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The effects of preoperative point-of-care focused cardiac ultrasound in high-risk patients: study protocol for a prospective randomised controlled trial

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ABSTRACT

INTRODUCTION: Perioperative mortality and morbidity remain substantial in acute surgery. Risk factors include known cardiovascular disease, but preoperative screening is insensitive to occult cardiopulmonary conditions. Focused cardiac ultrasound (FOCUS) can disclose both structural and functional cardiac disease and provides insight into the patient's haemodynamic status. This study aims to clarify whether preoperative FOCUS changes clinical outcomes in high-risk patients.

METHODS: This is a multi-centre, randomised, controlled, prospective study including patients ≥ 65 years of age scheduled for acute/emergency abdominal- or orthopaedic surgery. A total of 800 patients will be randomised to ± application of preoperative FOCUS. The primary endpoint is the proportion of patients admitted to hospital > 10 days or death within 30 days of surgery. The secondary endpoints include changes in the anaesthesia approach facilitated by FOCUS, biomarkers of organ function and perioperative complications.

CONCLUSIONS: The knowledge generated from this study may facilitate changes in the anaesthesia evaluation and decision process and, consequently, in the entire perioperative anaesthesia clinical practice. The study has the potential to reduce the risk of perioperative cardiopulmonary complications which directly implies improved patient outcome and reduced hospital costs.

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In non-cardiac surgery, major risk factors for morbidity and mortality include American Society of Anesthesiologists (ASA) classification [1], age, acute surgery and pre-existing cardiopulmonary disease [2-4]. These risk factors are occasionally readily available and, along with the type of surgery, allow anaesthesiologists to tailor anaesthetic drugs, fluid therapy and monitoring to the individual patient's need. However, cardiopulmonary disease may be occult or masked by other patient-related incapacities. Hence, identification of cardiopulmonary disease is an important priority during the preoperative anaesthesia evaluation. Routine preoperative anaesthesia evaluation includes screening with auscultation, blood tests and often electrocardiography. However, these exams are insensitive to detecting cardiopulmonary diseases that may be life-threatening during anaesthesia, including ischaemia [5], heart valve disease [6, 7] and left ventricular hypertrophy [7].

Point-of-care focused cardiac ultrasound (FOCUS) has been proposed as an effective method for filling out this obvious gap in rapid diagnostic capability, as FOCUS can detect both structural and functional cardiac disease as well as pleural effusion [8]. FOCUS performed by anaesthesiologists can identify unknown pathologies in surgical patients [9, 10] and identification of these pathologies enables prediction of perioperative morbidity [11]. Preoperative FOCUS has been shown to alter anaesthetic patient management including step-up in patient monitoring, anaesthesia technique, use of different anaesthetic drugs and changes in post-operative care [9, 12]. Although increasing knowledge of the patients' cardiovascular status seems to individualise and qualify patient management, it remains unclear whether the application of FOCUS has an impact on patient outcome [13].

This study aims to clarify whether preoperative FOCUS changes clinical outcomes in high-risk patients undergoing acute, non-cardiac surgery. A secondary aim is to answer whether the conjunctional use of FOCUS and biomarkers of organ function can identify patients at increased risk of post-operative complications.

The hypothesis of the present study is that preoperative FOCUS reduces the fraction of patients who are

