Tissue red blood cell perfusion (tRBCp)
the new target parameter for microcirculatory guided resuscitation.

Can Ince

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Laboratory of Translational Intensive Care

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Declared interests

I have the following financial relationships to disclose:

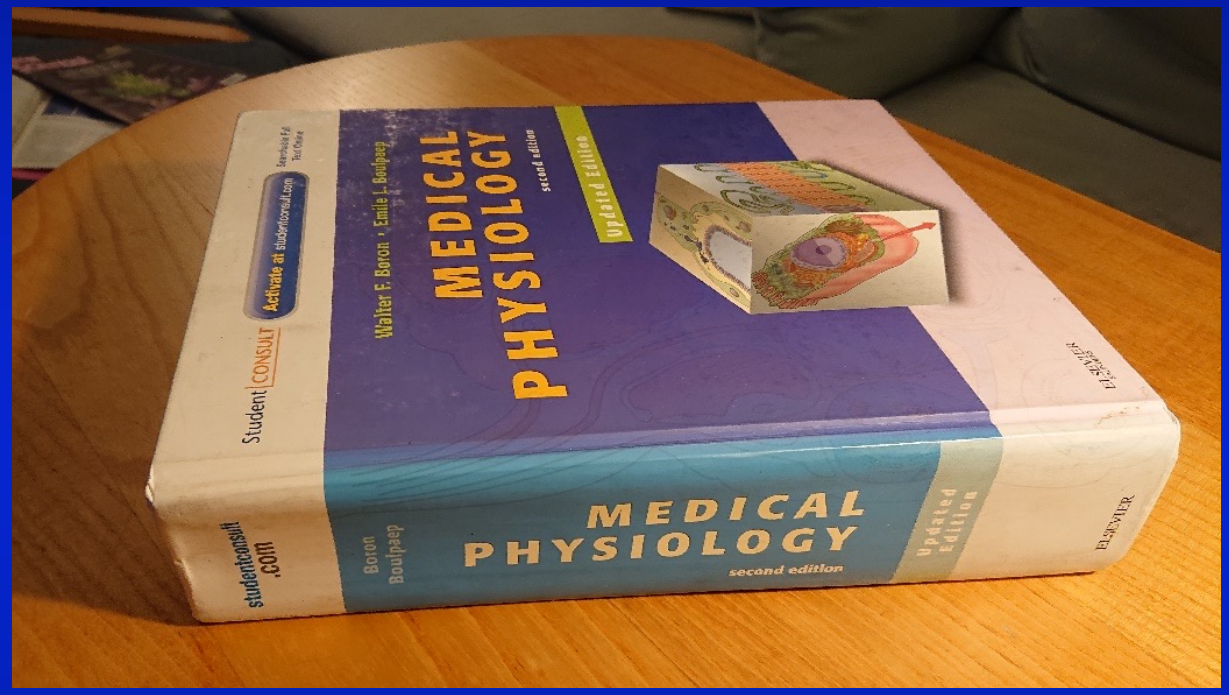
I am Chief Scientific Officer & Stockholder in: Active Medical BV (Oxycam device & MicroTools software for clinical microcirculation)

I have received educational grants and speakers fees for Cytosorbents

active_medical
unlocking the microcirculation

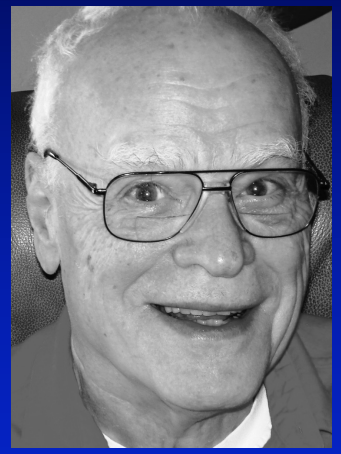
oxycam AI
ACTIVE MEDICAL

I am a physiologist!



"Physiology is the study of the dynamics of life"

Walter Boron



W Shoemaker

Role of Oxygen Debt in the Development of Organ Failure Sepsis, and Death in High-Risk Surgical Patients*

William C. Shoemaker, M.D.; Paul L. Appel, M.P.A
Harry B. Kram, M.D.

A Blalock

In 1922, Blalock defined shock as a failure of tissue perfusion and in experimental shock demonstrated

The data demonstrate a strong relationship between the magnitude and duration of the $\dot{V}O_2$ deficit in the intraoperative and early postoperative period and the subsequent appearance of organ failure and death.

Defecit = an excess of expenditure or liabilities over income or assets in a given period

(Chest 1992; 102:208-15)

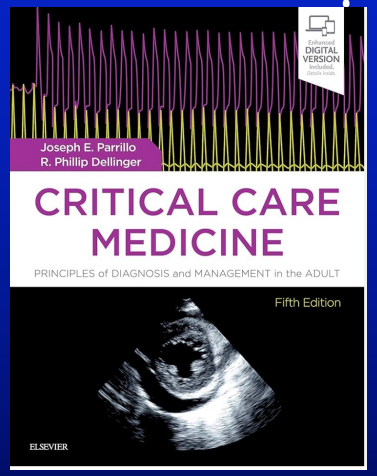
Kumar and Parrillo defined shock as the

‘‘state in which profound and widespread reduction of

effective tissue perfusion

leads first to reversible, and then if prolonged,
to irreversible cellular injury”

”

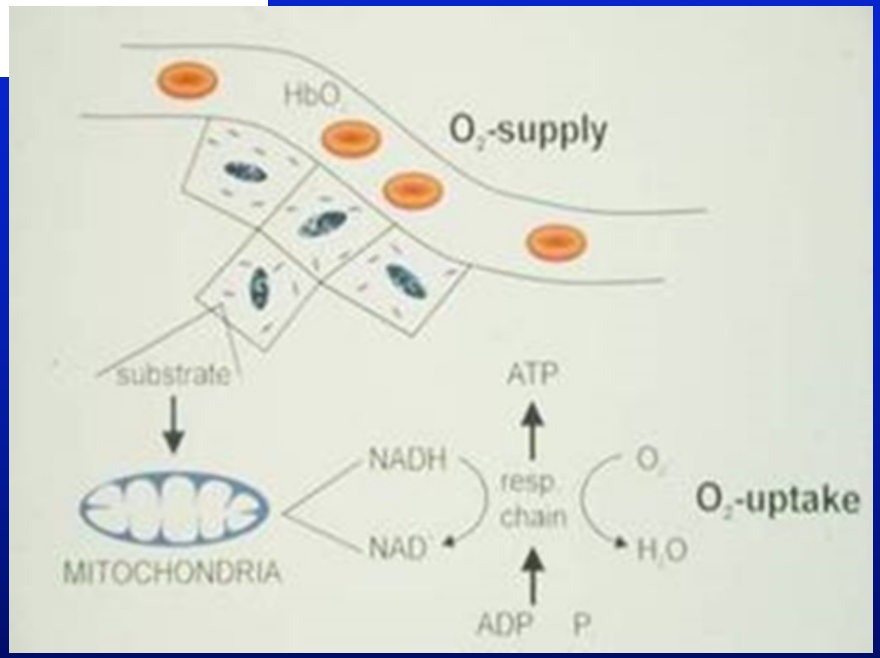


Kumar A, Parrillo JE. Shock: pathophysiology, classification and approach to management. In: Parrillo JE, Dellinger RP, editors. Critical care medicine: principles of diagnosis and management in the adult. St. Louis (MO): Mosby Publications; 2001. p. 371–420

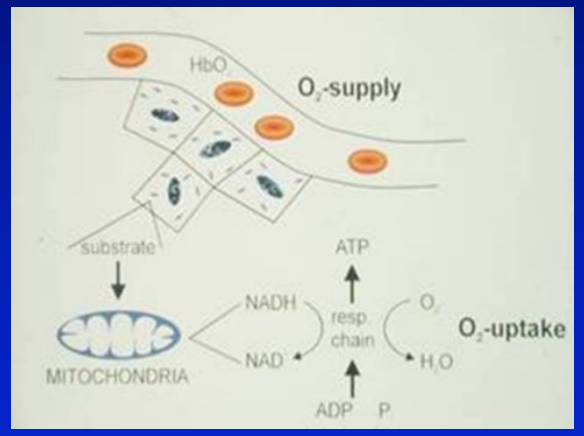
Maurizio Cecconi
Daniel De Backer
Massimo Antonelli
Richard Beale
Jan Bakker
Christoph Hofer
Roman Jaeschke
Alexandre Mebazaa
Michael R. Pinsky
Jean Louis Teboul
Jean Louis Vincent
Andrew Rhodes

Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine

Shock is a state in which the circulation is unable to deliver sufficient oxygen to meet the demands of the tissues, resulting in cellular dysfunction.



Intensive Care Med (2014) 40:1795–1815



Circulatory Shock

Jean-Louis Vincent, M.D., Ph.D., and Daniel De Backer,

FLUID RESUSCITATION

Fluid therapy to improve microvascular blood flow and increase cardiac output is an essential part of the treatment of any form of shock.

N Engl J Med 2013;369:1726-34.

CONFERENCE REPORTS AND EXPERT PANEL

Fluid administration for acute circulatory dysfunction using basic monitoring: narrative review and expert panel recommendations from an ESICM task force

Maurizio Cecconi[1,2*], Glenn Hernandez[3], Martin Dunser[4], Massimo Antonelli[5], Tim Baker[6,7], Jan Bakker
Jacques Duranteaum[12,13], Sharon Einav[14], A. B. Johan Groeneveld[15], Tim Harris[16,17], Sameer Jog[18],
Flavia R. Machado[19], Mervyn Mer[20], M. Ignacio Monge Garcia[21], Sheila Nainan Myatra[22], Anders Perner[23]
Jean-Louis Teboul[24,25], Jean-Louis Vincent[26] and Daniel De Backer[27]

Can arterial blood pressure help in the decision to start fluid resuscitation?

Can fluid-induced changes in arterial blood pressure during fluid administration help to assess the effects of fluid administration on cardiac output?

The physiological rationale when administering fluids in acute circulatory dysfunction is to **improve tissue perfusion.**

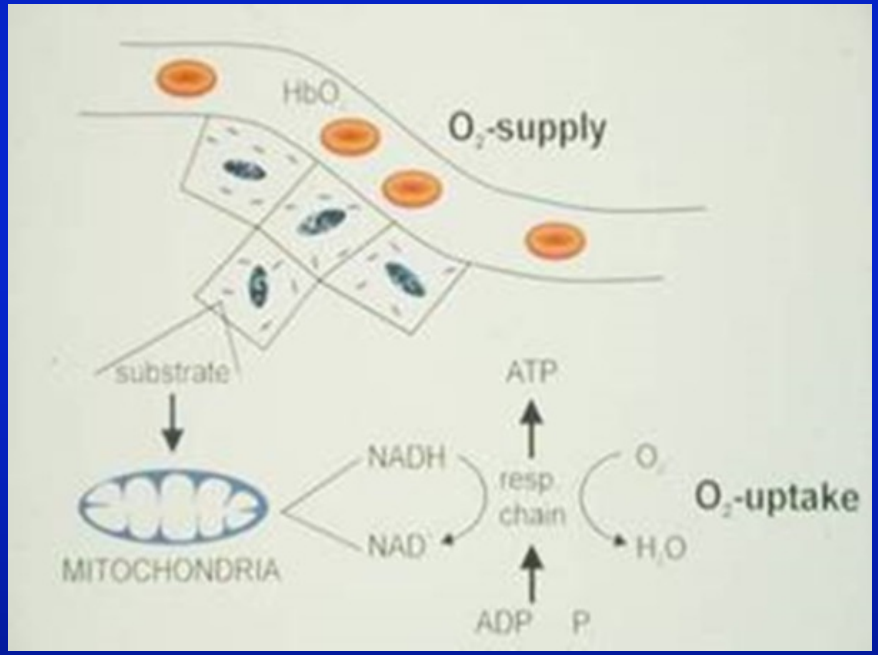
Does central venous pressure have a role in guiding fluid resuscitation?

Blood pressure-related triggers for fluid administration

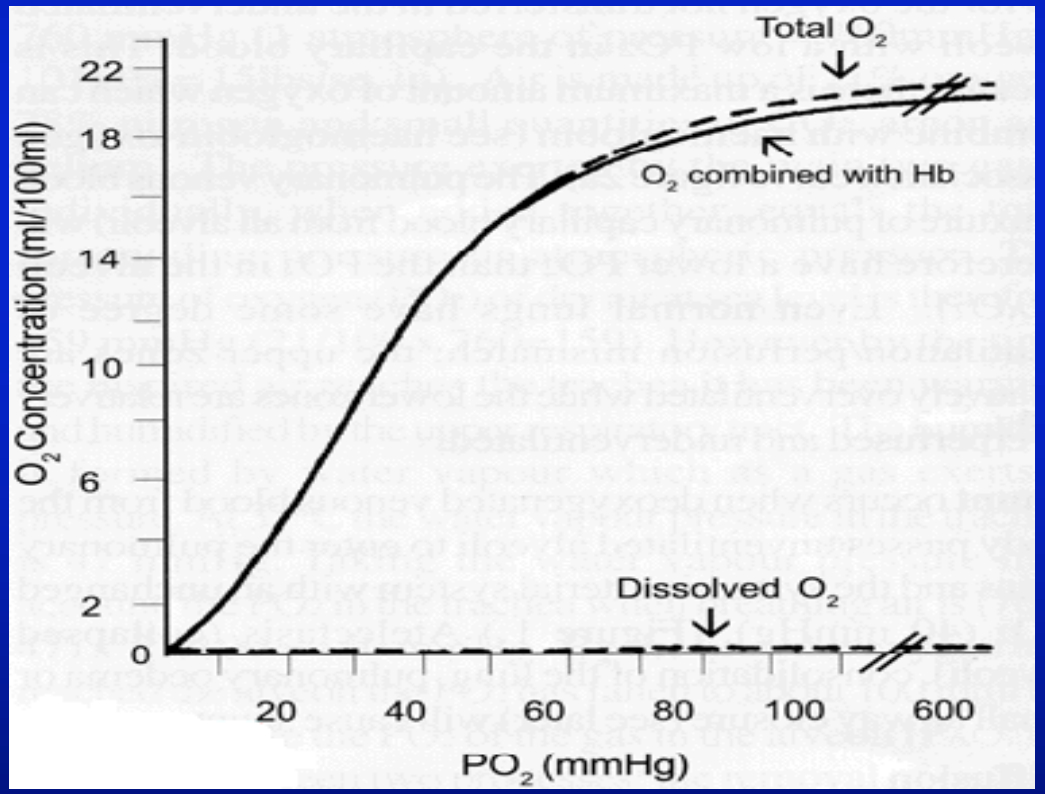
Jugular venous pressure (JVP)

Intensive Care Med
https://doi.org/10.1007/s00134-018-5415-2

What is tissue perfusion?



The main function of red blood cells is to transport oxygen to the tissue cells.



