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BJA

British Journal of Anaesthesia

Editor-in-Chief: Charles S. Reilly

SOUTH AFRICAN EXCERPTS EDITION

Volume 12 Number 1 2012

- **Is it time to implement preoperative platelet function testing before invasive procedures?**
- **Comparison of thromboelastometry (ROTEM®) with standard plasmatic coagulation testing in paediatric surgery**
- **Validity of the 6 min walk test in prediction of the anaerobic threshold before major non-cardiac surgery**

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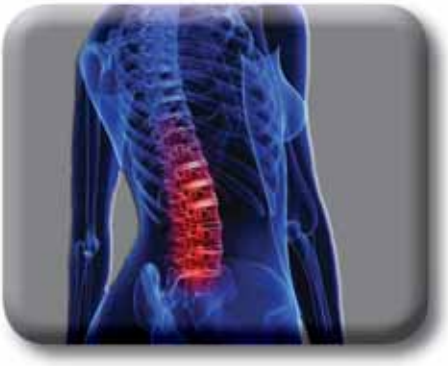

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References: 1. Dhillon S. Tramadol/paracetamol fixed-dose combination. *Clin Drug Investig* 2010;30(10):711-738. **2.** Jurnista® package insert. October 2011. **3.** Gupta S, Sathyan G. Providing constant analgesia with OROS® hydromorphone. *Journal of Pain and Symptom Management* 2007;33(25):S19-S24. **4.** Hale M, Tudor IC, Khanna S *et al.* Efficacy and tolerability of once-daily OROS® hydromorphone and twice-daily extended-release oxycodone in patients with chronic, moderate to severe osteoarthritis pain: results of a 6-week, randomized, open-label, non-inferiority analysis. *Clinical Therapeutic* 2007;29(5):874-888. **5.** Turgeon J, Gröning R, Sathyan G, *et al.* The pharmacokinetics of a long-acting OROS hydromorphone formulation. *Expert Opinion Drug Delivery* 2010;7(1):137-144. **6.** Drover DR, Angst MS, Valle M, *et al.* Input characteristics and bioavailability after administration of immediate and a new extended-release formulation of hydromorphone in healthy volunteers. *Anesthesiology* 2002; 97(4):827-836. **7.** Durogesic® package insert. April 2011. **8.** Kornick CA, Santiago-Palma J, Moryl N, *et al.* Benefit-risk assessment of transdermal fentanyl for the treatment of chronic pain. *Drug Safety* 2003;26(13):951-973.

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Comment

As this is the first edition of the ***British Journal of Anaesthesia (South African excerpts edition)*** would like to wish all of our readers a happy and prosperous 2012.

The selections featured in this month's Journal come from the December 2011 and January 2012 BJA editions and cover a wide range of areas of interest. The editorial by Tanaka1 asks the question as to whether or not the time has arrived for routine platelet monitoring in all patients receiving antiplatelet drugs. The basis for this editorial is an article that we could not feature for lack of space, but one that deals elegantly with the issues of possible mechanisms for assessment of platelet function and the residual effects of drugs such as clopidogrel following withdrawal.[2] Two further articles in the November BJA also address the issue of antiplatelet drugs. In the first the risk-benefit relationship between withholding clopidogrel and the risk of acute coronary syndromes in older patients with hip fractures is examined.[3] The second paper examines the risk of perioperative bleeding and acute coronary events related to continuation or withholding of aspirin.[4] Although we could not feature either of these articles, they are both strongly recommended as all anaesthetists in regular clinical practice certain to be faced with this dilemma on an ongoing basis in the future.

There is an excellent review article on thoracic epidurals which is compulsory reading for all examination candidates but also useful for all current clinical practitioners who use this technique in the perioperative period. An intriguing article on the use of large-volume nasal canulae, with high flow pharyngeal airway pressures also makes interesting reading as a simple way of avoiding postoperative reductions in lung volumes in patients undergoing cardiac surgery, although there is no reason why this should not apply to other patients as well.

To conclude, there are two paediatric anaesthesia articles, one featuring the value of fluid responsiveness as a measure of appropriate volume therapy in children. This remains a fairly contentious area and it is important that more articles of this nature come forward. The value of point of care coagulation testing is emphasised in the final selection for this month and this article provides further evidence that point of care coagulation testing can be more sensitive and specific than more traditional laboratory measures of coagulation as an indicator of clinical bleeding.

We hope that you will continue to enjoy the selections from the British Journal that we provide for you and find this month selection particularly helpful.

References

1. Tanaka KA, Dietrich W. Is it time to implement preoperative platelet function testing before invasive procedures? Br J Anaesth 2011; 107: 842-3
2. Benzon HT, McCarthy RJ, Benzon HA, et al. Determination of residual antiplatelet activity of clopidogrel before neuraxial injections. Br J Anaesth 2011; 107: 966-71
3. Collyer TC, Reynolds HC, Truyens E, Kilshaw L, Corcoran T. Perioperative management of clopidogrel therapy: the effects on in-hospital cardiac morbidity in older patients with hip fractures. Br J Anaesth 2011; 107: 911-5
4. Mantz J, Samama CM, Tubach F, et al. Impact of preoperative maintenance or interruption of aspirin on thrombotic and bleeding events after elective non-cardiac surgery: the multicentre, randomized, blinded, placebo-controlled, STRATAGEM trial. Br J Anaesth 2011; 107: 899-910

Editor, South African Excerpts Edition

Professor MFM James, Head of Department of Anaesthesia, Faculty of Medicine, University of Cape Town.

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References: **1.** Lloyd R, Derry S, Moore RA, McQuay HJ. Intravenous or intramuscular parecoxib for acute postoperative pain in adults (Review). *The Cochrane Collaboration* 2009; (1): 1-46. **2.** South African Rayzon package insert. **3.** Nussmeier NA, Whelton AA, Brown MT, Joshi GP, Langford RM, Singla NK *et al.* Safety and efficacy of the cyclooxygenase-2 inhibitors parecoxib sodium and valdecoxib after noncardiac surgery. *Anesthesiology* 2006; 104 (3): 518-526. **4.** Stoltz RR, Harris SI, Kuss ME, Lecomte D, Talwalker S, Dhadda S *et al.* Upper GI mucosal effects of parecoxib sodium in healthy elderly subjects. *Am J Gastroenterol* 2002; 97: 65-71. **5.** Noveck RJ, Laurent A, Kuss M, Talwalker S, Hubbard RC. Parecoxib sodium does not impair platelet function in healthy elderly and non-elderly individuals. *Clin drug invest* 2001; 21(7): 465-476. 41: 1111-1119.

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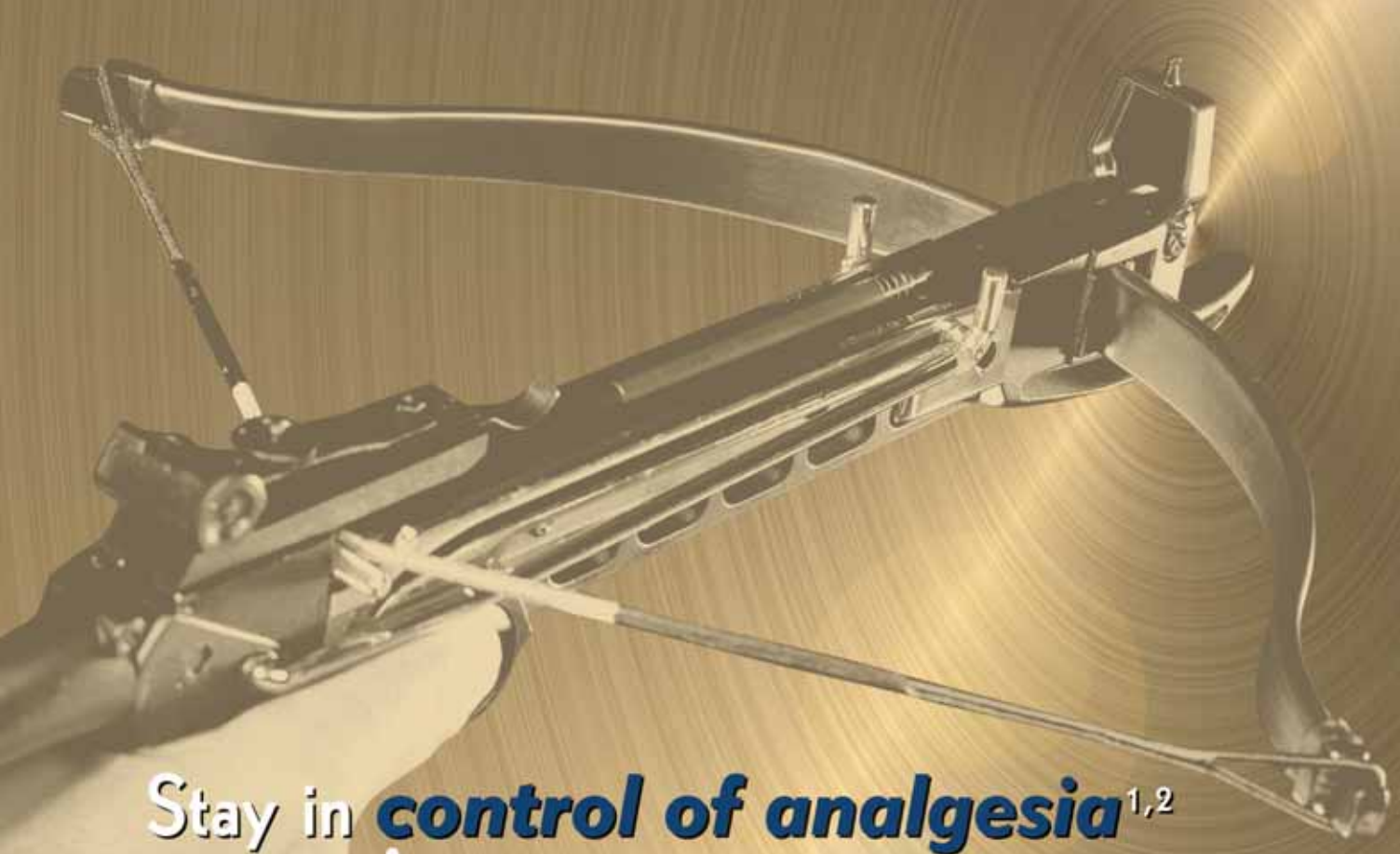

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References: 1. Lehmann A, Zeitler C, Thaler E, et al. Comparison of Two Different Anesthesia Regimens in Patients Undergoing Aortocoronary Bypass Grafting Surgery: Sufentanil-Midazolam Versus Remifentanil-Propofol. *J Cardiothorac Vasc Anesth* 2000;**14**(4):416-420. **2.** Scott LJ, Perry CM. Remifentanil. A Review of its Use During the Induction and Maintenance of General Anaesthesia. *Drugs* 2005;**65**(13):1793-1823.

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Elderly (over 65 years of age):** General anaesthesia - initial starting dose should be half the recommended adult dose and then titrated to individual patient need. Dose adjustment applies to use in all phases of anaesthesia, Cardiac anaesthesia and Intensive care - no initial dose reduction is required. **Obese patients:** For obese patients (greater than 20 % over their ideal body weight) the dosage should be reduced and based upon ideal body weight. **Renal impairment:** No dosage adjustment is necessary. **Hepatic impairment:** No dosage adjustment is necessary. Patients with severe hepatic impairment should be closely monitored and the dose titrated to individual's need. **SIDE-EFFECTS AND SPECIAL PRECAUTIONS:** Commonly reported side-effects are nausea, vomiting, hypotension, skeletal muscle rigidity, post-operative shivering, bradycardia, acute respiratory depression, apnoea, post-operative hypertension, and pruritis. Hypoxia, constipation, post-operative aches are infrequently reported. These adverse events resolve within minutes of discontinuing or decreasing the rate of administration. Allergic reactions including anaphylaxis, cases of cardiac arrest, asystole usually preceded by bradycardia, have been reported in patients receiving ULTIVA in conjunction with other anaesthetic agents. Patients with severe hepatic impairment are more sensitive to the respiratory depressant effects. For surgical procedures where post-operative pain is anticipated, appropriate analgesics should be administered prior to, or immediately following ULTIVA discontinuation, allowing sufficient time to reach the maximum effect of the longer-acting analgesic. Muscle rigidity related to the dose and rate of administration may occur. Bolus infusions should be administered over not less than 30 seconds. Muscle rigidity must be treated with appropriate supporting measures (refer to package insert for details). Analgesia is accompanied by marked respiratory depression and should be managed appropriately, including decreasing the rate of infusion by 50 %, or a discontinuation of the infusion. Ensure full consciousness and adequate spontaneous ventilation are achieved before patient is discharged from the recovery area. Hypotension and bradycardia may be managed by reducing the rate of infusion, or the dose of concurrent anaesthetics, or by using IV fluids, vasopressor or anticholinergic agents as appropriate. Debilitated, hypovolaemic and elderly patients are more sensitive to the cardiovascular effects. Interactions: If doses of concomitantly administered CNS depressant drugs are not reduced, patients may experience an increased incidence of adverse effects associated with these agents. The cardiovascular effects (hypotension and bradycardia), may be exacerbated in patients receiving concomitant cardiac depressant drugs, such as beta-blockers and calcium channel blocking agents. **MANAGEMENT OF OVERDOSAGE:** In the event of overdosage, discontinue administration, maintain a patent airway, initiate assisted or controlled ventilation with oxygen, maintain adequate cardiovascular function. If depressed respiration is associated with muscle rigidity, a neuromuscular blocking agent may be required. Intravenous fluids and vasopressor agents for the treatment of hypotension and other supportive measures may be employed. **APPLICANT:** GlaxoSmithKline South Africa (Pty) Ltd., (Co. reg. no. 1948/030135/07), 57 Sloane Street, Bryanston, 2021. Marketed by: Aspen Pharmacare, Building 12, Healthcare Park, Woodlands Drive, Woodmead, 2191. www.aspenpharma.com Medical Information Hotline: 0800 118 088. March 2010. UI/0310/135. A10828 02/10.

03/10 7693

British Journal of Anaesthesia **107** (6): 842–3 (2011)
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EDITORIAL II

Is it time to implement preoperative platelet function testing before invasive procedures?

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Antiplatelet therapy is the current standard for the prevention of cardiovascular ischaemia and stent thromboses. Owing to the widespread use of drug-eluting stents, increasing numbers of patients are maintained on life-long antiplatelet therapy with aspirin and clopidogrel. A clinical dilemma for pain physicians and anaesthetists arises when non-invasive pain treatments fail, and a neuraxial or regional blockade becomes one of the few options for patients on combined aspirin/clopidogrel therapy.

In their article in the current issue of *British Journal of Anaesthesia*,[1] Benzon and colleagues report the serial assessments of platelet function using the VerifyNow (Accumetrics, San Diego, CA, USA), and PFA-100 (Siemens Diagnostics, Deerfield, IL, USA) in 13 patients undergoing epidural injection after stopping clopidogrel (Table 1). The small sample size of this study limits implementing a specific interval for clopidogrel cessation before neuraxial blocks. Nevertheless, the authors should be congratulated for providing objective data on the time course of platelet recovery, which is rather difficult to obtain in the outpatient setting. Based on the extent of platelet inhibition on VerifyNow, the authors[1] empirically used three categories: >30% as therapeutic $P2Y_{12}$ inhibition, 11–29% as partial inhibition, and <10% as no inhibition. By the third day after stopping clopidogrel, only two of 13 patients had >30% inhibition, while seven had partial inhibition. Only three patients showed partial inhibition after the fifth day, and all recovered normal function from the seventh day after stopping clopidogrel. On the PFA-EPI assay, seven subjects on aspirin had abnormal closure time at baseline, which persisted for 7 days in two subjects. Only two of 13 patients had abnormal PFA-ADP closure time. None had any bleeding complication after epidural injections.

The clinical management in this study followed the current consensus guidelines.[2 3] Seven patients with coronary stents had been taking clopidogrel for at least 1 yr. The rate of cardiovascular events is highest within 90 days of stent placement, but becomes much lower after 1 yr.[4] In order to reduce bleeding risks associated with regional and neuraxial anaesthesia, a 7 day interval is recommended based on the pharmacology of clopidogrel. Aspirin monotherapy is not considered as a bleeding risk, but continuing both clopidogrel and aspirin can potentially increase haematoma formation or haemorrhage after neuraxial or other regional block procedures.[3] According to the present data,[1] it is possible that some patients only require 5 days for the return of platelet function, and 2 extra days could be hazardous in terms of thrombotic risks. Indeed, some patients with CYP2C19 genetic variations are poor metabolizers of clopidogrel, a pro-drug, and they can be more susceptible to cardiovascular events in the long term. Testing ADP-induced platelet aggregation may allow an individualized approach to periprocedural clopidogrel cessation, improving the balance between bleeding and thrombotic risks.[5–7]

Several points in this study are worthy of further comment. First, the sensitivity and specificity for platelet inhibition are variable for different platelet function tests.[6 7] Selecting a

Table 1 Characteristics of *in vivo* hemostasis, VerifyNow and PFA-100. WB, whole blood; AA, arachidonic acid; Epi, epinephrine; ADP, adenosine-5′-diphosphate; vWF, von Willebrand factor

	***In vivo* haemostasis**	**VerifyNow**	**PFA-100**
Blood	Native WB	Citrated WB	Citrated WB
Blood flow shear rate	300–1600 s^{-1} in artery, up to 10 000 s^{-1} in stenotic artery	Minimal	~5000 s^{-1}
Endpoint	Blood coagulation	Agglutination of fibrinogen-coated beads	Closure of a membrane aperture
Agonists	Collagen, thrombin, ADP, TxA_2, etc.	AA (aspirin test), ADP ($P2Y_{12}$ test)	Collagen/Epi, Collagen/ADP
Ligands	vWF, fibrinogen	Fibrinogen	vWF, fibrinogen

correct assay is important in evaluating the platelet recovery because VerifyNow, but not PFA-100 (collagen/ADP assay), was capable of demonstrating the effects of clopidogrel. Secondly, the efficacy of antiplatelet agents can be influenced by multiple factors. These include the location, type, or number of stents, severity of vascular disease, co-existing disease (e.g. diabetes, renal impairment), concomitant medication (e.g. statins), race, genetic factors, and compliance with the medication.[8 9] Lastly, platelet activation is involved in many aspects of physiological haemostasis and pathological vascular thrombosis. In contrast to multi-modal platelet activation *in vivo* (Table 1), platelet function testing only reflects platelet reactivity to a specific platelet agonist. The combination of an oral anti-Xa inhibitor, clopidogrel and aspirin, has been reported to increase the major bleeding events.[10] In this regard, optimal methods of monitoring, and withdrawal of concomitant antiplatelet and anticoagulant agents are largely unknown.

The question remains how platelet testing before a procedure can be efficiently implemented in the outpatient setting. Point-of-care platelet function assays are likely to help us establish more objective criteria for perioperative antiplatelet management,[11 12] but further studies of clinical and economic outcomes are necessary to justify their routine use.

Conflict of interest

None declared.

References

1 Benzon HT, McCarthy RJ, Benzon HA, *et al.* Determination of the residual antiplatelet activity of clopidogrel before neuraxial injections. *Br J Anaesth* 2011; **107**: 966–71

2 Grines CL, Bonow RO, Casey DE, *et al.* Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *Circulation* 2007; **115**: 813–8

3 Horlocker TT, Wedel DJ, Rowlingson JC, *et al.* Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med* 2010; **35**: 64–101

4 Rabbitts JA, Nuttall GA, Brown MJ, *et al.* Cardiac risk of noncardiac surgery after percutaneous coronary intervention with drug-eluting stents. *Anesthesiology* 2008; **109**: 596–604

5 Gurbel PA, Bliden KP, Samara W, *et al.* Clopidogrel effect on platelet reactivity in patients with stent thrombosis: results of the CREST Study. *J Am Coll Cardiol* 2005; **46**: 1827–32

6 Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, Ten Berg JM, Hackeng CM. High on-aspirin platelet reactivity as measured with aggregation-based, cyclooxygenase-1 inhibition sensitive platelet function tests is associated with the occurrence of atherothrombotic events. *J Thromb Haemost* 2010; **8**: 2140–8

7 Breet NJ, van Werkum JW, Bouman HJ, *et al.* Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. *J Am Med Assoc* 2010; **303**: 754–62

8 Barash P, Akhtar S. Coronary stents: factors contributing to perioperative major adverse cardiovascular events. *Br J Anaesth* 2010; **105**(Suppl. 1): i3–15

9 Chassot PG, Delabays A, Spahn DR. Perioperative antiplatelet therapy: the case for continuing therapy in patients at risk of myocardial infarction. *Br J Anaesth* 2007; **99**: 316–28

10 Alexander JH, Lopes RD, James S, *et al.* Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med* 2011; **365**: 699–708

11 Fleischmann KH, Kuter DJ, Coley CM, Rathmell JP. Practice guidelines often fail to keep pace with the rapid evolution of medicine: a call for clinicians to remain vigilant and revisit their own practice patterns. *Reg Anesth Pain Med* 2010; **35**: 4–7

12 Ferreiro JL, Sibbing D, Angiolillo DJ. Platelet function testing and risk of bleeding complications. *Thromb Haemost* 2010; **103**: 1128–35

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References: 1. Savarese JJ, Deriaz H, Mellinghoff H, *et al*. The pharmacodynamics of cisatracurium in healthy adults. *Curr Opin Anesth* 1996;**9**(Suppl.1):S16-S22. **2.** Taivanen T, Meakin GH, Meretoja OA, *et al*. The safety and efficacy of cisatracurium 0.15 mg/kg during nitrous oxide-opioid anaesthesia in infants and children. *Anaes* 2000;**55**:1047-1051. **3.** Wright PMC, Ornstein E. Pharmacokinetics, pharmacodynamics and safety of cisatracurium in elderly patients. *Curr Opin Anaesth* 1996; **9**(Suppl.1):S32-S35. **4.** Murray MJ, Cowen J, DeBlock H *et al*. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Crit Care Med* 2002; **30**(1):42-156.

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NIMBEX® has a shorter clinically effective duration and a faster spontaneous recovery profile than those observed in adults under similar anaesthetic conditions. *Maintenance:* A dose of 0.02 mg/kg provides approximately 9 minutes of additional clinically effective neuromuscular block during halothane anaesthesia. *Spontaneous Recovery:* Once recovery from neuromuscular block is underway, the rate is independent of the dose administered. *Reversal:* Neuromuscular block following administration is reversible with standard doses of anticholinesterase agents. **Use by intravenous infusion. Dosage in adults and children aged 2 to 12 years.** An initial infusion rate of 3 µg/kg/min (0.18 mg/kg/hr) is recommended to restore 89 - 99% T_1 suppression following evidence of spontaneous recovery. After an initial period of stabilisation of neuromuscular block, a rate of 1 - 2 µg/kg/min (0.06 – 0.12 mg/kg/hr) should be adequate to maintain block in this range in most patients. Reduction of the infusion rate by up to 40% may be required when administered during isoflurane or enflurane anaesthesia. Steady rate continuous infusion is not associated with a progressive increase or decrease in neuromuscular blocking effect. Following discontinuation of infusion, spontaneous recovery proceeds at a rate comparable to that following administration of a single bolus. **Dosage in elderly patients, renal impairment and hepatic impairment:** No dosing alterations required. **Dosage Recommendations in patients with cardiovascular disease and in ICU patients:** Refer to package insert. **For details on compatibility and dilution:** Refer to package insert. **SIDE-EFFECTS AND SPECIAL PRECAUTIONS:** Cutaneous flushing or rash, bradycardia, hypotension and bronchospasm, severe anaphylactic reactions have been reported. There have been some reports of persistent muscle weakness and/or myopathy following prolonged use in severely ill patients in the ICU. Great caution should be exercised in patients who have shown allergic hypersensitivity to other neuromuscular blocking agents. NIMBEX® has no clinically significant effect on heart rate and will not counteract the bradycardia produced by many anaesthetic agents or by vagal stimulation during surgery. Patients with myasthenia gravis and other forms of neuromuscular disease have shown increased sensitivity to non-depolarising blocking agents. An initial dose of not more than 0.02 mg/kg is recommended in these patients. Severe acid-base and/or serum electrolyte abnormalities may increase or decrease the sensitivity of patients to neuromuscular blocking agents. **Interactions:** *Increased effect:* enflurane, isoflurane and halothane, ketamine, other non-depolarising neuromuscular blocking agents. For other drugs, refer to package insert. *Decreased effect:* Prior chronic administration of phenytoin or carbamazepine, administration of suxamethonium to prolong the effects of non-depolarising neuromuscular blocking agents may result in a prolonged and complex block which can be difficult to reverse with anticholinesterases. Rarely, certain drugs may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; increased sensitivity to non-depolarising neuromuscular blocking agents might result. Refer to package insert for a list of such drugs. **MANAGEMENT OF OVERDOSAGE:** Prolonged muscle paralysis and its consequences are expected to be the main signs of overdosage. It is essential to maintain pulmonary ventilation and arterial oxygenation until adequate spontaneous respiration returns. Full sedation will be required since consciousness is not impaired. Recovery may be accelerated by the administration of anticholinesterase agents once evidence of spontaneous recovery is present. **APPLICANT:** GlaxoSmithKline South Africa (Pty) Ltd., (Co. reg. no. 1948/030135/07). 57 Sloane Street, Bryanston, 2021. Marketed by Aspen Pharmacare. Building 12, Healthcare Park, Woodlands Drive, Woodmead, 2191. www.aspenpharma.com Medical Information Hotline: 0800 118 088. March 2010. N/0310/065. A11055 03/10.

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BJA

Comparison of thromboelastometry (ROTEM®) with standard plasmatic coagulation testing in paediatric surgery

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Editor's key points

- Major surgery can result in significant blood loss and coagulopathy in children requiring rapid and accurate assessment of coagulation status.
- This observational study compared standard coagulation testing to rotational thromboelastometry in children undergoing major surgery.
- Standard coagulation testing did not correlate well with thromboelastometry testing except for fibrinogen levels with FibTEM.
- Further studies are needed to develop thromboelastometry-guided transfusion guidelines in children.

Background. Thromboelastometry (ROTEM®) might be useful to detect intraoperative coagulation disorders early in major paediatric surgery. This observational trial compares this technique to standard coagulation tests.

Methods. Intraoperative blood sampling was obtained in children undergoing elective major surgery. At each time point, standard coagulation tests [activated partial thromboplastin time (aPTT), prothrombin time (PT), and fibrinogen level] and ROTEM® analyses (InTEM, ExTEM, and FibTEM) were performed simultaneously by trained hospital laboratory staff.

Results. A total of 288 blood samples from 50 subjects were analysed. While there was a poor correlation between PT and aPTT to ExTEM clotting time (CT) and InTEM CT, respectively, a good correlation was detected between PT and aPTT to clot formation time, and a very good correlation between fibrinogen level and FibTEM assay ($r=0.882$, $P<0.001$). Notably, 64% of PT and 94% of aPTT measurements were outside the reference range, while impaired CT was observed in 13% and 6.3%, respectively. Standard coagulation test results were available after a median of 53 min [inter-quartile range (IQR): 45–63 min], whereas 10 min values of ROTEM® results were available online after 23 min (IQR: 21–24 min).

Conclusions. PT and aPTT cannot be interchangeably used with ROTEM® CT. Based on the results of ROTEM®, recommended thresholds for PT and aPTT might overestimate the need for coagulation therapy. A good correlation was found between the fibrinogen level and the FibTEM assay. In addition, ROTEM® offered faster turnaround times.

Keywords: blood, coagulation; complication, coagulopathy; measurement techniques, coagulation; measurement techniques, thrombelastograph

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Major surgical procedures in children are frequently associated with significant blood loss per kilogram body weight and the resulting need for transfusion of allogeneic blood products, which can be further aggravated by development of dilutional coagulopathy.[1] As a result, early detection of signs of coagulopathy is a major issue and challenge for paediatric anaesthetists. Standard coagulation tests [prothrombin time (PT), activated partial thromboplastin time (aPTT), and plasma fibrinogen level] in the perioperative setting are time-consuming,[2 3] which delays prompt haemostatic therapy.

