Continuous intra-arterial blood glucose monitoring using quenched fluorescence sensing in intensive care patients after cardiac surgery: phase II of a product development study

Lewis Macken, Oliver J Flower, Simon Bird, Naomi Hammond, Elizabeth Yarad, Frances Bass, Charles Fisher, Paul Strasma and Simon Finfer

Blood glucose (BG) control is an essential part of caring for critically ill patients. BG variability, hyperglycaemia and hypoglycaemia are all associated with adverse clinical outcomes in critically ill patients.[1-4] Intermittent BG measurement may allow hyperglycaemia and hypoglycaemia to develop undetected (because between-measurement changes may be missed[5]), leading to significant BG variability. Continuous glucose monitoring (CGM) offers the potential to improve BG control and such monitoring has the potential to improve clinical outcomes. CGM also offers the advantage of reducing nursing workload and patient discomfort by requiring fewer finger-pricks.[5,6]

In comparison with interstitial and intravenous monitoring, continuous arterial monitoring has the possible technical advantages of a rapid response time and not being affected by intravenous infusion of sugar-containing solutions. Possible risks include intra-arterial thrombus and interference with normal arterial catheter function. In a previous study, we assessed the Glu-Cath Intravascular CGM System (GluMetrics) for up to 24 hours in patients who had undergone cardiac surgery.[7] We found the system to be safe and to have no adverse effects on clinical care. We showed that 80.8% of sensor measurements met reference accuracy standards; the mean absolute relative difference (MARD) between the sensor and reference measurements was 13.0%. Identified device deficiencies were subsequently corrected, and the system monitors underwent both hardware and software changes. After these modifications, we extended the monitoring duration to up to 48 hours to further examine the safety and performance of the GluCath system in patients in the intensive care unit after cardiac surgery.

ABSTRACT

Purpose: Variations in blood glucose (BG), hyperglycaemia and hypoglycaemia are associated with adverse clinical outcomes in intensive care unit patients. Continuous glucose monitoring (CGM) offers the potential to improve BG control, leading to improved patient outcomes. In our product development study, we determined the safety and performance of the GluCath Intravascular CGM System for up to 48 hours in 20 patients admitted to the ICU after cardiac surgery.

Methods: The GluCath system uses a quenched chemical fluorescence mechanism to optically measure glucose in blood. After undergoing elective cardiac surgery, 20 patients had a GluCath sensor inserted through a pre-existing radial artery (RA) catheter, and BG was monitored for up to 48 hours. Qualitative measures included effects on patient care, blood pressure monitoring, and ease of blood sampling through the arterial catheter. Safety assessment of the sensor involved ultrasound (US) monitoring for intra-arterial thrombi. Quantitative measures were the accuracy of the sensor in comparison with the reference analyser, and the proportion of paired BG measurements that were compliant with the ISO15197:2003 and CLSI POCT 12-A3 accuracy reference standards. BG was managed according to usual protocols.

Results: Twenty sensors were successfully deployed through pre-existing RA catheters and stayed in the RA of the 20 patients for between 6 and 48 hours, with a median time of 45.0 hours (interquartile range, 42.0–47.3 hours). Sixteen of the inserted sensors (80%) remained in situ for more than 40 hours. Three catheters were removed due to clinically significant sampling difficulty or waveform dampening. Two patients had US evidence of a thrombus; in neither patient was the sensor removed early, and there were no significant sequelae or adverse effects detected. For the 758 paired measurements available for performance analysis, reference BG values ranged between 5.3 mmol/L and 12.8 mmol/L. Of the 758 paired sensor measurements, 735 (97.0%) met the ISO15197:2003 criteria (within 20% of a reference measurement when BG is ⩾ 4.2 mmol/L [75 mg/dL]), and 648 (85.5%) met the CLSI POCT 12-A3 criteria (within 12.5% of a reference measurement when the BG level is ⩾ 5.6 mmol/L [100 mg/dL] and within 0.67 mmol/L [12 mg/dL] when the BG level is < 5.6 mmol/L [100 mg/dL]). The aggregate mean absolute relative difference (MARD) between the sensor and the reference BG was 6.4%, with individual sensor MARDs ranging from 3.6% to 12.4%.

