危重症中体循环与微循环的关系

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何谓危重症？

- 衰竭的重要器官、系统急需支持
- 否则...死亡接踵而来
- 濒死状态

Critically ill patient

- **definition ——**

  Decompensation of the status of the patient leading without therapeutic intervention to the multiorganic failure and to death

何谓循环？

- **circulatory system is … heart, veins, capillaries, arteries, lymph vessels, lymph glands, …**
- **…to supply the body tissues with nourishment and collect waste materials**

体循环&微循环：大河——小溪？

- Systemic

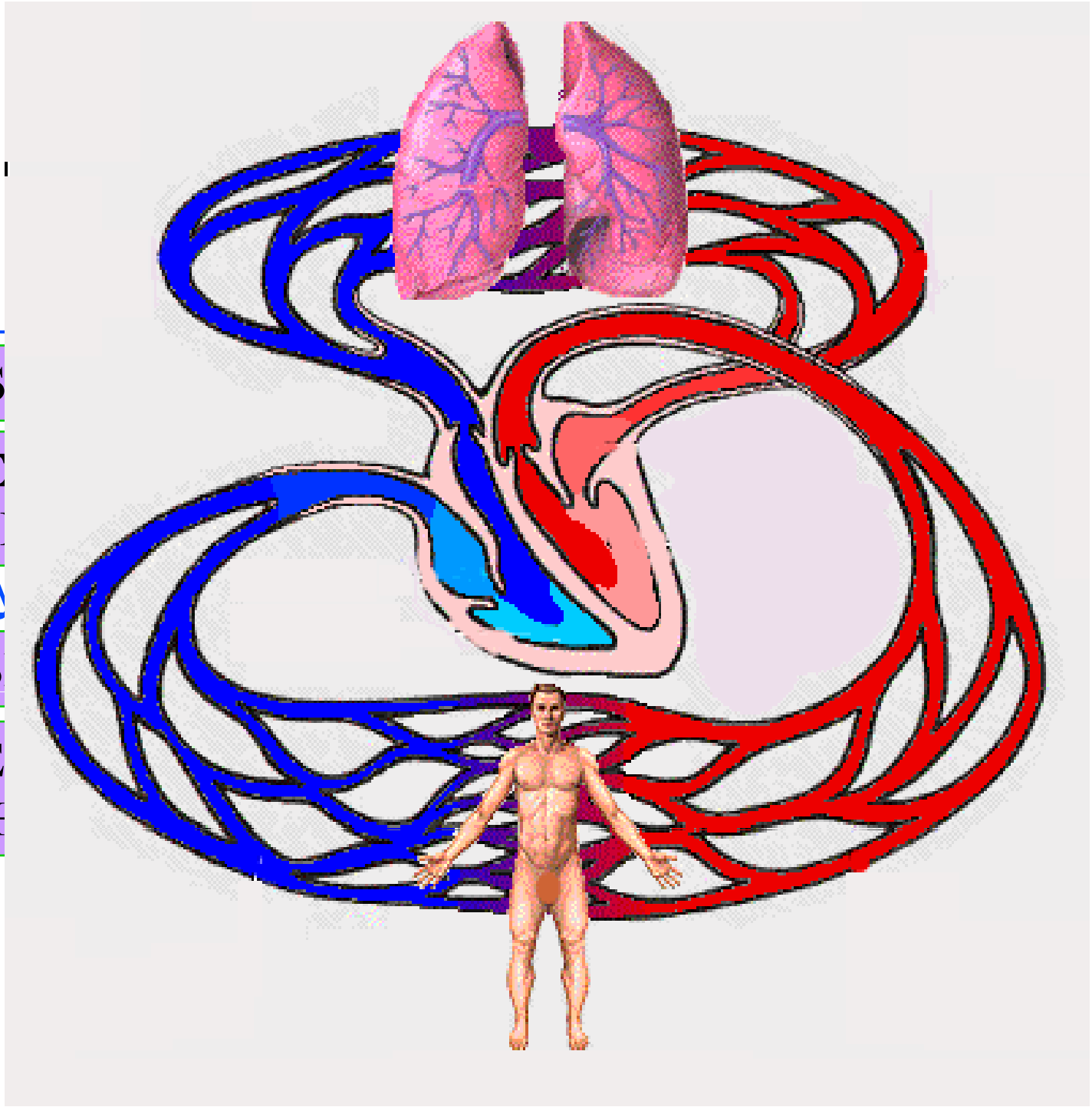
  HIGH RES

  HIGH PRE
  (120/80 mm
- Pulmonary

  LOW RES

  LOW PRE
  (25/10 mmH

heart



循环系统的功能

- **Heart**: pumps blood
- **Arterial System**: oxygenated blood to tissues
- **Venous system**: deoxygenated blood back to heart
- **Capillaries**: exchange gases, nutrients, and wastes

循环系统的功能

- **Distribute** nutrients through tissues of the body
- **Transport and exchange** oxygen and carbon dioxide
- **Remove** waste materials
- **Distribute** secretions of endocrine glands
- **Prevent** excessive bleeding
- **Prevent** infection
- **Regulate** body temperature

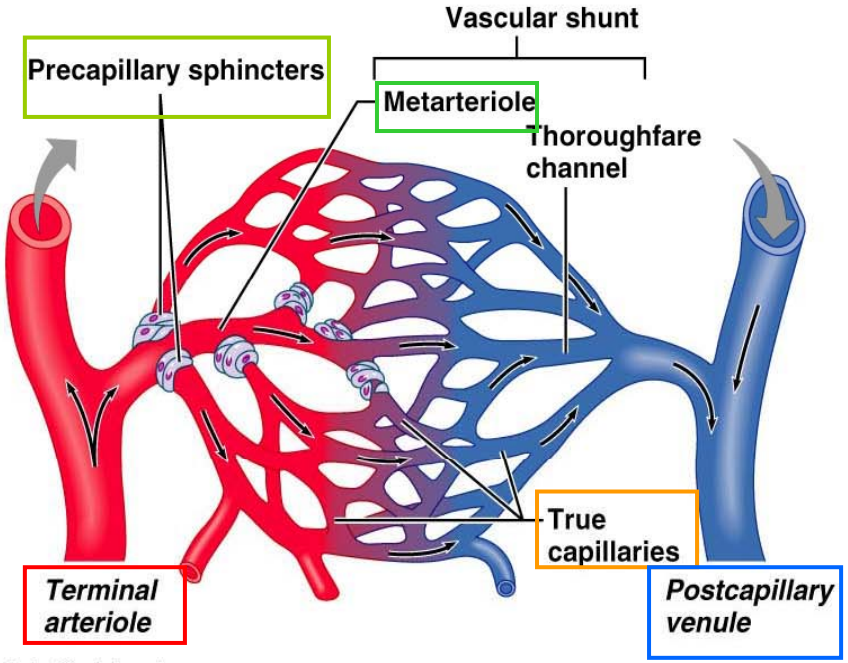
何谓微循环？

- 微循环（microcirculation）这个名词是1954年在美国召开的第一届国际微循环会议上正式提出的。指微（细）动脉和微（细）静脉之间微血管的血液循环。
- The microcirculation is the 血流 through 血管 smaller than 100 μm

Keywords:

管径 ≤100μm

微循环的构成



小动脉

(50~100 μm)

毛细血管

(5~10 μm)

小静脉

(~20 μm)

后小动脉

(10~20 μm)

毛细血管前括约肌

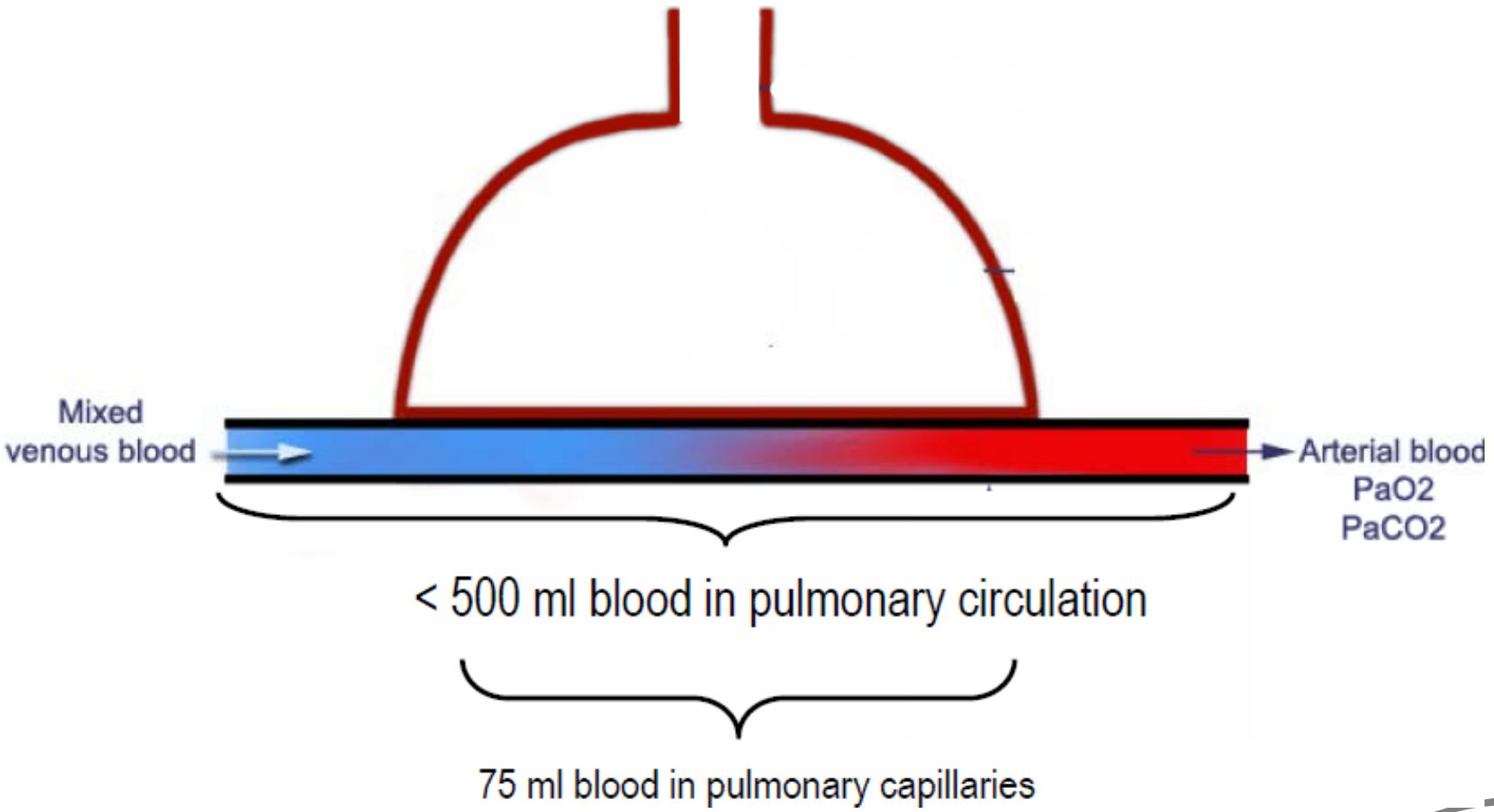
体循环和微循环

- **Pressure inside is 20~40 mmHg**
- **5% of the blood is in capillaries**
- **exchange of gases, nutrients, and wastes**
- **flow is slow and continuous**

Capillaries are close! Every cell in the body is no more than two cell diameters from a capillary.

