Dr Sau Yee Lam

BLOOD FLOW DISTRIBUTION AND MICROCIRCULATION IN CRITICALLY ILL

The Concept of Ventriculo-Arterial Coupling

Why do warm-blooded animals have a high systemic blood pressure?

Why do warm-blooded animals have a high systemic blood pressure?

Very "Expensive" Trait

- Requires increased muscular pumping
  - myocardial at risk of ischemia and infarction
- Stresses arterial conduits
  - stress degeneration
    - Atherosclerosis
    - Aneurysms
  - Rupture of congenital aneurysms
- End-organ dysfunction
  - Heart, brain, kidneys

Regulation of Organ Blood Flow

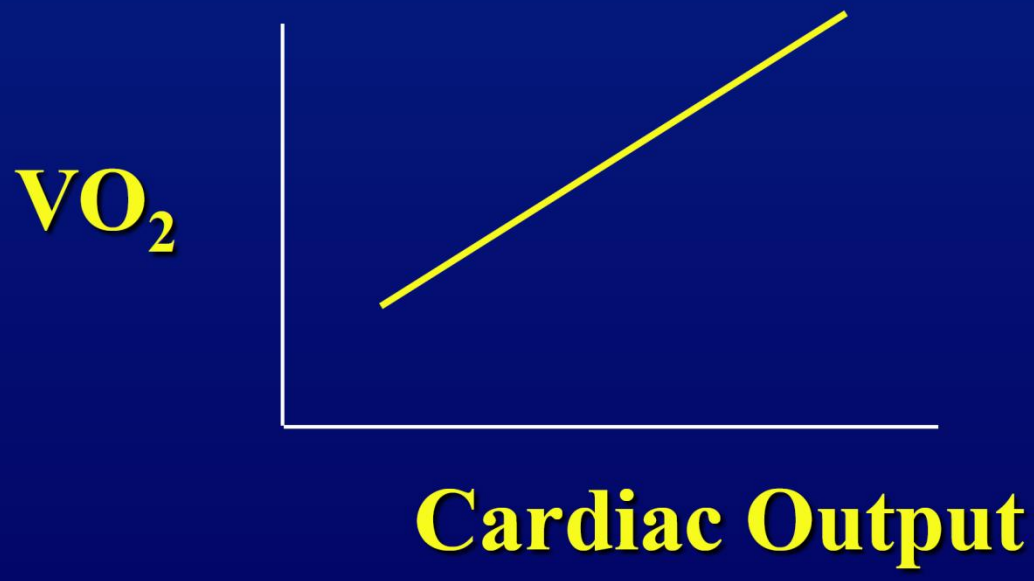
- High intra-organ input resistance
  - Arteriolar tone, precapillary sphincter
  - Tissue interstitial pressure
- High input pressure
- Primary method to increase organ blood flow
  - Local vasodilation in metabolically active tissues
  - Passive increase in arterial inflow

Cardiac output important only to maintain pressure

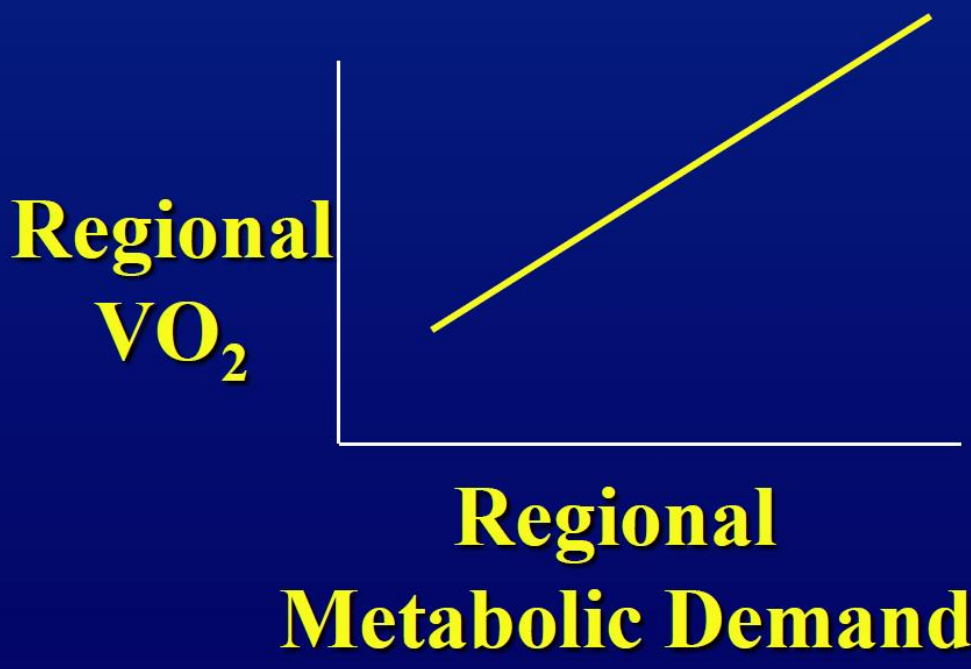
Rationale for defense of arterial pressure

Allows autoregulation of blood flow distribution

Cardiac Output is Proportional to Global Oxygen Uptake



Regional Blood Flow is Proportional to Regional Metabolic Demand



Global autonomic control important in optimizing TO_2

Vasoconstrictor tone alters the dysxoia threshold in hypoxic hypoxia

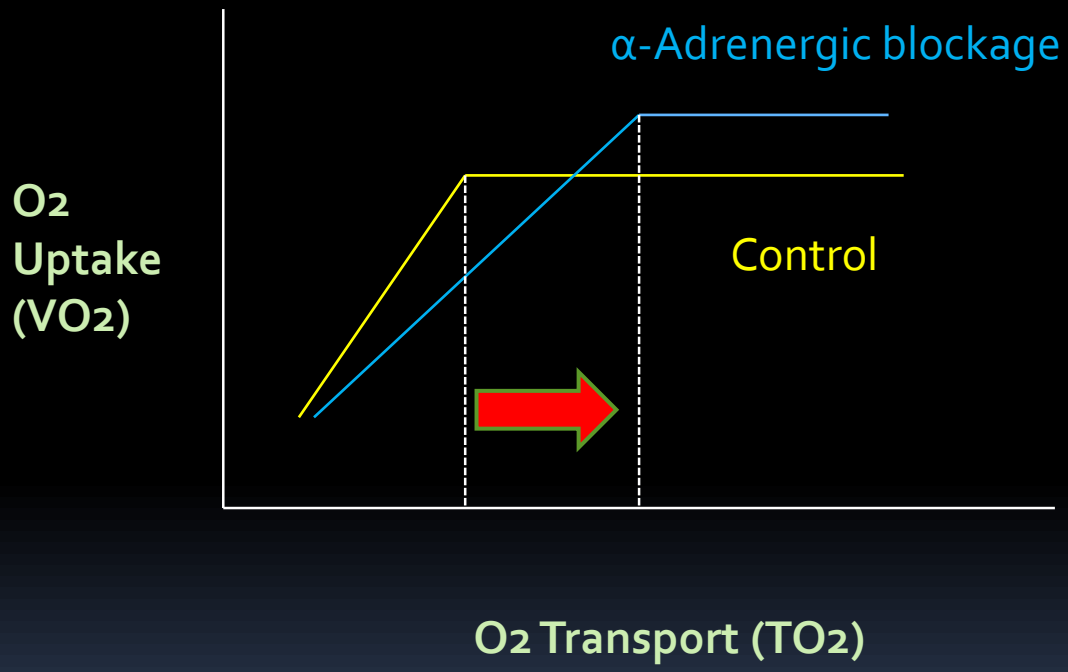
Cain et al. J Appl Physiol 45: 219-24, 1978

Adrenergic vasoconstriction augments tissue O_2 extraction during

reduction in O_2 delivery

Maginniss et al. J Appl Physiol 76: 1454-61, 1994

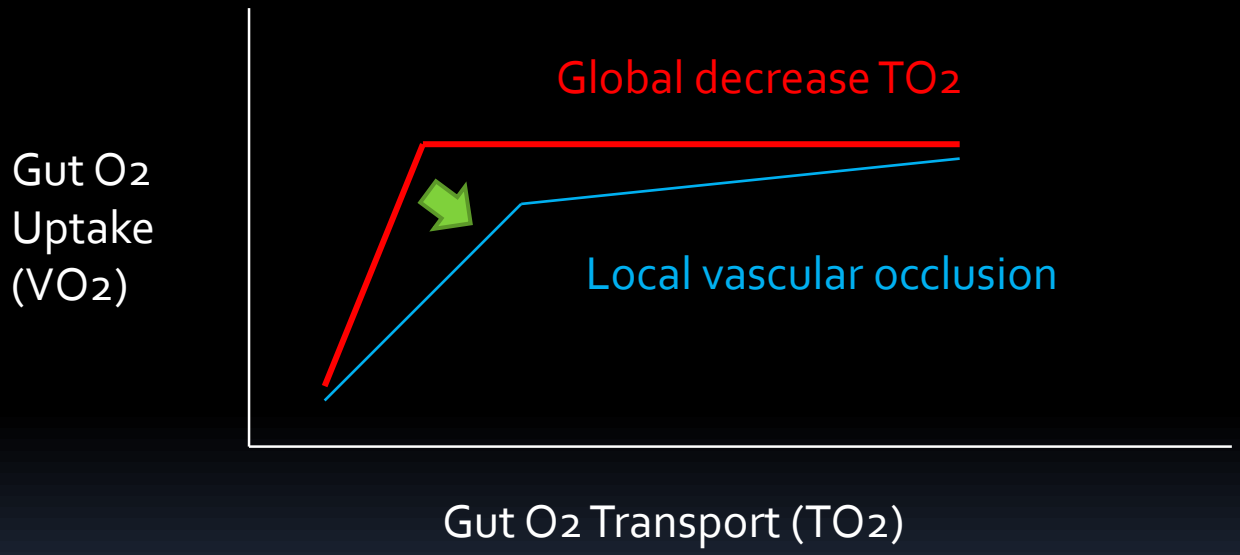
Loss of Autonomic Tone Impairs O2 Distribution



Cain et al. J Appl Physiol 45: 219-24, 1978

Increased Autonomic Tone (global decrease in TO_2)

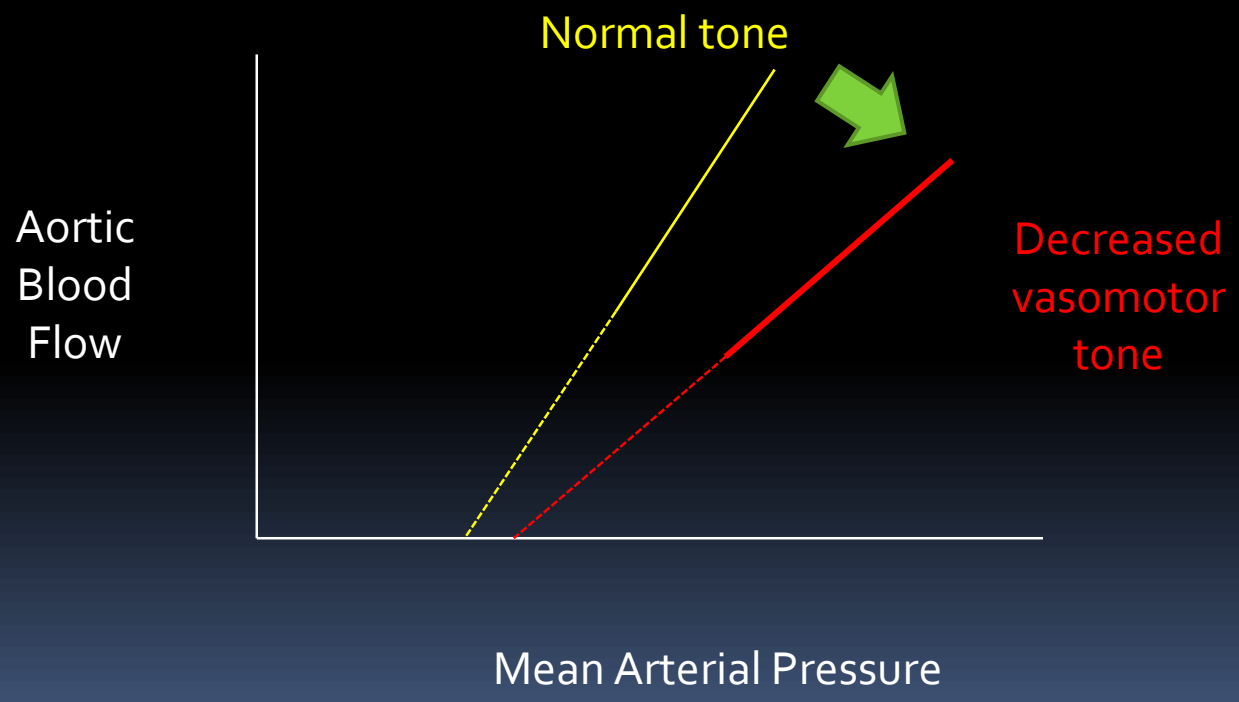
Improves O_2 Extraction



Maginniss et al/ J Appl Physiol 76:1451-64, 1994

Vascular Pressure-Flow Relations

Effect of Decreasing Vasomotor tone on Pressure-Flow Coupling



Control of Regional Blood Flow Distribution

Different vascular beds have different O2 extraction capacities (Regional VO_2/DO_2)

