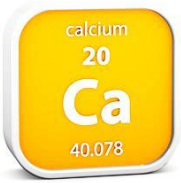
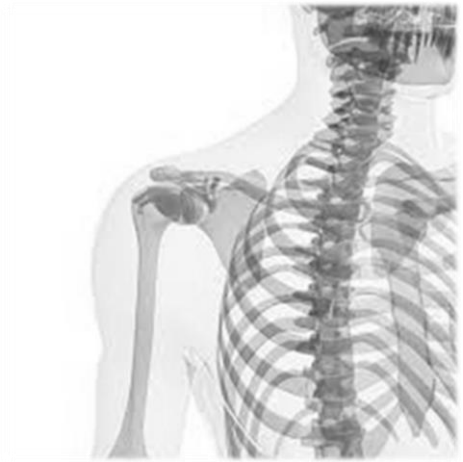
VÁPNÍK A HOŘČÍK

Jaroslav Raděj

17. ročník Colours of Sepsis – Sepse Ostrava 2015

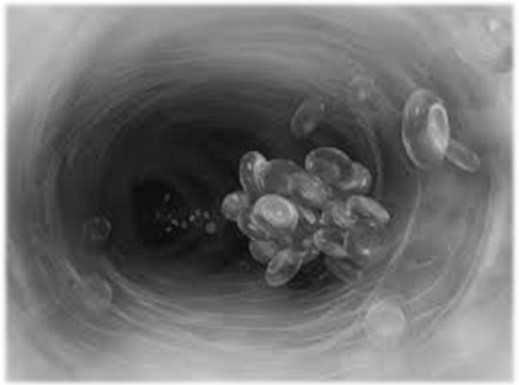


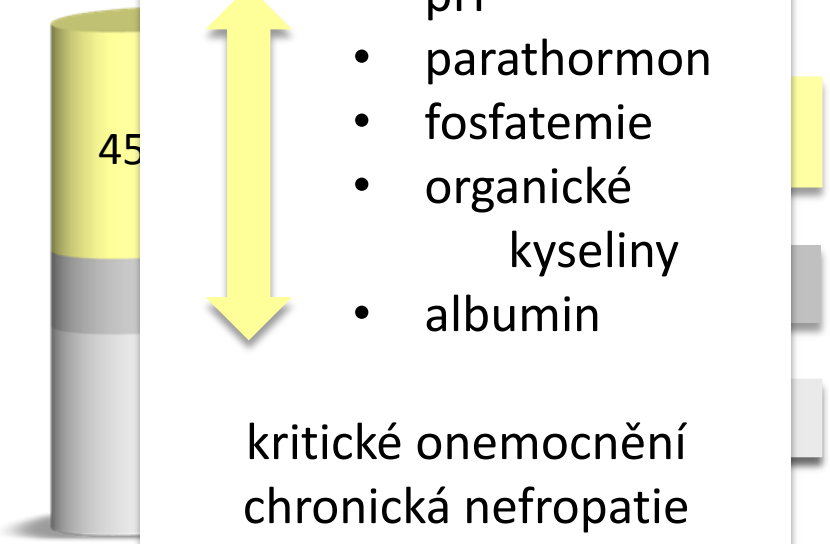


cca 1 kg ≈ > 99%

ECT ≈ 1%

plasma



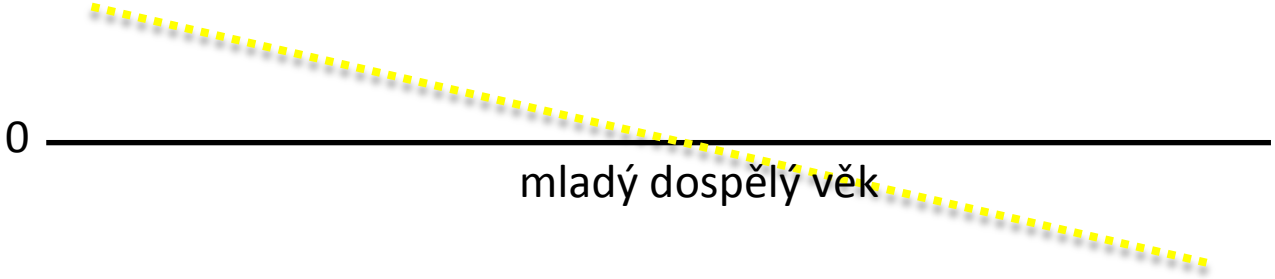


iCa nekoreluje

- pH
- parathormon
- fosfatemie
- organické kyseliny
- albumin

kritické onemocnění
chronická nefropatie

celková bilance vápníku



plasmatická hladina
iCa je konstantní

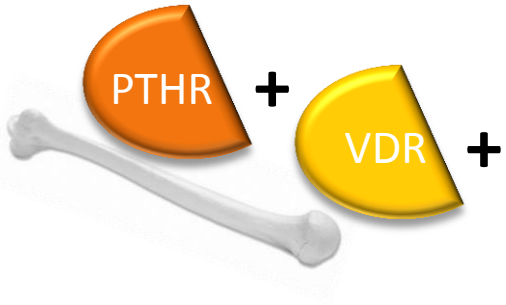
parathormon

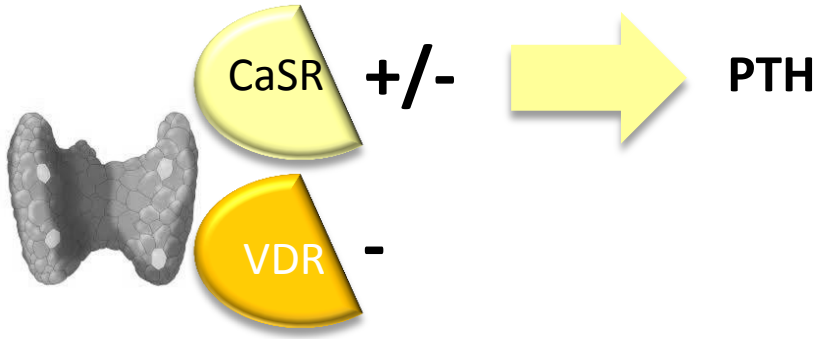
kalcitriol (vit. D3)

