Hemodynamic Consequences of Hemodialysis

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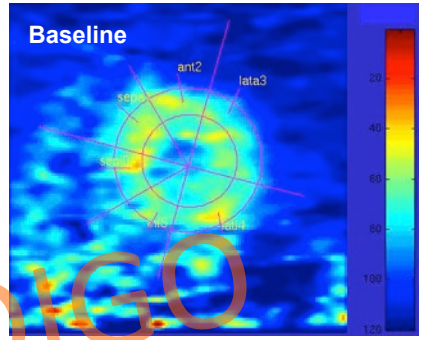
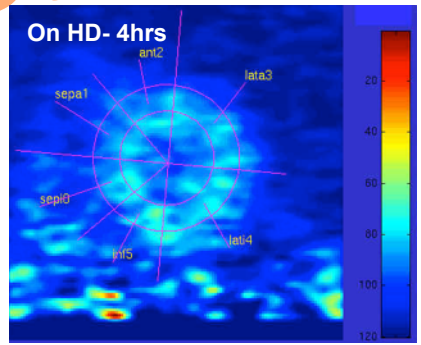
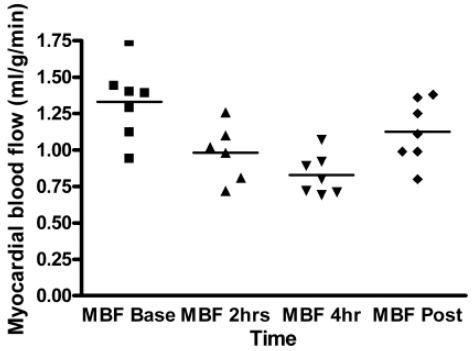
Outline

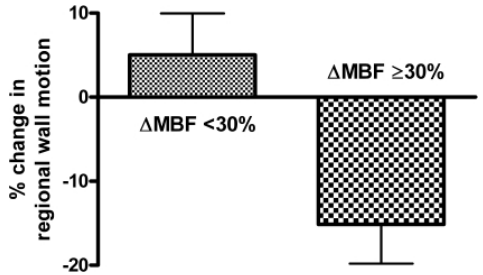
- Tour of the battlefield
- Injury is interconnected
- Making it better
- What we know is very limited
- Future approaches
- Conclusions

First direct study of HD-induced cardiac ischemia





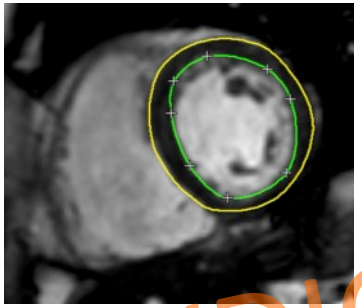




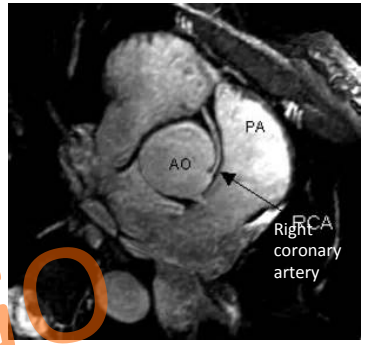
McIntyre CW et al. Clin J Am Soc Nephrol. 2008 Jan;3(1):19-26
McIntyre CW. Acute cardiac effects of haemodialysis. Kidney Int 2009

