Forced air warming during sedation in the cardiac catheterisation laboratory: a randomised controlled trial

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ABSTRACT
Objective Forced air warming (FAW) during general anaesthesia is a safe and effective intervention used to reduce hypothermia. The objective of this study was to determine if FAW reduces hypothermia when used for procedures performed with sedation in the cardiac catheterisation laboratory.

Methods A parallel-group randomised controlled trial was conducted. Adults receiving sedation in a cardiac catheterisation laboratory at two sites were randomised to receive FAW or usual care, which involved passive warming with heated cotton blankets. Hypothermia, defined as a temperature less than 36°C measured with a sublingual digital thermometer after procedures, was the primary outcome. Other outcomes were postprocedure temperature, shivering, thermal comfort and major complications.

Results A total of 140 participants were randomised. Fewer participants who received FAW were hypothermic (39/70, 56% vs 48/69, 70%, difference 14%; adjusted RR 0.75, 95% CI=0.60 to 0.94), and body temperature was 0.3°C higher (95% CI=0.1 to 0.5, p=0.004). FAW increased thermal comfort (63/70, 90% vs 51/69, 74%, difference 16%, RR 1.21, 95% CI=1.04 to 1.42). The incidence of shivering was similar (3/69, 4% vs 0/71 0%, difference 4%, 95% CI=−1.1 to 9.8). One patient in the control group required reintervention for bleeding. No other major complications occurred.

Conclusion FAW reduced hypothermia and improved thermal comfort. The difference in temperature between groups was modest and less than that observed in previous studies where use of FAW decreased risk of surgical complications. Therefore, it should not be considered clinically significant.

Trial registration number ACTRN12616000013460.

INTRODUCTION
Inadvertent perioperative hypothermia is considered an adverse effect of anaesthesia that should be avoided.1 Forced air warming (FAW) is a safe and effective intervention for the prevention of inadvertent perioperative hypothermia.2 It is recommended for use during general anaesthesia in clinical guidelines.2 3 The cardiac catheterisation laboratory (CCL) is similar to a perioperative environment in that patients are exposed for periods of time to low ambient room temperatures. Our recent review revealed that pharmacological agents used for procedural sedation and analgesia in the CCL, such as benzodiazepines, opioids and propofol, impair normal thermoregulation, but not to the same extent as doses used for general anaesthesia.4 5 For example, studies in healthy volunteers have shown that propofol and opioids markedly reduced the vasoconstriction and shivering thresholds, producing a linear decrease in core temperature.6–8 Administration of midazolam only minimally impacts thermoregulatory control9 but did produce a dose-dependent decrease in temperature due to core to peripheral heat redistribution.10 We have previously identified a moderate prevalence of hypothermia (defined as body temperature <36.0°C) after procedures performed with sedation in a CCL where passive warming with heated (or non-heated) cotton blankets was used.11 FAW increases body temperature during surgery in comparison with passive warming because it markedly reduces cutaneous heat loss. As a result, most patients who receive intraoperative FAW during surgery will meet the widely recommended goal for perioperative thermal management, which is for core temperature to be >36.0°C by the end of the procedure.12 The extent to which application of FAW would increase temperature during procedures performed in the CCL with sedation is unknown. We aimed to determine whether FAW reduces hypothermia when used for procedures performed with sedation in the CCL.

METHODS
Design
A randomised controlled trial was conducted to compare FAW with passive warming using heated cotton blankets during elective procedures performed under sedation in a CCL. Full details of the protocol for this study have been published,13 and it was prospectively registered (ACTRN12616000013460). Informed consent was obtained from each participant, and the study protocol conforms to the 1975 Declaration of Helsinki as reflected by the university and hospital human research ethics committee approvals (UCH HREC 1505; QUT HREC 1500000643; SVH HREC 15/263).

