



Acidosi metabolica ed effetti cardiovascolari

Ivo Casagranda.

D.E.A. Azienda Sanitaria Ospedaliera di Alessandria

S.Margherita Ligure 17 febbraio 2012

Agenda

Introduzione

Acidosi metabolica ed alterazioni cardiovascolari

Acidosi metabolica: da acidi inorganici
da acidi organici
da tossici } Quale terapia ?

Conclusioni

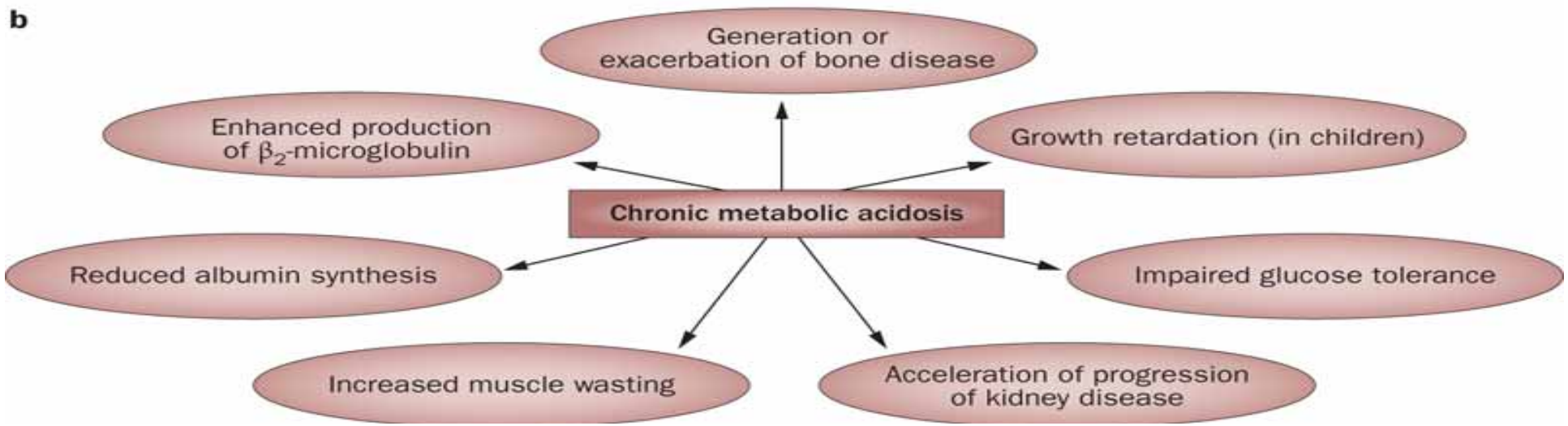
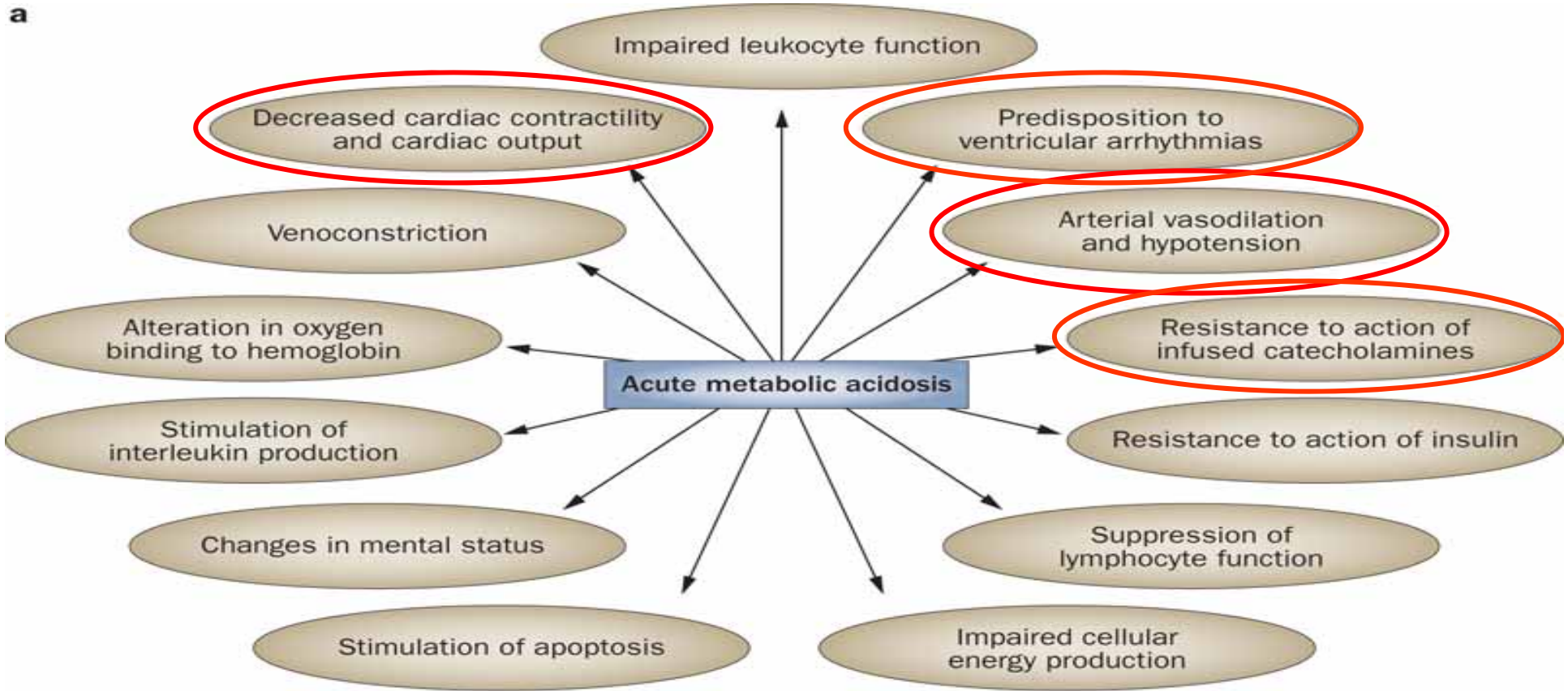
Introduzione

