Programska skupina P3-0323: Ledvične bolezni in nadomestna zdravljenja

Univerza v Ljubljani
Medicinska fakulteta

univerzitetni klinični center ljubljana
University Medical Centre Ljubljana

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Klinični oddelek za nefrologijo UKCL – Raziskovalna skupina 0312-024

- 212 zaposlenih (80% žensk)
- 21 specialistov nefrologov, 22 specializantov nefrologije (nefrologija 6 let – 2+4), 1 mlada raziskovalka (+1)
- 10 habilitiranih učiteljev – 2 redna profesorja, 6 izrednih profesorjev, 2 docenta (+1)
- 9 doktorandov
- 8 enot: ambulanta, hospitalni oddelek (32 postelj)
- 4 dializni centri: Center za akutno in komplicirano dializo (42 dializne postaje, 24/7), 2 satelitna dializna centra (15 in 10 dializnih mest), Center za peritonealno dializo
- Center for transplantacijo ledvic
- Ultrazvočna enota
- Prihodek v 2017: 21 milionov EUR

Programska skupina P3-0323

- 13 raziskovalcev
- 1 mlada raziskovalka (+1 v postopku zaposlitve)
- 4 tehnični sodelavci
- 9 doktorandov – mentorji člani programske skupine
- Področje raziskovanja: klinične in translacijske raziskave na področju ledvičnih bolezni, dialize in presaditve ledvic ter akutne ledvične okvare

Hemodializa

Regionalna citratna antikoagulacija

The International Journal of Artificial Organs / Vol. 31 / no. 5, 2008 / pp. 418-424

Artificial Kidney and Dialysis

Regional citrate anticoagulation for hemodialysis: calcium-free vs. calcium containing dialysate - A randomized trial

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Center for Dialysis, Department of Nephrology, University Medical Center Ljubljana, Ljubljana - Slovenia

Therapeutic Apheresis and Dialysis

Long-Term Citrate Anticoagulation in Chronic Hemodialysis Patients

Jakob Gubenšek, Janko Kovač, Miha Benedik, Andreja Marn-Pernat, Bojan Knap, Rafael Ponikvar, Jadranka Buturović-Ponikvar

First published: 30 May 2011 | https://doi.org/10.1111/j.1744-9987.2011.00951.x |

Artificial Organs

Main Text Article

Treatment Efficacy and Safety During Plasma Exchange With Citrate Anticoagulation: A Randomized Study of 4 Versus 15% Citrate

Manja Antonic, Jakob Gubensek, Jadranka Buturovic-Ponikvar, Rafael Ponikvar

First published: 14 September 2015 | https://doi.org/10.1111/aor.12559 |

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Therapeutic Apheresis and Dialysis

Original Article

Citrate Extended High Cut-Off Hemodiafiltration for Renal Recovery in Patients With Multiple Myeloma

Andreja Marn Pernat, Bojan Medved, Jakob Gubenšek, Vladimir Premru, Bojan Knap, Jadranka Buturovic-Ponikvar, Rafael Ponikvar

First published: 16 June 2016 | https://doi.org/10.1111/1744-9987.12432 |

Presented in part at the Symposium Celebrating 45 Years of Chronic Hemodialysis and Kidney Transplantation in Slovenia held November 19-21, 2015 in Ljubljana, Slovenia.

Regionalna citratna antikoagulacija

RESEARCH ARTICLE

Calcium Mass Balance during Citrate Hemodialysis: A Randomized Controlled Trial Comparing Normal and Low Ionized Calcium Target Ranges

Jakob Gubensek[1,2]*, Alesa Orsag[1], Rafael Ponikvar[1,2], Jadranka Buturovic-Ponikvar[1,2]

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RESEARCH ARTICLE

Influence of citrate concentration on the activation of blood cells in an *in vitro* dialysis setup

Jakob Gubensek[1,2]*, Karin Strobl[3], Stephan Harm[3], Rene Weiss[3,4], Tanja Eichhorn[3,4], Jadranka Buturovic-Ponikvar[1,2], Viktoria Weber[3,4], Jens Hartmann[3]

