

# GOAL DIRECTED THERAPY

SUMMARY OF LITERATURE

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## Summary of Goal-Directed Therapy Clinical Studies

*Goal Directed Therapy (GDT) is a term used to describe the use of cardiac output or similar parameters to perioperatively guide intravenous fluid and inotropic therapy.*

Investigator	Patient Type	Number of Patients	Control	GDT Protocol	P Value
<b>MORTALITY</b>					
Wilson	Major elective surgery	138	17% (8/46)	3% (3/92)	0.007
Rhodes	High risk surgery	106	7.5% alive @ 15 years	20.7% alive @ 15 years	0.09
Boyd	High risk surgery	107	22.7%	5.7%	0.015

### MORBIDITY (% OF PATIENTS) COMPLICATIONS (PER PATIENT)

Boyd	High risk surgery	107	1.35	0.68	0.008
Venn	Hip fracture repair	90	28%	7%	<0.5
Gan	Major elective surgery	100	7 (+/-3)	5 (+/-3)	0.03
Pearse	High risk surgery	122	68%	44%	0.003
Mayer	High risk patients	60	50%	20%	0.03

### LENGTH OF STAY (DAYS)

Boyd	High risk surgery	107	16	12.5	0.31
Pearse	High risk surgery	122	14 (11 - 27)	11 (7 - 15)	0.001
Mayer	High risk patients	60	19 (14 - 23.5)	15 (12 - 17.75)	0.006
Sinclair	Proximal femoral fracture	40	20 (10 to 61)	12 (9 to 15)	0.05
Lopes	High risk surgery	33	17	7	0.01

# Goal-Directed Therapy—Stroke Volume Variation (SVV) and Pulse Pressure Variation (PPV) as Predictors of Fluid Responsiveness

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## What are the potential clinical applications of Stroke Volume Variation (SVV) in the Anesthesiology setting?

Cardiac output optimization through goal-directed therapy has the ability to improve postoperative patients' outcome and to decrease the cost of surgery by reducing postoperative complications<sup>1</sup>. However, cardiac output optimization requires accurate predictors of fluid responsiveness. For that purpose, stroke volume variation has the ability to guide fluid management and to help in conducting goal directed therapy<sup>2</sup>. Using this index along with cardiac output monitoring ("From flying blind to flying right"<sup>3</sup>) has potential to improve our patients' outcome and to decrease the cost of surgery.

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### Rationale

Volume expansion is one of the most frequent clinical decisions performed every day by anesthesiologists. The goal of volume expansion is to increase left ventricular stroke volume and cardiac output and, consequently, to increase oxygen delivery to the tissues. However, if volume expansion can be beneficial to our patients when performed appropriately, we also know that inappropriate volume expansion can lead to tissue edema and to a decrease in oxygen extraction. Consequently, it is of major importance to be able to predict the effects of volume expansion before volume expansion is actually performed and there is a need for reliable predictors of fluid responsiveness in the anesthesiology setting. Most experts agree on the definition of responders to volume expansion as patients presenting more than 15 % increase in cardiac output following a 500 ml infusion of colloids<sup>4</sup>.

