Charles University in Prague
1st Faculty of Medicine

Biochemical diagnosis and monitoring of disorders of renal functions in critically ill patients

Ph.D. Thesis Summary

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Contents

List of abbreviations used in the text: SNa^+ (serum sodium), SK^+ (serum potassium), SOsm (serum osmolality), UNa^+ (urine sodium), UK^+ (urine potassium), $dU\text{-}Na^+$ (daily urine output of sodium), $dU\text{-}K^+$ (daily urine output of potassium), UU (concentration of urea in urine), dU-U (daily urine output of urea), UOsm (urine osmolality), UCr (urine creatinine), Ccr (clearance of creatinine), FE_H_2O (excretion fraction of free water), FE_Na^+ (excretion fraction of sodium), FE_K^+ (excretion fraction of potassium), UU/SU (concentration index of urea), C_Osm (clearance of osmotically active substances), C_H_2O (clearance of solute free water), C_El (electrolyte clearance), EWC (clearance of electrolyte free water), FE_Osm (excretion fraction of osmotically active substances), Vu (volume of urine), SAG (serum anion gap), UAG (urine anion gap), UOG (urine osmolal gap), CRRT (continuous renal replacement therapy), ECW (extracellular water), TBW (total body water)

Introduction

Alterations of renal functions affect approximately 3-25% of intensive care patients depending on the type of the unit, character of care provided and also on the diagnostic criteria used. Significantly increases morbidity as well as the short and long term mortality (1,2,3).

Few diagnostic entities has so developed and defined application as renal replacement therapy (RRT) however, precise definition of the failure of the organ which should be replaced by the technique is missing. The trend in research of the elimination techniques is towards monitoring of the homeostatic effects, inflammatory modulation, haemodynamic stabilization and ventilation improvement. No consensus exists in definition of renal and non-renal indication for renal replacement therapy (4,5). The influence of various modes of RRT on residual renal functions with possible influence on morbidity has not been explored yet. The problem of renal failure definition has been documented by the review of 28 studies on postoperative renal failure (6) where different diagnostic criteria are used in each study.

In an attempt to define precisely renal failure with the need for renal replacement therapy the definition proposed only on levels of catabolites and diuresis (5,6,7) should be completed with the broader spectrum of renal function tests. Neglecting better definition of renal failure may make assembling homogeneous study cohorts impossible. The absence of better definition of various types and levels of severity of renal dysfunction may also lower the impact of such studies (8). The detailed analysis of the broad spectrum of renal function tests would allow us not only to diagnose disorders of renal function but also disorders of ion and water homeostasis (9). The examination requires a quantitative urine collection together with the measurements of urine electrolytes, creatinine, urea and osmolality. Full utilisation of the biochemical parameters encompasses also a thorough analysis of homeostasis with the aid of calculated functional parameters (Tab.1).

A promising approach to renal function assessment is the measurement of low molecular weight proteins and middle molecules. Cystatin C is a newly proven marker of glomerular filtration. The impact of systemic inflammation on its levels in critically ill patients has not been fully excluded and its value in patients on renal replacement therapy has not been a matter of research yet (10,11,12,13). Besides ventricular filling pressures and atrial volumes the levels of natriuretic proteins are also significantly influenced by renal functions. The impact of renal failure and its severity has not been explored yet (14,15,16,17). The clinical benefit of renal replacement therapy depends also on the quality of extracorporeal circuit anticoagulation which should provide a functioning filter without the risk of bleeding for patient. Patients at risk for bleeding create almost 85% of all patients with the need of renal replacement in general intensive care setting. Some of the options available are regional circuit decalcification using 2.2% citrate solution or application of prostacyclin (18,19,20). The disoders of water and ion homeostasis go hand in hand with renal disoders. Systemic inflammation and loss of capillary wall integrity potentiates a cummulation of extracellular water (ECW) and increase of volume of distribution of drugs (21,22,23). The bedside estimate of increase of ECW by bioimpedance in patients with wide range of renal functions may have an impact on dosage of drugs distributed exclusively in ECW like antibiotics.

Tab.1: Normal levels of selected biochemical parameters in intensive care

Ccr	1.1-2.2 ml/s depending on age and gender
tub.resorbtion	97.5-99 %
FE_H_2O	1-2.5 %
FE_Na^+	1-2 %
FE_K^+	5-25 %
UU/SU	10-20
C_Osm	< 0.050 ml/s, i.e. < 4320 ml/24h
C_H_2O	-0.007 ml/s- - 0.027 ml/s , i.e. -610 ml/24h- - 2.330 ml/24h
C_El	0.5-3.0 l/24h
EWC	-1.1- +0.9 l/24h in normal osmolality
FE_Osm	< 3.5 %
Vu	2-4 l/24h
UNa$^+$	80-200 mmol/l
dU-Na$^+$	160-300 mmol
UK$^+$	30-80 mmol/l
dU-K$^+$	60-180 mmol
UU	120-300 mmol/l
dU-U	250-550 mmol
UCr	2.2 – 7.5 mmol/l
UOsm	400 - 900 mosm/kg
SAG	10 - 18 mmol/l
UAG	< +5 mmol/l
UOG	>150 mmol/l

Methods and Results

1. The first part deals in complex with the possible ways of application of renal function tests in the diagnosis of renal and homeostatic disorders in critically ill patients. The work was facilitated by the original computer programme „Kidney" designed and assembled in Visual Basic. The scheme of the programme with inputs and outputs is shown in Fig.1.