Rotation thromboelastometry (ROTEM®, TEM® Innovations, Munich, Germany) offers an alternative approach to assess perioperative coagulation disorders by means of visco-elastic analysis of clotting *in vitro*. First results are available within 10 min of test initiation, and clot formation can be observed online by a bedside monitor. The current recommendations for transfusion of fresh frozen plasma (FFP) or administration of prothrombin complex concentrates are mainly based on prolonged PT and aPTT.[4] Recently, results in trauma patients show good results using the ROTEM® clotting time (CT) instead of PT/aPTT to assess coagulation status.[5] Only limited data comparing the two approaches are available.

The aims of the current clinical observational study were (i) to compare standard coagulation measurements (PT, aPTT, and fibrinogen level) with ROTEM® testing and (ii) to compare the times required for performance of each method.

Methods

This prospective observational study project was approved by the institutional Ethics Committee of University Children's Hospital Zurich (KEK StV 27/08). Written informed consent was obtained from parents. The study was performed in paediatric patients undergoing elective major surgery with a high likelihood of considerable blood loss and the need for close intraoperative coagulation testing. Patients were excluded if preoperative standard coagulation tests or blood count were abnormal, or any history of hereditary or acquired coagulopathy including renal, hepatic, and bone marrow disease were known. No uniform transfusion protocol was used, as the main focus was the comparison between both coagulation measurements. Most anaesthetists used classical plasmatic coagulation intervention guidelines,[4] and some of the younger anaesthetists used ROTEM® to monitor fibrinogen concentration.

Blood samples were obtained at baseline in all subjects after general anaesthesia was induced and venous or arterial access was established, and thereafter at the discretion of the anaesthesiologist in charge during the entire surgical procedure. At each time point, two 3 ml tubes containing 0.14 ml citrate solution (S-monovettes®, Sarstedt, Nuembrecht, Germany) were taken for coagulation and ROTEM® tests and immediately transported manually to the hospital central laboratory. All intraoperative measurements were labelled as urgent on the form that was filled in for our laboratory personnel.

Citrated blood of one tube was analysed after centrifugation at 3000*g* for 15 min at 18°C on a STA Compact® coagulation analyser (Roche Diagnostics AG, Rotkreuz, Switzerland) to measure PT, aPTT, and fibrinogen. Simultaneously, thromboelastometry was performed in the hospital central laboratory by trained operators using the ROTEM® device. Technical details of the ROTEM® analyser have been described elsewhere.[6] The CT was defined from the start of measurement until the initiation of clotting after 20 μl of a buffered concentrated calcium chloride solution (StarTEM® reagent) and the activator was added to the whole blood sample.

To compare measurements of standard coagulation tests (PT, aPTT, and fibrinogen level), the following corresponding ROTEM® tests were defined:[6]

- CT and clot formation time (CFT) of the extrinsically activated ROTEM® assay (ExTEM CT and CFT, respectively); activation with 20 μl tissue factor to be compared with the PT;
- CT and CFT of the intrinsically activated ROTEM® assay (activation of 20 μl phospholipid–ellagic acid; InTEM CT and CFT, respectively); to be compared with the aPTT;
- Comparison of the functional fibrinogen test (Clauss assay) to be compared with the clot firmness after 10 min (FibTEM A10) and to the maximum clot firmness (FibTEM MCF) of the FibTEM assay. The FibTEM test was based on an ExTEM assay that also contains the platelet inhibitor cytochalasin D to separately evaluate functional fibrin polymerization without platelet activity.

In addition, platelet count was correlated to InTEM and ExTEM maximum clot firmness (MCF) and to the clot amplitude after 10 min (A10).

All devices were set up according to quality standards and underwent periodic quality controls. Immediately after results of standard coagulation measurements were available, the laboratory staff gave a call to the anaesthetist in charge and this time was noted for comparison of time of performance. In contrast, the ROTEM® device was connected to an intranet network that allows online display of the resulting curves at the anaesthesia monitoring device. The time was noted when the 10 min results of the ROTEM® assays were available online (A10 values).

The SPSS software package (Version 18.0; SPSS Inc., Chicago, IL, USA) was used for statistical analyses. After testing for Gaussian distribution revealed a non-parametric distribution of laboratory data, Spearman's correlation was used for analysis. Data are presented as median values with Q1 and Q3 quartiles if not otherwise noted.

Results

A total of 288 intraoperative coagulation analyses were obtained in 50 subjects undergoing major surgery. Surgical procedures included craniofacial ($n=23$), spine ($n=22$), complex hip ($n=2$), or cancer surgery ($n=3$). Subject characteristics and intraoperative transfusion requirements are presented in Table 1.

Overall correlation of the investigated assays and corresponding reference ranges are shown in Figures 1–3. As the reference ranges for standard coagulation tests and ROTEM® measurements are slightly different for each paediatric age group, we used a calculated mean value for displayed reference ranges in Figures 1–3 based on previous published data.[7 8]

PT showed a poor correlation to the CT of the extrinsically activated ROTEM® assay (ExTEM CT) ($r=-0.460$, $P<0.001$), but a high correlation to the CFT (ExTEM CFT; $r=-0.782$, $P<0.001$).

A slightly higher correlation was detected between results of activated partial thromboplastin time (aPTT) and CT and CFT of the intrinsically activated ROTEM® test (InTEM), $r=0.723$ ($P<0.001$) and $r=-7.89$ ($P<0.001$), respectively. Surprisingly, 94% of all aPTT values were outside the reference range, and according to the current guidelines, in 52%, prolongation of aPTT was designated to be clinically meaningful (>45 s). In contrast, increase in InTEM CT was only detected in 18 out of 285 analyses (6.3%). Since no conclusive threshold for CT has been published and validated, we defined CT values outside the normal range as abnormal.

The overall correlation of PT and ExTEM CT and of aPTT and InTEM CT was not significantly higher if only levels within the reference ranges were compared (calculations not shown).

Measurements of the functional fibrinogen tests using the Clauss assay and ROTEM® FibTEM A10 and MCF showed a

Table 1 Subject characteristics (n=50) and description of intraoperative transfusion therapy. Data are expressed as median (IQR) or number, as appropriate

Subject characteristics and intraoperative course	
Age (yr)	3.2 (0.8–10.7)
Gender (female/male)	24/26
Height (cm)	87.2 (72.2–118)
Weight (kg)	13.0 (9.0–22.5)
Total amount of infused crystalloids and colloids (ml kg^{-1})	128 (94.1–167)
Transfusion of RBC (ml kg^{-1}) (in 44 out of 50 patients)	40.0 (20.8–65.1)
Transfusion of FFP (ml kg^{-1}) (in 24 out of 50 patients)	21.9 (11.1–32.3)
Transfusion of platelets (ml kg^{-1}) (in 8 out of 50 patients)	16.7 (12.6–26.6)
Administration of human fibrinogen concentrate (mg kg^{-1}) (in 37 out of 50 patients)	44.5 (16.2–77.0)

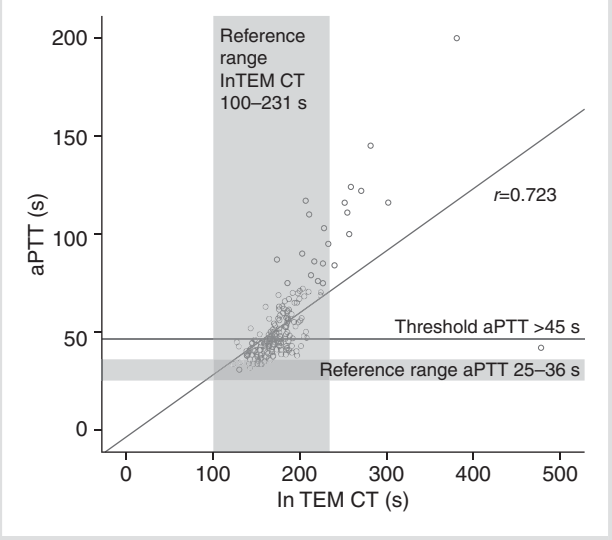

Fig 1 Correlation between ROTEM® InTEM CT and aPTT. Reference ranges are shown for each parameter. Critical threshold for aPTT according to the current guidelines[4 11] is displayed.

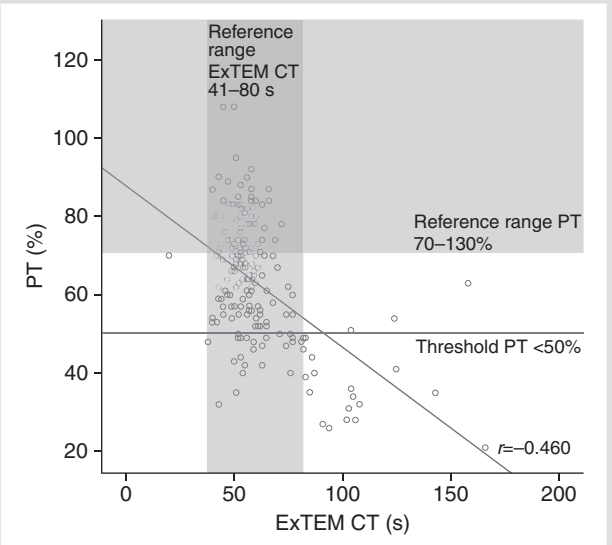

Fig 2 Correlation between ROTEM® ExTEM CT and PT. Reference ranges are shown for each parameter. Critical threshold for PT according to the current guidelines[4 11] is displayed.

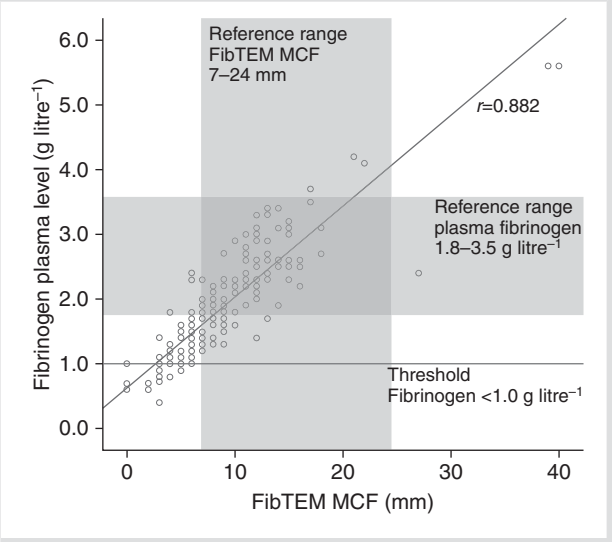

Fig 3 Correlation between ROTEM® FibTEM MCF and plasma fibrinogen level. Reference ranges are shown for each parameter. Critical threshold for plasma fibrinogen level according to the current guidelines[4] is displayed.

high overall correlation (r=0.823, P<0.001 and r=0.882, P<0.001). Both assays revealed impaired fibrin polymerization (FibTEM MCF <7 mm) and diminished plasma fibrinogen levels (Clauss assay <1.8 g litre^{-1}) in about 33% of all intraoperative coagulation analyses.

Clot amplitude A10 and MCF showed a high correlation to platelet count in the InTEM assay (r=0.9, P<0.001 and r=0.873, P<0.001, respectively) as well as in the ExTEM test (r=0.860, P<0.001 and r=0.77, P<0.001, respectively).

Results of standard coagulation measurements were transmitted immediately by phone call from the central laboratory which took a median of 53 min [inter-quartile range (IQR): 45–63 min] after blood sampling, whereas 10 min values of ROTEM® (A10) were available online after 23 min (IQR: 21–24 min).

Discussion

A major finding of this study is that only a moderate correlation exists between standard coagulation tests such as PT

or aPTT compared with the CTs using the extrinsically or intrinsically activated ROTEM® tests. Similar findings of only modest correlation are supported by results of other study groups.[7 9 10] Therefore, results of CT in ROTEM® tests and results of PT or aPTT cannot be used interchangeably for detecting intraoperative haemostatic disorders.

While impaired CT values were observed in only *X*% (37 out of 285 samples), more than 64% of PT measurements were outside the reference range (185 out of 288). PT values below a threshold of 50 s were observed in 22.6%. Impaired activation of the extrinsic pathway was uniformly detected with both assays in 37 out of 288 samples (13%). Even more surprisingly, 94% of all aPTT values were outside the reference range; and according to the current guidelines, in 52%, prolongation of aPTT levels was classified as clinically meaningful (>45 s).[11] In contrast, increase in InTEM CT was only detected in 18 out of 285 analyses (6.3%). This difference between tests might be explained by the fact that standard coagulation tests are performed in plasma while ROTEM® tests use whole blood. Apart from that, PT/aPTT measurements depend on the reagents used, incubation time, and the method of endpoint detection and show considerable variability between laboratories.

Tripodi and colleagues[12] stated that standard coagulation tests failed to reflect the balance between the actions of pro- and anticoagulant factors. Another aspect is that children in our study experienced different stages of dilutional coagulopathy, which is likely to be differently displayed by various coagulation measurements.

Notably, InTEM and ExTEM CFT showed a fairly high correlation to aPTT and PT, respectively. This was in accordance with the results from adult trauma patients that showed an excellent correlation between InTEM CFT and aPTT (r=0.91), while correlation between InTEM CT and aPTT was rather poor (r=0.47).[9] Despite a good correlation between clot strength after 15 min (ExTEM CA15) and PT in that investigation, the question of the optimal threshold for laboratory coagulation testing and ROTEM® measurements that reliably guides adequate haemostatic therapy remains. Recommendations of critical thresholds for PT and aPTT in current guidelines were based largely on expert opinion and sparse publications of clinical studies.[13–15] The PT or aPTT tests have been shown to overestimate the underlying coagulation factor activity if more than one factor is reduced,[16] which typically occurs in dilutional coagulopathy. Thus, impaired aPTT or PT values are a very common and early finding during intraoperative bleeding and haemodilution.[15 17] If these early abnormalities are not linked to relevant increase in bleeding, this might lead to considerable over-transfusion of FFP and other blood products. In adult liver transplantation, Wang and colleagues[18] showed a significant decrease in transfused allogeneic blood products following a transfusion algorithm using ROTEM® compared with standard laboratory tests. Data from Schöchl and colleagues revealed the effective use of ROTEM®-guided coagulation management in trauma patients by reducing the amount of allogeneic blood product transfusion.[5] However, there is a lack of data proving the usefulness of ROTEM®-guided coagulation management in children.[19 20]

Clot firmness analysed A10 or at maximum levels showed a very good correlation to platelet count. This finding is supported by data from liver transplantation in adults providing similar results (r=0.779, P<0.001).[21] Thus, MCF or even A10 values might serve as surrogate parameters to estimate platelet function.

Fibrinogen/fibrin is an important contributor to clot strength and is the first coagulation factor to become critically reduced during perioperative haemorrhage and dilutional coagulopathy.[17 22 23] In our study, plasma fibrinogen level assessed with the Clauss assay showed a high to a very high correlation to the FibTEM A10 and MCF. This finding is supported by other studies showing similar good correlations.[9 24] Impaired functional fibrinogen levels were observed in our study considerably more frequently based on the Clauss assay (54%), while the FiBTEM MCF showed impaired values in 37% of test results. Severe deterioration of plasma fibrinogen levels below 1.0 g litre^{-1} were observed in 11%. Although a minimum level of plasma fibrinogen of 1 g litre^{-1} was recommended by older guidelines[4 25], there is growing evidence that considerably higher fibrinogen levels (>1.5–2 g litre^{-1}) are necessary to control bleeding.[26–31] However, no universal threshold for minimum fibrinogen levels is supported by evidence-based data, and this could depend on other factors such as the type of surgery or concomitant coagulation factor activities. Another meaningful limitation of the Clauss assay is that fibrinogen levels can be considerably altered after massive fluid resuscitation and that colloids can induce erroneously increased levels of fibrinogen when using the photometric Clauss method.[28 32] Recently published data suggest that the mechanical detection principle of fibrinogen testing is more reliable than photometric techniques.[33]

Overall, there was a clear advantage for ROTEM® compared with standard coagulation tests in their shorter turnaround times, which will have an impact on timely and more targeted coagulation therapy.[19 24 28 34 35] Although point-of-care testing devices for the measurement of PT and aPTT might improve the time delay of standard laboratory testing, the other limitations of standard testing in the perioperative setting were still valid.

Some limitations in our study design need to be mentioned. First, ROTEM® analyses were performed not as bedside tests but in a central laboratory with a certain time delay for sample transport. However, previous studies using the ROTEM® have shown that blood samples remain stable over time.[36] Secondly, gelatin solution was exclusively used for fluid resuscitation in the majority of children, but not following a uniform strategy; thus, it was not possible to distinguish the impact on coagulation measurements from other causes for coagulopathy. Finally, this study was not designed to compare laboratory findings with clinical signs of increased bleeding. As a matter of course, transfusion therapy was not solely based on laboratory findings but additionally related to clinical observations. Difficulties in

distinguishing surgical from coagulopathic bleeding might increase the likelihood of more liberal transfusion regimens. Furthermore, a normal ROTEM® trace showed a high negative predictive value and might identify surgical bleeding early by distinguishing it from coagulopathic bleeding.[37] More effort to evaluate and standardize intraoperative visual assessment of coagulopathic bleeding in combination with coagulation measurements is required.

In conclusion, PT and aPTT cannot be used interchangeably to predict ROTEM® CT. Based on the results of ROTEM® testing, the currently recommended thresholds for PT and aPTT might overestimate the need for coagulation therapy. A good correlation was found between fibrinogen levels and the FibTEM assay. In addition, ROTEM® offers faster turnaround times, which can impact on timely monitoring and guiding coagulation therapy.

Declaration of interest

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References

1 Bolliger D, Gorlinger K, Tanaka KA. Pathophysiology and treatment of coagulopathy in massive hemorrhage and hemodilution. *Anesthesiology* 2010; **113**: 1205–19

2 Enriquez LJ, Shore-Lesserson L. Point-of-care coagulation testing and transfusion algorithms. *Br J Anaesth* 2009; **103**(Suppl. 1): i14–22

3 Haizinger B, Gombotz H, Rehak P, Geiselseder G, Mair R. Activated thrombelastogram in neonates and infants with complex congenital heart disease in comparison with healthy children. *Br J Anaesth* 2006; **97**: 545–52

4 Stainsby D, MacLennan S, Thomas D, Isaac J, Hamilton PJ. Guidelines on the management of massive blood loss. *Br J Haematol* 2006; **135**: 634–41

5 Schöchl H, Nienaber U, Hofer G, *et al.* Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. *Crit Care* 2010; **14**: R55

6 Luddington RJ. Thrombelastography/thromboelastometry. *Clin Lab Haematol* 2005; **27**: 81–90

7 Oswald E, Stalzer B, Heitz E, *et al.* Thromboelastometry (ROTEM(R)) in children: age-related reference ranges and correlations with standard coagulation tests. *Br J Anaesth* 2010; **105**: 827–35

8 Andrew M, Paes B, Johnston M. Development of the hemostatic system in the neonate and young infant. *Am J Pediatr Hematol Oncol* 1990; **12**: 95–104

9 Rugeri L, Levrat A, David JS, *et al.* Diagnosis of early coagulation abnormalities in trauma patients by rotation thrombelastography. *J Thromb Haemost* 2007; **5**: 289–95

10 Coakley M, Reddy K, Mackie I, Mallett S. Transfusion triggers in orthotopic liver transplantation: a comparison of the thromboelastometry analyzer, the thromboelastogram, and conventional coagulation tests. *J Cardiothorac Vasc Anesth* 2006; **20**: 548–53

11 Derivatives C-SGfTwBCaP. Cross-Sectional Guidelines for Therapy with Blood Components and Plasma Derivatives. *Transfus Med Hemother* 2009; **36**: 388–97

12 Tripodi A, Primignani M, Chantarangkul V, *et al.* The coagulopathy of cirrhosis assessed by thromboelastometry and its correlation with conventional coagulation parameters. *Thromb Res* 2009; **124**: 132–6

13 Ciavarella D, Reed RL, Counts RB, *et al.* Clotting factor levels and the risk of diffuse microvascular bleeding in the massively transfused patient. *Br J Haematol* 1987; **67**: 365–8

14 Murray DJ, Olson J, Strauss R, Tinker JH. Coagulation changes during packed red cell replacement of major blood loss. *Anesthesiology* 1988; **69**: 839–45

15 Murray DJ, Pennell BJ, Weinstein SL, Olson JD. Packed red cells in acute blood loss: dilutional coagulopathy as a cause of surgical bleeding. *Anesth Analg* 1995; **80**: 336–42

16 Dzik WH. Predicting hemorrhage using preoperative coagulation screening assays. *Curr Hematol Rep* 2004; **3**: 324–30

17 Mittermayr M, Streif W, Haas T, *et al.* Hemostatic changes following crystalloid or colloid fluid administration during major orthopedic surgery: role of fibrinogen administration. *Anesth Analg* 2007; **105**: 905–17

18 Wang SC, Shieh JF, Chang KY, *et al.* Thromboelastography-guided transfusion decreases intraoperative blood transfusion during orthotopic liver transplantation: randomized clinical trial. *Transplant Proc* 2010; **42**: 2590–3

19 Haas T, Fries D, Velik-Salchner C, Oswald E, Innerhofer P. Fibrinogen in craniosynostosis surgery. *AnesthAnalg* 2008; **106**: 725–31

20 Romlin BS, Wahlander H, Berggren H, *et al.* Intraoperative thromboelastometry is associated with reduced transfusion prevalence in pediatric cardiac surgery. *Anesth Analg* 2011; **112**: 30–6

21 Herbstreit F, Winter EM, Peters J, Hartmann M. Monitoring of haemostasis in liver transplantation: comparison of laboratory based and point of care tests. *Anaesthesia* 2010; **65**: 44–9

22 Moganasundram S, Hunt BJ, Sykes K, *et al.* The relationship among thromboelastography, hemostatic variables, and bleeding after cardiopulmonary bypass surgery in children. *Anesth Analg* 2010; **110**: 995–1002

23 Innerhofer P, Kienast J. Principles of perioperative coagulopathy. *Best Pract Res Clin Anaesthesiol* 2010; **24**: 1–14

24 Wegner J, Popovsky MA. Clinical utility of thromboelastography: one size does not fit all. *Semin Thromb Hemost* 2010; **36**: 699–706

25 American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. *Anesthesiology* 2006; **105**: 198–208

26 Rossaint R, Bouillon B, Cerny V, *et al.* Management of bleeding following major trauma: an updated European guideline. *Crit Care* 2010; **14**: R52

27 Fries D, Innerhofer P, Perger P, *et al.* Coagulation management in trauma-related massive bleeding. Recommendations of the Task Force for Coagulation (AGPG) of the Austrian Society of Anesthesiology, Resuscitation and Intensive Care Medicine (OGARI). *Anasthesiol Intensivmed Notfallmed Schmerzther* 2010; **45**: 552–61

28 Kozek-Langenecker SA. Perioperative coagulation monitoring. *Best Pract Res Clin Anaesthesiol* 2010; **24**: 27–40

29 Bolliger D, Szlam F, Molinaro RJ, Rahe-Meyer N, Levy JH, Tanaka KA. Finding the optimal concentration range for fibrinogen replacement after severe haemodilution: an in vitro model. *Br J Anaesth* 2009; **102**: 793–9

30 Fenger-Eriksen C, Lindberg-Larsen M, Christensen AQ, Ingerslev J, Sorensen B. Fibrinogen concentrate substitution therapy in patients with massive haemorrhage and low plasma fibrinogen concentrations. *Br J Anaesth* 2008; **101**: 769–73

31 Rahe-Meyer N, Pichlmaier M, Haverich A, *et al.* Bleeding management with fibrinogen concentrate targeting a high-normal plasma fibrinogen level: a pilot study. *Br J Anaesth* 2009; **102**: 785–92

32 Hiippala ST, Myllyla GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. *Anesth Analg* 1995; **81**: 360–5

33 Fenger-Eriksen C, Moore GW, Rangarajan S, Ingerslev J, Sorensen B. Fibrinogen estimates are influenced by methods of measurement and hemodilution with colloid plasma expanders. *Transfusion* 2010; **50**: 2571–6

34 Ganter MT, Hofer CK. Coagulation monitoring: current techniques and clinical use of viscoelastic point-of-care coagulation devices. *Anesth Analg* 2008; **106**: 1366–75

35 Johansson PI, Stissing T, Bochsen L, Ostrowski SR. Thrombelastography and thromboelastometry in assessing coagulopathy in trauma. *Scand J Trauma Resusc Emerg Med* 2009; **17**: 45

36 Lang T, Bauters A, Braun SL, *et al.* Multi-centre investigation on reference ranges for ROTEM thromboelastometry. *Blood Coagul Fibrinolysis* 2005; **16**: 301–10

37 Cammerer U, Dietrich W, Rampf T, Braun SL, Richter JA. The predictive value of modified computerized thromboelastography and platelet function analysis for postoperative blood loss in routine cardiac surgery. *Anesth Analg* 2003; **96**: 51–7

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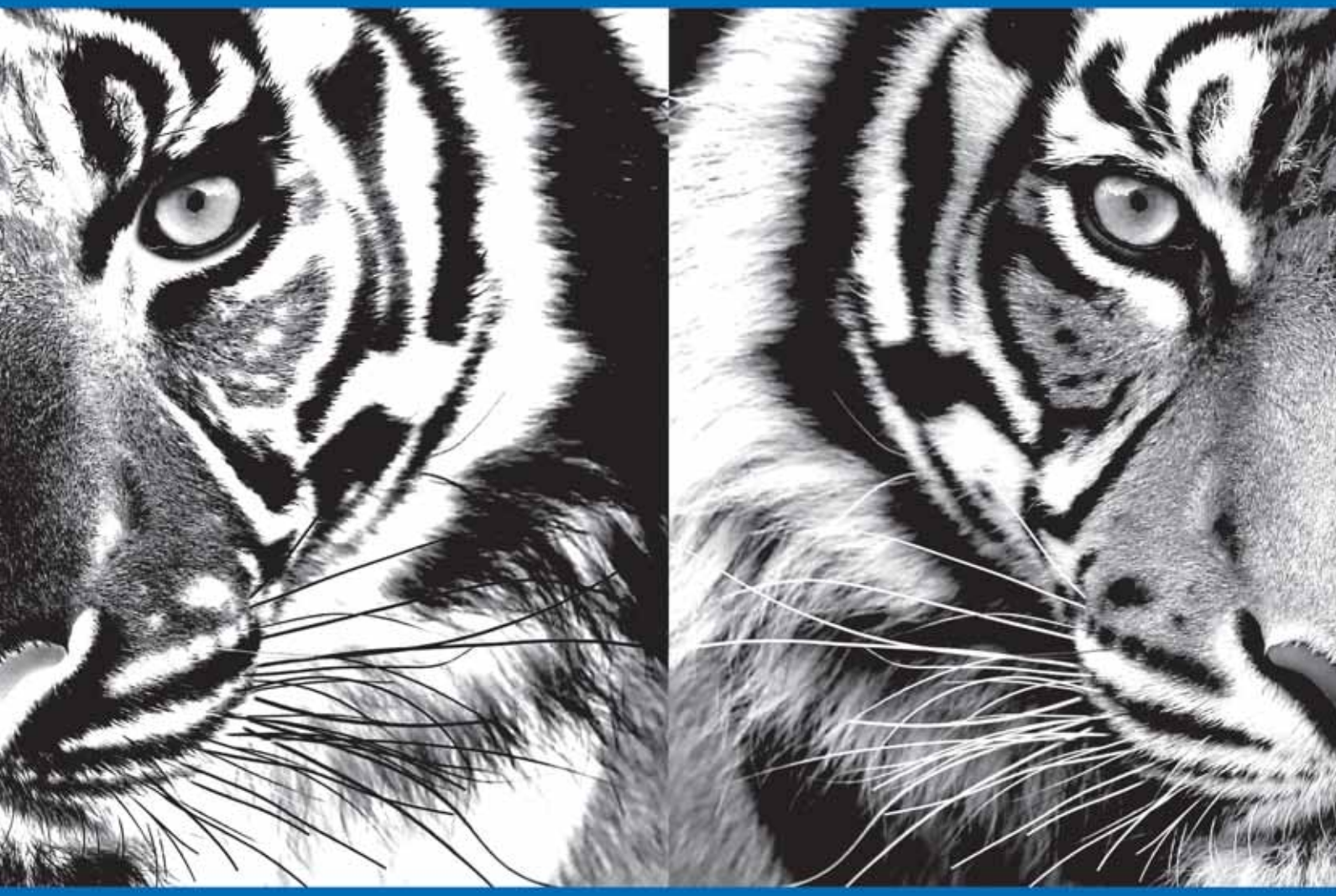

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References: 1. PreceDEX® package insert. **2.** Maze M, Morrison P. Redefining sedation. International Congress and Symposium Series 221. Royal Society of Medicine Press Limited; 1998. **3.** Bhana N, Goa KL, McClellan KJ. Dexmedetomidine. *Drugs* 2000; **59**(2): 263-268. SS **PRECEDEX® Dexmedetomidine HCl.** Each 1 ml of concentrated solution contains dexmedetomidine hydrochloride equivalent to 100 micrograms dexmedetomidine. Reg. No: 34/2.9/0239. **For full prescribing information refer to the package insert approved by the Medicines Regulatory Authority. Promo. No:** 0009-1009-1638-A-1096. **Date of Publication of this Promotional Material:** October 2009. Abbott Laboratories S.A. (Pty) Limited, Abbott Place, 219 Golf Club Terrace, Constantia Kloof, 1709. Tel: 011 858 2000.