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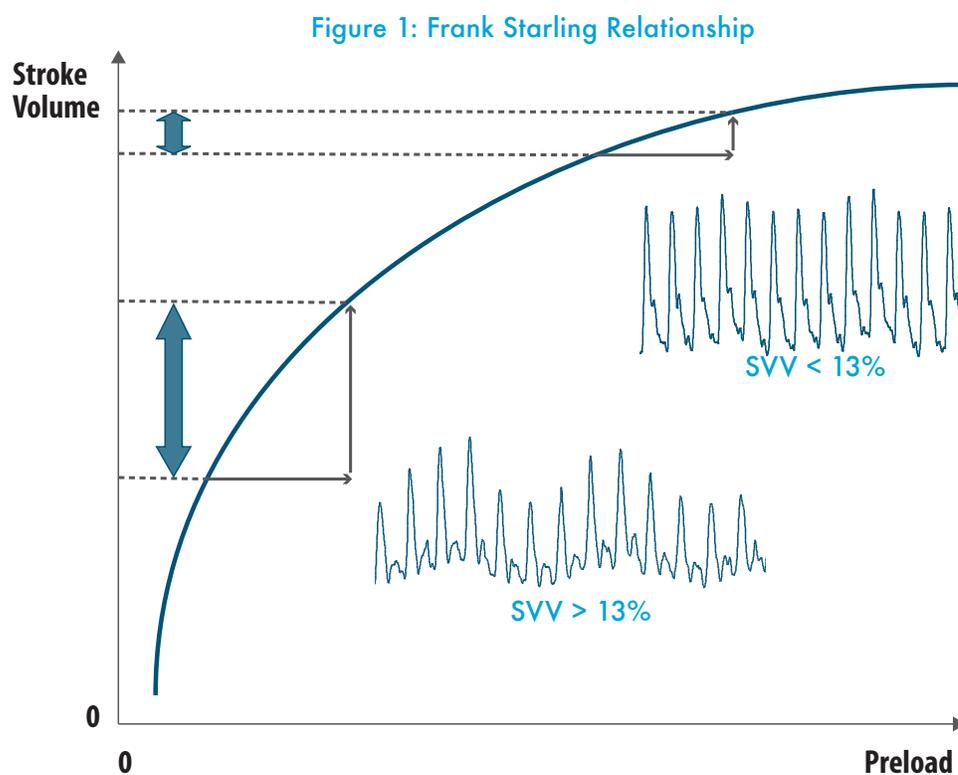
### How can we predict fluid responsiveness? From Static to Dynamic parameters

Historically, static parameters of fluid responsiveness have been used for fluid responsiveness prediction in the anesthesiology setting. These static parameters are basically preload parameters such as central venous pressure, pulmonary capillary wedge pressure, and/or left ventricular end-diastolic area. However, recent studies have suggested that these static parameters are poor predictors of fluid responsiveness in the anesthesiology setting and that central venous pressure should not be used anymore to make clinical decision regarding fluid management<sup>5</sup>.

More recently, dynamic parameters of fluid responsiveness relying on cardiopulmonary interactions in patients under general anesthesia and mechanical ventilation have been demonstrated to be the best predictors of fluid responsiveness in this setting<sup>6</sup>. In patients under general anesthesia, positive pressure ventilation induces cyclic changes in vena cava blood flow, pulmonary artery flow, and aortic blood flow.

During inspiration, vena cava blood flow (venous return) decreases and, according to the Frank-Starling relationship, pulmonary artery flow decreases. Depending on the position of the patient on the Frank-Starling relationship mechanical ventilation is going to induce either high respiratory variations in left ventricular stroke volume (when the patient is on the steep portion and more likely to be a responder to volume expansion) or low respiratory variations in left ventricular stroke volume (when the patient is on the plateau and more likely to be a non responder to volume expansion) (Figure 1).

To summarize this concept we can say that the more sensitive a ventricle is to preload (preload dependent) the more the little changes in preload induced by mechanical ventilation are going to impact left ventricular stroke volume. Classically, a stroke volume variation  $> 13\%$  is a strong predictor of fluid responsiveness while a stroke volume variation  $< 13\%$  is a strong predictor of fluid non responsiveness<sup>6</sup>.



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## What are the limitations of SVV?

Since stroke volume variation and pulse pressure variation require large changes in pleural and transpulmonary pressure, their use as a predictor of fluid responsiveness is limited to mechanically ventilated and deeply sedated patients. Smaller tidal volume (< 8 ml/kg of ideal body weight) or poor lung compliance will reduce the effect on venous return and subsequently the change in SV will be reduced. In patients with cardiac arrhythmias, right or left ventricular failure, changes in stroke volume may no longer reflect preload dependence<sup>4</sup>.