真正将血流从心血管系统运送到组织细胞的是微循环

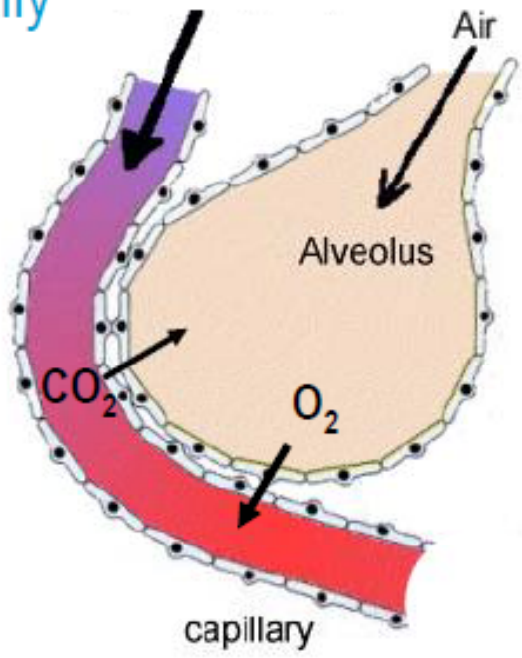
肺循环和微循环

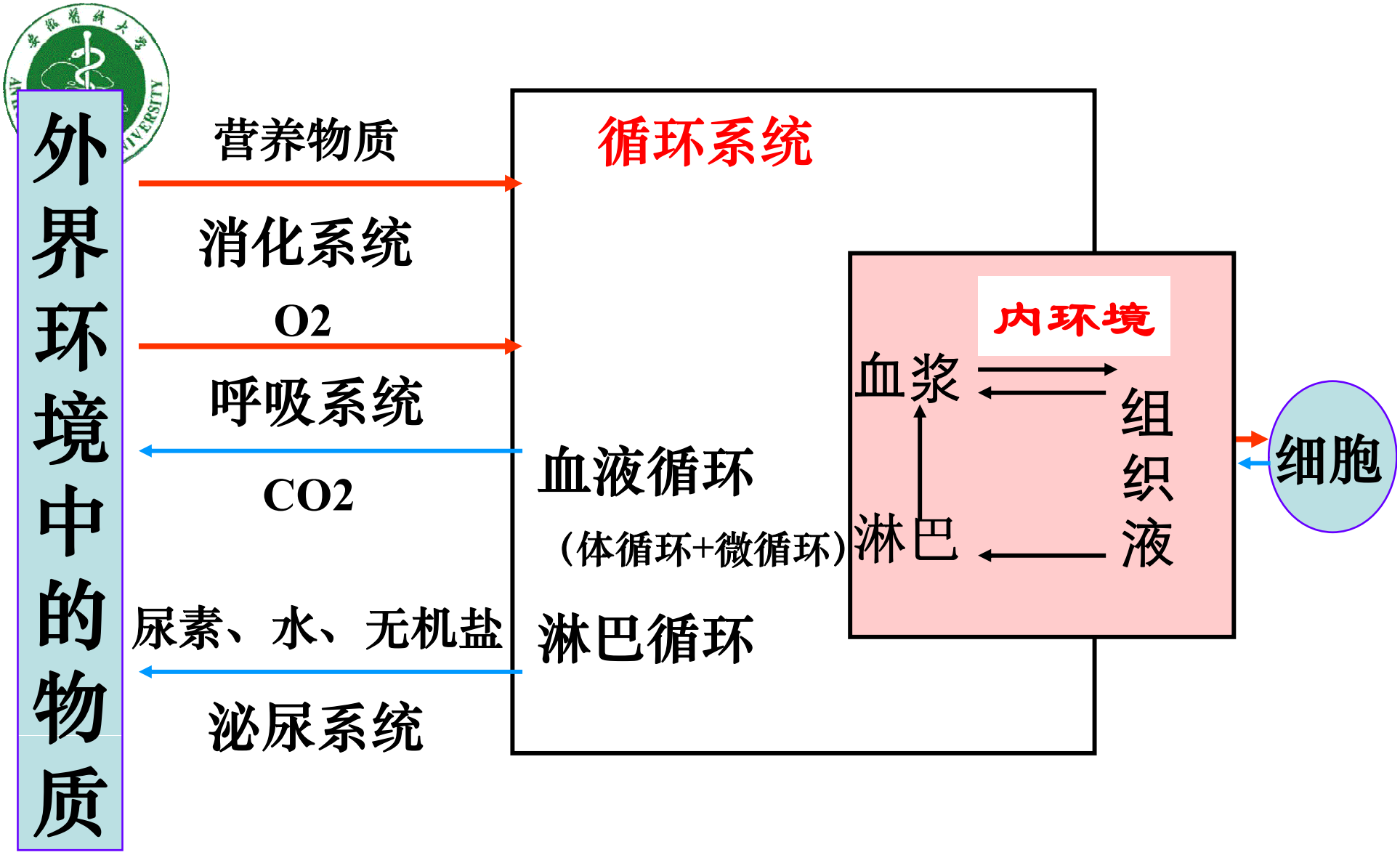

Mixed
venous blood
Arterial blood
PaO2
PaCO2
< 500 ml blood in pulmonary circulation
75 ml blood in pulmonary capillaries

肺循环和微循环

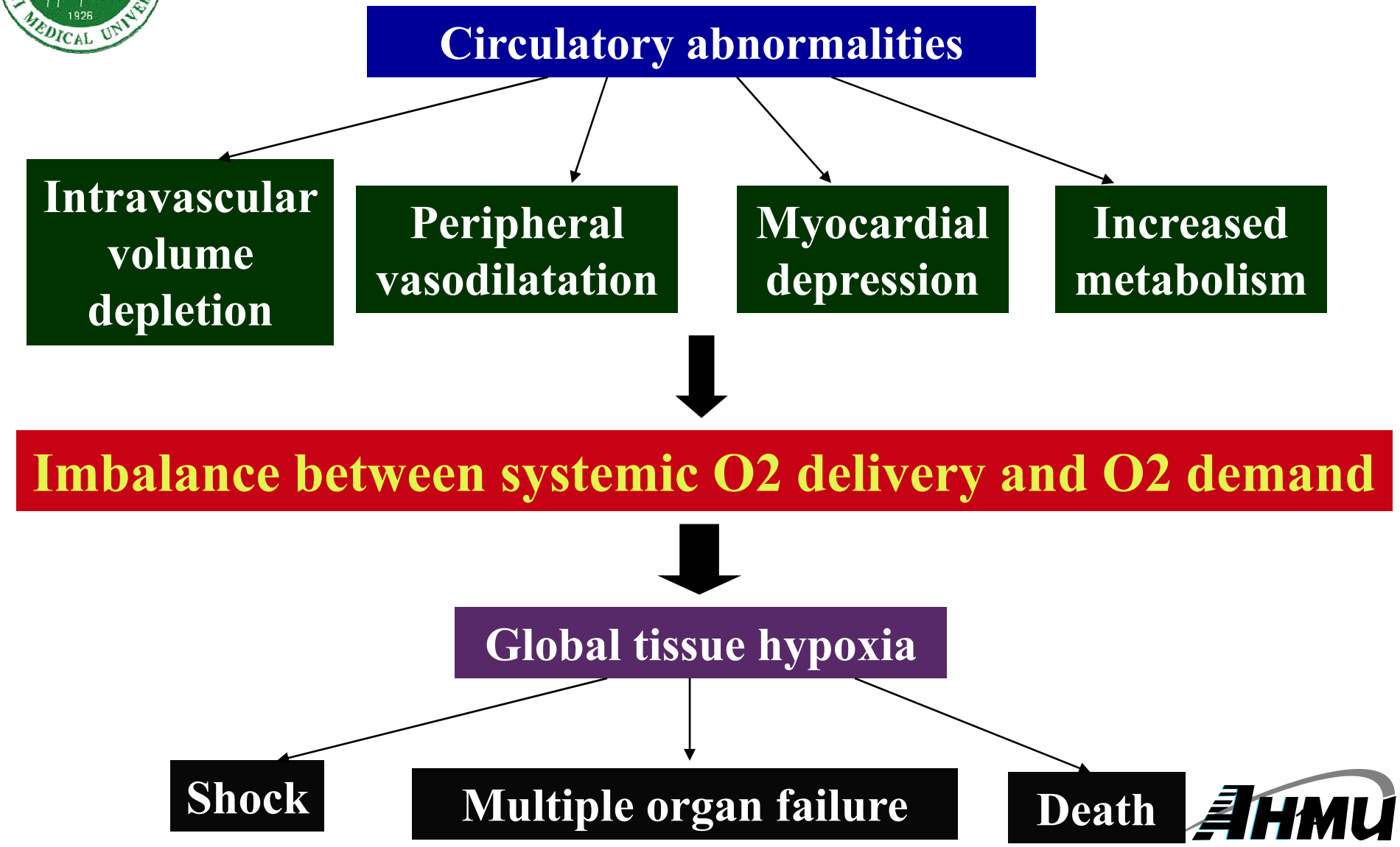
- gas exchange: across small pulmonary arterial vessels [histologically not capillaries-functionally capillaries] & pulmonary capillaries

