The Reference
in Prevention
for Animal Health

Disturbances of the Potassium and Phosphorus Metabolism in Periparturient Dairy Cows

Walter Grünberg

Similarities between Potassium and Phosphorus

- Predominantly intracellular electrolytes
- Balance strongly dependent on oral intake
- Important losses through the mammary gland
- Both associated with muscle function
- Disturbances of the electrolyte balance are common in periparturient dairy cows
- …

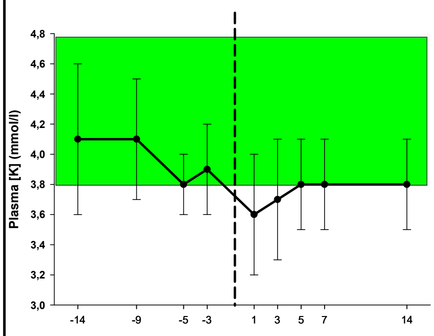
Dissimilarities

- **No storage form of potassium available in the body**
  – Large reserves of phosphorus in bone
- **Tight regulation of extracellular potassium concentration**
  – Plasma [Pi] not tightly regulated
- **Regulation of potassium homeostasis reasonably well understood**
  – Poor understanding of mechanisms regulating the P homeostasis
- **Symptoms of acute disturbances of the (extracellular) potassium homeostasis well defined**
  – Relevance of hypophosphatemia controversially debated

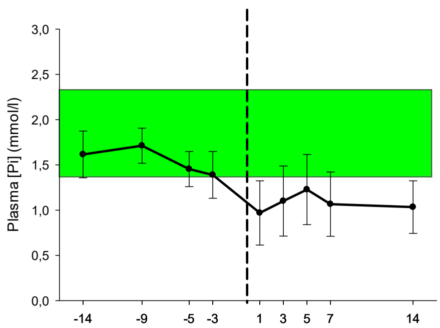
Potassium and Phosphate in Blood

Periparturient Period – Healthy Cow

Plasma Potassium



Plasma Phosphate



Grünberg et al. 2011

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Potassium and Phosphate in Blood

Periparturient Period – Sick Cow

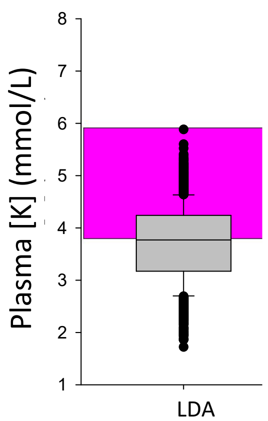
Left displaced abomasum

Plasma [Pi]	normal	57 %
	decreased	35 %
	increased	8 %
Plasma [K]	normal	45 %
	decreased	55 %
	increased	<1 %

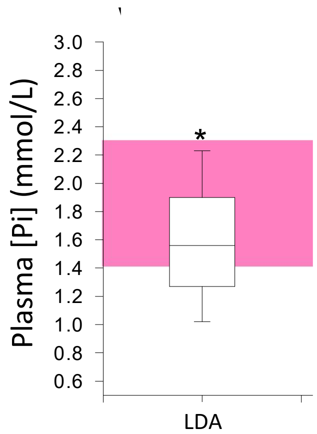
Grünberg et al. 2006 *Constable et al. 2013*

Potassium and Phosphate in Blood

Periparturient Period – Sick Cow



Constable et al. 2013



Grünberg et al. 2006

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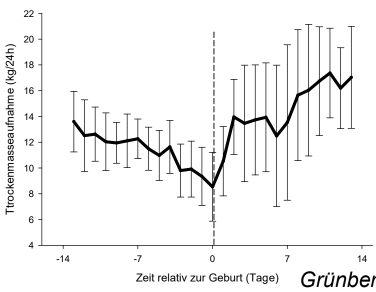
Relevance of a Disturbed Electrolyte Balance in Periparturient Cows

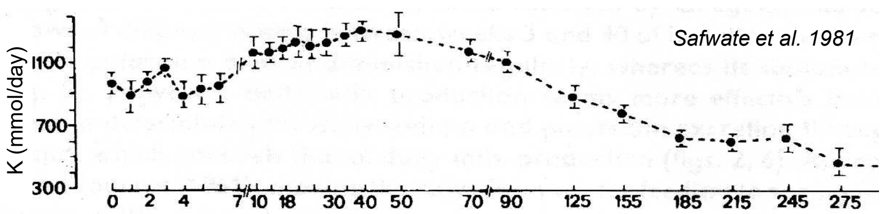
- **Hypokalemia**
  - **Membrane potential disturbances of excitable cells**
    - Altered function of striated and smooth muscles
    - Altered cardiac function
  - **Extracellular [K] sustained at expense of intracellular K?**
- **Hypophosphatemia**
  - **Relevance uncertain**
  - **Intracellular P balance is presumably more relevant**
    - Intracellular P sustained at expense of extracellular P?

Potassium Homeorrhesis in Early Lactation



Grünberg et al. 2011

- Feed intake at it's nadir around parturition
- Sudden onset of K losses through milk after parturition



Regulation of the Extracellular Potassium Balance

- **Counterregulation to hyperkalemia**
  - Compartmental shift of K into the cell
  - Renal excretion
  - Intestinal excretion

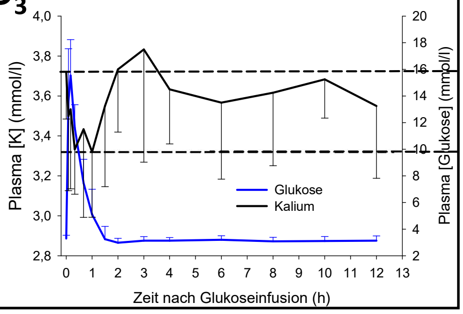
- **Counterregulation to hypokalemia**
  - Shift of K from intracellular to extracellular space
    - Less efficient with less muscle mass
  - Renal retention of K
    - Requires water and Na excretion
  - Reduced [K] in milk

Hypokalemia in Sick Cows

- **Etiology not entirely understood**
  - Decreased feed intake
  - Delayed gastrointestinal transit time
  - Alkalosis
  - Dehydration (Aldosterone)?
  - Iatrogenic (glucose, rehydration, glucocorticoids…)
  - …

