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Maintaining normoTHERMia during SEDation in the cardiac catheterisation laboratory: A randomised controlled trial

ABSTRACT

Aim

To determine whether applying forced air warming attenuates the impact of sedation-induced impairment of thermoregulation on core body temperature of patients who are sedated during interventional procedures in the cardiac catheterisation laboratory (CCL).

Background

A moderate proportion of sedated patients who undergo procedures in the CCL with only passive warming become hypothermic. Hypothermia in the surgical population is associated with increased risk of adverse cardiac events, infections, thrombotic and haemorrhagic complications and prolonged hospital stay. For this reason, investigation of the clinical benefits of preventing hypothermia in sedated patients using active warming is required.

Design

Randomised controlled trial.

Methods

140 participants undergoing elective interventional procedures with sedation in a cardiac catheterisation laboratory will be recruited from two hospitals in Australia. Participants will be randomised to receive forced air warming (active warming) or usual care (passive warming with heated cotton blankets) throughout procedures. The primary outcome is hypothermia (defined as temperature less than 36°C) at the conclusion of the procedure. Secondary outcomes are mean change in temperature from pre to post procedure, post-procedural shivering, thermal discomfort, major complications, disability-free survival to 30 days post-procedure, cost-effectiveness and feasibility of conducting a larger clinical trial.

Discussion

The results from this study will provide high-level evidence for practice in an area where there is currently no guidance. Findings will be easily translatable into clinical practice because most hospitals already have forced air warming equipment available for use during general anaesthesia.

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Why this study is needed

- Sedation is increasingly being utilised during many procedures for the diagnosis and treatment of diseases that once could only be performed with general anaesthesia.
- Current perioperative guidelines for temperature monitoring and management do not provide recommendations for procedures that are performed with sedation and analgesia in the procedural context due to a lack of available evidence to inform practice.
- This study will provide high-level evidence to inform current practice and future research regarding the prevention of hypothermia, which is a common adverse effect of the administration of sedation during interventional procedures.

INTRODUCTION

Inadvertent hypothermia is a known adverse effect of general and regional anaesthesia. It has been reported to occur in 50-90% of anaesthetised patients after surgery^{1, 2} and is associated with increased risk of adverse cardiac events, wound complications, thrombotic and haemorrhagic complications and prolonged hospital stay.³ Guidelines for promotion of normothermia during surgery are applicable for patients who receive general or regional anaesthetic in the CCL.^{4, 5} However, there are no guidelines for procedures that are performed with procedural sedation and analgesia (PSA) in this setting.

BACKGROUND

The CCL is similar to the perioperative environment in that patients can be exposed for long periods of time to a typically low ambient room temperature. We confirmed in a recent published review of the evidence that most pharmacological agents used for PSA in the CCL, such as benzodiazepines, opioids and propofol, impair normal thermoregulation.⁶⁻⁸ Following on from this review, we recently completed a single-centre prospective, observational study to identify the prevalence of hypothermia after procedural sedation in a cardiac catheterisation laboratory. Hypothermia ($<36.0^{\circ}\text{C}$) was present after 23.3% (n=93; 95%CI=19.2%-27.4%) of 399 procedures.⁹ Sedative regimens associated with the highest prevalence of hypothermia were any regimen that included propofol (n=35; 40.2%; 95%CI=29.9%-50.5%) and the use of fentanyl combined with midazolam (n=23; 20.3%; 95%CI=12.9%-27.7%).⁹

Potential clinical benefits of preventing hypothermia in sedated patients

Preventing hypothermia in sedated patients would be worthwhile in the CCL. This is because the harmful effects of hypothermia during surgery with either general or regional anaesthesia would likely also be associated with hypothermia during procedural sedation. A meta-analysis

