

Preload Response in Patients After Cardiac Surgery: A Comparison of Systolic Blood Pressure and Systolic Area Variability and Initial Volume of Distribution of Glucose

M. HARVEY*, L. VOSS†, J. SLEIGH*

*Department of Anaesthesia, Waikato Hospital, Hamilton, NEW ZEALAND

†Department of Anaesthetics and Intensive Care, University of Auckland, Waikato Clinical School, Hamilton, NEW ZEALAND

ABSTRACT

Objective: Estimation of stroke volume variation (e.g. systolic blood pressure and systolic area variability) and central extracellular compartment volume (e.g. initial volume of distribution of glucose, IVDG) may be useful in guiding fluid therapy in mechanically ventilated patients. The reliability of systolic blood pressure (SBP) variability has been well validated, but little is known about systolic area (SA) variability or IVDG. Our aim was to investigate SBP and SA variability and IVDG as predictors of preload responsive hypovolaemia in post-cardiac surgery patients.

Methods: Thirty-four mechanically ventilated patients undergoing preload enhancement post elective cardiac surgery were studied. The maximum-minimum difference and power spectral measurement of SBP and SA variability were derived from the arterial waveform trace and examined before and after rapid volume infusion. IVDG was determined prior to volume infusion from three-minute incremental glucose estimation and (with SBP and SA variability) correlated with subjects classified as hypotensive and preload responsive.

Results: Neither IVDG or SA and SBP variability were found to correlate with subjects identified as hypotensive and preload responsive. However, the power spectral measures of SBP and SA variability were significantly reduced ($p = 0.007$ and $p = 0.026$, respectively) following preload enhancement in fluid responsive subjects.

Conclusions: Our results indicate that neither IVDG, nor SBP and SA variability are predictive of preload responsive hypotension in post-cardiac surgery patients. Spectral analysis of SBP and SA may be more sensitive at assessing preload responsiveness in this patient group than traditional maximum-minimum measures. (*Critical Care and Resuscitation* 2003; 5: 171-176)

Key words: Cardiac output, pulse contour analysis, preload enhancement, stroke volume, systolic pressure variation, hypovolaemia, IVDG

Cardiac performance depends on adequate preload. Because the relationship between preload and cardiac output is not linear at a defined contractility, the ability

to predict if the heart will augment its function after preload enhancement is crucial in avoiding excess volume infusion. This is especially important in critic-

ally ill patients with multiple organ failure, in the presence of sepsis, or post cardiopulmonary bypass. The decision to undertake preload enhancement can be clinically difficult, and commonly used ventricular filling pressures are unreliable in predicting myocardial fibre stretch and subsequent response to volume infusion.^{1,2}

Alternative methods of predicting preload responsive hypotension have been proposed. For example, estimation of the intravascular volume from the initial volume of distribution of glucose (IVDG)³ has proven predictive of the development of post-operative hypovolaemic hypotension in patients following surgery for oesophageal carcinoma.⁴ If proved reliable IVDG may provide a simple, readily available measure of cardiac preload.

Measures of stroke volume variability have also been used to predict cardiac response to preload enhancement. Mechanical ventilation is known to cause cyclic variation of both right and left ventricular preload. The resulting fluctuations in stroke volume and systolic blood pressure (SBP) are exaggerated in hypovolaemia. Off-line quantification of SBP variability has been shown to accurately predict response to preload enhancement in animal models,⁶ and in human subjects.⁷⁻¹⁰ More recently, real-time monitoring of fluctuations in left ventricular stroke volume from pulse contour analysis (PiCCO system, pulse contour cardiac output, Pulsion Medical Systems, AG Munich, Germany) has proven useful in predicting response in patients undergoing volume infusion.^{11,12} The PiCCO system uses a complicated algorithm to estimate stroke volume from the systolic area (SA) of the arterial blood pressure waveform and is limited by the requirement for specialised thermodilution catheters and monitoring equipment.

To our knowledge SA variability *per se* has not been investigated as a predictor of fluid responsiveness and the reliability of IVDG as an indicator of hypovolaemic hypotension remains unproven. The aim of our study therefore, was to investigate the ability of SBP and SA variability and IVDG to predict fluid responsive hypotension in post-cardiac surgery patients.

METHODS

Patients

With the approval of the local ethics committee and written informed consent, 34 patients (27 male, 7 female) were studied after elective cardiac surgery. Patient demographics and operative procedures are presented in table 1.

