Prolonged concurrent hypotension and low bispectral index (‘double low’) are associated with mortality, serious complications, and prolonged hospitalization after cardiac surgery

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Abstract

Background: Low bispectral index (BIS) and low mean arterial pressure (MAP) are associated with worse outcomes after surgery. We tested the hypothesis that a combination of these risk factors, a ‘double low’, is associated with death and major complications after cardiac surgery.

Methods: We used data from 8239 cardiac surgical patients from two US hospitals. The primary outcomes were 30-day mortality and a composite of in-hospital mortality and morbidity. We examined whether patients who had a case-averaged double low, defined as time-weighted average BIS and MAP (calculated over an entire case) below the sample mean but not in the reference group, had increased risk of the primary outcomes compared with patients whose BIS and/or MAP were at or higher than the sample mean. We also examined whether a prolonged cumulative duration of a concurrent double low (simultaneous low MAP and BIS) increased the risk of the primary outcomes.

Results: Case-averaged double low was not associated with increased risk of 30-day mortality [odds ratio (OR) 1.73 [95% confidence interval (CI) 0.94–3.18] vs reference; P=0.01] or the composite of in-hospital mortality and morbidity [OR 1.47 (95% CI 0.98–2.20); P=0.01] after correction for multiple outcomes. A prolonged concurrent double low was associated with 30-day mortality [OR 1.06 (95% CI 1.01–1.11) per 10-min increase; P=0.001] and the composite of in-hospital mortality and morbidity [OR 1.04 (95% CI 1.01–1.07), P=0.004].

Conclusions: A prolonged concurrent double low, but not a case-averaged double low, was associated with higher morbidity and mortality after cardiac surgery.

Key words: arterial pressure; bispectral index monitor; cardiac surgical procedure; consciousness monitors; patient outcome assessment

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Patients who have cardiac surgery are at high risk for postoperative morbidity and mortality. Intraoperative anaesthetic and haemodynamic conditions might increase the risk for these complications. For example, deep anaesthesia, demonstrated by low bispectral index (BIS) scores, has been associated with increased risk for stroke, myocardial infarction, and mortality after cardiac surgery and non-cardiac surgery. Low intraoperative blood pressure is also associated with increased postoperative myocardial infarction, stroke, and mortality in cardiac surgical patients.

The ‘triple low’ condition, defined as the combination of deep anaesthesia (low BIS), hypotension [low mean arterial pressure (MAP)], and low minimum alveolar concentration of anaesthetic (MAC), is associated with increased morbidity and mortality after non-cardiac surgery. Two other investigations primarily in non-cardiac surgical patients provide conflicting results. A ‘double low’, defined as a combination of deep anaesthesia (low BIS) and low blood pressure (low MAP), was also associated with an increased risk of adverse outcome after non-cardiac surgery.

A recent study in non-cardiac surgical patients investigated whether an alert to the presence of a double low condition would trigger a clinical intervention to reduce double low duration and decrease 90-day mortality, but the alert was ineffective and the double low duration was unchanged. Nonetheless, the implications of the double low during cardiac surgery are unclear. We tested the primary hypothesis that case-averaged double low, defined as case-based time-weighted average BIS and MAP below the sample mean (and not in the reference group), and the cumulative duration of concurrent double low (simultaneous low MAP and BIS) was associated with increased 30-day mortality and a composite of in-hospital death and major complications after cardiac surgery.

Methods

Patient population and data collection

We included patients who had cardiac surgery at the Cleveland Clinic main campus in Cleveland, OH, USA between January 1, 2008 and October 18, 2013 and patients who had cardiac surgery at Mount Sinai Hospital, New York, NY, USA between January 1, 2008 and June 1, 2012. The study design, primary and secondary outcomes, and statistical analysis were defined a priori.

We included patients who had coronary artery bypass grafting, valve (aortic, mitral, and/or tricuspid) repair or replacement, combined coronary artery bypass graft and valve procedures, ascending aortic surgery, or left ventricular myomectomy with or without additional minor concomitant procedures (Maze procedure, closure of patent foramen ovale, etc.). We excluded patients who had heart or lung transplantation, ventricular assist device implantation, institution of extracorporeal membrane oxygenation, ventricular aneurysm repair, procedures requiring hypothermic circulatory arrest, or off-pump procedures. We also excluded patients who did not have BIS and/or MAP monitoring for at least 30 non-contiguous minutes during pre-cardiopulmonary bypass (CPB) (from the time of surgical incision to the start of initial CPB) and post-CPB (from the end of the final CPB to the end of surgery). Data from the Cleveland Clinic were obtained from the Cardiothoracic Anaesthesia Patient Registry using methods that have been reported previously. The requirement for written informed consent was waived by the institutional review board. The study protocol was reviewed and approved by both the Cleveland Clinic and Mount Sinai Institutional Review Boards.

