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Study design for a randomized crossover study investigating myocardial strain analysis in patients with coronary artery disease at hyperoxia and normoxemia prior to coronary artery bypass graft surgery (StrECHO-O_2)

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ABSTRACT

Background: Supplemental oxygen (O_2) is used routinely during anesthesia. In the treatment of acute myocardial infarction, it has been established that hyperoxia is to be avoided, whereas information on benefit and risk of hyperoxia in patients with stable coronary artery disease (CAD) remain scarce, especially in the setting of general anesthesia. This study will compare the immediate effects of normoxemia and hyperoxia on cardiac function, with a primary focus on changes in peak longitudinal left-ventricular strain, in anesthetized stable chronic CAD patients using peri-operative transesophageal echocardiography (TEE).

Methods: A single-center randomized cross-over clinical trial will be conducted, enrolling 106 patients undergoing elective coronary artery bypass graft surgery. After the induction of anesthesia and prior to the start of surgery, cardiac function will be assessed by 2D and 3D TEE. Images will be acquired at two different oxygen states for each patient in randomized order. The fraction of inspired oxygen (F_IO_2) will be titrated to a normoxemic state (oxygen saturation of 95–98%) and adjusted to a hyperoxic state ($F_IO_2 = 0.8$). TEE images will be analyzed in a blinded manner for standard cardiac function and strain parameters.

Conclusion: By using myocardial strain assessed by TEE, early and subtle signs of biventricular systolic and diastolic dysfunction can be promptly measured intraoperatively prior to the onset of severe signs of ischemia. The results may help anesthesiologists to better understand the effects of F_IO_2 on cardiac function and potentially tailor oxygen therapy to patients with CAD undergoing general anesthesia.

1. Introduction

1.1. Cardiac patients undergoing general anesthesia

Ischemic heart disease is an increasingly prevalent disease. Approximately 30% of patients undergoing extensive non-cardiac surgical procedures are at risk of or have diagnosed coronary artery disease (CAD) and a subsequent higher risk of perioperative cardiac complications [1]. Just the presence of cardiovascular disease places a patient higher on the perioperative risk score of the American Society of Anesthesiology (ASA), and increases perioperative mortality up to 5–24% [2]. A significant cardiac complication is perioperative myocardial ischemia after non-cardiac surgery (MINS). MINS is still an ongoing concern in the professional community and is associated with increased postoperative mortality, even though most patients do not exhibit ischemic symptoms [3]. Anesthesia in combination with surgical trauma lead to a complex perioperative scenario exposing the heart to many stimuli. Hemodynamics can be affected by anesthetics and vasoactive drugs [4], transitions from spontaneous to positive pressure ventilation, changes between normoxemia to hyperoxia, along with fluctuations in blood CO_2 and hemoglobin concentration [5,6]. However, the relative contribution of anesthesia management to the

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incidence of peri-operative outcomes has been notoriously difficult to quantify, since patients at risk are almost never exposed to general anesthesia (GA) without any surgery or intervention. Recently, more attention has been questioning the potential negative impact of iatrogenic hyperoxia and if it is a contributor to peri-operative myocardial injury.

1.2. Hyperoxia

Adverse sequelae of hyperoxia may be caused by increased activity of reactive oxygen species, which directly impair tissue function and trigger subsequent cell death [7]. Other problems may arise owing to direct vasoconstrictive effects of hyperoxia [8,9]. Until recently a supranormal inspired oxygen fraction was perceived to improve safety margins in acute medical care, and its unrestricted use was ubiquitous. Hyperoxia was not perceived by medical staff to be detrimental, due to conflicting evidence with randomized clinical trials reporting both negative effects of hyperoxia or no impact [10–14]. More recently, the European Society of Cardiology has revised previous guidelines for oxygen therapy in patients with acute coronary syndrome and recommends supplemental oxygen in NSTEMI [15] and STEMI [16] only for patients with a peripheral oxygen saturation (SpO_2) of less than 90% or in respiratory distress. Beyond acute cardiac care, there are various clinical scenarios, particularly in anesthesia and intensive care, where CAD patients may be exposed to supraphysiologic oxygen tensions, supporting the importance of further investigations. In the daily clinical practice, the arterial partial pressure of O_2 always varies widely during different stages of GA and surgery and between physicians [17]. However, such increased inspired O_2 concentrations during mechanical ventilation under GA often lead to supraphysiologic partial pressures of oxygen (paO_2) in arterial blood. There is insufficient information on benefit and risk of such hyperoxia in patients with stable CAD, especially when undergoing GA with endotracheal intubation.

We present a protocol for a new randomized cross-over clinical trial that will be conducted to investigate early functional surrogates of peri-operative myocardial ischemia during normoxemia and hyperoxia by echocardiographic strain analysis that may otherwise not be clinically apparent.

2. Study design and methods

2.1. Study design

A single-center randomized cross-over study with blinded image analysis will be conducted at the Inselspital, Bern University Hospital in Switzerland. In total 106 patients undergoing an elective CABG surgery will be enrolled to undergo a standardized perioperative TEE exam at an inspired oxygen fraction (F_IO_2) of 0.3 with further adjustment to target a peripheral normoxemic oxygen saturation of 95–98% and 0.8 for hyperoxia after induction of GA and prior to the start of surgery. This trial was approved by the local ethics research board of Bern (2020–00145, April 2020), registered on clinicaltrials.gov (NCT04424433, first posted June 2020) and on the Swiss National Clinical Trials Portal (SNCTP000003911). The recruitment status will be posted regularly on clinicaltrials.gov. Informed consent will be obtained at least the day prior to surgery. The work carried out will comply with the Declaration of Helsinki.

2.2. Study objectives

The overall objective of this study is to investigate effects of iatrogenic hyperoxia on myocardial function assessed by TEE in anesthetized patients with CAD prior to any surgical procedures. In particular, the primary aim of this study is to test the hypothesis if acute hyperoxia ($F_IO_2 = 0.8$) induced by and during general anesthesia leads to an attenuation in longitudinal peak systolic strain (%) as a measure of left-ventricular systolic function in comparison to normoxemia (SpO_2 95–98%).