Conclusions: The GluCath system, using quenched fluorescence sensing, was safe and showed acceptable accuracy when deployed for up to 48 hours in ICU patients after elective cardiac surgery.

Figure 1. GluCath sensor deployment within the radial artery via an arterial catheter
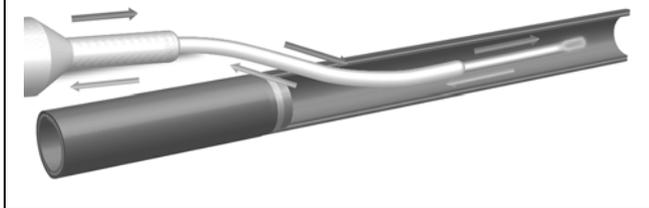
Methods

The purpose of this product development study was to determine the safety and performance of the GluCath Intravascular CGM System when used for up to 48 hours in patients admitted to the ICU after cardiac surgery. The outcome measures of this study were divided into qualitative and quantitative measures. Qualitative measures included assessment of any possible effects on patient care, blood pressure monitoring and blood sampling through the arterial catheter. Safety assessment involved monitoring for intra-arterial thrombi at the site of the catheter and sensor, and regular assessment of perfusion distal to the sensor. There were two quantitative outcome measures: the first was the assessment of the accuracy of the sensor measurements in comparison with measurements from the reference blood gas analyser (ABL800 Flex, Radiometer Medical ApS). The second quantitative outcome measure was the proportion of paired BG measurements that were compliant with the accuracy standards of the two reference standards for intermittent BG measurement machines (International Organization for Standardization [ISO] 15197:2003; and Clinical and Laboratory Standards Institute Point of Care Testing [CLSI POCT] 12-A3). The ISO 15197:2003 specifies that 95% of device results be within ±0.83 mmol/L (15 mg/dL) for reference glucose values < 4.2 mmol/L (75 mg/dL), and within 20% for reference glucose values ≥ 4.2 mmol/L (75 mg/dL). The CLSI POCT 12-A3 standard specifies that a measured BG value be within 12.5% of a reference meas-

Figure 2. A GluCath sensor in place within the radial artery, via an arterial catheter

Figure 3. Ultrasound of sensor in situ in radial artery, placed via an arterial catheter
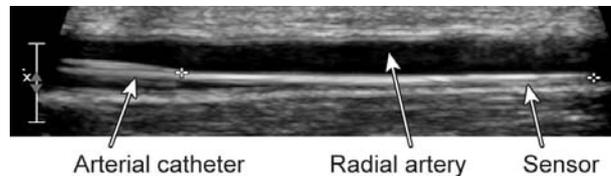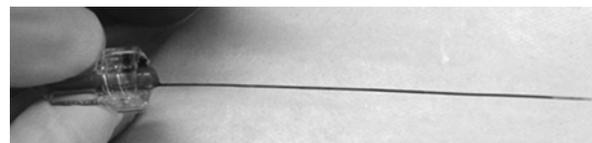

Figure 4. GluCath sensor after removal from arterial catheter

urement when the BG level is ≥ 5.6 mmol/L (100 mg/dL), and within 0.67 mmol/L (12 mg/dL) when the BG level is < 5.6 mmol/L (100 mg/dL).

The GluCath system

The GluCath system uses a quenched chemical fluorescence mechanism to optically measure glucose concentration in blood. Blue light is sent down an optical fibre to the distal tip of the sensor, and the sensing chemistry fluoresces green in proportion to the glucose concentration. The heparin-bonded arterial sensor is deployed through an arterial catheter, about 2 cm beyond the tip of the catheter (Figures 1 to 4). The GluCath system consists of the sensor, monitor and a sterile calibration solution. A more comprehensive description of the system has been published previously.[7]

The monitors used in our study had undergone revisions of both hardware and software, compared with the monitors used in previous studies. Most notably, the interval between measurements was reduced from 60 to 10 seconds, the optical signal measurement range was extended, and the user interface for recording blood sampling times and entering calibrations was modified. Also, a telescoping mechanism, which allowed the sensor to be inserted to varying depths, but which had caused technical problems, was removed.