Inputs

SNa$^+$ (mmol/l)
SK$^+$ (mmol/l)
SCl$^-$ (mmol/l)
SU (mmol/l)
SCr (umol/l)
SOsm (mosm/kg)
Vu (ml/h*x)
UNa$^+$ (mmol/l)
UK$^+$ (mmol/l)
UCl$^-$ (mmol/l)
UU (mmol/l)
UCr (mmol/l)
UOsm (mosm/kg)
Fluid input (ml/h*x)
Fluid output (ml/h*x)
aHCO_3^- (mmol/l)
albumin (g/l)

Outputs

Balance of fluids (ml/h*x)
Ccr (ml/s)
t. resorbtion (%)
FE_H_2O (%)
FE_Na^+ (%)
dU-Na$^+$ (mmol)
FE_K$^+$ (%)
dU-K$^+$ (mmol)
UU/SU
dU-U (mmol)
C_El (l/h*x)
EWC (l/h*x)
C_Osm (ml/s)
C_Osm (l/h*x)
C_H_2O (ml/s)
C_H_2O (l/h*x)
FE_Osm (%)
AG (mmol/l)
UAG (mmol/l)
UOG (mosm/l)

Fig.1: Original computer programme „Kidney", v.1.2, 1998. „x" represents the input of the period of urine collection in hours.

1.1. Glomerular filtration

Deterioration of renal functions often develops parallely with insignificant increase of serum creatinine (SCr) and urea (SU). This confirms well known limits of assessment of renal function using SCr a SU. The easiest way of glomerular filtration estimate is using the clearance of endogenous creatinine (Ccr) which is considered a valuable measure if urine is collected over 24 hour period. Certain factors influencing input variables must be considered when interpreting Ccr. An increased portion of creatinine excreted via tubular secretion and decrease of the serum concentration due to increased distribution volume in states of elevated extracellular water and decreased muscle mass may lead to the overestimation of the true level of glomerular filtration in critically ill subjects. The effects decreasing SCr become more significant with the progression of multiorgan dysfunction and are often paralleled with worsening of renal functions. This means that overestimation of glomerular filtration by measurement of Ccr is greater in deteriorating renal function and may double the true level in uremic patients (24). Problematic interpretation of the clearance of endogenous creatinine leads intensivists towards more accurate and less variable markers of glomerular filtration. The measurement of cystatine C appears to be a perspective option (vide infra).

1.2. Functional renal failure and its diagnostic importance

The presence or absence of the prerenal syndrome may help to diagnose renal hypoperfusion in individual patients (Tab.2). Clearance of electrolyte free water (EWC) is rather used as a supplementary parameter in relation to prerenal syndrome (25). A potential positive or negative correlate with clearance of solute free water and factors related are discussed in the following text. More than 80% of patients were prerenal on admission to the department. It is particularly related to the haemodynamic instability. Every biochemical parameter requires interpretation based on the knowledge of clinical status of a patient. Patient's volemic status and haemodynamic optimization using vasoactive agents may be also indicated after renal function assessment. On the other hand, the renal function can not be evaluated without knowledge of patientś clinical status and haemodynamic assessment.

Tab.2: Diagnosis of prerenal syndrome.

Parameter	Normal / non dg.	Prerenal	Renal
FE_Na^+	1-3%	< 1% (< 2%)	> 3%
t.resorbtion	97-99%	> 98%	< 97%
FE_H_2O	1-2.5%	< 2%	> 2.5%
UU/SU		> 10	< 5
C_H_2O	-0.007 – 0.027 ml/s	< - 0.007 ml/s	> - 0.007 ml/s
Uosm	400-600 mosm/kg	> 400 mosm/kg	< 400 mosm/kg
UNa$^+$	40-100 mmol/l	< 40 mmol/l	> 40 mmol/l

1.3. Tubular function and effects of diuretics

Diuretics belong to the most frequently used medications in intensive care setting. Their administration significantly influences renal functions and homeostasis (26). The diuretic administration appears to be rather invasive from the point of view of homeostatic monitoring based on the spectrum of renal function tests. On the other hand it influences the diagnosis of homeostasis with the aid of renal function tests.

1.4. Type of diuresis

The type of diuresis is defined with the aid of FE_H_2O, C_H_2O, EWC, FE_Osm and UOsm/SOsm. EWC was added to the classic criteria of the type of diuresis (Tab.3). Tubular osmotic diuresis is typical for the progressing renal insufficiency as compensatory, also accompanies therapy with loop diuretics, thiazides and acetazolamide. It also can be found as the overflow osmotic diuresis in glykosuria, hypercatabolism with high output of urea, therapy with manitol, after contrast administration or in bicarbonate escape in urine. The mixed water and osmotic diuresis represents secondary destruction of the kidney ability to concentrate urine. It is typical for progressing renal failure, severe tubulointersticial nephritis or secondary nephrogenic diabetes insipidus. Water diuresis represents central or

juvenile nephrogenic diabetes insipidus. It may be physiologic when high load of free water is excreted (27,28).

Tab.3: Definition of the type of diuresis. The impact of diuretics and infusion therapy must be evaluated in parallel. Parameters under the dashed line are added to the classic criteria according to Schück (28).