of randomised trials identified that forced air warming resulted in a large reduction (RR 0.37; 95% CI=0.27-0.55) in the risk of a composite of major complications after surgery (blood transfusions, cardiac events, wound infection and pressure injury).¹⁰ Of most concern is that cardiac events, including myocardial infarction, are more likely to occur in patients who became hypothermic.¹¹ Hypothermia is also likely to increase blood loss due to inhibition of platelet function and decreased activation of the clotting cascade.¹²⁻¹⁴ Bleeding complications are a major cause of mortality associated with CCL procedures.¹⁵ The prevalence of shivering observed in our sample (4.7%) was far less than in general or regional anaesthesia.¹⁶ However, it is still a cause for concern that some sedated patients experienced shivering after their procedure. Shivering significantly increases oxygen consumption and carbon dioxide production leading to increased myocardial workload.¹⁷ Shivering is potentially dangerous for patients who undergo procedures with sedation in the CCL, as they typically have cardiovascular disease as well as other comorbid severe systemic diseases making them susceptible to even subtle changes in metabolic requirements. Clinical trials investigating the clinical effectiveness of preventing hypothermia in sedated patients in the CCL are therefore required.¹⁸

Evidence base for the prevention of hypothermia using forced air warming

Authors of the American Society of PeriAnesthesia Nursing's guidelines for the promotion of normothermia reported that the evidence conclusively supports the effectiveness of forced air warming for the prevention of hypothermia during general and regional anaesthesia.⁵ The evidence regarding alternative methods of active warming is not as strong.⁵ The NICE guidelines on the prevention of hypothermia from the UK concur with American recommendations regarding the application of forced air warming.⁴ Evidence indicates that

forced air warming is safe, inexpensive and easy to use. It is also currently the most common active warming strategy used to maintain normothermia during general anaesthesia.¹⁹

AIM

To determine whether applying forced air warming attenuates the impact of sedation-induced impairment of thermoregulation on core body temperature of patients who are sedated during their procedure in the cardiac catheterisation laboratory.

Primary objective

To determine whether forced air warming:

1. Reduces the rate of hypothermia (defined as a temperature $<36^{\circ}\text{C}$), measured at the end of the procedure; and

Secondary objectives

1. To determine whether forced air warming reduces the mean change in core temperature from pre to post procedure.
2. To investigate the effect of forced air warming on thermal comfort.
3. To investigate the effect of forced air warming on shivering.
4. To investigate the effect of forced air warming on major complications.
5. To investigate the cost-effectiveness of forced air warming.
6. To investigate the effect of forced air warming on disability-free survival.
7. To determine the feasibility of using a similar methodology in a larger clinical trial powered to evaluate the clinical benefits of actively warming sedated patients during procedures in the CCL.

METHOD

Design

Single-blind (outcome assessors) randomised controlled trial of forced air warming versus usual care (passive warming with heated cotton blankets) in patients undergoing elective interventional procedures with sedation in a cardiac catheterisation laboratory.

Participants

Inclusion criteria

Patients undergoing an interventional procedure for cardiovascular disease in a CCL that is expected to require sedation and be of more than 30 minutes duration will be included. Interventional procedures include percutaneous coronary interventions, implantation of cardiac rhythm management devices (e.g. permanent pacemaker, implantable cardioverter-defibrillator) and ablation of cardiac arrhythmias. The trial will be conducted at two private hospitals in different metropolitan cities in Australia.

Exclusion criteria

Patients will be excluded from the study if they:

- are less than 18 years of age;
- are cognitively impaired (due to inability to provide informed consent);
- are unable to understand and speak English (due to inability to provide written informed consent);
- are undergoing an emergency procedure (e.g. percutaneous coronary intervention for ST elevation myocardial infarction);

- are undergoing a diagnostic procedure (e.g. coronary angiogram, electrophysiology study without ablation);
- have a current temperature above 37.5°C;
- are scheduled for general anaesthesia.

Intervention and control groups

All randomised participants will receive usual care, which involves passive warming with heated cotton blankets throughout the peri-procedural period that will be applied at the discretion of the nurses. No active warming is applied for sedated patients in current clinical practice.