At Cleveland Clinic, all data were collected daily, concurrent with patient care, on pre-printed forms, by experienced and specifically trained research personnel. Data were entered in an electronic database directly through tablet computers. Intraoperative data were obtained from the local Anaesthesia Information Management System (AIMS) [Anaesthesia Record Keeping System (ARKS), Cleveland Clinic, Cleveland, OH, USA], in which MAP was recorded at 1-min intervals for patients with an intra-arterial line and BIS was recorded at 1-min intervals.

Data were queried using SAS SQL and saved as SAS datasets (SAS Institute, Cary, NC, USA). Mortality data were derived from the US Social Security Death Index (SSDI).

Patient data from Mount Sinai were obtained from the Department of Anesthesiology Data Warehouse. Intraoperative data, including BIS and MAP at 15-sec intervals, were captured using the electronic record keeping system (CompuRecord, Philips, Andover, MA, USA). Vital signs in the Mount Sinai warehouse were kept in 15-sec increments. The median value for each minute for valid values of BIS and MAP was used. Validity was recorded by the local AIMS. MAPs <20 mm Hg and >200 mm Hg and BIS of zero were automatically invalidated.

Postoperative outcomes were retrieved from data collected by the Icahn School of Medicine at the Mount Sinai Department of Cardiovascular Surgery according to guidelines set by the New York State Department of Health (NYSDOH, State Cardiac Advisory Committee). The NYSDOH data registry represents a mandatory, verified, peer-reviewed data collection system that includes all cardiac surgery procedures in New York State. Medical chart review was performed to obtain additional information when necessary. Follow-up survival information to 30 days was obtained from the SSDI or by phone call to the patient’s referring cardiologist. Mortality data beyond 30 days were derived from the SSDI alone. Data were extracted from the perioperative data warehouse and local cardiac outcomes database using SQL queries.

Demographic, preoperative, and intraoperative variables from Cleveland Clinic sources were merged with variables with similar definitions from the Icahn School of Medicine at Mount Sinai. All patient identifiers were removed prior to statistical analysis. Patients with incomplete or unavailable data were excluded from the analysis.

Anaesthesia and surgery

Patients received standard anaesthesia care and monitoring, including arterial catheters for blood pressure monitoring and
either central venous or pulmonary artery catheters. Patients were typically premedicated with midazolam (1-4 mg), and anaesthesia was induced with etomidate (15-20 mg), sodium thiopental (3-5 mg kg\(^{-1}\)), or propofol (1-2 mg kg\(^{-1}\)). A total of 250-1000 \(\mu\)g of fentanyl was administered throughout surgery. Anaesthesia was usually maintained with isoflurane and a non-depolarizing muscle relaxant (rocuronium, vecuronium, cisatracurium, or pancuronium).

Surgery was performed through a full midline sternotomy or upper hemisternotomy. Routine strategies for heparinization and conduct of CPB were followed. At both Cleveland Clinic and Mount Sinai, heparin was administered to maintain an activated clotting time of >480 sec. At both centres, non-pulsatile CPB with membrane oxygenators were used. At Cleveland Clinic, normothermia was usually maintained, while at Mount Sinai, patient temperature was allowed to drift. Packed red blood cell transfusions were given at the discretion of the physicians, typically for haematocrit <21% on CPB or <24% after surgery. The target MAP during CPB was 60 mm Hg at Cleveland Clinic and 60-70 mm Hg with a target cardiac index of 2.4 litre min\(^{-1}\) m\(^{-2}\) at Mount Sinai. Inotropic and vasopressor support was with epinephrine, norepinephrine, and/or milrinone intravenous infusions given as necessary after separation from CPB for MAP <70-80 mm Hg and cardiac index <2.0 litre min\(^{-1}\) m\(^{-2}\). An intra-aortic balloon pump was inserted when low cardiac index persisted despite correction of hypovolaemia and inotropic support.

