients would

require follow-up postpartum to define more clearly the effects of pregnancy versus obesity per se.

A further limitation of the study was the absence of a sample size calculation. Previous work had groups with unbalanced numbers and smaller sample sizes. Also the obese women in these studies had lower BMI, and so were not comparable with our population. There was therefore little basis for establishing variability, and it was also difficult to estimate likely clinically important between-group differences in one or more echocardiographically measured parameter. Therefore, we decided upon 2 groups comprising equal numbers, and a larger sample size than in previous studies. To some extent, the upper limit of the sample size was limited by time constraints.

In summary, obese pregnant women had similar CO and CI to those with normal BMI. The LVM was higher, and SVI was lower, which indicates that these parturients may have limited adaptive reserve in clinical situations requiring an increase in CO. Obese women had minor decreases in septal LV tissue Doppler velocities, but the E/E' average values did not suggest clinically significant LV diastolic dysfunction. Further longitudinal studies are needed to determine to what extent the changes observed in obese parturients are related to obesity alone or to a combination of the pregnant state and obesity. Future investigations could establish whether these changes contribute to the increased cardiac morbidity in this population, and persist postpartum. This could inform the requirement for ongoing monitoring of cardiac structure and function, contributing to improved long term outcomes in morbidly obese women.

Key Points

- Obesity is a rapidly increasing threat to global health, recognised as a cardiovascular risk factor; we investigated whether there are cardiac structural and functional differences between term healthy and obese parturients.
- Morbidly obese pregnant women have significantly higher left ventricular mass and lower stroke volume index than pregnant women of normal body weight, and the basal intraventricular septum shows signs of remodelling as indicated by lower septal tissue Doppler velocities.
- These structural and functional cardiac differences could limit cardiovascular adaptation of obese patients in obstetric emergency situations.

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Tables for publication

Table 1: Patient characteristics by group			
	Controls (n=40)	Obese (n=40)	p-value
Age (years)	28.4 (6.2)	30.4 (4.9)	0.101
Gestation (weeks)	38.7 (1.4)	38.2 (1.7)	0.131
Ethnicity - African - Asian - Caucasian	 37 (92.5%) 2 (5.0%) 1 (2.5%)	 38 (95%) 1 (2.5%) 1 (2.5%)	1.000
Gravity - Primipara - Multipara	 8 (20%) 32 (80%)	 4 (10%) 36 (90%)	0.174
Parity - Nulliparous - Multiparous	 14 (35.0%) 26 (65.0%)	 7 (17.5%) 33 (82.5%)	0.117
Haemoglobin(g/dl)	11.4 (1.5)	11.58 (1.4)	0.708
BMI ($kg.m^{-2}$)	27.3 (24.2 –29.2)	42.9 (41.3 – 47.1)	
All values are mean (SD) except for BMI, which are median (interquartile range) *Fisher's exact or t-sample t-test* *Abbreviations: BMI, Body Mass Index*			

Table 2: Hemodynamic variables by group

	Controls (n=40)	Obese (n=40)	Mean difference (95% CI)	p-value
MAP (mmHg)	84 (9.49)	91 (8.42)	7 (3 to 11)	< 0.001
HR (beats/min)	79 (13)	84 (12)	5 (-1 to 10)	0.103
SV (mL)	59.52 (13.51)	64.38 (9.71)	4.85 (-0.39 to 10.09)	0.069
SVI ($mL.m^{-2}$)	34.25 (7.00)	30.14 (4.51)	-4.10 (-6.73 to -1.47)	0.003
CO ($mL.min^{-1}$)	4740 (1183)	5447 (1048)	707 (210 to1204)	0.006
CI ($L.min^{-1}.m^{-2}$)	2729 (623)	2551 (474)	-178 (-424 to 69)	0.156
TVR ($dynes.sec.cm^{-5}$)	1483 (358)	1367 (217)	-116 (-248 to 16)	0.084
TVRI ($dynes.sec.cm^{-5}m^{-2}$)	2559 (601)	2927 (519)	367 (117 to 617)	0.005
CW ($mmHg.L.min^{-1}$)	407.95 (120.92)	487.63 (115.14)	79.69 (27.13 to 132.251)	0.003
CWI ($mmHg.L.min^{-1}m^{-2}$)	233.81 (60.82)	229.01 (49.66)	-4.80 (-29.5 to 19.9)	0.700

