UNIVERSITEIT GENT

FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

# Goal Directed Perfusion:

## basic concepts and some examples

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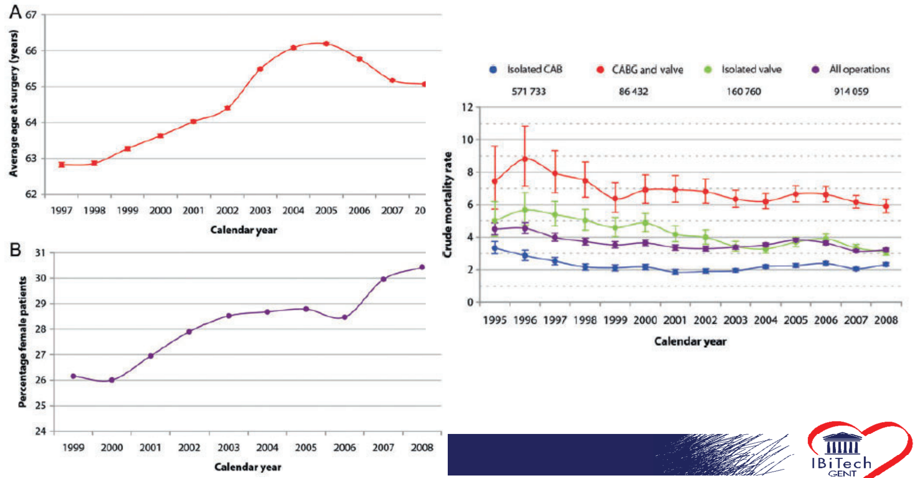
ORIGINAL ARTICLE

### The European Association for Cardio-Thoracic Surgery (EACTS) database: an introduction

Stuart J. Head[a], Neil J. Howell[b], Ruben L.J. Osnabrugge[a], Ben Bridgewater[c], Bruce E. Keogh[d], Robin Kinsman[e], Peter Walton[e], Jan F. Gummert[f], Domenico Pagano[b] and A. Pieter Kappetein[a,*]

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## Acute risk change for cardiothoracic admissions to intensive care: A new measure of quality in cardiac surgery

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Julian A. Smith, MS, FRACS,[e] and David Pilcher, MBBS, MRCP, FRACP, FCICM[a,c,f]

**Background:** Quality of cardiac surgical care may vary between institutions. Mortality is low and large numbers are required to discriminate between hospitals. Measures other than mortality may provide better comparisons.

**Objectives:** To develop and assess the Acute Risk Change for Cardiothoracic Admissions to Intensive Care (ARCTIC) index, a new performance measure for cardiothoracic admissions to intensive care units (ICUs).

**Methods:** The Australian and New Zealand Society of Cardiac and Thoracic Surgeons database and Australian and New Zealand Intensive Care Society Adult Patient Database were linked. Logistic regression was used to generate a predicted risk of death first from preoperative data using the previously validated Allprocscore and second on admission to an ICU using Acute Physiology and Chronic Health Evaluation III score. Change in risk as a percentage (ARCTIC) was calculated for each patient. The validity of ARCTIC as a marker of quality was assessed by comparison with intraoperative variables and postoperative morbidity markers.

**Results:** Sixteen thousand six hundred eighty-seven patients at 21 hospitals from 2008 to 2011 were matched. An increase in ARCTIC score was associated with prolonged cardiopulmonary bypass time ($P = .001$), intraoperative blood product transfusion ($P < .001$), reoperation ($P < .0001$), postoperative renal failure ($P < .0001$), prolonged ventilation ($P < .0001$), and stroke ($P = .001$).

**Conclusions:** The ARCTIC index is associated with known markers of perioperative performance and postoperative morbidity. It may be used as an overall marker of quality for cardiac surgery. Further work is required to assess ARCTIC as a method to discriminate between cardiac surgical units. (J Thorac Cardiovasc Surg 2014;■:1-6)

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# How do we know that blood flow meet the metabolic needs of a patient?

By retrospective analysis of organ function, blood markers and morbidity

"What we need is a multivariate online analysis of risk during cardiopulmonary bypass" *Charles Wildevuur*

Which parameters?

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## accp/sccm consensus conference

**Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis**

THE ACCP/SCCM CONSENSUS CONFERENCE COMMITTEE:
*Roger C. Bone, M.D., F.C.C.P., Chairman*
*Robert A. Balk, M.D., F.C.C.P.*
*Frank B. Cerra, M.D.*
*R. Phillip Dellinger, M.D., F.C.C.P.*
*Alan M. Fein, M.D., F.C.C.P.*
*William A. Knaus, M.D.*
*Roland M. H. Schein, M.D.*
*William J. Sibbald, M.D., F.C.C.P.*

- Body temperature: >38°C or <36°C
- Heart rate: >90 $min^{-1}$
- Hyperventilation: RR >20 $min^{-1}$ or $PaCO_2$ <32mmHg
- WBC: >12000 $\mu L^{-1}$ or <4000 $\mu L^{-1}$

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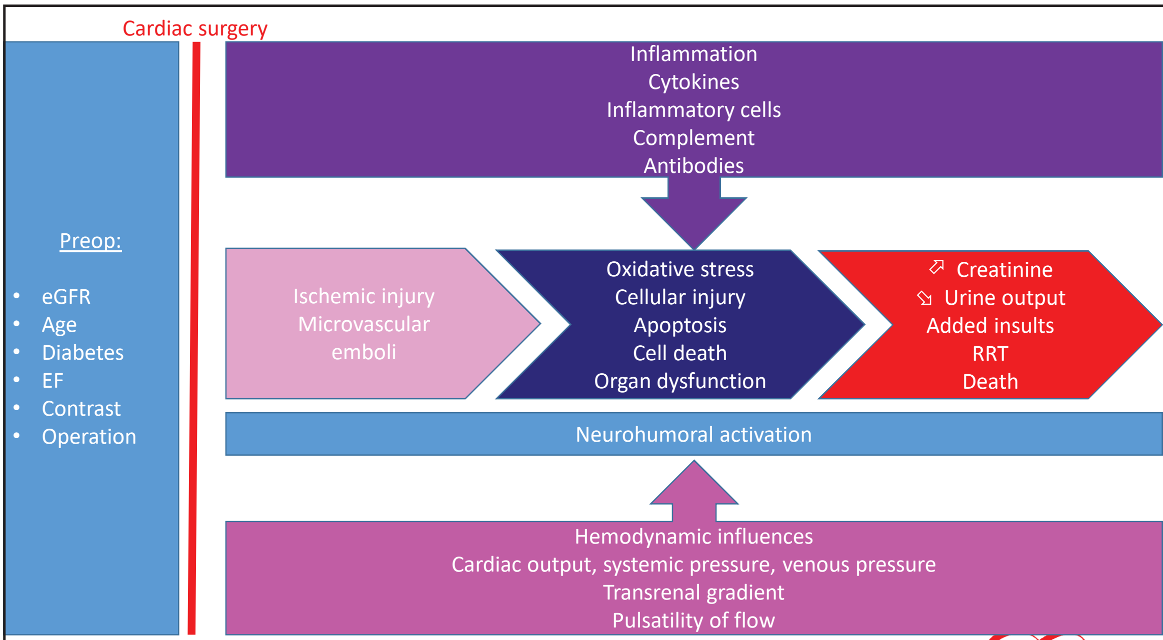
# PIRO concept

**Predisposition**: Premorbid illness with reduced probability of short term survival. Cultural or religious beliefs, age, gender.

**Insult**: Culture and sensitivity (infection) or infection pathogens; detection of disease amenable to source control.

**Response**: SIRS, other signs of sepsis, shock, CRP.

**Organ**: Organ dysfunction as number dysfunction of failing organs or composite score (e.g. MODS, SOFA, RIFLE).



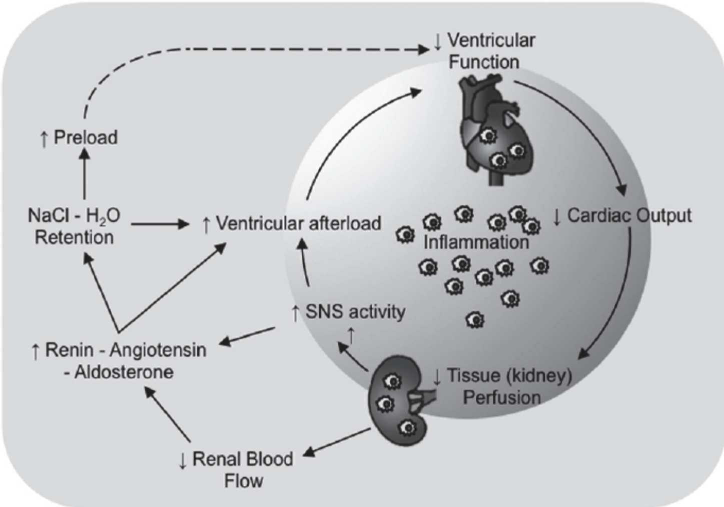

Bellomo 2008

# Cardiopulmonary bypass related injury

| Perioperative: | No AKI | AKI | | | |
|---|---|---|---|---|---|
| CABG | 2,080 (70.9) | 1,228 (64.7) | Ref | | |
| Valve | 488 (16.6) | 286 (15.1) | 1.18 | (0.98–1.41) | 0.080 |
| CABG/valve | 364 (12.4) | 385 (20.4) | 2.31 | (1.92–2.76) | <0.001 |
| Off-pump surgery | 210 (7.2) | 76 (4.0) | 0.43 | (0.32–0.58) | <0.001 |
| Number of valves, mean ± SD | 0.32 ± 0.52 | 0.39 ± 0.56 | 1.53 | (1.36–1.73) | <0.001 |
| Number of anastomoses, mean ± SD | 2.74 ± 1.67 | 2.86 ± 1.66 | 1.02 | (0.98–1.06) | 0.433 |
| Pump time (minutes), mean ± SD | 110 ± 54 | 124 ± 55 | 1.01 | (1.01–1.01) | <0.001 |
| Pump time >120 (minutes) | 1,093 (37.3) | 879 (46.3) | 2.07 | (1.81–2.36) | <0.001 |
| Cross-clamp time (minutes), mean ± SD | 69.7 ± 40.3 | 77.4 ± 38.6 | 1.01 | (1.01–1.01) | <0.001 |
| Cardioplegia time (minutes), mean ± SD | 20.1 ± 7.6 | 20.7 ± 6.6 | 1.02 | (1.01–1.03) | <0.001 |
| Blood cardioplegia | 2,439 (83.2) | 1,644 (86.6) | 1.22 | (1.01–1.46) | 0.038 |
| Cold cardioplegia | 1,482 (50.6) | 802 (42.2) | 0.88 | (0.77–1.01) | 0.068 |
| Cardioplegia hot shot | 2,558 (87.2) | 1,692 (89.1) | 1.11 | (0.90–1.36) | 0.333 |
| Retrograde autologous priming (RAP) | 1,722 (58.7) | 1,140 (60.0) | 0.85 | (0.75–0.98) | 0.023 |
| Volume of fluids on bypass (mL), mean ± SD | 1,925 ± 2,151 | 2,213 ± 2,494 | 1.00 | (1.00–1.00) | <0.001 |
| Prime volume (mL), mean ± SD | 1,150 ± 535 | 1,190 ± 559 | 1.00 | (1.00–1.00) | <0.001 |
| Blood prime units, mean ± SD | 0.09 ± 0.46 | 0.20 ± 0.65 | 1.56 | (1.36–1.79) | <0.001 |
| Number of pRBCs units, mean ± SD | 0.51 ± 1.24 | 0.87 ± 1.76 | 1.33 | (1.26–1.40) | <0.001 |
| Highest blood temperature, mean ± SD | 37.5 ± 0.41 | 37.5 ± 0.70 | 1.00 | (0.92–1.09) | 0.911 |
| Lowest venous saturation, mean ± SD | 69.87 ± 6.27 | 69.82 ± 6.35 | 1.00 | (0.99–1.01) | 0.549 |
| Total volume of heparin > 50,000 units | 1,031 (35.2) | 700 (36.9) | 0.97 | (0.84–1.11) | 0.619 |
| Last potassium on bypass, mean ± SD | 5.58 ± 3.32 | 5.58 ± 3.54 | 1.00 | (0.98–1.01 | 0.795 |
| Nadir hematocrit on bypass, mean ± SD | 23.24 ± 3.29 | 22.56 ± 3.39 | 0.91 | (0.90–.93) | <0.001 |
| Nadir hematocrit < 20 on bypass | 332 (11.3) | 320 (16.9) | 1.62 | (1.34–1.97) | <0.001 |
| Ultrafiltration (hemoconcentration on bypass) | 136 (4.6) | 139 (7.3) | 1.74 | (1.31–2.30) | <0.001 |
| Return to bypass | 219 (7.5) | 204 (10.7) | 1.61 | (1.28–2.03) | <0.001 |
| Aprotinin use | 1,157 (39.5) | 936 (49.4) | 2.08 | (1.82–2.37) | <0.001 |

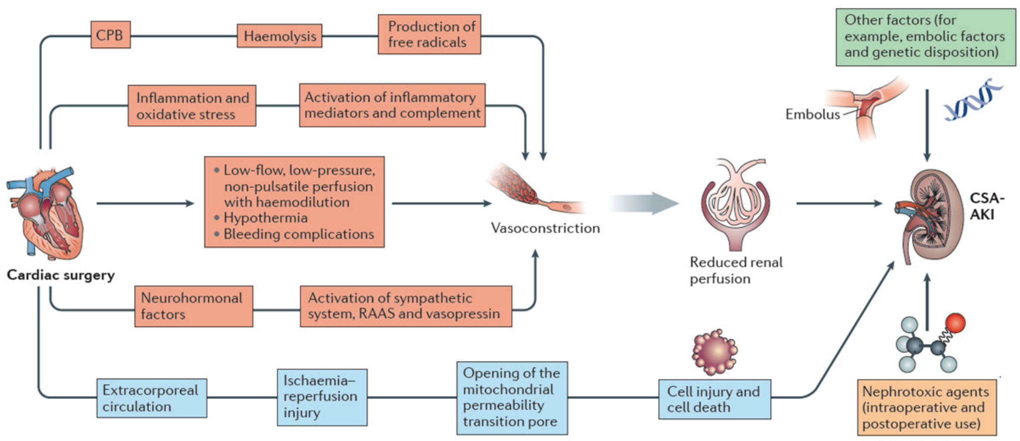
Brown 2012

# CardioRenal interrelationship in heart failure

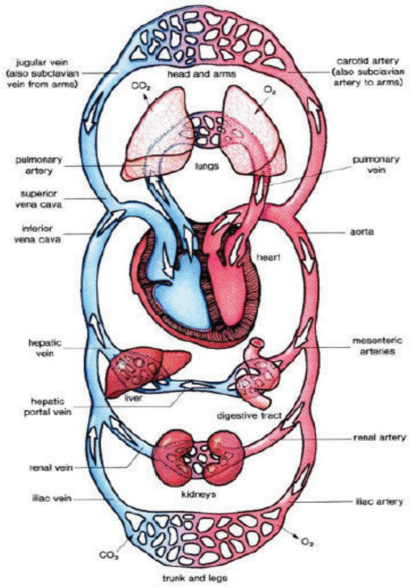



Boudoulas 2017

# Causes




Wang 2017




- Changes based on metabolic needs
- Usually in the range of 2.8 to 3.0 L/min/mq
- May increase up to 15 L/min/m²
- CO with arterial oxygen content, determines the oxygen delivery (DO2)
- Guaranty oxygen need (VO2)
- Pulsatile flow

- Hematocrit: 40 – 50%
- Normal cardiac function
- Normal vascular volume

Darling 1999

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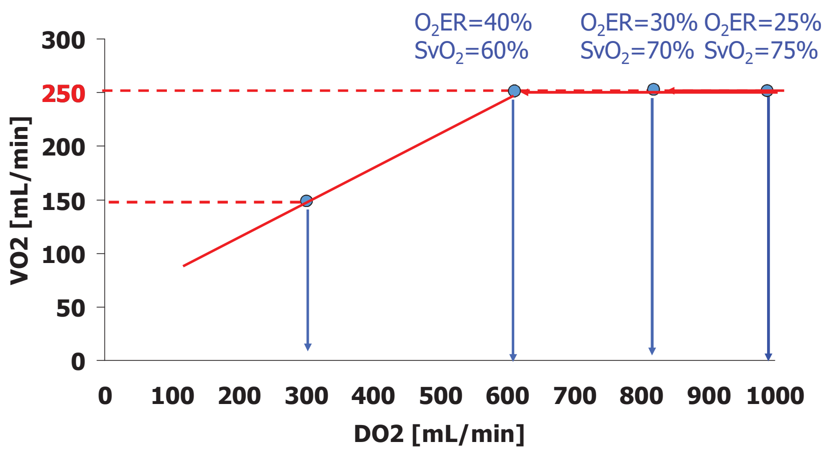
# $DO_2$ and $VO_2$

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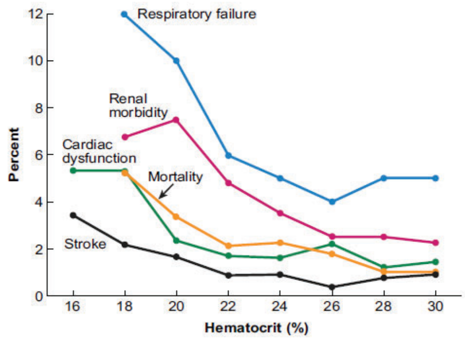
# Intraoperative anemia

TABLE 2. Investigations examining effect of intraoperative anemia on postoperative outcomes

| Groups | Design | n | Effect |
|---|---|---|---|
| Habib et al[21] | Observational | 5000 | Increased mortality and pulmonary, neurologic, renal, and cardiac morbidity |
| Habib et al[22] | Observational | 1760 | Increased renal injury |
| Ranucci et al[7] | Observational | 3003 | Major morbidity: prolonged ventilation, surgical reoperation, mediastinitis, renal dysfunction, stroke |
| DeFoe et al[23] | Observational | 6980 | Mortality, low output heart failure |
| Jonas et al[24] | Randomized controlled trial | 147 | Decreased cardiac index and psychomotor development; increased serum lactate and total body water |
| Swaminathan et al[25] | Observational | 1404 | Renal insufficiency |
| Karkouti et al[26] | Observational | 10,949 | Stroke |
| Bahrainwala et al[58] | Observational | 617 | Increased risk of stroke |
| von Heymann et al[27] | Randomized controlled trial | 54 | Similar oxygen delivery and morbidity |
| Berger et al[28] | Randomized controlled trial | 47 | Similar GI permeability and inflammatory response |

*GI*, Gastrointestinal.




Loor 2012

# Hematocrit on Cardiopulmonary Bypass and Outcome After Coronary Surgery in Nontransfused Patients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Departments of Cardiothoracic and Vascular Anesthesia and Intensive Care Unit and Cardiac Surgery, and Scientific Directorate, IRCCS Policlinico S. Donato, Milan, Italy



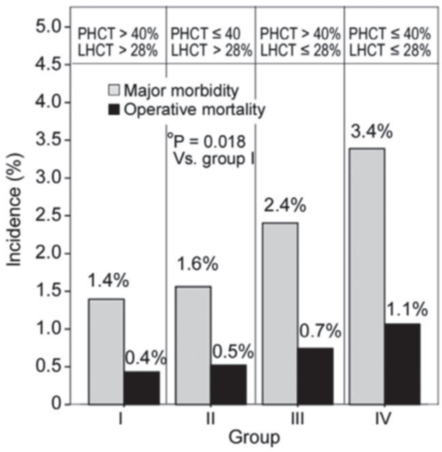
*Background.* Preoperative anemia and the lowest registered hematocrit value on cardiopulmonary bypass are recognized risk factors for morbidity and mortality after coronary operations. A low hematocrit often results in blood transfusions with all of the associated possible complications. The relative contribution of these three factors to long-term outcome is still not well established. This study aimed to identify the role of preoperative anemia and hemodilution during cardiopulmonary bypass as determinants of morbidity and mortality after coronary operations.

*Methods.* A consecutive series of 3,003 patients was analyzed. They had all undergone isolated coronary operations without receiving blood transfusions during their hospital stay. The preoperative hematocrit and the lowest hematocrit on cardiopulmonary bypass were analyzed in a multivariable model as predictors of major morbidity and operative mortality.

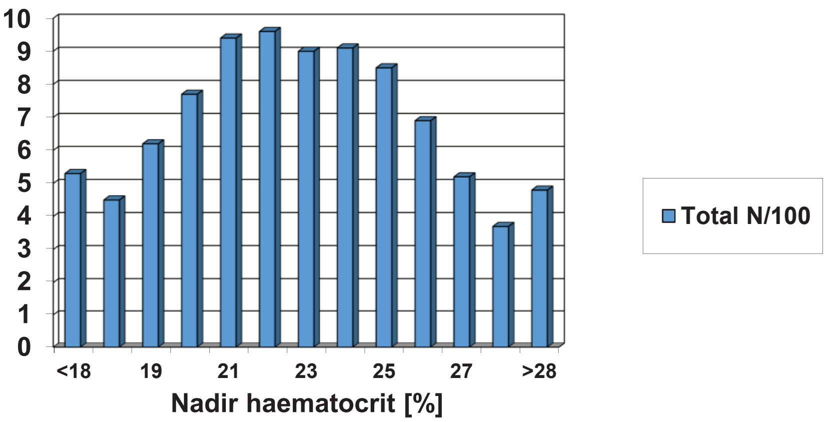
*Results.* After adjustment for the other explanatory variables, both the preoperative hematocrit and the lowest hematocrit on cardiopulmonary bypass were found to be independent risk factors for major morbidity, but not for operative mortality. However, low values of preoperative hematocrit were not associated with an increased morbidity, provided that the lowest hematocrit on cardiopulmonary bypass was maintained above 28%. Median values of the lowest hematocrit on cardiopulmonary bypass below 25% were associated with an increased major morbidity rate.

*Conclusions.* Excessive hemodilution during cardiopulmonary bypass is a risk factor for major morbidity even in the absence of blood transfusions. Techniques that aim to reduce the fall in hematocrit during cardiopulmonary bypass, including blood cardioplegia, may be useful, especially in patients with a low preoperative hematocrit.