Our study was conducted in the cardiothoracic ICU at the Royal North Shore Hospital, Sydney, Australia, and was approved by the Northern Sydney Local Health District Human Research Ethics Committee (protocol TP11-003REVC).

Inclusion criteria were age ≥ 18 years, planned ICU admission after elective cardiothoracic surgery, and agree-

ment to have a GluCath sensor inserted through a standard radial artery (RA) catheter. Exclusion criteria were an expected ICU stay of <24 hours, known pregnancy, or a known contraindication to heparin.

Patients participated in this study in three separate phases: prestudy screening and consent before the scheduled surgery day; the 48-hour period of BG monitoring after admission to the ICU after surgery; and a follow-up clinical examination within 48 hours of completing the glucose monitoring phase to exclude adverse effects of sensor insertion. Participation in the study concluded after the follow-up examination or resolution of any adverse event.

When the patient was deemed to be clinically stable after arrival in the ICU, ultrasound (US) examinations were performed on the RA in which the catheter had been inserted, and also on the ipsilateral ulnar artery. The GluCath sensor was then inserted through the radial arterial catheter, using aseptic technique, and connected to a normal saline flush bag containing heparin 1 U/mL. A repeat US was performed after sensor insertion. About 60 minutes after sensor insertion, the system was calibrated in vivo against the reference analyser. A calibration check was performed 1 hour later, and the system was recalibrated if the BG concentration was found to differ by 20% or more from the reference analyser. Sensors were calibrated again each morning during the BG monitoring period.

To avoid artefacts occuring during the drawing of blood samples and the subsequent flushing of the arterial catheter with saline, reference samples were paired with sensor readings recorded 1 minute before the blood draw. Arterial samples for reference BG measurements were obtained once every 60 minutes throughout the BG monitoring period. A maximum of 30 reference samples were collected per 24-hour period. The volume of blood withdrawn was minimised using a venous arterial blood management protection system (Edwards Lifesciences). BG was managed using the existing ICU protocol and standing orders for each patient. The BG values from the GluCath system were not displayed or used for patient care. The sensor was removed when the RA catheter was removed, or after 48 hours of continuous BG monitoring. A US examination was performed before sensor removal to determine the patency of the artery and the position of the sensor.

Statistical analysis

The degree of agreement between the GluCath system measurements and the corresponding measurement from the reference analyser was evaluated by the following composite difference statistics: the SD of the differences, the mean absolute difference (MAD), and the MARD. A modified Bland–Altman plot was also calculated.

Results

Twenty patients participated in the study between October 2012 and April 2013. Most patients were men (80%), with a mean age of 66 years (SD, 12.89 years). Coronary artery bypass surgery was the commonest procedure performed (70%) (Table 1).

All 20 arterial GluCath sensors were successfully deployed through pre-existing RA catheters, and stayed in the RAs of the 20 patients for between 6 and 48 hours, with a median time of 45.0 hours (interquartile range, 42.0–47.3 hours). Sixteen of the inserted sensors (80%) remained in situ for more than 40 hours (sensor 15 had an optical failure after 16 hours but remained in situ for 47 hours without problems, and four US examinations of this sensor showed no thrombus).

A total of 813 blood samples were collected from 20 patients, and 55 paired points were excluded: 23 samples (2.8%) were study-related exclusions (calibration samples and inadequate discarding of flush solution), and 32 (3.9%) were excluded due to GluCath-related device deficiencies. Consequently, 758 paired measurements were available for performance analysis (Figure 5).

Qualitative performance

There were 41 occurrences of difficult blood sampling recorded in 12 patients, and 42 instances of dampened pressure waveforms in 12 patients. Eleven patients experienced sampling difficulties and waveform dampening. Five per cent of all blood samples taken involved blood sampling difficulties, and 5.1% of all blood sampling times showed waveform dampening before the sample was taken. Three

Figure 5. Patient recruitment and data exclusions

20 patients recruited
20 sensors inserted

Total paired points excluded
(n = 55 [7%]):
- First sensor calibration for each patient (n = 20)
- Patient 15: optical failure of sensor after 16 hours, subsequent erroneous readings excluded (n = 28)
- Reference sample dilution due to inadequate discarding of flush solution in Patients 28, 30 and 32 (n = 3)
- Optical noise and artefacts in Patients 6 and 8 (n = 4)