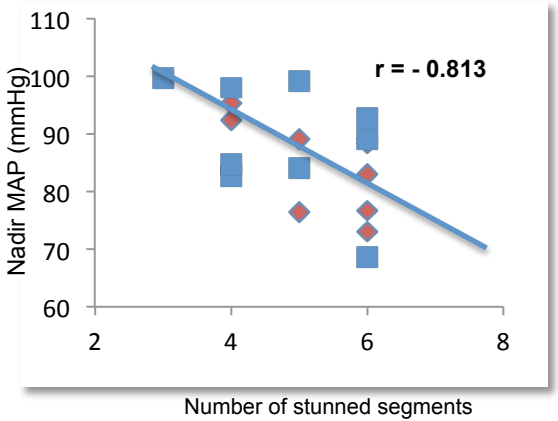
Cardiac MRI during hemodialysis

Global function

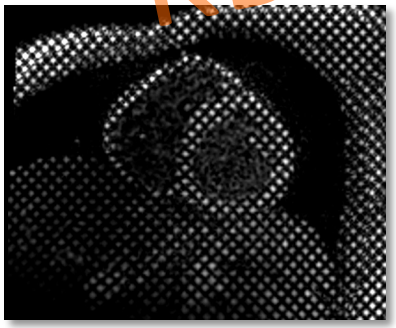


Coronary flow

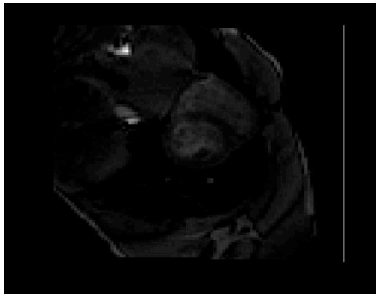


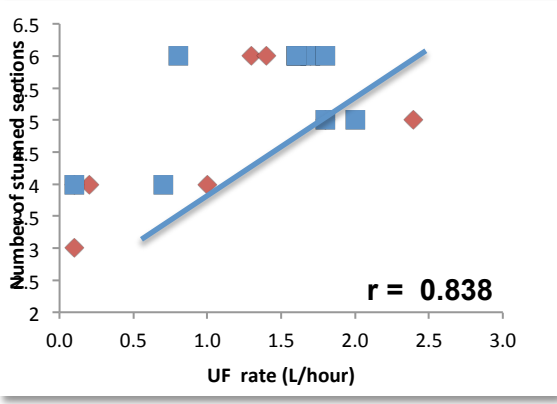


Segmental function



Myocardial perfusion

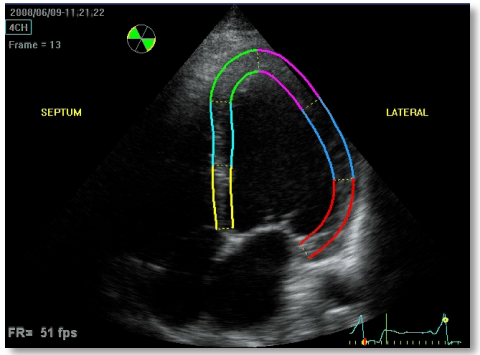


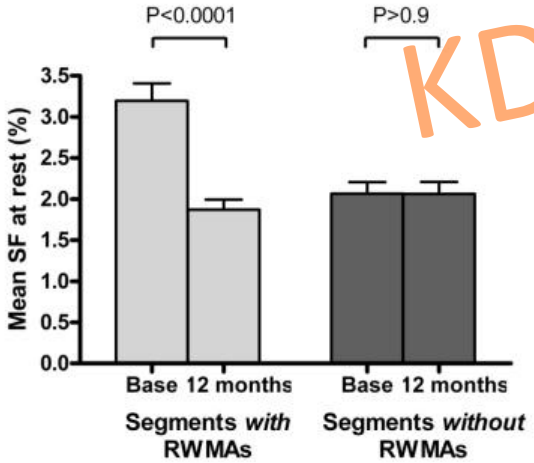


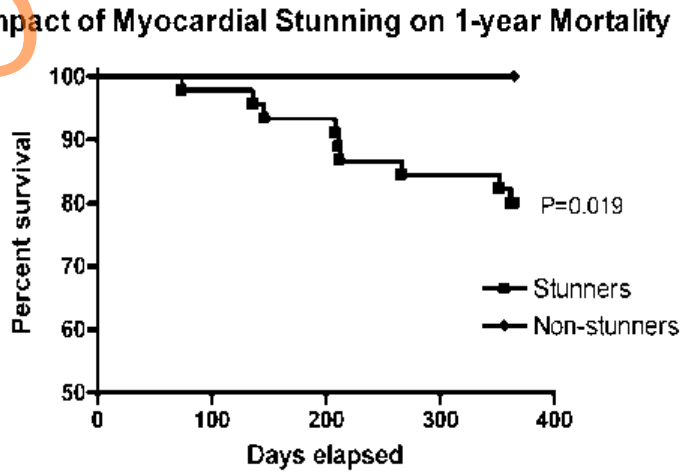
Buchanan C, Mohammed A, Köhler K, Canaud B, Taal MW, Selby NM, McIntyre CW. J Am Soc Nephrol. 2017 Apr;28(4):1269-1277

Longer term effects of recurrent cardiac injury- Heart failure

Factor associated with development of myocardial stunning	*OR*	*P value*
UF volume during HD of 1L	5.1	0.007
UF volume during HD of 1.5L	11.6	
UF volume during HD of 2L	26.2	
Max SBP reduction during HD of 10 mmHg	1.8	0.002
Max SBP reduction during HD of 20 mmHg	3.3	
Max SBP reduction during HD of 30 mmHg	6.0	

