ECMO for treatment of cardiotoxic intoxications

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Poisonings with cardiotoxicants

In the USA: AAPCC-NPDS 2015

Cardiovascular agents: 7th cause of exposures (3.9%) and 2th cause of death (fatality rate: 0.29%)

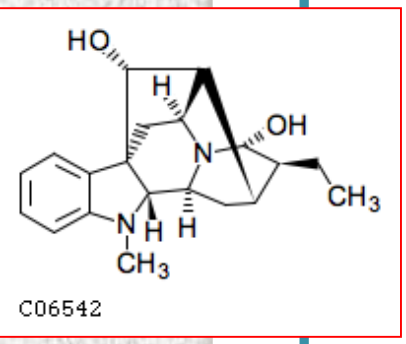
Mowry JB. *Clin Tox* 2016

- **Cardiovascular pharmaceuticals**
  - Sodium-channel blockers (Class I)
  - Beta-blockers (class II)
  - Potassium channel blockers (sotalol) (class III)
  - Calcium-channel antagonists (class IV)
  - Cardioglycosides (class V)
- **Non-cardiovascular pharmaceuticals**
- **Drugs of abuse**
- **Industrial toxicants**
- **Plants, household and over-the-counter toxicants**

The prognostic value of the ingested dose:
The example of ajmaline poisoning

Delay for symptom occurrence: 1 - 3 h
All patients in cardiac arrest died

Ingested tablets	N	Cardiac arrest
1 g	7	0
2 g	13	1
3 g	16	8



Conso F. *Press Med* 1980

Strategy of management of toxic cardiovascular failure

Diagnosis of shock

↓

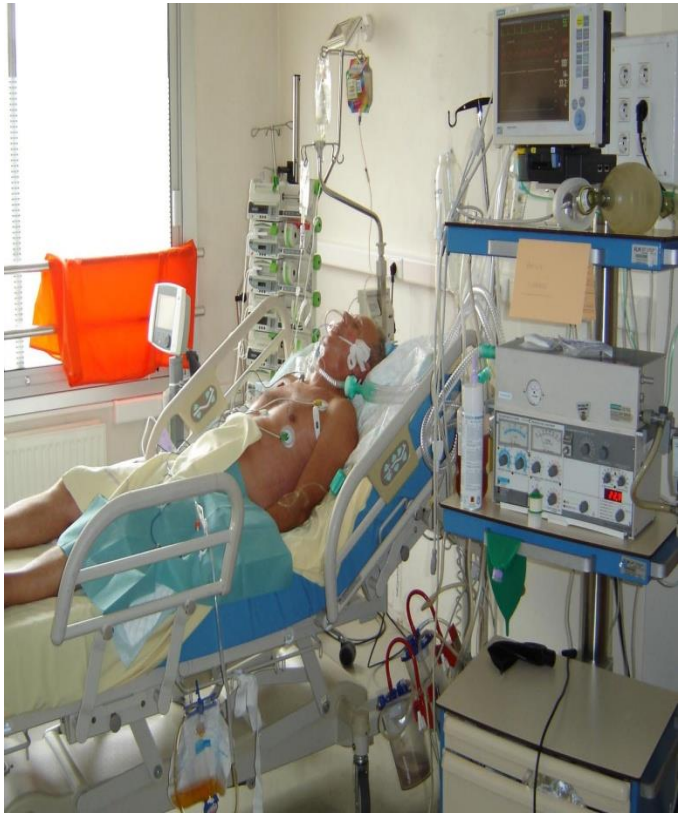
Determination of the mechanism of shock

↓

Definition of the optimal treatment

↓

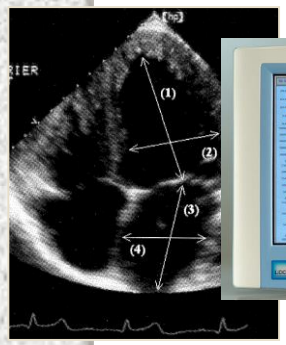
Diagnosis of the refractoriness of shock

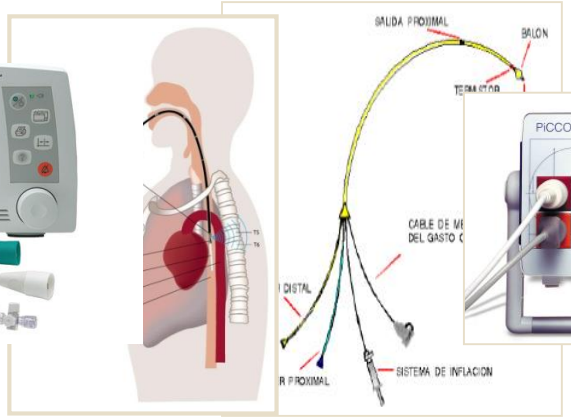


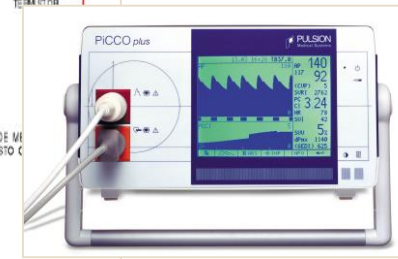
Hemodynamic monitoring of cardiotoxicant poisonings

Macrocirculation level:

- Measurement of blood pressure and cardiac index







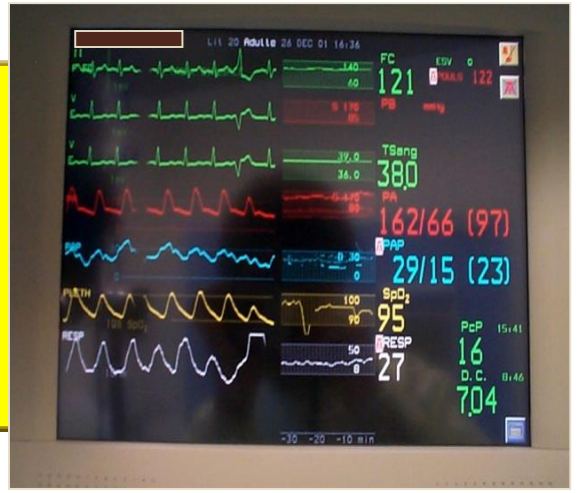
Microcirculation level:

- Simple signs: dizziness, transitory consciousness loss and collapse, skin discoloration, or even chest pain.

- More sophisticated signs requiring a close and repeated assessment of any change in the mental status, low urine output and routine clinical chemistry (lactate, creatinine and liver function tests).