Introduction

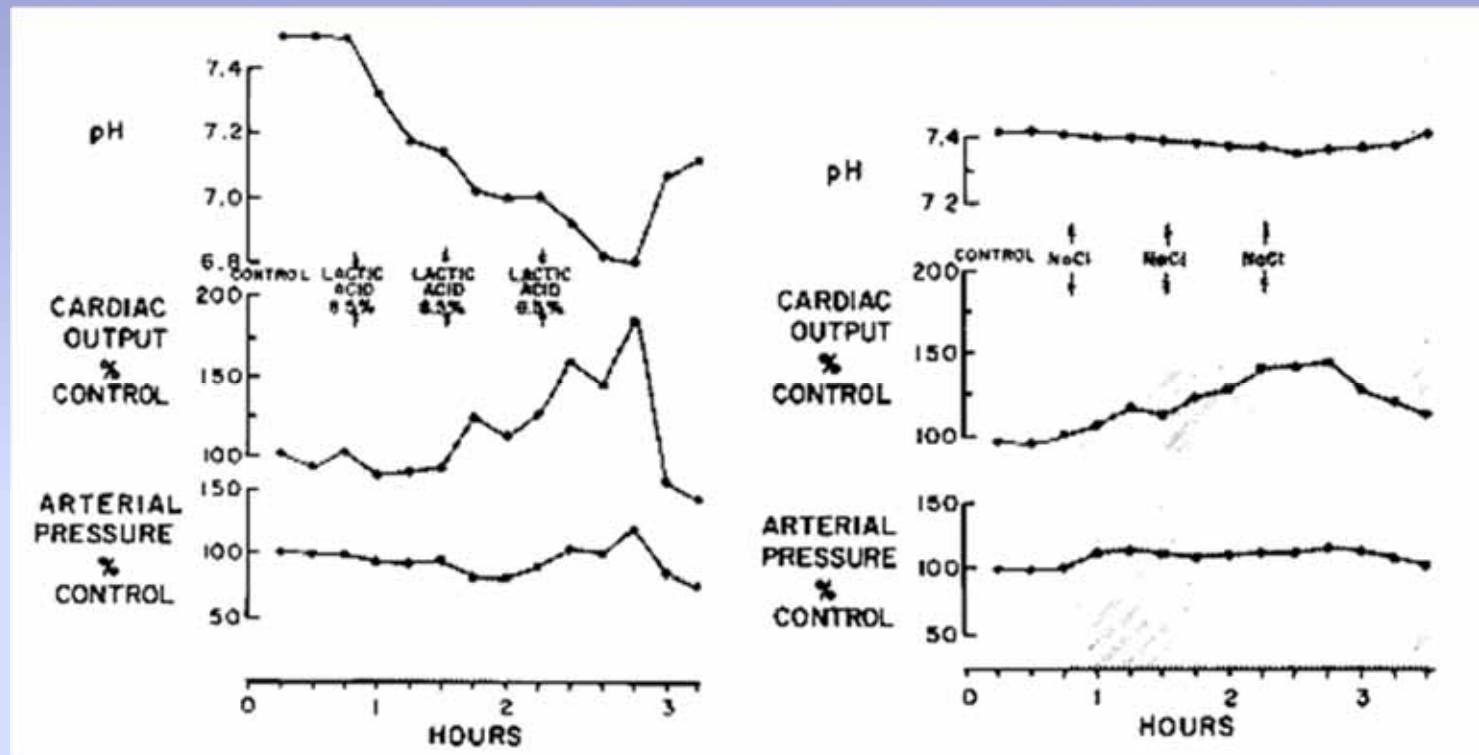
Disturbances in acid-base balance are commonly met problems in clinical medicine and decision about their treatment are of great importance in patients with cardio-pulmonary problems, in whom acid-base disturbances may be especially critical.

Similarly, cardiopulmonary function may be significantly compromised even in patients with no intrinsic heart or lung disease, in the face of acid-base disturbance.

Acidosi metabolica ed effetti cardiovascolari



Effect of metabolic acidosis on cardiac output



Metabolic acidosis: mean values from eight animals receiving 8.5% lactic acid

Control studies with NaCl. Mean values from five animals are illustrated.

Effect of metabolic acidosis on cardiac output

Metabolic acidosis induced by lactic acid injection, with reduction of pH to 6.8, resulted in a consistent increase in cardiac output and fall in peripheral resistance

Andersen MN et al. Ann Surg 1966

Isolated cardiac muscle and heart preparation in vitro invariably exhibit decreased contractile force during either metabolic or respiratory acidosis. The difference between the response of isolated hearts and intact animals are due primarily to sympathoadrenal factors.

Mitchell JH et al. Kidney Internat 1972

Effect of metabolic acidosis on myocardial contractility

Old experimental works show that acidosis depresses myocardial contractility. However, this effect is significant only when intracellular pH is less than 6,4.

Cooper DJ, et al. Am Rev Respir Dis 1993

Some Authors evaluated myocardial contractility using ultrasound examination during severe diabetic ketoacidosis and they find any significant sign of cardiac depression

Murray E, et al. N Engl J Med 1999

Cardiac failure may occur in a patient with severe hypoxic acidosis, but it is likely that the depressant myocardial effect is linked to hypoxia and not to acidosis

Levrant J and Grimaud D. Curr Opin Crit Care 2003

Effect of metabolic acidosis on myocardial contractility

It is generally agreed that myocardial contractility is depressed and the cardiovascular system becomes less responsive to catecholamines such as adrenaline or noradrenaline in the presence of acidosis, especially when the pH decreases less than 7.2.