Parameter	Type of diuresis Osmotic	Mixed	Water
FE_H_2O	> 2%	> 2%	> 2%
Uosm/SOsm	> 1	< 1	< 1
C_H_2O	< 0	> 0	> 0
FE_Osm	> 3.5%	> 3.5%	< 3.5%
C_El/EWC	> 3	< 3	< 3
FE_Na^+	> 2%	> 2%	1-2%

1.5. Ability to concentrate urine

The ability of kidneys to concentrate urine is evaluated comparing SOsm to C_H_2O and also to EWC which is important for understanding the shifts in effective osmolality (Tab.4). The factors disturbing the ability to concentrate urine can be divided into two groups. The first group causes parallel shift of C_H_2O and EWC when both are moving into positive or negative values. Thus failure of regulation can be diagnosed like disorders of hypothalamohypophyseal system (central diabetes insipidus, syndrome of inappropriate secretion of ADH) or disorders of renal tubular cell, receptors for ADH, aquaporine synthesis (nephrogenic diabetes insipidus) or more often failure of medullar osmotic gradient washed out by the prerenal insults and disturbed by administration of loop diuretics (secondary nephrogenic diabetes insipidus). Insufficient amount of fluid in the distal segment of nephron in renal failure has its impact as well. The second group of factors includes mostly intratubular osmotically active substances causing discrepant shift between C_H_2O and EWC. C_H_2O is typically lowered in positive EWC which can be found in high concentration of urea in urine, in relation to glycosuria, manitol therapy or in chronic acidosis with increased excretion of NH_4^+. The impact of X-ray contrast or higher concentration of ketons in urine must be also differentiated. The influence of certain antibiotics can not be excluded. The difference between C_H_2O and EWC is a function of concentration difference of these solutes. The examination of concentrating ability using C_H_2O without EWC leads in these clinical scenarios to underestimation of the clearance of free water (25,27,28).

Tab.4: Estimate of the ability of kidneys to concentrate urine. Parallel evaluation of C_{H_2O} and EWC in relation to SOsm is suggested.
According to Schück : Comparing C_{H_2O} and SOsm.

Sosm	C_{H_2O} increased	C_{H_2O} decreased
< 275 mosm/kg	Increased water intake, does not exlude disorder of the concentrating ability	Suspected disorder of the concentrating ability
> 295 mosm/kg	Suspected disorder of the concentrating ability	Does not exclude disoder of the concentrating ability

Method applying analysis of EWC (adapted from Shoker, 25):

Sosm	Normal response	Disoder of the concentrating ability
< 275 mosm/kg	C_EI </= EWC, EWC>0.9 l/24h	C_EI>EWC nebo EWC<0.9 l/24h, EWC<0.5 l/24h suggests contraregulation
>295 mosm/kg	C_EI/EWC>3 (not valid for negative EWC), EWC<0.4 l/24	C_EI/EWC<3 (not valid for negative EWC) or EWC>0.4 l/24h

The outlined approach has an importance for the differential diagnosis of any disorder of natremia and osmolality. Osmolal dysbalances are very frequent in critically ill patients. For example hyponatremia in central nervous system disease often associates with pathophysiologically joined syndroms of inappropriate secretion of ADH (IADHS) and cerebral salt wasting syndrome (CSWS). Their distinguishing is crucial for correct therapy of hyponatremia. Hypernatremia in central nervous system disease is often caused by central diabetes insipidus. A diffential diagnostic scheme of the tonicity disorders in cerebral pathology is shown in Tab.5. Routine monitoring of the renal function parameters together with rational infusion and diuretic therapy in those patients could lead to smaller shifts in tonicity and potentially reduce the risk of secondary brain injury (27,29,30).

Tab 5. Differential diagnosis of the selected syndromes.

	IADHS	CSWS	DI
sNa	< 135 mmol/l		> 145 mmol/l
sOsm	< 280 mosm/kg		> 295 mosm/kg
uNa	> 25 mmol/l		< 25 mmol/l
uOsm/sOsm	> 1		< 1
Ccr	increased	Normal	normal
EFH2O	norm., decreased	Increased	increased
EFNa	norm., decreased	Increased	norm., decreased
diuresis	norm., decreased	norm., increased	norm., increased
Cel	Normal	Increased	normal
EWC	decreased	norm.	increased
Cosm	norm.,increased	norm., increased	normal
CH2O	decreased	Decreased	increased
dUNa	< 100-150 mmol	> 150 mmol	=/< Na input
serum renin, aldosterone	Normal	norm.,increased	norm.,increased
ADH	increased, norm.	norm., increased	decreased
Serum uric acid	decreased	Normal	

The diagnostic value of the renal function parameters in relation to the defined syndromes is limited in case of:
- hypovolemia, hypotension, dehydratation, oedemas (cardiac, cirhosis)
- renal failure
- hypocorticalism, hypothyreosis
- diuretic use (thiazides)
- other osmotically active agents (manitol, hyperglycemia)

1.6. Examination of urine acidification

The examination consists of urine pH measurement, serum anion gap corrected for the level of albumin (SAG), urine anion gap (UAG) and urine osmolal gap (UOG). Renal tubular acidosis (RTA) may appear as a secondary disorder rising from rather broad spectrum of insults. The most frequent causes are nephrolithiasis, obstructive uropathy (prevalence up to 25%), another frequent cause is tubulointerstitial nephritis. The rate of secondary RTA was 5.8% in our study on critically ill patients. The differential diagnosis of hyperchloremic metabolic acidosis with normal anion gap after correction for serum albumin is shown in Tab.6. The exact distinguishing of proximal and distal RTA is not crucial in critically ill patients. The differentiation of hyperkalemic RTA and fourth type of RTA from the most frequent hypokalemic RTA seems to be more important. A significant laboratory finding is hyperchloremic metabolic acidosis with normal serum anion gap associated with hypernatremia, hypofosfatemia, hypocalcemia and normal or low magnesium levels (31,32).