1. Gan TJ, Soppitt A, Maroof M, el-Moalem H, Robertson KM, Moretti E, Dwane P, Glass PS. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. *Anesthesiology* 2002;97:820-6.
2. Cannesson M. Arterial Pressure Variation and Goal-Directed Fluid Therapy. *J Cardiothorac Vasc Anesth* 2009.
3. Cannesson M, Vallet B, Michard F. Pulse pressure variation and stroke volume variation: from flying blind to flying right? *Br J Anaesth* 2009;103:896-7; author reply 7-9.
4. Michard F. Changes in arterial pressure during mechanical ventilation. *Anesthesiology* 2005;103:419-28; quiz 49-5.
5. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness?: a systematic review of the literature and the tale of seven mares. *Chest* 2008;134:172-8.
6. 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.

## A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients

Owen Boyd, MRCP; R. Michal Grounds, MD FFARCS; E. David Bennett, FRCP  
St. George's Hospital, London, UK  
JAMA. 1993 Dec 8;270(22):2699-707.

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### Methods

This was a prospective, randomized study of 107 high risk surgical patients. Patients with similar demographics, hemodynamic values and surgical types were assigned to a treatment group (n = 53) that received deliberate increase of oxygen delivery to 600 mL/min per m<sup>2</sup> with the use of dopexamine hydrochloride infusion or to Control Group (n = 54) that received standard perioperative care. Outcome measures of mortality and complications were assessed at 28 days postoperatively.

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### Results

- Oxygen Delivery (median): 597 mL / m<sup>2</sup> in GDT group vs. 399 mL / m<sup>2</sup> in Control Group (p < 0.001)
- Mortality rate: 5.7% in GDT group vs. 22.2% in Control Group
- Mean # of complications: 0.68 per patient in GDT vs. 1.35 per patient in Control Group (p = 0.08)

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### Conclusions

*“Our data suggest that deliberately increasing CI and DO<sub>2</sub>I perioperatively leads to significant reduction in both mortality and morbidity in those patients who are at risk of both following surgery”*

## Goal-directed therapy in high-risk surgical patients: a 15-year follow-up study

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Intensive Care Med. 2010 Aug;36(8):1327-32. Epub 2010 Apr 8

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### Methods

This was a long term follow up of a previous study (Boyd, et al, 1993) to determine patients' length of survival in which Goal-directed therapy was used to deliberately increase oxygen delivery during surgery.

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### Results

Data from 106 of the original 107 patients (99%) were available for analysis.

- Long term (15 year) survival                      11 (20.7%) of the GDT patients vs, 4 (7.5%)  
of the Control Group (p = 0.09).

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- Median survival (GDT group)                      increased by 1,107 days (1,781 vs. 674 days, p = 0.005).

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- Factors influencing long-term survival          Age [hazard ratio (HR) 1.04 (1.02–1.07), p < 0.0001],  
Randomization to the GDT group [HR 0.61 (0.4–0.92), p = 0.02],  
Avoidance of a significant postoperative cardiac complication  
[HR 3.78 (2.16–6.6), p = 0.007].

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### Conclusions

*“Short-term goal-directed therapy in the perioperative period may improve long-term outcomes, in part due to its ability to reduce the number of perioperative complications.”*

## Reducing the risk of major elective surgery—randomized controlled trial of preoperative optimization of oxygen delivery

Jonathan Wilson, Ian Woods, Jayne Fawcett, Rebecca Whall,  
Wendy Dibbs, Chris Morris, Elizabeth McManus

Departments of Anesthetics and Intensive Care, York District Hospital, York, UK

British Medical Journal 1999 Vol: 318:1099-1103

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### Methods

This was a randomized, controlled study of high risk 138 patients undergoing major elective surgery. Patients were randomized into 3 groups. Two received invasive hemodynamic monitoring, fluid and either adrenaline or dopexamine to increase oxygen delivery. The third Control Group received routine perioperative care.