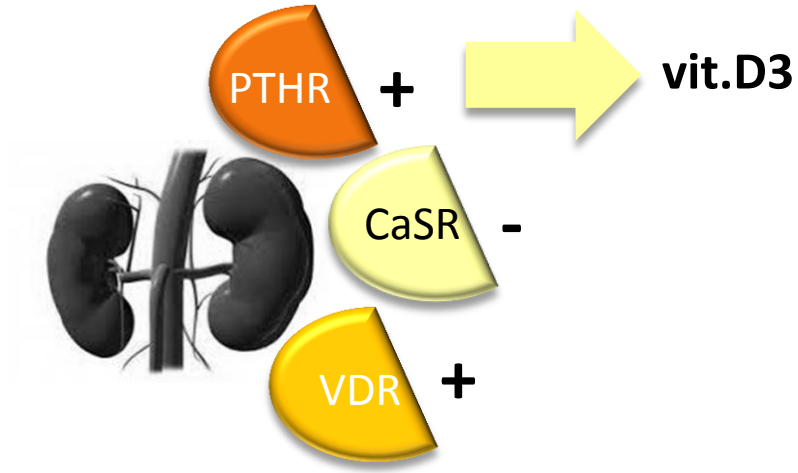
kalcitonin

estrogeny, adrenalin, FGF-23
prokalcitonin bez souvislosti

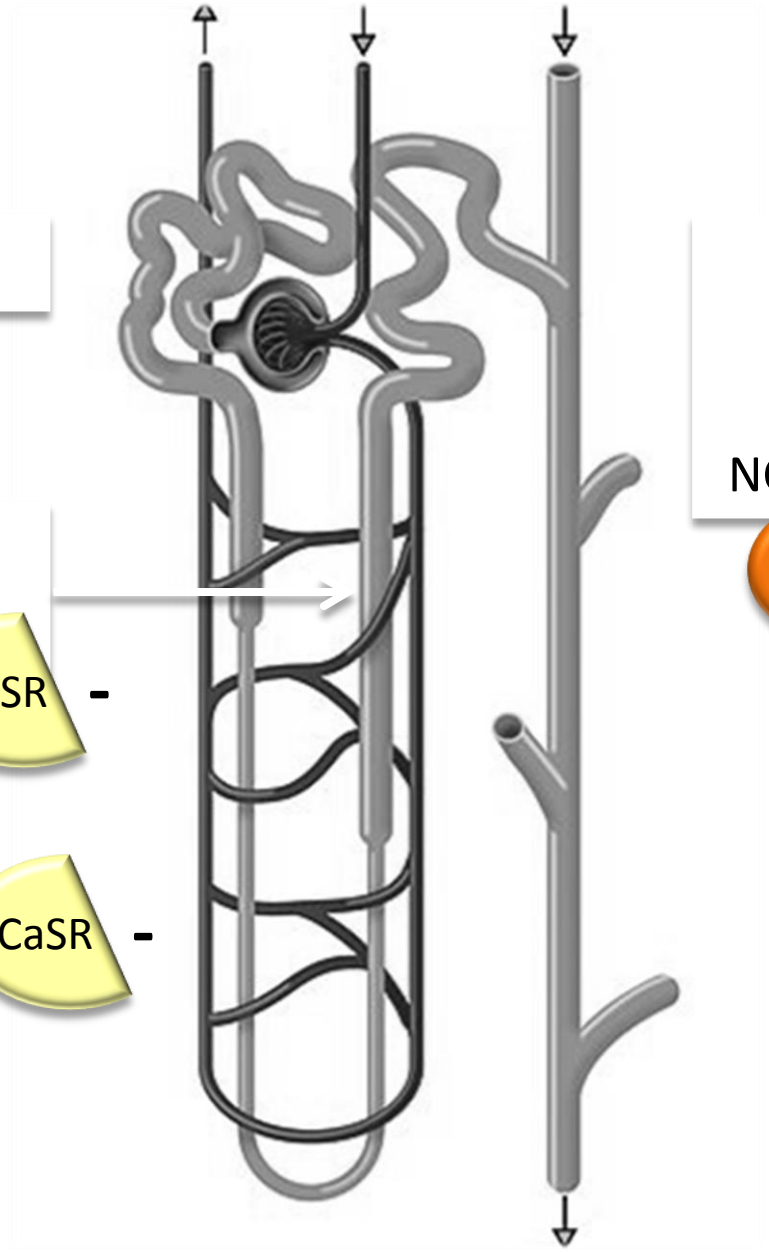
regulace iCa v plasmě







readsobce iCa



pasivně 70%

pasivně 20%
claudin 16/19

CaSR -

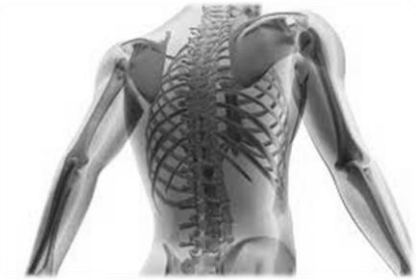
CaSR -

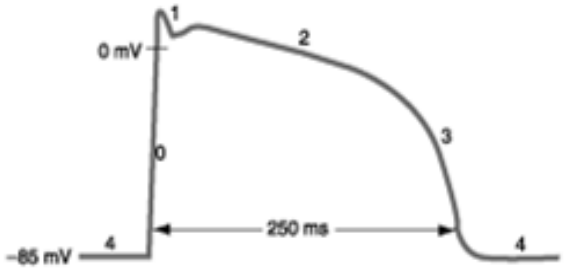
aktivně 10-15%
TRPV5 kanál
calbindin-D28k
NCX1 a PMCA1b kanál