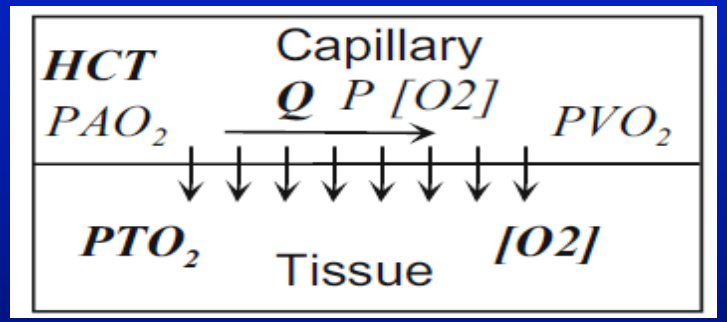
Of all oxygen in blood~97% is bound to Hb and ~3% bound to serum

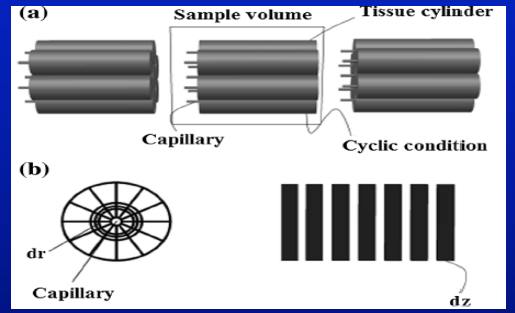
Blood Flow Versus Hematocrit in Optimization of Oxygen Transfer to Tissue During Fluid Resuscitation

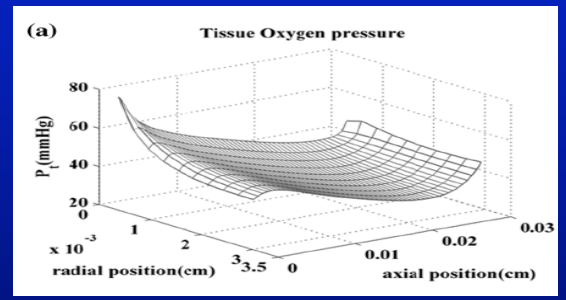
JAMAL SIAM,[1] MARWA KADAN,[1] RON FLAISHON,[2] and OFER BARNEA[1]

BMES BIOMEDICAL ENGINEERING SOCIETY

showed that oxygen content in blood is the dominant factor in oxygen transport to tissue and its effect is greater than the effect of flow. The integration of the capillary/tissue model with the hemodynamic model that links administered fluids with flow and blood dilution indicated that fluid resuscitation may reduce oxygen transport to tissue.



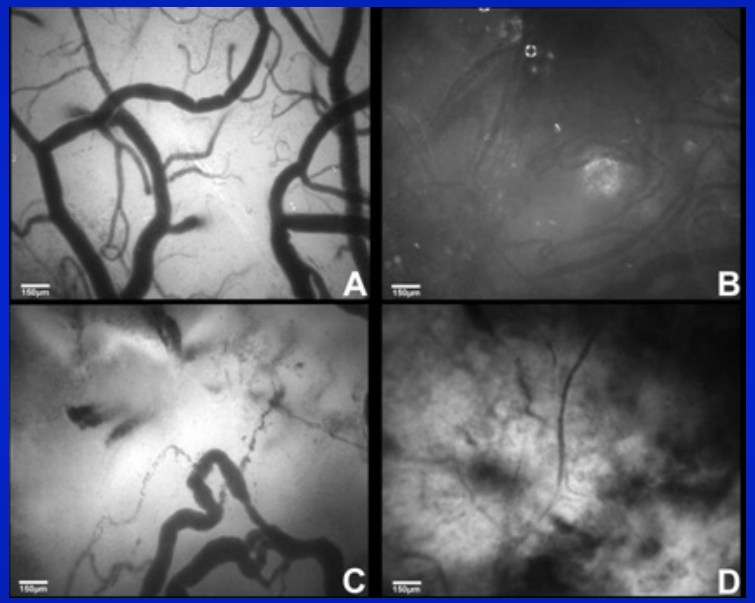


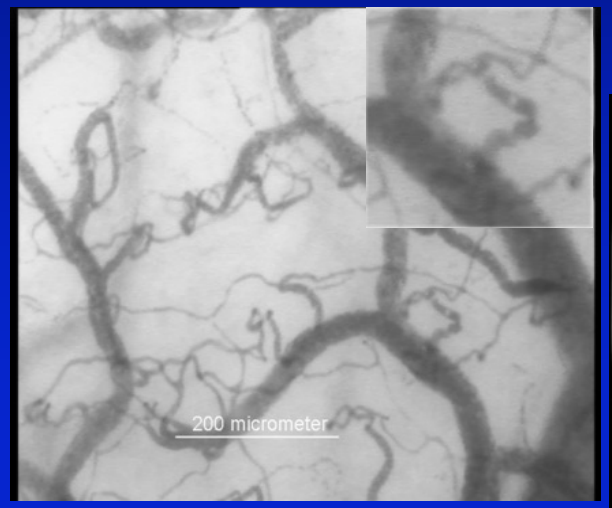


Cardiovascular Engineering and Technology, Vol. 6, No. 4, December 2015 (© 2015) pp. 474–484

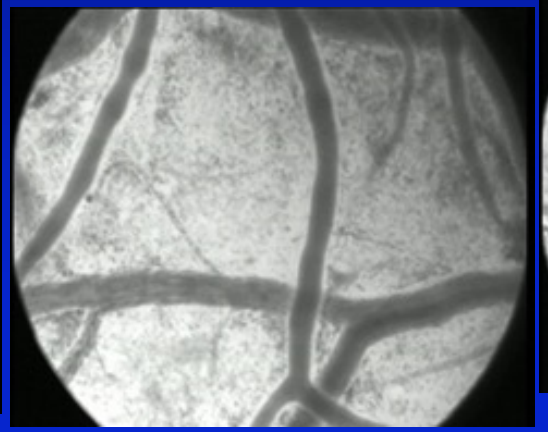
First direct visualizations of the microcirculation in human internal organs using OPS/SDF imaging.

Brain tumours

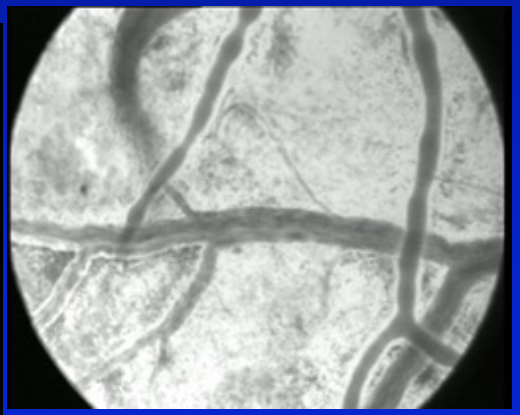




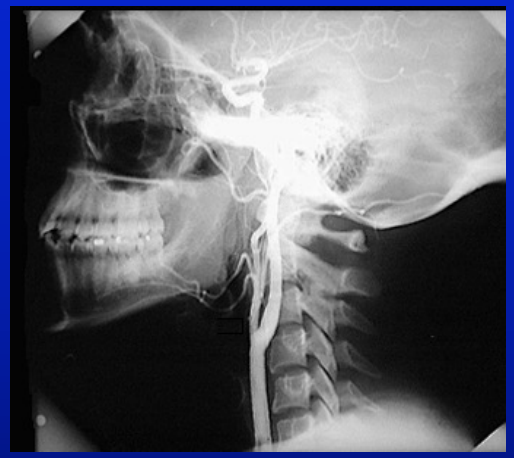
Subarachnoid hemh. cortex



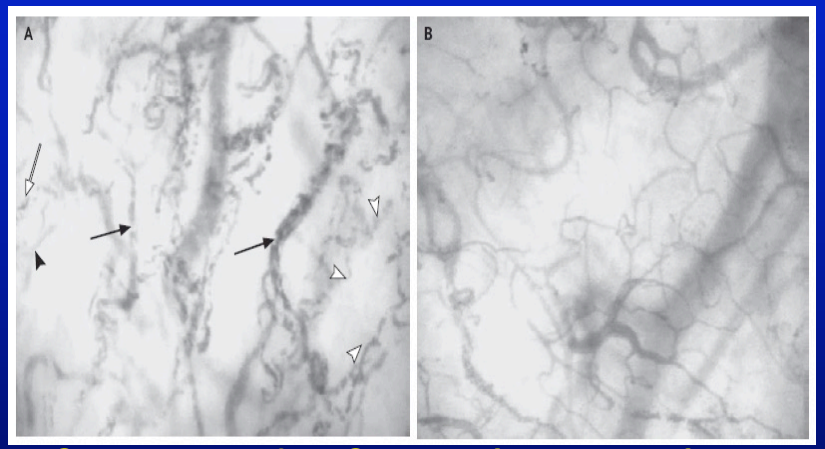
before HV



after HV



Leukemia



before and after chemotherapy

Groner et al. (1999) Nature Med 5:1209
Mathura et al. (2001) The Lancet 58:1698
Spronk et al. (2001) The Lancet 360:1395
Pennings et al. (2004) Stroke 35:1284
Meidema et al (2009) N Engl J Med 360:

Imaging the Microcirculation

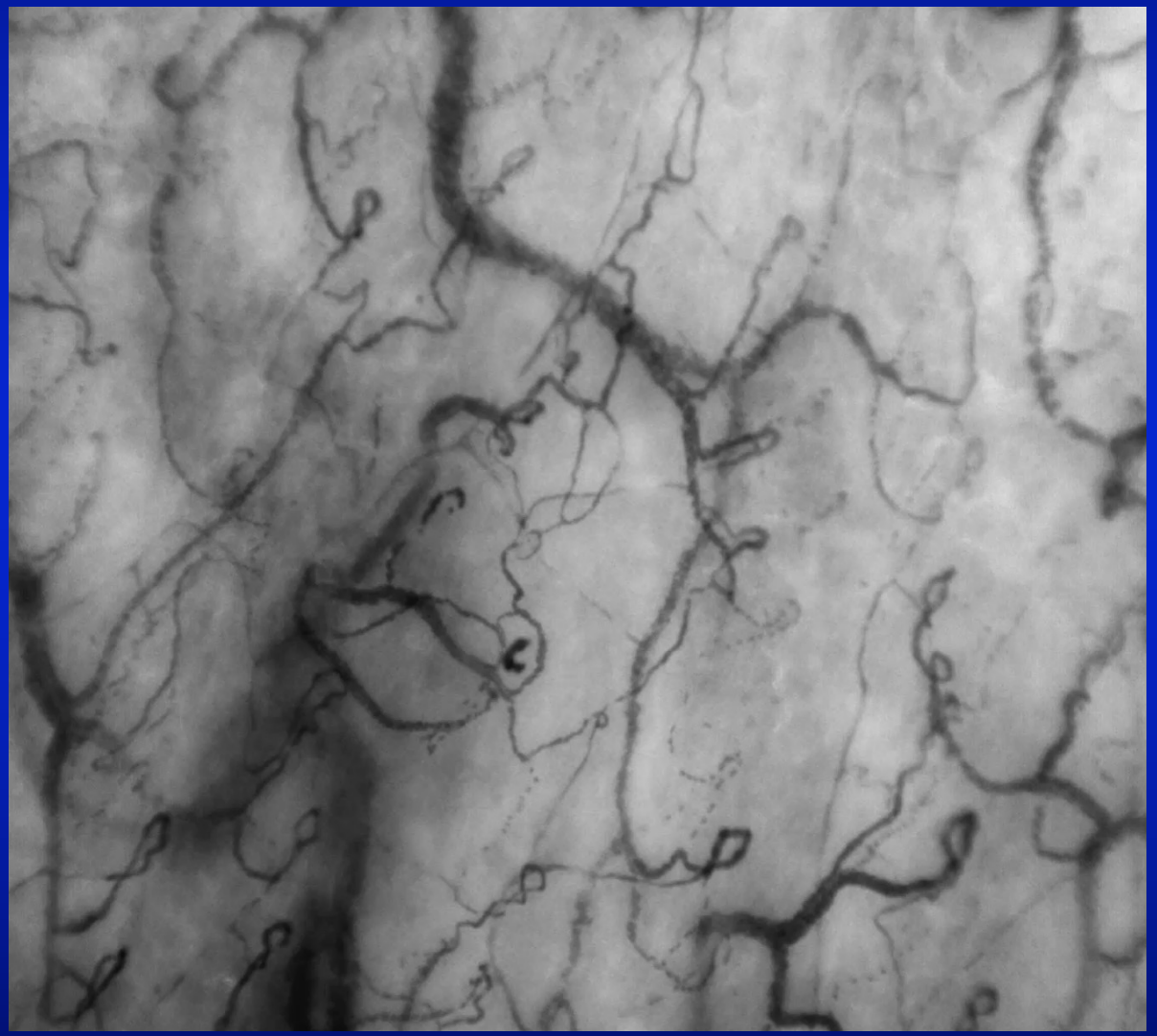
Physiology at the Bedside

CYTOMETRICS

Orthogonal Spectral (OPS) imaging

Braedius Medical

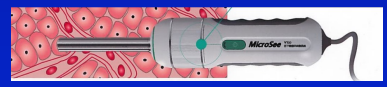
Incident dark field (IDF) imaging



MicroVision Medical

MicroSee 视微一看见微循环 组织灌注，一目了然

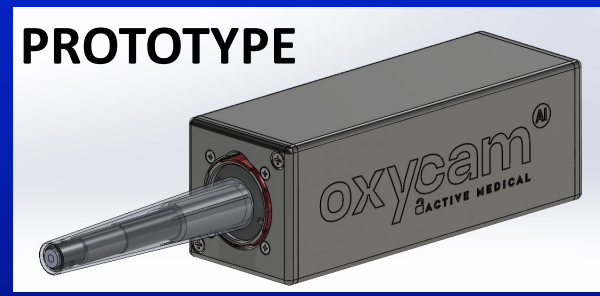
KK Technology



Sidestream dark field (SDF) imaging

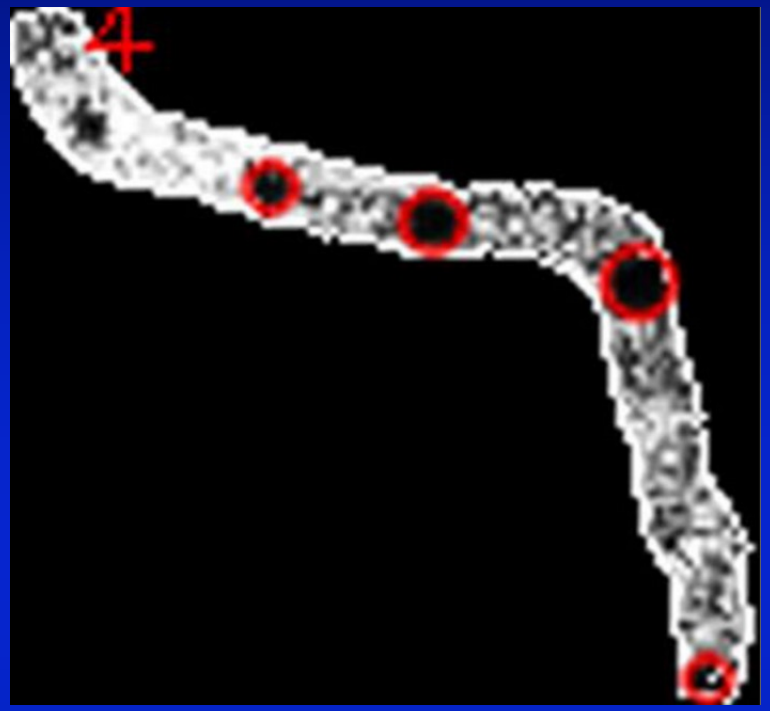
oxycam AI ACTIVE MEDICAL

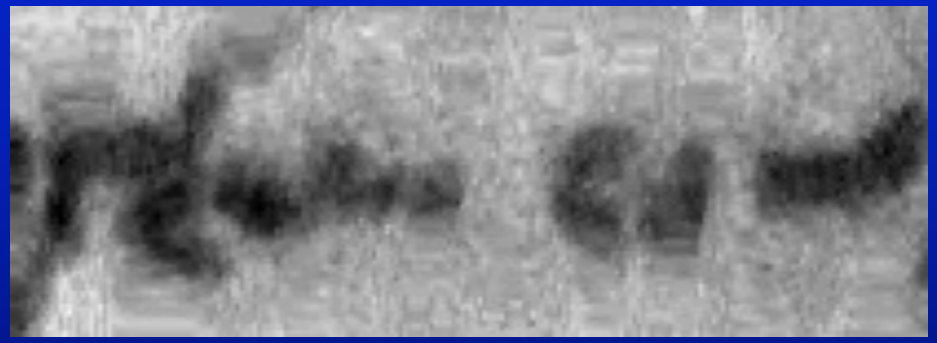
PROTOTYPE

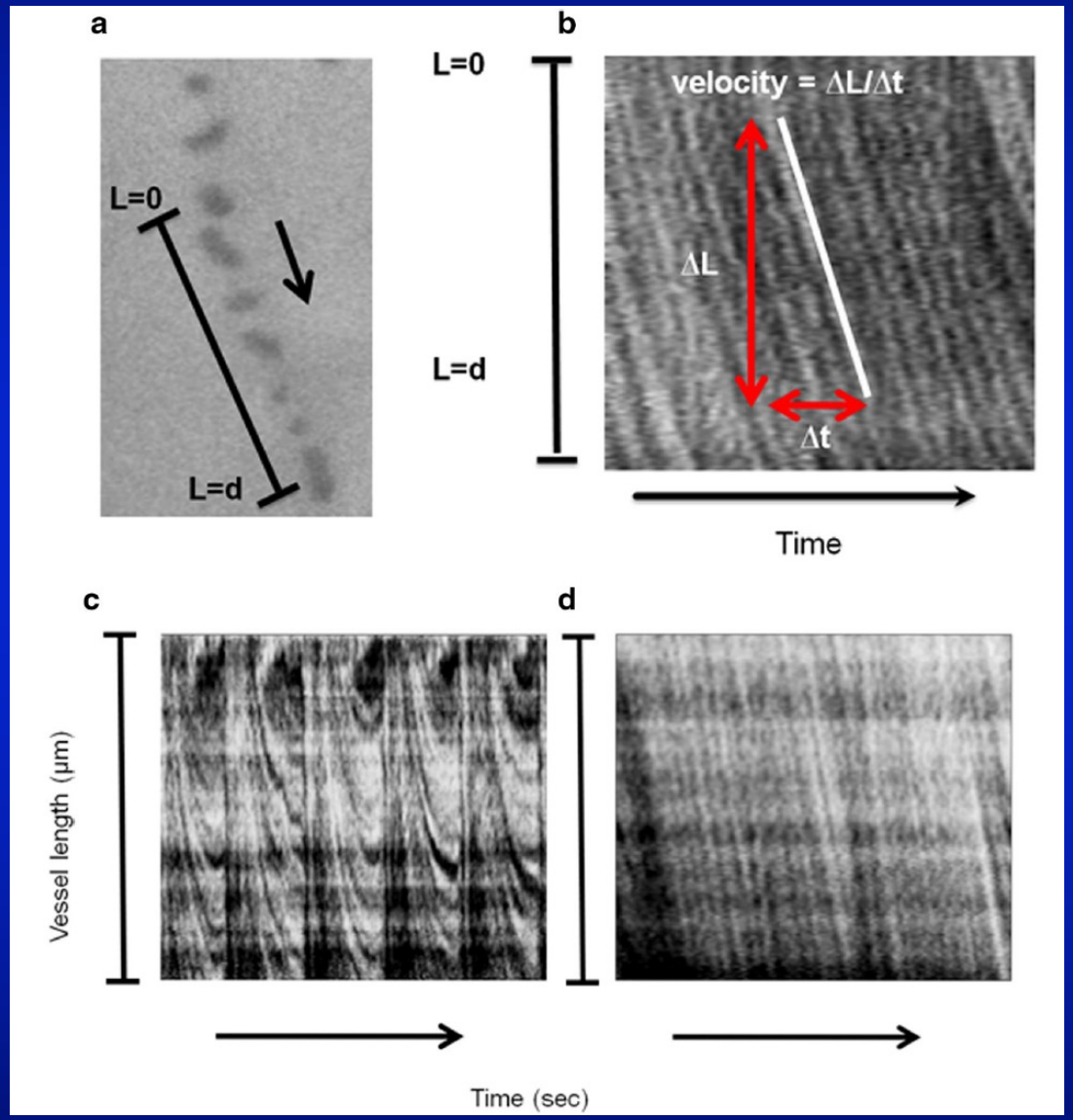


Incident dark field (IDF)
plus O2 saturation imaging

Space time diagrams allow quantitative measurement of red bloo



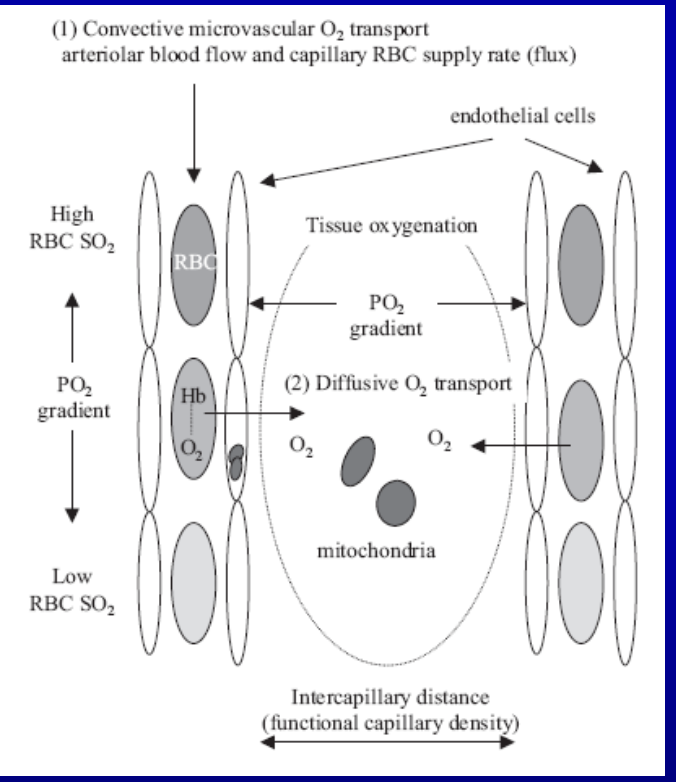




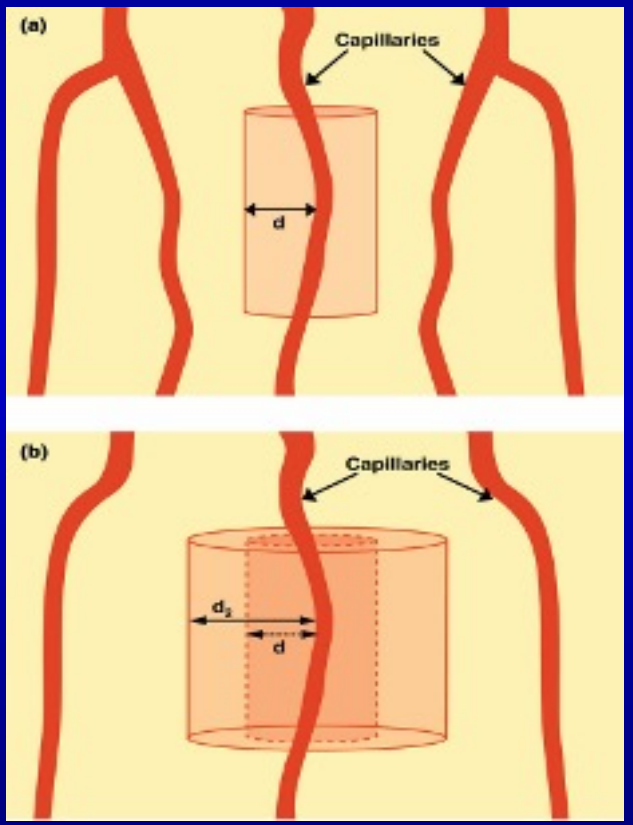
Critical Care 2018, **22(Suppl 1):**P278

Convection (flow) and Diffusion (functional capillary density) rate limit oxygen transport to the tissues.

$$VO_2 = \frac{D \times A\,(\,cappO_2 - mitpO_2)}{L}$$



VO_2	volume of transported O_2 by diffusion
D	diffusion constant
A	systemic capillary surface area
$cappO_2$	capillary pO_2
$mitpO_2$	mitochondrial pO_2
L	distance from RBC to mitochondria



heart failure normal diffusion low convection

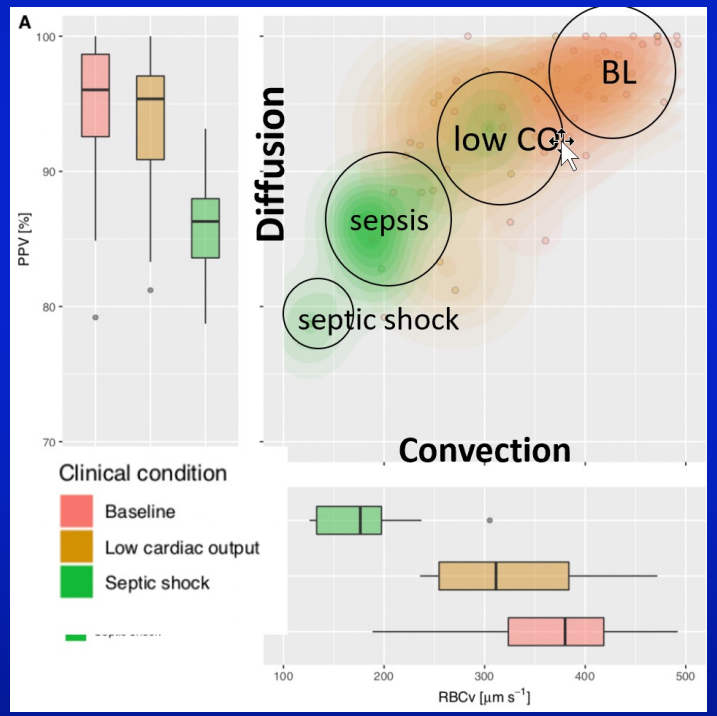
hemodilution large diffusion distance normal convection

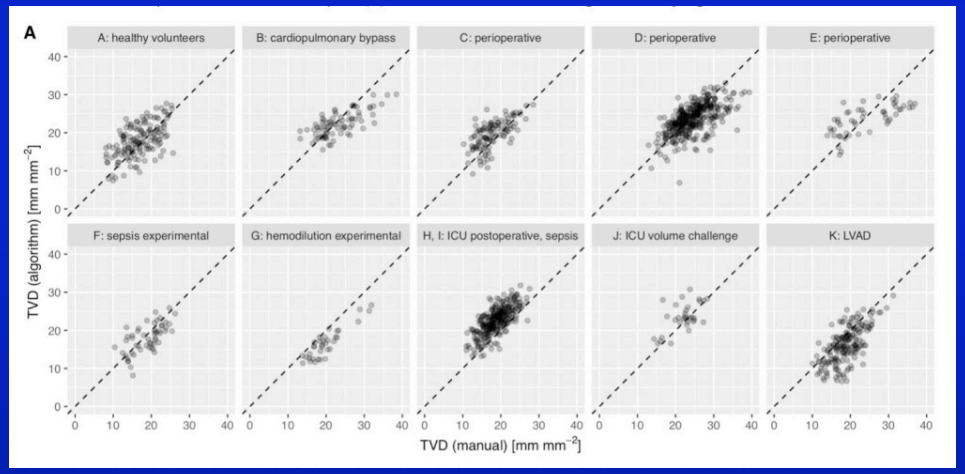
Automated Algorithm Analysis of Sublingual Microcirculation in an International Multicentral Database Identifies Alterations Associated With Disease and Mechanism of Resuscitation

Critical Care Medicine | 2020; 48:e864–e875

Matthias Peter Hilty, MD[1,2]; Sakir Akin, MD, PhD[1,3]; Christiaan Boerma, MD, PhD[4]; Abele Donati, MD, PhD[5]; Özge Erdem, MD[6]; Paolo Giaccaglia, MD[5]; Philippe Guerci, MD[1,7,8]; Dan MJ Milstein, PhD[9]; Jonathan Montomoli, MD, PhD[1,5]; Fevzi Toraman, MD[10]; Zuhre Uz, MD[11]; Gerke Veenstra, MD, PhD[4]; Can Ince, PhD[1]

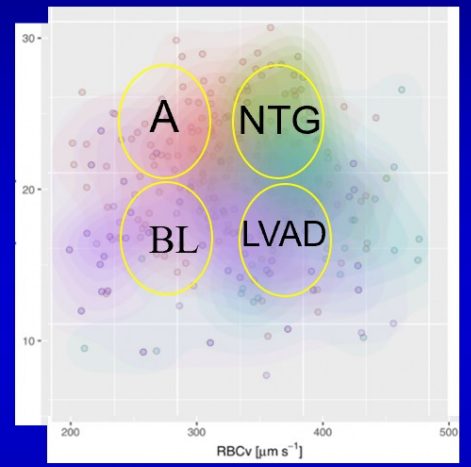
Differential diagnosis





267 adult and critically ill pediatric patients

Total vessel density (diffusion)



Red blood cell velocity (convection)

149,257 microscopy images were analyzed.

3.89×10^{12} RBC positions were tracked

Nature Research Communication & Biology 2019 Jun 19;2:217

Automated quantification of tissue red blood cell perfusion as a new resuscitation target

Matthias P. Hilty[a,b] *and Can Ince*[b]

- It is generally accepted that normalization of tissue perfusion is the ultimate endpoint for resuscitation of shock patients.