Iatrogenic Exacerbation of Hypokalemia

- **Parenteral Dextrose Infusion**
- **Parenteral Hypertonic NaCl**
  - Expect decline > 0.8 mmol/L with standard treatment
- **Administration of $NaHCO_3$**
- **Large volumes of fluid**
- **Corticoids**
- **....**



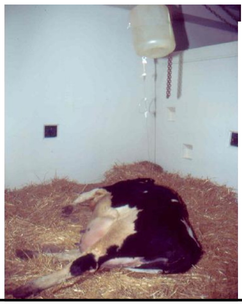
Clinical Implications of Hypokalemia

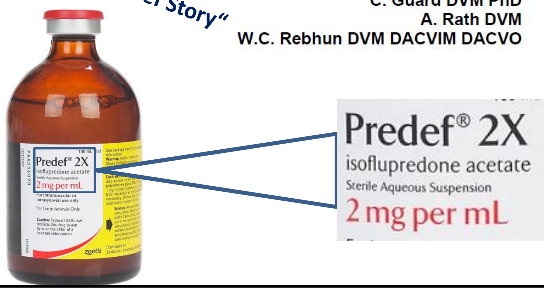
Preconvention Seminar 7: Dairy Herd Problem Investigation Strategies
AMERICAN ASSOCIATION OF BOVINE PRACTITIONERS
36th Annual Conference, September 15-17, 2003 - Columbus, OH

Hypokalemia, Muscle Weakness and Recumbency in Dairy Cattle (17 Cases 1991-1998)

S. F. Peek BVSc. PhD, DACVIM
T.J. Divers DVM DACVIM DACVECC
C. Guard DVM PhD
A. Rath DVM
W.C. Rebhun DVM DACVIM DACVO

"The Predef Story"



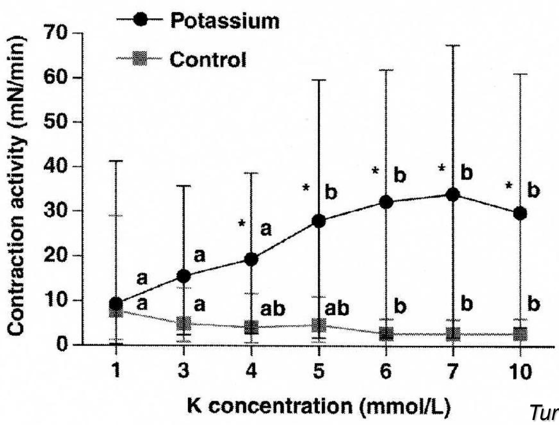


Hypokalemic Recumbency

- **Clinical presentation differs from milk fever**
- **Resembling botulism**
  - Decreased tone of tongue- and head / neck muscles
  - “Rubber neck” / head on the ground
- **Pronounced hypokalemia**
  - ➔ [K] < 2.0 mmol/L
- **Frequently associated with cardiac arrhythmia**
  - Atrial fibrillation