Participants randomised to the intervention group will also receive forced air warming for the duration of the procedure. The WarmTouch™ WT 6000 Warming Unit (Covidien, USA) will be used. The ‘upper body’ blanket attachment will be used for percutaneous coronary interventions and ablation of cardiac arrhythmias. The ‘lower body’ blanket attachment will be used for cardiac rhythm management device implantation procedures. Device temperature will be initially set at 43°C. Participants will be monitored for sweating, flushing and thermal discomfort so that the device temperature can be titrated accordingly. A step-down protocol for the warming device will be followed if a participant complains of feeling uncomfortable. Temperature will also be monitored at 30 minute intervals using an infrared aural canal thermometer for warming device titration purposes. If temperature rises above 37.5°C, active warming will be ceased. Active warming will be ceased at the end of procedures. Forced air warming will be used because it is safe, inexpensive and easy to use.¹⁹

Outcomes

Primary

- 1) Hypothermia (defined as temperature less than 36°C) at the conclusion of the procedure.

Secondary

- 1) Mean change in temperature from pre to post procedure
- 2) Shivering (post-procedure)
- 3) Thermal comfort (post-procedure)
- 4) Major complications at 30 days post-procedure, defined as:
 - a. Local infection that required re-intervention (not just antibiotics); or
 - b. Systemic infection/endocarditis.
 - c. Bleeding (TIMI major [symptomatic intracranial haemorrhage, clinically overt signs of bleeding associated with a drop in haemoglobin of more than 4g/dL or fatal bleeding] or required blood transfusion or procedural/surgical re-intervention)
 - d. Cardiovascular complications
 - i. Cardiac arrest (defined as ventricular fibrillation, asystole, electromechanical dissociation or ventricular tachycardia without cardiac output that required cardiopulmonary resuscitation and cardioversion)
 - ii. Myocardial infarction (defined as confirmed myocardial infarction distinct from index event)
- 5) Cost-effectiveness
- 6) Disability-free survival
- 7) Feasibility of conducting a larger clinical trial

Procedures

A flow chart describing the study procedures is presented in Figure 1.

Enrolment

A Research Assistant (RA) will review the theatre list to identify potential participants. Potential participants will have the study explained to them by the RA and also receive a Participant Information and Consent Form. Potential participants will be asked for permission to obtain relevant clinical and demographic information from their records for use only in this study. Consent for access to this information is also included in the Information Sheets and Consent Forms. Potential participants will be allowed as much time as they need to consider their involvement in the study, and if they agree to participate, written consent will be obtained. Potential participants will have the opportunity to ask questions before completing the consent form. Time of admission prior to procedures varies considerably. For this reason, there is no specific duration of time that the potential participants will be given to consider their participation. However, for the procedures that are conducted in the morning sessions, it is typical for patients to be admitted the previous day. The theatre list will be checked the day prior to the procedure and any potentially eligible participants who have been admitted will have the study explained to them and will be given a PICF so that they can consider their participation overnight. Potential participants who are admitted on the day of their procedure, which is typically performed in the afternoon session, will be approached as soon as possible after their admission to maximize the time for consideration of participation.

Screening

The RA will conduct a two-part screening process. First, the theatre list will be reviewed to identify patients undergoing interventional procedures that don't require a general anaesthetic.

Nursing staff will be consulted and the medical records will be reviewed to check for exclusion criteria (cognitive impairment, ability to understand and speak English, currently febrile).

Allocation sequence generation

All consented eligible patients will be allocated randomly to intervention and control groups. A statistician from the Institute of Health and Biomedical Innovation's Research Methods Group with no clinical involvement in the trial will generate a stratified (by site and into groups where an anaesthetist is going to be present during the procedure or not) block randomised sequence. Participants will be grouped into these strata because it will be important for the use of propofol to be balanced between the intervention and control groups. In our previous study we identified that the administration of propofol, which is only used when an anaesthetist is present, was an independent predictor of hypothermia.

Allocation concealment

Sealed opaque envelopes organized in sequential order will be used to conceal the allocation to intervention and control groups. The RA will hand the envelope to the Scout nurse only once eligibility and consent has been confirmed.

Data collection

Data will be collected at four time points: (T1) at baseline (prior to procedures); (T2) as soon as possible following the procedure; (T3) on hospital discharge; and (T4) 30-35 days after the procedure.