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Validity of the 6 min walk test in prediction of the anaerobic threshold before major non-cardiac surgery

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Editor's key points

- The 6 min walk test was compared with cardiopulmonary exercise testing (CPET) in predicting anaerobic threshold.
- The authors conclude that those walking >563 m do not require CPET, and those walking <427 m do.
- Patients who walk a distance between the two cut-off points need careful further evaluation.
- The findings of this study provide important validation of simple walk test in risk stratification and prognosis.

Background. For perioperative risk stratification, a robust, practical test could be used where cardiopulmonary exercise testing (CPET) is unavailable. The aim of this study was to assess the utility of the 6 min walk test (6MWT) distance to discriminate between low and high anaerobic threshold (AT) in patients awaiting major non-cardiac surgery.

Methods. In 110 participants, we obtained oxygen consumption at the AT from CPET and recorded the distance walked (in m) during a 6MWT. Receiver operating characteristic (ROC) curve analysis was used to derive two different cut-points for 6MWT distance in predicting an AT of <11 ml O_2 kg^{-1} min^{-1}; one using the highest sum of sensitivity and specificity (conventional method) and the other adopting a 2:1 weighting in favour of sensitivity. In addition, using a novel linear regression-based technique, we obtained lower and upper cut-points for 6MWT distance that are predictive of an AT that is likely to be ($P \geq 0.75$) <11 or >11 ml O_2 kg^{-1} min^{-1}.

Results. The ROC curve analysis revealed an area under the curve of 0.85 (95% confidence interval, 0.77–0.91). The optimum cut-points were <440 m (conventional method) and <502 m (sensitivity-weighted approach). The regression-based lower and upper 6MWT distance cut-points were <427 and >563 m, respectively.

Conclusions. Patients walking >563 m in the 6MWT do not routinely require CPET; those walking <427 m should be referred for further evaluation. In situations of 'clinical uncertainty' (≥427 but ≤563 m), the number of clinical risk factors and magnitude of surgery should be incorporated into the decision-making process. The 6MWT is a useful clinical tool to screen and risk stratify patients in departments where CPET is unavailable.

Keywords: anaerobic threshold; exercise test; oxygen consumption; preoperative care

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The assessment of exercise capacity before major non-cardiac surgery is recommended to help improve risk prediction perioperatively at the individual patient level.[1 2] There are two principal methods utilized in clinical practice in the UK: a cardiopulmonary exercise test (CPET) and patient-reported metabolic equivalent (MET) scores. A CPET is generally regarded as the 'gold standard' assessment, providing objective rather than subjective analysis of exercise capacity. Specific measurements obtained during testing have been validated in the prediction of perioperative risk for major non-cardiac surgery.[3–6] The anaerobic threshold (AT) currently has the largest evidence base with cut-off thresholds of <11 and <8 ml O_2 kg^{-1} min^{-1} generally regarded as representing high and very high perioperative risk, respectively.[4–7] A high-risk cut-off threshold of slope >34 for the ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$) has a more limited evidence base.[6] In thoracic surgery, a cut-off of <15 ml O_2 kg^{-1} min^{-1} for maximum oxygen consumption achieved ($\dot{V}O_2$ max) identifies high-risk cases.[8 9]

Service infrastructure costs may prohibit setting up a CPET service. Subjective functional assessment of METs, although a simpler alternative, has been shown to have user and physiological limitations.[10–12] An alternative, simple, objective measure of exercise capacity may therefore more robustly aid risk stratification, where CPET is unavailable. Ideally, such a test should be validated against measured CPET parameters.

A review of the validity data supporting functional exercise tests revealed the 6 min walk test (6MWT) to be the most extensively researched and established test for use in clinical or research contexts in the cardiorespiratory domain.[13] Previous studies have demonstrated a positive correlation between CPET measurements and distance walked in patients with cardiorespiratory disease.[14–17] Although the 6MWT has been shown to predict outcome after pulmonary resection[18] and lung volume reduction surgery,[19] there is no literature pertaining to major non-cardiac surgery. We believe that based on this evidence and pilot data from

our institution, the 6MWT might be suitable to provide the simple, objective assessment of exercise capacity outlined above.

The aim of this study was to assess the validity of the distance walked during the 6MWT in predicting the AT (and other parameters) derived from CPET.

Methods

The protocol for this concurrent validity study was approved by the National Research and Ethics Service in August 2008 (08/H1305/62). Trial registration: ISRCT 12656789.

Participants were recruited from the preoperative assessment clinics at the James Cook University Hospital between October 2008 and January 2010. After verbal explanation and a patient information sheet, written informed consent was obtained.

Participants included in the study were aged 50–85 yr and awaiting scheduled major non-cardiac surgery (Grade 3 or 4 surgery as defined by NICE guidance).[20] Exclusion criteria comprised: medical contraindication to CPET[21] or failure to complete a baseline CPET, lower limb claudication and inability to maintain a steady walking pace on level ground. After a medical screening examination, patients were invited to participate.

For a desired precision of estimation of ± 0.10 (95% confidence interval width) around a postulated validity correlation coefficient of $r=0.70$ (for 6MWT distance in the prediction of AT) derived from pilot work, a sample size of 100 patients was estimated. Allowing for an attrition rate of 25%, a final sample size of 125 participants was required. A total of 186 individuals were screened for inclusion. Of these, 129 participants were enrolled. Characteristics, co-morbid diseases, surgical procedures undertaken, and medications prescribed for participants completing both CPET and 6MWT (119 participants) are shown in Supplementary Table S1.

Participants were asked to complete two exercise tests: CPET (on a cycle ergometer) and a 6MWT. The CPET was performed first, in order to screen for significant cardiovascular pathology, thus ensuring the safe conduct of the 6MWT. To minimize participant inconvenience, both tests were undertaken on the same day. After CPET, patients were provided with refreshments and allowed an appropriate rest interval between tests. The 6MWT was only undertaken once the participants had reported that they had no residual fatigue from CPET. To avoid study bias, the 6MWT was administered by an investigator blinded to the results of the CPET.

Cardiopulmonary exercise test

The CPET was performed using the Medgraphics Ultima system (Tewkesbury, Gloucestershire, UK) and a Lode Corival V2 cycle ergometer (BV Medical Technology, Groningen, The Netherlands). Flow and gas calibrations were performed before each test session, which was subsequently conducted to our standard protocol (available in Supplementary material). All usual patient medication was continued. The test was terminated when the participant reached volitional exhaustion ($\dot{V}_{O_2}$ peak) or earlier if another termination criterion was fulfilled. The *V*-slope comparison plot was compiled using Breeze software (Medgraphics) and interpreted by two trained observers on completion of all study testing (G.R.D. and R.C.F.S.).

Six min walk test

After successful completion of CPET, participants performed the 6MWT as outlined in the guidance published by the American Thoracic Society (ATS).[22] Individuals walked to their own maximum pace along a flat corridor, marked with a 30 m track, aiming to cover as much distance as possible in the timed 6 min. Participants wore a MIROxi pulse oximeter (Medical International Research, Roma, Italy) to record heart rate response and oxygen saturations.

The ATS suggest that a practice test is not needed in most settings.[22] Furthermore, data from our pilot study (unpublished observation) confirmed that the test was highly reproducible, with an intraclass correlation coefficient (ICC 3.1) of 0.94, and a non-substantial mean bias of 18 m greater on a second walk. Thus, a single 6MWT was performed in the current study.

Test outcome measures recorded

- CPET—oxygen consumption at the AT (using the *V*-slope technique),[23] oxygen consumption at volitional exhaustion ($\dot{V}_{O_2}$ peak), the $\dot{V}E/\dot{V}_{CO_2}$ recorded at AT, and maximum heart rate achieved (HR_{max})
- 6MWT—maximal distance walked and HR_{max}

Statistical analysis

Ordinary least-squares linear regression models were applied to obtain the validity coefficient (*r*) and the standard error of the estimate (SEE)—the typical error associated with the prediction of AT (or $\dot{V}_{O_2}$ peak or $\dot{V}E/\dot{V}_{CO_2}$ slope) from 6MWT distance in an individual patient. Receiver operating characteristic (ROC) curve analysis was used to derive cut-points for 6MWT distance for the prediction of AT <11 ml O_2 kg^{-1} min^{-1}, AT <8 ml O_2 kg^{-1} min^{-1}, $\dot{V}_{O_2}$ peak <15 ml O_2 kg^{-1} min^{-1}, and a combination of AT <11 ml O_2 kg^{-1} min^{-1} and $\dot{V}E/\dot{V}_{CO_2}$ slope >34. The optimum cut-point was determined as the value corresponding with the greatest accuracy (highest sum of sensitivity plus specificity; i.e. with sensitivity and specificity weighted equally). When a test is to be used for screening purposes and risk stratification, however, a cut-off value with greater sensitivity (fewer false-negatives) may be desirable. Therefore, we derived an alternative cut-point by adopting a 2:1 weighting for sensitivity:specificity.

To refine the ROC-derived cut-offs, we used the obtained regression equation and SEE, to derive lower and upper cut-points for 6MWT distance that are predictive of an AT that is *likely to be* less than or greater than these prognostic AT thresholds. (A 6MWT distance falling between these two cut-points is assumed to be in an area of 'clinical uncertainty'.)

Herein, 'likely to be' is defined as a probability of $\geq$0.75 (odds of at least 3:1 in favour) of the patient's 'true' AT being less than (lower cut-point for 6MWT distance) or greater than (upper cut-point) 11 ml O_2 kg^{-1} min^{-1}, given the predicted AT from the regression equation and the observed prediction error (SEE).[24] This probability is derived from the disposition of the confidence interval for the predicted value to the prognostic value of 11 ml O_2 kg^{-1} min^{-1} and is calculated using the Student *t*-distribution. The required *t*-value is derived as the prognostic value for AT minus the predicted value from the regression and divided by the obtained SEE: (11–9.7)/1.9=0.68. The area under the *t*-distribution to the left of this value with the appropriate degrees of freedom is 0.75, providing the probability that the patient's true AT is $<$11 ml O_2 kg^{-1} min^{-1} if their predicted value from the regression was 9.7 ml O_2 kg^{-1} min^{-1}. Rearranging the derived linear regression equation gives the 6MWT distance predictive of an AT of 9.7 ml O_2 kg^{-1} min^{-1}; this is the lower cut-point. The upper cut-point was calculated in an identical fashion. All analyses were conducted using StatsDirect (Altrincham, UK; v. 2.7.8) and Medcalc (Mariakerke, Belgium; v. 11.5) software packages.

We adopted an objective criterion to identify and remove outliers with a standardized residual of $>$3.6 from the analysis. With the assumption of normality, this threshold identifies values that would occur only rarely ($<$5% of the time) with this sample size.[24]

Results

In total 119 of 129 recruited participants completed both exercise tests. Of the 10 individuals not completing: two withdrew consent after CPET, one failed to reach AT during CPET, five were unable to complete the full 6 min of walking, and two individuals had no reason documented. Of the 119 participants, an additional seven participants were eliminated from the analysis due to a persistently elevated respiratory exchange ratio (RER) likely a consequence of hyperventilation due to anxiety, poor accommodation to the mouthpiece, or both. In such cases, an AT is still detectable but it will be a 'pseudo-threshold' occurring before the actual AT resulting in an underestimation.[25] Screening for severe outliers resulted in the removal of one case for the AT analysis and one case for the $\dot{V}_{O_2}$ peak analysis, resulting in a data set of n=110 complete cases.

Exercise test results

The CPET and 6MWT results for study participants are presented in Table 1. The peak exercise challenge was comparable between the two tests as judged by the similar mean maximum heart rate. Figure 1 illustrates a scatter plot of AT *vs* 6MWT distance.

Linear regression analyses to predict the AT, $\dot{V}_{O_2}$ peak, and $\dot{V}E/\dot{V}_{CO_2}$ from the distance walked during the 6MWT are shown in Table 2, and the results of the ROC curve analyses are detailed in Table 3. The area under the ROC curve indicates that a randomly selected individual from the positive group (AT $<$11 ml O_2 kg^{-1} min^{-1}) has a 6MWT distance value (Y) smaller than that of a randomly chosen individual from the negative group (X) 85.2% of the time [$P(Y<X)$=0.852]. The likelihood ratios indicate that a 6MWT distance of $<$440 m is obtained around 15 times as frequently in patients with an AT of $<$11 ml O_2 kg^{-1} than in those with an AT above this threshold and that a 6MWT distance of $\geq$440 m is obtained approximately a third as frequently in patients with an AT of $<$11 ml O_2 kg^{-1} min^{-1} than in those with an AT above this value. The ROC curve for this analysis is shown in Figure 2, illustrating that the area under the curve is substantially larger than that of 'no

Table 1 Exercise test results [mean (SD)]. HR_{max}, maximum heart rate achieved; AT, anaerobic threshold; $\dot{V}_{O_2}$ peak, peak oxygen consumption

CPET	HR_{max} (beats min^{-1})	121 (24)
	AT (ml O_2 kg^{-1} min^{-1})	10.2 (2.6)
	$\dot{V}_{O_2}$ peak (ml O_2 kg^{-1} min^{-1})	14.8 (4.1)
	$\dot{V}E/\dot{V}_{CO_2}$	35.7 (5.6)
6MWT	HR_{max} (beats min^{-1}) (SD)	117 (22)
	Distance walked (m)	464.2 (94.5)

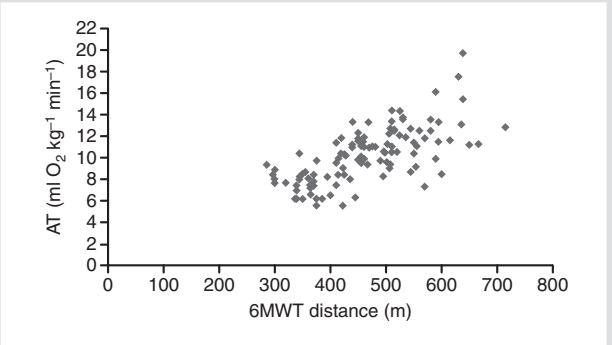

Fig 1 Scatter plot for 6MWT distance (m) *vs* AT (ml O_2 kg^{-1} min^{-1}).

Table 2 Linear regression analyses with 6MWT distance as the predictor. AT, anaerobic threshold; $\dot{V}E/\dot{V}_{CO_2}$, ventilatory equivalents for carbon dioxide; $\dot{V}_{O_2}$peak, peak oxygen consumption

Outcome	Slope	Intercept	Correlation coefficient (*r*) (95% CI)	Standard error of the estimate (SEE) (95% CI)
AT	0.019	1.598	0.68 (0.56–0.77)	1.9 (1.7–2.2) ml O_2 kg^{-1} min^{-1}
$\dot{V}_{O_2}$ peak	0.033	−0.326	0.75 (0.65–0.82)	2.7 (2.4–3.1) ml O_2 kg^{-1} min^{-1}
$\dot{V}E/\dot{V}_{CO_2}$	−0.028	48.479	0.46 (0.30–0.60)	5.0 (4.4–5.8)

Table 3 ROC curve analyses. AT, anaerobic threshold; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalents for carbon dioxide; $\dot{V}O_2$ peak, peak oxygen consumption

	CPET measurement (ml O_2 kg^{-1} min^{-1})							
	AT <11		**AT <8**		**AT <11 and $\dot{V}E/\dot{V}CO_2$ >34**		**$\dot{V}O_2$ peak <15**	
ROC curve sensitivity: specificity weighting	1:1	2:1	1:1	2:1	1:1	2:1	1:1	2:1
Prevalence (%)	58.2		19.1		36.4		51.8	
AUC	0.852		0.857		0.801		0.856	
95% CI	0.771–0.912		0.778–0.917		0.741–0.871		0.776–0.916	
Cut-point (m)	<440	<502	<411	<450	<440	<459	<450	<510
Sensitivity	0.641	0.844	0.857	0.952	0.725	0.825	0.702	0.895
95% CI	0.511–0.757	0.731–0.922	0.637–0.970	0.762–0.999	0.561–0.854	0.672–0.927	0.566–0.816	0.785–0.960
Specificity	0.957	0.674	0.843	0.697	0.800	0.686	0.868	0.566
95% CI	0.852–0.995	0.520–0.805	0.750–0.911	0.590–0.790	0.687–0.886	0.564–0.791	0.747–0.945	0.423–0.702
Positive likelihood ratio	14.73	2.59	5.45	3.14	3.63	2.62	5.31	2.06
95% CI	12.1–17.9	2.1–3.2	4.5–6.6	2.7–3.7	2.9–4.5	2.1–3.2	4.4–6.5	1.6–2.7
Negative likelihood ratio	0.38	0.23	0.17	0.07	0.34	0.26	0.34	0.19
95% CI	0.09–1.5	0.1–0.5	0.05–0.5	0.01–0.50	0.2–0.7	0.1–0.5	0.2–0.8	0.1–0.4

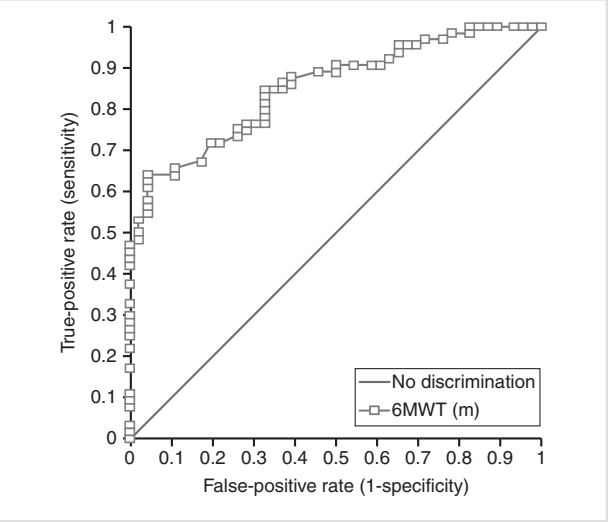

Fig 2 ROC curve for 6MWT distance (m) in discriminating between 'low' (<11 ml O_2 kg^{-1} min^{-1}) and 'high' (≥11 ml O_2 kg^{-1} min^{-1}) AT.

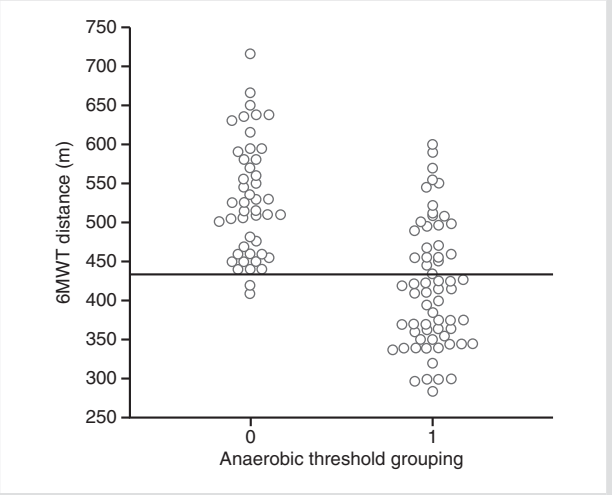

Fig 3 Dot plot of 6MWT distance (m) in patients with an AT <11 ml O_2 kg^{-1} min^{-1} ('1') and ≥11 ml O_2 kg^{-1} min^{-1} ('0'). The solid line represents the cut-point (<440 m) derived from the ROC curve analysis with sensitivity and specificity weighted equally.

discrimination' (0.50) indicated by the diagonal. Figure 3 shows the dot plot for 6MWT distance in the two groups.

Lower and upper cut-points for 6MWT distance derived from regression analysis

From the regression modelling, the lower and upper cut-points for 6MWT distance predictive of a true AT that is *likely to be* ($P \geq 0.75$) <11 or >11 ml O_2 kg^{-1} min^{-1}, respectively, were below 427 m (positive test) or above 563 m (negative test). For the 8 ml O_2 kg^{-1} threshold for the AT, the lower and upper cut-points were <269 and >405 m. For the $\dot{V}O_2$ peak <15 ml O_2 kg^{-1} min^{-1}, the lower and upper cut-points were <409 and >520 m.

Discussion

In this study, we have confirmed that the 6MWT may be a useful practical method for risk stratification, with a large effect size observed for the correlation between the distance walked during a 6MWT and oxygen consumption at both AT and $\dot{V}O_2$ peak. AT, measured during CPET, is presently recognized as the most robust endpoint to inform perioperative risk stratification.[4–7] For this reason, the majority of our analysis and inference focuses on the relationship between 6MWT distance and AT, rather than $\dot{V}O_2$ peak.

The ROC curve analyses for both the <11 and <8 ml O_2 kg^{-1} min^{-1} thresholds for AT revealed that the 6MWT

distance is an adequate discriminator between high and low AT patient groups. However, deriving an optimum single cut-point from ROC curve analysis is challenging and not ideally suited to a clinical context. Sensitivity can be weighted to reduce the false-negative rate, but we believe that the regression-based analysis represents a refinement of single ROC curve cut-points allowing for clinical variation and uncertainty. Using the regression method, a patient with a positive test (6MWT $<$427 m) is likely to be at high perioperative risk, and a patient with a negative test (6MWT $>$563 m) would be considered low risk. A patient completing a distance of $\geq$427 but $\leq$563 m is in a zone that we define as 'clinical uncertainty'. We can usefully incorporate these regression analysis-derived risk categories into clinical practice (see below).

The current international guidance[1 2] relies on subjective assessment of functional capacity, in the form of METs, as one of the three key variables in the decision-making process of risk stratification before non-cardiac surgery. A functional capacity of $<$4 METs (inability to climb a flight of stairs) represents the threshold to trigger the high-risk limb of the risk stratification pathways. In the current study only one of 101 individuals (1%) reported a functional capacity of $<$4 METs (14 ml O_2 kg min^{-1}), whereas 58.2% of our participants had an objectively measured AT of $<$11 ml O_2 kg min^{-1} during CPET. Interestingly, the individual reporting a functional capacity of $<$4 METs attained an AT and $\dot{V}O_2$ peak of 11.8 and 15.2 ml O_2 kg min^{-1}, respectively, thereby representing low risk based on objective testing. We believe that based on our data, the 6MWT represents a superior and more robust technique for risk stratification than a self-reported cut-point of $<$4 METs.

The other two key variables utilized to determine preoperative risk in the current international guidance are the number of clinical risk factors and nature of surgical intervention.[1 2] Utilizing this approach in combination with 6MWT distance could help identify the most at risk individuals before surgery. The major benefits would be the ease with which it could be administered, minimal staff training and equipment requirements, and simple and quick to perform. In addition, the test is repeatable,[22] is safe to perform, and entails a minimal increase in patient attendance time. Although not recommended as a replacement for CPET, the 6MWT could, in effect, act as a surrogate 'sieve' in identifying high-risk individuals who may require further assessment or optimization before surgery. In hospitals where CPET would perhaps not be utilized frequently, the 6MWT could be used as a cheap accurate alternative enabling identification and referral for CPET via loco-regional preoperative networked arrangements.

We believe that the upper and lower cut-points derived from the regression analysis provide the ideal platform in providing for such a model. For example, no further assessment would be required in an individual walking $>$563 m during the 6MWT (upper cut-point, true AT likely to be $>$11 ml O_2 kg min^{-1}), whereas a patient walking $<$427 m (lower cut-point, true AT likely to be $<$11 ml O_2 kg min^{-1}) would be considered high risk and should be referred for further functional assessment. In individuals walking a distance in the area of 'clinical uncertainty' ($\geq$427 but $\leq$563 m), it would be important to incorporate the number of clinical risk factors and magnitude of surgical intervention into this clinical decision-making process, before consideration of further investigation. Therefore, a patient walking, say, 500 m together with two to three clinical risk factors should be further assessed, whereas an individual walking the same distance with a good health profile would not.

Our study is unique in being the first to examine the use of the 6MWT before operation in patients undergoing non-cardio-thoracic surgery. However, we identified three studies within cardio-respiratory medicine reporting similar correlations between 6MWT distance and CPET measurements to ours.[14–16] These studies predominantly concentrated on correlations between peak oxygen consumption and 6MWT distance, reporting validity coefficients from r=0.64 to 0.88. The observed correlations between 6MWT distance and AT and $\dot{V}O_2$ peak in the current study are substantially larger than those reported in patients with chronic obstructive pulmonary disease.[26]

Our results appear to conflict with those reported from a study of the validity of an intermittent shuttle walk test in assessing fitness for surgery, with the authors concluding that the discriminatory ability of the test was poor.[27] However, a robust comparison of our findings with this study is not possible, as the patient group was substantially fitter (mean AT 12.7 *vs* 10.2 ml O_2 kg min^{-1}) than our sample, and the authors do not detail the method used to determine the single ROC cut-points, nor the sensitivity, specificity, and likelihood ratios associated with the derived cut-points.

It is important to acknowledge a number of limitations to our study. First, we are utilizing a specific cut-off value for AT to discriminate between high- and low-risk individuals (a threshold value of 11 ml O_2 kg min^{-1}). However, this threshold remains robust, despite being unchanged since proposed originally.[7] Indeed, Snowden and colleagues reported a very similar AT cut-point (10.1 ml O_2 kg min^{-1}) in prediction of increased postoperative morbidity.[4] Similarly, Wilson and colleagues[6] reported that an AT of $<$11 ml O_2 kg min^{-1} was a clinically significant predictor of mortality in major non-cardiac surgery patients.

Second, using the 6MWT as a surrogate provides limited diagnostic information on cardiorespiratory reserve, which can be obtained with CPET. We are however in effect suggesting the 6MWT as an improvement over a subjective cut-point of $<$4 METs in identifying high-risk individuals and not in replacement of CPET. With the current financial constraints on the National Health Service in the UK, we believe that the 6MWT represents a robust pragmatic improvement where CPET is unavailable. Indeed, identification of high-risk individuals utilizing the 6MWT may enable streamlined pathways of care at the loco-regional level as outlined above. Such a tertiary referral service would be more cost-effective and avoid unnecessary

duplication of tests. Third, the 6MWT is of limited utility in assessing patients with limb ischaemia or major limitation to exercise, for example, lower limb arthritis. Patients who cannot walk at a good pace have a resultant decreased 6MWT distance when compared with exercise results during non-weight-bearing cycle exercise. Finally, this study was designed to examine the prediction of CPET parameters from a 6MWT and not powered to predict perioperative outcome. We acknowledge that this might be considered an important direction for future research were the 6MWT to be adopted into regular clinical practice.

In conclusion, our results demonstrate that the 6MWT can be used robustly at preoperative assessment to assess exercise capacity. Where CPET is unavailable, we believe the regression analysis model presented provides an accurate, simple, and cheap way of clinically guiding further patient management as part of a preoperative screening process.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Declaration of interest

None declared.