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### Results

- Mortality: 3/92 (3%) in GDT Group (no difference in two treatment groups) vs. 8/46 (17%) in the Control Group (p = 0.007)

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- Complications 14/36 (30%) in patients in dopexamine group vs. 24/46 (52%) in the adrenaline group and 28 (61%) in the Control Group

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- Length of Stay 13 days in dopexamine group vs. 19 days in adrenaline group (p = 0.02) vs. 22 days in Control Group (p = 0.009)

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### Conclusions

*“Routine preoperative optimization of patients undergoing major elective surgery would be a significant and cost effective improvement in perioperative care...administration of fluid and inotropes, guided by invasive monitoring, can significantly reduce mortality, morbidity, and length of hospital stay...values for usage of intensive care beds and length of stay in hospital suggests there may be an overall savings in hospital costs when preoptimising patients for major elective surgery.”*

# Early goal-directed therapy after major surgery reduces complications and duration of hospital stay—a randomized controlled trial

Rupert Pearse, Deborah Dawson, Jayne Fawcett, Andrew Rhodes,  
R Michael Grounds and E David Bennett

Adult Intensive Care Unit, St George's Hospital, London, UK

Critical Care 2005, 9:R687-R693doi:10.1186/cc3887

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## Methods

This was a randomized, blinded study that measured the effects of post-operative goal-directed therapy (GDT) in high-risk patients undergoing major general surgery. The primary outcome measure was post-operative complications. Patients in the Control Group received 250 ml boluses of colloid to sustain an increase in CVP of at least 2mm Hg for 20 minutes. GDT patients received 250 ml boluses to sustain a rise in stroke volume of 10% for 10 minutes. The GDT group also received dopexamine if the oxygen delivery index (DO<sub>2</sub>I) failed to reach 600 ml/ml/min/m<sup>2</sup>. Cardiac output was measured by lithium indicator dilution and pulse power analysis. Sixty-two patients were randomized to GDT and 60 patients to control treatment and followed up for 60 days.

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## Results

- Postoperative complications: 27 patients (44%) in GDT group vs. 41 patients (68%) in Control Group (p = 0.003)
- Complications per patient: 0.7 per patient in GDT vs. 1.5 per patient in control group (p = 0.02)
- Mean duration of hospital stay: 11 days in GDT group vs 14 days in Control Group (p = 0.002)

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## Conclusions

*“Post-operative GDT is associated with reductions in post-operative complications and duration of hospital stays, but avoids the problems associated with pre-operative ICU admission and pulmonary artery catheterization.”*

## Goal-directed fluid management based on pulse pressure variation monitoring during high-risk surgery—a pilot randomized controlled trial

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Crit Care. 2007;11(5):R100.

### Methods

This was a single center, prospective, randomized study to determine if volume loading during high-risk surgery could improve outcomes. The variation in arterial pulse pressure ( $\Delta$ PP) induced by mechanical ventilation was used as an indicator of a patient's fluid responsiveness. Thirty-three patients undergoing high-risk surgery were randomized either to a Control Group (n = 16) or to a GDT intervention group (n = 17). In the GDT group,  $\Delta$ PP was continuously monitored during surgery and minimized to 10% or less by volume loading.

### Results

Both groups were comparable in terms of demographic data, American Society of Anesthesiology score, type, and duration of surgery.

- Pulse Pressure Variation  $\Delta$ PP decreased from  $22 \pm 75$  to  $9 \pm 1\%$  ( $P < 0.05$ ) in the monitored group.
- Duration of postoperative stay 7 days in GDT group) vs. 17 days in Control Group,  $P < 0.01$
- Postoperative complications per patient  $1.4 \pm 2.1$  complications per patient in GDT group vs.  $3.9 \pm 2.8$ , ( $P < 0.05$ ),
- Median duration of mechanical ventilation 1 day in GDT group vs. 5 days in Control Group, ( $P < 0.05$ )
- ICU stay 3 days in GDT group vs. 9 days in Control Group,  $P < 0.01$

### Conclusions

*“Monitoring and minimizing  $\Delta$ PP by volume loading during high-risk surgery improves postoperative outcome and decreases the length of stay in hospital.”*

## Cost analysis of a treatment policy of a deliberate perioperative increase in oxygen delivery in high risk surgical patients

J.F. Guest, O. Boyd, W.M. Hart, R.M. Grounds, E.D. Bennett

Adult Intensive Care Unit, St George's Hospital, Blackshaw Road, London, UK

Intensive Care Medicine 1997, Vol 23:85-90

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### Methods

A previous clinical trial (Boyd et al, 1993) demonstrated a significant reduction in mortality (5.7% vs 22.2%,  $p = 0.015$ ) and complications (0.68) vs (1.35),  $p = 0.008$ ) in high risk surgical patients in whom oxygen delivery was specifically targeted towards 600 ml/min per m<sup>2</sup> compared with conventional management. This current study retrospectively analyzed the medical cost of use of each patient in the trial.