Evaluation of the mechanism of the toxic shock

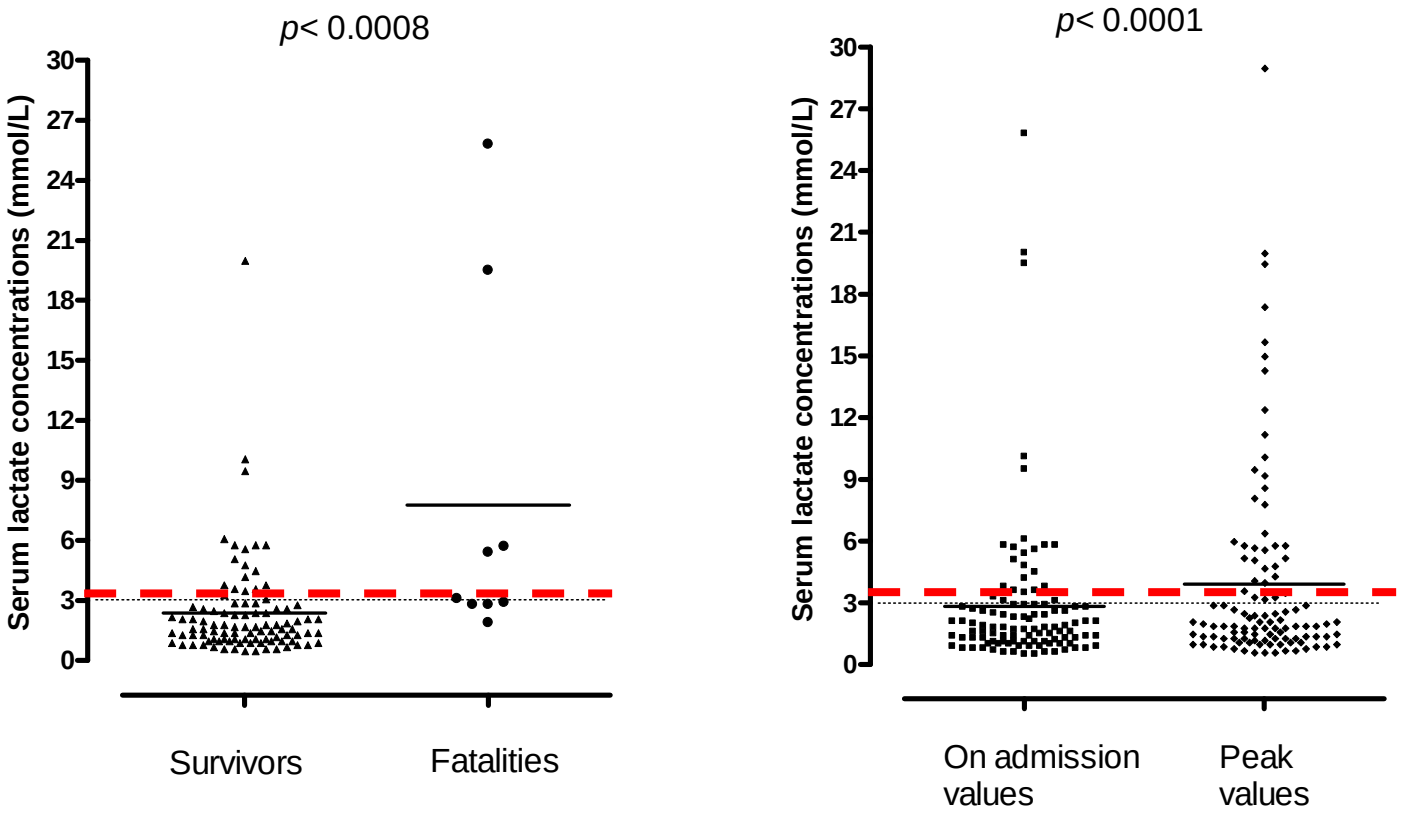
1- Hypotension: systolic BP < 90 mm Hg
or systolic BP decrease > 40 mmHg
or mean BP < 65 mmHg
2- Unresponsive to fluids
3- At least one sign of organ hypoperfusion



	Peripheral Shock	Cardiogenic Failure
Cardiac Index ($l.min^{-1}.m^{-2}$)	> 3.5	< 2.5
Systemic Resistance ($d.s^{-1}.cm^{-5}.m^2$)	< 1500	> 2000
P_{aw} (mmHg)	< 10	> 18
LVEF (%)	> 70	< 60

Beta-blocker poisonings

Prgnostic value of blood lactate on admission



The ROC-AUC of initial lactate for predicting mortality was 0.84 (0.74-0.94).

The cutoff point maximizing the sum of sensitivity and specificity was 2.7 mmol/L.

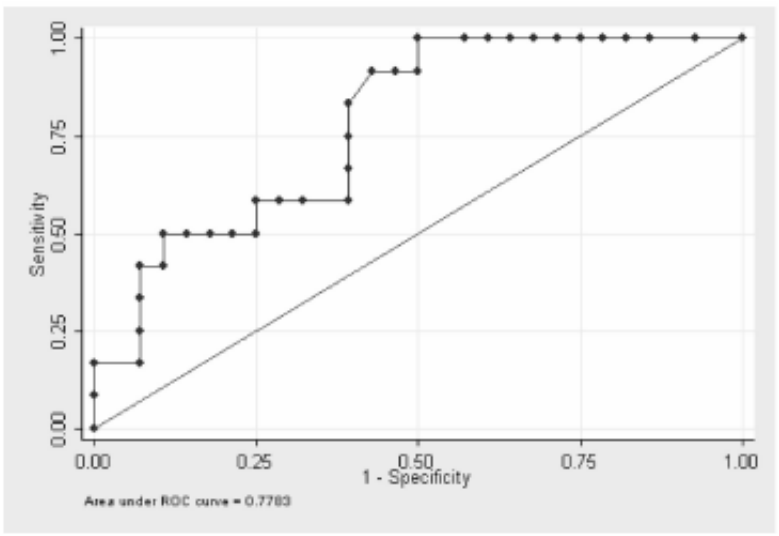
For the 3.0 mmol/L selected lactate cutoff point: 55% sensitivity, 80% specificity.

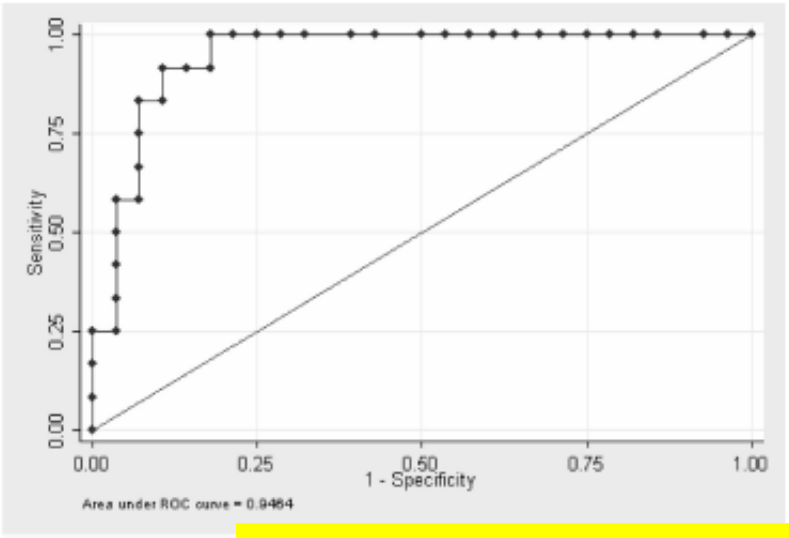
Mégarbane B. *Clin Tox* 2010

Calcium-channel antagonist poisonings
Predictive value of hyperglycemia

	No Composite End Point	Composite End point	*p* Value
Total, n	28	12	
Initial blood glucose, mg/dL[a]	129 (98.5–156.5)	188 (143.5–270.5)	.0058
Peak blood glucose, mg/dL[a]	145 (107.5–160.5)	364 (267.5–408.5)	.0001
Initial heart rate, beats/min[a]	60 (45–87)	50.5 (40–67.5)	.18
Minimal heart rate, beats/min[a,b]	58 (40–68)	40 (39–45)	.0589
Initial systolic blood pressure, mm Hg[a]	129 (100–144)	89 (60–113)	.0091
Lowest systolic blood pressure, mm Hg[a,b]	110.5 (94–130)	72 (60–84)	.0004

[a]Median (interquartile range); [b]lowest value during the first 24 hrs of admission.

