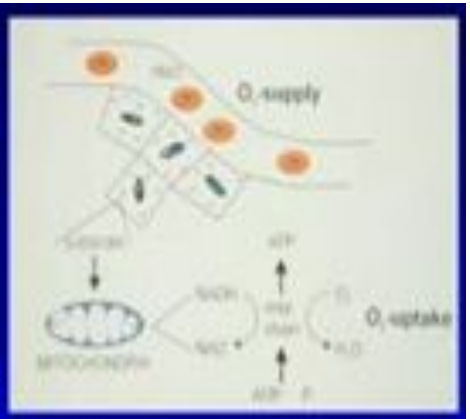
Physiopathologie des états de chocs

- **La physiopathologie est l’ étude des fonctions modifiées par la maladie**:
  - Les modifications.
  - Leurs amplitudes.
  - Leurs causes.
  - Leurs effet bénéfiques neutres ou délétères pour la survie de l’organisme.
  - Suggérer des cibles thérapeutiques.

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

CONFERENCE REPORTS AND EXPERT PANEL

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

SEPSIS-3 : définition du sepsis

❑ **Sepsis** : infection => réaction « dérégulée » de l'hôte => dysfonction(s) aiguë(s)

SEPSIS-3 : définition du choc septique

❑ **Choc septique** : sepsis => dysfonctions circulatoire et métabolique profondes malgré un RV

SEPSIS-3 : diagnostic du sepsis

Infection + score SOFA total ≥ 2

=> Mortalité >10%

	System	Score 0	1	2	3	4
1	Respiration					
	Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
2	Coagulation					
	Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
3	Liver					
	Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
4	Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
5	Central nervous system					
	Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
6	Renal					
	Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
	Urine output, mL/d				<500	<200

0 à 24 points

Singer et al. JAMA 2016

Seymour et al. JAMA 2016

SEPSIS-3 : diagnostic de choc septique

Sepsis

+

Vasoconstricteur pour PAM ≥ 65 mmHg

+

Lactatémie > 2 mmol/L

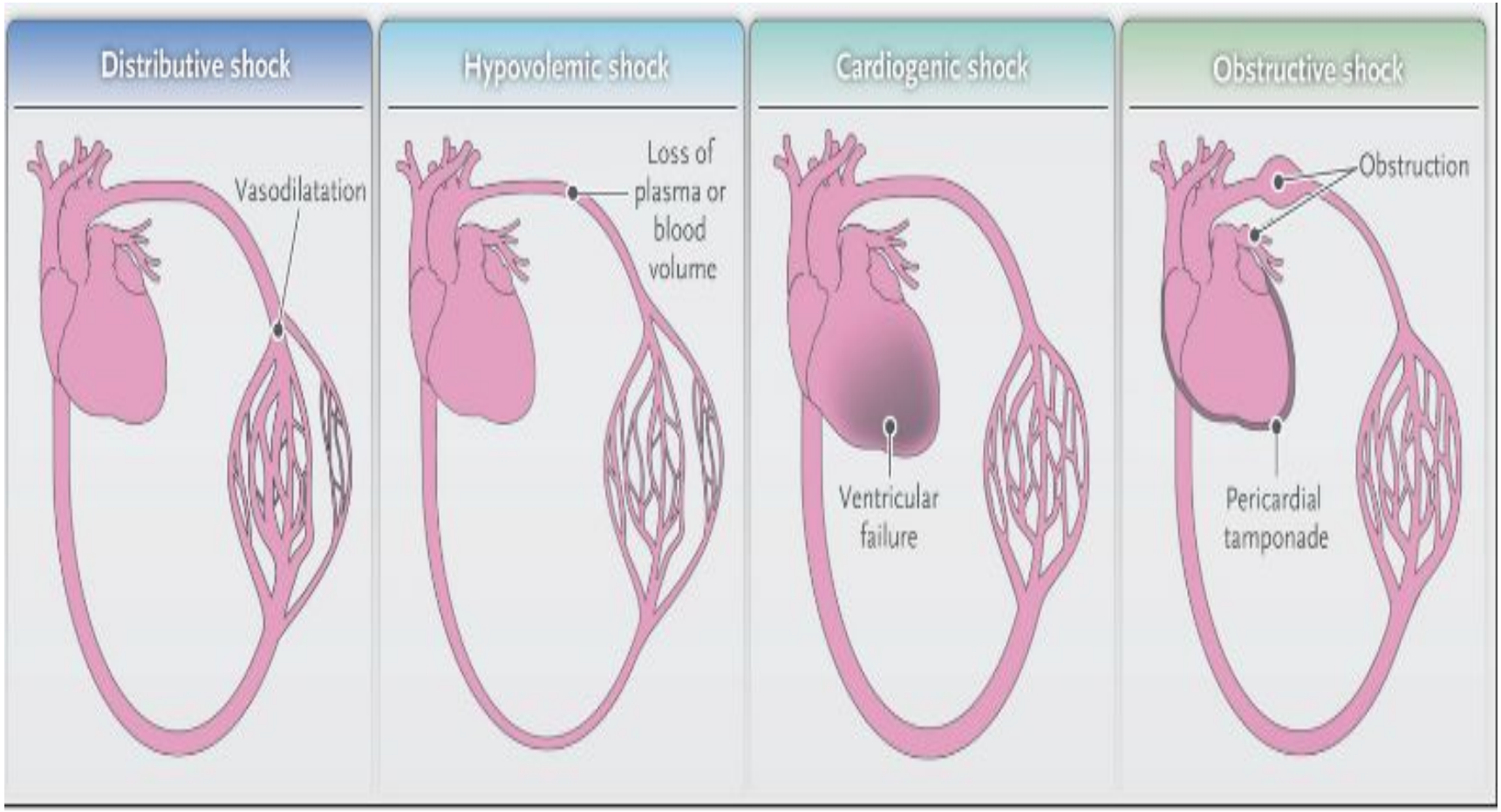
Malgré un RV « adéquat »

=> Mortalité 42 % (41% - 43%)

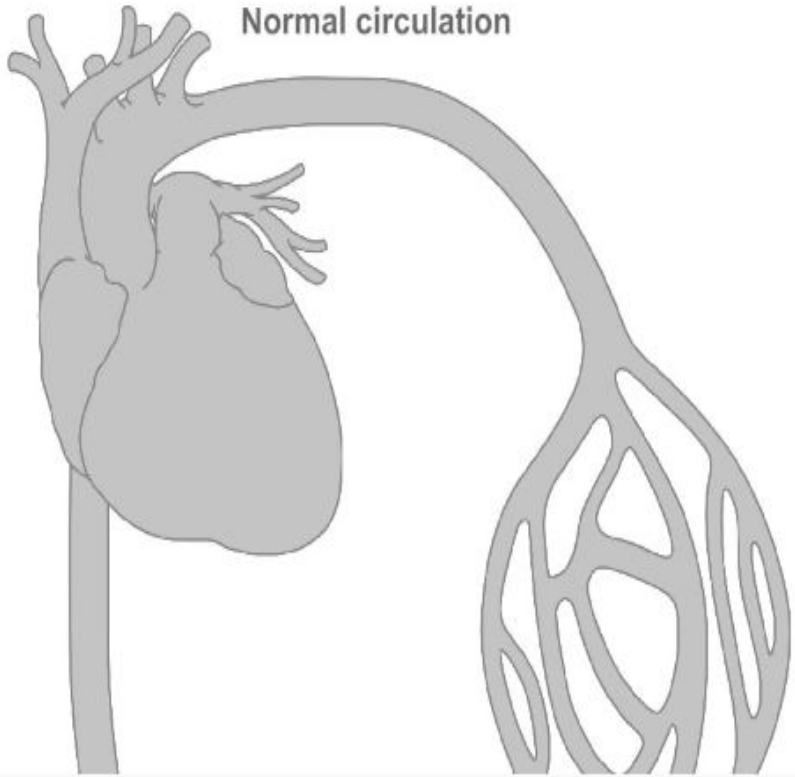
SEPSIS-3 : critères simplifiés …

Infection + score « quick SOFA » ≥ 2

Critères du score qSOFA	Points
Pression artérielle systolique ≤ 100 mmHg	1
Fréquence respiratoire ≥ 22 /min	1
Score de Glasgow ≤14	1


Distributive shock
Vasodilatation
Hypovolemic shock
Loss of plasma or blood volume
Cardiogenic shock
Ventricular failure
Obstructive shock
Obstruction
Pericardial tamponade

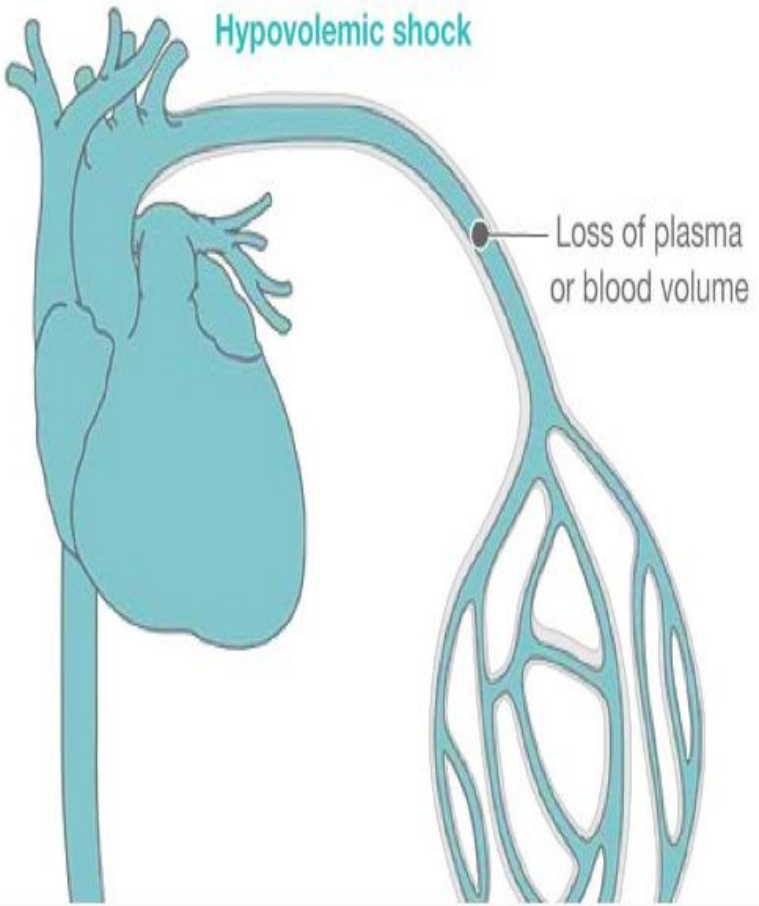
DIAGRAM



SIGNS OF CIRCULATORY SHOCK PATHWAY

Normal circulation

DIAGRAM



SIGNS OF CIRCULATORY SHOCK PATHWAY

Arterial hypotension and usually tachycardia

↓

Signs of tissue hypoperfusion present

- Altered mental state
- Mottled, clammy skin
- Oliguria
- Elevated blood lactate

↓

Circulatory shock

↓

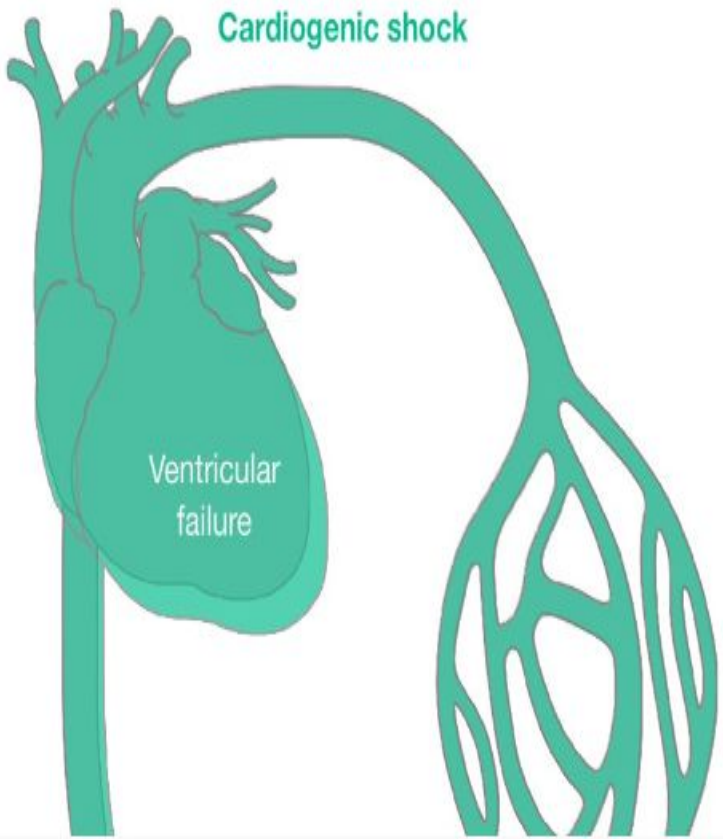
Low estimated cardiac output or SvO_2

↓

SYMPTOMS

Hypovolemic shock is characterized by internal or external fluid loss leading to organ failure.

DIAGRAM



SIGNS OF CIRCULATORY SHOCK PATHWAY

Arterial hypotension and usually tachycardia

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Signs of tissue hypoperfusion present

- Altered mental state
- Mottled, clammy skin
- Oliguria
- Elevated blood lactate

↓

Circulatory shock

↓

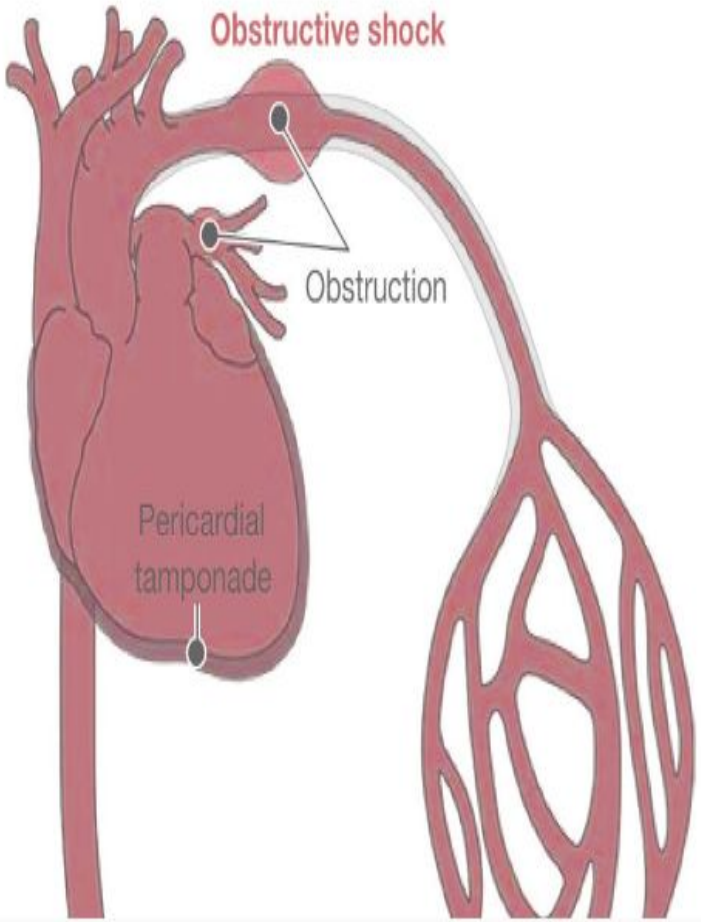
Low estimated cardiac output or SvO_2

↓

SYMPTOMS

Cardiogenic shock is characterized by low cardiac output and inadequate oxygen transport. It can be the result of a myocardial

DIAGRAM



SIGNS OF CIRCULATORY SHOCK PATHWAY

Arterial hypotension and usually tachycardia

↓

Signs of tissue hypoperfusion present

- Altered mental state
- Mottled, clammy skin
- Oliguria
- Elevated blood lactate

↓

Circulatory shock

↓

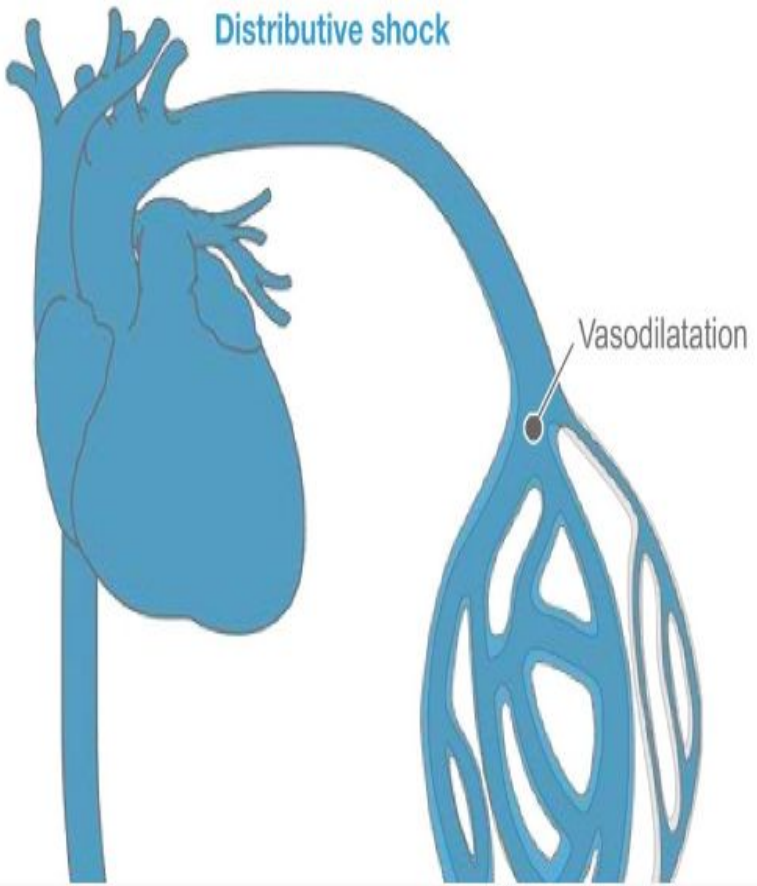
Low estimated cardiac output or SvO_2

↓

SYMPTOMS

Obstructive shock is characterized by a blockage in blood flow caused by a massive pericardial effusion, cardiac tamponade, or tension

DIAGRAM



SIGNS OF CIRCULATORY SHOCK PATHWAY

Arterial hypotension and usually tachycardia

↓

Signs of tissue hypoperfusion present

- Altered mental state
- Mottled, clammy skin
- Oliguria
- Elevated blood lactate

↓

Circulatory shock

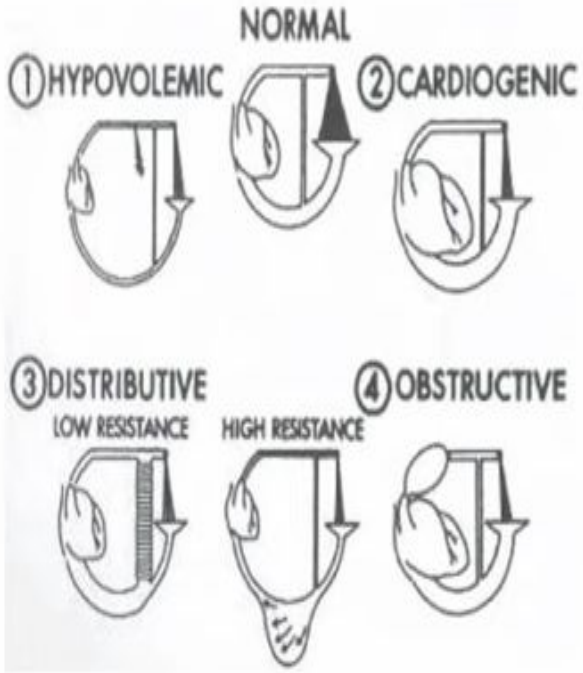
↓

Normal or high cardiac output or SvO_2

SYMPTOMS

Distributive shock is characterized by hypovolemia and hypotension. It is the result of vasodilatation and release of inflammatory mediators.

SHOCK: DIFFERENT TYPES?



CURRENT OPINION

What is microcirculatory shock?

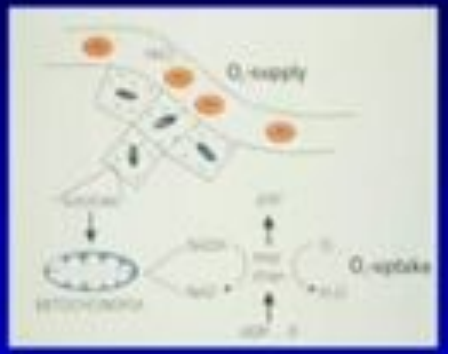
Vanina S. Kanoore Edul[a,b], Can Ince[b], and Arnaldo Dubin[b,c]

"The condition in which the microcirculation fails to support tissue oxygenation in the face of normal(ized) systemic hemodynamics"

Prolonged tissue hypoxia elicits an inflammatory response

Any type may eventually evolve into distributive shock

Finalité de la circulation



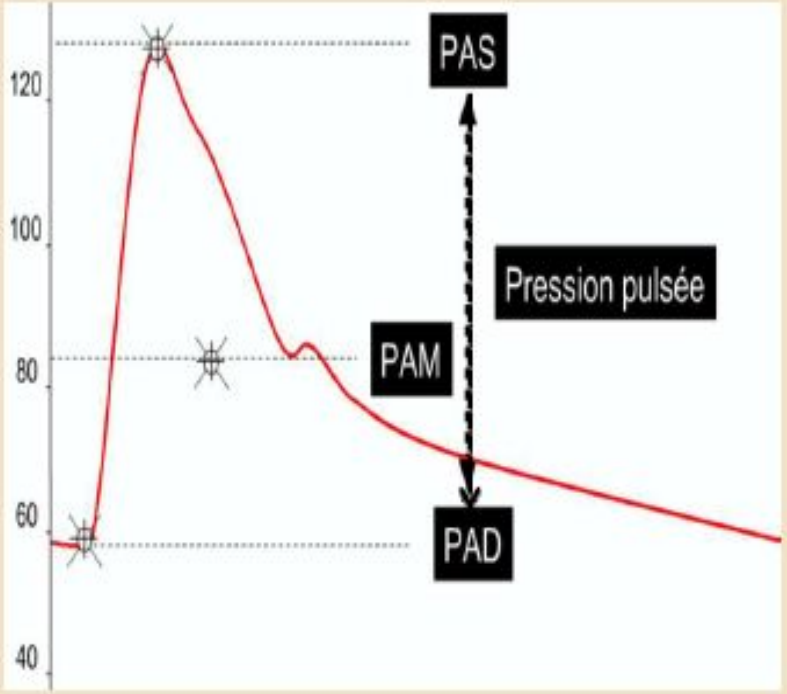
The ultimate purpose of the cardiovascular system is to provide the microcirculation with oxygen carrying red blood cells to provide tissue cells with oxygen needed to support oxidative phosphorylation.

Finalité de la circulation: PA

- Maintien distendu les parois du système artériel et assure l’ écoulement
- Son maintien assure une perfusion dans toute les circonstances
- Distribution du débit cardiaque (résistances)
- **La pression artérielle est régulée**.

Les différentes pressions

- Systolique
- Diastolique
- Moyenne
- Pression Pulsée



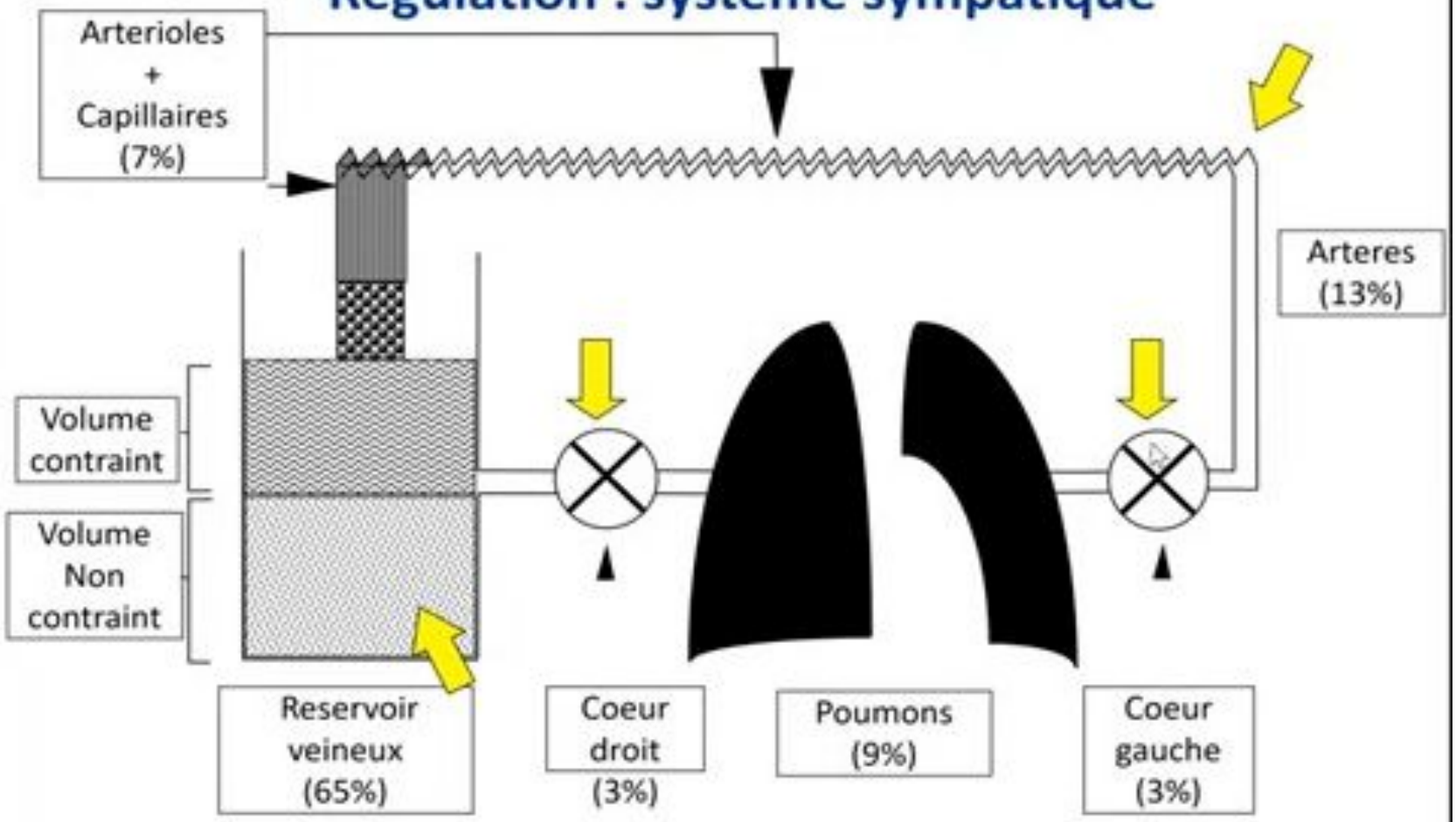
Finalité de la circulation: le débit

- Apports nutritifs
- Eliminer les déchets
- Régler au minimum
- **Le débit cardiaque est adapté**

Karl Ludwig (1816-95)

"... the **fundamental problems** in the circulation derive from the fact that the **supply of adequate amounts of blood** to the organs of the body is the **main purpose of the circulation** and the **pressures** that are necessary **to achieve it are of secondary importance**; but the **measurement of flow is difficult** while that of **pressure is easy** so that our knowledge of flow is usually derivatory."