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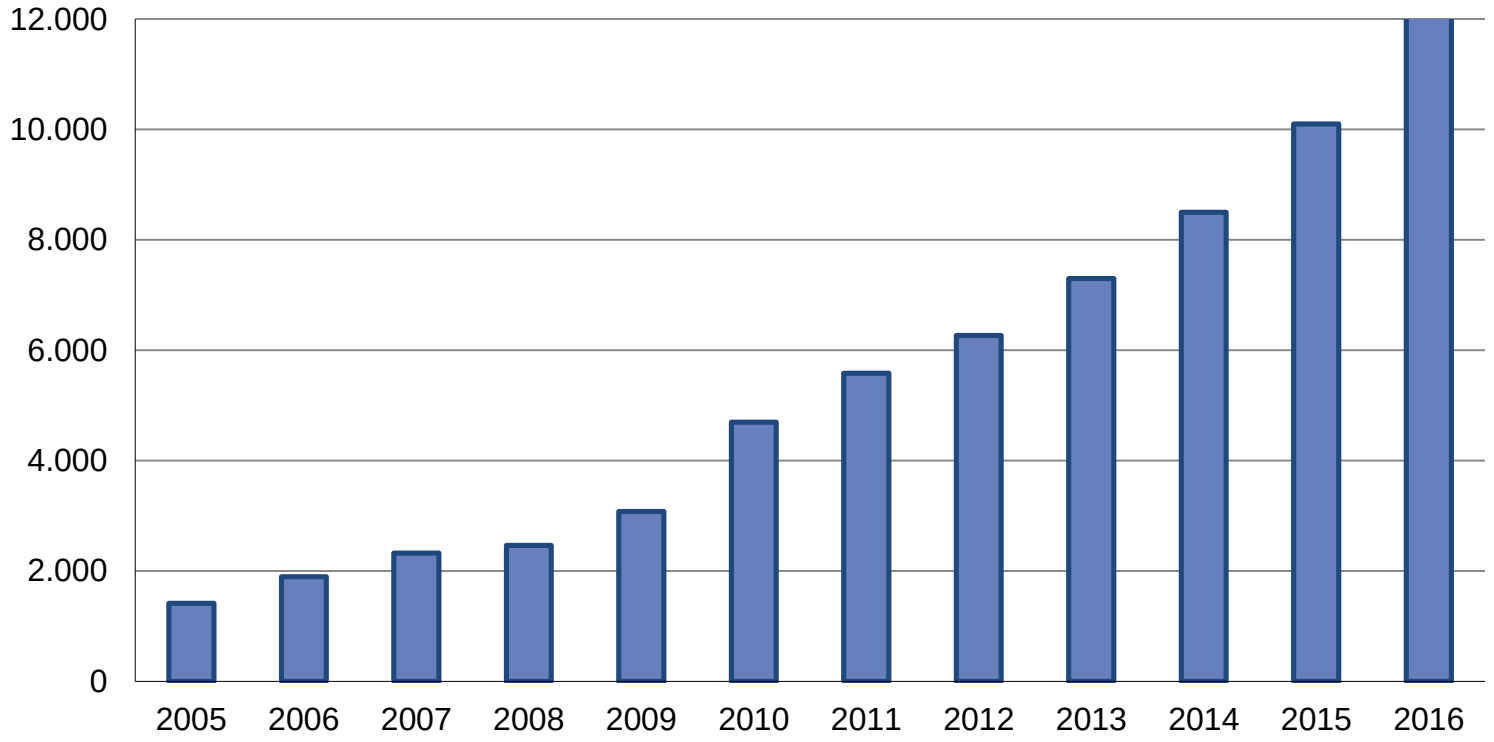