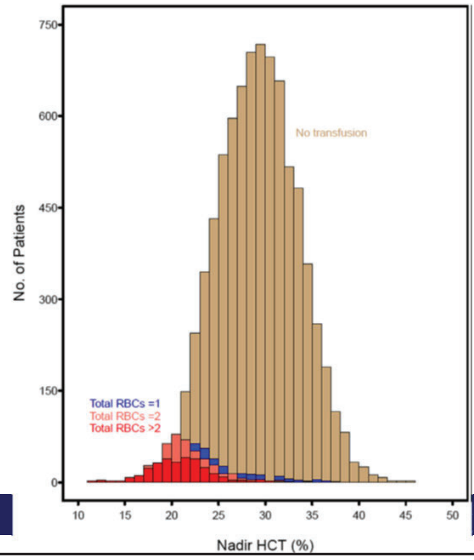

(Ann Thorac Surg 2010;89:11–8)




# Haematocrit during CPB



# Hematocrit during CPB




Loor 2013

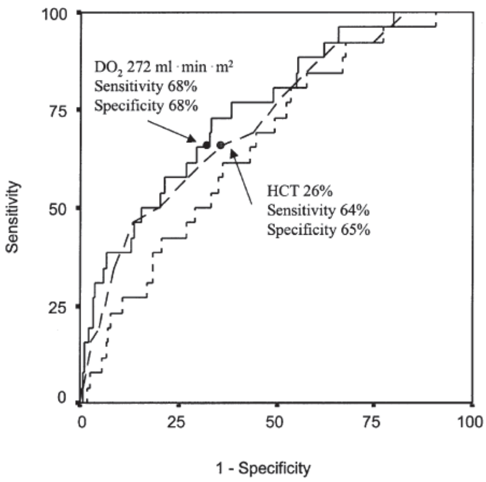
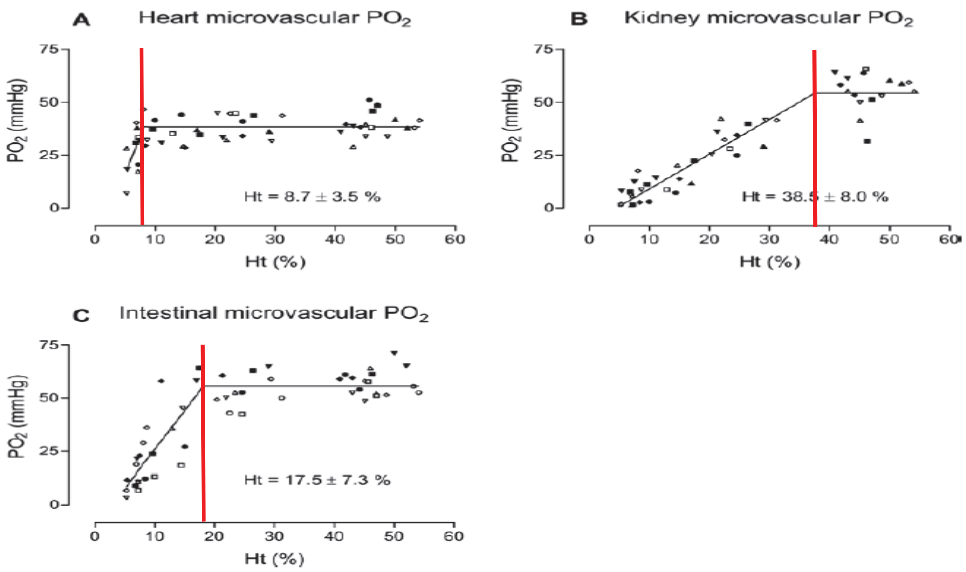


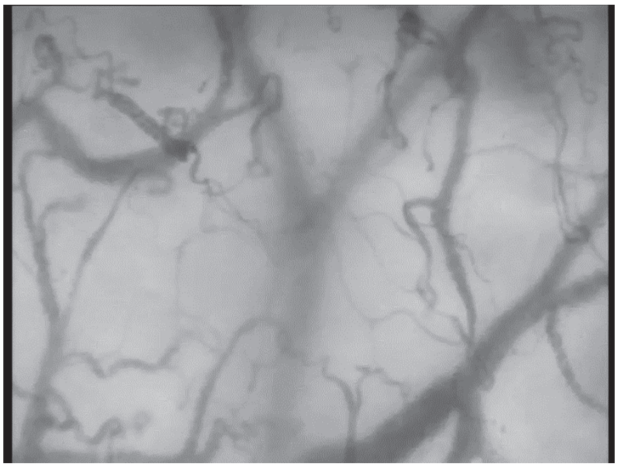

*Fig 2. Receiver operating characteristic curve for the three variables being identified as independent risk factors for acute renal failure. — — = lowest hematocrit on CPB; - - - - = pump flow indexed; —— = oxygen delivery indexed. (CPB = cardiopulmonary bypass; $DO_2$ = two determinants of oxygen delivery; HCT = hematocrit.)*

Ranucci 2005



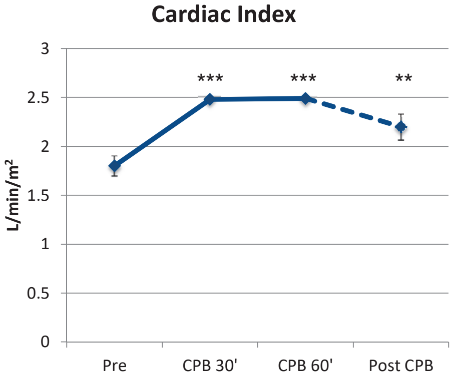

Van Bommel 2008

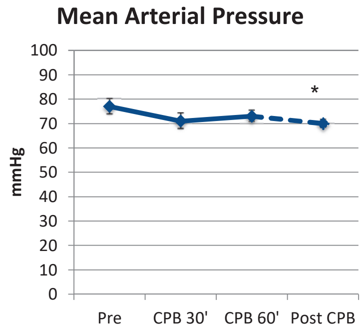
# Microcirculation

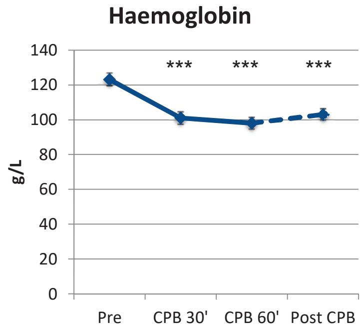


De Backer 2007

# Results – Systemic variables



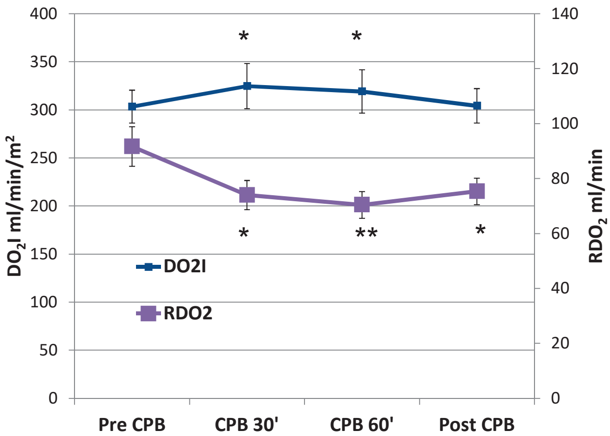




* p < 0.05, ** p < 0.01, ** p < 0.001

Lannemyr 2017

# Systemic and renal oxygen delivery




* p < 0.05, ** p < 0.01 vs Pre

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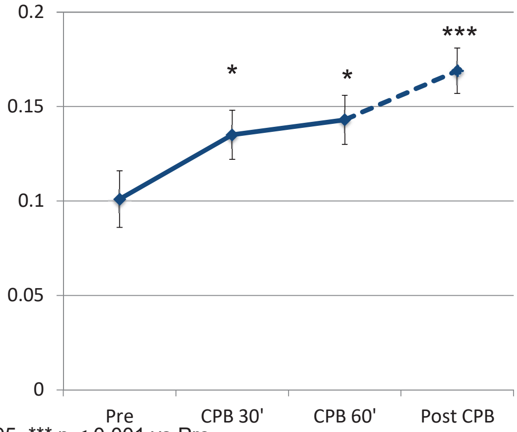
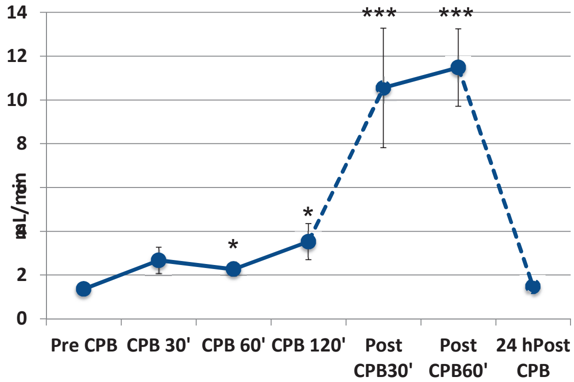
## Renal oxygen extraction




## NAG - Excretion




* p < 0.05, *** p < 0.001 vs Pre

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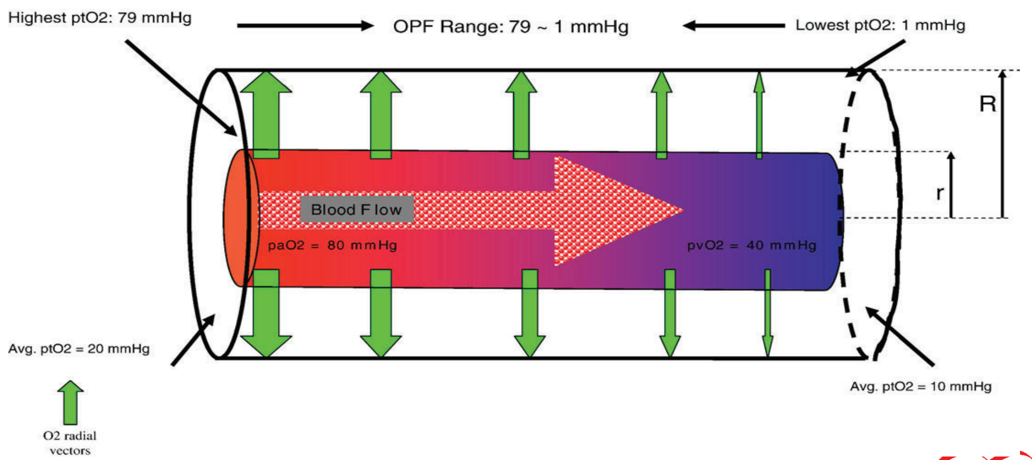
## Oxygen Pressure Field Theory: Krogh Cylinder Model

Capillary radius: r = 5µ
Capillary X-section : $A = \pi r^2 = 78.5\ \mu^2$

Cylinder radius: R = 10
Cylinder X-section: $A = \pi R^2 = 314\ \mu^2$

Ratio: $\frac{\text{Capillary X-section}}{\text{Cylinder X-section}} = 1/4$




Grist 2008

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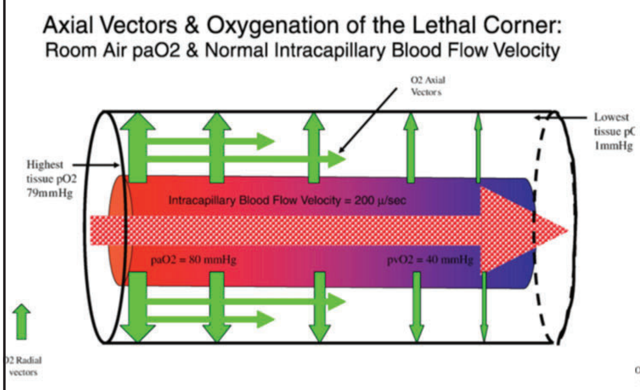
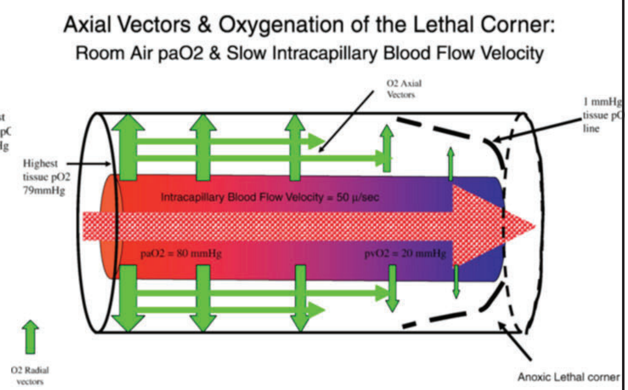
# Impact of velocity

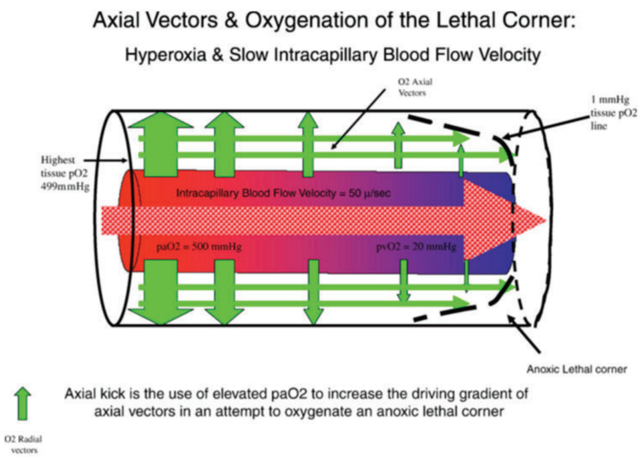



20% of oxygen supply venous end

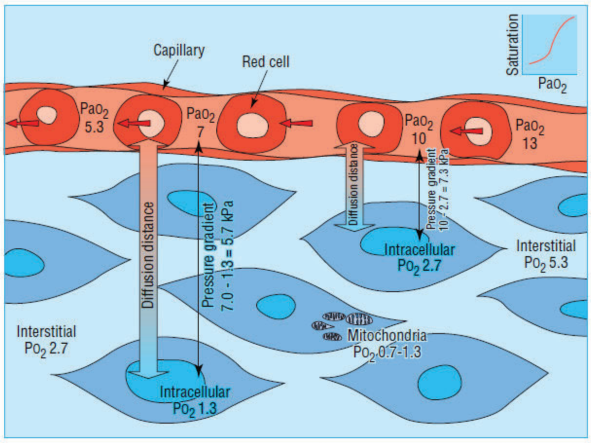



80% of oxygen supply venous end

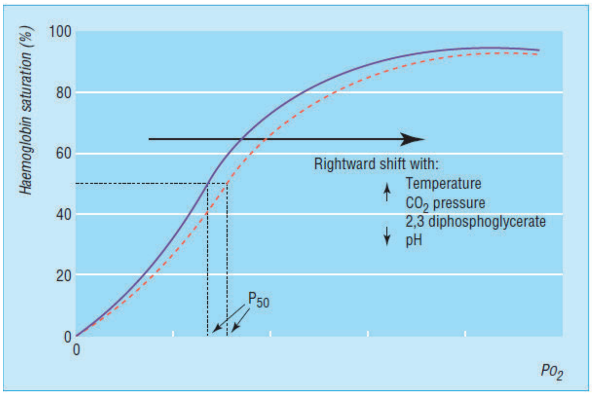
# Improve diffusion component



# Improve diffusion component

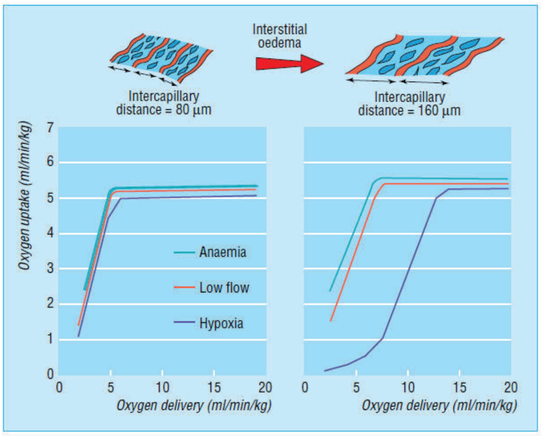



Effect of oxygen tension gradient and diffusion distance on availability of oxygen to cells

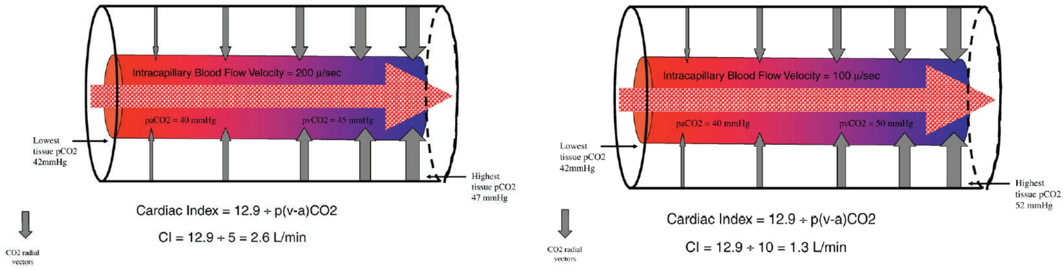



Oxygen-haemoglobin dissociation curve. The curve shifts to the right with increased temperature, acidosis, and 2,3-diphosphoglycerate concentrations

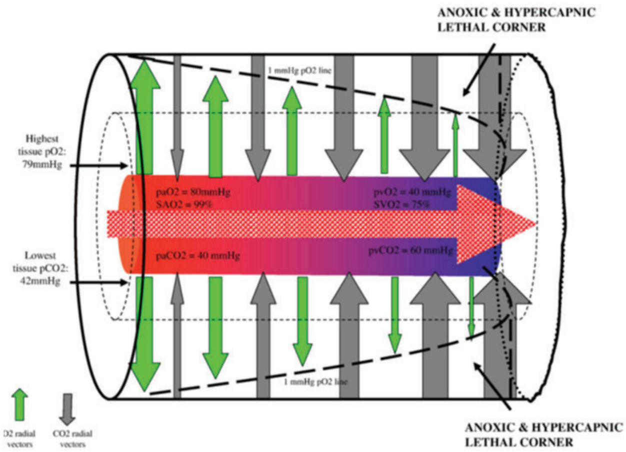
Leach 1998

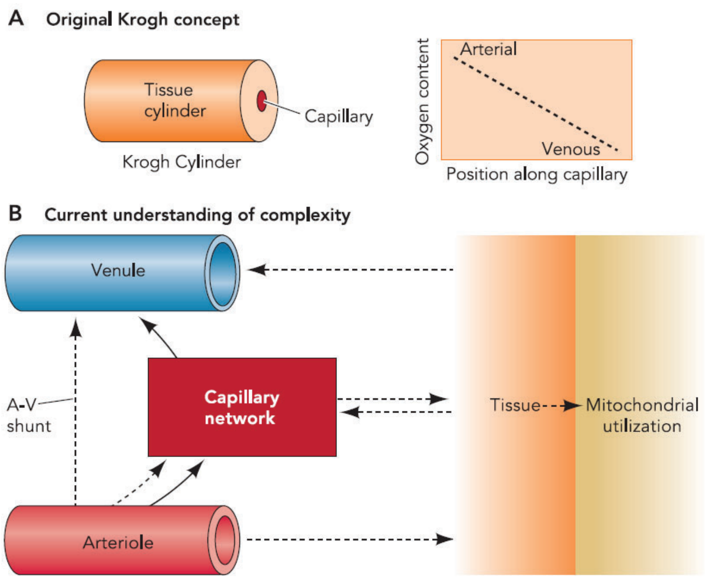


# $CO_2$ removal

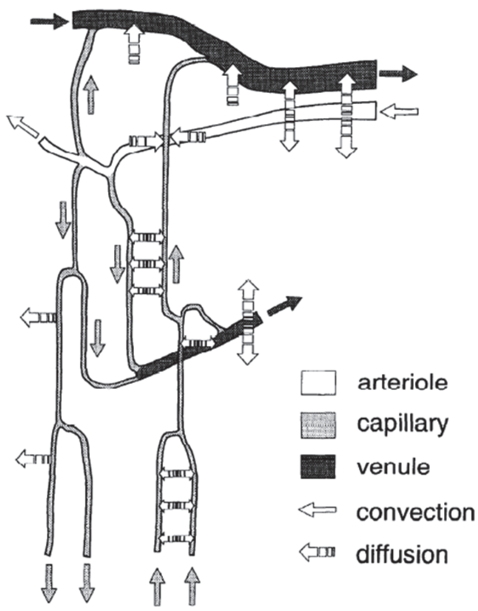



# Congestion and microcirculation



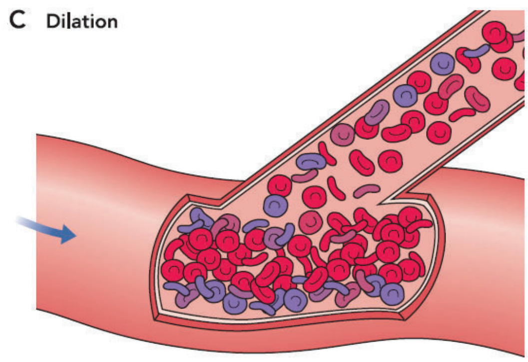


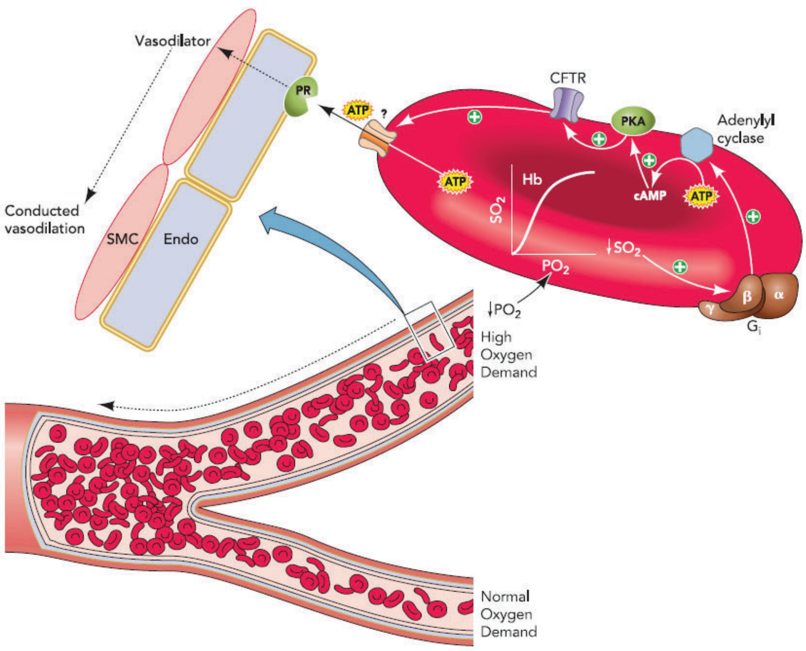

Ellsworth 2009



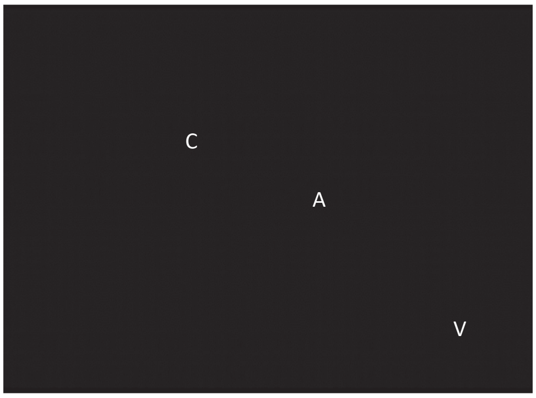

Ellsworth 1994

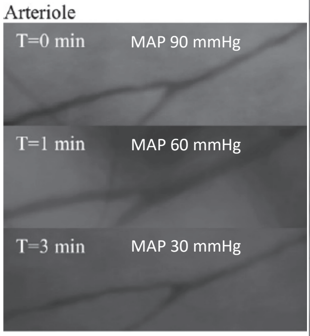
# Regulating mechanisms

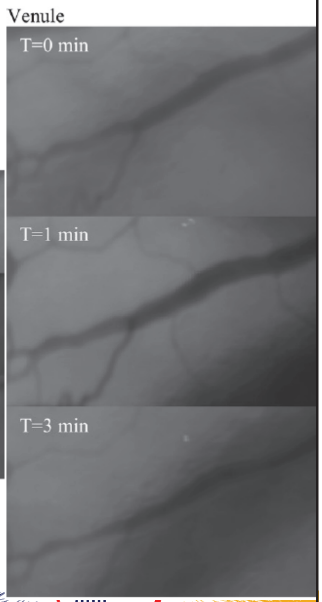


# MAP




Atasever 2011

# Hypoperfusion vs congestion

**Mean arterial and pulmonary arterial pressures (MAP and MPAP), pulmonary artery occlusion pressure (PAOP), cardiac output (CO), mixed venous oxygen saturation ($SvO_2$), and arterial pH and hematocrit (Ht) in SMAO (superior mesenteric artery occlusion, $n$ = 7) and SMVO (superior mesenteric vein occlusion, $n$ = 7) groups**

| | Group | BL | II-45 | R30 | R60 | R120 |
|---|---|---|---|---|---|---|
| MAP, mm Hg | SMAO | 122.7 ± 7.6 | 130.9 ± 9 | 122 ± 8.2 | 128.8 ± 7.2 | 128.3 ± 10.3 |
| | SMVO | 131 ± 8.1 | 95.7 ± 9.3[a,b] | 102 ± 9.2[a,b] | 106 ± 9.8[a,b] | 109 ± 7.5[a,b] |
| MPAP, mm Hg | SMAO | 14.5 ± 1.4 | 14.3 ± 1.8 | 15.8 ± 2 | 16.9 ± 1.6 | 19.1 ± 1.9[a] |
| | SMVO | 15.2 ± 1.9 | 12.0 ± 2.1 | 13.4 ± 2.2 | 13.4 ± 2.3[b] | 13.7 ± 2.8[b] |
| PAOP, mm Hg | SMAO | 7.3 ± 1.4 | 7.7 ± 1.7 | 7.4 ± 1.6 | 7.3 ± 1.7 | 7.5 ± 1.7 |
| | SMVO | 7.1 ± 1.2 | 5.4 ± 0.9[a] | 5.9 ± 1.6 | 4.6 ± 1.3[a,b] | 5.1 ± 1.1[a,b] |
| CO, L/min | SMAO | 2.9 ± 0.2 | 2.6 ± 0.2 | 2.3 ± 0.1 | 2.2 ± 0.2 | 2.3 ± 0.1 |
| | SMVO | 3.2 ± 0.2 | 2.1 ± 0.2[a] | 1.9 ± 0.2[a] | 1.6 ± 0.2[a,b] | 1.6 ± 0.2[a,b] |
| Arterial lactate, mmol/l | SMAO | 0.8 ± 0.1 | 0.8 ± 0.1 | 1.0 ± 0.1 | 0.8 ± 0.1 | 0.9 ± 0.3 |
| | SMVO | 1.2 ± 0.4 | 2.1 ± 0.4[a,b] | 2.2 ± 0.4[a,b] | 2.0 ± 0.3[a,b] | 1.7 ± 0.1[a,b] |
| Arterial pH | SMAO | 7.4 ± 0.02 | 7.42 ± 0.02 | 7.4 ± 0.02 | 7.39 ± 0.02 | 7.39 ± 0.01 |
| | SMVO | 7.37 ± 0.01 | 7.33 ± 0.01[a,b] | 7.29 ± 0.02[a,b] | 7.3 ± 0.01[a,b] | 7.29 ± 0.02[a,b] |
| Arterial Ht, % | SMAO | 35.3 ± 1.4 | 34.1 ± 0.6 | 36.9 ± 1.7 | 35.8 ± 2.1 | 35.5 ± 1.9 |
| | SMVO | 38.7 ± 1.1 | 35.8 ± 2.4 | 37.5 ± 2.1 | 38 ± 1.8 | 36.8 ± 2.4 |

*Notes:* Baseline (BL), 45 min after intestinal ischemia (II-45) and 30, 60, and 180 min after reperfusion (R30, R60, and R120, respectively). Data are presented as mean ± standard error of the mean.