Included in accuracy analysis:
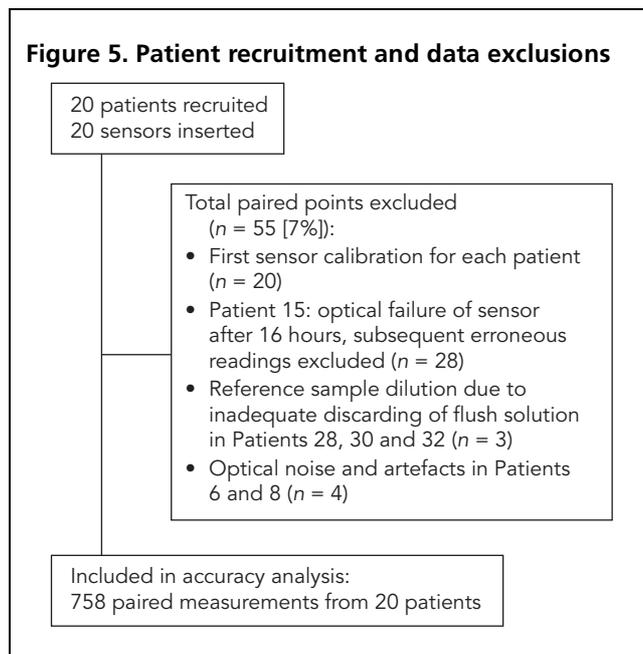758 paired measurements from 20 patients

Table 1. Patient characteristics and individual sensor performance

Patient	Sex	Operation	Age (years)	APACHE II score	Blood samples	Paired points	Mean glucose (mmol/L)	Mean bias (mmol/L)	SD (mmol/L)	MAD (mmol/L)	MARD (%)
1	M	CABG	80	12	35	34	8.6	0.3	0.5	0.5	5.8
2	M	CABG	59	7	52	51	9.0	−0.1	0.5	0.4	4.9
3	F	AVR	59	7	49	48	8.0	−0.4	0.7	0.7	8.5
4	M	CABG	53	11	43	42	7.9	−0.2	0.3	0.3	3.8
5	M	CABG/AVR/MVR	78	12	44	43	8.0	−0.1	0.4	0.3	3.7
6	M	CABG/AVR	78	15	47	43	8.6	−0.6	1.0	0.9	10.5
7	M	OPCABG	54	10	39	37	8.3	−0.3	0.6	0.6	6.8
8	M	CABG	58	9	41	39	8.2	−0.1	0.5	0.5	5.7
9	M	OPCABG	69	15	49	47	7.7	0.6	0.6	0.7	8.7
10	F	AVR	65	16	43	42	8.4	0.3	0.3	0.4	4.5
11	M	MVR	83	12	48	46	8.0	−0.4	0.8	0.7	7.6
12	M	OPCABG	65	13	21	20	10.0	1.1	0.8	1.1	12.4
13	M	AVR/MVR	32	9	45	44	7.5	−0.5	0.8	0.6	8.7
14	M	AVR	79	16	48	47	8.5	0.5	0.6	0.6	7.0
15	M	AVR	73	15	45	16	8.9	0.4	0.4	0.6	6.5
16	M	OPCABG	65	11	5	4	8.8	0.0	0.4	0.3	3.6
17	F	CABG	74	9	47	46	7.9	0.0	0.4	0.3	3.8
18	M	CABG	76	15	48	47	8.3	−0.1	0.5	0.4	4.7
19	M	CABG	48	10	20	19	9.2	0.2	0.4	0.4	4.9
20	F	CABG	72	9	44	43	8.0	0.0	0.6	0.5	5.9
Overall mean (SD)	−	−	66 (12.89)	11.65 (2.98)	813	758	8.3	0.0	0.7	0.5	6.4

APACHE = Acute Physiology and Chronic Health Evaluation. MAD = mean absolute difference. MARD = mean absolute relative difference. M = male. F = female. CABG = coronary artery bypass graft. AVR = aortic valve replacement. MVR = mitral valve replacement. OPCABG = off-pump coronary artery bypass graft.

catheters were removed due to clinically significant sampling difficulty or waveform dampening (Table 2). None of these three patients had evidence of a thrombus on US examination, and no clot or surface build-up was noted on the sensors after removal. With the exception of these three patients, all episodes of dampening or sampling difficulty were resolved by repositioning the hand or flushing the arterial catheter.