PROTOCOL ARTICLE

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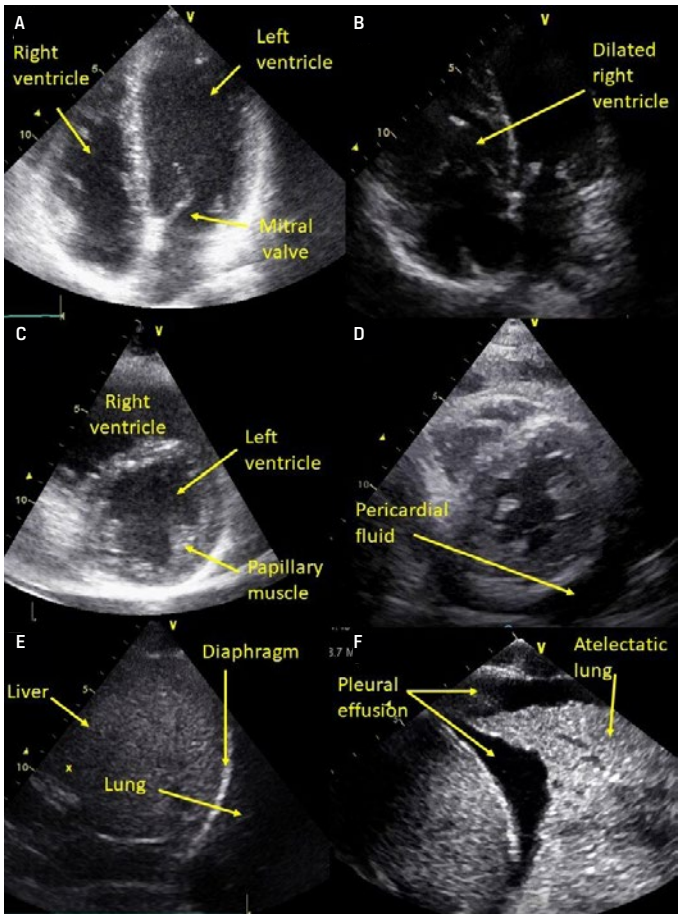

FIGURE 1 / Examples of normal, focused cardiac ultrasound findings and pathological findings. **A.** Normal apical four-chamber view. **B.** Four-chamber view with dilatation of the right ventricle indicative of either pressure- or volume overload. **C.** Normal parasternal short-axis view. **D.** Parasternal short-axis view with pericardial effusion. **E.** Normal right pleural view. **F.** Right pleural view with pleural effusion and consequent atelectasis of the lung.

admitted to hospital for more than ten days or die within 30 days after high-risk, non-cardiac surgery.

METHODS

This is a multi-centre, randomised, controlled, prospective study with sites in the towns of Randers and Aabenraa, Denmark. Patient inclusion commenced in May 2018 and follow-up is expected to complete in 2021. Progress and further details are available at the PreOpFOCUS homepage.

Eligibility criteria

The surgery schedules at Randers Regional Hospital and the Hospital of Southern Jutland (Aabenraa) are screened continuously for patients eligible for inclusion by the anaesthesiologists responsible for the preoperative anaesthesia evaluations. Eligible for inclusion are patients scheduled for emergency (< 6 hours) or urgent surgery (< 24 hours), scheduled for general or neuro-axial anaesthesia after the first anaesthesia visit, and with ASA classification 3 or 4 and age ≥ 65 years. The exclusion criteria are previous surgery performed during current hospital admission (including transfers from other hospitals than Randers Regional Hospital/ the Hospital of Southern Jutland), low-risk surgery defined by [14-16] or an expected surgery time < 30 min. or endoscopies, lack of consent from patient or proxy (in case of patient's mental incapacity), preoperative FOCUS not possible for logistical reasons or due to requirement for immediate surgery and previous participation in the study.

Intervention

Patients are randomised in a 1:1 ratio to either 1) FOCUS prior to anaesthesia or 2) no FOCUS performed (standard treatment).

FOCUS follows the principle formulated in the focused assessed transthoracic echocardiography (FATE) protocol [8]. In short, FOCUS provides information on cardiac status and pleural effusion by the following views: Apical four-chamber view, apical five-chamber view, parasternal long-axis view, parasternal short-axis view, subcostal four-chamber and inferior vena cava view, and bilateral pleural views. See **Figure 1** for examples of normal anatomy and common pathology. Two-dimensional grey-scale cine loops are stored from each view and the data extracted are fed into the web-based REDCap (Research Electronic Data Capture)

FOCUS performed 06-12-2818 18:20 by Peter Juhl-Olsen.

cpr.no 101010-1010	Participant no 570-32
Name: John Doe	Planned surgery:

	Left ventricle
Systolic function (average 3 views) is	Moderately reduced
End-diastolic dimension is	Increased and the end-diastolic diameter is 66 mm
Dyskinesia is	seen
Thickness of the septum and posterior wall is	Probably increased. The thickness of the septum is 13 mm The thickness of the posterior wall is 13 mm
Diastolic function is	Probably abnormal

	Right ventricle
End-diastolic dimension is	Increased and the end-diastolic dimension is 44 mm
Systolic function is	Reduced
Acute or chronic signs of pressure overload	No