Values are mean (SD), or mean difference (95% CI)

t-test with unequal variance. After adjustment for multiple comparisons (Bonferroni), p<0.005 is statistically significant

Abbreviations: CI, confidence interval; MAP, mean arterial pressure; HR, heart rate; SV, stroke volume; SVI, stroke volume index; CO, cardiac output; CI, cardiac index; TVR, total vascular resistance; TVRI, total vascular resistance index; CW, cardiac work; CWI, cardiac work index

Table 3: Left ventricular structural and functional variables by group

	Controls (n=40)	Obese (n=40)	Mean difference (95% CI)	p-value
IVSd (cm)	0.66 (0.13)	0.82 (0.10)	0.16 (0.11 to 0.22)	< 0.001
LVPWd (cm)	0.95 (0.13)	1.07 (0.16)	0.12 (0.06 to 0.19)	< 0.001
LVIDd (cm)	4.48 (0.36)	4.69 (0.39)	0.20 (0.04 to 0.37)	0.018
RWT	0.42 (0.06)	0.46 (0.10)	0.04 (0.00 to 0.08)	0.041
LVM (g)	115 (29)	152 (24)	37 (25 to 49)	< 0.001
LVMI ($g.m^{-2}$)	66 (15)	71 (12)	5 (1 to 11)	0.0978
LVM/height ($g.m^{-1)}$	71 (17)	95 (15)	24 (16 to 31)	< 0.001
$LVM/height^{2.7}$ ($g.m^{2.7}$)	32 (8)	43 (8)	11 (8 to 15)	< 0.001
FS (%)	35 (5.36)	32 (5.60)	-2.71 (-5.15 to -0.27)	0.030
FAC (%)	53 (6.41)	52 (5.11)	-0.44 (-3.02 to 2.15)	0.738
S' lateral ($cm.s^{-1}$)	8.95 (1.81)	9.13 (1.95)	0.18 (-0.66 to 1.01)	0.679
S' septal ($cm.s^{-1}$)	9.25 (1.64)	8.43 (1.20)	-0.83 (-1.47 to -0.18)	0.012

Values are mean (SD), or mean difference (95% CI)

t-test with unequal variance. After adjustment for multiple comparisons (Bonferroni), p<0.005 is statistically significant.

Abbreviations: CI, confidence interval; IVSd, interventricular septum in diastole; LVPWd, left ventricular posterior wall in diastole; LVIDd, left ventricular internal diameter in diastole; RWT, relative wall thickness; LVM, left ventricular mass; LVMI, left ventricular mass index; FS, fractional shortening; FAC, fractional area change

Table 4: Left ventricular diastolic variables by group

	Controls (n=40)	Obese (n=40)	Mean difference (95% CI)	p-value
E/A ratio	1.48 (0.35)	1.33 (0.32)	-0.16 (-0.31 to -0.01)	0.042
DT (ms)	180 (39)	194 (43)	14 (-4 to 33)	0.121
Septal E'	11.28 (3.18)	9.08 (1.69)	-2.20 (-3.34 to -1.06)	< 0.001
Lateral E'	12.78 (3.36)	12.08 (3.56)	-0.70 (-2.24 to 0.84)	0.369
Average E/E'	7.27 (1.68)	7.85 (1.77)	0.58 (-0.19 to 1.35)	0.137
Septal E'/A'	1.32 (0.44)	1.14 (0.31)	-0.18 (-0.35 to -0.01)	.039
Lateral E'/A'	1.70(.73)	1.61(.70)	-0.09 (-0.41 to 0.23)	.574
IVRT (ms)	61 (15)	73 (15)	12 (6 to 19)	< 0.001

Values are mean (SD), or mean difference (95% CI)

t-test with unequal variance. After adjustment for multiple comparisons (Bonferroni), p<0.005 is statistically significant