Eight catheters and sensors were removed deliberately before 48 hours, as the patients were ready for discharge from the ICU. In addition, the catheter and sensor in Patient 19 were unintentionally displaced after 21 hours of monitoring.

Table 2. Timing, reasons and patient details associated with unanticipated early removal of GluCath sensor

Patient no.	Sensor removal time and reason	Patient details
1	~ 37 h (RAC failure)	2 USs showed no thrombus; new RAC inserted without sensor
12	~ 20 h (RAC failure)	3 USs showed no thrombus. US before sensor removal showed RAC no longer in artery (sensor remained in situ), with associated new difficulties in aspirating blood and dampened waveform; RAC probably displaced after documented rolling of patient
16	~ 6 h (RAC failure)	3 USs showed no thrombus, but heavily calcified radial artery; new RAC inserted without sensor
19	Sensor and RAC unintentionally displaced at 21 h	US before sensor insertion showed 4 cm thrombus distal to tip of RAC. US 24 h after insertion showed new, non-occlusive, 2 cm thrombus over RAC; US unchanged 48 h after sensor insertion. No significant waveform or sampling problems while sensor in situ; no significant clinical sequelae

RAC = radial artery catheter. US = ultrasound.

Safety

Two of the 20 patients (Patients 14 and 19) had US evidence of thrombus. The sensor and catheter of Patient 14 remained in situ for 46 hours without significant sampling or waveform problems. In Patient 19, the catheter and sensor were unintentionally displaced after 21 hours of monitoring; before this there were no sampling or waveform problems. The US scans for Patient 14 showed a minor thrombus at the tip of the catheter 24 hours after insertion, resulting in a 25% arterial area reduction. However, the US performed after 48 hours (before sensor removal) showed no thrombus and the artery showed normal flow. The US scans for Patient 19 showed a thrombus within the RA before insertion of the sensor. Subsequent US scans showed an additional localised non-occlusive thrombus at the arterial cannula. These US findings were recorded as non-serious adverse events and monitored, but no treatment was required, nor were there clinical sequelae (Table 2).

Quantitative performance

A total of 758 blood samples were analysed from the 20 patients, with reference analyser concentrations of 5.3–12.8 mmol/L (95.4–230.4 mg/dL). The accuracy of the system was maintained across the different BG ranges (Table 3).

Of the 758 paired sensor measurements, 735 (97.0%) met the ISO 15197:2003 criteria and 648 (85.5%) met the CLSI POCT 12-A3 standard. Overall, aggregate results showed a MAD of 0.53 mmol/L and a MARD of 6.4%. Individual patient MARDs ranged from 3.6% to 12.4%, with 15 patients ⩽ 8%, four patients 8%–12%, one patient > 12%–16%, and no patients > 16% (Figure 6).

A modified Bland–Altman plot comparing the difference between the reference analyser and GluCath system on the y-axis, and the reference analyser alone on the x-axis, was constructed. The mean bias was < 0.1 mmol/L, with no correlation evident between the glucose difference and the reference glucose level. The upper limit of agreement was 1.4 mmol/L (24.8 mg/dL); the lower limit of agreement was −1.4 mmol/L (25.9 mg/dL) (Figure 7).

Discussion

This was a non-randomised, open-label, single-site, product development study in which we evaluated the performance of the GluCath CGM system for up to 48 hours. The system performed well against the current standards established for intermittent BG measurement. We found that