In a study dobutamine, but not adrenaline and noradrenaline, retains its inotropic effect in anesthetized dogs subjected to metabolic acidosis (pH 7.0) by infusing HCL or lactic acid.

Huang YG et al. Br J Anaesth 1995

Cause di acidosi metabolica

ANION GAP METABOLIC ACIDOSIS

K etosis	β -OH-Butyric & Ac Ac
U remia	Multiple organic & In acids
S alicylate	Multiple Organic Acids
M ethanol	Formic Acid
A ldehydes	Acetic Acid
L actate	l-Lactic Acid (d-Lactate)
E thylene Glycol	Glyoxylic & Oxalic Acid Pyroglutamic acid

HYPERCHLOREMIC METABOLIC ACIDOSIS

CAUSES:

GI Disorders

Diarrhea

Pancreatic Fistula

Ureteroenterostomy

Drugs

HCl & HCl Precursors

Acetazolamide

Cholestyramine

CaCl₂

Kidney Disorders

Early Kidney Failure

RTA

- Proximal (Type II)
- Distal (Type I)
- Type IV

Other

Post-Hypocapnia

Recovery from DKA

Toluene

ACIDOSI METABOLICHE

Quando vanno trattate ?

ACIDI INORGANICI



HCl
H₂SO₄
H₃PO₄

ESOGENI



TOSSICI

ACIDI ORGANICI

ENDOGENI



Ac. Lattico (D e L)
Chetoacidi

ACIDI INORGANICI

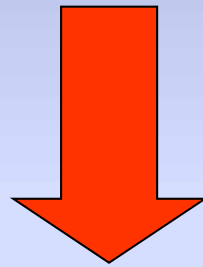


HCl

H₂SO₄

H₃PO₄

H⁺ IS BAD



ALKALI-THERAPY IS GOOD

ACIDOSI INORGANICHE (Cl^- , SO_4^{2-} , PO_4^{2-})

GAP ANIONICO NORMALE

Perdita di NaHCO_3

Gastroenterica

Diarrea
Fistole

Renale

RTA prossimale
ACZ
IRC precoce
US-stomia

Perdita di sali di Na
con ridotto H_e /GFR

RTA distale
RTA iperkaliemica

GAP ANIONICO ELEVATO

Perdita nefroni

IRA
IRC

ALCALI

ACIDI INORGANICI



Renal failure

Renal Failure and metabolic acidosis

- Moderate degree of RI (serum creatinine 2-4 mg/dl) causes a significant decline in serum bicarbonate although it remains within normal ranges; Once GFR declines to about 20 ml/min frank acidosis supervenes.

Physiopathology:

- In milder degrees of RI the organic ions that comprise the anion gap are excreted normally and the acidosis is **hyperchloremic** ;
- When renal failure worsens the kidney loses its ability to excrete sulfate, phosphates, and other anions, which results in their accumulation and an **increased anion gap**.

Renal Failure and metabolic acidosis

Treatment.

Anion gap metabolic acidosis

- Hemodialysis corrects acidosis by replacing bicarbonate while also maintaining euvolemia and normal serum concentration;
- In the rare patient with severe acidosis who does not have any other indication for dialysis , bicarbonate can be administered;

Hyperchloremic metabolic acidosis

- Type I (classic distal): bicarbonate is indicated;
- Type II: bicarbonate administration results in renal wasting;
- Type IV: correct hyperkalemia and replace bicarbonate if necessary.

ACIDI ORGANICI

ENDOGENI

Chetoacidi

Ac. Lattico (D e L)

H⁺ IS BAD



IS ALKALI-THERAPY GOOD ?