Instruments

Body temperature: It is not feasible to invasively monitor core temperature in this study. Instead, temperature will be measured non-invasively with an oral digital thermometer placed in the left or right sublingual pocket. This method of approximating core temperature has been

shown to be reliable when tested against readings from a pulmonary artery catheter (the ‘gold standard’ in core temperature assessment) and is considered more accurate than other non-invasive methods.²⁰ The thermometer will be calibrated as per the manufacturer’s instructions. Temperatures will be recorded from the same site (i.e. in either the right or left sub-lingual pocket at both T1 and T2) at each time-point.

Shivering: The presence or absence of shivering will be observed by the RA at T2.

Thermal comfort: Thermal comfort will be measured on a 5 point scale at T2. We used this type of rating scale effectively in our previous study in this setting. The RA will ask participants, using a standardised script, to score how comfortable they are with their body temperature (Too cold, cool, just right, warm, too warm).

Adverse effects: There is a risk of causing thermal injury to the skin if forced air warming is applied incorrectly. The scout nurse will monitor the patient and the forced air warming device throughout the procedure and also inspect intervention group participants’ skin at the end of procedures in order to assess whether any thermal injury has been sustained.

World Health Organization Disability Assessment Schedule 2.0 (WHODAS): The WHODAS measures limitations over the last 30 days across six major life domains: cognition, mobility, self-care, interpersonal relationships, work and household roles, and participation in society. WHODAS has excellent psychometric properties and can be administered in 5 min.^{21, 22} The survey will be administered in person at baseline and over the telephone at 30 days if the patient has been discharged.

EUROQOL 5D-5L (EQ-5D-5L): Quality of life will be measured in this study at baseline and 30 days post-procedure (T4) using the EQ-5D-5L. The EQ-5D-5L is a generic measure of health utility, which will be used to compare quality-adjusted life years between the intervention and control groups at 30 days and one year after procedures. There are five single item dimensions: 'mobility', 'self-care', 'usual function status', 'pain and/or discomfort', and 'anxiety and/or depression'. The survey will be administered over the telephone.

Healthcare resource utilisation and post-procedural complications case report forms: Most complications (with the exception of infection) will likely occur prior to discharge. For this reason, a medical chart review will be undertaken when the patient is discharged from hospital (T3). The following information will be extracted:

Major complications

- 1) Infection (confirmed by clinical diagnosis), categorised as a:
 - a. Local infection that required re-intervention (not just antibiotics); or
 - b. Systemic infection/endocarditis.
- 2) Bleeding (TIMI major [symptomatic intracranial haemorrhage, clinically overt signs of bleeding associated with a drop in haemoglobin of more than 4g/dL or fatal bleeding] or required blood transfusion or procedural/surgical re-intervention)
- 3) Cardiovascular complications
 - a. Cardiac arrest (defined as ventricular fibrillation, asystole, electromechanical dissociation or ventricular tachycardia without cardiac output that required cardiopulmonary resuscitation and cardioversion)
 - b. Myocardial infarction (defined as confirmed myocardial infarction distinct from index event)

Resource utilisation

- 4) Length of stay after index procedure in:
 - a. recovery
 - b. high dependency/ICU; and
 - c. hospital
- 5) Procedures that were performed after the index procedure
- 6) Survival (date and cause of death if known)

A telephone questionnaire (or face to face interview if re-admitted) will be undertaken at 30-35 days (T4) after participants' procedures to any major complications and resource utilisation that occurred post-discharge but within the 30 day follow-up period. If participants' answers to this questionnaire indicate a major complication had potentially occurred, hospital records will be accessed for confirmation according to the criteria outlined above.

The majority of health care costs arise from direct hospital and medical care, not pharmaceuticals. For this reason, the questionnaire will be used to capture just the major components of healthcare resources (e.g. hospital length of stay, ICU length of stay, medical procedures and general practitioner/specialist consultations). Medical records will be accessed, wherever practical, for confirmation regarding length of hospital stay and procedural details.

Potential confounders and biases: Demographic, procedural and disease factors will be measured, including age, gender, co-morbidities (Charlson comorbidity index), fasting status, procedure duration, room temperature and doses of sedative and analgesic medications used.