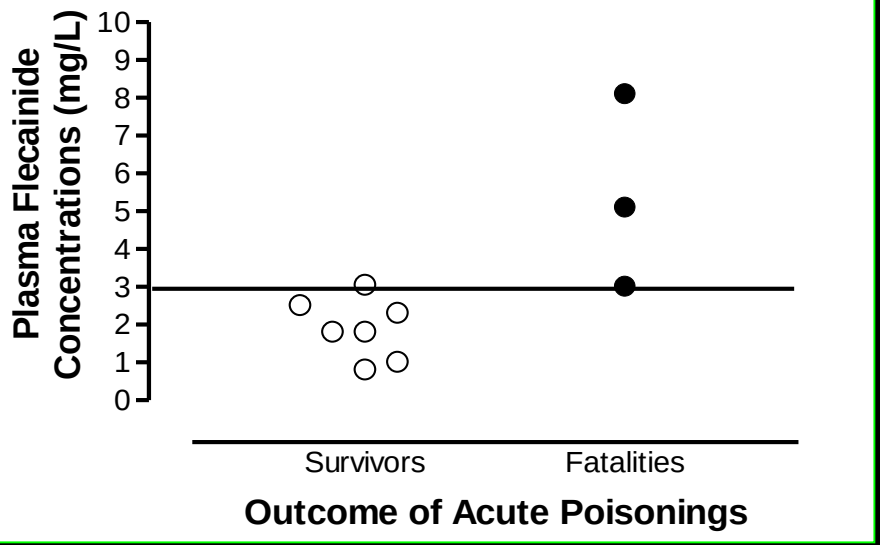




Levine M. *Crit Care Med* 2007

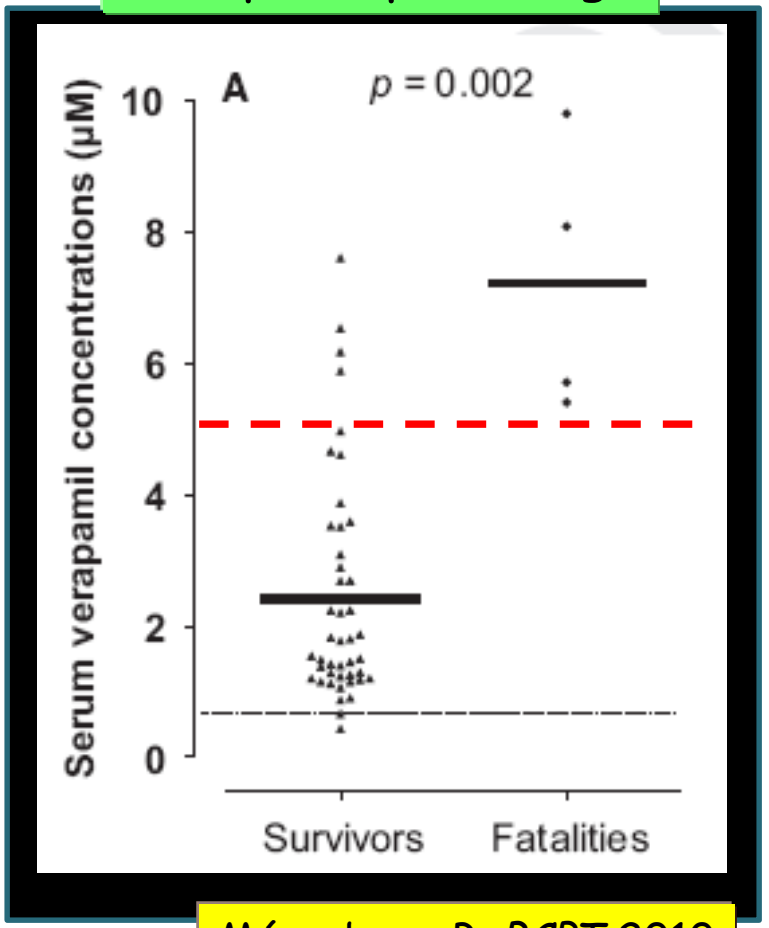
The prognostic value of plasma cardiotoxiant concentrations in acute poisonings

Flecainide poisonings



Mégarbane B. *Clin Tox* 2007

Verapamil poisonings



Mégarbane B. *BCPT* 2010

Conventional supportive treatments in ICU

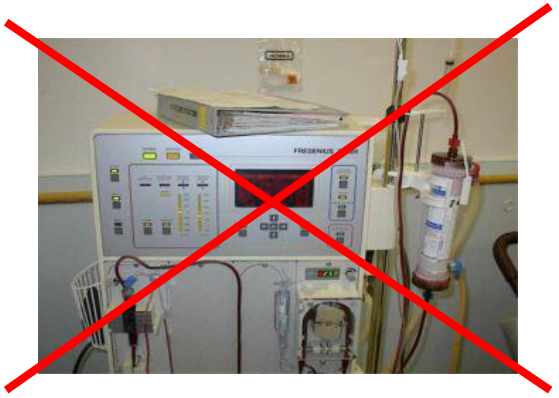
- **Intubation and mechanical ventilation :**
  - Severe arrhythmias and associated collapse
  - Coma, convulsions, respiratory failure
- **Treatment of collapse/shock**
  - Fluids + **adequate catecholamines**
- **Treatment of torsade-de-pointes**
  - Defibrillation, $MgSO_4$, titrated isoproterenol, cardiac pacing
  - Correction of electrolyte imbalance (K^+, Mg^{2+})
- **Treatment of monomorphic ventricular tachycardia**
  - Defibrillation, $MgSO_4$, lidocaine infusion
- **Cardiac pacing**
  - High degree AV block with preserved inotropism

Place of GI decontamination and elimination enhancement

- **Activated charcoal:** within 2 h following the ingestion

- **Repeated doses of charcoal:** Low-sustained forms

- **Dialysis:** limited interest as
  - Elevated protein binding
  - Elevated distribution volume
  - Liposolubility
  - Elevated endogenous clearance



Refractoriness requires failure of the optimal administration of antidotes in the ICU (1)

Beta-blockers

Dobutamine 5-20 µg/kg/min
Isoprenaline 1-5 mg/h (Sotalol)

↓

Glucagon 2-5 mg IV bolus
2-10 mg/h continuous infusion

↓

Epinephrine 0.5-10 mg/h

± **Cardiac Pacing**

Calcium channel blockers

Calcium chloride 1 g IV bolus /15 min
4 doses, 20-50 mg/kg/h infusion

↓

Insulin 1 IU/kg IV bolus
1-10 IU/kg/h continuous infusion

↓

Epinephrine 0.5-10 mg/h
Norepinephrine 0.5-10 mg/h

↓

Methylene blue 2 mg/kg bolus
1 mg/kg/h infusion

Refractoriness requires failure of the optimal administration of antidotes in the ICU (2)

Sodium channel blockers

Sodium bicarbonates 8.4%
250 ml to be repeated 3 times
+ 2g KCl / 250 ml
(cocaine: **Lidocaine** IV)

⬇

Epinephrine 0.5-10 mg/h
Norepinephrine 0.5-10 mg/h

Cardioglycosides

Atropine 0.5-1 mg to be repeated

⬇

Anti-digoxin Fab fragments
Semi-molar or molar dose
(if not available: ventricular pacing)

Lipid emulsion to treat cardiotoxicant drug-related toxicity

To treat severe anesthetics side-effects in the OR as well as membrane-stabilizing agent or calcium-channel blocker poisonings.

Dose regimen: 1.5 ml/kg IV bolus then 0.25 ml/kg/min infusion

Mechanisms:

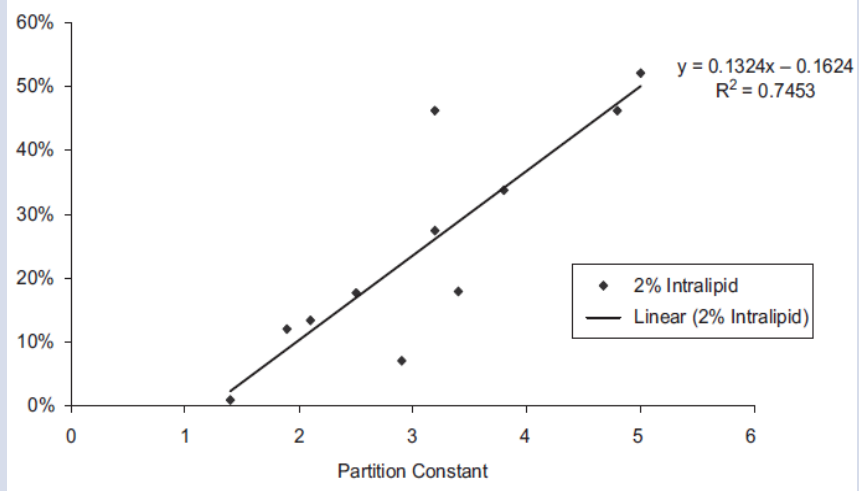
- Lipid sink / sponge: alteration of tissue distribution
- Modulator of myocardial energy, overcoming the inhibition of fatty acid-dependent metabolism
- Activator of myocardial Ca^{2+} channel increasing Ca^{2+} current
- Other toxin-specific mechanisms?