Secondary aims of this study are to assess differences in the impact of hyperoxia on other 2D and 3D systolic and diastolic strain parameters in comparison to traditional echocardiographic measures. Territorial strain discrepancies will also be compared between the healthy remote myocardium, myocardial territory subtended to previously revascularized vessels (by percutaneous intervention, excluding patients with previous CABG surgery) and myocardial territories subtended to stenosed vessel(s). Further aims are to identify patients at risk for hyperoxia-induced deterioration of strain parameters and association of such risk with baseline imaging measurements and demographic characteristics, such as sex, age, ejection fraction, cardiac output and index, comorbidities and medication.

2.3. Outcome measures

The primary measured outcome with be the change in longitudinal peak systolic strain (%) measured between identical TEE image acquisitions obtained in the same individual at normoxemia (SpO_2 95–98%) and hyperoxia (FiO_2 of 0.8).

Secondary outcome measures include the acquisition of the remaining TEE 2D and 3D systolic and diastolic strain parameters (i.e. time to peak strain, systolic and diastolic strain rates, displacements, velocities, torsion) and traditional TEE measures as well such as ventricular volumetry and function, stroke volume derived from the velocity time integral of the left ventricular outflow tract, tissue doppler and mitral valve inflow patterns to assess diastolic function, right ventricular fractional area change and tricuspid annular plane systolic excursion (detailed in Fig. 2). Anesthesia and hemodynamic parameters along with patient characteristics will also be collected.

2.4. Study population

In this study we will prospectively recruit patients scheduled for elective CABG surgery with angiographically documented coronary status, who will undergo general anesthesia and clinically indicated intra-operative TEE evaluation (Table 1). The patient population of the proposed study is ideally suited to answer this question, because a) the coronary status of these patients has been defined, b) these patients are routinely exposed to a variety of oxygen levels during induction and anesthesia for their coronary surgery, and c) they are undergoing indicated invasive hemodynamic, blood gas and TEE monitoring.

Table 1
Eligibility criteria.

Inclusion Criteria
• Elective coronary artery bypass graft (CABG) surgery
• Ability to provide informed consent
• Age > 18 years
Exclusion Criteria
• Absolute contraindication for TEE
• Emergency surgery, including but not limited to patients with unstable CAD: ST- and Non-ST-elevation myocardial infarction (STEMI, NSTEMI) and unstable angina
• Atrial fibrillation or significant arrhythmia
• Pacemaker, cardiac resynchronization therapy, left bundle branch block
• Severe-grade valvular disease
• Pericardial disease
• Previous cardiac or thoracic aortic surgery
• Previous chest radiation therapy, cardiotoxic or bleomycine chemotherapy
• Severe pulmonary hypertension, cor pulmonale, or right ventricular dysfunction, i.e., where high F_IO_2 might reduce pulmonary vascular resistance and right ventricular afterload.
• Patients where study explanation and informed consent cannot be performed/ obtained at the latest on the day before scheduled surgery.
• Females of child-bearing potential.

2.5. Sample size

As similar data investigating the impact of hyperoxia on myocardial strain in a GA environment has not been published, sample size is based off magnetic resonance imaging results in awake CAD patients [18]. An a priori conducted sample size analysis calculated 91 individuals would have an 80.1% power to reject the null-hypothesis with an effect size of 0.3 (based on a difference of 0.3 ± 1.0%) and a level of significance (alpha) of 0.05 with a two-sided general linear model with equal variance. We expect up to 15 subjects could be associated with premature dropouts, anatomical limitations to the TEE probe, or severe imaging artefacts and general bad image quality in which a full dataset cannot be analyzed. Therefore, 106 patients will be enrolled into the study.

2.6. Randomization protocol

In this crossover design, patients will be assigned to either a normoxemia-first (N) or a hyperoxia-first (H) on the day of surgery using a randomization procedure. The respective allocation will determine which oxygen level will be evaluated by TEE first, after which the other level will be assessed. No specific restrictions will be applied to the randomization, and the randomization procedure will occur in batches using a concealed envelope with the order of envelopes determined by a computer-generated algorithm. The anesthetist who acquires the TEE images will be aware of the randomization in order to target the gas levels and provide proper anesthetic management for the patient. The patient will not be aware of his/her group allocation, nor will the reader who analyzes coded images after the surgery.

2.7. Induction of GA

Patients will arrive at the operating room for their scheduled surgery. A finger pulse oximeter able to determine the oxygen reserve index (ORi, Radical®7, Masimo Inc.) will be mounted and monitored throughout induction and the study. Baseline SpO_2 and ORi will be noted at room air for comparison of the normoxemic state during the study induction. Induction of GA is performed according to standardized institutional guidelines. After arrival of the patient in the preparation area 1 mg of midazolam will be administered prior to placement of the arterial line. Prior to induction, patients will then be preoxygenated with 100% oxygen according to institutional and internationally accepted safety standards. A sufentanil bolus (0.5 μg/kg) will be administered during pre-oxygenation. At an end-tidal expiratory $F_{et}O_2 \geq 0.8$, the induction dose of 1-2 mg/kg propofol will be carefully titrated to reach anesthesia depth sufficient for intubation. Rocuronium (1 mg/kg) is used for muscle relaxation in all patients, after which endotracheal intubation is performed. After intubation, FiO_2 will then be adjusted to 0.8 and after 5 min of steady state SpO_2 and ORi will be recorded as a final baseline measure. Anesthesia will be maintained with inhalation of Isoflurane and continuous infusion of sufentanil (10–20 μg/kg/h). Appropriate dosing of anesthetics and vasopressor support by norepinephrine (goal of mean arterial pressure > 65 mmHg) are at the discretion of the attending anesthesiologist. Placement of all necessary central lines will occur, and the TEE probe will be inserted. Time from induction to acquisition of the first study images will be approximately thirty minutes. Afterwards, the study specific protocol will be performed prior to any surgical stimulus.