Régulation : système sympatique



Effets combinés du système sympathique

Cholley, 2002

REGULATION OF BLOOD FLOW

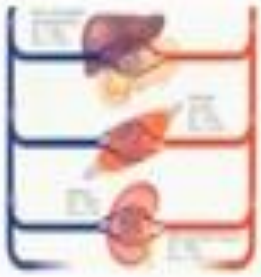
Central → **Regional** → **Local**

Cardiac Output

Preload

Contractility

Afterload



Vital ↔ NonVital organs

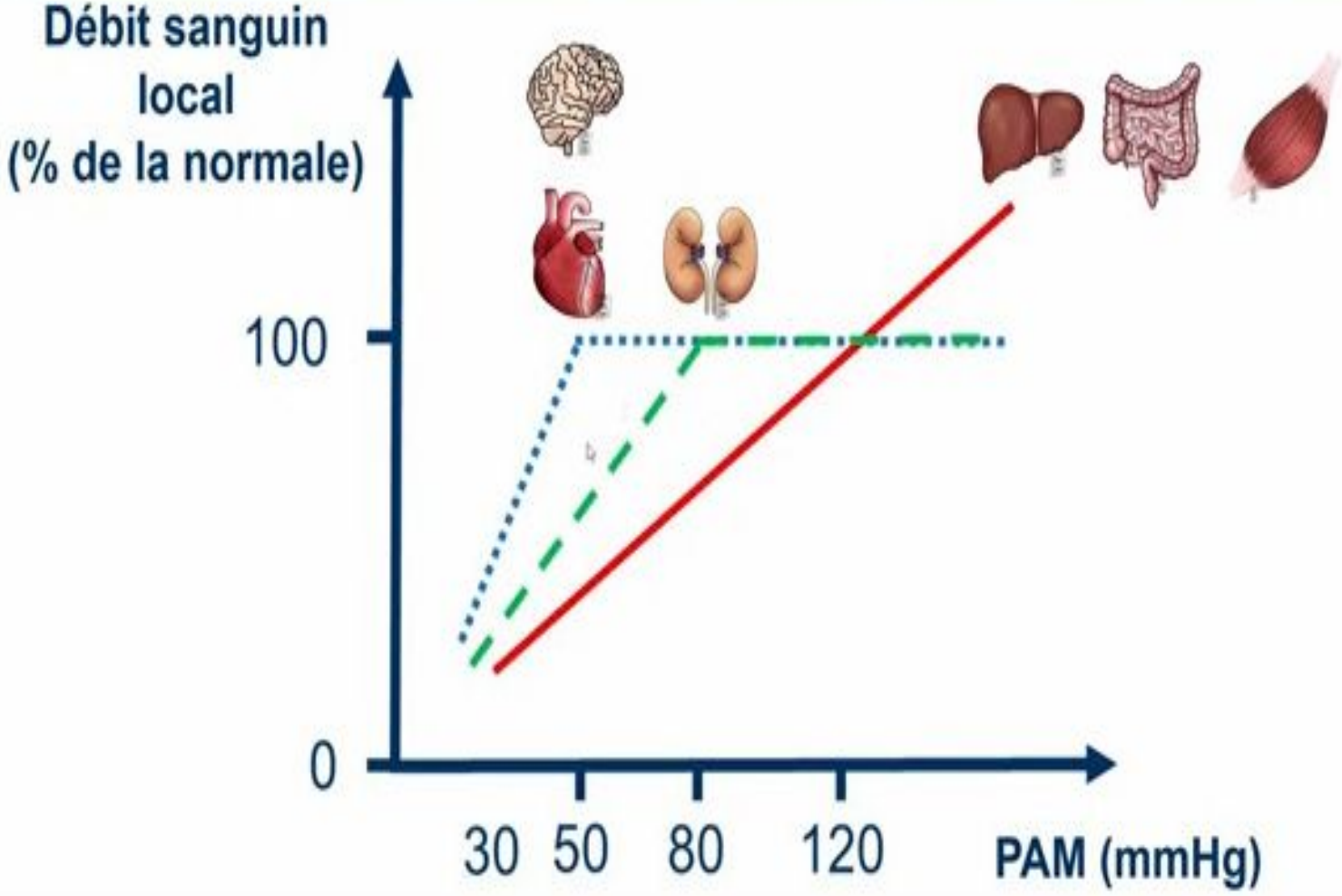
Resistances vessels

Sympathetic control

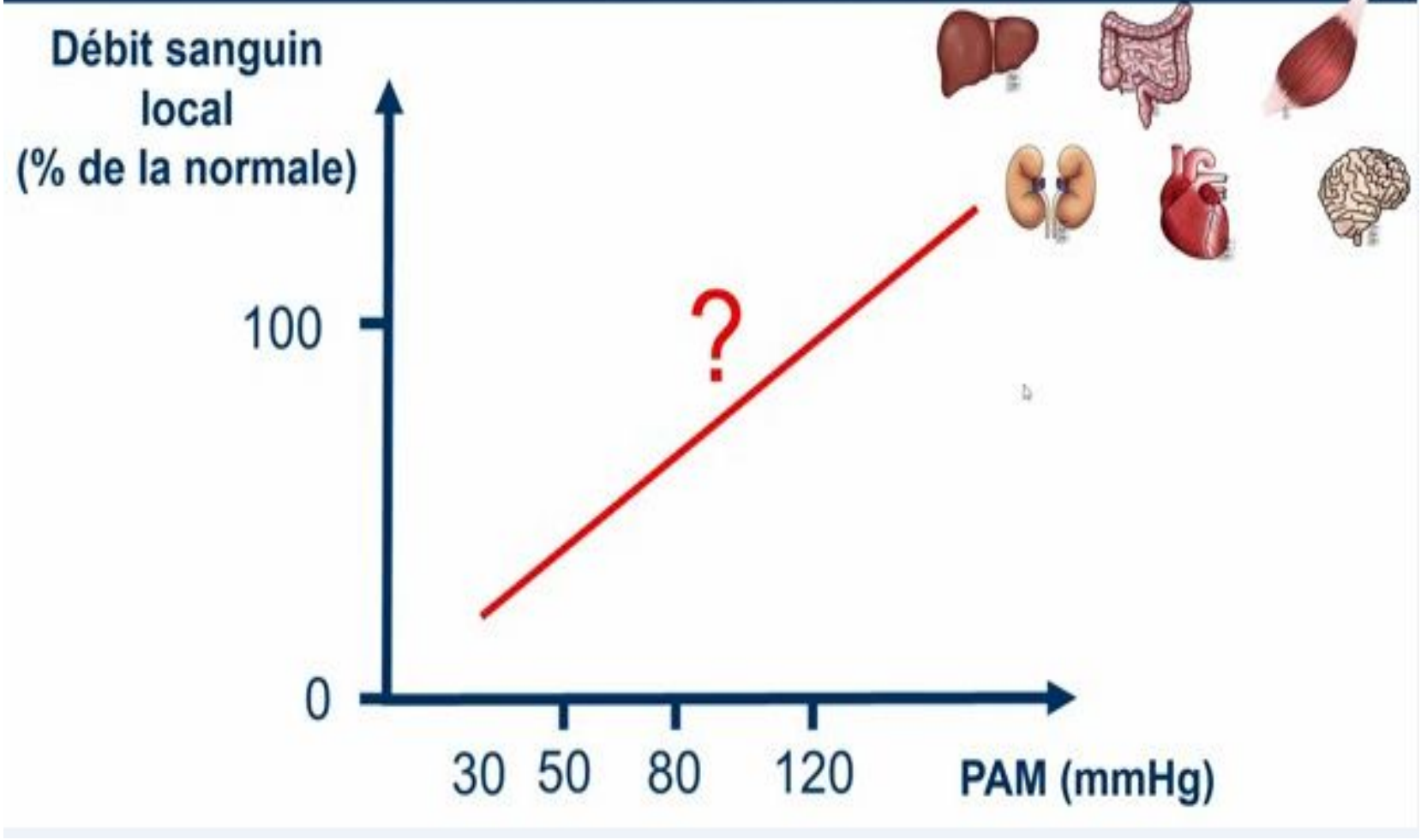
Functional capillary density

Extrinsic	**Intrinsec**
• Neural	• Metabolic
• Humoral	• Vascular

Autorégulation des débits régionaux

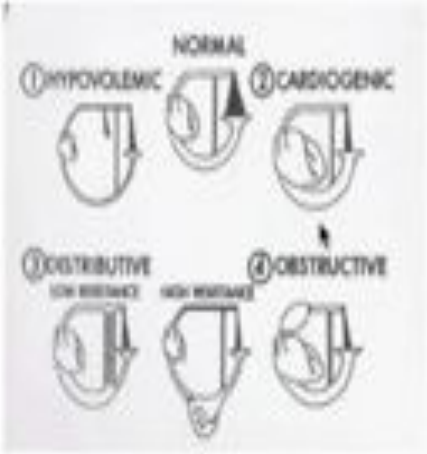


Débits régionaux



PROPOSED RECLASSIFICATION OF SHOCK STATES

With special reference to distributive defects



"Even though cardiac output may be substantial, ***if blood flow does not arrive at the exchange sites***, the ultimate metabolic detriment is not different from low cardiac output without shunt flow."

Dr. Max Harry Weil

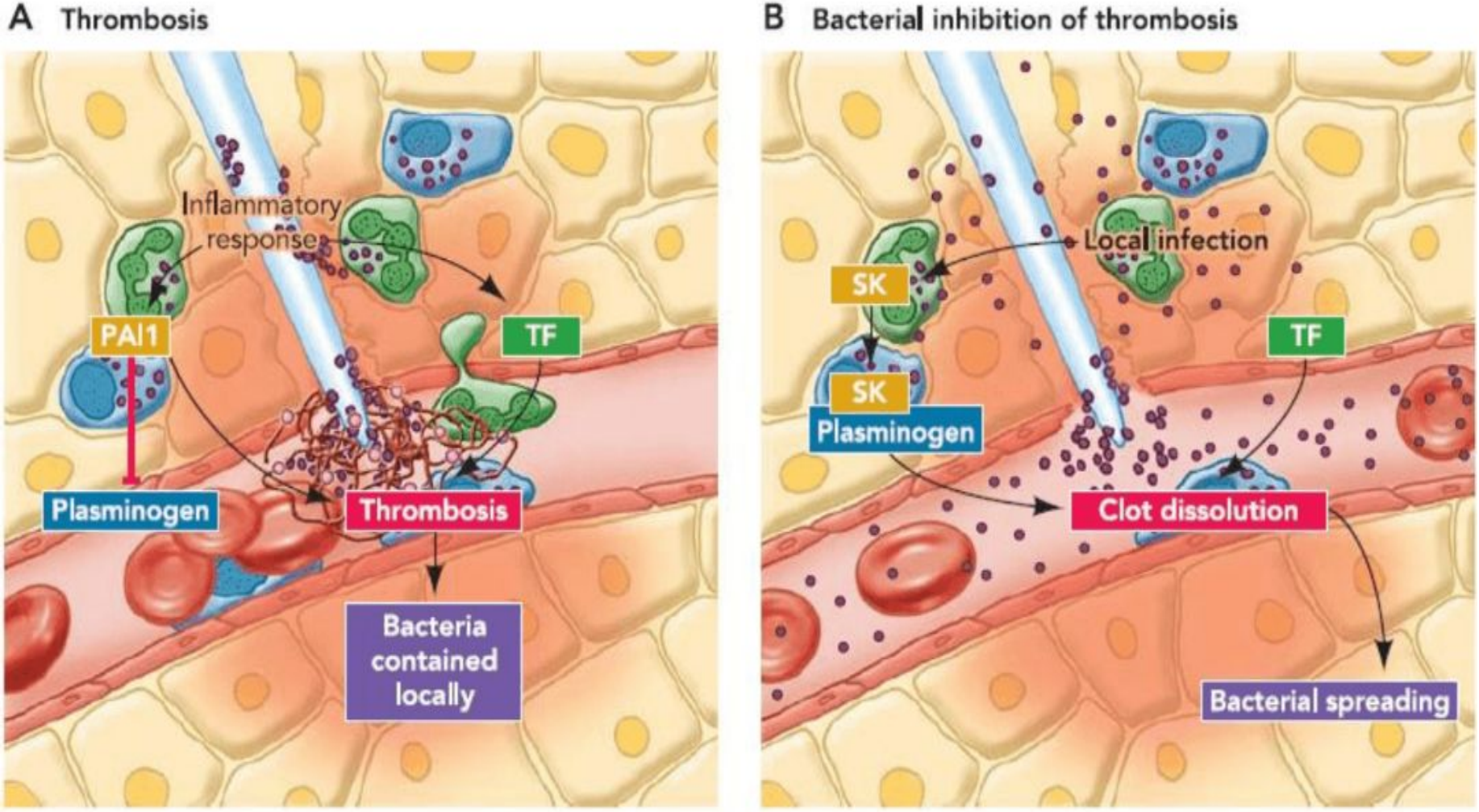
Septic shock → distributive alterations in tissue perfusion due to abnormal control of microvasculature

Weil MH, Shubin H (1971) Adv Exp Med Biol 23:13-23.

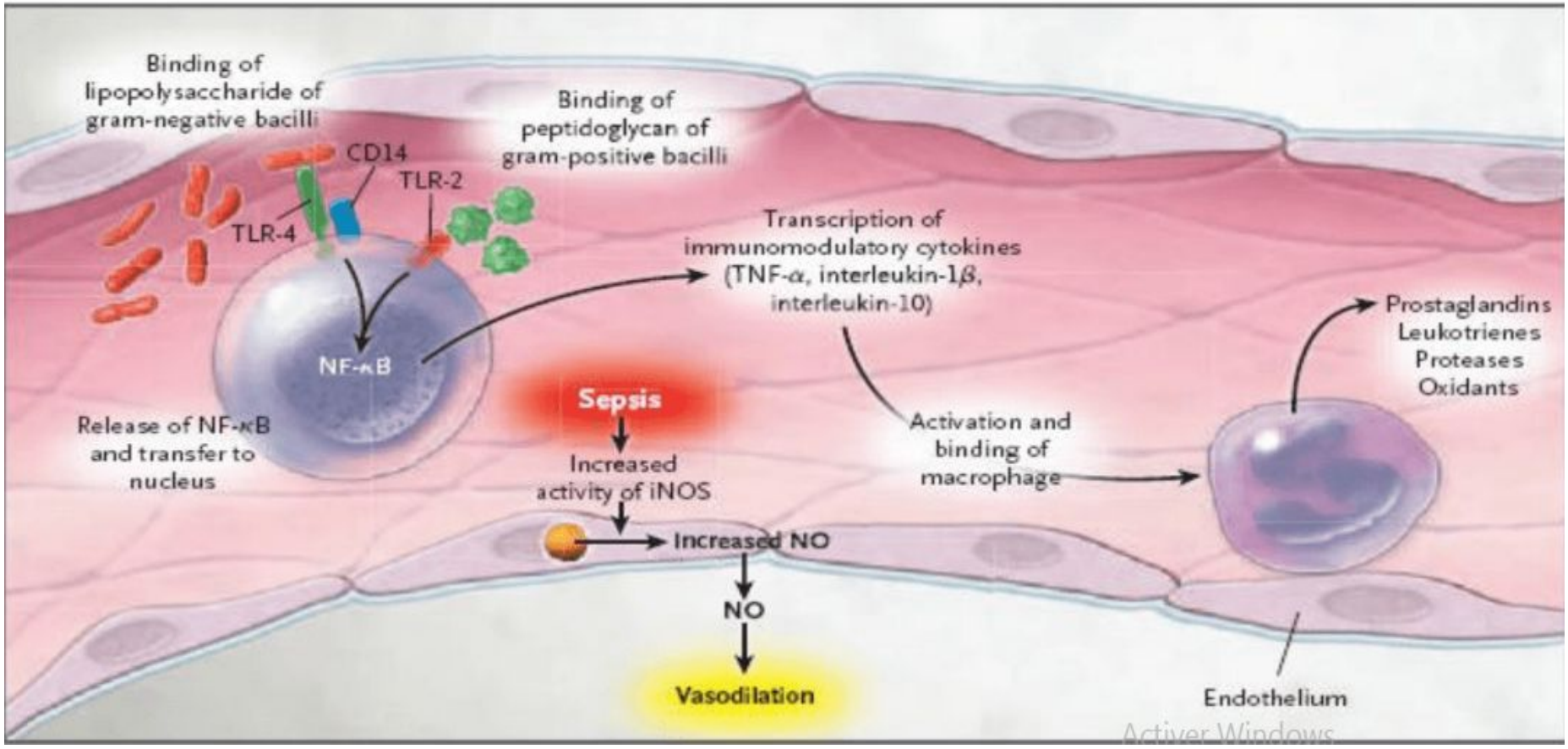
Physiopatholgie

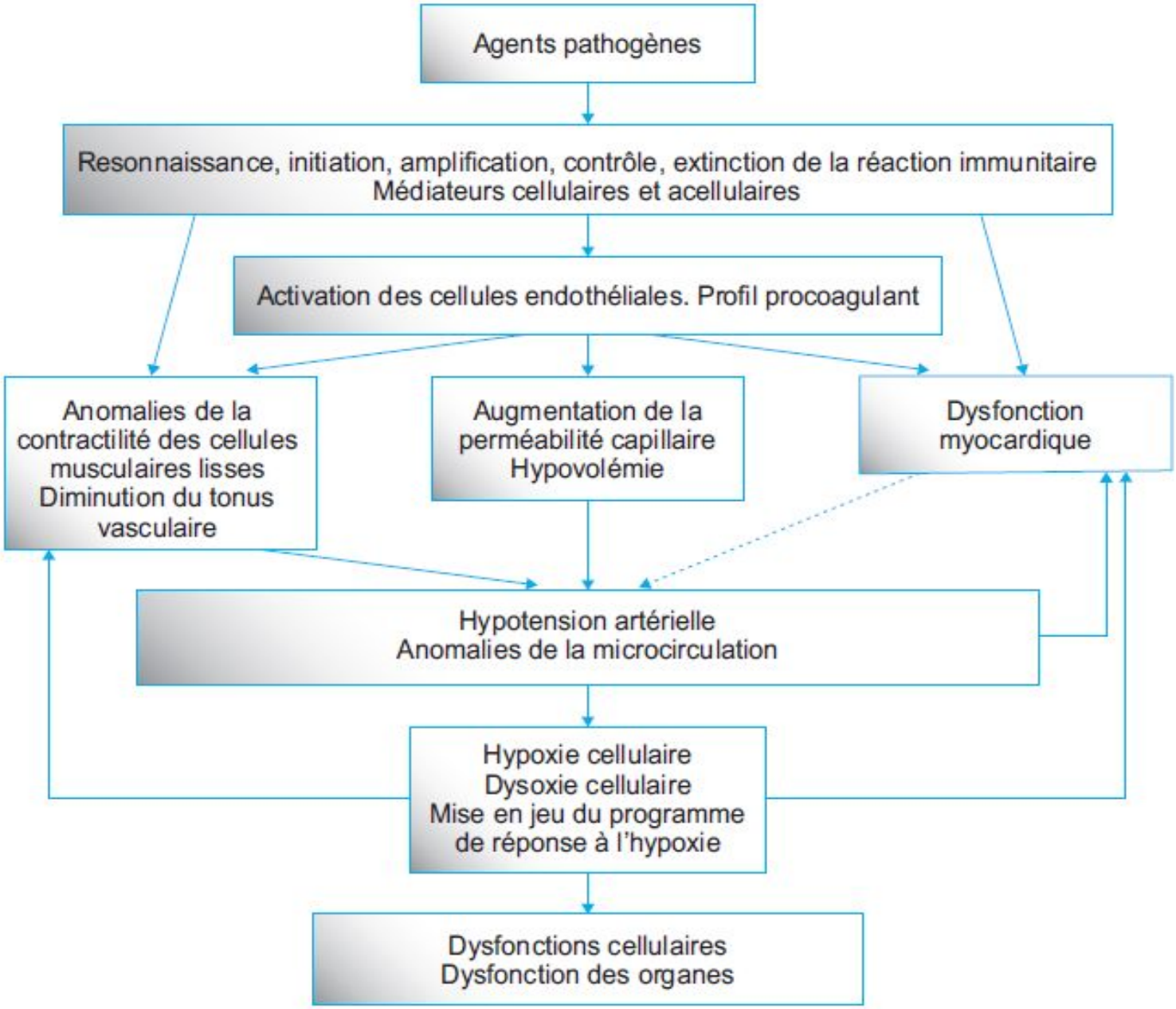
Compartimentalisation

Décompartimentalisation

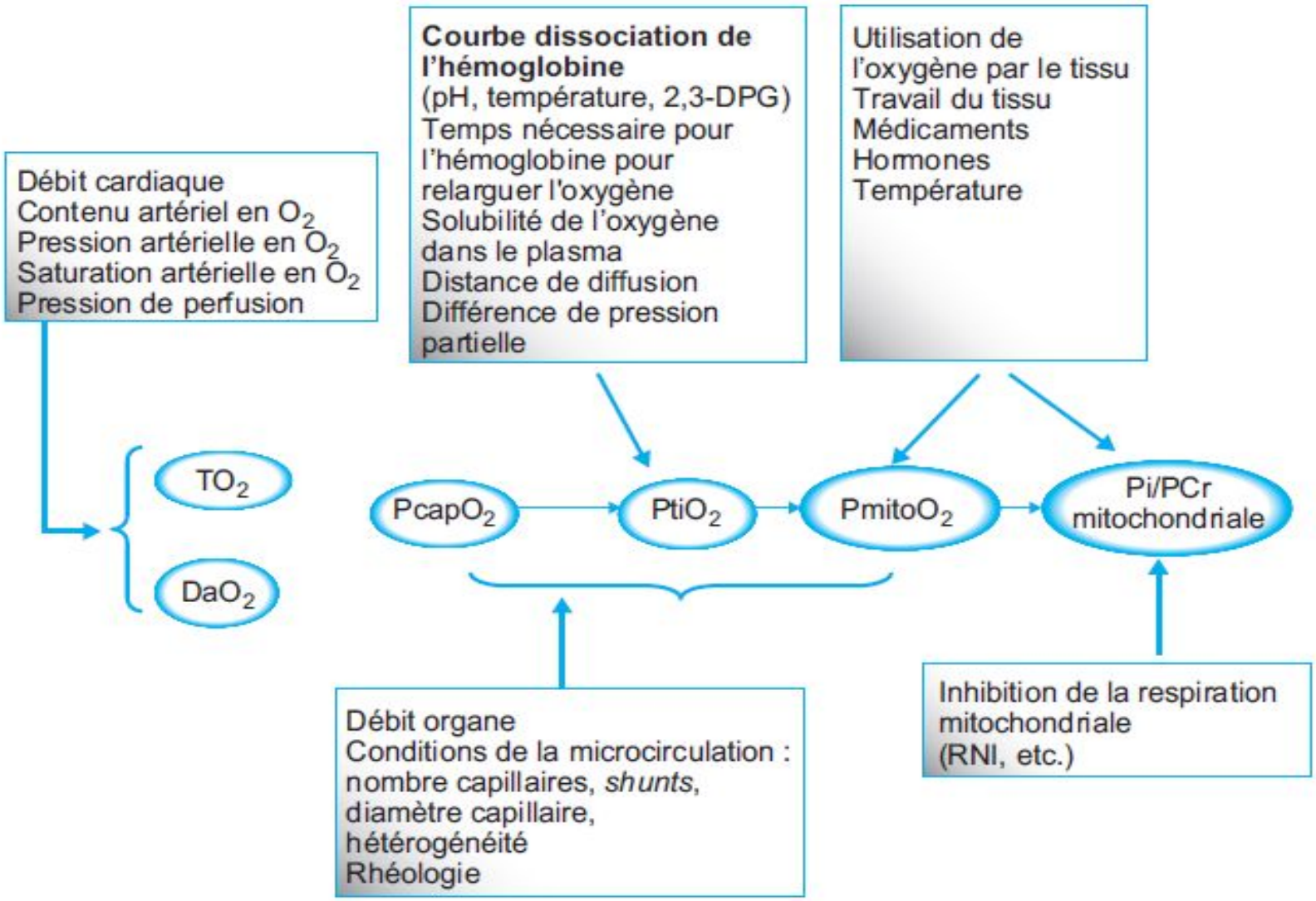


Inflammatory responses to sepsis




Agents pathogènes
Resonnaissance, initiation, amplification, contrôle, extinction de la réaction immunitaire
Médiateurs cellulaires et acellulaires
Activation des cellules endothéliales. Profil procoagulant
Anomalies de la contractilité des cellules musculaires lisses
Diminution du tonus vasculaire
Augmentation de la perméabilité capillaire
Hypovolémie
Dysfonction myocardique
Hypotension artérielle
Anomalies de la microcirculation
Hypoxie cellulaire
Dysoxie cellulaire
Mise en jeu du programme de réponse à l'hypoxie
Dysfonctions cellulaires
Dysfonction des organes

Transport et utilisation de l'oxygène



Transport artériel en Oxygène

$DO_2 = DC \bullet CaO_2$

$DC = VES \bullet FC$

$CaO_2 = (Hb \bullet SaO_2) + (PaO_2)$

- $(Hb \bullet SaO_2)$: O_2 lié (95%)
- (PaO_2) : O_2 libre (5%)

