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Dopexamine Has No Additional Benefit in High-Risk Patients Receiving Goal-Directed Fluid Therapy Undergoing Major Abdominal Surgery

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BACKGROUND: Dopexamine has been shown to reduce both mortality and morbidity in major surgery when it is used as part of a protocol to increase oxygen delivery in the perioperative period. A European multicenter study has examined the use of dopexamine in patients undergoing major abdominal surgery, showing a trend toward improved survival and reduced complications in high-risk patients when receiving low-dose dopexamine (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$). A reduced oxygen uptake at the anaerobic threshold (AT) has been shown to confer a significant risk of mortality in patients undergoing major abdominal surgery and allows objective identification of a high-risk operative group. In this study, we assessed the effects of low-dose dopexamine on morbidity after major abdominal surgery in patients who were at increased risk by virtue of a reduced AT.

METHODS: Patients undergoing elective major colorectal or urological surgery who had an AT of <11 $mL \cdot kg^{-1} \cdot min^{-1}$ or an AT of 11 to 14 $mL \cdot kg^{-1} \cdot min^{-1}$ with a history of ischemic heart disease were recruited. Before surgery, a radial arterial cannula was placed and attached to an Edwards Lifesciences FloTrac/Vigileo™ system for measuring cardiac output. Patients were given a 250-mL bolus of Voluven® (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride) until the stroke volume no longer increased by 10%, then received either dopexamine (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or saline 0.9% for 24 hours. During surgery, fluid boluses of Voluven were given if the stroke volume variation was $>10\%$. No crystalloid was given during surgery. A standardized postoperative fluid regime with Hartmann solution was prescribed at 1.5 $mL \cdot kg^{-1} \cdot h^{-1}$ for 24 hours. The primary outcome measure was postoperative morbidity measured by the Postoperative Morbidity Survey.

RESULTS: One hundred twenty-four patients were recruited over a 23-month period. The incidence of morbidity as measured by the Postoperative Morbidity Survey on day 5 was 55% in the control group versus 47% in the dopexamine group ($P = 0.14$). There was no significant reduction in morbidity on any measured postoperative day. Complication rates, mortality, and hospital length of stay were similar between the 2 groups; however, administration of dopexamine was associated with earlier return of tolerating an enteral diet.

CONCLUSION: With the effective use of goal-directed fluid therapy in elective surgical patients, the routine use of dopexamine does not confer an additional clinical benefit. (Anesth Analg 2011;112:130–8)

Dopexamine has been shown to reduce both mortality and morbidity in major surgery when it is used as part of a protocol to increase oxygen delivery (DO_2) in the perioperative period.[1,2] Further interest has been generated from these trials, because the use of dopexamine was associated with reductions in postoperative complications, mortality, and an associated decrease in hospital length of stay (LOS) that was specific to its use, yet not explained by the increase of DO_2.

A European multicenter study has examined the use of dopexamine in patients undergoing major abdominal surgery.[3] The majority of patients were deemed high risk based on the nature of their surgery alone, and no survival advantage was seen; however, those who underwent emergency surgery, or had >1 high-risk criterion showed a tendency toward improved outcomes when receiving low-dose dopexamine (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$).

Many criteria have been used to attempt to define a high-risk population and one of the most widely used is the Shoemaker criteria,[4] later simplified by Boyd et al.[1] These criteria contain a considerable subjective element, and many are either not applicable to an elective population, or occur intraoperatively and are therefore not useful as preoperative identifiers of a high-risk population, in which subsequent intervention may improve outcome. Additional scoring systems have been developed to specifically predict cardiac risk, but these predict only the incidence of cardiac events and not perioperative mortality or complications as a whole.[5]

Functional capacity has been shown to be a good predictor of outcome after both abdominal and thoracic

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surgery.[6–10] Cardiopulmonary exercise testing (CPET) provides an objective measurement of cardiorespiratory fitness, and hence functional capacity. A reduced oxygen uptake at the anaerobic threshold (AT) has been shown to confer a significant risk of mortality in patients undergoing major abdominal surgery. If AT is <11 mL · kg^{-1} · min^{-1} or between 11 and 14 mL · kg^{-1} · min^{-1} with ischemic heart disease (IHD), patients are at an increased risk of complications after surgery.[11] A recent large cohort study has shown that in patients undergoing nonvascular major abdominal surgery, a reduced AT is associated with a 6-fold relative risk of hospital mortality.[12] CPET can therefore identify a higher-risk surgical population in whom any potential benefits of dopexamine may be seen.