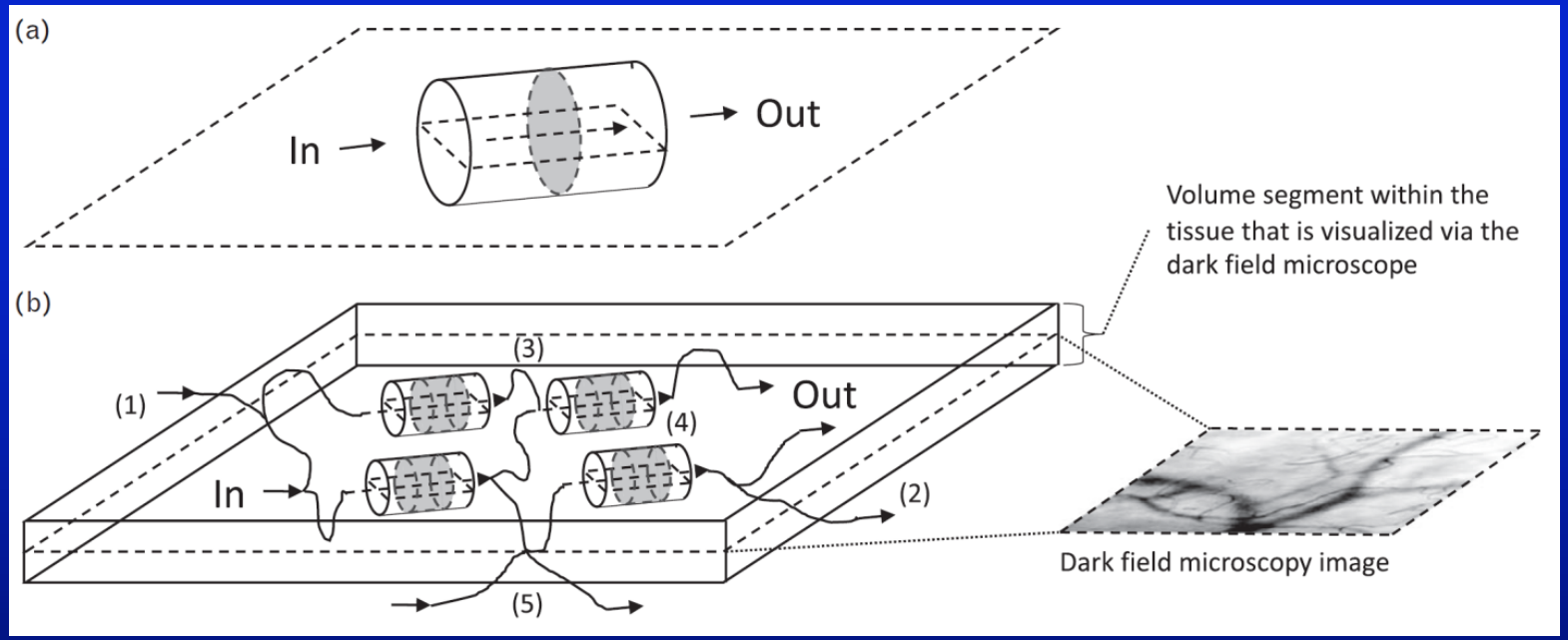
precise tissue perfusion parameter representing tissue RBC perfusion (*t*RBC*p*), combining the diffusive and convective component of tissue perfusion.

Curr Opin Crit Care 2020, 26:273–280

tissue RBC perfusion (tRBCp)

$$tRBCp = \frac{\sum_{i=0}^{n}(l_i \times \int s_i \; dt \times V_i \times c\mathrm{Hct})}{\sum_{i=0}^{n} l_i} \times (\mathrm{FOV} \times d)^{-1}$$

where s is the spatial displacement of blood within dt, l is the length of the vessel segment, V is the volume of the vessel segment, cHct is the capillary hematocrit, n the number of visualized vessel segments, and FOV is the field of view and d is the depth of the tissue volume visualized by the HVM image sequence.

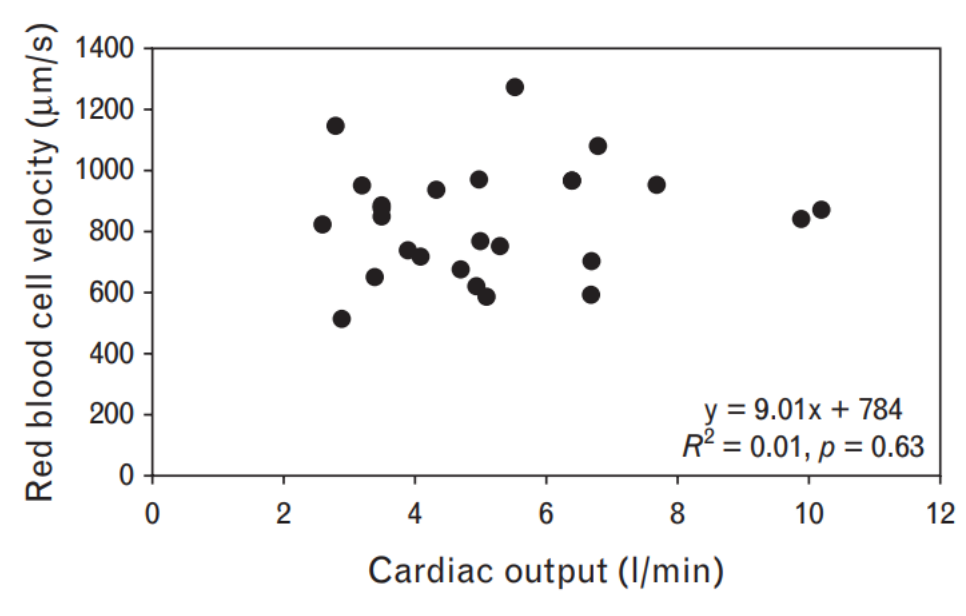


$1.546 \times 1.154 \times 0.050\,\mathrm{mm} = 0.089\,\mu\mathrm{l}$

three-dimensional catchment volume

What is microcirculatory shock?

Vanina S. Kanoore Edul[a,b], *Can Ince*[b], *and Arnaldo Dubin*[b,c]



Lack of correlation between cardiac output (CO) and red blood cell (RBC) velocity in patients with septic shock

KEY POINTS

- Microcirculatory shock is the failure of microcirculation to support tissue perfusion and oxygenation, despite a normal systemic hemodynamics.
- A severely disrupted microcirculation might coexist with a restored systemic hemodynamics.
- The adequacy of tissue sublingual perfusion does not guarantee a proper intestinal microcirculation.
- The basal state of the microcirculation might be useful to predict the response to fluids, vasopressors, and inotropes. The lower the microcirculatory blood flow, the better the response.

Curr Opin Crit Care 2015, 21:245–252

Hemodynamic coherence and the rationale for monitoring the microcirculation

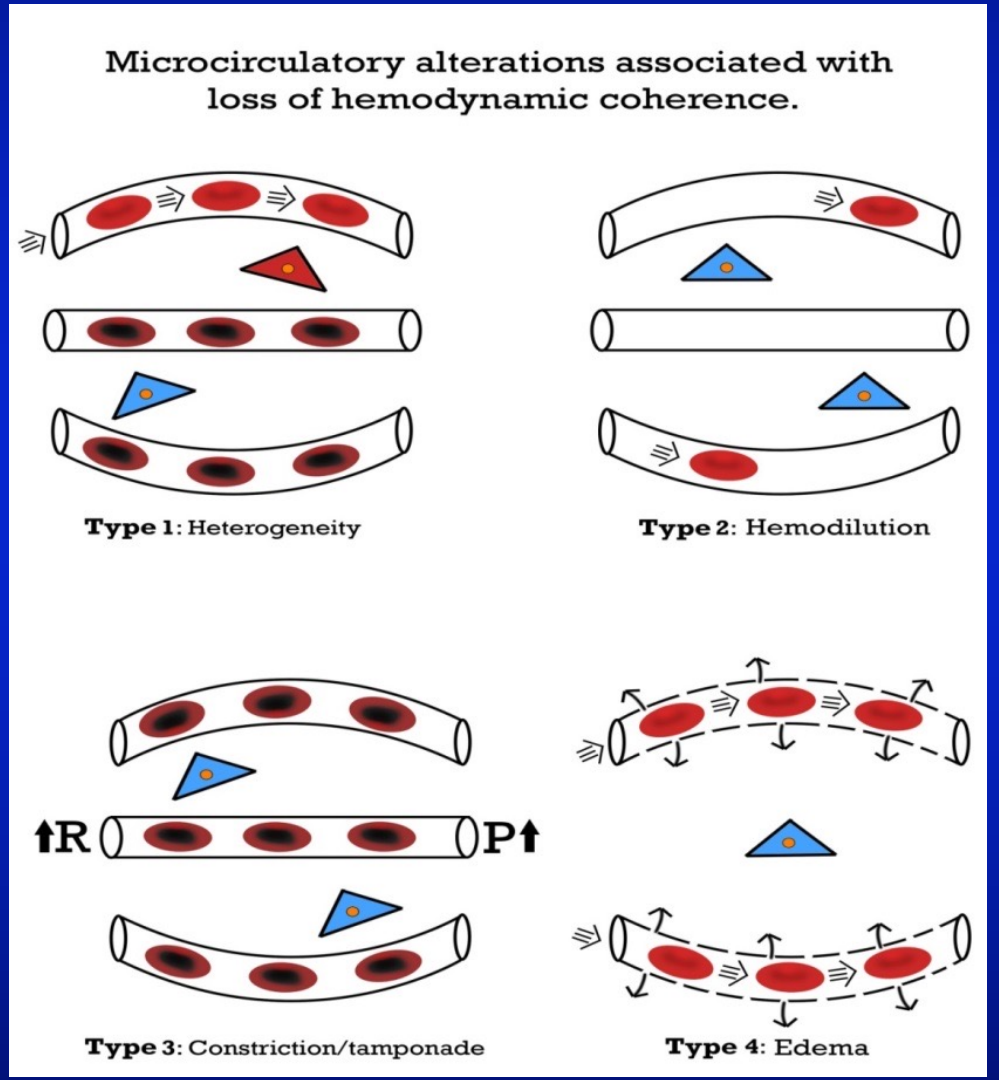
Can Ince

Hemodynamic Coherence is when

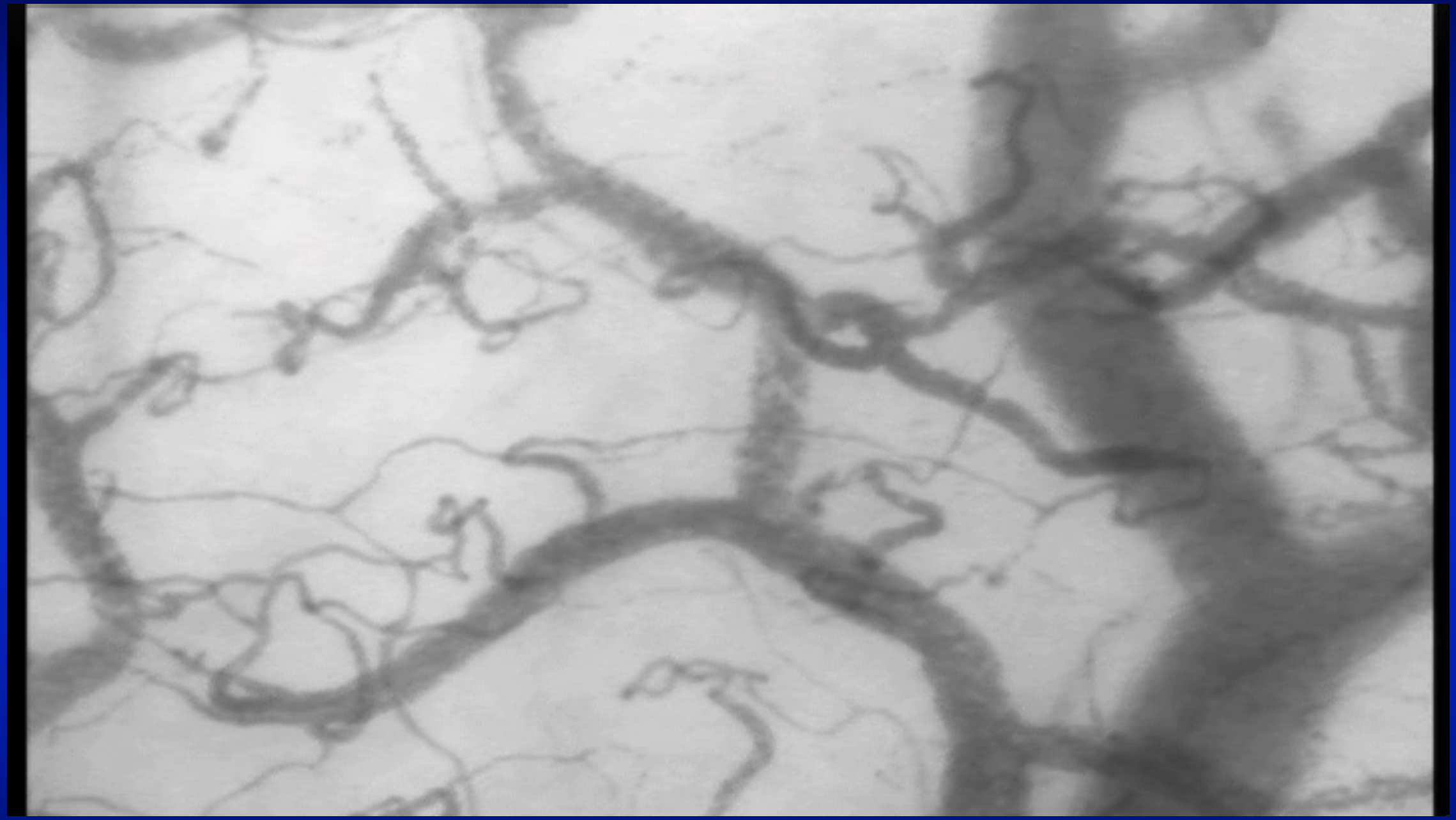
correction of the systemic hemodynamic
Results in a parallel improvement in the microcirculation.

Loss of Hemodynamic Coherence

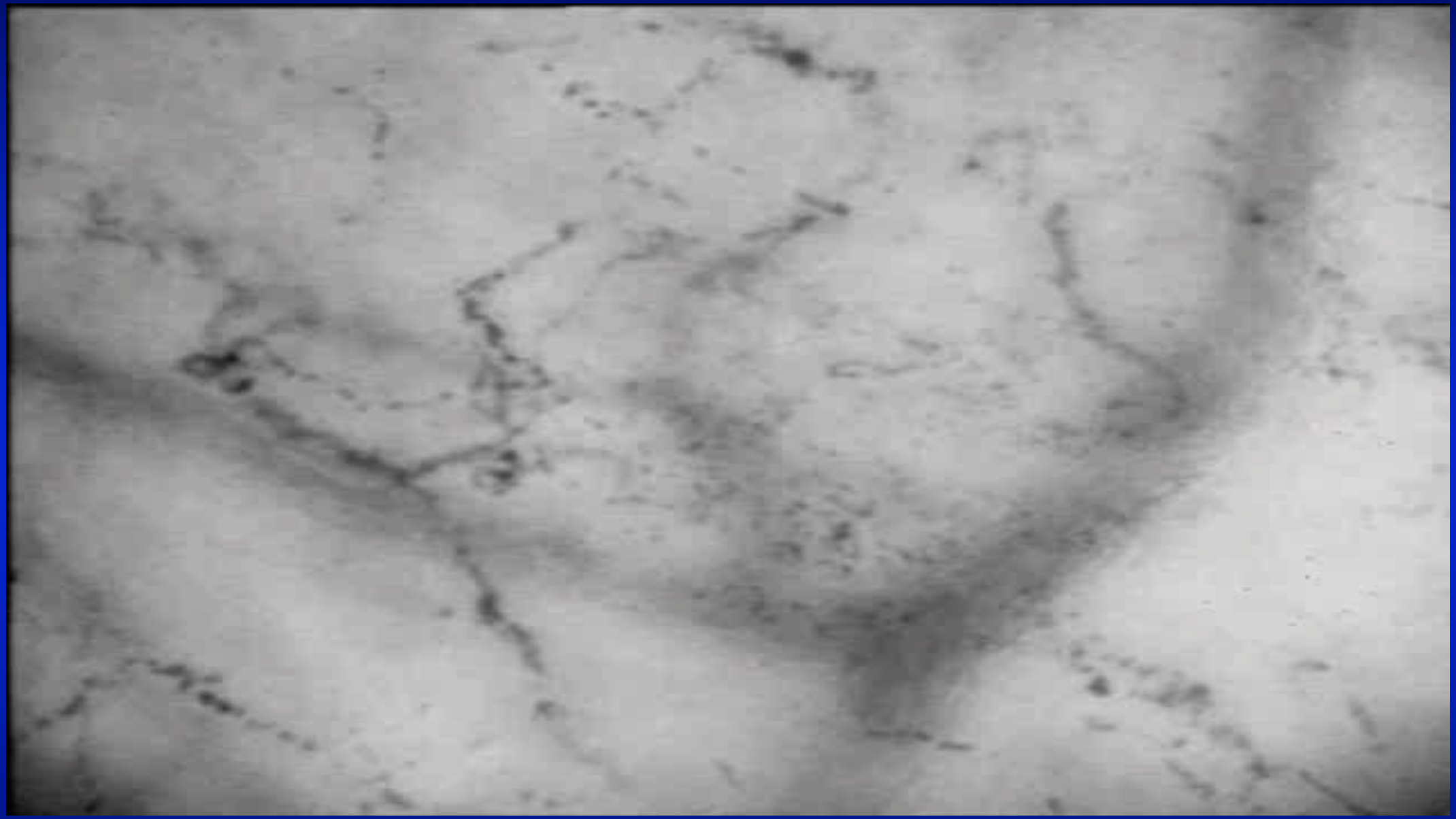
is when there is a disassociation of systemic Hemodynamics from the microcirculation