Endpoints

The two primary outcomes were all-cause 30-day mortality and a composite of major in-hospital outcomes that included all-cause in-hospital mortality and postoperative neurologic, renal, and infectious morbidities. Mortality was included in the major in-hospital outcomes composite to avoid survivorship bias (i.e., if a patient dies early, they are much less likely to have a non-death outcome than those who are discharged alive) and because of the potential relationship between exposure and mortality. The morbidity outcome variables for the composite of in-hospital outcomes had similar definitions in the Cleveland Clinic and Mount Sinai databases, and included neurologic morbidity defined as permanent new focal neurological deficit occurring either intra-operatively or within 24 h after surgery; renal morbidity, defined as the need for temporary or permanent renal replacement therapy of any type; and infectious morbidity, defined as sternal wound infection, sepsis (fever and positive blood cultures related to the procedure), or endocarditis (two or more positive blood cultures without other obvious source, demonstrated valvular vegetation, or acute valvular dysfunction caused by infection). Cardiac morbidity was excluded because the definitions differed at each institution and could not be merged.

Statistical analysis

In each analysis we considered all variables in Table 1 as potential confounding variables, including demographic information, medical history, and perioperative variables (Table 1; except for baseline haematocrit and creatinine, due to a large proportion of missing values) using backward variable selection (alpha-to-stay P-value=0.10). To assess the robustness of the final model, forward and stepwise variable selection techniques were used.

Case-averaged double low analysis

Intraoperative BIS and MAP values beginning at the time of surgical incision until the end of surgery were included in this analysis, with the exception of BIS and MAP between initiation and final separation of CPB, since MAP is typically maintained at >60 mm Hg by titration of CPB flow with administration of vasoactive agents. For each patient, time-weighted average (TWA) MAP and BIS were calculated using the trapezoidal rule to extrapolate between measurement points and account for differing lengths of time between measurements. TWA was thus calculated as the area under the curve (AUC) divided by the total time, that is, the time interval between the first and the last measurements.

Patients were then grouped into the following five BIS-MAP non-overlapping ‘exposure’ categories for analysis (Fig. 2 for examples and detail): reference (average BIS and MAP within 1 standard deviation (SD) of the sample mean), double low [both average BIS and MAP below the sample mean and not in the reference (i.e., one or both at least 1 SD below the mean)], low BIS/high MAP (average BIS below the mean, average MAP above the mean, and not in the reference), high BIS/low MAP (average BIS above the mean, average MAP below the mean, and not in the reference), and double high (both average MAP and BIS above the mean and not in the reference) (Fig. 2).

We assessed the relationship between each exposure group and the reference group on the primary outcome of 30-day mortality using multivariable logistic regression. The relationship between each exposure and the reference group on the composite of in-hospital mortality/morbidity was assessed using a multivariate (i.e., multiple outcomes per patient) generalized estimating equation (GEE) model with exchangeable covariance structure among the individual components of the composite. The model assumes a common effect across components, thus a single ‘common’ treatment effect odds ratio (OR) across the components was estimated.\(^{41}\) A separate GEE model was used to assess the heterogeneity of the BIS-MAP exposure across the components of the in-hospital mortality/morbidity composite by testing the BIS-MAP component interaction.

In addition, we conducted a sensitivity analysis in which we categorized patients into 9 BIS-MAP non-overlapping ‘exposures’ based on three levels for each BIS and MAP (high: >1 SD above the mean; normal: within 1 SD of the mean; low: >1 SD below the mean). Specifically, the double low group included those with both average BIS and MAP >1 SD below their respective means (Fig. 2, area A). The same statistical methods were used as above.

Secondary case-averaged analysis

Using the five exposure groups, we assessed relationships between BIS-MAP exposure and length of hospital stay after surgery by multivariable Cox proportional hazards regression, in which patients dying before discharge were considered having no event (i.e., no discharge alive) and were censored at the time of the longest length of stay of any patient.

