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Conflicts of Interest

- B. Braun
- Fresenius
- Siemens

Volume Depletion in Critically Ill Patients

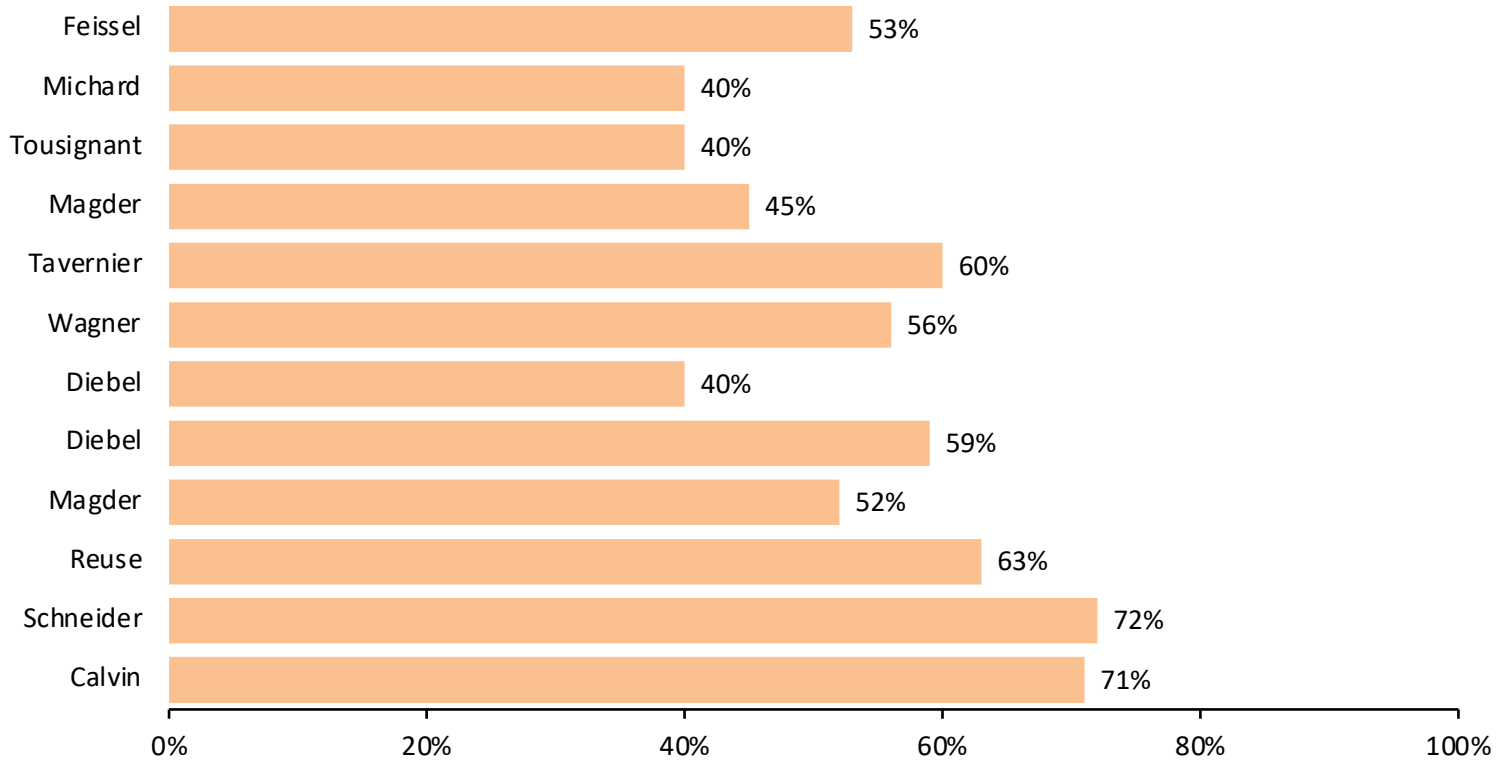
Absolute Hypovolemia

- External loss
 - hemorrhage
 - gastrointestinal
 - urinary
 - skin surface
- Internal loss
 - Third space loss

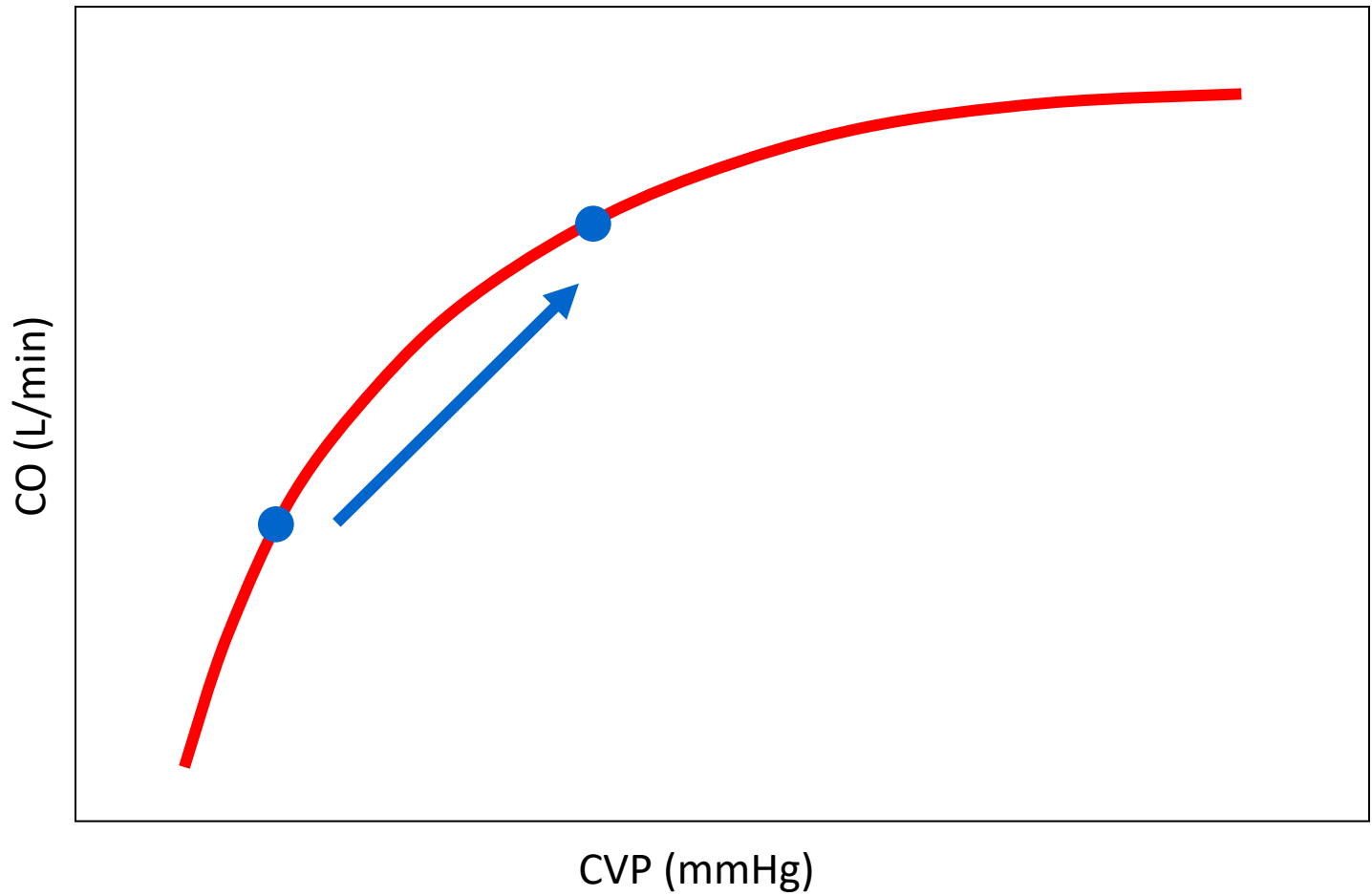
Relative Hypovolemia

- Increased venous capacity

Volume Depletion in Critically Ill Patients

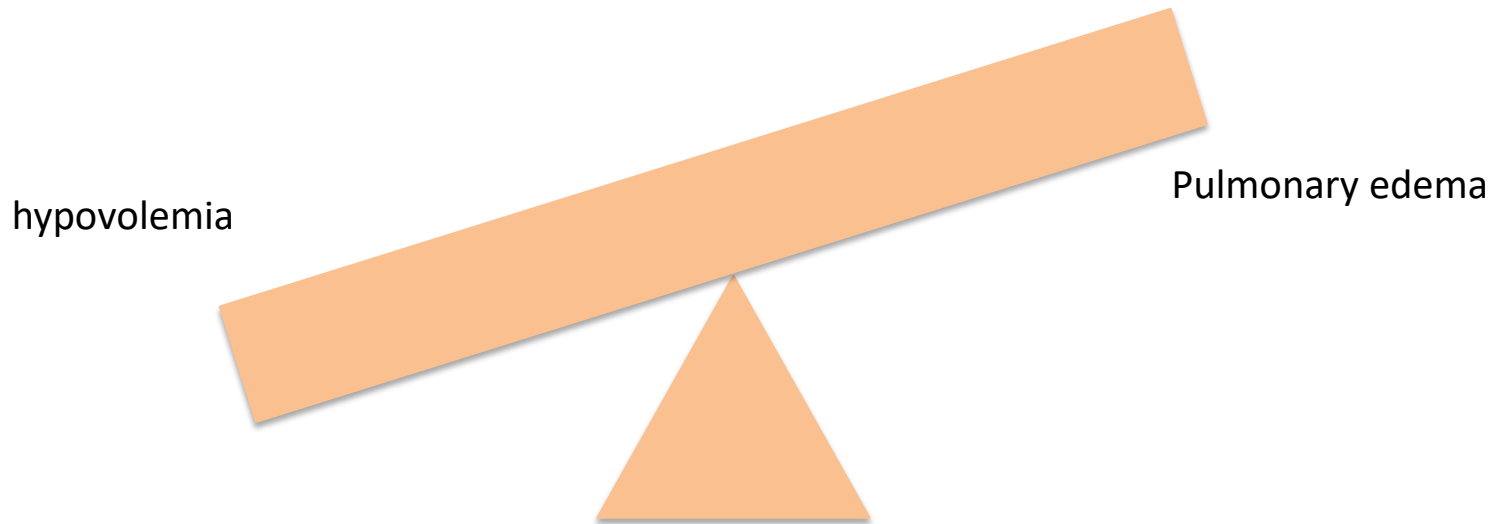


Why Should We Increase Preload



Fluid Management in Critically Ill Patients

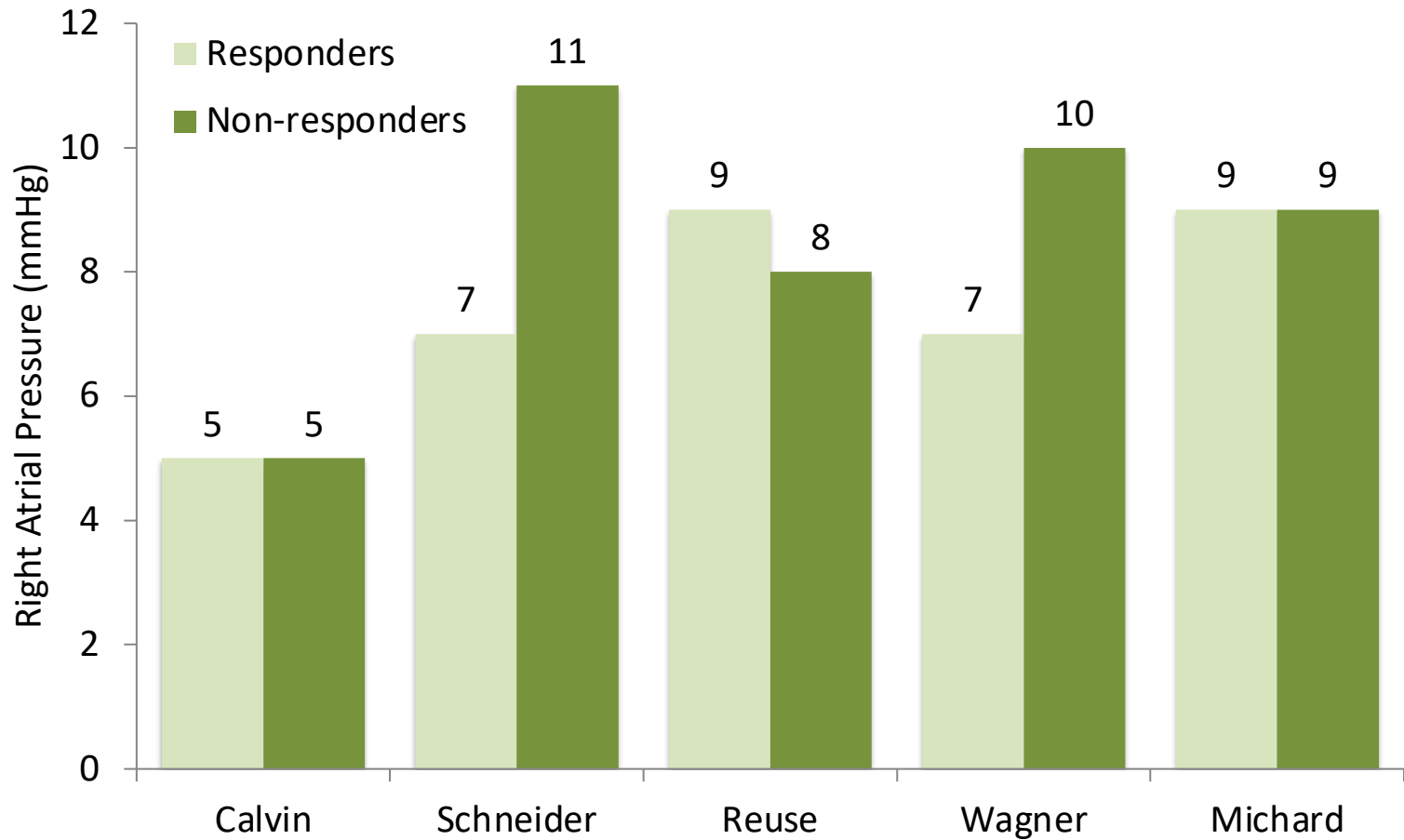
**52% of critically ill patients
responded to fluid challenge**