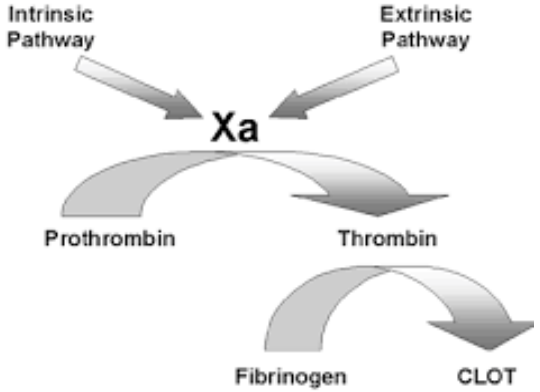
CaSR -

PTHR +

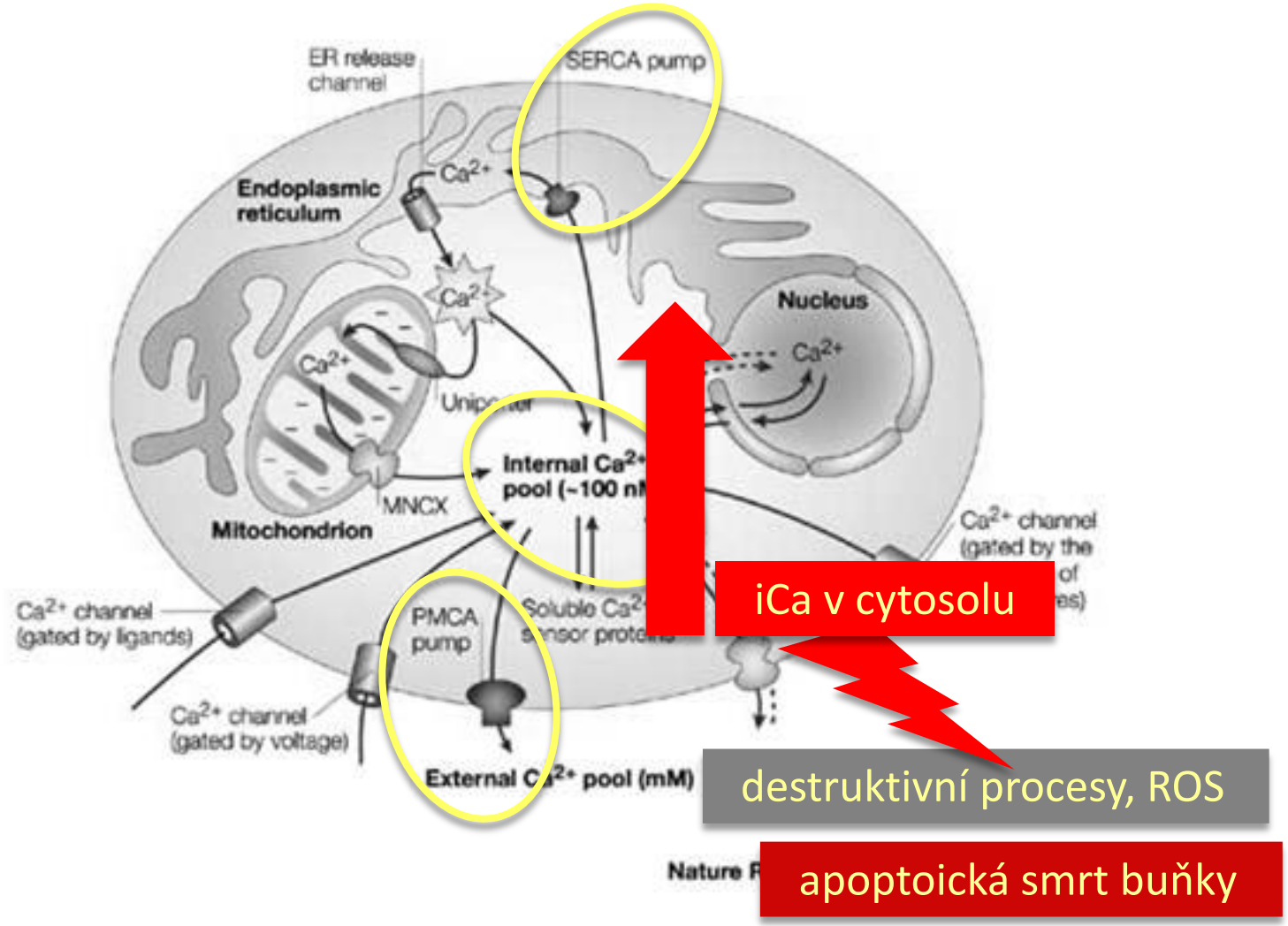
VDR +

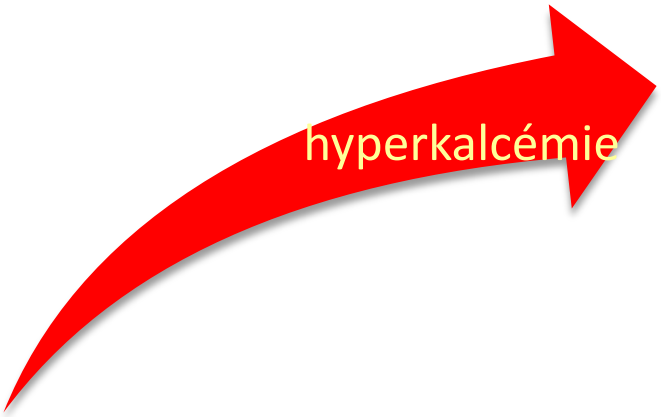






buněčný primární a sekundární messenger


ER release channel
SERCA pump
Endoplasmic reticulum
Ca2+
Nucleus
Mitochondrion
MNCX
Internal Ca2+ pool (~100 nM
Ca2+ channel (gated by ligands)
Ca2+ channel (gated by voltage)
PMCA pump
Soluble Ca2+ sensor proteins
External Ca2+ pool (mM)
iCa v cytosolu
destruktivní procesy, ROS
apoptoická smrt buňky



PTH-dependent.	PTH-independent.
✓ primární hyperparath.	✓ maligní onemocnění
✓ familiární poruchy	✓ gra… mm.
✓ terciální hyperparath.	✓ polékova
	✓ jiná endokrinopatie
	✓ imobilizace
	✓ vit. D intoxikace
	✓ milk-alkali syndrom

> 90%

> 3.25 mmol/l

v rámci kritického onemocnění vzácně

nespecifické pp., slabost

hodiny infuzní léčba krystaloidy
furosemid
calcitonin
hemodialýza

tipace, ulcerace

pankreatitis

DI, AKI

dny bisfosfonáty
glukokortikoidy specificky
kalcimimetika specificky

ofie, fibróza
nóza

úzkost, kognitivní funkce

kóma

zkrácení ST, hypertenze
kalcifikace, kardiomyopatie

arytmie

S-Vápník	1,91
S-Fosfor	1,11
S-Horcik	0,90

B-Ca ioniz.	1,07

hypokalcémie až u 50-80 % kriticky nemocných

- ✓ snížené uvolňování PTH a tvorba vit. D3 a rezistence cílových tkání
- ✓ hypomagnezémie i hypermagnezémie
- ✓ narušen kostní metabolismus s převahou resorpce
- ✓ léky (furosemid, heparin, propofol, antiepileptika, aj.)
- ✓ chelace (fosfor, laktát, citrát, mastné kyseliny)
- ✓ precipitace ve tkáních (pankreatitida, rabdomyolýza)
- ✓ přesun intracelulárně

nervosvalová dráždivost
svalová slabost
CIPNM

kardiovaskulární insuficience
arytmie

asymptomatický nezřídka při iCa 0,8 mmol/l

hypokalcémie kriticky nemocného, orgánové dysfunkce a mortalita

Afshinnia F1, Belanger K, Palevsky PM, Young EW. Ren Fail. 2013

Effect of ionized serum calcium on outcomes in acute kidney injury needing renal replacement therapy: secondary analysis of the acute renal failure trial network study. ATN Study

iCa < 1 mmol/l ≈ OR 1,70

Steele T, Kolamunnage-Dona R, Downey C, Toh CH, Welters I. Crit Care. 2013

Assessment and clinical course of hypocalcemia in critical illness.

bez vlivu na mortalitu, včetně suplementace

Zhang Z1, Xu X1, Ni H1, Deng H1. PLoS One. 2014

Predictive value of ionized calcium in critically ill patients: an analysis of a large clinical database MIMIC II.

iCa_{mean} 0,9-1,15 mmol/l ≈ OR 1,15; iCa_{mean} 0,8-0,9 mmol/l ≈ OR 2,52

Ionized calcium concentration and outcome in critical illness*

Moritoki Egi, MD; Inbyung Kim, PhD; Alistair Nichol, PhD; Edward Stachowski, MD; Craig J. French, MB; Graeme K. Hart, MD; Colin Hegarty, BSc; Michael Bailey, PhD; Rinaldo Bellomo, MD

Objective: To assess the association of abnormalities of ionized calcium levels with mortality in a heterogeneous cohort of critically ill patients.

Design: Retrospective, combined clinical and biochemical study.

Setting: Four combined medical/surgical intensive care units.

Patients: Cohort of 7,024 adult critically ill patients.

Interventions: None.