Tab.6: Diferential diagnosis of normal serum anion gap (SAG) metabolic acidosis. More homeostatic data than listed parameters are neccesary to establish the definitive diagnosis of renal tubular acidosis (RTA). UAG=UNa^++UK^+–UCl^-; UOG=[2*(UNa^++UK^+)+UU]-UOsm

SAG 10-18 mmol/l, hyperchloremia

1.) Exclusion of dilution etiology during rehydratation
2.) Exclusion of the increased intake of chloride (HCL, ArgCl, NH_4Cl, LysCl)
3.) Loss of bicarbonate through gut or kidneys (RTA), further division according to UAG a UOG

a.) UAG negative, UOG>150 – suspected gut loss (diarrhoea, duodenal drain, ileostomy, pankreatic fistula, ureterosigmoideostomy, neovesica)

b.) UAG positive, exclude presence of ketons, salicylates and peniciline antibiotics in urine, UOG<150, <100 respectively – suspected RTA
– K^+ normal or low, pH of urine>6.5 – hypokalemic RTA
– K^+ increased, pH of urine>6.5 – hyperkalemic RTA, RTA type IV to be excluded if pH of urine<6.5

1.7. The course of renal insufficiency and progression to renal failure in renal function parameters, margins of conservative therapy and early indication to CRRT based on renal function parameters

The renal function parameters were monitored in critically ill patients who developed delayed onset renal failure (33,34,35). The study resulted in proposal for the kidney functional model in multiple organ dysfunction syndrome (Fig.2). The cumulation of prerenal insults, septic and nephrotoxic effects consequently leads to decrease of glomerular filtration and to the induction of tubular osmotic diuresis. In case of further worsening of renal dysfunction and GF decrease a typical switch is seen from maximum induced compensatory tubular osmotic diuresis to mixed water and tubular osmotic diuresis with a loss of concentrating ability and isostenuria. This can be interpreted as a regulation through tubuloglomerular feedback and lowering of glomerular filtration in residual nephrons due to critically increased tubular flow in

overfilled tubules (36). The patients must have obviously had a maximum possible renoprotective regimen already before these signs appear in renal function tests. If the change of diuresis and loss of ability to concentrate urine is followed by further decrease of diuresis thus further decrease of GF is expected because patients are not able to increase urine concentration of creatinine. An increase of serum urea and creatinine invariably follows mostly accompanied with a decrease of diuresis and development of oliguric renal failure. If the number of surviving nephrons is sufficient patient may less often develop nonoliguric renal failure (37).

Based on this functional model a non standard indication scheme for CRRT administration was applied in following studies. This was defined as a decrease of glomerular filtration under 20% of normal for given age and gender, isostenuria and fall of daily urine output of urea under 250 mmol (38,39).

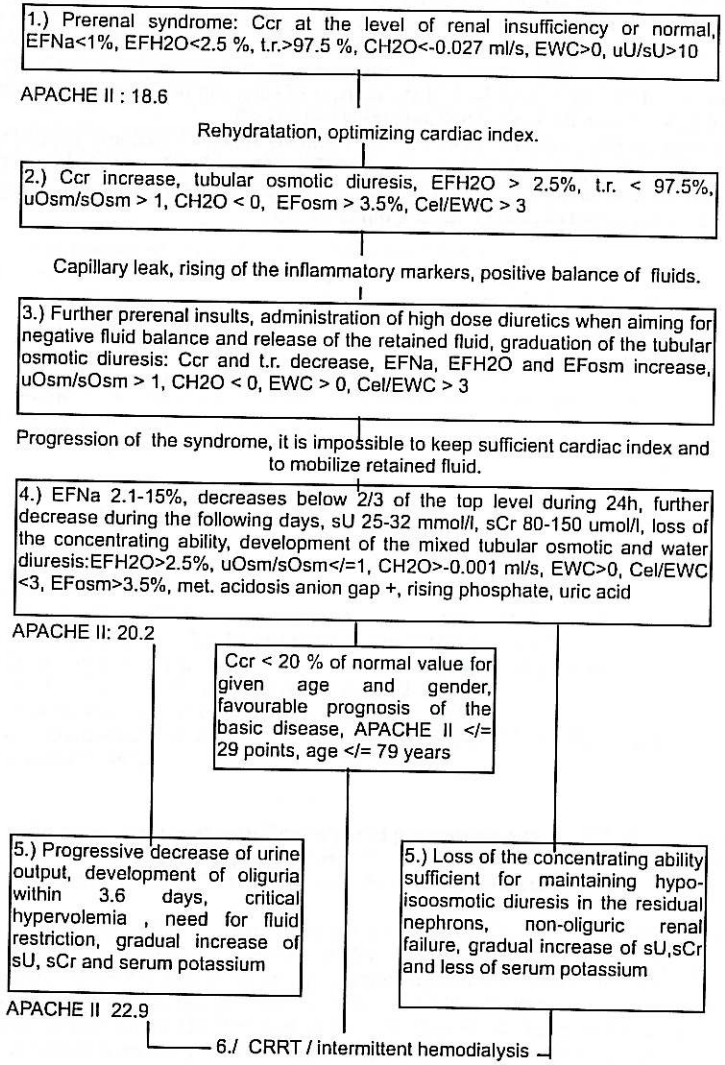

Fig.2: Functional kidney model in a typical SIRS/MODS patient. The index of Cel/EWC is valid only for EWC>0.