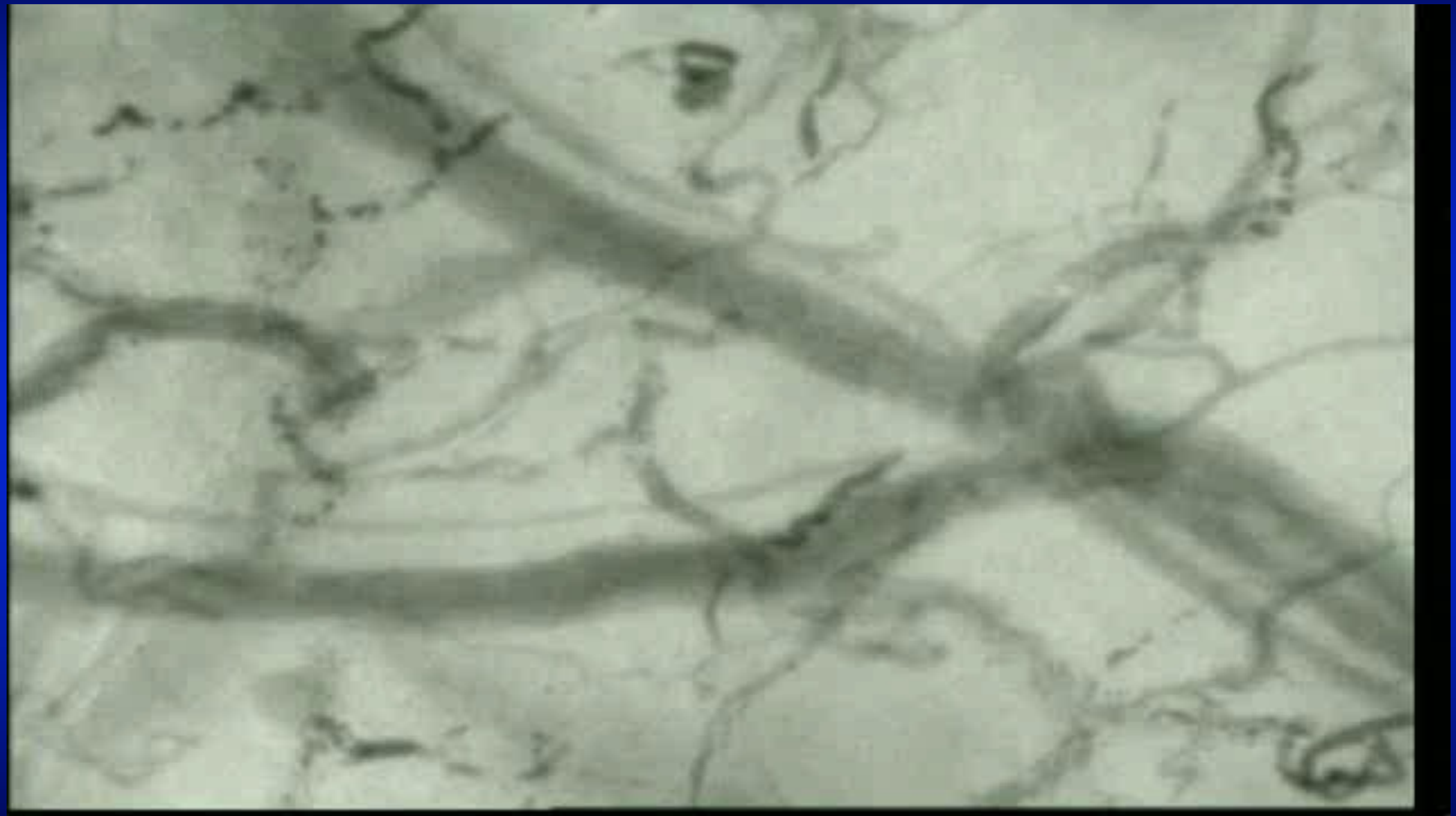
Critical Care (2015) 19:S8

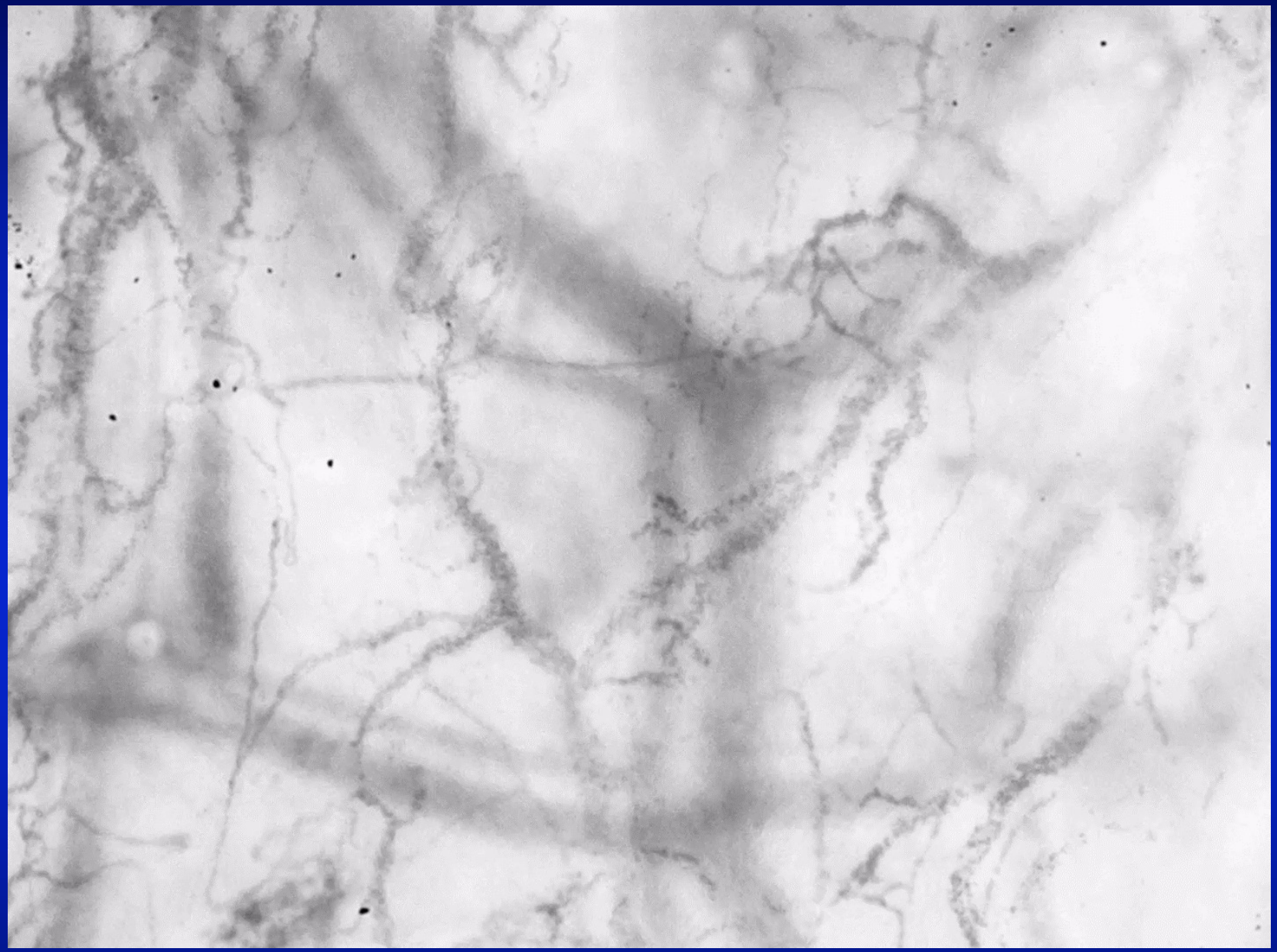


Health

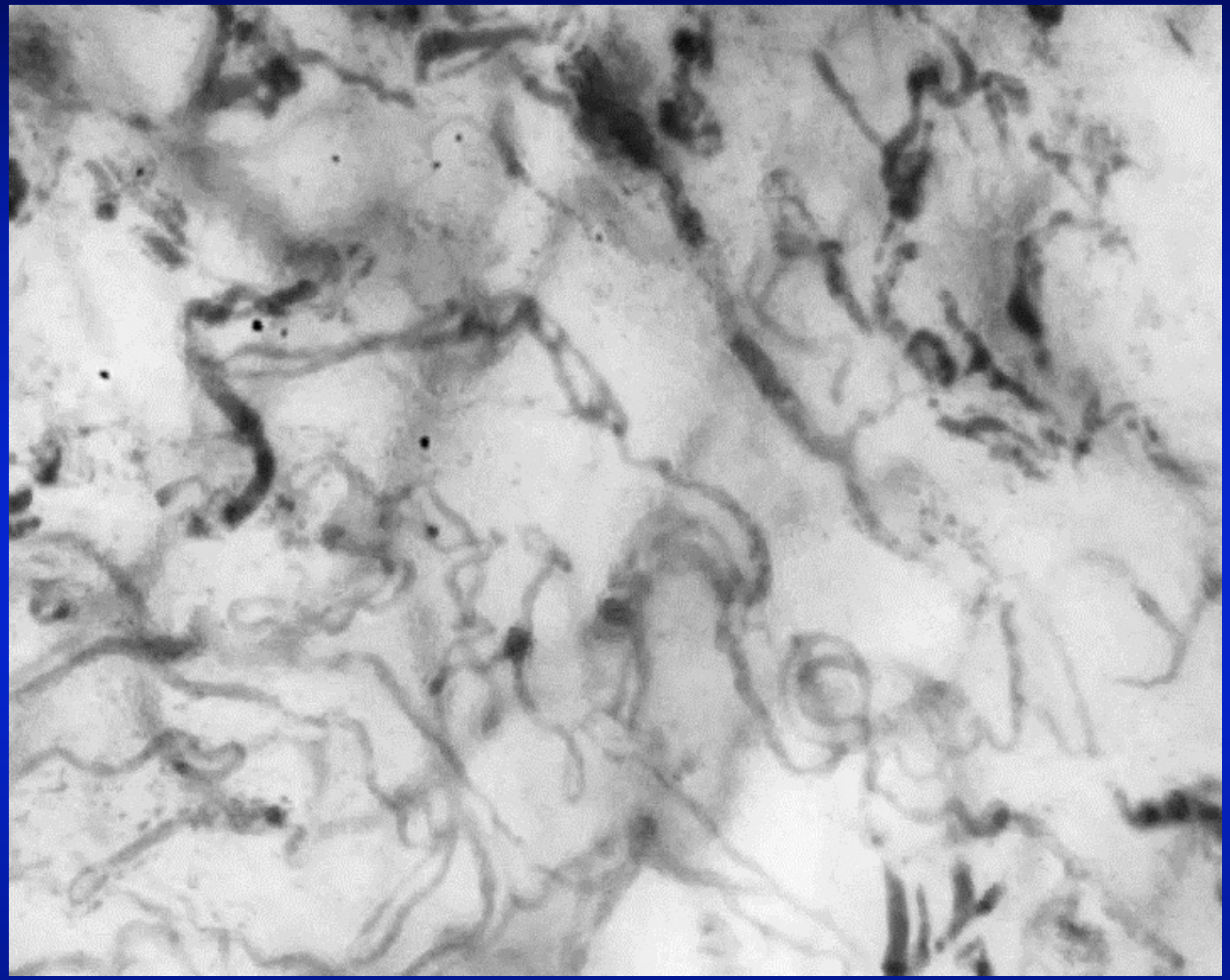


Sepsis





Vasoplegia following cardiac surgery

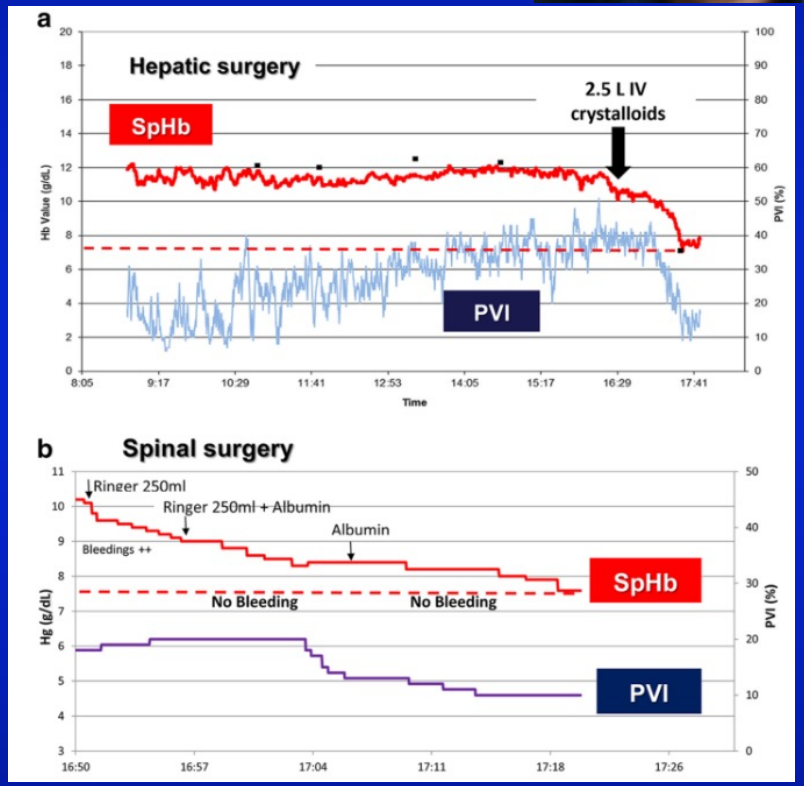


COVID 2

Iatrogenic hemodilution: a possible cause for avoidable blood transfusions?

Azriel Perel

The administration of large amounts of intravenous fluids may cause iatrogenic hemodilution and, at times, even a paradoxical decrease in DO2. The associated decrease in Hb values to below the acceptable transfusion threshold may lead to avoidable blood transfusions.