	Valves
Aortic valve appears	Normal
Mitral valve appears	Normal

	Miscellaneous
Volume status	No sign of gross volume overload or volume depletion seen
Pericardia! effusion	None seen
Pleural effusion	Right side: Seen and the calculated volume is 400 ml Left side: Seen and the calculated volume is 460 ml
Other pathology	None seen
Other comments:	
Did FOCUS provide new information?	Yes, the information was: left ventricle: systolic function left ventricle: diastolic function left ventricle: size right ventricle: systolic function right ventricle: size pleural effusion

FIGURE 2 / Example of a focused cardiac ultrasound (FOCUS) report made available to the anaesthesiologist responsible for patient anaesthesia. The FOCUS report is auto-generated from data put into the REDCap (Research Electronic Data Capture) data-monitoring tool by the physician performing the FOCUS examination.

data capture tool [17]. The data extracted are based on visual evaluation of cine loops including eye-balling, simple calibration and M-mode. Activation of Doppler modalities are not allowed. The data from each view are synthesised to automatically generate a FOCUS report that is made available to the anaesthesiologist ultimately responsible for providing anaesthesia to the patient. Please see **Figure 2** for a FOCUS report example. The report contains information on:

- Left ventricle: systolic function, myocardial dyskinesia, size, diastolic function and myocardial thickness
- Right ventricle: systolic function, size, signs of acute/chronic pressure overload
- Valves: aortic and mitral valve pathology
- Volume status, pericardial effusion, pleural effusion and other pathology.

The specific criteria for generating the individual components of the FOCUS report are given in **Figure 3**.

The anaesthesiologist performing the preoperative FOCUS can be, but is not required to be, the anaesthesiologist responsible for the anaesthesia given subsequently.

All other aspects of preoperative patient evaluation and handling, including referral for expert cardiology evaluation, will follow the department's standard practice.

As an absolute minimum, all anaesthesiologists performing FOCUS have undergone a one-day practical course in FOCUS and the use of cardiac ultrasound as an integral part of daily patient handling and have been screened by the study initiators for adequate competency level.

FIGURE 3 / Definition of the possible output in the focused cardiac ultrasound (FOCUS) report made available to the anaesthesiologist responsible for patient anaesthesia

Definitions	
Left ventricle	
Systolic function	Normal: 52% ≤ EF ≤ 72% Slightly reduced: 41% ≤ EF ≤ 51% Moderat reduced: 40% ≤ EF ≤ 30% Severely reduced: EF < 30% Hyperdynamic: EF > 72%
Dyskinesia of the myocardium	Seen NOT seen
End-diastolic diameter is	Normal: Men ≤ 58 mm; women: ≤ 52 mm Dilated: Caliber is provided
Myocardial thickness is	Probably normal (<13 mm) Probably increased. The calibered thickness of the septum and posterior wall is provided
Diastolic function	Probably normal: Thickness of the posterior wall AND septum <13 mm AND left atrial sizes ≤ 23 cm^2 / 39 mm May be abnormal: Thickness of the posterior wall OR septum ≥ 13 mm OR left atrial size > 23 cm^2 / 39 mm Probably abnormal*: Thickness of the posterior wall OR septum ≥13 mm AND left atrial size > 23 cm^2 / 39 mm *) in case of permanent/paroxysmal atrial fibrillation patients cannot be categorized as "probably abnormal"
Right ventricle	
Systolic function	Normal: TAPSE ≥ 17 mm Reduced: TAPSE < 17 mm
End-diastolic dimension is	Normal: ≤ 41mm Dilated: Caliber is provided
Signs of acute or chronic pressure overload	No: Eccentricity index ~ 1. NO D-configuration of the left ventricle Yes: Eccentricity index < 1. D-configuration of the left ventricle
Valves	
Aortic valve	Normal: Sufficient opening of cusps, sufficient closure of cusps. 20 grey scale May be stenotic: Cusps seem calcified and restricted in motion May be insufficient: Signs of insufficient closure of cusps in diastole. 20 grey scale May be BOTH stenotic and insufficient: Combination of the above
Mitra l valve	See aortic valve for criteria
Miscellaneous	
Volume status	No sign of gross volume overload or volume depletion seen Signs of volume overload: No collapse of the inferior vena cava with respiration** Signs of volumen depletion: Total collapse of the inferior vena cava inferior with respiration ANO a hyperdynamic left ventricle **) Unspecific sign in case of concomitant decompensated heart failure
Pericardia! fluid	Not seen Seen, but there are NOT echocardiographic signs of haemodynamic significance. Maximal caliber of pericardia l fluid < 10 mm, no compression of cardiac chambers, respiratory variation of the inferior vena cava Seen, and there ARE echocardiographic signs of haemodynamic significance. Maximal caliber of pericardia l fluid ≥ 10 mm, compression of cardiac chambers, no respiratory variation of the inferior vena cava
Pleural fluid	Not seen Seen on the right side. The calculated volume on the right side is: Seen on the left side. The calculated volume on the left side is: Volume of pleural fluid is estimated as 20 × pleural parietal-visceral distance in mm. The patient is in a 15° supine position