Participants
Patients were eligible for inclusion if they were undergoing an interventional procedure of more than 30 min duration with sedation. Procedures were percutaneous coronary interventions, cardiovascular implantable electronic device procedures...
with a drop in haemoglobin of more than 4 g/dL or fatal cranial haemorrhage, clinically overt signs of bleeding associated

2 Conway A, the manufacturer’s instructions) was used to measure tempera-

3000 in direct measurement mode and calibrated according to oral digital thermometer placed in the sublingual pocket (Filac

Data collection was conducted blinded to group assignment. An

data were reviewed on discharge and readmission within the follow-up period.

Intervention and control groups

All participants received passive warming with heated cotton blankets, which were applied by the nurses as part of their usual practice. No restrictions on the use of passive warming were in place.

Intervention group participants received FAW during their procedures using a WarmTouch WT 6000 Warming Unit (Covidien, Minneapolis, Minnesota, USA) with either an ‘upper body’ or a ‘lower body’ blanket attachment. The temperature of the FAW unit was set at 45°C. Nursing staff monitored participants for signs of hyperthermia (sweating and flushed skin) and thermal discomfort so that the temperature of the device could be titrated according to a step-down protocol. An infrared aural canal thermometer was used to monitor temperature every 30 min so that active warming could be ceased if temperature rose above 37.5°C. Active warming was discontinued when procedures were completed.

Outcomes

The rate of hypothermia (temperature less than 36°C) at the conclusion of the procedure was the primary outcome. Other outcomes included postprocedure temperature, shivering, thermal comfort and major complications at 30 days postpro-

cedure (defined as local infection that required reintervention or systemic infection/endocarditis, bleeding (symptomatic intracranial haemorrhage, clinically overt signs of bleeding associated with a drop in haemoglobin of more than 4 g/dL or fatal bleeding or required blood transfusion or procedural/surgical reintervention), cardiovascular complications (ventricular fibrillation, asystole, electromechanical dissociation or ventricular tachycardia without cardiac output that required cardiopulmonary resuscitation) and cardioversion or myocardial infarction (defined as confirmed myocardial infarction distinct from index event)).

Procedures

Allocation sequence generation

An independent statistician generated a stratified (by presence of an anaesthetist and site) block randomised sequence (two to four in each block). These strata were used to ensure that the use of propofol was balanced between groups.

Allocation concealment

The group allocations were concealed using sequentially ordered sealed opaque envelopes. The research assistant handed the envelope to the Scout nurse (nurse responsible for intraproce-

dural care) just prior to procedure commencement.

Data collection

Data collection was conducted blinded to group assignment. An oral digital thermometer placed in the sublingual pocket (Filac 3000 in direct measurement mode and calibrated according to the manufacturer’s instructions) was used to measure tempera-

ture. Temperatures were taken from the same site before and

after procedures. Participants were observed after procedures to detect shivering, and researchers assessed thermal comfort on a 5-point scale (too cold, cool, just right, warm and too warm). Data about use of warming methods used in active and passive warming groups were collected. This included the number of times the temperature of the FAW device was titrated during procedures as well as the number of heated cotton blankets and towels used during and after procedures in the recovery area for both groups. Medical records were reviewed on discharge

Statistical analysis

Intention-to-treat principles were used in the analyses. Absolute differences as well as relative risks with 95% CIs were calculated for the primary outcome of hypothermia and the secondary outcome of thermal comfort (classified as a rating of ‘just right’) using Poisson regression with robust variance estimation to adjust for the stratified variables (site and use of monitored anaesthesia care) as well as preprocedural temperature. As there were too few events to use a regression model to compare the rates of shivering between groups, a Fisher’s exact test was used without adjustment for stratification. Analysis of covariance, adjusting for baseline temperature and stratification variables, was used to compare postprocedure temperatures. A subgroup analysis was conducted by including an interaction term in the model for use of propofol.

RESULTS

There were 598 patients screened for eligibility between April 2016 and March 2017 (figure 1). The major reasons patients were not enrolled in the study included the use of general anaes-

thesia (n=88) or an anticipated procedural duration of less than 30 min (n=341). A total of 140 participants were randomised. Demographic and clinical characteristics are presented in table 1.