Subclinical Implications of Hypokalemia

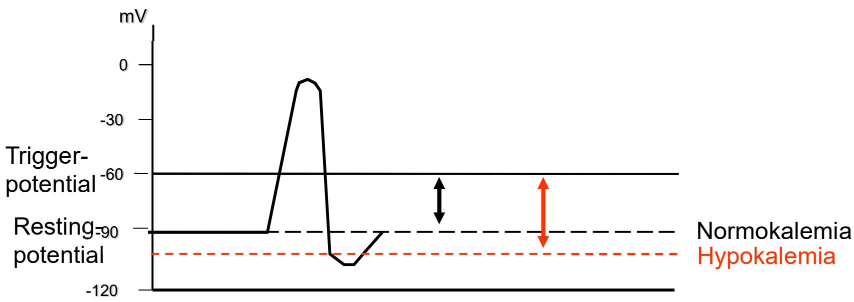
Hypokalemia and Abomasal Motility



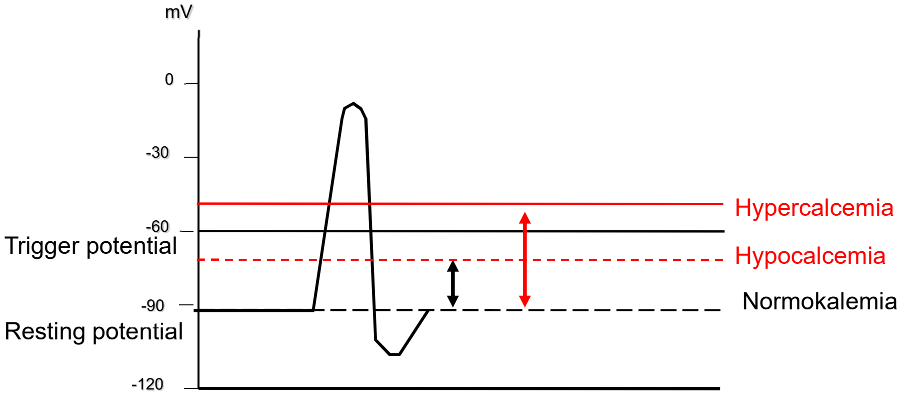
Turck & Leonhard-Marek 2010

Potential Clinical Implications of Hypokalemia

Decreased Resting-Membrane Potential of Excitable Cells

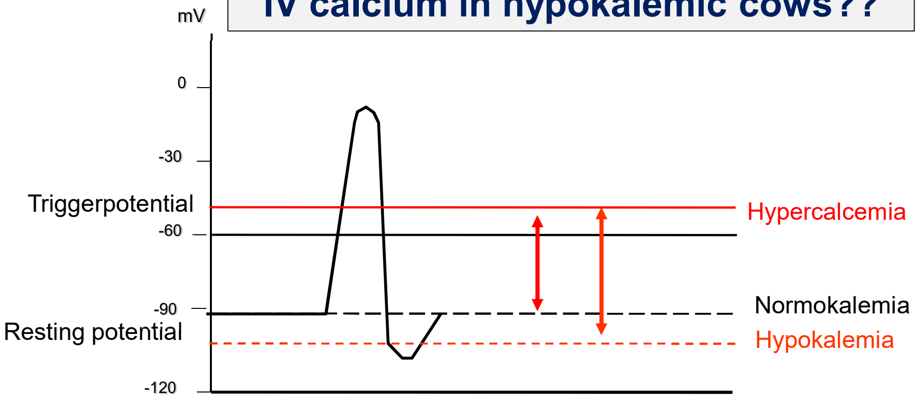


Potassium as Ca-Antagonist with Hypercalcemia

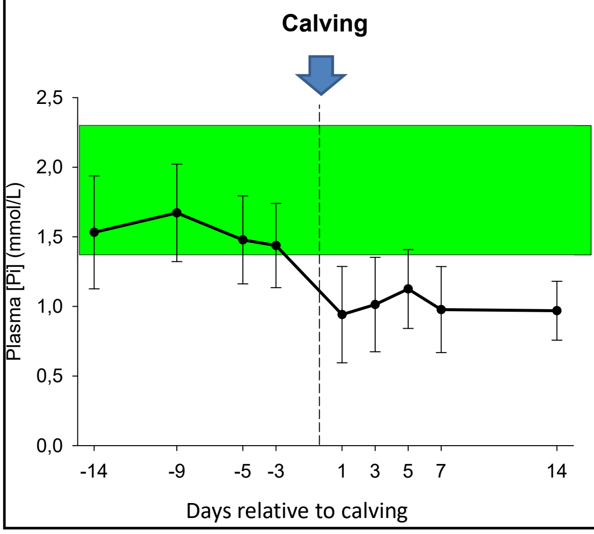


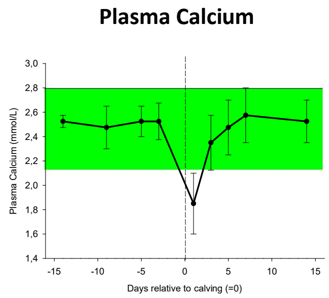
Potassium as Ca-Antagonist with Hypercalcemia

Increased risk of complications after IV calcium in hypokalemic cows??



Plasma Phosphate (Pi) in Healthy Periparturient Dairy Cows



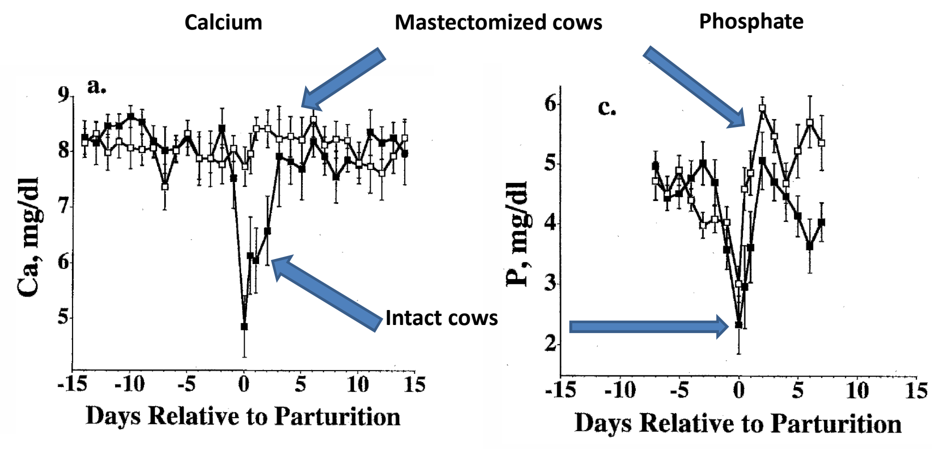


Grünberg et al. 2011

Mechanisms Presumed behind Periparturient Hypophosphatemia

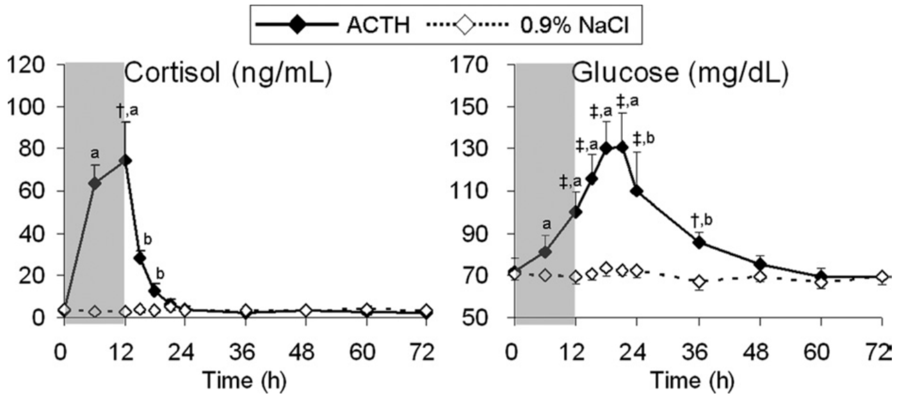
- **Loss of P through udder**
- **Decreased feed intake**
- **Decreased GI motility**
- **Hormonal adaptation**
  - PTH
  - Cortisol
- **Lag time of counter regulation**
- **…**

Plasma Calcium and Phosphate at the Onset of Lactation



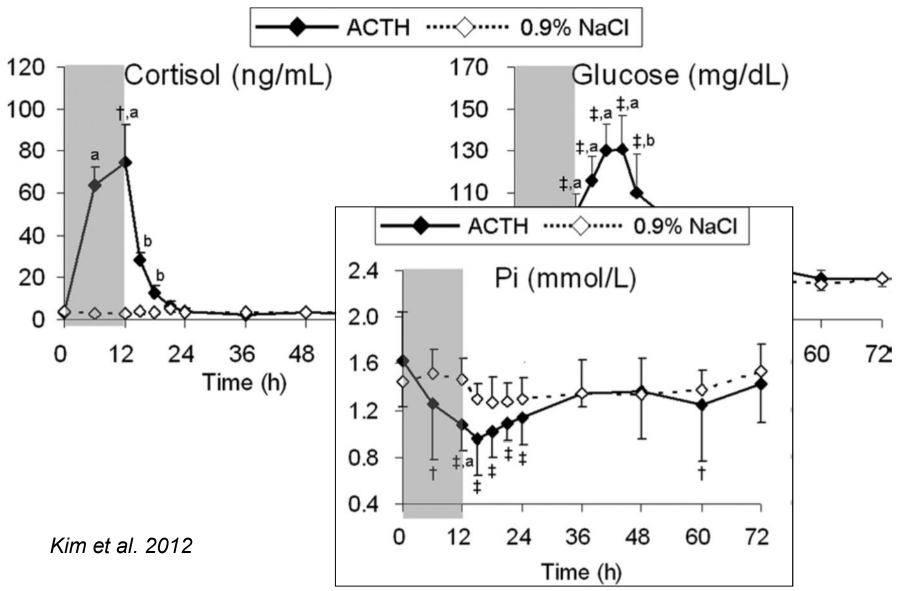
Goff et al. 2002

Plasma Phosphate and Cortisol



Kim et al. 2012

Plasma Phosphate and Cortisol



Kim et al. 2012

Incidence of Periparturient Hypophosphatemia

Metabolic Profiling of Clinically Healthy Dairy Cows

- **54% on the day of calving** *Staufenbiel 2002*
- **Over 15% in the first 10 days of lactation**
- **10% between 10 and 20 days of lactation**