Schelichtig et al J Appl Physiol 70:169-78, 1991

Different vascular beds have different passive pressure-flow relations (regional P/Q)

Kramer et al. Am Rev Respir Dis 139: A540, 1989

The absolute amount of blood flow redistribution is limited in stress states

Romand et al. Am J Respir Crit Care Med 153:203-10, 1996

Blood flow is diverted away from vascular bed that can most avidly extract O_2

Marked decrease in muscle and liver blood flow

Lesser decrease in kidney and gut blood flow

- If perfusion pressure is maintained

No decease in brain blood flow

- If perfusion pressure is maintained

Schlichtig et al J Appl Physiol 70: 169-78, 1991

A lower DO_2 crit than predicted, if proportional flow to all organs remained the same as global flow decreased

Active blood flow redistribution among organs during hemorrhage improves O_2 extraction efficiency

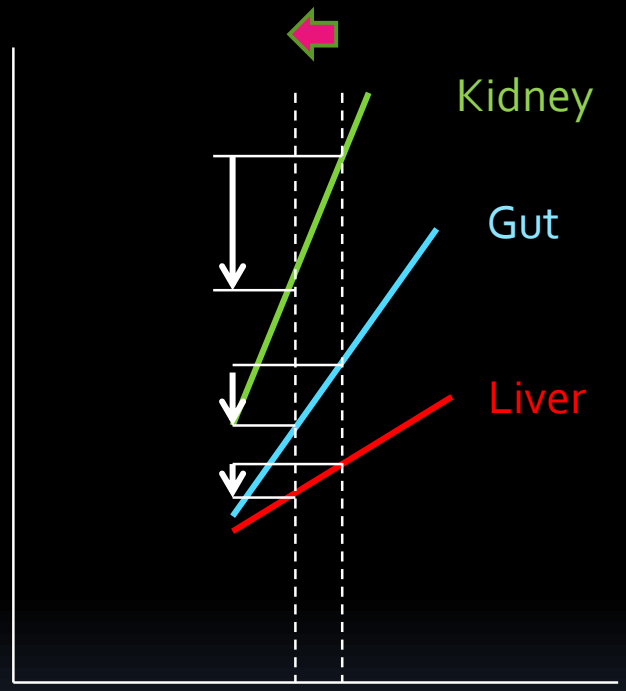
Blood flow tends to be distributed away from organs with better O_2 extraction capacities

Maximizing DO_2crit as global DO_2 declines

Liver → Gut → Kidney

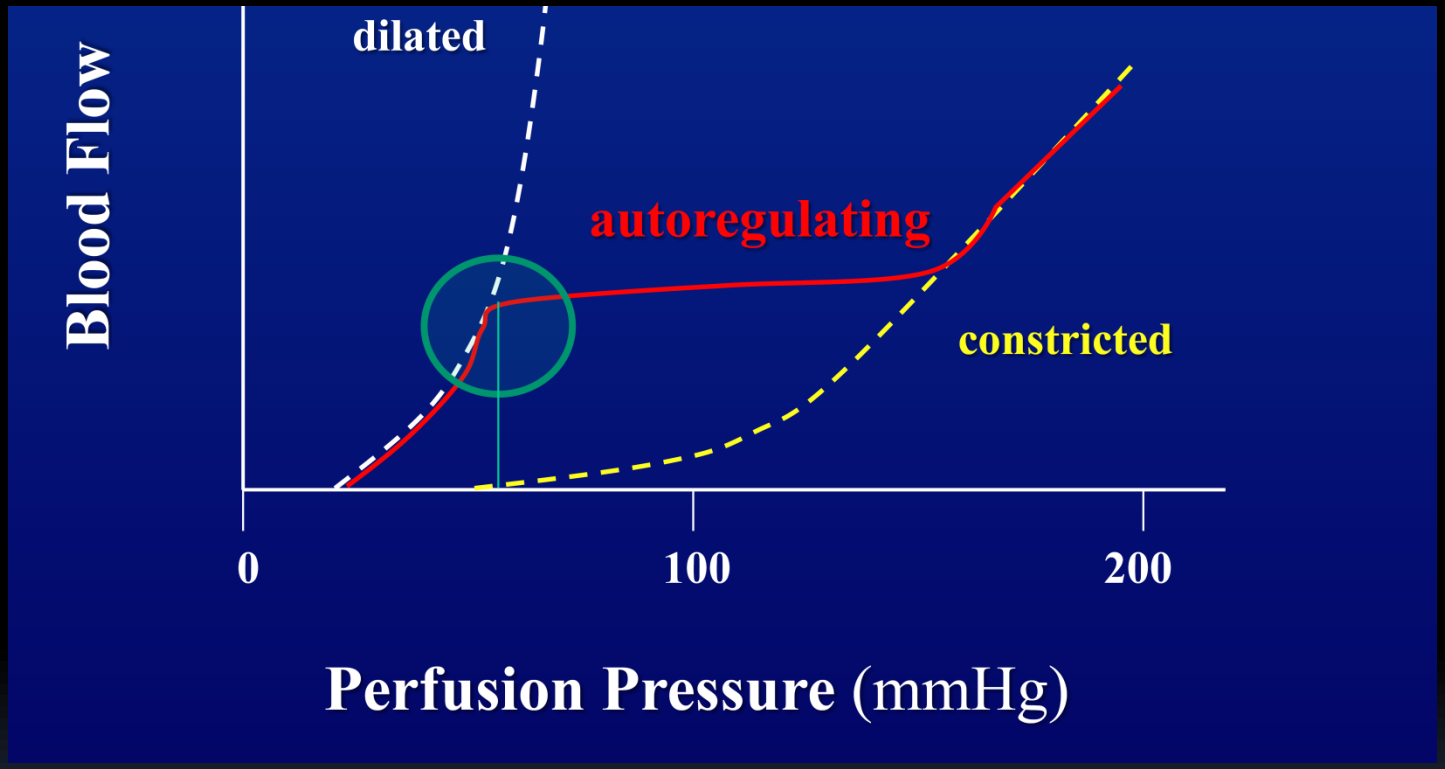
Schlichtig et al J Appl Physiol 70: 169-78, 1991

Passive Pressure-Flow Relations



Phenobarbal-aneasthetized, canine, n=8

Organ Specific Autoregulation



Mean Arterial Pressure is NOT Organ Perfusion Pressure

Relation Between MAP & Perfusion Pressure

- MAP = Diastolic pressure + 1/3 pulse pressure
- Perfusion pressure = Input – Output Pressure

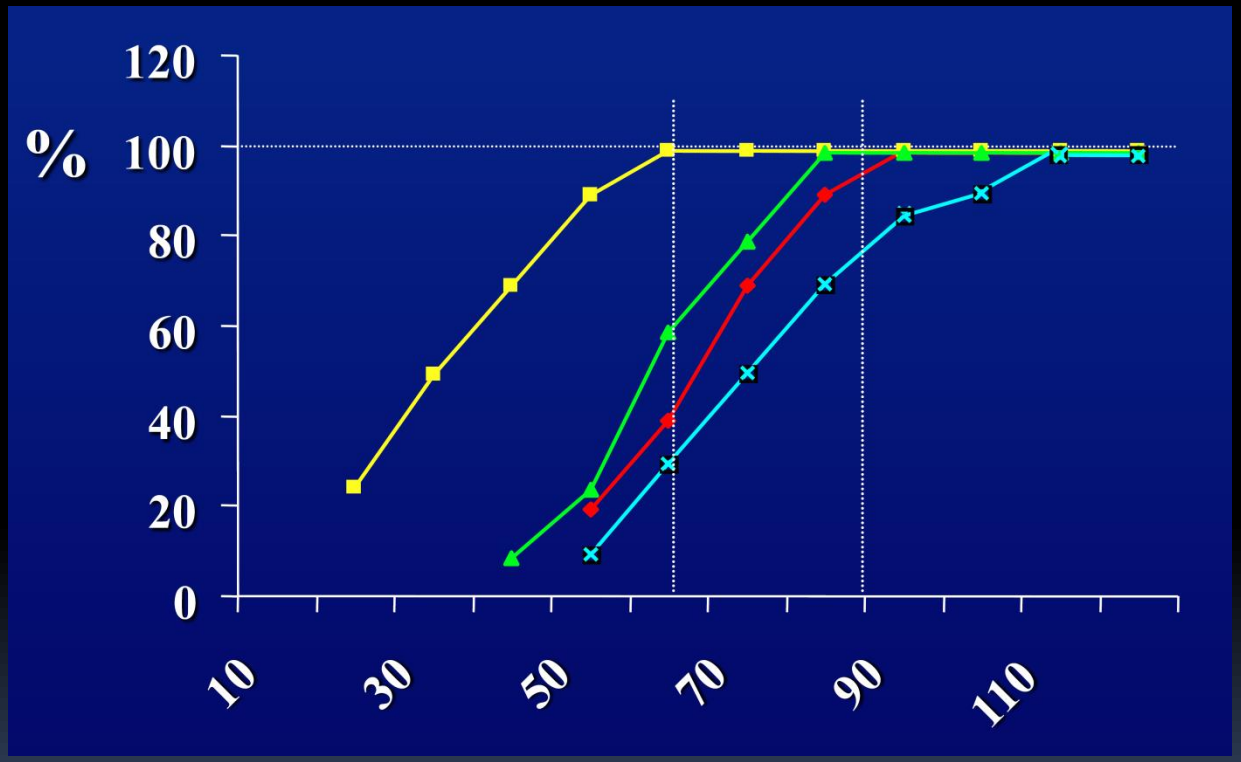
Organ	Input Pressure	Output Pressure
Brain	MAP	CVP(ITP) or ICP
Heart	Diastolic arterial pressure	CVP (ITP)
Kidney, Gut	MAP	CVP or Intra-abd pressure
Skeletal Muscle	MAP	CVP or Interstitial Pressure

Kato & Pinsky. Ann Intensive Care Med 5:41, 2015

Perfusion Pressure and Organ Flow

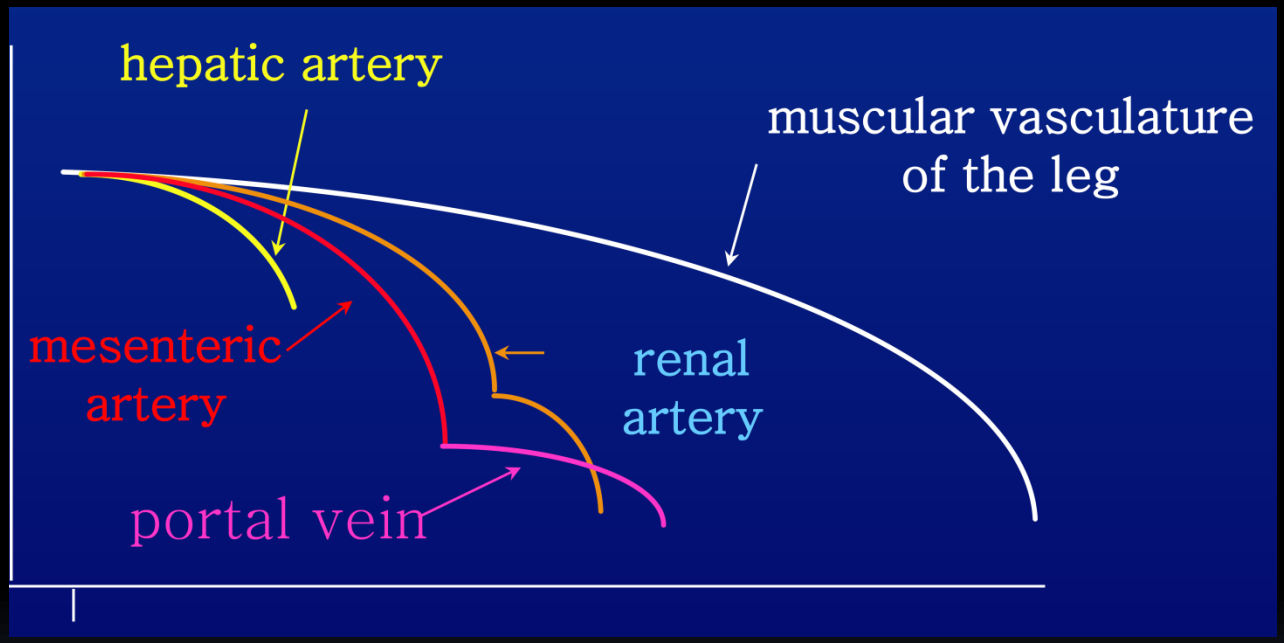
Coronary PP = DAP – LVEDP

Renal PP = MAP – Tissue Pressure



Organ Perfusion Pressure (mmHg)