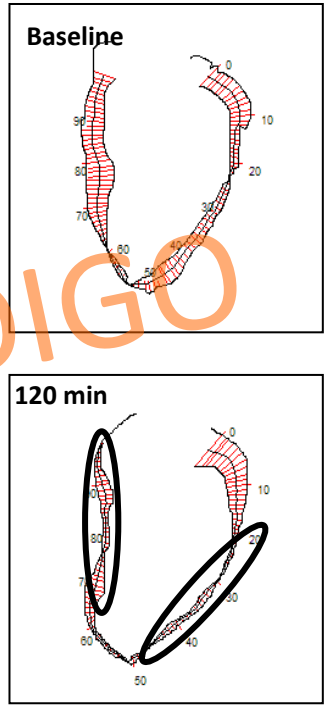


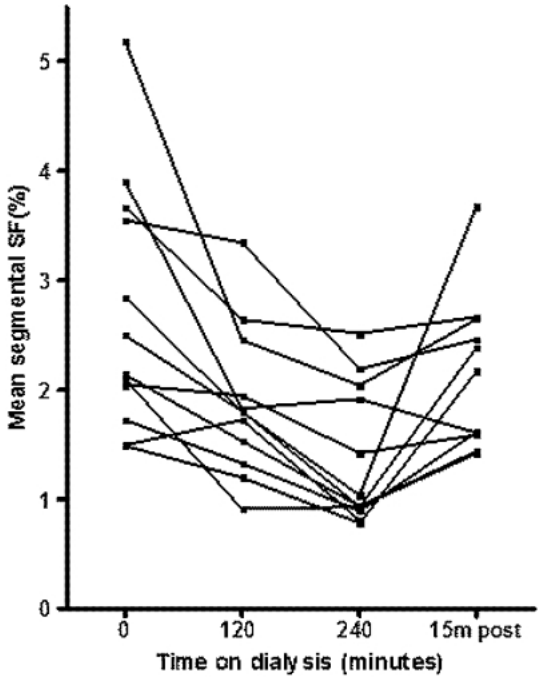




Burton JO, Korsheed S, McIntyre CW. Clin J Am Soc Nephrol. 2009 May;4(5):914-20
Burton JO, Jefferies HJ, *McIntyre CW* . Clin J Am Soc Nephrol. 2009 Dec;4(12):1925-31

Children on dialysis- Uremia *without* classical CAD





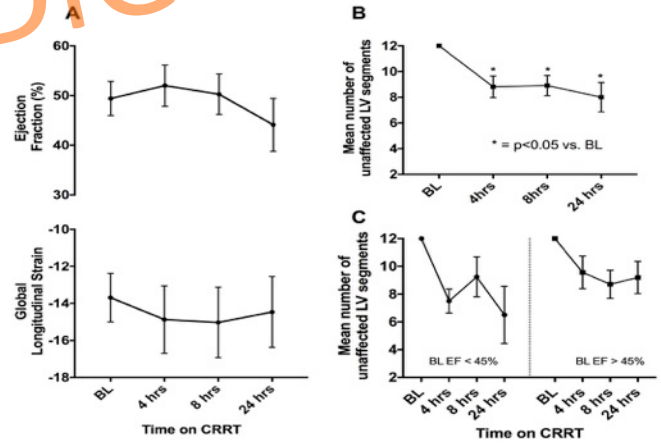
Hothi D, Rees L, McIntyre CW. Clin J Am Soc Nephrol 2009

Intensive Care Med
DOI 10.1007/s00134-017-4768-2

Myocardial stunning occurs during intermittent haemodialysis for acute kidney injury

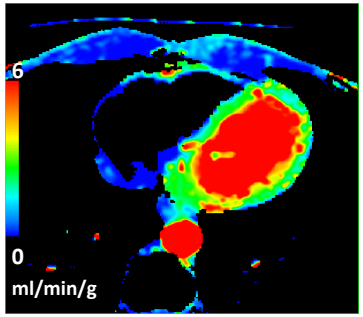
Huda Mahmoud[1,2*], Lui G. Forni[3], Christopher W. McIntyre[4] and Nicholas M. Selby[1,2]