DC : débit cardiaque

VES : volume d 'éjection systolique

FC : fréquence cardiaque

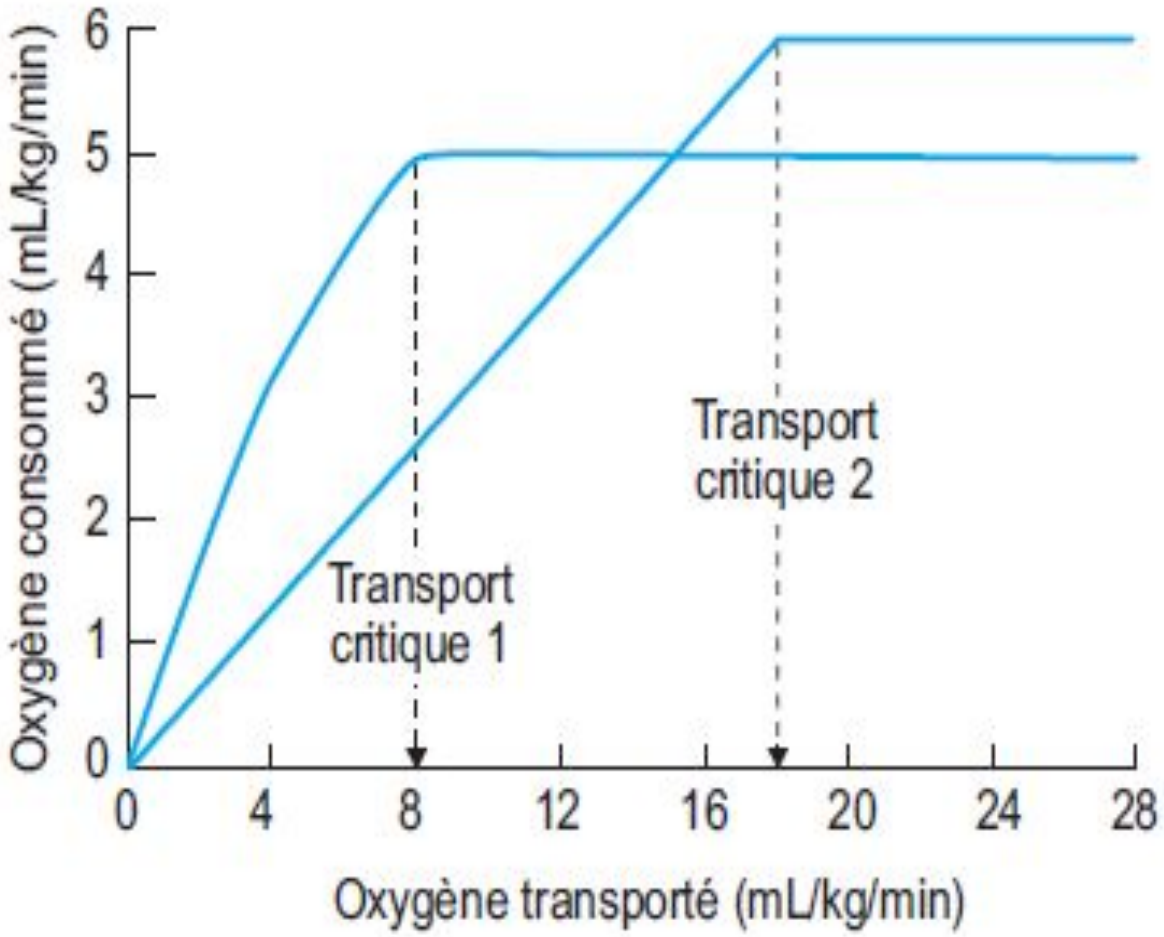
CaO_2 : contenu artériel en O_2

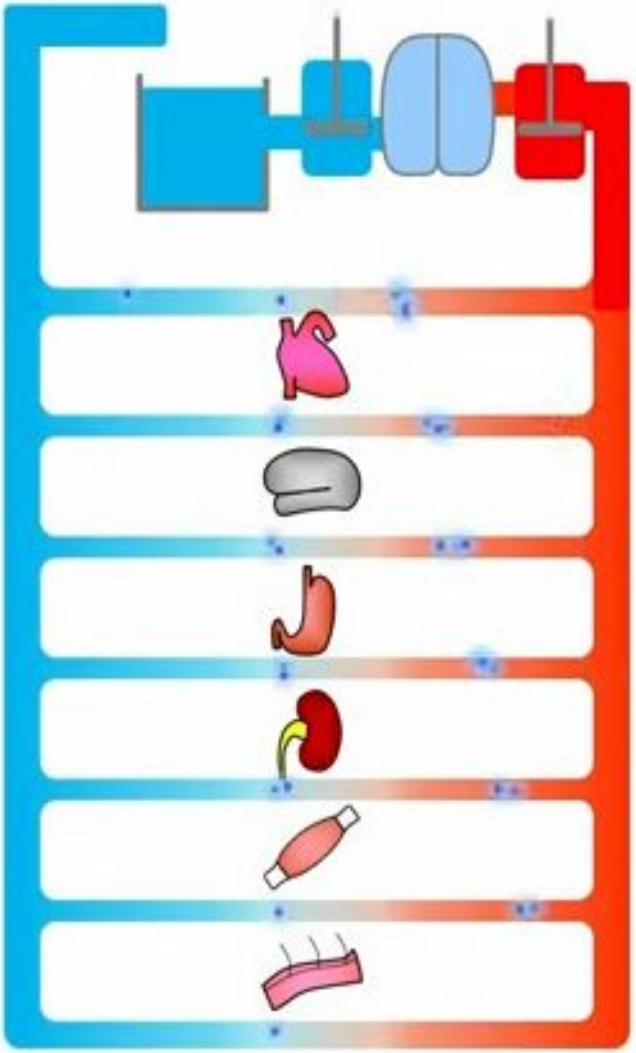
Hb : hémoglobinémie

SaO_2 : saturation artérielle en O_2

PaO_2 : pression en O_2 du sang artériel.

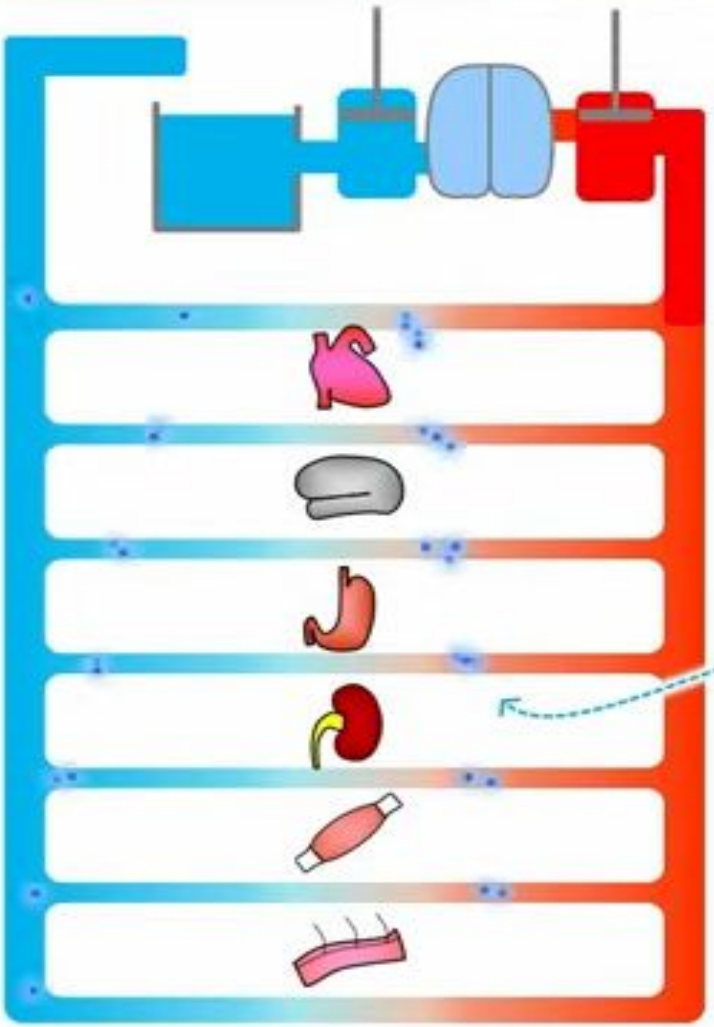
- Seul le débit cardiaque a un système de régulation
- Contenu artériel en O_2 très dépendant de l'Hb.


Oxygène consommé (mL/kg/min)
0
1
2
3
4
5
6
0
4
8
12
16
20
24
28
Oxygène transporté (mL/kg/min)
Transport critique 1
Transport critique 2



Défaillance circulatoire

Définition



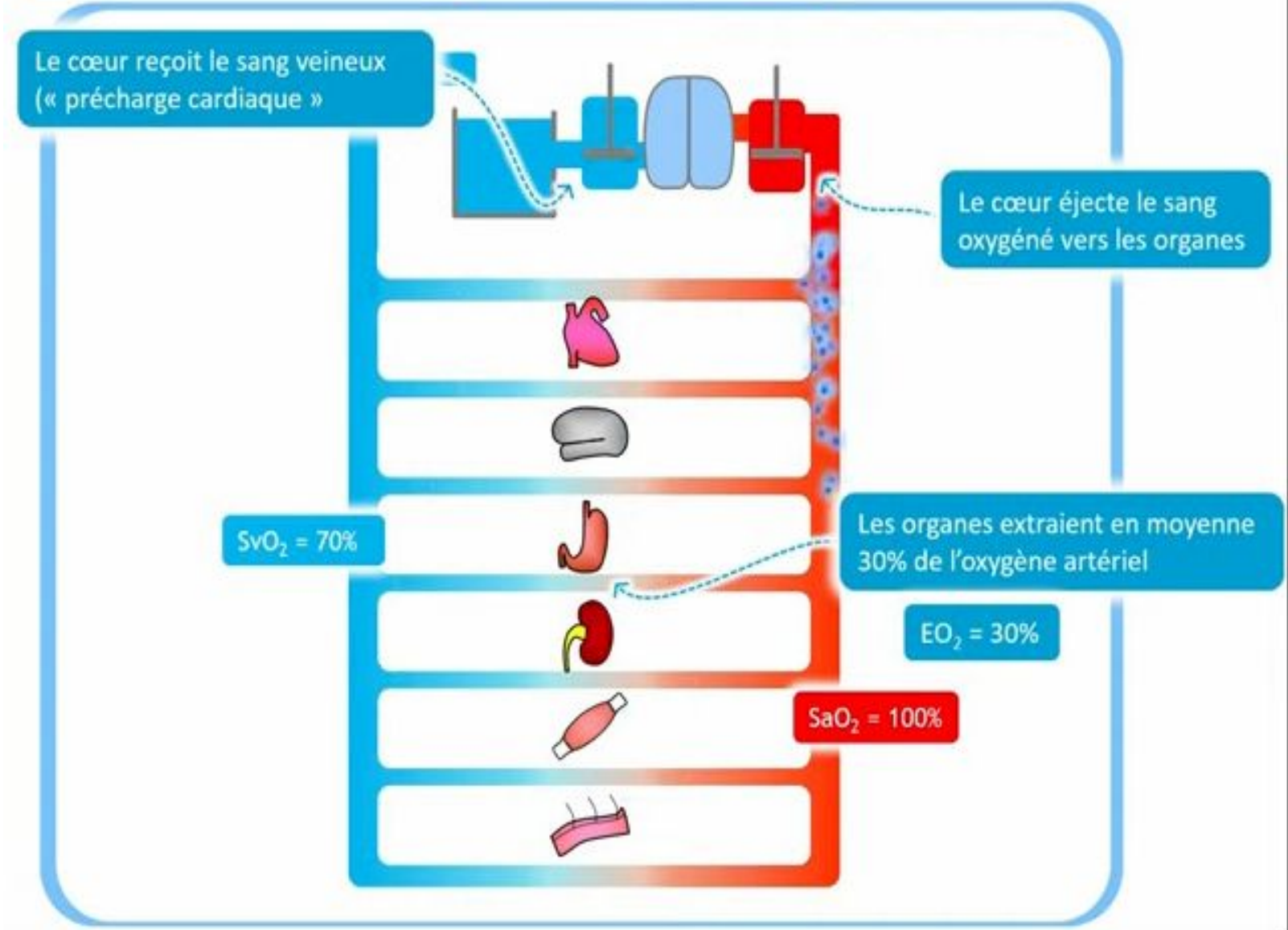
↘ perfusion des organes

Conduisant à une **inadéquation entre apports et besoins en O_2 des tissus**

Défaillance circulatoire

Mécanismes de base

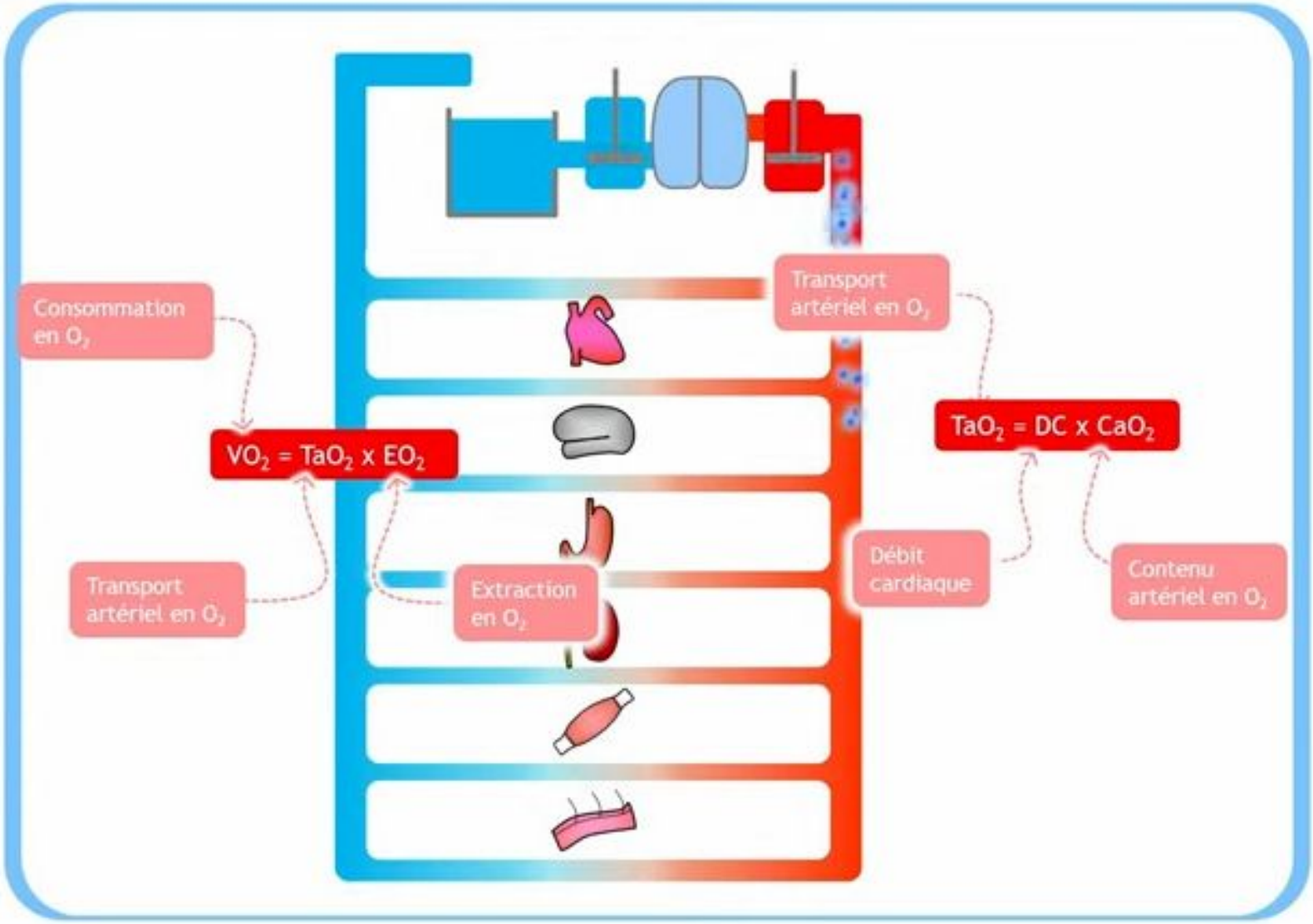
A l'état normal



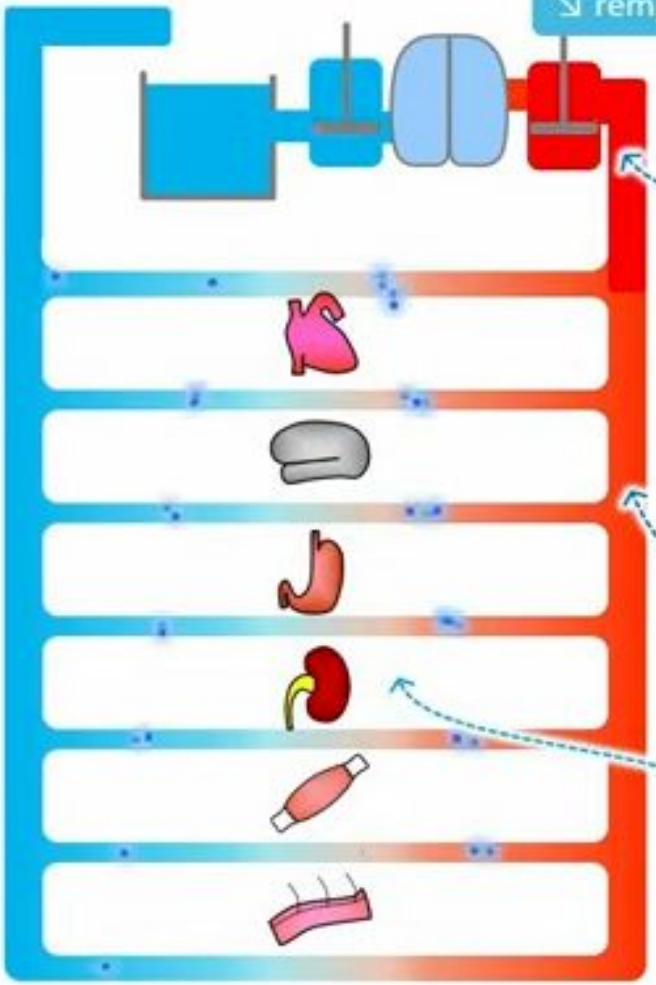
Défaillance circulatoire

Mécanismes de base

A l'état normal



Défaillance circulatoire | Mécanismes de base | Etat de choc



↘ remplissage

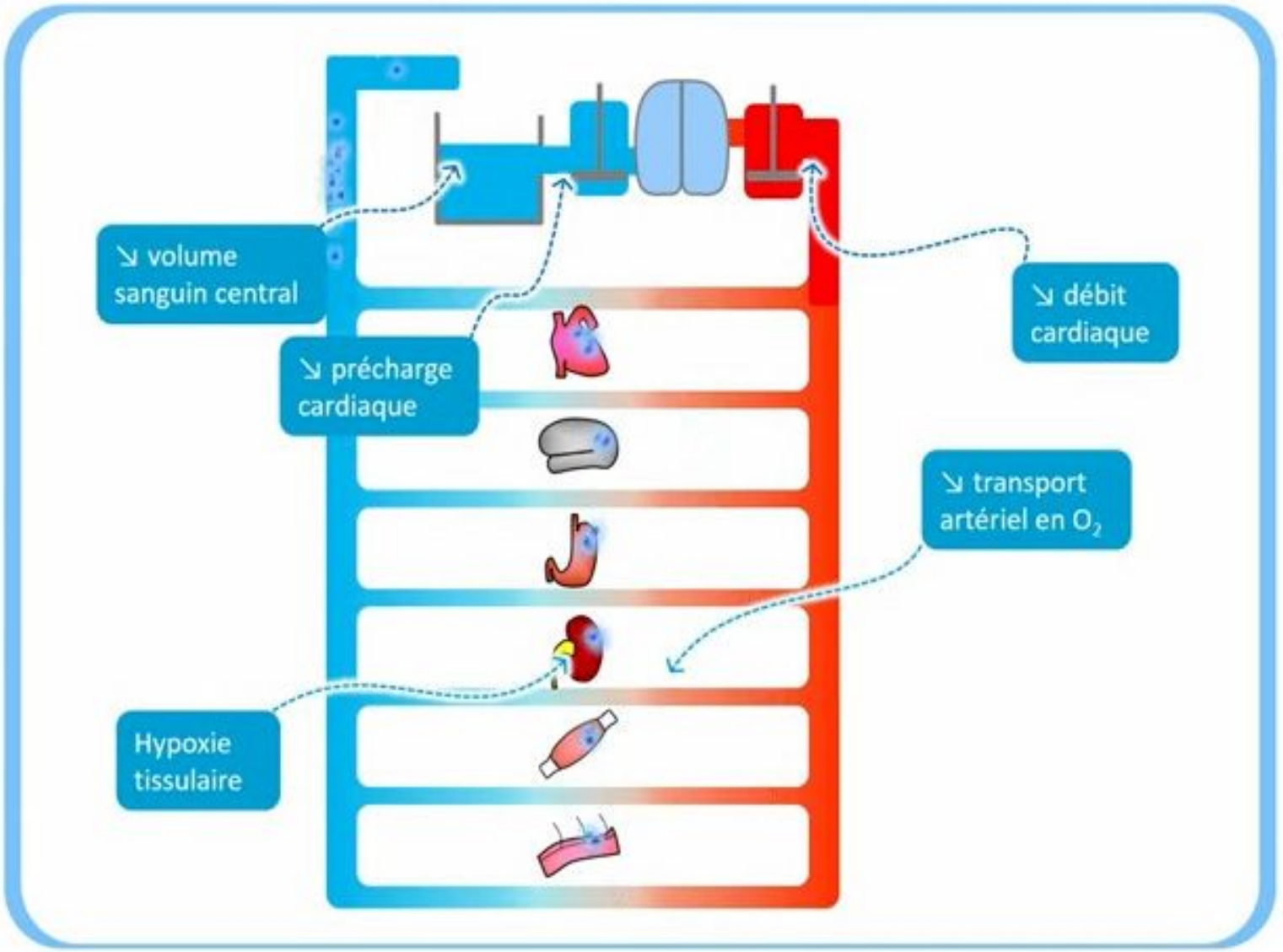
↘ contractilité

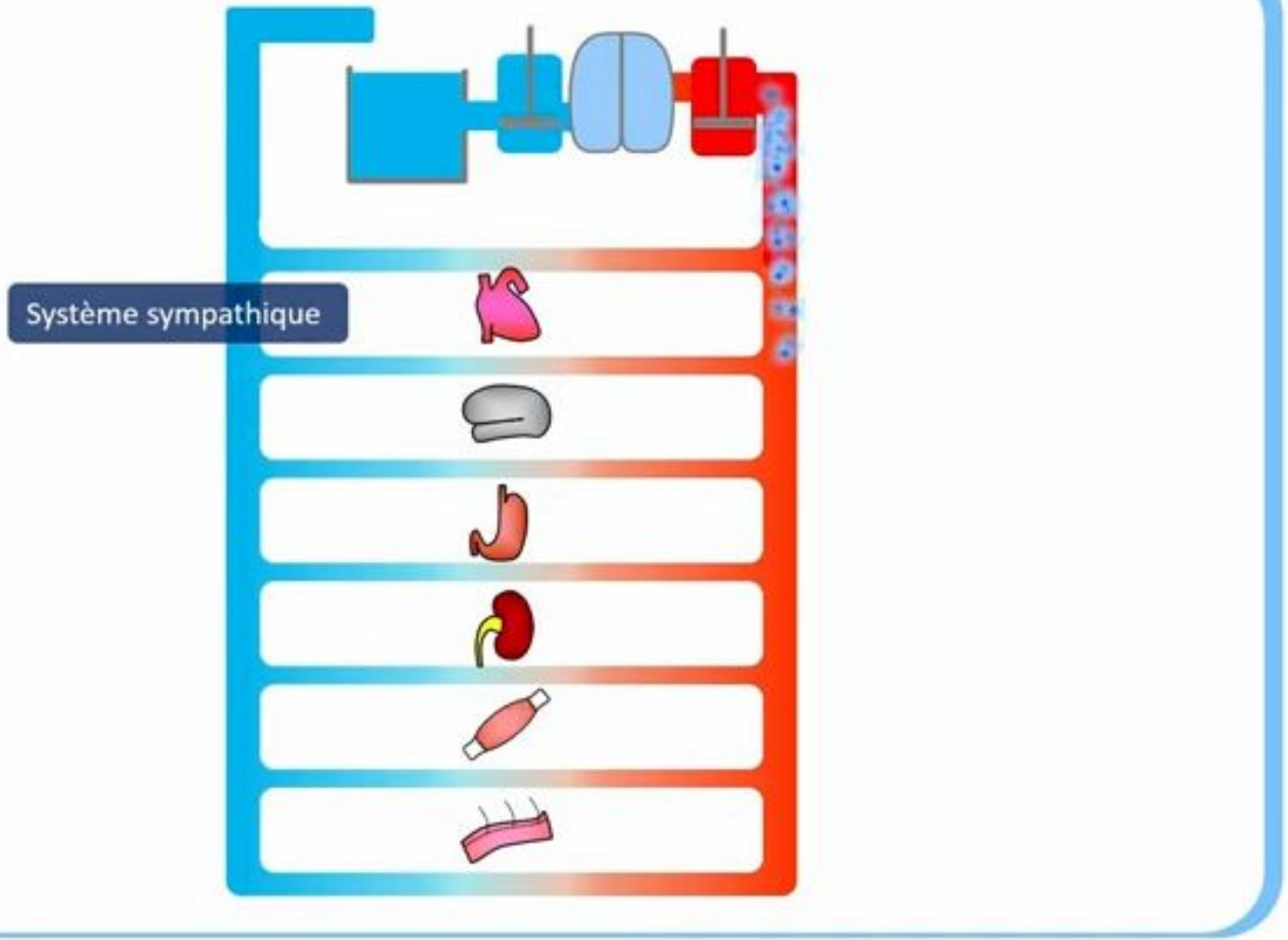
↘ débit cardiaque

Vasodilatation

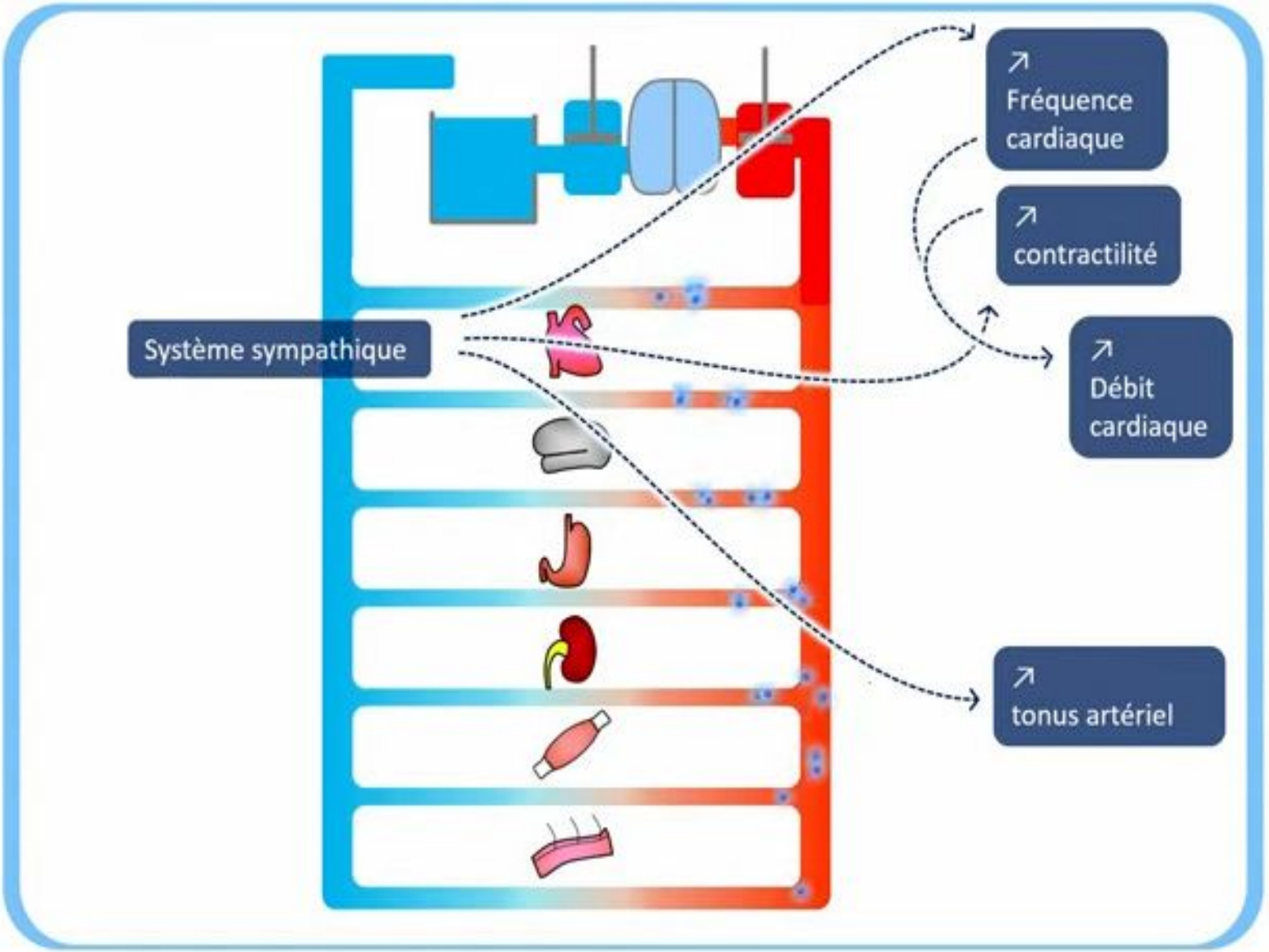
↘ pression artérielle

Les organes reçoivent moins d'O_2


↘ volume sanguin central
↘ précharge cardiaque
↘ débit cardiaque
↘ transport artériel en O_2
Hypoxie tissulaire