2. The contribution of low molecular weight proteins and middle molecules to the diagnosis of renal functions

A problematic estimate of glomerular filtration based on clearance of creatinine, using inuline or isotopes leads to the search for other more reliable and more sensitive markers for diagnosis of renal dysfunction in intensive care. Cystatin C (cysC) represents a newly proven marker of glomerular filtration. CysC is a nonglycosylated basic protein produced at a constant rate by all nucleated cells. It is freely filtered by the renal glomeruli and catabolized in tubuli. No secretion or re-uptake in tubuli was described. The serum concentration is independent of age, gender and muscle mass. CysC is a more sensitive marker of glomerular filtration than creatinine. It is suitable for early detection of even small decreases of GF. SCr seems to offer more advantage for detection of transient changes of GF in patients with existing chronic renal disease (10,11,12,13). The subject of research (38) was the unexplored relationship between cysC and residual diuresis in patients already developing acute renal failure. Residual renal functions in patients on continuous renal replacement therapy could be considered as one of the markers of succesful application of the technique. The aim of these therapeutic modalities is to stabilize critically ill patient and to help returning residual diuresis. A relationship was found between residual diuresis and levels of cysC (Fig.3) and between mortality and levels of cysC. The initial decrease of levels after the start of CRRT could be explained by the adsorbtion on the filter and extracorporeal circuit because elimination on the filter was negligible. The impact of sepsis and systemic inflammation on levels of cysC is uncertain. The levels of septic controls in our study were higher than the levels of nonseptic controls however, the difference did not reach statistic significance. At present another author's study takes place at Westmead Hospital in Sydney exploring the influence of systemic inflammation on the levels of low molecular weight proteins in patients with various severity of renal insufficiency.

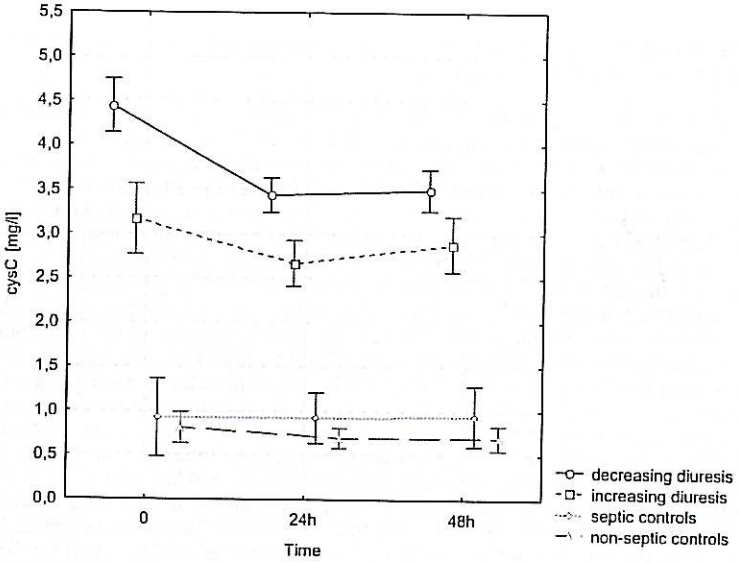

Fig.3: Repeated measures ANOVA for data comparison between group with decreasing diuresis (circles), group with increasing diuresis (squares), septic control group (diamonds) and non-septic control group (triangles). The symbols represent mean levels; the whiskers extend to the highest and lowest values if no outliers are present.

Natriuretic peptides are classified as middle molecules and are discussed in relation to the renal functions. Their importance lays particularly in diagnosis of heart failure. The influence of renal deterioration on the levels of natriuretic peptides has not been fully clarified. The release of BNP is related to the increased enddiastolic pressure in ventricles while major stimulus for ANP secretion is increased atrial pressure and activation of heart endocardium. A renoprotective, natriuretric and diuretic properties of natriuretic peptides are presumed. The effect upon kidney functions is based on a tubular natriuretic effect and a favourable impact on glomerular filtration by means of the filtration fraction increase. ANP decreases renin secretions in the kidney, reduces the effects of angiotensin and the vascular effects of vasopressin and endothelins. BNP and ANP given parenterally as diuretics exert favourable effect on morbidity and the need for dialysis in oliguric renal failure (14,15,16,17,40).

The causes of the loss of residual diuresis after commencing of the elimination technique are not clarified even in nephrologic patients (41). One of the theories is the elimination of natriuretic peptides on the filter. Author's study (39) showed high sensitivity of BNP for the diagnosis of renal insufficiency when levels 60-70 times higher than in the control group were found. The levels of ANP were also high but the increase of ANP better correlated with the loss of residual renal functions than the change of BNP. Natriuretic peptides were significantly higher in patients with

decreasing diuresis in contrast to patients with preserved residual diuresis or in patients where diuresis increased after start of CRRT. Both proteins were not eliminated during continuous haemodiafiltration and therefore the theory about elimination of natriuretic peptides and loss of residual diuresis was not confirmed. Parallel echocardiographic monitoring proved relationship between levels of natriuretic peptides and ejection fraction of the left ventricle even under conditions of renal failure. The study also proved a relationship between ANP, BNP and mortality in patients treated with combination of mechanical ventilation and CRRT.