A meta-regression analysis of data from all the available dopexamine trials in major abdominal surgery has shown a statistically significant improvement both in mortality and hospital LOS for low-dose dopexamine use (≤ 1 μg · kg^{-1} · min^{-1})[13]; however, a meta-analysis of the same data showed no overall benefit,[14] leaving an uncertainty as to whether dopexamine confers a survival advantage or reduction in perioperative complications. The reason for this difference in outcomes in what is essentially the same data lies within the chosen methods of analysis. Gopal et al.[14] chose to express the data as more conservative relative risk, whereas Pearse et al.,[13] using a meta-regression analysis, were confined to using odds ratio.[15] Odds ratio can potentially exaggerate treatment effects when the event rate is high. Caution is required when interpreting results when the odds ratio is <0.5, and the event rate is $>10\%$ as in the dopexamine trials.[16] This may be why such dichotomous conclusions were reached. Therefore, the aim of this study was to clarify the role of dopexamine by assessing whether a low fixed dose reduces morbidity after major abdominal surgery in patients who are at increased risk by virtue of a reduced AT.

METHODS

The protocol was approved by an NHS research ethics committee and sponsored by York Teaching Hospitals NHS Foundation Trust. Clinical trial authorization was obtained from the Medicines and Health Regulation Authority. The trial was placed on the ISRCTN register before patient recruitment (ISRCTN33549216, accepted August 8, 2006). A member of the research team screened patients for eligibility, and informed written consent was obtained from patients before surgery.

Inclusion and Exclusion Criteria

All patients older than 50 years scheduled for major abdominal surgery in this institution underwent CPET as part of their standard preoperative assessment. From this cohort, we recruited patients scheduled to undergo elective major colorectal or urological surgery who after CPET had an AT of <11 mL · kg^{-1} · min^{-1}, or an AT of 11 to 14 mL · kg^{-1} · min^{-1} with a significant history of IHD, or electrocardiogram changes during CPET. A significant history of IHD was defined as a history of angina, myocardial infarction, positive exercise test findings, prior documentation of cardiac ischemia on nuclear or echocardiographic stress testing, or coronary artery angiographic evidence of vessel stenosis $>50\%$ of the vessel diameter. Electrocardiogram changes deemed significant during CPET were defined as ST depression of >2 mm from baseline in 2 adjacent leads, ventricular tachycardia, or new onset atrial fibrillation.

We excluded patients younger than 55 years without comorbidities; those with hypertrophic cardiomyopathy, significant aortic stenosis, a low preoperative platelet count ($<150 \times 10^9$/L), pheochromocytoma, or monoamine oxidase inhibitor use within the last 14 days; or those deemed unable to give informed consent.

Significant comorbidities were recorded and included a history of IHD as defined above: prior coronary artery bypass graft surgery, atrial fibrillation, hypertension requiring treatment with ≥ 1 antihypertensive medication, peripheral vascular disease (intermittent claudication known to be caused by atherosclerotic disease, a history of lower extremity arterial bypass surgery, or angiographic evidence demonstrating $>70\%$ stenosis), diabetes requiring current treatment either by insulin or oral hypoglycemics, renal insufficiency with a preoperative creatinine of >150 μmol · L^{-1}, cerebrovascular disease (history and/or radiological evidence of cerebral infarction or hemorrhage, or a clinical history of transient ischemic attack), and chronic obstructive pulmonary disease (clinical history and documented forced expiratory volume in 1 second/forced vital capacity $<70\%$).

Protocol

On arrival in the theater suite, IV cannulae were inserted into forearm veins for administration of fluid and study drug. An arterial cannula was placed into a radial artery for continuous arterial blood pressure measurement, and connected to an Edwards Lifesciences FloTrac/Vigileo™ system (Edwards Lifesciences, Irvine, CA; software version 1.10) for measuring stroke volume and preload responsiveness via stroke volume variation (SVV).

Baseline measures of hemodynamic variables were recorded before induction of anesthesia (heart rate, stroke volume, arterial blood pressure), and an arterial blood sample was taken for analysis. Patients were then given a 250-mL bolus of colloid (Voluven®; Fresenius Kabi, Bad Homburg, Germany). If the stroke volume increased 10% or more above baseline, then the bolus was repeated until no further increases in stroke volume were seen.

Anesthesia was then induced with propofol (1–2 mg · kg^{-1}) and fentanyl (1–2 μg · kg^{-1}) and was maintained with isoflurane in oxygen-enriched air. Analgesia was provided by epidural infusion. The intraoperative management of the epidural was at the discretion of the clinician. Epidural analgesia was continued postoperatively with a standardized infusion (0.1% bupivacaine with fentanyl 2 μg · mL^{-1} at 6–10 mL · h^{-1}) for pain relief. Patients who refused epidural analgesia, or in whom it was contraindicated or deemed inappropriate, received an infusion of remifentanil intraoperatively and a morphine sulfate patient-controlled analgesia system postoperatively.