Sirianni AJ. *Ann Emerg Med* 2008
Finn SD. *Anesthesia* 2009
Weinberg GL. *Anesthesiology* 2009

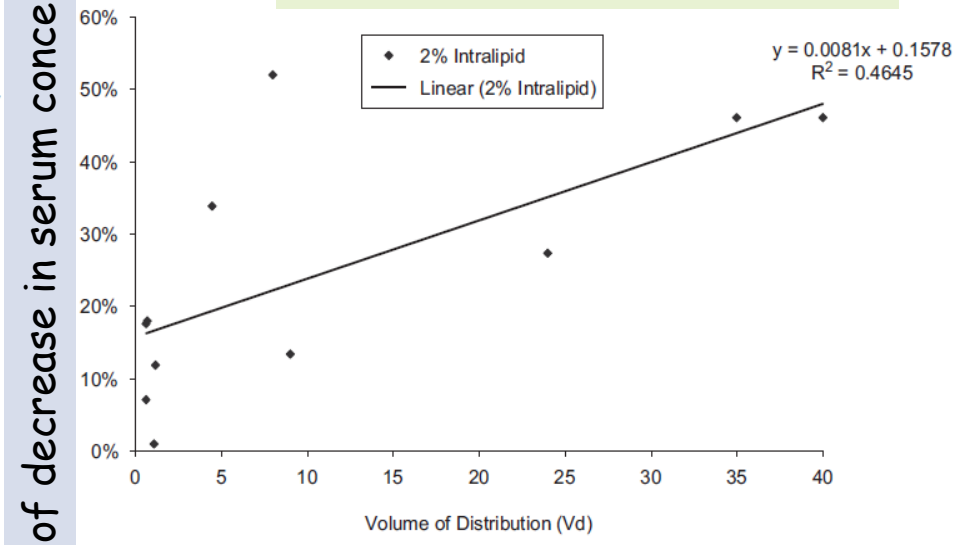
Partition constant and volume of distribution as predictors of ILE efficacy for toxicological emergencies

Serum drug concentration decrease plotted against the partition constant and the volume of distribution of eleven drugs with 2% Intralipid® added to the sample

Partition constant



Volume distribution



French D. *Clin Tox* 2011

Evidence-based recommendations on the use of intravenous lipid emulsion therapy in poisoning

For the management of cardiac arrest:
We recommend using ILE with bupivacaine toxicity, while our recommendations are neutral regarding its use for all other toxins.

For the management of life-threatening toxicity:
- We suggest using ILE as a part of treatment in bupivacaine toxicity and we recommend its use if other therapies fail;
- We suggest using ILE if other therapies fail for toxicity due to other local anesthetics, amitriptyline, and bupropion;
- Our recommendations are neutral for all other toxins.

In the treatment of non-life-threatening toxicity, recommendations varied according to the balance of expected risk/benefit for each toxin

Gosselin S. *Clin Tox* 2016

Refractoriness to the conventional therapies (supportive care + catecholamine + antidotes)

F, 17 years, severe propranolol poisoning

Sedation + mechanical ventilation + FiO_2 100%

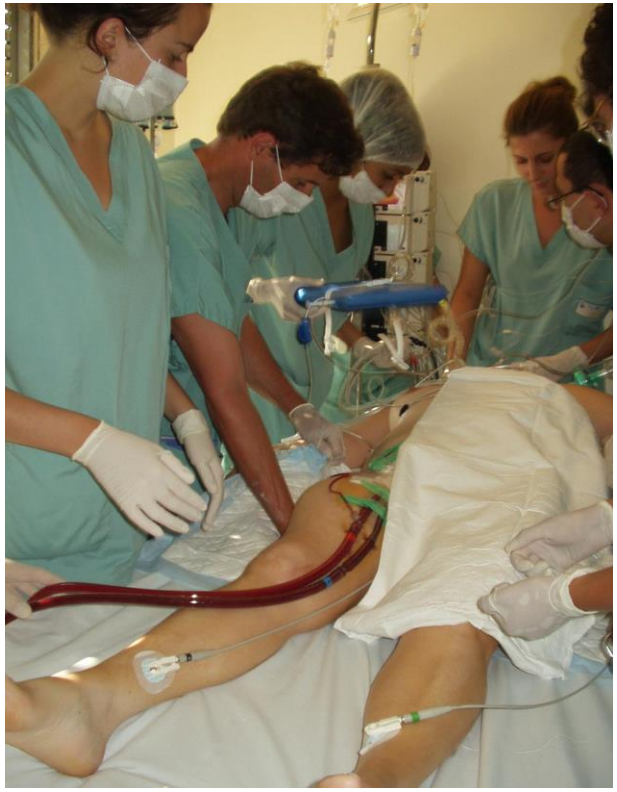
		Epinephrine 1.5 mg/h	Dobutamine 15 µg/kg/min	
BP	S	93	56	mmHg
	D	64	33	mmHg
	M	75	43	mmHg
P_{RA}		7	6	cmH_2O
P_{AP}	S	27	19	cmH_2O
	D	19	11	cmH_2O
	M	23	15	cmH_2O
P_{cw}		17	13	cmH_2O
Cardiac Index		1.4	1.8	$l/min/m^2$
Systemic resistances		50.3	20.3	UI

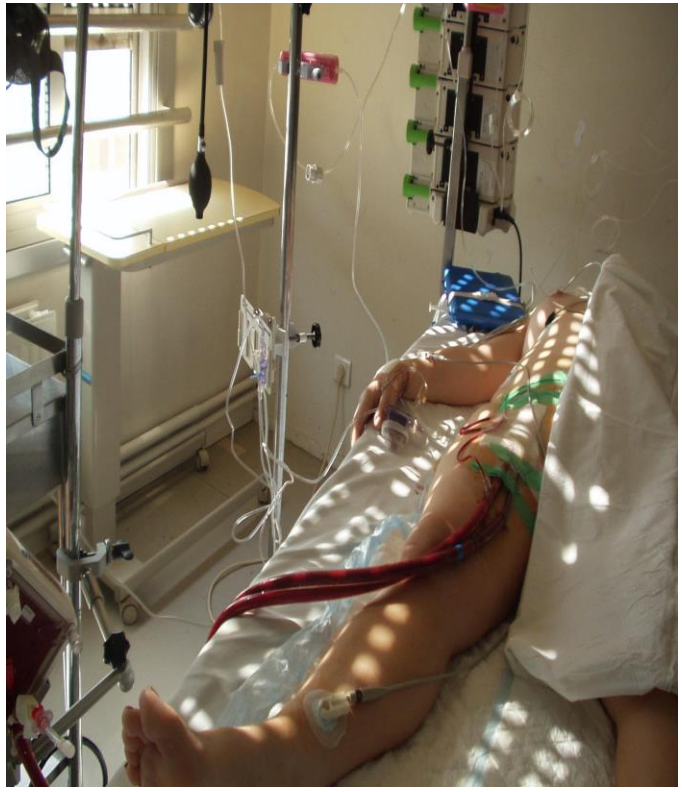
30 min later

Dramatic decrease in BP ...