Clinical procedures and monitoring

Prior to surgery, all patients underwent central ven-

ous catheterisation and arterial catheterisation for continuous intraoperative and postoperative haemodynamic monitoring.

Table 1. Patient demographics

| | <i>Median (range)</i> |
|-------------------------------------|-----------------------|
| Weight (kg) | 82.5 (40 - 127) |
| Age (yr) | 65 (42 - 85) |
| Body surface area (m ²) | 1.96 (1.57 - 2.46) |
| Operation: | |
| 27 CABG | |
| 3 AVR | |
| 1 ASD repair | |
| 3 CABG/valve replacement | |

CABG = Coronary artery bypass graft, AVR = aortic valve replacement, ASD = atrial septal defect

Arterial pressure was monitored using a 20G radial artery catheter connected in standard fashion (Solar 9500 monitor, Marquette Medical Systems, WI U.S.A.). Because we were aiming to study the system under routine clinical conditions of use, we did not examine the frequency response of the system in detail, but checked that the system was not grossly under-, or over-, damped by visual examination of the arterial waveform and square-wave test. Intraoperative fluid management was determined by each anaesthetist, who was unaware of the contents of the study. All patients were returned to the intensive care unit in a state of clinical haemodynamic stability. On arrival the arterial pressure monitor was connected to standard personal computer via Stobes APC (Wellington, NZ) for digitalised recording and subsequent off-line analysis. All patients were studied while intubated and sedated with a continuous propofol infusion. Ventilator settings provided tidal volumes of 5 - 7 mL/kg and ventilator rate of 10 breaths/min in the absence of positive end expiratory pressure. Maintenance fluid was 5% dextrose solution at 1 mL/kg/hour. If commenced in the operating room, inotropic and vasoactive infusions (e.g. adrenaline in 1 patient, milrinone in 3 patients and noradrenaline in 11 patients) were continued in the intensive care unit. Infusion rates remained unchanged during the acquisition of study data.

IVDG protocol

Immediately after admission to the intensive care unit, blood was sampled via an indwelling arterial line and estimation of glucose concentration performed via the glucose oxidase method (Bayer 856 analyser, Bayer Diagnostics division, Leverkusen Germany). Twenty mL of 25% glucose solution (5g) was administered as a bolus over 30 seconds via a central venous catheter. At

an interval of 180 seconds a further blood glucose estimation was performed and IVDG calculated according to the formula $IVDG = 24.44 \times e^{-0.0298 \times dGL} + 2.70$ (where dGL = incremental glucose level at 180 s after i.v. glucose).¹³

Volume expansion protocol

Volume expansion was undertaken to maintain haemodynamic parameters [mean arterial pressure (MAP) > 65 mmHg], or at the discretion of the attending intensivist [maintenance of CVP, urine output]. Volume expansion was achieved by rapid infusion of 250 - 500 mL Hemohes® (Pentastarch 10 g/100 mL in 0.9% saline). Infused volume and external haemorrhage for the time of infusion were recorded with calculated net volume equalling the difference. Retrospectively, episodes of preload enhancement were classified into two groups based on patient response to the infused volume. If the patient fulfilled the following criteria: MAP ≤ 65 mmHg accompanied by either tachycardia (pulse rate > 110 bpm in unpaced subjects) or oliguria (urine output < 30 mL/hr), and correcting (MAP ≥ 70 mmHg, pulse ≤ 100 bpm or urine output ≥ 30 mL/hr as appropriate) with rapid volume infusion they were presumed hypovolaemic and classified as being 'preload responsive'. Patients who did not fulfil all these criteria were classified as 'preload unresponsive'.

Each episode of rapid volume infusion was studied. Recordings of haemodynamic variables, in addition to continuous 120-second arterial waveform traces, were saved immediately prior to, and subsequent completion of volume infusion. The arterial waveform traces were digitized at 100 samples/sec (AD 512, Humusoft, Novakovich, Czech Republic) and stored for later off-line analysis using Matlab (version 6, Mathworks, USA) computational and data analysis software.