2.8. Study intervention

During the study intervention under GA, positive end-expiratory pressure (PEEP) is set at a minimum of 5 mmHg, tidal volume set at 6-8 ml/kg per normal predicted bodyweight, with ventilation rate set to maintain a normal end-expiratory CO_2 (35-40 mmHg), and then further adjusted if required. Based on the randomization protocol (Fig. 1), either normoxemia (Group N) or hyperoxia (Group H) will be targeted first,

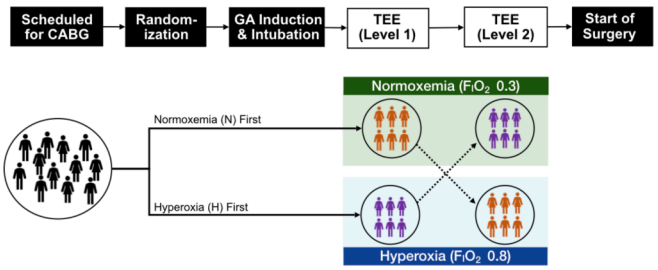

Fig. 1. Study Pathway.
Transesophageal echocardiography (TEE) images will be acquired at both an inspired fraction of oxygen (F_IO_2) of initially 0.3 with further adjust to target SpO_2 of 95–98% if necessary and 0.8 in the time frame between induction and the start of surgery. Patients will be randomized to receive normoxemia (**N**, $F_IO_2 = 0.3$) first, or hyperoxia first (**H**, $F_IO_2 = 0.8$).

followed by the remaining gas level.

- Group N: F_IO_2 will be initially reduced to 0.3 and further titrated until ORi returns to 0 and SpO_2 ranges from 95 to 98% to ensure normoxemia. If an F_IO_2 of 0.3 yields a $SpO_2 > 98\%$ F_IO_2 may be further reduced to 0.25. If an F_IO_2 of 0.3 will results in an $SpO_2 <$ 95% lung recruitment maneuvers will be performed, followed by a stepwise increase in PEEP to a maximum of 8 mmHg before F_IO_2 is allowed to be further increased in 0.05 increments to target normoxemic SpO_2. Continuous SpO_2 and ORi readings will be monitored to confirm a stable blood gas level has been reached. After 5 min of steady-state F_IO_2 and maintaining target readings of SpO_2 and ORi, arterial oxygen saturation and paO_2 will be confirmed with an arterial blood gas analysis, and all pertinent imaging will be obtained (Fig. 2). F_IO_2 will then be increased to 0.8 to target hyperoxia as the second level. The resultant ORi and will be monitored to confirm stabilization, and hyperoxia will be confirmed by arterial blood gas analysis after 5 min of steady state. TEE acquisition will then be repeated identically to the acquisition at normoxemia.
- Group H: Procedures targeting gas levels will be the same as described for group 1 (N), however in the case of the second group, the hyperoxic level will be targeted first after the induction. After data acquisition, F_IO_2 will be reduced to target normoxemia as the second level.

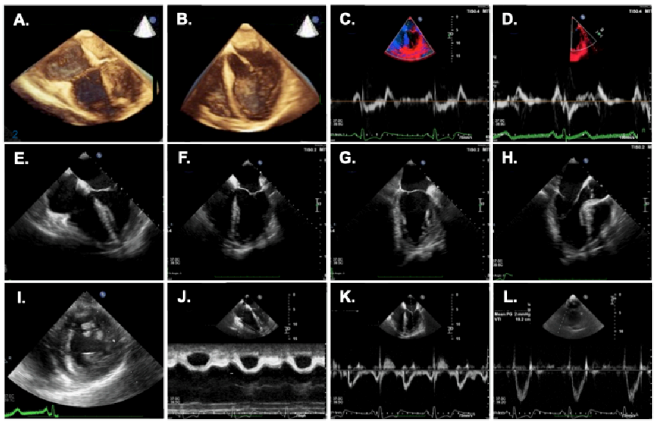

Fig. 2. Transesophageal Echocardiography.
A. Right ventricular 3D cine, B. Left ventricular 3D cine, C. Septal tissue doppler velocity, D. Lateral wall tissue doppler velocity. E. Right ventricular centered 4-chamber cine, F. Left ventricular centered 4-chamber cine, G. 2-chamber cine, H. 3-chamber cine/long axis view, I. short-axis cine (acquired in 3 planes), J. Tricuspid annular plane systolic excursion using anatomic M-Mode, K. Mitral inflow, L. Left ventricular outflow tract velocity time integral.

Once images and data measurements are acquired from the second level, the participant has completed the study protocol. The expected time of the experimental procedure is approximately up to 25 min. Thereafter F_IO_2 is selected at the discretion of the attending anesthesiologist and normal clinical routine and surgery will begin.

2.9. Image acquisition protocol

All images are acquired intra-operatively by cardiovascular anesthesiologists certified in TEE by the European Association of Cardiovascular Imaging (EACVI) and European Association of Cardiothoracic Anesthesiology and Intensive Care (EACTAIC) with Philips EPIQ 7c (X7-2t probe) or EPIQ CVx (X8-2t probe, EPIQ ultrasound system, Philips Medical Systems, Andover, USA), while hemodynamic readings and blood gases are stable as monitored by SpO_2, ORi and confirmed by arterial blood gas analysis. Standard two-dimensional (2D) data will be acquired to measure biventricular systolic and diastolic function. This includes mid-esophageal left and right ventricular centered 4-chamber views, 2-chamber, long-axis 3-chamber; and trans-gastric basal, mid-ventricular and apical short-axis views. Tricuspid annular plane systolic excursion will be acquired using anatomical M-Mode from the right cantered 4-chamber view or with conventional M-Mode from the deep trans-gastric view. Diastolic function will be assessed by acquiring tissue doppler imaging velocities of the septal and lateral mitral valve insertion points, together with the mitral inflow pattern using pulsed wave doppler. In addition, left ventricular stroke volume will be assessed by velocity time integral measurements in the left ventricular outflow tract from a trans-gastric long-axis view or a deep trans-gastric 4-chamber view. Additionally, a 3D cine volume (6 beats during apnea) of the left and right ventricle will be acquired for subsequent analysis of 3D strain and volumetry (Fig. 2). This imaging protocol is acquired at each gas level.