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References

1 Fleisher LA. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. *Circulation* 2007; **116**: 1971–96

2 Poldermans D. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery. European Society of Cardiology Guidelines. *Eur Heart J* 2009; **30**: 2769–812

3 Carlisle J, Swart M. Mid-term survival after abdominal aortic aneurysm surgery predicted by cardiopulmonary exercise testing. *Br J Surg* 2007; **94**: 966–9

4 Snowden C, Prentis J, Anderson H, *et al.* Submaximal cardiopulmonary exercise testing predicts complications and hospital length of stay in patients undergoing major surgery. *Ann Surg* 2010; **251**: 535–41

5 Older P, Hall A, Hader R. Cardiopulmonary exercise testing as a screening test for perioperative management of major surgery in the elderly. *Chest* 1999; **116**: 355–62

6 Wilson RJT, Davies S, Yates D, Redman J, Stone M. Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery. *Br J Anaesth* 2010; **105**: 297–303

7 Older P, Smith R, Courtney P. Pre-operative evaluation of cardiac failure and ischaemia in elderly patients by cardiopulmonary exercise testing. *Chest* 1993; **104**: 701–4

8 Bayram A, Candan T, Gebitekin C. Preoperative maximal exercise oxygen consumption test predicts postoperative pulmonary morbidity following major lung resection. *Respirology* 2007; **12**: 505–10

9 Armstrong P, Congleton J, Fountain SW, *et al.* BTS guidelines: guidelines on the selection of patients with lung cancer for surgery. *Thorax* 2001; **56**: 89–108

10 McGlade D, Poon A, Davies M. The use of a questionnaire and simple exercise test in the pre-operative assessment of vascular surgery patients. *Anaesth Intensive Care* 2001; **29**: 520–6

11 Byrne N, Hills A, Hunter R, *et al.* Metabolic equivalent: one size does not fit all. *J Appl Physiol* 2005; **99**: 1112–9

12 Savage P, Toth M, Ades P. A re-examination of the metabolic equivalent concept in individuals with coronary heart disease. *J Cardiopulm Rehabil* 2007; **27**: 143–8

13 Solway S, Brooks D, Lacasse E, Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. *Chest* 2001; **119**: 256–70

14 Riley M, McParland J, Stanford CM, *et al.* Oxygen consumption during corridor walk testing in chronic cardiac failure. *Eur Heart J* 1992; **13**: 789–93

15 Miyamoto S, Nagaya N, Satoh T, *et al.* Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. *Am J Respir Crit Care Med* 2000; **161**: 487–92

16 Cahalin LP, Mathier MA, Semigram MJ, *et al.* The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. *Chest* 1996; **110**: 325–32

17 Wijkstra PJ, TenVergert EM, van der Mark TW, *et al.* Relation of lung function, maximal inspiratory pressure, dyspnoea, and quality of life with exercise capacity in patients with chronic obstructive pulmonary disease. *Thorax* 1994; **49**: 468–72

18 Holden DA, Rice TW, Stelmach K, Meeker DP. Exercise testing, 6-min walk and stair climb in the evaluation of patients at high risk for pulmonary resection. *Chest* 1992; **102**: 1174–9

19 Szekely LA, Oelberg DA, Wright C, *et al.* Preoperative predictors of operative morbidity and mortality in COPD patients undergoing bilateral lung volume reduction surgery. *Chest* 1997; **111**: 550–8

20 NICE guidelines: Preoperative tests: the use of routine preoperative tests for elective surgery. Appendices. 2003

21 Weisman I. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003; **167**: 211–77

22 American Thoracic Society statement: guidelines for the six minute walk test. *Am J Respir Crit Care Med* 2002; **166**: 111–7

23 Beaver W, Wasserman K, Whipp B. A new method of detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1996; **60**: 2020–7

24 Hopkins WG, Marshall SW, Batterham AM, Hanin J. Progressive statistics for studies in sports medicine and exercise science. *Med Sci Sports Exerc* 2009; **41**: 3–12

25 Ozcelik O, Ward SA, Whipp B. Effect of altered body CO_2 stores on pulmonary gas exchange dynamics during incremental exercise in humans. *Exp Physiol* 1999; **84**: 999–1011

26 Chaung M, Lin I, Wasserman K. The body weight-walking distance product as related to lung function, anaerobic threshold, and peak VO_2 in COPD patients. *Respir Med* 2001; **95**: 618–26

27 Struthers R, Erasmus P, Holmes K, Warman P, Collingwood A, Sneyd JR. Assessing fitness for surgery: a comparison of questionnaire, incremental shuttle walk, and cardiopulmonary exercise testing in general surgical patients. *Br J Anaesth* 2008; **101**: 774–80

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Oxygen delivery through high-flow nasal cannulae increase end-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients

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Editor's key points

- High-flow nasal cannulae (HFNCs) used for oxygen therapy increases pharyngeal airway pressures but the effect on lung volumes is unknown.
- In this study of patients after cardiac surgery, HFNC increased end-expiratory lung impedance, suggesting increased lung volumes and functional residual capacity.
- Oxygenation improved and the benefits were greatest in patients with high BMIs.
- Further data are required to assess the clinical significance of these data.

Background. High-flow nasal cannulae (HFNCs) create positive oropharyngeal airway pressure, but it is unclear how their use affects lung volume. Electrical impedance tomography allows the assessment of changes in lung volume by measuring changes in lung impedance. Primary objectives were to investigate the effects of HFNC on airway pressure (P_{aw}) and end-expiratory lung volume (EELV) and to identify any correlation between the two. Secondary objectives were to investigate the effects of HFNC on respiratory rate, dyspnoea, tidal volume, and oxygenation; and the interaction between BMI and EELV.

Methods. Twenty patients prescribed HFNC post-cardiac surgery were investigated. Impedance measures, P_{aw}, $Pa_{O_2}/F_{I_{O_2}}$ ratio, respiratory rate, and modified Borg scores were recorded first on low-flow oxygen and then on HFNC.

Results. A strong and significant correlation existed between P_{aw} and end-expiratory lung impedance (EELI) ($r=0.7$, $P<0.001$). Compared with low-flow oxygen, HFNC significantly increased EELI by 25.6% [95% confidence interval (CI) 24.3, 26.9] and P_{aw} by 3.0 cm H_2O (95% CI 2.4, 3.7). Respiratory rate reduced by 3.4 bpm (95% CI 1.7, 5.2) with HFNC use, tidal impedance variation increased by 10.5% (95% CI 6.1, 18.3), and $Pa_{O_2}/F_{I_{O_2}}$ ratio improved by 30.6 mm Hg (95% CI 17.9, 43.3). A trend towards HFNC improving subjective dyspnoea scoring ($P=0.023$) was found. Increases in EELI were significantly influenced by BMI, with larger increases associated with higher BMIs ($P<0.001$).

Conclusions. This study suggests that HFNCs reduce respiratory rate and improve oxygenation by increasing both EELV and tidal volume and are most beneficial in patients with higher BMIs.
Australia and New Zealand Clinical Trial Registry.
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Pulmonary complications after cardiac surgery are common[1] and are associated with adverse outcomes, including prolonged mechanical ventilation times, increased use of sedation, increased risk of ventilator-associated pneumonia, and prolonged intensive care unit and hospital lengths of stay.[2 3] Alveolar collapse and atelectasis is observed in up to 90% of post-surgical cases[4] and subsequently results in a reduction in functional residual capacity (FRC) of ~20%.[1] Physiotherapy and early mobilization may provide some benefit, but respiratory dysfunction is still commonplace.[5] Non-invasive ventilation can be useful in avoiding reintubation in such patients, but this treatment prevents early mobilization; is associated with gastric distension which may further reduce FRC; restricts effective communication and oral nutrition; and is poorly tolerated in some patients.[6]

High-flow nasal cannulae (HFNCs) deliver high-flow humidified air and oxygen via wide-bore nasal cannulae at a prescribed fraction of inspired oxygen ($F_{I_{O_2}}$). Whereas conventional nasal prongs are generally limited to flows of 5 litre min^{-1} due to the potential drying effects of cold oxygen on the nasal mucosa,[7] oxygen at up to 50 litre min^{-1} may be delivered when the warmed gas is optimally humidified, making it less irritant to the nasal mucosal. The therapy is well established in neonatal and paediatric populations[8 9] and HFNC use has recently been described in adult populations.[10 11]

A number of studies have described the generation of positive airway pressure at the level of the pharynx associated with HFNC.[12–14] However, there are no data regarding the translation of this pharyngeal positive pressure effect to the lungs, nor any data describing associated changes in lung volumes. This is essential in understanding whether HFNC provide any clinically relevant benefit.

Electrical impedance tomography (EIT) is a non-invasive radiation-free bedside imaging technique used to provide real-time images and data of regional lung ventilation and lung volumes (Fig. 1).[15] Its use has been validated in a number of clinical applications including optimization of mechanical ventilatory strategies such as lung recruitment manoeuvres;[16] detection of pulmonary complications including lung collapse, pleural effusion, and pneumothorax;[17 18] and ensuring correct placement of the endotracheal tube.[19] EIT can provide an indication of changes in lung volumes associated with HFNC usage.

The primary aims of this prospective interventional study were to compare the differences in airway pressure (P_{aw}) and end-expiratory lung volume (EELV) between HFNC and low-flow oxygen and to determine any relationship between changes in P_{aw} and EELV. Secondary aims were to investigate the changes in respiratory rate, subjective rating of dyspnoea (modified Borg score), tidal volume (V_t), and oxygenation (Pa_{o_2}/FI_{o_2} ratio) between the two therapies. Owing to the association between increased BMI and decreased FRC in the postoperative period,[20] we assessed the interaction between BMI and changes in EELV in patients receiving HFNC.

Methods

After approval from the Institutional Human Research and Ethics Committee (EC27105), this study was conducted at a tertiary referral hospital in Australia specializing in cardiothoracic surgery and medicine. The study was registered with the Australian Clinical Trials Registry (Clinical Trial No.: ACTRN12609000037202).

Participants

Written informed consent was obtained from all participants. Patients were included in the study if they were deemed by the treating intensive care specialist to be displaying signs of respiratory dysfunction [including one or more of decreasing Pa_{o_2} (Pa_{o_2}/FI_{o_2} ratio of <300), subjective dyspnoea, increased use of accessory muscles, increase in respiratory rate] and requiring HFNC; post-cardiac surgery (performed on cardiopulmonary bypass); and ≥ 18 yr of age. Patients were excluded if they had ongoing air leak post-surgery, a requirement for electrical cardiac pacing or an open sternum.

Electrical impedance tomography

Lung volume changes were assessed using EIT. Previous studies have demonstrated that changes in end-expiratory lung impedance (EELI) as measured by EIT have a strong linear correlation with changes in EELV.[21 22] Similarly, V_t changes are correlated with tidal impedance variation (VARt).[22] Therefore, the effect of HFNC at a pulmonary, rather than an oropharyngeal airway level, can be assessed.

EIT measurements were performed with the EIT Evaluation Kit 2 (Dräger Medical, Lübeck, Germany) which had been calibrated and self-tested according to the manufacturer's instructions. EIT files were automatically saved to the device's hard drive, analysed by the Dräger review software V5.1 and then downloaded as a Microsoft™ Excel spreadsheet.

Study protocol

Patients were assessed in an upright position either in bed (at a head of bed elevation of at least 45° as measured by an angle measurement device) or sitting in a straight backed chair. Pain levels were assessed, and analgesia administered if necessary, to ensure that patients could breathe without discomfort and restriction. After instillation of Co-phenylcaine Forte Nasal spray into the nares, an 8 Fr feeding tube (Unomedical, Sydney, Australia) was inserted nasally to the level of the oropharynx. Correct placement was confirmed both by visual inspection and capnography (Marquette monitor, GE Medical Systems Information Technologies Inc., WI, USA). The tube was then connected to a precision pressure transducer (PPT-001, DWWW2V, Honeywell International Ltd, Minneapolis, MN, USA) to measure P_{aw} and the data downloaded directly to a Microsoft™ Excel spreadsheet. Figure 2 shows a representative example of the airway pressure tracing obtained.

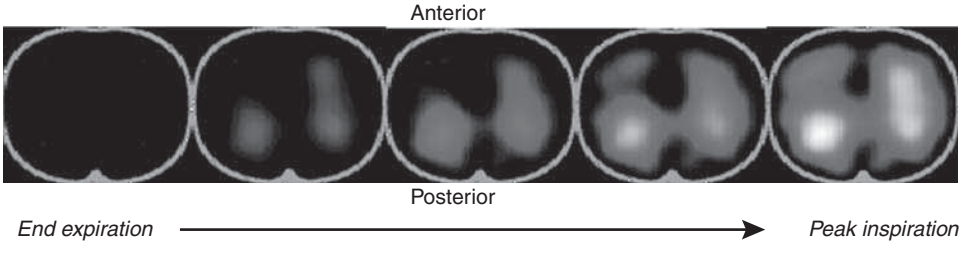

Fig 1 EIT ventilation image from end expiration (left) to peak inspiration (right).

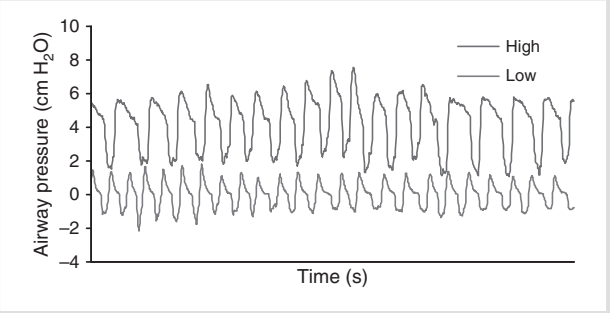

Fig 2 Oropharyngeal airway pressure tracing on HFNC and low-flow oxygen over 1 min. For this participant, mean airway pressure on HFNC was 4.4 cm H_2O and on low-flow oxygen was 0 cm H_2O.

An appropriately sized electrode belt was placed around the circumference of the patient's chest, at the level of the anterior intercostal space 5–6, and an optimal EIT signal was confirmed before data collection. For female patients, the placement of the belt was standardized to underneath the breast tissue. Data were collected first on low-flow oxygen, then on HFNC. The order of data collection was unable to be randomized as the participants were requiring HFNC as part of their treatment. Before the measurement of the low-flow oxygen data, patients were asked to rate their dyspnoea level using the Modified Borg Dyspnoea Scale[23] and asked to keep their mouth closed if possible during the measurement period. The patient's mouth status (open or closed) was tracked every 30 s during the measurement period. Simultaneous 2 min P_{aw}, EELI, and VARt readings were then recorded while the patient was receiving oxygen therapy via a low-flow system (either nasal cannula or Hudson face mask) at the flow rate the patient was receiving before HFNC prescription. $F_{I_{O_2}}$ on low flow was estimated using a previously described standardized algorithm.[24] An arterial blood gas (ABG) was taken at this time in all patients if an intra-arterial line (IAL) was *in situ*.

HFNCs (Optiflow™ system, MR850 heated humidified, RT202 delivery tubing and RT050/051 nasal cannulae, Fisher and Paykel Healthcare Ltd, Auckland, New Zealand) were applied with the humidifier temperature set to 37°C to optimize humidification. The $F_{I_{O_2}}$ was titrated to patient need to maintain $S_{p_{O_2}} \geq 95\%$ and flow was commenced at 35 litre min^{-1}. This flow rate was titrated upwards to a maximum of 50 litre min^{-1} as determined by patient tolerance, as is the clinical practice in the unit. A 15 min washout period was used between therapies to counter any cumulative treatment effect. The patient was again asked to score their dyspnoea while reminded to keep their mouth closed if possible. After optimal signals were confirmed on both the EIT and pressure transducer, simultaneous 2 min EIT and P_{aw} measurements were repeated in addition to ABG analysis.

Supplementary data included patient characteristics, including height and weight to assess BMI. Data analysed from the EIT files were EELI, VARt, and respiratory rate. The mean P_{aw} was measured in cm H_2O from the pressure transducer files.

Initially, the investigators chose to exclude patients requiring cardiac pacing as there was no safety data regarding the interaction between EIT and cardiac pacing. After consultation with colleagues who routinely use EIT to study post-cardiac surgical neonates with temporary epicardial pacing, it was found that in a 12 month period, no adverse events occurred. Therefore, late in the study, this exclusion criterion was removed. Only one patient was recruited using the amended exclusion criteria.

Statistical analysis

To investigate the changes in lung volumes (EELI and VARt) for the EIT data, a mixed-effects regression model was used. A mixed model extends a standard regression model by allowing repeated results from the same individual which we modelled using a random intercept. The dependent variable was EIT and the independent variable was HFNC (yes/no). Spearman's correlation coefficient was used to determine any correlation between EELI and P_{aw} change. A second independent variable of mouth closed (yes/no) was added to test its effect on EELI. An interaction term was included to examine whether the effectiveness of the HFNC depended on BMI. To investigate changes in V_t, respiratory rate, modified Borg score, and $Pa_{O_2}/F_{I_{O_2}}$ ratio, a paired *t*-test was used. Adjustments were made for multiple comparisons using the Bonferroni method; therefore, any *P*-values <0.008 (0.05/6 outcome variables$=0.008$) were considered significant. Data were assessed using an intention-to-treat analysis. All analyses were performed using the R statistical software (www.r-project.org).

Results

Twenty-seven patients were eligible for inclusion into the study and were approached for informed consent. Two patients refused insertion of the nasopharyngeal catheter, two patients required epicardial pacing to be commenced just before the study period, one male patient could not be fitted with a correctly sized EIT belt due to their chest circumference, and the EIT was unable to pass the manufacturer's self test in a further two patients. Therefore, 20 patients who were prescribed HFNC by the intensive care specialist post-cardiac surgery were recruited, 15 of whom were males. The mean (range) age of participants was 65.3 (51–77) yr, height was 171.1 (160–183) cm, weight was 93.3 (60–123) kg, and BMI was 32 (22–45) kg m^{-2}. Selected clinical variables are shown in Table 1. Two patients were unable to provide complete data due to the absence of an IAL in one patient and the inability to tolerate the nasopharyngeal catheter in the other. Using an intention-to-treat analysis, the data from these two patients were included.

When compared with a low-flow oxygen device, HFNC increased mean P_{aw} by 3.0 cm H_2O [95% confidence interval (CI) 2.4, 3.7; paired *t*-test $P<0.001$] and EELI by 1517

Table 1 Patient characteristics. CABG, coronary artery bypass graft; AVR, aortic valve replacement; MVR, mitral valve replacement

Patient	Sex	BMI	APACHE 2 Score	Surgery	Respiratory parameters on low-flow oxygen		
					$F_{I_{O_2}}$	$Pa_{O_2}/F_{I_{O_2}}$	Respiratory rate
1	M	32	10	CABG×3	0.32	269	22
2	M	26	16	AVR, CABG×3	0.5	132	31
3	F	43	8	AVR, replacement of ascending aorta	0.4	187	23
4	F	45	16	AVR, replacement of aortic root	0.6	263	17
5	M	33	9	CABG×3	0.5	110	24
6	M	34	16	CABG×3, AVR	0.36	189	16
7	M	34	8	AVR	0.6	268	18
8	M	28	18	CABG×4	0.6	–	18
9	F	22	18	CABG×3, MVR	0.6	125	31
10	M	32	27	CABG×3	0.6	137	18
11	M	35	16	CABG×4	0.6	128	16
12	M	34	16	CABG×4	0.4	157	19
13	M	29	17	AVR	0.6	105	22
14	M	26	14	CABG×1	0.4	190	22
15	M	25	24	AVR, replacement of aortic root	0.4	152	21
16	M	36	10	CABG×4	0.5	152	14
17	M	34	20	CABG×4	0.5	110	22
18	F	34	12	CABG×2, MVR	0.7	110	20
19	F	24	18	CABG×4	0.6	130	20
20	M	31	15	CABG×2	0.6	127	21

Table 2 Outcome variables. Low-flow oxygen compared with HFNCs

Variable	Low-flow oxygen [mean (SD)]	HFNC [mean (SD)]	Mean difference [mean (SD)]	95% confidence interval	*P*-value
End-expiratory lung impedance (units)	419 (212.5)	1936 (212.9)	1517 (46.6)	1425, 1608	<0.001
Mean airway pressure (cm H_2O)	−0.3 (0.9)	2.7 (1.2)	3.0 (1.3)	2.4, 3.7	<0.001
Respiratory rate (bpm)	20.9 (4.4)	17.5 (4.6)	−3.4 (2.8)	−2.0, −4.7	<0.001
Borg score					
0–10	2.7 (2.6)	1.9 (2.3)	−0.8 (1.2)	−0.1, −1.4	0.023
Tidal variation (units)	1512 (195.0)	1671 (195.1)	159 (21.6)	117, 201	<0.001
$Pa_{O_2}/F_{I_{O_2}}$ ratio (mm Hg)	160 (53.7)	190.6 (57.9)	30.6 (25.9)	17.9, 43.3	<0.001

impedance units (95% CI 1425, 1608; mixed model $P<0.001$) (Table 2). This translates to an increase in EELI of 25.6% (95% CI 24.3, 26.9; mixed model $P<0.001$) on HFNC, suggesting a similar increase in EELV. No statistically significant difference was found in EELI when the patients' mouth was closed or open (mixed model $P=0.99$). No significant correlation was found between P_{aw} and mouth open or closed ($P=0.99$). A strong and significant correlation was found between P_{aw} and EELI ($r=0.7$, $P<0.001$). Respiratory rate was lowered by 3.4 bpm (95% CI 1.7, 5.2; paired *t*-test $P<0.001$) and the Borg dyspnoea score by 0.8 points (95% CI 0.1, 1.4; paired *t*-test $P=0.023$). HFNC significantly increased VARt by 159 impedance units (95% CI 117, 202; mixed model $P<0.001$), translating to a 10.5% increase (95% CI 6.1, 18.3; mixed model $P<0.001$). This finding suggests a similar increase in V_t. The $Pa_{O_2}/F_{I_{O_2}}$ ratio was improved by 30.6 (95% CI 17.9, 43.3; paired *t*-test $P<0.001$) even though 95% of patients were receiving an equal or lower $F_{I_{O_2}}$ while on HFNC than when on low-flow oxygen.

Higher gas flow rates were found to result in larger increases in EELI. For every 1 litre min^{-1} increase in flow rate, the difference in EELI between low-flow oxygen device and HFNC increases by a further 0.7% (95% CI 0.1, 1.3; mixed model *P*-value=0.023).

BMI significantly influenced the positive effect of HFNC on EELI (mixed model $P<0.001$). A BMI of 25 resulted in a mean increase in EELI of 13.3% (high *vs* low flow), whereas with a BMI of 40, the increase was 24.4%. Figure 3 shows the mean increases in EELI (expressed as a percentage increase) by BMI.

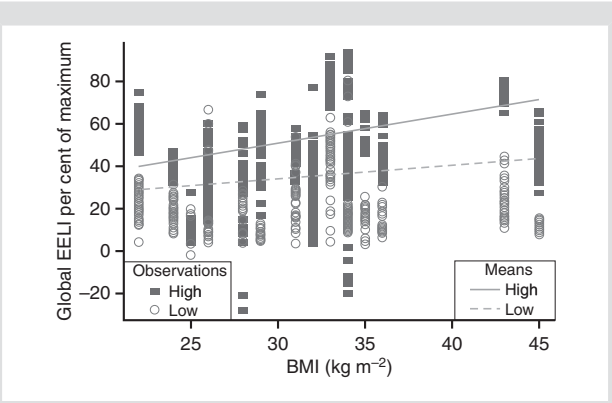

Fig 3 Average global end-expiratory lung impedance (EELI) (as a per cent of maximum) by BMI on low-flow oxygen (low) and HFNCs (high).

Discussion

These data indicate for the first time that HFNC are associated with an increase in EELI in patients post-cardiac surgery, suggesting an increase in EELV and hence FRC. The increase in EELV was found to be significantly greater in those subjects with a higher BMI. The generation of positive oropharyngeal P_{aw} by HFNC reported in earlier studies[12–14] was confirmed. A significant decrease in respiratory rate was recorded in addition to a trend towards decreasing subjective dyspnoea levels. Significant increases were recorded in V_t and oxygenation. The benefits of positive airway pressure and the resultant increase in EELV include a reduction in work of breathing, prevention of small airway closure, and improved oxygenation due to reduced pulmonary shunting.[25] This increase in EELV, coupled with the reduction in respiratory rate and the patients' perceived dyspnoea, could mean that HFNC use after cardiac surgery may be of substantial clinical benefit in the patient with borderline respiratory function after extubation.

HFNC have been shown to generate between 0.2 and 4.8 cm H_2O of positive P_{aw} in neonatal and paediatric populations.[26 27] In healthy adult volunteers, HFNC generated between 5.1 and 8.7 cm H_2O pharyngeal P_{aw}.[12 14] The findings of our study are similar to the only other published work investigating the effects of HFNC on P_{aw} in adult intensive care patients.[13] We found no significant correlation between P_{aw} and mouth open or closed ($P=0.99$) in this study, which is at odds with previous studies.[12 14] We believe that this may be due to the small sample of mouth open data leading to the data sample being underpowered to detect a difference in this variable (21% *vs* 79% of total data).

EELI was found to increase with the transition from low- to high-flow oxygen delivery in 90% of the participants in this study. Owing to the strong linear relationship between changes in EELI and EELV demonstrated in previous EIT studies,[21 22] it can therefore be concluded that the use of HFNC increases EELV. This increase in EELV may be explained by the recruitment of alveoli, and prevention of further alveolar collapse, as a result of the low-level positive P_{aw} generated by HFNC. Additionally, the increase could be attributed to further expansion of partially recruited alveoli.

With a mean BMI of 32 kg m^{-2} in the study cohort, the increase in EELV was significantly greater in those patients with higher BMI (Fig. 3). Obese patients are predisposed to postoperative atelectasis and this atelectasis resolves more slowly than in patients with normal body weight.[28] Additionally, this group of patients is prone to reduced FRC with an increased risk of developing further respiratory complications.[29] Therefore, it appears that patients with higher BMIs may derive particular benefit from the low-level positive airway pressure and increase in EELV that HFNCs produce. This may be explained by the pre-existing derangement in respiratory mechanics displayed in obese patients, specifically the higher closing volumes and subsequent reduction in lung volume due to excessive unopposed intra-abdominal pressure.[30] Subsequently, the obese patient will have a higher number of recruitable alveoli than a patient with a normal BMI and this may account for the beneficial effects seen in the obese group. More work in this area is required to further explore and describe the interaction observed between EELV and BMI, particularly as more than one third of patients undergoing cardiac surgery at this institution have a BMI of $\geq$30.

A statistically significant reduction in respiratory rate was observed on HFNC. While no formal measurements of work of breathing were used, the mean decrease in respiratory rate of 3.4 bpm may result in a reduction in work of breathing.[31] An improvement in lung compliance and FRC could be contributing factors in the trend towards an improvement in subjective dyspnoea and may also be partially responsible for the observed decrease in respiratory rate.

A higher $Pa_{O_2}/F_{I_{O_2}}$ ratio was demonstrated in patients using HFNC. This could be attributed in part to the observed increase in EELV and resultant increase in alveolar ventilation. However, the $Pa_{O_2}/F_{I_{O_2}}$ ratio would also be improved by the use of higher inspired oxygen concentration, as is seen in high-flow oxygen devices. During high flow, it is likely that there is less air entrainment, and this may also be a contributor. In our study, 95% of patients were receiving an equal or lower $F_{I_{O_2}}$ while on HFNC than when on low-flow oxygen, with 50% receiving a lower $F_{I_{O_2}}$ while on HFNC.

Gas flow rates, which determine inspired oxygen concentration particularly at lower flows, were not standardized across patients in this study. Instead, a clinically driven protocol was chosen which reflected clinical practice and management of these patients and clinical usage of the device. The assessment of the effects of HFNC at different flow rates may be of interest in future studies to further delineate optimal flows.