Concurrent double low analysis

A was defined as the simultaneous occurrence of low BIS and low MAP, where BIS and MAP were below the mean of the time-weighted average for all patients (i.e., <43 and <75 mm Hg, respectively) and BIS and/or MAP were at least 1 SD below the time-weighted average for all patients (i.e., <37 and/or <69 mm Hg, respectively).
### Table 1 Demographic characteristics, medical history, baseline laboratory, and perioperative variables by case-averaged BIS-MAP category (N = 8239). Statistics are mean ± SD, median [Q1, Q3], or percentage, as appropriate. *Both time-weighted average BIS and MAP within 1 SD of the mean (i.e. 43.4 ± 6.6 and 74.7 ± 5.5 mm Hg, respectively). aPearson’s chi-squared test, unless specified, banalysis of variance, and cKruskal–Wallis analysis of variance by ranks. †11% of patients had missing values.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Reference* (N = 4225)</th>
<th>Double low (N = 916)</th>
<th>Low BIS/ high MAP (N = 1090)</th>
<th>High BIS/ low MAP (N = 1100)</th>
<th>Double high (N = 908)</th>
<th>P-value*</th>
</tr>
</thead>
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#### Demographics
- Age (years) 64 (14) 61 (16) 60 (13) 62 (16) 61 (14) < 0.001
- Male (%) 67 57 62 65 73 < 0.001
- Caucasian (%) 84 82 82 83 80 0.07

#### Medical history/condition
- Hypertension (%) 64 57 60 63 64 0.001
- Congestive heart failure (%) 24 32 20 30 20 < 0.001
- Myocardial infarction (%) 21 18 20 19 17 0.11
- Cardiogenic shock (%) 1 3 1 1 1 < 0.001
- Normal: EF > 60% 37 39 40 38 42 0.04
- Mild: EF = 50–59% 34 30 32 35 31
- Mildly moderate: EF = 46–49% 1 1 1 0 1
- Moderate: EF = 41–45% 5 5 4 6 4
- Moderate severe: EF = 35–40% 7 8 6 5 6
- Severe: EF < 35% 16 17 18 15 16
- Left main coronary stenosis (>70%) (%) 3 2 3 3 4 0.21
- Moderate or severe mitral insufficiency (%) 44 48 37 49 42 < 0.001
- Atrial fibrillation/flutter (%) 22 27 18 24 16 < 0.001
- Chronic obstructive pulmonary disease (%) 10 13 10 10 9 0.07
- Pulmonary hypertension (%) 16 22 12 19 13 < 0.001
- Diabetes mellitus (%) 14 13 14 13 11 0.07
- Peripheral vascular disease (%) 3 2 3 3 4 < 0.001
- Stroke (%) 10 10 9 8 6 0.02
- Dialysis (%) 2 6 2 4 2 < 0.001

#### Preoperative laboratory values
- Haematocrit% (%) 40 (5) 37 (6) 40 (5) 39 (6) 41 (5) < 0.001
- Creatinine* (mg/dL) 1.0 [0.8, 1.2] 1.0 [0.8, 1.3] 1.0 [0.8, 1.2] 1.0 [0.8, 1.1] 1.0 [0.8, 1.1] 0.02

#### Surgical variables
- Previous cardiac surgery (%) 19 23 13 23 12 < 0.001
- Emergency procedure (%) 1 5 2 2 2 < 0.001

#### Type of procedure (%)
- Coronary artery bypass graft 39 30 34 37 38 < 0.001
- Internal mammary artery graft 30 18 26 24 29 < 0.001
- Saphenous vein graft 35 26 29 33 34 < 0.001
- Aortic valve repair/replacement 34 41 33 38 29 < 0.001
- Mitral valve replacement 9 16 7 14 6 < 0.001
- Mitral valve repair 34 33 31 33 34 0.41
- Tricuspid valve repair/replacement 18 26 14 20 12 < 0.001
- Aortic surgery 11 12 12 10 6 < 0.001
- Myomectomy 5 4 8 5 9 < 0.001
- Maze procedure 11 11 10 11 9 0.52