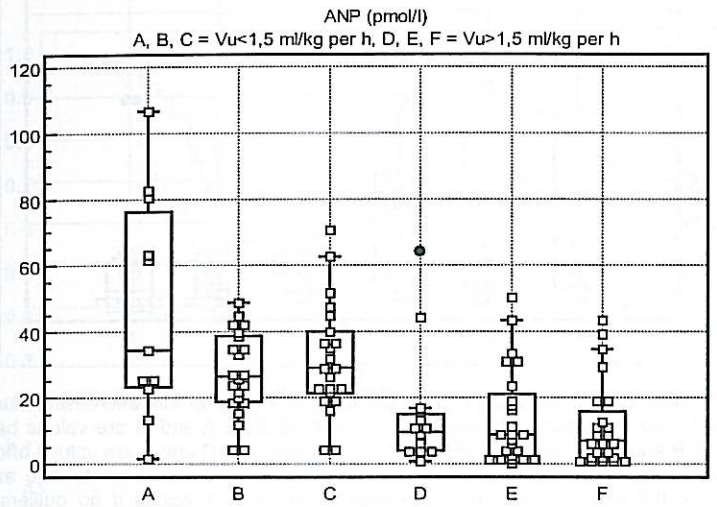

Fig.4: Box and Whiskers plot of the ANP levels in the group with decreasing diuresis (A,B,C) and the group with increasing diuresis (D,E,F). A and D are values before CRRT. B, and E are values after 24 hours of therapy and C and F are values after 48 hours. The boxes represent 25th to 75th percentile with a horizontal line at the median; the whiskers extend to the highest and lowest values if no outliers are present.

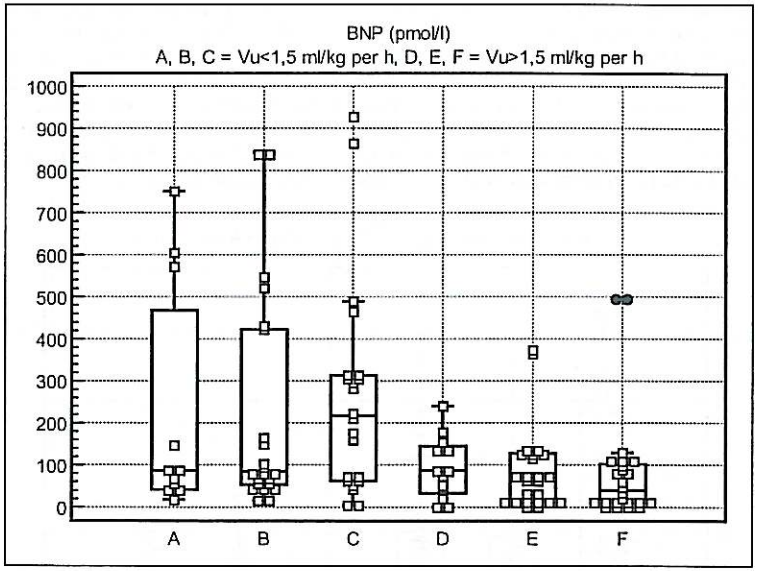

Fig.5: Box and Whiskers plot of the BNP levels in the group with decreasing diuresis (A,B,C) and the group with increasing diuresis (D,E,F). A and D are values before CRRT. B and E are values after 24 hours of therapy and C and F are values after 48 hours. The boxes represent 25th to 75th percentile with a horizontal line at the median; the whiskers extend to the highest and lowest values if no outliers are present.

3. The impact of anticoagulation on effective and safe performance of extracorporeal elimination technique in critically ill subjects

Continuous renal replacement therapy requires anticoagulation of the extracorporeal circuit which brings with it the risk of bleeding in high risk patients. Patients at risk of bleeding are those after trauma or surgery, or those with intracranial pathology, acute pancreatitis, patients with gastric ulcers, history of GIT bleeding, pericarditis, endocarditis and severe diabetic retinopathy. A special approach is required in patients with thrombocytopenia, coagulopathy and heparin induced platelet antibodies (HITTS). Anticoagulation of CRRT should ideally exert minimum effects on coagulation outside the circuit and provide ideally filter survival beyond 24 hours. The monitoring should be rapid, simple, and in the case of complications anticoagulation should be rapidly reversible (42,43,44). Authors study was based on the experience with the regional circuit decalcification using citrate (18) which we compared with epoprostenol - a product registered in Czech Republic in 2002. Prostacykline anticoagulation inhibits aggregation and adhesion of platelets in extracorporeal circuit, plasmatic halftime is 2.5-4 minutes (19,20). Epoprostenol

was administered with a low dose of unfractionated heparin (5-6 $IU.kg^{-1}.h^{-1}$) and control group was anticoagulated with citrate. Median filter survival was 26 h (interquartile range 16-37) in prostacyklin group and 36.5 h (interquartile range 23-50) in citrate group, $p<0.01$. Citrate does not influence haemodynamics, platelets and is cheaper comparing to prostacyclin. Gradual increasing of dosage of PGI_2 up to the average of 8.7 $ng.kg^{-1}.min^{-1}$ did not escalate haemodynamic side effects. Prostacyklin has no impact on intermediate metabolism and patients nutrition compared to citrate and may be safely used in patient with liver dysfunction (45).