Analysis of SBP and SA variability

Pre- or post-infusion arterial recordings of 8 episodes of rapid volume infusion (5 preload responsive by study criteria, 3 non-preload responsive) were unsuitable for further analysis due to excessive motion artifact, and were excluded from paired analysis. From the 42 remaining recordings, a 24 s artifact-free time window (representing 4 respiratory cycles) was chosen from the original 120 s for further analysis. From these truncated data segments, systolic blood pressure (SBP) and the area subtending the systolic component of the arterial pressure waveform (calculated from the onset of systole to the dicrotic notch) were determined for each cardiac cycle. Accurate SBP and dicrotic notch detection for all cardiac cycles was confirmed by visual inspection for all 24 s segments before the data was further analysed. SBP and SA variability were calculated in two ways. Firstly, the difference between the maximum and minimum SBP for a respiratory cycle was obtained equalling systolic

pressure variability (SPV). In like manner the maximum and minimum SA for the similar period was calculated and termed systolic area variability (SAV). Secondly, power spectra of the SBP and SA data was computed by Discrete Fourier Transformation and the peak power at the respiratory frequency obtained for both variables. This we called systolic blood pressure power (SBP_{power}) and systolic area power (SA_{power}) respectively.

Statistical analysis

Statistical analysis of all variables were performed using SPSS for Windows (version 10.0, SPSS, Chicago, IL). Correlation of haemodynamic variables were assessed using Pearson's linear correlation coefficient (r). Mean differences in continuous variables were evaluated using paired Student's t-tests. A p value of 0.05 or less was deemed significant.

RESULTS

Thirty-four patients provided 50 episodes of rapid volume infusion. Seventeen episodes were in response to preload responsive hypotension as defined by the study protocol, 33 were in response to intensivist direction. Net volume infusion was 350.5 mL (4.43 mL/kg) in those developing preload responsive hypotension and 334.1 mL (4.13 mL/kg) in those undergoing rapid volume infusion for another indication.

Prediction of preload responsive hypotension

The blood glucose concentration prior to intravenous glucose administration was 7.32 mmol/L (5.10 - 11.3 mmol/L). No correlation was observed between the initial blood glucose and subsequent IVDG. No significant difference in IVDG was observed between patients who developed preload responsive hypotension and those who did not (132.7 vs. 117.7 mL/kg respectively, p = 0.331). No significant difference was observed in total infusion volume in 24 hours or blood loss for the same period between preload responsive and non responsive groups. No significant difference was observed in CVP between preload responsive and non-responsive groups (8.31 vs. 10.8 mmHg respectively, p = 0.098). All of our measures of SBP and SA variability showed a trend towards higher variability in subjects diagnosed as preload responsive versus non responsive, however none of these differences reached statistical significance.

Haemodynamic responses to volume infusion (Table 2)

In the preload responsive group, SA_{power} and SBP_{power} were significantly reduced following volume infusion (p = 0.007 and 0.026 respectively) (table 2). There was no significant change in either SPV or SAV following volume infusion in the preload responsive group (table 2). No significant change in any of the SBP or SA measures of variability were observed in the non-preload responsive group with volume infusion (table 2).

Table 2. Pre- and post-infusion variables \pm SD

| | Fluid-responsive | | p | Non Fluid-responsive | | p |
|---|------------------------|---------------------------|-------|--------------------------|---------------------------|--------|
| | Pre infusion (n=12) | Post infusion (n = 12) | | Pre infusion (n = 30) | Post infusion (n = 30) | |
| Pulse rate (bpm) | 75.3 \pm 14.8 | 76.0 \pm 13.5 | 0.057 | 78.8 \pm 9.4 | 80.7 \pm 9.9 | 0.076 |
| CVP (mmHg) | 8.31 \pm 2.7 | 11.3 \pm 3.0 | 0.001 | 10.8 \pm 3.7 | 13.3 \pm 3.6 | 0.0001 |
| MAP (mmHg) | 63.4 \pm 2.5 | 76.0 \pm 6.0 | 0.001 | 76.8 \pm 6.9 | 79.6 \pm 8.5 | 0.04 |
| SPV (mmHg) | 7.90 \pm 3.1 | 6.70 \pm 2.2 | 0.168 | 6.70 \pm 2.7 | 8.5 \pm 9.3 | 0.326 |
| SAV (msmmHg) | 43.0 \pm 19.3 | 43.0 \pm 19.4 | 0.504 | 39.0 \pm 18 | 41 \pm 17 | 0.767 |
| Systolic area/BSA (msmmHg/m ²) | 96 \pm 39 | 107 \pm 31.0 | 0.541 | 86.0 \pm 27 | 93 \pm 35 | 0.075 |
| SBP _{power} (mmHg ²) | 4.30 \pm 4.1 | 1.80 \pm 1.2 | 0.026 | 3.70 \pm 6.1 | 3.4 \pm 6.4 | 0.571 |
| SA _{power} (msmmHg ²) | 142 \pm 110 | 64.0 \pm 53 | 0.007 | 77.0 \pm 79 | 71 \pm 87 | 0.590 |

CVP = Central venous pressure, MAP = Mean arterial pressure, SPV = systolic pressure variability, SAV = systolic area variability, BSA = body surface area, SBP_{power} = power spectral measure of systolic blood pressure variability, SA_{power} = power spectral measure of systolic area variability

SA_{power} and measures of systolic pressure variability (SPV and SBP_{power}) show good correlation [$r = 0.459$, $p < 0.01$ for SPV; $r = 0.780$, $p < 0.01$ for SBP_{power} (figure 1)].