Système sympathique

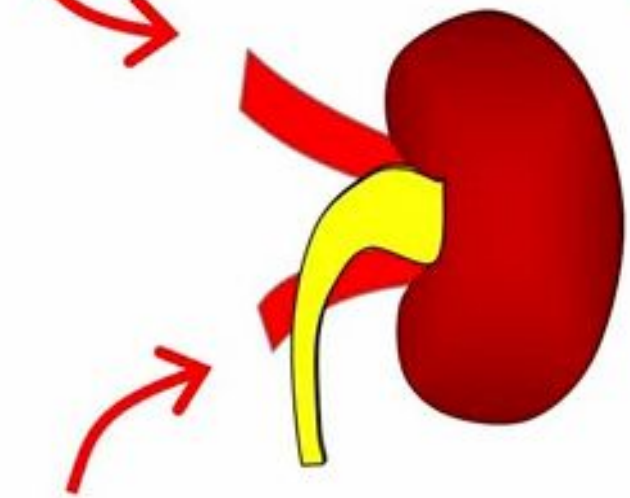
Défaillance circulatoire | Choc hypovolémique | Mécanismes adaptatifs



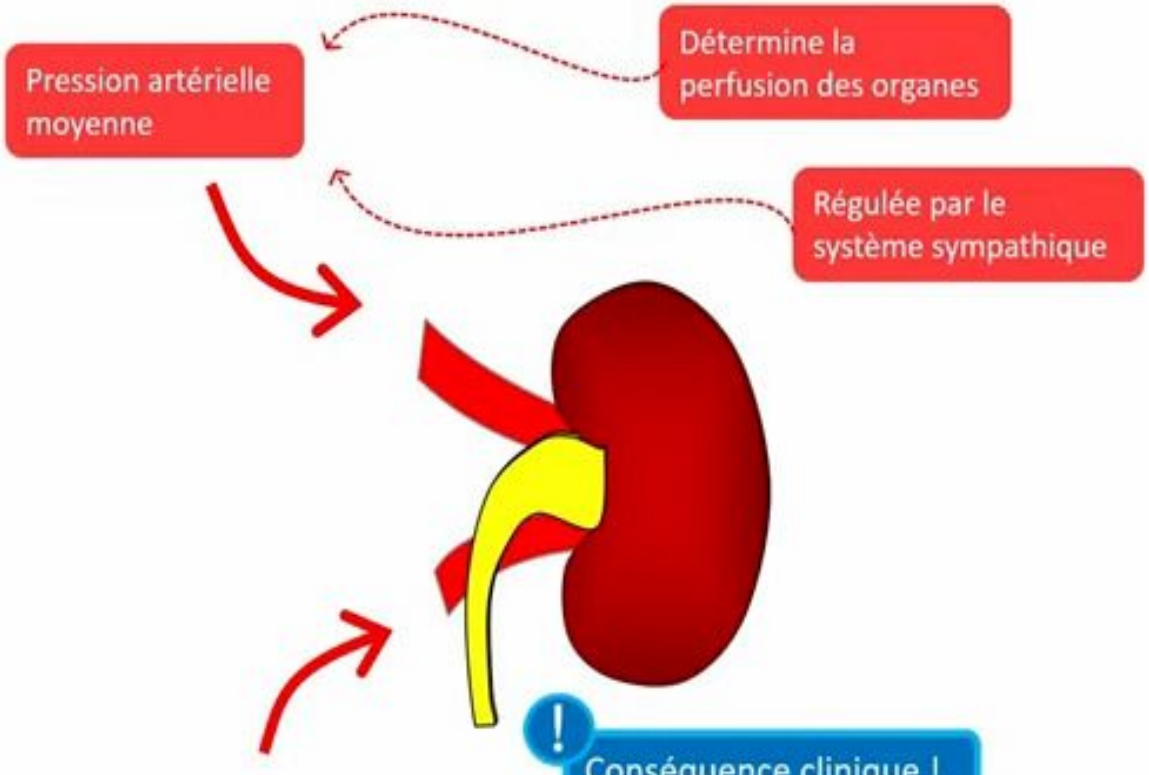
Pression artérielle moyenne

Détermine la perfusion des organes

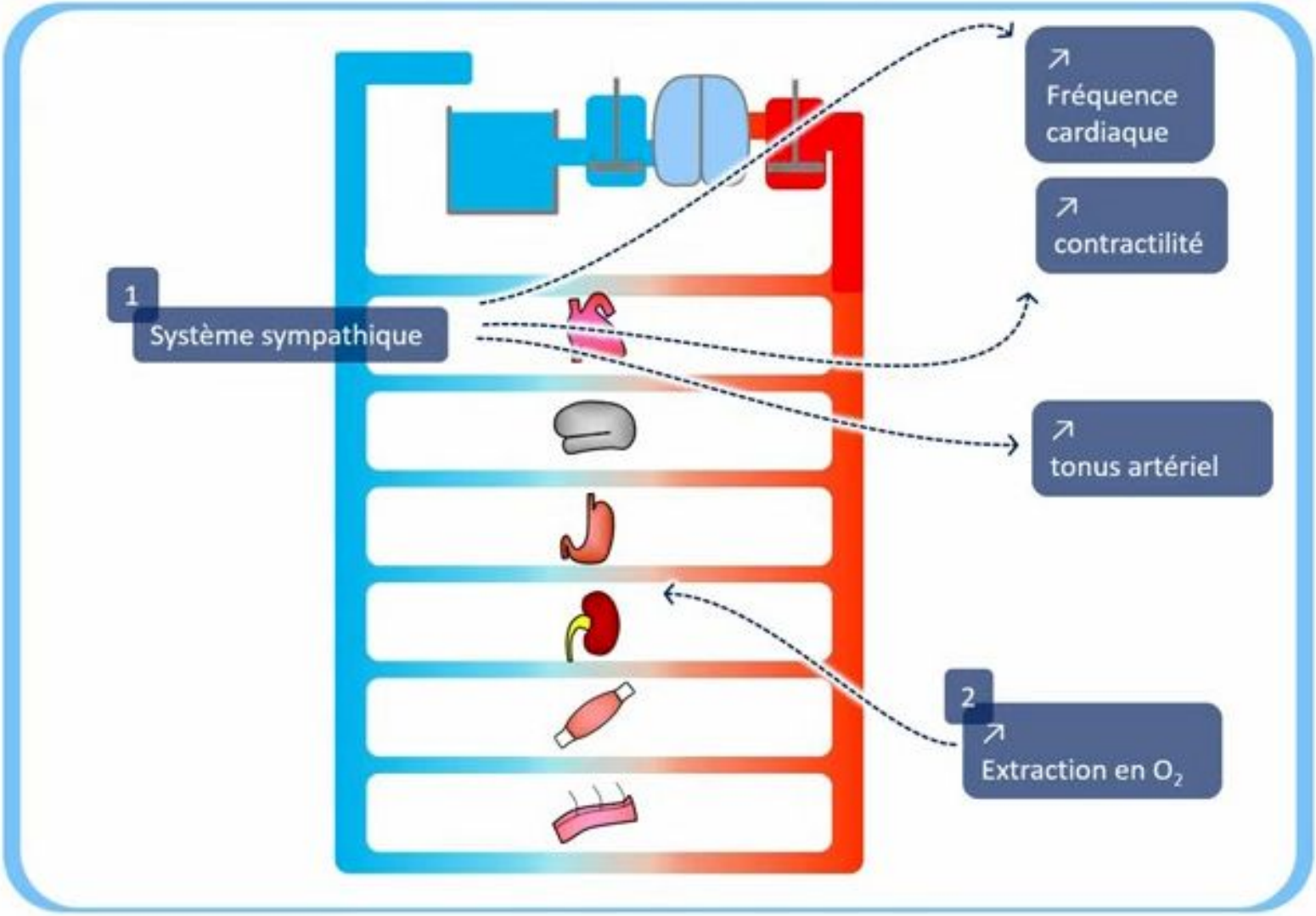
Régulée par le système sympathique



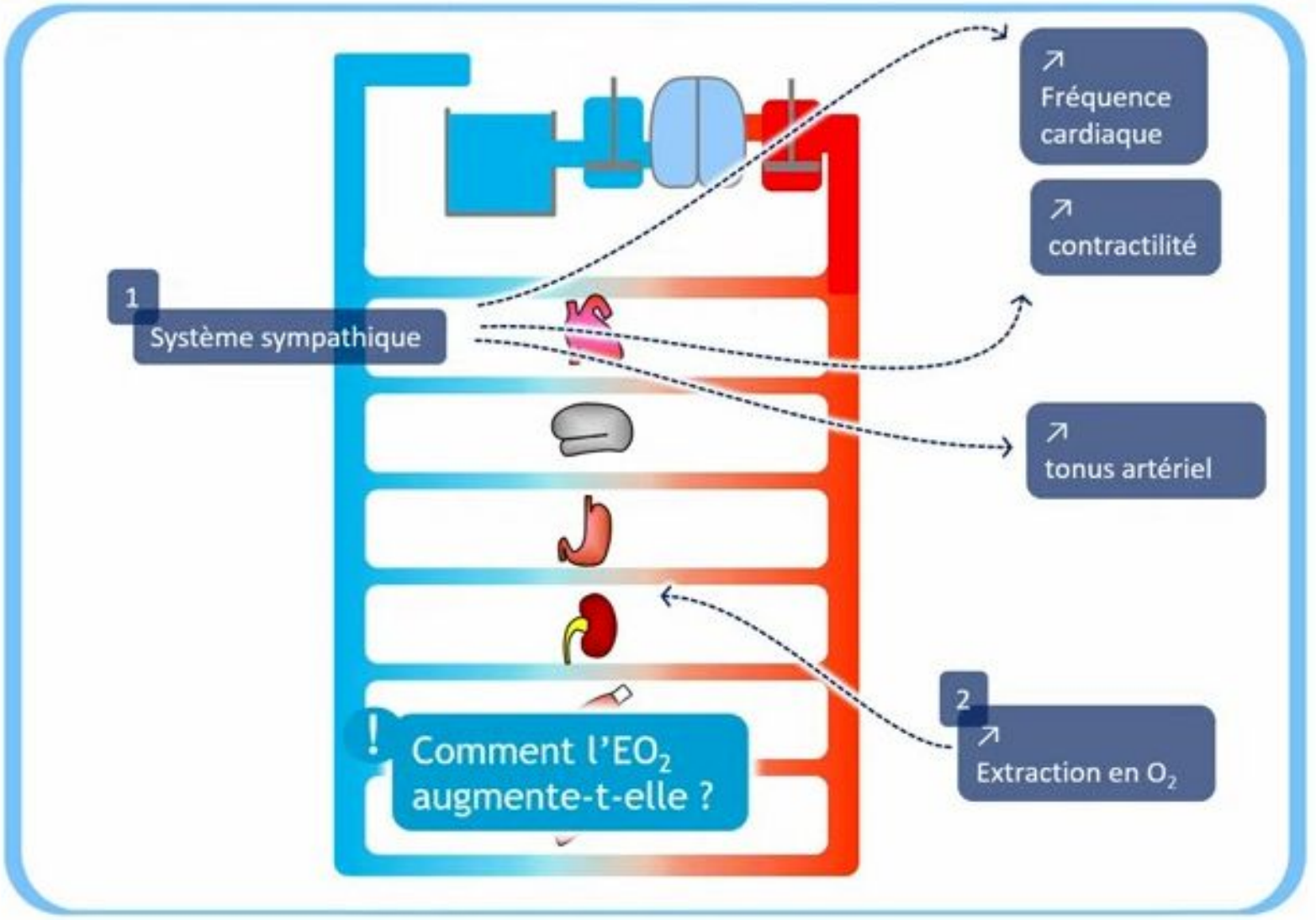
Défaillance circulatoire | Choc hypovolémique | Mécanismes adaptatifs



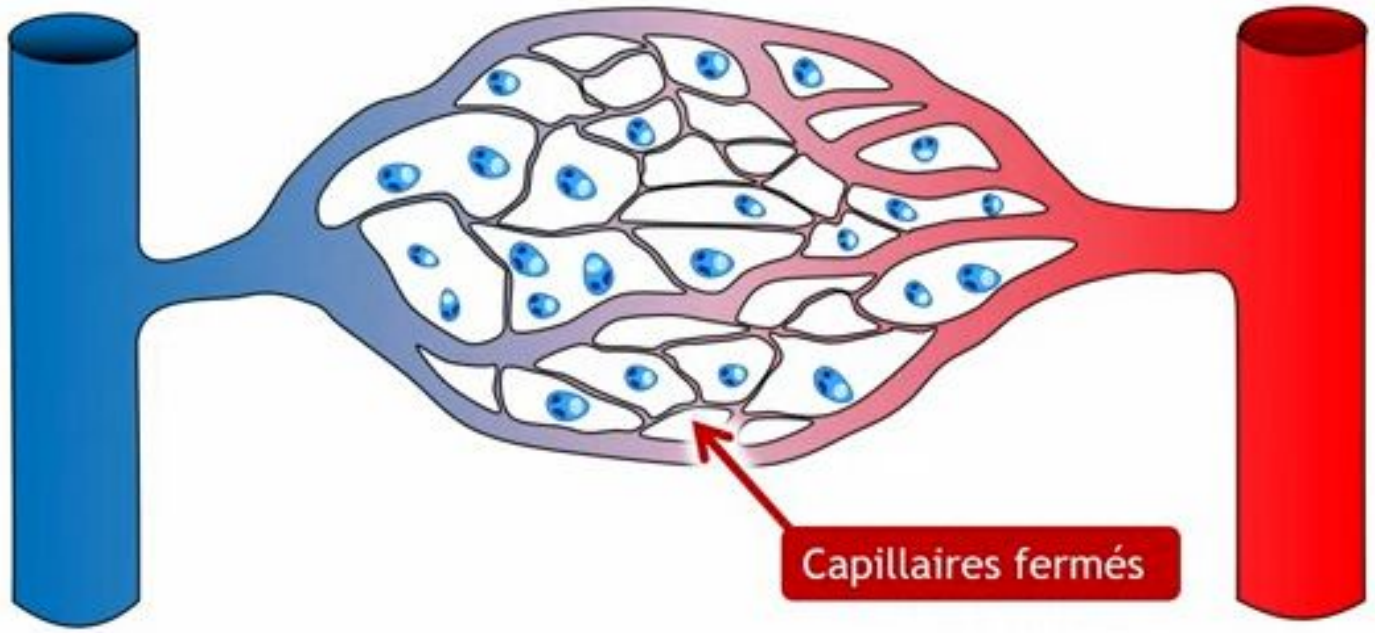
Défaillance circulatoire | Choc hypovolémique | Mécanismes adaptatifs



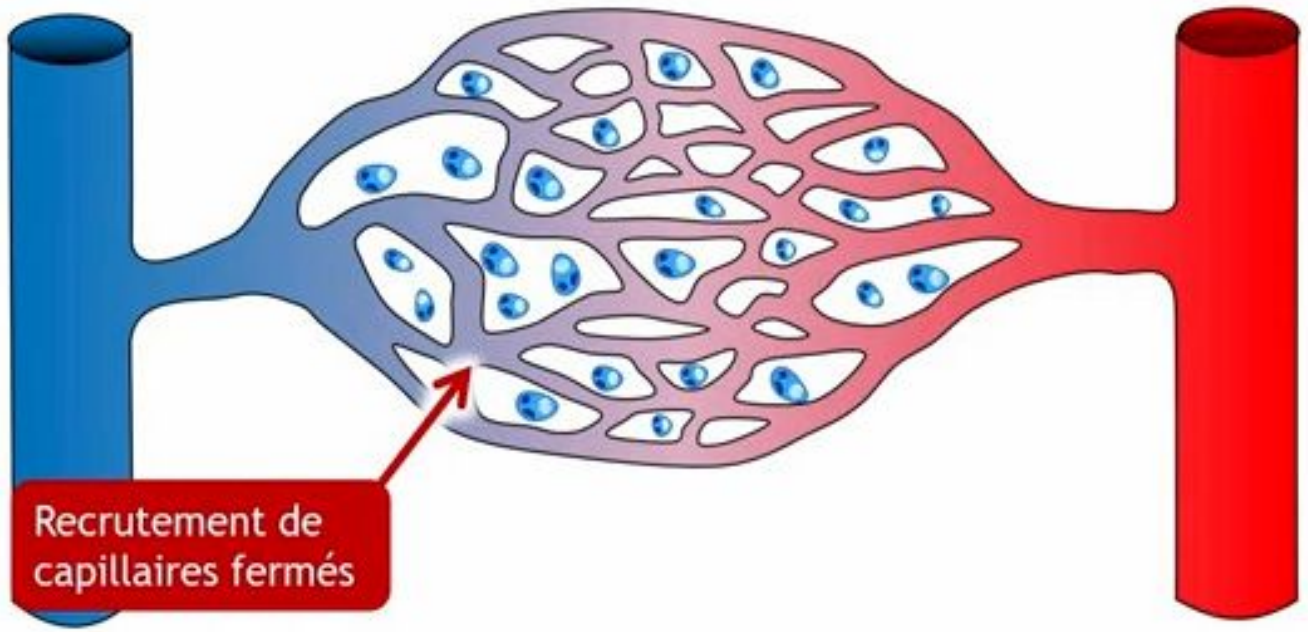
Défaillance circulatoire | Choc hypovolémique | Mécanismes adaptatifs



La microcirculation protège contre l'hypoxie tissulaire

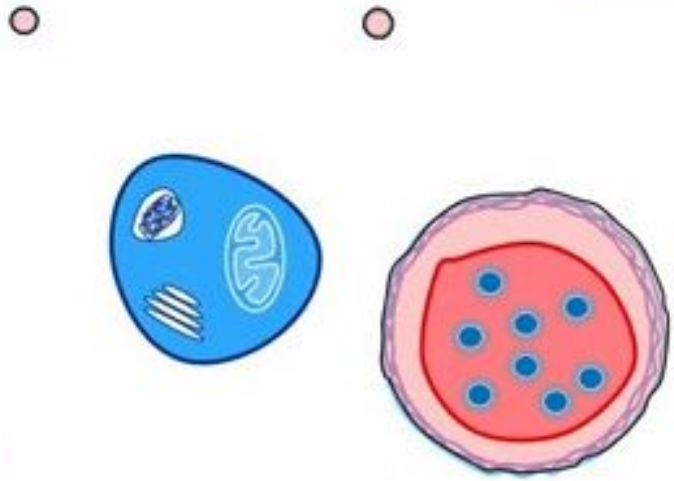


La microcirculation protège contre l'hypoxie tissulaire

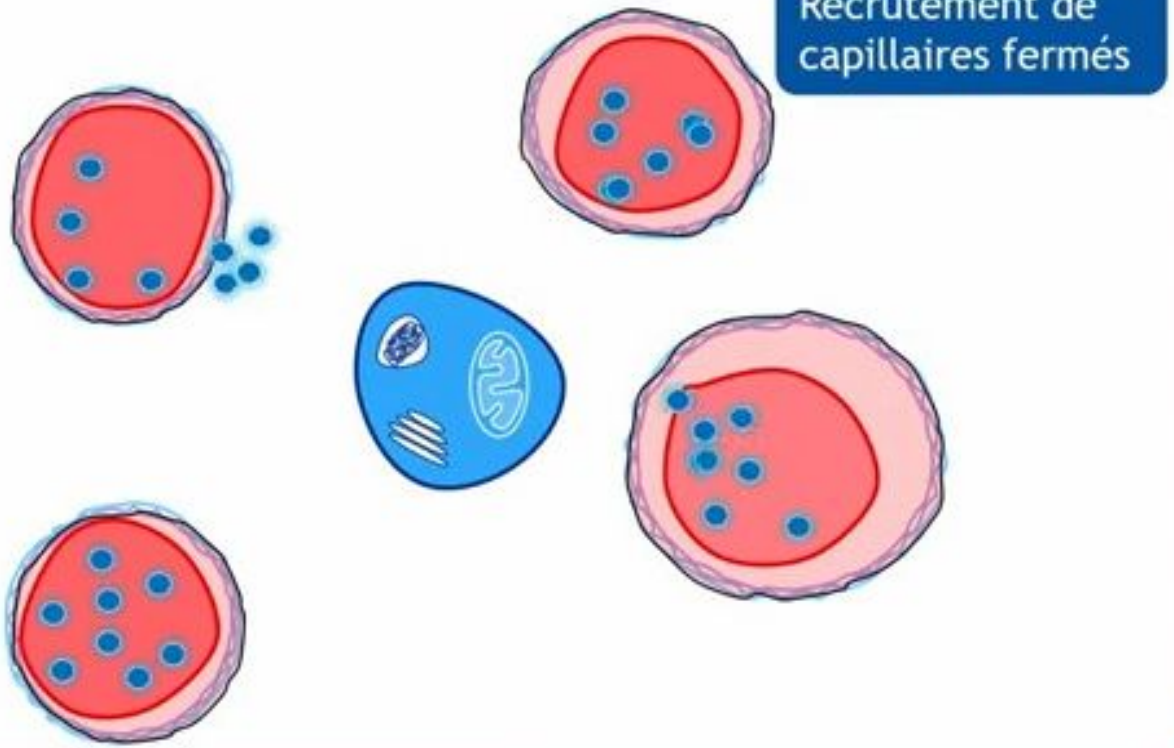


La microcirculation protège contre l'hypoxie tissulaire

Recrutement de capillaires fermés



La microcirculation protège contre l'hypoxie tissulaire



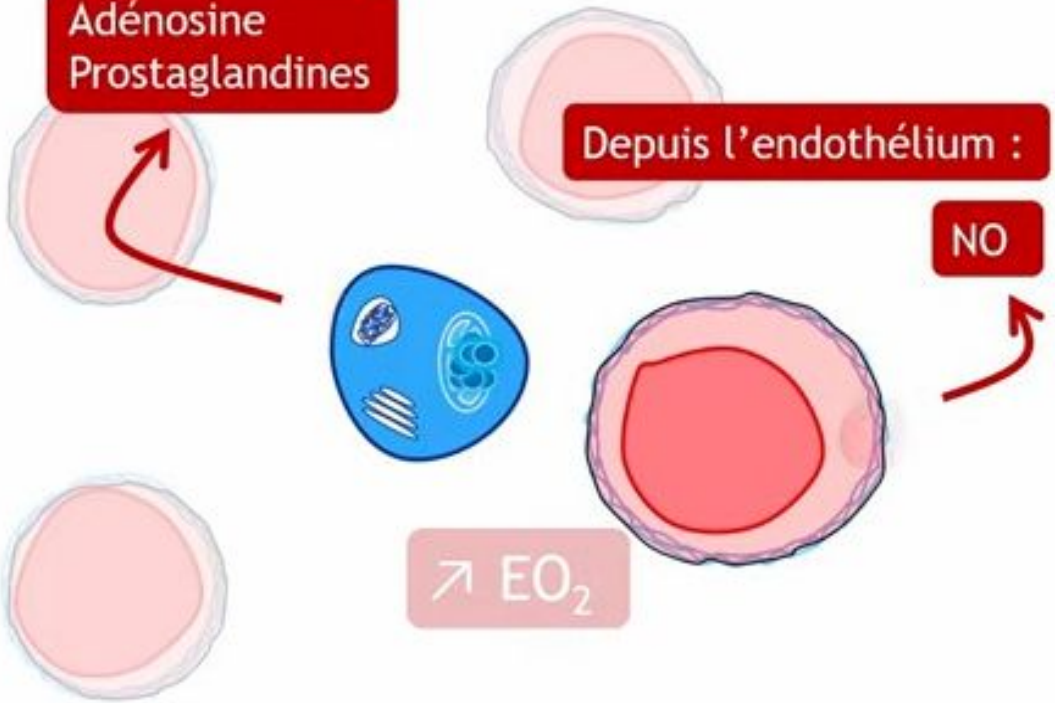
La microcirculation protège contre l'hypoxie tissulaire