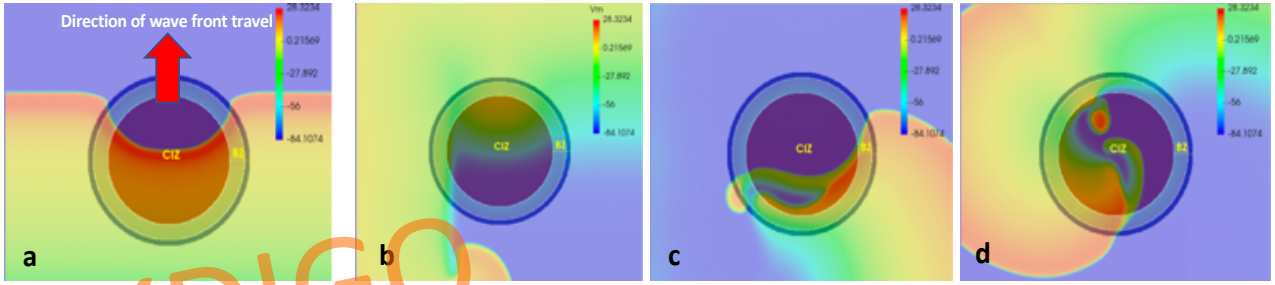
KDIGO

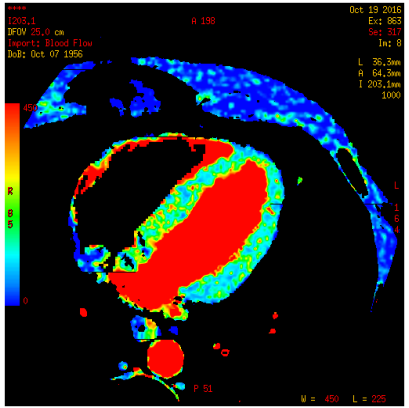


Slasserev M, Salerno F, McIntyre CW. SA-PO554 ASN 2018

Importance of tissue perfusion patterns- beyond HF







KDIGO

Renal Failure, 30:701–709, 2008

ISSN: 0886-022X print / 1525-6049 online
DOI: 10.1080/08860220802212908

informa
healthcare

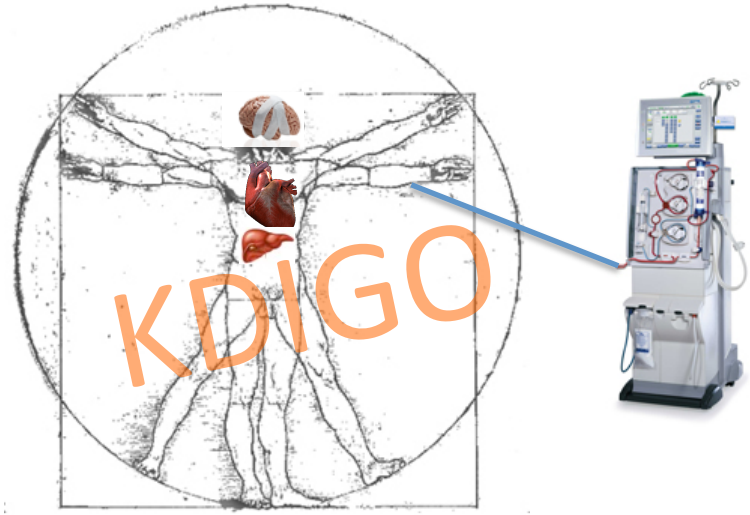
CLINICAL STUDY

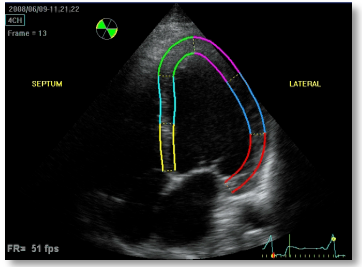
Hemodialysis-Induced Left Ventricular Dysfunction Is Associated with an Increase in Ventricular Arrhythmias

Dying to Feel Better: The Central Role of Dialysis–Induced Tissue Hypoxia

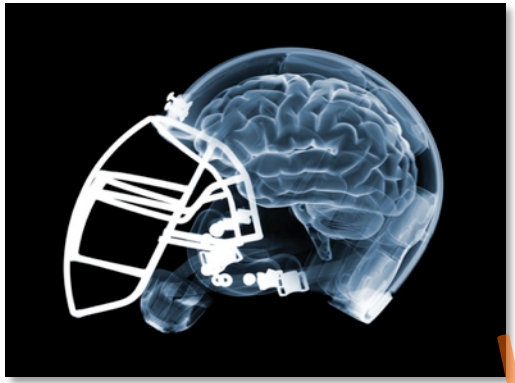
Christopher McIntyre and Lisa Crowley

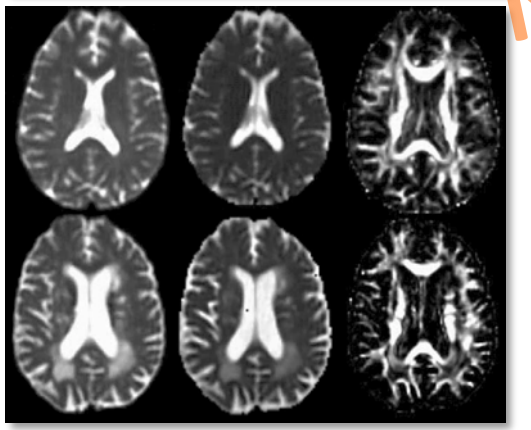
Clin J Am Soc Nephrol 11: ●●●–●●●, 2016. doi: 10.2215/CJN.01380216





HD- associated brain injury





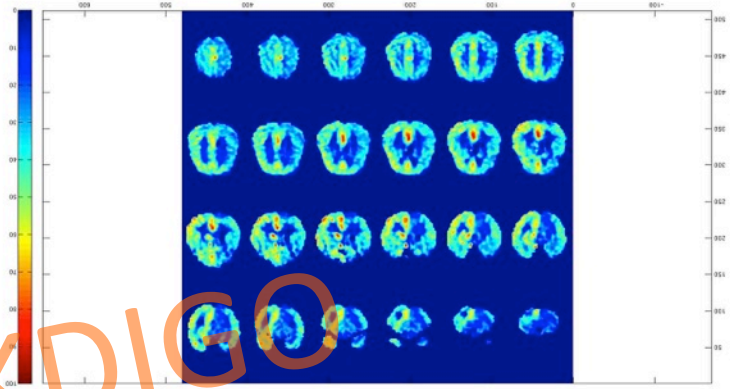
- Universal
- Functionally significant
- Progressive
- Directly proportional to white matter changes
- Independently associated to hemodynamic instability

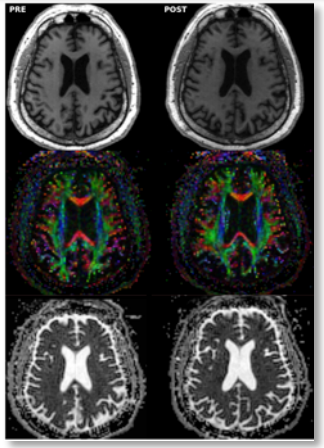
McIntyre CW, Goldsmith DJ. Kidney Int. 2015 Jun;87(6):1109-15
Eldehni MT, Odudu A, McIntyre CW. J Am Soc Nephrol. 2015 Apr;26(4):957-65
Eldehni MT, McIntyre CW.Semin Dial. 2012 May;25(3):253-6