#### Intraoperative variables
- Total cardiopulmonary bypass time (min) 105 [79, 137] 118 [86, 162] 97 [73, 129] 114 [84, 152] 97 [72, 126] < 0.001
- Total aortic cross-clamp time (min) 79 [56, 104] 88 [61, 122] 71 [50, 95] 83 [60, 115] 72 [52, 96] < 0.001
- Requirement for inotropic agents (%) 11 20 10 18 9 < 0.001
- Red blood cell transfusion (units) 0 [0, 0] 0 [0, 2] 0 [0, 0] 0 [0, 1] 0 [0, 0] < 0.001
- Fresh frozen plasma transfusion (units) 0 [0, 0] 0 [0, 0] 0 [0, 0] 0 [0, 0] 0 [0, 0] < 0.001
- Platelet transfusion (units) 0 [0, 0] 0 [0, 1] 0 [0, 0] 0 [0, 0] 0 [0, 0] < 0.001
We assessed the association between cumulative concurrent double low time in minutes (concurrent double low condition was not necessarily contiguous) and the outcomes described above using logistic regression, GEE models, and Cox proportional hazards regression. We further assessed the interaction between clinical site (Cleveland Clinic or Mount Sinai) and both BIS-MAP categories and the duration of the double low condition on each of the primary outcomes.

**Sensitivity analysis for 30-day mortality**

The 30-day mortality data were derived from the US SSDI. In 2011, the Social Security Administration redacted records derived from state sources. This resulted in a decrease in overall reported deaths. Therefore, we conducted a sensitivity analysis where we included only patients who had surgery prior to 2011.

**Significance criterion**

The overall significance level was 0.025 for each of the two primary outcomes (30-day mortality and in-hospital morbidity/mortality) for both case-averaged double low and concurrent double low analyses, and the significance criterion within outcome was further adjusted for pairwise comparisons (P<0.00625, i.e. 0.025/4, Bonferroni correction) for comparing four BIS-MAP exposure groups vs the reference. Likewise, for the secondary outcome, the significance criterion was 0.0125 (i.e. 0.05/4) for comparing four BIS-MAP exposure groups vs the reference. All the reported CIs were appropriately adjusted by Bonferroni correction. Throughout we refer to them as 95% confidence intervals to indicate that the significance level was controlled at 5% within both primary and secondary hypotheses (although separate adjustment was used for assessing both time-based and case-based analyses as primary, as these are highly correlated). The significance criterion for assessing interactions was P<0.10.

**Power analysis**

With 4225 patients in the reference group and 916 patients in the double low group, we had ~90% power at the 0.025 significance level to detect an OR ≥2.25 for having 30-day mortality.
using a reference incidence of 1.6%. With 5.4% of patients in the reference group expected to have at least one of the major events in our in-hospital morbidity/mortality vector endpoint, we had ~90% power at the 0.025 significance level to detect an OR between the double low and reference groups of ≥1.65. The actual power we had for the in-hospital morbidity/mortality vector endpoint in our study was likely similar to the above, since analysing an outcome as a set of individual endpoints rather than a traditional ‘collapsed composite’ endpoint (any vs none) is at least as powerful under most conditions. 14,15

SAS software version 9.3 for Windows (SAS Institute, Cary, NC, USA) and R software version 2.12.1 for Windows (R Foundation for Statistical Computing, Vienna, Austria) were used for all statistical analyses.

Results

The final cohort of the study included 5875 cardiac surgery patients from the Cleveland Clinic Foundation (CCF) and 2364 from Mount Sinai (Fig. 1). In the overall study population of 8239 cardiac surgical patients, intraoperative BIS was a mean of 43 (SD 7) [CCF: 44 (SD 7); Mount Sinai: 43 (SD 6)] and the MAP was a mean of 75 (SD 6) mm Hg [CCF: 75 (SD 5); Mount Sinai: 75 (SD 6)] averaged over the pre- and post-CPB periods. The period of CPB was managed in a standard fashion at both institutions by adjusting CPB flows to maintain a MAP >60 mm Hg.

Case-averaged double low analysis

Patients were categorized into five non-overlapping BIS-MAP exposure categories as previously defined (Fig. 2). Demographics, baseline, and perioperative characteristics are summarized by the five BIS-MAP categories in Table 1. The observed incidences of 30-day mortality and of the composite in-hospital mortality/morbidity outcome are shown in Table 2.

After adjusting for multiple comparisons, there was no difference in 30-day mortality between the BIS-MAP exposure groups compared with the reference group as listed in Table 2 and shown in Figure 3. The lack of an association between BIS-MAP exposure groups with 30-day mortality outcome was consistent across the two enrolling sites (BIS-MAP x site interaction P=0.69). Sensitivity analysis using patients who had surgery prior to 2011 did not affect these results (Table 2).