Patients were randomized to receive dopexamine hydrochloride 1 mg · mL^{-1} (Dopacard; Elan Pharma, Dublin, Ireland) or dextrose 5% (control) at an equivalent infusion rate. The hospital pharmacy department prepared the blinded drugs, using a block of 4 treatment allocation. The

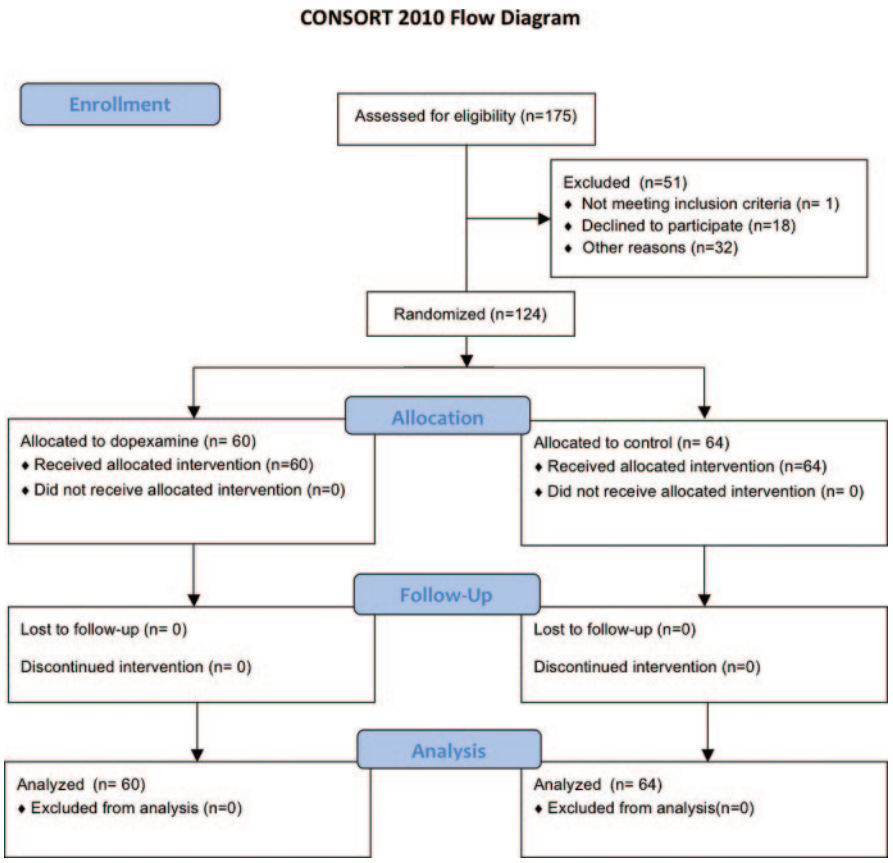

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) trial flow diagram.

study drug was commenced after induction of anesthesia at a rate of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and maintained for 24 hours after the start of surgery.

Patients' lungs were ventilated with a tidal volume of ≥ 7 mL $\cdot kg^{-1}$, and further fluid boluses of Voluven 250 mL were given if the SVV measured by the anesthesiologist was >10%. No maintenance crystalloid was given intraoperatively. A target arterial blood pressure was not set and was left to the individual clinicians' discretion. Packed red cells were given to maintain a hemoglobin of >8 g $\cdot dL^{-1}$. Samples of arterial blood were taken at the start of surgery, hourly thereafter, and at the end of surgery along with hemodynamic measurements so that DO_2 could be calculated. The study drug was maintained at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ unless an increase in heart rate of >30% of the baseline was seen with no other identifiable cause, in which case the infusion was reduced to 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Postoperatively patients were returned to the postanesthetic care unit. Measurements of DO_2 were taken on arrival and again 1 hour later. A standardized fluid regime was commenced in which patients received 1.5 mL $\cdot kg^{-1} \cdot h^{-1}$ Hartmann solution for 24 hours, and Voluven 250 mL if urine output was <0.5 mL $\cdot kg^{-1} \cdot h^{-1}$ for 2 consecutive hours. If the patient was to return to the critical care unit, then the arterial cannula remained in situ; otherwise, it was removed before the patient returned to the ward. The patient's surgical and anesthetic team determined all other aspects of the patient's care.

A member of the research team followed up patients on postoperative days 1, 3, 5, 8, 10, 12, and 15. The primary outcome measure was the incidence of postoperative morbidity (defined as the occurrence of any 1 of the criteria in any of the 9 domains) on day 5 as measured by the Postoperative Morbidity Survey (POMS) described by Bennett-Guerrero et al.[17] Secondary outcome measures including hospital LOS, POSSUM (physiological and operative severity score for the enumeration of mortality and morbidity),[18] and P-POSSUM (a modified version of the original scoring system using the same parameters, but different weightings)[19] predicted standardized morbidity and mortality ratios, perioperative hemodynamic variables, fluid balance, and recovery parameters. Complications are defined in the Appendix.