[a]$P < 0.05$ *versus* baseline.

[b]$P < 0.05$ *versus* SMAO.

Cruz 2010

# Hypoperfusion vs congestion

**Intestinal oxygen delivery, consumption and extraction ratio ($DO_2$intest, $VO_2$intest and $O_2$ERintest), and mesenteric vein pH and hematocrit (Ht) in SMAO (superior mesenteric artery occlusion, $n = 7$) and SMVO (superior mesenteric vein occlusion, $n = 7$) groups**

| | Group | BL | II-45 | R30 | R60 | R120 |
|---|---|---|---|---|---|---|
| $DO_2$ intest, mL/min | SMAO | 67.7 ± 9.9 | - | 45.4 ± 6.8[a] | 45.5 ± 7.5[a] | 38.8 ± 5.3[a] |
| | SMVO | 79.9 ± 10.5 | - | 15.8 ± 1.9[a,b] | 14.6 ± 10.5[a,b] | 16.4 ± 2.4[a,b] |
| $VO_2$ intest, mL/min | SMAO | 4.9 ± 0.2 | - | 5.8 ± 1.3 | 5.1 ± 0.3 | 4.2 ± 1.1 |
| | SMVO | 5.8 ± 1.2 | - | 2.6 ± 0.7[a,b] | 3.2 ± 0.6[a,b] | 3.3 ± 0.6[a,b] |
| $O_2$ER intest, % | SMAO | 5.0 ± 1.1 | - | 10.1 ± 1.9[a] | 10.9 ± 2.1[a] | 12.4 ± 2.7[a] |
| | SMVO | 5.7 ± 1.6 | - | 22.7 ± 3.8[a,b] | 29.0 ± 4.8[a,b] | 22.9 ± 3.8[a,b] |
| Mesenteric lactate, mmol/l | SMAO | 0.9 ± 0.1 | 1.4 ± 0.3[a] | 1.7 ± 0.3[a] | 1.2 ± 0.2 | 1.3 ± 0.3 |
| | SMVO | 1.5 ± 0.4 | 5.3 ± 0.9[a,b] | 4.0 ± 0.7[a,b] | 3.2 ± 0.6[a,b] | 2.6 ± 0.3[a,b] |
| Mesenteric vein pH | SMAO | 7.38 ± 0.02 | 7.36 ± 0.02 | 7.35 ± 0.02 | 7.35 ± 0.02 | 7.35 ± 0.02 |
| | SMVO | 7.35 ± 0.02 | 7.18 ± 0.03[a,b] | 7.21 ± 0.03[a,b] | 7.2 ± 0.02[a,b] | 7.22 ± 0.01[a,b] |
| Mesenteric vein | SMAO | 37.2 ± 1.7 | 34.3 ± 1.5 | 37.7 ± 1.3 | 36.7 ± 2.3 | 36.8 ± 1.5 |
| Ht, % | SMVO | 39.2 ± 1.2 | 66.4 ± 0.9[a,b] | 40.3 ± 2.6 | 39.4 ± 1.9 | 37.1 ± 2.0 |

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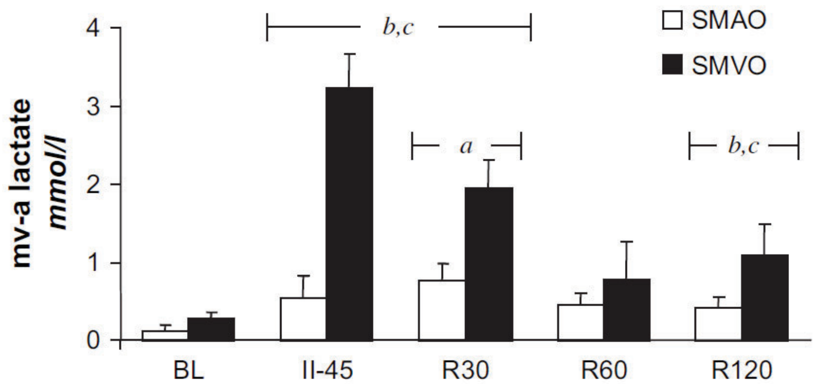
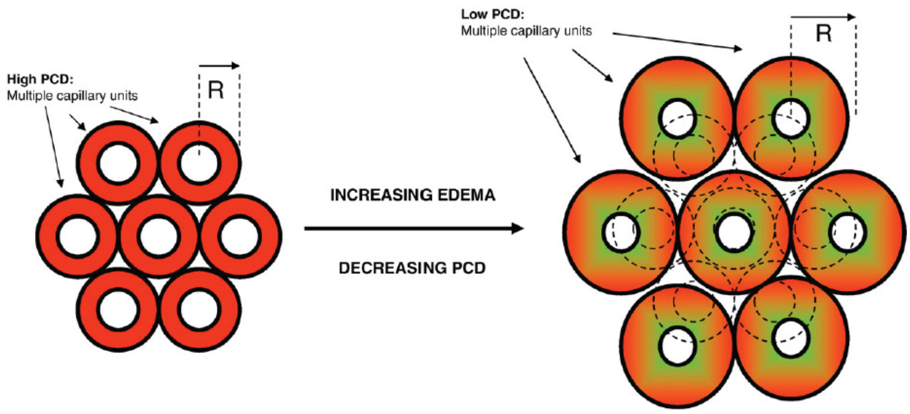
# Hypoperfusion vs congestion

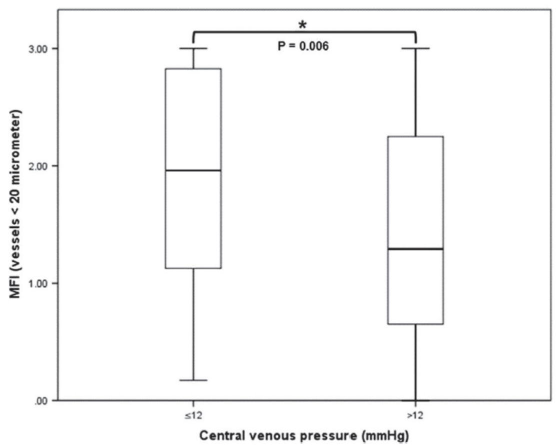



IBiTech GENT

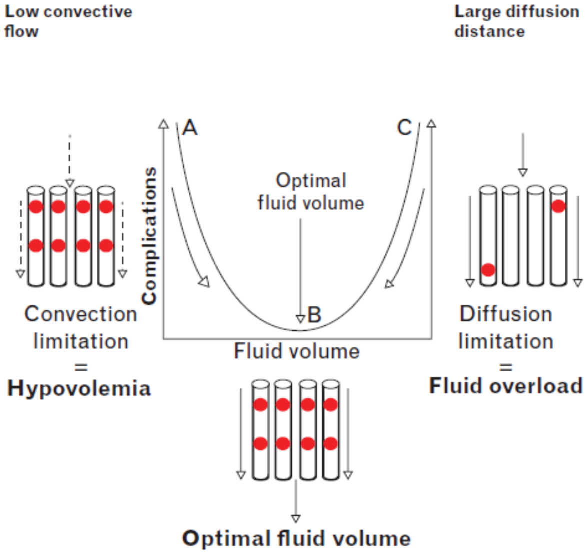
# Congestion

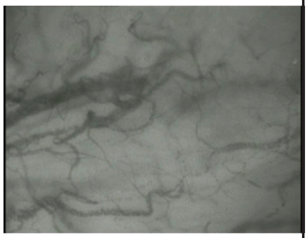



# Increased RAP



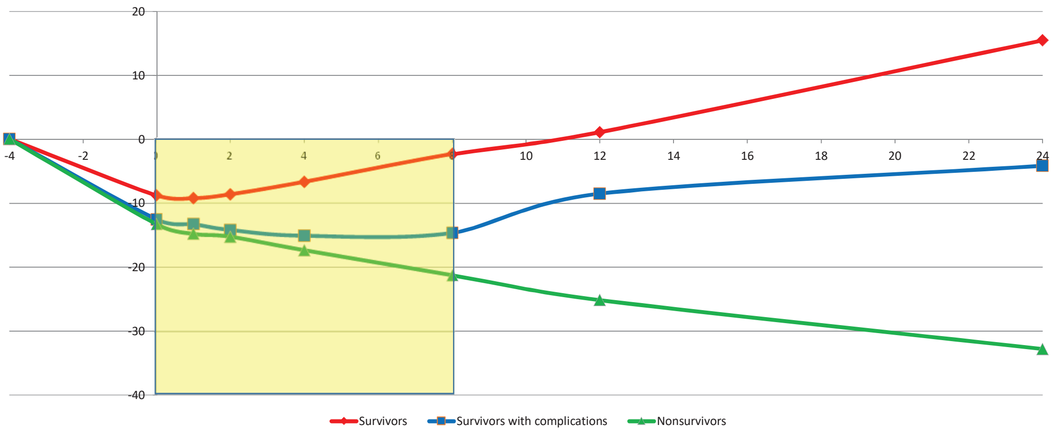

Vellinga 2013



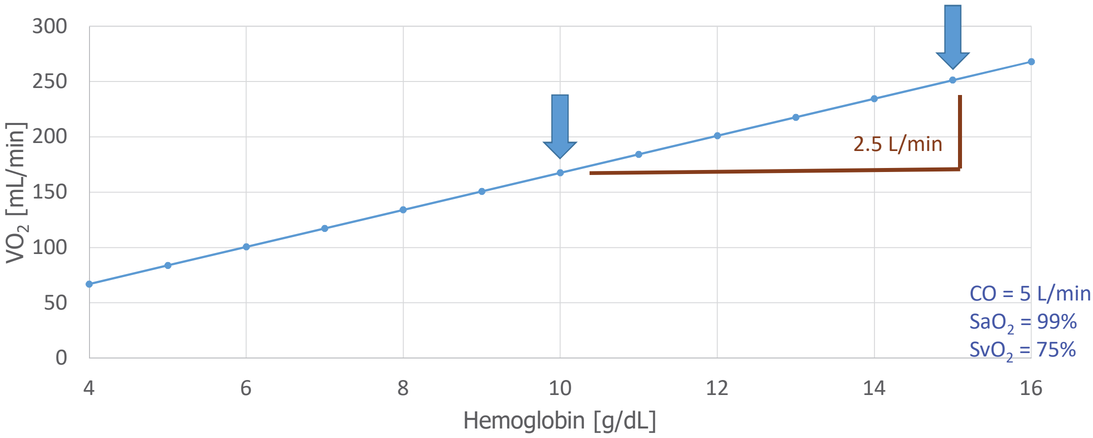
Ince 2014

# Perioperative oxygen debt

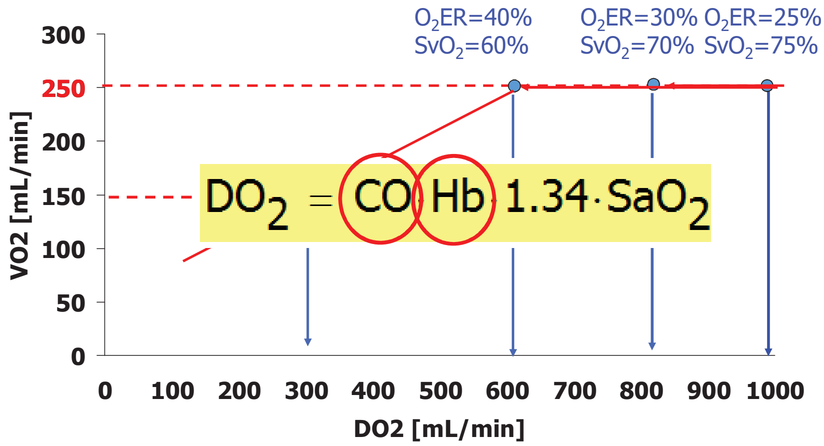



Shoemaker 1991

# $VO_2$ and hemoglobin




# $DO_2$ and $VO_2$



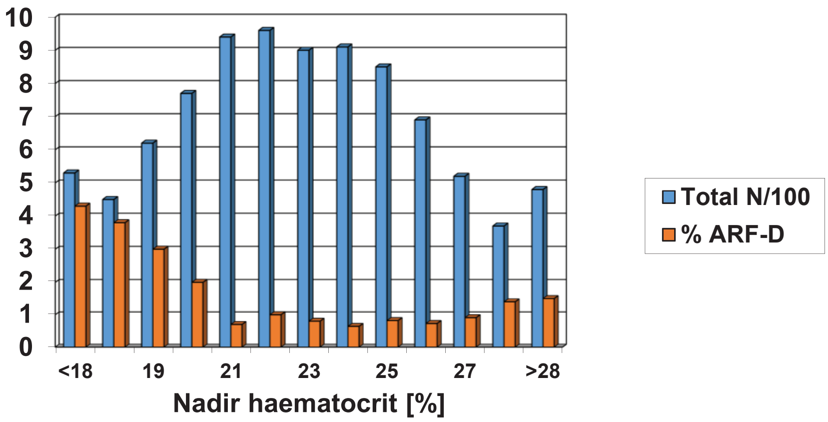
# Hypothesis

- If $DO_2$ is a prime variable
- If most perfusionists work with a fixed CI

↓

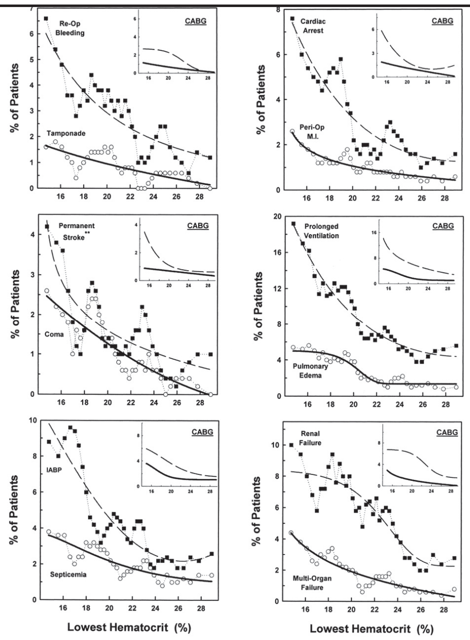
Must hemoglobin influence quality of Perfusion

# Haematocrit during CPB




Karkouti 2005

# Hematocrit during CPB




Lowest HCT on CPB is associated to:

- Reopening
- Bleeding
- Perioperative MI
- Cardiac arrest
- Stroke
- Coma
- Prolonged ventilation
- IABP
- Renal failure
- MOF

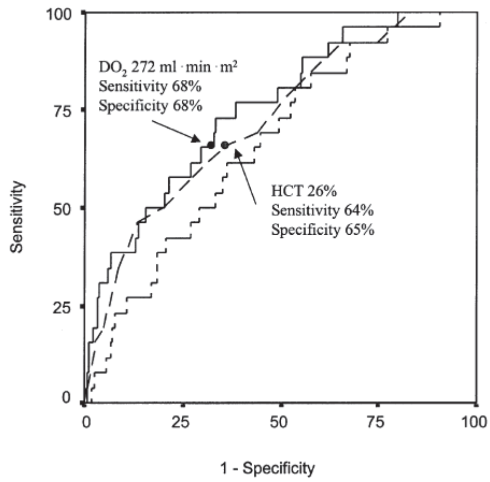
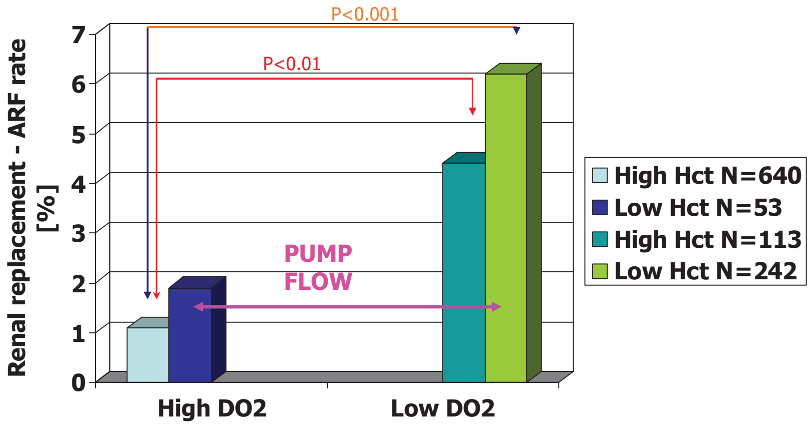



*Fig 2. Receiver operating characteristic curve for the three variables being identified as independent risk factors for acute renal failure. — — = lowest hematocrit on CPB; - - - - = pump flow indexed; —— = oxygen delivery indexed. (CPB = cardiopulmonary bypass; $DO_2$ = two determinants of oxygen delivery; HCT = hematocrit.)*

Ranucci 2005

# Optimal flow and outcome




Ranucci 2005

# Optimal flow and outcome

**Basic patient characteristics**

| Characteristic | Hematocrit 25% | | Hematocrit 20% | | p |
|---|---|---|---|---|---|
| | Median | IQR | Median | IQR | |
| Age (years) | 60 | 55–67 | 65 | 58–71 | 0.10 |
| Gender (male/-female) | 28/2 | | 26/0 | | 0.49 |
| Height (m) | 1.78 | 1.73–1.81 | 1.75 | 1.72–1.79 | 0.35 |
| Weight (kg) | 93 | 80–100 | 87 | 80–100 | 0.52 |
| Body mass index (kg/m²) | 27.9 | 26.0–32.2 | 28.8 | 26.7–29.9 | 0.72 |
| Preoperative hematocrit (%) | 41.8 | 40.2–43.0 | 42.1 | 39.4–45.4 | 0.88 |
| Duration of anesthesia (minutes) | 300 | 290–320 | 310 | 290–325 | 0.26 |
| Duration of surgery (minutes) | 190 | 160–220 | 205 | 175–250 | 0.09 |
| CPB time (minutes) | 72 | 55–83 | 73 | 63–81 | 0.50 |
| Aortic cross clamp time (minutes) | 45 | 33–56 | 45 | 38–49 | 0.93 |
| APACHE II score | 14 | 9–19 | 16 | 13–27 | 0.09 |

APACHE, Acute Physiology and Chronic Health Evaluation; CPB, cardiopulmonary bypass; IQR, interquartile range.

von Heymann 2006

**Outcome measures in the intensive care unit**

| Outcome measure | Hematocrit 25% | | Hematocrit 20% | | *p* |
|---|---|---|---|---|---|
| | Median | IQR | Median | IQR | |
| Number of transfused patients | 1 | | 5 | | 0.10 |
| Drainage loss (ml) | 382 | 265–530 | 400 | 290–620 | 0.28 |
| Patients with postoperative stroke (*n*) | 0 | | 0 | | 0.99 |
| Patients with agitated arousal reaction (*n*) | 3 | | 3 | | 0.99 |
| Patients with myocardial infarction (*n*) | 0 | | 0 | | 0.99 |
| CK/CK-MB ratio (%) | 6.25 | 4.8–7.2 | 5.9 | 4.4–7.0 | 0.99 |
| Patients with catecholamines on admission to ICU (*n*) | 10 | | 7 | | 0.57 |
| Patients with catecholamines 6 h after admission to ICU (n) | 5 | | 2 | | 0.42 |
| Patients with dopamine 18 h after admission to ICU (*n*) | 2 | | 1 | | 0.53 |
| Patients with respiratory failure (*n*) | 3 | | 3 | | 0.99 |
| Duration of ventilator support (hours) | 10 | 8–12,5 | 10 | 10–12 | 0.36 |
| Patients with renal failure (*n*) | 1 | | 1 | | 0.99 |
| Creatinine 18 h after admission to ICU (mg/dl) | 0.92 | 0.82–1.19 | 1.06 | 0.90–1.14 | 0.30 |
| Urine volume in ICU (ml) | 2.810 | 2.390–3.469 | 2.815 | 2.100–3.600 | 0.82 |
| Combined endpoint of organ failure (*n*) | 8 | | 10 | | 0.57 |
| Duration of ICU stay (hours) | 22 | 21–24 | 23 | 21–28 | 0.24 |
| Mortality (*n*) | 0 | | 1 | | 0.48 |

CK, creatine kinase; CK-MB, myocardial creatine kinase; ICU, intensive care unit; IQR, interquartile range.

von Heymann 2006

# Optimal flow and outcome

**Intraoperative outcome measures**

| Outcome measure | Hematocrit 25% | | Hematocrit 20% | | *p* |
|---|---|---|---|---|---|
| | Median | IQR | Median | IQR | |
| CI during CPB (l/m²/minute) | 3.2 | 3.0–3.7 | 3.2 | 3.0–3.5 | 0.57 |
| Temperature during CPB (°C) | 35.6 | 35.0–36.0 | 36.8 | 35.4–36.0 | 0.12 |
| Cumulative norepinephrine dosage during CPB (mg) | 0.08 | 0.06–0.10 | 0.03 | 0.0–0.08 | 0.13 |
| Dopamine dosage for weaning from CPB (µg/kg/minute) | 1.0 | 0.0–3.0 | 1.5 | 0.0–3.0 | 0.92 |
| Patients with catecholamines for weaning from CPB (*n*) | 16 | | 16 | | 0.79 |
| Patients with intraaortic balloon pump for weaning from CPB (*n*) | 2 | | 0 | | 0.49 |
| Patients with acute cardiac failure during weaning from CPB (*n*) | 3 | | 2 | | 1.00 |
| Urine volume during CPB (ml) | 159 | 97–354 | 165 | 102–440 | 0.57 |

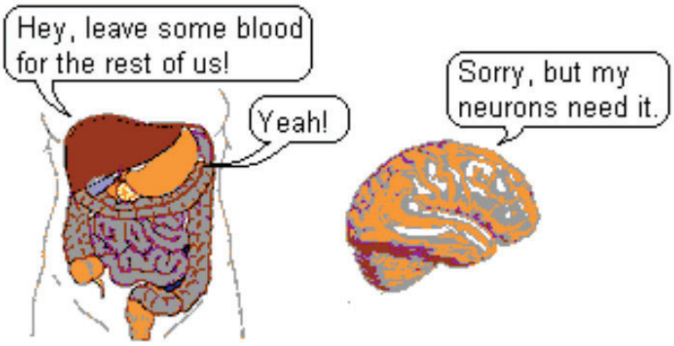
CI, cardiac index; CPB, cardiopulmonary bypass; IQR, interquartile range.