Acute effects of HD on brain- PET/MR imaging

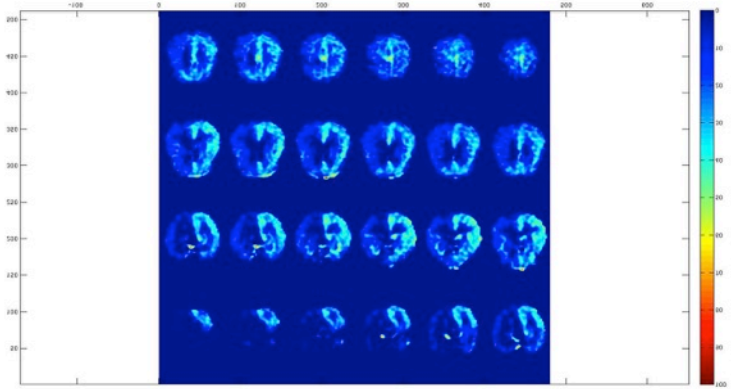
HEART & STROKE FOUNDATION OF CANADA
Finding answers. For life.

Pre-HD



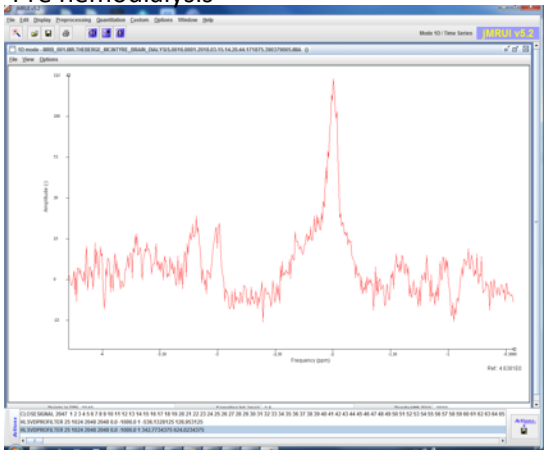


Peak stress-HD

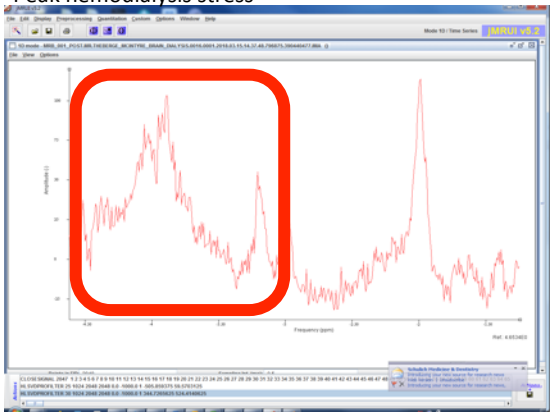


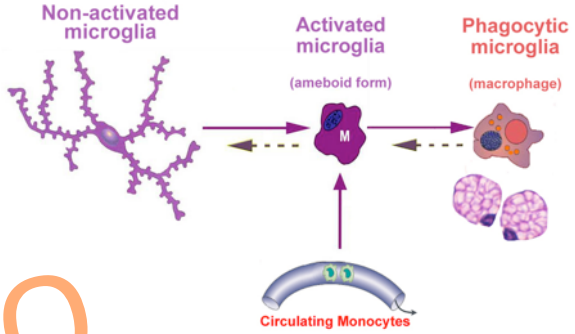
Toxic neurotransmitter release and Inflammation