How to Predict Fluid Responsiveness

- **Static parameters** central venous pressure (CVP), pulmonary artery wedge pressure (PAWP), left ventricular end-diastolic area (LVEDA)
- **Conventional dynamic parameters** orthostatic hypotension, fluid challenge
- **Functional hemodynamic parameters** pulse pressure variation (PPV), systolic pressure variation (SPV), Δ down, stroke volume variation (SVV), respiratory variation of inferior vena cava (Δ IVC), respiratory variation of superior vena cava (Δ SVC), pleth variability index
- **Passive leg raising** cardiac index, pulse pressure
- **End-expiratory occlusion test** cardiac index, pulse pressure
- **Other parameters** pre-ejection period variation, artery peak velocity variation

RAP Before Volume Expansion



Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest 2002; 121: 2000-2008

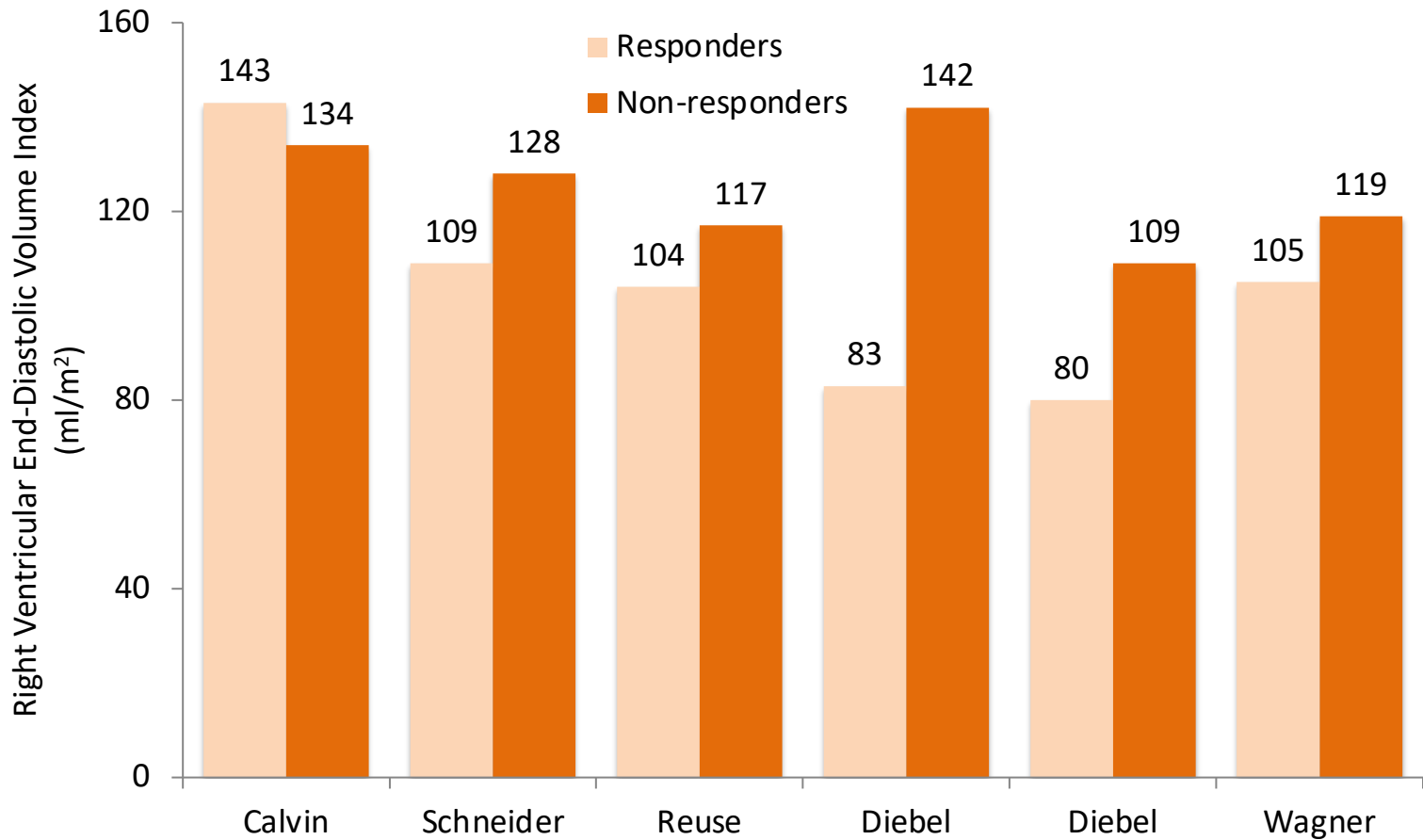
PAWP Before Volume Expansion

Source	PAOP, mm Hg	
	Responders	Nonresponders
Calvin et al ²	8 ± 1	7 ± 2
Schneider et al ³	10 ± 1	10 ± 1
Reuse et al ⁴	10 ± 4	10 ± 3
Diebel et al ⁶	14 ± 7	7 ± 2†
Diebel et al ⁷	16 ± 6	15 ± 5
Wagner and Leatherman ⁸	10 ± 3	14 ± 4†
Tavernier et al ⁹	10 ± 4	12 ± 3
Tousignant et al ¹¹	12 ± 3	16 ± 3†
Michard et al ¹²	10 ± 3	11 ± 2

*Values are expressed as mean ± SD, except for the study of Schneider et al³ (mean ± SEM).

†p < 0.05 responders vs nonresponders.

RVEDV Index Before Volume Expansion



Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest 2002; 121: 2000-2008

LVEDA Before Volume Expansion

Table 4—LVEDA Before Volume Expansion in Responders and Nonresponders*

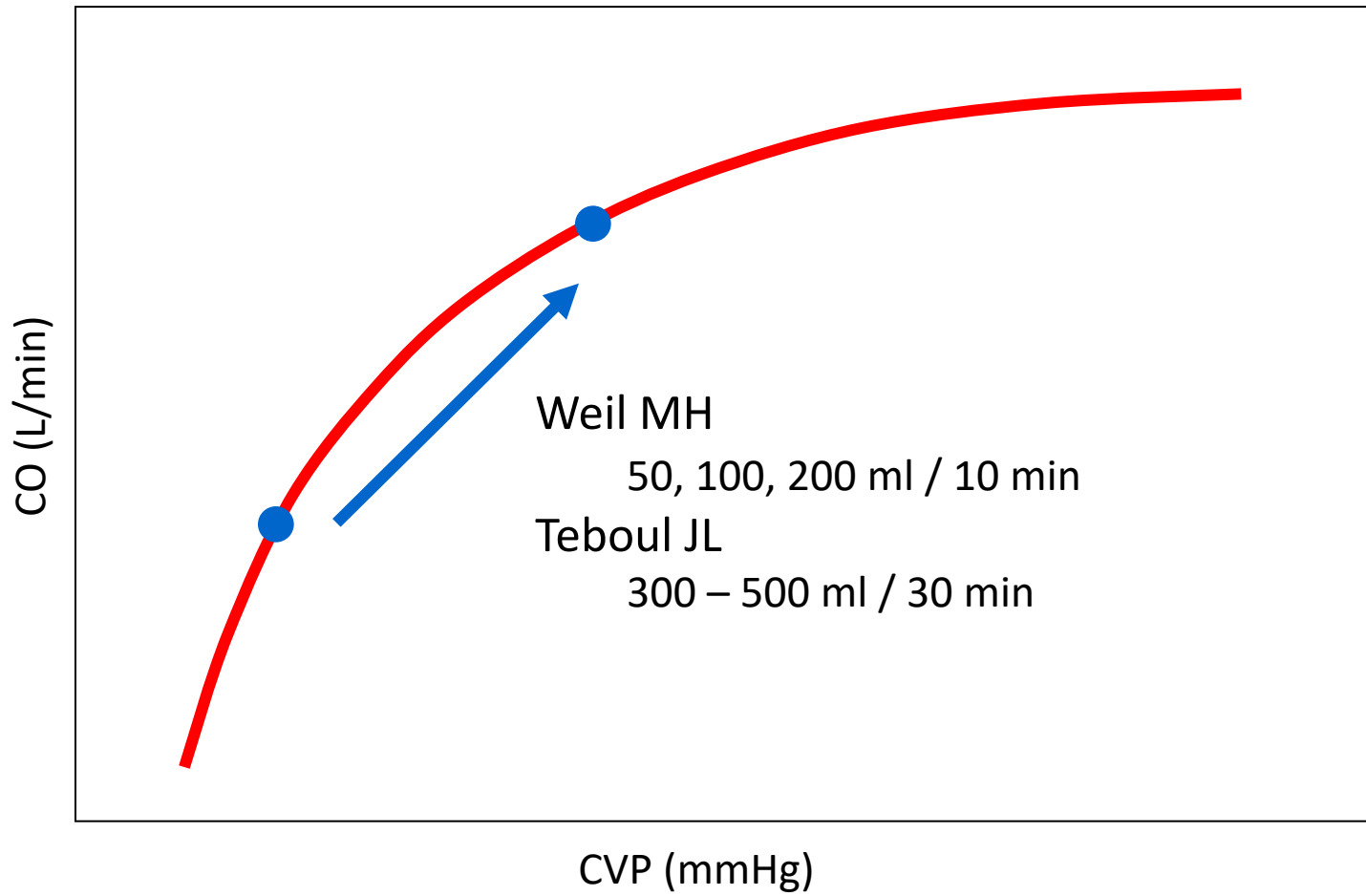
Source	LVEDA, cm ² /m ²	
	Responders	Nonresponders
Tavernier et al ⁹	9 ± 3	12 ± 4†
Tousignant et al ¹¹	15 ± 5‡	20 ± 5†‡
Feissel et al ¹³	10 ± 4	10 ± 2

*Data are presented as mean ± SD.

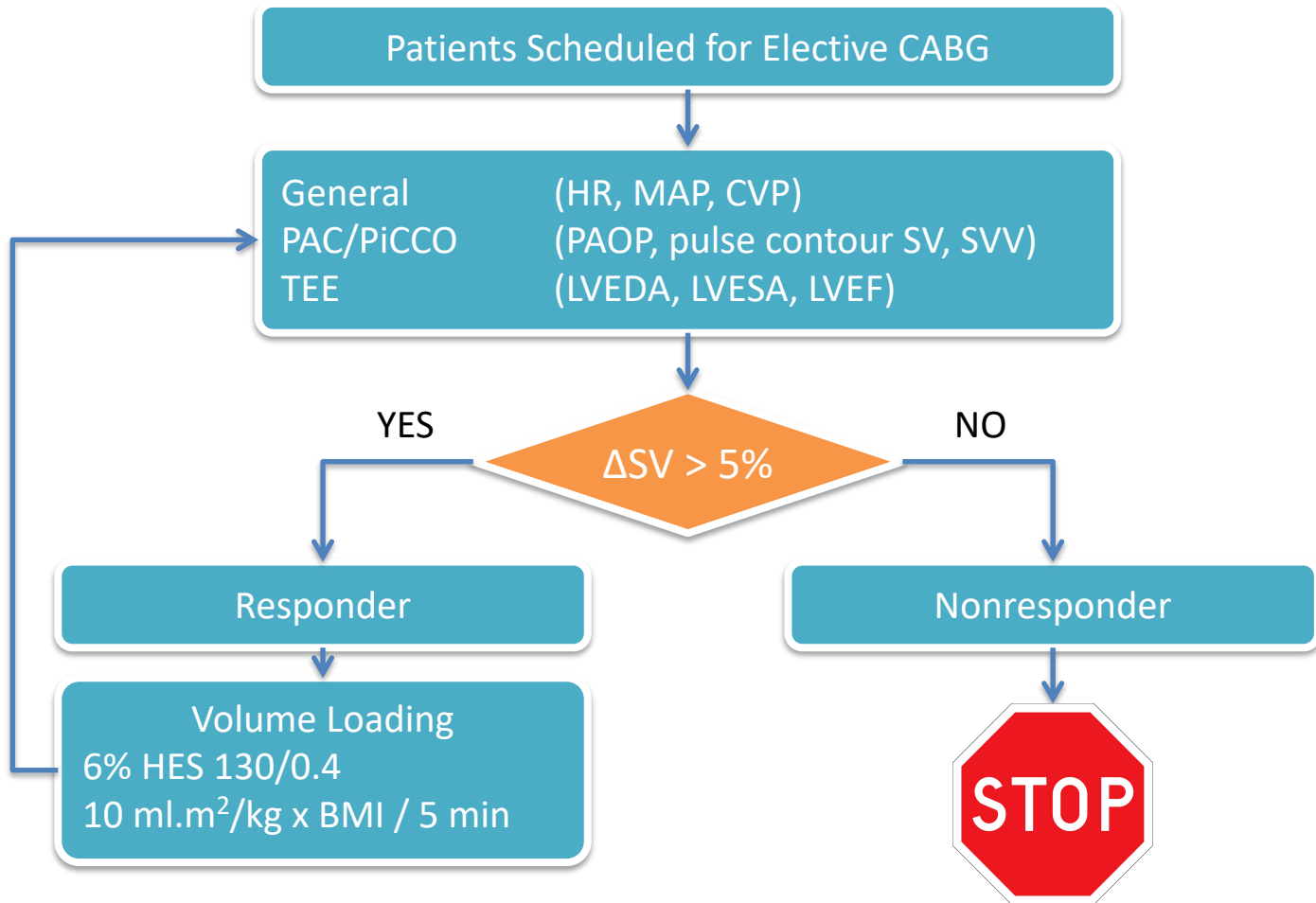
†p < 0.05 responders vs nonresponders.

‡Area expressed in centimeters squared.

Fluid Challenge



In Patients with Cardiac Dysfunction...