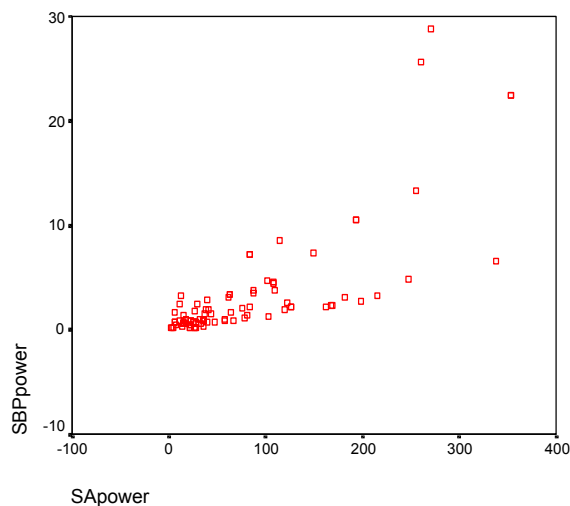


Figure 1. Linear correlation analysis of the relationship between SA_{power} and SBP_{power}

Pre- and post- rapid volume infusion heart rates remained unchanged in preload responsive and non responsive groups. Central venous pressures increased significantly from 8.31 to 11.25 mmHg in the preload responsive group and from 10.79 to 13.32 mmHg in the non responsive group. Mean increase in MAP was 12.6

mmHg in patients diagnosed with preload responsive hypotension, and 2.5 mmHg in patients undergoing rapid volume infusion for an alternative indication (Table 2). Both increases are statistically significant. The greater increase in MAP in those diagnosed as hypovolaemic reflects augmented cardiac performance during a state of preload responsiveness (see criteria). Mean stroke volume, estimated from systolic area/body surface area (SA/BSA), was not significantly affected by volume infusion in either preload responsive or non responsive groups.

DISCUSSION

Optimising cardiac preload and subsequent end-diastolic volume is crucial in the maintenance of cardiac output. We have evaluated peripherally-acquired pulse contour analysis as compared to previously validated systolic blood pressure variation. Our results demonstrate primarily the ability of power spectral measures of SBP and SA variability (SA_{power} and SBP_{power}, respectively) to assess response to preload enhancement with greater sensitivity than the traditionally used (maximum-minimum) difference measures (SPV and SAV). Power spectral analysis of SBP or SA variability may thus provide a more accurate reflection of ventricular stroke volume variation. Good correlation is shown to exist between SA_{power} and measures of systolic pressure variability (SPV and SBP_{power}). These findings are consistent with a previously documented correlation between stroke volume variability and SPV.¹¹

In patients diagnosed clinically with preload responsive hypotension, preload enhancement resulted in a reduction in SA_{power} to levels approximating those of non-hypovolaemic individuals [64 vs. 77 msmmHg² (table 2)] with associated resolution of hypotension, tachycardia and/or oliguria. Real-time monitoring of the SA power spectra may thus prove useful in evaluating endpoints for fluid resuscitation in hypovolaemic individuals. This requires further study.

Routine use of standard invasive arterial blood pressure monitoring equipment renders the technique of peripheral pulse contour analysis readily available to intensive care unit patients undergoing routine monitoring. The ability of maximum-minimum difference SBP variation (SPV) to assess and predict response to preload enhancement is well validated.^{6-7,9-10} That our results did not demonstrate a significant difference in SPV following rapid volume infusion is surprising, especially given the significant difference observed in SBP_{power}, which also evaluates SBP variability. It is difficult to explain this apparent discrepancy without a recognised gold standard measure of cardiac preload (e.g. trans-oesophageal assessment of end-diastolic dimension) as comparison. However, we may speculate that our utilisation of standard radial waveform trace may have resulted in inaccuracies in the arterial recordings and contributed to the lack of observed difference in SPV.