- there are about 280 billion pulmonary capillaries for about 300 million alveoli resulting in a gas exchange surface of about 60-100 m²]

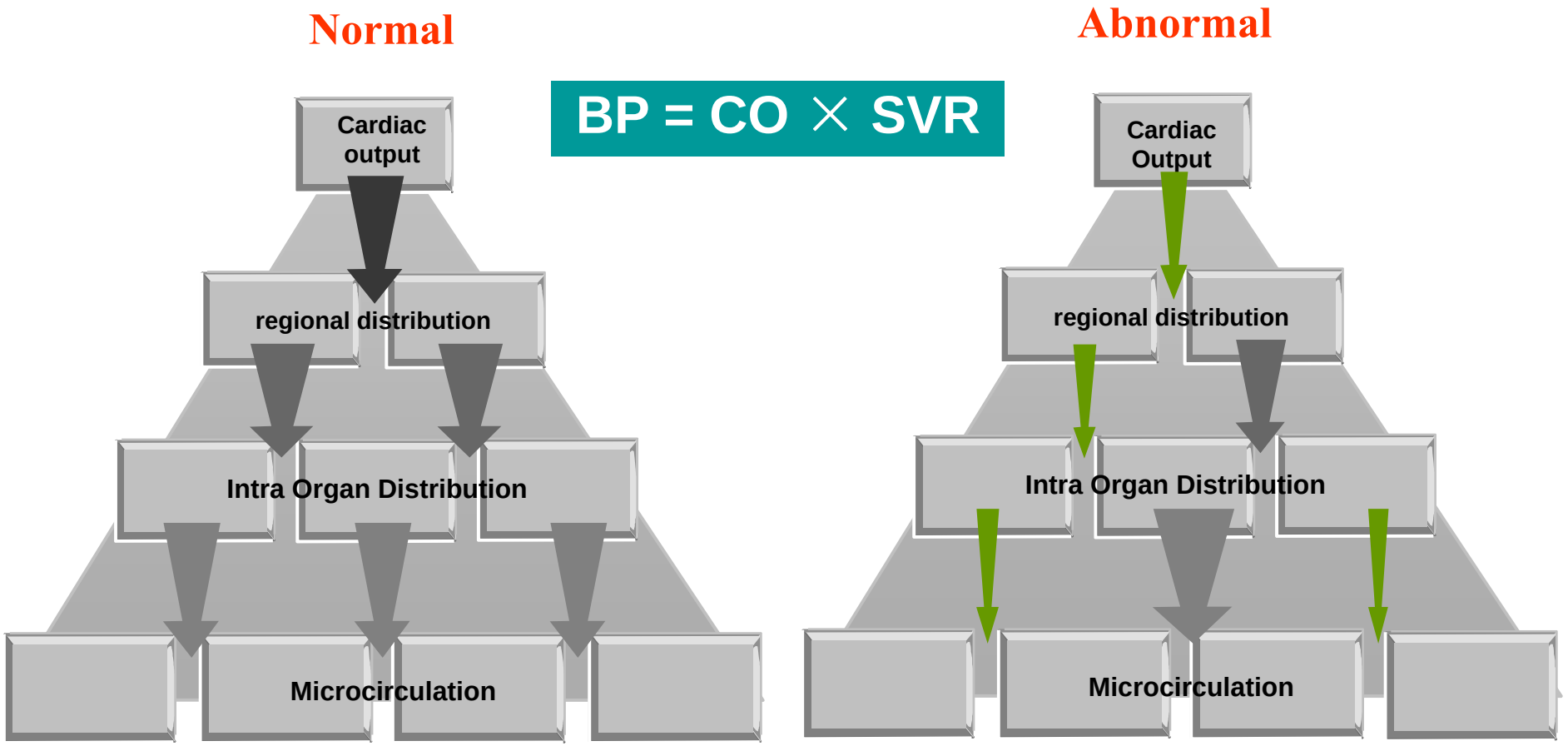



外界环境中的物质
营养物质
消化系统
O2
呼吸系统
CO2
尿素、水、无机盐
泌尿系统
循环系统
血液循环
（体循环+微循环）
淋巴循环
内环境
血浆
组织液
淋巴
细胞