DO2 @ 25% = 356 mL/min/m²    DO2 @ 20% = 287 mL/min/m²

> 270 mL/min/m²

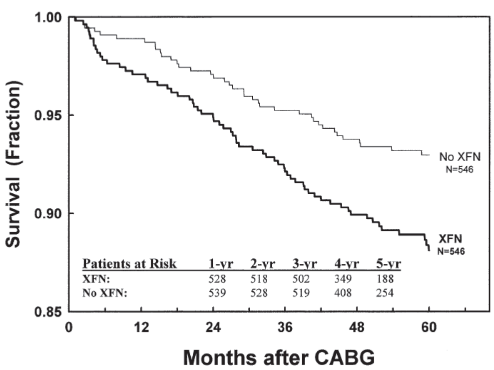
von Heymann 2006

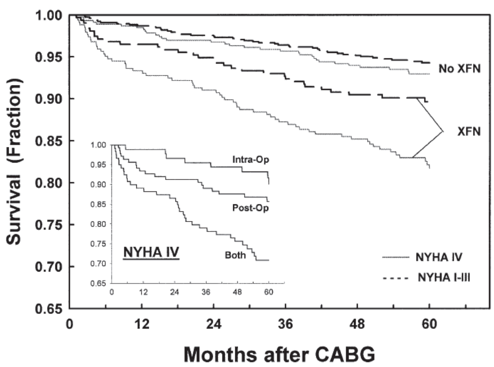
# What if flow cannot augmented?




https://faculty.washington.edu/chudler/vessel.html

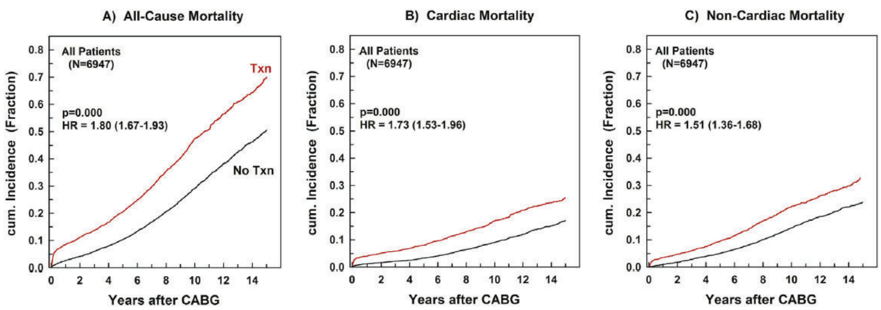
# Blood transfusion: the answer?



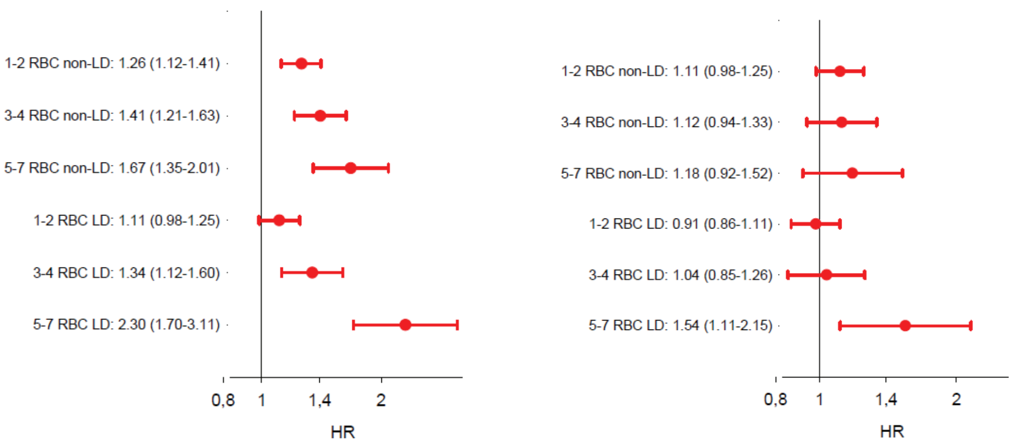

Engoren 2002

# Blood transfusion the answer?




Schwann 2016

# Blood transfusion: the answer?



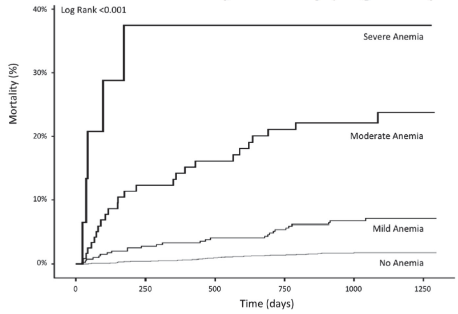

Bjursten 2016

# Association Between Anemia, Bleeding, and Transfusion with Long-term Mortality Following Noncardiac Surgery

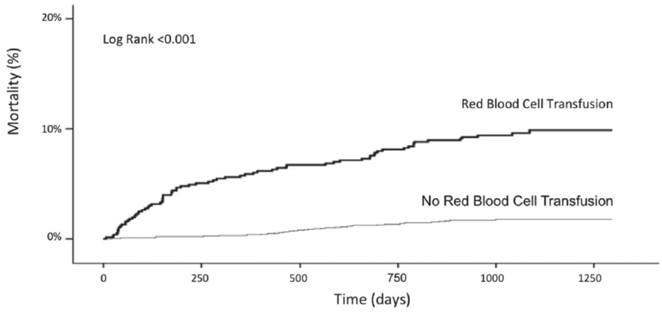
CrossMark

Nathaniel R. Smilowitz, MD,[a] Brandon S. Oberweis, MD,[b] Swetha Nukala, MBBS,[c] Andrew Rosenberg, MD,[d] Sibo Zhao, MS,[a] Jinfeng Xu, PhD,[a] Steven Stuchin, MD,[e] Richard Iorio, MD,[e] Thomas Errico, MD,[e] Martha J. Radford, MD,[a,f,g] Jeffrey S. Berger, MD, MS[a,h]

*[a]Division of Cardiology, Department of Medicine, New York University School of Medicine, New York; [b]Division of Cardiology, Department of Medicine, Columbia University Medical Center, New York, NY; [c]Division of Vascular Surgery, Department of Clinical Quality and Clinical Effectiveness, [d]Division of Vascular Surgery, Department of Anesthesiology, [e]Division of Vascular Surgery, Department of Orthopedic Surgery, [f]Chief Quality Officer, Division of Vascular Surgery, [g]Division of Vascular Surgery, Department of Population Health, and [h]Division of Vascular Surgery, Department of Surgery, New York University School of Medicine, New York.*

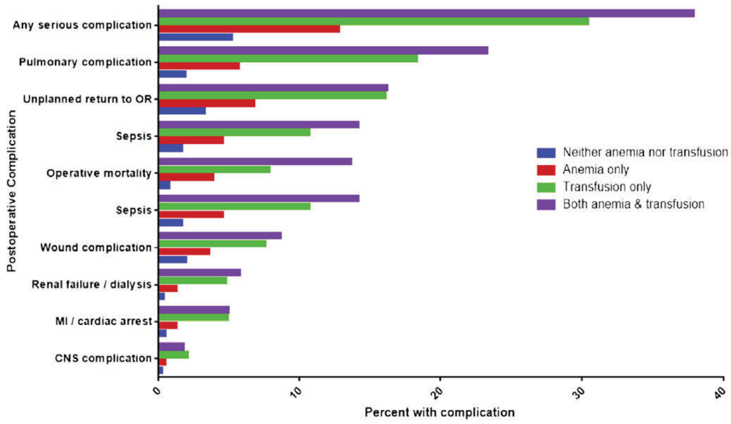



| At Risk: | 2722 | 2683 | 2662 | 2643 | 2070 | 284 |
|---|---|---|---|---|---|---|
| No Anemia: | 2185 | 2176 | 2164 | 2155 | 1678 | 226 |
| Mild Anemia: | 400 | 389 | 384 | 379 | 302 | 35 |
| Moderate Anemia: | 121 | 107 | 103 | 98 | 83 | 22 |
| Severe Anemia: | 16 | 11 | 11 | 11 | 7 | 1 |




| At Risk: | 3050 | 3007 | 2982 | 2960 | 2319 | 306 |
|---|---|---|---|---|---|---|
| RBCT: | 766 | 728 | 716 | 706 | 542 | 68 |
| No RBCT: | 2284 | 2279 | 2266 | 2254 | 1777 | 238 |

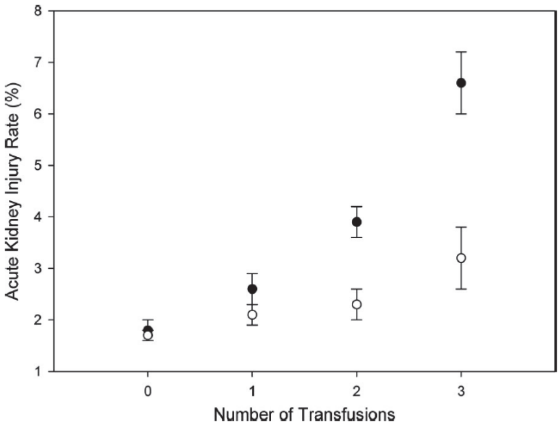
# Transfuse or not?




Ferraris 2015

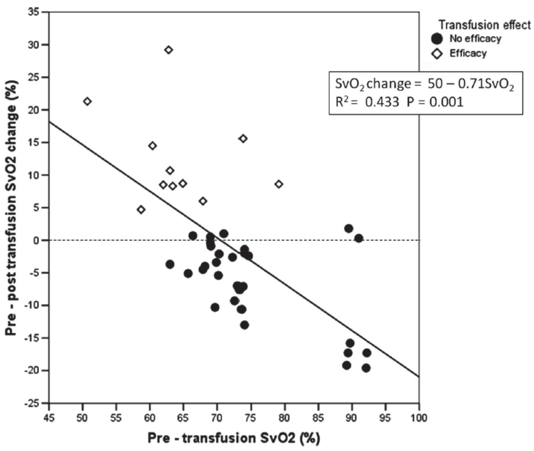
IBiTech GENT

# AKI, anemia and transfusion




Karkouti 2011

# Was transfusion efficacious?




Ranucci 2011

# Acute Kidney Injury and Hemodilution During Cardiopulmonary Bypass: A Changing Scenario

Marco Ranucci, MD, FESC, Tommaso Aloisio, MD, Giovanni Carboni, CCP, Andrea Ballotta, MD, FESC, Valeria Pistuddi, Lorenzo Menicanti, MD, and Alessandro Frigiola, MD, for the Surgical and Clinical Outcome REsearch (SCORE) Group

Departments of Cardiothoracic and Vascular Anesthesia and Intensive Care and Department of Cardiac Surgery, IRCCS Policlinico San Donato, Milan, Italy

*Background.* Severe hemodilution during cardiopulmonary bypass (CPB) is a risk factor for acute kidney injury (AKI) after heart operations. Many improvements to CPB technology have been proposed during the past decade to limit the hemodilution-related AKI risk. The present study is a retrospective analysis of the relationship between hemodilution during CPB and AKI in cardiac operations in the setting of different interventions applied over 14 years.

*Methods.* We retrospectively analyzed 16,790 consecutive patients undergoing heart operations from 2000 to 2013. Various risk factors for AKI were collected and analyzed, together with a number of interventions as possible modifiers of the relationship between a nadir hematocrit (HCT) value during CPB and AKI.

*Results.* The relationship between the nadir HCT value during CPB and AKI was confirmed in a multivariable analysis, with the relative risk of AKI increasing by 7% per percentage point of decrease of the nadir HCT value during CPB. The relative risk of AKI decreased by 8% per year of observation ($p = 0.001$) despite a significantly increased risk of AKI ($p = 0.001$). A sensitivity analysis based on differences before and after different interventions demonstrated a beneficial effect of the application of goal-directed perfusion (aimed at preserving oxygen delivery during CPB), with a reduction in the AKI rate from 5.8% to 3.1% ($p = 0.001$). A policy restricting angiographic examination on the day of operation was also useful (reduction of AKI rate from 4.8% to 3.7%; $p = 0.029$).

*Conclusions.* A bundle of interventions mainly aimed at limiting the renal impact of hemodilution during CPB is effective in reducing the AKI rate.

(Ann Thorac Surg 2015;100:95–100)


*Table 2. Demographics and Renal Risk Factors of the Patient Population in the Different Periods Considered*

| Period (No. of patients) | Age (y) | eGFR (mL/min) | LVEF (%) | Diabetes (%) | Redo Operations (%) | Nonelective Operations (%) | Nonisolated CABG (%) | IABP Use (%) | CPB time (min) |
|---|---|---|---|---|---|---|---|---|---|
| 2000–2001 (2,714) | 64.4 (10.7) | 56.8 (23) | 51.6 (11.8) | 12.6 | 4.0 | 2.4 | 42.9 | 0.3 | 71.7 (37) |
| 2002–2003 (2,694) | 65.6 (11.3) | 71.8 (34) | 50.4 (11.6) | 14.1 | 5.4 | 4.0 | 49.6 | 0.4 | 71.8 (36) |
| 2004–2005 (3,006) | 66.5 (11.6) | 74.3 (36) | 51.6 (11.9) | 13.8 | 5.5 | 6.5 | 49.3 | 0.8 | 75.1 (38) |
| 2006–2007 (2,313) | 66.3 (11.8) | 77.2 (33) | 52.0 (11.1) | 12.1 | 6.2 | 4.5 | 49.8 | 0.8 | 80.4 (39) |
| 2008–2009 (1,829) | 65.9 (12.3) | 78.7 (36) | 53.9 (11.8) | 14.1 | 6.1 | 3.1 | 57.1 | 0.9 | 83.1 (37) |
| 2010–2011 (2,157) | 65.9 (13.5) | 76.9 (40) | 53.1 (12.0) | 18.5 | 6.6 | 3.6 | 63.7 | 2.0 | 87.1 (44) |
| 2012–2013 (2,077) | 66.3 (13.0) | 75.6 (35) | 53.5 (11.5) | 18.1 | 8.1 | 8.2 | 68.7 | 1.3 | 86.0 (42) |
| p value (between periods)[a] | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 |

[a] Analysis of variance or Pearson's $\chi^2$ test. Data expressed as mean (standard deviation) or percentage.

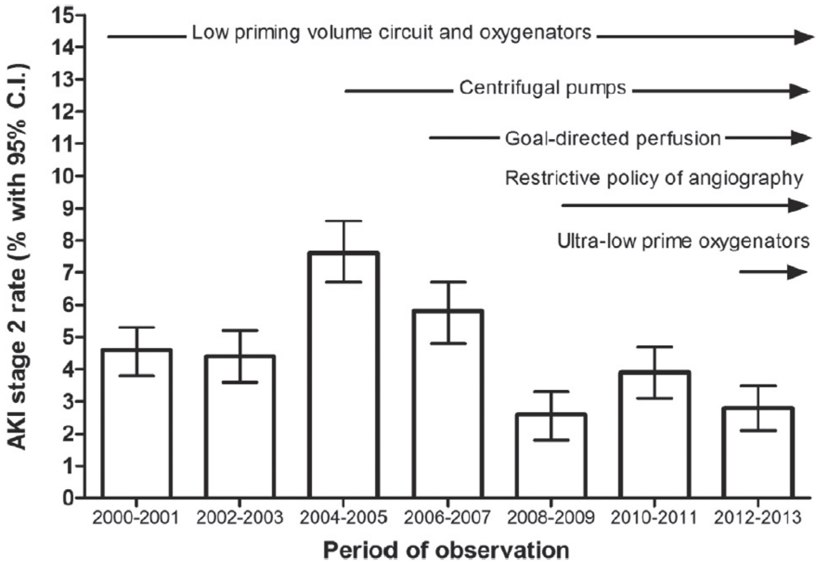
CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; eGFR = estimated glomerular filtration rate; IABP = intraaortic balloon pump; LVEF = left ventricular ejection fraction.

*Table 3. Renal Risk and Renal Outcome of the Patient Population in the Different Periods Considered*

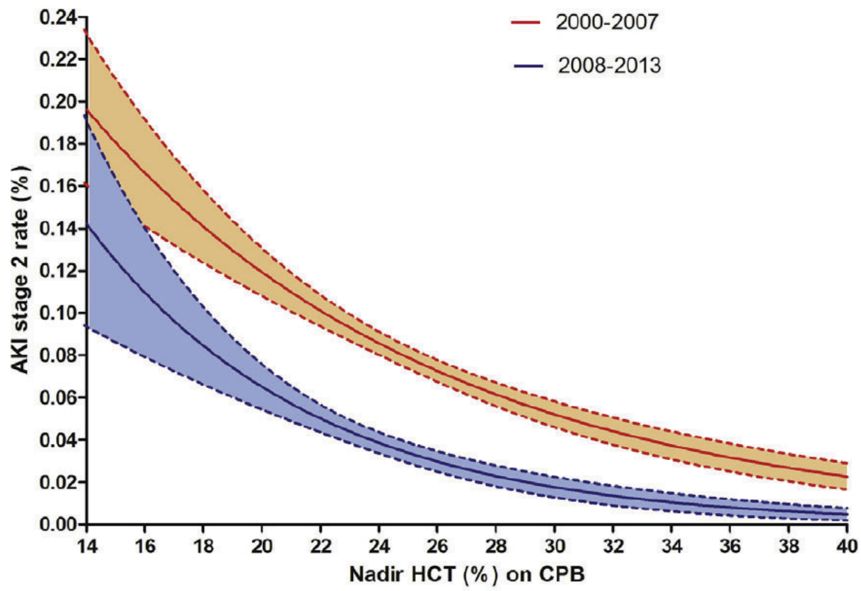
| Period | No. of Patients | RRS | AKI Rate | Nadir HCT Value During CPB (%) | AKI Rate at Nadir < 24% | Odds Ratio (95% CI) for AKI As a Function of Nadir HCT Value | p Value for Univariate Association |
|---|---|---|---|---|---|---|---|
| 2000–2001 | 2,714 | 1.49 (1.1) | 124 (4.6) | 25.9 (4.1) | 48 (6.7) | 0.92 (0.88–0.96) | 0.001 |
| 2002–2003 | 2,694 | 1.36 (1.1) | 118 (4.4) | 27.8 (3.7) | 28 (8.0) | 0.89 (0.84–0.93) | 0.001 |
| 2004–2005 | 3,006 | 1.36 (1.1) | 229 (7.6) | 26.6 (3.6) | 57 (9.0) | 0.95 (0.91–0.98) | 0.005 |
| 2006–2007 | 2,313 | 1.25 (1.1) | 133 (5.8) | 26.2 (3.4) | 45 (8.3) | 0.93 (0.89–0.98) | 0.010 |
| 2008–2009 | 1,829 | 1.34 (1.0) | 47 (2.6) | 26.1 (3.7) | 26 (5.5) | 0.85 (0.79–0.93) | 0.001 |
| 2010–2011 | 2,157 | 1.51 (1.1) | 84 (3.9) | 26.1 (3.7) | 34 (6.3) | 0.85 (0.80–0.91) | 0.001 |
| 2012–2013 | 2,077 | 1.70 (1.2) | 58 (2.8) | 28.0 (4.1) | 14 (4.7) | 0.91 (0.86–0.97) | 0.006 |
| Total | 16,790 | | | | | | |
| p value (between periods)[a] | | 0.001 | 0.001 | 0.001 | 0.001 | | |

[a] Analysis of variance or Pearson's $\chi^2$ test. Data are expressed as mean (standard deviation) or number (%).

AKI = acute kidney injury; CI = confidence interval; CPB = cardiopulmonary bypass; HCT = hematocrit; RRS = renal risk score.