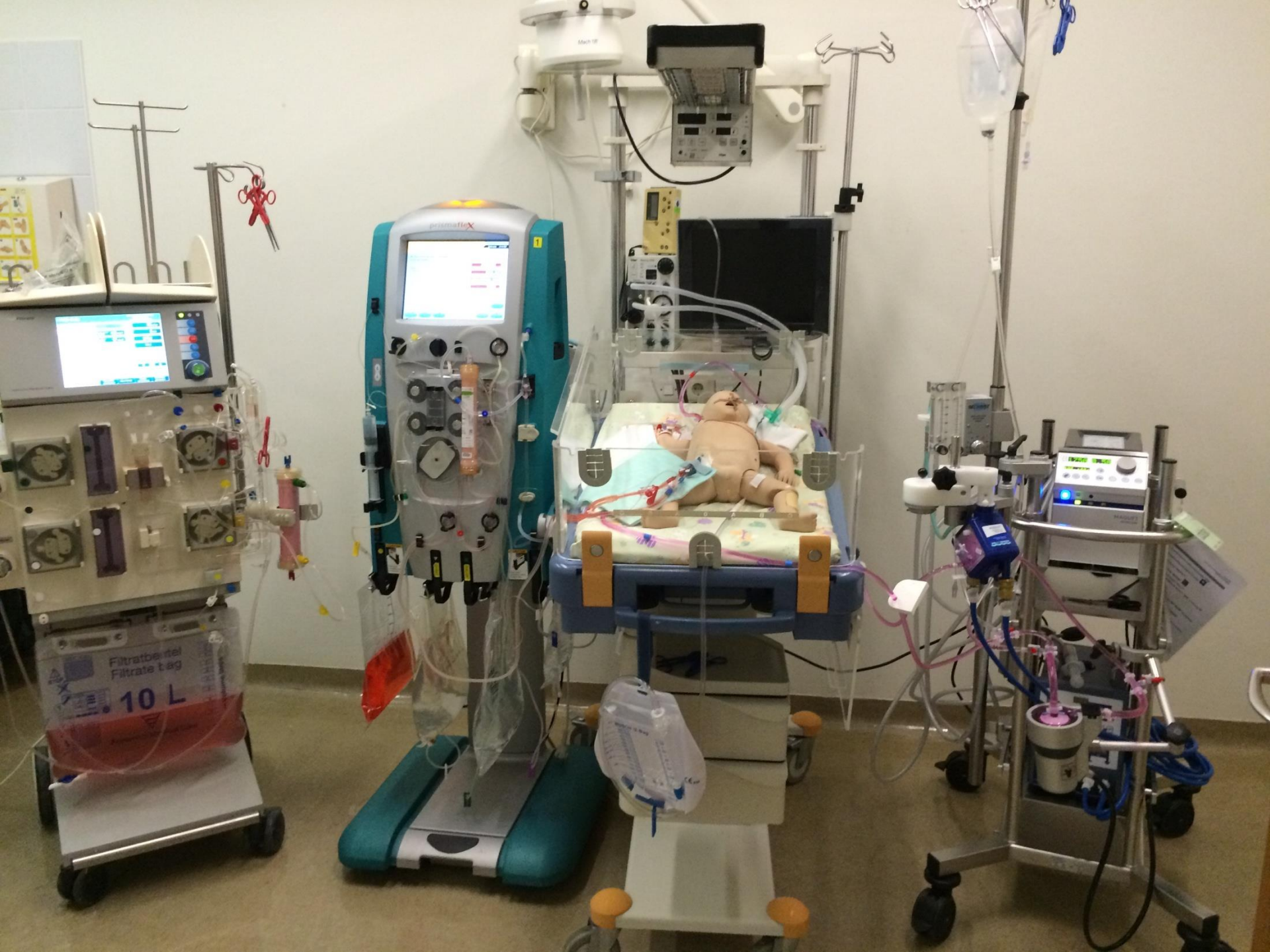
Gubensek J , Buturović-Ponikvar J et al. Plos One 2016 & 2018