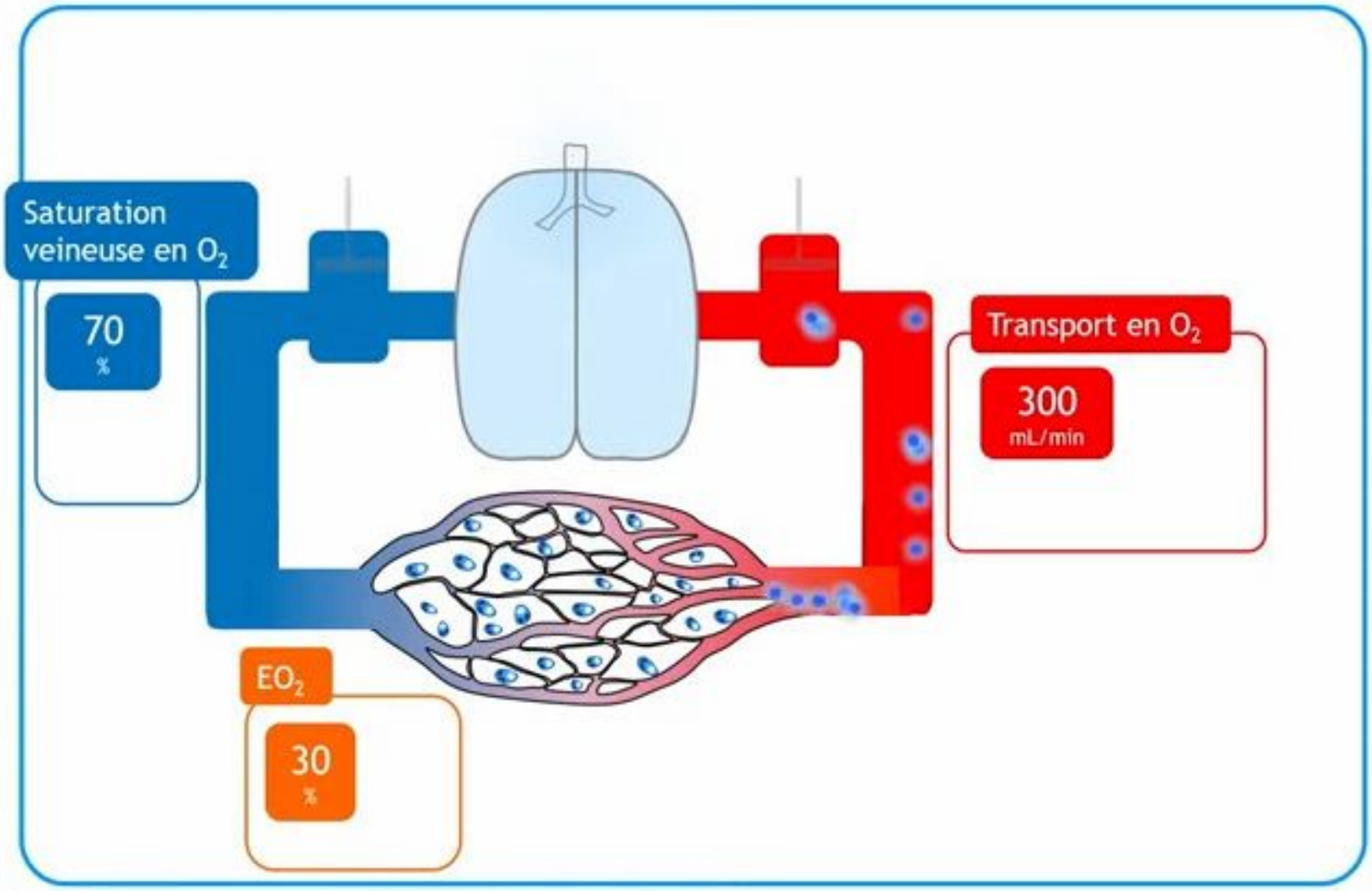
Depuis la cellule :

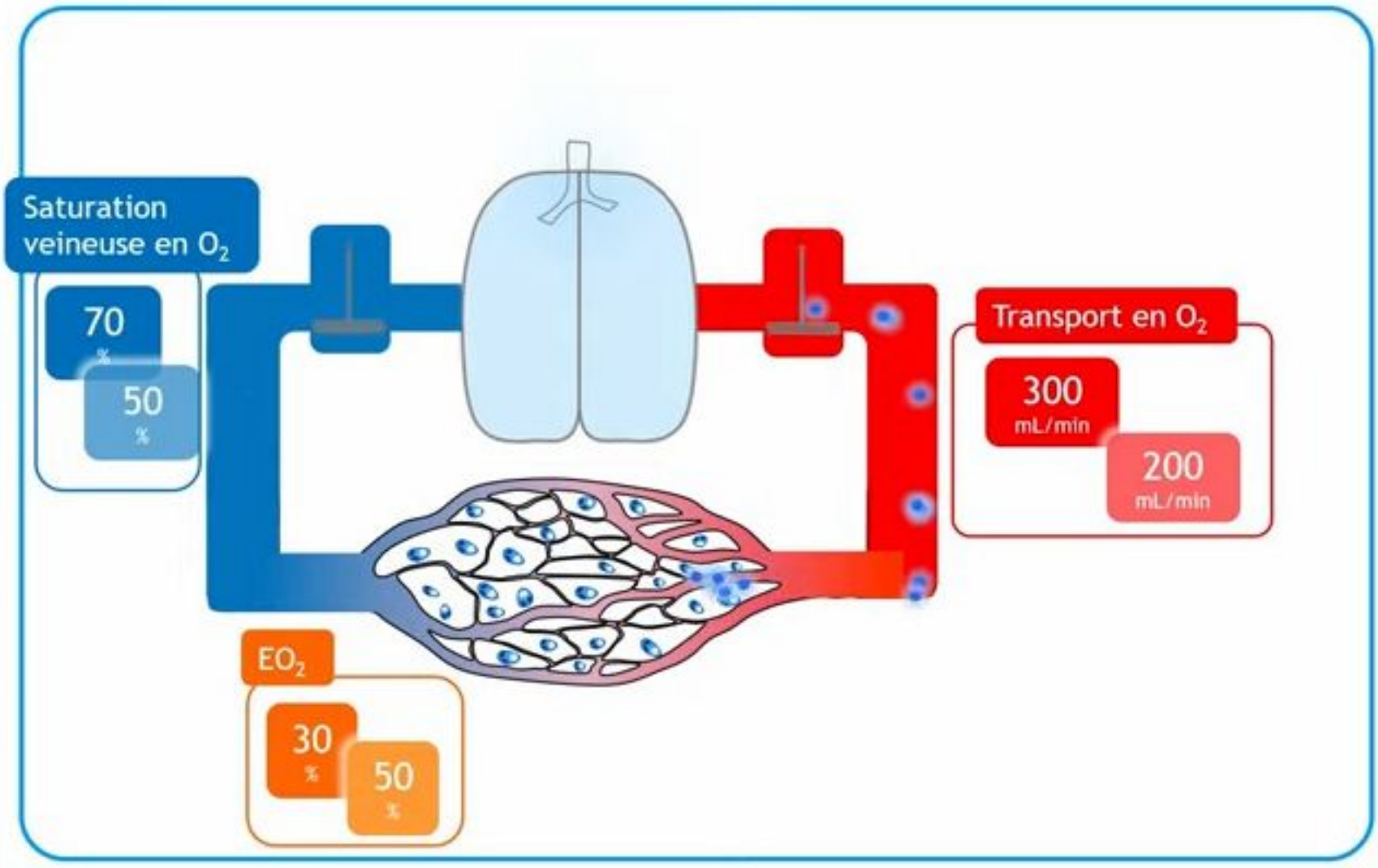
Adénosine
Prostaglandines

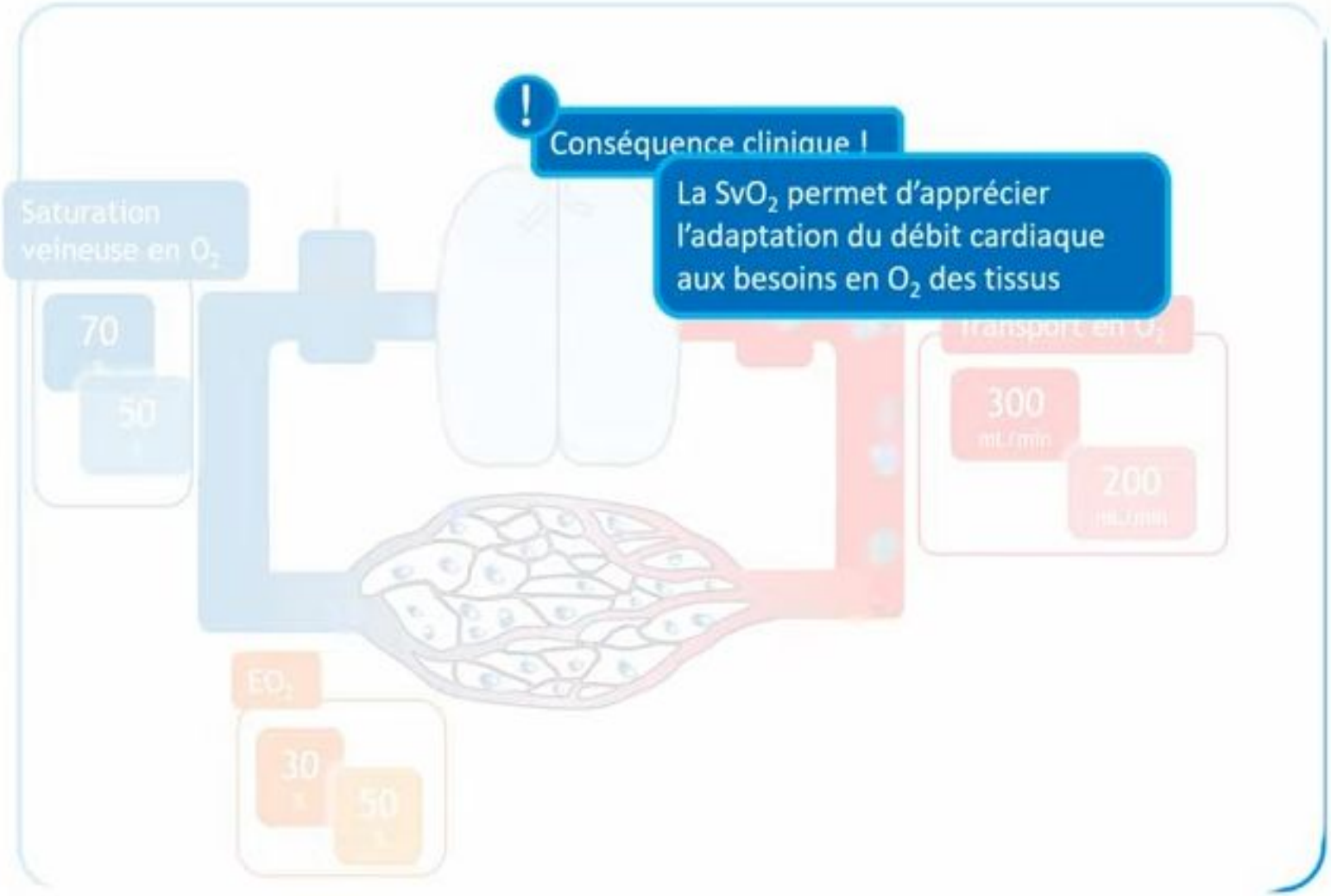
Depuis l'endothélium :

NO

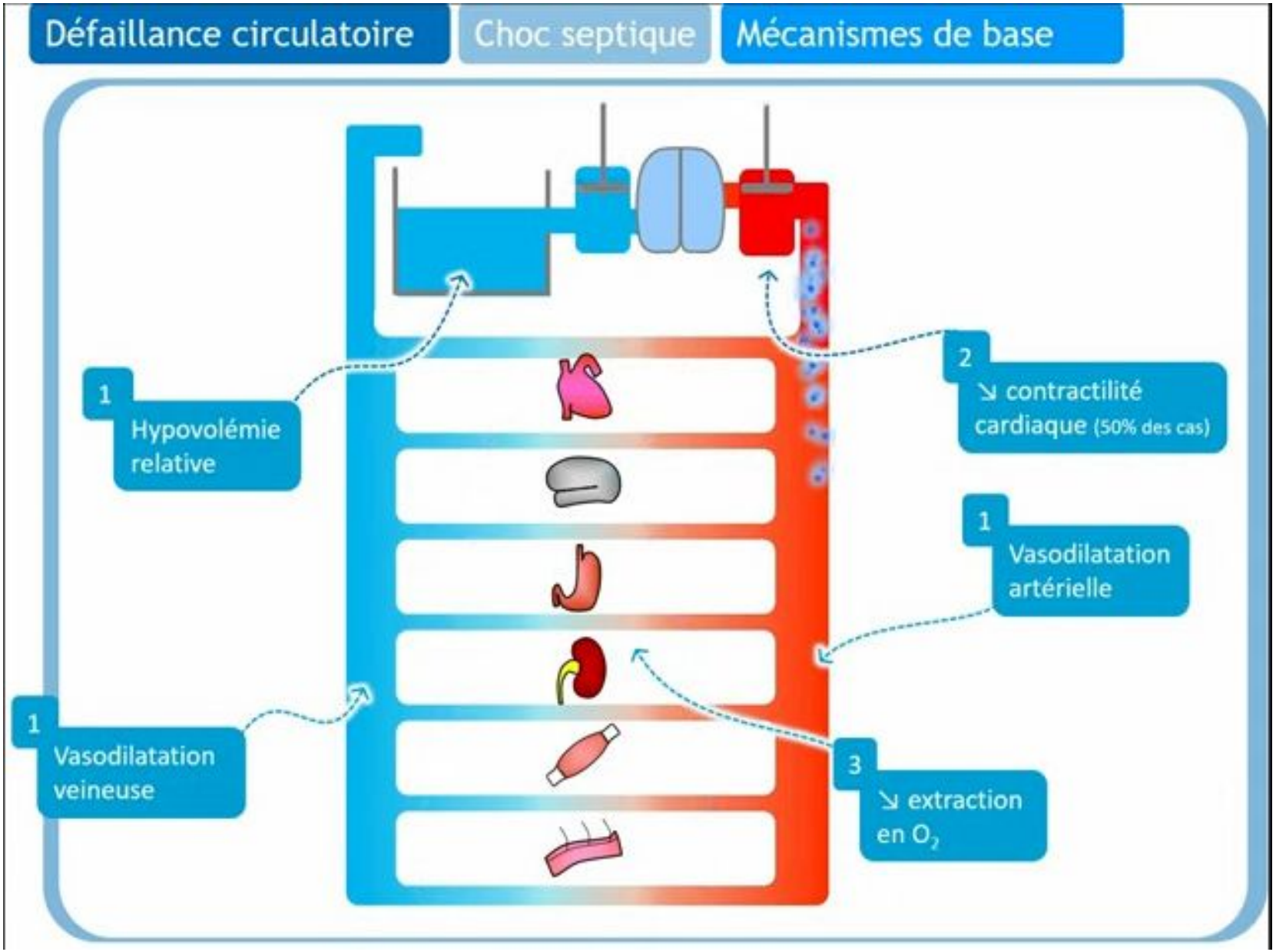


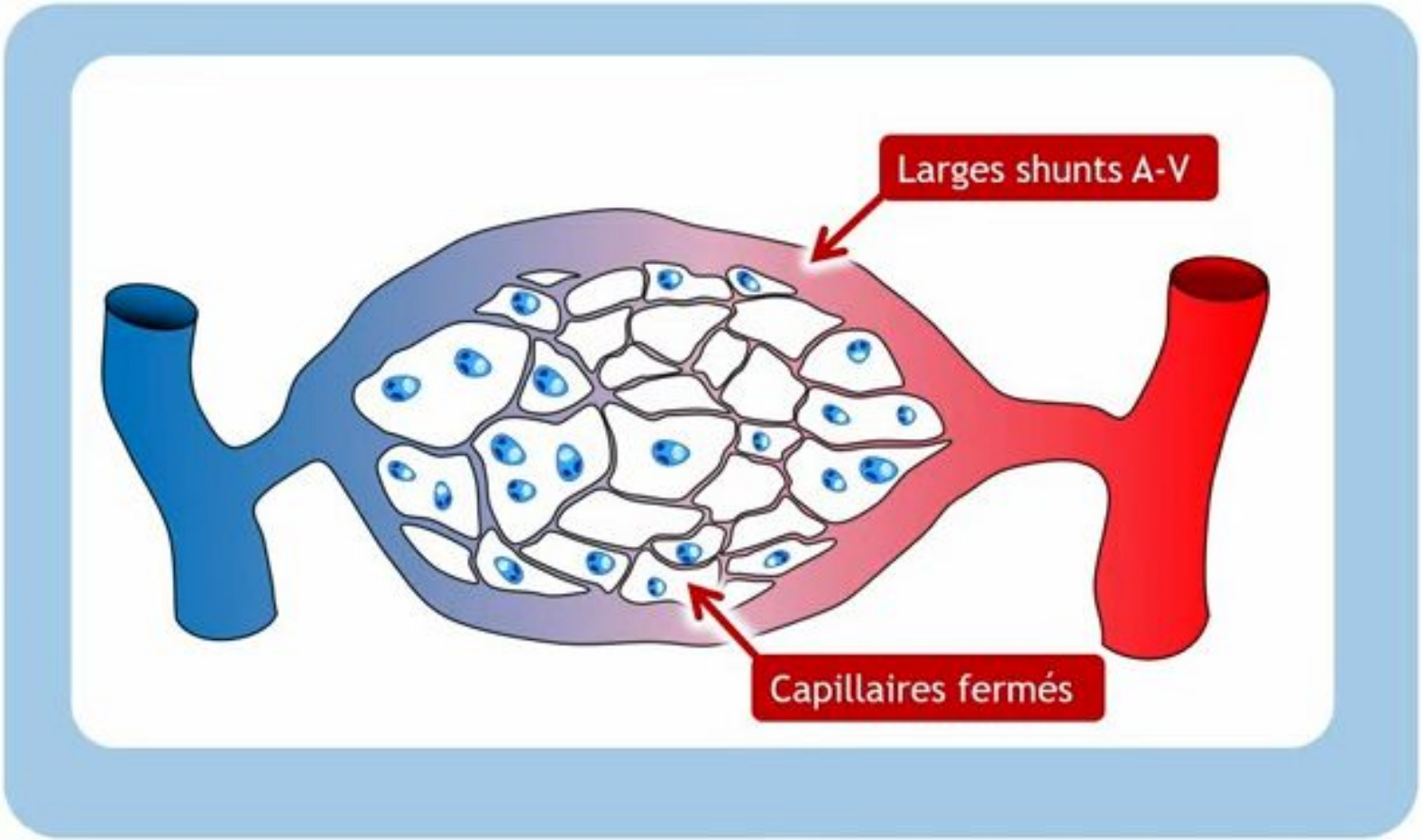

Saturation veineuse en O_2
70
%
Transport en O_2
300
mL/min
EO_2
30
%


Saturation veineuse en O_2
70 %
50 %
Transport en O_2
300 mL/min
200 mL/min
EO_2
30 %
50 %

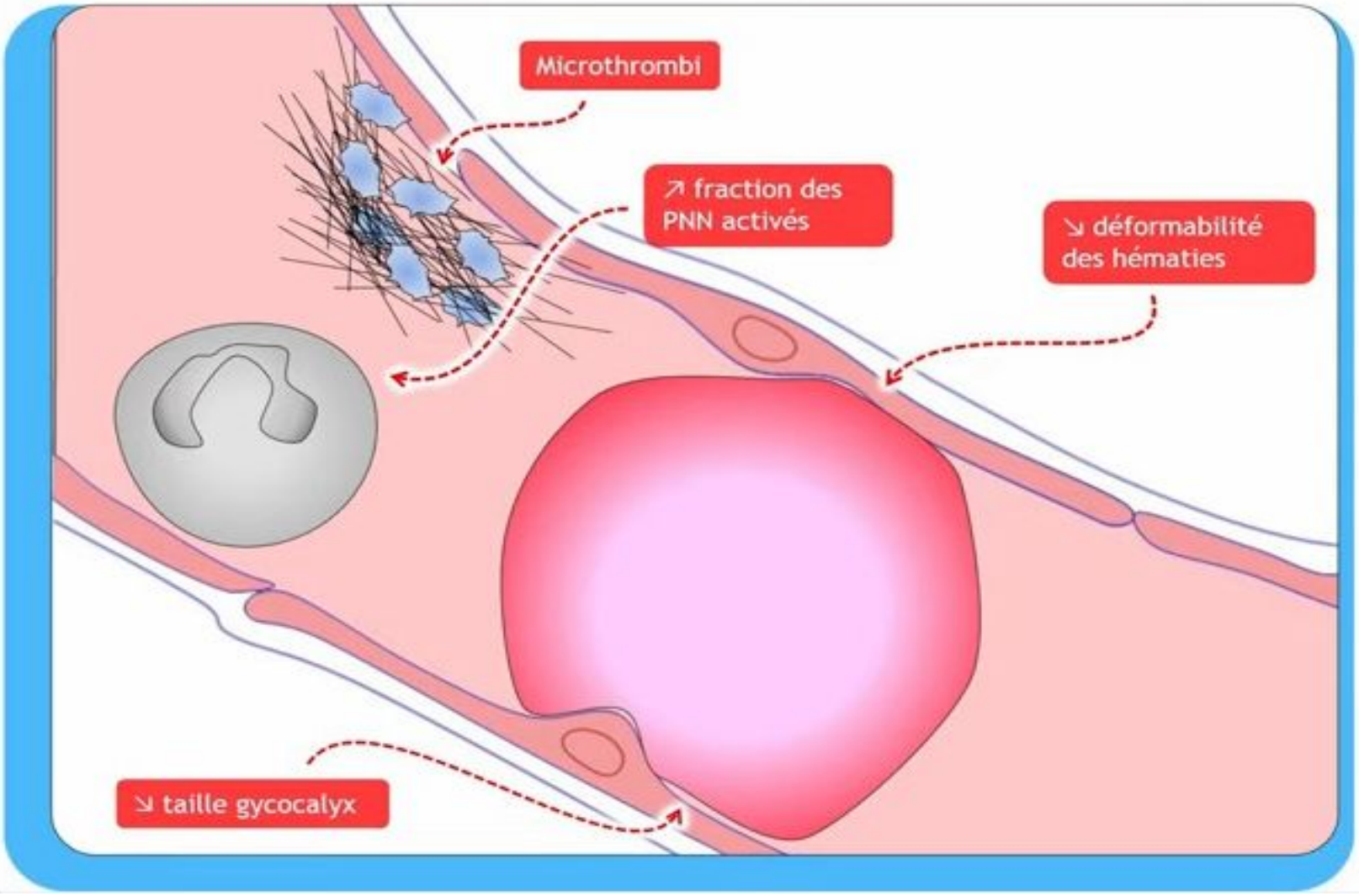

!
Conséquence clinique !
La SvO_2 permet d'apprécier l'adaptation du débit cardiaque aux besoins en O_2 des tissus
Saturation veineuse en O_2
70
50
300
200
30
50

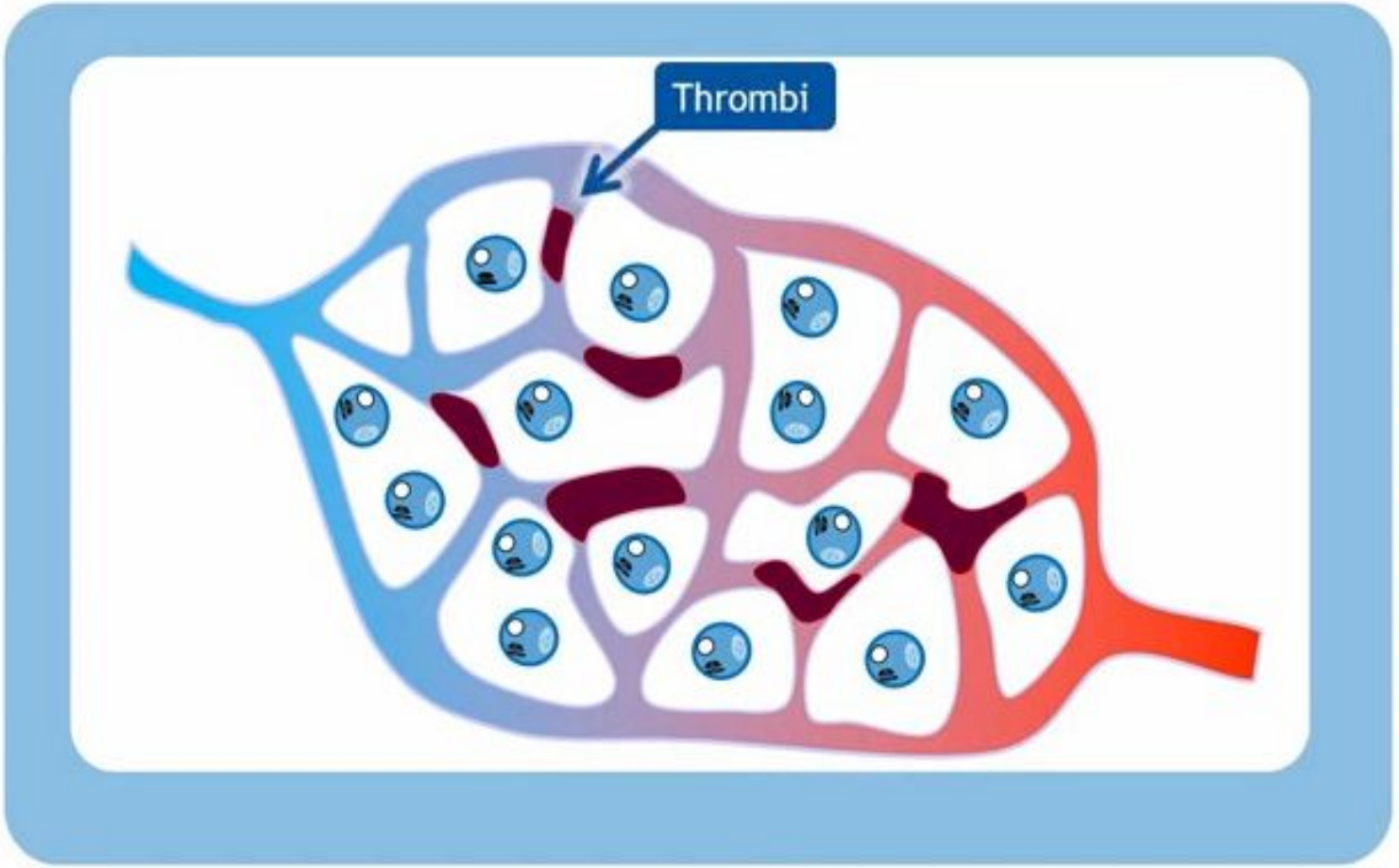
Défaillance circulatoire | Choc septique | Mécanismes de base