2.10. Monitoring safety outcomes

As described in the section *Study Intervention*, FiO_2 and SpO_2 are used to target normoxemia. We will also obtain blood gas analysis to measure paO_2 levels as a third measure to monitor safety thresholds. As a safety margin, a paO_2 of 80 mmHg will be considered a lower threshold for the normoxemia level at which corrective action to increase paO_2 will be taken. Lower paO_2 levels <60 mmHg during normoxemia will be considered an adverse event. PaO_2 levels at or above 60 mmHg is considered normal for the typical age range of the target patient population [19]. Vital parameters will be monitored and recorded continuously. This includes heart rate, 5-lead electrocardiogram, respiratory mechanics and inspiratory and expiratory end-tidal gas analysis for O_2 and CO_2, SpO_2 and ORi, processed electroencephalogram parameters, invasive arterial pressures, arterial blood gas analysis and oximetry. Signs or symptoms of new-onset acute myocardial ischemia during study interventions will be monitored and recorded. This includes, for instance, new hemodynamic instability, significant ST-elevation or depression, new-onset severe wall motion abnormality in >2 segments. If these events occur during the study, the current blood gas level will be aborted, and the previous more stable gas level will immediately re-installed.

2.11. Data analysis

Tricuspid annular plane systolic excursion, septal and lateral tissue doppler velocities, E (early component) and A (atrial component) mitral influx velocities using pulsed wave doppler and left ventricular outflow tract velocity time integral will be analyzed on the echocardiography machine right after completion of the study intervention for both blood gas levels.

For the remaining assessments readers will be blinded to both patient identity and medical history, along with the oxygen level. All TEE image datasets at normoxemia and hyperoxia will be analyzed in batches a period of time after the surgery using clinically validated software (TomTec-Arena, TomTec Imaging Systems, Unterschleissheim, Germany). Analysis will include measures of biventricular volumetry and ejection fraction from 3D datasets, left ventricular ejection fraction from the 2D 4-chamber and 2-chamber views using the Simpson method of discs as well as right ventricular fractional area change from the right ventricular centered 4-chamber view. For both 2D and 3D acquisitions, systolic as well as diastolic global and segmental longitudinal, radial and circumferential strain parameters will be analyzed (Fig. 3). Strain measurements will be acquired for global measures of both ventricles. The primary measured parameter will be global longitudinal left-ventricular peak systolic strain. Moreover, parameters of the left ventricle will be further reported for regional analysis by using the myocardial American Heart Association (AHA) 16 segment model. After unblinding, these segments will then be categorized as post-stenotic, reperfused or remote territory based on the status of the perfusing coronary artery according to coronary angiography report. Coronary lesions visually assessed with a diameter stenosis greater than 50% will be localized to the corresponding segment of the coronary artery and classified as proximal, mid, distal or in a subsequent branch. Based on the pattern of coronary dominance the allocation of myocardial segments will follow Fig. 4. Data will then be matched to the gas level and analyzed according to the primary and secondary outcomes. Further arterial blood gases, ORi, heart rate, blood pressure and other anesthetic measurements at the time of image acquisition as well as coronary status, demographic data, medication and comorbidities will be obtained for statistical analysis.

Interobserver variability will be assessed with 20 datasets to compare the readings of the anesthesiology study team with a collaborator from cardiology experienced with 2D and 3D strain analysis.

2.12. Statistical analysis

Continuous variables will be reported as mean and standard deviation or median with interquartile ranges, while categorical variables are reported as frequency and percentages.

For the primary endpoint, to investigate if there is a difference in global peak longitudinal strain between normoxemia and hyperoxia, a mixed effects general linear model will be used that includes the randomized group category as a variable to account for any possible order effect with the gas levels. Inclusion for significant covariates will be made if appropriate.

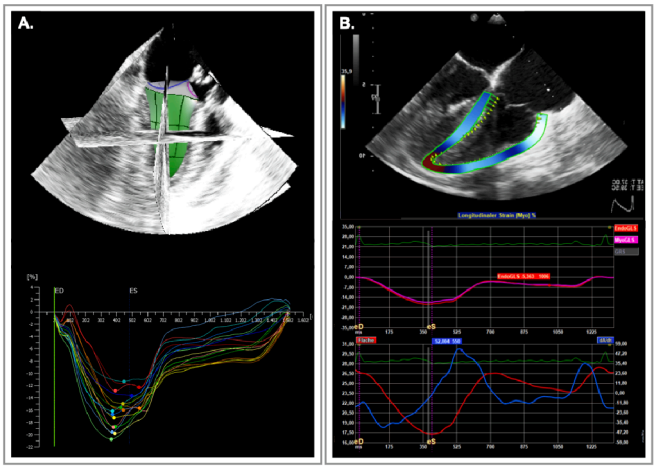

Fig. 3. Myocardial Strain Analysis.
A. Left ventricular longitudinal strain from a 3D TEE image with segmental strain curves in the lower panel. B. 2D right ventricular global longitudinal peak strain and ventricular area and area change over time.

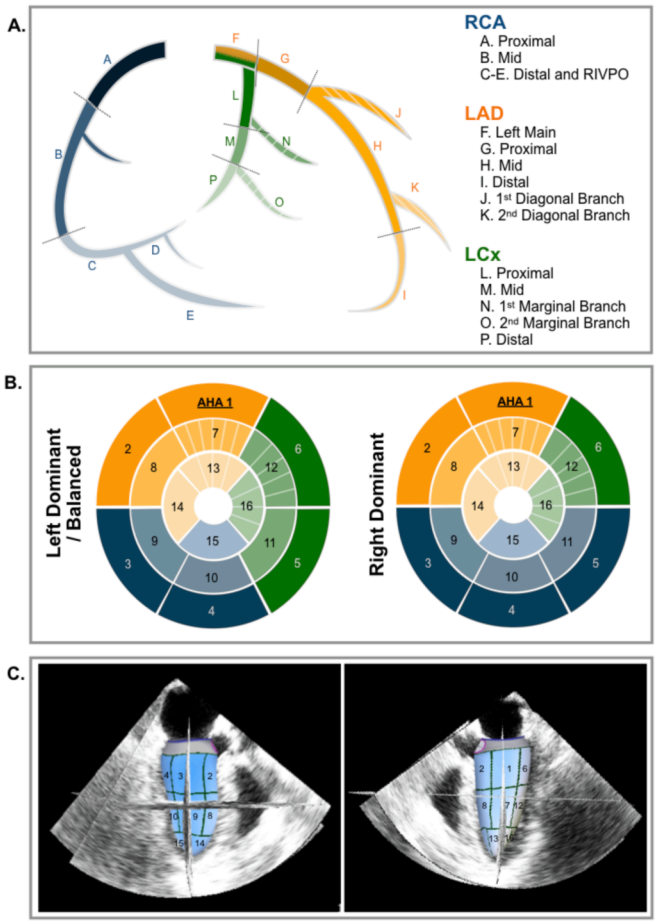

Fig. 4. Allocating Coronary Angiogram Findings to Myocardial Strain.
A. Locations of epicardial stenoses will be allocated to the coronary tree segments for the right coronary artery (RCA, blue), left anterior descending (LAD, yellow) and left circumflex (LCx, green) coronary artery. B. According to the coronary dominance, the myocardial American Heart Association (AHA) segments will be matched to the coronary tree segments, with lesions in the proximal portion of the coronary artery (dark shading) impacting the basal segments and downstream myocardium. Lesions in the distal portion of the coronary artery (light shading) will impact only apical segments, while striped segments represent perfusion by the diagonal and marginal branches. C. Myocardial AHA segments are shown on a strain overlay from a 3D left ventricular acquisition.