Regionalna citratna antikoagulacija

HD procedures with regional citrate anticoagulation at UMC Ljubljana



Buturović-Ponikvar J et al.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Regionalna citratna antikoagulacija

ERA-EDTA NEWS / ISSUE 2 / JUNE 4th, 2017 / page 18

Is regional citrate anticoagulation the future of hemodialysis?

JADRANKA BUTUROVIC-PONIKVAR
Ljubljana, Slovenia

Citrate has many characteristics of the ideal anticoagulant for hemodialysis. Its anticoagulant effect (mediated through depletion of Ca++) is immediate, complete and limited to the dialysis circuit. Citrate has a very specific antidote: calcium. In addition to inhibiting coagulation, citrate reduces platelet deposition on the dialyzer membrane. The dialysis membrane examined with a scanning electron microscope showed negligible thrombus formation after regional citrate anticoagulation (RCA). In contrast, pronounced cell adhesion and thrombus formation were demonstrated after standard heparin or nadroparine anticoagulation. By chelating calcium and magnesium, citrate may reduce complement activation induced by the interaction of blood with the artificial membrane, thus improving the biocompatibility of the dialysis circuit. Unlike heparin, citrate has no antigenicity. Citrate is easily dialyzable (molecular weight of trisodium citrate is 294 Da), with more than 80 % removal through the high-flux membrane. The cost of citrate is low.

the complexity of the RCA procedure with safety concerns. Today the risk of metabolic complications (alkalosis, acidosis, hypo- or hypercalcemia, hypernatremia) is greatly reduced by the use of high-flux dialyzers with high citrate clearance, adjustment of sodium and bicarbonate offered by modern hemodialysis monitors, and wide availability of point-of-care ionometers. The latter, together with good protocols and availability of precise infusion pumps, reduce the complexity of the procedure.

RCA during intermittent hemodialysis is usually performed using calcium-free dialysate, trisodium-citrate infusion (as close to the patient as possible), and calcium infusion just before the blood is returned to the patient (distally from the venous bubble trap) (Figure 1). The dose of citrate is calculated as the percentage of blood flow and adjusted according to the post-dialyzer (or pre-dialyzer) ionized calcium level, targeted to 0.3– 0.4 mmol/l. This level of ionized calcium is enough to prevent clotting. With higher hematocrit, lower citrate doses are needed.

Post-dialyzer ionized calcium level is lower than pre-dialyzer because of the calcium efflux from the plasma dialyzed against calcium-free dialysate. Of course, it is a vital necessity to replace calcium before the hypocalcemic blood is returned to the patient. Maintaining normal ionized calcium in the patient's blood is the most

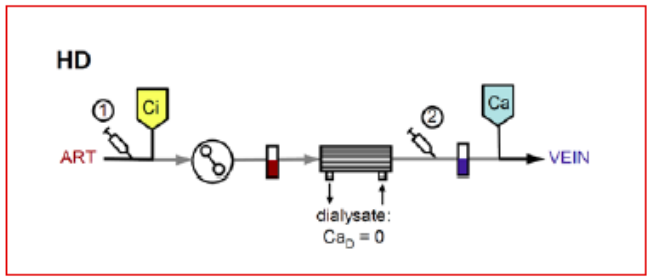


Figure 1: Scheme for regional citrate anticoagulation during double-needle hemodialysis: (1) sampling point for patient's ionized calcium; (2) sampling point for dialysis circuit (i.e. post-filter) ionized calcium; Ci=citrate; Ca=calcium; CaD=dialysate calcium © Buturovic Ponikvar, Gubensek

ferred citrate to heparin-free dialysis with saline flushes (the main option for patients at risk of bleeding before introduction of citrate). The major reason was a perfectly 'clean' dialysis circuit after dialysis, usually without any clots. Dialyzer and bloodlines after hemodialysis with RCA often looked as if they had not been used. This was achieved in parallel with patient safety and acceptable procedure complexity.

In 2016, more than 12,000 RCA procedures (>1000 per month, >30 per day) were performed by our Centre for Acute and Complicated Dialysis at University Medical Centre Ljubljana. RCA hemodialysis is routinely performed at other in-hospital Slovenian dialysis centers, and also at some free-standing hemodialysis units,

As an anticoagulant, citrate has many advantages over heparin in hemodialysis

In conclusion, citrate has many advantages over heparin as an anticoagulant in hemodialysis. Although the citrate module is not (yet) routinely available for intermittent hemodialysis (as it is for CRRT), strict protocols, trained nurses, precise infusion pumps, point-of-care ionometers and high citrate clearance in high-flux dialyzers all guarantee the safety of the procedure, with minimal risk of metabolic complications. This allows for the expansion of RCA in intermittent hemodialysis, and the exploration of potential beneficial effects of citrate beyond anticoagulation. ■