Input Arterial Pressure Varies Across Vascular Circuits



Perfusion Pressure

Length of Vessel

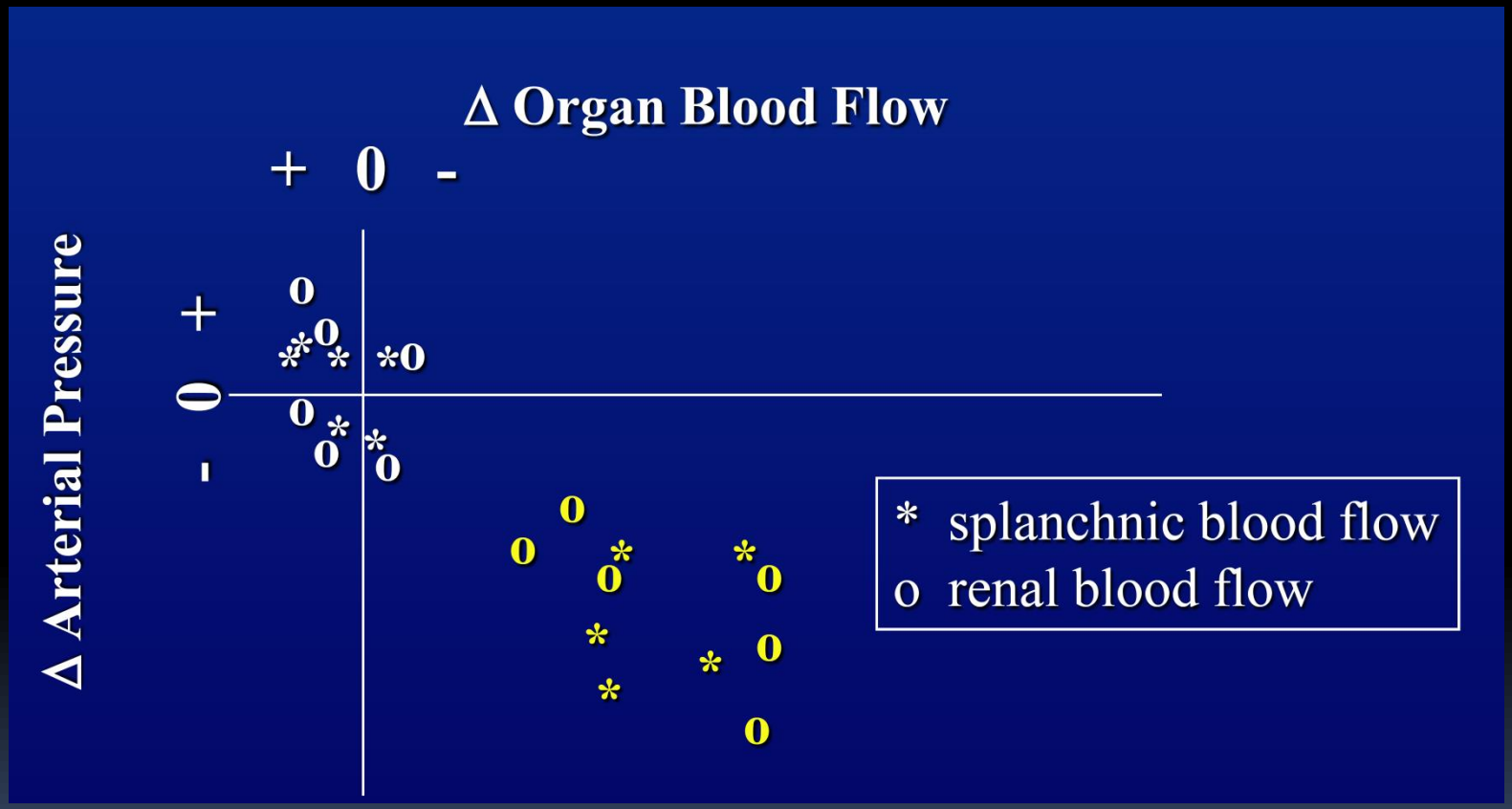
Perfusion Pressure is the Primary Determinants of Local Blood Flow

Blood flow redistribution is limited

- Active blood flow redistribution occurs early in hemorrhage and is limited
- Once established, further reductions in blood flow decrease organ blood flow only if perfusion pressure also decreases

Romand et al. Am J Respir Crit Care Med 153:203-10, 1996

Arterial Pressure is the primary determinate of visceral organ blood flow following hemorrahge during remote exercise



Romand et at. AJRCCM 153:203-210, 1996

Regional blood flow distribution in sepsis

- Dissociation between blood flow and metabolic demand
- Dissociation between nutrient flow and cellular uptake and utilization

Sepsis alters vasomotor tone

- Decreased adrenergic responsiveness
- Pathologic vasoconstriction
  - PGF_2
  - Thromboxane A2
  - Platelet activating factor
  - Leukotrienes
- Pathologic vasodilation
  - Nitric oxide synthase
  - Leukotrienes, 20-HETE

Sepsis alters arteriolar tone

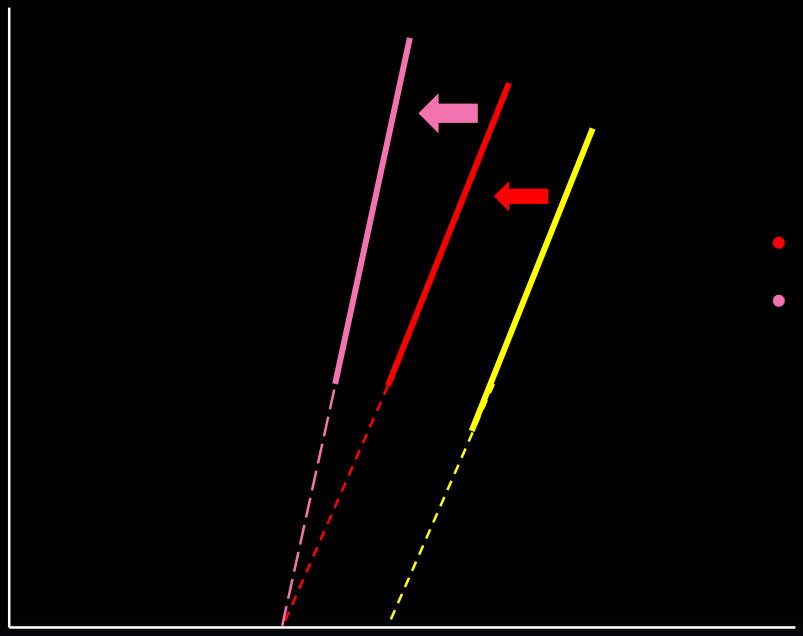
Acute endotoxemia decreases critical closing pressure)Pzf) but does not alter the slope of the pressure-flow (P/Q) relation (<6h)

Pinsky MR & Matuschak GM. J Crit Care 1:18-31, 1986

Sustained sepsis and endotoxemia decreases both Pzf and the slope of P/Q relation (arterial resistance) via systemic iNOS expression

Petros et at. Lancet 338:1557, 1991

Effect of endotoxin of arterial pressure-flow relations



- Initial decrease in Pzf
- Subsequent decrease in slope once iNOS upregulated

Pinsky MR & Matuschak GM. J Crit Care 1:18-31, 1986

Petros et at. Lancet 338:1557, 1991

Sepsis alters the pressure-flow relations among organs

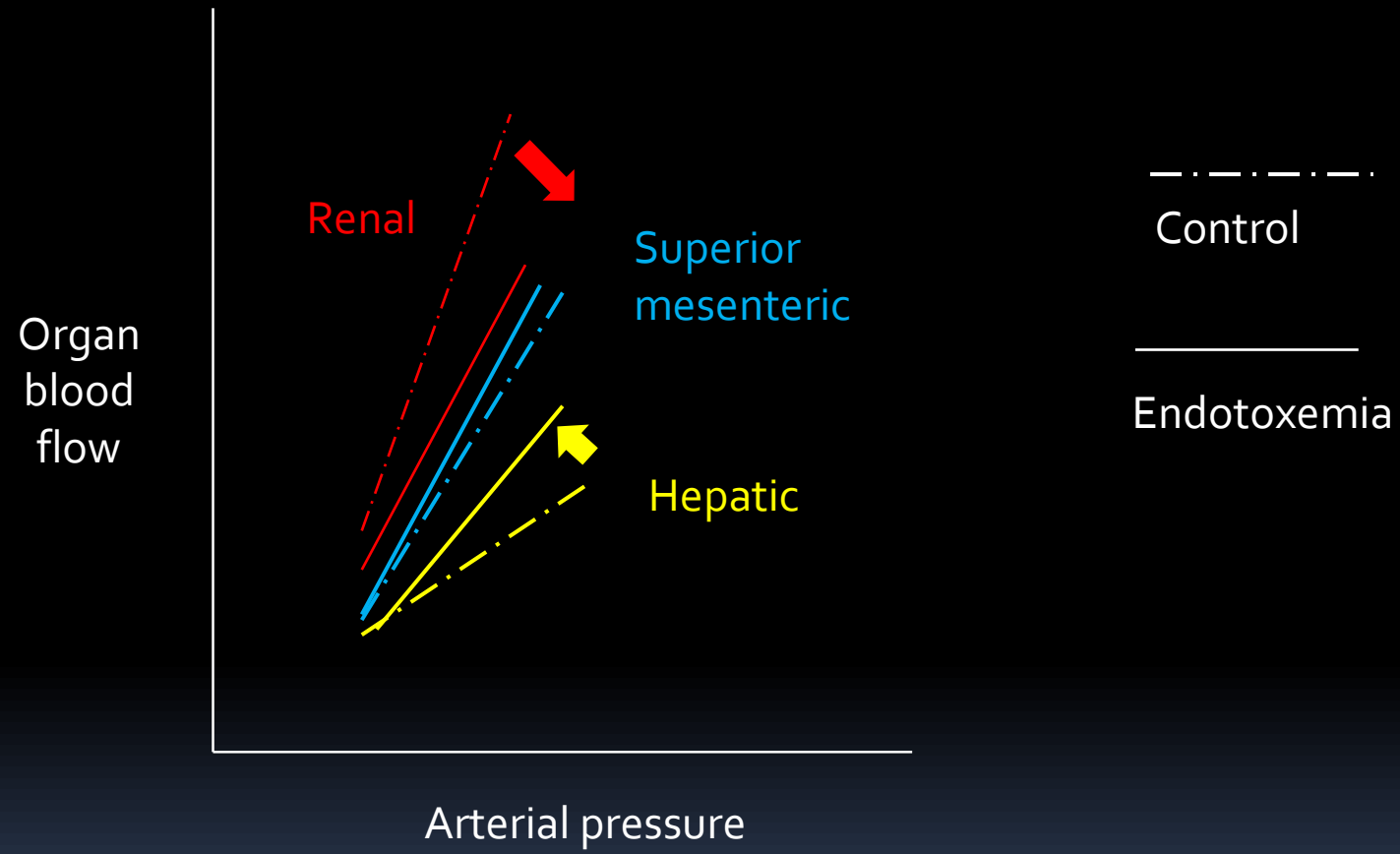
- Blood flow redistribution varies in a non-uniform fashion among visceral organs