Measurements and Main Results: We studied 177,578 ionized calcium measurements, from 7024 patients, with a mean value of 1.11 mmol/L (ionized calcium measured every 4.5 hrs on average). The unadjusted lowest and highest ionized calcium reported during intensive care unit stay were significantly different between intensive care unit survivors and nonsurvivors ($p < .001$). If hypocalcemia occurred at least once during the intensive care unit stay, the probability of intensive care unit mortality increased by 46%, 108%, and 150% for ionized calcium levels <1.15, 0.90, and 0.80 mmol/L, respectively. If hypercalcemia occurred at least once during the intensive care unit stay, the probability of intensive care unit mortality increased by 100%, 162%, and 190% for ionized calcium levels >1.25, 1.35, and 1.45 mmol/L, respectively. Similar trends were seen for hospital mortality. However, from multivariate logistic regression analysis, only an ionized calcium <0.8 mmol/L or an ionized calcium >1.4 mmol/L were independently associated with intensive care unit and hospital mortality.

Conclusions: Within a broad range of values, ionized calcium concentration has no independent association with hospital or intensive care unit mortality. Only extreme abnormalities of ionized calcium concentrations are independent predictors of mortality. (Crit Care Med 2011; 39:314–321)

KEY WORDS: calcium; ionized calcium; hypocalcemia; hypercalcemia; intensive care unit; critical illness; mortality

A normal ionized calcium (iCa) concentration in blood is important to many fundamental physiologic regulatory mechanisms (1–5). However, abnormalities of iCa concentration are common in critically ill patients (6–9). The vast majority of these abnormalities are due to hypocalcemia (5–24), but hypercalcemia has also been reported (25).

Hypocalcemia has been associated with increased mortality in critically ill patients (5, 7, 10–17, 23, 24, 26). However, this relationship is derived from univariate analyses or relatively small single center studies (7, 10–17). Additionally, there are only a few small studies on the association between hypercalcemia and mortality in critically ill patients (1, 27). Thus, the independent relationship between abnormalities of iCa and outcome is currently poorly understood.

Despite this limitation, correction of hypocalcemia with exogenous calcium has been advocated to prevent neurologic and cardiovascular complications (28, 29). However, the administration of exogenous

MATERIALS AND METHODS

The data collection for this study was part of an established quality assurance activity. The data collection and the data analysis for this study were approved by the local institutional ethic committee, which waived the need for informed consent. The Austin Hospital Ethics Committee approved this investigation and its submission for publication.

Study Population and Data Sources. The current study is a multicenter, retrospective, and observational investigation of 7024 ICU patients. Four hospitals, three in Melbourne and one in Sydney, Australia participated in this study. All patients admitted to the ICUs of these hospitals from February 2, 2000 to October 20, 2004 were included. Patients admitted during periods when arterial blood gas data were not electronically stored in a given

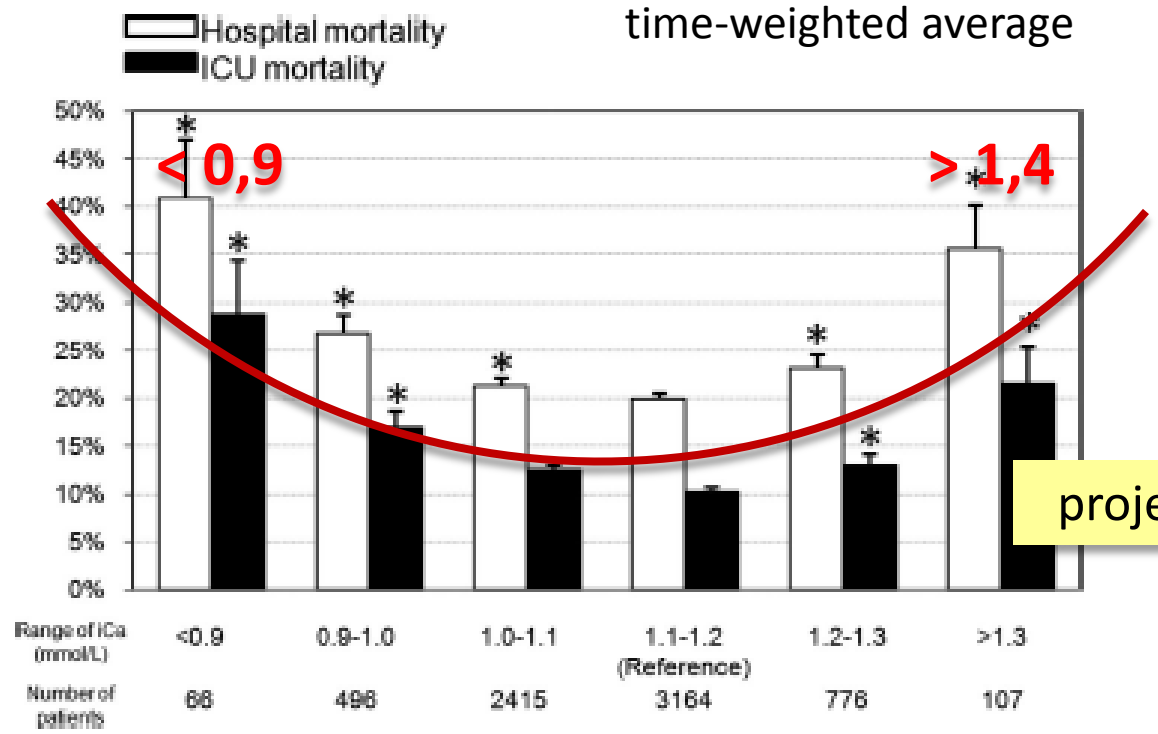
*See also p. 406.

From the Department of Anesthesiology and Resuscitology (ME), Okayama University Hospital,

7 024 pacientů

iCa_{mean} 1,11 mmol/l

< 1,15 mmol/l	**88,4%**
< 0,9	10,8%
< 0,8	3,3%
> 1,25 mmol/l	22,7%
> 1,35	6,7%
> 1,45	2,0%



projev tíže onemocnění ?!

zvýšená koncentrace iCa v cytosolu u septických

yeed MM, Song SK, Thompson M, Zaloga GP

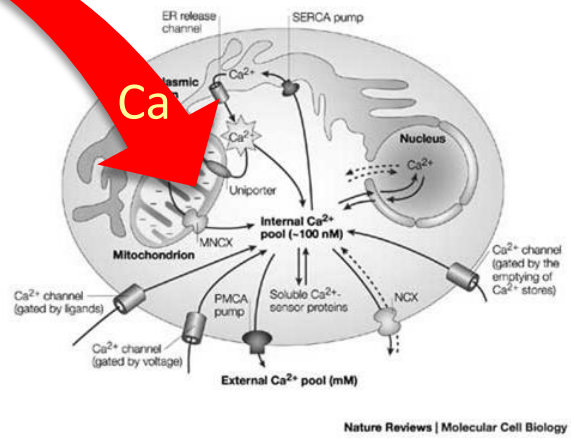
rfuzi

hara Y, Marban E, Steenbergen C

sepse škodí

rlstedt F, Malcolm DS, Zaloga GP

Ca



hypokalcémie je protektivní mechanismus v době kritického onemocnění ?