Reuter DA, Kirchner A, Felbinger TW, et al. Usefulness of left ventricular stroke volume variation to assess fluid responsiveness in patients with reduced cardiac function. Crit Care Med 2003; 31: 1399-1404

In Patients with Cardiac Dysfunction...

Table 2. Hemodynamic data at baseline and before the nonresponder volume loading step

	Study Group (EF <35%) (n = 12)		Control Group (EF >50%) (n = 14)	
	Baseline	Nonresponder	Baseline	Nonresponder
MAP, mm Hg	77 ± 6.4 ^a	87 ± 12 ^{a,b}	82 ± 7	95 ± 12 ^b
HR, beats/min	98 ± 10	97 ± 9	93 ± 7	93 ± 6
SVI, mL ² /m ²	31.9 ± 6.3	39.1 ± 5.2 ^{a,b}	33.5 ± 4.8	44.2 ± 5.8 ^b
SVV, %	13.1 ± 4.8	7.8 ± 2.3 ^b	15.3 ± 4.2	7.9 ± 2.2 ^b
LVEFA, %	25 ± 9 ^a	27 ± 10 ^a	68 ± 11	69 ± 10 ^b
CVP, mm Hg	7 ± 3	9 ± 3 ^b	8 ± 3	11 ± 3
PAOP, mm Hg	6 ± 3	8 ± 4 ^b	6 ± 4	9 ± 4 ^b
LVEDAI, cm ² /m ²	28.9 ± 9.6 ^a	32.5 ± 7.8 ^{a,b}	15.1 ± 3.4	19.4 ± 4.1 ^b
SVRI, dynes sec/cm ⁵	1847 ± 599	1751 ± 478	1960 ± 556	1804 ± 539

Preoperative LVEF

27.4 ± 5.8%

64.8 ± 8.7%

Reuter DA, Kirchner A, Felbinger TW, et al. Usefulness of left ventricular stroke volume variation to assess fluid responsiveness in patients with reduced cardiac function. Crit Care Med 2003; 31: 1399-1404

In Patients with Cardiac Dysfunction...

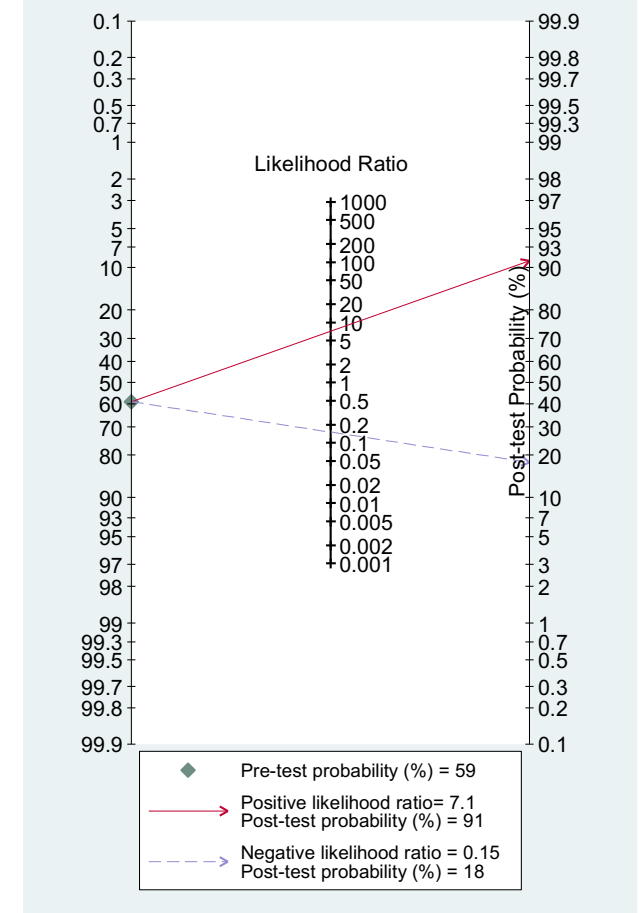
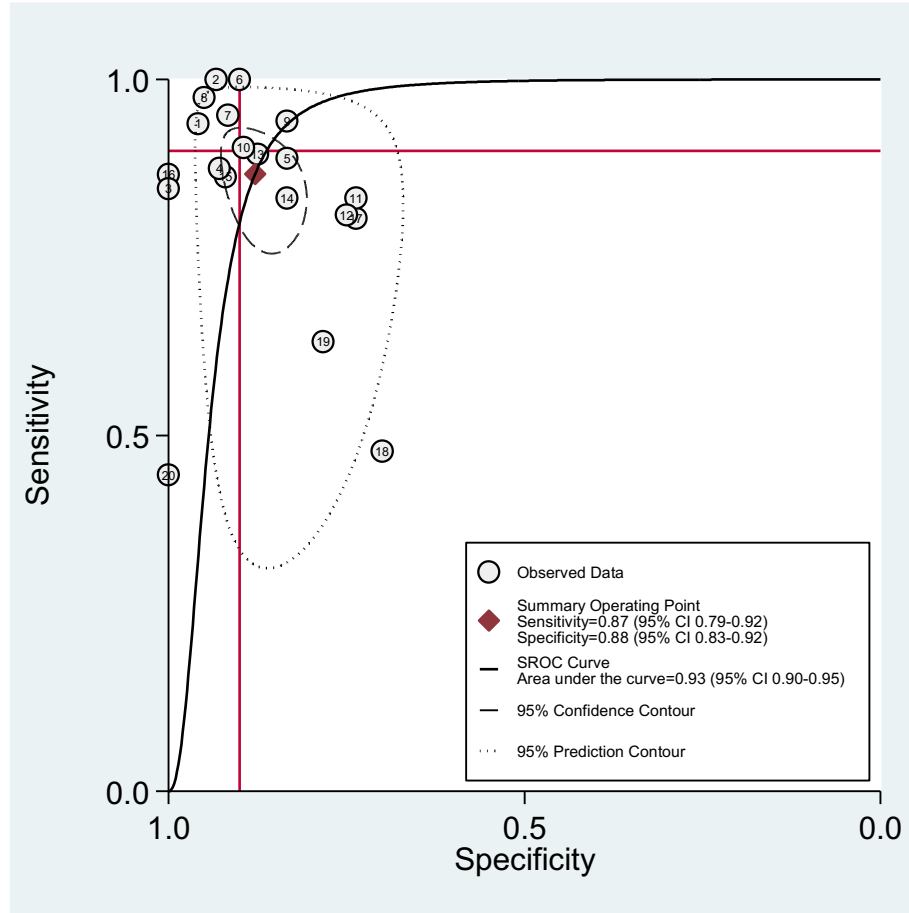
- Functional hemodynamics
 - PPV
 - SVV
 - ...
- Passive leg raising

PPV to Predict Fluid Responsiveness

Author	Year	Threshold	TP	FP	FN	TN	Sen	Spe
Michard	2000	13%	15	1	1	23	94%	96%
Kramer	2004	11%	6	1	0	14	100%	93%
Feissel	2005	17%	11	0	2	9	85%	100%
Monnet	2006	12%	14	1	2	13	88%	93%
Charron	2006	10%	8	2	1	10	89%	83%
Feissel	2007	12%	18	1	0	9	100%	94%
Wyffels	2007	11.3%	19	1	1	11	95%	92%
Auler	2008	12%	38	1	1	19	97%	95%
Vistisen	2009	6.5%	16	1	1	5	94%	83%
Loupec	2011	13%	19	2	2	17	90%	89%
Cecconi	2012	13%	10	5	2	14	83%	74%
Fellahi	2012	10%	17	1	4	3	81%	75%
Biais	2012	10%	17	2	2	14	89%	88%
Khwannimit	2012	12%	20	3	4	15	83%	83%
Monnet	2012	10%	19	2	3	23	88%	91%
Monnet	2012	12%	13	0	2	11	85%	100%
Yazigi	2012	11.5%	33	5	8	14	80%	74%
Ishihara	2013	8.5%	11	6	12	14	50%	71%
Fischer	2013	14%	36	5	21	18	64%	78%
Fischer	2013	16%	12	0	15	10	44%	100%

Yang X, Du B. Does pulse pressure variation predict fluid responsiveness in critically ill patients? A systematic review and meta-analysis. Crit Care 2014; 18: 650

PPV to Predict Fluid Responsiveness



Yang X, Du B. Does pulse pressure variation predict fluid responsiveness in critically ill patients? A systematic review and meta-analysis. Crit Care 2014; 18: 650

PPV and SVV to Predict Fluid Responsiveness

	Pulse Pressure Variation (PPV)	Stroke Volume Variation (SVV)
Sensitivity	0.84 (0.62 – 0.95)	0.82 (0.59 – 0.93)
Specificity	0.83 (0.58 – 0.94)	0.84 (0.62 – 0.95)
ROC AUC	0.88 (0.84 – 0.92)	0.84 (0.79 – 0.89)

Hong J, He H, Chen Z, et al. Comparison of stroke volume variation with pulse pressure variation as a diagnostic indicator of fluid responsiveness in mechanically ventilated critically ill patients. Saudi Med J 2014; 35: 261-268

PPV and SVV to Predict Fluid Responsiveness

- Confounding factors
 - Spontaneous breathing activity
 - Cardiac arrhythmias
 - Low tidal volume
 - Respiratory frequency
 - Increased intraabdominal pressure

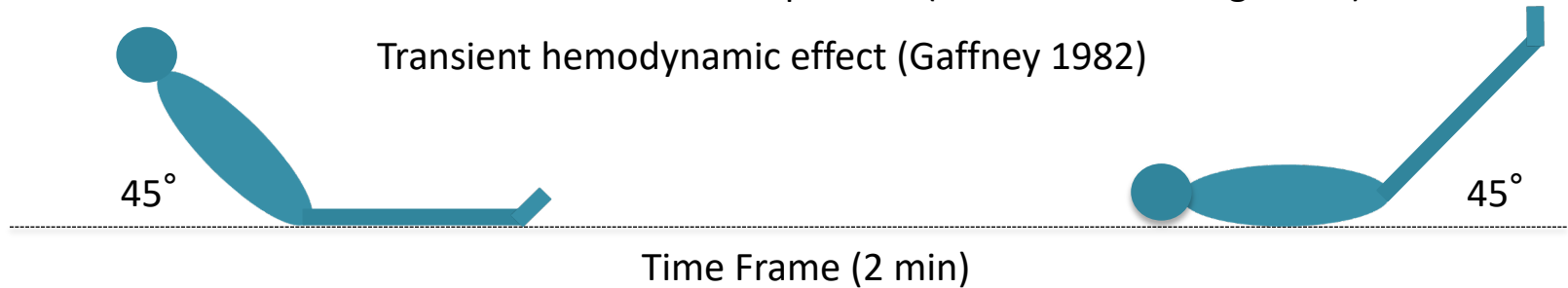
PLR to Predict Fluid Responsiveness

Promote venous return (Rutlen et al 1981; Reich et al 1989)

Increase right ventricular preload (Thomas et al 1965)

Increase left ventricular preload (Rocha 1987; Takagi 1989)

Transient hemodynamic effect (Gaffney 1982)



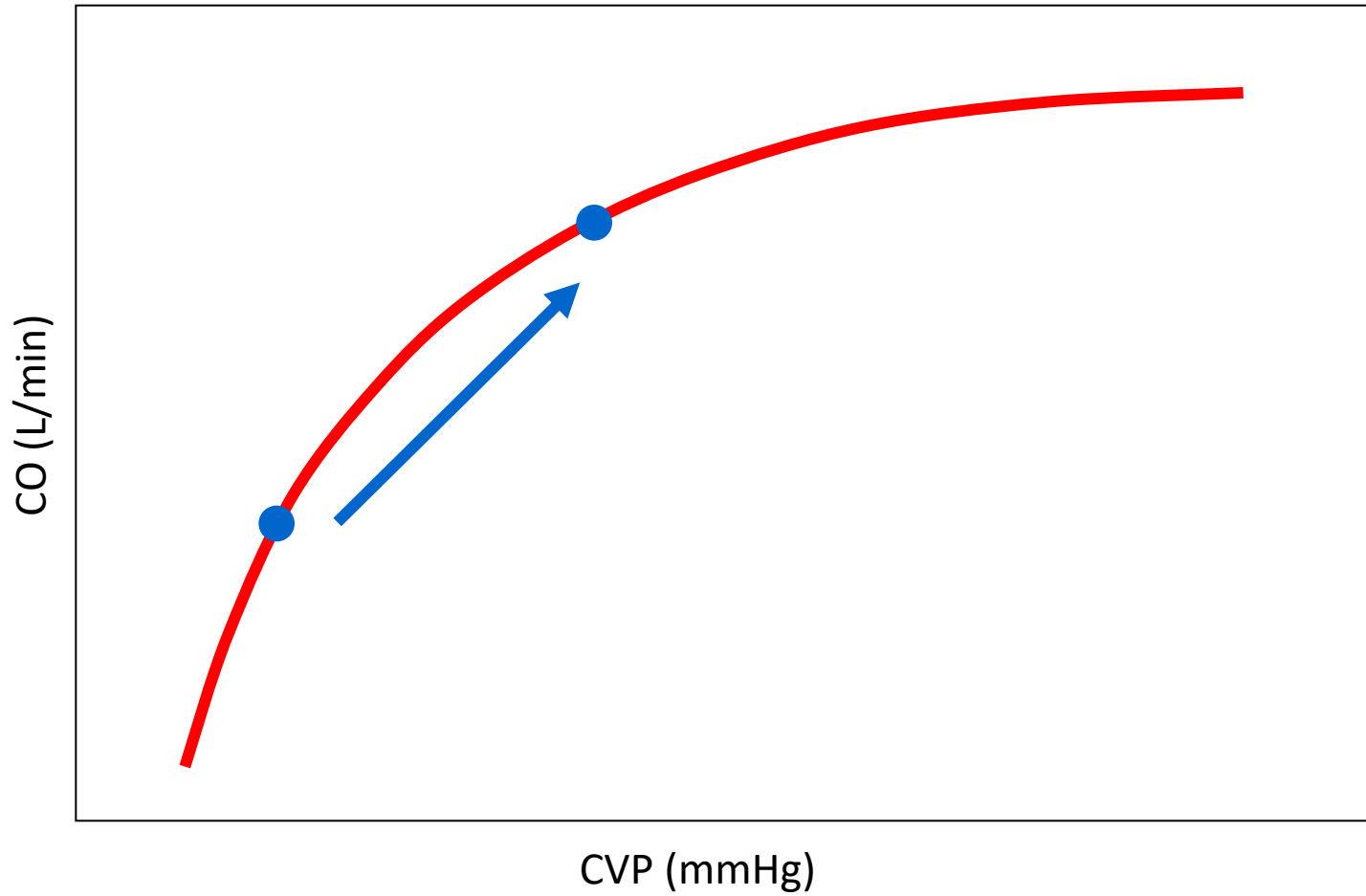
	Cutoff	SEN	SPE	DOR	AUROC
cCO	8 – 15%	89.4% (84.1 – 93.4%)	91.4% (85.9 – 95.2%)	89.0 (40.2 – 197.3)	0.95 (0.92 – 0.97)
cPP	9 – 12%	59.5% (47.4 – 70.7%)	86.2% (75.3 – 93.5%)	10.8 (4.4 – 26.1)	0.76 (0.67 – 0.86)