Kramer et al. Chest 96:293S, 1989

- Blood flow redistribution not altered by Norepinephrine

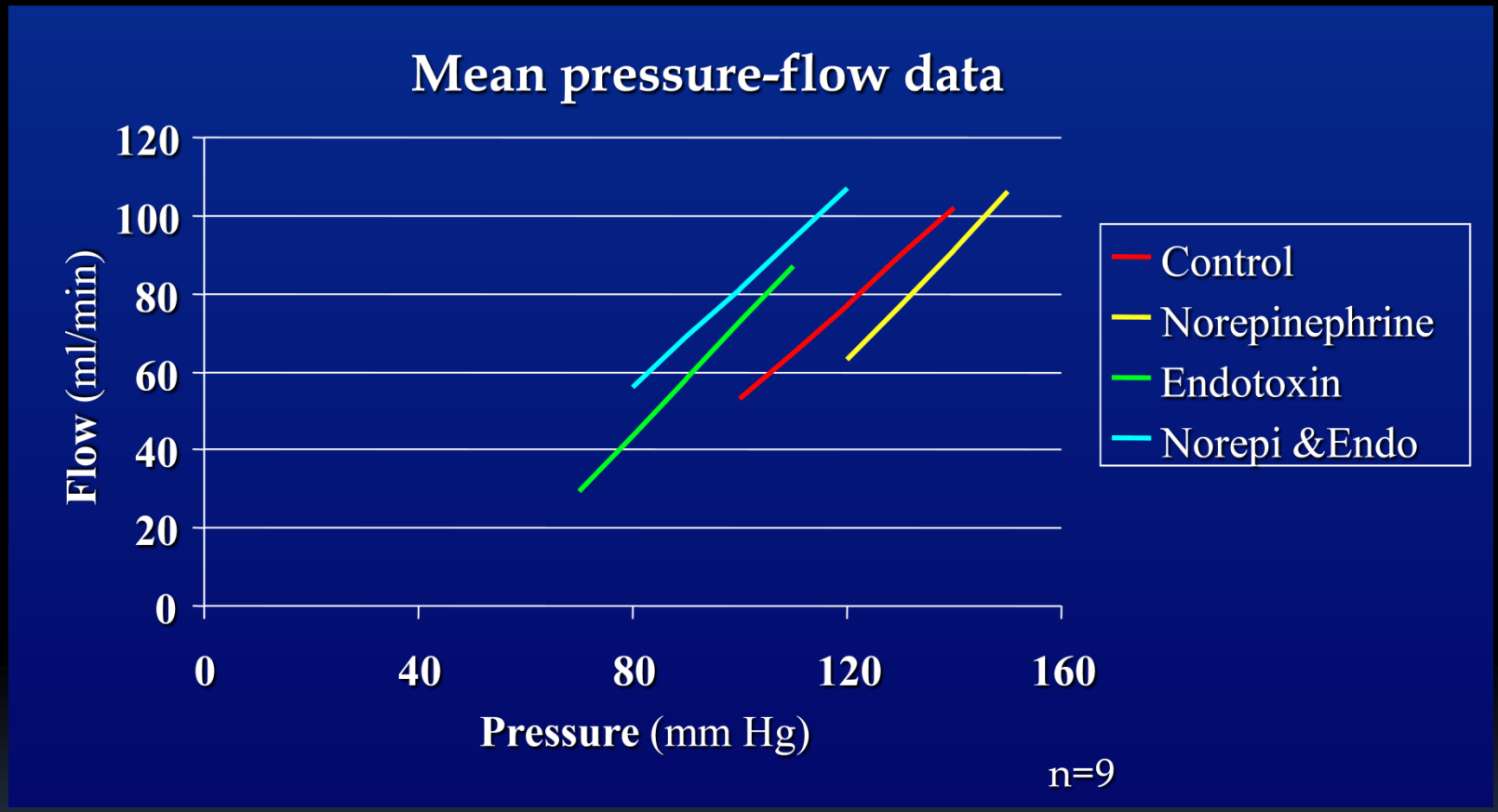
Belloma et al. AJRCCM 159:1186-92, 1999

Effect of endotoxin on visceral arterial pressure-flow relations



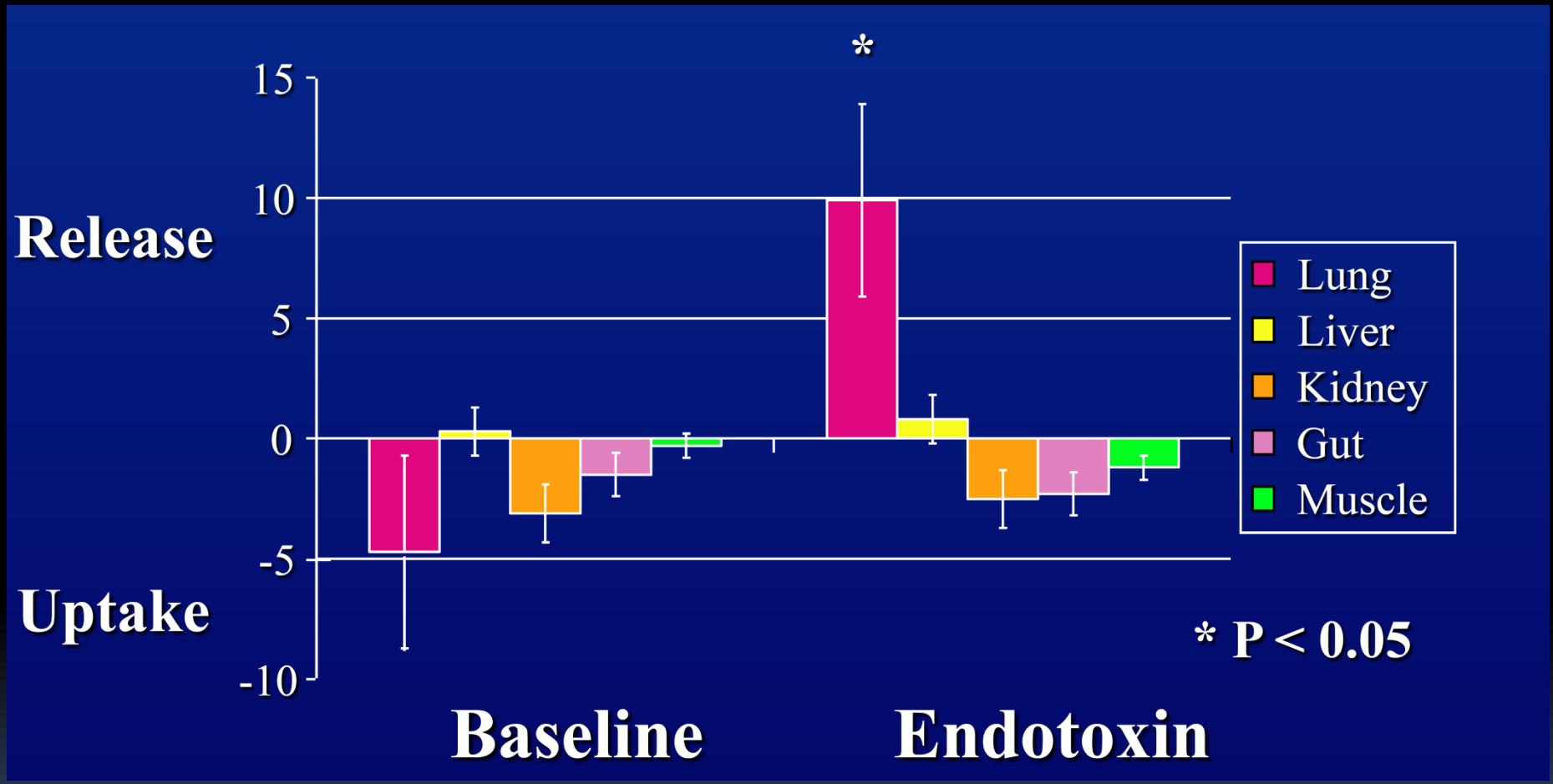
Kramer et al. Chest 96:293S, 1989

Endotoxin and renal blood flow



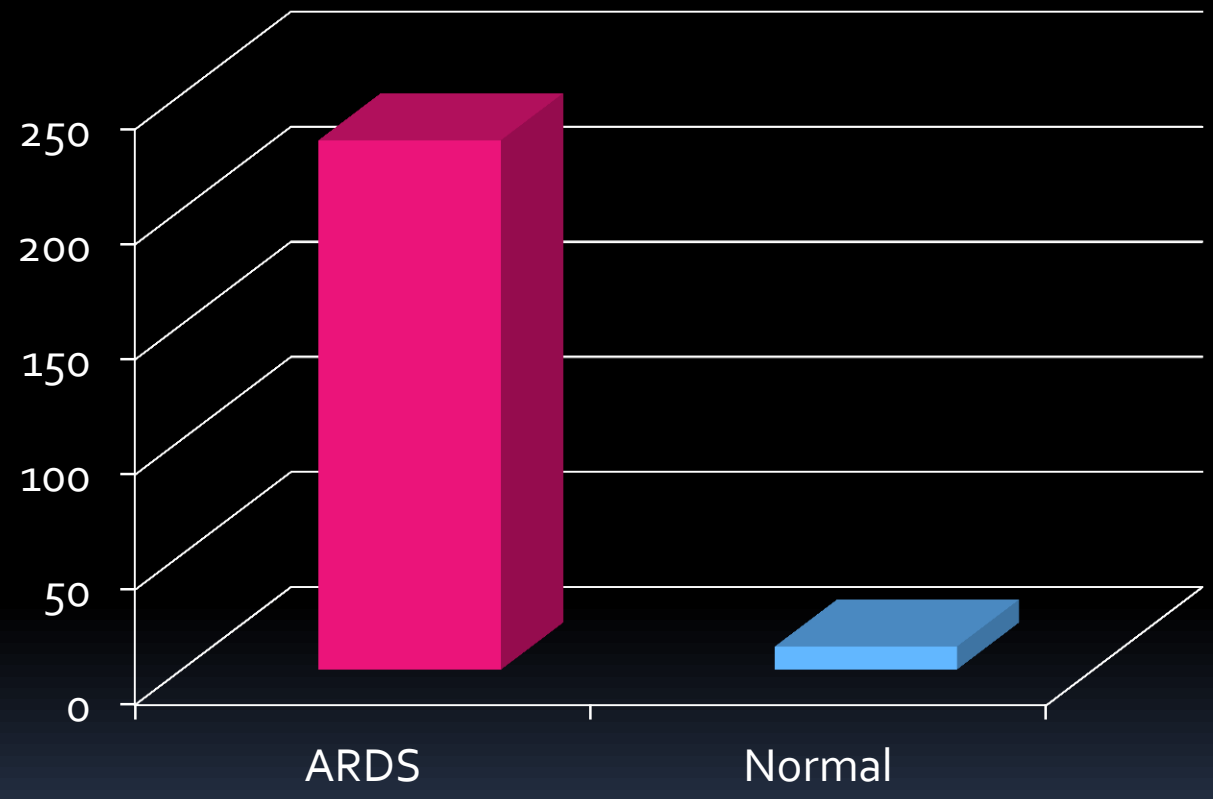
Belloma et al. AJRCCM 159:1186-92, 1999

Lactate flux across various organ beds



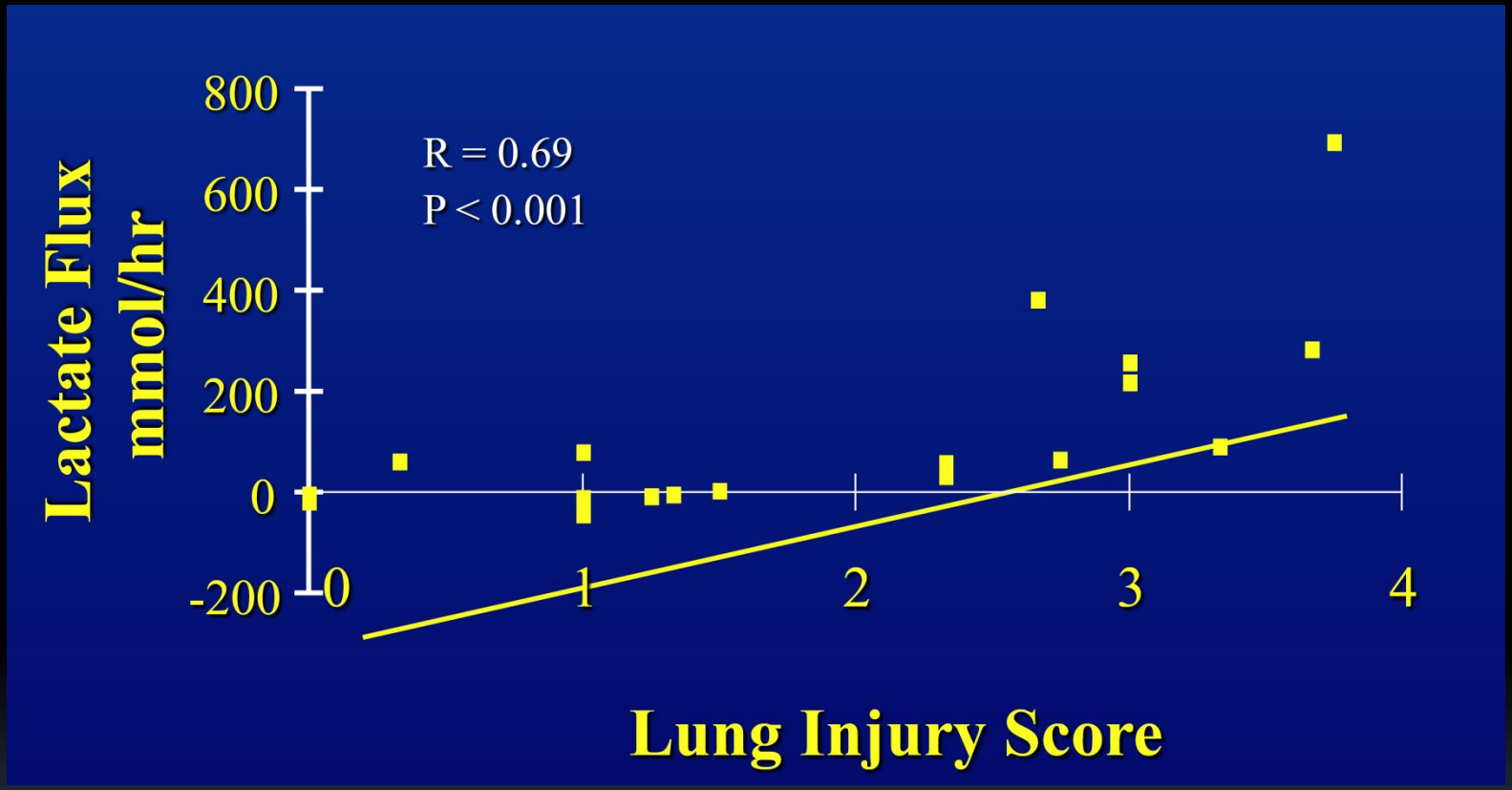
Bellomo et al. Chest 110:198-204, 1996

Lactate release by the lung



Kellum JA, et al. Chest 111:1301-5, 1997

Lung lactate and lung injury



Kellum JA, et al. Chest 111:1301-5, 1997

Lung is a source of lactate

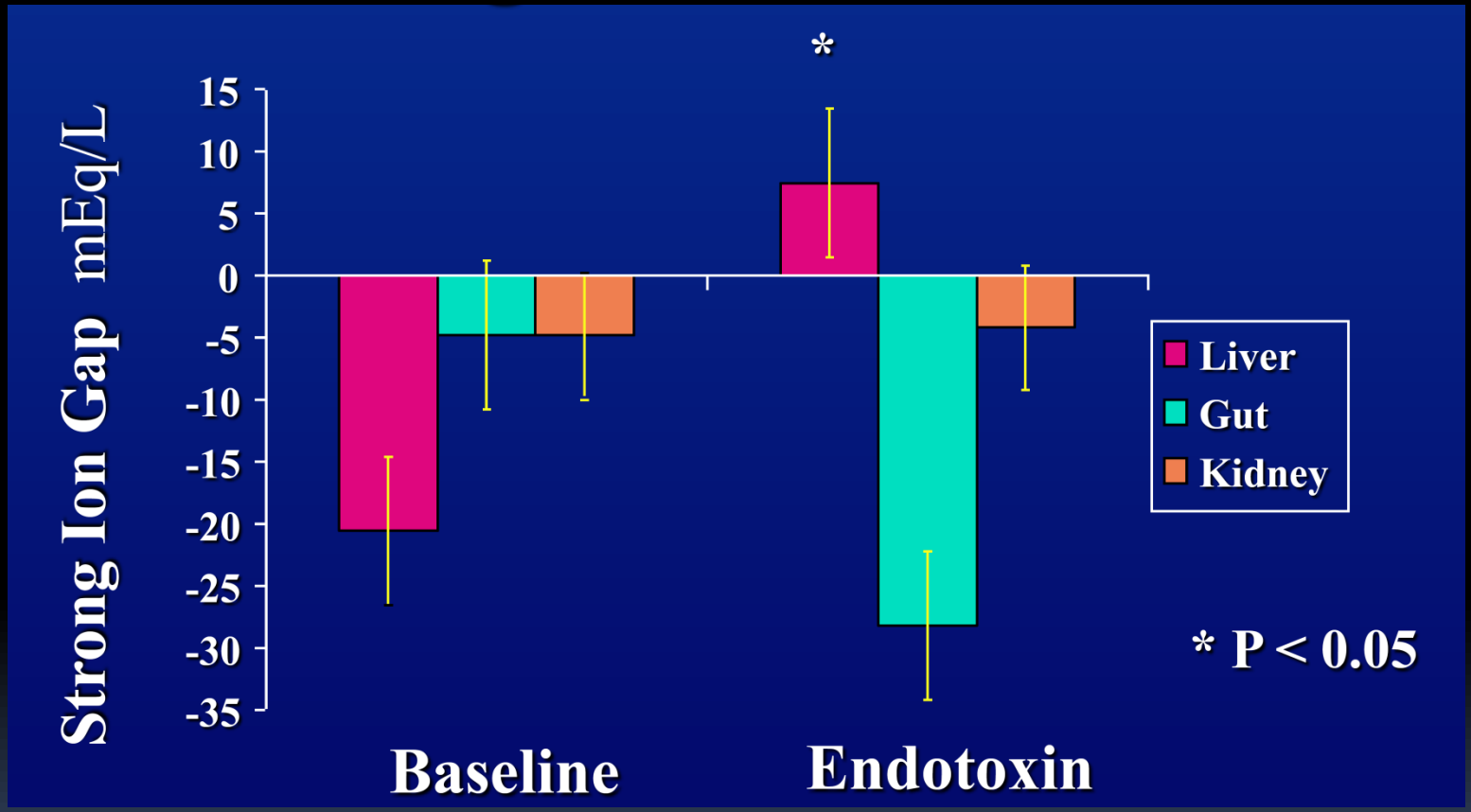
- Experimental endotoxemia

- Sayeed. Circ Shock 9:335-41, 1982
- Bowles et al J Crit Care 7:95-104, 1992
- Bellomo et al. Chest 110: 198-204, 1996

- Clinical studies of sepsis

- Brown et al. J Crit Care 11:2-8, 1996
- Kellum et al. Chest 111:1301-5, 1997
- De Backer et al. Am J Resp Crit Care Med 156:1099-105, 1997

Change in Anion Flux following Endotoxin Infusion



Kellum et al: J Appl Physiol 78:2212-9, 1995

Metabolic acidosis

Lactate may reflect either ischemic lactate release, aerobic lactate production, or normal metabolism by anaerobic WBCs