Patients experiencing a double high had lower odds of the composite in-hospital mortality and morbidity outcome compared with the reference group. No other BIS-MAP exposure group was significantly different on the composite mortality/morbidity compared with the reference group (Table 2 and Fig. 3). The final model selected via the backward variable selection technique was robust; very similar sets of covariables were selected via the forward and stepwise variable selection techniques (Appendix A). For informational purposes, we report the ORs for the double low group vs each of the other four BIS-MAP categories in Appendix B.

Fig 2 Plot of time-weighted average bispectral index (BIS) vs time-weighted average mean arterial pressure (MAP) during pre- and post-cardiopulmonary bypass periods for the case-averaged double low analysis. Patients were grouped into the following five BIS-MAP “exposure” categories for analysis: reference group (both BIS and MAP within 1 SD of the mean, red region); double low [both BIS and MAP below the mean and not in the reference region (i.e. both below the mean and one or both at least 1 SD below the mean); blue region]; low BIS/high MAP (BIS below the mean, MAP above the mean, and not in reference region, green region); high BIS/low MAP (BIS above the mean, MAP below the mean, and not in the reference region, black region); and double high (both BIS and MAP above the mean, and not in the reference region, purple region). Each data point represents the case-based results for one patient. Note that by definition of being “not in the reference region” the double low region includes three kinds of patients, those that were >1 SD below the mean for both BIS and MAP (area A), those that were ≥1 SD below the mean for MAP but within the mean and mean – 1 SD for BIS (area B), and those that were within the mean – 1 SD for MAP but below the mean – 1 SD for BIS (area C).
likely to have 30-day mortality as compared with the reference patients in the double low group, and 8 (IQR 5–13) days for reference patients. The estimated median days from surgery to hospital discharge derived from the Kaplan–Meier curves was 7 (IQR 5–10) days for patients in the double high group, and 77 (1.8%) reference patients died during hospitalization. Hospital discharges for those patients were considered as non-events and censored at the longest observed length of stay. The estimated median days from surgery to hospital discharge derived from the Kaplan–Meier curves were 10 (interquartile range (IQR) 6–18) days for patients in the double low group, 7 (IQR 5–11) days for patients in the low BIS/high MAP group, 8 (IQR 6–15) days for patients in the high BIS/low MAP group, 7 (IQR 5–10) days for patients in the double high group, and 8 (IQR 5–13) days for reference patients. Patients in the double low group were an estimated 23% less likely [hazard ratio (HR) 0.77 (95% CI 0.70–0.85), P<0.001] to be discharged from the hospital compared with the reference patients at any given time point postoperatively after adjusting for covariables (Table 3).

 Concurrent double low analysis
Cumulative duration of simultaneous occurrence of low BIS and low MAP was associated with increased odds of having 30-day mortality and the composite endpoint of in-hospital mortality and morbidity. A 10-min increase in the simultaneous double low duration was associated with an estimated 6% higher odds of 30-day mortality (OR 1.06 (95% CI 1.01–1.11), P<0.001), consistent with the sensitivity analysis using patients who had surgery prior to 2011 (OR 1.05 (95% CI 1.01–1.10), P<0.01). A longer duration of simultaneous double low was associated with an increased odds of the composite of in-hospital mortality/morbidity [OR 1.04 (95% CI 1.01–1.07) per 10-min increase, P<0.004]. The observed median total time that a patient experienced a simultaneous double low condition was 25 (IQR 10–47) min.

Secondarily, we found that a longer duration of the concurrent double low was associated with a longer hospital stay. The estimated median days from surgery to hospital discharge derived from the Kaplan–Meier curves was 7 (IQR 5–11) days for patients with a double low duration of <10 min (first quartile) and 7 (IQR 5–12), 8 (IQR 5–13), and 9 (IQR 6–16) days for patients in the second, third, and fourth quartiles (double low durations...
of 10–25, 25–47, and ≥47 min, respectively). For a 10-min increase in the concurrent double low duration, patients were 3% less likely to be discharged from the hospital at any given time point postoperatively after adjusting for covariables [HR 0.97 (95% CI 0.97–0.98), P<0.001; Table 3].