Cavallaro F, Sandroni C, Marano C, et al. Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies. *Intensive Care Med* 2010; 36: 1475-1483

PLR to Predict Fluid Responsiveness

- PRO
 - No need to sedation
 - No requirement for spontaneous breathing and/or cardiac arrhythmia
- CONS
 - Arterial blood pressure unable to predict CO change
 - Real-time cardiac output monitoring
 - Contraindication of changes of body position
 - Intraabdominal hypertension

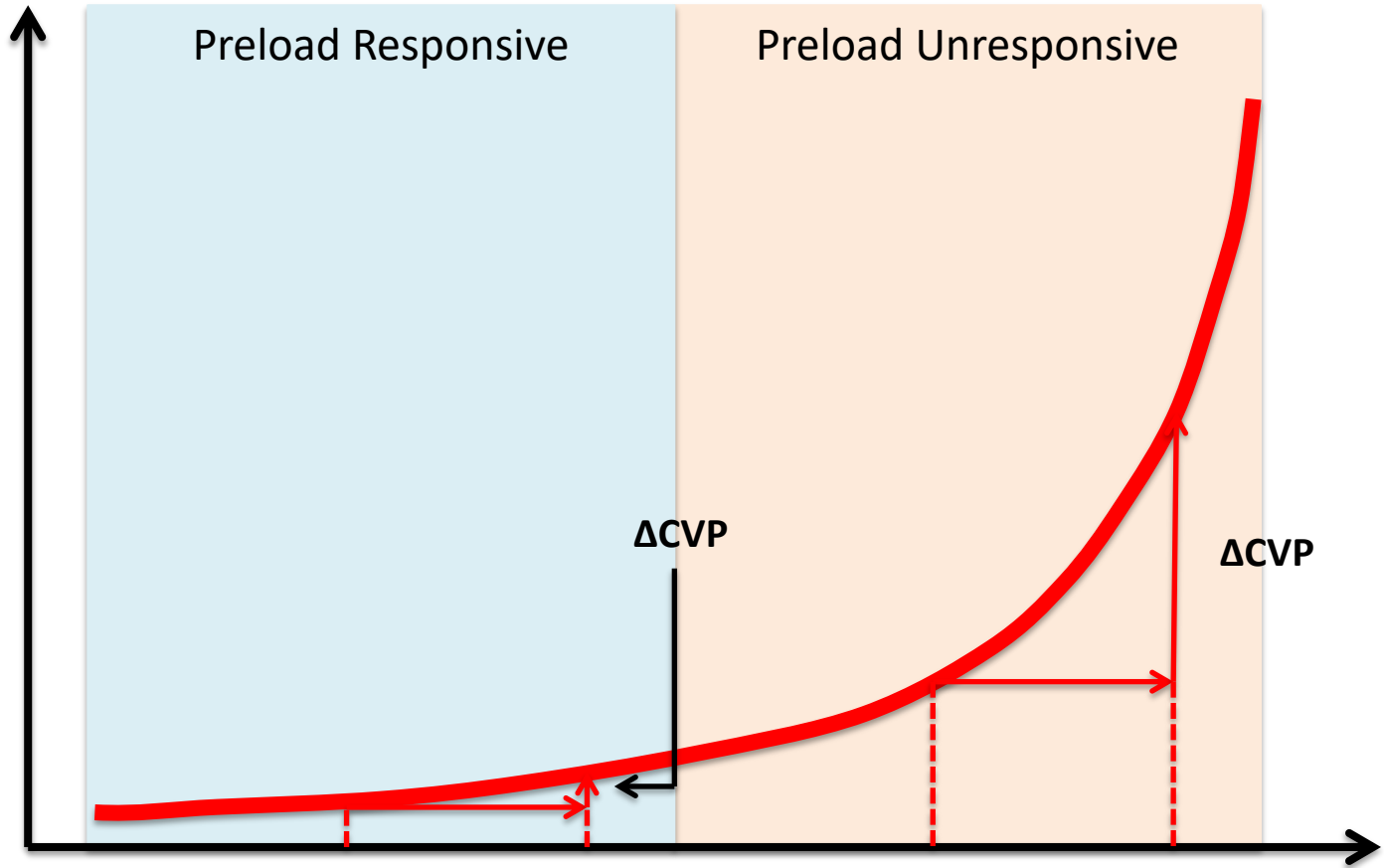
Why Should We Increase Preload



CVP 2 – 5 Rule

Time	CVP (mm Hg)	Gelofusine fluid challenge
Initial reading	<14	200 ml
	≥14	100 ml
During fluid challenge	Increase >5	Stop fluid challenge and WAIT
Following fluid challenge	Increase >3	WAIT
	≤3	Repeat fluid challenge as per initial reading

CVP 2 – 5 Rule



CVP 2 – 5 Rule Never Validated

Fluid challenge in ICU patients

- # of patients 39
- Male sex 22
- Age 64 ± 16
- APACHE II 25 ± 9
- Non-surgical 30
- Vasopressor 37
- Invasive MV 36
- CRRT 14
- Death 22

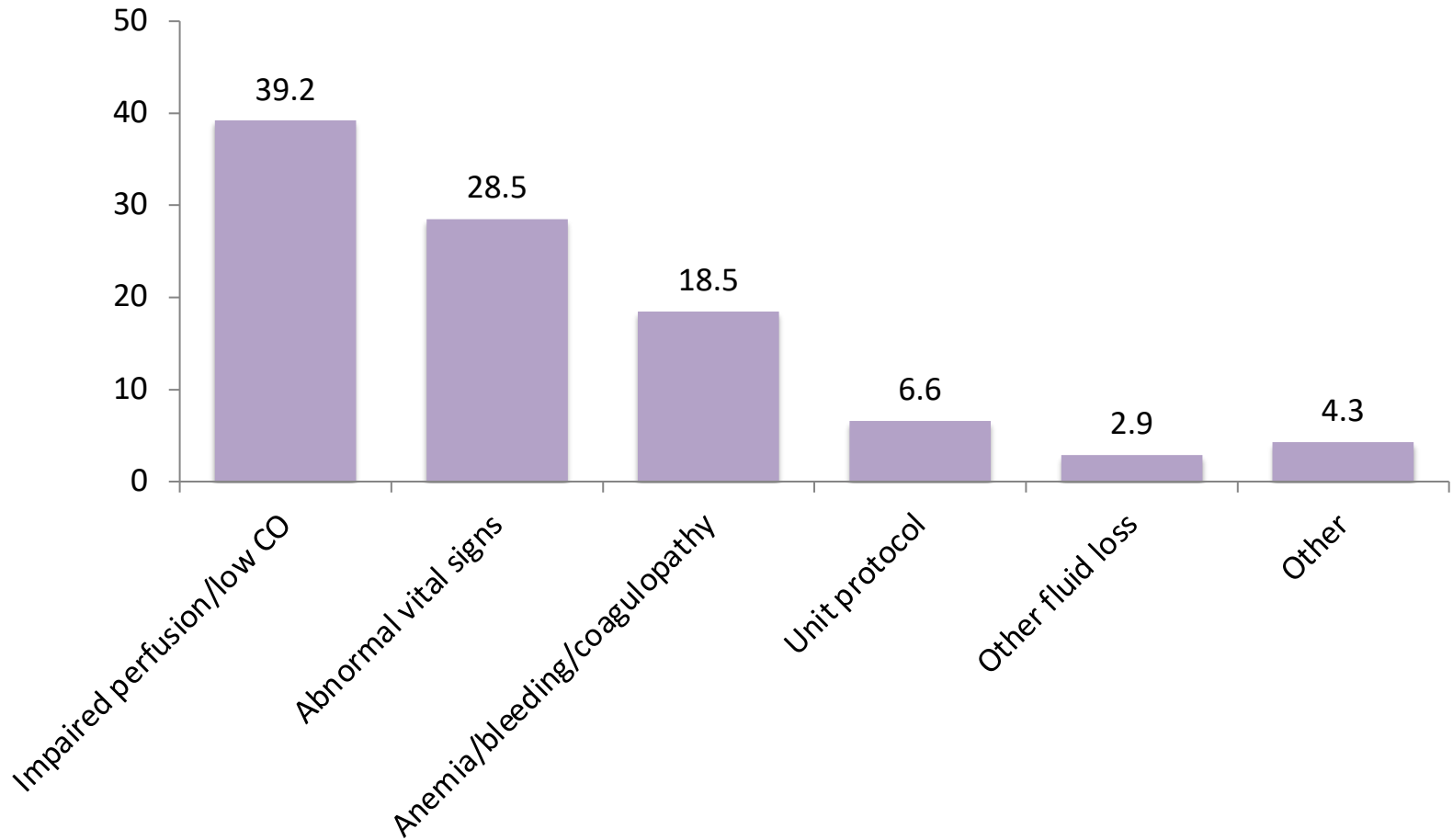
	ΔCVP	
	2 mmHg	5 mmHg
sensitivity	32.6%	17.5%
specificity	67.5%	73.9%
PPV	53.6%	36.8%
NPV	46.6%	50.7%

Data on file. Medical ICU, Peking Union Medical College Hospital

Fluid Challenge in Critically Ill Patients

**Do We Have Other Surrogate Markers
of Increased Cardiac Output
at the Bedside?**

Indications for Fluid Resuscitation



Finfer S, Liu B, Taylor C, et al. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. Crit Care 2010; 14: R185

Assessment of Fluid Challenge

INDICATIONS

CO/CI/SV ↘

HR ↗

MAP ↘

CVP ↘

pH ↘

UO ↘

LA ↗

≠

ASSESSMENT

CO/CI/SV ↗

HR ↘

MAP ↗

CVP ↗

pH?

UO?

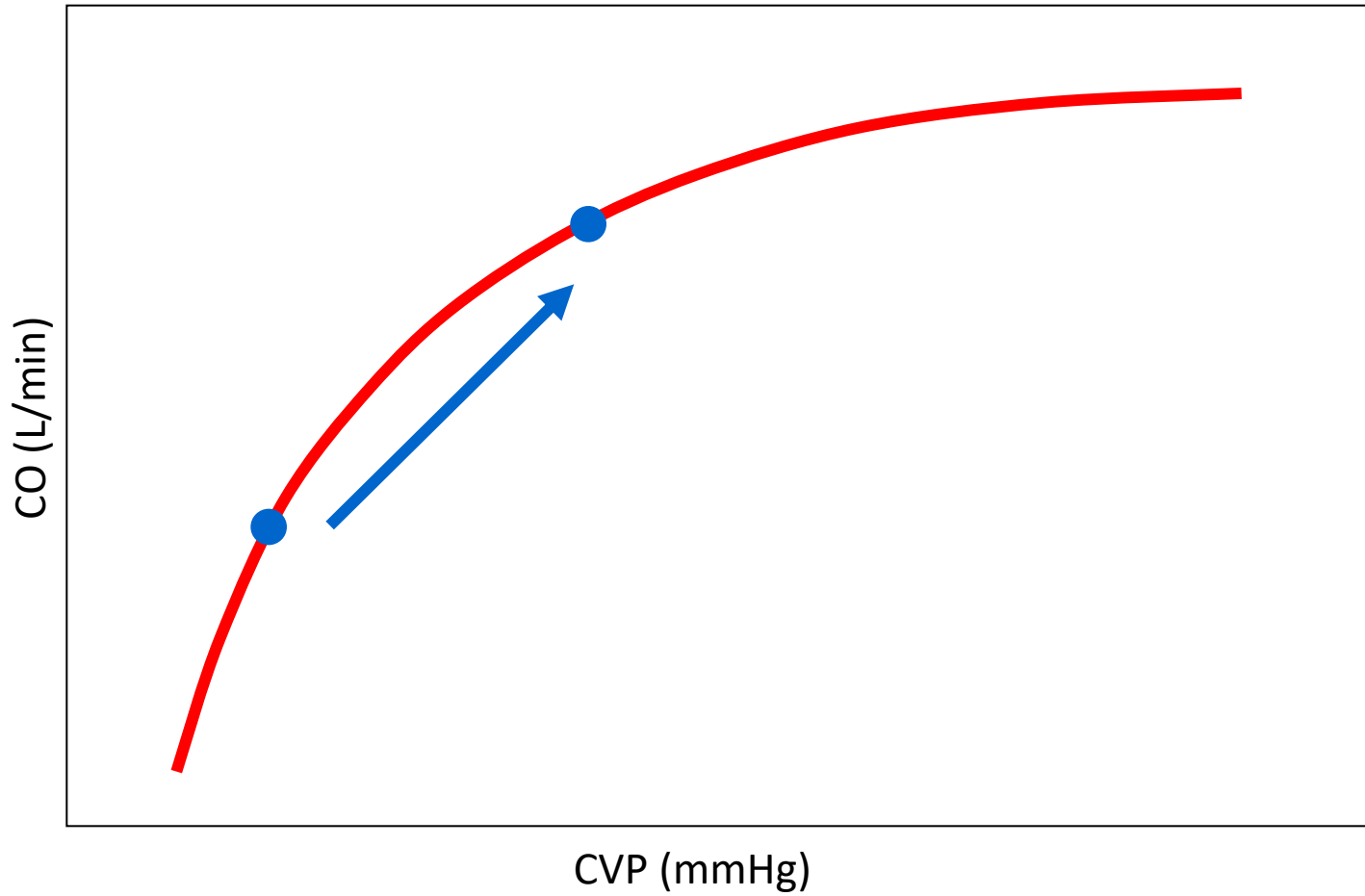
LA?