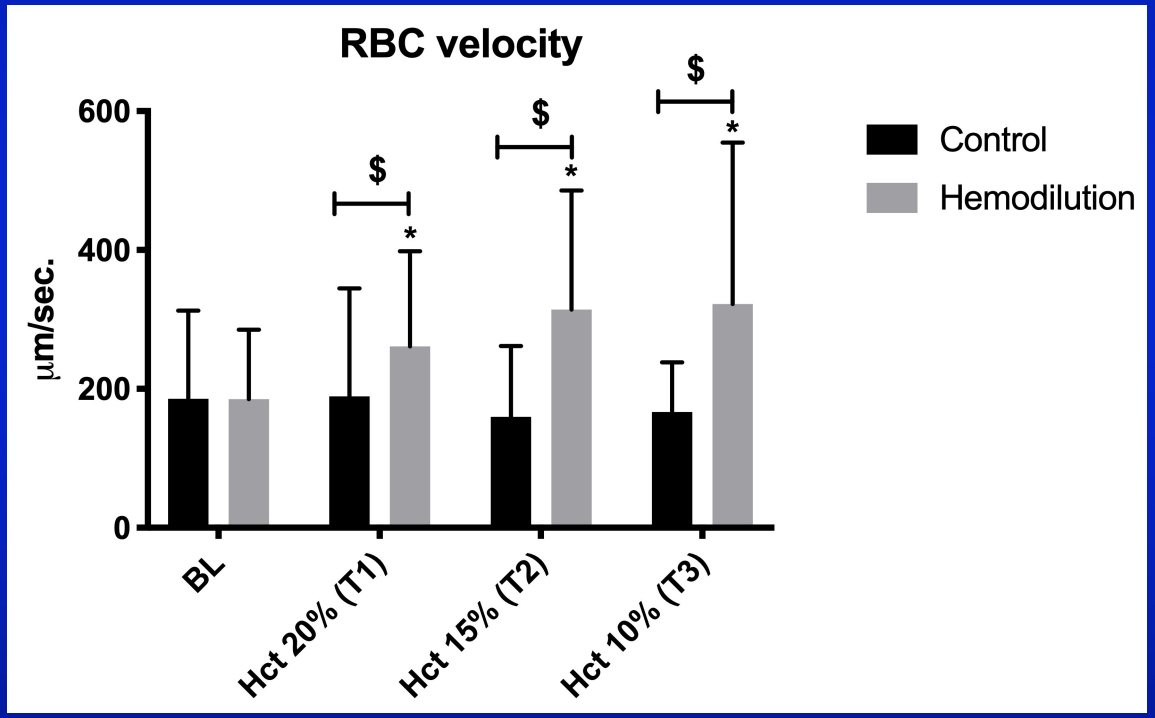
Continuous hemoglobin (SpHb) and Pleth Variability Index (PVI)

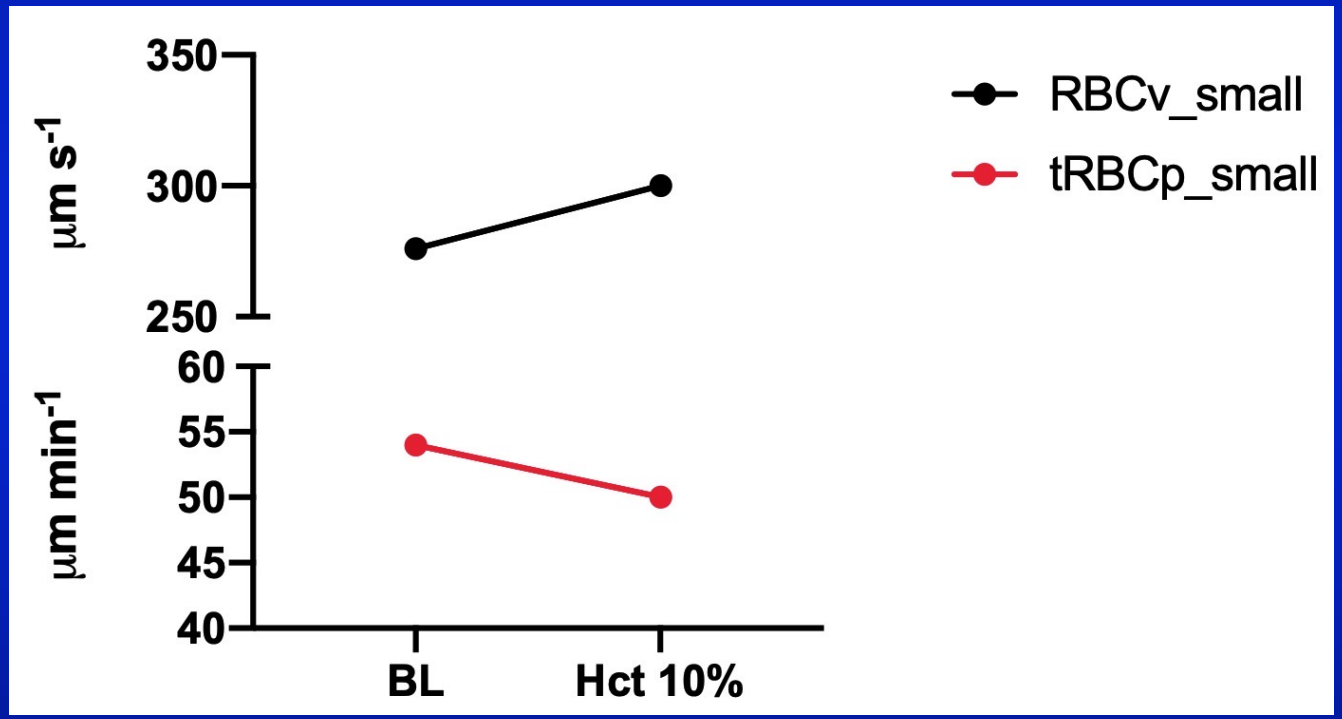
administration of 500 ml of fluids may acutely decrease the Hb concentration by about 1 g/dl, or about 8%

excessive values (close to 40%) signifies the development of hypovolemia

Critical Care (2017) 21:291

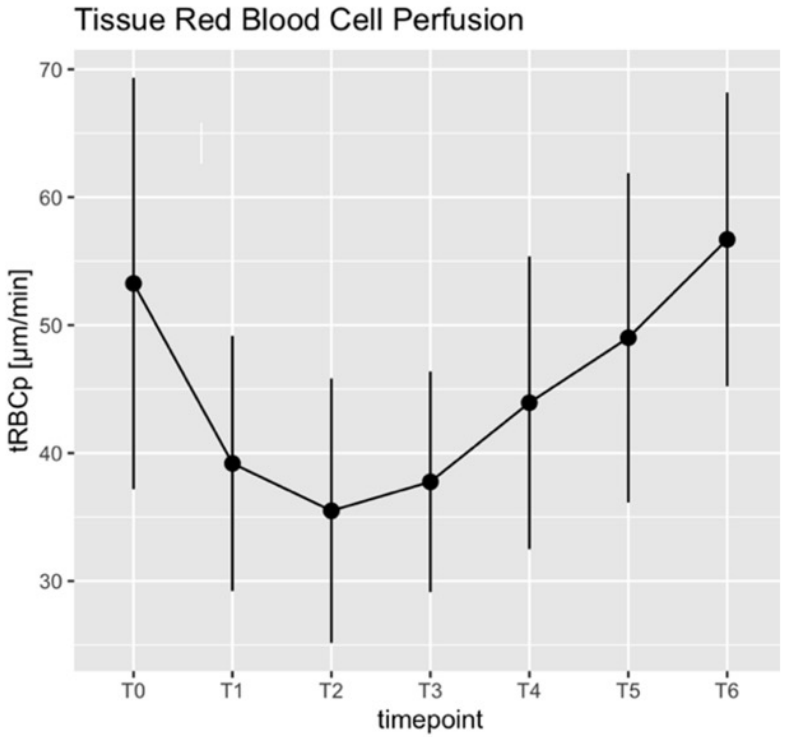
Hemodilution in pigs increases tissue RBC velocity at the expens tissue RBC perfusion (tRBCp) calculated using MicroTools.

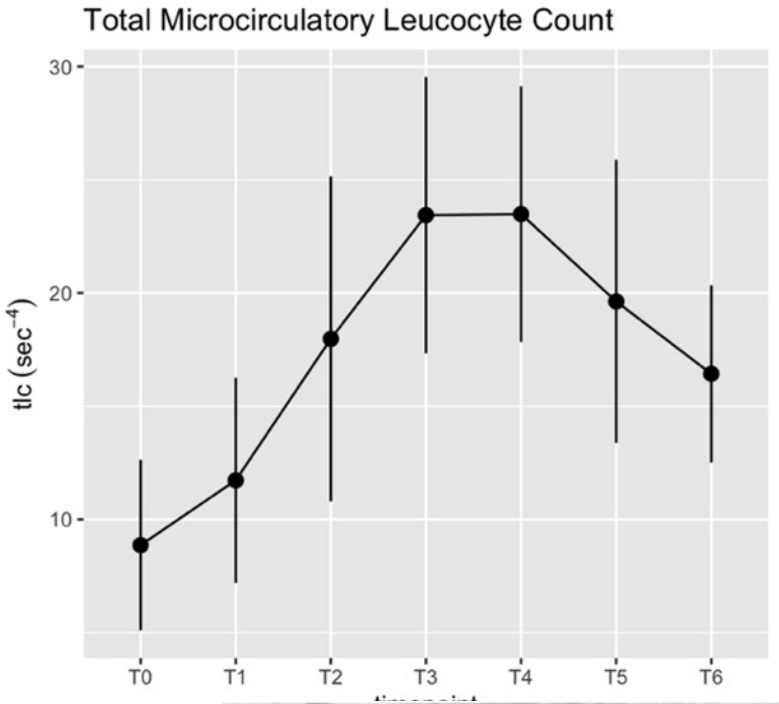




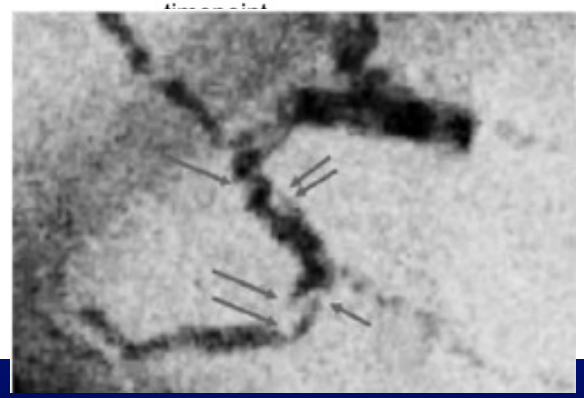
Microcirculatory response among patients undergoing elective cardiac surgery with cardiopulmonary-bypass.

Favaron E, Ince C, Montomoli J, van Boven WJ





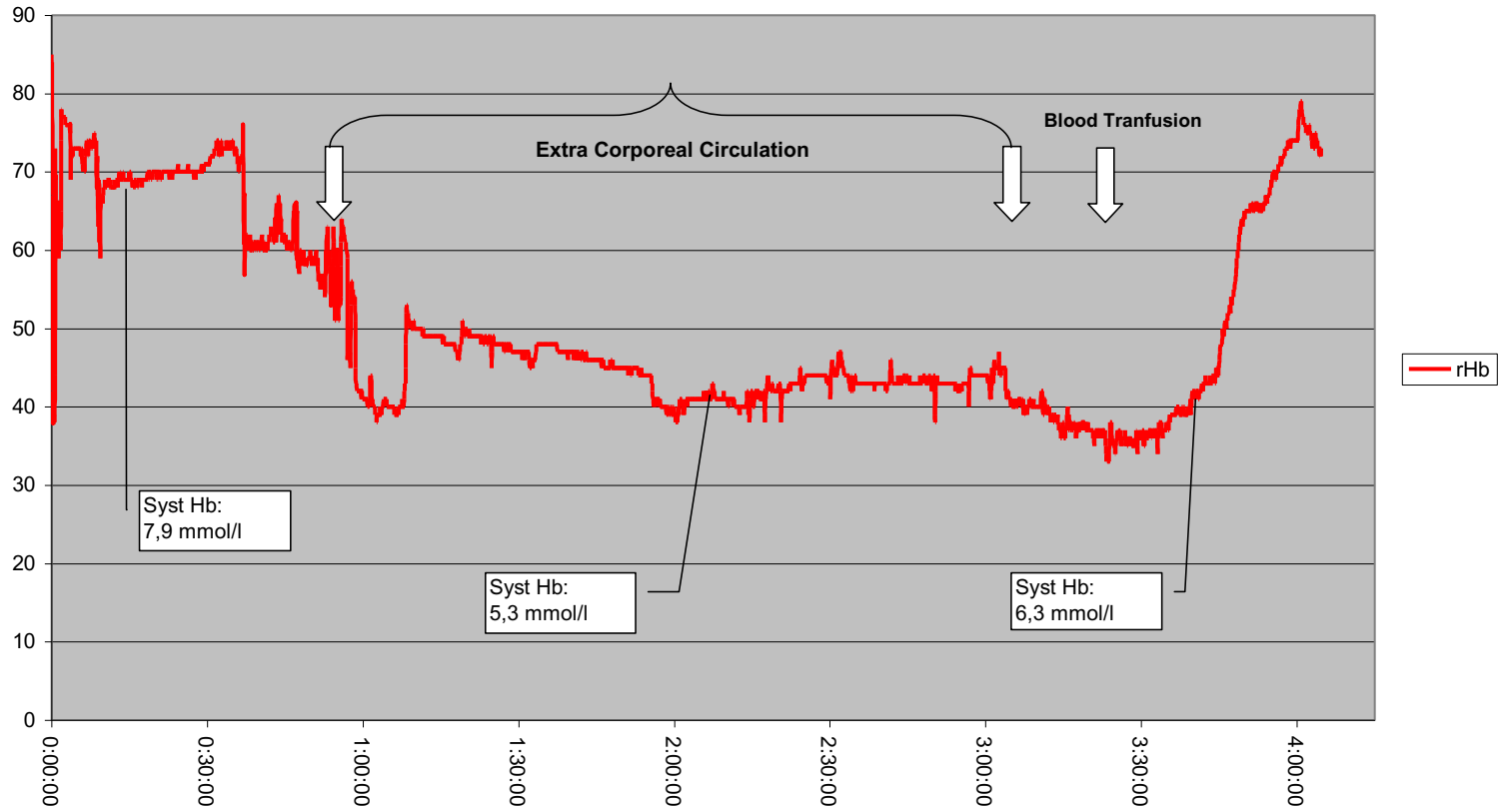
Before surgery (T0)
Induction of anaesthesia (T1),
10 minutes after induction of the CPB (T2),
After removal of aortic clamp (T3),
End of surgery (T4).