Circulation

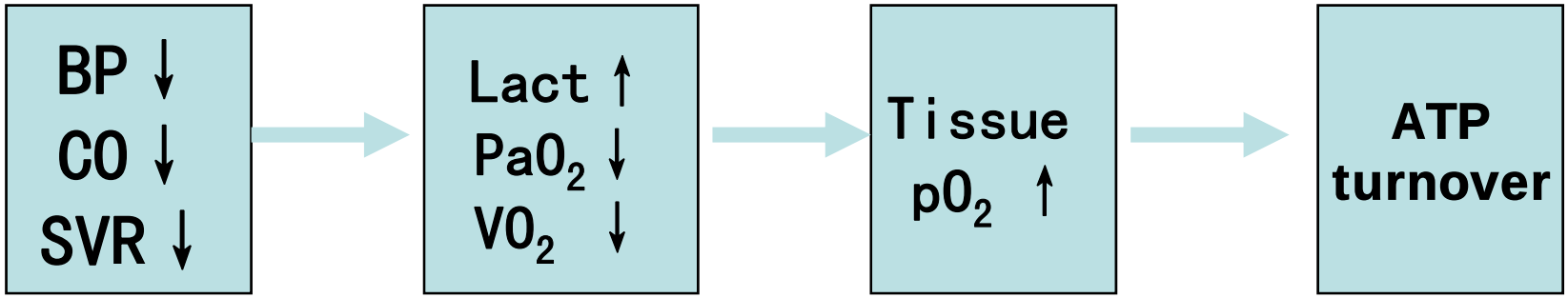


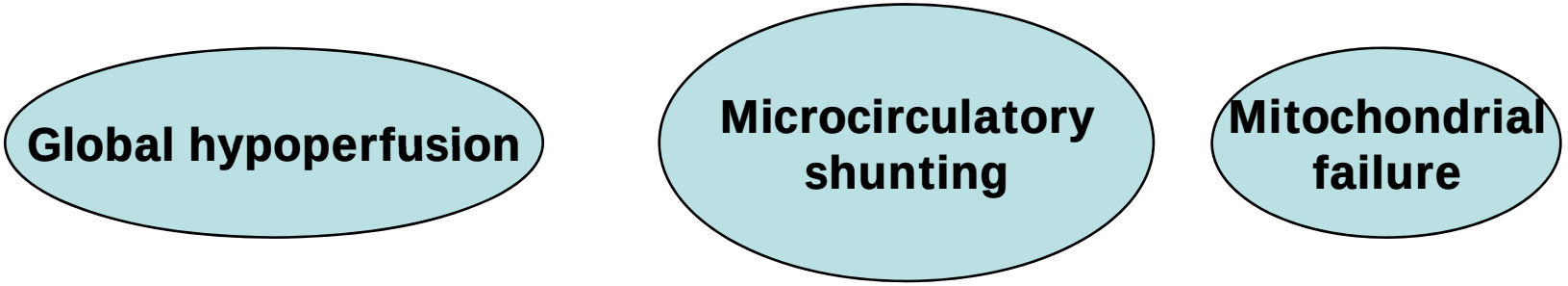
O_2输送的调节



QO2 = Flow ×O2 content

Mechanism of regional tissue dysoxia（细胞病性缺氧）





Crit Care Med 1995; 23: 1217

Lancet 2002; 360: 219

Seven Stages of Cell Death

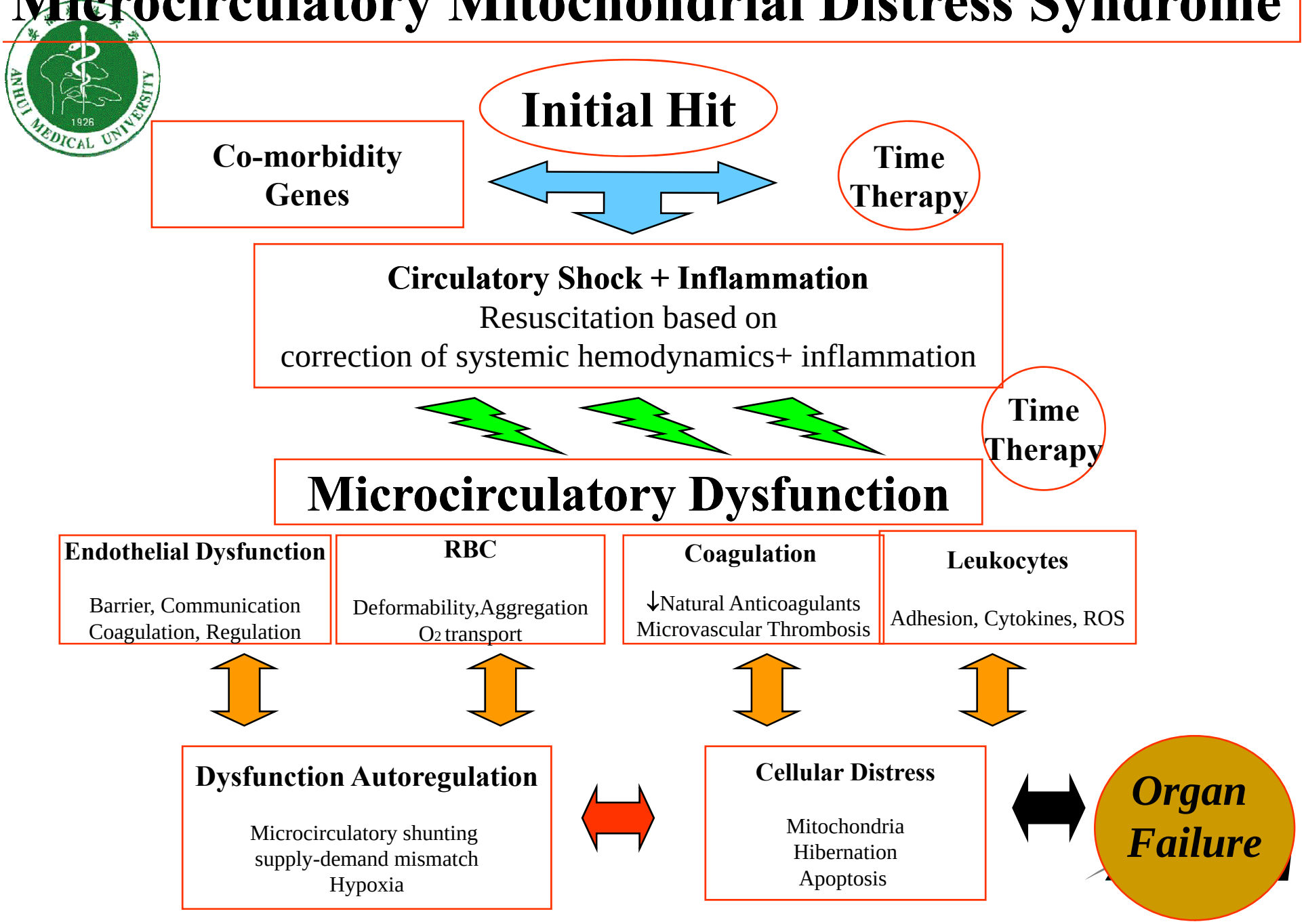
- 1. Normal cell

  Normal sodium –potassium pump
- 2. Hypoxia: intracellular ischemia occurs; anaerobic metabolism begins; lactic acid builds up in cell; leading to metabolic acidosis; causes the sodium potassium pump to fail.
- 3. Ion shift occurs Sodium rushes into the cell bringing water with it.

Seven Stages of Cell Death

- 4. **Cell swelling** occurs.
- 5. **Mitochondrial swelling** occurs; production of ATP ceases.
- 6. **Intracellular disruption** releases lysosomes, cell membrane begins to break.
- 7. **Cell destruction** begins leading to **tissue death**.

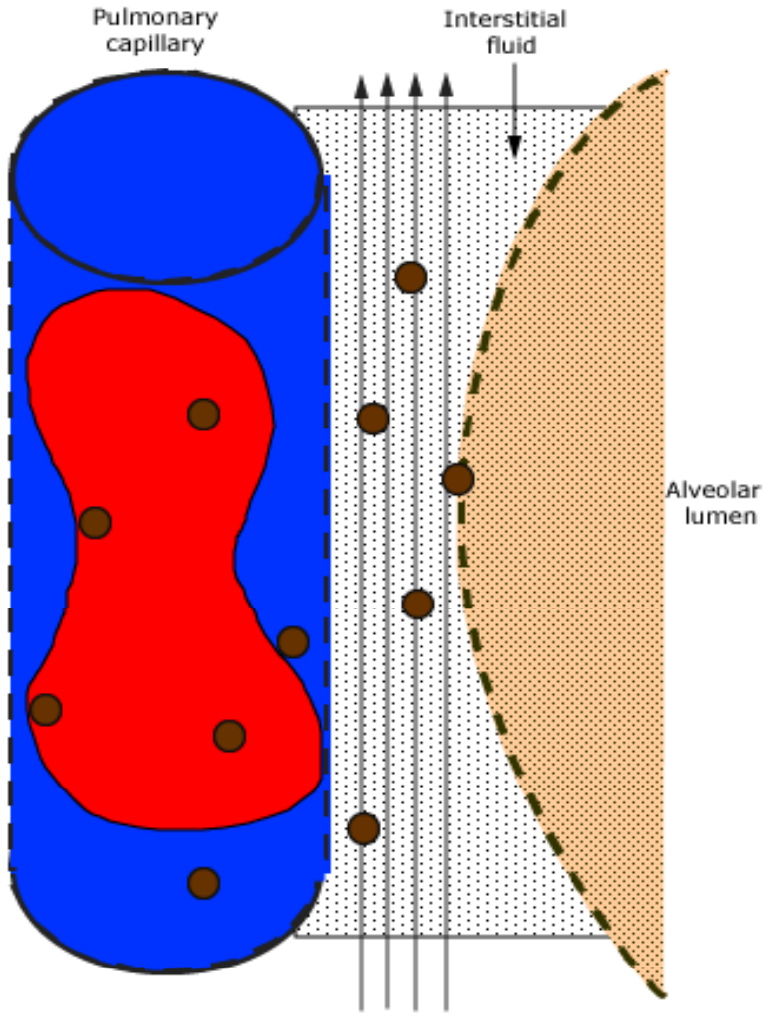
Microcirculatory Mitochondrial Distress Syndrome

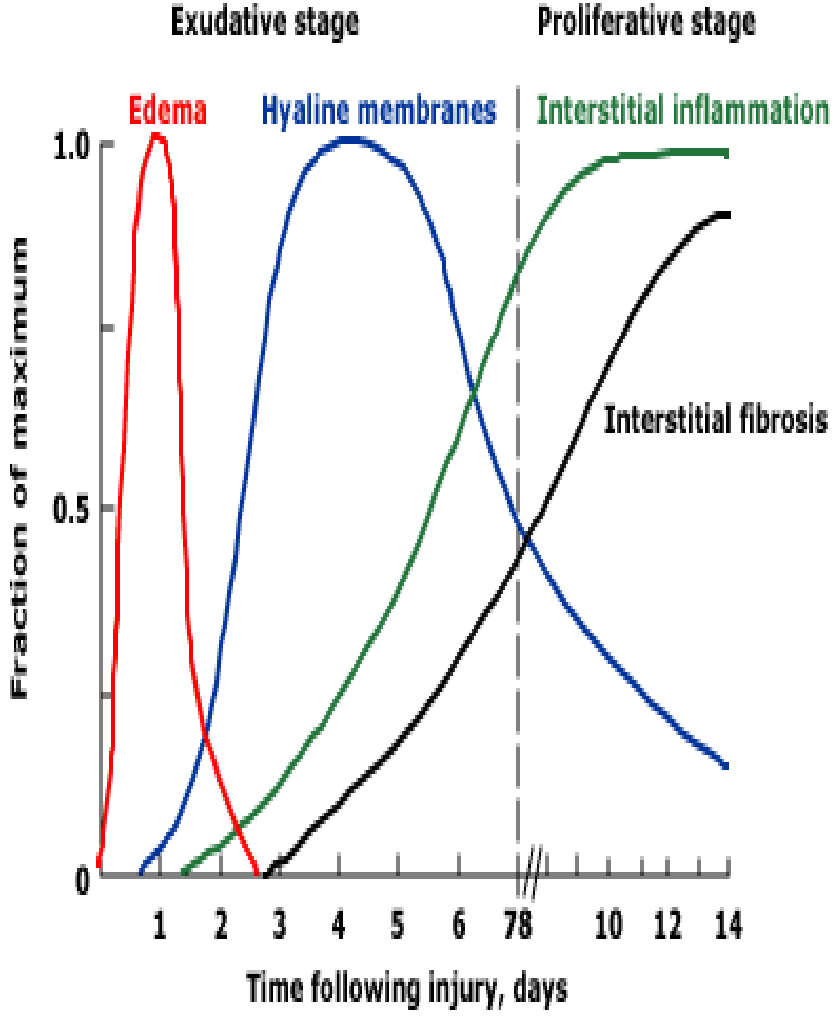


Specific organ failure

- Circulation
- Lung
- GI tract
- Liver
- Kidney
- Nervous system

肺（Lung）


Pulmonary capillary
Interstitial fluid
Alveolar lumen


Exudative stage
Proliferative stage
Edema
Hyaline membranes
Interstitial inflammation
Interstitial fibrosis
Fraction of maximum
1.0
0.5
0
1
2
3
4
5
6
7
8
10
12
14
Time following injury, days