Lactate as Surrogate Marker?

	Responders (<i>n</i> =33)		Non-responders (<i>n</i> =27)	
	Baseline	Fluids	Baseline	Fluids
Heart rate, bpm	97 [89–108]	95 [84–102]+	87 [78–114]	86 [74–109]
Mean arterial pressure, mmHg	68 [61–76]	78 [69–78]++	70 [60–81]	75 [66–81]
Mean pulmonary art press, mmHg	24 [15–32]	28 [23–36]++	26 [22–29]	29 [24–36]++
PAOPend expiratory, mmHg	12 [10–14]	16 [12–19]++	14 [12–16]*	18 [11–22]+
PAOPcorrected, mmHg	10 [8–13]	12 [9–15]++	13 [10–15]*	16 [10–18]++
RAP, mmHg	10 [7–12]	13 [11–15]	12 [9–15]	13 [11–16]
Delta PP, %	13.6 [7.8–22.7]	4.1 [1.1–7.6]+++	5.3 [2.3–12.8]***	5.3 [3.1–8.0]\$\$\$
Cardiac index, l/min m ²	2.54 [2.08–3.56]	3.09 [2.58–4.33]+++	2.83 [2.00–3.42]	2.87 [2.16–3.76]\$\$\$
SvO ₂ , %	63 [56–69]	69 [60–73]++	66 [62–70]	68 [64–70]
Hemoglobin concentrations, g/dl	9.3 [8.2–10.6]	8.7 [7.9–9.8]+	9.9 [8.6–10.7]	9.4 [8.1–10.4]+
Lactate concentrations, mEq/l	3.1 [1.5–3.9]	3.0 [1.5–3.8]	1.9 [1.4–2.5]	1.9 [1.3–2.4]
Tidal volume, ml/kg	7.5 [6.3–8.9]		7.3. [6.3–8.9]	
PEEPtot, cm H ₂ O	6 [5–10]		5 [4–10]	

De Backer D, Heenen S, Piagnerelli M, et al. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med* 2005; 31: 517-523

Why Should We Increase Preload



If CO Monitor Available...

- Volume expansion-related stroke volume change (ΔSV)
 - > 0% Calvin, Schneider
 - > 10% Wagner & Leatherman
 - > 15% Tavernier
 - > 20% Tousignant
- Volume expansion-related cardiac output change (ΔCO)
 - > 250 ml/min Magder
 - > 0% Reuse
 - > 10% Diebel
 - > 15% Michard, Feissel

If CO Monitor Unavailable...

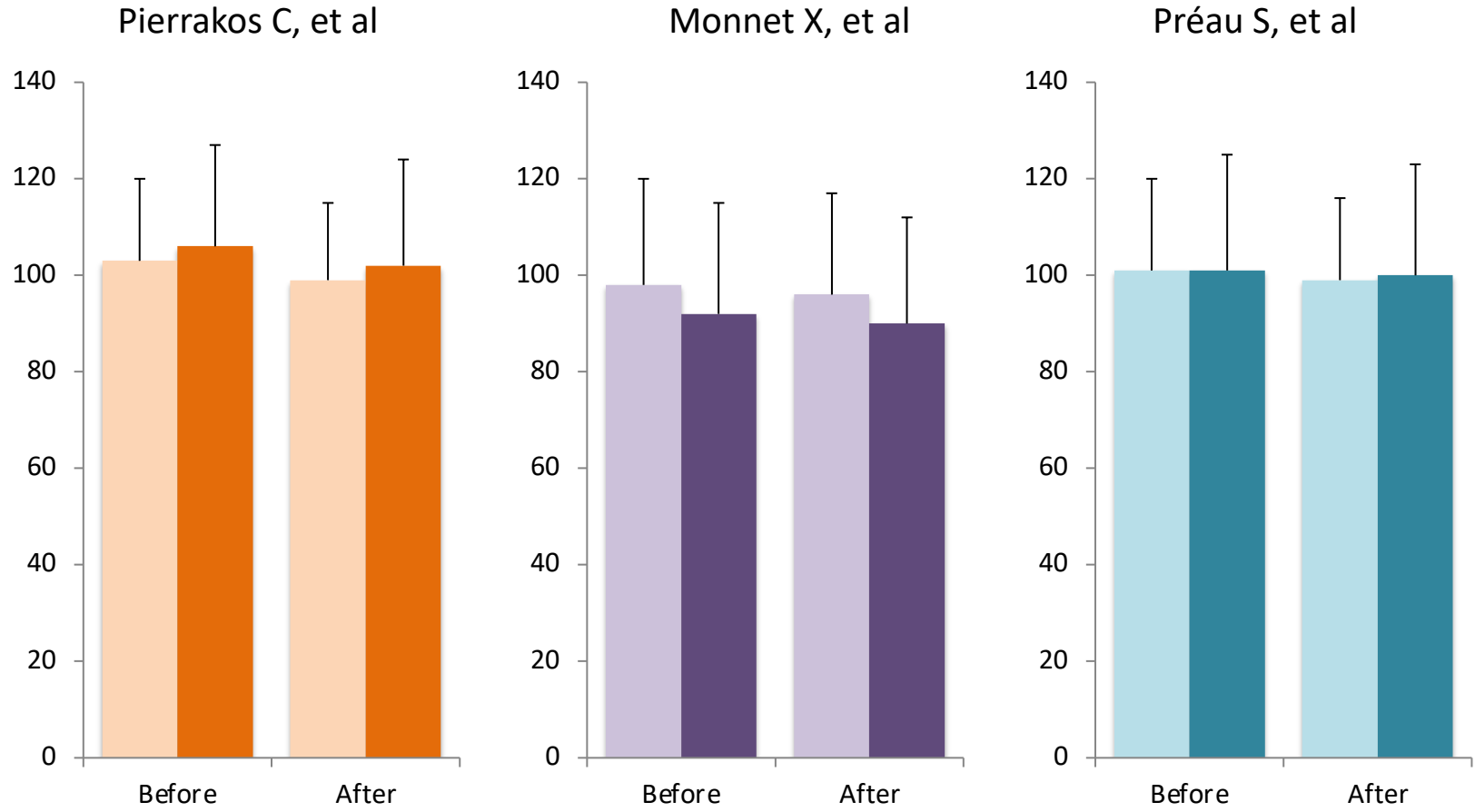
Functional hemodynamics

- SVV
- SPV
- PPV
- Δ down
- Passive leg raising
- ...

Traditional hemodynamics

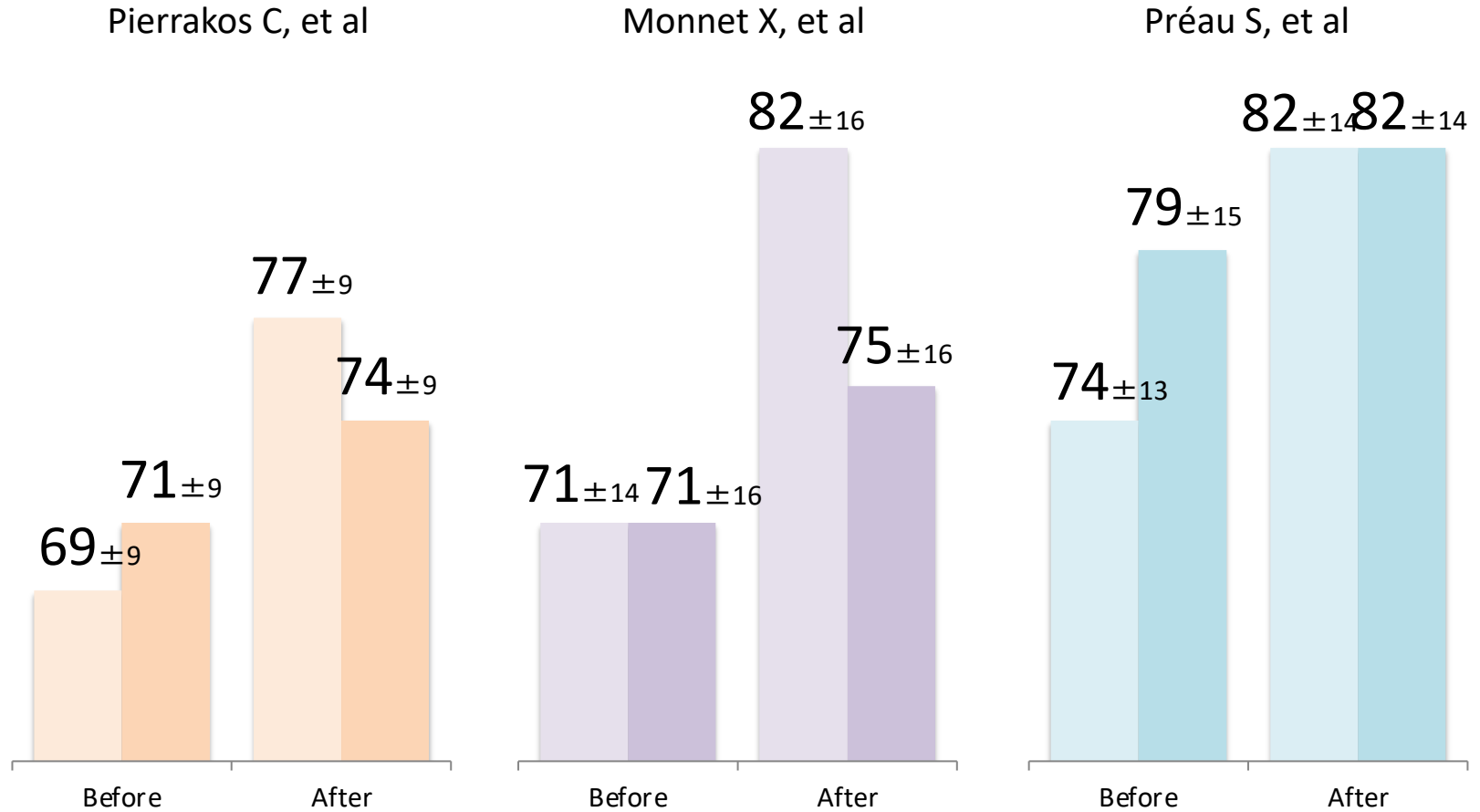
- Δ CVP
- Δ HR
- Δ BP
- ...

Heart Rate to Detect CO Changes



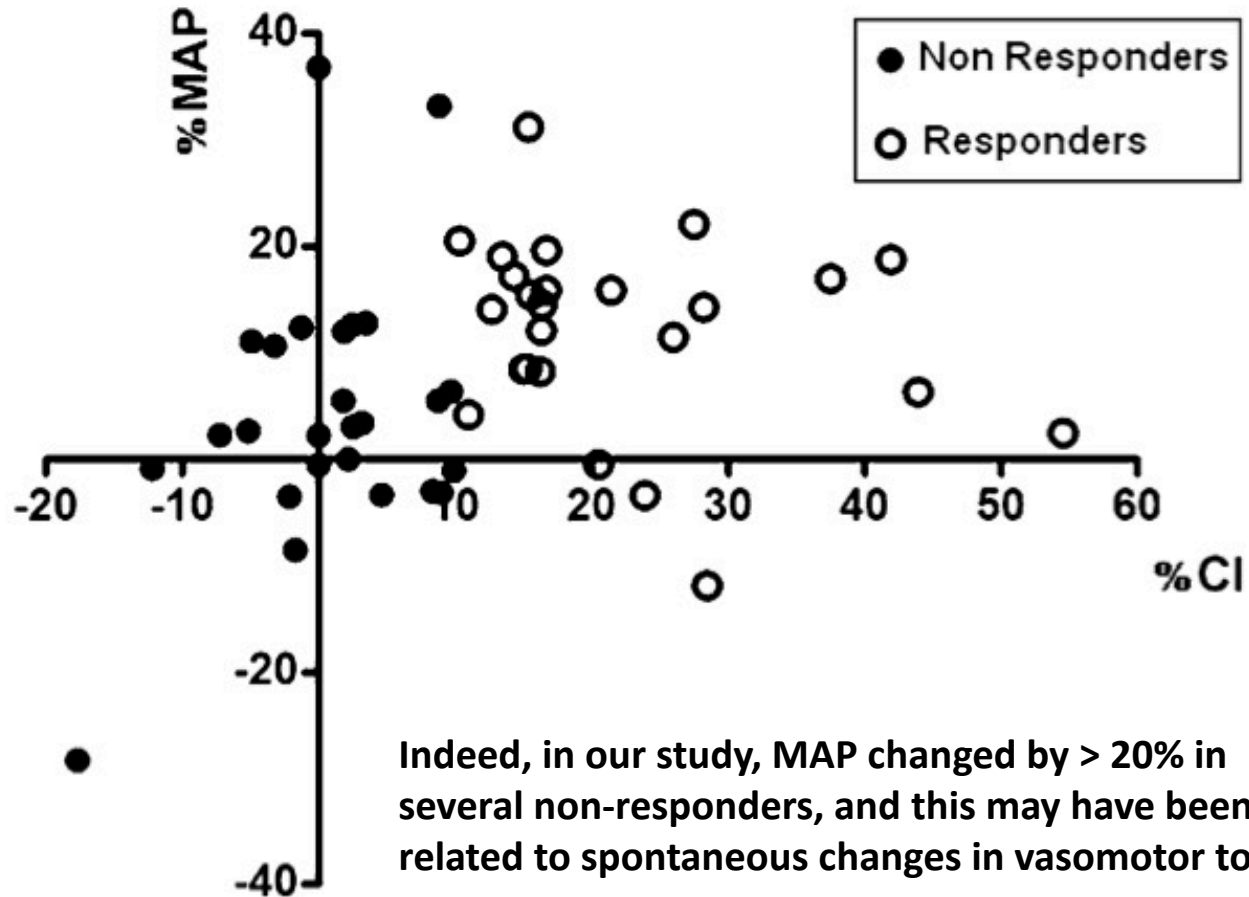
1. Préau S, Saulnier F, Dewavrin F, et al. Passive leg raising is predictive of fluid responsiveness in spontaneously breathing patients with severe sepsis or acute pancreatitis. Crit Care Med 2010; 38: 819-825. 2. Monnet X, Letierce A, Hamzaoui O, et al. Arterial pressure allows monitoring the changes in cardiac output induced by volume expansion but not by norepinephrine. Crit Care Med 2011; 39: 1394-1399. 3. Pierrakos C, Velissaris D, Scolletta S, et al. Can changes in arterial pressure be used to detect changes in cardiac index during fluid challenge in patients with septic shock? Intensive Care Med 2012; 38: 422-428