Abbreviations: CI, confidence interval; DT, deceleration time; IVRT, isovolumetric relaxation time

Table 5: Right ventricular variables by group

	Controls (n=37)	Obese (n=39)	Mean difference (95% CI)	p-value
TAPSE (cm)	2.41 (0.44)	2.37 (0.41)	-0.04 (-0.23 to 0.15)	0.698
S' ($cm.s^{-1}$)	15.05 (2.92)	14.72 (2.72)	-0.34 (-1.63 to 0.96)	0.606
RV E'/A'	1.29 (0.32)	1.07 (0.47)	-0.23 (-0.41 to -0.04)	0.016

Values are mean (SD), or mean difference (95% CI)

t-test with unequal variance. After adjustment for multiple comparisons (Bonferroni), p<0.005 is statistically significant

Abbreviations: CI, confidence interval; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle

Chapter 3

Appendix 1 – HREC Approval letter

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences

Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: nosi.tsama@uct.ac.za
Website: www .health.uct.ac.za/fhs/research/humanethics/forms

21 January 2016

HREC REF:021/ 2016

Prof R Dyer
D23, Anaesthesia
NGSH

Dear Prof Dyer

PROJECT TITLE: THE IMPACT OF OBESITY ON CARDIAC FUNCTION IN PREGNANCY

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

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 30'" January 2017.

The HREC note that recruitment for this study will also occur at Groote Schuur Hospital.

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 Africa n Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABP),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/ 135/95) and FDA Code Federal Regulation Part 50, 56 and 3 12.

Appendix 2 - Consent form for control group

Title of Project: The Impact of obesity on cardiac function in pregnancy

Principal Investigator: Prof Robert Dyer

Contact details: Department of Anaesthesia, University of Cape Town
Groote Schuur Hospital, Anzio Road, Observatory, Cape Town, 7700
Tel: 021 4045001

Participant's Printed Name:

We are inviting you to take part in a research study that will be done at Mowbray Maternity Hospital during the period January to March 2016.

The purpose of the study is to find out if an increased weight affects the function of a woman's heart during pregnancy.

It is known that both pregnancy and weight gain may affect the function of a person's heart. We would like to do research to look at how the combination of increased weight and pregnancy affect the function of a woman's heart.

In order to do this we will examine both women of normal and increased weight to be able to compare the results. You are asked to participate in the control group which includes women of normal body weight.

We will do this by doing an ultrasound of your heart, also known as an echo. This is similar to the ultrasound we do of your baby during pregnancy. It takes 20-30 minutes and is safe for you and your baby. We will do this at a time when it will not affect any routine medical care.

The echo will give us information about how well your heart is working and coping with pregnancy.
The study may be beneficial to you, because if we find a problem we will inform your obstetric doctor and you will receive appropriate treatment of the problem.

When the study is normal it will still be useful and reassuring to have extra information about your health status.

You will not be charged or compensated for this study.
The study is funded by the Department of Anaesthesia.

We will record health information about you that will include your age, gender, ethnicity, 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.
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.
The only reason we need to have your name is in order to be able to inform the obstetric doctors if we find any problems that may need treatment.

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.

We will keep your participation in this research study confidential to the extent permitted by law. 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

Taking part in this study is entirely voluntary. Giving or withholding consent for this study will not affect the quality of health care given to you. If you decide to participate you must sign this form to give your consent.

You have the right to ask any questions you may have about this research. If you have questions, complaints or concerns please contact the investigator at the telephone number provided above.

If you have questions regarding your rights as a research participant or you have concerns or general questions about the research, you can also contact the Human Research Ethics Committee at the number provided above.

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
_____	_____	_____ _____
Signature of witness 2	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 3 - Consent form for study group (obese pregnant women)

Title of Project: The Impact of obesity on cardiac function in pregnancy

Principal Investigator: Prof Robert Dyer

Contact details: Department of Anaesthesia, University of Cape Town
Groote Schuur Hospital, Anzio Road, Observatory, Cape Town, 7700
Tel: 021 4045001

Participant's Printed Name:

We are inviting you to take part in a research study that will be done at Mowbray Maternity Hospital during the period January to March 2016.
The purpose of the study is to find out if an increased weight affects the function of a woman's heart during pregnancy.