While the sample size of this study was small, the investigators were able to describe significant differences in clinical markers between low-flow oxygen and HFNC usage in a typical post-cardiac surgical cohort. A larger sample size will be necessary to investigate the effects of HFNC on longer term outcomes. Our cohort consisted of more males

than females at a ratio of 3:1, which is reflective of global trends in cardiac surgery.[32]

This study confirms that HFNCs are effective in providing modest levels of positive airway pressure and, for the first time, clearly demonstrates that this translates to increases in EELV. These increases in lung volume, and the associated improvements in respiratory rate, subjective dyspnoea, and oxygenation, necessitate further investigation if the clinical significance of HFNC usage and its impact on patients' longer term outcomes is to be established. These questions will be addressed in a subsequent randomized controlled trial which will examine the effects of HFNC on postoperative atelectasis in patients with a BMI of $\geq$30 (Australian Clinical Trials Registry, Clinical Trial No.: ACTRN12610000942055).

Conclusions

HFNCs generate statistically and clinically relevant increases in oropharyngeal airway pressure and increases in EELV and tidal volume as demonstrated by changes in lung impedance, particularly in patients with higher BMIs. These changes are associated with reduced respiratory rate, less dyspnoea, and improved oxygenation. Thus, HFNC may be a useful treatment option for patients experiencing respiratory dysfunction post-cardiac surgery, particularly those patients who cannot tolerate non-invasive ventilation and those with a higher BMI.

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Conflict of interest

None declared.

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References

1 Ng CS, Wan S, Yim AP, Arifi AA. Pulmonary dysfunction after cardiac surgery. *Chest* 2002; **121**: 1269–77

2 Joshi J, Fraser JF, Mullany DV. The high risk cardiac surgical patient. *Curr Anaesth Crit Care* 2005; **16**: 369–83

3 Taylor GJ, Mikell FL, Moses HW, *et al.* Determinants of hospital charges for coronary artery bypass surgery: the economic consequences of postoperative complications. *Am J Cardiol* 1990; **65**: 309–13

4 Bendixen HH, Hedley-Whyte J, Laver MB. Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation. A concept of atelectasis. *N Engl J Med* 1963; **269**: 991–6

5 O'Connor ED, Walsham J. Should we mobilise critically ill patients? A review. *Crit Care Resusc* 2009; **11**: 290–300

6 Gregoretti C, Confalonieri M, Navalesi P, *et al.* Evaluation of patient skin breakdown and comfort with a new face mask for non-invasive ventilation: a multi-center study. *Intensive Care Med* 2002; **28**: 278–84

7 Lellouche F, Maggiore SM, Deye N, *et al.* Effect of the humidification device on the work of breathing during noninvasive ventilation. *Intensive Care Med* 2002; **28**: 1582–9

8 Holleman-Duray D, Kaupie D, Weiss MG. Heated humidified high-flow nasal cannula: use and a neonatal early extubation protocol. *J Perinatol* 2007; **27**: 776–81

9 Woodhead DD, Lambert DK, Clark JM, Christensen RD. Comparing two methods of delivering high-flow gas therapy by nasal cannula following endotracheal extubation: a prospective, randomized, masked, crossover trial. *J Perinatol* 2006; **26**: 481–5

10 McGinley BM, Patil SP, Kirkness JP, Smith PL, Schwartz AR, Schneider H. A nasal cannula can be used to treat obstructive sleep apnea. *Am J Respir Crit Care Med* 2007; **176**: 194–200

11 Tiruvoipati R, Lewis D, Haji K, Botha J. High-flow nasal oxygen *vs* high-flow face mask: a randomized crossover trial in extubated patients. *J Crit Care* 2010; **25**: 463–8

12 Groves N, Tobin A. High flow nasal oxygen generates positive airway pressure in adult volunteers. *Aust Crit Care* 2007; **20**: 126–31

13 Parke R, McGuinness S, Eccleston M. Nasal high-flow therapy delivers low level positive airway pressure. *Br J Anaesth* 2009; **103**: 886–90

14 Williams AB, Ritchie JE, Gerard C. Evaluation of a high flow nasal oxygenation system: gas analysis and pharyngeal pressures. *Intensive Care Med* 2006; **32**: S219

15 Victorino JA, Borges JB, Okamoto VN, *et al.* Imbalances in regional lung ventilation: a validation study on electrical impedance tomography. *Am J Respir Crit Care Med* 2004; **169**: 791–800

16 Grant CA, Fraser JF, Dunster KR, Schibler A. The assessment of regional lung mechanics with electrical impedance tomography: a pilot study during recruitment manoeuvres. *Intensive Care Med* 2009; **35**: 166–70

17 Costa EL, Chaves CN, Gomes S, *et al.* Real-time detection of pneumothorax using electrical impedance tomography. *Crit Care Med* 2008; **36**: 1230–8

18 Hahn G, Just A, Dudykevych T, Frerichs I, *et al.* Imaging pathologic pulmonary air and fluid accumulation by functional and absolute electrical impedance tomography. *Physiol Meas* 2006; **27**: S187–98

19 Steinmann D, Stahl CA, Minner J, *et al.* Electrical impedance tomography to confirm correct placement of double-lumen tube: a feasibility study. *Br J Anaesth* 2008; **101**: 411–8

20 Jones RL, Nzekwu MM. The effects of body mass index on lung volumes. *Chest* 2006; **130**: 827–33

21 Hinz J, Hahn G, Neumann P, *et al.* End-expiratory lung impedance change enables bedside monitoring of end-expiratory lung volume change. *Intensive Care Med* 2003; **29**: 37–43

22 van Genderingen HR, van Vught AJ, Jansen JR. Estimation of regional lung volume changes by electrical impedance pressures tomography during a pressure–volume maneuver. *Intensive Care Med* 2003; **29**: 233–40

23 American Thoracic Society. ATS statement: guideline for the 6 minute walk test. *Am J Respir Crit Care Med* 2002; **166**: 111–7

24 Wilkins RL, Stoller JK, Kacmarek RM, eds. *Egan's Fundamentals of Respiratory Care*. St Louis: Mosby, 2009

25 Duke GJ, Bersten AD. Non Invasive ventilation for adult acute respiratory failure. Part 1. *Crit Care Resusc* 1999; **1**: 198

26 Lampland AL, Plumm B, Meyers PA, Worwa CT, Mammel MC. Observational study of humidified high-flow nasal cannula compared with nasal continuous positive airway pressure. *J Pediatr* 2009; **154**: 177–82

27 Spence KL, Murphy D, Kilian C, McGonigle R, Kilani RA. High-flow nasal cannula as a device to provide continuous positive airway pressure in infants. *J Perinatol* 2007; **27**: 772–5

28 Eichenberger A, Proietti S, Wicky S, *et al.* Morbid obesity and postoperative pulmonary atelectasis: an underestimated problem. *Anesth Analg* 2002; **95**: 1788–92

29 Damia G, Mascheroni D, Croci M, Tarenzi L. Perioperative changes in functional residual capacity in morbidly obese patients. *Br J Anaesth* 1988; **60**: 574–8

30 Pelosi P, Croci M, Ravagnan I, *et al.* Respiratory system mechanics in sedated, paralyzed, morbidly obese patients. *J Appl Physiol* 1997; **82**: 811–8

31 Otis AB. The work of breathing. *Physiol Rev* 1954; **34**: 449–58

32 Cheng DC, Bainbridge D, Martin JE, Novick RJ. Does off-pump coronary artery bypass reduce mortality, morbidity, and resource utilization when compared with conventional coronary artery bypass? A meta-analysis of randomized trials. *Anesthesiology* 2005; **102**: 188–203

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Prediction of fluid responsiveness in infants and neonates undergoing congenital heart surgery

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Editor's key points

- Dynamic tests of preload are increasingly used to assess fluid responsiveness (FR) in adults.
- This study compared several static and dynamic measures in infants undergoing surgery to correct congenital heart defects.
- Pulse pressure variability predicted FR before and after surgery.
- Stroke volume variability and static variables were less useful.

Background. Dynamic variables reliably predict fluid responsiveness (FR) in adults, but no data are available regarding their performance in infants. The aim of this prospective study was to assess whether pulse pressure variation (PPV) and stroke volume variation (SVV), in contrast to central venous pressure (CVP) and global end-diastolic volume (GEDV), are applicable in infants undergoing congenital heart surgery and to assess threshold values that may help to guide fluid administration in these patients.

Methods. Twenty-six anaesthetized infants, mean (SD) weight 9.7 (4.3) kg, were studied during closed-chest conditions and changing loading conditions before and after repair of congenital heart disease. Stroke volume index was measured by transoesophageal echocardiography (SVI_{TOE}), CVP was measured via a central venous line, GEDV index (GEDVI) was measured by transpulmonary thermodilution, and PPV and SVV were monitored using the PiCCO monitoring system.

Results. Fifteen infants had increased SVI_{TOE} with fluid loading $\geq$15% (responders); 11 infants were defined as non-responders. Analysing the relationship between CVP, GEDVI, SVV, and PPV at baseline with volume-induced percentage change in SVI_{TOE}, only PPV was significantly correlated with ΔSVI_{TOE} both before ($r=0.54$, $P=0.004$) and after ($r=0.73$, $P>0.0001$). As assessed by receiver-operating characteristic curve analysis, only PPV accurately predicted FR before surgical repair [area under the curve (AUC): 0.79, $P=0.01$] and after surgical repair (AUC: 0.86, $P=0.002$).

Conclusions. PPV, in contrast to SVV, CVP, and GEDVI, predicted FR in infants undergoing congenital heart surgery both before and after repair of congenital heart disease.

Keywords: echocardiography; haemodynamics; infants; neonates; physiological monitoring; pulse pressure

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Since hypovolaemia is a common cause of perioperative circulatory failure in both adults and infants, the assessment of the volume status in the critically ill is of paramount importance. Apart from clinical skills, traditional variables such as central venous pressure (CVP) and mean arterial pressure (MAP) are mainly used to guide fluid therapy in infants and neonates.[1] However, numerous studies have shown that the measurement of preload and change in preload alone is not sufficient to show whether a patient will increase stroke volume index (SVI) after a fluid bolus or not.[2–4] More recently, variables such as pulse pressure variation (PPV) and stroke volume variation (SVV), which are based on the heart–lung interaction induced by mechanical ventilation, have been shown to reliably predict the response to a fluid load in adults in different clinical scenarios.[5–7] Whether these dynamic variables are able to predict fluid responsiveness (FR) also in infants and neonates is not yet known. Some experimental data using a paediatric porcine model are available, demonstrating conflicting results in comparison with adults.[4 8 9] This emphasizes the need for a clinical study regarding the application of dynamic variables in infants and neonates. We hypothesized that the predictive power of these variables is not necessarily conferrable to infants and neonates, since there are fundamental differences in physiology between them and adults.

The aim of this study was to investigate whether PPV and SVV in comparison with the static variables CVP and global end-diastolic volume (GEDV) are reliable indicators of FR in paediatric patients undergoing congenital heart surgery.

Methods

The study was conducted in accordance with the principles of the Declaration of Helsinki and the Guidelines for Good

Clinical Practice. The protocol was approved by our institutional Ethics committee (Christian Albrecht University Kiel) and all parents gave informed consent for participation in the study.

We studied 26 mechanically ventilated children with congenital heart disease with a mean (SD) age of 14 (12) months and weight of 9.7 (4.3) kg, undergoing elective congenital heart surgery [secundum atrial septal defect (ASD), ventricular septal defect (VSD)] after induction of general anaesthesia. Exclusion criteria were: any contraindication for transoesophageal echocardiography (TOE), atrial fibrillation and/or ventricular arrhythmias distorting variation in SV or its surrogates, and acute need for inotropic drugs after induction of anaesthesia. Induction and maintenance of anaesthesia were standardized. Anaesthesia was induced with etomidate (0.4–0.6 mg kg^{-1}) followed by a bolus of sufentanil (0.5–1 $\mu g\ kg^{-1}$) and rocuronium (0.6–0.9 mg kg^{-1}), and thereafter infants were intubated and their lungs mechanically ventilated with a fixed tidal volume of 10 ml kg^{-1} and a frequency adapted to age and to maintain the Pa_{CO_2} between 4.5 and 5.5 kPa. Positive end-expiratory pressure was set between 3 and 5 cm H_2O and $F_{I_{O_2}}$ maintained between 0.3 and 0.5. Anaesthesia was then maintained with sevoflurane and boluses of sufentanil (0.5–1 $\mu g\ kg^{-1}$) before and after cardiopulmonary bypass, whereas during cardiopulmonary bypass, sufentanil was combined with a continuous infusion of propofol (3–5 mg $kg^{-1}\ h^{-1}$).

A 4–5.5 Fr central venous catheter was inserted in the right internal jugular vein or alternatively in the right or left subclavian vein to measure CVP. A 7 cm 3 Fr thermistor-tipped catheter for arterial pressure tracing, for arterial thermodilution, and for pulse contour analysis (PiCCO Plus®, Version 6.0, Pulsion Medical Systems, Munich, Germany) was inserted percutaneously into the right or left femoral artery. The arterial catheter allows discontinuous measurement of transpulmonary thermodilution cardiac index (CI_{TPTD}), SVI (SVI_{TPTD}), and global end-diastolic volume index (GEDVI) as described previously.[10] Additionally, PPV and SVV were monitored continuously. SV was calculated based on a modified algorithm originally described by Wesseling and colleagues.[11] This algorithm enables continuous calculation of SV by measuring the systolic portion of the aortic pressure waveform and dividing the area under the curve (AUC) by the aortic impedance. Initially, the specific aortic impedance is determined by transpulmonary thermodilution.[10] Five millilitres of ice cold saline were injected three times at random points in the respiratory cycle into the proximal port of the central venous catheter to assess CI_{TPTD} and to calibrate pulse contour-derived CI. All thermodilution curves were analysed and accepted or, if necessary, rejected and calibration repeated.

The PiCCO monitor also calculates the mean transit time (mtt) and the down-slope time (dst) of the aortic thermodilution curve which enables GEDV calculation.[12] GEDV is calculated according to:

$$\mathrm{GEDV} = \mathrm{CO} \times (\mathrm{mtt} - \mathrm{dst})$$

SVV is generated from the mean values of four minimum and maximum SVs averaged during the last 30 s as follows:

$$\mathrm{SVV}(\%) = 100 \times \frac{(\mathrm{SV_{max}} - \mathrm{SV_{min}})}{[(\mathrm{SV_{max}} + \mathrm{SV_{min}})]/2}$$

Additionally, PPV can be determined during the same time interval:

$$\mathrm{PPV}(\%) = 100 \times \frac{(\mathrm{PP_{max}} - \mathrm{PP_{min}})}{[(\mathrm{PP_{max}} + \mathrm{PP_{min}})]/2}$$

A paediatric multiplane probe (dimensions of 10.7×7.5 mm, 5 MHz) was used in all children (GE Vivid 7; GE Vingmed Ultrasound AS, N-3190; GE, Horten, Norway). Echocardiographic images were recorded together with the ECG. In all children undergoing elective congenital heart surgery, echocardiography approved the presence of a left-to-right shunt and the absence of any right-to-left shunt. Using a mid-oesophageal long-axis approach, the diameter of the left ventricular outflow tract (LVOT) was obtained for estimation of LVOT area. Conventional pulsed-wave Doppler was performed to measure velocity–time integrals (VTI) in the LVOT, using a longitudinal transgastric position of the echo probe at an angle of 110–130° (Fig. 1). To rule out unforeseeable effects on the accuracy of SVI_{TOE} obtained in the presence of a perimembranous VSD, a deep transgastric approach was aimed alternatively to obtain the diameter and the pulsed-wave Doppler flow of the ascending aorta (Fig. 1). Before each measurement, the probe position was verified to ensure optimal acquisition of the maximal velocity signal. SVI_{TOE} was calculated multiplying the area of the LVOT, respectively, the area of the ascending aorta, with the corresponding VTI of the Doppler measurement. Cardiac index (CI_{TOE}) then was automatically computed by the echo machine as SVI_{TOE} times heart rate. This method was originally described by Darmon and colleagues[13] and has been confirmed by several investigators.[14–16] None of the children had a significant residual shunt as demonstrated by colour Doppler echocardiography at the end of the operation. All TOE measurements were obtained by one experienced investigator and analysed offline by two investigators blinded for the haemodynamic data.

Data collection was performed during closed-chest conditions at the following time points: after induction of anaesthesia and instrumentation of the patients including all required catheters and the transoesophageal echo probe, the first data collection was performed and this time point was defined as baseline before surgical repair of the congenital heart defect (BL-BSR). The second time point during closed-chest conditions was defined after a fluid load with 10 ml kg^{-1} of hydroxylethyl starch 6% (FL-BSR). The third and fourth time points of data collection took place after surgical repair of the congenital heart defect at the end of the operative procedure also during closed-chest conditions: BL after surgical repair of the congenital heart defect (BL-ASR) and after FL with 10 ml kg^{-1} of hydroxylethyl starch 6% (FL-ASR). Haemodynamic measurements were obtained

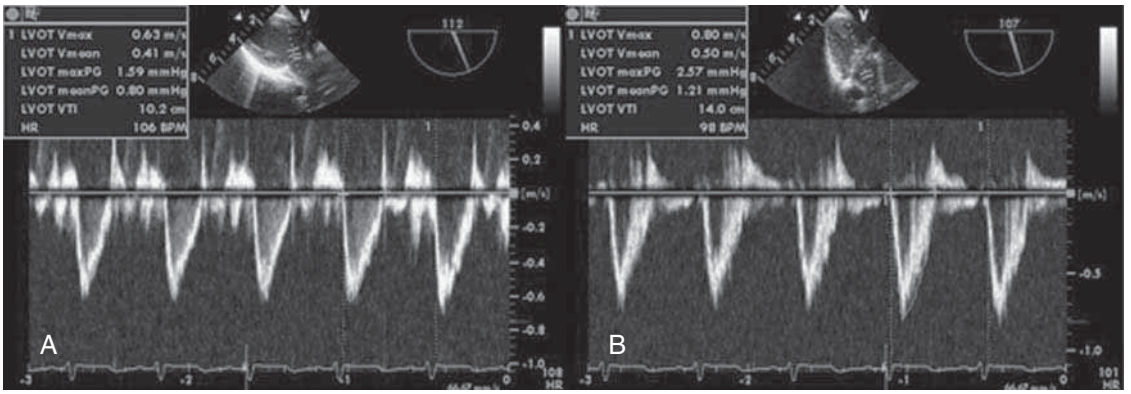

Fig 1 Measurement of Doppler velocity time integral in the LVOT (A) and in the ascending aorta (B).

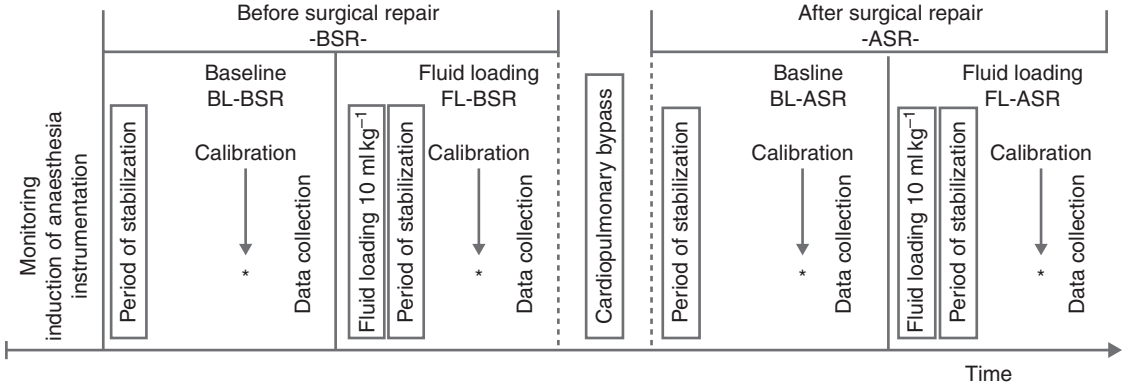

Fig 2 Study design. BSR, before surgical repair; ASR, after surgical repair.

after a short period of stabilization (~3 min) within 10 min after the end of the fluid load and after recalibration of the PiCCO system (Fig. 2). CVP was measured at end-expiration. Children with increased $SVI_{TOE} \geq 15\%$ in response to fluid administration were considered to be responders; the remaining ones were defined as non-responders.

Statistical analysis

Data are expressed as mean (SD). Statistical comparisons were performed using commercially available statistics software (GraphPad Prism 5, GraphPad Software Inc., San Diego, CA, USA). One-way analysis of variance was used to analyse data both before and after surgical repair and volume loading, followed by the Bonferroni correction for multiple comparisons. To assess the ability of a variable to identify responders and non-responders, receiver-operating characteristic (ROC) curves were generated, and an optimal threshold value (the value that maximizes the sum of both sensitivity and specificity) was determined. Areas under the ROC curves were calculated and compared as described previously.[17] Pearson correlation coefficients were calculated for static and dynamic variables and subsequent changes in SVI after fluid loading. Values of $P<0.05$ were considered statistically significant.

Results

Twenty-six patients were included in the study: 18 were undergoing VSD closure and eight underwent surgical correction of an ASD. Mean (SD) age, weight, height, and body surface area (BSA) were: age: VSD: 7.8 (3.8) months, ASD: 30.6 (9.4) months; weight: VSD: 7.2 (1.6) kg, ASD: 15.5 (2.7) kg; height: VSD: 71.7 (10.7) cm, ASD: 98.2 (11.7) cm; BSA: VSD: 0.37 (0.06) cm^2, ASD: 0.64 (0.08) cm^2. Details of all patient characteristics regarding congenital heart disease, age, body weight, height, and BSA are described in Supplementary Table S1. None of the children needed continuous vasoactive drugs before the beginning of cardiopulmonary bypass. Infants undergoing surgical repair of the VSD received a single dose of enoximone (0.5 mg kg^{-1}) before weaning from cardiopulmonary bypass in addition to a low dose of epinephrine (0.02–0.05 μg kg^{-1} min^{-1}). Haemodynamic variables are presented in Table 1. Fifteen children

Table 1 Haemodynamic variables [mean (SD)] in all children before and after surgical repair of congenital heart disease. BL-BSR, baseline before surgical repair; FL-BSR, fluid loading before surgical repair; BL-ASR, baseline after surgical repair; FL-ASR, fluid loading after surgical repair; HR, heart rate; MAP, mean arterial pressure; SVRI, systemic vascular resistance index; CI_{TPTD}, cardiac index derived from transpulmonary thermodilution; SVI_{TPTD}, stroke volume index derived from transpulmonary thermodilution; CI_{TOE}, cardiac index obtained by transoesophageal echocardiography; SVI_{TOE}, stroke volume index obtained by transoesophageal echocardiography; CVP, central venous pressure; GEDVI, global end-diastolic volume index; SVV, stroke volume variation; PPV, pulse pressure variation. *Significantly different from BL-BSR; †significantly different from BL-ASR. *P*-value indicated for one-way analysis of variance followed by the Bonferroni correction for multiple comparisons

Variables	BL-BSR	FL-BSR	BL-ASR	FL-ASR
HR (min^{-1})	102 (18)	100 (18)	126 (17)	124 (19)
MAP (mm Hg)	62 (9)	68 (12)	55 (7)	62 (10)†
SVRI (dyne s cm^{-5} m^{-2})	2050 (1053)	1989 (980)	1448 (725)	1398 (692)
CI_{TPTD} (litre min^{-1} m^{-2})	3.1 (1.5)	3.6 (1.0)	3.7 (0.9)	4.5 (1.1)
SVI_{TPTD} (ml min^{-1} m^{-2})	31.0 (12)	37.1 (9)	30.9 (9)	35.8 (8)
CI_{TOE} (litre min^{-1} m^{-2})	3.5 (1.1)	4.2 (1.0)*	3.9 (1.0)	4.6 (0.9)
SVI_{TOE} (ml min^{-1} m^{-2})	33.8 (7.5)	41.8 (9.5)*	32.1 (9.0)	40.7 (9.2)†
CVP (mm Hg)	7.5 (1.9)	11.1 (3.3)*	9.7 (2.2)	11.6 (3.3)†
GEDVI (ml m^{-2})	299 (129)	391 (128)*	415 (167)	595 (223)†
SVV (%)	14.5 (3.2)	10.4 (3.0)*	14.7 (3.5)	11.2 (3.1)†
PPV (%)	16.3 (4.9)	12.2 (3.7)*	16.4 (4.8)	11.4 (2.7)†

showed increased SVI_{TOE} ≥15% in response to a fluid load (responders: VSD: n=11; ASD: n=4), whereas in the remaining 11 children, SVI_{TOE} increased by ≤15% (non-responders: VSD: n=7; ASD: n=4). Fluid loading induced significant changes in CI_{TOE}, SVI_{TOE}, CVP, GEDVI, SVV, and PPV before surgical repair and in MAP, SVI_{TOE}, CVP, GEDVI, SVV, and PPV after surgical repair of congenital heart defect (Table 2).

Analysing the relationship between CVP, GEDVI, SVV, and PPV and volume-induced percentage change in SVI (ΔSVI_{TOE}) before repair of the congenital heart defect, only PPV significantly correlated with ΔSVI_{TOE} (r=0.54, P=0.004). After surgical repair, GEDVI (r=−0.64, P=0.0005), SVV (r=0.57, P=0.02), and PPV (r=0.73, P<0.0001) significantly correlated with ΔSVI_{TOE} in contrast to CVP (r=−0.03, P=0.81) (Table 2).

At BSR, the best AUC to identify a ≥15% increase in SVI_{TOE} was seen for PPV (AUC=0.79). The optimal threshold value given by ROC analysis was ≥16% for PPV: a value of ≥16% predicted an increase in SVI_{TOE} ≥15% with a sensitivity of 61% and a specificity of 96%. After surgical repair of the congenital heart defect, the best AUC to discriminate between responders and non-responders was seen for PPV (AUC: 0.86), SVV (AUC: 0.78), and GEDVI (AUC: 0.77) (Figs 3 and 4). The optimal threshold value given by ROC analysis was ≥15% for PPV (sensitivity: 93% and specificity: 72%), ≥15% for SVV (sensitivity: 60% and specificity: 81%), and for GEDVI, ROC analysis yielded a threshold value of ≤400 ml m^{-2} (sensitivity: 66% and specificity: 78%).

Table 2 Correlation between preload variables and volume-induced percentage change in SVI_{TOE} ≥15% before and after surgical repair of congenital heart disease in SVI at different PEEP levels. BSR, before surgical repair; ASR, after surgical repair; SVI_{TOE}, stroke volume index obtained by transoesophageal echocardiography; CVP, central venous pressure; GEDVI, global end-diastolic volume index; PPV, pulse pressure variation; SVV, stroke volume variation

Preload variables	BSR		ASR	
	r	*P*-value	*r*	*P*-value
CVP (mm Hg)	−0.17	0.42	−0.03	0.81
GEDVI (ml m^{-2})	−0.13	0.52	−0.64	0.0005
PPV (%)	0.54	0.004	0.73	<0.0001
SVV (%)	0.30	0.14	0.57	0.02

Discussion

The main findings of this study are:

(i) the static variable CVP does not predict FR in infants before and after ASD/VSD closure.

(ii) GEDVI and SVV failed to predict FR in the presence of an intracardiac left-to-right shunt. After surgical repair of the intracardiac shunt, however, both variables enhanced their predictive power.

(iii) PPV in contrast to SVV was the only dynamic variable of FR in this setting and accurately predicted the response to fluid loading both before and after repair of an intracardiac shunt.