Blood Pressure to Detect CO Changes

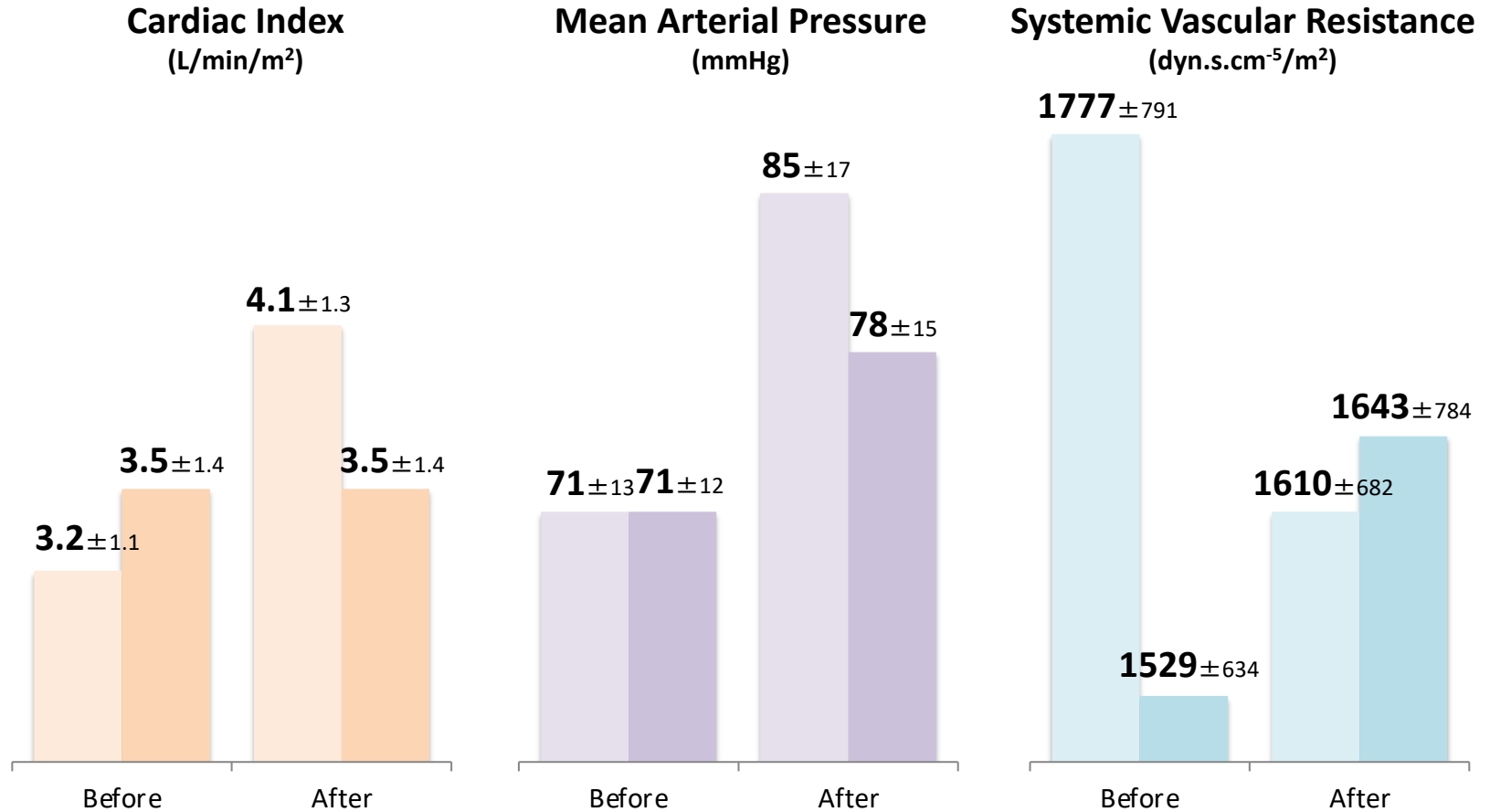


1. Préau S, Saulnier F, Dewavrin F, et al. Passive leg raising is predictive of fluid responsiveness in spontaneously breathing patients with severe sepsis or acute pancreatitis. Crit Care Med 2010; 38: 819-825. 2. Monnet X, Letierce A, Hamzaoui O, et al. Arterial pressure allows monitoring the changes in cardiac output induced by volume expansion but not by norepinephrine. Crit Care Med 2011; 39: 1394-1399. 3. Pierrakos C, Velissaris D, Scolletta S, et al. Can changes in arterial pressure be used to detect changes in cardiac index during fluid challenge in patients with septic shock? Intensive Care Med 2012; 38: 422-428

Blood Pressure to Detect CO Changes



Blood Pressure to Detect CO Changes



Lakhal K, Ehrmann S, Perrotin D, et al. Fluid challenge: tracking changes in cardiac output with blood pressure monitoring (invasive or non-invasive). Intensive Care Med 2013; 39: 1953-1962

Blood Pressure to Detect CO Changes

Abstract

Background: Mean arterial pressure above 65 mmHg is recommended for critically ill hypotensive patients whereas they do not benefit from supranormal cardiac output values. In this study we investigated if the increase of mean arterial pressure after volume expansion could be predicted by cardiovascular and renal variables. This is a relevant topic because unnecessary positive fluid balance increases mortality, organ dysfunction and Intensive Care Unit length of stay.

Methods: Thirty-six hypotensive patients (mean arterial pressure < 65 mmHg) received a fluid challenge with hydroxyethyl starch. Patients were excluded if they had active bleeding and/or required changes in vasoactive agents infusion rate in the previous 30 minutes. Responders were defined by the increase of mean arterial pressure value to over 65 mmHg or by more than 20% with respect to the value recorded before fluid challenge. Measurements were performed before and at one hour after the end of fluid challenge.

Results: Twenty-two patients (61%) increased arterial pressure after volume expansion. Baseline heart rate, arterial pressure, central venous pressure, central venous saturation, central venous to arterial PCO₂ difference, lactate, urinary output, fractional excretion of sodium and urinary sodium/potassium ratio were similar between responder and non-responder. Only 7 out of 36 patients had valuable dynamic indices and then we excluded them from analysis. When the variables were tested as predictors of responders, they showed values of areas under the ROC curve ranging between 0.502 and 0.604. Logistic regression did not reveal any association between variables and responder definition.

Conclusions: Fluid challenge did not improve arterial pressure in about one third of hypotensive critically ill patients. Cardiovascular and renal variables did not enable us to predict the individual response to volume administration.

Trial registration: ClinicalTrials.gov: NCT00721604.

Cardiac Filling Pressure as Safety Limits

	Baseline	+ 10 min	+ 20 min
Type of fluid: RL			
Rate of infusion: 500 ml/30 min			
Clinical endpoint: MAP 75 mmHg	65	70	75
Pressure safety limits: CVP 15 mmHg	12	13	14



Successful Fluid Challenge

Cardiac Filling Pressure as Safety Limits

	Baseline	+ 10 min	+ 20 min
Type of fluid: RL			
Rate of infusion: 500 ml/30 min			
Clinical endpoint: MAP 75 mmHg	65	67	60
Pressure safety limits: CVP 15 mmHg	12	14	15



Unsuccessful Fluid Challenge

If CO Monitor Unavailable...

Functional hemodynamics

- SVV
- SPV
- PPV
- Δ down
- Passive leg raising
- ...

Traditional hemodynamics

- Δ CVP?
- Δ HR?
- Δ BP?
- ...

Oxygen Delivery and Oxygen Consumption

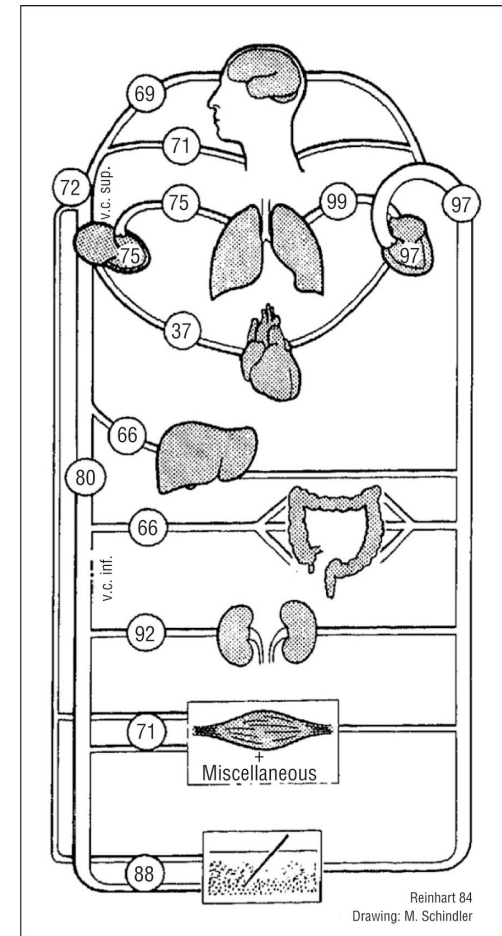
$$DO_2 = CO \times Hb \times SaO_2$$

$$VO_2 = CO \times Hb \times (SaO_2 - SvO_2)$$

$$SvO_2 = SaO_2 - VO_2 / (CO \times Hb)$$

Condition	SvO ₂	ScvO ₂	r	n	SvO ₂ -ScvO ₂
Total	53 ± 16	52 ± 15	0.96	29531	3.7 ± 2.9
Control	59 ± 14	57 ± 15	0.98	14167	2.8 ± 2.0
Hemorrhage	33 ± 14	37 ± 12	0.94	1490	6.0 ± 3.1
Resuscitation	51 ± 12	50 ± 11	0.91	9838	4.2 ± 2.7
Hypoxia	27 ± 12	31 ± 10	0.78	1897	5.9 ± 5.9
Hyperoxia	63 ± 12	61 ± 14	0.96	1899	3.5 ± 2.6

*Values are mean ± SD; all correlations (r) significant at p < .001; SvO₂, mixed venous O₂ saturation; ScvO₂, central venous O₂ saturation; n, number of comparisons; |SvO₂-ScvO₂|, mean difference.



Reinhart 84
Drawing: M. Schindler

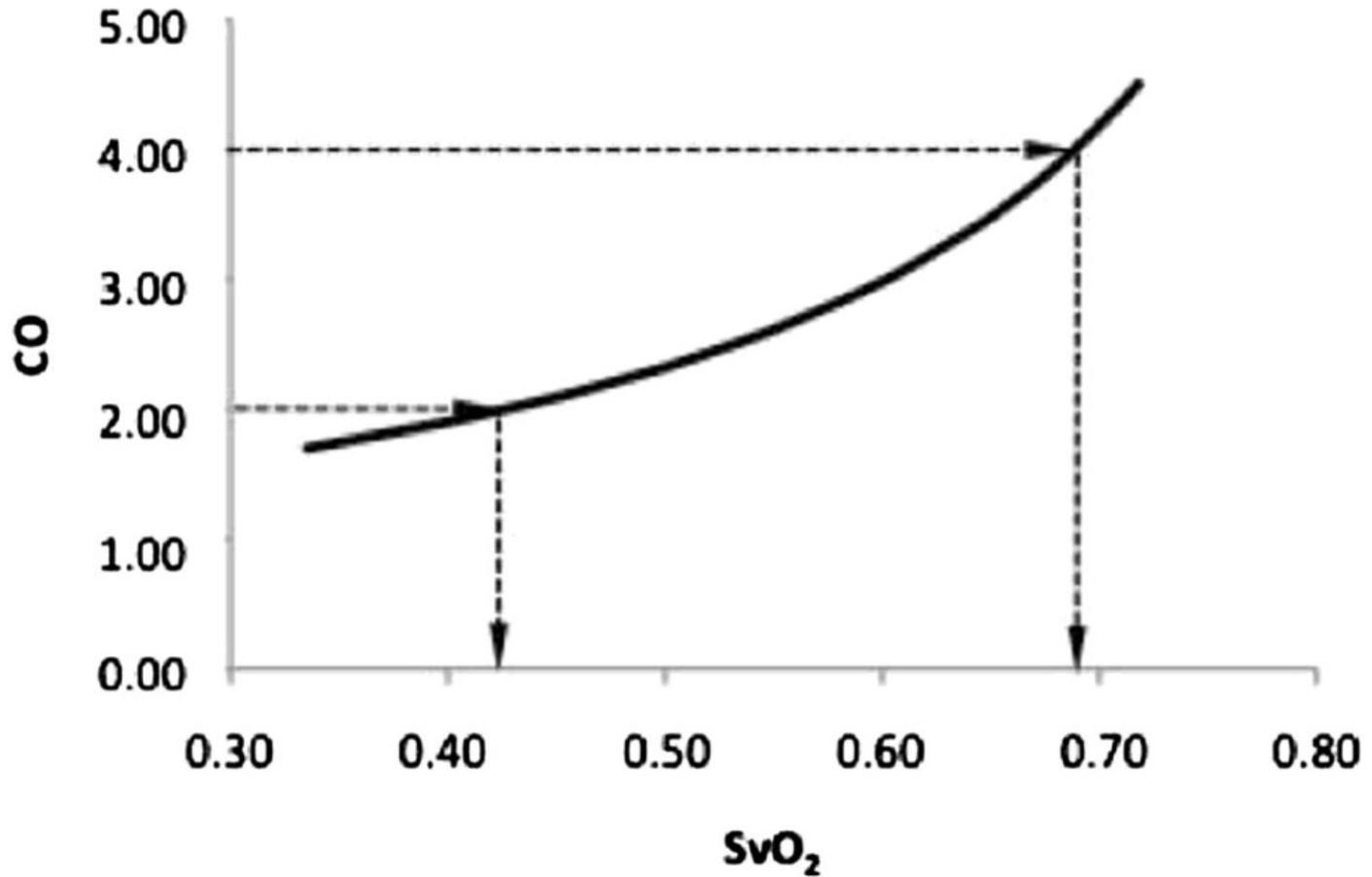
SvO₂ to Detect Cardiac Output Changes

$$\text{SvO}_2 = \text{SaO}_2 - \text{VO}_2 / (\text{CO} \times \text{Hb})$$

If SaO₂, VO₂, and Hb are stable

$$\text{SvO}_2 \propto \text{CO}$$

Correlation between SvO₂ and CO



Squara P. Central venous oxygenation: when physiology explains apparent discrepancies. Crit Care 2014; 18: 579