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### Results

- Mortality: 5.7% in GDT group vs. 22.2% in Control Group ( $p = 0.015$ )
- Morbidity: 0.68 in GDT group vs. 1.35 in Control Group
- Median Cost of Treatment: GDT group = £6,525 vs. £7,784 in Control Group
- Median Cost of Treating Complications: £213 in GDT group vs. £668 in Control Group

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### Conclusions

*“Perioperative increase in oxygen delivery in high risk surgical patients not only improves survival, but also provides an actual and relative cost savings. This may have important implications for the management of these patients and the funding of intensive care”*

## Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery

Tong J. Gan, Andrew Soppitt, Mohammed Maroof, Habib El-Moalem, Kerri Robertson, Eugene Moretti, Peter Dwane, Peter Glass

Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina

Anesthesiology 2002, Vol: 97:820-826

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### Methods

One hundred patients who were to undergo major elective surgery with an anticipated blood loss greater than 500 ml were randomly assigned to a Control Group (n = 50) that received standard intraoperative care or to a protocol (GDT) group (n = 50). The GDT group received intraoperative plasma volume expansion to maintain maximal stroke volume, monitored by transesophageal Doppler. Length of postoperative hospital stay and postoperative surgical morbidity were assessed.

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### Results

- End Of Surgery Cardiac Output: GDT Group = 5.8 + 1.6 vs. Control = 5.1 + 1.4 (p < 0.05)

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- End Of Surgery Stroke Volume: GDT Group = 76 + 19 vs. Control = 67 + 17 (p < 0.05)

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- Duration of Hospital Stay: GDT Group = 5 + 3 vs. Control = 7 + 3 (p = 0.03)

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- Oral Intake of Solid Food: GDT Group = 3 + 0.5 vs. Control = 4.7 + 0.5 (p = 0.01)

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- Severe postoperative vomiting: GDT Group = 7/50 (14%) vs. Control = 18/50 (35%), )p <0.05)

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### Conclusions

*“Goal directed intraoperative fluid administration results in earlier return to bowel function, lower incidence of postoperative nausea and vomiting, and a decrease in the length of postoperative hospital stay”*

## Intraoperative intravascular fluid optimization and length of hospital stay after repair of proximal femoral fracture—randomized controlled trial

Susan Sinclair, Sally James, Mervyn Singer

Departments of Intensive Care and Orthopaedics, University College London Hospital, London, UK

British Medical Journal 1997, Vol: 315:909-912

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### Methods

This was a prospective, randomized controlled trial that compared conventional intraoperative fluid management with repeated fluid challenges to maximize stroke volume in 40 patients undergoing hip fracture repair. Stroke volume was monitored by transesophageal Doppler.

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### Results

- Operative Changes in Cardiac Output: GDT Group = +1.2 L/min vs. Control Group = -0.41 L/min ( $p < 0.05$ )
- Operative Changes in Stroke Volume: GDT Group = +13 ml vs. Control Group = -5 ml ( $p < 0.001$ )
- Hospital Stay: GDT Group = 12 days vs. Control Group = 20 days ( $p < 0.05$ )

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### Conclusions

*“Intraoperative intravascular volume loading to optimal stroke volume resulted in a more rapid postoperative recovery and a significantly reduced hospital stay.”*

## Goal-directed intraoperative therapy based on auto calibrated arterial pressure waveform analysis reduces hospital stay in high-risk surgical patients—a randomized controlled trial

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Department of Anesthesiology and Intensive Care Medicine,  
Klinikum Ludwigshafen, Ludwigshafen, Germany

Critical Care 2010, 14:R18 doi:10.1186/cc8875

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### Methods

60 high-risk patients scheduled for major abdominal surgery were randomized into an enhanced hemodynamic monitoring group using a cardiac index based intraoperative optimization protocol (GDT-group, n = 30) or a standard management group (Control-group, n = 30), based on standard monitoring data.