It is known that both pregnancy and weight gain may affect the function of a person's heart. We would like to do research to look at how the combination of increased weight and pregnancy affect the function of a woman's heart.

In order to do this we will examine both women of normal and increased weight to be able to compare the results. You are asked to participate in the group of women with increased weight.

We will do this by doing an ultrasound of your heart, also known as an echo. This is similar to the ultrasound we do of your baby during pregnancy. It takes 20-30 minutes and is safe for you and your baby. We will do this at a time when it will not affect any routine medical care.

The echo will give us information about how well your heart is working and coping with pregnancy.
The study may be beneficial to you, because if we find a problem we will inform your obstetric doctor and you will receive appropriate treatment of the problem.

When the study is normal it will still be useful and reassuring to have extra information about your health status.

You will not be charged or compensated for this study.
The study is funded by the Department of Anaesthesia.

We will record health information about you that will include your age, gender, ethnicity, 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.
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.
The only reason we need to have your name is in order to be able to inform the obstetric doctors if we find any problems that may need treatment.

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.

We will keep your participation in this research study confidential to the extent permitted by law. 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

Taking part in this study is entirely voluntary. Giving or withholding consent for this study will not affect the quality of health care given to you. If you decide to participate you must sign this form to give your consent.

You have the right to ask any questions you may have about this research. If you have questions, complaints or concerns please contact the investigator at the telephone number provided above.

If you have questions regarding your rights as a research participant or you have concerns or general questions about the research, you can also contact the Human Research Ethics Committee at the number provided above.

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
_____	_____	_____ _____
Signature of witness 2	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 4 – STROBE Checklist

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

	Item No	Recommendation	Comments
Title and abstract	1✓	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	See abstract – p.3-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2✓	Explain the scientific background and rationale for the investigation being reported	See introduction – p.5
Objectives	3✓	State specific objectives, including any prespecified hypotheses	p.6 paragraph 2
Methods			
Study design	4✓	Present key elements of study design early in the paper	p.7 paragraph 1
Setting	5✓	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p.7 paragraph 1
Participants	6✓	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	p.7 paragraph 1
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7✓	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
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:	Echocardiography protocol – p.8
Bias	9✓	Describe any efforts to address potential sources of bias:	p.10 paragraph 1

Study size	10✓	Explain how the study size was arrived at: *Prior studies were examined – this further discussed in the manuscript*	p.7 paragraph 1
Quantitative variables	11✓	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.	p.8 paragraph 1
Statistical methods	12✓	(*a*) Describe all statistical methods, including those used to control for confounding	p.8 paragraph 1
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	p.11 paragraph 1
		(*e*) Describe any sensitivity analyses	N/A
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	This was a straightfoward recruitment of 40 patients in each group; no patients refused consent
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14✓	(a) Give characteristics of study participants (eg demographic, clinical, social) and	p.11 paragraph 1 Table 1

		information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15✓	Report numbers of outcome events or summary measures over time	N/A
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	N/A
		(*b*) Report category boundaries when continuous variables were categorized	p.11 paragraph 1, BMI limits defined
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17✓	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18✓	Summarise key results with reference to study objectives	p.13 paragraph 1
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	Discussion p.13-14
Interpretation	20✓	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion p.13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	

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	p.2 – Title page, funding detailed

*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 5 – Instruction to authors, Anesthesia & Analgesia

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	http://www.stard-statement.org/ http://www.tripod-statement.org/

	Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis	
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 ≤ 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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- **Drug Names and Equipment**
- **Statistical Analysis**
- **Patient Identification**

Permissions

Language Editing Services

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

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

- *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 <u>PubMed</u>
- 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 (<u>Back to Top</u>)

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

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

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

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 (Back to Top)

- 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 · kg^{-1} · 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)

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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.
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- 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.
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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 ≤ 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 ≤ 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, a written 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 (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 ≤ 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, 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 (<u>Back to Contents</u>)

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 (**<u>see above</u>**).
8. The above noted word count, reference count, and table/figure count limits are not followed for a specific article type.