造血系统（Hepatosplanic system）

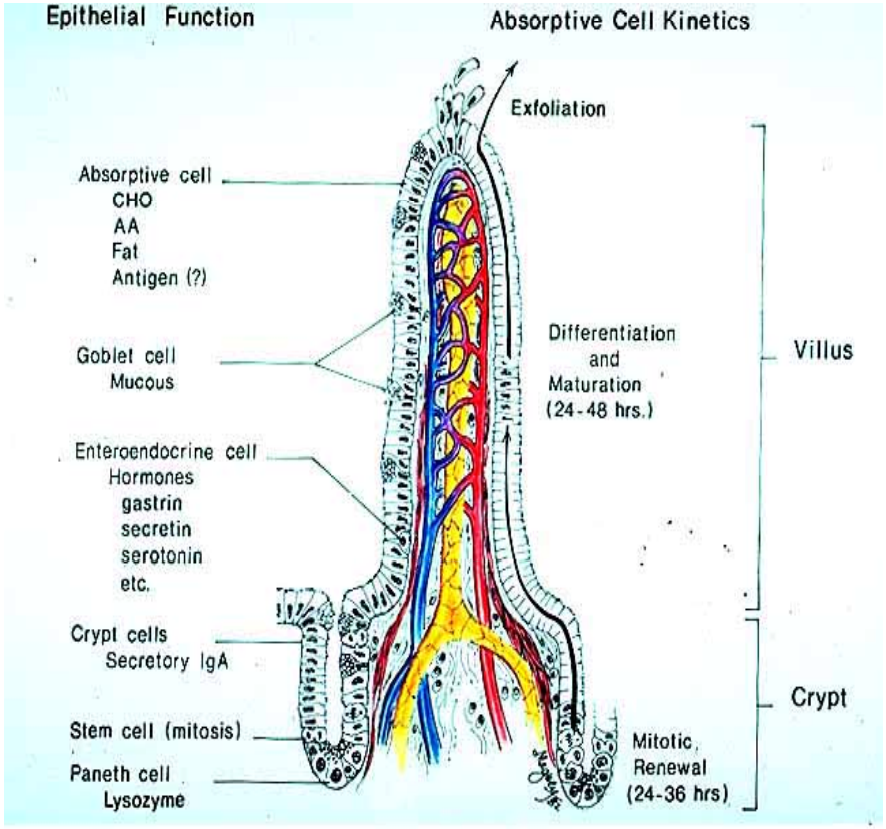
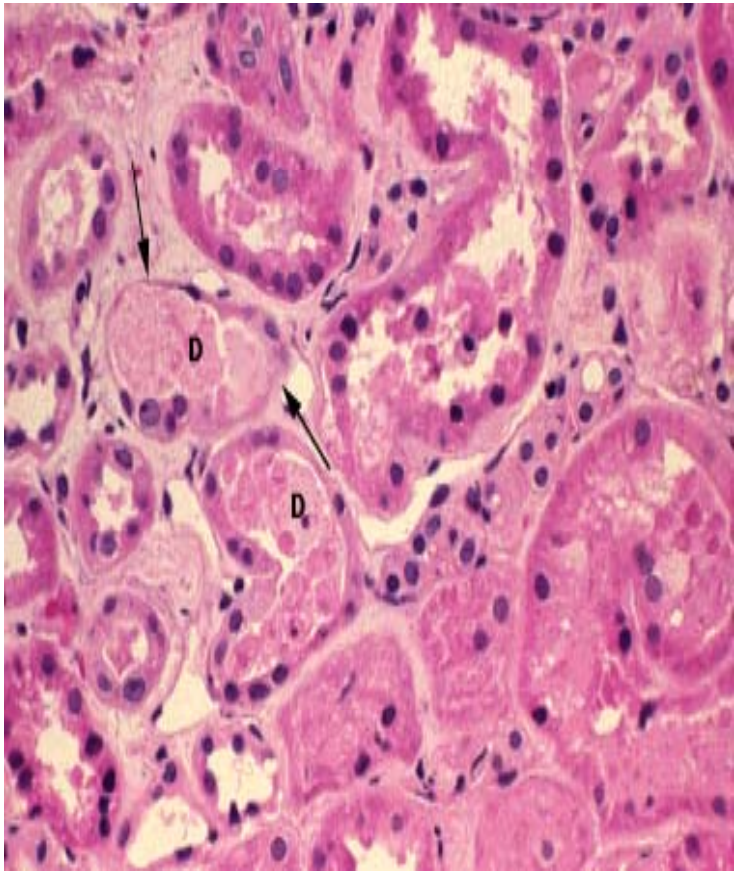


Figure 16. Diagram of the epithelium of an intestinal villus and crypt.

- **Feedback loop**
- **Sepsis depress the gut's normal barrier**

（肾脏）Kidney



- Acute tubular necrosis
- Systemic hypotension
- direct renal vasoconstriction,
- cytokines :TNF
- Endotoxin ,FMLP, a three amino acid (fMet-Leu-Phe) chemotactic peptide…

神经系统（Nervous system）

- **Encephalopathy: agitation,confusion,coma**
- **NO in the brain induce apoptosis in neurons**
- **Hypothalamic-pituitary-adrenal axis**

  Sympathetic nervous system

  Cholinergic anti-inflammatory pathway

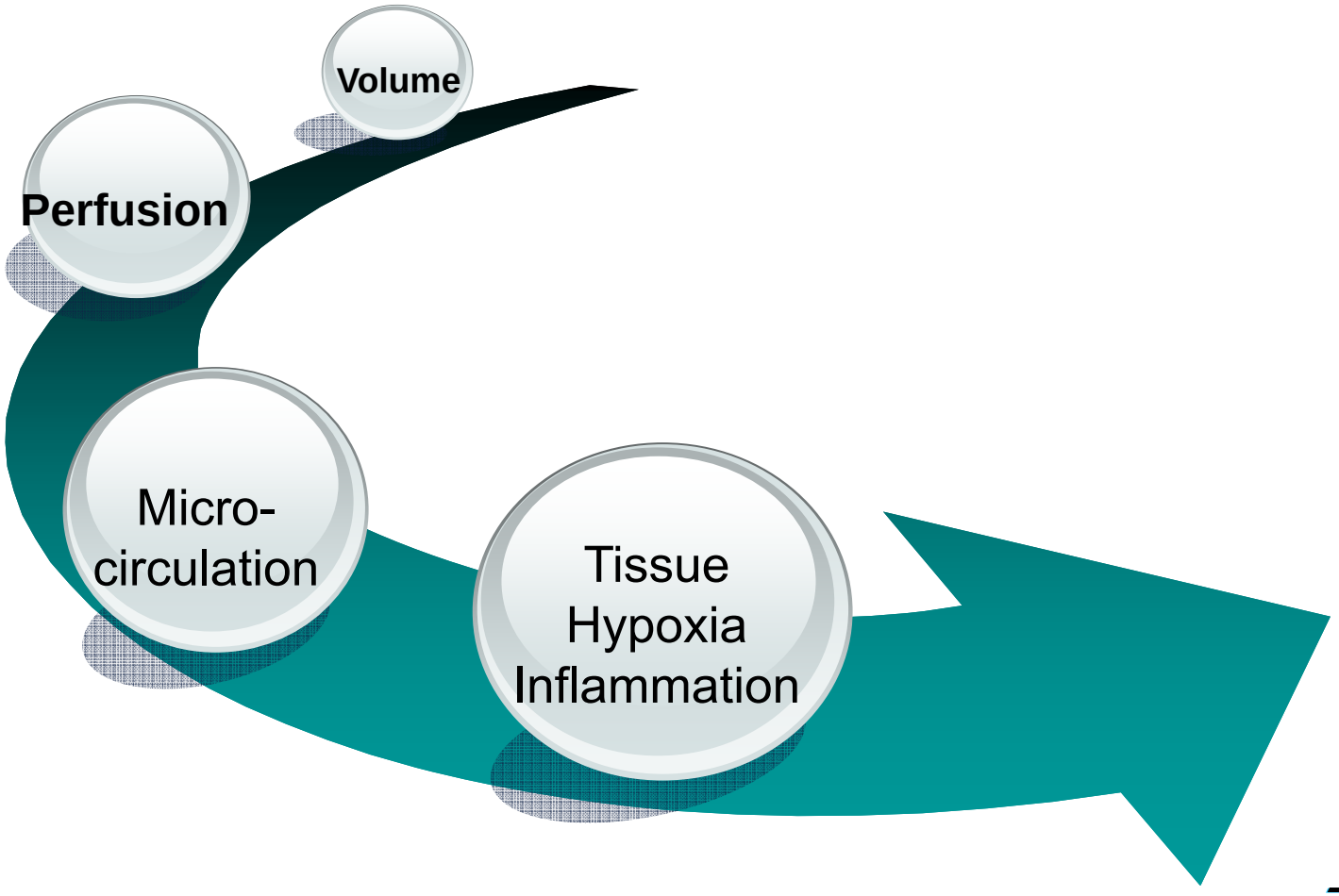
代谢变化（Metabolic alternations）

- **Intensive insulin therapy with tight glycemic control resulted in survival benefit**
- **GLUT-1,2,3 :insulin-independent**

  hepatocyte, neurons, gut mucosal,renal tubular,immune and endothelial cell
- **GlUT-4:insulin-dependent**

  hear, skeletal muscle, adipose tissue

体循环-微循环-细胞病性缺氧



循环障碍的急诊管理策略

- 评估（院前、急诊抢救室、ICU）
- 动态监测
- 综合治疗措施

血流动力学监测

- Microcirculation
- Esophageal Doppler
- NICO (partial CO_2 rebreathing method)
- PiCCO
- RVEF PAC – RVEDV/RVEDVI
- $ScvO_2$ CVP

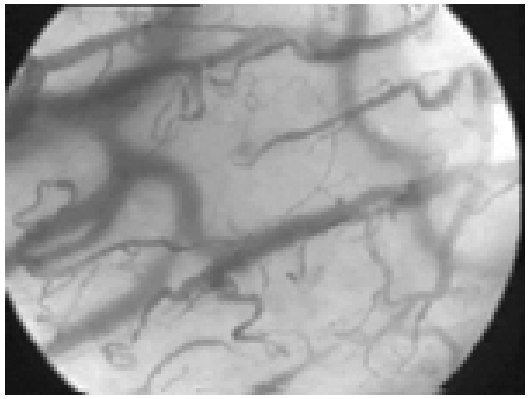
- HR
- BP
- T
- RR
- Urine output
- Response
- Lactate

微循环监测

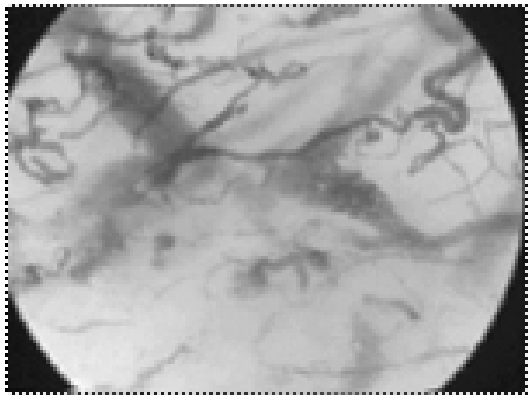
- Nailfold videomicroscopy
- Laser doppler (skin, muscle, gut)
- GI tonometry (pCO2)
- Near-infrared spectroscopy
- Oxygen electrodes (pO2)
- Orthogpnal polarization spectral imaging (sublingual mucosa)

Orthogonal polarization spectral (OPS)