VA-ECMO in cardiogenic schock

The purpose of VA-ECMO is to take over heart function until recovery can occur, minimizing myocardial work, improving organ perfusion and maintaining the renal and biliary elimination of the toxicant





Baud FJ. *Crit Care* 2007

ECLS indications in acute poisonings

Which patients to treat with ECLS ?

Numerous risks

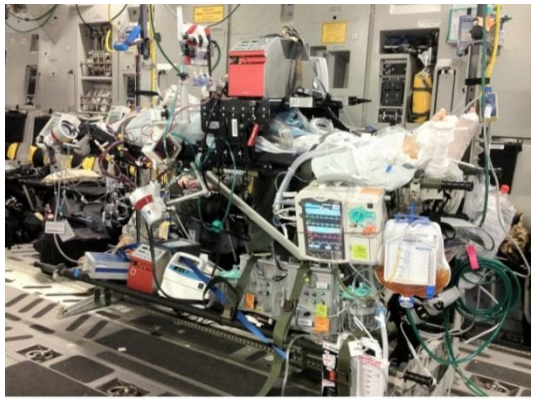
Too late : To result in anoxic brain injury or multiorgan failure

Undiscriminated use: to treat patients who would spontaneously have had favorable outcome with pharmacological treatments

Two options to bring ECMO to the patient

To transfer the patient to Cardiac Surgery Department

To implement ECMO by mobile TCS team



To develop an ECMO program in the ICU in our hospital devoid of cardiac surgery

Specialized team in ICU

Toxic cardiac arrest or failure is announced

Warning

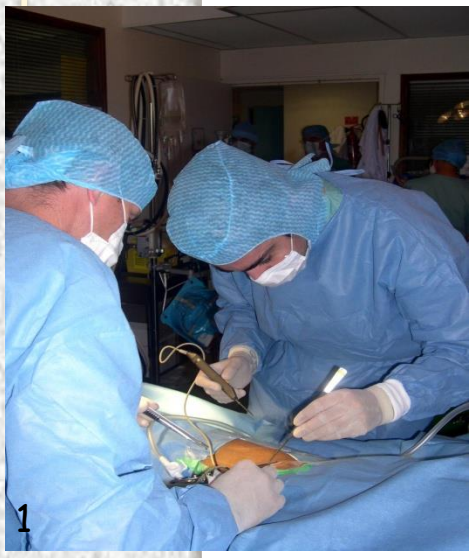
Perfusionist — Surgeons — ICU Physician — Cardiologists — Nurses

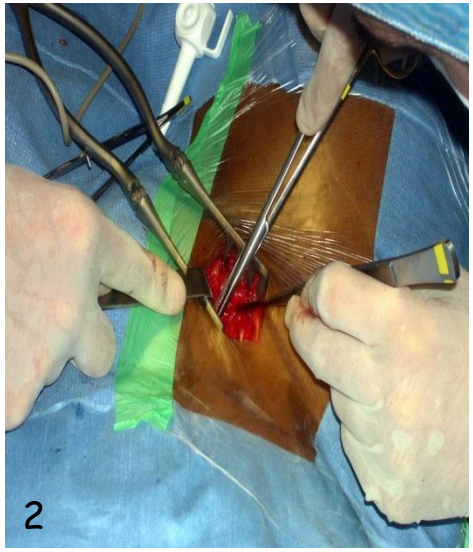
DISPONIBILITY

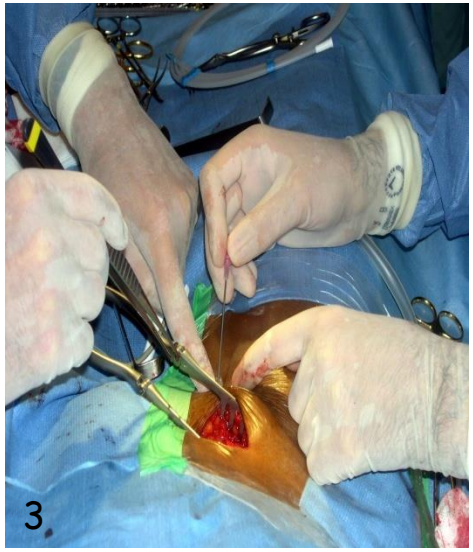
morning — night

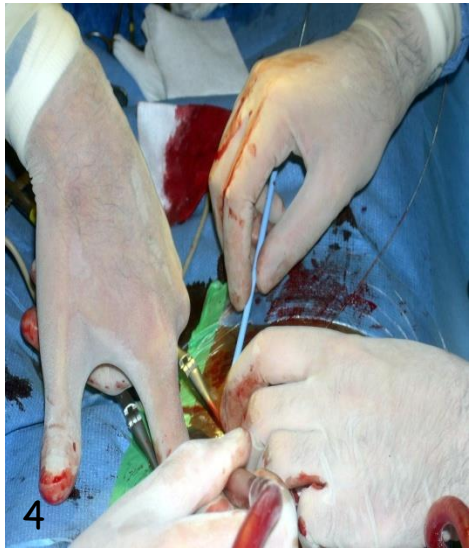
working days — week ends

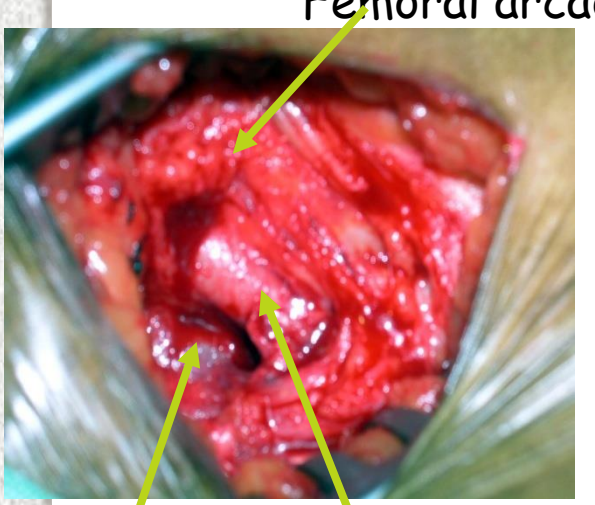
Cannulation of femoral vessels in medical ICU