Macrae et al. 2006
Macrae et al. 2012

Incidence of Periparturient Hypophosphatemia

Metabolic Profiling of
Healthy Dairy Cows

Hypophosphatemia, so what?!?

- **54% on th**
- **Over 15% in the first**
- **10% between 10 and 20 days o**

002

Macrae et al. 2006
Macrae et al. 2012

Incidence of Hypophosphatemia in Recumbent Periparturient Dairy Cows

Electrolyte status		Study			
Ca	P	Bostedt et al. 1973	Bostedt et al. 1979	Stolla 2000	Metzner and Klee 2005
[Ca] ↓	[Pi] ↓	60,2%	67,5%	64,4%	62,4
[Ca] ↓	[Pi] →	10,8%	12,1%	1,0%	4,1%
[Ca] →	[Pi] ↓	18,2%	13,7%	28,7%	18,4%
[Ca] →	[Pi] →	10,8%	6,7%	5,9%	15,1%

Incidence of Hypophosphatemia in Recumbent Periparturient Dairy Cows

Electrolyt status		Study			
Ca	P	Bostedt e…	[illegible]	Stolla 2000	Metzner and Klee 2005
[Ca] ↓	[Pi] ↓	60,2%	[illegible]	[illegible]	62,4
[Ca] ↓	[Pi] →	10,8%	12,1%	[illegible]	[illegible]
[Ca] →	[Pi] ↓	18,2%	13,7%	28,7%	[illegible]
[Ca] →	[Pi] →	10,8%	6,7%	5,9%	15,1…

> 80% of recumbent periparturient cows are hypophosphatemic…

Hypophosphatemia and Periparturient Recumbency

Table 1

Median values of the variables [age, calcium (Ca), phosphorus (P), magnesium (Mg), potassium (K)] compared between the positive response (PR) and negative response (NR-ADC) groups in the study

Variables	Age (years)		Ca (mmol/L)		P (mmol/L)		Mg (mmol/L)		K (mmol/L)	
Response	PR	ADC	PR	ADC	PR	ADC	PR	ADC	PR	ADC
Median	8.0	8.1	1.41	1.40	.85[a]	.50[a]	1.11	1.03	4.20	4.14
Cows (*n*)	50	36	50	36	50	36	50	36	50	36
P-value	0.387		0.378		**0.019**		0.260		0.326	

[a] Median values with superscripts are significantly different at the 0.05 level (Wilcoxon Rank-Sum Test)

PR= Positive responders
ADC= Alert Downer Cows

Ménard and Thompson 2007

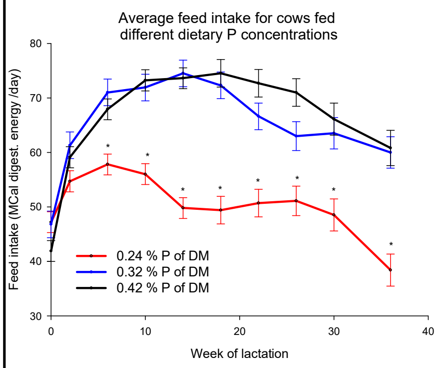
What Happens if Dairy Cows are <u>Transiently</u> P-Deprived?

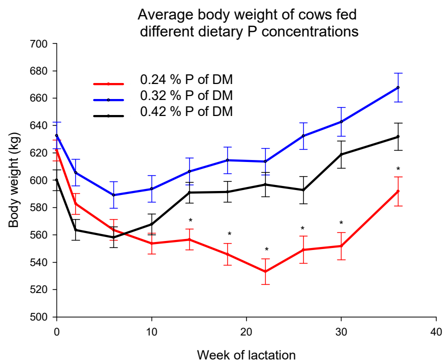
Some experimental results of the past years….

What Happens if Dairy Cows are Transiently P-Deprived?