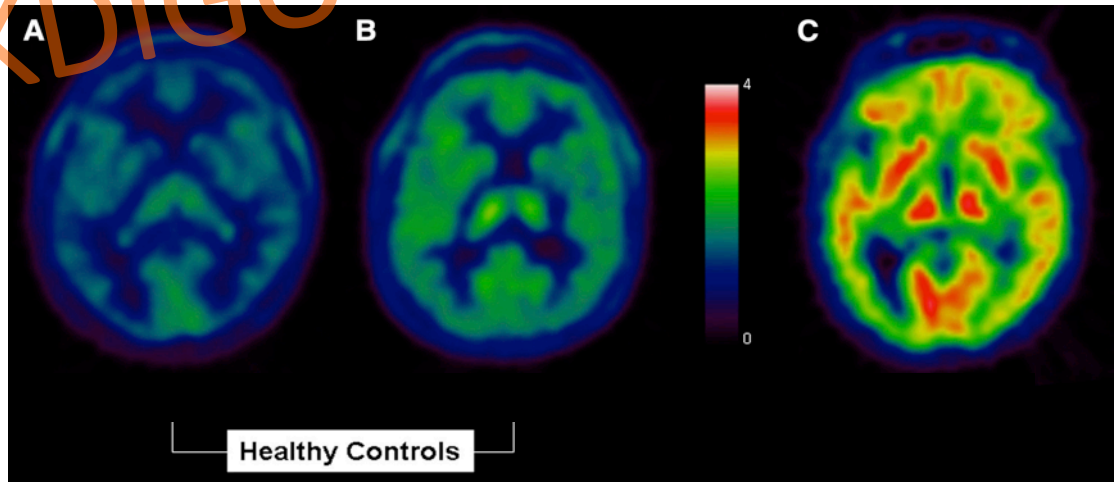
Pre hemodialysis



Peak hemodialysis stress







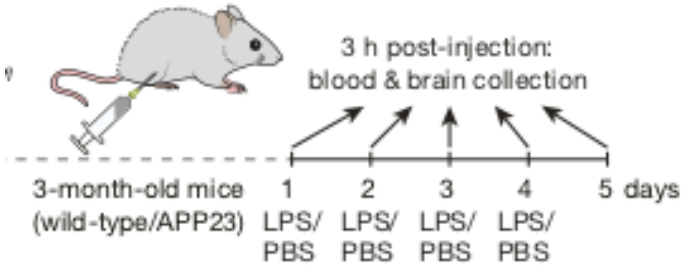
ARTICLE

NATURE | www.nature.com/nature

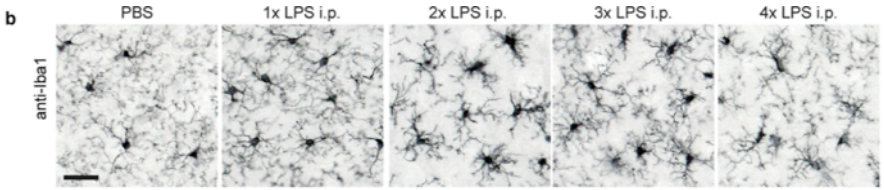
https://doi.org/10.1038/s41586-018-0023-4

Innate immune memory in the brain shapes neurological disease hallmarks

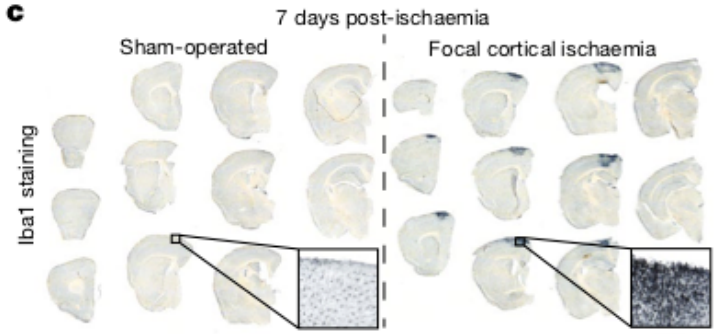
Ann-Christin Wendeln[1,2,3,12], Karoline Degenhardt[1,2,3,12], Lalit Kaurani[4,5], Michael Gertig[4,5], Thomas Ulas[6], Gaurav Jain[5,7], Jessica Wagner[1,2,3], Lisa M. Häsler[1,2], Katleen Wild[1,2], Angelos Skodras[1,2], Thomas Blank[8], Ori Staszewski[8], Moumita Datta[8], Tonatiuh Pena Centeno[5,7], Vincenzo Capece[5,7], Md. Rezaul Islam[5], Cemil Kerimoglu[5], Matthias Staufenbiel[1,2], Joachim L. Schultze[6,9], Marc Beyer[10], Marco Prinz[8,11], Mathias Jucker[1,2], André Fischer[4,5] & Jonas J. Neher[1,2]*



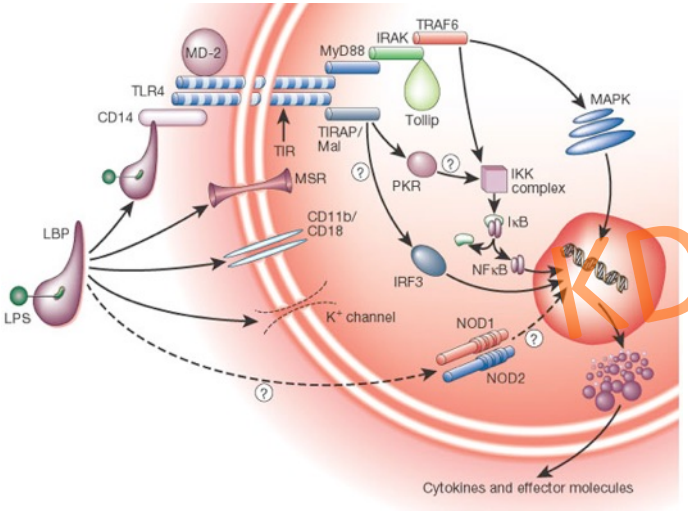
Microglia are recruited and activated- with memory