Calcium Supplementation During Sepsis Exacerbates Organ Failure and Mortality via Calcium/Calmodulin-Dependent Protein Kinase Kinase Signaling

Richard D. Collage, BS[1]; Gina M. Howell, MD[1]; Xianghong Zhang, PhD[1]; Jennifer L. Stripay, BS[1]; Janet S. Lee, MD[2]; Derek C. Angus, MD, MPH[3]; Matthew R. Rosengart, MD, MPH[1,3]

Background: Calcium plays an essential role in nearly all cellular processes. As such, cellular and systemic calcium concentrations are tightly regulated. During sepsis, derangements in such tight regulation frequently occur, and treating hypocalcemia with parenteral calcium administration remains the current practice guideline.
Objective: We investigated whether calcium administration worsens mortality and organ dysfunction using an experimental murine model of sepsis and explored the mechanistic role of the family of calcium/calmodulin-dependent protein kinases in mediating these physiological effects. To highlight the biological relevance of these observations, we conducted a translational study of the association between calcium administration, organ dysfunction, and mortality among a cohort of critically ill septic ICU patients.
Design: Prospective, randomized controlled experimental murine study and observational clinical cohort analysis.
Setting: University research laboratory and eight ICUs at a tertiary care center.
Patients: A cohort of 870 septic ICU patients.
Subjects: C57Bl/6 and CaMKK$^{-/-}$ mice.
Interventions: Mice underwent cecal ligation and puncture polymicrobial sepsis and were administered with calcium chloride (0.25 or 0.25 mg/kg) or normal saline.
Measurements and Main Results: Administering calcium chloride to septic C57Bl/6 mice heightened systemic inflammation and vascular leak, exacerbated hepatic and renal dysfunction, and increased mortality. These events were significantly attenuated in CaMKK$^{-/-}$ mice. In a risk-adjusted analysis of septic patients, calcium administration was associated with an increased risk of death, odds ratio 1.92 (95% CI, 1.00–3.68; $p = 0.049$), a significant increase in the risk of renal dysfunction, odds ratio 4.74 (95% CI, 2.48–9.08; $p < 0.001$), and a significant reduction in ventilator-free days, mean decrease 3.29 days (0.50–6.08 days; $p = 0.02$).
Conclusions: Derangements in calcium homeostasis occur during sepsis that is sensitive to calcium administration. This altered calcium signaling, transduced by the calmodulin-dependent protein kinase kinase cascade, mediates heightened inflammation and vascular leak that culminates in elevated organ dysfunction and mortality. In the clinical management of septic patients, calcium supplementation provides no benefit and may impose harm. (*Crit Care Med* 2013; 41:e352–e360)
Key Words: calcium; calcium/calmodulin-dependent protein kinase; infection; inflammation; mortality; organ failure; sepsis

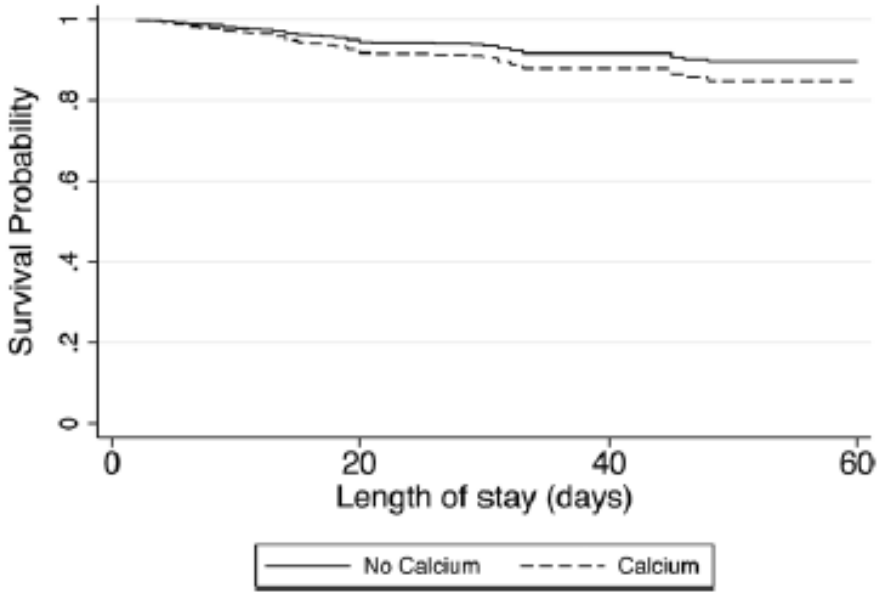
Calcium plays an essential role in nearly all biological processes. As such, ionized calcium concentration

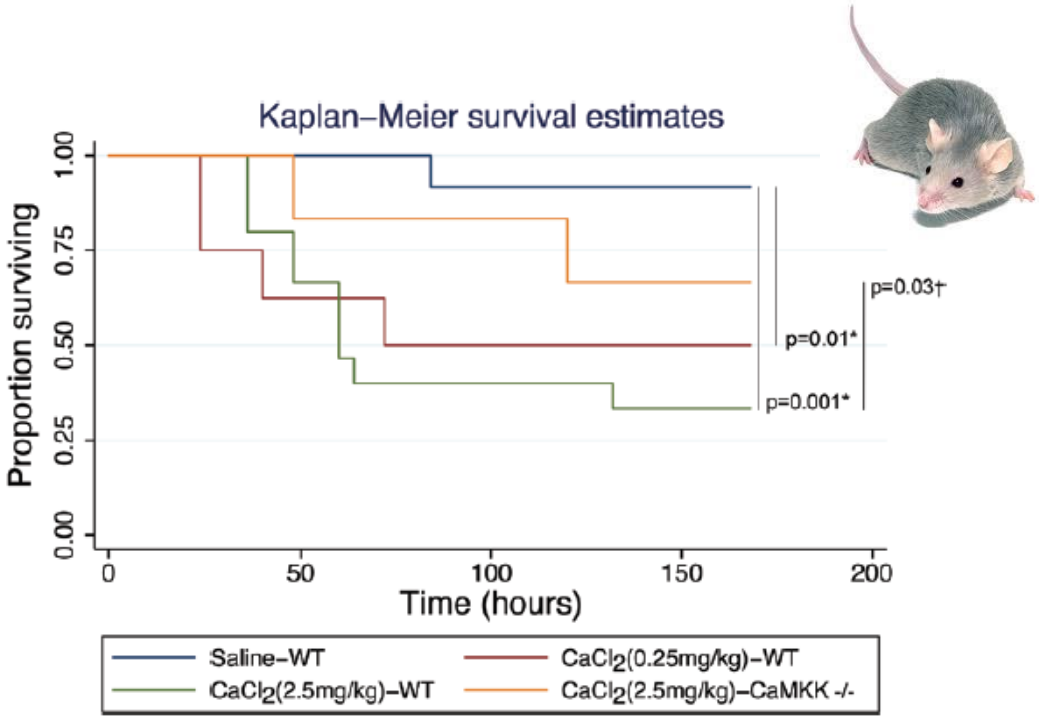
526 septických pacientů
iCa_{mean} 1,09±0,14 mmol/l
iCa < 1,15 mmol/l 71,7%