Make the difference between transient (acute) and chronic phosphate deficiency

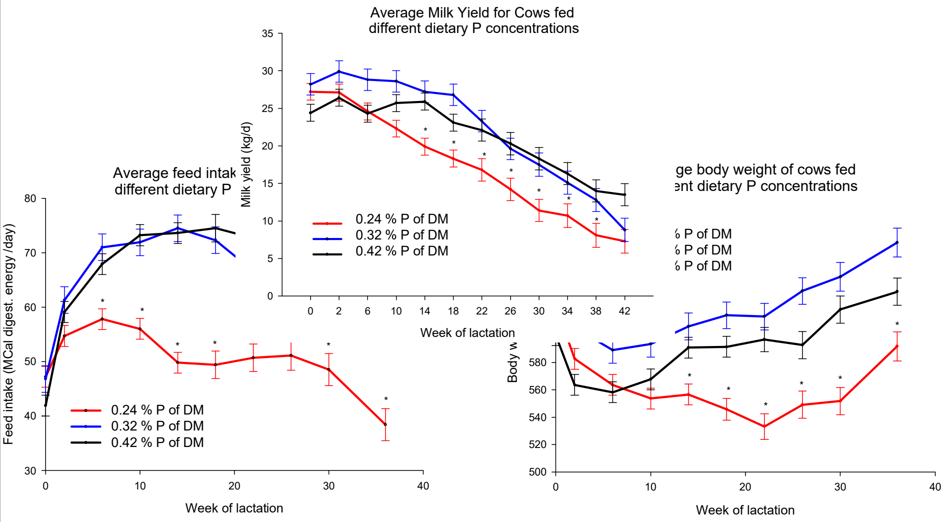
Chronic Dietary P-Deprivation





Call et al. 1987

Chronic Dietary P-Deprivation



Call et al. 1987

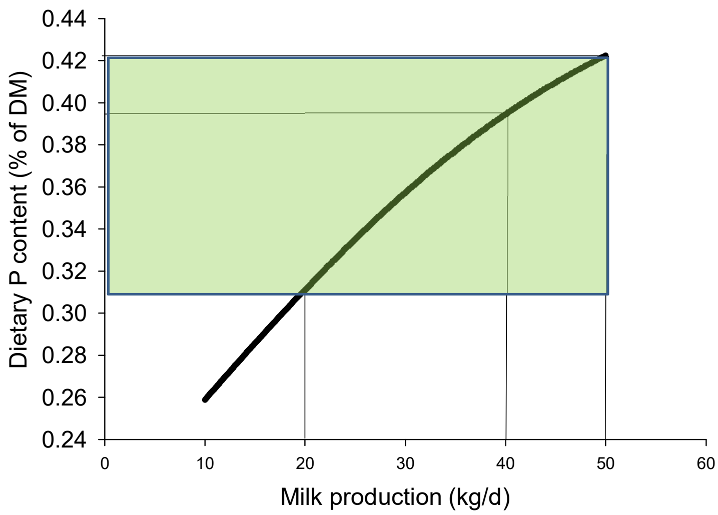
Recommendation Standards for Dietary P in the Industrialized World

Lactation

		UK		D		USA		NL	
Milk (kg/d)	DMI (kg/d)	g P/d	% DM	g P/d	% DM	g P/d	% DM	g P/d	% DM
15	17	56	0,33	46	0,27	51	0,30	40	0,24
25	20,3	77	0,38	65	0,32	65	0,32	55	0,27
35	23,6	99	0,42	84	0,36	83	0,35	69	0,29
45	26,9	121	0,45	103	0,38	96	0,36	83	0,31
55	30	142	0,47	121	0,40	114	0,38	97	0,32

modified from Pfeffer et al. 2005

Phosphorus-Recommendation Standards for Dairy Cattle



* P-Digestibility = 70 %

Concerns with Transient P-Deficiency in Periparturient Cows

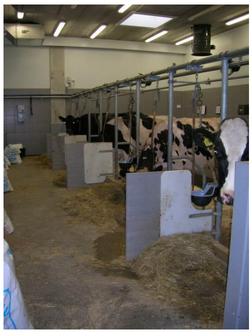
- **Postparturient Hemoglobinuria**
- **Downer Cow Syndrome**
- **Disturbed liver function**

The Reference in Prevention for Animal Health

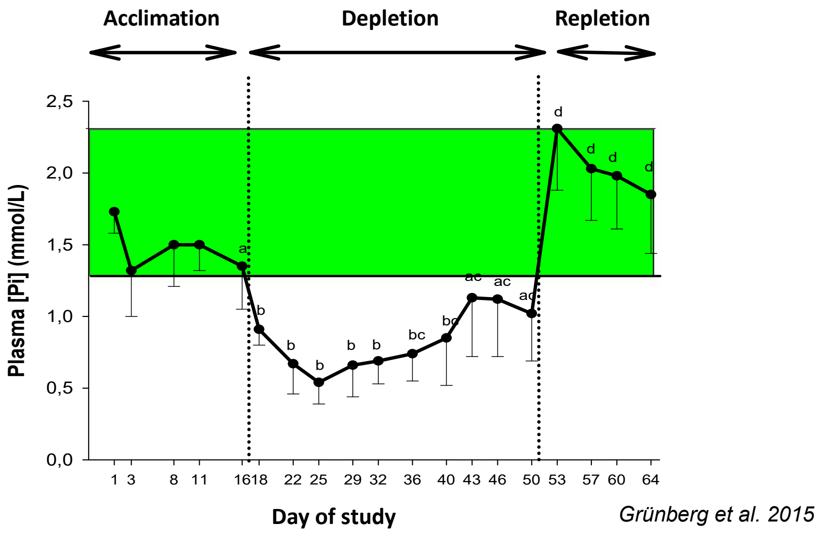
Dietary P-Depletion of non-periparturient Dairy Cows

Pilot-Study on 10 past-peak Dairy Cows

- Fed a P-deficient diet for 5 weeks
  - Ration with 0.18 % P in DM
- Then supplemented with P for 2 weeks
  - Ration with 0.47 % P/in DM



Dietary P-Depletion of non-periparturient Dairy Cows



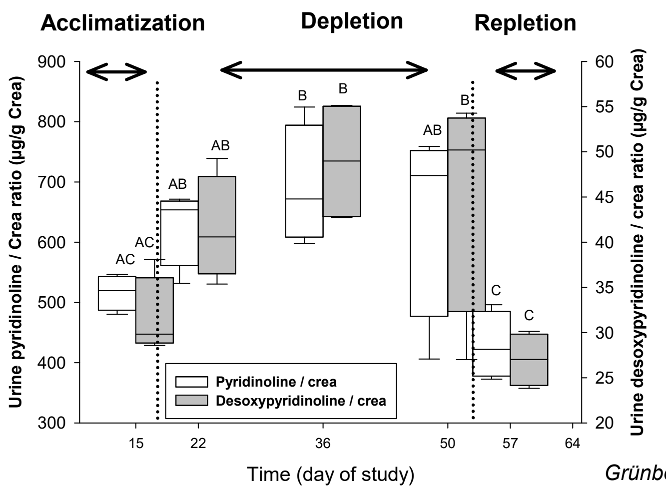
Grünberg et al. 2015

Clinical Signs

- **No altered demeanor**
- **No clinical disease**
- **No noticeable drop in feed intake or milk production**
  - DMI: 20.4 ± 2.5 kg DM/day
  - Milk: 23.6 ± 3.7 kg Milk/day
- **No signs of muscle weakness**
- **No signs of anemia or hemolysis**