IS ALKALI-THERAPY *ALWAYS* GOOD ?

Chetoacidosi diabetica

Gestione della chetoacidosi diabetica

1. Ripristinare di liquidi persi
2. Somministrare insulina e.v.
3. Correggere il potassio
4. Valutare se è il caso di correggere l'acidosi metabolica (bicarbonato)

Perché non somministrare bicarbonato

- Stimola, a livello epatico, la chetogenesi con aumento della chetonemia

Okuda Y, Adroguè HJ. Et al. J Clin Endocrinol Metab 1996;81:314-320

- Determina acidosi intracellulare nei tessuti

Viallon A, Zeni F et al. Crit Care Med 1999;27:2690-2693

- Aumento dell'affinità per l'ossigeno da parte dell'emoglobina con ipossia tessutale periferica

BellingamAJ et al. Trans Assoc Am Phys 1970;83:113-120

Terapia con bicarbonato

L'evidenza

Studio	Disegno	Conclusione	Livello di evidenza
Gamba G, Osguerra J Bicarbonate therapy in severe diabetic ketoacidosis. A double blind, randomized, placebo controlled trial. Rev Invest Clin 1991;43:234-38	20 pz Random (pH <7.15)	Nessuna differenza	A
Lever E, Jaspan JB Sodium bicarbonate therapy in severe diabetic ketoacidosis AM J Med 1983;75:263-8	73pz Retrospektivo	Nessuna differenza	B
Morris LR, Murphy MB, Kitabachi AE Bicarbonate therapy in severe diabetic ketoacidosis Diabetes Care 1980;3: 53-56	21 pz Random (ph 6.9-7.14)	Nessuna differenza	A

Terapia con bicarbonato

Somministrare sodio bicarbonato solo se:

- $\text{pH} < 6,9$

Continuare la somministrazione fino a che:

- Il valore del bicarbonato sierico si raddoppia
- Il valore del bicarbonato si avvicina a 8 mEq/l
- Δ bicarbonatemia $\times 0,5 \times$ peso corporeo

La concentrazione di HCO_3 non aumenta per qualche ora per la titolazione degli H^+ intracellulari e per la diluizione secondaria alla somministrazione di soluzione salina

Perché non somministrare bicarbonato

- I bicarbonati sono rigenerati dal metabolismo del lattato, dei chetoacidi e dell'aceto-acetato con il trattamento patogenetico

Halperin ML et al. Metabolism 1983;32:308-15

- Il pH risponde rapidamente al trattamento con fluidi e glucosio

Miller PD et al. Arch. Intern. Med. 1978; 138:67-72

Conclusioni

L'evidenza

- Per la gestione della chetoacidosi diabetica la letteratura offre un certo numero di RCT's anche se le casistiche inserite sono piccole
- Per la chetoacidosi alcolica non esistono RCT's e in alcune parti ci si è riferiti agli studi condotti per la chetoacidosi diabetica

Acidosi lattica

Lactic acidosis

Lactic acidosis, defined as a lactate concentration $> 5\text{mmol/L}$ and a pH < 7.35 , commonly complicates critical illness.

Its causes are legion, including sepsis, cardiogenic shock, severe hypoxemia, hepatic failure, and intoxication. Many of these share reduced delivery of oxygen to cells or impaired use of oxygen mitochondria, yet some are based in more complex derangements.