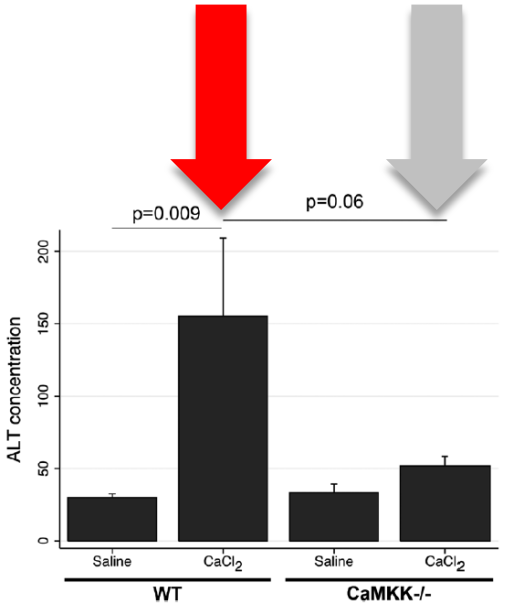
bez vlivu na mortalitou, renální dysfunkci, plicní dysfunkci

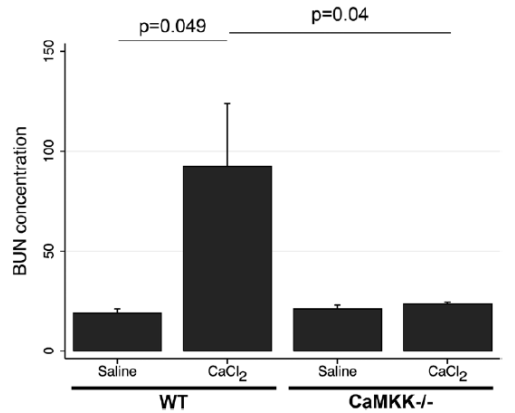
substituce 17,7% pacientů

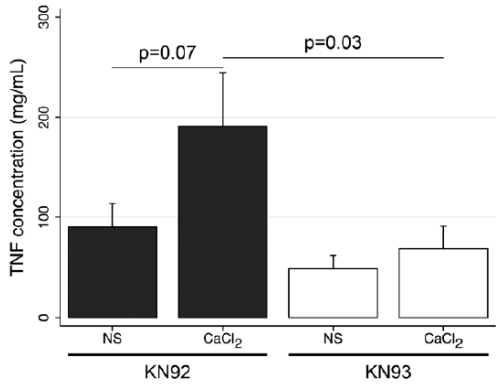
zvýšení mortality ≈ OR 1,92, korelace s dávkou
renální dysfunkce ≈ OR 4,74, korelace s dávkou
redukce neventilovaných dní ≈ snížení o 3,29 d




Kaplan–Meier survival estimates
Proportion surviving
0.00
0.25
0.50
0.75
1.00
0
50
100
150
200
Time (hours)
p=0.03†
p=0.01*
p=0.001*
Saline–WT
CaCl2(0.25mg/kg)–WT
CaCl2(2.5mg/kg)–WT
CaCl2(2.5mg/kg)–CaMKK -/-


p=0.009
p=0.06
ALT concentration
0
50
100
150
200
Saline
CaCl2
Saline
CaCl2
WT
CaMKK-/-


p=0.049
p=0.04
BUN concentration
0
50
100
150
Saline
CaCl2
Saline
CaCl2
WT
CaMKK-/-


p=0.07
p=0.03
TNF concentration (mg/mL)
0
100
200
300
NS
CaCl2
NS
CaCl2
KN92
KN93

substituce kalcia

symptomatický pacient  a pacient s těžkou hypokalcémií 

živo

into

prin

rutinní využití v **ALS CPR**
(kromě PEA při hyper-K, hypo-Ca, intoxikaci CCBs)
ERC guidelines 2010

nekrotizující **pankreatitis**
ACG guidelines 2013

léčba levosimendanem

cílová plasmatická hladina iCa při regionální citrátové antikoagulace

EAACI guidelines 2014

rutinní **hemodynamická podpora**

skelet ≈ 50%

svaly a jiné tkáně ≈ 49,…%

intracelulárně 8-10 mmol/l

92% Mg vázané

plasma ≈ 0,3%

55% Mg^{2+} [0,52-0,60 mmol/l]

relevantní ukazatel? iMg?