Warming methods

The temperature of the FAW device was titrated down during the procedure in accordance with the step-down protocol for eight of the intervention group participants. One patient randomised to the control group undergoing an electrophysiology procedure received FAW at the discretion of the anaes-

thesist because the patient expressed thermal discomfort prior to procedure commencement. Nurses used a total of 150 heated cotton blankets and 36 heated towels during and after procedures for the 69 participants randomised to the control group. Nurses used 115 heated blankets and 37 heated towels during and after procedures for the 71 participants randomised to the intervention group.

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Primary outcome
Fewer participants who received FAW were hypothermic (39/70, 56% vs 48/69, 70%, difference 14%) after their procedures. This difference was statistically significant in the model with adjustment for variables used for stratification and baseline temperature (adjusted RR 0.75, 95% CI=0.60 to 0.94, p=0.011).

Secondary outcomes
Body temperature was 0.3°C higher (95% CI=−0.5 to −0.1, p=0.004) in the FAW group (table 2). The interaction between allocation group and use of propofol was not significant (p=0.564).

Forced air warming reduced shivering (0/71 0% vs 3/69, 4%, difference 4%, 95% CI=−1.1 to 9.8, p=0.117) and increased self-reported thermal comfort (63/70, 90% vs 51/69, 74% difference 16%, adjusted RR 1.21, 95% CI=1.04 to 1.42, p=0.014). One patient in the control group required reintervention for bleeding. No major infections or cardiovascular complications occurred in either group. There was no evidence of thermal injury to skin after procedures in the FAW group.

DISCUSSION
Using FAW during interventional procedures performed with sedation in the CCL decreased rates of hypothermia by 14% (a 25% relative risk reduction) as a result of increasing temperature by 0.3°C on average compared with passive warming. The increase in body temperature in the FAW group should be considered modest. It is similar to those arising from testing of this intervention with sedated patients in controlled experimental conditions and with application of active warming during neuraxial anaesthesia. A recent meta-analysis of eight trials with 1189 participants who received neuraxial anaesthesia found that active warming increased postoperative temperature by 0.36°C in comparison with passive warming (95% CI=0.16 to 0.55) and reduced risk of hypothermia by 29% (RR 0.71, 95% CI=0.61 to 0.83).

A positive effect of active warming in our trial was increased thermal comfort. This result is consistent with a meta-analysis conducted in a recent Cochrane review. Active body surface warming increased ratings of thermal comfort in a meta-analysis of four trials with 364 participants (standardised mean difference 0.72, 95% CI=0.29 to 1.24). The relative contributions to thermal comfort of core and skin temperatures is about equal. As such, our finding that FAW increased ratings of thermal comfort in comparison with passive warming would be due to the effect of this device on skin temperature in addition to the 0.3°C increase in body temperature that was induced.

The increase in temperature in the group of participants randomised to receive FAW in our trial was less than that...
observed in previous studies where the use of this intervention decreased risk of surgical complications.\textsuperscript{20,21} It is likely that the underlying mechanisms for the protective effects of active warming on surgical outcomes are influenced by the degree to which core temperature is increased. For example, the relationship between core temperature and immune function is implicated in the development of postoperative infection.\textsuperscript{22} Moreover, recent research has shown that greater reductions in temperature during surgery were associated with increased likelihood of blood transfusion requirement.\textsuperscript{12} It is therefore not likely that increasing temperature with FAW by only a few tenths of a degree during sedation would improve clinical outcomes for this population.