Sample Size and Statistical Analysis

A sample size of 62 patients per group was calculated on the basis of previous work in which the incidence of POMS on day 5 was 0.35 in the dopexamine group compared with 0.6 in the control group. Sixty-two patients per group gives a statistical power of 88.1% to detect a difference with an α error level of 5%.

Continuous data were analyzed using the Student t test and within-group comparison of cardiovascular measurements analyzed with the paired t test. Nonparametric data were analyzed using the Mann-Whitney U test. Incidences were calculated using the χ^2 test. A P value <0.05 was considered significant. Where appropriate, 95% confidence intervals were calculated.

Statistical analysis was performed with GraphPad Prism (GraphPad Prism version 5.0b for Mac OS X; GraphPad Software, San Diego, CA).

Table 1. Patient Details

	Control (n = 64)	Dopexamine (n = 60)
Age (median, range)	76 (57–89)	74 (49–89)
Sex (male/female)	38/26	30/30
Weight (kg)	76.2	78.6
Anaerobic threshold ($mL \cdot kg^{-1} \cdot min^{-1}$) (SD)	9.5 (1.35)	9.6 (1.25)
Epidural analgesia (%)	94	90
Comorbidity		
Ischemic heart disease (previous myocardial infarction or angina)	21 (33%)	18 (30%)
Previous coronary artery surgery	6 (14%)	3 (5%)
Atrial fibrillation	8 (13%)	7 (12%)
Hypertension	47 (73%)	35 (58%)
Peripheral vascular disease	2 (3%)	2 (3%)
Diabetes	12 (19%)	9 (15%)
Renal insufficiency	13 (20%)	9 (15%)
Cerebrovascular disease	5 (8%)	6 (10%)
Chronic obstructive pulmonary disease	9 (14%)	4 (7%)
Medication		
β-Blockers	22 (34%)	21 (35%)
Aspirin	28 (43%)	27 (45%)
Statin	26 (41%)	27 (45%)
Angiotensin enzyme converting inhibitor	18 (28%)	20 (33%)
POSSUM data (median, interquartile range)		
Physiology score	23 (19–30)	22 (18–26)
Operative Score	12 (11–16)	11 (11–16)
Total score	35 (32–42)	36 (31–40)
POSSUM-predicted in-hospital morbidity (%)	54 (39–79)	54 (35–70)
POSSUM-predicted in-hospital mortality (%)	12 (6–17)	12 (7–26)
P-POSSUM–predicted in-hospital mortality (%)	5 (2–13)	5 (2–10)

POSSUM = physiological and operative severity score for the enumeration of mortality and morbidity.

Table 2. Surgical Details

	Control (n = 64)	Dopexamine (n = 60)
Surgical procedure		
Anterior resection	12	19
Abdominal perineal resection	6	3
Cystectomy	2	2
Hartmann procedure	3	0
Other	3	2
Colonic resection	24	26
Radical nephrectomy	14	8
Intraoperative data (median, interquartile range)		
Blood loss (mL)	393 (200–700)*	155 (106–189)
Operation duration (min)	155 (106–189)	130 (96–180)

* $P < 0.001$ compared with dopexamine group.

RESULTS

One hundred twenty-four patients were recruited over a 23-month period from January 2007 to December 2009 (Fig. 1). No differences were seen between the groups in terms of AT, preoperative morbidities, and medications (Table 1). Table 2 shows operations performed. There was a significant increase in intraoperative blood loss in the control group (determined from weighed swabs and suction volume minus wash used).

Perioperative hemodynamic variables are shown in Figure 2. There were no differences in baseline values between the 2 groups. There were no differences in stroke volume (Fig. 2A) or mean arterial blood pressure (Fig. 2B) between the 2 groups throughout the monitored perioperative period. The dopexamine group showed a larger reduction in stroke volume from baseline compared with the control group postoperatively (Table 3). A significantly higher DO_2 was seen in the dopexamine group at 2 and 3 hours intraoperatively, but this did not extend into the recovery period (Fig. 2C).

The dopexamine group showed a significantly more rapid heart rate compared with the control group from 1 hour intraoperatively onward (Fig. 2D), and showed a significant increase from baseline values (Table 3). There were no significant changes in DO_2, cardiac index, base excess, lactate, or hemoglobin between the 2 groups (Table 3).