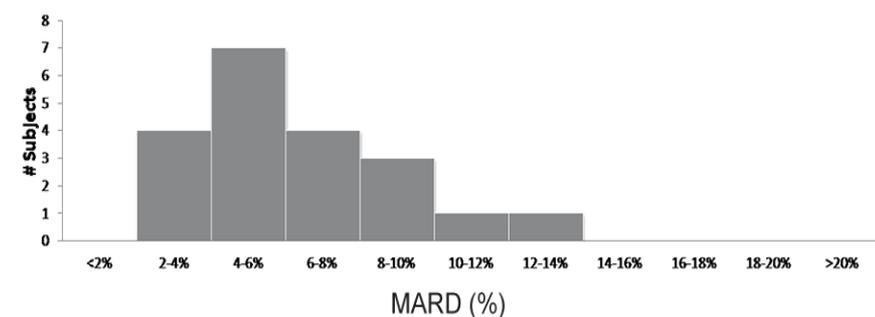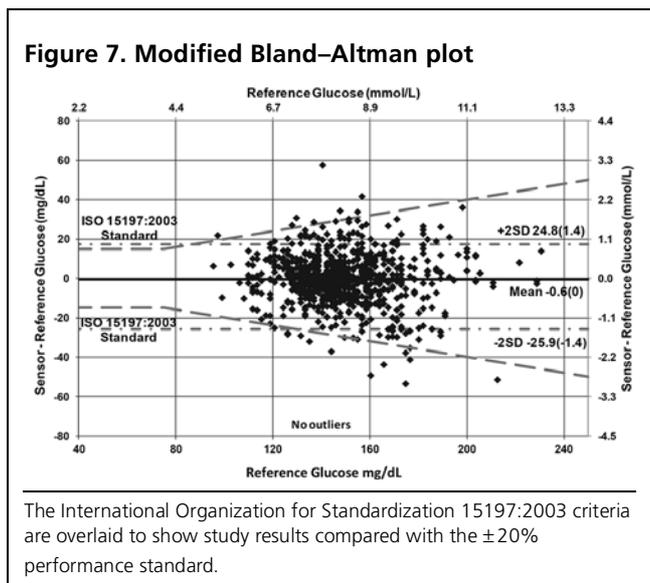**Figure 6. Frequency of mean absolute relative difference (MARD) for all patients**

Table 3. Sensor performance, overall and by BG range

Performance variable	Reference BG level (mmol/L)				
	< 4	4–6	6–10	> 10	All
Paired points	0	6	694	58	758
Mean bias (mmol/L)	na	0.11	−0.04	0.10	−0.03
SD (mmol/L)	na	0.05	0.65	0.23	0.72
MAD (mmol/L)	na	0.53	0.52	0.66	0.53
MARD (%)	na	9.5	6.4	6.2	6.4
CLSI POCT 12-A3 (%)*	na	83.3	85.6	84.5	85.5
ISO 15197:2003 (%)†	na	83.3	97.0	98.3	97.0

BG = blood glucose. na = not applicable. MAD = mean absolute difference. MARD = mean absolute relative difference. CLSI POCT = Clinical and Laboratory Standards Institute Point of Care Testing. ISO = International Organization for Standardization. * Specifies that a measured BG level be within 12.5% of a reference measurement when the BG level is ⩾ 5.6 mmol/L (100 mg/dL), and within 0.67 mmol/L (12 mg/dL) when the BG level is < 5.6 mmol/L (100 mg/dL). † Specifies that 95% of device results be within ± 0.83 mmol/L (15 mg/dL) for reference BG values < 4.2 mmol/L (75 mg/dL), and within 20% for reference BG values ⩾ 4.2 mmol/L (75 mg/dL).

Figure 7. Modified Bland–Altman plot

The International Organization for Standardization 15197:2003 criteria are overlaid to show study results compared with the ±20% performance standard.

97.0% of paired sensor measurements met ISO15197:2003 criteria and 85.5% met the CLSI POCT 12-A3 standard, with a MARD of 6.4%. This was an improvement on the results of our previous 24-hour study using an earlier version of the GluCath system, in which we found that 80.8% of paired measurements met ISO15197:2003 criteria and 59.3% met CLSI POCT 12-A3 criteria. We presume that this improvement reflects refinements in the software and hardware of the monitor, and the increase in frequency with which the system recorded the BG concentration. It is encouraging to note that the accuracy of the system has improved with a longer arterial dwell-time, as this 48-hour duration is more likely to reflect the clinical need for continuous BG monitoring in ICU practice for critically ill patients.