Cardiogenic Shock

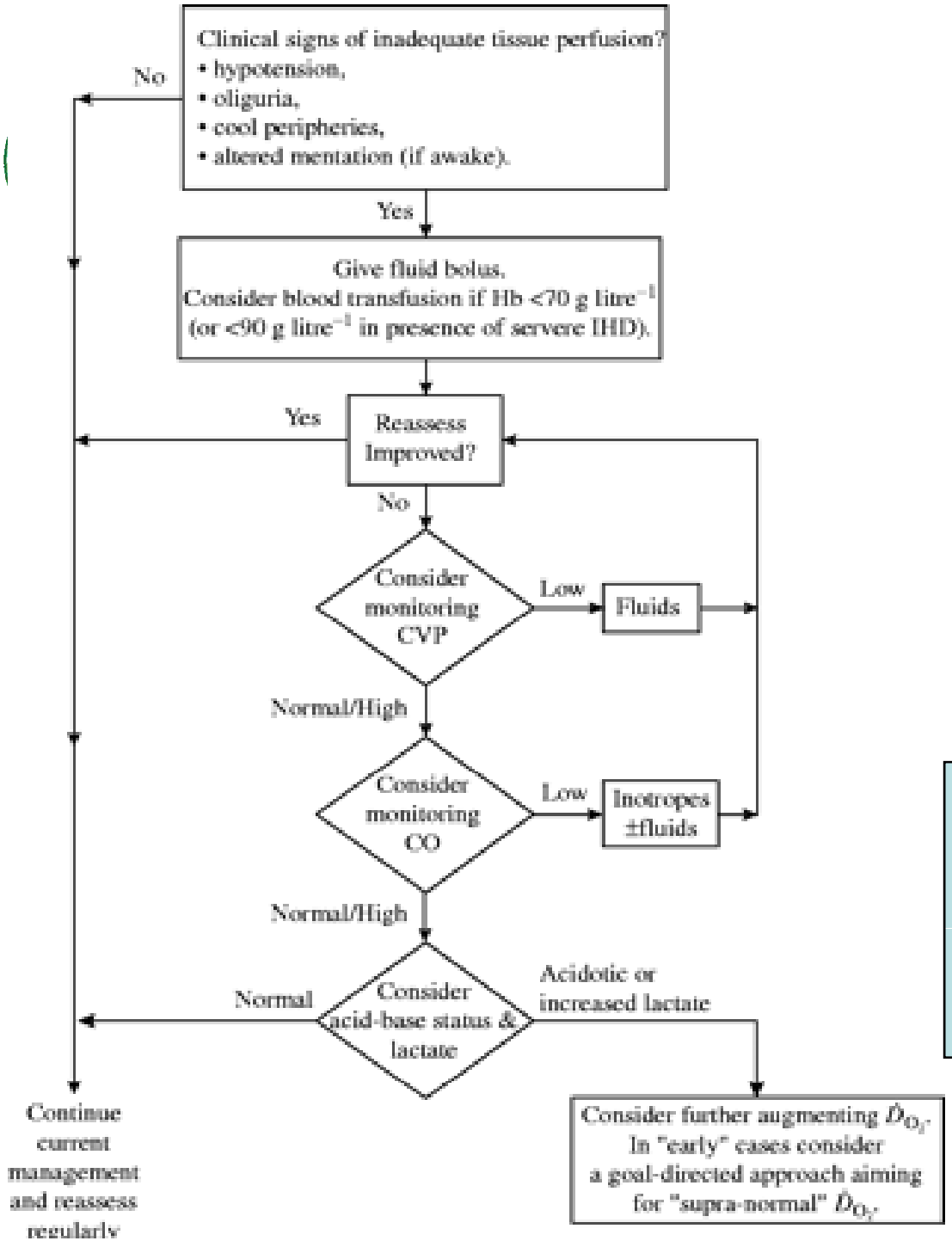


Normal Tongue



Cadiogenic Shock

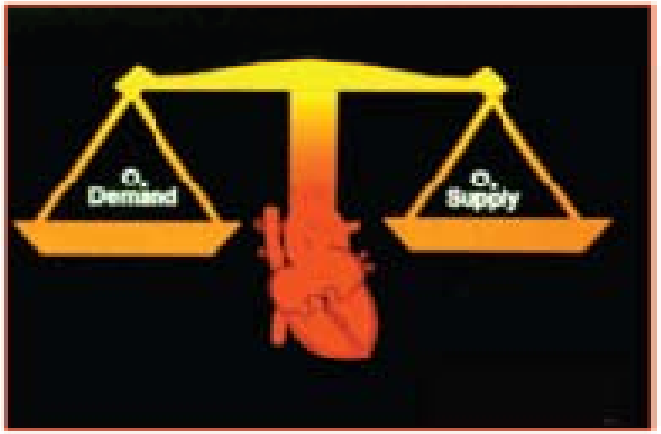
Curr Opin Crit Care. 2001 Jun;7(3):200-3
Curr Opin Crit Care. 2005 Jun;11(3):240-4



Goal-Directed Therapy

大河满了——小溪？

Goal-directed Therapy



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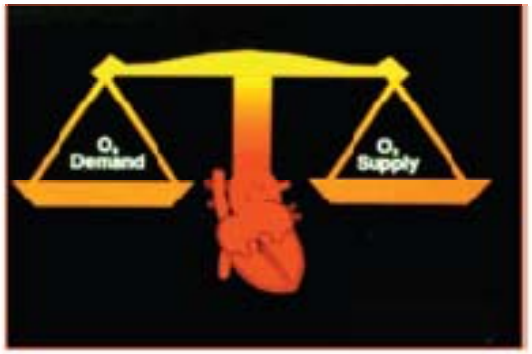

"Upstream" endpoints of resuscitation

Hemodynamic parameters
- Preload (CVP, PCWP)
- Afterload (MAP, SVR)
- Contractility (SV)
- Heart rate (BPM)
- Shock index (HR/SBP)
- Coronary perfusion pressure

DO_2 parameters
- PaO_2
- Hemoglobin
- Cardiac output

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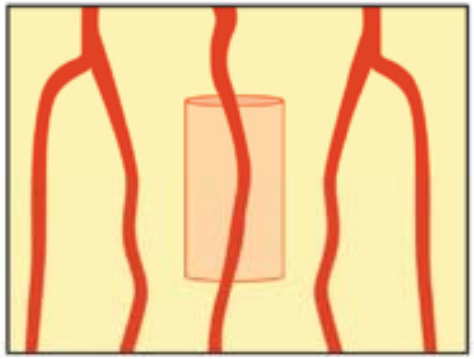
Microcirculation



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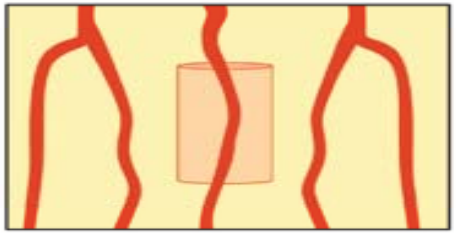
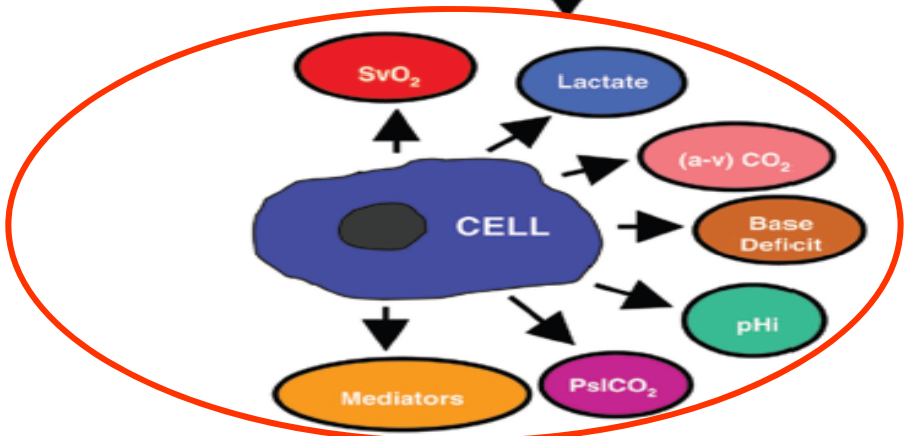
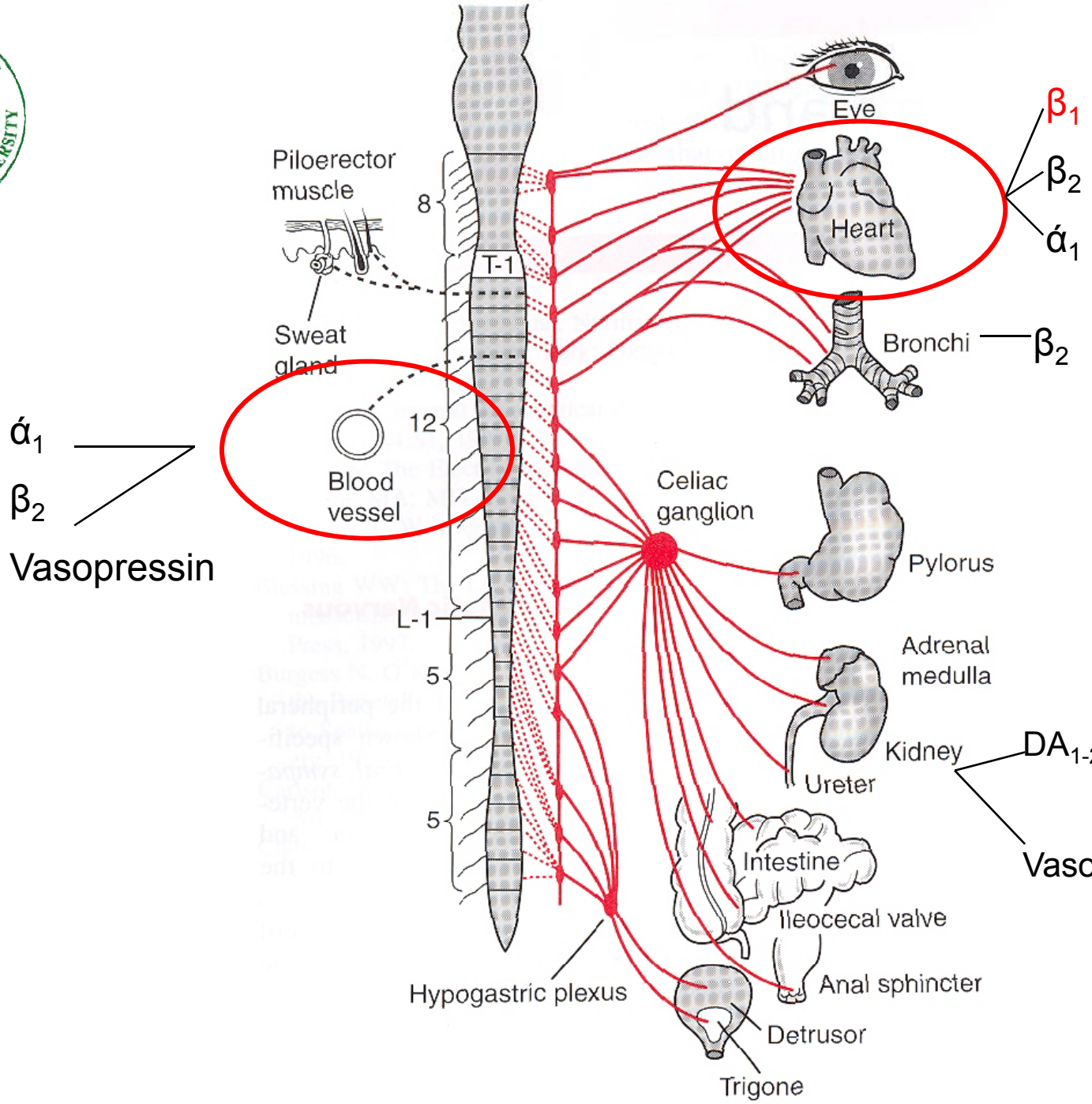