readsorbce iMg

pasivně 15–25%

aktivně 5-10%

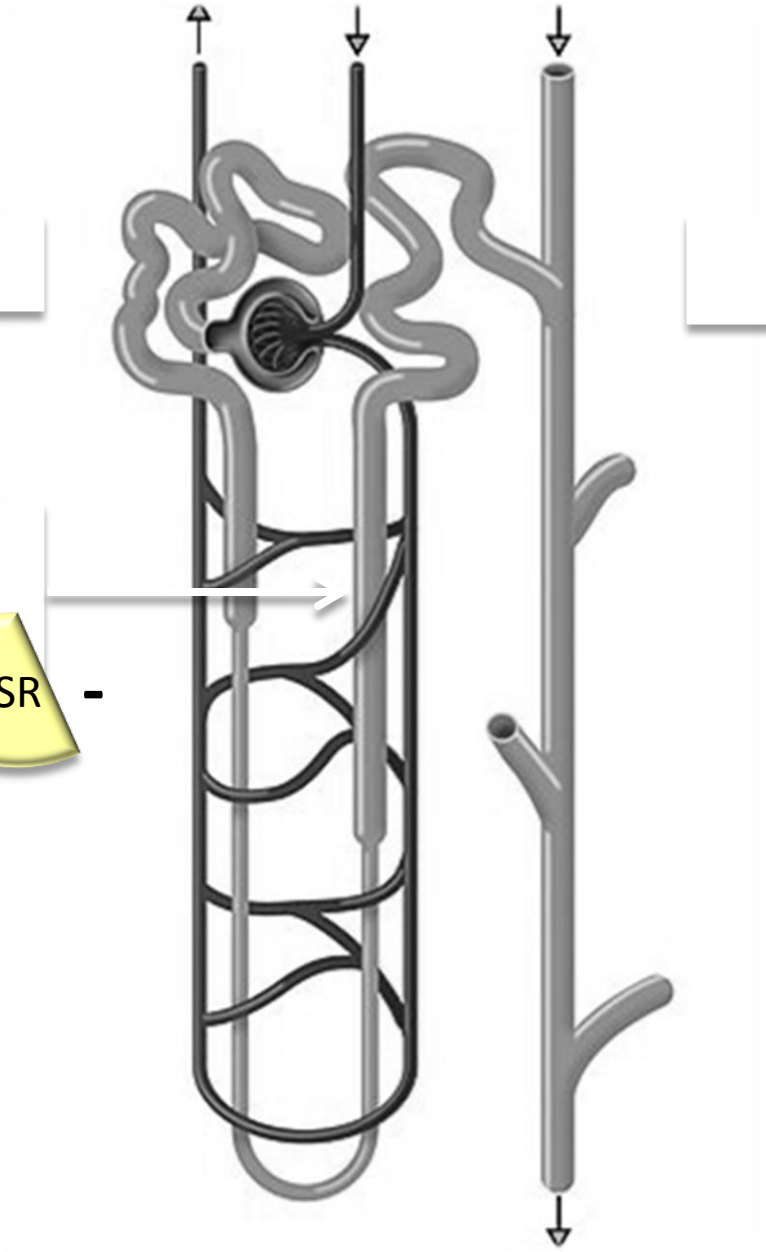
pasivně 60–70%

claudin 16/19

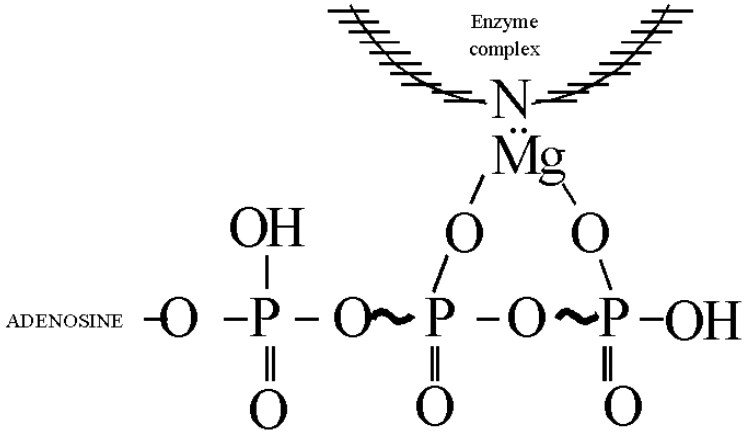
CaSR -

hydratace

furosemid



Mg-ATP komplex



uchování energie

enzymatické procesy

pohyb ostatních elektrolytů

imunitní procesy

hypomagnezémie

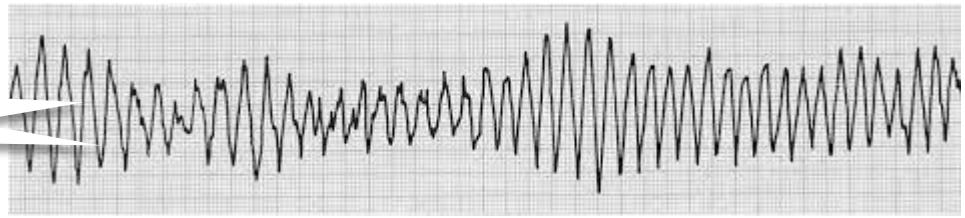
hypokalcémie

refrakterní hypokalémie

zpravidla < 0,5 mmol/l celkového plasm. Mg

neuromuskulární projevy

kardiovaskulární projevy

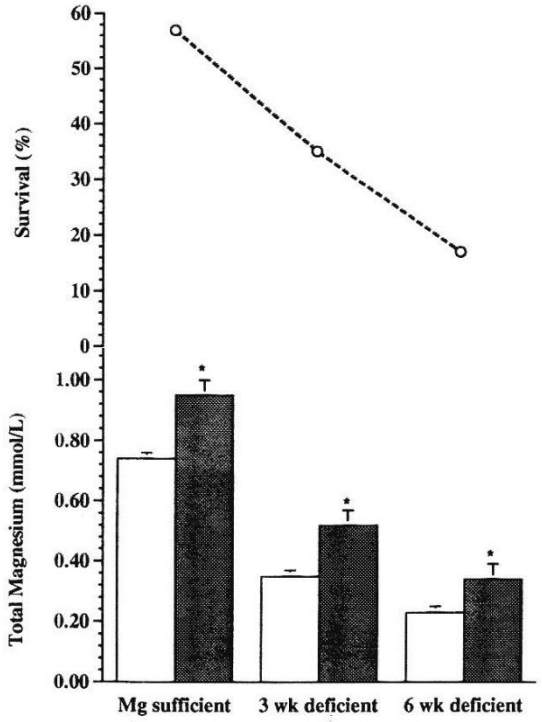


léčba u preeklampsie a eklampsie, fibrilace síní
arteriální hypertenze, inzulinorezistence, bronchodilatace, neuroprotekce?

imunomodulace v sepsi? intracelulární kalciový antagonista

Salem M1, Kasinski N, Munoz R, Chernow B. Crit Care Med. 1995

Progressive magnesium deficiency increases mortality from endotoxin challenge: protective effects of acute magnesium replacement therapy.



hypomagnezémie jako nezávislý faktor mortality u kriticky nemocných?

Rubeiz GJ, Guerin C, Soliman HM

Nephrol Dial Transplant (2013) 28: 910–916
doi: 10.1093/ndt/gfs268
Advance Access publication 4 July 2012

Hypomagnesemia as a risk factor for the non-recovery of the renal function in critically ill patients with acute kidney injury

Sarah Cascaes Alves[1],
Cristiane Damiani Tomasi[1],
Larissa Constantino[1],
Vinícius Giombelli[1],
Roberta Candal[1],
Maria de Lourdes Bristot[1],
Maria Fernanda Topanotti[1],
Emmanuel A. Burdmann[2],
Felipe Dal-Pizzol[1,3],
Cassiana Mazon Fraga[1,3]
and Cristiane Ritter[1,3]

Correspondence and offprint requests to: Cassiana Mazon Fraga; E-mail: cmzf@ig.com.br

[1]Laboratório de Fisiopatologia Experimental, Instituto Nacional de Ciência e Tecnologia Translacional em Medicina, Programa de Pós-Graduação em Ciências da Saúde, Unidade Acadêmica de Ciências da Saúde, Universidade do Extremo Sul Catarinense, Criciúma, SC, Brazil,
[2]Division of Nephrology, University of Sao Paulo Medical School, Sao Paulo, Brazil and
[3]Unidade de Terapia Intensiva, Hospital São José, Criciúma, SC, Brazil

Keywords: acute kidney injury, hypomagnesemia, ICU, recovery, RIFLE, magnesium

ABSTRACT

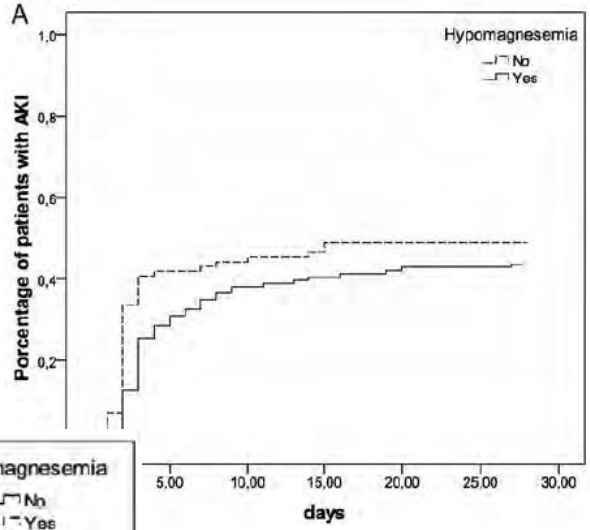
Background. The aim of this study was to evaluate the role of hypomagnesemia as a risk factor for the development of acute kidney injury (AKI) and non-recovery of renal function