### Discussion

We demonstrate that a prolonged cumulative concurrent double low is associated with increased odds of 30-day mortality and composite morbidity/mortality. The case-averaged double low condition, however, was not significantly associated with adverse postoperative outcomes. We believe that the concurrent double low, the simultaneous occurrence of low BIS and MAP, is more relevant to clinical practice because it is immediately apparent to the anaesthesia team and can trigger a clinical intervention. This contrasts with a case-averaged double low, which is calculated after conclusion of the surgical case and is thus not immediately apparent. However, both case-averaged double low and prolonged cumulative duration of the concurrent double low were significant predictors of prolonged hospitalization in patients having cardiac surgery (Table 3). Our overall results are similar to our previously published work that demonstrated that mortality, and especially hospital length of stay, progressively increased with prolonged cumulative duration of the triple low.5

After correction for multiple outcomes, we did not find an association between case-averaged double low, calculated by the time-weighted average of BIS and MAP over the entire case, and 30-day mortality or in-hospital morbidity and mortality after cardiac surgery. Aside from the obvious possibility that there simply was no association, two factors might have contributed to the lack of significance. The first was that our analysis conservatively adjusted for multiple comparisons and used an a priori significance criterion of 0.00625 (a Bonferroni correction for two primary outcomes with four comparisons). The second is that the current cardiac surgical analysis included only a third of the number of the patients that were included in our previous non-cardiac triple low analysis. That is, our current analysis might simply be underpowered. Nonetheless, there was an impressive ‘dose–response’ relationship with progressively worsened mortality and composite outcome from double high through the two single highs to double low (Fig. 3). This pattern mimics our previously reported triple low results in non-cardiac surgery patients.

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### Table 3 Secondary results. Associations between time to discharge from hospital and case-averaged BIS-MAP category and total concurrent double low time (N=8239). *Both time-weighted average BIS and MAP within 1 SD of the mean (i.e. 43.4±6.6 and 74.7±5.5 mm Hg, respectively). Hazard ratios <1 indicate less likely to be discharged early and thus prolonged length of stay compared with the reference group. *All the factors listed in Table 1 were considered for model inclusion via the backward selection procedure using alpha-to-stay at 0.10. Confidence intervals were Bonferroni adjusted. The overall significance level was 0.025 for comparing four BIS-MAP exposure groups versus the reference group. We refer to them as 95% confidence intervals to indicate that the overall significance level was controlled at 5%. Hazard ratios from a multivariable analysis of 30-day mortality were calculated by the time-weighted average of BIS and MAP over the entire case, and 30-day mortality or in-hospital morbidity and mortality after cardiac surgery. Aside from the obvious possibility that there simply was no association, two factors might have contributed to the lack of significance. The first was that our analysis conservatively adjusted for multiple comparisons and used an a priori significance criterion of 0.00625 (a Bonferroni correction for two primary outcomes with four comparisons). The second is that the current cardiac surgical analysis included only about a third of the number of the patients that were included in our previous non-cardiac triple low analysis. That is, our current analysis might simply be underpowered. Nonetheless, there was an impressive ‘dose–response’ relationship with progressively worsened mortality and composite outcome from double high through the two single highs to double low (Fig. 3). This pattern mimics our previously reported triple low results in non-cardiac surgery patients.

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### Fig 3 Odds ratio of 30-day mortality and “common effect” odds ratio across the individual in-hospital outcomes were plotted for each of the four case-averaged BIS-MAP exposure groups in the reference group. All the factors listed in Table 1 were considered for model inclusion via the backward selection procedure using alpha-to-stay at 0.10. Confidence intervals were Bonferroni adjusted. The overall significance level was 0.025 for comparing four BIS-MAP exposure groups versus the reference group. We refer to them as 95% confidence intervals to indicate that the overall significance level was controlled at 5%.
A limitation of our study was the approach to defining the BIS-MAP categories. Outside of the reference group, a patient could only be grouped into low or high BIS or MAP (split at the mean); there was no normal. This may be one of the reasons for the lack of a significant association between the double low and the reference. It would be more precise to categorize patients into nine BIS-MAP categories based on three levels for both BIS and MAP (i.e. high: >1 SD above the mean, low: >1 SD below the mean, and normal: within 1 SD of the mean). However, there were not enough patients in each of the nine categories to ensure a sufficiently powered analysis; for example, only 2% (163 of 8299) of patients had both BIS and MAP >1 SD below the mean and would thus be categorized into the double low group. In a sensitivity analysis, the difference between the double low group only including these 163 patients and the reference patients was indeed large (8.6% vs 1.6% for 30-day mortality and 14.1% vs. 5.4% for the composite of in-hospital mortality/morbidity).