Secondary endpoints investigating changes in other echocardiographic parameters between gas levels will be assessed with similar statistical models as the primary endpoint.

Post-hoc analysis accounting for multiple comparisons within patient myocardium will be applied to investigate the changes in regional strain across the myocardium. General linear models will be used to investigate the association of pre-operative or baseline values with a change in strain due to hyperoxia, and receiver operating characteristic curves will be used for the determination of cut-off values if appropriate.

For interobserver and intraobserver reproducibility, reliability will be determined with an intra-class correlation (ICC) for absolute agreement. Agreement between reads will be further tested with Bland-Altman analysis for the mean bias and 95% limits of agreement.

In the case of non-normal distribution, non-parametric tests will be applied if applicable. Statistical significance is defined with a two-sided *p*-value of <0.05. GraphPad Prism version (GraphPad Software, La Jolla California USA), and IBM SPSS Statistics 26 (IBM, Armonk, NY, USA) are planned to be used for analysis.

3. Discussion

3.1. Oxygen dose rational

In this study we use F_IO_2 to target the oxygen levels (0.3 and 0.8), guided by SpO_2 and ORi. Except for induction of general anesthesia, there is no consensus on mandatory perioperative hyperoxygenation in patients with stable CAD, nor for during maintenance of general anesthesia in a general patient population. In 2017 the WHO stipulated that F_IO_2 should be set to 0.80 in all adults undergoing endotracheal general anesthesia, in order to reduce the incidence of surgical site infection [20]. These recommendations have been disputed by experts in the fields of anesthesiology and critical care medicine, and remain controversial [21]. Since high-quality evidence is lacking for a beneficial effect of a F_IO_2 of 0.60 or higher on surgical site infection, Wetterslev et al. and the Cochrane Anesthesia Group performed a meta-analysis in 2015 on the effects of perioperative inspiratory oxygen fraction in adult surgical patients. They came to the conclusion that there was insufficient evidence to support the routine use of a high F_IO_2 (0.6 to 0.9) beyond what is needed to maintain normal arterial oxygen saturation (generally 0.3 to 0.4) [22]. A survey showed that anesthesiologists feel that a safe F_IO_2 for their patients ranges between 0.40 and 0.60 [17,23]. Thus, current F_IO_2 dosing practice is rather eminence- than evidence-based.

The F_IO_2 levels selected in this study proposal lie within existing clinical recommendations, and safe oxygenation levels will be monitored using continuous pulse oximetry and ORi, which can detect imminent deoxygenation 30s before it becomes apparent in SpO_2 monitoring [24]. In this regard, our protocol is in close accordance with the published multi-center PROXI trial [14]. These F_IO_2 targets are also similar to other ongoing trials investigating other peri and post-operative outcomes in relation to hyperoxia (NCT04808401, NCT03388957 [25], NCT03494387 [26]).

3.2. Advantages of myocardial strain

While several hyperoxia studies focus on outcome or serum markers, which may take a few hours to develop from the onset of myocardial insult, this study will implement strain analysis on peri-operative images as a novel assessment to investigate the immediate impact of peri-operative hyperoxia on cardiac function. In various cohorts strain able to detect subtle myocardial dysfunction and is an incremental prognostic marker beyond traditional measurements such as ejection fraction [27–29], and is increasingly incorporated as a key endpoint for clinical trials [30,31]. Systolic and diastolic function parameters can be assessed in longitudinal, circumferential and radial orientation, thus providing information on the different layers of the myocardium. What is also another benefit of strain beyond ejection fraction and volumetry is that it quantifies regional dysfunction. This is particularly beneficial in the case of our CAD population where myocardium downstream of significant epicardial lesions may be more at risk to ischemic events. Discordance in myocardial function caused by underlying infarct or inducible ischemia can lead to post-systolic shortening [32] and a widespread mechanical dispersion [33]. Moreover we will incorporate both 2D and 3D imaging. While 2D is the universal application, 3D is a developing field as it provides comprehensive coverage of the heart, and can be rapidly acquired, generally using 6-heart beats to provide sufficient temporal resolution.

While there are currently multiple publications assessing the diagnostic use of strain in a non-anesthesia setting, there are many benefits of peri-operative assessments of myocardial deformation as well detailed in a review by Duncan et al. [34]. In this study strain is analyzed outside of the operating room, so that analysis can be blinded and performed in batches, thus removing any analyzers bias. Nevertheless, strain analysis is also feasible intra-operatively to get an assessment of current myocardial function. Perioperative changes in both left ventricular [35,36] and right ventricular strain [37] are now reported to

depict the development of peri-operative myocardial dysfunction, even in cases when changes in ejection fraction are not noted. Thus, we propose that the ability of strain to detect subtle dysfunction may shed more light on the inconclusive findings of the impact of hyperoxia on cardiac function during general anesthesia.