IVDG estimation on arrival in the intensive care unit did not prove predictive of the later development of preload responsive hypotension nor the net intravenous volume requirement in the 24 hours following surgery. Calculated values of 132.7 and 117.7 mL/kg for patients developing preload responsive hypotension and those who did not respectively are consistent with the haemodynamic stability displayed at the time of initial estimation. The critical IVDG for the development of hypovolaemic hypotension has previously been reported as 105 mL/kg post radical surgery for oesophageal carcinoma, with a normal range of 110 - 130 mL/kg.¹⁴

IVDG is known to correlate poorly with cardiac output in patients with congestive heart failure.^{3,15} No patient in our population was diagnosed with heart failure preoperatively, however three patients required milrinone infusion and one patient adrenaline infusion post operatively to maintain cardiac output. Transient myocardial dysfunction consequent to the attendant stress of cardiac surgery may have impacted on the ability of IVDG to reliably predict cardiac preload in these patients. It is also worth noting that single IVDG estimation would not predict the development of relative hypovolaemia resulting from peripheral vasodilatation associated with rapid rewarming.

In conclusion, power spectral evaluation of SA and SBP variability may prove useful measures of response to preload enhancement in mechanically ventilated patients. Neither single IVDG estimation, nor SA or SBP variability are predictive of the development of preload responsive hypotension in post cardiac surgery patients.

Received: 20 June 2003

Accepted: 6 July 2003

REFERENCES

1. Sakka S C, Bredle D L, Reinhart K et al. Comparison between intrathoracic blood volume and cardiac filling pressures in the early phase of hemodynamic instability of patients with septic shock. *J Crit Care* 1999;14:78-83.
2. Shippy C R, Appel P L, Shoemaker W L. Reliability of clinical monitoring to assess blood volume in critically ill patients. *Crit Care Med* 1984;12:107-112.
3. Ishihara H, Takamura K, Iwakawa T, Tsubo T, Matsuki A. Does the initial distribution of glucose reflect the central ECF volume status in critically ill patients. *Infusionther* 1996;23:196-201.
4. Suzuki A, Ishihara H, Okawa H et al. Can initial distribution volume of glucose predict hypovolaemic hypotension after radical surgery for oesophageal cancer. *Anaesth Analg* 2001;92:1146-1151.
5. Jardin F, Farcot J C, Gueret P, Frost J F, Ozier Y, Bourdarias J P. Cyclic changes in arterial pressure during respiratory support. *Circulation* 1983;83:266-274.
6. Perel A, Pizov R, Cotev S. Systolic blood pressure variation is a sensitive indicator of hypovolaemia in ventilated dogs subject to graded hemorrhage. *Anesth* 1987;67:498-502.
7. Rooke G A, Schwid H A, Shapira Y. The effect of graded hemorrhage and intravascular volume replacement on systolic pressure variation in humans during mechanical and spontaneous ventilation. *Anaesth Analg* 1995;80:925-932.
8. Stone D J. Physiology and monitoring of intravascular volume status in the neurosurgical patient. *Anesth Analg* 1999;88:98-103.
9. Tavernier B, Makhotine O, Lebuffe G et al. Systolic pressure variation as a guide to fluid therapy in patients with sepsis induced hypotension. *Anesthesiol* 1998;89:1313-1321.
10. Michard F, Boussat S, Chemla D et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am J Resp Crit Care Med* 2000;162:134-138.
11. Berkenstadt H, Margalit N, Hadani M et al. Stroke volume variation as a predictor of fluid responsiveness in patients undergoing brain surgery. *Anesth Analg* 2001;92:984-989.
12. Reuter D A, Felbinger T W, Kilger E et al. Optimizing fluid therapy in mechanically ventilated patients after cardiac surgery by on-line monitoring of left ventricular stroke volume variations. Comparison with aortic

- systolic pressure variations. *Br J Anesth* 2002;88:124-126.
13. Hirota K, Ishihara H, Tsubo T et al. Estimation of the initial distribution volume of glucose by an incremental plasma glucose level at 3 min after i.v. glucose in humans. *Br J Clin Pharmacol* 1999;47:361-364.
 14. Ishihara H, Suzuki A, Okawa H et al. The initial distribution volume of glucose rather than indocyanine green derived plasma volume is correlated with cardiac output following major surgery. *Intensive Care Med* 2000;26:1441-1448.
 15. Ishihara H, Shimodate Y, Koh H, Isozaki K, Tsubo T, Matsuki A. The initial distribution volume of glucose and cardiac output in the critically ill. *Can J Anaesth* 1993;40:28-31.