It should be noted that the average preoperative temperature was low in our sample, at about 36.1°C. A recent analysis of preoperative temperatures from seven prospective studies also revealed an unexpectedly high incidence of preoperative hypothermia.\textsuperscript{23} In this analysis, independent predictors of preoperative hypothermia were male sex and being aged over 52 years.\textsuperscript{23} The majority of participants included in our sample were male (66%), and the average age was 72. As such, the demographic characteristics of our sample likely explain the low preoperative temperatures that were observed. As the average preprocedural temperature was low, further research on the added benefit of preoperative warming on patients undergoing sedation in the CCL may be warranted. In a recent Cochrane Review on the effectiveness of active warming for preventing hypothermia in surgical patients, the authors concluded that the addition of preoperative full-body warming for a period of 30 min had an extra protective benefit over intraoperative warming.\textsuperscript{18} Several other studies highlight the role of preoperative warming for preventing perioperative hypothermia.\textsuperscript{24,25}

### Limitations

The rates of hypothermia used for the sample size calculation were different to those observed in our study. We attribute this to the type of thermometer used. There was a lower incidence of postprocedural hypothermia observed in our previous study where an infrared aural canal thermometer was used.\textsuperscript{11} We used a sublingual digital thermometer in this randomised controlled trial because it is a more accurate non-invasive temperature measuring device for postanaesthetic patients compared with infrared aural canal thermometers.\textsuperscript{26}

A further potential limitation is that we did not blind participants or clinicians to group assignment. The technical challenges of achieving double blinding in trials of warming strategies have been acknowledged previously.\textsuperscript{27} Importantly, outcome assessors were blinded to group assignment to reduce the risk of detection bias in our trial.

It should also be noted that we only included patients undergoing procedures with an anticipated duration of more than 30 min. Extrapolation of our findings to other procedures performed in procedural settings is not recommended, as it is likely that the effect of FAW on body temperature is dependent on contextual factors, including the length of procedures and ambient temperature to which the patients have been exposed. The ambient temperature during procedures was 20°C on average. Active warming may have less of an effect on body temperature and thermal comfort in comparison with passive warming in procedural suites where the ambient temperature is higher.

### Table 1 Baseline characteristics

| Variable                              | Forced air warming (n=71), mean (SD) or n (%) | Passive warming (n=69), mean (SD) or n (%) |
|---------------------------------------|----------------------------------------------|-------------------------------------------|
| Age                                   | 72 (13)                                      | 73 (13)                                   |
| Males                                 | 49 (69)                                      | 44 (64)                                   |
| BMI                                   | 27 (5)                                       | 27 (6)                                    |
| Charlson Comorbidity Score            | 1.6 (1.6)                                    | 1.8 (2.2)                                 |
| ASA class >2                          | 64 (90)                                      | 62 (90)                                   |
| Procedure duration (min)              | 57 (39)                                      | 56 (29)                                   |
| PCI                                    | 16 (23)                                      | 16 (23)                                   |
| Cardiac implantable electronic device | 34 (48)                                      | 32 (46)                                   |
| Electrophysiology study and/or ablation of cardiac arrhythmia | 8 (11)                                      | 7 (10)                                    |
| Peripheral intervention               | 8 (11)                                       | 9 (13)                                    |
| Structural heart procedure            | 5 (7)                                        | 5 (7)                                     |
| Monitored anaesthesia care            | 34 (48)                                      | 33 (48)                                   |
| Propofol used                         | 27 (38)                                      | 29 (42)                                   |
| Total midazolam dose                  | 2.1 (0.9)                                    | 2 (0.9)                                   |
| Total fentanyl dose                   | 50 (35)                                      | 45 (32)                                   |
| Propofol bolus amount                 | 43 (88)                                      | 38 (81)                                   |
| Propofol target controlled infusion used | 9 (13)                                      | 9 (13)                                    |
| Room temperature                      | 19.8 (1.0)                                   | 20 (1.1)                                  |

ASA, American Society of Anesthesiologists; BMI, body mass index; PCI, percutaneous coronary intervention.