In critically ill infants and neonates, adequate fluid therapy is a particular challenge for the anaesthetist and critical care physician, since fluid homeostasis is maintained in a narrow range and physiological compensation of both hypervolaemia and hypovolaemia is limited. Therefore, assessment of each subject's individual position on the Starling curve in order to optimize cardiac preload and avoid deleterious fluid overload is of utmost importance. The basic principle of a dynamic approach to challenge the individual

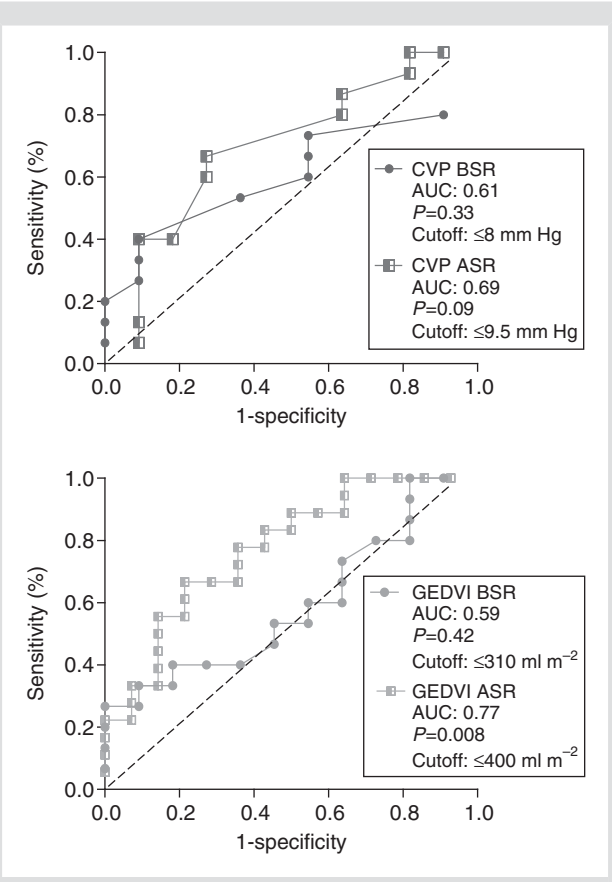

Fig 3 Prediction of FR: area under the ROC curve (AUC) for predicting a ≥15% increase in SVI. BSR, before surgical repair; ASR, after surgical repair; CVP, central venous pressure; GEDVI, global end-diastolic volume index. The straight line indicates line of identity. AUC=0.5: prediction of FR not better than chance; AUC=1.0: best prediction. Cut-off value maximizes the sum of both sensitivity and specificity, helping to discriminate between responders and non-responders.

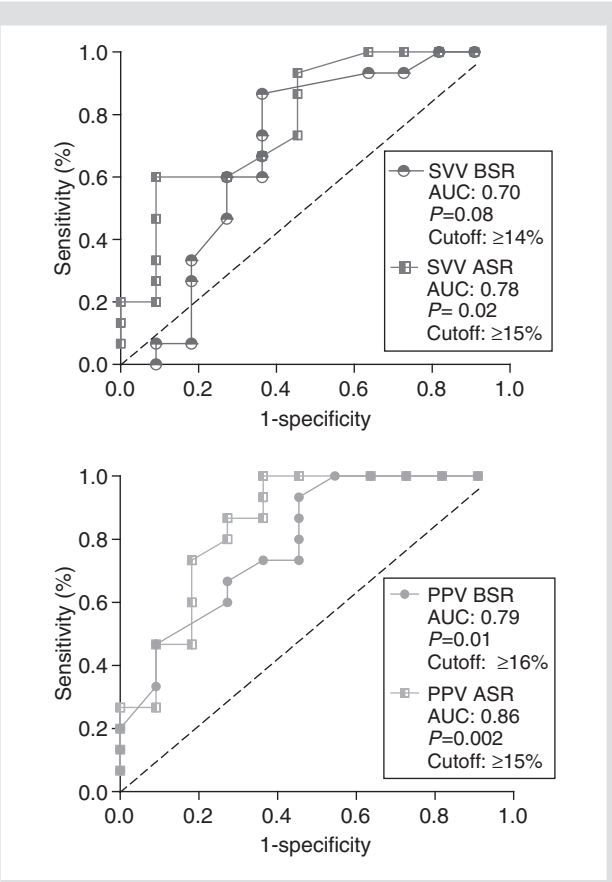

Fig 4 Prediction of FR: area under the ROC curve (AUC) for predicting a ≥15% increase in SVI. BSR, before surgical repair; ASR, after surgical repair; PPV, pulse pressure variation; SVV, stroke volume variation. The straight line indicates line of identity. AUC=0.5: prediction of FR not better than chance; AUC=1.0: best prediction. Cut-off value maximizes the sum of both sensitivity and specificity, helping to discriminate between responders and non-responders.

Frank–Starling curve at the bedside is to induce a cyclical change in cardiac preload induced by mechanical ventilation. Positive pressure ventilation intermittently decreases right ventricular end-diastolic volume and consequently decreases left ventricular preload due to a reduction in venous return.[18] SVV and PPV have been introduced as dynamic variables of FR, which reflect ventilation-induced cyclic changes in left ventricular SV. Several recent studies have shown that SVV and PPV are superior to the measurement of static filling pressures.[4–7 19 20] However, only a few animal studies[4 8 9] and one clinical observation[21] are available in infants and neonates addressing the impact of volumetric and dynamic variables on preload assessment and prediction of FR.

In the present study, we challenged the ability of the static variables CVP and GEDVI and the dynamic variables PPV and SVV to predict FR in this particular patient population. These variables were monitored during two completely different circulatory conditions: the presence of an intracardiac shunt, that is, left-to-right shunt, and after surgical treatment, in the absence of an intracardiac shunt.

In terms of the static variable CVP, our results are in good agreement with previous investigations in adults[2 22] and in a paediatric porcine model.[4] On the basis of these and several other studies, a systematic review concluded that dynamic variables are superior to static filling pressures in predicting FR.[3] In our study, CVP was not able to predict FR either with or without an intracardiac shunt. The static volumetric variable GEDVI was not superior to CVP in the presence of left-to-right shunt. After closure of the shunt, however, the predictive power of GEDVI in terms of FR was substantially improved. The area under the ROC curve was significant only after surgical repair of the congenital heart defect, yielding a sensitivity of 66% and a specificity of 78%. As with any thermodilution technique, intracardiac shunts, substantial valvular insufficiencies, or both may affect absolute values of CI and additionally absolute values of GEDVI. Although both variables are derived from the same thermodilution curve, it has been shown that the mean transit time of an indicator may change independently of changes in CI, disarming the assumption of mathematical coupling between CI

and GEDVI.[23–25] In the presence of a left-to-right shunt, recirculation of the indicator prolonged the thermodilution curve resulting in an underestimation of CI, which is in accordance with our investigation. Conversely, Cecchetti and colleagues demonstrated a significant linear correlation between CI and GEDVI in infants with haemorrhagic and cardiogenic shock.[26] Our data support the findings of Cecchetti and colleagues in at least two ways, first, since the accuracy of SVI_{TPTD} compared with SVI_{TOE} has been enhanced after closure of the intracardiac shunt, one could assume that the accuracy of GEDVI obtained by the same thermodilution curve has been improved likewise. This might explain the ability of GEDVI to predict FR after the intracardiac shunt was eliminated. Currently, normal values for intracardiac and intrathoracic blood volumes in infants and neonates have not yet been defined. In a study of infants after cardiac surgery, values of GEDVI [427 (38) ml m^{-2}] were comparable with values obtained in our study.[27]

Regarding the ability of PPV and SVV to discriminate between responders and non-responders, only PPV met the criteria of a reliable dynamic variable of FR both before and after repair of the intracardiac shunt. At BSR, a threshold value of PPV $\geq$16% reliably predicted an increase in SVI_{TOE} $\geq$15% with a sensitivity of 73% and a specificity of 63%. The predictive power of PPV was increased at ASR, yielding a threshold value of $\geq$15% with a sensitivity of 93% and a specificity of 72%. An SVV value of $\geq$15% was able to predict FR only in the absence of an intracardiac shunt with a sensitivity of 60% and a specificity of 90%, indicating a less predictive power compared with PPV. These findings differ, at least in part, to previously reported results. Our group recently showed in a paediatric porcine model applying different loading conditions that SVV but not PPV was able to accurately predict FR, when animals' lungs were ventilated with a tidal volume of 10 ml kg^{-1}.[4] Since these findings were counterintuitive compared with previously reported results in adults, we hypothesized that they may be explained by differences between the physiology in young *vs* adult subjects, specifically heart rate, chest wall compliance, mean arterial pressure and pulse pressure, arterial vasomotor tone, and aortic compliance and elastance, all of which may influence pulse pressure and PPV in a differing way compared with adults. Moreover, frequent calibration of the PiCCO monitoring system used to obtain SVV repeatedly adjusted pulse contour-derived SVV to potential changes in arterial elastance and compliance, giving SVV an edge over PPV in this setting. Accordingly, it was suggested that though PPV is still a surrogate of SVV, the influence of vasomotor tone on PPV and systolic pressure variation (SPV) is more pronounced compared with SVV.[28]

Durand and colleagues investigated 26 infants with a median age of 26 months requiring ventilation and volume expansion. They showed that respiratory variations of aortic blood flow obtained by echocardiography accurately predicted FR, whereas PPV and SPV did not.[21] They hypothesized that at least one physiological factor may have contributed to the low predictive power of PPV and SPV in their observation: based on the physiology of the Windkessel model, pulse pressure is directly proportional to left ventricular SV and inversely related to arterial compliance.[29 30] Therefore, they speculated that PPV or SPV in their responder group was limited in their predictive power due to the higher arterial elastic properties observed in children. In addition, the children in Durand's study were ventilated with a mean tidal volume of 7.4 ml kg^{-1}, a tidal volume that has been shown to be too low to induce meaningful intrathoracic pressure swings, since cyclic variations in left ventricular pressure highly depend on absolute value of tidal volume applied.[4 20]

In a recent systematic review of the literature, it was pointed out that PPV, SVV, and SPV are highly reliable variables of FR and that the diagnostic accuracy of PPV appears to be significantly superior compared with SVV and SPV.[31] The findings of our investigation emphasize the robustness of PPV compared with SVV to reliably predict FR in different clinical scenarios and in different patient populations. Although still a surrogate variable of SVV, PPV is a simple measure of pulse pressure (defined as the difference between the systolic and diastolic pressure). In contrast, SVV is a variable based on a complex algorithm obtained by pulse contour analysis, consequently highly dependent on changes in aortic compliance.[32] With respect to the impact of dynamic variables of FR in optimizing fluid management, it must be kept in mind that there are clearly defined limitations. In a recent review on PPV, Cannesson and colleagues[33] stressed the importance of a sound knowledge about physiological and technological background essential to accurately interpret dynamic variables, that is, PPV. A newly introduced and recently improved non-proprietary and publicly available algorithm for automatic determination of PPV from arterial pressure signals has been compared with the PiCCO system in an experimental setting of rapid haemodynamic changes due to severe haemorrhagic shock.[34] The PiCCO system, that is, PPV performed well during haemodynamic stable conditions; however, the systems failed to accurately estimate the PPV during severe haemorrhage and during aggressive fluid administration. These findings, however, do not affect our results, since the two time points of data collection were not during severe haemorrhage. Especially data collection before surgical repair was performed under stable haemodynamic conditions. Also the second time point of data collection after surgical repair at the end of the operation was characterized by stable haemodynamics, even though some children received inotropic pharmacological support. Moreover, in a recent investigation, Pinsky and colleagues were able to show in patients after cardiac surgery requiring fluid administration, vasoactive support, or both that both SVV and PPV appear to be unaffected by varying doses of vasopressor and inotropic agents.[35]

Our results are limited by the lack of an experimental gold standard for SVI determination, such as an ultrasound flow probe measuring instantaneous aortic blood flow. Instead, we used a clinical acceptable method to determine CI and

SVI, TOE. In paediatrics, echocardiography has been proven to be interchangeable with the Fick and pulmonary artery thermodilution method with a bias of around 10%.[36] An advantage of using TOE as the reference method for CO determination, however, is the possibility to determine instantaneous blood flow in the LVOT or in the ascending aorta, independent from the amount of the shunt fraction and beyond this to rule out any residual shunt at the end of the surgical procedure. Furthermore, the type of congenital heart defect (i.e. ASD/VSD) and consequently the associated specific pathologies regarding right and/or left atrial and ventricular compliance may influence the performance of dynamic variables of FR in different ways. Since we did not obtain data on atrial, ventricular, or both compliance, we cannot substantially comment on this particular point of interest. Further investigations highlighting these specific questions would be very helpful to more precisely define indications and limitations of dynamic variables of FR in infants. By implication, our results cannot be extrapolated to critically ill infants without congenital heart disease. However, we have chosen children with intracardiac shunts that benefit from curative surgery and consequently make them more comparable with infants and neonates being critically ill due to different diagnosis. Nevertheless, more data are needed in different paediatric clinical scenarios to more clearly define the relevance of dynamic variables of FR helping to guide fluid administration more precisely.

In conclusion, in infants and neonates undergoing congenital heart surgery, PPV but not SVV, CVP, and GEDVI accurately predicted FR both before and after repair of an intracardiac shunt.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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References

1 Tibby SM, Hatherill M, Murdoch IA. Use of transesophageal Doppler ultrasonography in ventilated pediatric patients: derivation of cardiac output. *Crit Care Med* 2000; **28**: 2045–50

2 Kumar A, Anel R, Bunnell E, *et al.* Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. *Crit Care Med* 2004; **32**: 691–9

3 Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest* 2002; **121**: 2000–8

4 Renner J, Cavus E, Meybohm P, *et al.* Pulse pressure variation and stroke volume variation during different loading conditions in a paediatric animal model. *Acta Anaesthesiol Scand* 2008; **52**: 374–80

5 Cannesson M, Attof Y, Rosamel P, *et al.* Respiratory variations in pulse oximetry plethysmographic waveform amplitude to predict fluid responsiveness in the operating room. *Anesthesiology* 2007; **106**: 1105–11

6 Hofer CK, Muller SM, Furrer L, Klaghofer R, Genoni M, Zollinger A. Stroke volume and pulse pressure variation for prediction of fluid responsiveness in patients undergoing off-pump coronary artery bypass grafting. *Chest* 2005; **128**: 848–54

7 Michard F. Changes in arterial pressure during mechanical ventilation. *Anesthesiology* 2005; **103**: 419–28, quiz 49–5

8 Renner J, Gruenewald M, Meybohm P, *et al.* Effect of elevated PEEP on dynamic variables of fluid responsiveness in a pediatric animal model. *Paediatr Anaesth* 2008; **18**: 1170–7

9 Renner J, Meybohm P, Hanss R, Gruenewald M, Scholz J, Bein B. Effects of norepinephrine on dynamic variables of fluid responsiveness during hemorrhage and after resuscitation in a pediatric porcine model. *Paediatr Anaesth* 2009; **19**: 688–94

10 Godje O, Hoke K, Goetz AE, *et al.* Reliability of a new algorithm for continuous cardiac output determination by pulse-contour analysis during hemodynamic instability. *Crit Care Med* 2002; **30**: 52–8

11 Wesseling KH, Purschke R, Smith NT, Wust HJ, de Wit B, Weber HA. A computer module for the continuous monitoring of cardiac output in the operating theatre and the ICU. *Acta Anaesthesiol Belg* 1976; **27**(Suppl.): 327–41

12 Sakka SG, Ruhl CC, Pfeiffer UJ, *et al.* Assessment of cardiac preload and extravascular lung water by single transpulmonary thermodilution. *Intensive Care Med* 2000; **26**: 180–7

13 Darmon PL, Hillel Z, Mogtader A, Mindich B, Thys D. Cardiac output by transesophageal echocardiography using continuous-wave Doppler across the aortic valve. *Anesthesiology* 1994; **80**: 796–805, discussion 25A

14 Estagnasie P, Djedaini K, Mier L, Coste F, Dreyfuss D. Measurement of cardiac output by transesophageal echocardiography in mechanically ventilated patients. Comparison with thermodilution. *Intensive Care Med* 1997; **23**: 753–9

15 Perrino AC Jr, Harris SN, Luther MA. Intraoperative determination of cardiac output using multiplane transesophageal echocardiography: a comparison to thermodilution. *Anesthesiology* 1998; **89**: 350–7

16 Poelaert J, Schmidt C, Van Aken H, Hinder F, Mollhoff T, Loick HM. A comparison of transoesophageal echocardiographic Doppler across the aortic valve and the thermodilution technique for estimating cardiac output. *Anaesthesia* 1999; **54**: 128–36

17 Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983; **148**: 839–43

18 Morgan BC, Martin WE, Hornbein TF, Crawford EW, Guntheroth WG. Hemodynamic effects of intermittent positive pressure respiration. *Anesthesiology* 1966; **27**: 584–90

19 Berkenstadt H, Friedman Z, Preisman S, Keidan I, Livingstone D, Perel A. Pulse pressure and stroke volume variations during severe haemorrhage in ventilated dogs. *Br J Anaesth* 2005; **94**: 721–6

20 De Backer D, Heenen S, Piagnerelli M, Koch M, Vincent JL. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med* 2005; **31**: 517–23

21 Durand P, Chevret L, Essouri S, Haas V, Devictor D. Respiratory variations in aortic blood flow predict fluid responsiveness in ventilated children. *Intensive Care Med* 2008; **34**: 888–94

22 Kramer A, Zygun D, Hawes H, Easton P, Ferland A. Pulse pressure variation predicts fluid responsiveness following coronary artery bypass surgery. *Chest* 2004; **126**: 1563–8

23 Buhre W, Kazmaier S, Sonntag H, Weyland A. Changes in cardiac output and intrathoracic blood volume: a mathematical coupling of data? *Acta Anaesthesiol Scand* 2001; **45**: 863–7

24 McLuckie A, Bihari D. Investigating the relationship between intrathoracic blood volume index and cardiac index. *Intensive Care Med* 2000; **26**: 1376–8

25 Walsh TS, Lee A. Mathematical coupling in medical research: lessons from studies of oxygen kinetics. *Br J Anaesth* 1998; **81**: 118–20

26 Cecchetti C, Lubrano R, Cristaldi S, *et al.* Relationship between global end-diastolic volume and cardiac output in critically ill infants and children. *Crit Care Med* 2008; **36**: 928–32

27 Egan JR, Festa M, Cole AD, Nunn GR, Gillis J, Winlaw DS. Clinical assessment of cardiac performance in infants and children following cardiac surgery. *Intensive Care Med* 2005; **31**: 568–73

28 Pinsky MR. Probing the limits of arterial pulse contour analysis to predict preload responsiveness. *Anesth Analg* 2003; **96**: 1245–7

29 Berne RM, Levy MN. The arterial system. In: Berne RM, Levy MN, eds. *Physiology*. St Louis: Mosby Inc., 1998; 415–28

30 Chemla D, Hebert JL, Coirault C, *et al.* Total arterial compliance estimated by stroke volume-to-aortic pulse pressure ratio in humans. *Am J Physiol* 1998; **274**: H500–5

31 Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med* 2009; **37**: 2642–7

32 Wesseling KH, Jansen JR, Settels JJ, Schreuder JJ. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. *J Appl Physiol* 1993; **74**: 2566–73

33 Cannesson M, Aboy M, Hofer CK, Rehman M. Pulse pressure variation: where are we today? *J Clin Monit Comput* 2011; **25**: 45–56

34 Aboy M, McNames J, Thong T, Tsunami D, Ellenby MS, Goldstein B. An automatic beat detection algorithm for pressure signals. *IEEE Trans Biomed Eng* 2005; **52**: 1662–70

35 Hadian M, Severyn DA, Pinsky MR. The effects of vasoactive drugs on pulse pressure and stroke volume variation in postoperative ventilated patients. *J Crit Care* 2011; **26**: 328.e1–8

36 Chew MS, Poelaert J. Accuracy and repeatability of pediatric cardiac output measurement using Doppler: 20-year review of the literature. *Intensive Care Med* 2003; **29**: 1889–94

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Risks and benefits of thoracic epidural anaesthesia

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Editor's key points

- Thoracic epidurals are used widely for intraoperative- and postoperative pain control.
- Perceived benefits such as improved outcome, lower mortality and morbidity, and better gastrointestinal function are likely but difficult to prove.
- The major risks of bleeding and infection are now better quantified and understood.
- The authors conclude that the benefits outweigh the risks if guidelines are followed.

Summary. Thoracic epidural anaesthesia (TEA) reduces cardiac and splanchnic sympathetic activity and thereby influences perioperative function of vital organ systems. A recent meta-analysis suggested that TEA decreased postoperative cardiac morbidity and mortality. TEA appears to ameliorate gut injury in major surgery as long as the systemic haemodynamic effects of TEA are adequately controlled. The functional benefit in fast-track and laparoscopic surgery needs to be clarified. Better pain control with TEA is established in a wide range of surgical procedures. In a setting of advanced surgical techniques, fast-track regimens and a low overall event rate, the number needed to treat to prevent one death by TEA is high. The risk of harm by TEA is even lower, and other methods used to control perioperative pain and stress response also carry specific risks. To optimize the risk–benefit balance of TEA, safe time intervals regarding the use of concomitant anticoagulants and consideration of reduced renal function impairing their elimination must be observed. Infection is a rare complication and is associated with better prognosis. Close monitoring and a predefined algorithm for the diagnosis and treatment of spinal compression or infection are crucial to ensure patient safety with TEA. The risk–benefit balance of analgesia by TEA is favourable and should foster clinical use.

Keywords: cardiovascular risk; epidural anaesthesia; infection; intestinal; bleeding

Thoracic epidural anaesthesia (TEA) has been established as a cornerstone in the perioperative care after thoracic and major abdominal surgery providing most effective analgesia.[1 2] Beyond its analgesic properties, TEA's effects on the postoperative neurohumoural stress response, cardiovascular pathophysiology, and intestinal dysfunction have been in the focus of both clinical and experimental investigations for years.[3–7] However, the use of TEA is related to specific complications and contraindications.

This review aims to outline the risks of TEA and its benefits with respect to the perioperative pathophysiology, outcome, and organ protection.

Increased sympathetic activity and the stress response

The increased sympathetic activity associated with injury induces distinct changes in the host's hormonal and immune response and in the coagulation system.[8–11] These highly conserved defence mechanisms can turn against the host in the case of coexisting cardiovascular disease.[12] A number of synergistic mechanisms are involved in cardiac complications during stress. Increased catecholamine levels increase left ventricular afterload and heart rate, while decreasing the time for coronary perfusion.[13] Altered and stenotic coronary arteries do not respond to sympathetic stimulation.[14] Raised corticotropin-releasing hormone levels reduce cardiac NO release and increase endothelin production. This aggravates coronary endothelial dysfunction.[15] After both minimally invasive and major open surgery increased serum levels of stress hormones have been recorded.[7 16 17] Stress induces a pro-coagulatory state in the absence of any trauma.[18] This effect is prolonged with increasing age and may persist for weeks after surgery.[17 19–21] Finally, early after stressful events, a pro-inflammatory response may lead to plaque instability via activation of matrix metalloproteinases.[22 23] This triad triggers acute coronary syndrome and myocardial infarction during and after stressful events. Consequently, cardiovascular causes account for 63% of perioperative mortality in a high-risk patient population and are still responsible for 30% of perioperative mortality in low-risk patients.[24]

TEA and sympathetic block

A segmental temporary sympathetic block during TEA is assumed to be an important mediator of the perioperative effects of TEA.[13 25] However, both clinical and experimental data on sympathetic activity during TEA need careful interpretation. Methodological problems limit objective assessment of sympathetic activity in the perioperative

period.[26] Microneurography allows a direct and quantitative insight into sympathetic activity. It is, however, an invasive technique and limited in spatial resolution.[27–29] Indirect techniques such as skin conductance response and heart rate variability rely on altered effector organ function during a sympathetic block.[26 27 30] Most measurements are based on the assessment of skin perfusion. This, however, may be affected by the microvascular anatomy, emotional and thermoregulatory state, or presence of general anaesthesia.[27 31 32]

There are limited data on the presence and segmental spread of a thoracic sympathetic block during TEA. Altered skin temperature regulation was shown by thermography in TEA[33] and a cardiac sympathetic block was demonstrated for 6 days during TEA after oesophagectomy.[34] It is unclear whether the sympathetic block is characterized by a limited segmental spread during TEA. This is based on experimental findings in animals demonstrating a segmental sympathetic block with compensatory increase in sympathetic activity in the unblocked area.[29] In humans, a sympathetic block involving splanchnic and lower limb nerves occurred during a limited upper thoracic sensory block with high TEA after injection of 4.2 ml of 0.75% bupivacaine.[35] Midthoracic TEA with 10 ml of 0.25% bupivacaine induced a thoracic sympathetic block that included the legs.[33] In contrast, only segmental sympathetic block was found with a high thoracic TEA using 4 ml bupivacaine 0.5%.[27] The concentration and volume of the local anaesthetic may determine the intensity and the limits of the sympathetic block.[35 36]

Anti-ischaemic effects of TEA in cardiac and non-cardiac surgery

TEA has been shown to decrease adverse perioperative cardiac events.[3 37] Better pain relief with concomitant reduction in the postoperative stress response and systemic sympathetic activity may contribute to this effect.[1 38 39] Regional sympathetic block including the cardiac sympathetic nerves reduces not only ischaemic pain but preserves coronary perfusion during cold pressor testing. This effect was most pronounced in stenotic vessels.[40 41] These data support findings of perioperative anti-ischaemic effects of TEA in both cardiac and non-cardiac surgery. TEA improved diastolic function in patients with coronary artery disease undergoing operative revascularization.[42] Diastolic dysfunction has been reported to be an early sign of cardiac ischaemia. While in this study no effect on systolic function was recorded, an earlier study showed improved systolic function and wall motion in coronary artery disease. Troponin release and long-term survival after coronary artery bypass grafting underline the cardioprotective potential of TEA in that study.[43] In experimental myocardial ischaemia, TEA reduced infarct size.[13] Clinical data on myocardial ischaemia and mortality are inconclusive. In a randomized trial, TEA did not reduce the 30 day complication rate after cardiac surgery.[44] In this study, TEA was only used for $<$24 h in most patients. In contrast, after off-pump coronary artery bypass grafting, TEA used for 72 h reduced arrhythmia and improved postoperative pain control and recovery.[45] The biggest prospective trial of the outcome effects of TEA did not show a survival benefit.[46] However, the trial is underpowered to show the moderate outcome effect of TEA, and interpretation of the results may be compromised.[47] Some meta-analyses suggest that TEA may decrease cardiac morbidity and mortality after cardiac and major non-cardiac surgery.[37 48 49] However, others do not confirm this and emphasize reduced morbidity such as respiratory complication or cardiac arrhythmias after cardiac surgery.[50]

Intestinal perfusion

Safeguarding intestinal perfusion is a critical issue in the maintenance of intestinal function and the integrity of the mucosal barrier. However, the influence of TEA on intestinal perfusion is not understood, with both improvement and deterioration of tissue perfusion being demonstrated.