Metabolic acidosis may reflect dilutional acidosis, anionic protein release or true lactic acidosis

Does resuscitation restore organ blood flow in sepsis?

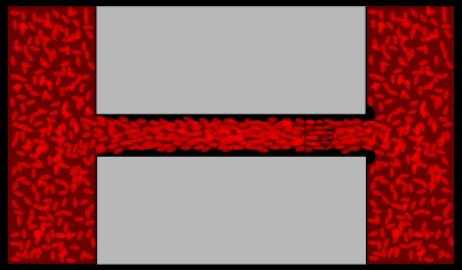
Within organ blood flow redistribution

- Mucosal tissue hypoxia not improved by resuscitation, despite restoration of mesenteric blood flow to basal levels
- Serosal surface oxygenation restored

Vallet et al. J Appl Physiol 76:793-800, 1994

Determinants of Capillary Blood Flow

- Fahraeus Effect (30% reduction in Hct)



-Obligatroy Film of plasma over endothelium

Klitzman & Duling. Am J Physiol 237:H481-90, 1979

- Heterogeneity of flow distribution

-Streaming and branch point effects

Cockelet. Microcirculation 2:1-18, 1982

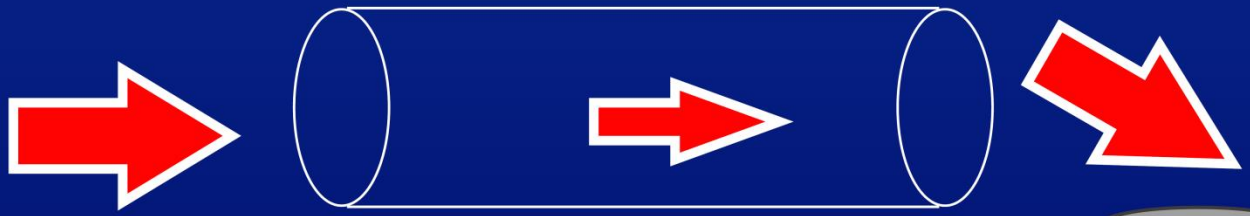
- Retardation of plasma flow

Duling et al. Int J Microcirc Circ Exp 1:409-24, 1982

Dejardins & Duling Am J Physiol 258:H 647-54, 1990

Fahraeus Effect

Obligatory Film of Plasma on Capillary Endothelial Surface



Whole Blood Hematocrit 45%

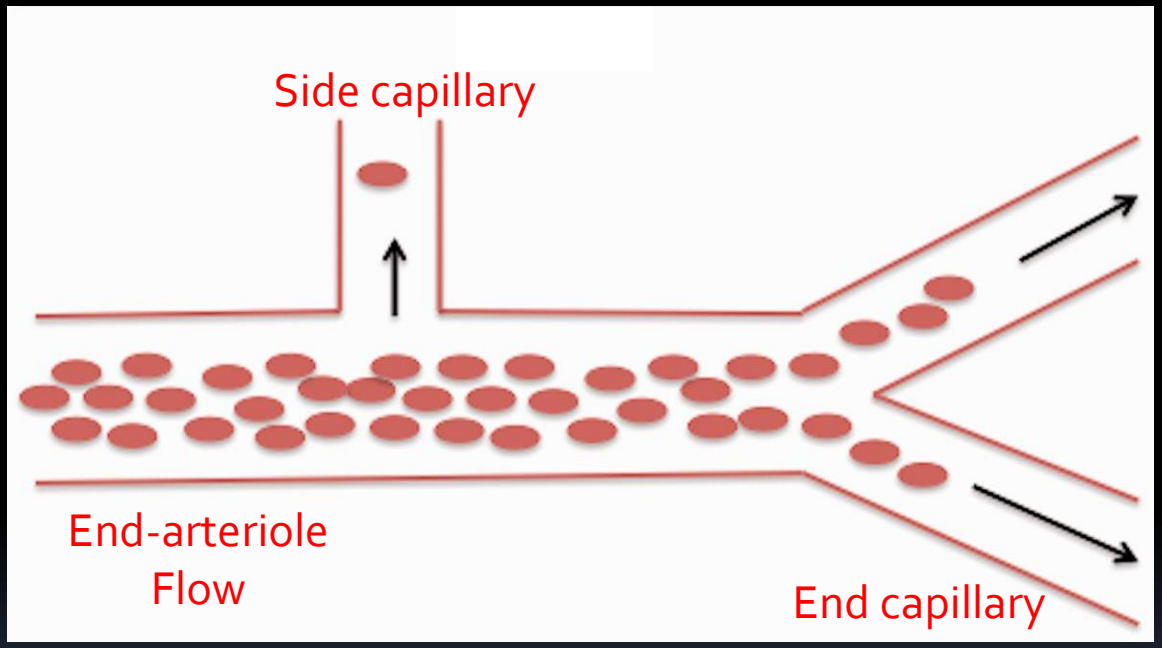
Tube Hemotocrit 30%

Outflow Hematocrit 45%

As cross-sectional area of vessel gets smaller, the effect of this PLASMA layer increases

Capillary Streaming at Branch Points

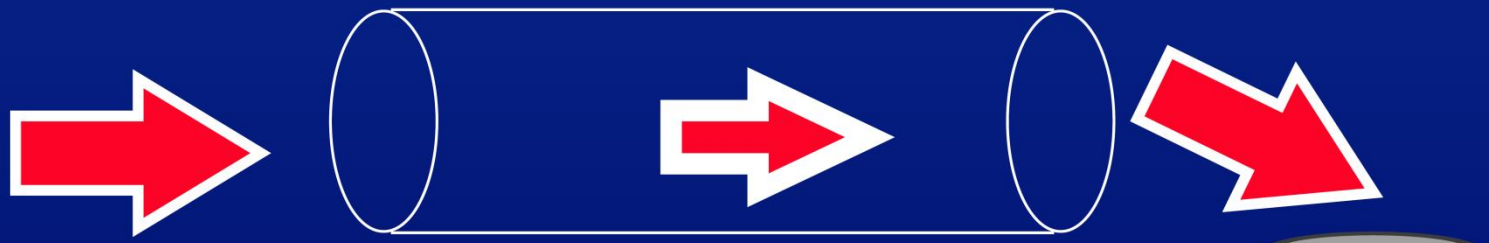
Gut microvilli supplied by side capillaries