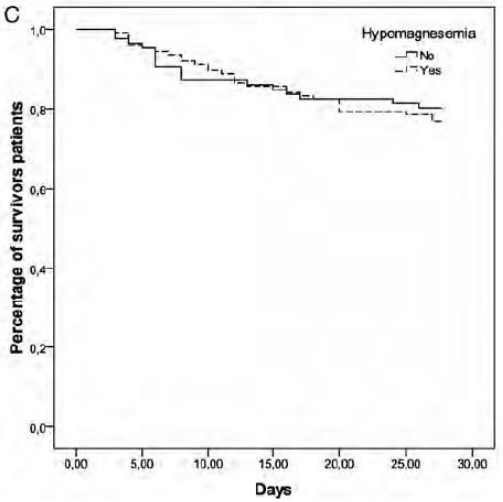
P = 0.003). A multivariate analysis identified hypomagnesemia as an independent risk factor for non-recovery of renal function (P = 0.005). Patients with and without hypomagnesemia had similar mortality rates (P = 0.63).

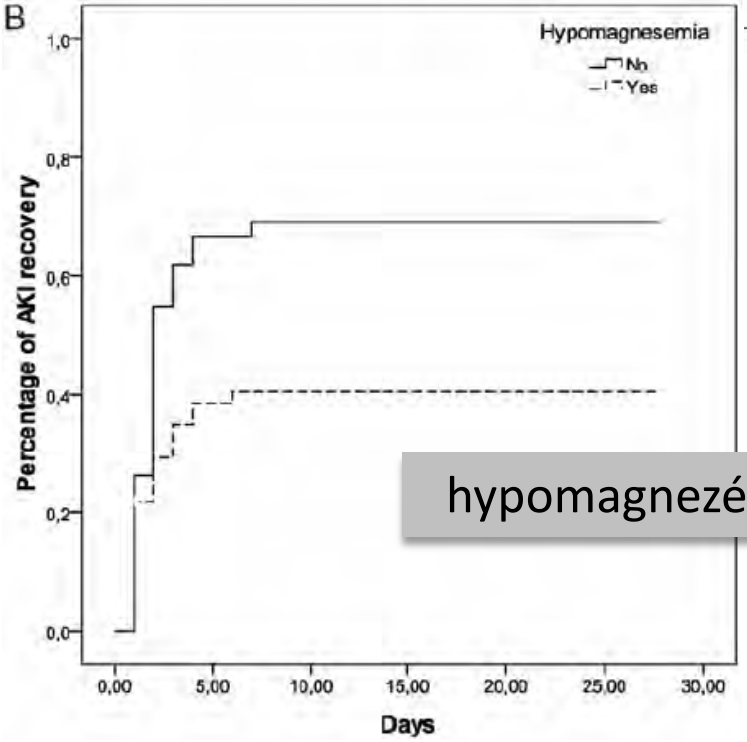
Conclusions. Hypomagnesemia was an independent risk factor for non-recovery of renal function in a cohort of criti-

232 pacientů, septických 14%

Mg < 0,7 mmol/l 63%







hypomagnezémie rizikový faktor nereparace reální funkce

4,8 (1,79-16,43)

sledováno také u pacientů s AIDS, po Tx ledviny

hypomagnezémie až u 50-60 % kriticky nemocných

FEMg > 2% <

ztráty ledvinami

- ✓ volumexpanze
- ✓ akutní tubulární dysfunkce
- ✓ kličkové diuretikum
- ✓ aminoglykosidy
- ✓ amphotericin B, aj.
- ✓ polyurie různé etiologie
- ✓ hyperkalcémie
- ✓ leptospiroza
- ✓ vrozené defekty

ztráty gastrointestinálním traktem

- ✓ zvracení
- ✓ gastrická derivace
- ✓ maladsorbce
- ✓ průjmy, IBD
- ✓ inhibitory protonové pumpy

jiné

- ✓ akutní pankreatitis
- ✓ popáleniny
- ✓ hypofosfatémie
- ✓ polytransfuze
- ✓ hungry bone syndrome

predisponovaní pacienti s diabetem mellitus, chronickým etylismem, malnutricí

hypermagnezémie

nepřiměřený příjem

zastavit příjem
hydratace
kličkové diuretikum
hemodialýza
100-200 mg element. kalcia

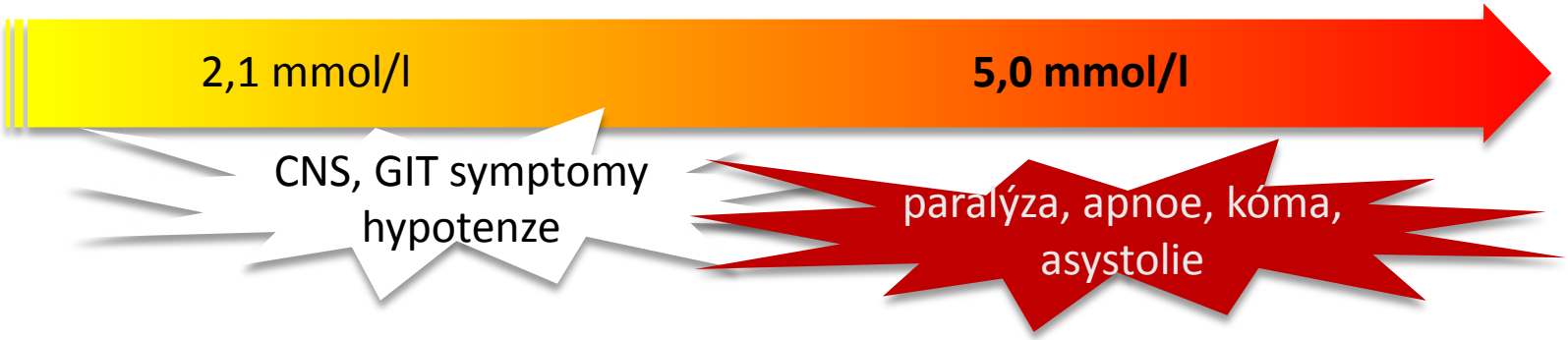
nízká renální eliminace

- ✓ konečné selhání ledvin
- ✓ intoxikace lithiem, theofylinem
- ✓ endokrinopatie

jiné

- ✓ tumor lysis syndrom
- ✓ hyperkatabolismus
- ✓ sepse

predisponovaní pacienti s postižením ledvin, zánětlivým postižením GIT



Ionizovaná kalcémie dobře odráží iontovou poruchu.

Neznáme klinickou relevanci hypokalcémie u kriticky nemocných.

Korekce asymptomatické mírné a střední hypokalcémie u kriticky nemocných je neopodstatněná, riziková a pravděpodobně škodlivá.

Magnezémie neodráží zcela skutečný obsah hořčíku v cílových tkáních.

Substituce hořčíkem může být bezpečná a prospěšná v řadě klinických situací, zejména u pacienta v riziku deficitu.

Substituce hořčíkem patří do léčby závažné hypokalémie a hypokalcémie. Často je nutné opakované podání či kontinuální infuze.