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### Results

- The median duration of hospital stay: 15 days (GDT) vs. 19 days (Control) (P = 0.006)
- Complications: 6 patients (GDT) vs. 15 patients (Control) P = 0.03].
- The total number of complications: 17 versus (GDT) vs. 49 complications, P = 0.001).

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### Conclusions

*“In high-risk patients undergoing major abdominal surgery, implementation of an intraoperative goal-directed hemodynamic optimization protocol...was associated with a reduced length of hospital stay and a lower incidence of complications compared to a standard management protocol.”*

## Randomized controlled trial to investigate influence of the fluid challenge on duration of hospital stay and perioperative morbidity in patients with hip fractures.

Venn R, Steele A, Richardson P, Poloniecki J, Grounds M, Newman P.

Department of Anaesthesia and Intensive Care, Worthing Hospital, W. Sussex UK

Br J Anaesth. 2002 Jan;88(1):65-71.

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### Methods

This was a prospective, randomized controlled study comparing conventional fluid management with two methods of advanced hemodynamic monitoring. A total of 90 patients undergoing proximal femoral fracture repair were randomized into three groups. Two groups received colloid fluid challenges by CVP monitoring (CVP, n=31) or esophageal Doppler monitoring (DOP, n=30). The Control Group received conventional fluid management (CON, n=29). Outcome measures included hospital stay and postoperative complications.

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### Results

- Days before medically fit for discharge: CVP group = 10.0, DOP Group = 7.7, CON Group = 13.9 (p = 0.035)
- Severe intraoperative hypo tension: CVP group = 9%, DOP Group = 7%, CON Group = 28% (p = 0.048).

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### Conclusions

*“Invasive intraoperative hemodynamic monitoring with fluid challenges during repair of femoral fracture under general anaesthetic shortens time to being medically fit for discharge”*

## NORMAL ADULT HEMODYNAMIC PARAMETERS

Abbreviation	Parameter	Equation	Normal Range
SBP	Systolic Blood Pressure		90 - 140 mmHg
DBP	Diastolic Blood Pressure		60 - 90 mmHg
MAP	Mean Arterial Pressure	$SBP + (2 \times DBP)/3$	70 - 105 mmHg
CVP	Central Venous Pressure		5 - 10 mmHg
PPV	Pulse Pressure Variation	$(PP_{max} - PP_{min}) / [(PP_{max} + PP_{min}) / 2] \times 100$	<10% unlikely to be fluid responsive >13-15% likely to be fluid responsive
SVV	Stroke Volume Variation	$(SV_{max} - SV_{min}) / [(SV_{max} + SV_{min}) / 2] \times 100$	<10% unlikely to be fluid responsive >13-15% likely to be fluid responsive
CO	Cardiac Output	$HR \times SV / 1000$	4.0 - 8.0 l/min
CI	Cardiac Index	$CO / BSA$	2.5 - 4.0 l/min/m <sup>2</sup>
SV	Stroke Volume	$CO / HR \times 1000$	60 - 100 ml/beat
SVI	Stroke Volume Index	$CI / HR \times 1000$	33 - 47 ml/m <sup>2</sup> /beat
SVR	Systemic Vascular Resistance	$80 \times (MAP - RAP) / CO$	800 - 1200 dynes · sec/cm <sup>5</sup>
SVRI	Systemic Vascular Resistance Index	$80 \times (MAP - RAP) / CI$	1970 - 2390 dynes · sec/cm <sup>5</sup> /m <sup>2</sup>
HR	Heart Rate		60-120 bpm
BSA	Body Surface Area	$BSA(m^2) = 0.007184 \times wt (kg)^{0.425} \times ht (cm)^{0.725}$	Men 1.9 m <sup>2</sup> Women 1.6 m <sup>2</sup>
EF	Ejection Fraction	$SV / EDV$	55-75%
SaO <sub>2</sub>	Arterial Oxygen Saturation		95 - 100%
SvO <sub>2</sub>	Mixed Venous Saturation		60 - 80%

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