"Downstream" markers of the effectiveness of resuscitation



关注“下游”标志物

- SvO2
- Lactate
- (a-v)CO2
- Base deficit
- pHi
- PslCO2
- mediators


Eye
β1
β2
α1
Heart
Piloerector muscle
8
T-1
Sweat gland
Bronchi
β2
α1
β2
Vasopressin
12
Blood vessel
Celiac ganglion
Pylorus
L-1
5
Adrenal medulla
Kidney
DA1-2
Ureter
5
Intestine
Ileocecal valve
Vasopressin
Anal sphincter
Hypogastric plexus
Detrusor
Trigone

血管活性药物

- 提供充足的组织氧供
- 维持重要器官功能
- 维持全身血压

The main factors influencing blood pressure are:

  - **Cardiac output (CO)**▸驱因，正性肌力药物
  - **Peripheral resistance (PR)** ▸血管活性药物
  - **Blood volume** ▸晶、胶体，血制品

- 联合用药减少不良反应

Catecholamines and Sites of Action

Drug	Site of Action	Dose Range (μg/kg/min)	Hemodynamic Effects	Adverse Effects
Isoproterenol	β_1- and β_2-receptors No α_1 effects	0.05-0.5 (β only)	↑ inotropy, ↑ HR, ↓ MAP via β_1- and β_2-receptors Reduced PVR and SVR	Tachycardia and arrhythmias
Dopamine	β_1- and β_2-receptors α_1-receptors in periphery DA_1 and DA_2 receptors in the kidney	0.5-5 (dopaminergic); 5-10 (β and dopaminergic); >10 (α and β); >20 (α)	↑ inotropy, ↑ MAP, ↑ PVR. At <10 μg/kg, inotropic effects predominate Renal effects at <3 μg/kg	Tachycardia post-CPB Increasing α effects >10 μg/kg/min leads to increases in SVR and PVR. Tissue necrosis
Dobutamine	β_1- and β_2-receptors ($\beta_1 > \beta_2$)	5-10 (α and β)	↑ inotropy, ↑ HR via β_1- and β_2-receptors Dilates coronary arteries	Tachycardia post-CPB. Vasodilator effects may
Epinephrine	β_1-, β_2-, and α_1-receptors Minimal β_2 effects	0.01-0.02 (β); 0.02-0.5 (α and β)	↑ inotropy, ↑ HR and MAP via β_1-receptors. Vasodilator at low doses via β_2-receptors	Tachycardia Vasoconstiction at higher doses via α-receptors Hyperglycemia Myocardial necrosis increased afterload

CPB, cardiopulmonary bypass; HR, heart rate; MAP, mean arterial pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

Bohn (2006). Inotropic Agents in Heart Failure in Children and Young Adults. Chang & Towbin.

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Norepinephrine	α_1- and β_1-receptors Minimal β_2 effects	0.01-0.5 (α and β)	↑ MAP via α_1-receptors	Vasoconstriction and increased afterload

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		5-10 (β and dopaminergic);	At <10 μg/kg, inotropic effects predominate	>10 μg/kg/min leads to increases in
	DA_1 and DA_2 receptors in the kidney	>10 (α and β); >20 (α)	Renal effects at <3 μg/kg	SVR and PVR. Tissue necrosis
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Drug	Site of Action	Dose Range (μg/kg/min)	Hemodynamic Effects	Adverse Effects
Isoproterenol	β_1- and β_2-receptors No α_1 effects	0.05-0.5 (β only)	↑ inotropy, ↑ HR, ↓ MAP via β_1- and β_2-receptors Reduced PVR and SVR	Tachycardia and arrhythmias
Dopamine	β_1- and β_2-receptors α_1-receptors in periphery DA_1 and DA_2 receptors in the kidney ($\beta_1 > \beta_2$) Minimal α_1 effects	0.5-5 (dopaminergic); 5-10 (β and dopaminergic); >10 (α and β); >20 (α)	↑ inotropy, ↑ MAP, ↑ PVR. At <10 μg/kg, inotropic effects predominate Renal effects at <3 μg/kg	Tachycardia post-CPB Increasing α effects >10 μg/kg/min leads to increases in SVR and PVR. Tissue necrosis
Dobutamine	β_1- and β_2-receptors ($\beta_1 > \beta_2$) Minimal α_1 effects	5-10 (α and β)	↑ inotropy, ↑ HR, β_1- and β_2-receptors ↓ PVR and SVR Dilates coronary arteries	Vasodilator effects may result in reduced MAP
Epinephrine	β_1-, β_2-, and α_1-receptors	0.01-0.02 (β); 0.05-0.5 (α and β)	↑ inotropy, ↑ HR and Vasodilator at low doses via β_2-receptors	Tachycardia Hyperglycemia Myocardial necrosis
Norepinephrine	α_1- and β_1-receptors Minimal β_2 effects	0.01-0.5 (α and β)	↑ MAP via α_1-receptors	Vasoconstriction and increased afterload

CPB, cardiopulmonary bypass; HR, heart rate; MAP, mean arterial pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

Bohn (2006). Inotropic Agents in Heart Failure. Heart Failure in Children and Young Adults. Chang & Towbin.

肾上腺素&微循环

- 肾上腺素：减少微循环血流，导致缺血；可能是导致心肺复苏后神经功能恢复差的原因之一！

Research

Open Access

Increasing arterial blood pressure with norepinephrine does not improve microcirculatory blood flow: a prospective study

Arnaldo Dubin[1,2], Mario O Pozo[3], Christian A Casabella[1], Fernando Pálizas Jr[3], Gastón Murias[3], Miriam C Moseinco[1], Vanina S Kanoore Edul[1,2], Fernando Pálizas[3], Elisa Estenssoro[1] and Can Ince[5]

Abstract

Introduction Our goal was to assess the effects of titration of a norepinephrine infusion to increasing levels of mean arterial pressure (MAP) on sublingual microcirculation.

Methods Twenty septic shock patients were prospectively studied in two teaching intensive care units. The patients were mechanically ventilated and required norepinephrine to maintain a mean arterial pressure (MAP) of 65 mmHg. We measured systemic hemodynamics, oxygen transport and consumption (DO_2 and VO_2), lactate, albumin-corrected anion gap, and gastric intramucosal-arterial PCO_2 difference (ΔPCO_2). Sublingual microcirculation was evaluated by sidestream darkfield (SDF) imaging. After basal measurements at a MAP of 65 mmHg, norepinephrine was titrated to reach a MAP of 75 mmHg, and then to 85 mmHg. Data were analyzed using repeated measurements ANOVA and Dunnett test. Linear trends between the different variables and increasing levels of MAP were calculated.

Results Increasing doses of norepinephrine reached the target values of MAP. The cardiac index, pulmonary pressures, systemic vascular resistance, and left and right ventricular stroke work indexes increased as norepinephrine infusion was augmented. Heart rate, DO_2 and VO_2, lactate, albumin-corrected anion gap, and ΔPCO_2 remained unchanged. There were no changes in sublingual capillary microvascular flow index (2.1 ± 0.7, 2.2 ± 0.7, 2.0 ± 0.8) and the percent of perfused capillaries (72 ± 26, 71 ± 27, $67 \pm 32\%$) for MAP values of 65, 75, and 85 mmHg, respectively. There was, however, a trend to decreased capillary perfused density (18 ± 10,17 ± 10,14 ± 2 vessels/mm², respectively, ANOVA $P = 0.09$, linear trend $P = 0.045$). In addition, the changes of perfused capillary density at increasing MAP were inversely correlated with the basal perfused capillary density ($R^2 = 0.95$, $P < 0.0001$).

Conclusions Patients with septic shock showed severe sublingual microcirculatory alterations that failed to improve with the increases in MAP with norepinephrine. Nevertheless, there was a considerable interindividual variation. Our results suggest that the increase in MAP above 65 mmHg is not an adequate approach to improve microcirculatory perfusion and might be harmful in some patients.

去甲肾上腺素&微循环

- 去甲肾上腺素：MAP升高，但乳酸仍高，毛细血管密度降低！

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Key Concepts

- The predominant β-AR in the heart is the β_1-AR (75%).
- β_2-ARs are largely found in vascular smooth muscle.
- Ά$_1$-ARs predominate in vascular smooth muscle although they are present in the neonatal myocardium.