As no standards for point accuracy have been formalised for inpatient continuous BG monitors, it is reasonable to compare the accuracy of the GluCath system with criteria established for intermittent monitoring systems. A 2013 critical care consensus document suggested that 98% of readings should be within 12.5% of a reference standard, and the MARD should be < 14%.[5,8] Our results are close to these recommendations. However, rate-trend accuracy (the accuracy of measurement of rate of change in BG) is specific to CGM systems, and agreed criteria had not been established at the time of our study.

While the sensor's design enabled blood pressure monitoring and hourly arterial blood sampling, waveform dampening and difficulty withdrawing blood over the sensor were observed. Most of the sensors and catheters remained in situ for more than 40 hours. Three arterial catheters were removed because of difficulties with monitoring or sampling, but none of these catheters or sensors had an associated thrombus formation. We found that two patients had evidence of a thrombus on routine US despite a normally functioning arterial catheter, and no adverse consequences were detected during follow-up clinical examination. This is probably consistent with usual clinical practice when using arterial catheters. One review has reported an overall mean incidence of temporary arterial occlusion after RA catheterisations of 19.7%, and permanent occlusion occurring with a mean incidence of 0.09% of catheterisations.[9,10] Although a comparison of coagulation study results and arterial catheter patency duration was not part of the study plan, patency may have been maintained by the use of heparin flush solution and by the prescription of antiplatelet agents for many of these postcardiac surgery patients.

Our study had limitations, including that it was performed in a single centre, studying only patients undergoing elective cardiac surgery. Our patients had BG measurements of 4.8–13.5 mmol/L, thus precluding determination of the accuracy of the GluCath system for BG measurements outside this range. Furthermore, few reference blood samples were obtained outside the ICU target BG control range of 6–10 mmol/L, reflecting the fact that BG was managed in the usual way, using existing ICU protocols. Similarly, the accuracy of BG measurements outside the range of the GluCath device (BG measurements < 4 mmol/L and > 13.3 mmol/L are recorded as low or high, respectively) could not be evaluated. The performance of the GluCath system in the hypoglycaemic range was previously evaluated in outpatient studies.[11,12] The study plan did not assess for any change in accuracy of the sensor over time, but no degradation in performance was noted by the investigators. Further quantitative analysis would be needed to assess the performance of the sensor as a function of time since insertion and time since last calibration. Finally, the qualitative outcome measurement of the system involves subjective assessments and hence such conclusions have inherent limitations. Further research assessing the performance and safety of CGM is warranted, particularly in ICU patient populations other than postcardiac surgery patients.

Conclusions

Our product development study has shown the safety and potential utility of continuous intra-arterial BG monitoring using quenched fluorescence sensing. Future research should address whether CGM improves BG control and patient outcomes.

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Competing interests

Simon Finfer receives research funding and refund of study-related travel expenses paid to his employer from GluMetrics, equipment for research provided to his employer from Dipylon Medical (Eirus), travel expenses and consulting fees paid to his employer from Edwards Life Sciences, and equipment for research provided to his employer from Nova Biomedical (StatStrip). Oliver Flower, Simon Bird, Lewis Macken, Naomi Hammond, Elizabeth Yarrad, Frances Bass and Charles Fisher receive research funding paid to their employer from GluMetrics. Simon Bird received a refund of study-related travel expenses from GluMetrics. Paul Strasma was an employee of GluMetrics.

Author details

Lewis Macken, Senior Intensive Care Specialist[1]
Oliver J Flower, Intensive Care Specialist[1]
Simon Bird, Research Coordinator[1]
Naomi Hammond, Research Manager[1,2]
Elizabeth Yarad, Research Coordinator[1]
Frances Bass, Research Manager[1]
Charles Fisher, Vascular Surgeon[1]
Paul Strasma, Vice President, Marketing and Clinical Affairs[3]
Simon Finfer, Senior Intensive Care Specialist,[1] and Professor[2,4]

1 Royal North Shore Hospital, Sydney, NSW, Australia.

2 The George Institute for Global Health, Sydney, NSW, Australia.

3 GluMetrics, Irvine, Calif., United States.

4 University of Sydney, Sydney, NSW, Australia.

Correspondence: lewis.macken@health.nsw.gov.au

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