Δ ScvO₂ to Detect Cardiac Output Changes

Baseline	Responders (n = 18)	Nonresponders (n = 22)
HR (bpm)	122 ± 29	114 ± 16
MAP (mmHg)	80 ± 7	87 ± 17
CVP (mmHg)	11 ± 4	12 ± 4
PCO ₂ gap (mmHg)	5.6 ± 5.0	4.8 ± 3.0
ScvO ₂ (%)	69.6 ± 9.8	71.0 ± 13.8

Data on file. Medical ICU, Peking Union Medical College Hospital

ΔScvO_2 to Detect Cardiac Output Changes

	Responders (n = 18)	Nonresponders (n = 22)
ΔCI (L/min/m ²)	1.0 \pm 0.5	0.0 \pm 0.3 p < 0.001
ΔHR (bpm)	-5 \pm 7	-3 \pm 5 p = 0.289
ΔMAP (mmHg)	13 \pm 13	6 \pm 6 P = 0.033
ΔSBP (mmHg)	23 \pm 22	8 \pm 9 P = 0.014

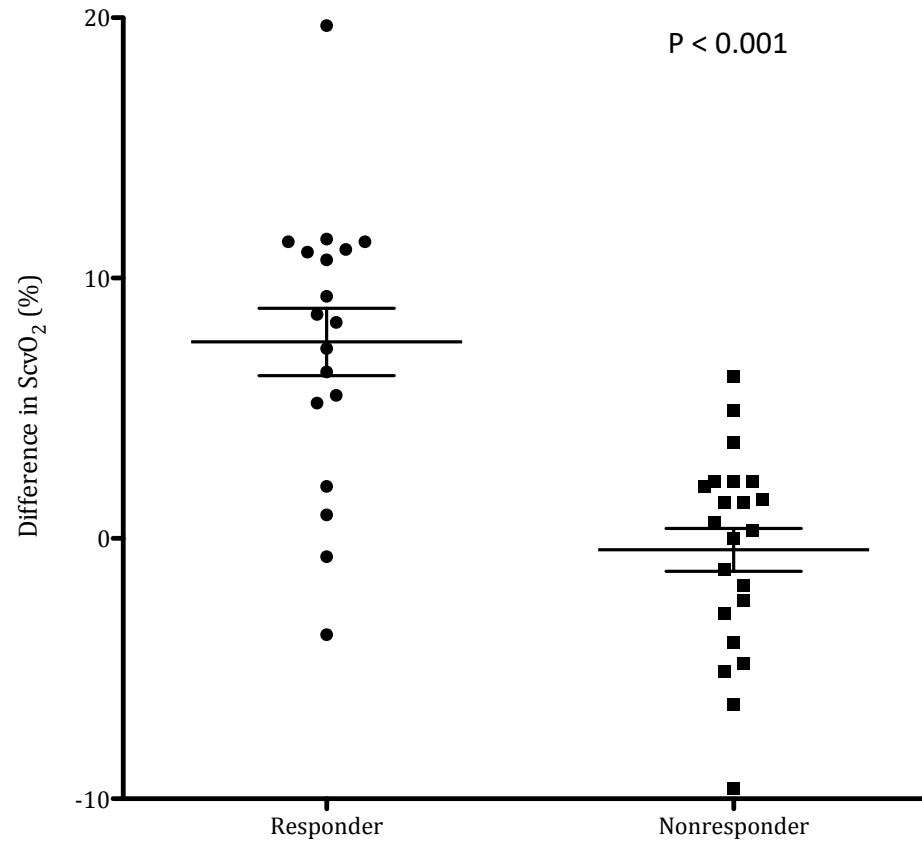
Data on file. Medical ICU, Peking Union Medical College Hospital

ΔScvO_2 to Detect Cardiac Output Changes

	Responders (n = 18)	Nonresponders (n = 22)
ΔCVP (mmHg)	3 \pm 1	4 \pm 2 P = 0.151
ΔPCO_2 gap (mmHg)	1.5 \pm 3.6	0 \pm 2.6 P = 0.157
ΔScvO_2 (%)	7.5 \pm 5.5	-0.4 \pm 3.9 P < 0.001

Data on file. Medical ICU, Peking Union Medical College Hospital

ΔScvO_2 to Detect Cardiac Output Changes

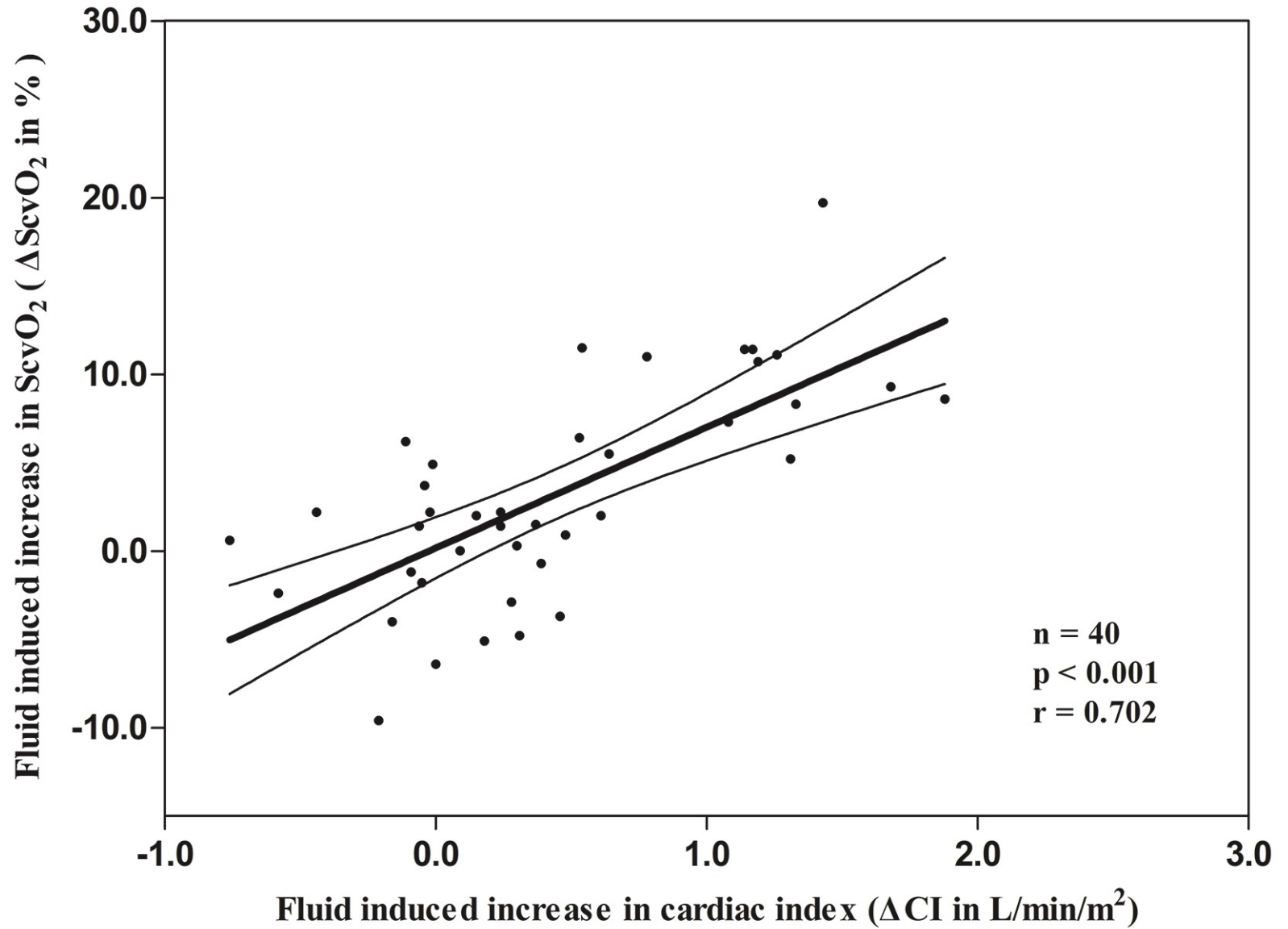


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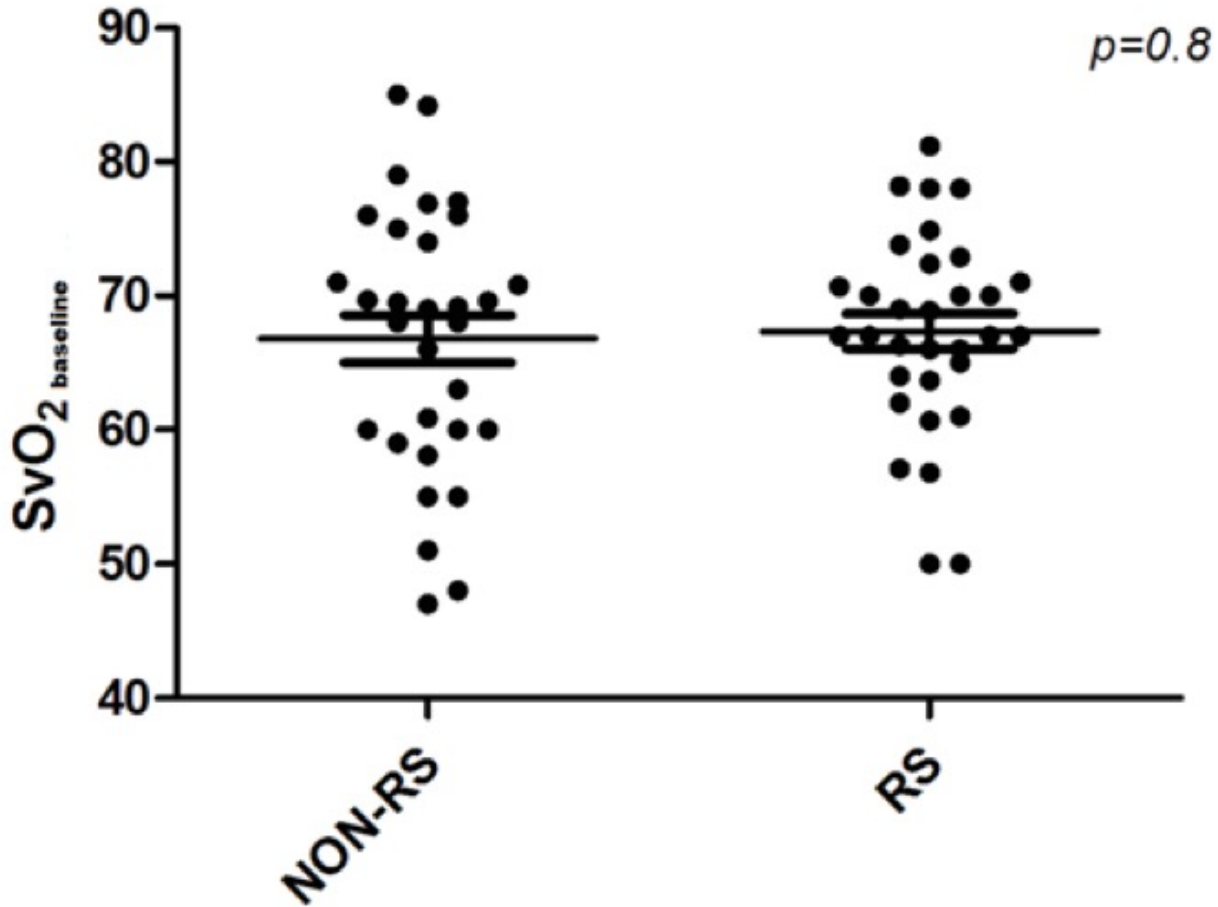
ΔScvO_2 to Detect Cardiac Output Changes

	Cutoff Value	AUROC	SEN/SPE
ΔCVP (mmHg)	2	0.63 _(0.46 – 0.80)	0.89/0.18
ΔMAP (mmHg)	7	0.70 _(0.53 – 0.86)	0.67/0.68
PCO_2 gap (mmHg)	7.5	0.63 _(0.45 – 0.81)	0.44/0.76
ΔScvO_2 (%)	5.0	0.88 _(0.76 – 0.99)	0.78/0.95

Data on file. Medical ICU, Peking Union Medical College Hospital



Baseline ScvO₂ Not Predictive of Fluid Responsiveness



Velissaris D, Pierrakos C, Scolletta S, et al. High mixed venous oxygen saturation levels do not exclude fluid responsiveness in critically ill septic patients. Crit Care 2011; 15: R177