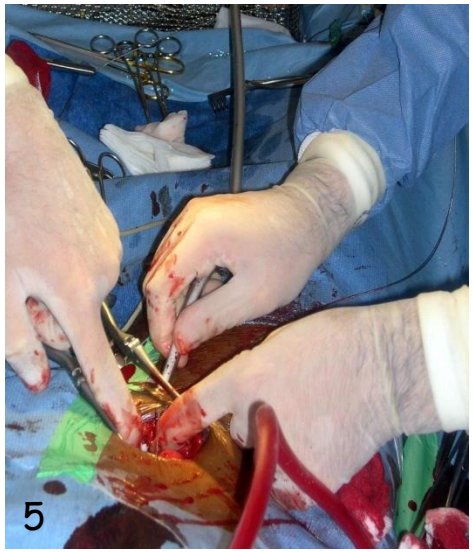


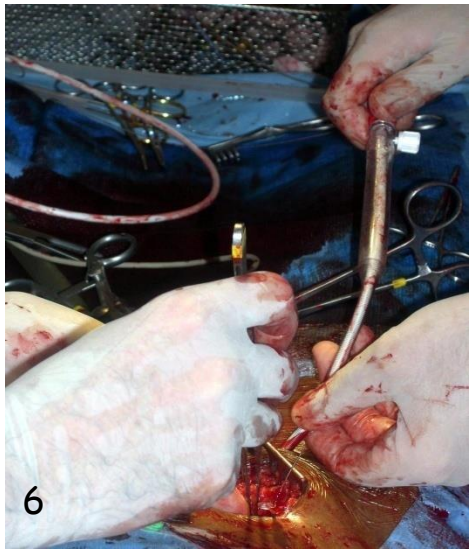






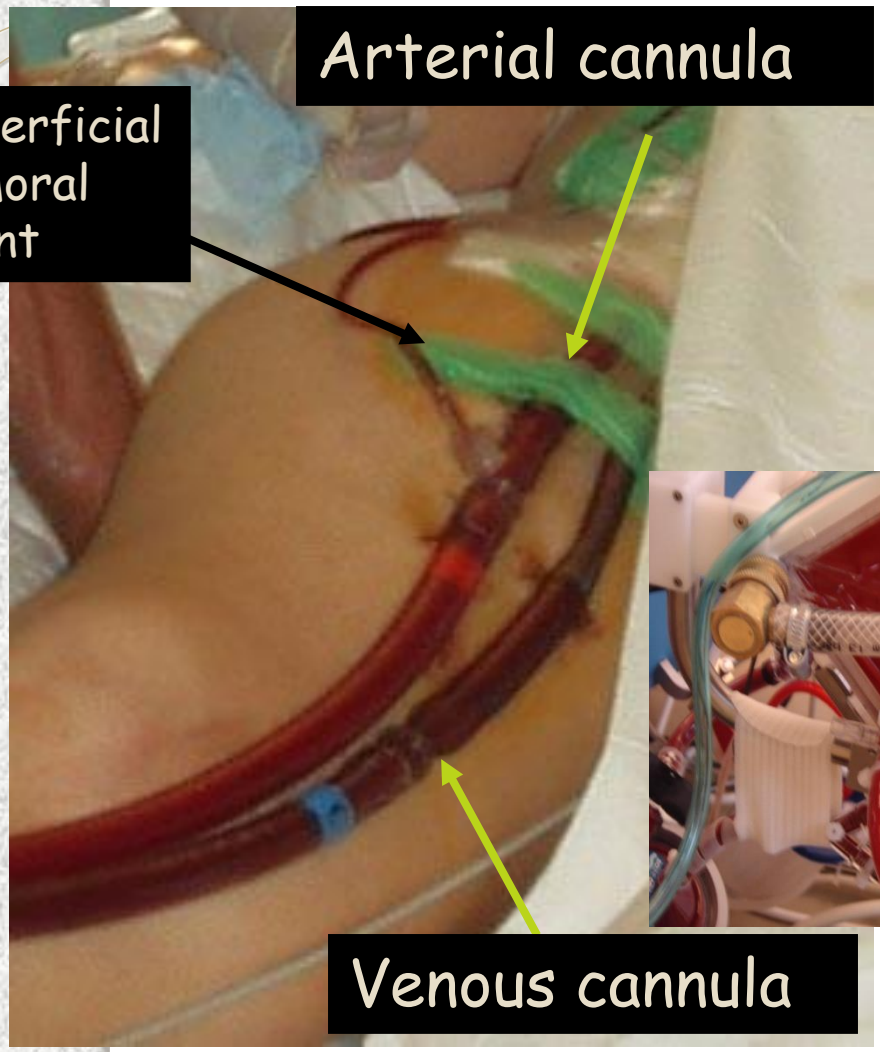


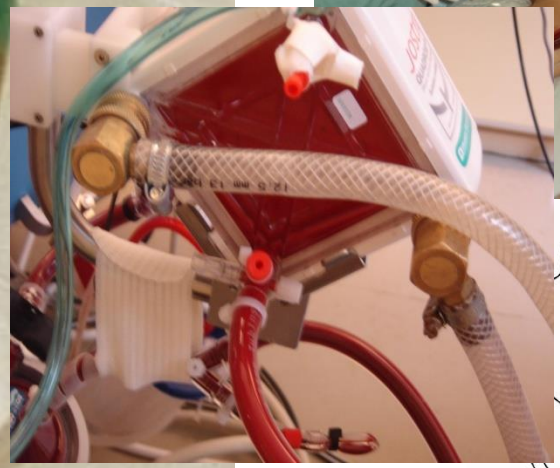


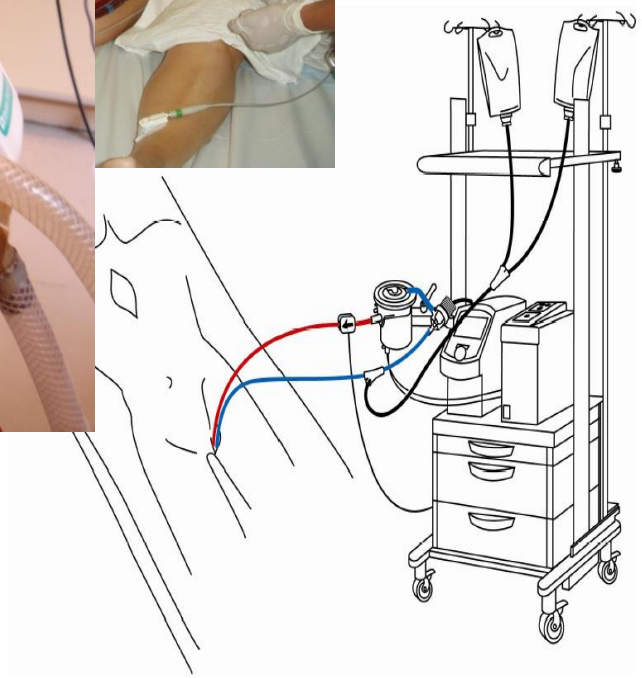


Mégarbane B. *Intensive Care Med* 2007

va-ECMO in the ICU

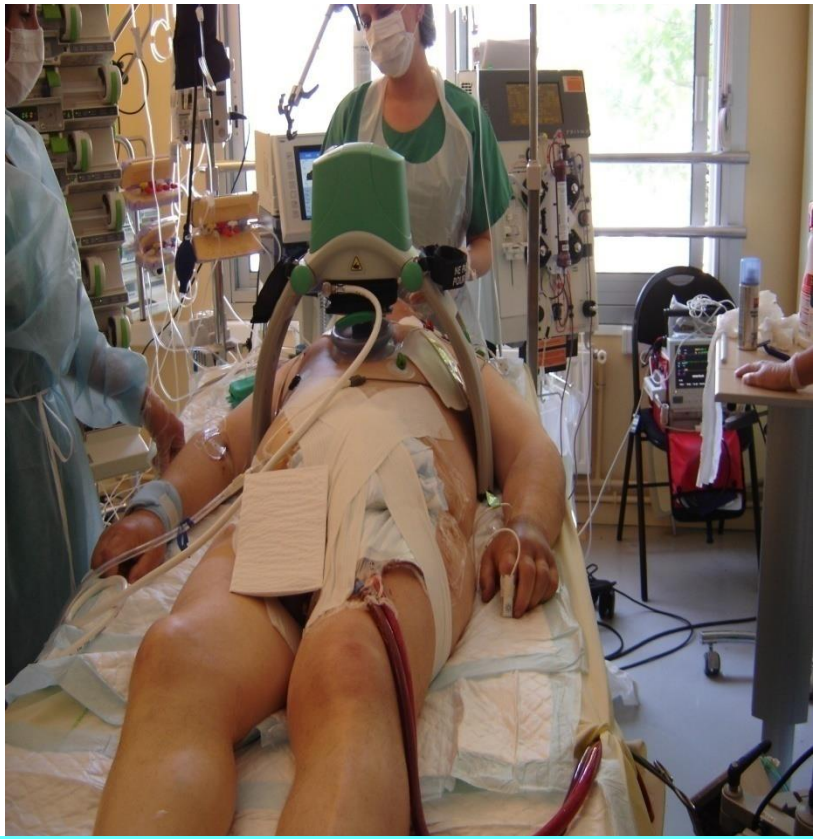






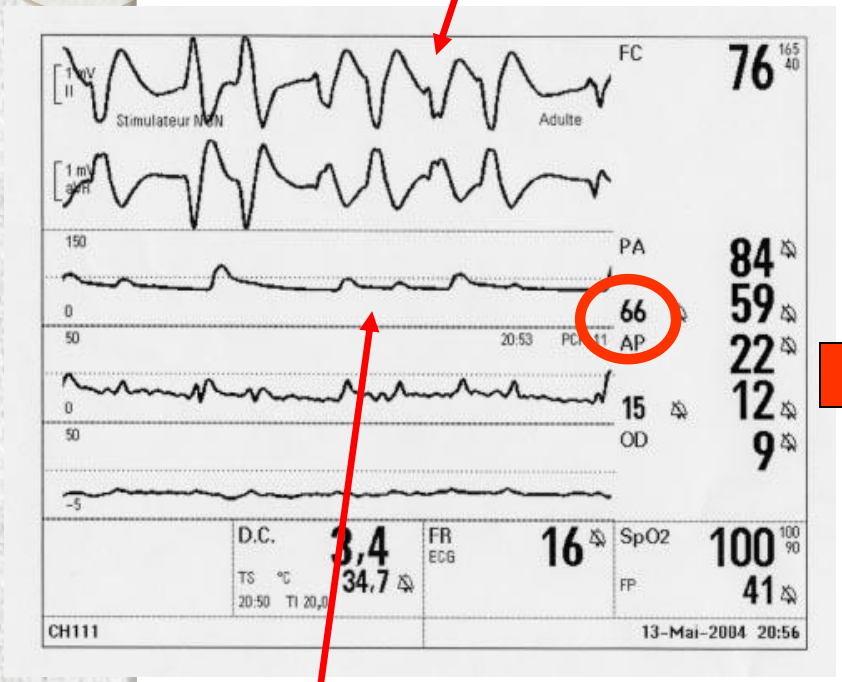
Babatasi G. *Arch Mal Cœur Vx* 2001
Mégarbane B. Intensive Care Med 2007

Adequate cardiac massage and ACLS are the keys for good prognosis in patients with cardiac arrest before va-ECMO implementation



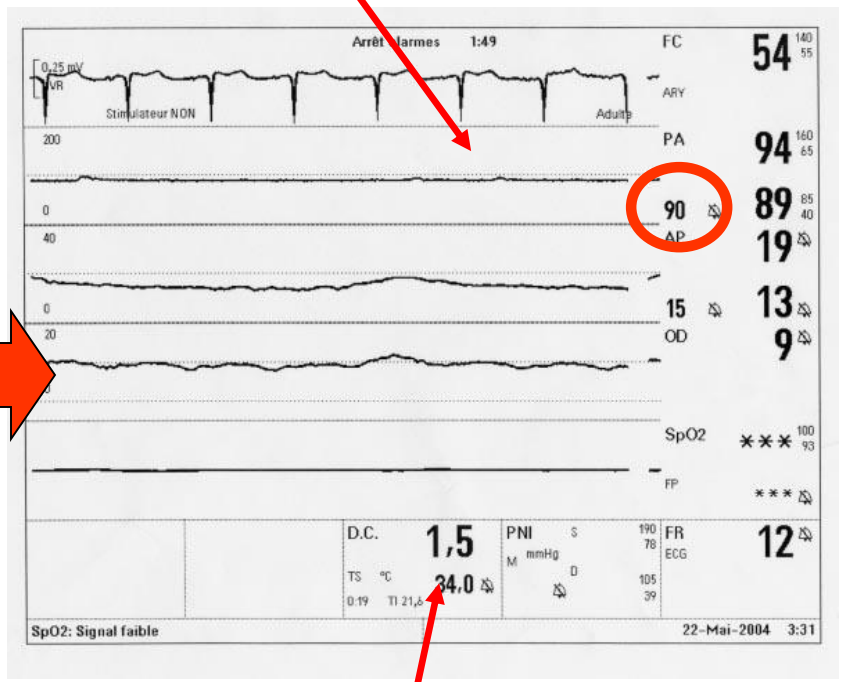
va-ECMO monitoring in the ICU

Spontaneous cardiac rhythm