Key Concepts

- Catacholamines are good in the short term for hemodynamic support but most increase myocardial oxygen demand, increase diastolic pressures, and can lead to apoptosis

- PDE inhibitors, while increasing intracellular Ca^{+}, are lusiotropic and inotropic agents that do not increase myocardial O_2 demand and are not associated with tachyphylaxis.

Key Concepts

- A strategy of combining a PDE inhibitor with a catecholamine may be the best approach to support of the myocardium and circulation.

- Most inotropic agents to date have a common final intracellular pathway of increased intracellular Ca^{+}, which may ultimately lead to cell (myocyte) death.

something better?

- A new generation of inotropic agents known as calcium-sensitizing agents achieve their positive inotropic effects without an increase in intracelluar Ca^{+} or myocardial O_2 consumption. Unfortunately they early studies of the first of these drugs demonstrated less benefit than was anticipated

Levosimendan

复苏

- **Resuscitation**
  - Resuscitation goals
    - Time
    - CV parameters
  - Fluid management
    - Crystalloid vs. colloid
  - Vasopressor management
- **“Low-dose” corticosteroid therapy**
- **Microvascular circulation**

复苏目标

- **BP** **MAP>65 mmHg/SBP>90 mmHg**
- **CVP** **8-12 mmHg**
- **Urine output** **0.5-1 ml/kg/hr**
- **ScvO2** **>70%**
- **Hgb** **>70-100 g/L**
- **pH** **>7.30**
- **Lactate** **<4**

However time frame is likely as important as absolute goals!!

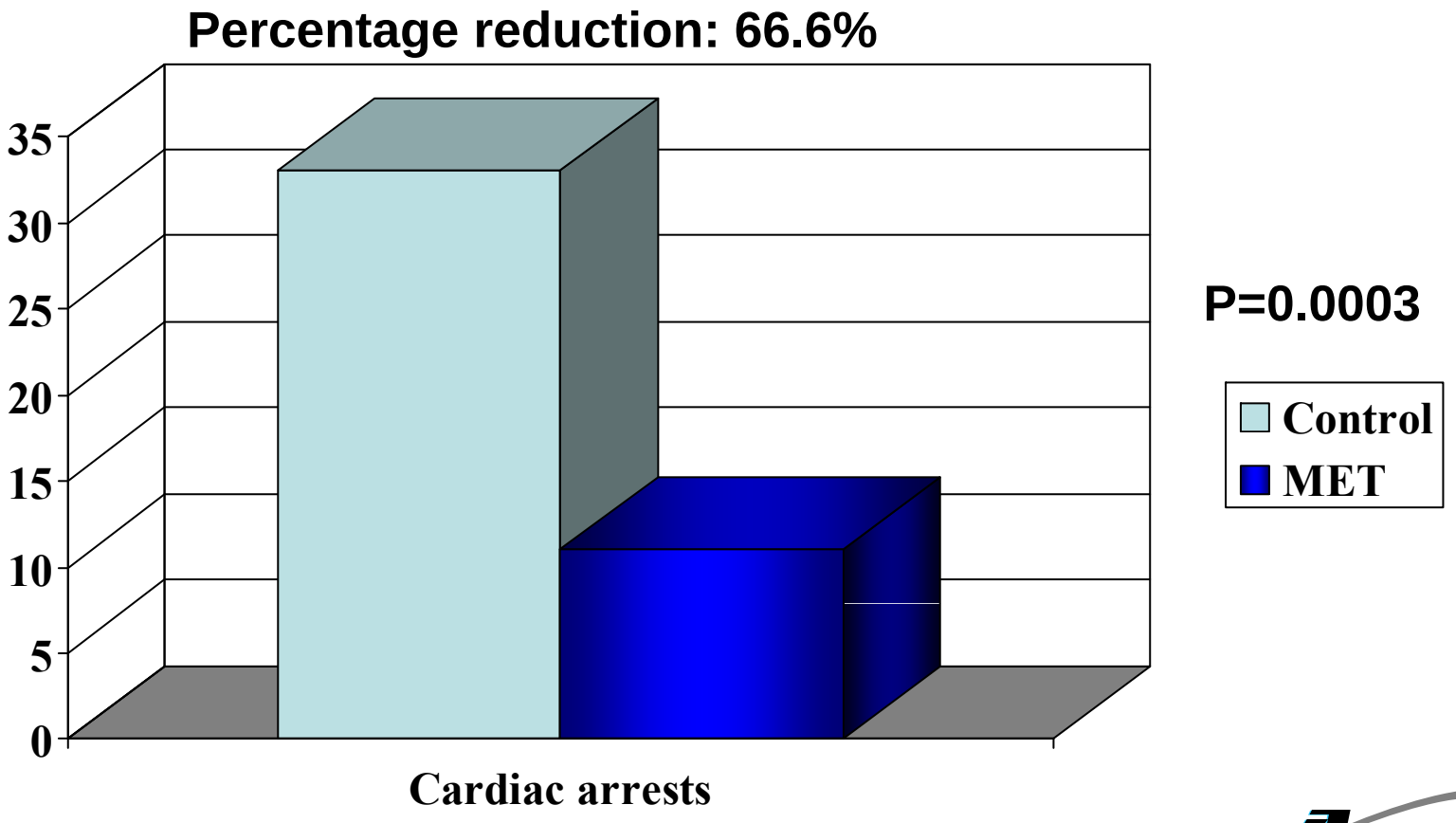
Conclusion

- **Prevention**
- **MET (medical emergent team)**
- **Early goal directed management**
- **Sepsis protocol**
- **Organ supportive and replacement treatment**

"Microcirculation Recruitment Manoeuvres"

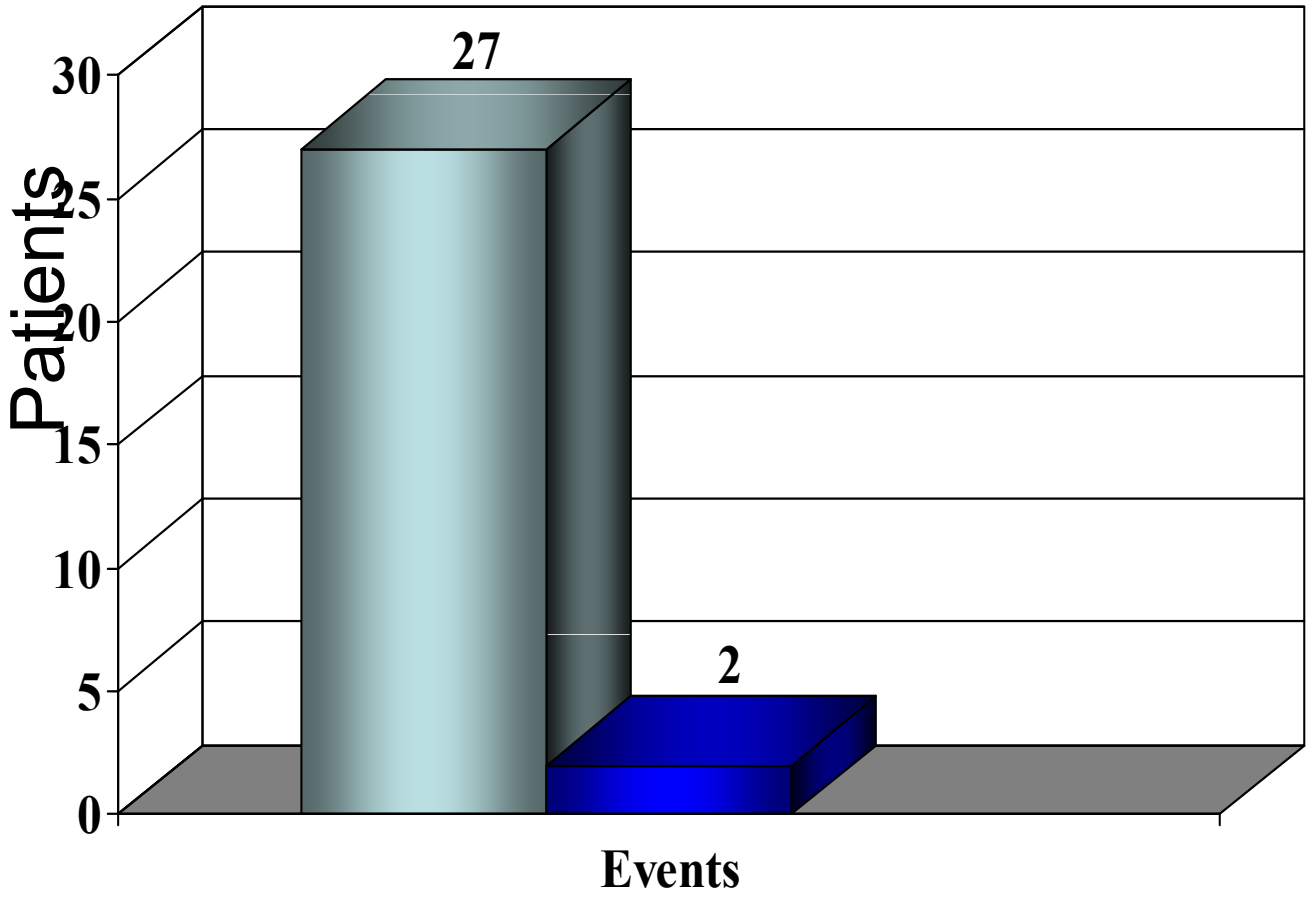
Open the microcirculation and keep it open by support of the pump, fluids, vasodilators and restricted use of vasopressor agents.

Impact of medical emergency team on unexpected cardiac arrests



Bellomo R et al. *Crit Care Med* 2004;32:916-921.

Impact of Medical Emergency Team on ARF requiring Renal Replacement Therapy



p<0.001

Bellomo R et al. *Crit Care Med* 2004;32:916-921.

存在问题

- 究竟有无疗效确切的改善微循环的药物？
- 改善微循环，微循环能否充分复苏？
- 微循环充分复苏，患者预后能否切实得到改善？

路漫漫其修远兮，
吾将上下而求索！

Thank you for your attention!