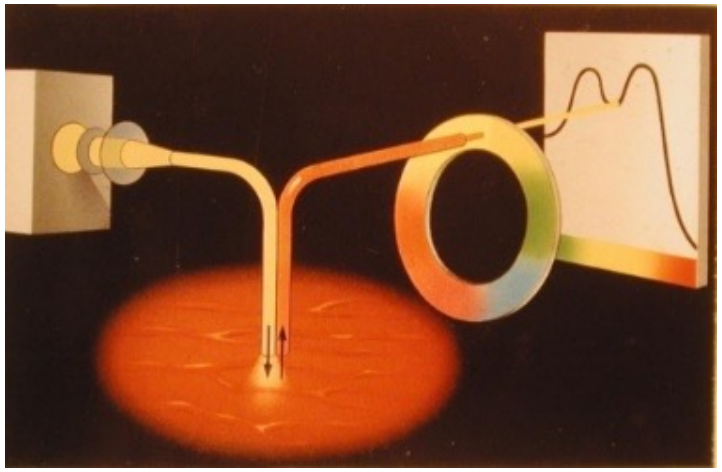


The effect of blood transfusion on sub-lingual microcirculatory Hb concentration measured by reflectance spectrophotometry during on-pump cardiac surgery,

Emre Almac

RBC

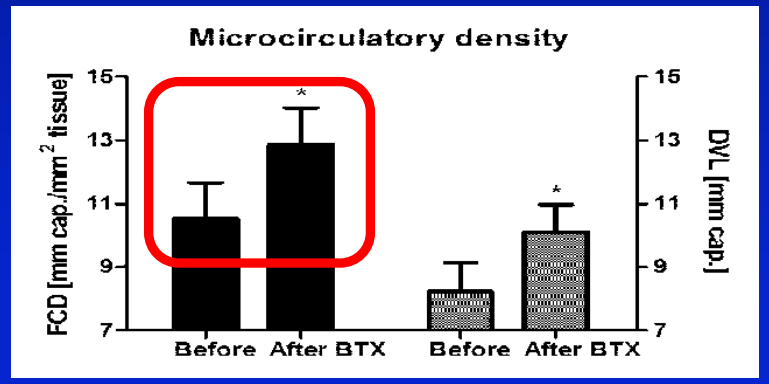


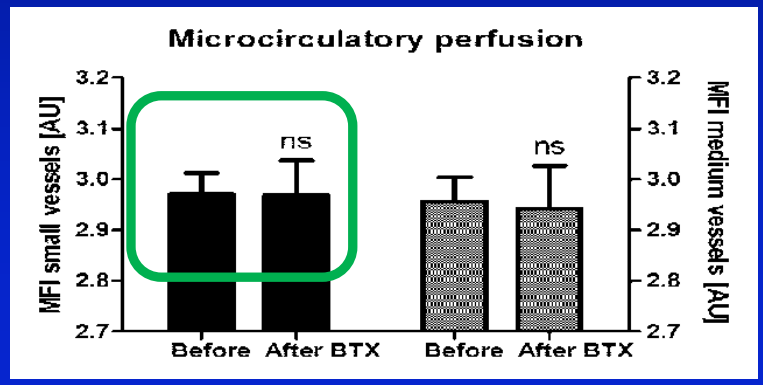


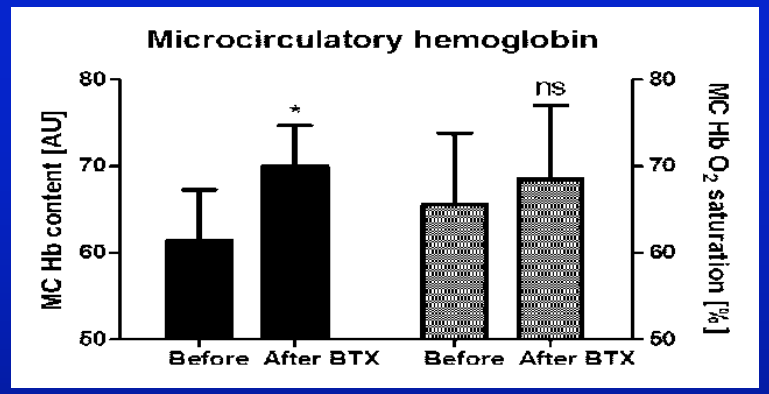
The only effective way in increasing oxygen content in the microcirculation is by a blood transfusion.

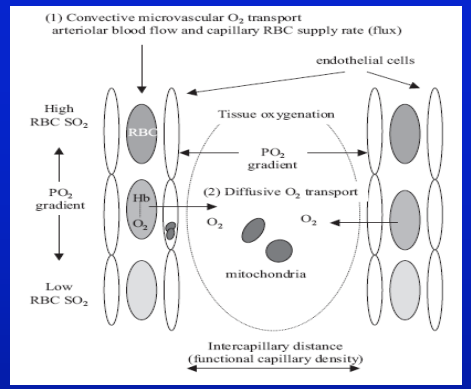
Blood transfusions recruit the microcirculation during cardiac surgery

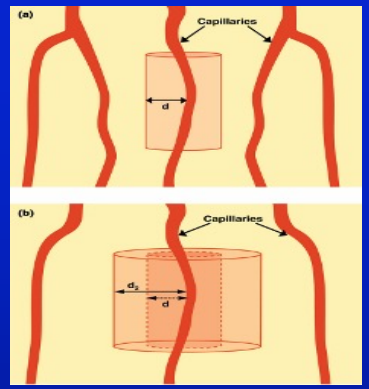
Koray Yuruk, Emre Almac, Rick Bezemer, Peter Goedhart, Bas de Mol, and Can Ince











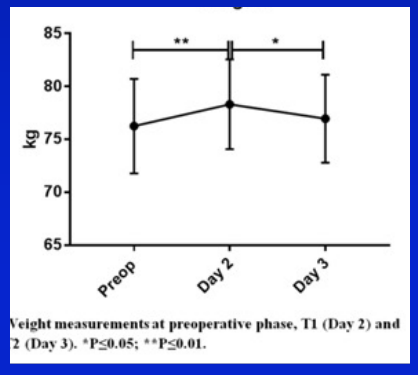
Results show that blood transfusion s improve oxygen tranport by reducing diffusion distances and not by augmenting convection.

Transfusion (2010) 51(5):961-7.

Sublingual microcirculation reveals fluid overload and leukocytosis in a post-cardiac surgery patient

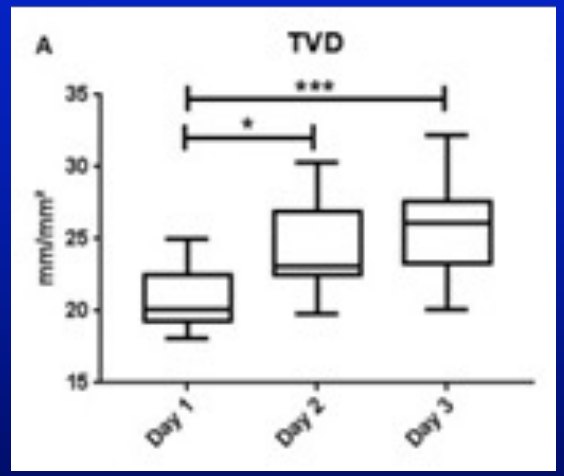
Zühre Uz,[1] Bastianus AJM de Mol,[2] Thomas M van Gulik,[1] Can Ince[1]

weight

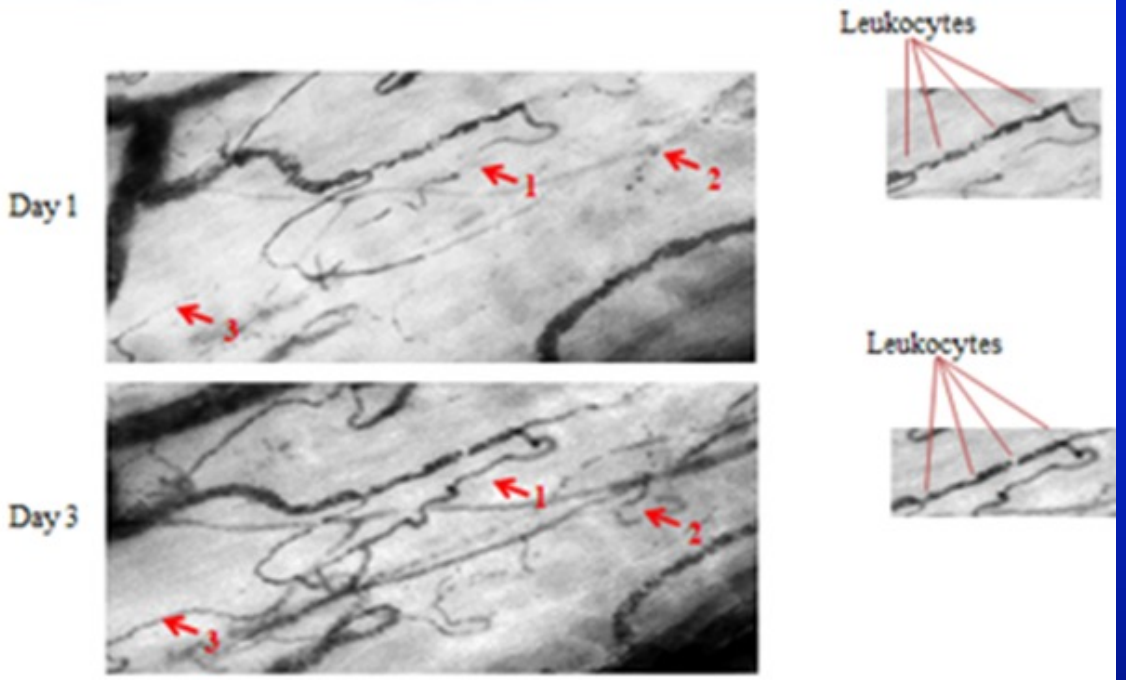


Weight measurements at preoperative phase, T1 (Day 2) and T2 (Day 3). *P≤0.05; **P≤0.01.

microcirculatory density



Furosemide therapy recruits the microcirculation in post cardiac surgery patient.



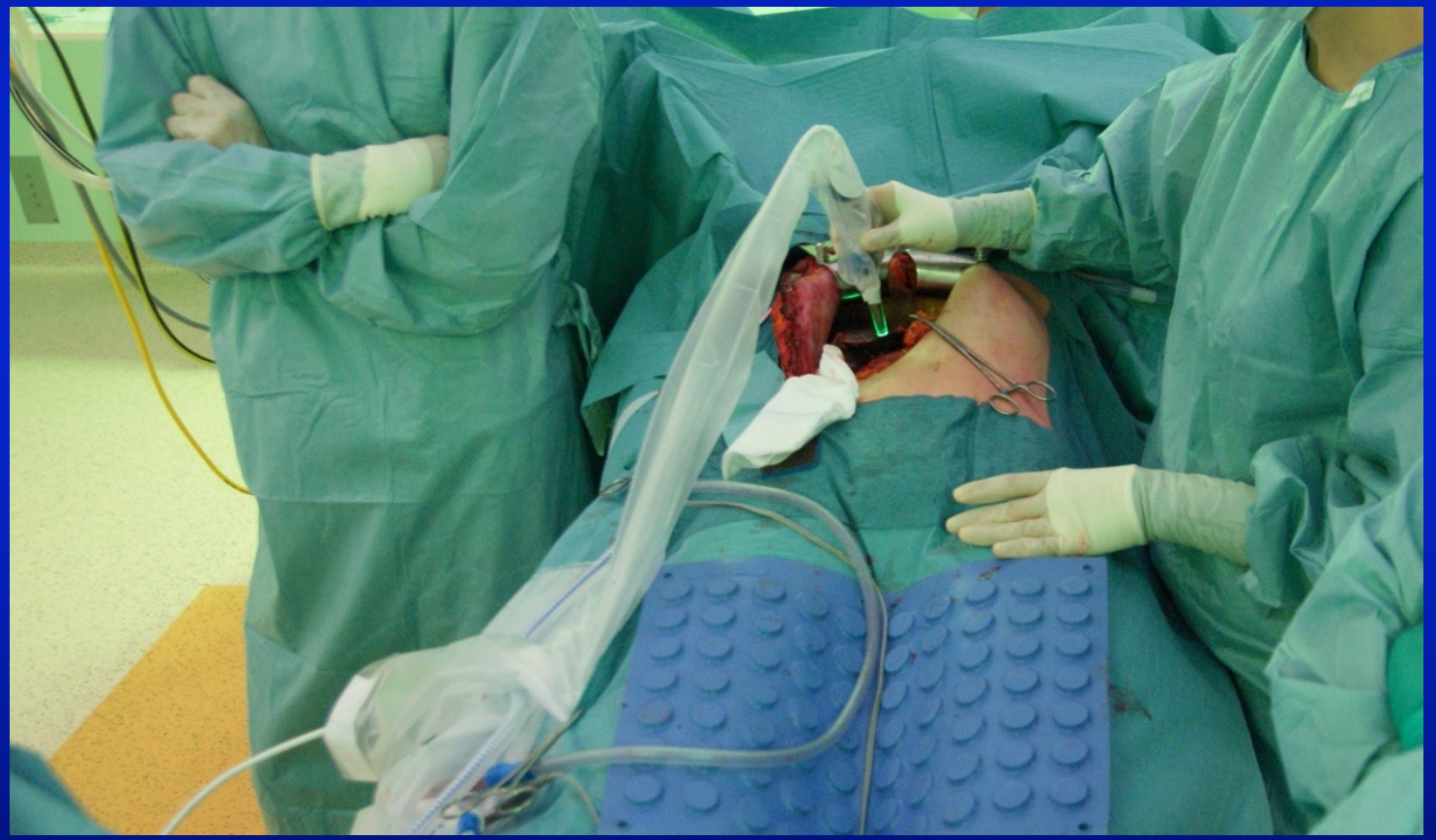
Learning points

- Fluid overload is a common complication after cardiac surgery caused by haemodynamic resuscitation performed during the surgical procedure.
- Patients with a severe aortic stenosis suffer from left ventricular hypertrophy requiring careful fluid management.
- Sublingual microcirculation monitoring may provide an additional check on optimal filling status in critically ill patients apart from recording fluid balance and weight control.

Uz Z, *et al*. *BMJ Case Rep* 2018. doi:10.1136/bcr-2017-223681

Real-time observation of microcirculatory leukocytes in patients undergoing major liver resection

Zühre Uz[1,2]✉, C. Ince[2,3], L. Shen[2,3], B. Ergin[3] & T. M. van Gulik[1]



Scientific Reports | (2021) 11:4563

Low CVP guided fluid therapy has better tRBCp than SV guided fluid therapy in abdominal surgery

Uz Z, Jongerius I, Shen L, Mungroop T, Veelo D, van Gulik T, Ince C

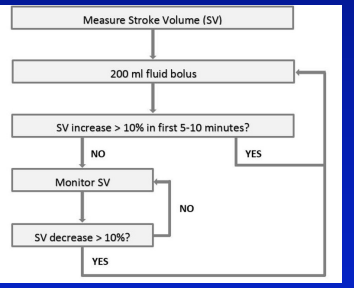
Low CVPDFT

furosamide

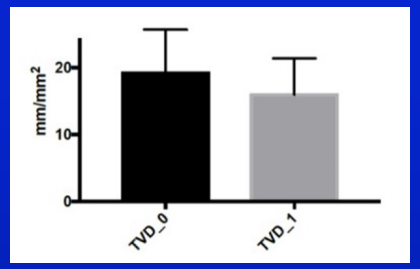
nitroglycerine

The cumulative fluid balance was >higher in the ***SV***DFT (+620±760 ml) group than in the lo***CVP***DFT (-200±560 ml) group, p <0.01).