Low priming volume circuit and oxygenators
Centrifugal pumps
Goal-directed perfusion
Restrictive policy of angiography
Ultra-low prime oxygenators
AKI stage 2 rate (% with 95% C.I.)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
2000-2001
2002-2003
2004-2005
2006-2007
2008-2009
2010-2011
2012-2013
Period of observation

2000-2007
2008-2013
AKI stage 2 rate (%)
0.00
0.02
0.04
0.06
0.08
0.10
0.12
0.14
0.16
0.18
0.20
0.22
0.24
14
16
18
20
22
24
26
28
30
32
34
36
38
40
Nadir HCT (%) on CPB

## Maintain red blood cell mass

- Low priming volume
- Retrograde autologous priming
- Limit fluid delivery
- Ultrafiltration

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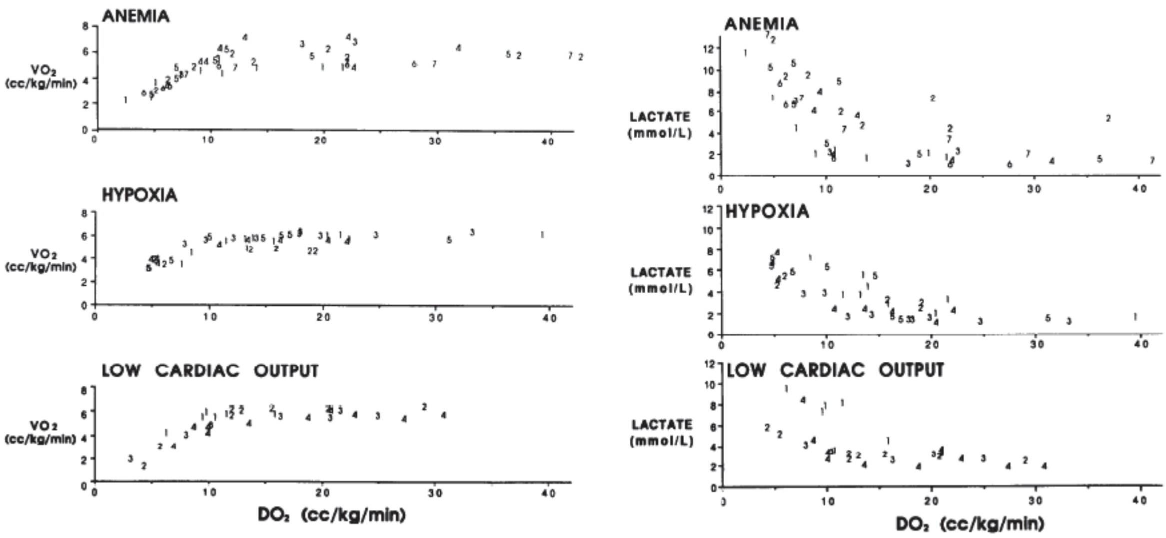
## $DO_2$ as a goal

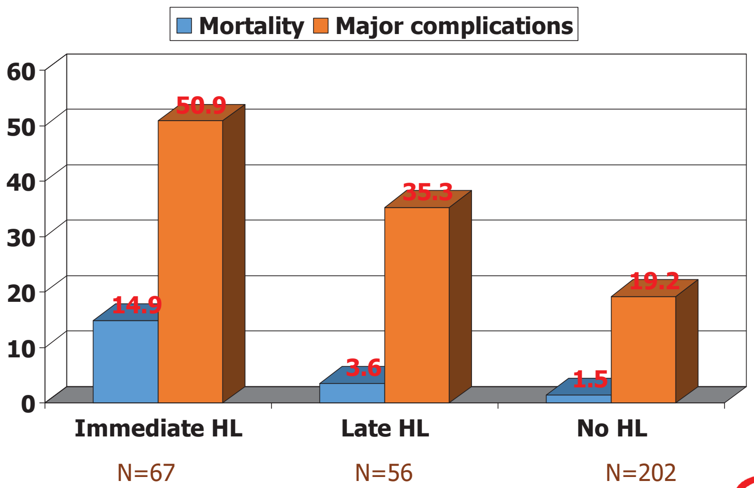
- Scarce information on $DO_2$ during CPB
- With a constant pump flow, $DO_2$ is direct related to Hct
- Most CPB cases are performed at 32 - 34°C
- Pump flow = 2 - 3 L/min/m²
- => Hct = cte => $DO_2$ varies with 50%

IBiTech GENT

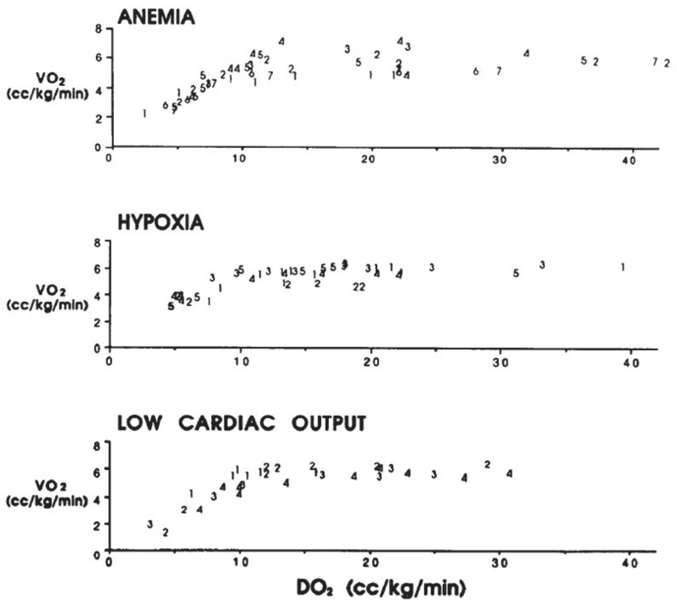



Cilley 1991

# Lactate as marker

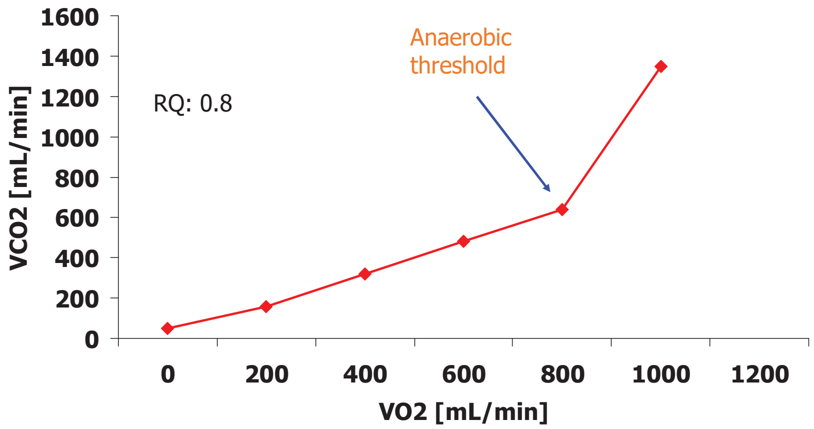


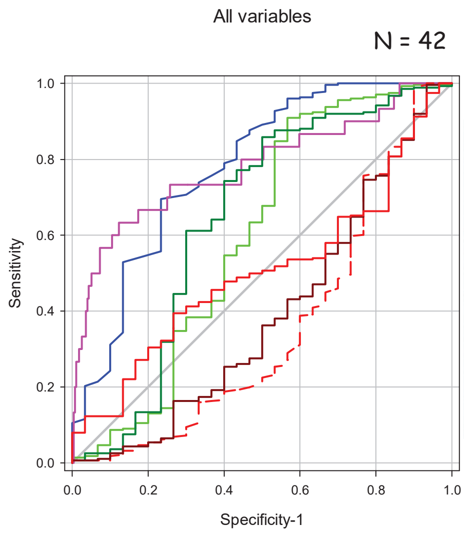

Maillet 2003

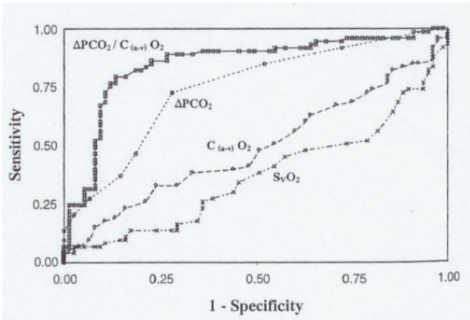



Cilley 1991

# $VCO_2 – VO_2$






Mekonso-Dessap 2002

# How do we know that blood flow meet the metabolic needs of a patient?

By retrospective analysis of organ function, blood markers and morbidity

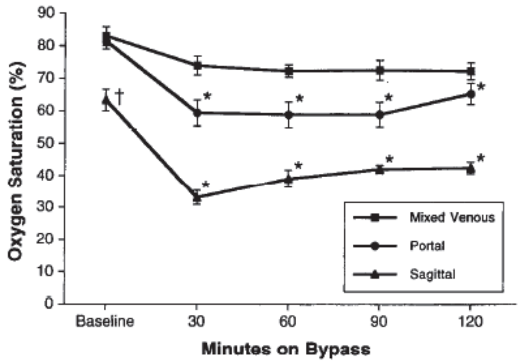
"What we need is a multivariate online analysis of risk during cardiopulmonary bypass" *Charles Wildevuur*

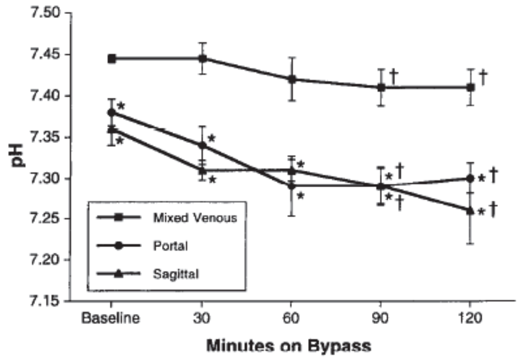
$DO_2i$ => what we give to the patient

$VCO_2i$ => what we get from the patient

| Variable | Baseline | Bypass interval (min) 30 | 60 | 90 | 120 |
|---|---|---|---|---|---|
| pH | 7.46 ± 0.02 | 7.47 ± 0.1 | 7.45 ± 0.1 | 7.46 ± 0.2 | 7.46 ± 0.1 |
| $Paco_2$ | 37.3 ± 2.4 | 32.4 ± 1.9 | 34.3 ± 1.8 | 33.8 ± 1.8 | 33.4 ± 1.9 |
| $Pao_2$ | 310 ± 20.1 | 312 ± 34.1 | 244 ± 32.7 | 269 ± 42.1 | 284 ± 42.0 |
| Arterial bicarbonate | 27.1 ± 1.2 | 24.4 ± 0.8* | 23.9 ± 0.8* | 23.4 ± 0.6* | 22.0 ± 0.7* |
| Hct | 26.3 ± 2.2 | 14.6 ± 1.6* | 15.9 ± 1.5* | 16.4 ± 1.6* | 14.4 ± 1.5* |
| Temperature (°C)[a] | 37.3 ± 0.4 | 37.4 ± 0.3 | 37.6 ± 0.1 | 37.6 ± 0.2 | 37.6 ± 1.4 |

Hct = hematocrit.
[a] Temperature was measured nasopharyngeally.
* $P < 0.05$ compared with baseline value.




McDaniel 1995

"current guidelines for calculating pump flow during normothermic bypass may be reconciled to better match prebypass systemic oxygen delivery with oxygen delivery during CPB."

McDaniel 1995

*Table 2. Univariate Analysis of Oxygen-Carbon Dioxide Derived Parameters and Other Intraoperative Variables at Arterial Lactate Determinations Below or Above the Threshold Value (3 mmol/L).*

| Parameter | Arterial Lactates ≤ 3 mmol/L (n = 130) | Arterial Lactates > 3 mmol/L (n = 37) | $p$ |
|---|---|---|---|
| $Pao_2$ (mmHg) | 225 ± 56 | 228 ± 44 | 0.7 |
| $Svo_2$ | 0.78 ± 0.76 | 0.76 ± 0.8 | 0.15 |
| $VCO_2i$ (mL · $min^{-1}$ · $m^{-2}$) | 51.4 ± 15.2 | 82.1 ± 38.4 | < 0.001 |
| $DO_2i/VCO_2i$ | 6.35 ± 1.7 | 4.14 ± 1.2 | < 0.001 |
| $VCO_2i/VO_2i$ | 0.77 ± 0.22 | 1.35 ± 0.68 | < 0.001 |
| Aortic cross-clamp on | 72% | 46% | 0.003 |
| BSA ($m^2$) | 1.85 ± 0.2 | 1.62 ± 0.45 | 0.005 |
| CPB time (min) | 44.7 ± 36.3 | 68.9 ± 47.7 | 0.006 |

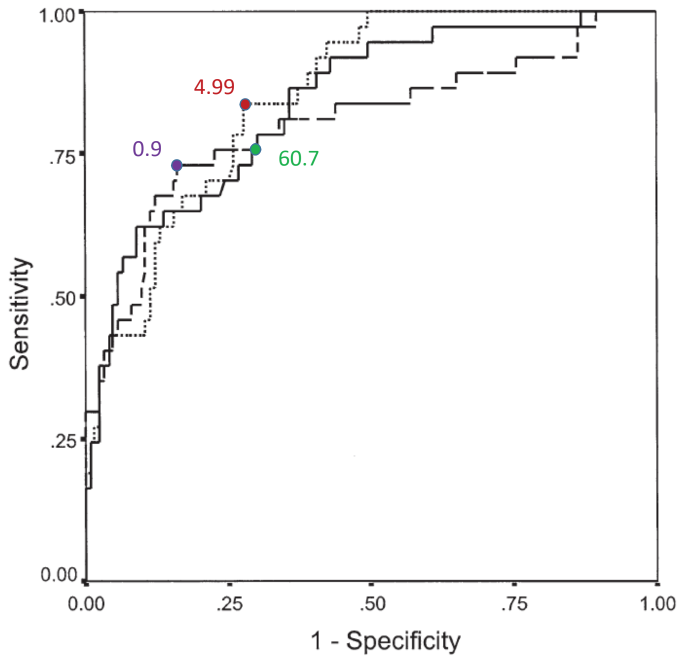
BSA = body surface area; CPB = cardiopulmonary bypass; $Do_2i/Vco_2i$ = oxygen delivery indexed/carbon dioxide elimination indexed; $Pao_2$ = arterial oxygen tension; $Svo_2$ = mixed venous oxygen saturation; $Vco_2i$ = carbon dioxide elimination indexed; $Vco_2i/Vo_2i$ = respiratory quotient.

*Table 3. Receiver Operating Characteristic Analysis and Relative Cutoff Values*

| Factor | AUC | $p$ | Cutoff Value | Sensitivity | Specificity |
|---|---|---|---|---|---|
| $Do_2i/Vco_2i$ | 0.852 | < 0.001 | 4.99 | 78.4% | 74% |
| $Vco_2i$ | 0.838 | < 0.001 | 60.7 | 75.7% | 70.7% |
| $Vco_2i/Vo_2i$ | 0.803 | < 0.001 | 0.90 | 75.7% | 77.2% |

AUC = area under the curve; $Do_2i/Vco_2i$ = oxygen delivery indexed/ carbon dioxide elimination indexed; $Vco_2i$ = carbon dioxide elimination indexed; $Vco_2i/Vo_2i$ = respiratory quotient.

Ranucci 2006



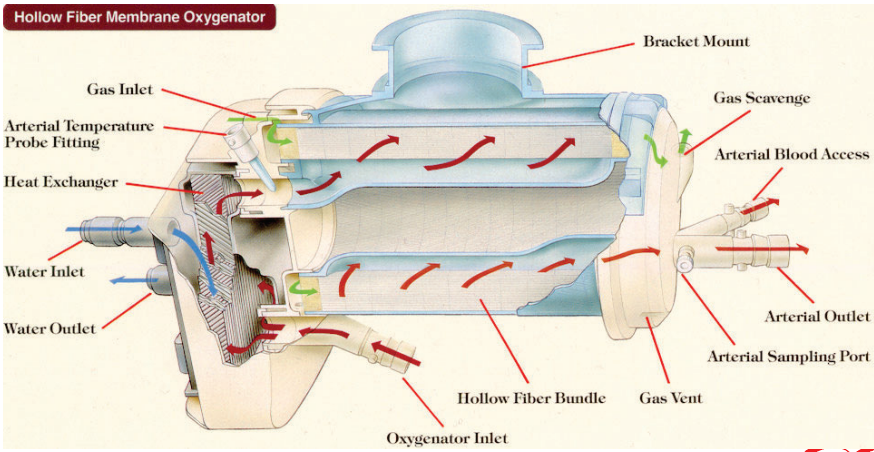

Ranucci 2006

# $CO_2$ can be measured in real time

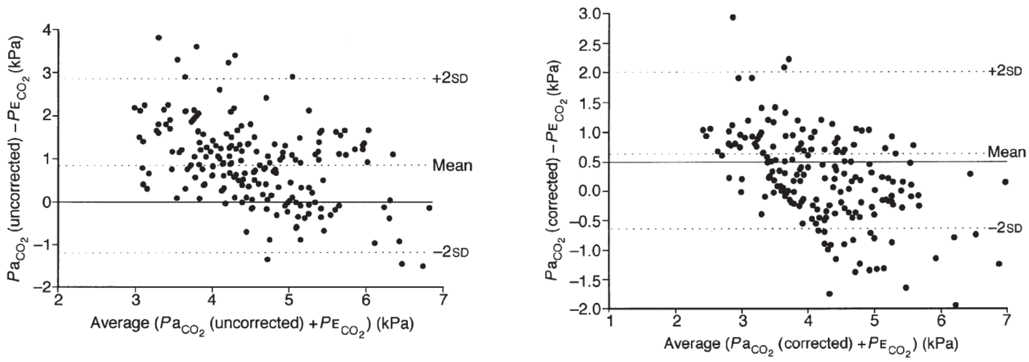

# $CO_2$ production

$$VCO_2 = Q_{gas} \cdot \frac{e_{CO2}}{P_{baro}}$$

# Capnography: potential problems

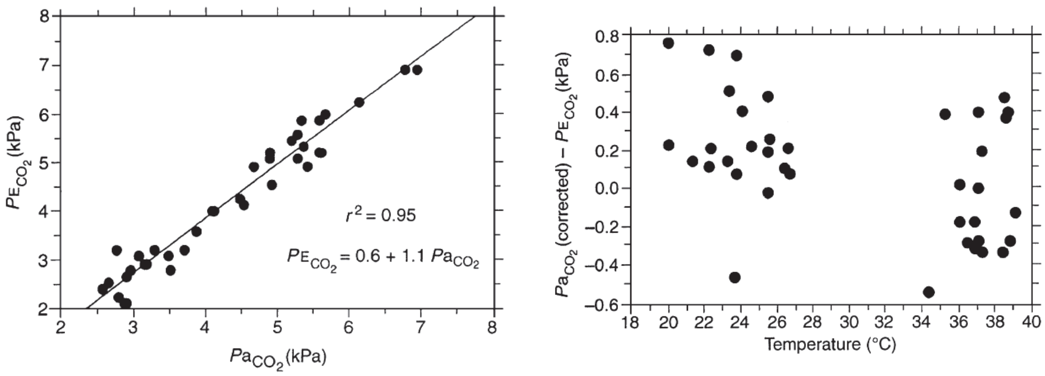



# Capnography oxygenator exhaust




O'Leary 1999

# Capnography oxygenator exhaust




Weightman 1999

- ATP: Ambient Temperature Pressure (room air)
- ATPS: Ambient Temperature Pressure Saturated ($H_2O$)
- BTPS: Body Temperature Pressure Saturated ($H_2O$)
- STPD: Standard Temperature (0°C), Pressure (1ATM), Dry

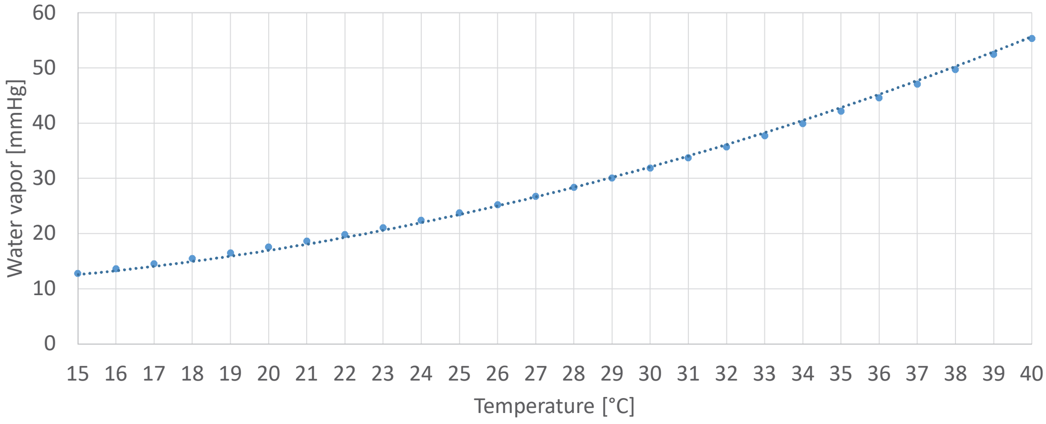
# Gas laws

$$P_1 \cdot \frac{V_1}{T_1} = P_2 \cdot \frac{V_2}{T_2} \rightarrow \frac{P_2 \cdot T_1 \cdot V_2}{T_2 \cdot V_1}$$

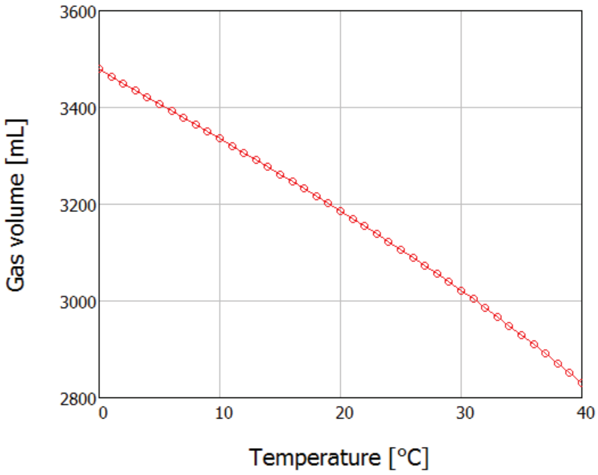
$$V_{STPD} := \frac{(P_{baro} - P_{H2O}) \cdot 273.15K}{P_{baro} \cdot (T_{art})} = 0.826$$

$T_{art}$ in K

# Water vapor and temperature



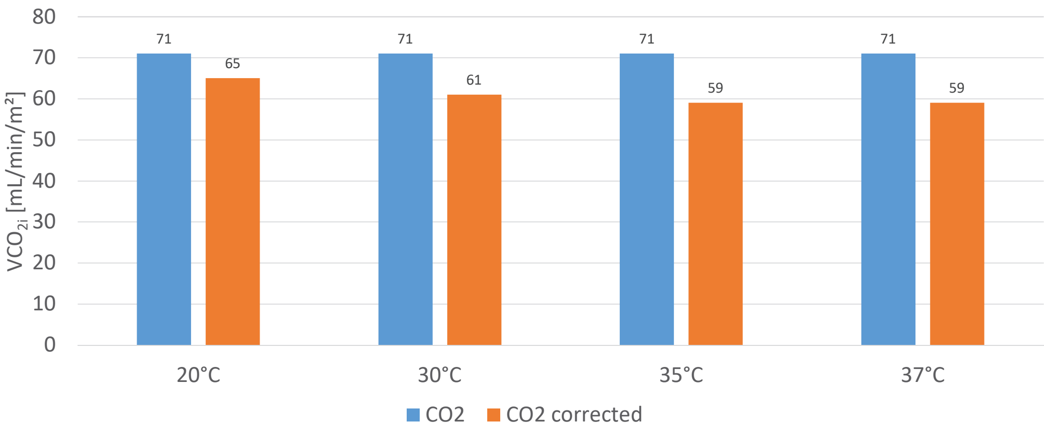
# Conversion ATPS to STPD




# Example

- $eCO_2$ = 36 mmHg/760 mmHg = 4.7%
- $Q_{gas}$ = 3000 mL/min
- $P_{barometric}$ = 760 mmHg
- $T_{art}$ = 20°C
- BSA = 2 m²

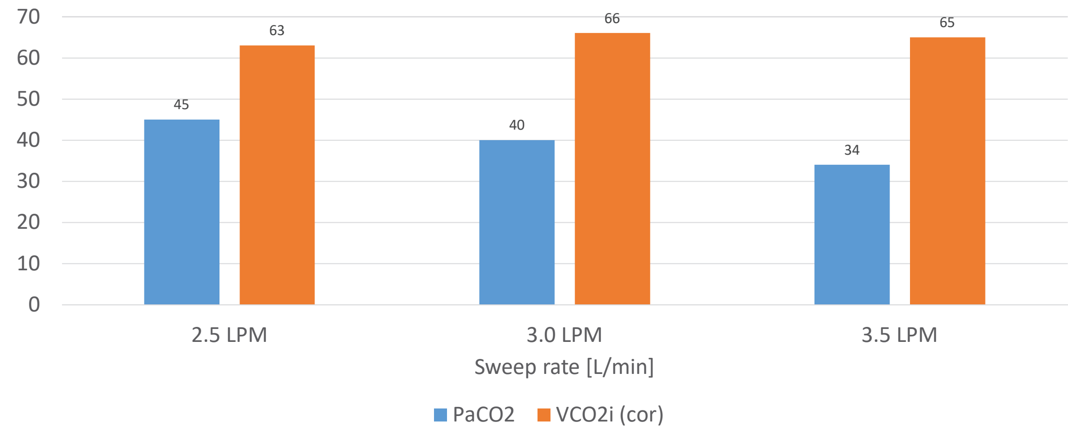
# ATPS versus STPD




for venous return. Lowest core body temperature during CPB varied from 27°C to 37°C as requested by the surgeon. Body temperature was measured at the naso-pharingeal site and at the rectal site. This last temperature was considered for correcting the values of blood gas analyses. The perfusate temperature was measured at the oxygenator site and used for correcting the values of exhaled carbon dioxide. Antegrade intermittent cold

mm Hg. The gas flow was initially settled at 50% oxygen to air ratio and a 1:2 flow ratio with the pump flow indexed, and subsequently arranged in order to maintain an arterial oxygen tension greater than 150 mm Hg and an arterial carbon dioxide tension between 33 and 38 mm Hg.