Data analysis

Sample size

Previous studies of forced air warming during general anaesthesia have reduced hypothermia from 69% to 13% (>80% relative reduction).²³ Therefore, the sample size for the THERMISED Pilot Study has been calculated to detect an 80% relative difference in the rate of hypothermia. 128 patients (64 in each group) will be required to detect an 80% reduction in hypothermia from 20% in the intervention group to 4% in the control group (assuming type I error of 5% (two-tailed) and power of 80%). The mean change in temperature from pre to post-procedure that was observed in sedated patients included in our previous study was -0.27°C (SD 0.45).⁹ Assuming the control group's mean change in temperature from pre to post-procedure will be -0.25°C , a standard deviation of 0.5°C , type I error of 5% and 80% power, a sample of 128 participants will be able to detect even a small difference in the mean change in temperature from pre to post-procedure between intervention and control groups (effect size 0.25).

Feasibility

Assuming an 80% participation rate, approximately 170 patients will need to be invited to participate over the 6-month period allocated for data collection. This is feasible based on the number of procedures performed with sedation at this site (about 100 per month).

Statistical analysis

Data will firstly be transferred from the case report forms into STATA v13 for analysis (Statacorp, Texas, USA). Analyses will be performed using intention-to-treat principles. Descriptive statistics (frequencies and percentages) will be used to summarise categorical data while means and standard deviations or median and inter-quartile range will be calculated to describe continuous data. Relationships between baseline variables and outcomes will be investigated using t-tests or ANOVAs for continuous variables and chi-square tests for categorical variables to identify confounders.

Primary outcome

A cut point of $<36.0^{\circ}\text{C}$ will be used to classify patients as hypothermic. To determine the effect of forced air warming on the risk of hypothermia, relative risk regression analyses will be performed to calculate relative risks with 95% confidence intervals. Multivariable adjustment will be performed using log binomial regression in order to estimate adjusted relative risk ratios if confounders are identified.

Secondary outcomes

Although the sample size is unlikely to be sufficient to detect statistically significant differences for all the secondary outcome measures, exploratory analysis of these data will be used to inform the design of future research in this area. The mean change in core temperature from pre to post procedure will be compared between the intervention and control groups using a t-test. Multivariable adjustment will be performed using linear regression if confounders are identified. Separate relative risk regression analyses will be used to calculate relative risks with 95% confidence intervals for secondary outcomes of thermal discomfort (either too hot or too cold), shivering, major complications and disability-free survival at 30 days. Disability will be

classified as an increase from baseline of >8% in the WHODAS score, which has been identified as a minimum clinically important difference in previous research.²⁴ Multivariable adjustment will be performed using log binomial regression in order to estimate adjusted relative risk ratios if confounders are identified. A separate analysis of the overall change in WHODAS score over time (baseline and 30 days), between groups (forced air warming and standard care) and (time by group) interaction effects will be examined using Linear Mixed Models (LMMs) with adjustment for identified confounders. LMM will be used because this statistical technique allows the inclusion of all available data, including those subjects who do not complete all assessments.^{25, 26}

The cost-effectiveness analysis will be undertaken from the perspective of the Australian health care funder. The net monetary benefit (NB) for the alternate treatment options will be calculated by multiplying the effect by the willingness-to-pay threshold minus the cost. The cost-effective intervention will be the one that yields the highest expected NB. The willingness-to-pay per quality adjusted life-year gained will be AUD\$50,000. Although there will not likely be statistically significant differences in survival or quality of life between treatment groups within a trial of this size, the data collected will provide an estimate of the baseline quality of life in this population that can be augmented by data on quality of life and cost associated with hypothermia-associated complications derived from literature review.^{4, 10} Longer term costs and quality-adjusted life-years will then be modelled using this information. To quantify model uncertainty, Monte-Carlo samples will be drawn from probability distributions specified for all model parameters.