Severe hypotension despite high dose catecholamine

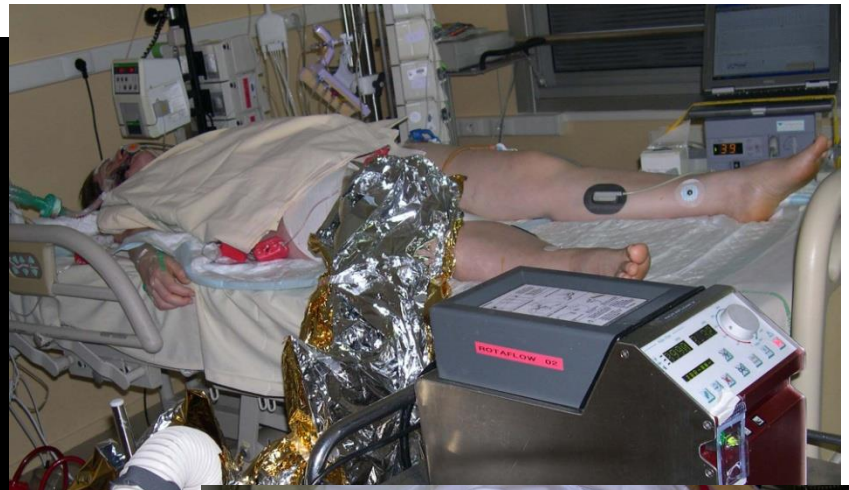
ECLS completely dependent cardiac flow (around 5-6 l/min)

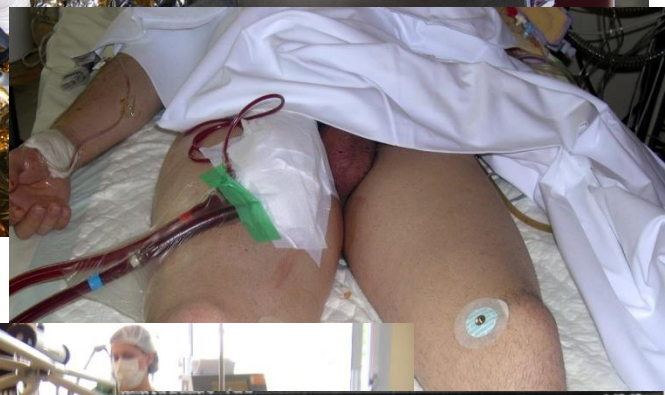


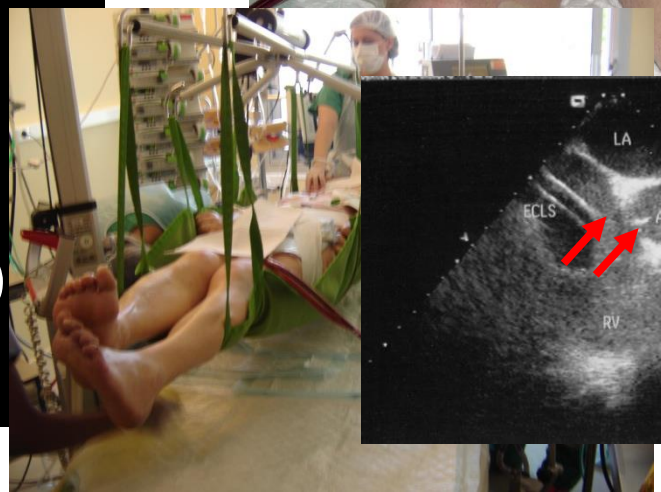
Spontaneous cardiac flow

Monitoring of VA-ECMO-treated patients in the ICU

- Efficient anticoagulation:
  heparin to obtain ACT = 2N
- Catecholamines
  for mean BP = 60-70 mmHg +
  dobutamine to facilitate LV discharge
- Adequate transfusions
- Adapted Mechanical ventilation
  ABG monitoring by radial catheter
- Temperature control
- Canulated lower limb monitoring
- Echocardiography:
  weaning criteria
- Neurological evaluation (EEG, clinical)
- Care, nursing