TAPSE = tricuspid annular plane systolic excursion.

Data collection & management

The following demographic data will be obtained: age, sex, ASA physical classification, echocardiography < 12 months available, smoking status (yes/no/previous), type of surgery (subspecialty & surgery specification), indication for surgery, creatinine and the verified presence of the following conditions: hypertension (requiring medication), heart valve disease (any including previous surgery), coronary artery disease (verified by coronary artery angiography, exercise test or myocardial scintigraphy), systolic heart failure (ejection fraction < 55% previously), atrial fibrillation (persistent or paroxysmal), peripheral artery disease, stroke, chronic obstructive lung disease, asthma, restrictive lung disease, diabetes mellitus (oral or insulin treatment demanding) and chronic renal failure (estimated glomerular filtration rate 60 ml/min./1.73 m^2 > 3 months).

Demographic data and data on all endpoints are available from the Central Denmark Region/Region of Southern Denmark electronic patient journals and hard copy patient anaesthesia journals. All data are recorded electronically in REDCap.

Randomisation & blinding

A randomisation table with stratification for age (65-74 years/≥ 75 years), surgical subspecialty (orthopaedic or abdominal/gynaecological surgery) and study site has been generated prior to study commencement using STATA (College Station, Texas, USA). Individual patients undergo actual randomisation upon formal study inclusion. Physicians, patients and study personnel responsible for data registration are not blinded to allocation.

Endpoints

All endpoints are censored at 30 days after the day of surgery and confined to patients' admittance to hospital including transfers to other hospitals than Randers Regional Hospital or the Hospital of Southern Jutland, including re-admissions, unless otherwise stated. Clinical endpoints follow the definitions formulated by the European Society of Intensive Care Medicine/European Society of Anaesthesiology where applicable [18]. The primary endpoint is the proportion of patients 1) admitted to hospital > 10 days (defined as the date of discharge minus the date of surgery) or 2) death within 30 days of surgery.

Secondary endpoints are comprised by events and measurements in the pre-, intra- and post-operative period. Emphasis is on the changes in patient therapy directly facilitated by FOCUS and the frequency of complications that might explain individual pathways leading to a potential difference in the primary endpoint. Endpoints pertaining to changes in patient therapy because of FOCUS include preoperative volume therapy, changes in anaesthesia type, step-up or step-down in patient haemodynamic monitoring level, postponement/cancellation of surgery and perioperative admission to the intensive care unit. Post-operative complications and events noted include pulmonary, cardiac, cerebrovascular and renal complications and the frequency of wound infections. Likewise, the duration of intensive care therapy will be recorded along with the rate of hospital readmission.

To describe whether the conjunctional use of FOCUS and biomarkers of organ function can identify patients at an increased risk of pos-toperative complications (secondary aim), a panel of biomarkers is obtained on the day before surgery and on the first post-operative day. Blood samples are frozen, and pooled analyses of these biomarkers are performed every 12-24 months. Hence, they cannot influence the effects of FOCUS. The biomarkers taken are given in **Table 1**.

TABLE 1 / Organ specific biomarkers obtained in relation to the preperative point-of-care focused cardiac ultrasound (PreOpFOCUS) study. All samples are drawn prior to surgery and on the day following surgery.