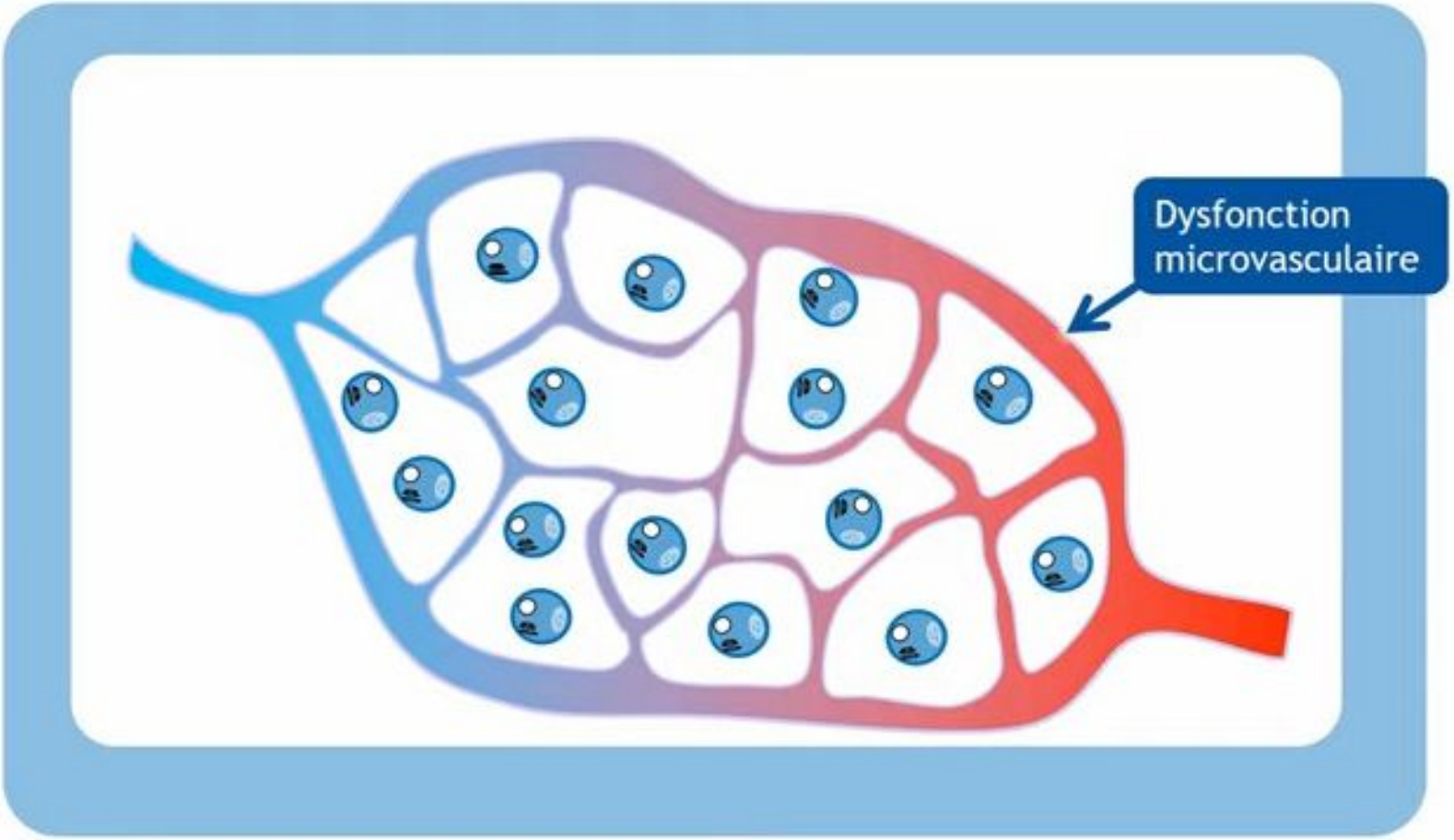



Larges shunts A-V
Capillaires fermés

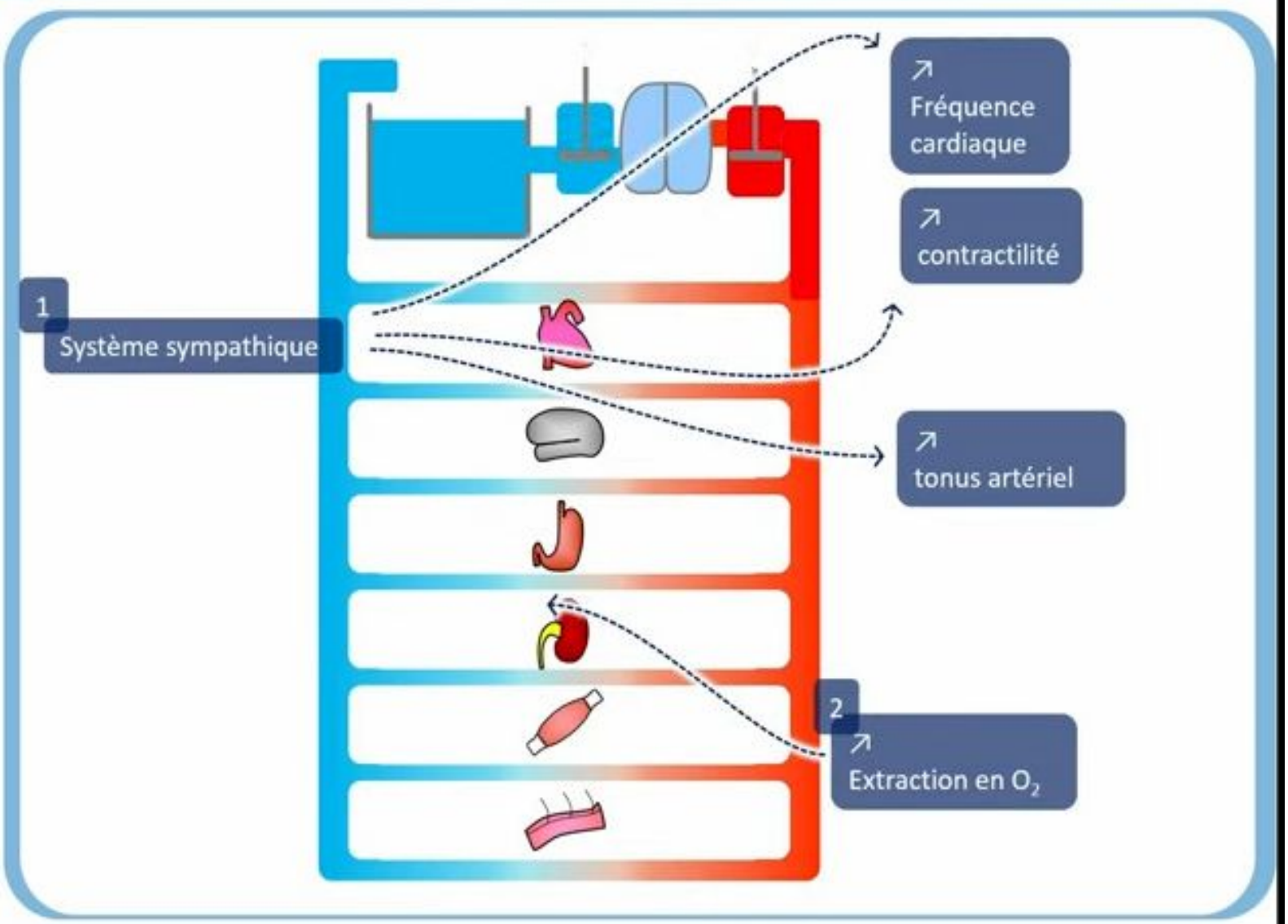
Défaillance circulatoire | Choc septique | Mécanismes de base




Thrombi

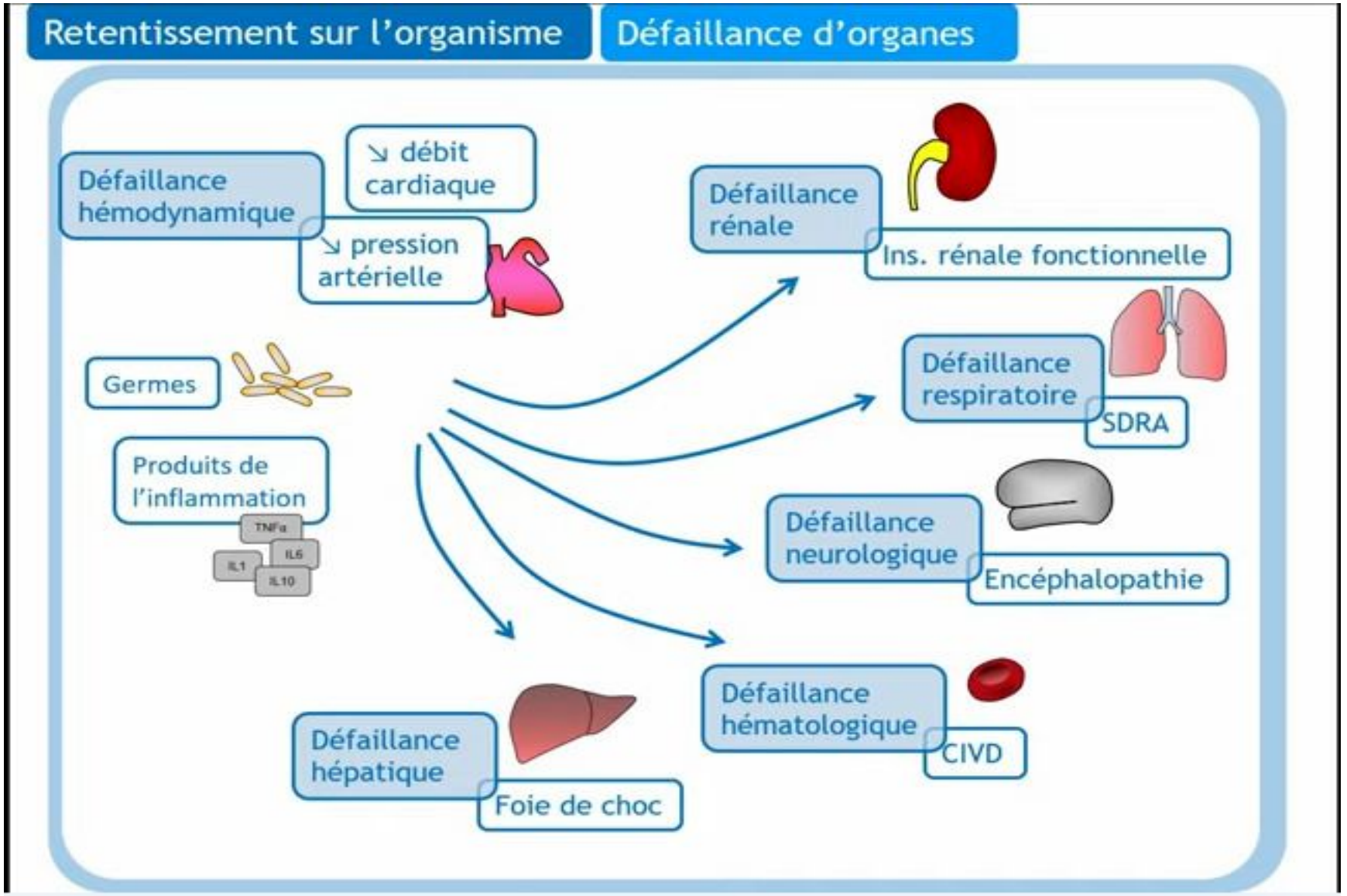

Dysfonction
microvasculaire

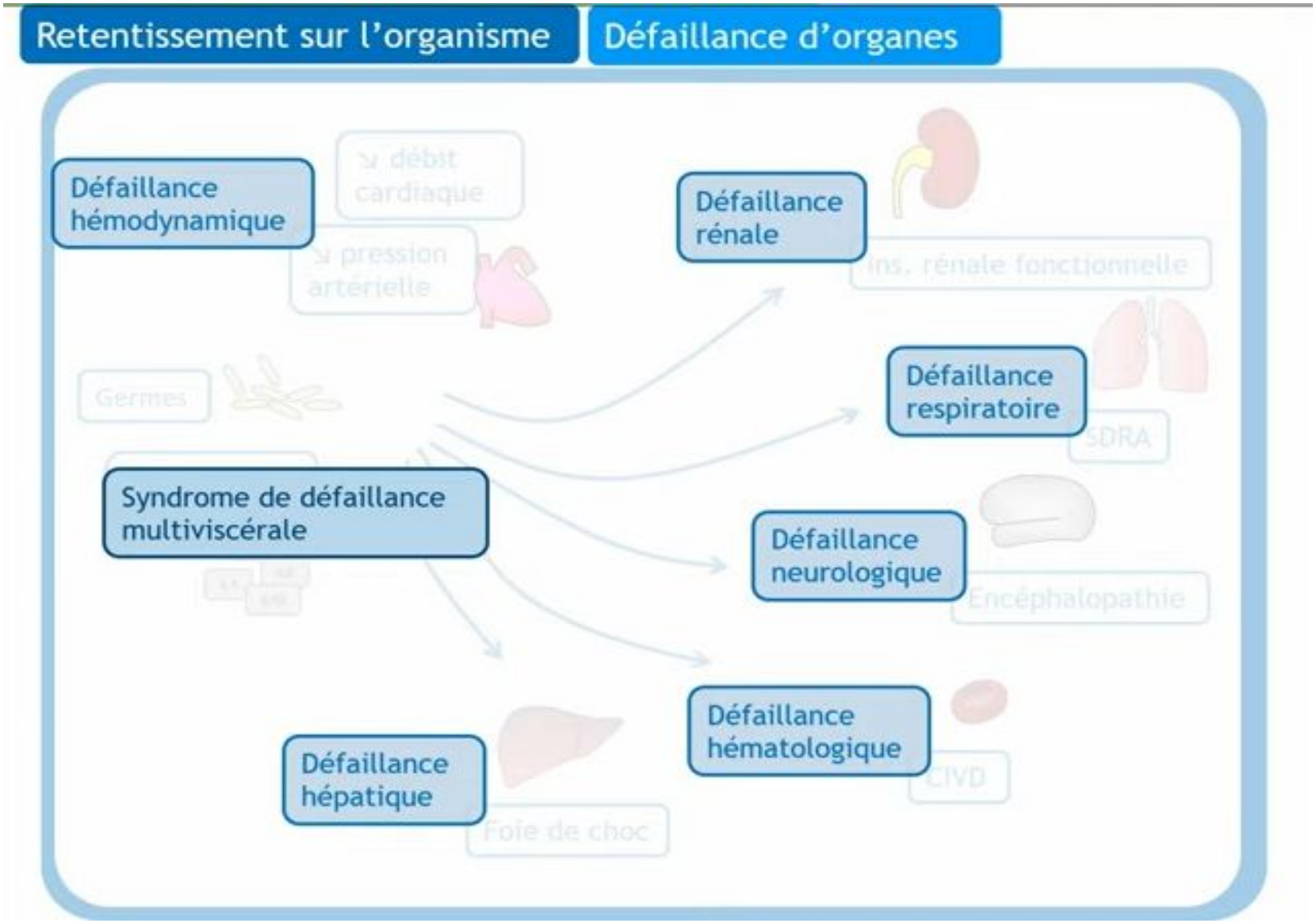
Défaillance circulatoire | Choc septique | Mécanismes adaptatifs

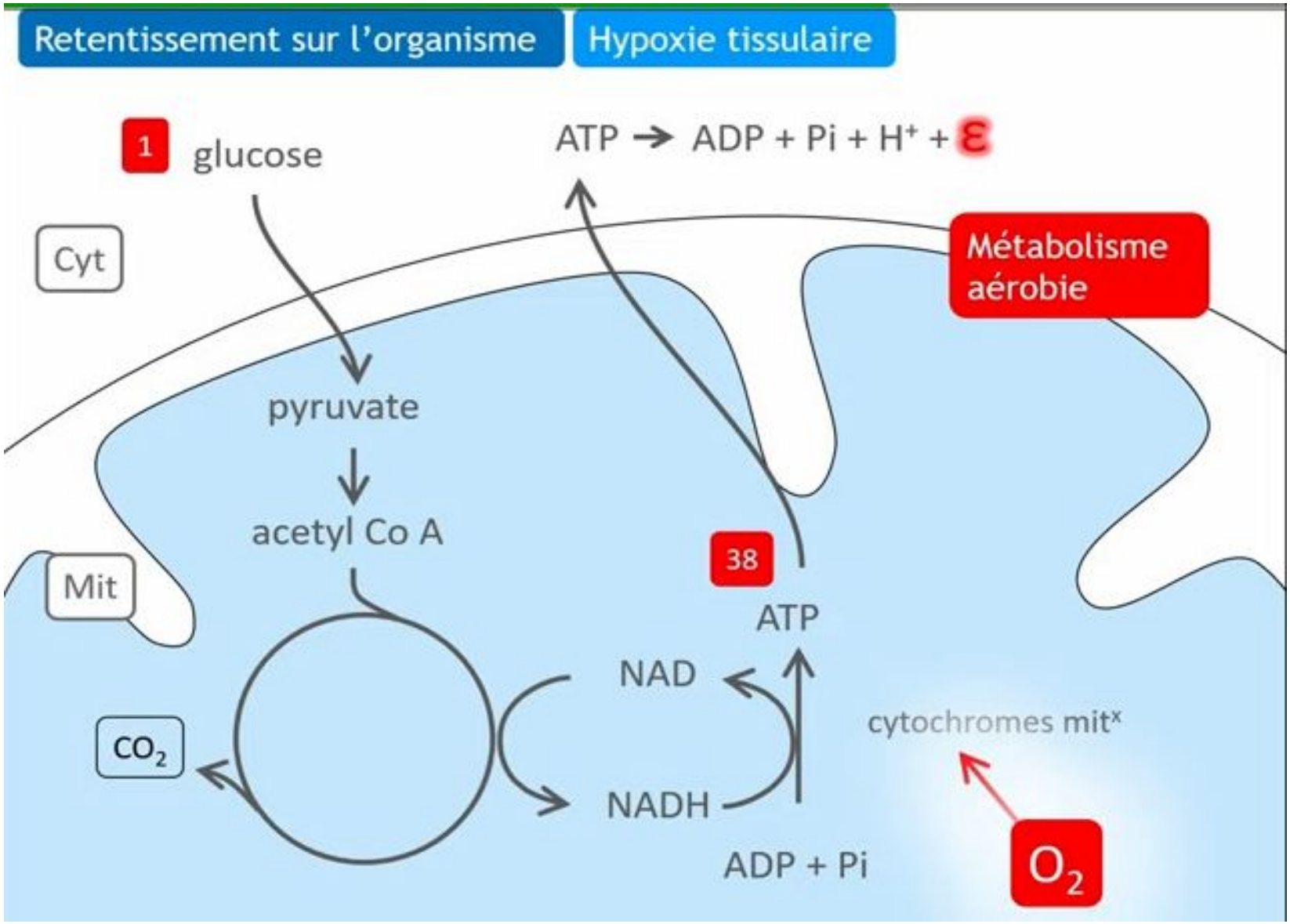


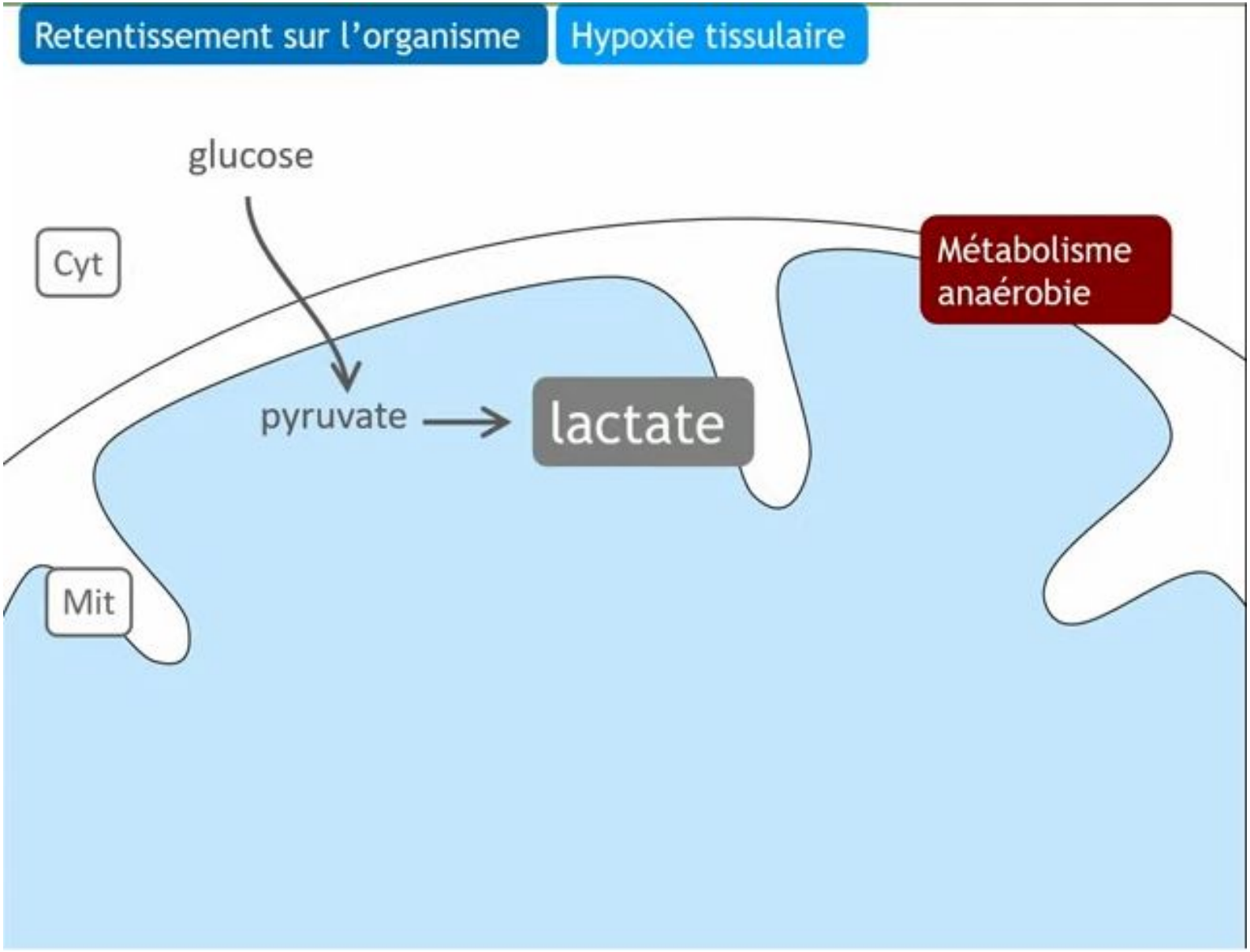
Retentissement sur l'organisme

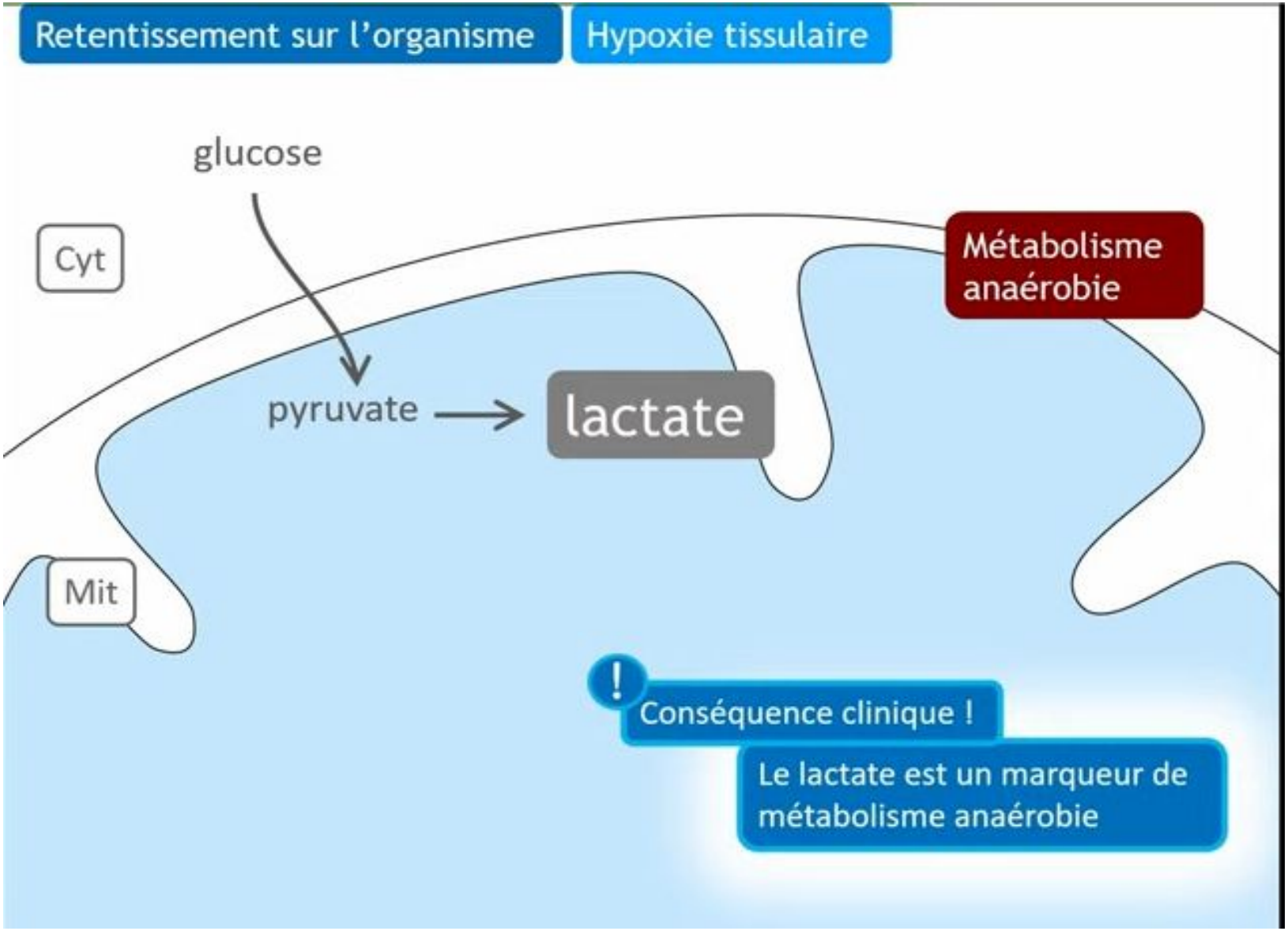
Défaillance d'organes



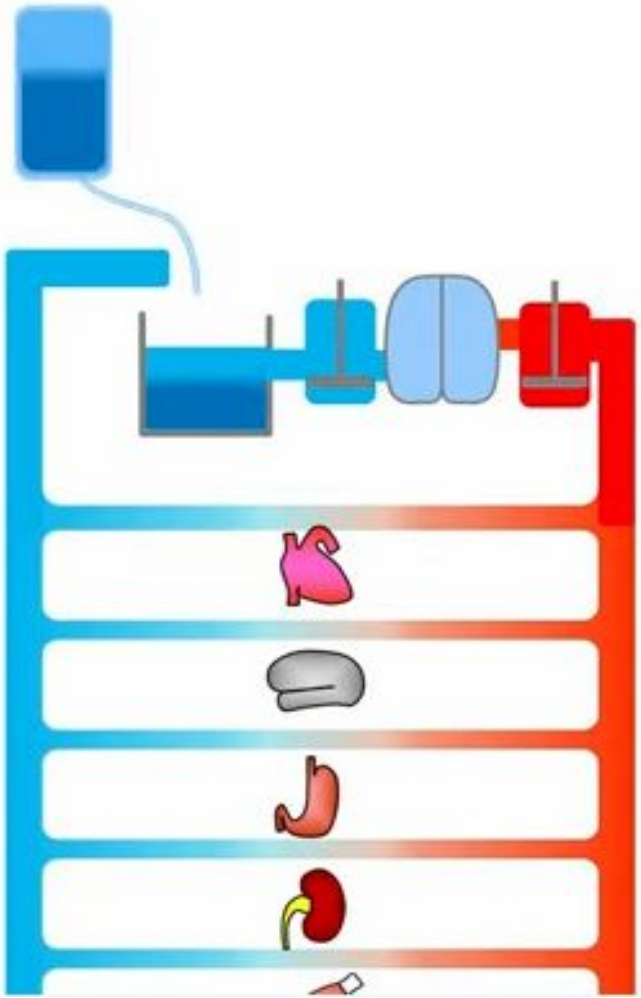

Retentissement sur l'organisme
Défaillance d'organes
Défaillance hémodynamique
↘ débit cardiaque
↘ pression artérielle
Défaillance rénale
Ins. rénale fonctionnelle
Défaillance respiratoire
SDRA
Germes
Syndrome de défaillance multiviscérale
Défaillance neurologique
Encéphalopathie
Défaillance hématologique
CIVD
Défaillance hépatique
Foie de choc