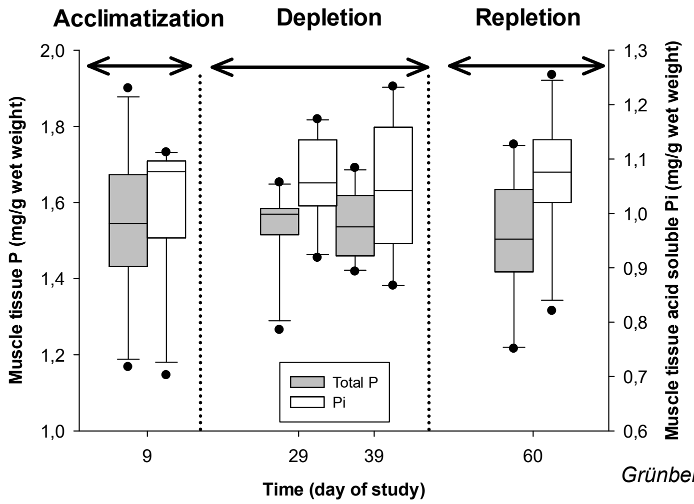
Counterregulatory Mechanisms

Bone Mobilization



Grünberg et al. 2015

Phosphorus in Muscle Tissue



Grünberg et al. 2015

Electromyography

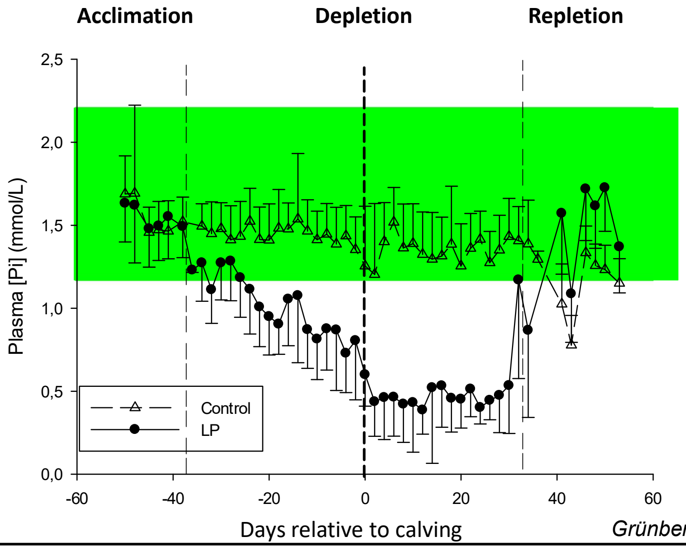
- **No apparent signs of muscle weakness**
- **EMG-results did not suggest energy deficiency**
  (ATP or creatine phosphate-depletion)
- **Increased occurrence of pathologic spontaneous activity (PSA) in muscle fibers**
  – Suggestive membrane instability or neuromyopathy

Grünberg et al. 2015

Dietary P-Deprivation in Transition Dairy Cows

- **Two groups**
  - **Group C**
  - **Group LP (low-phosphate)**
- **Study period from 6 weeks ante- to 6 weeks post-partum**
  - P-deficient diet for LP cows from 4 weeks a.p. to 4 weeks p.p.
    - 0.15 % P in DM antepartum
    - 0.20 % P in DM postpartum

Dietary P-Deprivation in Transition Dairy Cows



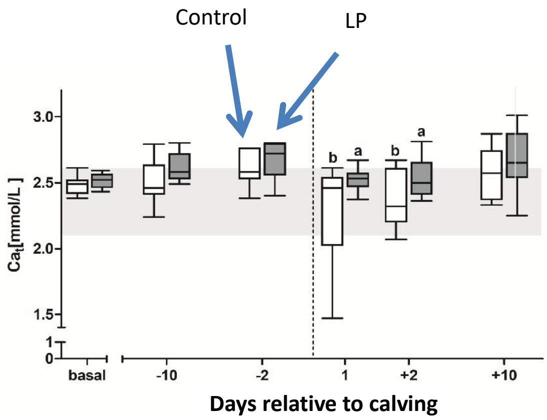
Grünberg et al. 2018

Clinical Findings

- **No abnormal demeanor until parturition**
  - No disease occurrence
  - No feed intake depression
  - No signs of muscle weakness

- **Periparturient period**
  - **Control:** 4 /18 Cows with clinical hypocalcemia (stage I and II)
  - **Group LP**: Uneventful parturition, no clinical hypocalcemia, no recumbencies

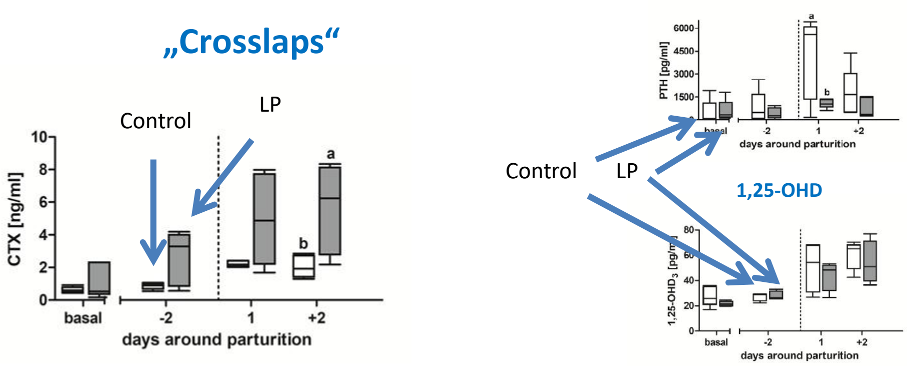
Periparturient Calcium Balance in P-deprived Dairy Cows



Cohrs et al. 2018

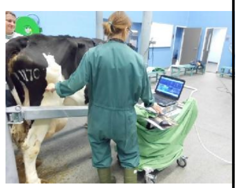
Mechanisms of periparturient Ca-Mobilisation

Bone Mobilization Despite of Blunted Increases in PTH



Muscle Tissue Composition and Function

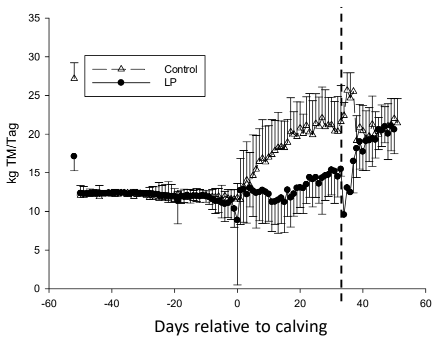
- No clinical signs of muscle function disturbance
- P-deprivation does not alter muscle tissue P, Pi, ATP, ADP, AMP or creatine phosphate content