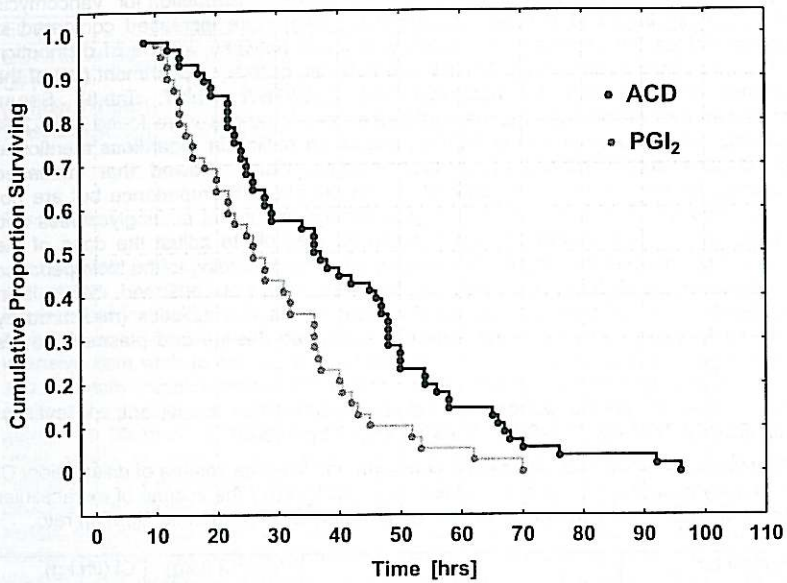

Fig. 6: Kaplan-Meier curves of time to haemofilter clotting (according to the anticoagulation used, $p<0.01$).

4. The impact of renal function disorders and changes in water homeostasis on the volume of distribution of nephrotoxic drugs

Sepsis and multiple organ dysfunction induce an increase in the water content of the body mainly in the extracellular space. Antibiotics are primarily distributed in extracellular water (ECW), therefore antimicrobial prescribing in sepsis must take into account the increase in volume of distribution and variable drug clearance. At different stages of the disease process, antibiotic requirements in septic ICU patients may be similar, less or greater than in patients on the conventional ward. Subtherapeutic antibiotic concentrations in those patients may account for treatment failures and may contribute towards emergence of bacterial resistance (21,22,23). Measurement of serum levels of antibiotics is recommended for drugs with a low

therapeutic index and is routinely practiced in the ICU for antibiotics like aminoglycosides and glycopeptides. Avoiding toxic levels and effective dosage for rather limited time is a part of renoprotective approach to critically ill patient (46,47).

Authors study (48) evaluated the relationship between volume of distribution monitored with the aid of two compartment pharmacokinetic model and volume of extracellular water (ECW) taken with bioimpedance (49) in mechanically ventilated patient with sepsis and syndrome of increased capillary permeability. ECW was increased and represented 45.6-46.6% of total body water (TBW). The total balance of fluids between two measurements correlated with a change of ECW ($r=0.82$, $p<0.0001$) and TBW ($r=0.74$, $p<0.0001$). The volumes of distribution for vancomycin (0.677±0.339 l/kg) and netilmicin (0.505±0.172 l/kg) were increased compared to normal values. An important correlation was found between volume of distribution (Vd_{area}) of vancomycin and ECW/TBW and between central compartment (V_1) of the volume of distribution for netilmicin and ECW/TBW (Tab.7, Tab.8). Serum concentrations higher than recommended therapeutic ranges were found in 81.2 % patients on vancomycin and in 50.0% patients on netilmicin regardless mentioned correlations and increased distribution volumes. Study showed that increased volumes of distribution can be estimated with the aid of bioimpedance but are not associated with the requirement for higher dosage in case of aminoglycosides and glycopeptides. The hypothesis that it would be possible to adjust the dose of the nephrotoxic antibiotics in terms of increasing the dose according to the bioimpedance estimate of the distribution volume of the agent was not confirmed. Study is in agreement with data on sub therapeutic tissue levels of antibiotics (measured by microdialysis) found in septic patients with adequate dosage and plasmatic levels (50).

Tab.7: Results of the vancomycin study. r correlation coefficient; p level of significance; *p<0.02; ** p<0.02; *** p<0.0001; **** p<0.0001

Abbreviations: V1 central distribution compartment; Vd-area volume of distribution; Cl total body clearance; ECW extracellular water, ECW/TBW the volume of extracellular water expressed as percentage of total body water; GFR glomerular filtration rate.

Parameter		V1 (l/kg)	Vd-area (l/kg)	Cl (l/h.kg)
	mean±SD	0.212±0.100	0.677±0.339	0.037±0.018
ECW (l)	22.75±6.04	r = 0.15	r = 0.41 *	r = 0.42 **
ECW/TBW (%)	45.56±4.67	r = 0.15	r = 0.70 ***	r = 0.33
GFR (ml/min.1.73m^2)	67.76±25.73			r = 0.83 ****
Body weight (kg)	84.6±18.2			

Tab.8: Results of the netilmicin study. r correlation coefficient; p level of significance; *p<0.003; ** p<0.04; *** p<0.0001

Abbreviations: V1 central distribution compartment; Vd-area volume of distribution; Cl total body clearance; ECW extracellular water, ECW/TBW the volume of extracellular water expressed as percentage of total body water; GFR glomerular filtration rate.