References

1. Hofbauer R, et al. Kidney Int 1999; 56: 1578– 83
2. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Chapter 5.3. Anticoagulation. Kidney Int Suppl 2012; 2(Suppl 1): 95– 100
3. Gubensek J et al. PLoS One 2016; 11: e0168593

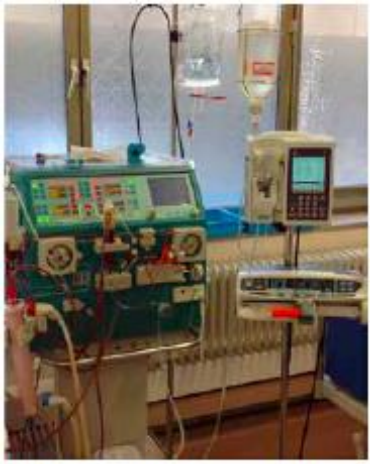


Figure 2. Regional citrate anticoagulation during double-needle hemodialysis: blood flow 250 ml/min, 8 % trisodium citrate (1000 ml polypropylene bottle) 150 ml/h, 1 M calcium chloride 13 ml/h © Buturovic Ponikvar

Regionalna citratna antikoagulacija

Ongoing trials

- efficacy and safety of different citrate concentrations in chronic hemodialysis
- randomized trial comparing efficacy and safety of chronic hemodiafiltration during citrate and heparin anticoagulation

Citrate as a locking solution for HD catheters

Ongoing trials

- In collaboration with Institute for cell biology, Faculty of Medicine, University of Ljubljana
- randomized trial comparing two different citrate concentrations (4% vs. 30%) on catheter biofilm formation assessed by scanning electron microscopy