Muscles supplied by end capillaries

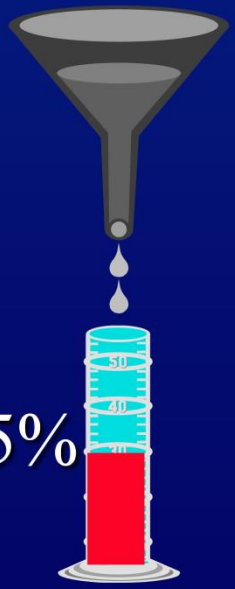
Capillary Hematocrit

RBC gating into capillary and
increased RBC velocity relative to plasma



Whole Blood
Hematocrit 45%

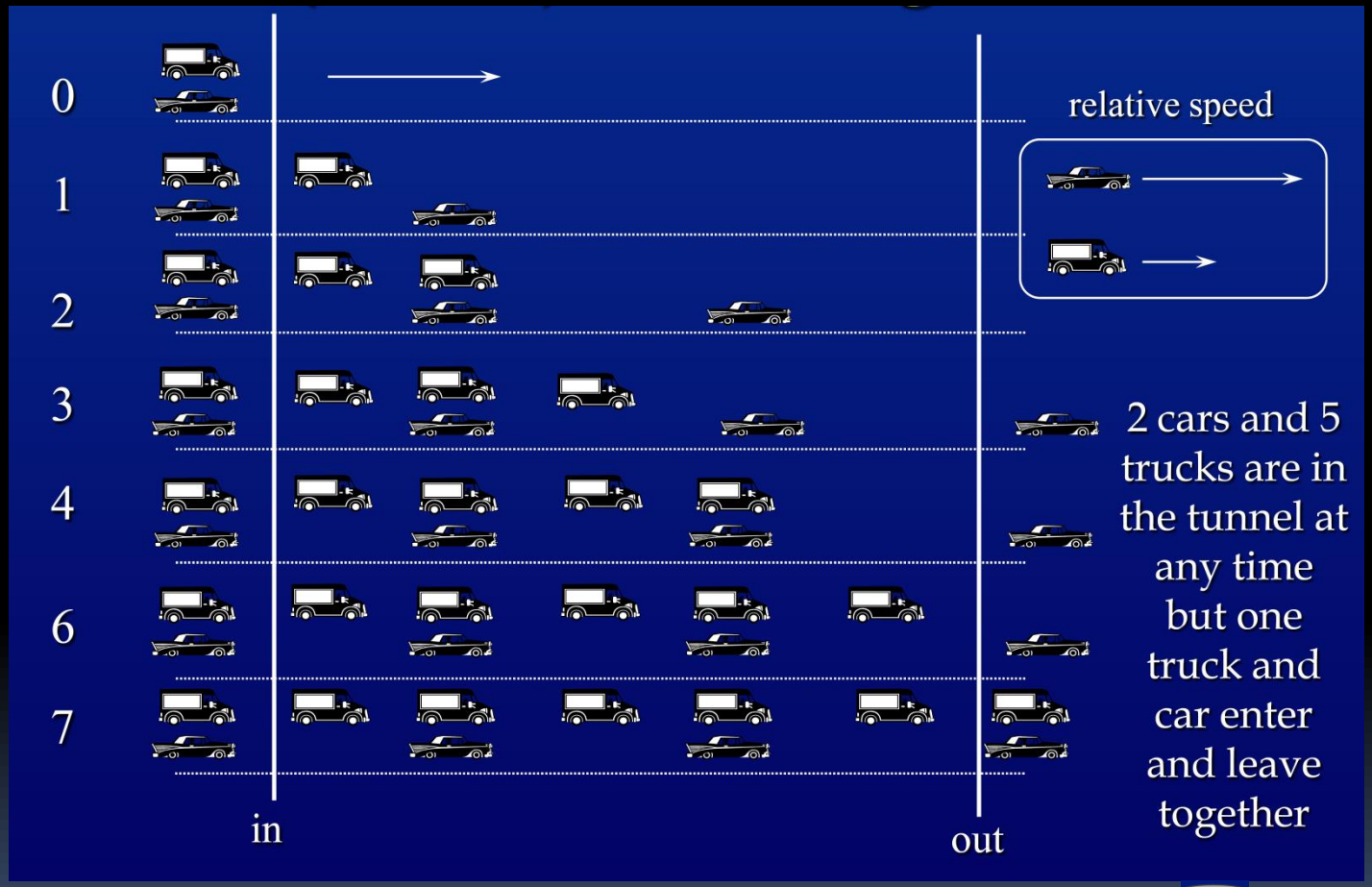
Capillary Hematocrit 10%



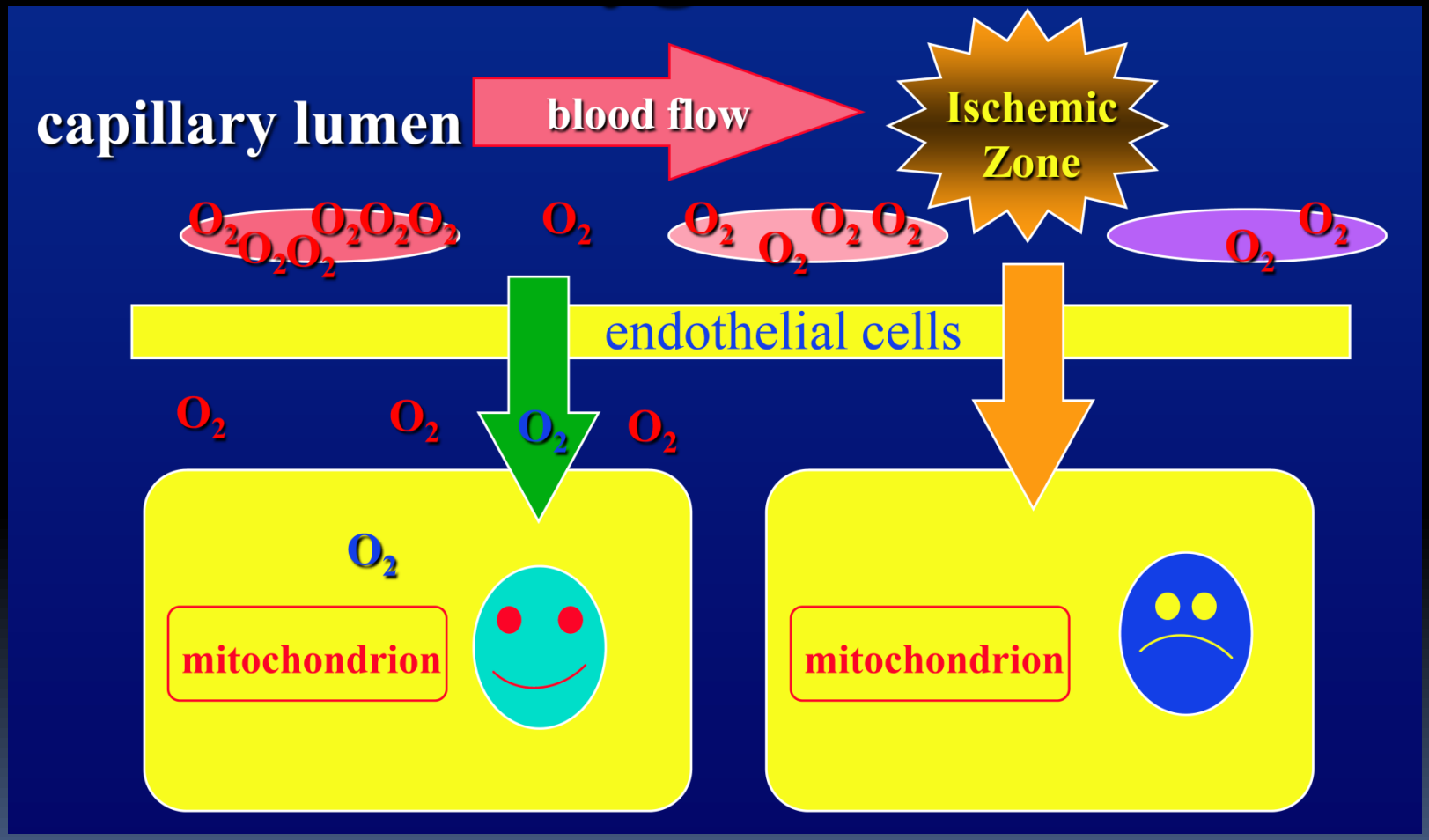
Outflow
Hematocrit 45%

Although RBC flux higher than plasma
Ischemia risk from RBC-free
plasma space depleted of O_2

Capillary Hct as RBC (Cars) & Plasma (Trunks) Traversing a Tunnel



Capillary Hematocrit and Tissue oxygenation



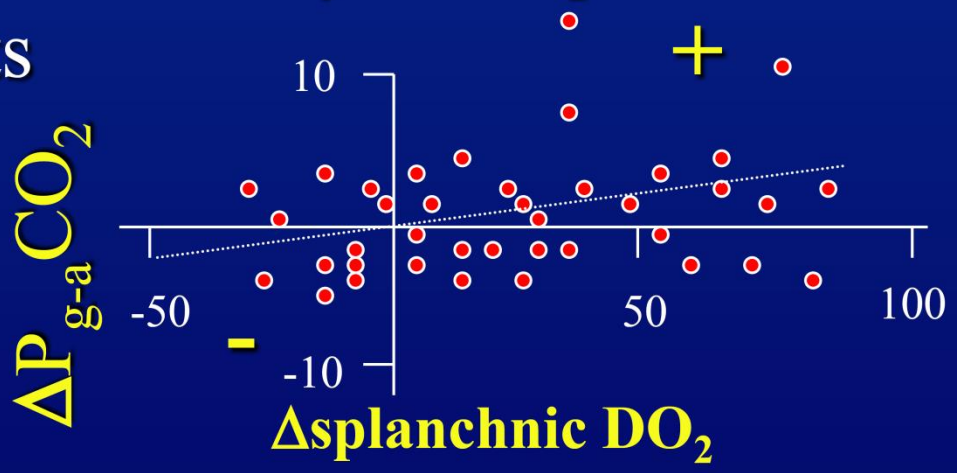
Beyond global oxygen supply-demand relations in search of measures of dysoxia

- Global measures of VO_2/DO_2 do not reflect regional blood flow
- Regional markers have yet to be shown superior to global markers in defining therapeutic effectiveness

Pinsky, Intensive Care Med 20:1-3 1994

Gastric-arterial PCO_2 gradients do not reflect systemic and splanchnic hemodynamics or DO_2

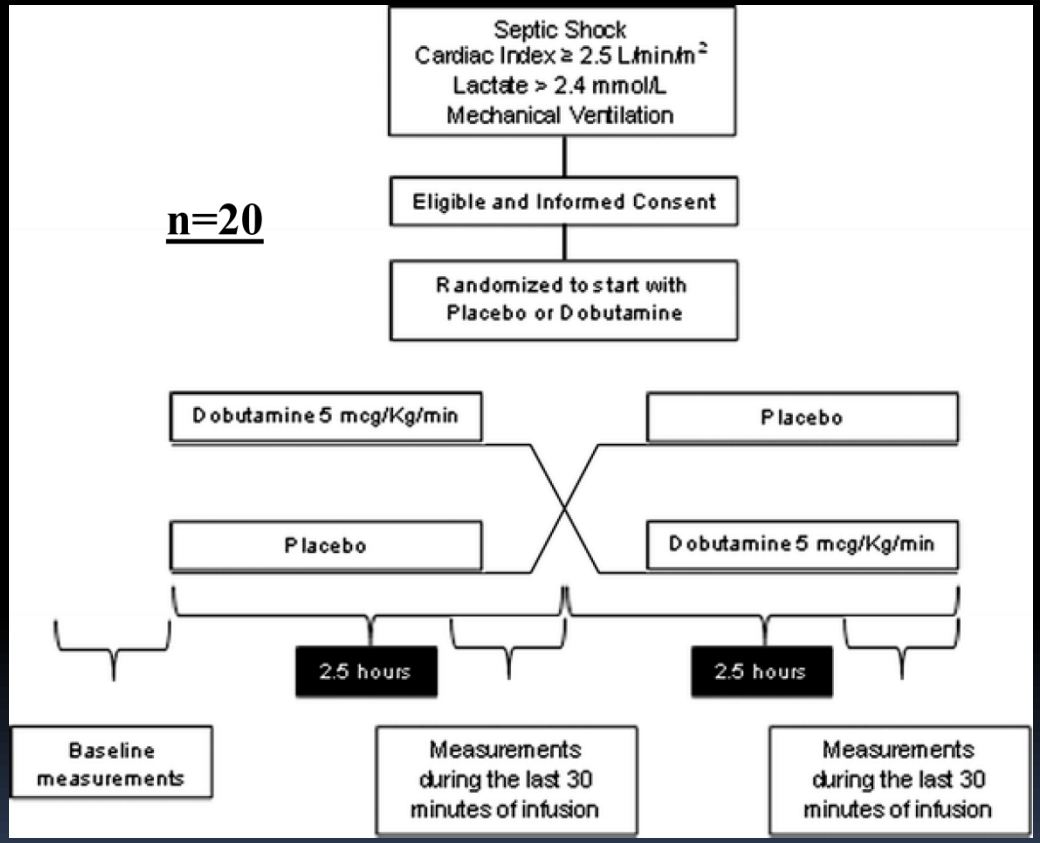
- Prospective study of 30 post-cardiac surgery patients



No relationship between change in $\Delta Pg\text{-}aCO_2$ and Δ splanchnic DO_2

Uusaro et al. Shock 14:13-7, 2000

Do macro-circulatory parameters reflect organ perfusion?



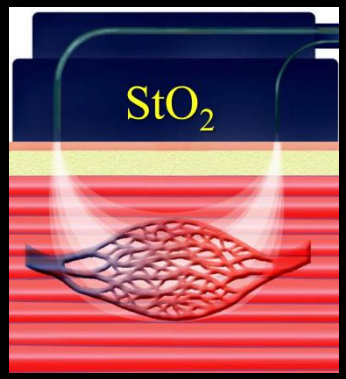
Hernandez et al. Intensive Care Med 39:1435-43, 2013

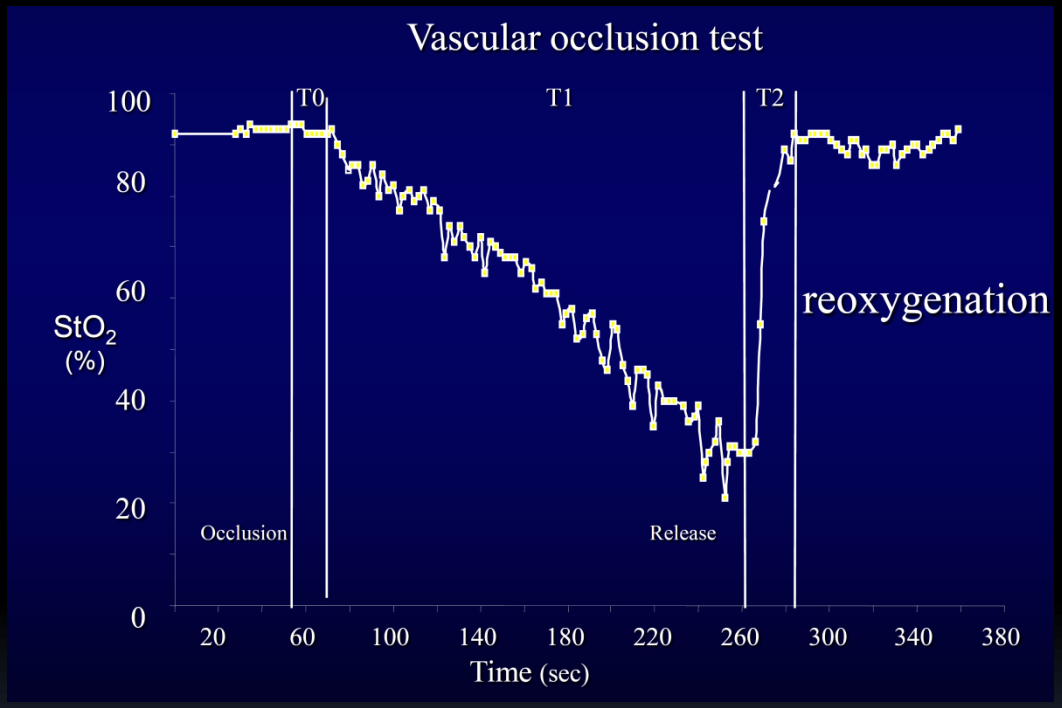
Do macro-circulatory parameters reflect organ perfusion?