# Do NOT treat $PaCO_2$

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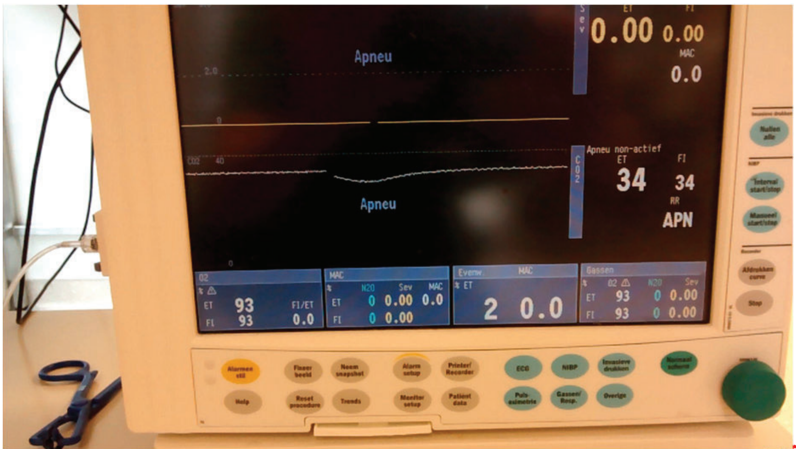
# Scavenging of volatile anesthetics and capnography

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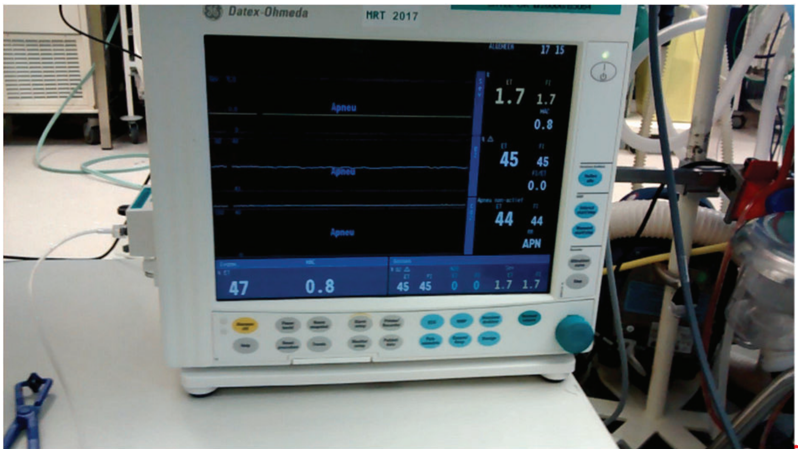
# Scavenging of volatile anesthetics and capnography

# Scavenging of volatile anesthetics and capnography



# Calculation $DO_2$ and $VCO_2$

$Hb = 8\frac{gm}{dL}$ — Hemoglobin concentration

$cte = 1.34\frac{mL}{gm}$ — Maximum transport capacity hemoglobin

$SaO_2 = 99\%$ — Arterial oxygen saturation

$CO = 5\frac{L}{min}$ — cardiac output or pump flow

$k_{blood} = 3.666 \cdot 10^{-5}\frac{mL}{mmHg \cdot mL}$ — oxygen solubility in blood

$PaO_2 = 150mmHg$ — Partial oxygen tension

$$DO_2 = \left[\left(Hb \cdot cte \cdot SaO_2\right) + \left(PaO_2 \cdot k_{blood}\right)\right] \cdot CO = 558\frac{mL}{min}$$

$V_{gas} = 2\frac{L}{min}$ — Gas flow

$e_{CO2} = 40mmHg$ — Oxygenator exhaust $CO_2$

$P_{baro} = 760mmHg$ — Barometric pressure

$V_{CO2} = V_{gas} \cdot \frac{e_{CO2}}{P_{baro}} = 105\frac{mL}{min}$ — Uncorrected $VCO_2$

$P_{H2O} = 39.9mmHg$ — Water vapor tension @ $T_{blood}$

$T_{blood} = 34\ °C$ — Arterial blood temperature

$V_{STPD} = \frac{\left(P_{baro} - P_{H2O}\right) \cdot 273.15K}{P_{baro} \cdot \left(T_{blood}\right)} = 0.843$ — Conversion to STPD, CAVE $T_{blood}$ is converted to K (°C + 273.15)

$V_{CO2c} = V_{CO2} \cdot V_{STPD} = 89\frac{mL}{min}$ — Corrected $VCO_2$

$$\frac{DO_2}{V_{CO2c}} = 6.3$$

Oxygenation

$Hb = 80\frac{gm}{L}$ $\quad Q_{Blood} = 4.5\frac{L}{min}$ $\quad BSA = 1.8m^2$

$SaO_2 = 99\%$ $\quad PaO_2 = 150mmHg$ $\quad k_{Blood} = 3.666\cdot10^{-5}\frac{mL}{mmHg\cdot mL}$

$CO_2$

$Q_{gas} := 2\frac{L}{min}$ $\quad e_{CO2} := 40mmHg$ $\quad P_{Baro} := 760mmHg$

$T_{Blood} := 34\,°C$ $\quad P_{H2O} := 39.9mmHg$

Spectrum

$$DO2_{M4} = \frac{\left(Hb\cdot1.34\cdot\frac{mL}{gm}\cdot SaO_2\right)\cdot Q_{Blood}}{BSA} = 265\cdot\frac{\frac{mL}{min}}{m^2}$$

$$V_{CO2\_M4} = \frac{Q_{gas}\cdot\frac{e_{CO2}}{P_{Baro}}}{BSA} = 58\cdot\frac{\frac{mL}{min}}{m^2}$$

$$\frac{DO2_{M4}}{V_{CO2\_M4}} = 4.537$$

Connect

$$DO2_{Connect} = \frac{\left[\left(Hb\cdot1.36\cdot\frac{mL}{gm}\cdot SaO_2\right)+\left(PaO_2\cdot k_{Blood}\right)\right]\cdot Q_{Blood}}{BSA} = 283\cdot\frac{\frac{mL}{min}}{m^2}$$

$$V_{CO2\_Connect} = \frac{\frac{\left(P_{Baro}-P_{H2O}\right)\cdot273.15K}{P_{Baro}\cdot T_{Blood}}\cdot Q_{gas}\cdot\frac{e_{CO2}}{P_{Baro}}}{BSA} = 49.276\cdot\frac{\frac{mL}{min}}{m^2}$$

$$\frac{DO2_{Connect}}{V_{CO2\_Connect}} = 5.744$$

# Develop an algorithm

$DO_2/VCO_2$ ratio <5

↓

Augment pump flow

Increase Hb content

Decrease T, check anesthesia level

de Somer *et al. Critical Care* 2011, **15**:R192
http://ccforum.com/content/15/4/R192

CRITICAL CARE

RESEARCH Open Access

# $O_2$ delivery and $CO_2$ production during cardiopulmonary bypass as determinants of acute kidney injury: time for a goal-directed perfusion management?

Filip de Somer[1], John W Mulholland[2], Megan R Bryan[2], Tommaso Aloisio[3], Guido J Van Nooten[1] and Marco Ranucci[3*]

**Abstract**

**Introduction:** Acute kidney injury (AKI) is common after cardiac operations. There are different risk factors or determinants of AKI, and some are related to cardiopulmonary bypass (CPB). In this study, we explored the association between metabolic parameters (oxygen delivery ($DO_2$) and carbon dioxide production ($VCO_2$)) during CPB with postoperative AKI.

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| Outcome | All cases N=354 | DO2 < 280 mL/min/m² N= 181 | DO2 ≥ 280 mL/min/m² N= 173 | P |
|---|---|---|---|---|
| Any AKI | 75 (21.2%) | 54 (29.8%) | 21 (12.1%) | 0.001 |
| AKI stage 1 | 31 (8.8%) | 23 (12.7%) | 8 (4.6%) | 0.007 |
| AKI stage 2-3 | 44 (12.4%) | 31 (17.1%) | 13 (7.5%) | 0.006 |

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# Goal Directed Perfusion:
## What we know

- Patients who experience a nadir DO2 on CPB < 272 mL/min/m2 have a higher rate of AKI following cardiac surgery
- This information is coming from retrospective trials, and registries
- This is called «an association»

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# Goal Directed Perfusion:
## What we don't know

- If we intentionally avoid low levels of DO2 through a GDP technique, will we be able to reduce the AKI rate?
- This is called «causative effect»
- To demonstrate that a strategy, a drug, a technique, is able to change the outcome, we need a RCT

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# GIFT

- Prospective, randomized, controlled trial
- Multicenter
- 10 Institutions in Europe, USA, New Zealand
- Co-ordinating Institution: IRCCS PSD
- Ethics Committee Approval at IRCCS PSD
- Registered at clinicaltrials.gov NCT02250131
- Centralized data collection at IRCCS PSD
- Statistical analysis at IRCCS PSD
- Spontaneous study with the external support of Sorin Group.
- Sorin Group shall provide resources for steering committee meetings and GDP monitor

GIFT
The GIFT investigators

# The GDP Trial – protocol

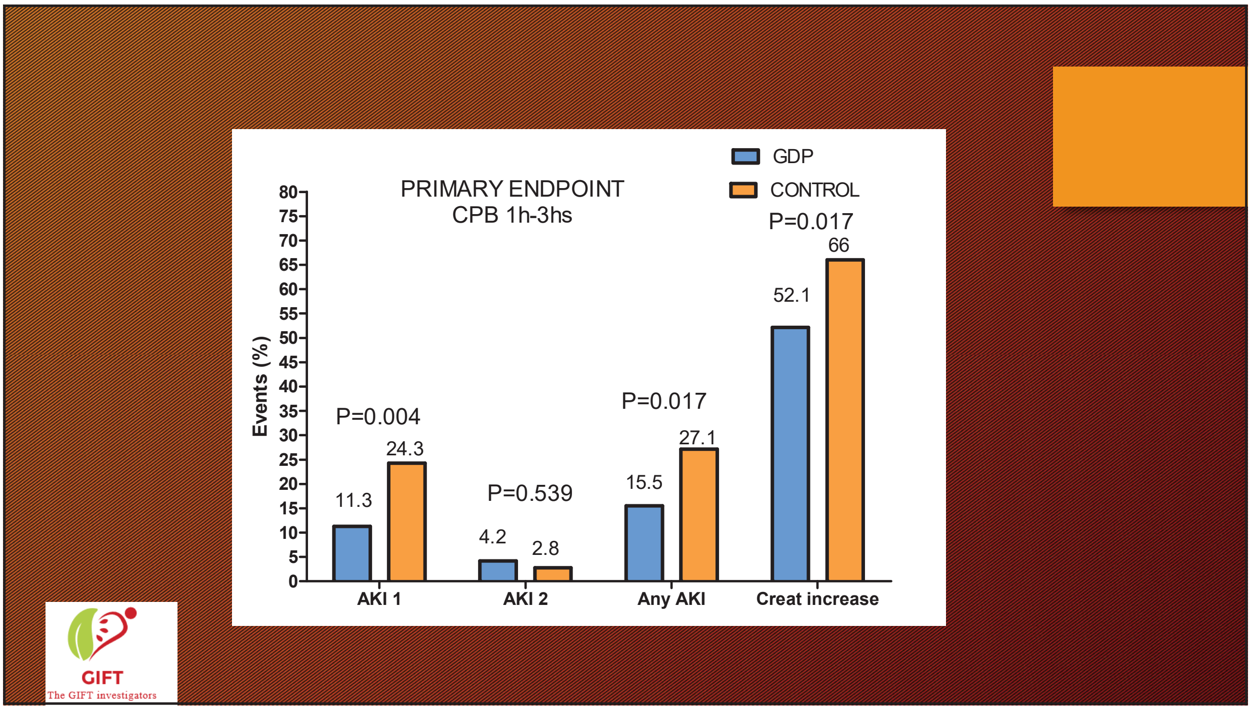
| CONTROL (N=350) | TREATMENT (N=350) |
|---|---|
| GDP monitor | GDP monitor |
| NO Blood prime (withdrawal) | NO Blood prime (withdrawal) |
| Priming volume and nature according to local standards | Priming volume and nature according to local standards |
| Perfusion targeted on BSA and °C | Perfusion targeted on DO2 > 280 mL/min/m2 |
| Perfusion pressure according to local standards | Perfusion pressure according to local standards |
| Transfusion triggered by HCT according to local standards (<20%?) | Transfusion triggered by HCT < 21% and SVO2 < 68% and/or O2ER > 40% |
| Postoperative care according to local standards | Postoperative care according to local standards |

GIFT
The GIFT investigators

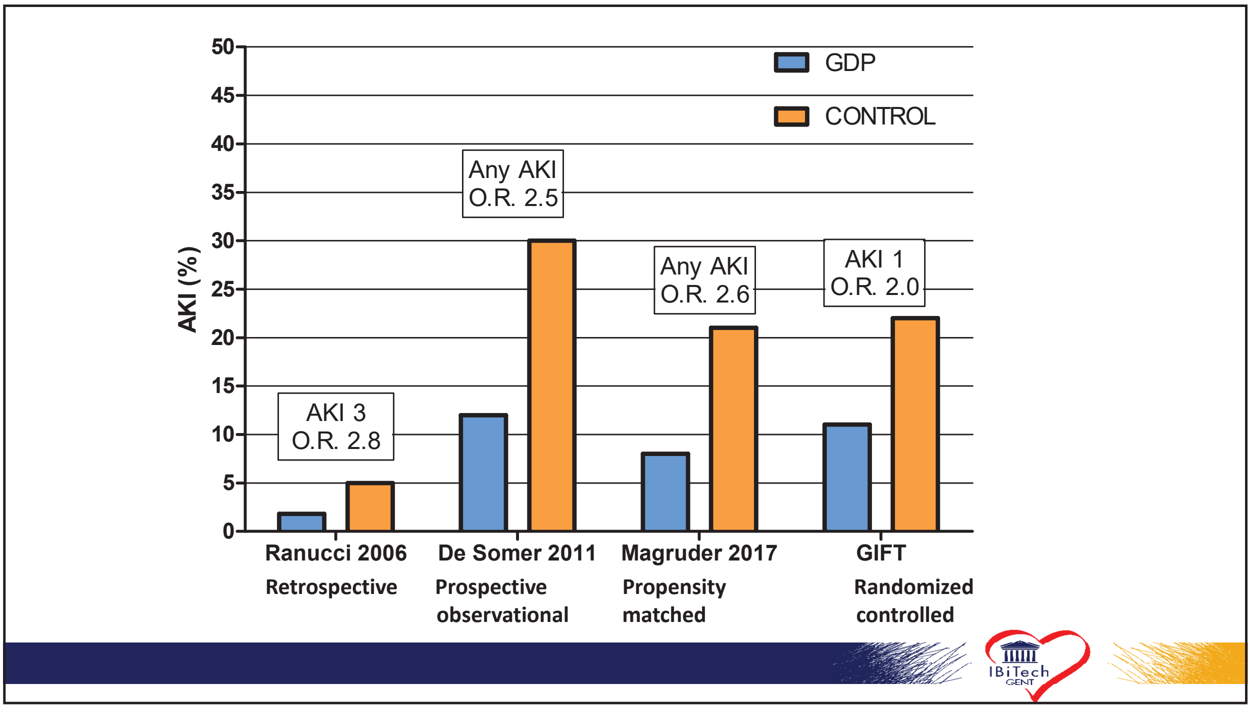
## DO2, VCO2, and DO2/VCO2 data adjudication

- NADIR DO2: maintained for at least 10 minutes (2 consecutive measures)
- Same for VCO2, and DO2/VCO2

GIFT
The GIFT investigators



PRIMARY ENDPOINT
CPB 1h-3hs
GDP
CONTROL
Events (%)
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
P=0.004
11.3
24.3
P=0.539
4.2
2.8
P=0.017
15.5
27.1
P=0.017
52.1
66
AKI 1
AKI 2
Any AKI
Creat increase
GIFT
The GIFT investigators

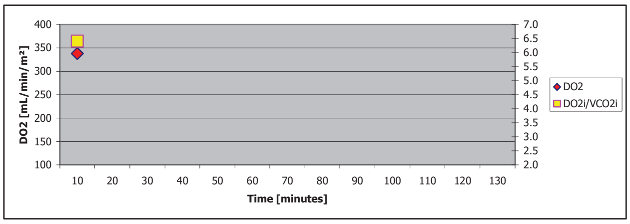



AKI (%)
50
45
40
35
30
25
20
15
10
5
0
GDP
CONTROL
AKI 3
O.R. 2.8
Any AKI
O.R. 2.5
Any AKI
O.R. 2.6
AKI 1
O.R. 2.0
Ranucci 2006
Retrospective
De Somer 2011
Prospective
observational
Magruder 2017
Propensity
matched
GIFT
Randomized
controlled
IBiTech
GENT

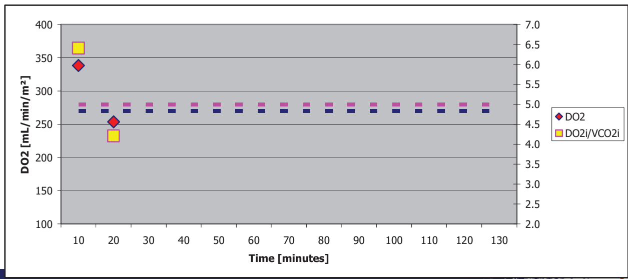
# Example

- 45 y female
- 45 kg, 1.49 m²
- CI (2.4 LPM/m²) = 3.6
- Baseline Hb: 10.7 g/dL
- AVR + MVR

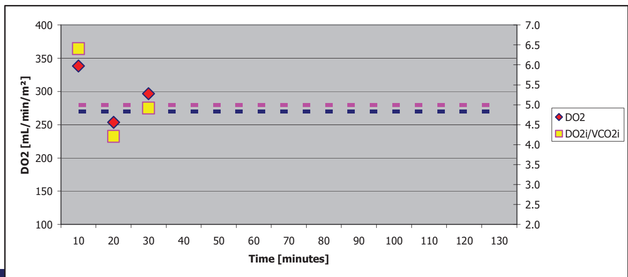
| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| BSA [m²] | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 |
| Qblood [mL/min] | 3600 | | | | | | | | | |
| Ta [°C] | 33 | | | | | | | | | |
| PaO2 [mmHg] | 128 | | | | | | | | | |
| Hb [gm/dL] | 10.7 | | | | | | | | | |
| $SaO_2$ [%] | 97.5 | | | | | | | | | |
| $PvO_2$ [mmHg] | 45.1 | | | | | | | | | |
| $SvO_2$ [%] | 76.1 | | | | | | | | | |
| Qgas [mL/min] | 1750 | | | | | | | | | |
| $eCO_2$ [mmHg] | 40 | | | | | | | | | |
| VO2 [mL/min] | 119.71 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| $DO_2$ [mL/min] | 503.26 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| $DO_{2i}$ [mL/min/m²] | 338 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| $VCO_2$ [mL/min] | 78.53 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| $VCO_{2i}$ [mL/min] | 52.8 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| $DO_{2i}/VCO_{2i}$ | 6.4 | #DIV/0! | #DIV/0! | #DIV/0! | #DIV/0! | #DIV/0! | #DIV/0! | #DIV/0! | #DIV/0! | #DIV/0! |
| Lactaat [mg/dL] | 18.7 | | | | | | | | | |
| Lactaat [mmol/L] | 2.0757 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



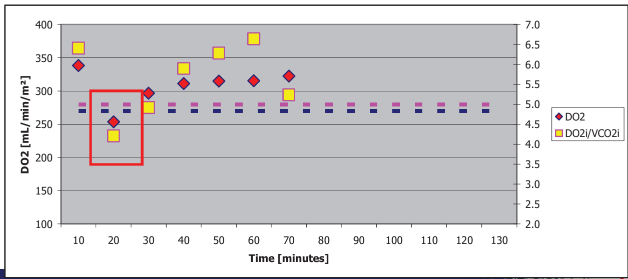
| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| BSA [m²] | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 |
| Qblood [mL/min] | 3600 | 3600 | | | | | | | | |
| Ta [°C] | 33 | 33 | | | | | | | | |
| PaO2 [mmHg] | 128 | 180 | | | | | | | | |
| Hb [gm/dL] | 10.7 | 8 | | | | | | | | |
| $SaO_2$ [%] | 97.5 | 97.8 | | | | | | | | |
| $PvO_2$ [mmHg] | 45.1 | 45 | | | | | | | | |
| $SvO_2$ [%] | 76.1 | 76 | | | | | | | | |
| Qgas [mL/min] | 1750 | 2000 | | | | | | | | |
| $eCO_2$ [mmHg] | 40 | 40 | | | | | | | | |
| VO2 [mL/min] | 119.71 | 99.20 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| $DO_2$ [mL/min] | 503.26 | 377.43 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| $DO_{2i}$ [mL/min/m²] | 338 | 254 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| $VCO_2$ [mL/min] | 78.53 | 89.74 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| $VCO_{2i}$ [mL/min] | 52.8 | 60.3 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| $DO_{2i}/VCO_{2i}$ | 6.4 | 4.2 | #DIV/0! | #DIV/0! | #DIV/0! | #DIV/0! | #DIV/0! | #DIV/0! | #DIV/0! | #DIV/0! |
| Lactaat [mg/dL] | 18.7 | 20 | | | | | | | | |
| Lactaat [mmol/L] | 2.0757 | 2.22 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



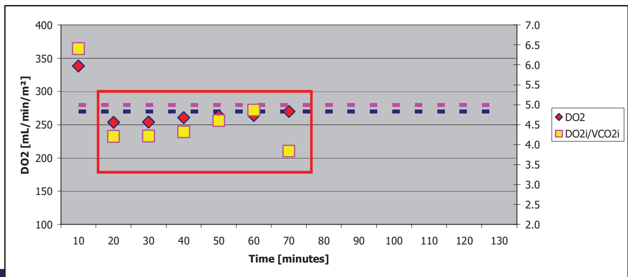

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| BSA [m²] | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 |
| Qblood [mL/min] | 3600 | 3600 | 4200 | | | | | | | |
| Ta [°C] | 33 | 33 | 33 | | | | | | | |
| PaO2 [mmHg] | 128 | 180 | 168 | | | | | | | |
| Hb [gm/dL] | 10.7 | 8 | 8 | | | | | | | |
| $SaO_2$ [%] | 97.5 | 97.8 | 98 | | | | | | | |
| $PvO_2$ [mmHg] | 45.1 | 45 | 45 | | | | | | | |
| $SvO_2$ [%] | 76.1 | 76 | 80 | | | | | | | |
| Qgas [mL/min] | 1750 | 2000 | 2000 | | | | | | | |
| $eCO_2$ [mmHg] | 40 | 40 | 40 | | | | | | | |
| VO2 [mL/min] | 119.71 | 99.20 | 97.06 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| $DO_2$ [mL/min] | 503.26 | 377.43 | 441.24 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| $DO_{2i}$ [mL/min/m²] | 338 | 254 | 296 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| $VCO_2$ [mL/min] | 78.53 | 89.74 | 89.74 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| $VCO_{2i}$ [mL/min] | 52.8 | 60.3 | 60.3 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| $DO_{2i}/VCO_{2i}$ | 6.4 | 4.2 | 4.9 | #DIV/0! | #DIV/0! | #DIV/0! | #DIV/0! | #DIV/0! | #DIV/0! | #DIV/0! |
| Lactaat [mg/dL] | 18.7 | 20 | 20 | | | | | | | |
| Lactaat [mmol/L] | 2.0757 | 2.22 | 2.22 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