### Table 2 Effect of forced air warming on temperature (°C) for the main comparison and use of propofol subgroup analysis

|                          | Forcic air warming | Passive warming | Difference between means (95% CI) | p Value | p Value for interaction |
|--------------------------|--------------------|-----------------|----------------------------------|---------|------------------------|
| Total                    |                    |                 |                                  |         |                        |
| Baseline                 | 36.1 (0.5)         | 36.2 (0.5)      | 0.1                              | 0.2     | 0.07                   |
| Postprocedure            | 35.8 (0.7)         | 35.6 (0.7)      | −0.2 (−0.4 to 0.01)              | 0.07    | 0.004                  |
| ANCOVA (adjusting for baseline temperature and stratification variables) | | | | | |
| Propofol used            |                    |                 |                                  |         |                        |
| Baseline                 | 36 (0.3)           | 36.1 (0.4)      | 0.1                              | 0.2     | 0.033                  |
| Postprocedure            | 35.6 (0.4)         | 35.5 (0.5)      | −0.1 (−0.4 to 0.1)               | 0.185   | 0.004                  |
| ANCOVA (adjusting for baseline temperature and stratification variables) | | | | | |
| Propofol not used        |                    |                 |                                  |         |                        |
| Baseline                 | 36.1 (0.5)         | 36.2 (0.5)      | 0.1                              | 0.2     | 0.04                   |
| Postprocedure            | 35.9               | 35.7            | −0.2 (−0.6 to −0.1)              | 0.194   | 0.564                  |
| ANCOVA (adjusting for baseline temperature and stratification variables) | | | | | |

ANCOVA, analysis of covariance.
What is already known on this subject?
The pharmacological agents used for procedural sedation and analgesia in the cardiac catheterisation laboratory impair normal thermoregulation. As a result, inadvertent hypothermia (defined as body temperature <36.0°C) is common after procedures performed with sedation in a cardiac catheterisation laboratory.

What might this study add?
Using forced air warming during interventional procedures performed with sedation in the cardiac catheterisation laboratory decreased rates of hypothermia by 14% as a result of increasing temperature by 0.3°C on average compared with passive warming. Forced air warming also increased thermal comfort.

How might this impact on clinical practice?
Using forced air warming during procedures performed with sedation in the cardiac catheterisation laboratory would reduce postprocedural hypothermia (temperature <36.0°C) and improve thermal comfort. However, it is unlikely that increasing temperature by only a few tenths of a degree with active warming will improve clinical outcomes.

CONCLUSIONS
FAW can be recommended for use during procedures performed with sedation in the CCL to reduce postprocedural hypothermia and to improve thermal comfort. However, the difference in temperature between active and passively warmed patients is not clinically important, as it is unlikely that increasing temperature by only a few tenths of a degree will reduce risk of procedural complications.

Contributors
AC, JD and JS designed the study. AC and SE collected data. AC analysed the data and wrote the first draft of the manuscript. All authors contributed important intellectual content to the drafted manuscript and approved it for publication.

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Competing interests
None declared.

Patient consent
Obtained.

Ethics approval
Informed consent was obtained from each participant, and the study protocol conforms to the 1975 Declaration of Helsinki as reflected by the university and hospital human research ethics committee approvals (UCH HREC 1505; QUT HREC 150000646; SVH HREC 15s/263).