Feasibility of conducting a larger clinical trial

Descriptive statistics will be used to calculate rate of recruitment, the number of eligible patients who agreed to participate, the number of patients who received the correct protocol and the number of patients who completed the trial. Acceptability of the intervention will be evaluated by using descriptive statistics to determine the number of intervention group participants who did not tolerate the active warming device for the whole procedure. Feasibility of utilising disability-free survival as a primary outcome in a larger clinical trial will be determined by evaluating the completeness of follow-up at 30 days after participants' procedures.

Ethical considerations

University and hospital human research ethics committee approvals were obtained in 2015 (UCH HREC 1505; QUT HREC 1500000643; SVH HREC 15/263). Participation in this study is voluntary and will not affect any aspect of a participant's treatment by their clinicians. There will be no cost to the participant from being involved in the study. As participants who are cognitively impaired, as confirmed by diagnosis noted in medical record or by a treating clinician, do not have the capacity to consent, these patients will be excluded from the study. The risk is the potential for thermal injury to the skin from the forced air warming device. If the manufacturer's instructions are followed, this risk will be minimized. If thermal injury does occur, it is likely to be minor and not require any treatment, but it may cause some discomfort. There is a potential risk for discomfort associated with having a probe sit beneath participants' tongue for about 30 seconds in order to measure body temperature. This is a non-invasive method for measuring body temperature which is routinely used in clinical practice. For this reason, the potential benefits associated with preventing hypothermia in sedated patients seem to outweigh the potential risk of discomfort.

Validity and reliability

This study will be conducted in compliance with Good Clinical Practice guidelines, the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research, The Australian Code for the Responsible Conduct of Research and the Declaration of Helsinki.

Patient Identification

All patients screened for the study will be entered on the Patient Screening Log. In the event a patient is excluded from study participation, the reason will be documented on the screening log. Each consenting patient will be assigned a participant ID number on randomisation to the study. This number and the patient information are to be entered on the case report forms (CRFs). All other data will only use the ID number and stored separately from the CRFs.

Case Report Forms

All required data must be clearly recorded on the appropriate CRFs. Every effort must be made to ensure that the dates recorded on CRFs are accurate. The study will be conducted using either digital or paper CRFs. Data will be recorded on the paper CRFs using black/blue ballpoint pen and any errors requiring correction must be clearly crossed out (no white-out is permitted), initialled and dated.

Data handling and record keeping

Unique project codes will be assigned to participants on entry to the project, and stored securely and separately from participant data. During each data collection, research staff will enter participant data into a database. At no time will identifiable study information be reported or available to persons other than the research personnel.

Interim analysis

As participants for this trial are not anticipated to be recruited over an extended period of time and the safety of forced air warming has already been established in the surgical setting, interim analyses for safety or efficacy will not be conducted.

Adverse event reporting

Any adverse events that arise, whether related to the study intervention or not, will in the first instance be reported to the Clinical Nurse Manager and to the investigators who will then submit a report of the event to the HREC. The standard reporting system for will also be followed (Riskman® notification).

DISCUSSION

It is important to note that the impact of using forced air warming on clinical outcomes of sedated patients may be less pronounced compared with the populations in which this technology has been investigated previously (i.e. patients undergoing major surgery with general and/or regional anaesthesia). There is a smaller absolute change in temperature from pre to post-procedure in sedated patients compared with those who receive general anaesthesia.⁹ The underlying mechanisms for the adverse effects of hypothermia on surgical outcomes are influenced by the degree to which core temperature is reduced. For example, there is a negative linear association between core temperature and neutrophil oxidative and phagocytic activity.²⁷ It is therefore unknown whether more modest impairment of immune function resulting from a smaller reduction in temperature induced by sedation would have a clinically relevant impact on the rate of post-procedural infections. That said, a recent large retrospective observational study suggests even small amounts of hypothermia are still clinically relevant. Actively warmed patients undergoing surgery who experienced small reductions in temperature had an increased risk of requiring a blood transfusion.²⁸

Another factor to consider in designing a trial to evaluate the clinical effectiveness of forced air warming for sedated patients undergoing interventional cardiovascular procedures is that the overall procedural complication rate is low. For example, major infections occurred in only 1.7% of 1081 patients after implantable cardioverter-defibrillator replacement.²⁹ As a result, a very large sample size would be required to detect a statistically significant difference in the rate of complications between forced air warming and control groups. For this reason, this study has also been designed to provide other valuable information that could be used to inform alternative research designs with the similar aim of determining the clinical effectiveness of using forced air warming for sedated patients undergoing interventional cardiovascular procedures.