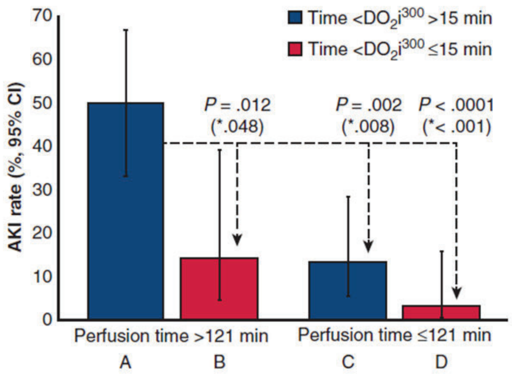
| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| BSA [m²] | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 |
| Qblood [mL/min] | 3600 | 3600 | 4200 | 4300 | 4300 | 4300 | 4300 | | | |
| Ta [°C] | 33 | 33 | 33 | 33 | 33 | 33 | 34 | | | |
| PaO2 [mmHg] | 128 | 180 | 168 | 175 | 176 | 200 | 176 | | | |
| Hb [gm/dL] | 10.7 | 8 | 8 | 8.2 | 8.3 | 8.4 | 8.5 | | | |
| $SaO_2$ [%] | 97.5 | 97.8 | 98 | 98 | 98 | 97 | 98 | | | |
| $PvO_2$ [mmHg] | 45.1 | 45 | 45 | 45 | 43 | 45 | 40 | | | |
| $SvO_2$ [%] | 76.1 | 76 | 80 | 82 | 80 | 81 | 79 | | | |
| Qgas [mL/min] | 1750 | 2000 | 2000 | 1750 | 1750 | 1750 | 1750 | | | |
| $eCO_2$ [mmHg] | 40 | 40 | 40 | 40 | 38 | 36 | 47 | | | |
| VO2 [mL/min] | 119.71 | 99.20 | 97.06 | 92.93 | 103.81 | 98.10 | 111.19 | 0.00 | 0.00 | 0.00 |
| $DO_2$ [mL/min] | 503.26 | 377.43 | 441.24 | 463.03 | 468.68 | 469.49 | 479.97 | 0.00 | 0.00 | 0.00 |
| $DO_{2i}$ [mL/min/m²] | 338 | 254 | 296 | 311 | 315 | 315 | 323 | 0 | 0 | 0 |
| $VCO_2$ [mL/min] | 78.53 | 89.74 | 89.74 | 78.53 | 74.60 | 70.67 | 91.68 | 0.00 | 0.00 | 0.00 |
| $VCO_{2i}$ [mL/min] | 52.8 | 60.3 | 60.3 | 52.8 | 50.1 | 47.5 | 61.6 | 0.0 | 0.0 | 0.0 |
| $DO_{2i}/VCO_{2i}$ | 6.4 | 4.2 | 4.9 | 5.9 | 6.3 | 6.6 | 5.2 | #DIV/0! | #DIV/0! | #DIV/0! |
| Lactaat [mg/dL] | 18.7 | 20 | 20 | 17 | | | | | | |
| Lactaat [mmol/L] | 2.0757 | 2.22 | 2.22 | 1.887 | 0 | 0 | 0 | 0 | 0 | 0 |




| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| BSA [m²] | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 | 1.49 |
| Qblood [mL/min] | 3600 | 3600 | 3600 | 3600 | 3600 | 3600 | 3600 | | | |
| Ta [°C] | 33 | 33 | 33 | 33 | 33 | 33 | 34 | | | |
| PaO2 [mmHg] | 128 | 180 | 168 | 175 | 176 | 200 | 176 | | | |
| Hb [gm/dL] | 10.7 | 8 | 8 | 8.2 | 8.3 | 8.4 | 8.5 | | | |
| $SaO_2$ [%] | 97.5 | 97.8 | 98 | 98 | 98 | 97 | 98 | | | |
| $PvO_2$ [mmHg] | 45.1 | 45 | 45 | 45 | 43 | 45 | 40 | | | |
| $SvO_2$ [%] | 76.1 | 76 | 80 | 82 | 80 | 81 | 79 | | | |
| Qgas [mL/min] | 1750 | 2000 | 2000 | 2000 | 2000 | 2000 | 2000 | | | |
| $eCO_2$ [mmHg] | 40 | 40 | 40 | 40 | 38 | 36 | 47 | | | |
| VO2 [mL/min] | 119.71 | 99.20 | 83.19 | 77.80 | 86.91 | 82.13 | 93.09 | 0.00 | 0.00 | 0.00 |
| $DO_2$ [mL/min] | 503.26 | 377.43 | 378.20 | 387.66 | 392.38 | 393.06 | 401.84 | 0.00 | 0.00 | 0.00 |
| $DO_{2i}$ [mL/min/m²] | 338 | 254 | 254 | 260 | 264 | 264 | 270 | 0 | 0 | 0 |
| $VCO_2$ [mL/min] | 78.53 | 89.74 | 89.74 | 89.74 | 85.26 | 80.77 | 104.78 | 0.00 | 0.00 | 0.00 |
| $VCO_{2i}$ [mL/min] | 52.8 | 60.3 | 60.3 | 60.3 | 57.3 | 54.3 | 70.4 | 0.0 | 0.0 | 0.0 |
| $DO_{2i}/VCO_{2i}$ | 6.4 | 4.2 | 4.2 | 4.3 | 4.6 | 4.9 | 3.8 | #DIV/0! | #DIV/0! | #DIV/0! |
| Lactaat [mg/dL] | 18.7 | 20 | 20 | 17 | | | | | | |
| Lactaat [mmol/L] | 2.0757 | 2.22 | 2.22 | 1.887 | 0 | 0 | 0 | 0 | 0 | 0 |



# Importance of time




Mukaida 2019

45 y.o. female, 45 Kg., 1.49 $m^2$
2.4 CI = 3.58 LPM, AVR MVR, Sorin Inspire™ 6
Baseline Hgb = 10.7

| Time | BQ | RQ | Temp | $SvO_2$ | HCT | $DO_2i$ | $VO_2$ | $VO_2i/DO_2i$ | $DO_2/VCO_2$ | $VCO_2i$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 5 | 3.64 | 99 | 35.2 | 88 | 24 | 299 | 79.4 | 18.3 | 4.8 | 61.9 |
| 25 | 3.51 | 98 | 3[illegible] | [illegible] | [illegible] | [illegible] | 75.5 | 19 | 4.8 | 57.5 |
| 40 | 3.69 | 103 | [illegible] | [illegible] | [illegible] | [illegible] | 73.4 | 16.8 | 6.6 | 46 |
| 45 | 3.59 | 100 | [illegible] | [illegible] | [illegible] | [illegible] | 79.8 | 19 | 6.5 | 44.4 |
| 70 | 3.6 | 100 | [illegible] | [illegible] | [illegible] | [illegible] | 72.5 | 18 | 5.8 | 47.6 |
| 100 * | 3.9 | 109 | [illegible] | [illegible] | [illegible] | [illegible] | 103 | 25.5 | 4.6 | 60.3 |
| 120 | 3.9 | 109 | [illegible] | [illegible] | [illegible] | [illegible] | 126.2 | 27 | 4.8 | 64.2 |
| 140 | 4 | 112 | 36.5 | 78 | 24 | 328 | 94.3 | 19.3 | 7.5 | 43.5 |

AKI Score

Pre-op creatinine = 1.07 mmol/l

Peak post creatinine = 0.77 mmol/l

* 1 unit PRBC at 110 minutes, low volume , absolute Hgb trigger reached

35 y.o. male, 136 Kg., 2.55 m², BMI = 45
2.4 CI = 6.1 LPM, IBW = 75 Kg, IBSA = 1.9, Ideal 2.4 CI = 4.56 LPM
Redo PVR RVOT repair, Baseline Hgb = 12 g/dL

| Time | BQ | RQ | 2 | $VO_2i/DO_2i$ | $DO_2/VCO_2$ | $VCO_2i$ |
|---|---|---|---|---|---|---|
| 5 | 4.6 | 0.75 | 5 | 17 | 6.1 | 43 |
| 30 | 5.0 | 0.82 | 1 | 15.4 | 6.9 | 41 |
| 60 | 5.0 | 0.82 | 8 | 13.2 | 6.8 | 44 |
| 90 | 5.2 | 0.85 | 2 | 16.3 | 6.4 | 46 |
| 125 | 5.0 | 0.82 | 2 | 18.4 | 5.4 | 52 |

AKI Score

Pre-op creatinine = 0.97 mmol/l

Peak post creatinine = 1.12 mmol/l

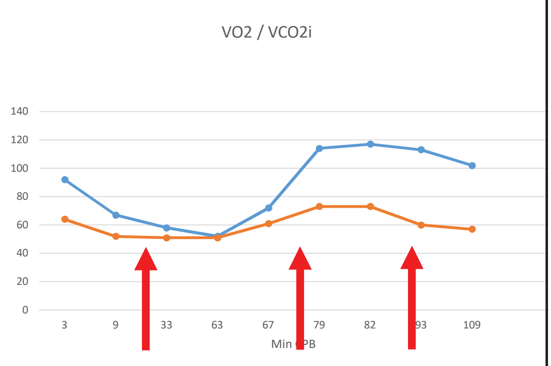
73 y.o female, 61 Kg. critical AS, baseline HCT 27%, CBF Risk
$Q_b$ 100% = 3.72 LPM , BSA = 1.55 M²
MAP goal > 70 mmHg

| Time | $Q_b$ | T | Hct | $DO_{2i}$ | $VO_{2i}$ | $VCO_{2i}$ | $DO_{2i}/VCO_{2i}$ | $VCO_{2i}/VO_{2i}$ | SVR |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 4.4 | 36 | | | | | | 1.08 | 1572 |
| 9 | 4.4 | 34 | | | | | | 1.20 | 1290 |
| 33 | 4.2 | 32 | | | | | | 1.36 | 1314 |
| 63 | 3.77 | 32 | | | | | | 1.52 | 1633 |
| 67 | 4.12 | 34 | | | | | | 1.31 | 1430 |
| 79 | 4.3 | 35 | | | | | | 0.99 | 1302 |
| 82 | 4.4 | 36 | 23 | 308 | 117 | 73 | 4.2 | 0.97 | 1204 |
| 93 | 4.62 | 36 | 24 | 324 | 113 | 60 | 5.4 | 0.83 | 1043 |
| 109 | 4.42 | 36.5 | 26 | 340 | 102 | 57 | 5.9 | 0.87 | 1170 |

AKI Score

Pre-op creatinine = 0.86 mmol/l

Peak post creatinine = 1.11 mmol/l



# Why does it not always work?

What we need is a multivariate online analysis of risk during cardiopulmonary bypass *Charles Wildevuur*

Which parameters?

IBiTech GENT

## Effect of mean arterial pressure, haemoglobin and blood transfusion during cardiopulmonary bypass on post-operative acute kidney injury

Michael Haase[1,2], Rinaldo Bellomo[3], David Story[4], Angela Letis[4], Katja Klemz[1], George Matalanis[5], Siven Seevanayagam[5], Duska Dragun[1], Erdmann Seeliger[6], Peter R. Mertens[2] and Anja Haase-Fielitz[2]

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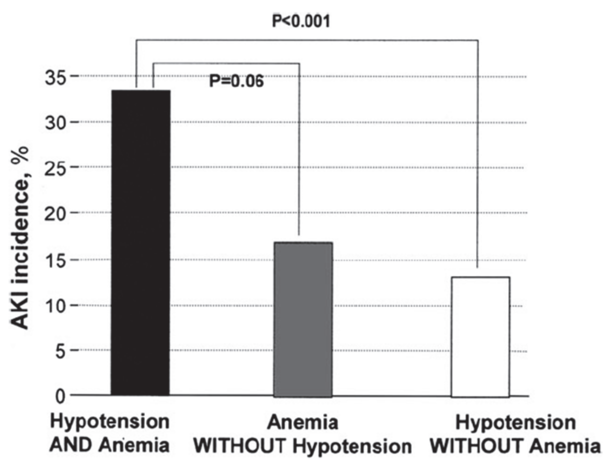
IBiTech GENT

| Variable | AKI (*N* = 179) | No AKI (*N* = 741) | P univariate | Adjusted OR (95% CI) | P multivariate |
|---|---|---|---|---|---|
| Model 0 | | | | | |
| AKICS Score, points [3][b] | 5.8 (3.9–8.1) | 4.3 (2.6–6.3) | <0.001 | 1.09 per point increase (1.04–1.15) | <0.001 |
| Emergency[c] | 25 (13.8%) | 22 (3.1%) | <0.001 | 4.36 (2.31–8.22) | <0.001 |
| Return to operating room, *n* | 34 (19.0%) | 52 (7.0%) | <0.001 | 2.74 (1.68–4.49) | <0.001 |
| Atrial fibrillation, *n* | 47 (26.3%) | 69 (9.3%) | <0.001 | 2.66 (1.69–4.17) | <0.001 |
| Intra-aortic balloon pump, *n* | 19 (10.6%) | 25 (3.4%) | <0.001 | 1.27 (0.61–2.66) | 0.521 |
| Intraoperative variables added to Model 0 | | | | | |
| Haemoglobin concentration, g/dL[d] | | | | | |
| Median[e] | 8.1 (7.4–9.3) | 8.7 (7.7–9.7) | <0.001 | 1.18 per g/dL decrease (1.02–1.34) | 0.028 |
| Lowest[e] | 7.4 (6.4–8.6) | 8.2 (7.0–9.3) | <0.001 | 1.16 per g/dL decrease (1.03–1.31) | 0.018 |
| Variability, %[e] | 1.2 (0.6–2.2) | 0.9 (0.5–1.5) | <0.001 | 1.10 per % increase (0.94–1.28) | 0.239 |
| Arterial $O_2$ content, mL/dL[d] | | | | | |
| Median[e] | 12.2 (11.2–13.9) | 13.0 (11.6–14.4) | <0.001 | 1.13 per mL/dL decrease (1.02–1.26) | 0.027 |
| Lowest[e] | 10.9 (9.6–12.5) | 12.0 (10.4–13.5) | <0.001 | 1.11 per mL/dL decrease (1.02–1.22) | 0.018 |
| Variability, %[e] | 1.7 (0.8–3.0) | 1.2 (0.7–2.1) | <0.001 | 1.07 per % increase (0.96–1.20) | 0.241 |
| $SaO_2$, % | 99.7 (99.6–99.8) | 99.7 (99.6–99.8) | 0.949 | N/A | N/A |
| $PaO_2$, mmHg | 324 (274–385) | 319 (272–375) | 0.543 | N/A | N/A |
| Red blood cell transfusion, mL[d] | 750 (500–1000) | 500 (250–750) | <0.001 | 1.001 per mL (1.000–1.002) | 0.013 |
| Vasopressors | | | | | |
| Metaraminol, mg | 3.5 (1.9–6.5) | 3.5 (1.5–6.0) | 0.852 | N/A | N/A |
| Phenylephrine, mg | 4.9 (2.2–8.5) | 2.3 (1.3–4.5) | 0.007 | 1.05 (0.95–1.16) | 0.334 |
| MAP, mmHg | | | | | |
| Median[e] | 68.5 (64.0–73.0) | 68.0 (64.0–73.0) | 0.841 | N/A | N/A |
| Lowest[e] | 31.0 (25.0–36.0) | 32.0 (25.5–36.5) | 0.554 | N/A | N/A |
| Variability, %[e] | 16.7 (14.1–19.7) | 17.0 (14.3–19.6) | 0.390 | N/A | N/A |
| AUC MAP, min × mmHg | | | | | |
| <50 mmHg[e] | 0.32 (0.13–0.66) | 0.37 (0.17–0.69) | 0.304 | N/A | N/A |
| <60 mmHg[e] | 1.49 (0.86–2.68) | 1.51 (0.93–2.58) | 0.673 | N/A | N/A |
| <70 mmHg[e] | 5.27 (3.55–7.46) | 5.17 (3.51–7.38) | 0.986 | N/A | N/A |



Circulation

ORIGINAL RESEARCH ARTICLE

# High-Target Versus Low-Target Blood Pressure Management During Cardiopulmonary Bypass to Prevent Cerebral Injury in Cardiac Surgery Patients

## A Randomized Controlled Trial

Editorial, see p 1781

**BACKGROUND:** Cerebral injury is an important complication after cardiac surgery with the use of cardiopulmonary bypass. The rate of overt stroke after cardiac surgery is 1% to 2%, whereas silent strokes, detected by diffusion-weighted magnetic resonance imaging, are found in up to 50% of patients. It is unclear whether a higher versus a lower blood pressure during cardiopulmonary bypass reduces cerebral infarction in these patients.

**METHODS:** In a patient- and assessor-blinded randomized trial, we allocated patients to a higher (70–80 mm Hg) or lower (40–50 mm Hg) target for mean arterial pressure by the titration of norepinephrine during cardiopulmonary bypass. Pump flow was fixed at 2.4 $L \cdot min^{-1} \cdot m^{-2}$. The primary outcome was the total volume of new ischemic cerebral lesions (summed in millimeters cubed), expressed as the difference between diffusion-weighted imaging conducted preoperatively and again postoperatively between days 3 and 6. Secondary outcomes included diffusion-weighted imaging–evaluated total number of new ischemic lesions.

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Lars S. Rasmussen, DMSc, PhD, MD
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Olaf B. Paulson, DMSc, MD
Theis Lange, PhD, MSc
Carsten Thomsen, DMSc, MD
Peter Skov Olsen, DMSc, MD
Hanne Berg Ravn, DMSc, PhD, MD
Jens C. Nilsson, PhD, MD

| | Low-Target Group (n=99) | High-Target Group (n=98) |
|---|---|---|
| Age, y | 65.0±10.7 | 69.4±8.9 |
| Male sex, n (%) | 93 (93.9) | 84 (85.7) |
| Nonwhite race, n (%) | 2 (2.0) | 0 (0) |
| Previous myocardial infarction, n (%)* | 37 (37.4) | 37 (37.8) |
| Recent myocardial infarction (past 2 wk), n (%) | 30 (30.3) | 25 (25.5) |
| Aortic valvular disease, n (%) | 34 (34.3) | 34 (34.7) |
| Angina, CCS score >1, n (%)† | 64 (64.6) | 47 (48.0) |
| Current or previous atrial fibrillation, n (%) | 14 (14.1) | 13 (13.3) |
| Hypertension, n (%) | 83 (84.8) | 87 (88.8) |
| Diabetes mellitus, type 1 or 2 (insulin treated), n (%) | 10 (10.1) | 10 (10.2) |
| Diabetes mellitus, type 2 (non–insulin treated), n (%) | 14 (14.1) | 14 (14.3) |
| Chronic lung disease, n (%) | 9 (9.1) | 12 (12.2) |
| Current smoker, n (%) | 18 (18.2) | 15 (15.3) |
| Current alcohol abuse, n (%) | 7 (7.1) | 7 (7.1) |
| BMI, kg/m²‡ | 27.0 (3.8) | 27.6 (4.0) |
| Left ventricular ejection fraction, n (%) | | |
| >50% | 54 (54.5) | 50 (51.5) |
| 35%–50% | 32 (32.3) | 40 (41.2) |
| 20%–34% | 12 (12.1) | 7 (7.2) |
| <20% | 1 (1.0) | 0 (0) |

| | Low-Target Group (n=98) | High-Target Group (n=97) |
|---|---|---|
| Hematocrit, before start of surgery, % | 40.3±5.9 | 40.6±4.7 |
| MAP before anesthesia induction, mm Hg | 92.3±15.7 | 96.9±13.4 |
| MAP during bypass, mm Hg | 44.7±4.7 | 66.8±4.9 |
| MAP below target during bypass, n (%)* | 2 (2.0) | 18 (18.5) |
| MAP above target during bypass, n (%)† | 5 (5.1) | 0 (0) |
| Blood flow rate during bypass, $L \cdot min^{-1} \cdot m^{-2}$ | 2.69±0.1 | 2.69±0.1 |
| Hematocrit, mean level during bypass, % | 31.5±3.8 | 33.1±4.2 |
| Nadir hematocrit sampling value during bypass, % | 28.7±3.7 | 29.2±4.0 |
| Surgery time, min | 184.9±50.8 | 194.3±66.6 |
| Bypass time, min | 94.0±33.0 | 105.6±77.4 |
| Cross-clamp time, min‡ | 63.3±26.9 | 64.8±32.6 |
| Peak lactate level during surgery, mmol | 2.25±0.83 | 2.16±0.82 |
| Norepinephrine infused in the OR, μg/kg | 2.65±6.01 | 17.43±20.14 |
| Patients receiving norepinephrine in the OR, n (%) | 35 (35.7) | 90 (92.7) |

# MAP: high vs low

| | Low-Target Group, n | | High-Target Group, n | | Difference (95% CI) | OR (95% CI) | *P* Value |
|---|---|---|---|---|---|---|---|
| Primary outcome | | | | | | | |
| Total volume of new cerebral lesions, $mm^3$ | | | | | | | |
| Complete cases, median (IQR) | 89 | 25 (0 to 118) | 80 | 29 (0 to 143) | 0 (−25 to 0.028)* | | 0.41 |
| Excluding 3 outliers, median (IQR) | 88 | 24 (0 to 118) | 78 | 28 (0 to 134) | | | |
| Complete cases, mean (SD) | 89 | 415 (2682) | 80 | 488 (2539) | 8 (−978 to 994)† | | 0.99‡ |
| Excluding 3 outliers, mean (SD) | 88 | 133 (313) | 78 | 144 (265) | | | |
| Secondary outcome | | | | | | | |
| Total number of new cerebral lesions | | | | | | | |
| Complete cases, median (IQR) | 89 | 1 (0 to 2) | 80 | 1 (0 to 2) | 0 (0 to 0)* | | 0.54 |
| Complete cases, mean (SD) | 99 | 1.82 (3.62) | 98 | 2.25 (4.41) | 0.23 (−0.99 to 1.46)† | | 0.71‡ |
| Patients with new infarcts in watershed border zones, n (%)§ | 89 | 32 (36.0) | 80 | 33 (41.3) | | | 0.49 |
| Stroke, n (%) | | 1 (1.1) | | 6 (7.0) | | 6.64 (0.78 to 310.75) | 0.06 |
| Symptoms on awakening | 97 | 0 | 92 | 4 | | | |
| Symptom onset between days 2 and 30 | 97 | 1 | 92 | 2 | | | |
| POCD, n (%) | | | | | | | |
| At 7 d | 91 | 21 (23.1) | 78 | 27 (34.6) | | 1.76 (0.90 to 3.47) | 0.12 |
| At 90 d | 89 | 8 (9.0) | 75 | 5 (6.7) | | 0.72 (0.23 to 2.31) | 0.77 |

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# MAP: high vs low

| | Low-Target Group | High-Target Group | OR (95% CI) | *P* Value |
|---|---|---|---|---|
| Length of stay in ICU, h, median (IQR) | 21 (20–26) | 21 (19–22) | | 0.82 |
| ICU stays >36 h, n (%) | 11 (11.5) | 12 (12.6) | 1.12 (0.42–2.97) | 0.82 |
| Lactate, peak value at POD 1, mmol | 2.61±1.17 | 2.90±1.70 | | 0.16 |
| Inotropes >24 h, n (%) | 4 (4.1) | 10 (10.4) | 2.72 (0.75–12.32) | 0.10 |
| Vasopressors >24 h, n (%) | 3 (3.1) | 10 (10.4) | 3.66 (0.90–21.37) | 0.05 |
| Time to extubation, h, median (IQR) | 4.6 (2.9–6.7) | 4.6 (3.2–7.9) | | 0.43 |
| Atrial fibrillation, n (%) | 49 (49.5) | 52(53.1) | 1.18 (0.65–2.16) | 0.57 |
| Creatinine, peak value, mmol/L | 118.0±47.4 | 121.9±48.6 | | 0.57 |
| Creatinine, doubling of baseline value, n (%) | 2 (2.0) | 9 (9.4) | 4.93 (1.02–48.12) | 0.03 |
| Hallucinations or delirium, n (%)* | 7 (7.1) | 10 (10.5) | 1.53 (0.50–4.95) | 0.45 |
| Length of stay in cardiac surgery ward, d | 6 (5–8) | 6 (5–7.75) | | 0.92 |

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Kanji *et al. Journal of Cardiothoracic Surgery* 2010, **5**:71
http://www.cardiothoracicsurgery.org/content/5/1/71

JOURNAL OF CARDIOTHORACIC SURGERY

RESEARCH ARTICLE Open Access

# Difference between pre-operative and cardiopulmonary bypass mean arterial pressure is independently associated with early cardiac surgery-associated acute kidney injury

Hussein D Kanji[1], Costas J Schulze[1,2], Marilou Hervas-Malo[3], Peter Wang[1], David B Ross[1,2], Mohamad Zibdawi[1,2,4], Sean M Bagshaw[2,3,4*]