Preoperative and intraoperative fluid administration was similar between the groups; however, postoperatively, the dopexamine group required less colloid boluses, and 24-hour positive fluid balance was reduced compared with the control group (Table 4).

The incidence of morbidity as measured by POMS on day 5 was 55% in the control group compared with 47% in the dopexamine group ($P = 0.14$; Fig. 3). There was no significant reduction in morbidity on any measured postoperative day. Complication rates, mortality, and hospital LOS were similar between the 2 groups. Administration of dopexamine was associated with earlier return to tolerating an enteral diet; however, other measures of gut function (time to passing flatus and defecation) showed no difference (Table 5).

A reduction in the observed standardized morbidity ratio as calculated by the POSSUM score was seen in both groups; however, this was only significant in those who received dopexamine. There was a significant overlap in the 95% confidence intervals between the groups and therefore no clear benefit effect can be postulated.

DISCUSSION

Low-dose dopexamine does not significantly reduce all-cause morbidity measured by POMS after major abdominal surgery in high-risk patients who have had intraoperative fluid therapy guided by SVV.

The main strengths of this study are that it was a double-blind placebo controlled trial. Fluid therapy was also standardized across both groups. This is an important factor because optimization of circulating volume improves outcome,[1,11,20,21] and therefore the only variable within the trial was the administration of dopexamine.

Patient selection was concentrated on a high-risk group as measured by CPET rather than based on age or the nature of surgery. This is the group that had shown a tendency toward improved outcomes in the study by Takala et al.[3] In addition, a previous study by our group evaluated the perioperative effects of dopexamine,[22] and although using a lower dose than Takala et al. used, had shown a tendency toward improvement in outcome. However, randomization failed in this study, leading to a 3-fold

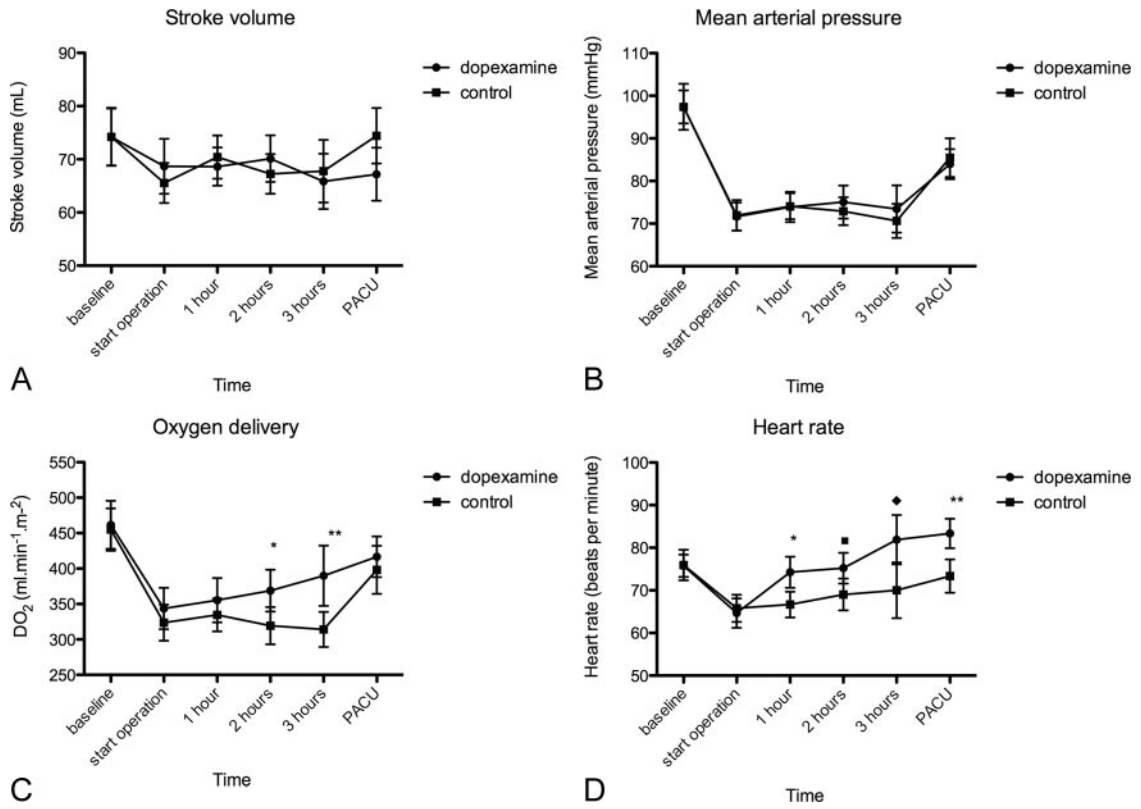

Figure 2. Perioperative hemodynamic variables. A, stroke volume. B, mean arterial blood pressure. C, oxygen delivery. D, heart rate. *$P = 0.003$, **$P < 0.001$, ■$P = 0.02$, ◆$P = 0.01$. PACU = postanesthesia care unit.