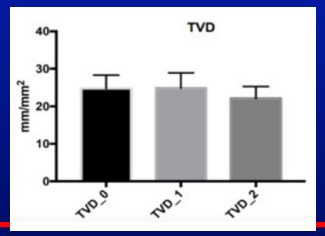
SVDFT

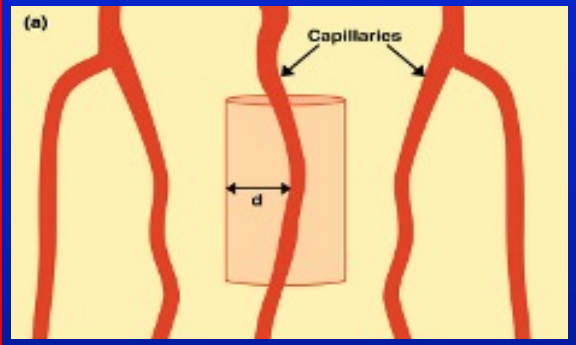


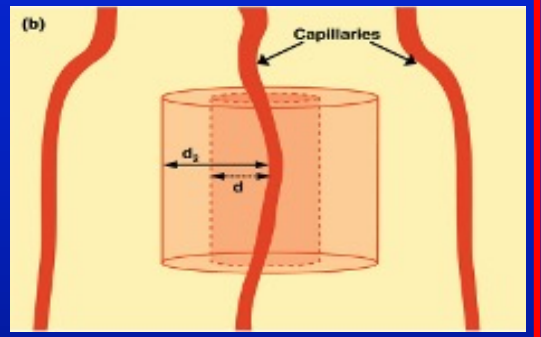
Intestinal tRBC unchanged during low-CVPDFT



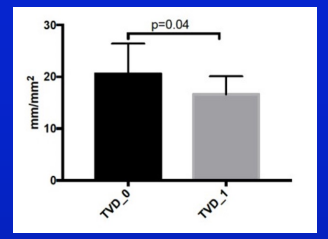
Sublingual tRBC unchanged after 24 hours



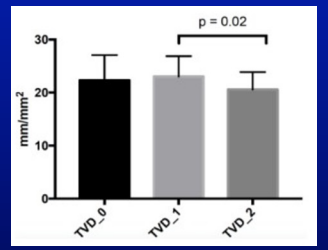




Intestinal tRBC lower after surgery SVDFT



Sublingual tRBC lower after surgery SVDFT



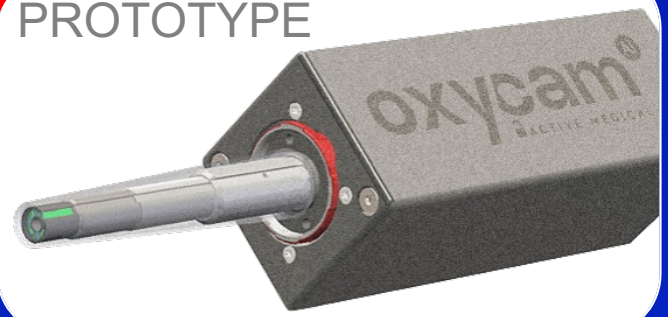
Introducing

oxycam AI

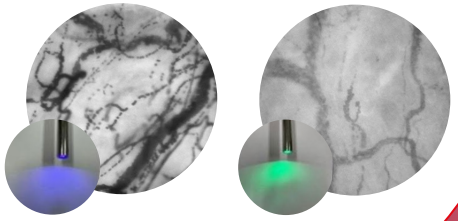
ACTIVE MEDICAL

powered by MicroTools

PROTOTYPE

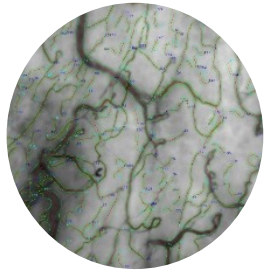


Better image quality with blue illumination



Dual-wave length ratio imaging allows visualization of microcirculatory Hb oxygen saturation images

Embedded automatic Microtools AI analysis clinically validated quantitative microcirculatory values

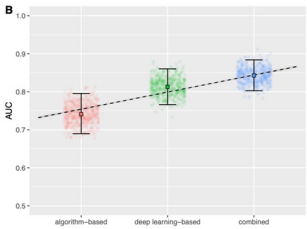


International database for Machine Learning

The microcirculation network

Embedded MicroTools-AI for identification of disease

Microcirculation alterations in critically ill COVID-19 patients analyzed using artificial intelligence; *Critical Care (2022) 26:311*



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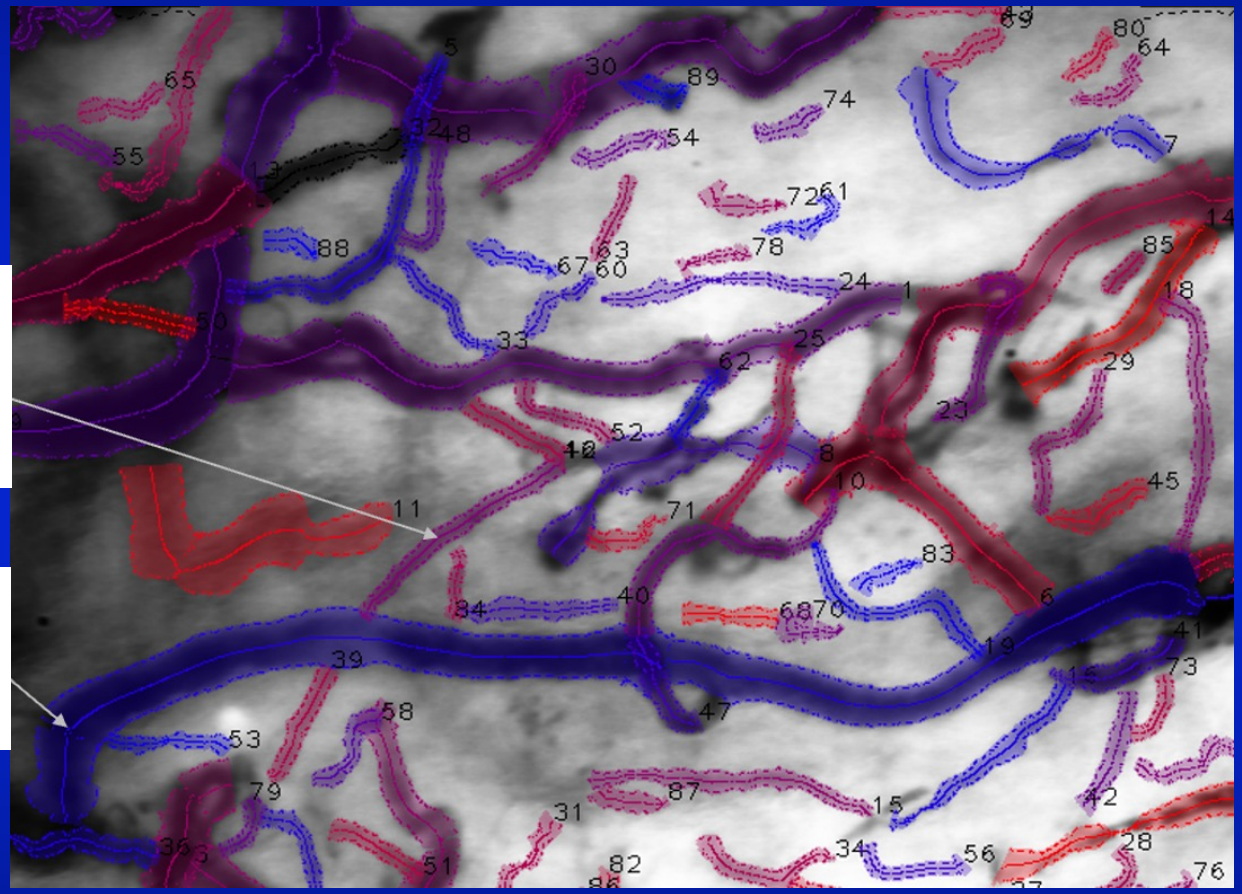
Two-wavelength ratio imaging: Tissue oxygen delivery and consumption

→**Tissue oxygen delivery**
→**Tissue oxygen extraction**
→**Tissue oxygen shunting**

Oxygen delivery and extraction in individual capillaries

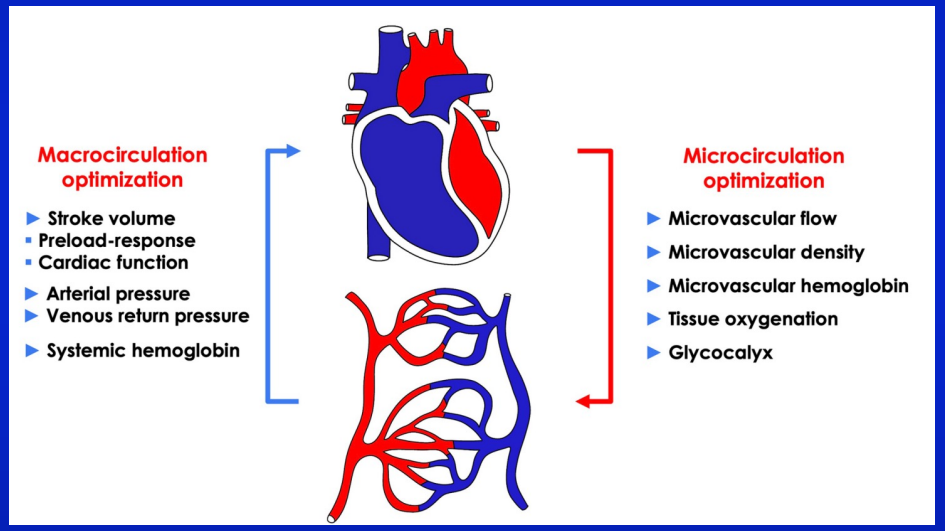
Output oxygen saturation in venules

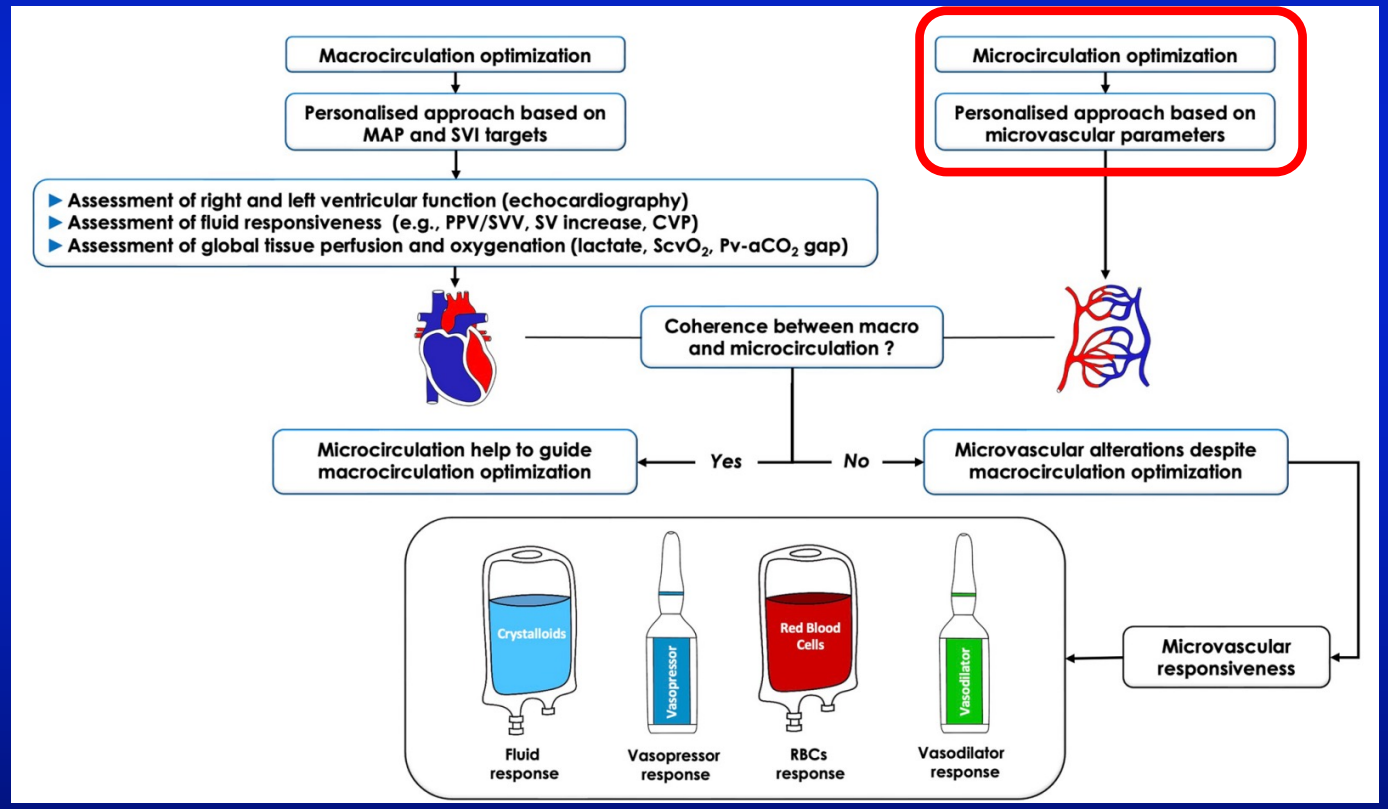


λ_{peak} = 470 nm λ_{peak} = 527 nm

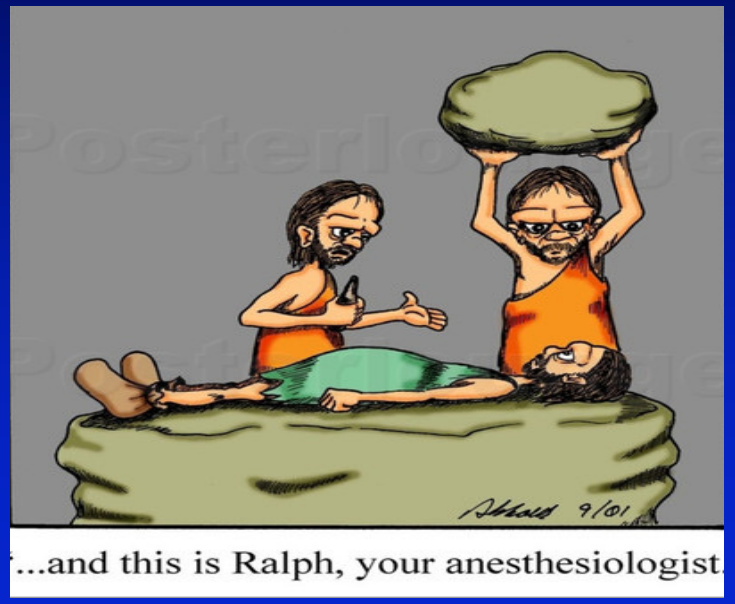
The future of intensive care: the study of the microcirculation will help to guide our therapies

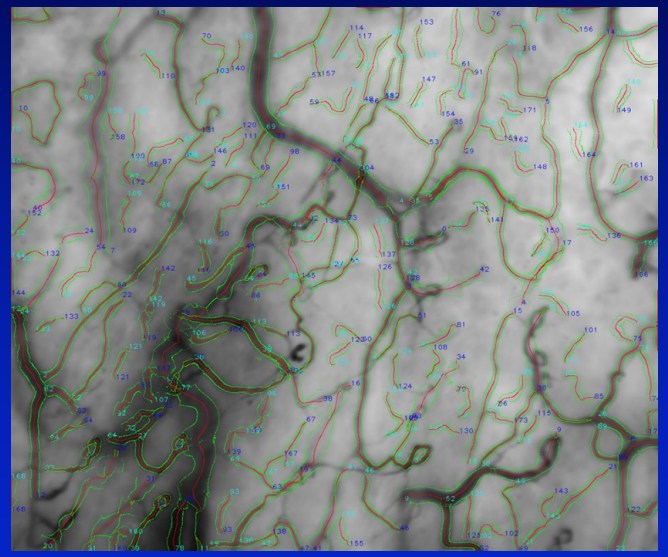
J. Duranteau[1*], D. De Backer[2], K. Donadello[3], N. I. Shapiro[4], S. D. Hutchings[5,6], A. Rovas[7], M. Legrand[8], A. Harrois[1] and C. Ince[9]





Critical Care (2023) 27:190





Thank you for your attention.