Cardiopulmonary system
Brain natriuretic peptide
High-sensitivity troponin T/I
N-terminal-pro-brain natriuretic peptide
Midregional pro-adrenomedullin
Soluble vascular endothelial growth factor receptor-1
Galectin-3
Lactate
Cardiovascular system
High-density lipoprotein
Low-density lipoprotein
Somatostatin receptor subtype 2
Transforming growth factor-β
Intercellular adhesion molecule-1
Vascular cell adhesion protein-1
Inflammation
Mononuclear cell count
Interleukin-3
Interleukin-6
Interleukin-8
Interleukin-10
Tumour necrosis factor-α
Macrophage migration inhibitory factor/protein
Liver
C-reactive protein
Bilirubin
Fibrinogen
Activated partial thromboplastin time
International normalised ratio
Kidneys
Creatinine
Glomerular filtration rate
Cystatin C
Urine albumin
Metabolism
Glucose
Triglycerides

Statistical considerations

A data extract from The Randers Regional Hospital covering a three-month period (September – November 2015) showed that 32 out of 96 patients (33%) meeting the study participation criteria remained admitted to hospital for more than ten days or died within 30 days. A clinically relevant reduction of this proportion to 22%, given a power of 90%, a significance level of 5% and an allocation ratio of 1:1, required 362 participants in each arm (724 participants in total). In order to increase power and to compensate for potential surgery cancellations after inclusion, we decided to include 800 participants.

Analyses will be performed both according to the intention-to-treat principle and, secondarily, including only patients actually operated on and hence subjected to the inherent risk. The following tests are planned a priori:

Logistic regression will be used for analyses of the primary endpoint and other categorical data. Numer-

ical data will be analysed with linear regression and, if the assumption of normality is violated, a transformation leading to non-violation of this assumption will be attempted such as logarithm, square root or another power transformation.

For all regression analyses, the effects of predefined subgroup analyses of age (65-74 years, ≥ 75 years), surgical subspecialty (orthopaedic or abdominal/gynaecological surgery) and study site will be incorporated for both primary and secondary endpoints. Baseline characteristics (mentioned above) associated with endpoints will be identified and given $p < 0.1$. These endpoints will be included in a multivariate analysis of the effect of the intervention (± FOCUS) with subsequent backward elimination at a $p < 0.05$ threshold.

A p value < 0.05 will be considered statistically significant and two-sided tests will be used throughout. Data will be presented as odds ratios and means for logistic regressions and linear regressions, with the corresponding confidence intervals. In case of transformation, means with the appropriate confidence intervals will be given upon back-transformation, thus representing median values. No interim analysis is planned.

Ethical considerations

The study was approved by the Central Denmark Region's Committee on Biomedical Research (record no 1-10-72-338-16). All participants or their proxies give written and oral consent prior to enrolment and the study is conducted in accordance with the Helsinki II Declaration.

Trial registration: NCT03501927.

DISCUSSION

FOCUS is disseminating quickly into clinical practise, and there is an urgent need for scientific documentation of its effects related to clinical patient outcome and not surrogate endpoints. Otherwise, another ill-proven intervention may become standard treatment, precluding further evidence-based validation.

Current guidelines address only *known* pathology and insensitive patient screening diagnostics [14]. The influence of *unknown* pathology on patient outcome remains to be described, but as reflected by the substantial perioperative morbidity and mortality in acute surgery [15], the potential for improvement is significant. Revelation of unknown pathology and further insight into the individual patient's haemodynamic status may be key. Recently, a pilot trial on the effects of FOCUS in 102 patients with femoral neck fractures showed promising results in regard to a composite endpoint of all-cause death, acute injury or cardiovascular morbidity within 30 days after surgery [19]. The knowledge generated from our study may facilitate changes in the anaesthesia evaluation and decision process and, consequently, the entire perioperative anaesthesia clinical practice. The study has the potential to reduce the risk of perioperative cardio-pulmonary complications, which directly implies improved patient outcome and reduced hospital costs.

Furthermore, organ-specific biomarkers can provide information, which, in conjunction with FOCUS, may help identify patients who are at increased risk for complications and aid anaesthesiologists in choosing an organ-protective anaesthesia strategy in the right patients.

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