3.3. Added relevance to reported studies of peri-operative hyperoxia

As the awareness of potential detrimental effects of supplemental O_2 arise, there is still conflicting evidence about the perioperative effects of hyperoxia in patients undergoing GA between studies and within a study population itself. Peri-operative and post-operative studies investigating hyperoxia have initially focused on surgical site infections, where hyperoxia was reported to be beneficial for some procedures, whereas more recent findings are inconclusive or show no difference related to oxygen fraction [38,39]. Similarly, inconclusive results have been observed with pulmonary complications as a cause of hyperoxia [40–42]. A few published anesthesia trials have also focused on long-term cardiac specific or overall survival outcomes. During CABG, a randomized control trial reported there was no difference in serum markers or hypoxic events between groups maintained at a paO_2 target of 200-220 mmHg versus 120-150 mmHg during cardiopulmonary bypass [43]. However, it has to be noted that the difference between both oxygen levels is small and the lower paO_2 group had already mild hyperoxic paO_2. After abdominal surgery, the Danish PROXI trial, found an increase in long-term mortality after exposure to perioperative hyperoxia [44]. In addition, further analysis of the PROXI trial described an increased incidence of new acute coronary syndrome and long term risk of myocardial infarction in the F_IO_2 group of 0.80 vs 0.30 group [45]. Two randomized clinical trials (HOT-ICU and ICU-ROX) have investigated even lower oxygen targets in patients with acute hypoxemic respiratory failure in the intensive care unit, and found adverse events were the same when targeting conservative oxygen targets of a paO_2 of 60 mmHg or maximal SpO_2 of 90% in comparison to paO_2 of 90 mmHg or SpO_2 of 97% respectively [42,46]. However, investigating markers that don't arise until a period of time after oxygen administration doesn't provide information on the direct cause and effect relationship as perioperative anemia, hypotension and postoperative distress with tachycardia from pain may also result in ischemia. The added relevance of our proposed study to the current literature is that it will investigate the peri-operative impact of hyperoxia and assess if there is an immediate impact of the FiO_2 level on biventricular function. The intent is to investigate if subtle dysfunction occurs, especially prior to the development of severe symptoms of ischemia that may lead to increased morbidity and mortality.

Utilizing invasive measures and cardiac magnetic resonance imaging in an anesthetized swine model with an acutely induced significant coronary artery stenosis we have previously reported hyperoxia ($paO_2 > 300$ mmHg) decreased coronary flow, consequently impairing both regional myocardial oxygenation and wall motion measured by strain analysis in the myocardium distal to the stenosis [9]. In a non-anesthesia setting, independent groups reported inhaling O_2 for 20 min compromised cardiac output and other hemodynamic measures in awake heart failure patients [47]. Using more advanced imaging modalities, myocardial perfusion and cardiac output also decreased in healthy controls breathing supplemental oxygen [48]. Similarly we have previously investigated the immediate impact of hyperoxia in awake patients with stable CAD, and there was no global benefit or impairment in the acute response to hyperoxia when investigating systolic markers such as ejection fraction and peak strain using magnetic resonance [18]. However, when patients had underlying myocardial injury as shown by myocardial tissue characterization, or if they had compromised myocardial strain at baseline, these patients developed a myocardial oxygenation heterogeneity and subsequent reduction in myocardial function after a brief period of O_2 [18]. Moreover many studies focus on systolic measures, yet we observed a significant decrease in diastolic function in the awake CAD group [18]. While the focus on myocardial function is primarily on systolic function, diastolic function may play an important role, especially as it is earlier in the ischemic pathway, and should theoretically arise prior to overt systolic abnormalities and more severe signs of myocardial injury including ST elevations and rises in serology markers such as troponins [49]. However, these human studies investigated awake participants without the complex environment associated with GA, and it is unknown if the same findings may be observed.

4. Conclusion & rationale for the study

Existing recommendations on appropriate intraoperative oxygenation targets during general endotracheal anesthesia are aimed at prevention of surgical site infections [50]. Evidence regarding other benefits or adverse effects of iatrogenic hyperoxia during general anesthesia in patients with known heart disease is minimal, with current publications relying on various outcomes that often arise post-surgery. Using TEE-based strain analysis, we will be able to detect early signs of myocardial ischemia during the perioperative period and determine whether the worsening of myocardial function occurs significantly more frequently during controlled intraoperative hyperoxia. Although this study investigates patients undergoing CABG surgery, all study interventions are performed prior to the start of any surgical procedure, thus these findings are relevant to patients with CAD undergoing general anesthesia for all types of cardiac surgery. Moreover, as the confounding effects associated with surgery will not impact the results, these findings will primarily demonstrate the impact of factors associated with anesthetic procedures. Thus, this study may show if perioperative hyperoxia is one of the puzzle pieces leading to myocardial injury during general anesthesia and may help anesthesiologists to better weigh risks and benefits when selecting an inspired oxygen fraction.

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Declaration of Competing Interest

All authors have nothing to declare.

References

[1] S.D. Kristensen, J. Knuuti, A. Saraste, et al., 2014 ESC/ESA guidelines on non-cardiac surgery: cardiovascular assessment and managementThe joint task force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA), Eur. Heart J. 35 (35) (2014) 2383–2431, https://doi.org/10.1093/eurheartj/ehu282.

[2] U. Wolters, T. Wolf, H. Stützer, T. Schröder, ASA classification and perioperative variables as predictors of postoperative outcome, Br. J. Anaesth. 77 (2) (1996) 217–222.

[3] F. Botto, P. Alonso-Coello, M.T.V. Chan, et al., Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes, Anesthesiology. 120 (3) (2014) 564–578, https://doi.org/10.1097/ALN.0000000000000113.

[4] D.P. Guensch, K. Fischer, C. Jung, et al., Relationship between myocardial oxygenation and blood pressure: experimental validation using oxygenation-sensitive cardiovascular magnetic resonance, PLoS One 14 (1) (2019), e0210098, https://doi.org/10.1371/journal.pone.0210098.

[5] K. Ruetzler, A.K. Khanna, D.I. Sessler, Myocardial injury after noncardiac surgery: preoperative, intraoperative, and postoperative aspects, implications, and directions, Anesth. Analg. 131 (1) (2020) 173–186, https://doi.org/10.1213/ANE.0000000000004567.

[6] P.J. Devereaux, W. Szczeklik, Myocardial injury after non-cardiac surgery: diagnosis and management, Eur. Heart J. 41 (32) (2020) 3083–3091, https://doi.org/10.1093/eurheartj/ehz301.