Table 3. Perioperative Hemodynamic Measurements

	Baseline values		Recovery values (arrival in PACU)		Change from baseline	
	Control ($n = 64$)	Dopexamine ($n = 60$)	Control ($n = 64$)	Dopexamine ($n = 60$)	Control ($n = 64$)	Dopexamine ($n = 60$)
Heart rate (bpm)	76 (72–80)	76 (73–78)	73 (69–77)	83 (80–87)*†	−5 (−10 to 0)	8 (5–10)‡
Stroke volume (mL)	74 (69–80)	74 (69–80)	74 (69–80)	67 (62–72)	1 (−3 to 5)	−6 (−11 to −2)§
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	3.0 (2.8–3.1)	2.9 (2.8–3.1)	2.9 (2.8–3.1)	3.0 (2.9–3.2)	−0.0 (−0.17 to 0.13)	0.17 (0–0.34)
Oxygen delivery ($mL \cdot min^{-1} \cdot m^{-2}$)	455 (425–485)	462 (428–496)	398 (364–432)‖	416 (389–445)¶	−56 (−87 to −24)	−35 (−63 to −8)
Base excess	0.61 (0.07–1.15)	0.47 (−0.09 to 1.04)	−2.54 (−3.17 to −1.90)#	−2.39 (−2.94 to −1.84)#	−3.1 (−3.6 to −2.6)	−2.9 (−3.3 to −2.4)
Lactate	0.96 (0.85–1.01)	0.89 (0.8–0.98)	0.94 (0.81–1.07)	0.99 (0.82–1.17)	0 (−0.1 to 0.1)	0 (−0.2 to 0.3)
Hemoglobin ($g \cdot dL^{-1}$)	13.5 (10.0–17.1)	12.3 (11.8–12.7)	10.2 (9.7–10.6)	10.4 (10.0–10.8)#	−1.5 (−2.1 to −0.9)	−1.9 (−2.2 to −1.5)

Values are mean (95% confidence intervals).
PACU = postoperative anesthesia care unit.
* $P < 0.001$ compared with control.
† $P < 0.0001$ compared with baseline.
‡ $P < 0.001$ compared with control.
§ $P = 0.0263$ compared with control.
‖ $P = 0.01$ compared with baseline.
¶ $P = 0.04$ compared with baseline.
# $P < 0.001$ compared with baseline.

increase in patients with IHD in the dopexamine group, which in our experience is associated with an increased relative risk of mortality.[12]

A reduced AT has been shown to be a significant risk factor for patients undergoing major surgery in terms of increased mortality, particularly in those who have no other cardiac risk factors and have a relative risk of >10.[12] Functional capacity as measured by CPET variables other than AT has also been shown to be of prognostic benefit in other surgical groups.[6,7] We would expect that the exclusion of low-risk patients would have increased the signal strength of any benefit from dopexamine, if truly present.

We have previously investigated fixed-dose dopexamine at 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in goal-directed fluid therapy, because the majority of patients in our previous trial achieved their targeted DO_2 at this dose in combination with fluid loading.[2] We chose to investigate the higher dose

Table 4. Perioperative Fluid Administration and Balance

	Control (n = 64)	Dopexamine (n = 60)
Preoperative fluid (median, interquartile range)		
Colloid (mL)	250 (250–500)	250 (250–250)
Intraoperative fluid		
Colloid (mL) (median, interquartile range)	1250 (750–1750)	1000 (750–1500)
Packed red cells (mL) (mean, 95% CI)	261 (157–364)	251 (123–380)
Postoperative (1st 24 h)		
Crystalloid (mL) (mean, 95% CI)	2301 (2154–2447)	2346 (2207–2485)
Colloid (mL) (median, interquartile range)	500 (0–1000)	250 (0–500)*
Urine output (mL) (mean, 95% CI)	1396 (1256–1536)	1637 (1433–1841)
Fluid balance (mL) (mean, 95% CI)	2541 (2290–2792)	2048 (1734–2363)*

CI = confidence interval.
* P = 0.02.