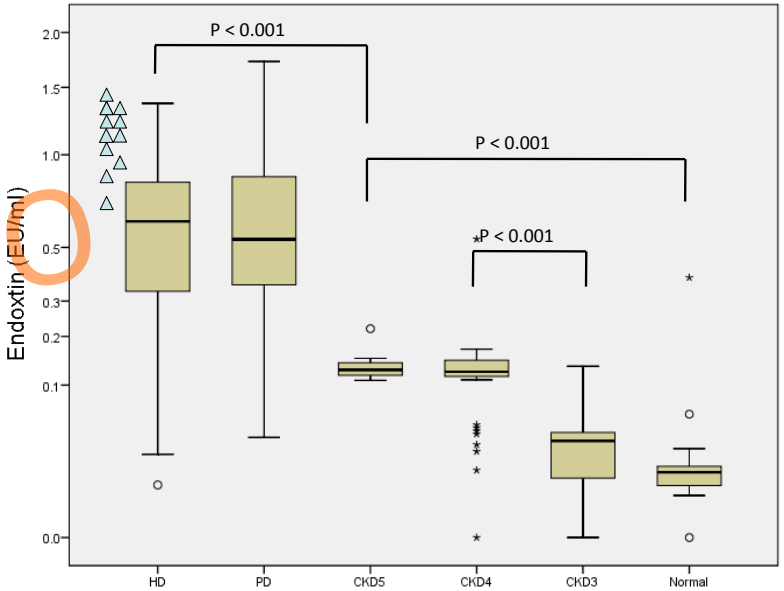


This aggravates neurological injury



Gut derived endotoxin in CKD





Jonathan Cohen *Nature* 420, 885-891(19 December 2002

McIntyre CW, Harrison LE, Eldehni MT et al. Clin J Am Soc Nephrol. 2011 Jan;6(1):133-41

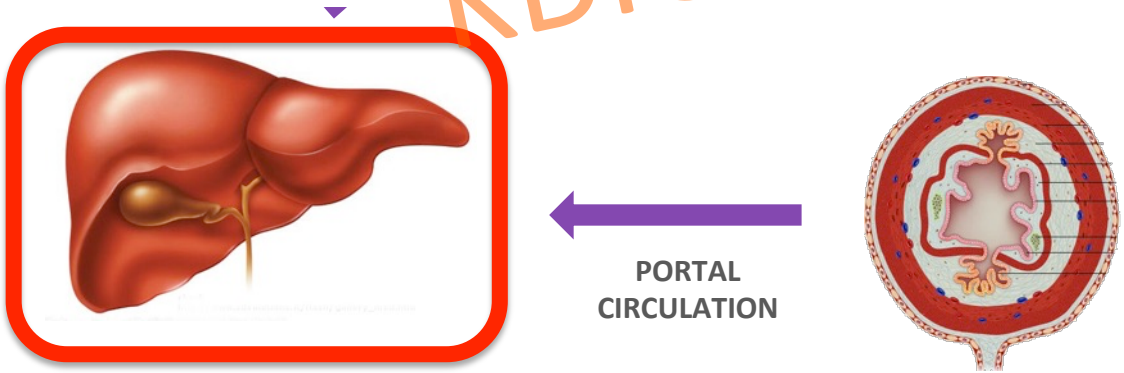
Harrison LEA, McIntyre CW. Nephron 2014

REVIEW www.jasn.org

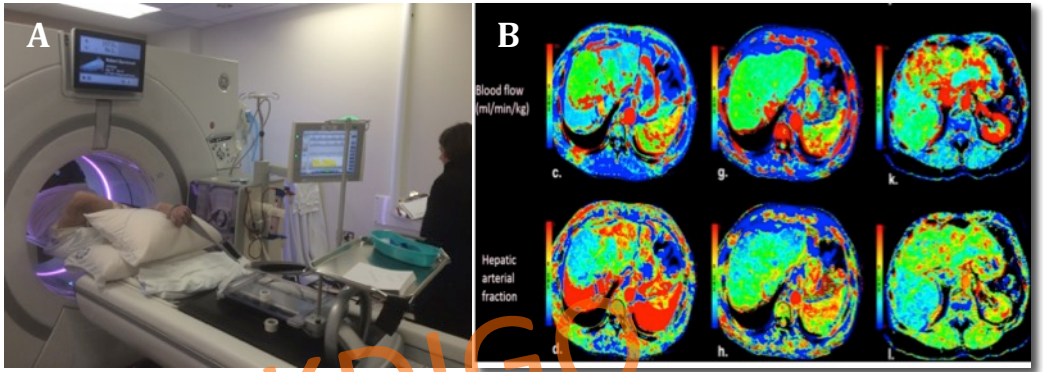
J Am Soc Nephrol **29:** 1601–1608, 2018