Using a primary endpoint that will provide a robust estimate of the clinical effectiveness of using forced air warming for sedated patients but not require a very large sample size is one alternative. There is the potential that a smaller sample size would be required to obtain adequate statistical power if disability-free survival was used as the primary outcome in a clinical trial aiming to determine the clinical effectiveness of forced air warming in sedated patients due to the rate of disability that would likely be present among this cohort. A previous study identified a prevalence of pre (27%) and post-operative (22%) disability among patients undergoing a broad range of surgery.²² It is likely that similar rates of disability will be present in a population of patients undergoing procedures for the treatment of cardiovascular disease with sedation, due to the typically advanced age and multi-morbidity profile of this cohort. This study will provide estimates of pre and post-procedural disability (calculated from WHODAS scores) that would be required to conduct a sample size calculation using disability-free survival as the primary outcome measure in a future trial of the clinical effectiveness of forced air warming for sedated patients undergoing interventional procedures in a cardiac catheterisation laboratory.

Limitations

A limitation of this study is the inability to directly measure core body temperature. Previous trials of forced air warming in surgical populations used tympanic membrane thermocouples to measure core body temperature.^{11, 18} Although measuring core temperature at the tympanic membrane with a thermocouple can be tolerated by awake patients, there is a risk of perforation. It was decided that the slightly more accurate measurement that could be derived from this device did not justify this risk for the participants. A higher level of sedation than is required for the procedures would need to be induced to invasively measure core temperature at other sites (e.g. oesophagus), so these approaches were not considered feasible for this study. For these reasons, we decided to non-invasively measure temperature using a sublingual digital thermometer. Sublingual digital thermometry was found to be an accurate non-invasive temperature measuring device for post anaesthetic patients.³⁰ Zero-heat-flux thermometers, which are also non-invasive, might provide more precise estimates of core temperature compared with oral thermometers.^{31, 32} However, these devices are not currently commercially available for use in Australia, so we could not source them for use in the trial.

The primary outcome (rate of hypothermia post- procedure) will be measured for each participant in our trial at a different time interval relative to the start of their procedures. In order to take the variability in the time from baseline to post-procedure temperature measurements into account, log binomial and linear regression will be used. A potential alternative we had considered was to measure temperatures at baseline (pre-procedure) and then at pre-defined time intervals throughout and post-procedures. However, in the clinical context in which this intervention is being applied, it would not be feasible for temperatures to be measured intra-procedurally without risking detection bias (the outcome assessor would be ‘unblinded’ because it would be clearly visible that participants were receiving forced air

warming). In addition, procedures would need to be interrupted for at least one minute or potentially longer to accurately measure temperature intra-procedurally with a sublingual thermometer. To avoid procedural interruptions and reduce risk of detection bias, we chose not to measure temperatures intra-procedurally at pre-defined time intervals for the primary outcome. Intra-procedural temperature will be measured only in the intervention group with an infrared aural canal thermometer at 30 minute intervals (procedures will not be required to be stopped for this measurement to occur) to facilitate warming device titration for safety reasons (i.e. if hyperthermia is detected, the device will be turned off). It should be noted, though, that clinical guideline recommendations for perioperative temperature management support our choice of the time-point at which the primary outcomes for this trial will be measured. It is recommended that temperature above 36°C should be targeted throughout the peri-procedural period, with a specific emphasis placed on this temperature target being reached by the end of the procedure in order to prevent hypothermia-induced post-procedural complications such as shivering, thermal discomfort and adrenergic stress (adrenergic stress is hypothesised to be the cause of increased risk of adverse cardiac events in patients who become hypothermic during surgery).^{11, 28}

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Figure 1. Study procedures (RA = Research assistant)