Parameter	Placebo	Dobutamine	*p* value
Heart rate (bpm)	93 (84-108)	108 (97-122)	<0.01
Mean arterial pressure (mmHg)	71 (68-80)	69 (65-75)	0.52
Central venous pressure	13 (11-16)	11 (9-14)	0.13
Pulmonary Artery Occlusion P	13 (10-15)	12 (10-15)	0.15
Cardiac index (l/min/m^2)	3.7 (3.2-4.1)	4.2 (3.5-5.0)	<0.01
LV ejection fraction (%)	63 (58-72)	74 (64-78)	0.02
Pulse pressure variation (%)	6 (2-8)	6 (3-8)	0.16
Urine output (ml)	90 (51-119)	52 (25-220)	0.39
Norepi dose (mcg/kg/min)	0.15 (0.07-0.33)	0.16 (0.06-0.42)	0.39

Hernandez et al. Intensive Care Med 39:1435-43, 2013

Identifying Cardiovascular Reserve: StO2 during an vascular occlusion test





Do macro-circulatory parameters reflect organ perfusion?

Parameter	Placebo	Dobutamine	*p* value
Capillary Refill Time (s)	3 (2-4)	3 (2-5)	0.67
Central-to-Toe Temp (°C)	3.3 (1.5-3.8)	3.6 (0.4-4.6)	0.45
Thenar muscle O_2 saturation (%)	82 (74-88)	84 (75-88)	0.10
StO_2 recovery slope after VOT (%/s)	2.5 (1.2-3.4)	2.1 (1.1-3.1)	0.01

Hernandez et al. Intensive Care Med 39:1435-43, 2013

Do macro-circulatory parameters reflect organ perfusion?

Parameter	Placebo	Dobutamine	*p* value
Mixed venous O_2 saturation (%)	77 (72-81)	78 (75-81)	0.05
Mixed venous-arterial pCO_2 gradient (mm Hg)	3.3 (1.5-3.8)	3.6 (0.4-4.6)	0.45
Arterial lactate (mmol/l)	2.8 (2.4-3.9)	2.8 (2.4-4.0)	0.20
O_2 Delivery (ml/min/m^2)	566 (374-722)	717 (419-771)	0.02
O_2 Consumption (ml/min/m^2)	129 (100-156)	140 (106-167)	0.35
ICG plasma disappearance rate*	18.8 (11.7-24.6)	14.4 (9.5-25.6)	0.03
ICG retention rate at 15 min (%)	6.0 (2.8-17.4)	11.5 (2.3-24.3)	0.06
Gastric-arterial pCO_2 (mmHg)	13 (7-18)	13 (7-29)	0.52
Intraabdominal pressure (mmHg)	12 (8-16)	12 (9-17)	0.39

*(%/min)

Hernandez et al. Intensive Care Med 39:1435-43, 2013

Do macro-circulatory parameters reflect organ perfusion?

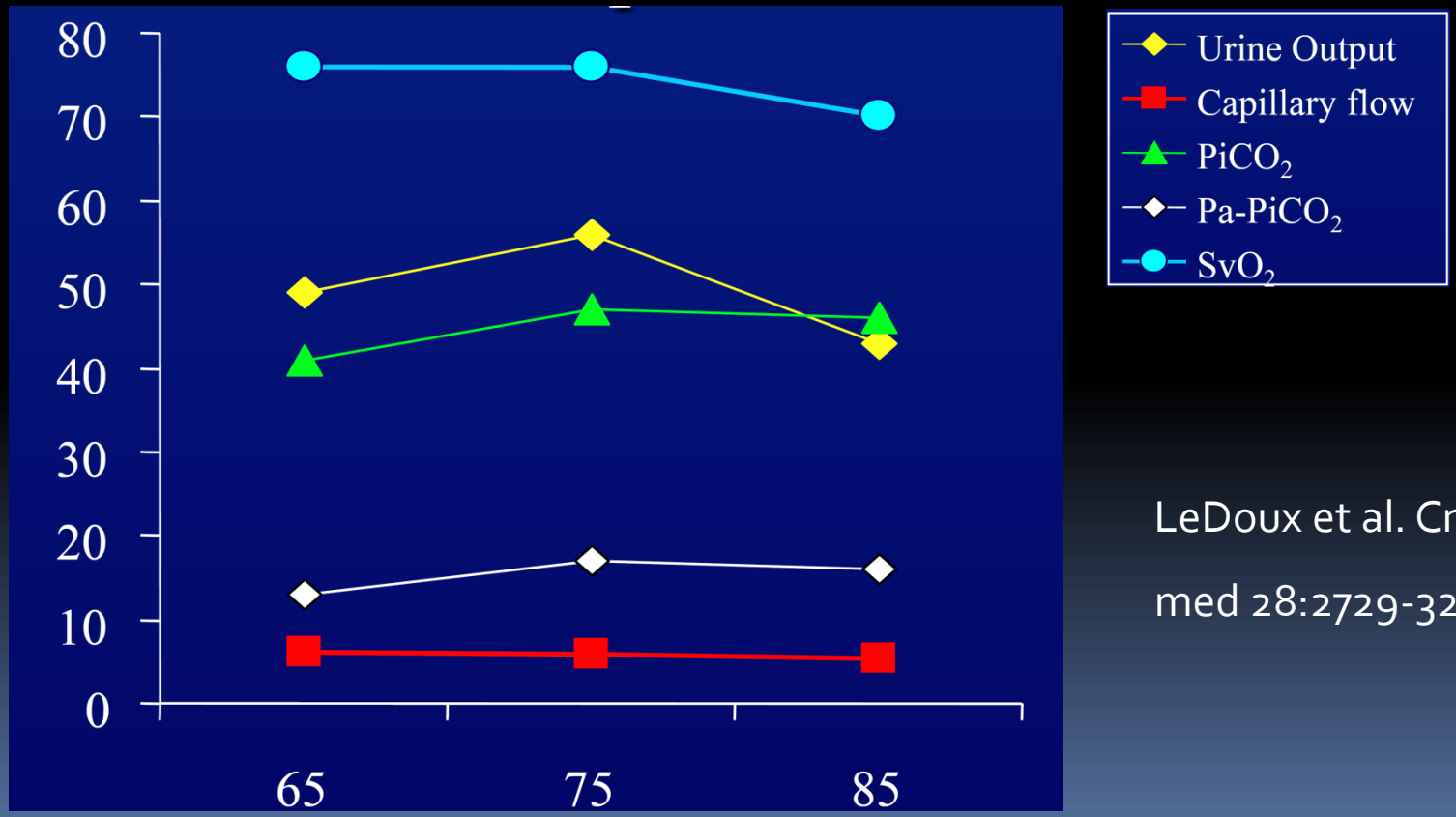
Sublingual microcirculatory parameters

Parameter	Placebo	Dobutamine	*p* value
Total microcirculatory density (n/mn)	11.8 (10.2-12.5)	11.9 (9.7-12.5)	0.91
Perfused vessel density (n/mn)	9.1 (7.9-9.9)	9.1 (7.9-10.1)	0.24
Proportion of perfused microvessels (%)	75 (69-79)	79 (72-84)	0.09
Microvascular flow index	2.1 (1.9-2.5)	2.1 (1.8-2.5)	0.73
Heterogeneity of microvascular flow	0.58 (0.46-0.73)	0.47 (0.40-0.86)	0.52

Hernandez et al. Intensive Care Med 39:1435-43, 2013

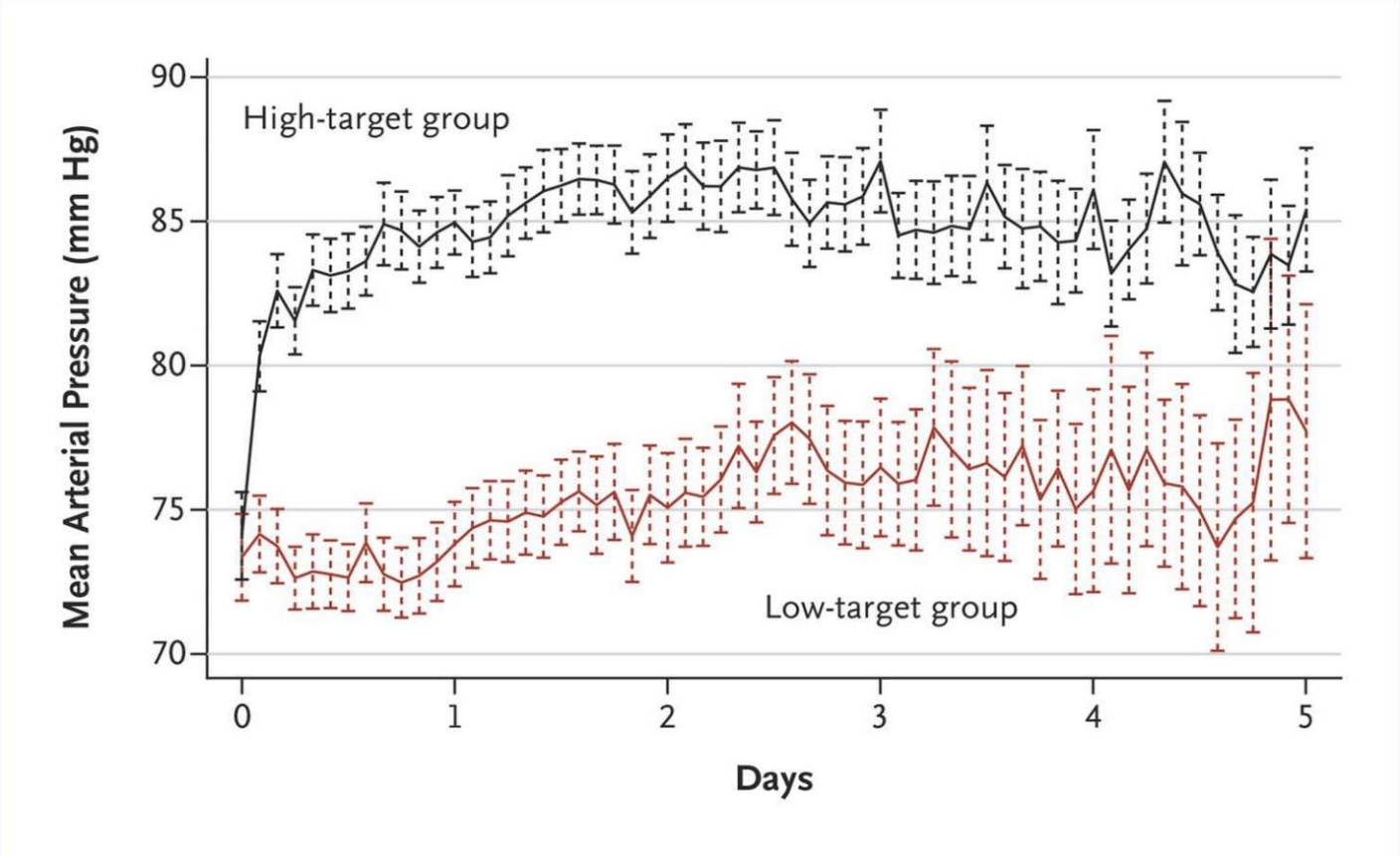
Organ Perfusion Pressure is important

- Increasing MAP > 65mmHg with noradrenaline improves tissue perfusion in septic shock
- Increasing MAP further, >75 or 85 mmHg does not increase tissue perfusion further