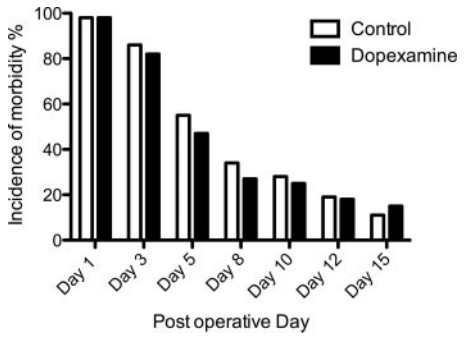

Figure 3. Incidence of postoperative morbidity as measured by the Postoperative Morbidity Survey.

of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in this series of patients, because this was the dose received by high-risk patients who showed a tendency toward improved outcomes in the European multicenter trial.[3] Both this study and the study by Stone et al.[22] have shown a statistically significant increase in heart rate from baseline in patients receiving dopexamine. Data from the other trials do not report this variable; however, it is an increase of <10 beats per minute in both this study and in the previous work by Stone et al. Should we therefore exercise a degree of caution when using dopexamine in patients with IHD? Whereas there was a statistically nonsignificant increase in the number of patients with cardiovascular complications in this study, other studies have shown a reduction in cardiovascular morbidity in those who received dopexamine.[2,22,23] Therefore, low-dose dopexamine seems not to confer an increased cardiovascular risk.

Previous studies using dopexamine have shown dose-dependent increases in cardiac output and stroke volume,[24] and in the study by Takala et al., DO_2 was increased in the protocol groups that received dopexamine. There was no difference in cardiac output between the 2 groups as seen in the trial by Stone et al., and hence one could speculate no difference in DO_2. However, compared with baseline, both groups increased their cardiac index with volume therapy. None of these finding are replicated in this study. The reason for this is unclear but may represent differences in the technology used to measure cardiac output.

The measurement of cardiac output by the FloTrac/Vigileo system has shown acceptable bias in validation studies; however, the percentage error has often been greater than the clinically acceptable 30%, limiting its use as a primary measure of cardiac output.[25–28] A software update (v1.10) to the system as used in this trial has shown in limited studies a clinically acceptable percentage error.[29] Although cardiac output measured by the FloTrac system was not used as a targeted goal in this study, the hemodynamic data are presented in the results and should be interpreted with this in mind. However, the changes in cardiac output seem to be tracked by the FloTrac system with good correlation.[25,26]

Table 5. In-Hospital Patient Complications

	Control (n = 64)	Dopexamine (n = 60)
Infection		
Clostridium difficile infection	2	0
Deep infection	3	1
Chest infection	5	5
Pyrexia of unknown origin	0	2
Urinary infection	6	5
Wound infection	7	2
Respiratory		
Chest infection	5	5
Pleural effusion	2	3
Respiratory failure	2	2
Cardiovascular		
Atrial fibrillation	5	8
Cardiac failure	2	3
Cerebrovascular accident	1	1
Hypotension	1	1
Myocardial infarction	1	1
TIA	0	1
Abdominal		
Anastomotic leak	2	2
Wound dehiscence	2	3
Other		
Acute renal failure	6	2
Total complications	51	46
Patients with ≥1 complication (%)	26 (41)	18 (30)
Death in hospital (%)	3 (4.7)	3 (5)
POSSUM-derived standardized ratios for in-hospital morbidity		
Predicted morbidity %	54	54
Actual morbidity %	41	30
Standardized morbidity ratio	0.76 (0.51–1.1)	0.55 (0.34–0.87)
Hospital length of stay (median, interquartile range)	9 (7–15)	8 (6–14)
Recovery variables (median, interquartile range)		
Time to diet (d)	3 (2–4)	2 (1–3)*
Time to flatus (d)	2 (2–4)	2 (1–3)
Time to defecation (d)	4 (3–5)	4 (3–5)

TIA = transient ischemic attack; POSSUM = physiological and operative severity score for the enumeration of mortality and morbidity.
* P = 0.01.

We chose to use the FloTrac/Vigileo system over other more validated forms of cardiac output monitoring such as the esophageal Doppler for 2 main reasons. First, it allowed measurement of hemodynamics and fluid optimization in awake patients, and timing of fluid therapy may well be key in outcome benefits.[21] Second, cardiac output measurements in patients with epidural anesthesia, which the majority of our patients had, have been shown to be overestimated by esophageal Doppler.[30]

The targeted volume optimization variable SVV is validated in terms of improving clinical outcome, and protocols incorporating SVV have reduced hospital LOS and complication rates.[31,32] SVV has been shown to be an accurate predictor of fluid responsiveness.[25,33]