**Table 2 Summary of intra-operative variables stratified by post-operative CSA-AKI**

| Variable | No AKI (n = 92) | AKI (n = 65) | p-value |
|---|---|---|---|
| Valve only surgery (%) | 26 (28.3) | 12 (18.5) | 0.16 |
| Combined (valve + CABG) (%) | 43 (46.7) | 21 (32.3) | 0.07 |
| Re-operation (%) | 8 (8.7) | 6 (9.2) | 0.91 |
| # Grafts (mean [± SD]) | 3.4 ± 1.1 | 3.5 ± 1.1 | 0.77 |
| Duration of CPB (min, mean [± SD]) | 126.6 ± 52 | 127.2 ± 63.2 | 0.69 |
| Duration of cross clamp (min, mean [± SD]) | 90.9 ± 46.9 | 88.7 ± 57.1 | 0.42 |
| Average CPB MAP (mmHg, mean [± SD]) | 57.8 ± 5.1 | 56.9 ± 4.9 | 0.25 |
| Minutes <MAP 60 mmHg (median [± IQR]) | 59 ± 65 | 56 ± 45 | 0.49 |
| Minutes <MAP 50 mmHg (median [± IQR]) | 2.5 ± 10 | 5.0 ± 15 | 0.35 |
| Delta MAP (mmHg, mean [± SD]) | 28.0 ± 13.2 | 31.3 ± 13.8 | 0.10 |
| PRBC transfusions (units, mean [± SD]) | 1.8 ± 1.5 | 2.4 ± 2.3 | 0.27 |
| Patients transfused with PRBC (%) | 23 (25) | 19 (29.2) | 0.56 |
| Insulin dose (Units, mean [± SD]) | 3.3 ± 1.3 | 3.6 ± 3.1 | 0.72 |
| Furosemide dose (mg, n = 9, n = 7, mean [± SD]) | 22.8 ± 10.3 | 27.1 ± 12.5 | 0.50 |
| Ultrafiltration (mL, n = 34, n = 25, mean [± SD]) | 1440 ± 1049 | 1470 ± 1344 | 0.98 |
| Received tranexamic acid (%) | 83 (90.2) | 58 (89.2) | 0.84 |
| Received aprotinin (%) | 0 (0) | 0 (0) | NS |
| Use of side-biting clamp (%) | 16 (17.4) | 21 (32.2) | 0.03 |
| Average flow (mL/kg/min, mean[± SD]) | 60.9 ± 7.1 | 55.5 ± 8.4 | 0.001 |
| Average temperature (°C, mean [± SD]) | 35.3 ± 1.4 | 35.5 ± 1.1 | 0.75 |

**Table 3 Univariate Factors associated with early CSA-AKI**

| Predictor | Odds Ratio | 95% CI | P-value |
|---|---|---|---|
| Male Sex | 1.06 | 0.5-2.1 | 0.87 |
| Age (per year) | 1.01 | 0.99-1.04 | 0.25 |
| Age ≥ 75 years (present) | 1.7 | 0.8-3.5 | 0.15 |
| BMI (kg/m$^2$)(per 1 point) | 1.2 | 0.8-3.5 | < 0.0001 |
| BMI ≥25 kg/m$^2$ (present) | 4.4 | 1.9-10.2 | 0.0007 |
| Valve disease (present) | 0.55 | 0.3-1.0 | 0.06 |
| DM (present) | 2.2 | 1.1-4.2 | 0.025 |
| PVD (present) | 1.9 | 0.9-3.3 | 0.19 |
| HTN (present) | 1.7 | 0.9-3.3 | 0.12 |
| Delta MAP (per 1 mmHg) | 1.02 | 0.99-1.04 | 0.14 |
| Delta MAP ≥26 mmHg (present) | 2.1 | 1.1-4.2 | 0.024 |
| Flow ≥54 per mL/kg/min (present) | 0.2 | 0.1-0.5 | 0.0002 |
| pH | 1.4 | 0.8-2.7 | 0.26 |
| Pre-operative ACE inhibitor (present) | 0.6 | 0.3-1.1 | 0.1 |
| Valve Surgery (present) | 0.5 | 0.3-1 | 0.07 |
| Peak CPB-MAP | 0.5 | 0.2-0.97 | 0.04 |
| Pre-operative Systolic BP (≥111 mmHg) | 2.1 | 0.99-4.6 | 0.05 |
| Duration of CPB MAP ≤60 (per 1 min) | 1.99 | 0.9-4.4 | 0.89 |

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PHYSIOLOGICAL REVIEWS

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Cerebral Blood Flow and Oxygen Consumption In Man

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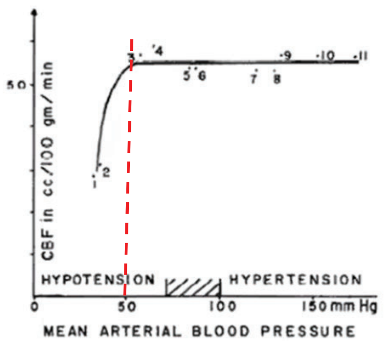


# Cerebral Autoregulation

- Summarized results of 11 studies
- Plotted CBF versus MAP
- Manually drew line at 50 mmHg, lower limit of autoregulation

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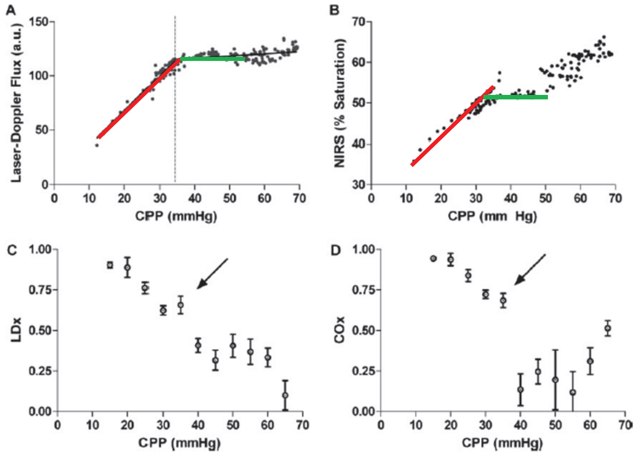
# Quantification of autoregulation




- When Cox approaches 1, autoregulation is disturbed.
  - COx > 0.30 -> no autoregulation
- When COx approaches 0, blood pressure is in the autoregulation range.
  - COx < 0.30 -> cerebral autoregulation

Brady 2007

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BJA

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Cardiovascular

## Comparison of different metrics of cerebral autoregulation in association with major morbidity and mortality after cardiac surgery

Xiuyun Liu[1,2,*], Joseph Donnelly[3], Ken M. Brady[4], Kei Akiyoshi[1], Brian Bush[1], Raymond C. Koehler[1], Jennifer K. Lee[1], Charles W. Hogue[5], Marek Czosnyka[6,7], Peter Smielewski[6] and Charles H. Brown IV [1,*]

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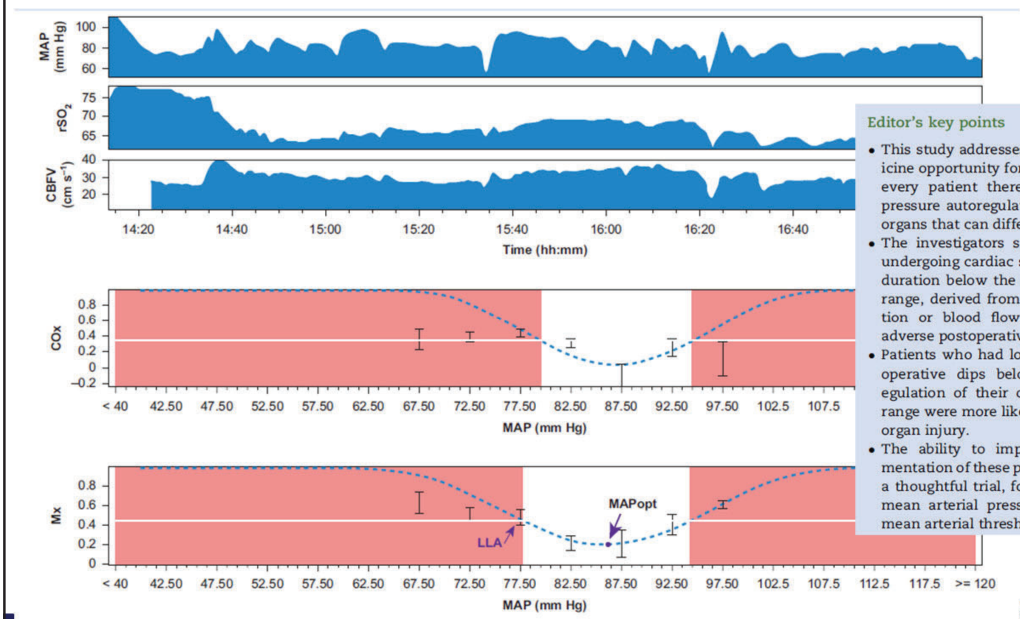



**Editor's key points**

- This study addresses a fundamental precision medicine opportunity for perioperative management: for every patient there is an optimal mean arterial pressure autoregulatory range for perfusion of vital organs that can differ substantially among people.
- The investigators sought to establish, in patients undergoing cardiac surgery, whether the extent and duration below the optimal mean arterial pressure range, derived from measures of cerebral oxygenation or blood flow, were associated with major adverse postoperative outcomes.
- Patients who had longer and more extensive intraoperative dips below the lower limit of autoregulation of their optimal mean arterial pressure range were more likely to suffer major postoperative organ injury.
- The ability to impact outcomes through implementation of these physiological insights will require a thoughtful trial, for example comparing precision mean arterial pressure thresholds with a generic mean arterial threshold.

Liu 2022

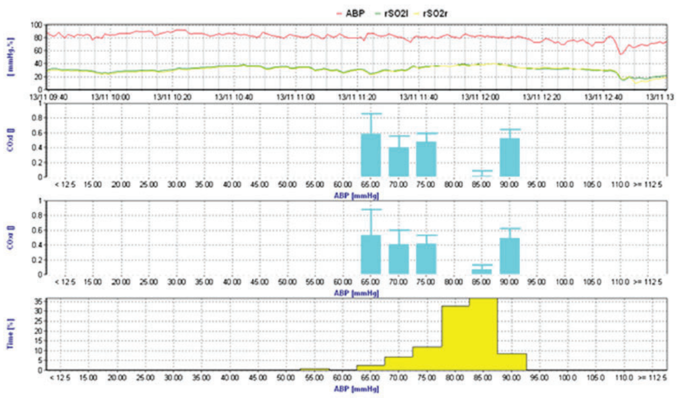
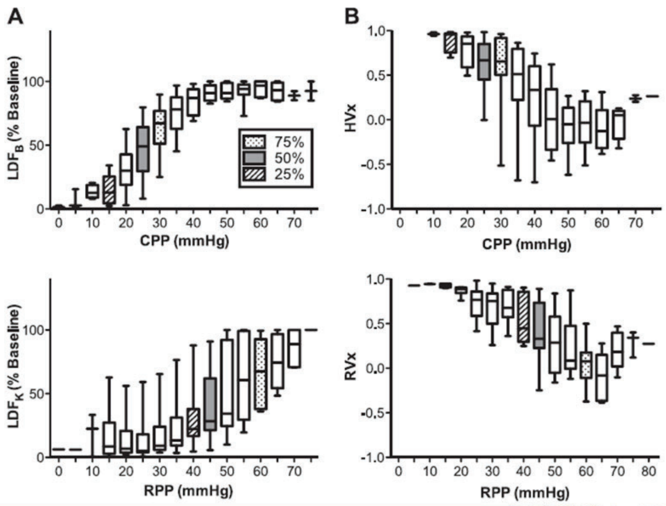



**TABLE 3. Specific complication rates for patients with major morbidity and mortality after surgery and relationship to duration and magnitude of mean arterial pressure below the lower limit of cerebral blood flow autoregulation measured with the cerebral oximetry index**

| | | $AUC_{MAP<LLA}$ (mm Hg × min/h) | | |
|---|---|---|---|---|
| **Complication** | **Patients (n)** | **With complication** | **Without complication** | ***P* value** |
| Stroke | 18 (4.1) | 20.2 ± 26.5 | 9.5 ± 9.3 | .056 |
| Renal failure | 16 (3.6) | 15.5 ± 12.7 | 9.7 ± 10.6 | .030 |
| Mechanical ventilation >48 h | 31 (7.1) | 16.5 ± 15.1 | 9.4 ± 10.2 | <.001 |
| Inotrope use >24 h or new IABP insertion | 47 (10.8) | 11.7 ± 13.1 | 9.7 ± 10.4 | .108 |
| Operative death | 15 (3.4) | 15.1 ± 19.1 | 9.8 ± 10.3 | .081 |

Ono 2014

# Autoregulation of the kidney




Rhee 2012

## Influence of variations in systemic blood flow and pressure on cerebral and systemic oxygen saturation in cardiopulmonary bypass patients

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**Editor's key points**

- Maintenance of adequate tissue perfusion and oxygenation is important during anaesthesia.
- In patients undergoing cardiopulmonary bypass, the authors independently manipulated blood flow and systemic arterial pressure.
- Cerebral and systemic oxygenation were positively correlated with flow but not with pressure.

**Background.** Although both pressure and flow are considered important determinants of regional organ perfusion, the relative importance of each is less established. The aim of the present study was to evaluate the impact of variations in flow, pressure, or both on cerebral and whole-body oxygen saturation.

**Methods.** Thirty-four consenting patients undergoing elective cardiac surgery on cardiopulmonary bypass were included. Using a randomized cross-over design, four different haemodynamic states were simulated: (i) 20% flow decrease, (ii) 20% flow decrease with phenylephrine to restore baseline pressure, (iii) 20% pressure decrease with sodium nitroprusside (SNP) under baseline flow, and (iv) increased flow with baseline pressure. The effect of these changes was evaluated on cerebral ($Sc_{O_2}$) and systemic ($Sv_{O_2}$) oxygen saturation, and on systemic oxygen extraction ratio (OER). Data were assessed by within- and between-group comparisons.

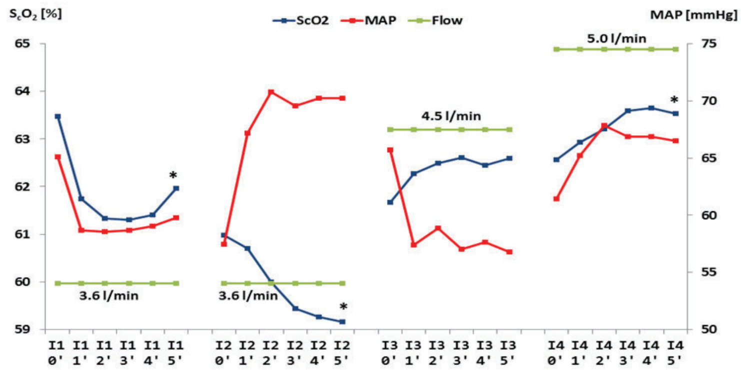
**Results.** Decrease in flow was associated with a decrease in $Sc_{O_2}$ [from 63.5 (7.4) to 62.0 (8.5) %, $P<0.001$]. When arterial pressure was restored with phenylephrine during low flow, $Sc_{O_2}$ further decreased from 61.0 (9.7) to 59.2 (10.2) %, $P<0.001$. Increase in flow was associated with an increase in $Sc_{O_2}$ from 62.6 (7.7) to 63.6 (8.9) %, $P=0.03$, while decreases in pressure with the use of SNP did not affect $Sc_{O_2}$. $Sv_{O_2}$ was significantly lower ($P<0.001$) and OER was significantly higher ($P<0.001$) in the low flow arms.

**Conclusions.** In the present elective cardiac surgery population, $Sc_{O_2}$ and $Sv_{O_2}$ were significantly lower with lower flow, regardless of systemic arterial pressure. Moreover, phenylephrine administration was associated with a reduced cerebral and systemic oxygen saturation.

**Keywords:** cardiopulmonary bypass; oximetry; phenylephrine; spectroscopy, near-infrared

Accepted for publication: 28 March 2013

# Results

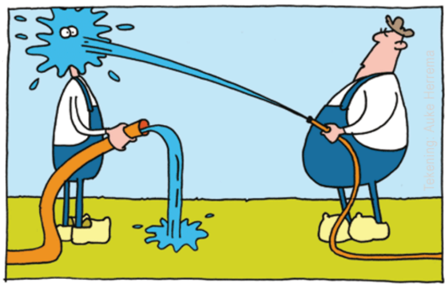



# Analysis

| $Q_{blood}$ L/min | $DO_{2i}$ mL/min/m² | $VO_{2i}$ mL/min/m² | $VO_{2i}/DO_{2i}$ |
|---|---|---|---|
| 3.6 BL -20% | 256 | 46 | 0.18 |
| 3.6 BL -20% + PE | 256 | 46 | 0.18 |
| 4.5 BL+NSP=> -20%P | 320 | 49 | 0.15 |
| 5.0 BL+20%=>MAP | 356 | 47 | 0.13 |

# Conclusion pressure vs flow

- Cerebral and venous oxygen saturations are more dependent on flow than on pressure
- Change in paradigm “pressure vs flow”



# Multivariate model

| Risk Factor | Points |
|---|---|
| Female gender | 1 |
| Congestive heart failure | 1 |
| Left ventricular ejection fraction <35% | 1 |
| Preoperative use of IABP | 2 |
| COPD | 1 |
| Insulin-requiring diabetes | 1 |
| Previous cardiac surgery | 1 |
| Emergency surgery | 2 |
| Valve surgery only (reference to CABG) | 1 |
| CABG + valve (reference to CABG) | 2 |
| Other cardiac surgeries | 2 |
| Preoperative creatinine 1.2 to <2.1 mg/dl (reference to 1.2) | 2 |
| Preoperative creatinine ≥2.1 (reference to 1.2) | 5 |

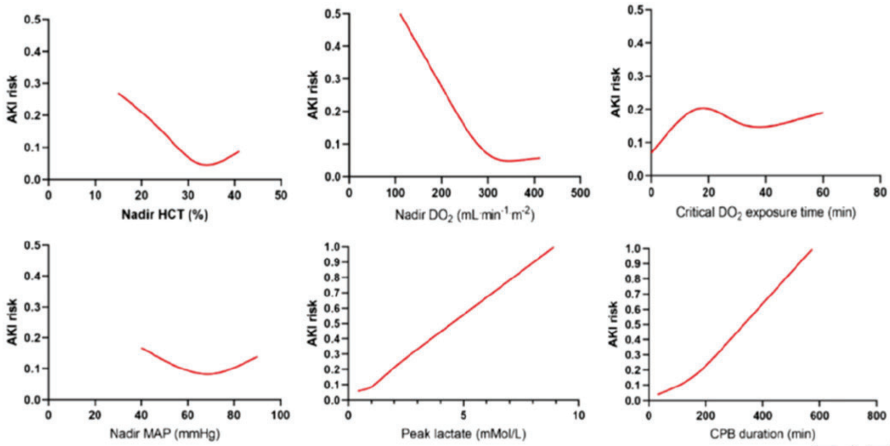
| Item | Regression coefficient | Odds ratio |
|---|---|---|
| Nadir hematocrit risk | 0.578 | 1.78 |
| Nadir oxygen delivery risk | 3.797 | 44.6 |
| Time of exposure to critical oxygen delivery risk | −0.284 | 0.75 |
| Cardiopulmonary bypass duration risk | 4.552 | 94.8 |
| Nadir mean arterial pressure risk | 0.498 | 1.65 |
| Peak lactates risk | 4.197 | 66.5 |
| Red blood cell transfusion risk | 3.652 | 38.5 |
| Constant | −4.112 | — |

$$\frac{\exp(-1.079 + 0.079{*}CRS + 0.035{*}Age - 0.095{*}HCT)}{(1 + \exp[-1.079 + 0.079{*}CRS + 0.035{*}Age - 0.095{*}HCT])}$$

$$\text{MDPI CSA} - \text{AKI risk} = \frac{\exp(-3.35 + 4.17{*}SRM + 5.37{*}DPR)}{1 + \exp[-3.3 + 4.17{*}SRM + 5.37{*}DPR]}$$

Ranucci 2022

# Multivariate model




Ranucci 2022

# Conclusions

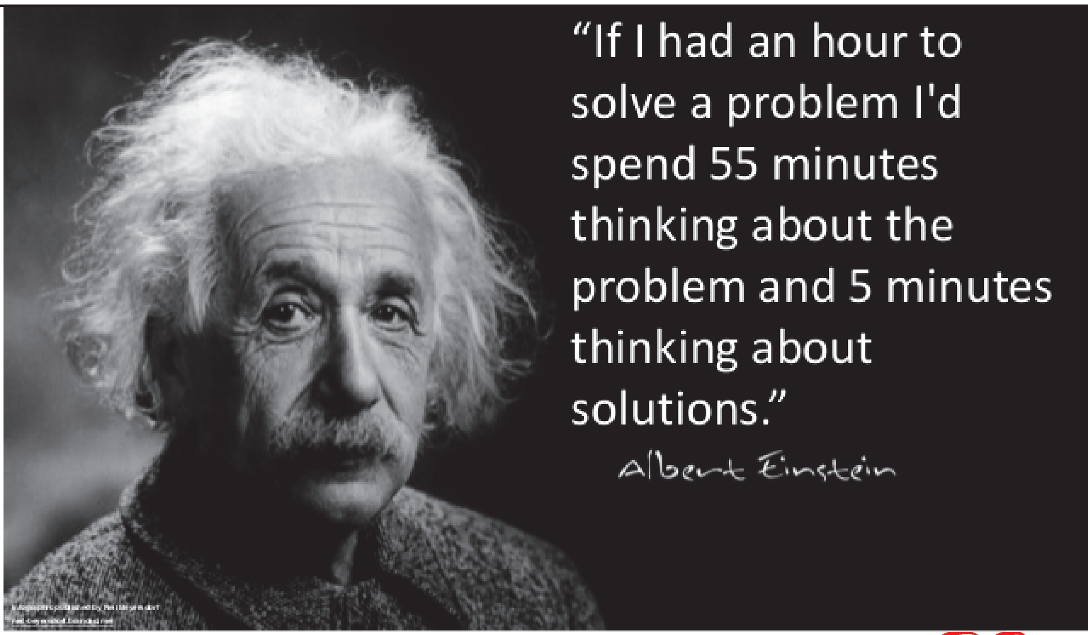
- GDP should be based upon oxygen delivery and CO2 production
- Increased RQ is indicative for a disturbed microcirculation
- MAP should stay in the autologous regulation
- Flow is more important than pressure

## Conclusions

- GDP reduces postoperative morbidity
- GDP is a multivariate online analysis of risk
- More variables are needed

## Goal Directed Perfusion

Wants to preserve organ function
by influencing host response
but this asks for
continuous markers

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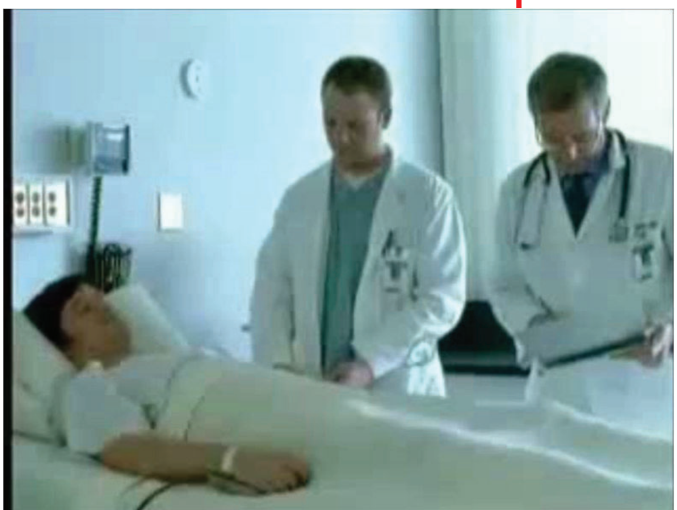
# Correct communication helps!



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