[7] M. Wenk, H. Van Aken, A. Zarbock, The New World health organization recommendations on perioperative Administration of Oxygen to prevent surgical

site infections, Anesth. Analg. 125 (2) (2017) 682–687, https://doi.org/10.1213/ANE.0000000000002256.
[8] P.H. McNulty, N. King, S. Scott, et al., Effects of supplemental oxygen administration on coronary blood flow in patients undergoing cardiac catheterization, Am. J. Phys. Heart Circ. Phys. 288 (3) (2005) H1057–H1062, https://doi.org/10.1152/ajpheart.00625.2004.
[9] D.P. Guensch, K. Fischer, N. Shie, J. Lebel, M.G. Friedrich, Hyperoxia exacerbates myocardial ischemia in the presence of acute coronary artery stenosis in swine, Circ. Cardiovasc. Interven. 8 (10) (2015) 1–8, https://doi.org/10.1161/CIRCINTERVENTIONS.115.002928.
[10] R. Moradkhan, L.I. Sinoway, Revisiting the role of oxygen therapy in cardiac patients, J. Am. Coll. Cardiol. 56 (13) (2010) 1013–1016, https://doi.org/10.1016/j.jacc.2010.04.052.
[11] D. Stub, K. Smith, S. Bernard, et al., Air versus oxygen in ST-segment-elevation myocardial infarction, Circulation. 131 (24) (2015) 2143–2150, https://doi.org/10.1161/CIRCULATIONAHA.114.014494.
[12] S. de Jonge, M. Egger, A. Latif, et al., Effectiveness of 80% vs 30–35% fraction of inspired oxygen in patients undergoing surgery: an updated systematic review and meta-analysis, Br. J. Anaesth. 122 (3) (2019) 325–334, https://doi.org/10.1016/j.bja.2018.11.024.
[13] D.K. Chu, L.H.-Y. Kim, P.J. Young, et al., Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis, Lancet 391 (10131) (2018) 1693–1705, https://doi.org/10.1016/S0140-6736(18)30479-3.
[14] C.S. Meyhoff, J. Wetterslev, L.N. Jorgensen, et al., Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery: the PROXI randomized clinical trial, JAMA. 302 (14) (2009) 1543–1550, https://doi.org/10.1001/jama.2009.1452.
[15] M. Roffi, C. Patrono, J.-P. Collet, et al., 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation, Eur. Heart J. 37 (3) (2016) 267–315, https://doi.org/10.1093/eurheartj/ehv320.
[16] B. Ibanez, S. James, S. Agewall, et al., 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation, Eur. Heart J. 39 (2) (2018) 119–177, https://doi.org/10.1093/eurheartj/ehx393.
[17] C.M. Morkane, H. McKenna, A.F. Cumpstey, et al., Intraoperative oxygenation in adult patients undergoing surgery (iOPS): a retrospective observational study across 29 UK hospitals, Perioper. Med. 7 (1) (2018) 17, https://doi.org/10.1186/s13741-018-0098-3.
[18] Dominik P. Guensch, Fischer Kady, Yamaji Kyohei, et al., Effect of hyperoxia on myocardial oxygenation and function in patients with stable multivessel coronary artery disease, J. Am. Heart Assoc. 9 (5) (2020), e014739, https://doi.org/10.1161/JAHA.119.014739.
[19] J.A. Hardie, W.M. Vollmer, A.S. Buist, I. Ellingsen, O. Mørkve, Reference values for arterial blood gases in the elderly, Chest. 125 (6) (2004) 2053–2060.
[20] Global Guidelines for the Prevention of Surgical Site Infection, 2016.
[21] O. Akca, L. Ball, F.J. Belda, et al., WHO needs high FIO2? Turkish J. Anaesthesiol. Reanimat. 45 (4) (2017) 181–192, https://doi.org/10.5152/TJAR.2017.250701.
[22] J. Wetterslev, C.S. Meyhoff, L.N. Jørgensen, C. Gluud, J. Lindschou, L. S. Rasmussen, The effects of high perioperative inspiratory oxygen fraction for adult surgical patients, Cochrane Database Syst. Rev. 6 (2015), CD008884, https://doi.org/10.1002/14651858.CD008884.pub2.
[23] L. Ball, A.B. Lumb, P. Pelosi, Intraoperative fraction of inspired oxygen: bringing back the focus on patient outcome, Br. J. Anaesth. 119 (1) (2017) 16–18, https://doi.org/10.1093/bja/aex176.
[24] T.W.L. Scheeren, F.J. Belda, A. Perel, The oxygen reserve index (ORI): a new tool to monitor oxygen therapy, J. Clin. Monit. Comput. 32 (3) (2018) 379–389, https://doi.org/10.1007/s10877-017-0049-4.
[25] C. Reiterer, B. Kabon, M.F. von Sonnenburg, et al., The effect of supplemental oxygen on perioperative brain natriuretic peptide concentration in cardiac risk patients – a protocol for a prospective randomized clinical trial, Trials. 21 (2020), https://doi.org/10.1186/s13063-020-04336-9.
[26] C. Petersen, F.C. Loft, E.K. Aasvang, et al., Hyperoxia and antioxidants during major non-cardiac surgery and risk of cardiovascular events: protocol for a 2 × 2 factorial randomised clinical trial, Acta Anaesthesiol. Scand. 64 (3) (2020) 400–409, https://doi.org/10.1111/aas.13518.
[27] P. Gunasekaran, S. Panaich, A. Briasoulis, S. Cardozo, L. Afonso, Incremental value of two dimensional speckle tracking echocardiography in the functional assessment and characterization of subclinical left ventricular dysfunction, Curr. Cardiol. Rev. 13 (1) (2017) 32–40, https://doi.org/10.2174/1573403X12666160712095938.
[28] I. Eitel, T. Stiermaier, T. Lange, et al., Cardiac magnetic resonance myocardial feature tracking for optimized prediction of cardiovascular events following myocardial infarction, JACC Cardiovasc. Imaging 11 (10) (2018) 1433–1444, https://doi.org/10.1016/j.jcmg.2017.11.034.
[29] K. Fischer, S.J. Obrist, S.A. Erne, et al., Feature tracking myocardial strain incrementally improves prognostication in myocarditis beyond traditional CMR imaging features, J. Am. Coll. Cardiol. Img. 13 (9) (2020) 1891–1901, https://doi.org/10.1016/j.jcmg.2020.04.025.