Causes of Lactic acidosis

Type A

Decreased oxygen delivery

- Hypotension
 - Volume depletion
 - Blood loss
 - Cardiogenic shock
 - Septic shock
- Severe anemia
- Severe hypoxemia
- Carbon monoxide

Increase oxygen demands

- Exercise
- Seizures
- Shivering

Causes of Lactic acidosis

Type B

Inadequate oxygen utilization

- **SIRS**
- **Diabetes mellitus**
- **Malignancy**
- **Total parenteral nutrition**
- **Thiamine deficiency**

- **Congenital lactic acidosis**
- **Mitochondrial myopathies**
- **HIV infection**
- **Malaria**
- **Drug/toxins**

Other

D-lactic acidosis

Causes of Lactic acidosis

Type B

Drugs/toxins

- **Biguanids**
- **Propofol**
- **Salycilate**
- **Simvastatin**
- **Lactulose**
- **Propylene glicole**
- **Theophylline**
- **Nalidix acid**
- **Nitroprusside**
- **Ethanol**
- **β -2 Agonists**
- **Niacin**
- **Cyanide**
- **Antiretroviral drugs**
- **Vasoactive drugs**
- **Isoniazide**
- **Acetaminophen**
- **Linezolid**

Those who continue to advocate the use of sodium bicarbonate for lactic acidosis generally use the following chain of reasoning.

1. A low pH, in and of itself, is harmful (most notably by impairing cardiovascular function).
2. Sodium bicarbonate can increase the pH when infused IV.
3. Raising the pH with sodium bicarbonate improves cardiovascular function or some other relevant outcome.
4. Any adverse effects of sodium bicarbonate are outweighed by its benefits

1. A low pH, in and of itself, is harmful (most notably by impairing cardiovascular function).

- Numerous studies , concerning very different cells, have shown that anoxic or ischemic cells placed in a buffer of pH 6.5 to 7 are able to survive during several hours.

If the same anoxic cells are incubated in a buffer of pH 7.40, they all die in less than an hour.

- Anoxic cells placed in a acidic buffer begin to die when the pH of the medium (pH paradox)

2. Raising the pH with sodium bicarbonate improves cardiovascular function or some other relevant outcome.

No controlled study has shown improved hemodynamics attributable to sodium bicarbonate infusion regardless of effect on pH, and many show worsening of some hemodynamic variable.

It is significant that such negative findings include two studies in critically ill humans receiving infused catecholamines, subset of patients of patients who might be expected to benefit most dramatically

2. Raising the pH with sodium bicarbonate improves cardiovascular function or some other relevant outcome.

- Paradoxical lowering of intracellular pH despite a rise in extracellular pH when bicarbonate is administered
- This is due to the fact that when bicarbonate combines with hydrogen ions, it forms carbonic acid.



CO_2 diffuses into cells, worsening intracellular pH

Conclusion

- Sodium bicarbonate is clearly effective in raising the arterial pH in critically ill patients with lactic acidosis;
- The impact on intracellular pH is unknown in such patients, but extrapolation from extensive animal studies suggests that it is negative;
- Despite the correction of arterial acidemia, sodium bicarbonate has no favorable effects, even for patients with severe acidemia and receiving continuous infusion of catecholamines.
- Clinicians universally agree that the most important step in the treatment of lactic acidosis is to treat the underlying conditions

ACIDI ORGANICI



ESODOGENI



Tossici

Treatment of metabolic acidosis

The treatment of the metabolic acidosis with base has been recommended by most experts.

The delivery of base with dialysis might be preferred to lesser complications of base therapy

Kraut JA and Kurtz I. Clin J Am Soc Nephrol 2008

Conclusions -1

- It is difficult to claim that acidosis by itself is able to deeply depress the myocardial activity;
- In the acidotic models there is a reduction in myocardial responsiveness to adrenaline or noradrenaline but not to dobutamine;
- Several electrophysiologic studies have shown that acidosis promote some arrhythmia, notably the reentrant arrhythmia

Conclusions -2

- Alkali therapy should be restricted to severe mineral metabolic acidosis ($BE \leq 10$ mmol/L) because it seems to be safe
- The benefit of alkali therapy has never been clinically demonstrated during severe organic metabolic acidosis
- Metabolic acidosis and the systematic symptomatic correction of all severe organic metabolic acidosis by alkali is undoubtedly a serious mistake
- In toxic metabolic acidosis the alkali therapy is recommended by most experts