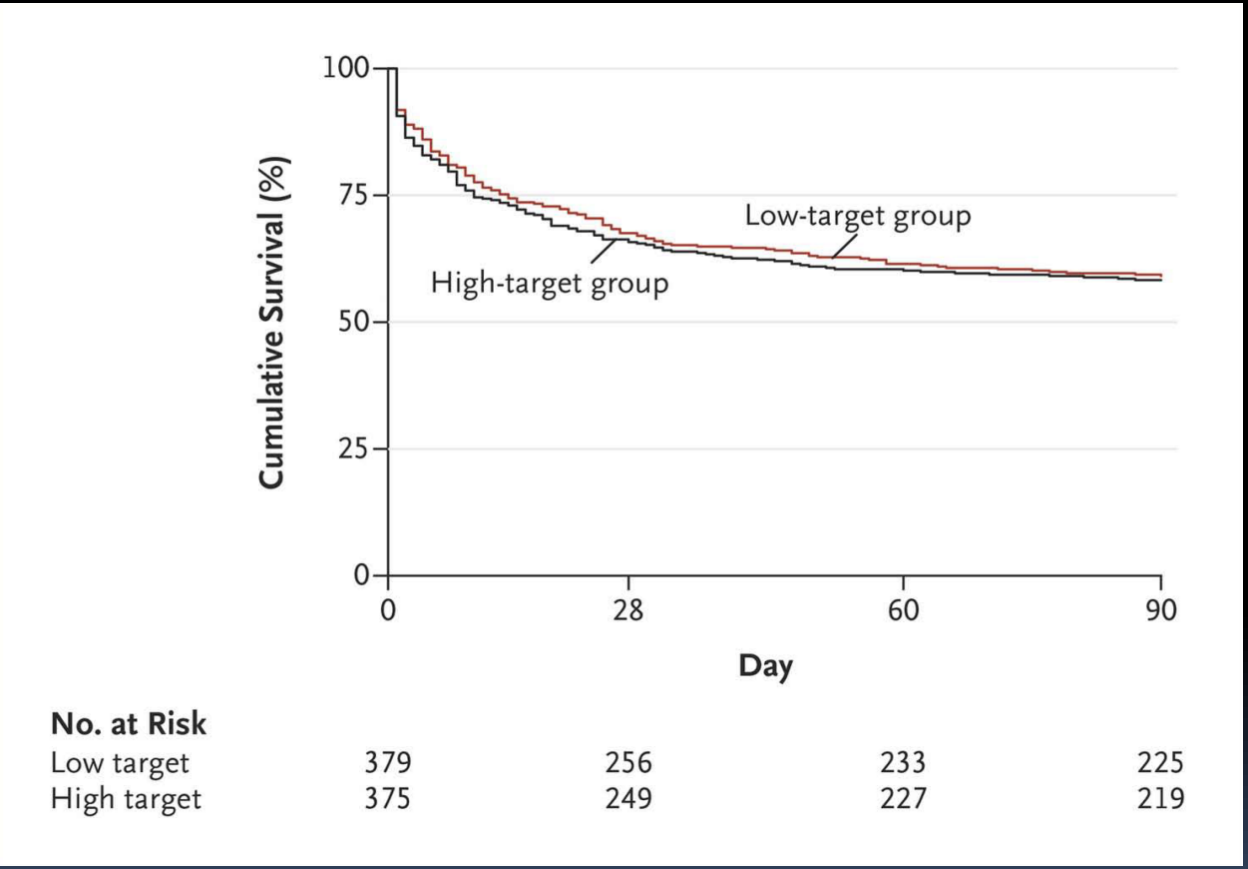
LeDoux et al. Crit Care med 28:2729-32, 2000

High Blood Pressure (80-85mmHg) vs Low Blood Pressure (65-75 mmHg) Targets in Septic Shock



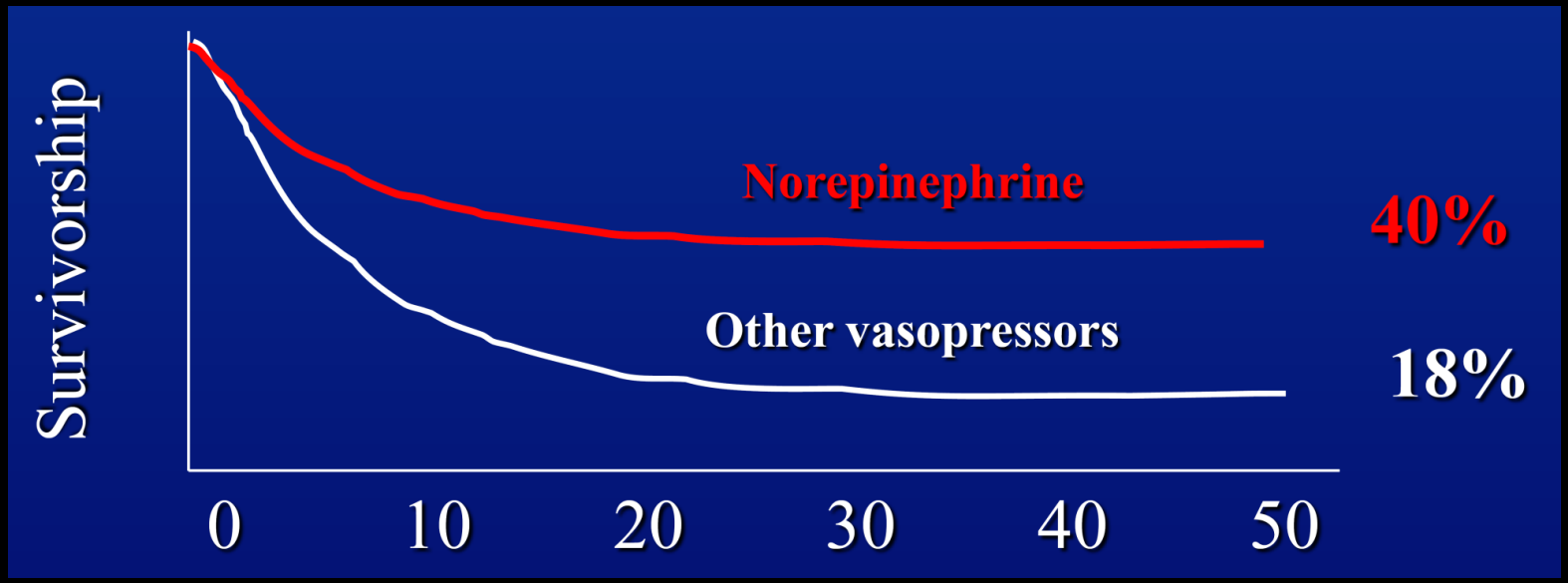
Asfar et al NEJM 370:1583-93, 2014

High Blood Pressure (80-85mmHg) vs Low Blood Pressure (65-75 mmHg) Targets in Septic Shock



Asfar et al NEJM 370:1583-93, 2014

Noradrenaline improves outcome from septic shock

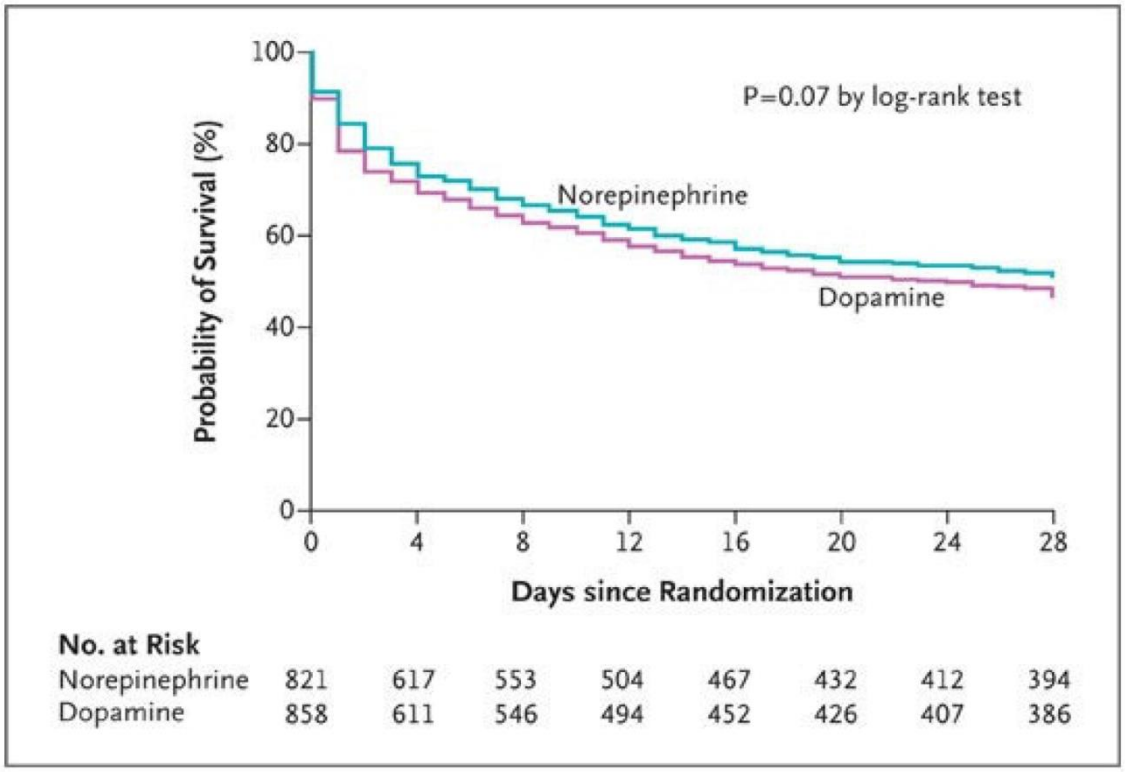


- Prospective observational study n=97
- Use of norepinephrine strongly associated with a favorable outcome when controlled for MAP

Martin et al Crit Care Med 28:2758-65, 2000

Comparison of Norepinephrine to Dopamine in Patients in Shock

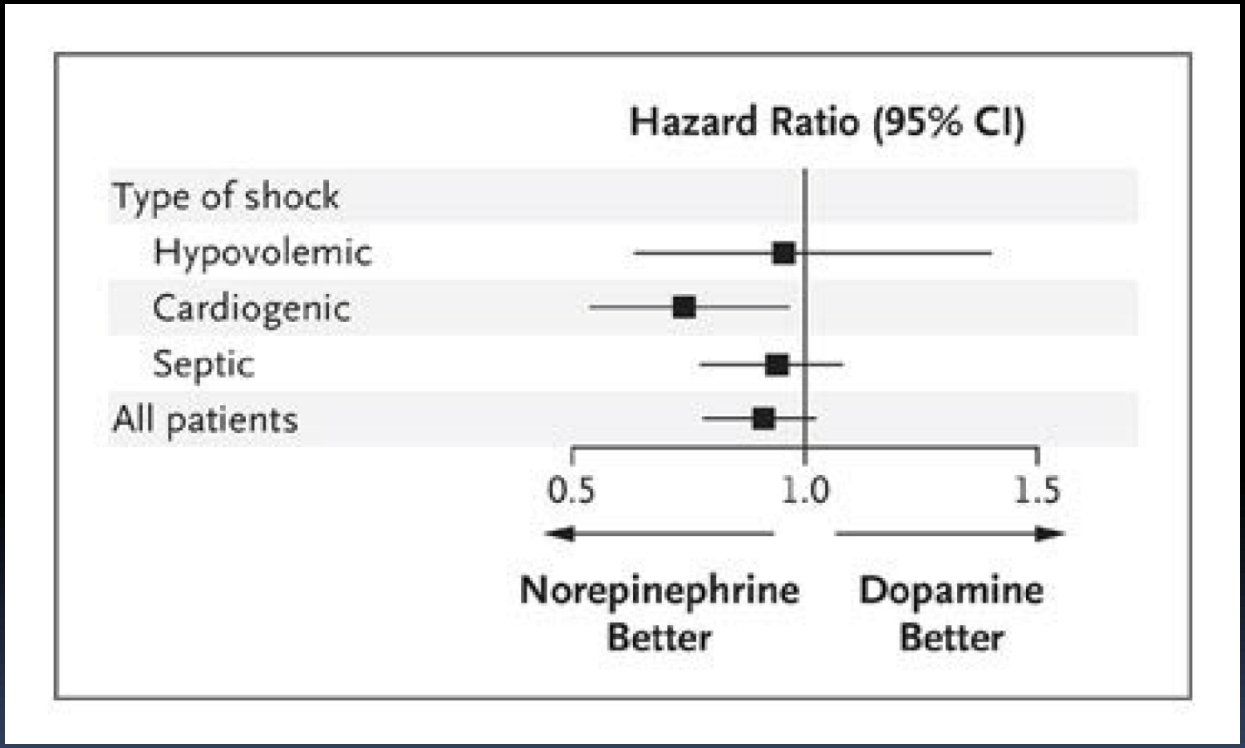
Kaplan-Meier Curves for 28-day Survival in the ITT Population



De Backer et al NEJM 362:779-89, 2010

Comparison of Norepinephrine to Dopamine in Patients in Shock

Forest Plot for Predefined Subgroup Analysis According to Type of Shock



De Backer et al NEJM 362:779-89, 2010

The way in which organ perfusion pressure is maintained is important

- Increasing MAP >65mmHg improves outcome in patients in septic shock better if vasopressor is norepinephrine
- Evidence of pre-existent organ injury (low uo), inflammation (serum lactate) also determine outcome

Martin et al Crit Care Med 28:2758-65, 2000

De Backer et al NEJM 362:779-89, 2010

Recommendations

- Monitoring
- Measure real perfusion performance variables
  - ✓ Uo, MAP, capillary refill, sensorium
- Measure surrogates variables for collaboration not confirmation
  - ✓ Gut tonometry, serum lactate, $ScvO_2$, v-aPCO_2
- Trends my be more important than absolute values
- Management
  - Fluids and vasopressor to keep MAP >65mmHg
  - Norepinephrine is the drug of choice
  - Consider increasing inotropy if cardiac output remains low and evidence of tissue hypoperfusion