Published cases of va-ECMO-treated acute poisonings:

- Beta-blockers
- CCB
- Sodium channel blockers

De Lange DW. *Clin Tox* 2013

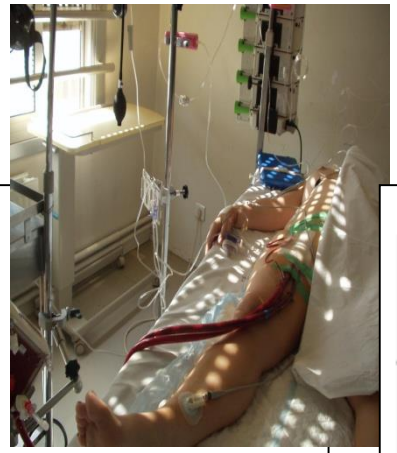
Agent	References
Acebutalol	29,37
Amiodarone	38
Antidepressants (tricyclic)	15,29,39–41
Arsenic	42
Atenolol	29
Bisoprolol	29
Bupropion	43
Calcium Channel Blockers	1,44–49
Carbamazepine	29,50
Carbon monoxide	51
Chloroquine	15,52
Cibenzoline	29,53
Citalopram	29
Cocaine	54
Disopyramide	29,55
Diltiazem	29
Flecainide	29,56–58
Hydrocarbon products	59–63
Ibuprofen	64
Lidocaine	65
Mepivacaine	66
Methadone	67
Metoprolol	29
Opioids	67–69
Organophosphates	70
Paraquat	31,32
Paroxetine	29
Phosphine	71
Propafenone	15,29
Propranolol	29,72–74
Quetiapine	75
Quinidine	76
Radiocontrast material (intravenous)	77
Sotalol	29,78
Taxus	79
Venlafaxine	29
Verapamil	29
Zinc chloride	80
Zotepine	81

Outcome of poisoned patients treated with ECLS

	Total (N=112)	Cardiac failure (N=41)	Refractory arrest (N = 71)
Survival	35 (31%)	22 (54%)	13 (18%)
Neurological sequellae	4	3	1
Hemorrhagic accidents	18	4	14
Thombo-embolic complications	6	4	2
Lower limb ischemia	8	6	2

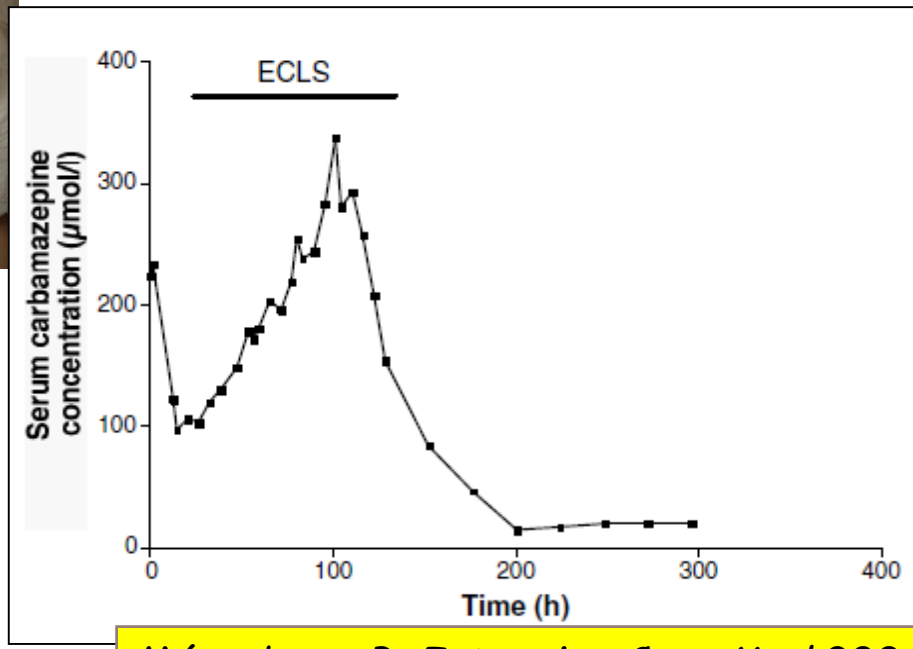
Toxicokinetics in severe poisonings requiring ECMO

Propafenone poisoning



- $T_{1/2}$: 30 h (pharmacology: 4 h)
- Vd: 151 l/kg
- Clearance: 262 l/h

Carbamazepine poisoning



Mégarbane B. *Intensive Care Med* 2006

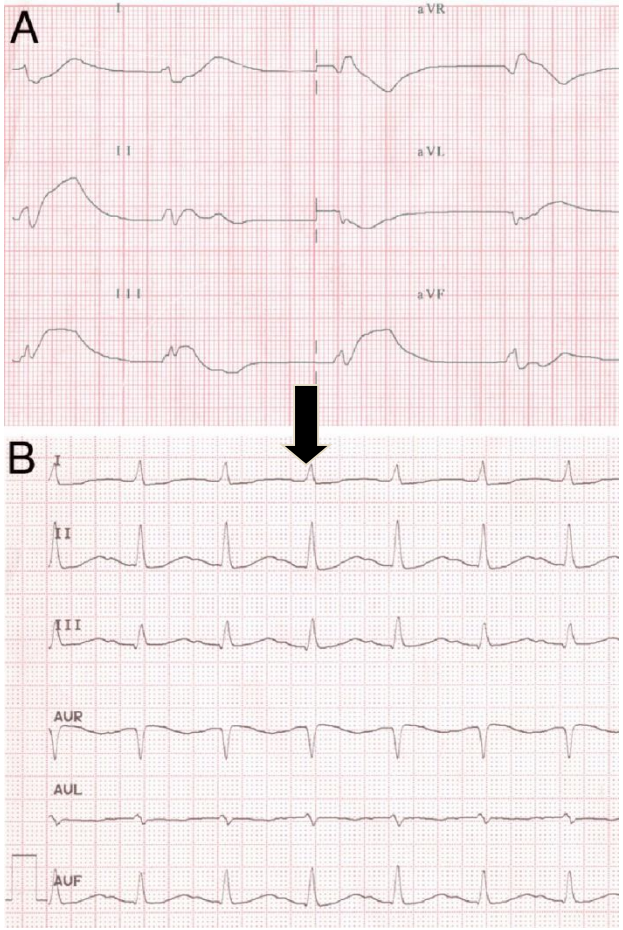
- Concentration on admission: 224 µmol/l
- Peak concentration: 338 µmol/l at 101 h
- Prolonged absorption despite MDAC
- $T_{1/2}$: 22.6 h (pharmacology: 12-20 h)

Death of ECLS-treated poisoned patients

- Death resulted from multiorgan failure, anoxic encephalopathy or capillary leak syndrome if ECLS was performed under cardiac massage.

- Four patients presented documented brain death, allowing organ donation in 2 cases.

- The heart of one flecainide-poisoned patient was successfully transplanted, after normalization of ECG and myocardial function as well as toxicant elimination under ECLS.



Vivien B. Ann Emerg Med 2010

Take home messages

- Shock and arrhythmias following poisonings with cardiotoxicants (especially with digitalis, sodium-channel, and calcium channel blockers) may lead to life-threatening symptoms and death.

- Adequate monitoring of severity and assessment of prognostic criteria are mandatory to improve patient management.

- Treatment is mainly supportive. Despite the absence of high-level of evidence, administration of antidotes is life-saving.

- ECMO should be considered in refractory cardiovascular failure or cardiac arrest although its definitive benefit needs to be evaluated.

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