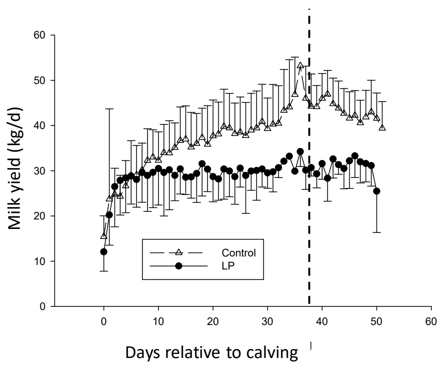
- No biochemical indication of muscle cell damage
- Increased occurrence of pathological spontaneous activity (PSA) in muscle fibers

Feed Intake and Milk Production

Feed Intake

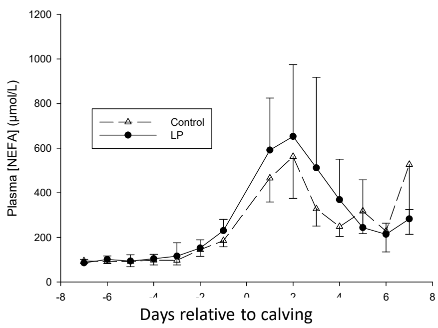


Milk Production

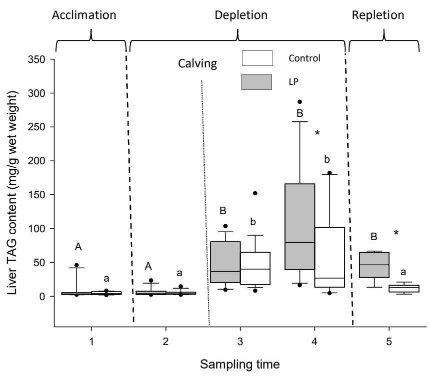


Negative Energy Balance

Plasma [NEFA]

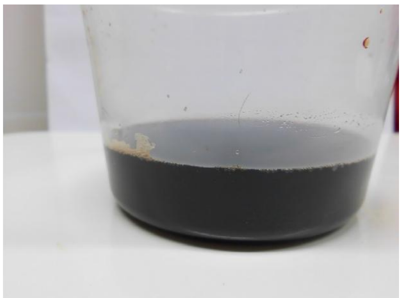


Liver Triacylgylcerol (TAG)



Postparturient Hemoglobinuria

- 5/18 P depleted cows
- Always in 2. week of lactation
- Duration 3 – 5 days



Postparturient Hemoglobinuria

Preliminary Conclusions

- **Hemolysis occurred in narrow time window relative to calving**
- **Predisposition?**
  - P-Deprivation seems to play a role
  - Other factors?
- **Destruction of specific erythrocytes?**
  - Cannot be controlled
  - After lysis of specific erythrocytes, normal regenerative activity even during sustained P-deprivation

Disturbances of the Potassium and Phosphorus Metabolism in Periparturient Dairy Cows

Synopsis

Synopsis

- **Homeostasis of phosphorus and potassium are both challenged in periparturient cows**
  - Even more so in cows with feed intake depression
- **Homeostatic disturbances may well be consequence rather than cause of a primary problem**
- **Clinical and subclinical effect of balance disorders for these electrolytes are poorly defined**

Synopsis

- For both electrolytes increasing the supply in late gestation to prevent deficiencies in early lactation IS NOT an option
- Supplying these minerals (case by base basis) in cows off feed should be considered as supportive care treatment

Treatment Options

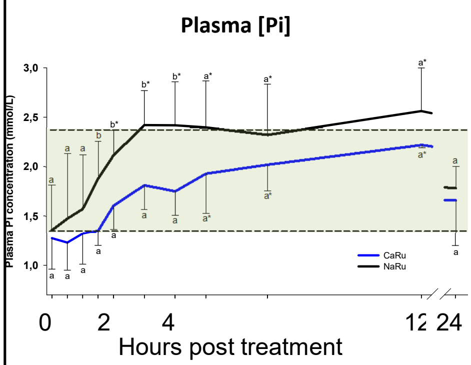
- For both minerals parenteral treatment is unsuitable for the field situation
  - Phosphorus
    - No products containing PO_4 commercially available
    - Bolus IV-infusion of PO_4-solutions short lived effect (and off label)
  - Potassium
    - Bolus IV-infusion not an option
    - Drip infusion requires constant monitoring of plasma [K]
- Oral supplementation of both minerals is
  - safe
  - effective
  - (relatively) inexpensive

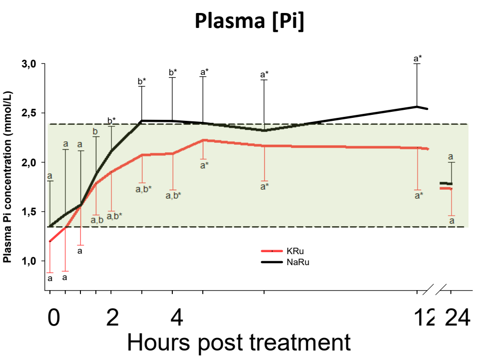
Solubility of Various Phosphate Salts

Phosphate salt		Solubility in g/100 g H_20 at 25 °C
NaH_2PO_4	Monosodium phosphate	94.9
Na_2HPO_4	Disodium phosphate	11.8
$CaHPO_4$	Dicalcium phosphate	0.043
$Ca(H_2PO_4)_2$	Monocalcium phosphate	1.8
KH_2PO_4	Monopotassium phosphate	25.0
K_2HPO_4	Dipotassium phosphate	149.0
$MgHPO_4$	Magnesium phosphate	0,025