Baseline ScvO₂ Not Predictive of Fluid Responsiveness

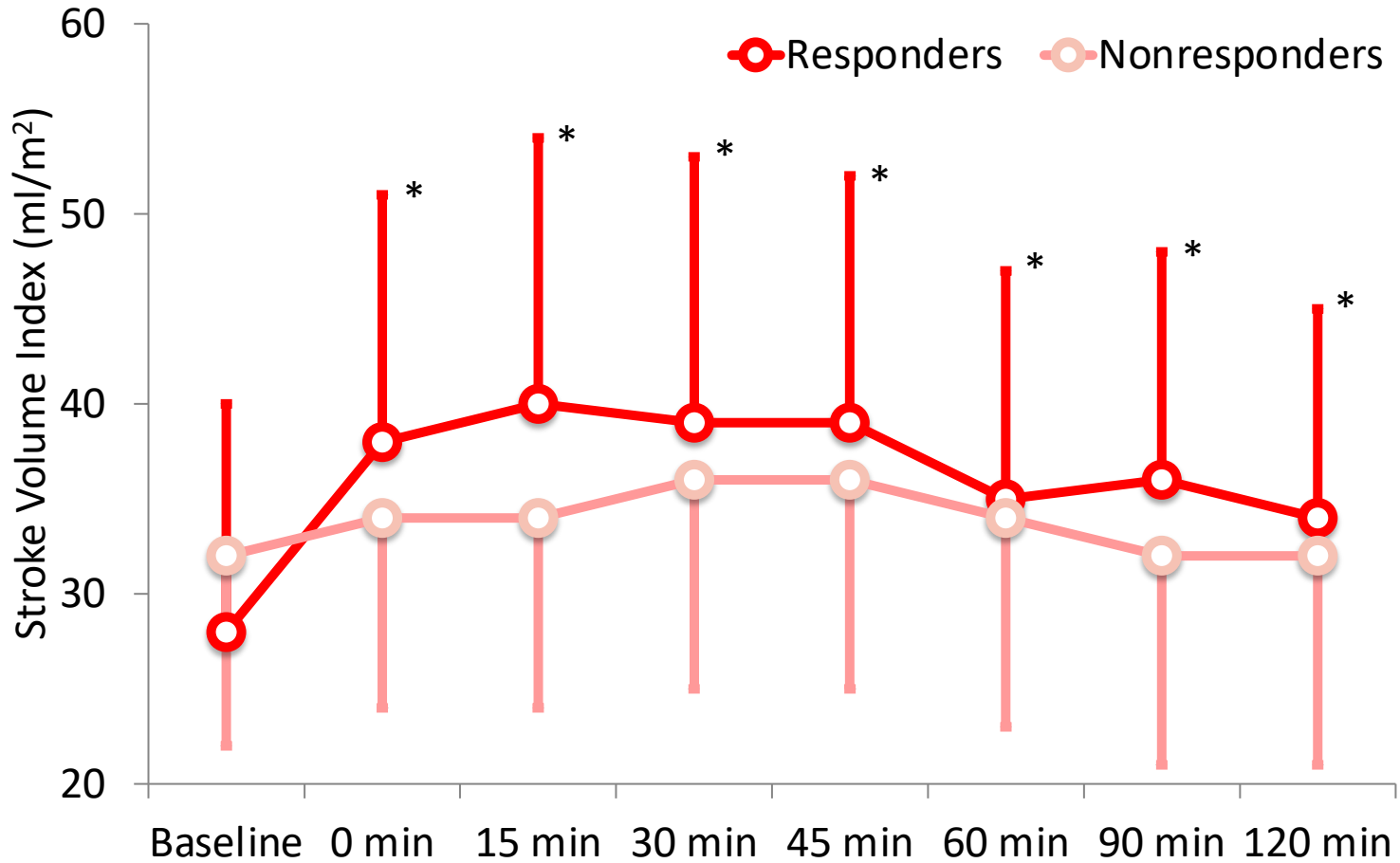
	Cutoff value	AUROC	SEN/SPE
Δ CVP (mmHg)	2	0.63 _(0.46 – 0.80)	0.89/0.18
Δ MAP (mmHg)	7	0.70 _(0.53 – 0.86)	0.67/0.68
ScvO ₂ (%)	55	0.55 _(0.37 – 0.73)	0.56/0.55
Δ ScvO ₂ (%)	5.0	0.88 _(0.76 – 0.99)	0.78/0.95

Data on file. Medical ICU, Peking Union Medical College Hospital

ΔScvO_2 to Detect Cardiac Output Changes

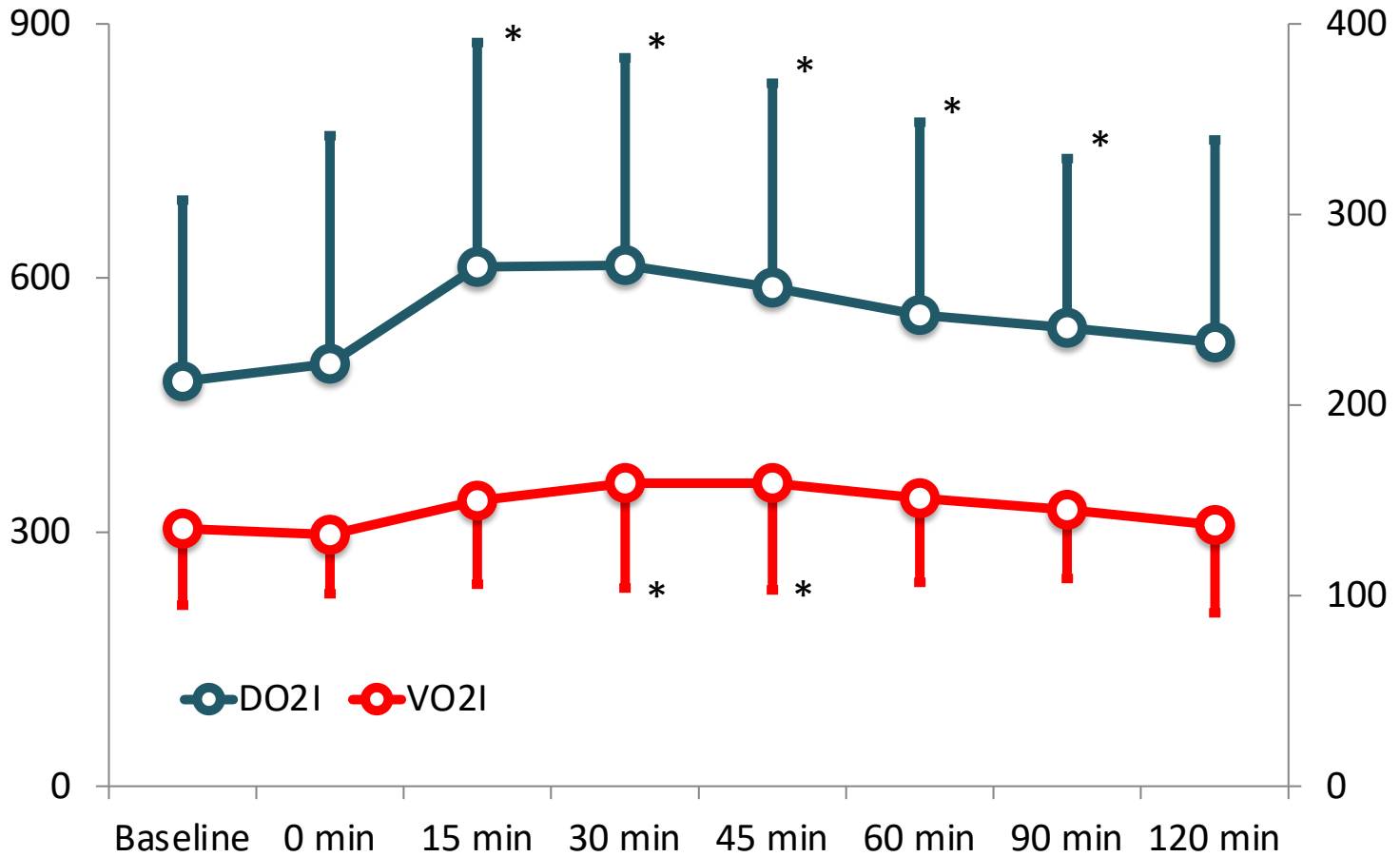
- PROS
 - Devices (blood gas analyzer with cooximeter) readily available
 - Wide spectrum of patients
 - Spontaneous breathing vs. mechanical ventilation
 - Cardiac arrhythmia vs. sinus rhythm
 - Low tidal volume vs. high tidal volume
 - ...
- CONS
 - Hemodilution effect of fluid challenge ($\text{ScvO}_2 \downarrow$)
 - Increase in oxygen consumption due to improved oxygen delivery ($\text{ScvO}_2 \downarrow$)

Stroke Volume After Fluid Challenge



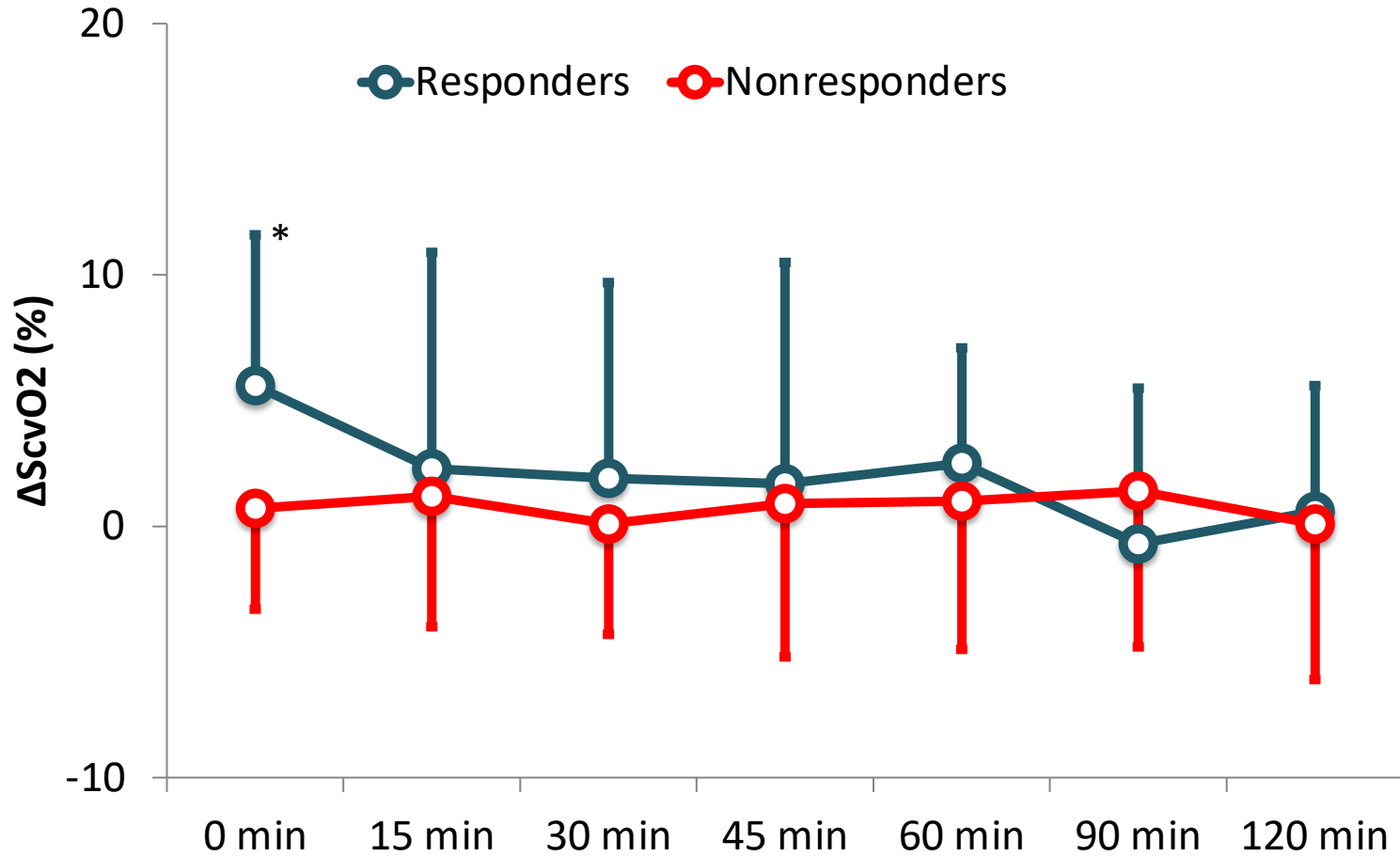
Data on file. Medical ICU, Peking Union Medical College Hospital

Oxygen Metabolism in Responders



Data on file. Medical ICU, Peking Union Medical College Hospital

Transient Diagnostic Value of ScvO₂



Data on file. Medical ICU, Peking Union Medical College Hospital

Pharmacodynamics of Fluid Challenge

Cardiac Output	Responders	Nonresponders	$\Delta(R - NR)$
dmax (L/min)	0.87 (0.51 – 1.22)	0.58 (0.27 – 0.90)	0.29 (-0.20 – 0.75) 0.89
Tmax (min)	1.16 (-0.56 – 2.84)	3.77 (2.28 – 5.28)	-2.61 (-4.86 – -0.39) 0.01
E _{max} (L/min)	5.65 (5.29 – 6.00)	5.37 (5.06 – 5.69)	0.28 (-0.20 – 0.74) 0.88
d ₁₀ (L/min)	0.23 (-0.99 – 0.55)	0.15 (-0.12 – 0.43)	0.08 (-0.35 – 0.50) 0.65

Pharmacodynamics of Fluid Challenge

- Why does the effect of fluid challenge diminish after only 10 minutes?
 - Patient population: postoperative
 - Choice of fluid: crystalloid
 - Rate of fluid infusion: 250 mL/5 min
 - ...

Doctors are men who prescribe medicines of which they know little, to cure diseases of which they know less, in human beings of whom they know nothing



François-Marie Arouet Voltaire