Parameter		V1 (l/kg)	Vd-area (l/kg)	Cl (l/h.kg)
	mean±SD	0.243±0.069	0.505±0.172	0.050±0.033
ECW (l)	20.97±3.86	r = 0.36	r = 0.22	r = 0.29
ECW/TBW (%)	46.56±4.03	r = 0.60 *	r = 0.44 **	r = 0.13
GFR (ml/min.1.73m^2)	67.01±35.93			r = 0.92 ***
Body weight (kg)	75.8±11.8			

Discussion

Entire project is inspired by certain gaps in full utilisation of biochemical parameters in intensive care. A certain imbalance between the amount of biochemical investigations and their effective application and cost exists. A deeper look into renal function parameters would be neccessary if physicians working in intensive care wish to monitor the effects of renoprotective measures, indicate early and correctly renal replacement therapy and assemble cohorts of patients with similar type and degree of renal insufficiency for research purposes. The estimate of glomerular filtration by means of clearance of endogennous creatinine, evaluation of renal ability to concentrate urine, urine outputs of catabolites and ionts and evaluation of renal acidification are mainstay of renal monitoring in critically ill patients. The thesis is based on author's published studies which are subject to similar problems as most of research originating from the field of intensive care medicine. These are particularly inhomogenity of groups of patients from the point of view of basic diagnosis, variability of type and grade of renal injury. The last factor was partially solved by the inclusion of the definition of renal failure based on the renal function parameters (clearance of endogenous creatinine, type of diuresis and outputs of catabolites in urine). Another limitation (38,39) rises from the type of elimination technique used. Continuous venovenous haemodiafiltration is used very often however, convective mode of elimination in the form of continuous venovenous haemofiltration may prevail in many intensive care units. More significant elimination of middle molecules and low molecular proteins on the filter would be expected thus limiting their use for diagnosis of residual renal functions. Rather unexplored modality of elimination of above mentioned molecules is adsorbtion on the walls of the extracorporeal circuit and filter. The effect of adsorbtion was presumed in authors papers but not objectively verified. The experiment was targeted on drugs with exclusive distribution in ECW when monitoring the effects of ECW expansion on drug levels. A correlate between the grade of ECW expansion and volume of distribution of the antibiotics was found however, to our surprise without the need for dosage escalation. Again variability of the basic disease plays its significant role. Time is an important factor after the start of antibiotic treatment when the volume of distribution can be saturated after initial several dozens of hours. Patient's survival in critical care

often depends on efficient dosage of drugs like antibiotics. A conclusion impeaching studies suggesting to increase dosage of the antibiotics in patients with the increase of ECW is rising from the author's study.

Summary

Aims: A systematic approach to renal function monitoring using information taken by means of renal function tests calculated from examination of serum and urine specimen has not been comprehensively explored. The application of analysis of natriuretic peptides or low molecular weight proteins like cystatin C in diagnosis of advanced renal failure requiring renal replacement therapy has not been tested in critically ill patients. The performance of continuous renal replacement therapy depends on the adequate anticoagulation of the extracorporeal circuit. Prostacyclin as one of the newer agents has not been compared to citrate which may be considered a standard agent in many intensive care units. Changes of distribution volume of antibiotics have been a matter of debate in terms of dosage alteration but have not been assessed clinically at the bedside using other tools than a pharmacokinetic model.

Methods: Establishing computer programme evaluating various renal functions allowed us to monitor the effects of diuretics, osmolality shifts, disorders of urine acidification and progression of renal insufficiency towards acute renal failure. Creating a functional model of acute renal failure serves as a tool for further studies on renal replacement therapy in the intensive care setting. A relationship between residual diuresis and levels of natriuretic peptides and cystatin C were studied before and during first 48 hours of continuous venovenous haemodiafiltration. Prostacycline circuit anticoagulation together with low dose unfractionated heparin was compared to regional citrate decalcification of the circuit. Septic patients with generalised capillary leak syndrome were given glycopeptide or aminoglycoside antibiotic. A distribution volume of the antibiotic estimated by the pharmacokinetic model was correlated with the volume of extracellular fluid taken by bioimpedance.

Results: The study outlined available ways of monitoring of the diuretic administration which seems to be rather invasive in terms of the impact on homeostasis. Renal function tests appeared as an available monitoring tool for a diagnosis of tonicity disoders in cerebral disease. Prevalence of urine acidification disorders is not negligible in intensive care patients and renal function monitoring allows quick differential diagnosis. Application of function monitoring for the diagnosis of acute renal failure in critically ill patients may clarify renal failure from other confounding effects of non renal factors. A hypothesis that natriuretic peptides may stimulate residual diuresis in acute renal failure was not confirmed. Their importance lays in the diagnosis of acute renal failure per se and differentiation of oliguric and non oliguric form with preserved residual diuresis. An indirect relationship between residual diuresis and levels of natriuretic peptides was found. Cystatin C may also differentiate patients on renal replacement therapy in terms of preserved residual diuresis and prognosis. Prostacycline does not offer comparable filter survival to citrate and may interfere with platelet function in certain patients however, its application with low dose heparin is a safe option of circuit anticoagulation. An increased distribution volume of aminoglycoside and glycopeptide antibiotics in sepsis is not associated with requirement for dosage escalation.

Conclusion: This study is the result of clinical research performed on critically ill patients. It attempts to contribute to medically and financially effective diagnostics at the departments which create only about 10% of hospital capacity but at the same time require inproportionally more medical resources. Homeostasis interpretation and prevention of renal failure in the form of renoprotective regimen including monitoring of nehrotoxic antibiotics together with correctly indicated and terminated renal

replacement therapy goes hand in hand with improved patient´s survival and cost effectivity of patient´s treatment.

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