TEA reversed impaired intraoperative intestinal oxygenation during major surgery and protected intestinal barrier function in experimental hypoxaemia.[51 52] In acute experimental pancreatitis and in sepsis, TEA improved mucosal capillary perfusion.[53 54] In healthy rats, a shift from intermittent to continuous capillary perfusion during mild hypotension was recorded during TEA.[55] Similarly, in patients undergoing oesphagectomy, continuous epidural infusion of bupivacaine without a bolus dose increased anastomotic mucosal blood flow compared with the control group.[56] In these studies, TEA was associated with no or only moderate hypotension. After oesphagectomy, the postoperative increase in cardiac output during the weaning procedure was blunted by TEA, suggesting altered haemodynamic regulation.[56]

However, a number of clinical and experimental studies suggest adverse effects of TEA on measures of intestinal perfusion.[57–60] In 10 patients undergoing oesphagectomy, TEA reduced blood flow in the distal gastric tube mucosa.[61] These studies reported substantial deterioration in systemic haemodynamics. The mean arterial pressure was reduced by 20–50% after induction or during maintenance of TEA.[57 58 60 61] Cardiac output remained stable in one study,[60] but was decreased up to 35% in two.[57 61] Animal studies show that the adverse perfusion effects of TEA are related to an extended or total sympathetic block.[57 58] The clinical study[59] had a sensory block to T4, and as the sympathetic block exceeds the sensory block in epidural anaesthesia, this suggests an almost complete sympathetic block in these patients.[33]

TEA appears to exert beneficial effects on intestinal perfusion as long as its haemodynamic consequences are adequately controlled. The maintenance of systemic perfusion pressure by small doses of norepinephrine has been shown not to compromise intestinal perfusion in experimental abdominal surgery under general anaesthesia.[62] Similarly, systemic hypotension and impaired colonic perfusion after induction of TEA were reversed by vasopressor therapy.[60]

Intestinal motility

After operation, paralytic ileus and abdominal sepsis can be life-threatening and have a major economic impact.[63] Pain, increased sympathetic tone, the use of systemic opioid analgesia, and intestinal neuroinflammatory processes contribute to intestinal hypomotility.[64] The available data on postoperative intestinal function with TEA involve small studies including both thoracic and lumbar epidural anaesthesia, different epidural drug regimens with or without epidural opioids, and covering a wide range of surgical procedures. These studies have been the subject of meta-analyses in the last decade.[65–68] In 2007, a systematic update did not retrieve any major study (group size >100) addressing intestinal function as a primary or secondary outcome.[6] These meta-analyses showed accelerated recovery of intestinal function in all cumulated studies and subsets of studies in major vascular and colorectal surgery.[65 66 68] TEA resulted in a faster resolution of postoperative ileus after major non-intestinal surgery.[69] Epidural infusion of local anaesthetics alone or in combination with opioids was shown to be equally effective in accelerating intestinal recovery and superior to systemic and to epidural opioids alone.[65 70 71] The faster resolution of postoperative ileus after major open surgery has been attributed to superior pain therapy, reduced opioid consumption, and sympathetic block.[6 65]

In the last decade, systemic lidocaine has been studied [72 73] and shown to improve postoperative intestinal motility and hospital stay after surgery.[74 75] Two small studies compared systemic lidocaine with epidural anaesthesia. After colonic surgery, pain control and intestinal recovery were more effective with TEA than with systemic lidocaine.[76] In contrast, a recent study found that both were equally effective.[77] In the latter study, TEA was not used continuously but only started 1 h before the end of the procedure. Furthermore, in many countries the perioperative use of lidocaine for analgesic purposes is unlicensed (off-label-use).

The use of TEA in fast-track and minimally invasive approaches for major procedures has been questioned.[6] Two recent studies of TEA after laparoscopic surgery reported improved bowel motility,[78 79] while another showed no effect.[80] However, differences in the study design, technique of TEA, and the surgical procedures do hinder comparison and interpretation of the data. The faster resolution of ileus was demonstrated on the background of a non-accelerated standard care. Surgery lasted about 3 h and the surgical cases included major resections, such as hemicolectomy, in 12–55%.[78 79] In contrast to this, TEA failed to exert beneficial effects when added to an established fast-track programme after laparoscopic sigmoidal resection with a duration of surgery of 2 h.[80] Pain was significantly lower in the TEA groups in all of the mentioned studies.

Further studies of laparoscopic fast-track regimens are needed to define the role of TEA in comparison with techniques such as transversus abdominis plane (TAP) block or wound catheters and systemic lidocaine infusion.[68] In open upper abdominal surgery, TEA resulted in significantly less opioid consumption compared with a TAP block three times daily.[81] In thoracic and breast surgery, a paravertebral block might be a valuable addition to the portfolio of regional anaesthesia.[82 83] However, similar precautions as in neuraxial anaesthesia must be taken into account.

Anastomotic perfusion and patency

The impact of TEA on anastomotic perfusion and healing of the anastomosis is unclear.

In colorectal surgery, TEA has been found to decrease anastomotic blood flow and to improve gastric and transverse colonic blood flow.[59] After oesphagectomy, reduction in the already compromised mucosal circulation of the proximal end of the gastric tube was more pronounced compared with the distal end.[61] In both studies, however, significant systemic haemodynamic alterations were present. In contrast to this, 1 h (sedated patients) and 18 h (awake and extubated patients) anastomotic mucosal blood flow was increased in TEA after oesophageal resection.[56]

Data on anastomotic patency are also equivocal until today. In 2001, a meta-analysis of 12 clinical trials comparing epidural and systemic analgesia with respect to anastomotic breakdown was unable to show either improved or impaired anastomotic healing due to considerable heterogeneity in the studies.[84] Only two of these studies included more than 30 patients in each group. The drugs used differed between the studies and both lumbar and thoracic epidurals were tested in different surgical procedures. In two larger retrospective case–control studies including 259 mixed gastrointestinal (GI) anastomoses and 400 rectal cancer resections, TEA did not influence anastomotic healing.[85 86]

Recently, TEA was shown to reduce the rate of anastomotic insufficiency after emergency laparotomy.[87] A retrospective analysis of oesophageal anastomosis demonstrated a 70% risk reduction for anastomotic leak in the TEA group.[88] A retrospective analysis of GI surgery found a significantly reduced rate of anastomotic leak.[89] These protective effects might be of great importance in the light of the fivefold increase in mortality in patients with anastomotic leak. However, large randomized controlled trials are needed.

TEA and outcome

TEA provides better pain relief in a wide range of thoracic and abdominal surgery.[1] However, irrespective of better pain control, improvement in the clinical postoperative course by TEA seems to be procedure-specific. While the efficacy of TEA in open colonic resection is well documented, little benefit is reported after hysterectomy.[90] However, in both procedures, TEA significantly improved pain control for up to 2 weeks after surgery.[78–80] Superior pain control and reduced metabolic response are related to an improved quality of life after colonic resection.[91 92] TEA improves the short-term quality of recovery and may affect long-term psychic well being.[45 93] A recent meta-analysis of the pulmonary effects of TEA showed a reduced rate of pneumonia

after TEA, probably due to earlier mobilization, reduced opioid consumption, and improved cough.[94]

A 30% relative risk reduction in fatal outcome was shown after surgery in unselected patients with neuraxial anaesthesia.[3] These findings are in agreement with a retrospective analysis which demonstrated reduced mortality in a TEA group after colectomy or lung resection.[95 96] In cardiac surgery, a meta-analysis showed reduced myocardial ischaemia and mortality and a reduced need for ventilation with TEA for cardiac surgery.[48] While a recent study demonstrated reduced early morbidity after off-pump cardiac surgery, a study including >600 patients with or without epidural anaesthesia during cardiopulmonary bypass did not demonstrate differences in the long-term outcome.[44 45] However, in the latter study, TEA was used only for 24 h. In a very large retrospective analysis in intermediate- and high-risk procedures, TEA resulted in a mild but significant reduction in perioperative mortality.[49]

TEA and tumour spread

Tumour resection is important in the treatment of cancer, but the procedure has significant risks as surgical manipulation promotes systemic spread of tumour cells, which predicts a poor outcome [97 98] Surgical stress impairs the host's immune function and ability to eliminate circulating tumour cells. This includes suppression of natural killer cell function, increased Th2 T-cell activity, and reduced innate immune reactivity.[99] These studies attracted attention to techniques of regional anaesthesia such as TEA or paravertebral block as a potential tool to influence the long-term outcome by perioperative measures.[100]

Four retrospective studies recently demonstrated reduced tumour recurrence rate and improved survival after TEA or paravertebral block.[101–104] Additional retrospective data from colonic surgery suggest that age might influence the effects of TEA on cancer recurrence.[105] The most recent data describe a reduced cancer recurrence only when TEA is used intraoperatively.[106] Prolonged TEA was not better than general anaesthesia alone in this patient population. A disputed *post hoc* analysis of a subpopulation of the MASTER trial patients revealed no difference in oncological outcome.[107] However, there is an urgent need for further scientific effort to clarify this important issue. Morphine has been repeatedly shown to reduce natural killer cell activity and to promote growth in experimental colonic cancer metastasis and experimental breast cancer.[108–111] However, animal experimental data demonstrate that the immunological effects of opioids are only partially understood.[112–115]

Adrenergic response also promotes experimental tumour growth.[116] Social stress increases metastatic growth partially by sympathetic activity.[117] Tumour growth can be prevented by an effective sympathetic block and analgesia in mice.[118] β-Adrenergic inhibition reduces experimental tumour growth, whereas β-adrenergic stimulation increased metastatic growth.[119 120] The observed protective effects of regional anaesthesia might be therefore based on both an opioid-sparing effect and reduced neurohumoral stress response.

Risks of TEA

The benefits of TEA can be demonstrated in large patient populations only. An uneventful perioperative course in a high-risk patient can never be attributed solely to the use of TEA. The procedural complications, however, are highly specific to TEA. Complications can result in severe impairment from spinal cord injury. Consequently, patient safety issues are a dominant aspect in the clinical use and patient perception of TEA. However, the risk of harm as a result of TEA is lower than that of other perioperative treatment strategies. For example, the POISE study of perioperative β-blocker therapy resulted in death or persistent neurological deficit in one of 98 treated patients.[121] This risk greatly exceeds that of TEA, but its manifestations are far more unspecific and usually not clearly related to the therapeutic intervention, which leads to caution in the use of TEA in critically ill patients, despite potential benfits.[122]

Epidural bleeding after TEA

Until today, the risk of bleeding complications both after epidural anaesthesia in general and specifically after TEA is not known. However, there is increasing evidence that the overall number of vertebral canal haematomas after epidural block might be misleading in clinical decision-making. The overall incidence of bleeding within the vertebral canal in the 1990s was 1:18 000 in Sweden.[123] This number, however, includes obstetric epidural patients who have a low risk of vertebral column bleeding after epidural puncture both in the retrospective analysis and in the most recent prospective National Audit Project 3 (NAP3) in the UK.[123 124] The risk of epidural bleeding in the perioperative patient population in the retrospective study was higher, reaching a risk of 1:10 200 for surgical patients,[123] which matches the prospective NAP3 data. In that study, the estimated risk of vertebral canal haematoma ranged between 1:5747 (pessimistic estimation) and 1:12 195 (optimistic estimation) in the perioperative population.[124] In a recent single-centre database analysis, the incidence ranged between 1:2700 and 1:4761.[1 123 125]

These numbers, however, include both lumbar epidurals and TEA. In the Swedish study, haematoma occurred after eight TEAs and 17 lumbar epidural punctures.[123] However, it is not clear how often the respective procedures were performed, and estimation of the risk of TEA is not possible. In NAP3, five of eight bleeding complications occurred after TEA, but again the underlying numbers of TEA and lumbar epidurals are not available. Assuming a less frequent use of TEA, the authors suggest a higher risk of bleeding complications with TEA compared with lumbar epidural block.[124] This is supported by a retrospective analysis of 8100 patients, in which three vertebral column haematomas occurred after TEA but none after lumbar epidural puncture. The total

numbers of the respective procedures, however, are not provided.[125] In contrast, no epidural bleeding was reported in 10 000 cases of TEA, but three occurred after lumbar epidural anaesthesia resulting in a risk of 1:832.[1] Patient age and sex seem to be a major influence in vertebral column haematoma after TEA.[1 123–127] In a case series of 3736 orthopaedic patients, predominantly older women, no bleeding complications were reported.[128] The higher risk for older patients may be related to different causative factors such as reduced epidural space or degeneration of the spine, resulting in more frequent traumatic puncture. However, the higher rate of concomitant use of anticoagulant or antiplatelet drugs in combination with (unrecognized) impairment of renal function may be important. Consequently, the available data allow a reasonable estimation of the overall risk of epidural anaesthesia but do not allow conclusions on the specific incidence of bleeding complications with TEA.

TEA in patients receiving an anticoagulant, antiplatelet, or fibrinolytic drug needs to be performed with caution. The sudden increase in bleeding complications in the presence of twice-daily low-molecular-weight heparin (LMWH) led to the first national guidelines on the use of neuraxial blockade in anticoagulated patients. In 2010, the European guidelines were updated and now cover most recently introduced antiplatelet and anticoagulant drugs.[129] All recommendations refer to patients with normal drug elimination. In patients with (unrecognized) organ dysfunction, for example, renal insufficiency, adapted risk evaluation and careful patient selection are warranted. Glomerular filtration can be assessed from serum creatinine by the simplified equation validated in the Modification of Diet in Renal Disease (MDRD) trial.[130] The higher risk of bleeding after epidural anaesthesia in older women in major studies underlines this necessity.[1 123–126] For example, even mild impairment of renal function increases the time of effective anticoagulation by LMWH from 6.6 to 9.9 h. In severe chronic renal disease, LMWH lasts $>$15 h.[131] In these patients, a 50% dose reduction in LMWH is required. Most elective surgical cases are not in hospital for more than 1 day before surgery; therefore, prophylactic anticoagulation can be started the evening after surgery.[129 132] This ensures the maximal safety of TEA even in older patients with impaired renal function.

The withdrawal of antiplatelet drugs leads to rebound effects with an increased rate of thromboembolic events.[133–135] This rebound effect is aggravated by the prothrombotic and pro-inflammatory state induced by surgery. Stopping antiplatelet drugs within 3 weeks after stenting results in a mortality of 30–86%.[136] Late stent thrombosis after stopping antiplatelet drugs can occur more than 1 yr after stenting.[137 138] Consequently, a consensus has been reached to continue antiplatelet medication in almost all surgical cases other than in emergency intracranial, spinal, and intraocular surgery, where bleeding is potentially catastrophic and bridging with tirofiban and heparin is recommended.[136] In patients taking acetylsalicylic acid, the European and US guidelines allow neuraxial blockade without restrictions on the timing and dosage.[129 139] In all guidelines, the additional risk of the concomitant use of acetylsalicylic acid and other anticoagulant drug is emphasized.

While acetylsalicylic acid is regarded as safe antiplatelet therapy, thienopyridine derivates such as clopidogrel are not recommended 5–7 days before TEA. This warning is based on the increased incidence of surgical bleeding under thienopyridines and two cases of vertebral column haematoma after a neuraxial block under clopidogrel medication.[129 139 140] Recently, however, a case series of 309 vascular surgery patients treated with lumbar epidural anaesthesia was published.[141] Of them, 217 were on dual platelet aggregation inhibition with additional acetylsalicylic acid. None of these patients showed any sign of epidural or spinal bleeding. There are two cases of epidural catheter removal after commencement of a dual antiplatelet therapy due to postoperative myocardial infarction.[142 143] An uneventful course after spinal anaesthesia during dual antiplatelet therapy has been described.[144] In contrast, a number of case reports of spontaneous spinal haematomas during dual antiplatelet therapy without any anaesthetic manipulation raise serious concerns.[145–147] Additionally, spontaneous spinal haematomas have been described both with clopidogrel and acetylsalicylic acid alone.[140 148] Thus, the case series must not lead to an assumption of safety.

Complications due to infection

TEA is an invasive analgesic technique and as such is inevitably associated with the risk of complications due to infection. Iatrogenic pathogen inoculation and haematogenous infection of the insertion site or the epidural catheter are the potential causes of infection within the vertebral canal.[149] Estimates of incidence vary widely.[149] Recent data from Germany report an incidence of one abscess in 10 000 patients with TEA.[1] In the UK, an incidence of 1:24 000 epidural abscesses was found after perioperative neuraxial blockade with 10 of 13 cases in the study period related to epidural anaesthesia.[124] In paediatric postoperative pain therapy, epidural infections and abscesses are also rare.[150] Epidural abscess with spinal cord and radicular compression is the predominant complication after TEA and usually caused by *Staphylococcus aureus*. Meningitis has also been reported with a lower incidence. It is usually caused by *Streptococcus*.[149 151] Infectious complications may occur as early as day 2 but more commonly from day 4. They may be accompanied by signs of infection at the insertion site but usually present with non-specific symptoms. This frequently results in delayed diagnosis and underlines the necessity of close clinical observation and a high level of suspicion.[124] The prognosis of complications due to infection is better than that for epidural bleeding. All patients with meningitis had full recovery and $\sim$50% of the patients with epidural abscesses recover without permanent disability.[124]

Practical patient safety measures

Recent data from the UK reported delayed diagnosis in four of five cases of epidural haematoma with persistent harm. Only one patient was treated in time and reached full recovery.[124] Renal function must be checked in patients receiving TEA to detect any impairment. As catheter removal is a critical phase which may trigger epidural bleeding, neurological monitoring must be continued until 24 h after catheter removal. Regular neurological assessment must be an integral part of postoperative care for TEA. Patients and medical and nursing personnel in the surgical wards must be aware of the early signs of neurological complications during or early after TEA. Thoracic catheter insertion and the consequent use of low concentrations of local anaesthetic further foster timely suspicion of epidural complications as there will be a low incidence of dense motor blocks. Any new or unexpectedly dense motor block must trigger an algorithm including discontinuation of epidural drug administration, frequent clinical reassessment, and low threshold for urgent magnetic resonance imaging of the epidural space in the case of persistent signs. Preparation of epidural drug solutions should only be provided by a pharmacy without the further need of manipulation.[152]

In conclusion, TEA provides optimal pain therapy in a wide range of surgical procedures and may reduce perioperative morbidity and mortality after major abdominal and thoracic surgery. TEA may influence tumour progression after oncological surgery. However, the low event rate and changes in the surgical technique and perioperative management mean that a large number of patients would be required to prove the effects of TEA in a randomized controlled trial.[49] The available studies vary with respect to surgical procedures, insertion level of epidural anaesthesia, choice of epidural drugs and infusion regimen, measurement parameters, and methodological quality. Therefore, with respect to perioperative outcome and pathophysiology, large retrospective analyses or meta-analyses are often still the best available evidence. Large prospective studies and retrospective analyses of TEA have allowed accurate estimation of the risk of neuraxial damage and persistent neurological deficits. Rigid adherence to good operating procedures and a high level of awareness can largely improve the safety of TEA in patients receiving antiplatelet and anticoagulant drugs. The available data suggest a high level of safety when TEA is used as established in guidelines. The additional beneficial effects on intestinal, cardiovascular, and immune function and on better pain control must be considered along with the background of safety.

Conflict of interest

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References

1 Popping DM, Zahn PK, Van Aken HK, Dasch B, Boche R, Pogatzki-Zahn EM. Effectiveness and safety of postoperative pain management: a survey of 18 925 consecutive patients between 1998 and 2006 (2nd revision): a database analysis of prospectively raised data. *Br J Anaesth* 2008; **101**: 832–40

2 Royse C, Royse A, Soeding P, Blake D, Pang J. Prospective randomized trial of high thoracic epidural analgesia for coronary artery bypass surgery. *Ann Thorac Surg* 2003; **75**: 93–100

3 Rodgers A, Walker N, Schug S, *et al.* Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. *Br Med J* 2000; **321**: 1493

4 Liu SS. Anesthesia and analgesia for colon surgery. *Reg Anesth Pain Med* 2004; **29**: 52–7

5 Kozian A, Schilling T, Hachenberg T. Non-analgetic effects of thoracic epidural anaesthesia. *Curr Opin Anaesthesiol* 2005; **18**: 29–34

6 Liu SS, Wu CL. Effect of postoperative analgesia on major postoperative complications: a systematic update of the evidence. *Anesth Analg* 2007; **104**: 689–702

7 Brodner G, Van Aken H, Hertle L, *et al.* Multimodal perioperative management—combining thoracic epidural analgesia, forced mobilization, and oral nutrition—reduces hormonal and metabolic stress and improves convalescence after major urologic surgery. *Anesth Analg* 2001; **92**: 1594–600

8 Holte K, Kehlet H. Epidural anaesthesia and analgesia—effects on surgical stress responses and implications for postoperative nutrition. *Clin Nutr* 2002; **21**: 199–206

9 Sedowofia K, Barclay C, Quaba A, *et al.* The systemic stress response to thermal injury in children. *Clin Endocrinol (Oxf)* 1998; **49**: 335–41

10 Woolf PD, McDonald JV, Feliciano DV, Kelly MM, Nichols D, Cox C. The catecholamine response to multisystem trauma. *Arch Surg* 1992; **127**: 899–903

11 Leor J, Poole WK, Kloner RA. Sudden cardiac death triggered by an earthquake. *N Engl J Med* 1996; **334**: 413–19

12 Wilbert-Lampen U, Leistner D, Greven S, *et al.* Cardiovascular events during World Cup soccer. *N Engl J Med* 2008; **358**: 475–83

13 Meissner A, Rolf N, Van Aken H. Thoracic epidural anesthesia and the patient with heart disease: benefits, risks, and controversies. *Anesth Analg* 1997; **85**: 517–28

14 Nabel EG, Ganz P, Gordon JB, Alexander RW, Selwyn AP. Dilation of normal and constriction of atherosclerotic coronary arteries caused by the cold pressor test. *Circulation* 1988; **77**: 43–52

15 Wilbert-Lampen U, Straube F, Trapp A, Deutschmann A, Plasse A, Steinbeck G. Effects of corticotropin-releasing hormone (CRH) on monocyte function, mediated by CRH-receptor subtype R1 and R2: a potential link between mood disorders and endothelial dysfunction? *J Cardiovasc Pharmacol* 2006; **47**: 110–16

16 Marana E, Scambia G, Colicci S, *et al.* Leptin and perioperative neuroendocrine stress response with two different anaesthetic techniques. *Acta Anaesthesiol Scand* 2008; **52**: 541–6

17 Kobayashi M, Tsujitani S, Kurisu Y, Kaibara N. Responses of cytokines and coagulation-fibrinolytic states to surgical stress following esophagectomy. *Hepatogastroenterology* 2004; **51**: 1376–8

18 von Kanel R, Mills PJ, Ziegler MG, Dimsdale JE. Effect of beta2-adrenergic receptor functioning and increased norepinephrine on the hypercoagulable state with mental stress. *Am Heart J* 2002; **144**: 68–72

19 Wirtz PH, Redwine LS, Baertschi C, Spillmann M, Ehlert U, von Kanel R. Coagulation activity before and after acute psychosocial stress increases with age. *Psychosom Med* 2008; **70**: 476–81

20 Dahl OE. Mechanisms of hypercoagulability. *Thromb Haemost* 1999; **82**: 902–6

21 Sweetland S, Green J, Liu B, *et al.* Duration and magnitude of the postoperative risk of venous thromboembolism in middle aged women: prospective cohort study. *Br Med J* 2009; **339**: b4583

22 Sambola A, Osende J, Hathcock J, *et al.* Role of risk factors in the modulation of tissue factor activity and blood thrombogenicity. *Circulation* 2003; **107**: 973–7

23 Gidron Y, Gilutz H, Berger R, Huleihel M. Molecular and cellular interface between behavior and acute coronary syndromes. *Cardiovasc Res* 2002; **56**: 15–21

24 Bangalore S, Wetterslev J, Pranesh S, Sawhney S, Gluud C, Messerli FH. Perioperative beta blockers in patients having non-cardiac surgery: a meta-analysis. *Lancet* 2008; **372**: 1962–76

25 Clemente A, Carli F. The physiological effects of thoracic epidural anesthesia and analgesia on the cardiovascular, respiratory and gastrointestinal systems. *Minerva Anestesiol* 2008; **74**: 549–63

26 Cook PR, Malmqvist LA, Bengtsson M, Tryggvason B, Lofstrom JB. Vagal and sympathetic activity during spinal analgesia. *Acta Anaesthesiol Scand* 1990; **34**: 271–5

27 Magnusdottir H, Kirno K, Ricksten SE, Elam M. High thoracic epidural anesthesia does not inhibit sympathetic nerve activity in the lower extremities. *Anesthesiology* 1999; **91**: 1299–304

28 Hogan QH, Kulier A, Bosnjak ZJ, Kampine JP. Sympathetic and mesenteric venous responses to baroreceptor or chemoreceptor stimulation during epidural anesthesia in rabbits. *Anesthesiology* 1996; **85**: 1413–21

29 Taniguchi M, Kasaba T, Takasaki M. Epidural anesthesia enhances sympathetic nerve activity in the unanesthetized segments in cats. *Anesth Analg* 1997; **84**: 391–7

30 Introna R, Yodlowski E, Pruett J, Montano N, Porta A, Crumrine R. Sympathovagal effects of spinal anesthesia assessed by heart rate variability analysis. *Anesth Analg* 1995; **80**: 315–21

31 Adolphs J, Schmitt TK, Schmidt DK, *et al.* Evaluation of sympathetic blockade after intrathecal and epidural lidocaine in rats by laser Doppler perfusion imaging. *Eur Surg Res* 2005; **37**: 50–9

32 Eisenach JH, Pike TL, Wick DE, *et al.* A comparison of peripheral skin blood flow and temperature during endoscopic thoracic sympathotomy. *Anesth Analg* 2005; **100**: 269–76

33 Freise H, Meissner A, Lauer S, *et al.* Thoracic epidural analgesia with low concentration of bupivacaine induces thoracic and lumbar sympathetic block: a randomized, double-blind clinical trial. *Anesthesiology* 2008; **109**: 1107–12

34 Simeoforidou M, Vretzakis G, Bareka M, *et al.* Thoracic epidural analgesia with levobupivacaine for 6 postoperative days attenuates sympathetic activation after thoracic surgery. *J Cardiothorac Vasc Anesth* 2011; **25**: 817–23

35 Hopf HB, Weissbach B, Peters J. High thoracic segmental epidural anesthesia diminishes sympathetic outflow to the legs, despite restriction of sensory blockade to the upper thorax. *Anesthesiology* 1990; **73**: 882–9

36 Ginosar Y, Weiniger CF, Kurz V, Babchenko A, Nitzan M, Davidson E. Sympathectomy-mediated vasodilatation: a randomized concentration ranging study of epidural bupivacaine. *Can J Anaesth* 2009; **56**: 213–21

37 Beattie WS, Badner NH, Choi P. Epidural analgesia reduces postoperative myocardial infarction: a meta-analysis. *Anesth Analg* 2001; **93**: 853–8

38 Holte K, Kehlet H. Effect of postoperative epidural analgesia on surgical outcome. *Minerva Anestesiol* 2002; **68**: 157–61

39 Kehlet H. The endocrine-metabolic response to postoperative pain. *Acta Anaesthesiol Scand Suppl* 1982; **74**: 173–5

40 Olausson K, Magnusdottir H, Lurje L, Wennerblom B, Emanuelsson H, Ricksten SE. Anti-ischemic and anti-anginal effects of thoracic epidural anesthesia versus those of conventional medical therapy in the treatment of severe refractory unstable angina pectoris. *Circulation* 1997; **96**: 2178–82

41 Nygard E, Kofoed KF, Freiberg J, *et al.* Effects of high thoracic epidural analgesia on myocardial blood flow in patients with ischemic heart disease. *Circulation* 2005; **111**: 2165–70

42 Schmidt C, Hinder F, Van Aken H, *et al.* The effect of high thoracic epidural anesthesia on systolic and diastolic left ventricular function in patients with coronary artery disease. *Anesth Analg* 2005; **100**: 1561–9

43 Berendes E, Schmidt C, Van Aken H, *et al.* Reversible cardiac sympathectomy by high thoracic epidural anesthesia improves regional left ventricular function in patients undergoing coronary artery bypass grafting: a randomized trial. *Arch Surg* 2003; **138**: 1283–90; discussion 91

44 Svircevic V, Nierich AP, Moons KG, *et al.* Thoracic epidural anesthesia for cardiac surgery: a randomized trial. *Anesthesiology* 2011; **114**: 262–70

45 Caputo M, Alwair H, Rogers CA, *et al.* Thoracic epidural anesthesia improves early outcomes in patients undergoing off-pump coronary artery bypass surgery: a prospective, randomized, controlled trial. *Anesthesiology* 2011; **114**: 380–90

46 Rigg JR, Jamrozik K, Myles PS, *et al.* Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. *Lancet* 2002; **359**: 1276–82

47 Van Aken H, Gogarten W, Brussel T, Brodner G. Epidural anaesthesia and analgesia in major surgery. *Lancet* 2002; **360**: 568; author reply 9

48 Bignami E, Landoni G, Biondi-Zoccai GG, *et al.* Epidural analgesia improves outcome in cardiac surgery: a meta-analysis of randomized controlled trials. *J Cardiothorac Vasc Anesth* 2009; **23**: 594–9

49 Wijeysundera DN, Beattie WS, Austin PC, Hux JE, Laupacis A. Epidural anaesthesia and survival after intermediate-to-high risk non-cardiac surgery: a population-based cohort study. *Lancet* 2008; **372**: 562–9