Transplantacija ledvic

Standardiziran UZ-Doppler transplantirane ledvice

Standardized US-Doppler of the allograft

Serial measurements at predefined time points

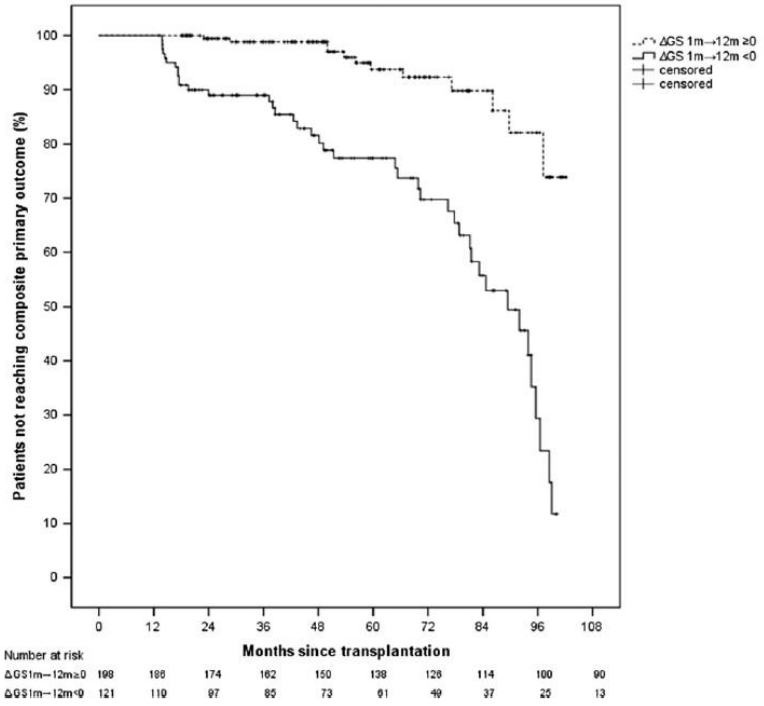
Original Clinical Science

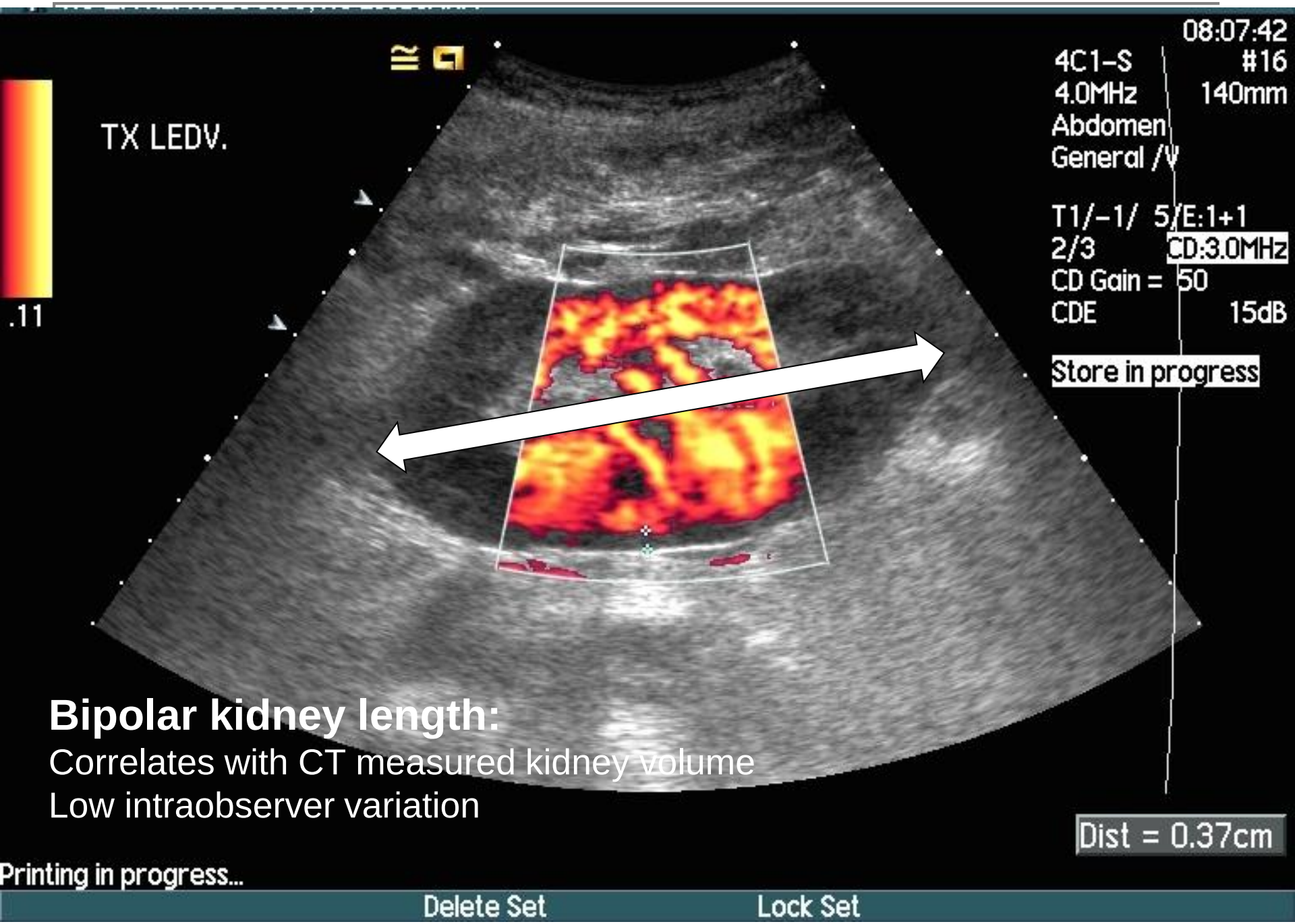
OPEN

Decrease in 1-year Kidney Graft Size Predicts Inferior Outcomes After Deceased Donor Kidney Transplantation

Senka Černe, MD,[1,2] Miha Arnol, MD, PhD,[1,3] Aljoša Kandus, MD, PhD,[1,3] and Jadranka Buturović-Ponikvar, MD, PhD[1,3]