[30] M.J. Tugman, J.H. Narendra, Q. Li, et al., Ultrafiltration-profiled hemodialysis to reduce dialysis-related cardiovascular stress: study protocol for a randomized controlled trial, Contemp. Clin. Trials Commun. 15 (2019) 100415, https://doi.org/10.1016/j.conctc.2019.100415.
[31] G.J. Ong, T.H. Nguyen, J. Stansborough, et al., The N-AcetylCysteine and RAMipril in Takotsubo syndrome trial (NACRAM): rationale and design of a randomised controlled trial of sequential N-Acetylcysteine and ramipril for the management of Takotsubo syndrome, Contemp. Clin. Trials. 90 (2020) 105894, https://doi.org/10.1016/j.cct.2019.105894.
[32] E. Rumbinaite, A. Karuzas, D. Verikas, et al., Detection of functionally significant coronary artery disease: role of regional post systolic shortening, J. Cardiovasc. Echogr. 30 (3) (2020) 131–139, https://doi.org/10.4103/jcecho.jcecho_55_19.
[33] B. Kvisvik, E.N. Aagaard, L. Mørkrid, et al., Mechanical dispersion as a marker of left ventricular dysfunction and prognosis in stable coronary artery disease, Int. J. Card. Imaging 35 (7) (2019) 1265–1275, https://doi.org/10.1007/s10554-019-01583-z.
[34] A.E. Duncan, A. Alfirevic, D.I. Sessler, Z.B. Popovic, J.D. Thomas, Perioperative assessment of myocardial deformation, Anesth. Analg. 118 (3) (2014) 525–544, https://doi.org/10.1213/ANE.0000000000000088.
[35] J. Labus, J. Winata, T. Schmidt, et al., Perioperative course of two-dimensional left ventricular global longitudinal strain in coronary artery bypass surgery, J. Cardiothorac. Vasc. Anesth. 34 (2020) S49, https://doi.org/10.1053/j.jvca.2020.09.069.
[36] Fischer Kady, Kauert-Willms Annegret, Heinisch Paul Philipp, et al. Resolution of strain abnormalities during extracorporeal rewarming from accidental hypothermic cardiac arrest following avalanche burial. JACC: Case Rep. 0(0). doi: https://doi.org/10.1016/j.jaccas.2020.09.033.
[37] M. Donauer, J. Schneider, N. Jander, F. Beyersdorf, C. Keyl, Perioperative changes of right ventricular function in cardiac surgical patients assessed by myocardial deformation analysis and 3-dimensional echocardiography, J. Cardiothorac. Vasc. Anesth. 34 (3) (2020) 708–718, https://doi.org/10.1053/j.jvca.2019.08.026.
[38] A. Kurz, T. Kopyeva, I. Suliman, et al., Supplemental oxygen and surgical-site infections: an alternating intervention controlled trial, Br. J. Anaesth. 120 (1) (2018) 117–126, https://doi.org/10.1016/j.bja.2017.11.003.
[39] C.S. Meyhoff, Perioperative hyperoxia: why guidelines, research and clinical practice collide, Br. J. Anaesth. 122 (3) (2019) 289–291, https://doi.org/10.1016/j.bja.2018.12.016.
[40] K. Mattishent, M. Thavarajah, A. Sinha, et al., Safety of 80% vs 30–35% fraction of inspired oxygen in patients undergoing surgery: a systematic review and meta-analysis, Br. J. Anaesth. 122 (3) (2019) 311–324, https://doi.org/10.1016/j.bja.2018.11.026.
[41] R.P. Weenink, S.W. de Jonge, R.A. van Hulst, et al., Perioperative hyperoxyphobia: justified or not? benefits and harms of hyperoxia during surgery, J. Clin. Med. 9 (3) (2020), https://doi.org/10.3390/jcm9030642.
[42] O.L. Schjørring, T.L. Klitgaard, A. Perner, et al., Lower or higher oxygenation targets for acute hypoxemic respiratory failure, N. Engl. J. Med. 384 (14) (2021) 1301–1311, https://doi.org/10.1056/NEJMoa2032510.
[43] B. Smit, Y.M. Smulders, M.C. de Waard, et al., Moderate hyperoxic versus near-physiological oxygen targets during and after coronary artery bypass surgery: a randomised controlled trial, Crit. Care 20 (1) (2016) 55, https://doi.org/10.1186/s13054-016-1240-6.
[44] C.S. Meyhoff, L.N. Jorgensen, J. Wetterslev, K.B. Christensen, L.S. Rasmussen, PROXI trial group. Increased long-term mortality after a high perioperative inspiratory oxygen fraction during abdominal surgery: follow-up of a randomized clinical trial, Anesth. Analg. 115 (4) (2012) 849–854, https://doi.org/10.1213/ANE.0b013e3182652a51.
[45] S. Fonnes, I. Gögenur, E.S. Søndergaard, et al., Perioperative hyperoxia - long-term impact on cardiovascular complications after abdominal surgery, a post hoc analysis of the PROXI trial, Int. J. Cardiol. 215 (2016) 238–243, https://doi.org/10.1016/j.ijcard.2016.04.104.
[46] ICU-ROX Investigators the Australian and New Zealand Intensive Care Society Clinical Trials Group, D. Mackle, R. Bellomo, et al., Conservative oxygen therapy during mechanical ventilation in the ICU, N. Engl. J. Med. 382 (11) (2020) 989–998, https://doi.org/10.1056/NEJMoa1903297.
[47] Wasim A. Haque, Boehmer John, S. Clemson Barry, A. Leuenberger Urs, H. Silber David, I. Sinoway Lawrence, Hemodynamic effects of supplemental oxygen administration in congestive heart failure, J. Am. Coll. Cardiol. 27 (2) (1996) 353–357, https://doi.org/10.1016/0735-1097(95)00474-2.
[48] S. Bodetoft, M. Carlsson, H. Arheden, U. Ekelund, Effects of oxygen inhalation on cardiac output, coronary blood flow and oxygen delivery in healthy individuals, assessed with MRI, Eur J Emerg Med 18 (1) (2011) 25–30, https://doi.org/10.1097/MEJ.0b013e32833a295e.
[49] R.W. Nesto, G.J. Kowalchuk, The ischemic cascade: temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia, Am. J. Cardiol. 59 (7) (1987) C23–C30, https://doi.org/10.1016/0002-9149(87)90192-5.
[50] B. Allegranzi, B. Zayed, P. Bischoff, et al., New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective, Lancet Infect. Dis. 16 (12) (2016) e288–e303, https://doi.org/10.1016/S1473-3099(16)30402-9.