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REFERENCES
1 Sessler DI. Perioperative thermoregulation and heat balance. Lancet 2016;387:2655–64.
2 NICE. The management of inadvertent perioperative hypothermia in adults. UK: National Institute for Health and Care Excellence, 2008.
3 Torossian A, Bräuer A, Höcker J, et al. Preventing inadvertent perioperative hypothermia. Dtsch Arztebl Int 2015;112:166.
4 Conway A, Rolley JX, Page K, et al. Trends in nurse-administered procedural sedation and analgesia across Australian and New Zealand cardiac catheterisation laboratories: results of an electronic survey. Aust Crit Care 2014;27:4–10.
5 Conway A. A review of the effects of sedation on thermoregulation: insights for the cardiac catheterisation laboratory. J Perinat Nurs 2016;31:226–36.
6 Matsukawa T, Kurz A, Sessler DI, et al. Propofol linearly reduces the vasconstriction and shivering thresholds. Anesthesiology 1995;82:1169–80.
7 Leslie K, Sessler DI, Björksten AR, et al. Propofol causes a dose-dependent decrease in the thermoregulatory threshold for vasconstriction but has little effect on sweating. Anesthesiology 1994;81:353–60.
8 Kurz A, Go JC, Sessler DI, et al. Alfentanil slightly increases the sweating threshold and markedly reduces the vasconstriction and shivering thresholds. Anesthesiology 1995;83:293–9.
9 Kurz A, Sessler DI, Annadata R, et al. Midazolam minimally impairs thermoregulatory control. Anesth Analg 1995;81:393–8.
10 Matsukawa T, Hanagata K, Ozaki M, et al. I.m. midazolam as premedication produces a concentration-dependent decrease in core temperature in male volunteers. Br J Anaesth 1997;78:396–9.
11 Conway A, Kennedy W, Sutherland J. Inadvertent hypothermia after procedural sedation and analgesia in a cardiac catheterisation laboratory: a prospective observational study. J Cardiothorac Vasc Anesth 2015;29:1285–90.
12 Sun Z, Honar H, Sessler DI, et al. Intraoperative core temperature patterns, transfusion requirement, and hospital duration in patients warmed with forced air. Anesthesiology 2015;122:276–85.
13 Conway A, Duff J. Forced air warming to maintain normothermia during SEDation in the cardiac catheterization laboratory: protocol for the THERMISED pilot randomized controlled trial. J Adv Nurs 2016;72:2547–57.
14 Horn EP, Bein B, Bihm R, et al. The effect of short time periods of pre-operative warming in the prevention of peri-operative hypothermia. Anaesthesia 2012;67:612–7.
15 Zou G, A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004;159:702–6.
16 Sato H, Yamakage M, Okugami K, et al. Forced-air warming effectively prevents midazolam-induced core hypothermia in volunteers. Eur J Anaesthesiol 2009;26:566–71.
17 Shaw CA, Steelman VM, DeBer G, et al. Effectiveness of active and passive warming for the prevention of inadvertent hypothermia in patients receiving neuraxial anaesthesia: a systematic review and meta-analysis of randomized controlled trials. J Clin Anesth 2015;27:93–104.
18 Madri E, Urmüha G, Roqué i Figuls M, et al. Active body surface warming systems for preventing complications caused by inadvertent perioperative hypothermia in adults. Cochrane Database Syst Rev 2016;4:CD009016.
19 Frank SM, Raja SN, Bulcao CC, et al. Relative contribution of core and cutaneous temperatures to thermal comfort and autonomic responses in humans. J Appl Physiol 1999;86:1588–93.
20 Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. N Engl J Med 1996;334:1209–16.
21 Schmied H, Kurz A, Sessler DI, et al. Mild hypothermia increases blood loss and transfusion requirements during total hip arthroplasty. Lancet 1996;347:289–92.
22 Wenzich C, Nairz E, Sessler DI, et al. Mild intraoperative hypothermia reduces production of reactive oxygen intermediates by polymorphoneuclear leukocytes. Anesth Analg 1996;82:810–6.
23 Wetzel AJ, Perl T, Brandes IF, et al. Unexpectedly high incidence of hypothermia before induction of anesthesia in elective surgical patients. J Clin Anesth 2016;24:282–9.
24 Horn EP, Bein B, Broch Q, et al. Warming before and after epidural block before general anaesthesia for major abdominal surgery prevents perioperative hypothermia: a randomised controlled trial. Eur J Anaesthesiol 2016;33:334–40.

Conway A, et al. Heart 2017;0:1–6. doi:10.1136/heartjnl-2017-312191
25 Steelman VM, Perkhounkova YS, Lemke JH. The gap between compliance with the quality performance measure “perioperative temperature management” and normothermia. Journal for healthcare quality: official publication of the national J Healthcare Qual 2015;37:333–41.

26 Langham GE, Maheshwari A, Contrera K, et al. Noninvasive temperature monitoring in postanesthesia care units. Anesthesiology 2009;111:90–6.

27 Akhtar Z, Hesler BD, Fiffick AN, et al. A randomized trial of prewarming on patient satisfaction and thermal comfort in outpatient surgery. J Clin Anesth 2016;33:376–85.
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