50 Svircevic V, van Dijk D, Nierich AP, *et al.* Meta-analysis of thoracic epidural anesthesia versus general anesthesia for cardiac surgery. *Anesthesiology* 2011; **114**: 271–82

51 Ai K, Kotake Y, Satoh T, Serita R, Takeda J, Morisaki H. Epidural anesthesia retards intestinal acidosis and reduces portal vein endotoxin concentrations during progressive hypoxia in rabbits. *Anesthesiology* 2001; **94**: 263–9

52 Kapral S, Gollmann G, Bachmann D, *et al.* The effects of thoracic epidural anesthesia on intraoperative visceral perfusion and metabolism. *Anesth Analg* 1999; **88**: 402–6

53 Daudel F, Freise H, Westphal M, *et al.* Continuous thoracic epidural anesthesia improves gut mucosal microcirculation in rats with sepsis. *Shock* 2007; **28**: 610–4

54 Freise H, Lauer S, Anthonsen S, *et al.* Thoracic epidural analgesia augments ileal mucosal capillary perfusion and improves survival in severe acute pancreatitis in rats. *Anesthesiology* 2006; **105**: 354–9

55 Sielenkamper AW, Eicker K, Van Aken H. Thoracic epidural anesthesia increases mucosal perfusion in ileum of rats. *Anesthesiology* 2000; **93**: 844–51

56 Michelet P, Roch A, D'Journo XB, *et al.* Effect of thoracic epidural analgesia on gastric blood flow after oesophagectomy. *Acta Anaesthesiol Scand* 2007; **51**: 587–94

57 Schwarte LA, Picker O, Hohne C, Fournell A, Scheeren TW. Effects of thoracic epidural anaesthesia on microvascular gastric mucosal oxygenation in physiological and compromised circulatory conditions in dogs. *Br J Anaesth* 2004; **93**: 552–9

58 Adolphs J, Schmidt DK, Korsukewitz I, *et al.* Effects of thoracic epidural anaesthesia on intestinal microvascular perfusion in a rodent model of normotensive endotoxaemia. *Intensive Care Med* 2004; **30**: 2094–101

59 Sala C, Garcia-Granero E, Molina MJ, Garcia JV, Lledo S. Effect of epidural anesthesia on colorectal anastomosis: a tonometric assessment. *Dis Colon Rectum* 1997; **40**: 958–61

60 Gould TH, Grace K, Thorne G, Thomas M. Effect of thoracic epidural anaesthesia on colonic blood flow. *Br J Anaesth* 2002; **89**: 446–51

61 Al-Rawi OY, Pennefather SH, Page RD, Dave I, Russell GN. The effect of thoracic epidural bupivacaine and an intravenous adrenaline infusion on gastric tube blood flow during esophagectomy. *Anesth Analg* 2008; **106**: 884–7, table of contents

62 Hiltebrand LB, Koepfli E, Kimberger O, Sigurdsson GH, Brandt S. Hypotension during fluid-restricted abdominal surgery: effects of norepinephrine treatment on regional and microcirculatory blood flow in the intestinal tract. *Anesthesiology* 2011; **114**: 557–64

63 Fruhwald S, Holzer P, Metzler H. Gastrointestinal motility in acute illness. *Wien Klin Wochenschr* 2008; **120**: 6–17

64 Bauer AJ. Mentation on the immunological modulation of gastrointestinal motility. *Neurogastroenterol Motil* 2008; **20**(Suppl. 1): 81–90

65 Jorgensen H, Wetterslev J, Moiniche S, Dahl JB. Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. *Cochrane Database Syst Rev* 2000; CD001893

66 Nishimori M, Ballantyne JC, Low JH. Epidural pain relief versus systemic opioid-based pain relief for abdominal aortic surgery. *Cochrane Database Syst Rev* 2006; **3**: CD005059

67 Werawatganon T, Charuluxanun S. Patient controlled intravenous opioid analgesia versus continuous epidural analgesia for pain after intra-abdominal surgery. *Cochrane Database Syst Rev* 2005; CD004088

68 Marret E, Remy C, Bonnet F. Meta-analysis of epidural analgesia versus parenteral opioid analgesia after colorectal surgery. *Br J Surg* 2007; **94**: 665–73

69 Blumenthal S, Min K, Nadig M, Borgeat A. Double epidural catheter with ropivacaine versus intravenous morphine: a comparison for postoperative analgesia after scoliosis correction surgery. *Anesthesiology* 2005; **102**: 175–80

70 de Leon-Casasola OA, Karabella D, Lema MJ. Bowel function recovery after radical hysterectomies: thoracic epidural bupivacaine-morphine versus intravenous patient-controlled analgesia with morphine: a pilot study. *J Clin Anesth* 1996; **8**: 87–92

71 Liu SS, Carpenter RL, Mackey DC, *et al.* Effects of perioperative analgesic technique on rate of recovery after colon surgery. *Anesthesiology* 1995; **83**: 757–65

72 Hahnenkamp K, Herroeder S, Hollmann MW. Regional anaesthesia, local anaesthetics and the surgical stress response. *Best Pract Res Clin Anaesthesiol* 2004; **18**: 509–27

73 Marret E, Rolin M, Beaussier M, Bonnet F. Meta-analysis of intravenous lidocaine and postoperative recovery after abdominal surgery. *Br J Surg* 2008; **95**: 1331–8

74 Herroeder S, Pecher S, Schonherr ME, *et al.* Systemic lidocaine shortens length of hospital stay after colorectal surgery: a double-blinded, randomized, placebo-controlled trial. *Ann Surg* 2007; **246**: 192–200

75 Harvey KP, Adair JD, Isho M, Robinson R. Can intravenous lidocaine decrease postsurgical ileus and shorten hospital stay in elective bowel surgery? A pilot study and literature review. *Am J Surg* 2009; **198**: 231–6

76 Kuo CP, Jao SW, Chen KM, *et al.* Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. *Br J Anaesth* 2006; **97**: 640–6

77 Swenson BR, Gottschalk A, Wells LT, *et al.* Intravenous lidocaine is as effective as epidural bupivacaine in reducing ileus duration, hospital stay, and pain after open colon resection: a randomized clinical trial. *Reg Anesth Pain Med* 2010; **35**: 370–6

78 Taqi A, Hong X, Mistraletti G, Stein B, Charlebois P, Carli F. Thoracic epidural analgesia facilitates the restoration of bowel function and dietary intake in patients undergoing laparoscopic colon resection using a traditional, nonaccelerated, perioperative care program. *Surg Endosc* 2007; **21**: 247–52

79 Zingg U, Miskovic D, Hamel CT, Erni L, Oertli D, Metzger U. Influence of thoracic epidural analgesia on postoperative pain relief and ileus after laparoscopic colorectal resection: benefit with epidural analgesia. *Surg Endosc* 2009; **23**: 276–82

80 Turunen P, Carpelan-Holmstrom M, Kairaluoma P, *et al.* Epidural analgesia diminished pain but did not otherwise improve enhanced recovery after laparoscopic sigmoidectomy: a prospective randomized study. *Surg Endosc* 2009; **23**: 31–7

81 Niraj G, Kelkar A, Jeyapalan I, *et al.* Comparison of analgesic efficacy of subcostal transversus abdominis plane blocks with epidural analgesia following upper abdominal surgery. *Anaesthesia* 2011; **66**: 465–71

82 Powell ES, Cook D, Pearce AC, *et al.* A prospective, multicentre, observational cohort study of analgesia and outcome after pneumonectomy. *Br J Anaesth* 2011; **106**: 364–70

83 Messina M, Boroli F, Landoni G, *et al.* A comparison of epidural vs. paravertebral blockade in thoracic surgery. *Minerva Anestesiol* 2009; **75**: 616–21

84 Holte K, Kehlet H. Epidural analgesia and risk of anastomotic leakage. *Reg Anesth Pain Med* 2001; **26**: 111–17

85 Zakrison T, Nascimento BA Jr, Tremblay LN, Kiss A, Rizoli SB. Perioperative vasopressors are associated with an increased risk of gastrointestinal anastomotic leakage. *World J Surg* 2007; **31**: 1627–34

86 Jestin P, Pahlman L, Gunnarsson U. Risk factors for anastomotic leakage after rectal cancer surgery: a case–control study. *Colorectal Dis* 2008; **10**: 715–21

87 Tyagi A, Seelan S, Sethi AK, Mohta M. Role of thoracic epidural block in improving post-operative outcome for septic patients: a preliminary report. *Eur J Anaesthesiol* 2011; **28**: 291–7

88 Michelet P, D'Journo XB, Roch A, *et al.* Perioperative risk factors for anastomotic leakage after esophagectomy: influence of thoracic epidural analgesia. *Chest* 2005; **128**: 3461–6

89 Zugel N, Bruer C, Breitschaft K, Angster R. Effect of thoracic epidural analgesia on the early postoperative phase after interventions on the gastrointestinal tract. *Chirurg* 2002; **73**: 262–8

90 Kehlet H, Wilkinson RC, Fischer HB, Camu F. PROSPECT: evidence-based, procedure-specific postoperative pain management. *Best Pract Res Clin Anaesthesiol* 2007; **21**: 149–59

91 Carli F, Mayo N, Klubien K, Schricker T, Trudel J, Belliveau P. Epidural analgesia enhances functional exercise capacity and health-related quality of life after colonic surgery: results of a randomized trial. *Anesthesiology* 2002; **97**: 540–9

92 Lattermann R, Carli F, Schricker T. Epidural blockade suppresses lipolysis during major abdominal surgery. *Reg Anesth Pain Med* 2002; **27**: 469–75

93 Royse C, Remedios C, Royse A. High thoracic epidural analgesia reduces the risk of long-term depression in patients undergoing coronary artery bypass surgery. *Ann Thorac Cardiovasc Surg* 2007; **13**: 32–5

94 Popping DM, Elia N, Marret E, Remy C, Tramer MR. Protective effects of epidural analgesia on pulmonary complications after abdominal and thoracic surgery: a meta-analysis. *Arch Surg* 2008; **143**: 990–9; discussion 1000

95 Wu CL, Rowlingson AJ, Herbert R, Richman JM, Andrews RA, Fleisher LA. Correlation of postoperative epidural analgesia on morbidity and mortality after colectomy in Medicare patients. *J Clin Anesth* 2006; **18**: 594–9

96 Wu CL, Sapirstein A, Herbert R, *et al.* Effect of postoperative epidural analgesia on morbidity and mortality after lung resection in Medicare patients. *J Clin Anesth* 2006; **18**: 515–20

97 Liu Z, Jiang M, Zhao J, Ju H. Circulating tumor cells in perioperative esophageal cancer patients: quantitative assay system and potential clinical utility. *Clin Cancer Res* 2007; **13**: 2992–7

98 Lurje G, Schiesser M, Claudius A, Schneider PM. Circulating tumor cells in gastrointestinal malignancies: current techniques and clinical implications. *J Oncol* 2010; **2010**: 392652

99 Vallejo R, Hord ED, Barna SA, Santiago-Palma J, Ahmed S. Perioperative immunosuppression in cancer patients. *J Environ Pathol Toxicol Oncol* 2003; **22**: 139–46

100 Snyder GL, Greenberg S. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. *Br J Anaesth* 2010; **105**: 106–15

101 Christopherson R, James KE, Tableman M, Marshall P, Johnson FE. Long-term survival after colon cancer surgery: a variation associated with choice of anesthesia. *Anesth Analg* 2008; **107**: 325–32

102 Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? *Anesthesiology* 2006; **105**: 660–4

103 Biki B, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. *Anesthesiology* 2008; **109**: 180–7

104 Wuethrich PY, Hsu Schmitz SF, Kessler TM, *et al.* Potential influence of the anesthetic technique used during open radical prostatectomy on prostate cancer-related outcome: a retrospective study. *Anesthesiology* 2010; **113**: 570–6

105 Gottschalk A, Ford JG, Regelin CC, *et al.* Association between epidural analgesia and cancer recurrence after colorectal cancer surgery. *Anesthesiology* 2010; **113**: 27–34

106 de Oliveira GS Jr, Ahmad S, Schink JC, Singh DK, Fitzgerald PC, McCarthy RJ. Intraoperative neuraxial anesthesia but not postoperative neuraxial analgesia is associated with increased relapse-free survival in ovarian cancer patients after primary cytoreductive surgery. *Reg Anesth Pain Med* 2011; **36**: 271–7

107 Myles PS, Peyton P, Silbert B, Hunt J, Rigg JR, Sessler DI. Perioperative epidural analgesia for major abdominal surgery for cancer and recurrence-free survival: randomised trial. *Br Med J* 2011; **342**: d1491

108 Gupta K, Kshirsagar S, Chang L, *et al.* Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth. *Cancer Res* 2002; **62**: 4491–8

109 Yeager MP, Colacchio TA. Effect of morphine on growth of metastatic colon cancer in vivo. *Arch Surg* 1991; **126**: 454–6

110 Yeager MP, Colacchio TA, Yu CT, *et al.* Morphine inhibits spontaneous and cytokine-enhanced natural killer cell cytotoxicity in volunteers. *Anesthesiology* 1995; **83**: 500–8

111 Farooqui M, Li Y, Rogers T, *et al.* COX-2 inhibitor celecoxib prevents chronic morphine-induced promotion of angiogenesis, tumour growth, metastasis and mortality, without compromising analgesia. *Br J Cancer* 2007; **97**: 1523–31

112 Borman A, Ciepielewski Z, Wrona D, *et al.* Small doses of morphine can enhance NK cell cytotoxicity in pigs. *Int Immunopharmacol* 2009; **9**: 277–83

113 Martucci C, Panerai AE, Sacerdote P. Chronic fentanyl or buprenorphine infusion in the mouse: similar analgesic profile but different effects on immune responses. *Pain* 2004; **110**: 385–92

114 Carrigan KA, Saurer TB, Ijames SG, Lysle DT. Buprenorphine produces naltrexone reversible alterations of immune status. *Int Immunopharmacol* 2004; **4**: 419–28

115 Saurer TB, Ijames SG, Carrigan KA, Lysle DT. Neuroimmune mechanisms of opioid-mediated conditioned immunomodulation. *Brain Behav Immun* 2008; **22**: 89–97

116 Ben-Eliyahu S, Shakhar G, Rosenne E, Levinson Y, Beilin B. Hypothermia in barbiturate-anesthetized rats suppresses natural killer cell activity and compromises resistance to tumor metastasis: a role for adrenergic mechanisms. *Anesthesiology* 1999; **91**: 732–40

117 Vegas O, Garmendia L, Arregi A, Beitia G, Azpiroz A. Effects of antalarmin and nadolol on the relationship between social stress and pulmonary metastasis development in male OF1 mice. *Behav Brain Res* 2009; **205**: 200–6

118 Bar-Yosef S, Melamed R, Page GG, Shakhar G, Shakhar K, Ben-Eliyahu S. Attenuation of the tumor-promoting effect of surgery by spinal blockade in rats. *Anesthesiology* 2001; **94**: 1066–73

119 Ben-Eliyahu S, Shakhar G, Page GG, Stefanski V, Shakhar K. Suppression of NK cell activity and of resistance to metastasis by stress: a role for adrenal catecholamines and beta-adrenoceptors. *Neuroimmunomodulation* 2000; **8**: 154–64

120 Glasner A, Avraham R, Rosenne E, *et al.* Improving survival rates in two models of spontaneous postoperative metastasis in mice by combined administration of a beta-adrenergic antagonist and a cyclooxygenase-2 inhibitor. *J Immunol* 2010; **184**: 2449–57

121 Devereaux PJ, Yang H, Yusuf S, *et al.* Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008; **371**: 1839–47

122 Schug S. The effect of neuraxial blockade on peri-operative mortality and major morbidity: an updated meta-analysis. *Anaesth Intensive Care* 2005; **33**: 675

123 Moen V, Dahlgren N, Irestedt L. Severe neurological complications after central neuraxial blockades in Sweden 1990–1999. *Anesthesiology* 2004; **101**: 950–9

124 Cook TM, Counsell D, Wildsmith JA. Major complications of central neuraxial block: report on the Third National Audit Project of the Royal College of Anaesthetists. *Br J Anaesth* 2009; **102**: 179–90

125 Christie IW, McCabe S. Major complications of epidural analgesia after surgery: results of a six-year survey. *Anaesthesia* 2007; **62**: 335–41

126 Cameron CM, Scott DA, McDonald WM, Davies MJ. A review of neuraxial epidural morbidity: experience of more than 8,000 cases at a single teaching hospital. *Anesthesiology* 2007; **106**: 997–1002

127 Vandermeulen EP, Van Aken H, Vermylen J. Anticoagulants and spinal-epidural anesthesia. *Anesth Analg* 1994; **79**: 1165–77

128 Liu SS, Bieltz M, Wukovits B, John RS. Prospective survey of patient-controlled epidural analgesia with bupivacaine and hydromorphone in 3736 postoperative orthopedic patients. *Reg Anesth Pain Med* 2010; **35**: 351–4

129 Gogarten W, Vandermeulen E, Van Aken H, Kozek S, Llau JV, Samama CM. Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology. *Eur J Anaesthesiol* 2010; **27**: 999–1015

130 Levey AS, Coresh J, Greene T, *et al.* Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem* 2007; **53**: 766–72

131 Sanderink GJ, Guimart CG, Ozoux ML, Jariwala NU, Shukla UA, Boutouyrie BX. Pharmacokinetics and pharmacodynamics of the prophylactic dose of enoxaparin once daily over 4 days in patients with renal impairment. *Thromb Res* 2002; **105**: 225–31

132 Geerts WH, Bergqvist D, Pineo GF, *et al.* Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133**: 381S–453S

133 Beving H, Zhao C, Albage A, Ivert T. Abnormally high platelet activity after discontinuation of acetylsalicylic acid treatment. *Blood Coagul Fibrinolysis* 1996; **7**: 80–4

134 Burger W, Chemnitius JM, Kneissl GD, Rucker G. Low-dose aspirin for secondary cardiovascular prevention—cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation—review and meta-analysis. *J Intern Med* 2005; **257**: 399–414

135 Oscarsson A, Gupta A, Fredrikson M, *et al.* To continue or discontinue aspirin in the perioperative period: a randomized, controlled clinical trial. *Br J Anaesth* 2010; **104**: 305–12

136 Chassot PG, Delabays A, Spahn DR. Perioperative antiplatelet therapy: the case for continuing therapy in patients at risk of myocardial infarction. *Br J Anaesth* 2007; **99**: 316–28

137 McFadden EP, Stabile E, Regar E, *et al.* Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004; **364**: 1519–21

138 Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis. *J Am Coll Cardiol* 2005; **45**: 456–9

139 Horlocker TT, Wedel DJ, Rowlingson JC, *et al.* Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med* 2010; **35**: 64–101

140 Breivik H, Bang U, Jalonen J, Vigfusson G, Alahuhta S, Lagerkranser M. Nordic guidelines for neuraxial blocks in disturbed haemostasis from the Scandinavian Society of Anaesthesiology and Intensive Care Medicine. *Acta Anaesthesiol Scand* 2010; **54**: 16–41

141 Osta WA, Akbary H, Fuleihan SF. Epidural analgesia in vascular surgery patients actively taking clopidogrel. *Br J Anaesth* 2010; **104**: 429–32

142 Bergmann L, Kienbaum P, Gorlinger K, Peters J. Uneventful removal of an epidural catheter guided by impedance aggregometry in a patient with recent coronary stenting and treated with clopidogrel and acetylsalicylic acid. *Reg Anesth Pain Med* 2007; **32**: 354–7

143 Tank S, Gottschalk A, Radtke P, Nickler E, Freitag M, Standl T. Removal of an epidural catheter under ongoing antithrombotic therapy. *Anasthesiol Intensivmed Notfallmed Schmerzther* 2006; **41**: 274–7

144 Herbstreit F, Peters J. Spinal anaesthesia despite combined clopidogrel and aspirin therapy in a patient awaiting lung transplantation: effects of platelet transfusion on clotting tests. *Anaesthesia* 2005; **60**: 85–7

145 Lim SH, Hong BY, Cho YR, *et al.* Relapsed spontaneous spinal epidural hematoma associated with aspirin and clopidogrel. *Neurol Sci* 2011; **32**: 687–9

146 Moon HJ, Kim JH, Kwon TH, Chung HS, Park YK. Spontaneous spinal epidural hematoma: an urgent complication of adding clopidogrel to aspirin therapy. *J Neurol Sci* 2009; **285**: 254–6

147 Omori N, Takada E, Narai H, Tanaka T, Abe K, Manabe Y. Spontaneous cervical epidural hematoma treated by the combination of surgical evacuation and steroid pulse therapy. *Intern Med* 2008; **47**: 437–40

148 Finsterer J, Seywald S, Stollberger C, *et al.* Recovery from acute paraplegia due to spontaneous spinal, epidural hematoma under minimal-dose acetyl-salicylic acid. *Neurol Sci* 2008; **29**: 271–3

149 Schulz-Stubner S, Pottinger JM, Coffin SA, Herwaldt LA. Nosocomial infections and infection control in regional anesthesia. *Acta Anaesthesiol Scand* 2008; **52**: 1144–57

150 Sethna NF, Clendenin D, Athiraman U, Solodiuk J, Rodriguez DP, Zurakowski D. Incidence of epidural catheter-associated infections after continuous epidural analgesia in children. *Anesthesiology* 2010; **113**: 224–32

151 Horlocker TT, Wedel DJ. Infectious complications of regional anesthesia. *Best Pract Res Clin Anaesthesiol* 2008; **22**: 451–75

152 Pogatzki-Zahn EM, Wenk M, Wassmann H, Heindel WL, Van Aken H. Complications of regional anesthesia: diagnostic and management. *Anasthesiol Intensivmed Notfallmed Schmerzther* 2007; **42**: 42–52

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OROS® hydromorphone prolonged release for the management of chronic, moderate to severe pain

Hydromorphone is a semisynthetic derivative of morphine, which may be used as an alternative to morphine in the treatment of severe chronic pain. OROS® hydromorphone prolonged release uses OROS® (osmotic-controlled release oral delivery system) technology, which provides stable plasma concentrations and avoids fluctuating plasma drug levels that may lead to adverse events and breakthrough pain. With once-daily administration, the OROS® delivery system releases hydromorphone at a near constant rate to provide 'around-the-clock' analgesia and reduce the necessity for breakthrough pain medication.

OROS® hydromorphone is indicated for use in patients with severe pain. It is contraindicated in patients with acute or postoperative pain. Although hydromorphone is a more potent analgesic agent than morphine, differences between individual agents and opioid formulations mean that a fixed dose ratio cannot be relied on when switching patients from other opioids to OROS® hydromorphone and careful patient monitoring and dose titration is required. The manufacturer's prescribing information recommends that the total daily dose of morphine (or the morphine-equivalent daily dose of any opioid) is multiplied by a conversion factor of 0.2 when converting from oral morphine to OROS® hydromorphone. As with other opioids, there is no ceiling effect with hydromorphone and the analgesic efficacy increases with increasing dose. The only restriction on escalating dose is the emergence of adverse effects.

OROS® hydromorphone is contraindicated with concomitant use of monoamine oxidase inhibitors and the combined opioid receptor agonists/antagonists (e.g. buprenorphine). Concomitant use with CNS depressants may lead to respiratory depression, hypotension and profound sedation. Also, because of the risk of respiratory depression, OROS® hydromorphone should be avoided in combination with muscle relaxants.

The analgesic efficacy of OROS® hydromorphone has been demonstrated in patients with chronic moderate to severe low back pain, cancer pain and non-malignant pain, where patients were converted from standard opioid medication to OROS® hydromorphone using a conversion ratio of 5:1 morphine equivalents to hydromorphone. Once daily administration provided consistent analgesia over a 24 hour period in patients with cancer pain, which was at least equivalent to morphine. Pain scores indicated that pain relief may have been better with OROS® hydromorphone in the evening when morphine was at trough levels and hydromorphone was at the midpoint of the dosing period. A 1-year, open-label trial extension trial indicated that pain relief could be sustained in the long-term with continued use of OROS® hydromorphone.

Pharmacoeconomic analyses suggest that OROS® hydromorphone was a cost-effective option to oxycodone CR in patients with chronic, severe osteoarthritis pain and relative to other opioids in patients with severe, chronic malignant or non-malignant pain.

The tolerability profile of OROS® hydromorphone is manageable, with most adverse events being mild to moderate and typical of those expected with an opioid medication. The most commonly reported adverse events in clinical trials included constipation, nausea, somnolence, dizziness, vomiting and fatigue. Adverse events reported with long-term use are similar to those experienced with short-term use. In general, serious adverse events were infrequent. Respiratory depression was rarely reported, occurring in ≥1 in 10 000, but <1 in 1000 patients, but hypotension was more common occurring in ≥1 in 100, but <1 in 10. As with all opioids, there is a potential for the development of tolerance or physical dependence. Abrupt discontinuation of OROS® hydromorphone may result in withdrawal symptoms and to prevent this, dosage should be reduced by 50% every 2 days until the lowest possible dose is reached when the drug may be stopped.

Chronic pain can significantly impair quality of life and interfere with normal daily functioning, both socially and at work. OROS® hydromorphone has been developed with the aim of improving analgesia and providing the convenience of a once daily dose, with a lower potential for abuse or dependence compared with short-acting opioid alternatives.

Reference:
Carter NJ, Keating GM. OROS® hydromorphone prolonged release. A review of its use in the management of chronic, moderate to severe pain. CNS Drugs 2010; 24(4): 337-361.

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References • **1.** Bharti N, Chari P, Thingnam SKS, Arora S. Comparison of Haemodynamic and Cardiovascular Effects of VIMA with Sevoflurane Versus TIVA with Propofol in Patients Undergoing Coronary Artery Bypass Surgery. *Indian J Anaesth* 2008; **52**(6): 805-812 • **2.** De Hert SG, ten Broecke PW, Mertens E, Van Sommeren EW, De Blier IG, Stockman BA, *et al.* Sevoflurane but Not Propofol Preserves Cardiac Function in Coronary Surgery Patients. *Anesthesiol* 2002; **97**: 42-9 • **3.** De Hert S, Vlasselaers D, Barbé R, Ory J-P, Dekegel D, Donnadonni R, *et al.* A comparison of volatile and non volatile agents for cardioprotection during on-pump coronary surgery. *Anaesth* 2009; **64**: 953-960 • **4.** Hemmerling T, Olivier J-F, Le N, Prieto I, Bracco D. Myocardial protection by isoflurane vs. sevoflurane in ultra-fast-track anaesthesia for off-pump aortacoronary bypass grafting. *European Journal of Anaesthesiology* 2008; **25**: 230-236 • **5.** Cromheecke S, Pepermans V, Hendrickx E, Lorsomradee S, ten Broecke PW, Stockman BA *et al.* Cardioprotective Properties of Sevoflurane in Patients Undergoing Aortic Valve Replacement with Cardiopulmonary Bypass. *Anesth Analg* 2006; **103**: 289-296 • **6.** Garcia C, Julier K, Bestmann L, Zollinger A, von Segesser LK, Pasch T *et al.* Preconditioning with sevoflurane decreases PECAM-1 expression and improves one-year cardiovascular outcome in coronary artery bypass graft surgery. *Br J Anaesth* 2005; **94**: 159-165 • **7.** Delgado-Herrera L, Ostroff RD, Rogers SA. Sevoflurane: Approaching the Ideal Inhalational Anesthetic. A Pharmacologic, Pharmacoeconomic, and Clinical Review. *CNS Drug Reviews* 2001; **7**(1): 48-120 • **8.** De Baerdemaeker LEC, Jacobs S, Den Blauwen N, *et al.* Postoperative Results after Desflurane or Sevoflurane Combined with Remifentanil in Morbidly Obese Patients. *Obesity Surg* 2006; **16**: 728-733 • **9.** O'Keeffe NJ, Healy TEJ. The role of new anesthetic agents. *Pharmacol Ther* 1999; **84**: 233-248 • **10.** Wild MR, Gornall CB, Griffiths DE, Curran J. Maintenance of anaesthesia with sevoflurane or isoflurane effects on adverse airway events in smokers. *Anaesth* 2004; **59**: 891-893 •

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