Retentissement sur l'organisme
Hypoxie tissulaire
1
glucose
ATP → ADP + Pi + H+ + ε
Cyt
Métabolisme aérobie
pyruvate
acetyl Co A
Mit
38
ATP
NAD
CO2
cytochromes mitx
NADH
ADP + Pi
O2

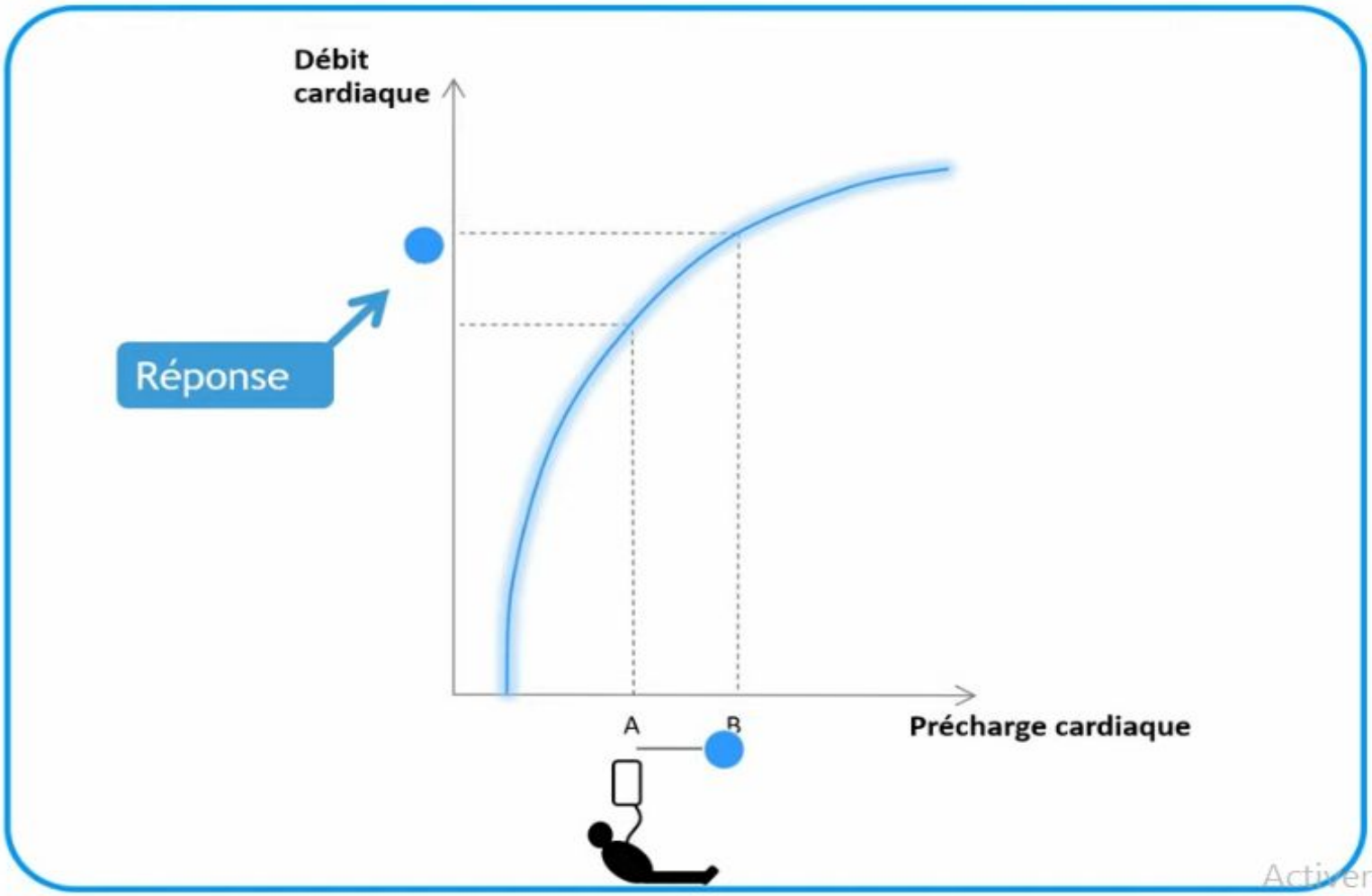

Retentissement sur l'organisme
Hypoxie tissulaire
glucose
Cyt
Métabolisme anaérobie
pyruvate
lactate
Mit

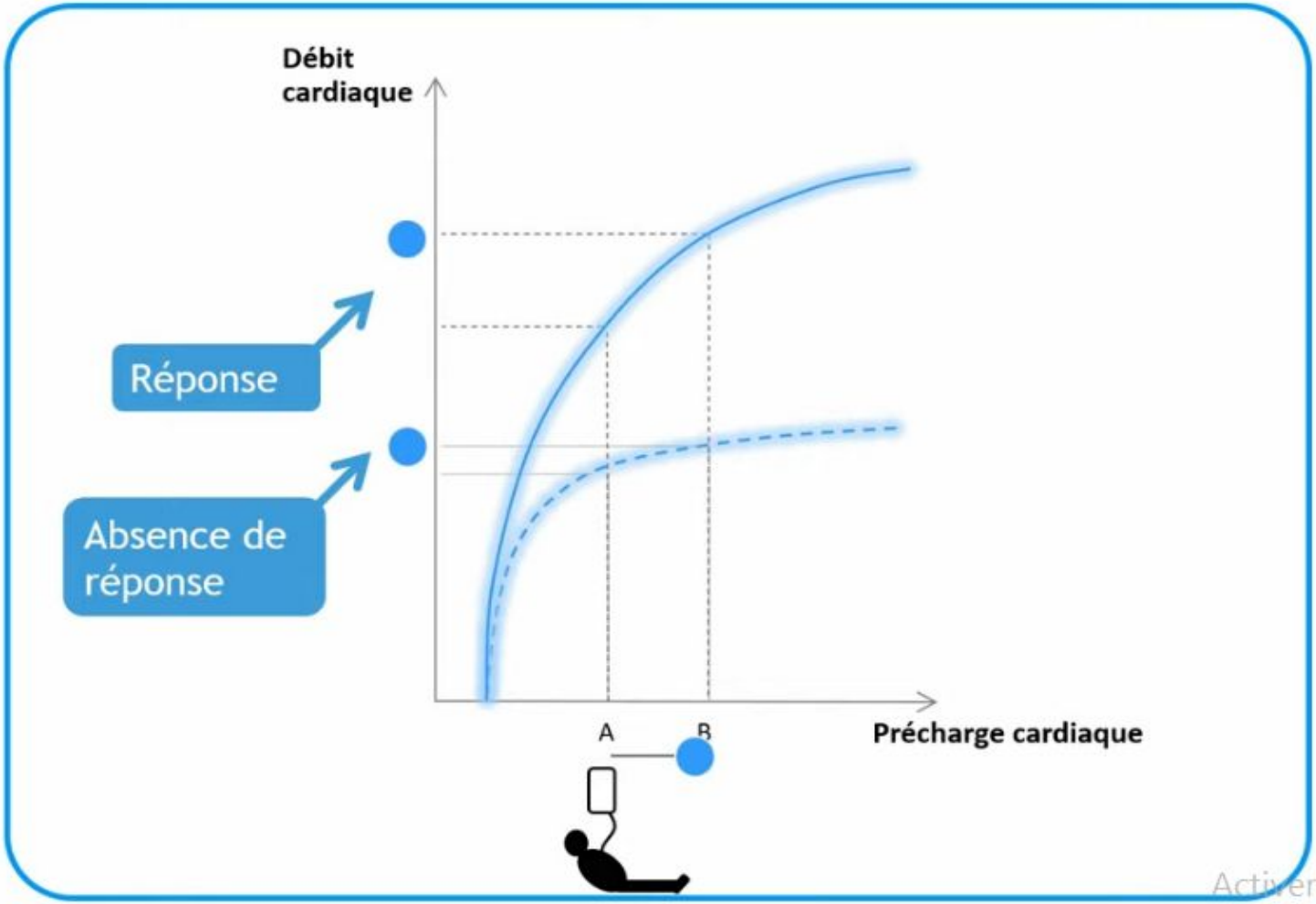

Retentissement sur l'organisme
Hypoxie tissulaire
glucose
Cyt
Métabolisme anaérobie
pyruvate
lactate
Mit
!
Conséquence clinique !
Le lactate est un marqueur de métabolisme anaérobie

Défaillance circulatoire | Choc septique | Traitement

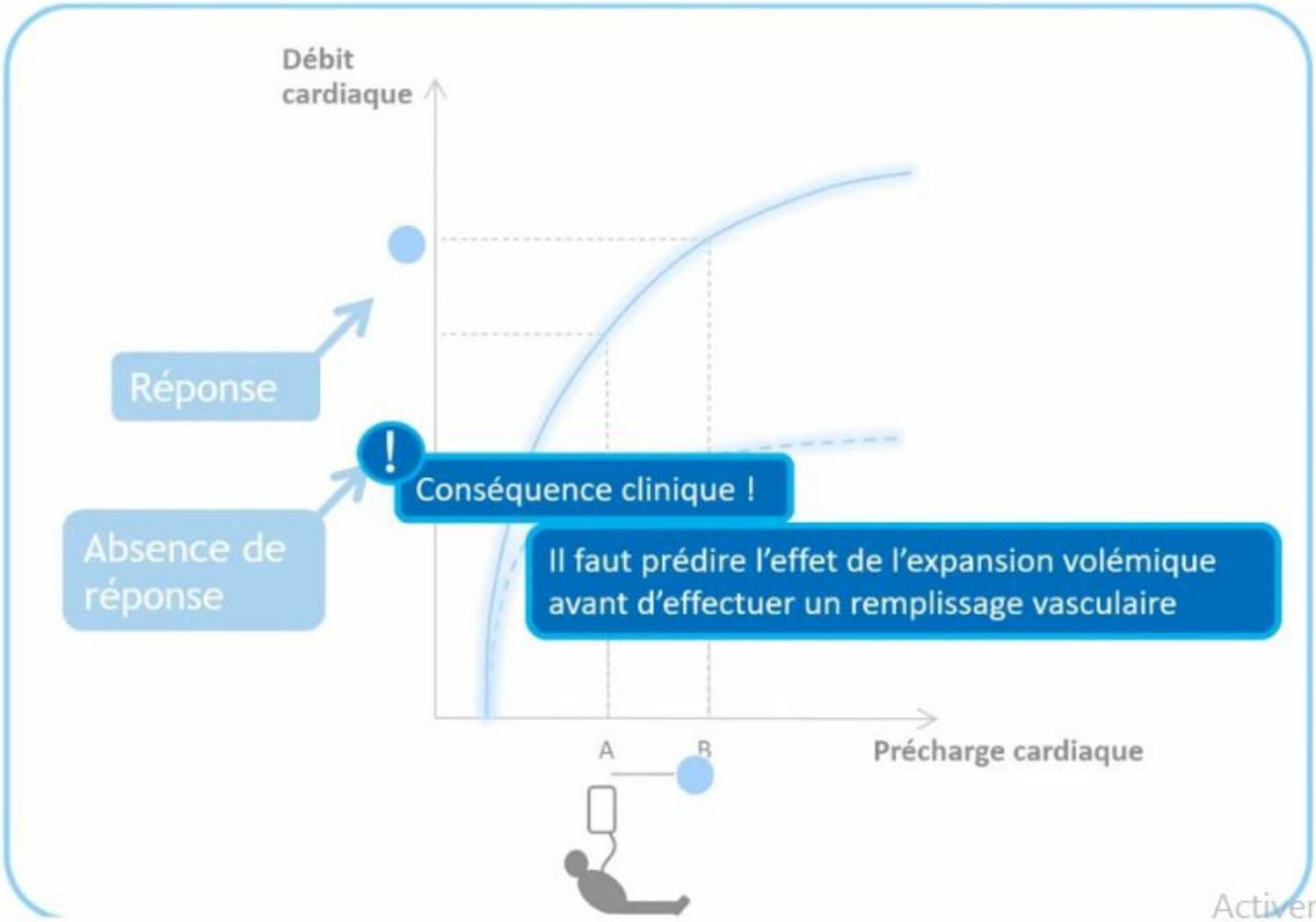


Défaillance circulatoire | Choc septique | Traitement

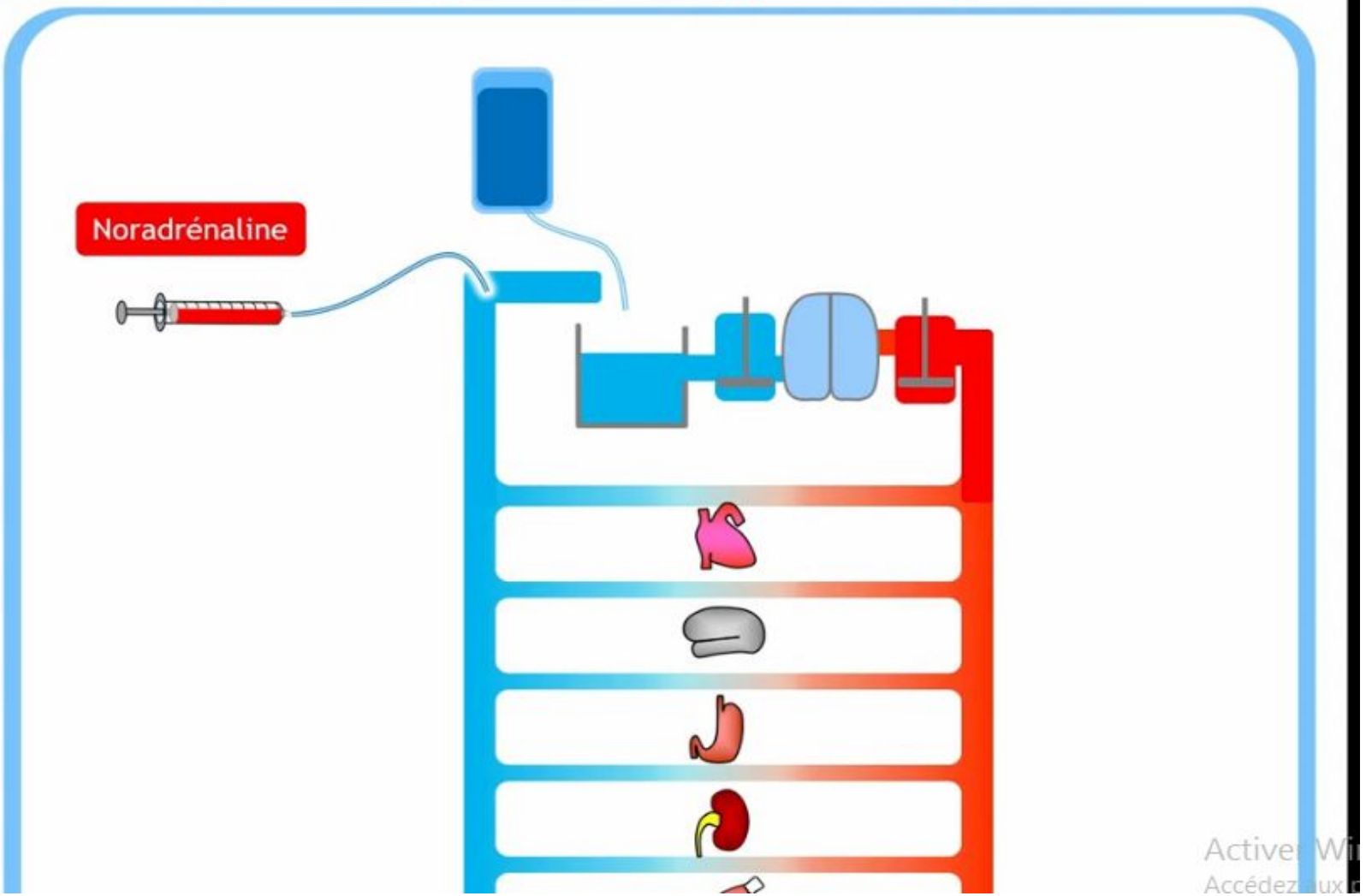




Défaillance circulatoire | Choc septique | Traitement



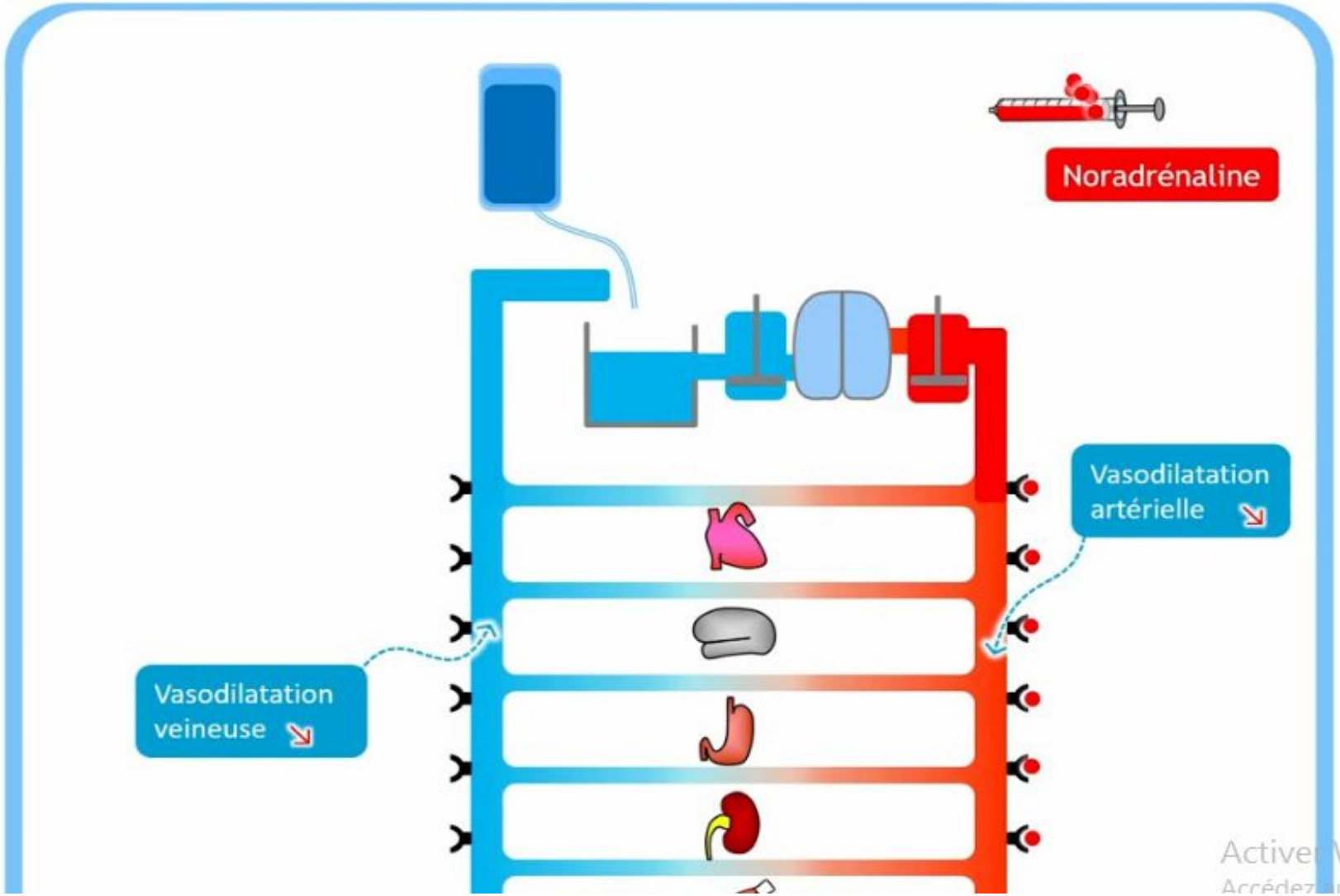
Défaillance circulatoire | Choc septique | Traitement



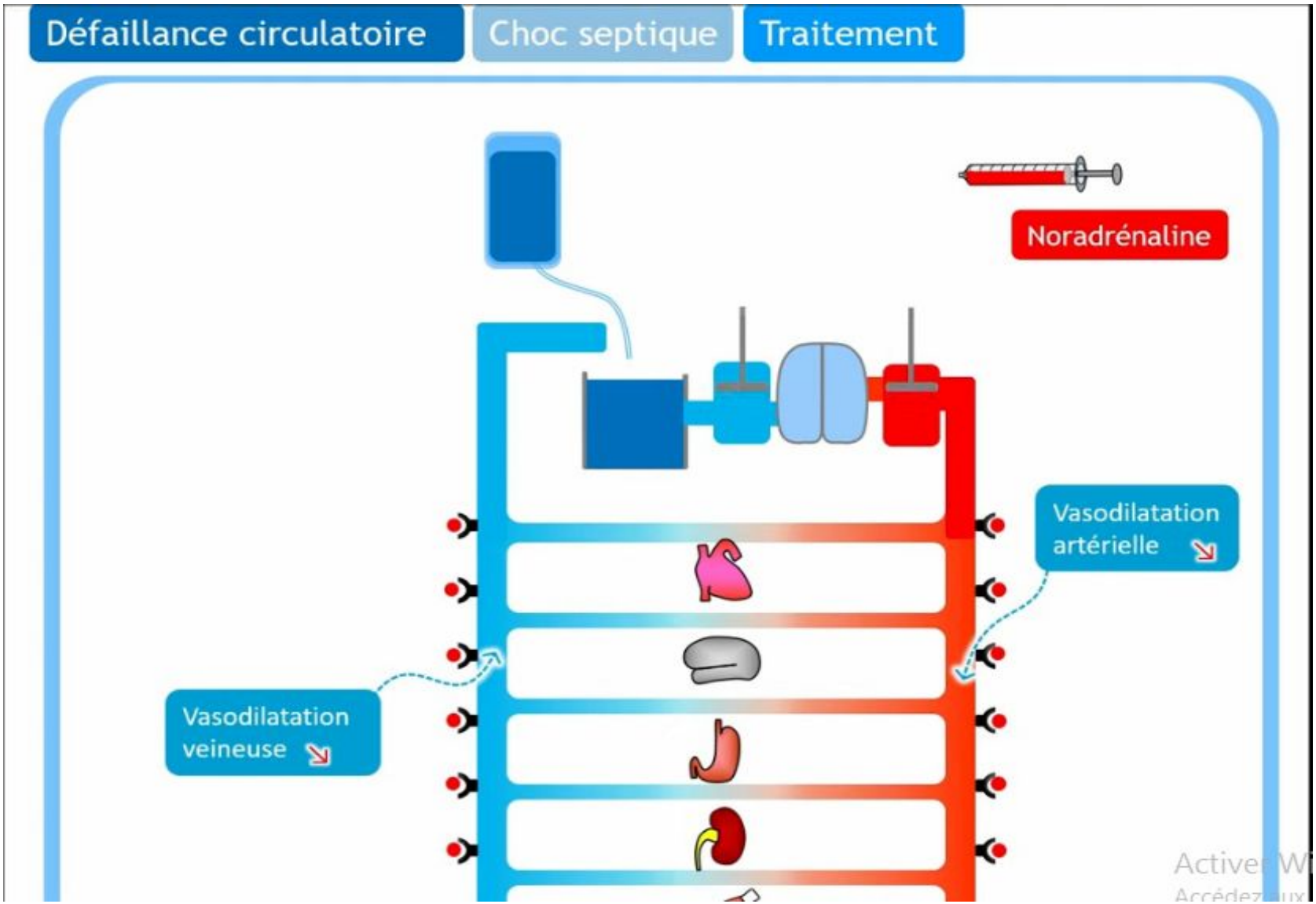
La noradrénaline

1. Entraîne une vasoconstriction artérielle
2. Entraîne une vasoconstriction veineuse
3. Exerce un effet synergique avec le remplissage vasculaire

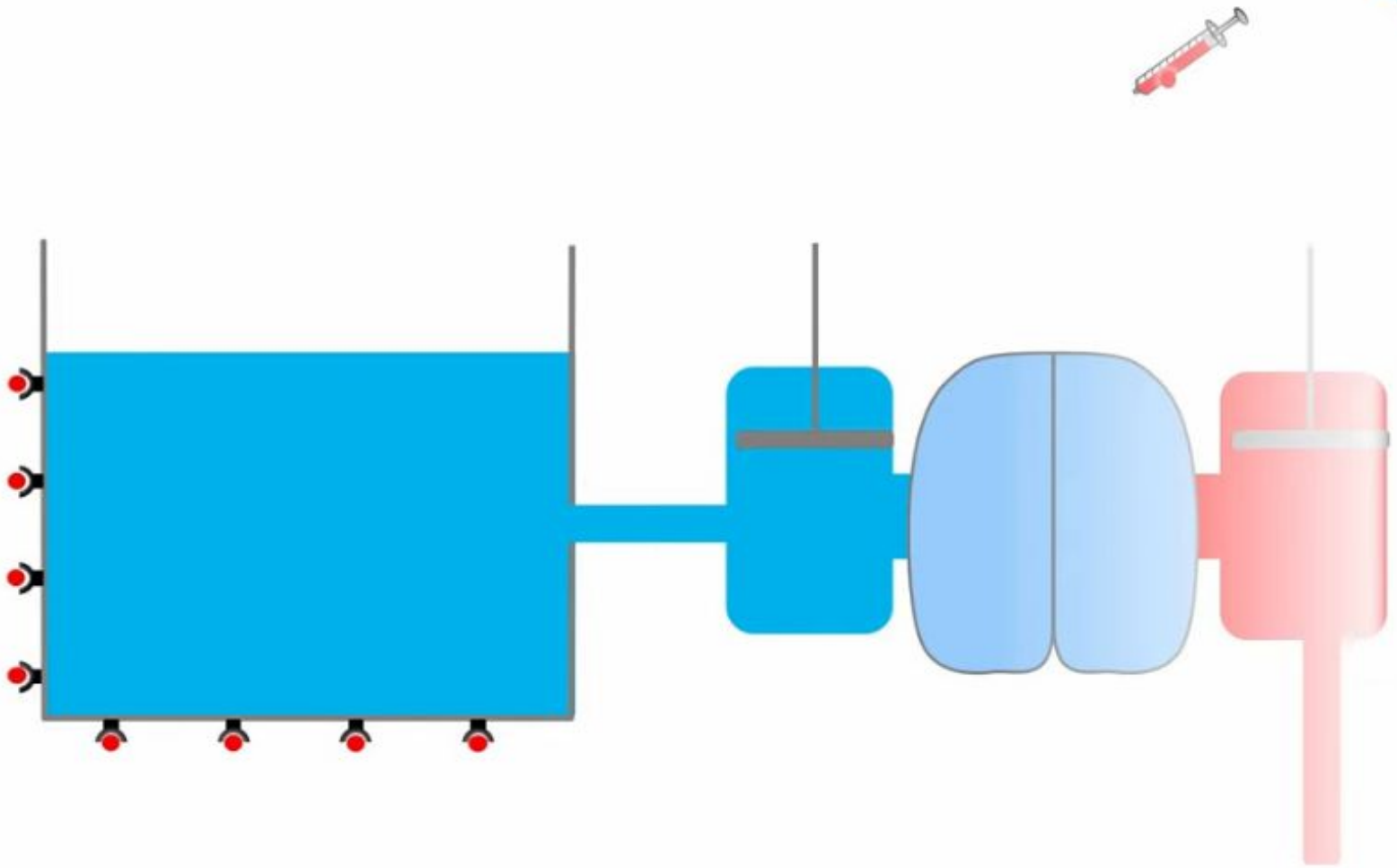
Défaillance circulatoire | Choc septique | Traitement