Hypotension is a known predictor of worse postoperative outcomes. Gold and colleagues reported a greater than two-fold increase in cardiac and neurologic complications in patients who were randomized to a low MAP of 50–60 mm Hg vs a higher MAP of 80–100 mm Hg during CPB. Others have reported that an intraoperative MAP <60 mm Hg predicted postoperative mortality after cardiac surgery. Gottesman and colleagues observed that cardiac surgical patients with an intraoperative decrease in MAP of at least 10 mm Hg were four times more likely to have bilateral watershed cortical infarcts than other infarct patterns. In our study, average MAP in the double low group was ~69 mm Hg, which is not considered significant hypotension in conventional clinical practice and is higher than that associated with worse outcomes in previously reported work. The combination of low MAP and low BIS (double low) might therefore be a stronger predictor of worse outcomes than MAP alone.

Our results are similar to those in non-cardiac surgery patients, but not identical. Aside from the obvious distinction between triple and double lows, divergence might have resulted from varying anaesthetic techniques in cardiac and non-cardiac surgery patients, since use of high-dose opioids, muscle relaxants, and hypothermia during cardiac surgery can decrease BIS. Invasive haemodynamic monitoring is routine during cardiac surgery and allows earlier diagnosis and treatment of hypotension and thus frequent use of inotropic and vasopressor infusions might have reduced the duration of hypotension; the range of MAP was much smaller in our current cardiac patients (range 69–81 mm Hg) than in our previous non-cardiac analysis (78–96 mm Hg), suggesting tighter haemodynamic control; cardiac surgery patients presumably had more life-threatening illness and, of course, had extremely invasive surgery; and absence of MAC data precluded distinguishing patients who were deeply anaesthetized (low BIS and high MAC) from those who were sensitive to anaesthesia (low BIS and low MAC).

It is worth considering why low MAC and low BIS might separately or together be associated with death, complications, and prolonged hospitalization. There is considerable patient-to-patient variability in the MAP needed for adequate brain perfusion during cardiac surgery, and some patients require considerably greater than average pressures, which cannot be predicted simply by using standard definitions for hypotension. Inadequate cerebral perfusion in an individual patient might manifest as low BIS. To the extent that brain perfusion is inadequate and consequently lowers BIS, the condition should be amenable to interventions that increase blood pressure. Low BIS values might also identify patients who, because of underlying illness, are especially sensitive to anaesthesia.

While our investigation demonstrated that a prolonged cumulative concurrent double low condition during cardiac surgery is associated with increased morbidity and mortality, whether treatment of this condition improves outcomes is unclear. McCormick and colleagues attempted to answer this important question in non-cardiac surgical patients by using an alert to notify the anaesthesia providers of a double low condition. The intraoperative alert, however, did not provide a clinically meaningful reduction in the duration of double low. It remains possible that use of a more effective alerts or perhaps educating anaesthesia providers to aggressively treat the double low condition will improve postoperative outcomes after non-cardiac surgery. Whether patients having cardiac surgery benefit from reduction of the double low condition requires further investigation.

We included a large number of cardiac surgical patients from two high-volume centres. Similar results at each suggest that our findings are reasonably generalizable. Because cardiac surgical complications are prospectively collected, numerous potential confounding factors were accurately recorded and included as adjustments in our analysis. Nonetheless, the most serious limitation for this type of observational association is the potential for unobserved confounding.

In summary, prolonged cumulative concurrent double low was associated with higher morbidity and mortality after cardiac surgery. Case-average double low, defined as low time-weighted average BIS and MAP, was not associated with worse outcomes. Whether intervening to reduce the duration of simultaneous double low improves outcomes can only be determined by a randomized trial.

Authors’ contributions
A.M.: study design, interpretation, manuscript preparation, and revision.
P.J.M.: study design, data procurement, interpretation, and manuscript preparation.
D.I.S.: study design, analysis, and manuscript preparation.
D.L.R.: study design, interpretation, and manuscript preparation.
J.Y.: data procurement, statistical analysis, manuscript preparation, and revision.
E.J.M.: interpretation of data, statistical analysis, and manuscript preparation.
M.A.L.: data procurement, interpretation, and manuscript preparation.
J.G.C.: data procurement, interpretation, and manuscript preparation.
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All authors were involved in final approval of the manuscript.

Supplementary material
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