Background. Longest bipolar length of the kidney graft is routinely measured for ultrasonographic assessment of graft size (GS), although the value of the graft length remains unclear. **Patients and Methods.** In a single-center, observational study involving 319 deceased-donor kidney transplant recipients, we assessed variations in absolute and adjusted GS (corrected for body surface area) between 1 and 12 months after transplantation ($\Delta GS_{1m \rightarrow 12m}$). We tested whether variations in GS during the first year were predictive of the composite outcome of a reduction of 50% or more in the estimated glomerular filtration rate or end-stage graft failure. **Results.** At 1 year after transplantation, 121 patients (38%) had a decrease in GS ($\Delta GS_{1m \rightarrow 12m} < 0$), and 198 patients (62%) had an increase in GS ($\Delta GS_{1m \rightarrow 12m} \geq 0$). After a median follow-up of 53 months, 41 patients with a decrease in GS reached the composite outcome as compared with 12 patients with an increase in GS (34% and 6%, respectively; $P < 0.001$). Areas under the receiver operating characteristics curves of absolute and adjusted $\Delta GS_{1m \rightarrow 12m}$ for composite outcome were 0.81 (95% confidence interval [95% CI], 0.74-0.88) and 0.78 (95% CI, 0.70-0.86), respectively. In multivariate analysis, the risk of the composite outcome was significantly higher among patients with a decrease in GS during the first year after transplantation (hazard ratio, 4.55; 95% CI, 2.35-8.81; $P < 0.001$). **Conclusions.** A decrease in kidney GS during the first year after transplantation, as compared with an increase in GS, is a powerful predictor of subsequent graft dysfunction or end-stage graft failure.





Bipolar kidney length:

Correlates with CT measured kidney volume

Low intraobserver variation

Standardized US-Doppler of the allograft

Serial measurements at predefined time points

- daily protocol US-Doppler of the kidney allograft in the early post-transplant period

- the evolution of US-Doppler parameters in patients with immediate and delayed graft function and their associations with allograft function and histology

Transplantacija ledvice

Klinični biomarkerji zavrnitve

Detection of subclinical de-novo DSA & MVI

Urine protein and complement in de-novo patients

Research Project

Spot urine protein and Complement excretion in a prospective cohort of kidney transplant recipients during the first year after transplant

Detection of subclinical de-novo DSA & MVI

Urine albumin and tubular protein excretion

Research Project

- Spot urine albumin and tubular protein (*NAG, alpha-1-microglobulin*) excretion in a prospective cohort of kidney transplant recipients during the first year after transplant

Transplantacija ledvice – molekularni markerji zavrnitve

Detection of subclinical de-novo DSA & MVI

Intracellular vesicles - Inlammasome

Javna agencija za raziskovalno dejavnost Republike Slovenije

Slovenian Research Agency

univerzitetni klinični center ljubljana
University Medical Centre Ljubljana

Univerza v Ljubljani
Medicinska fakulteta
Department of Biochemistry

- ***Inflammasome*** as a biomarker of kidney graft injury in a prospective cohort of kidney transplant patients

Raziskovalna oprema

- Področje raziskovanja so predvsem opazovalne in interventne klinične raziskave
- Oprema predvsem v povezavi s kliničnim delom (ultrazvočno monitorji, point-of-care laboratorijski aparati….)
- Hladilnik za biološke vzorce z veliko kapaciteto za shranjevanje (-80 ° C)
- Centrifuga za krvne vzorce

Primer dobre prakse

- Doktorska naloga asist. Dr. Željke Večerić Haler, v sodelovanju z Inštitutom za Biologijo celice MF
- Preučevanje protektivnega učinka matičnih celic pri akutni ledvični okvari pri miškah
- V pripravi pilotski projekt uporabe mezenhimskih matičnih celic pri kronični humoralni zavrnitvi presajene ledvice, v sodelovanje bo vključen ZTM

Dodana vrednost sodelovanja z MF, OI, ZTM

- Visoka ekspertnost ustanov
- Mednarodna uveljavljenost raziskovalcev
- Prepletenost sodelovanja na kliničnih in drugih področjih
- Neposredna bližina ustanov
- Izjemna priložnost za dodatne sinergije na področju kliničnega in translacijskega raziskovanja
- Priložnost za usklajen nastop na domačih in mednarodnih razpisih