Défaillance circulatoire | Choc septique | Traitement

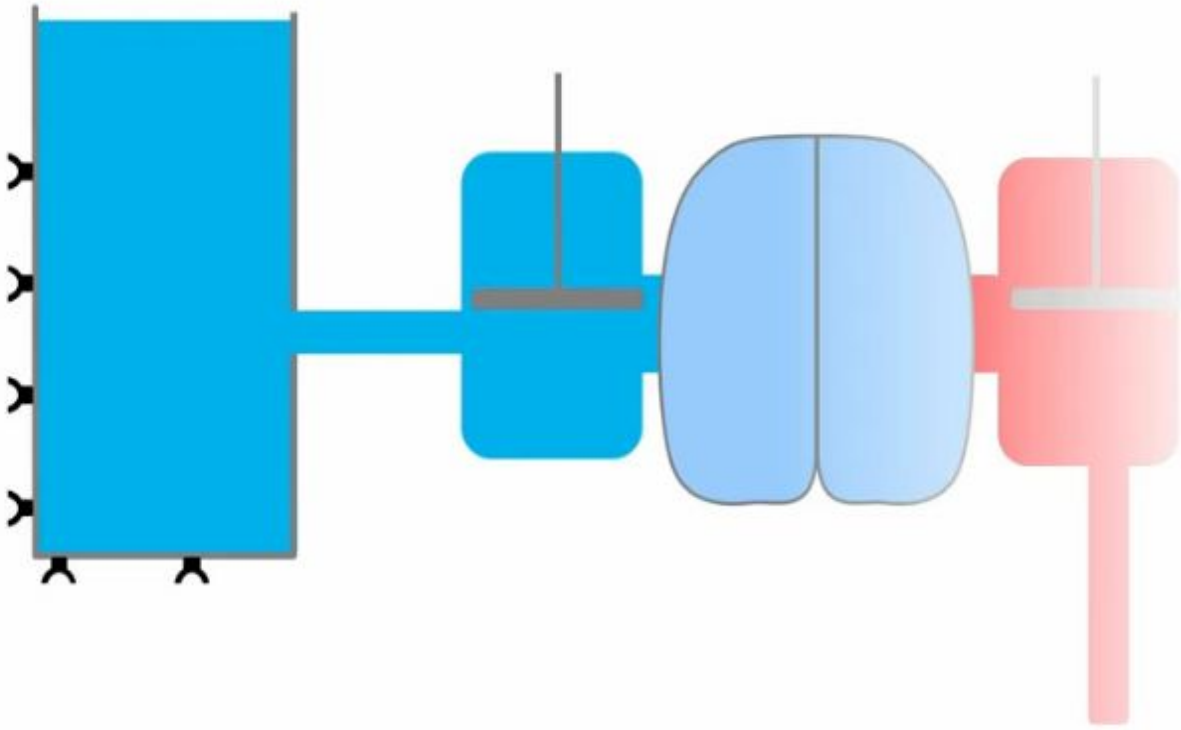


Défaillance circulatoire | Choc septique | Traitement



Conséquence clinique !

L'administration précoce de noradrénaline permet de réduire le volume de fluide administré



Classification of vasopressors

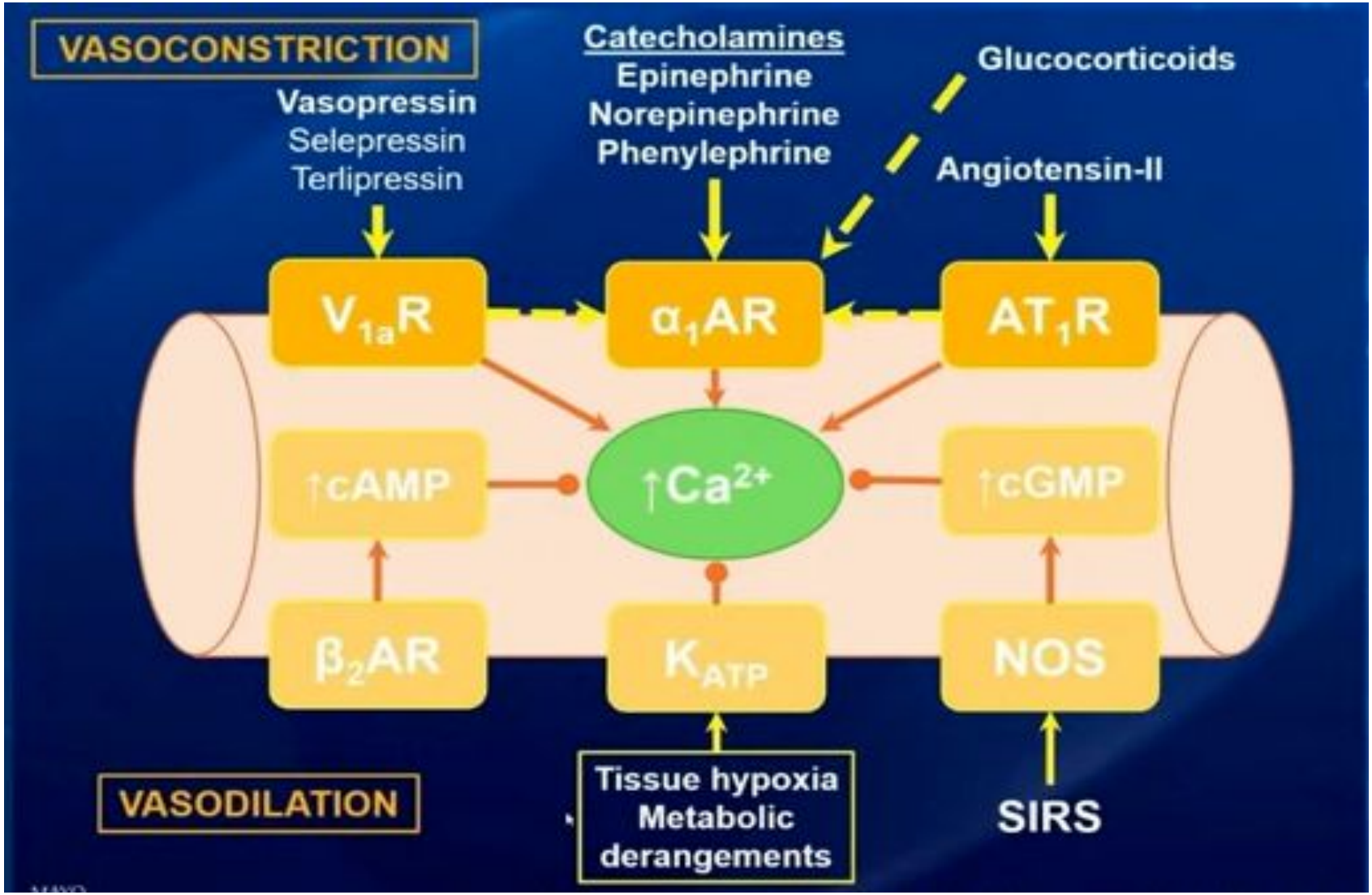
Peripheral vascular & direct cardiac effects

Vasopressors increase arterial pressure via peripheral vasoconstriction (increased SVR)

- Pure vasoconstrictors lack inotropic effects
  - **Phenylephrine**
  - **Vasopressin**
  - **Angiotensin-II**

  } **No direct cardiac toxicity**
- Catecholamines have beta1 inotropic effects
  - **Epinephrine** (strong)
  - **Norepinephrine** (weak)
  - **Dopamine** (strong)

  } **Risk of cardiac toxicity**


VASOCONSTRICTION
Vasopressin
Selepressin
Terlipressin
Catecholamines
Epinephrine
Norepinephrine
Phenylephrine
Glucocorticoids
Angiotensin-II
V1aR
α1AR
AT1R
↑cAMP
↑Ca2+
↑cGMP
β2AR
KATP
NOS
VASODILATION
Tissue hypoxia
Metabolic
derangements
SIRS

Catecholamine-sparing vasopressors

First-line for catecholamine-resistant shock

Characteristic	Vasopressin	Angiotensin-II
Dose range	0.01-0.03 U/min	5-80 ng/kg/min
Typical use	Fixed dose?	Titrated
Receptor	Vasopressin-1a	Angiotensin-1
Advantages	May reduce mortality Lower risk of AKI* Reduces arrhythmias*	May reduce mortality (if high renin or RRT)** Improves severe AKI
Disadvantages	Excessive vasoconstriction (mesenteric/skin +/- coronary)	Thrombosis risk Cost
Onset	~10-20 minutes	~1-2 minutes
Response rate	>50%	~70%, esp. high renin
Ideal use	Catecholamine-resistant septic shock	Catecholamine-refractory septic shock

Vasopressors & septic shock

Don't wait until resistant/refractory shock

MILD – NE <0.1 mcg/kg/min

- Only NE needed in most patients

MODERATE – NE 0.1-0.19 mcg/kg/min

- Check $S_{cv}O_2$, echo, ionized Ca, arterial pH
- Consider whether to add 2nd vasopressor

SEVERE – NE 0.2-0.29 mcg/kg/min

- Add second vasopressor
- Adjunctive stress-dose corticosteroids

RESISTANT – NE 0.3-0.5 mcg/kg/min

REFRACTORY – NE >0.5 mcg/kg/min

Which second vasopressor to add?
Catecholamine vs. catecholamine-sparing

Characteristic	Epinephrine	Vasopressin	Angiotensin-II
Dose	0.05-0.2 μg/kg/min	0.03 U/min*	10-20 ng/kg/min
Cost in USA	$	$$	$$$
Heart rate	↑↑	↓	↓
Cardiac output	↑	↓	↓
PVR	↑	↔	?
Cardiac toxicity	++	–	–
Lactate/glucose	↑	–	–
Mortality?	↔	Probable ↓	Possible ↓
Predict benefit?	**Low $ScvO_2$**	**Acidemia**	**High renin**
Ideal use	*Moderate/severe septic shock with low HR / CO*	*Severe/resistant septic shock, esp. high HR / CO*	*Resistant or refractory septic shock, esp. AKI*

Individualizing second-line therapy

How to select add-on vasopressors

EPINEPHRINE – selected patients

- ✓ **Low CO, low S_vO_2, low HR, LV dysfunction**
- ❖ Ischemia, arrhythmia, lactic acidosis, DKA

VASOPRESSIN – preferred

- ✓ **High HR, arrhythmia, acidemia, vasoplegia**
- ❖ Low CO/S_vO_2, LV dysfunction, gut ischemia

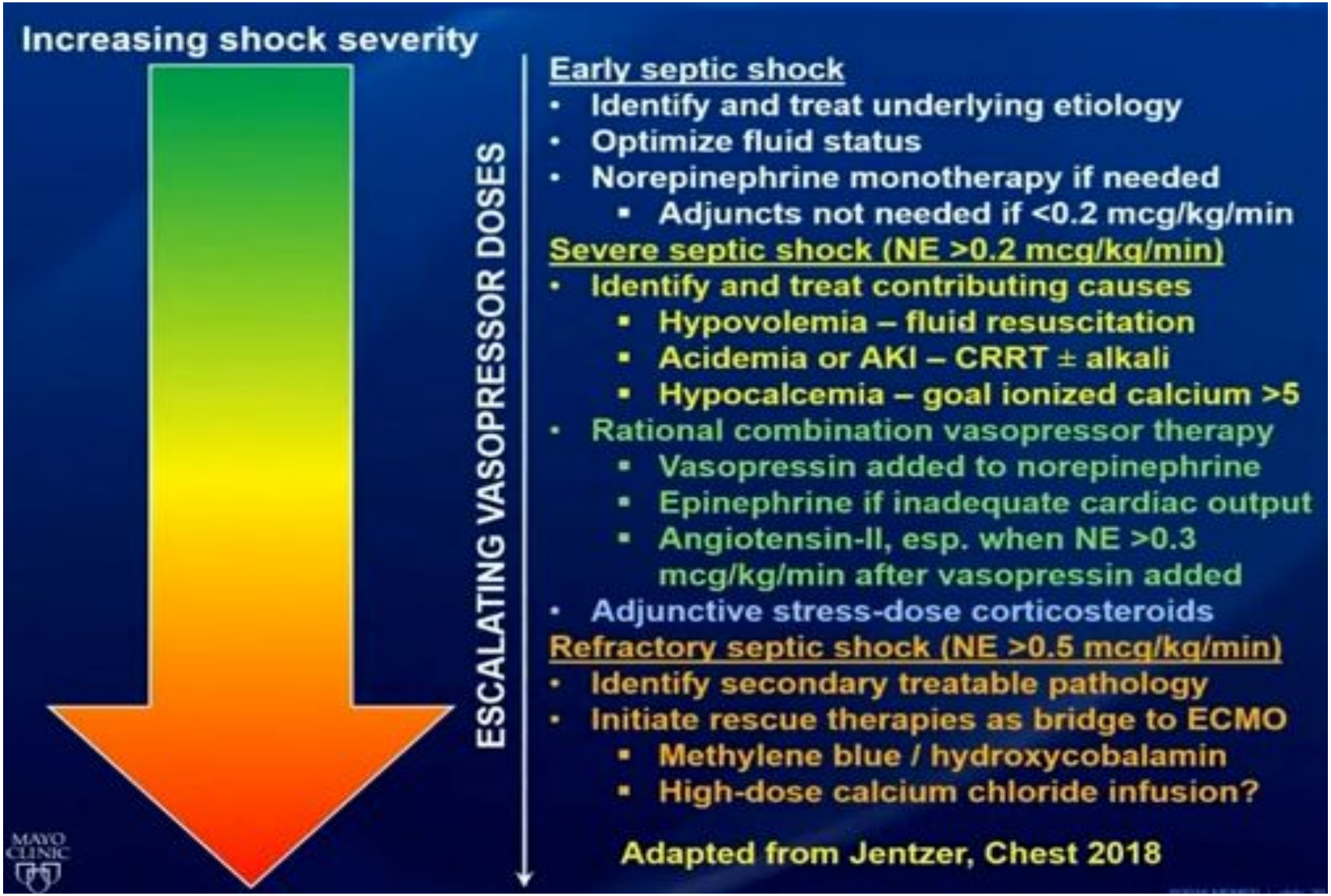
ANGIOTENSIN-II – alternative

- ✓ **High renin, AKI on CRRT, refractory shock**
- ❖ Low CO/S_vO_2, LV dysfunction, thrombosis

Clinical pearls – tips & tricks

How to optimize vasopressor therapy

- **If catecholamine doses are rapidly rising:**
  - ✓Be sure you know what you are treating!
    - ➢Rule out & treat acidemia or low ionized Ca
  - ✓Add a catecholamine-sparing vasopressor
    - ➢When adding 2nd vasopressor, add steroids
- **Vasopressin/angiotensin don't always work**
  - ✓If no response in 1 hour, switch agents
- **Weaning catecholamines before stopping vasopressin reduces risk of hypotension**
  - ✓Wean vasopressin gradually (not abruptly)


Increasing shock severity
ESCALATING VASOPRESSOR DOSES
Early septic shock
• Identify and treat underlying etiology
• Optimize fluid status
• Norepinephrine monotherapy if needed
▪ Adjuncts not needed if <0.2 mcg/kg/min
Severe septic shock (NE >0.2 mcg/kg/min)
• Identify and treat contributing causes
▪ Hypovolemia – fluid resuscitation
▪ Acidemia or AKI – CRRT ± alkali
▪ Hypocalcemia – goal ionized calcium >5
• Rational combination vasopressor therapy
▪ Vasopressin added to norepinephrine
▪ Epinephrine if inadequate cardiac output
▪ Angiotensin-II, esp. when NE >0.3 mcg/kg/min after vasopressin added
• Adjunctive stress-dose corticosteroids
Refractory septic shock (NE >0.5 mcg/kg/min)
• Identify secondary treatable pathology
• Initiate rescue therapies as bridge to ECMO
▪ Methylene blue / hydroxycobalamin
▪ High-dose calcium chloride infusion?
Adapted from Jentzer, Chest 2018
MAYO CLINIC

What is microcirculatory shock?

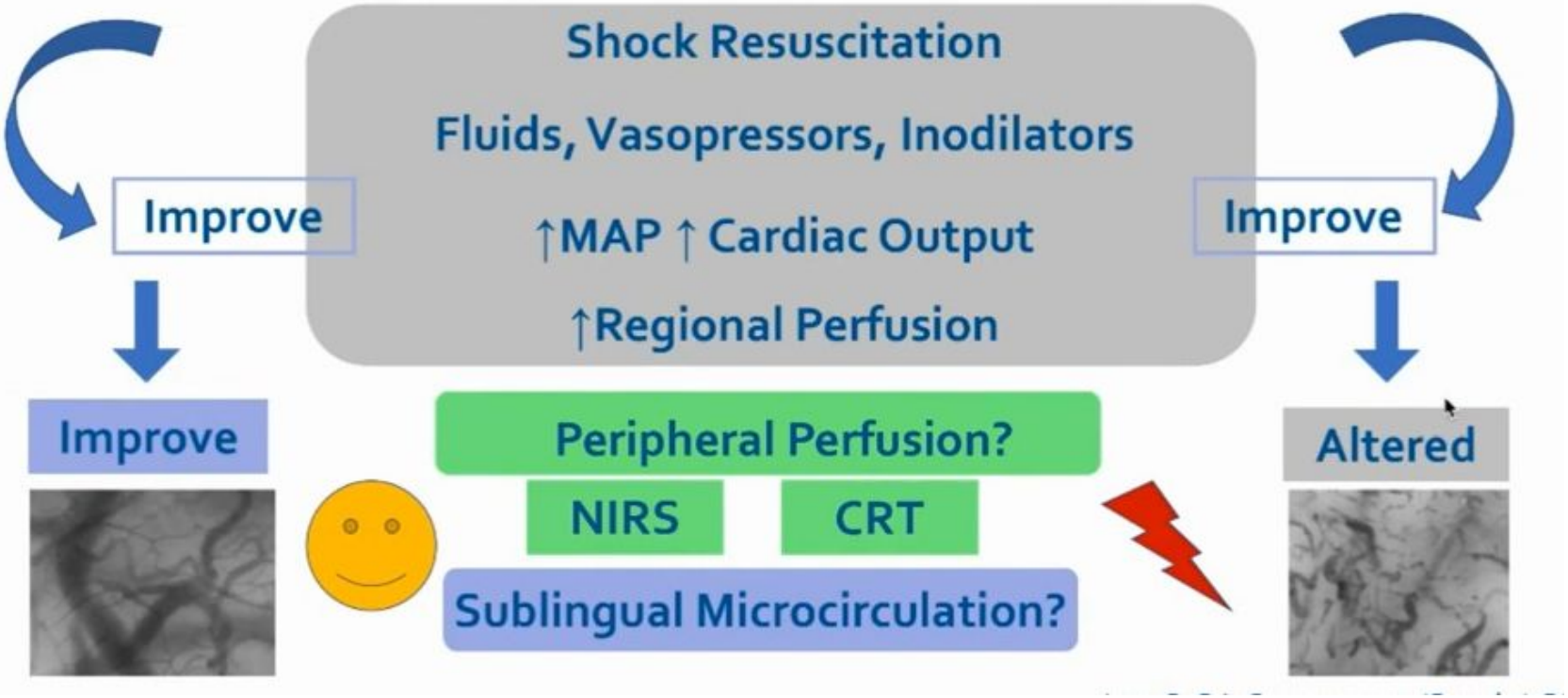
Vanina S. Kanoore Edul[a,b], Can Ince[b], and Arnaldo Dubin[b,c]

"The condition in which the microcirculation fails to support tissue oxygenation in face of normal(ized) systemic hemodynamics"

Distributive shock is microcirculatory shock

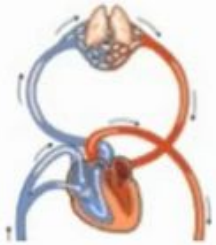
Monitoring of microcirculation during resuscitation seems necessary to guarantee the restoration of tissue perfusion and oxygenation

HEMODYNAMIC COHERENCE CONCEPT



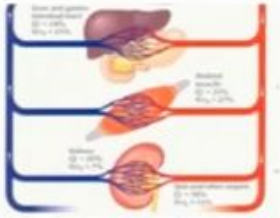
REGULATION OF BLOOD FLOW

Central



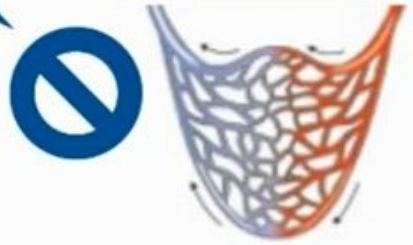
Cardiac Output
Preload
Contractility
Afterload

Regional



Vital ↔ NonVital organs
Resistances vessels
Sympathetic control

Local



↓ Functional capillary density

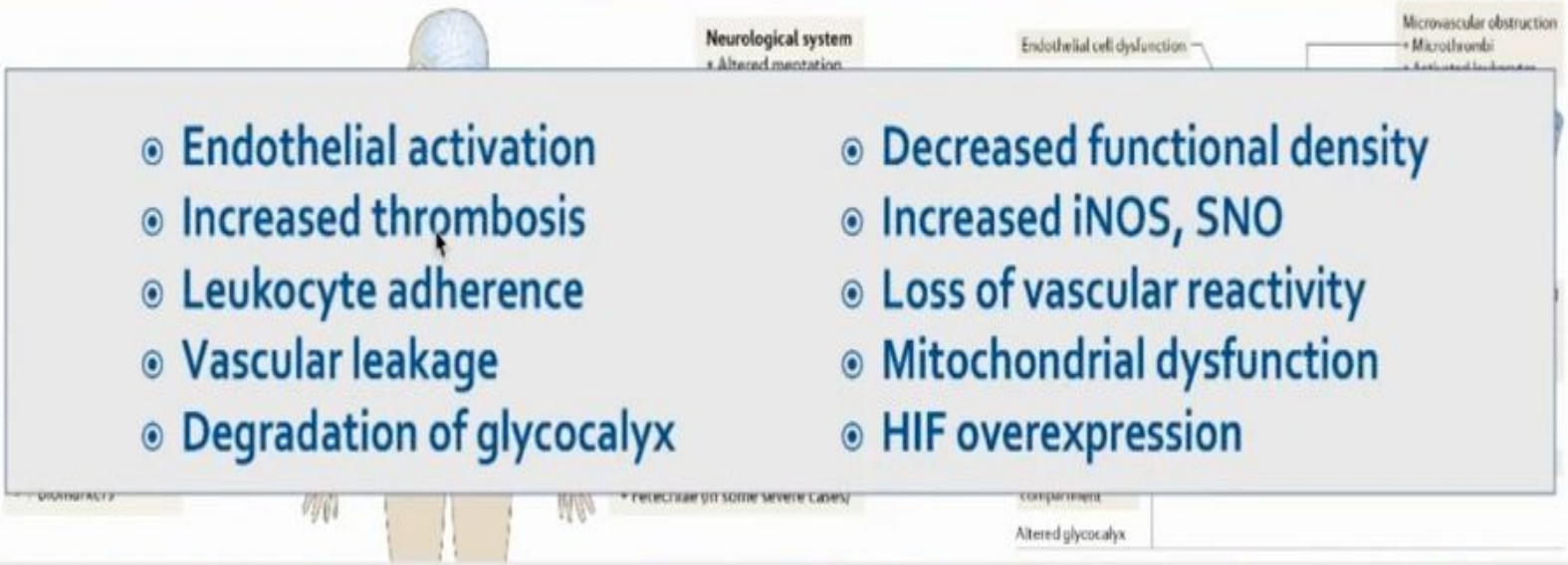
Loss of Vascular Reactivity

Microthrombosis

↑ Capillary permeability

MECHANISMS OF DISCONNECTION

Sepsis occurs when a dysregulated host response to an infection results in life-threatening tissue damage and organ dysfunction



- Endothelial activation
- Increased thrombosis
- Leukocyte adherence
- Vascular leakage
- Degradation of glycocalyx
- Decreased functional density
- Increased iNOS, SNO
- Loss of vascular reactivity
- Mitochondrial dysfunction
- HIF overexpression

Alterations in each organ can range from mild dysfunction to complete organ failure

The mechanisms that underlie organ dysfunction in sepsis are similar for all organs

DETERMINANTS OF MICROVASCULAR OXYGEN TRANSPORT

μDO_2

Convection

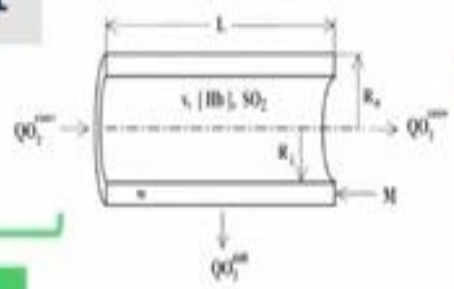
Diffusion

μ Blood Flow

μ O_2 content

Arteriolar Tone

Capillary Hct



Cap – Mit PO_2

Diffusion Distance

Area gas exchange

μΔP= Precapillary - Venular

Vasoconstriction → ↓ Flow and Hct

REGULATION OF BLOOD FLOW

Central → Regional → Local

Cardiac Output

Preload, Contractility, Afterload, Heart Rate

Vital ↔ NonVital organs

Resistance vessels

Sympathetic control

Functional Capillary Density

Extrinsic	Intrinsec
• Neural	• Metabolic
• Humoral	• Vascular

⇩ DO_2 → ⇧CO → Redistribution of Flow → ⇧ O_2ER