One possible benefit seen from dopexamine in this study was an improvement in gut function, with a reduced time to tolerating oral diet despite any difference in hemodynamic variables. The clinical significance of this finding, however, is debatable, because other markers of gut recovery such as time to passing flatus and defecation were not altered by dopexamine infusion, and the overall hospital LOS was not improved. The gut is unusually sensitive to reduced tissue perfusion because of its higher critical oxygen requirement, and the villi are particularly at risk.[34,35] In low cardiac output states, the splanchnic circulation is very sensitive to change, and the splanchnic blood flow decreases out of proportion to the overall decrease in cardiac output. Dopexamine has been shown to reduce gastrointestinal permeability,[36] increase splanchnic blood flow without an increase in systemic cardiac output,[37] and reduce α-mediated arterial small bowel vasoconstriction.[38] Clinically, Poeze et al.[39] showed that gastric intramucosal pH (pHi) used as a marker of splanchnic flow predicted outcome from major abdominal surgery. In the group that had a poor pHi, dopexamine infusion improved this measurement and significantly reduced the incidence of multiorgan failure without a systemic increase in DO_2 and oxygen consumption. However, fluid optimization of stroke volume alone can also improve gastric pHi,[40] and therefore dopexamine may not provide any additional benefit over this strategy.

The observed POSSUM-derived standardized morbidity ratios were reduced in both groups; however, this was only significant in the dopexamine-treated patients. The clinical significance of this is unclear because the confidence intervals for the 2 groups significantly overlap, and therefore the true means may be identical. If there is reduced morbidity from receiving dopexamine, it is likely to be of minor importance only, and is not reflected in the POMS, or hospital LOS, and is therefore of dubious clinical significance.

Mortality is one of the most common primary outcome measures used in clinical trials; however, low elective surgical mortality even in high-risk groups limits its use because of the numbers of patients who would need to be enrolled in a trial to show a statistical benefit from an intervention. Morbidity is a more useful measure of outcome because of the significantly higher event rate, but reporting of adverse events varies in its quality. Hospital LOS is often used as a surrogate marker of postoperative morbidity; however, it can be influenced by other factors such as social care and therefore may not be a true measure of the quality of recovery after major surgery.[41,42]

The POMS prospectively assesses short-term morbidity after major surgery, and has been shown to identify the majority of patients with prolonged hospitalization independent of procedure.[43] The POMS is a 9-domain survey containing 18 items that confirms the presence or absence of various items. It has been shown to accurately identify 98% of patients with prolonged hospitalization independent of surgical procedure type, and is starting to be used in outcome and effectiveness research.[22,44] Although this approach offers a consistent approach to composite outcome, the survey has had limited validation.

In conclusion, with the effective use of goal-directed fluid therapy in elective surgical patients, the routine use of dopexamine does not confer an additional clinical benefit.

AUTHOR CONTRIBUTIONS

SJD and RJTW helped with study design, data analysis, conduct of study, and manuscript preparation; DY helped with data analysis, conduct of study, and manuscript preparation.

APPENDIX: DEFINITIONS OF COMPLICATIONS

1. Anastomotic leak: discharge of bowel contents via the drain, wound, or abnormal orifice.
2. Acute renal failure: an increase in serum creatine of >30% from the preoperative value.
3. Atrial fibrillation: new onset atrial fibrillation on electrocardiogram (ECG).
4. *Clostridium difficile* infection: difficile toxin detected in feces.
5. Cardiac failure: clinical (i.e., any of the following signs: increased jugular venous pressure, respiratory rates, crepitations, or presence of S3) and radiographic evidence (e.g., vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema).
6. Chest infection: production of purulent sputum with positive bacteriological culture, with or without chest radiographic changes or pyrexia, or consolidation seen on chest radiograph.
7. Cerebrovascular accident: a new focal neurologic deficit thought to be vascular in origin with signs and symptoms lasting >24 hours.
8. Hypotension: a systolic blood pressure <90 mm Hg requiring fluid resuscitation.
9. Deep infection: the presence of an intraabdominal collection confirmed clinically or radiologically.
10. Ischemic bowel: nonviable bowel as a result of vascular disruption.
11. Myocardial infarction: detection of increase of troponin T above the 99th percentile of the upper reference limit with at least 1 of the following: symptoms of ischemia, ECG changes indicative of new ischemia (new left bundle branch block or new ST-T changes), and development of pathological Q waves in the ECG.
12. Pleural effusion: effusion in the pleural space requiring drainage.
13. Pyrexia of unknown origin: any temperature >37°C for >24 hours occurring after the original pyrexia from surgery had resolved for which no obvious cause can be found.

14. Respiratory failure: respiratory difficulty requiring either intermittent positive pressure ventilation or noninvasive positive pressure ventilation.
15. Septicemia: positive blood culture.
16. Transient ischemic attack: a new focal neurologic deficit thought to be vascular in origin with signs and symptoms lasting <24 hours.
17. Urinary infection: the presence of $>10^5$ bacteria/mL with the presence of white cells in the urine in previously clear urine.
18. Wound dehiscence: superficial or deep wound breakdown requiring resuturing.
19. Wound infection: wound cellulitis or the discharge of purulent exudate.

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