Oral Treatment of Hypophosphatemia

NaH_2PO_4 — $Ca(H_2PO_4)_2$ — $KHPO_4$





Idink and Grünberg 2014

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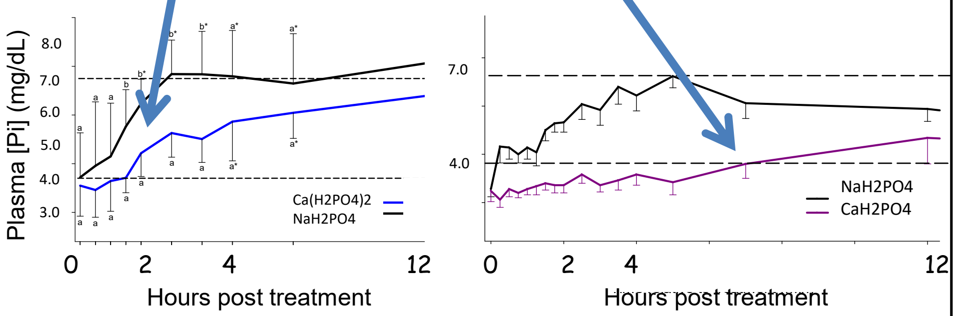
Oral Treatment of Hypophosphatemia

Monocalciumphosphate ($Ca(H_2PO_4)_2$)

vs. Dicalciumphosphate (CaH_2PO_4)

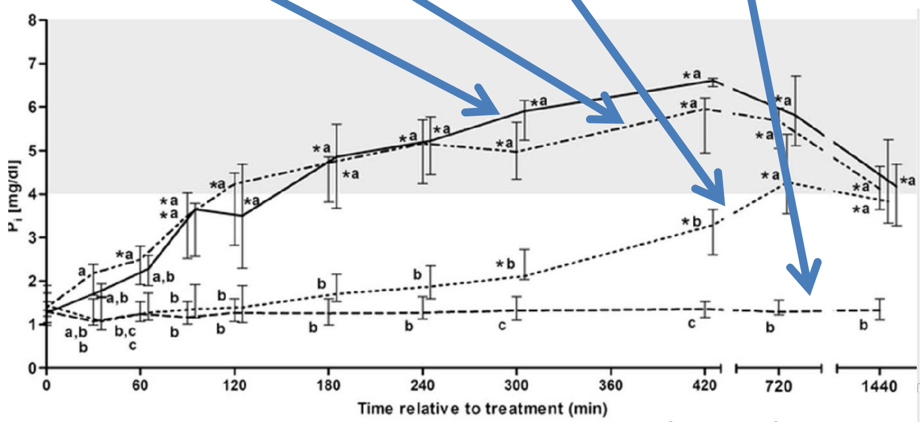


Idink and Grünberg 2014

Grünberg et al. 2013

Oral Treatment of Hypophosphatemia

NaH_2PO_4, Na_2HPO_4, $MgHPO_4$, and Control



Cohrs and Grünberg 2018

Oral Treatment of Hypophosphatemia

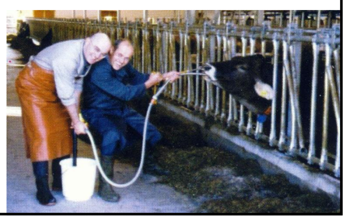
Treatment recommendation: 50-60 g P orally every 12-24h in the form of:

- **NaH_2PO_4 → 250-300 g (First choice)**
- **Na_2HPO_4 → 280-340 g**
- KH_2PO_4 → 200-250 g (with concomitant hypokalemia)
- $Ca(H_2PO_4)_2$ →200-240 g (less effective, but may provide Ca)
- $CaHPO_4$ → 300-330 g (unsuitable for rapid correction of hypophosphatemia)
- $MgHPO_4$ → 300-330 g (unsuitable for rapid correction of hypophosphatemia)

Oral Administration of Potassium

KCl as Bolus- or Drench

- **Rapid onset (ruminal absorption)**
- **Safe to dose**
- **Duration of effect? Treatment interval?**
- **Avoid massive over dosage**
  - Hyperkalemia
  - Osmotic diarrhea
  - Mucosal irritation?



Oral KCl

Recommended Dosage

- Recommendations are mostly empirical!
- **Mild / moderate Hypokalemia: 60-90 g/600 kg/ KCl**
- Moderate / severe hypokalemia: 90-150 g KCl / 600 kg
- **Avoid single doses > 250 g KCl / 600 kg**
- **Treatment interval: 8-12h?**

Oral KCl

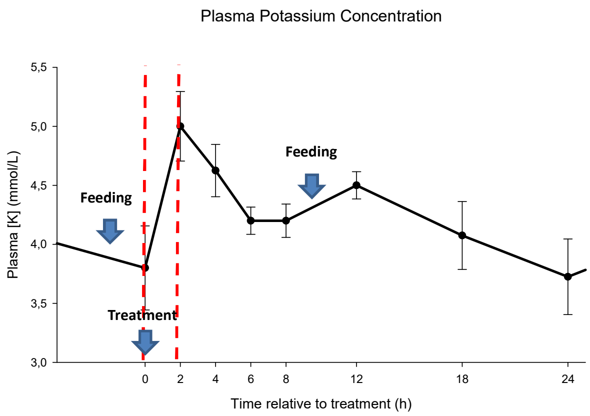
Pay Attention to Difference between K and KCl

- Approx. 50% of the mass of KCl is K!

  ➔ x g KCl ≈ x/2 g K
- Content of K on the label often given as amount K (NOT as KCl)
- To treat even mild hypokalemia a drench powder needs to contain at least 30 g K (or 60 g KCl) / dose

Oral Treatment with KCl

200 g of KCl as Drench



Grünberg unpublished

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Recommendation Standards for Dietary P

Dry Cow

- **2.5 - 3.0 g/kg** (0.25-0.30%) **DM (US)**
- **2.5 - 2.8 g/kg** (0.25-0.28%) **DM (D)**
- **2.0 - 2.5 g/kg** (0.20-0.25%)**DM (NL)**
- **Ca:P ratio considered obsolete in bovine**
- **Avoid excess of P (> 4.2 g/kg DM in close-up)**

P below 2.0 g kg/DM is probably deficient in the dry-cow ration

Dietary P-Deprivation in Transition Dairy Cows

Dietary P-content

- **Acclimation (dry cow)**
  - 2,8 g P/kg DM both groups
- **Dry cow-period (4-5 weeks)**
  - Group LP: 1,5g P/kg DM
  - Group C: 2,8g P/kg DM
- **Early lactation (4-5 weeks)**
  - Group LP: 2,0g P/kg DM
  - Group C: 4,2g P/kg DM
- **Repletion (2 weeks)**
  - 4,2g P/kg DM both groups