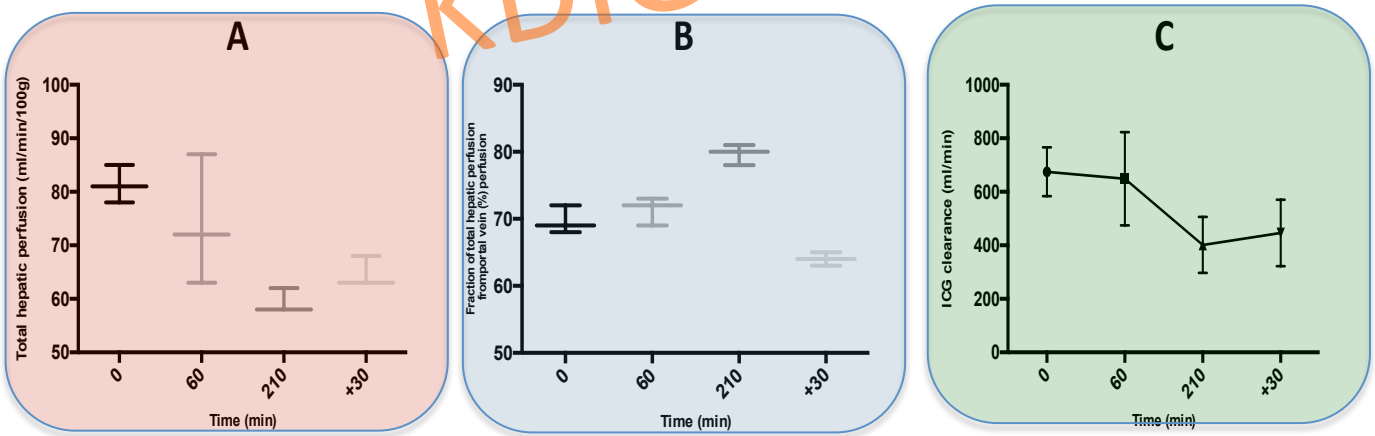
Circulating Bacterial Fragments as Cardiovascular Risk Factors in CKD

Cheuk-Chun Szeto,[1] Christopher William McIntyre,[2] and Philip Kam-Tao Li[1]



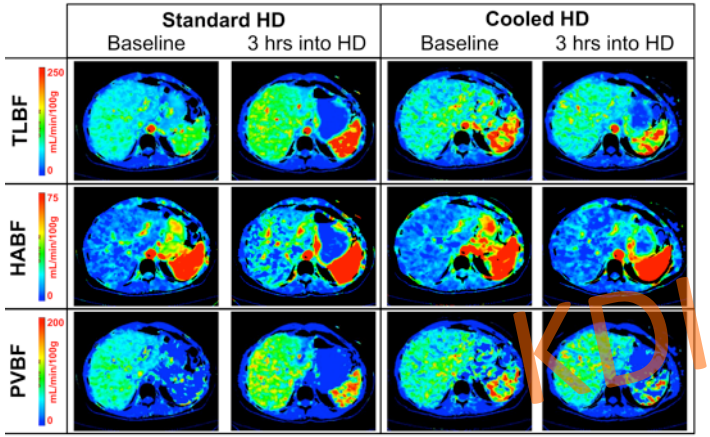
HD effects on hepatic perfusion- the selfish liver

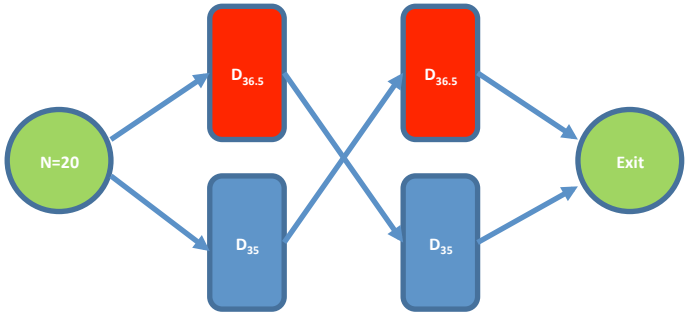


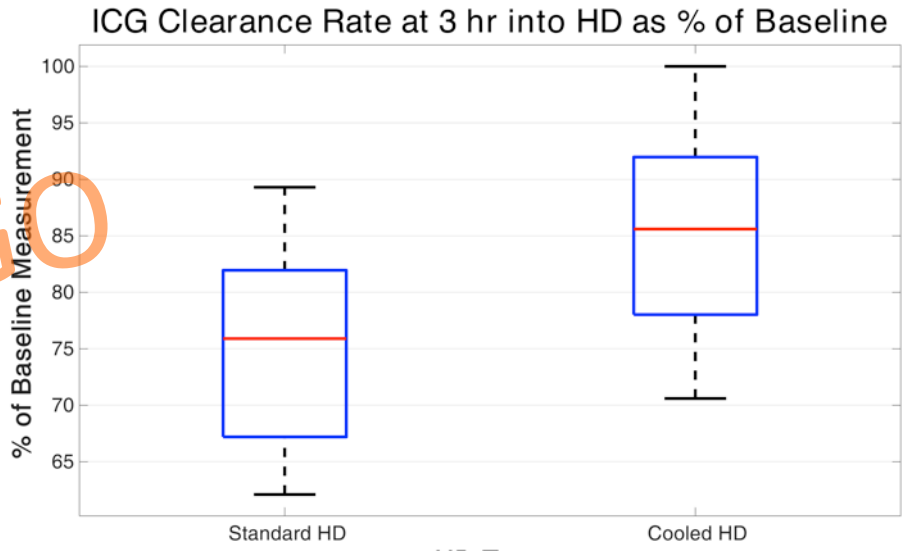


Grant CA, McIntyre CW. Seminars in Dialysis 2019

RCT of dialysate cooling to improve hepatic and GIT perfusion during HD

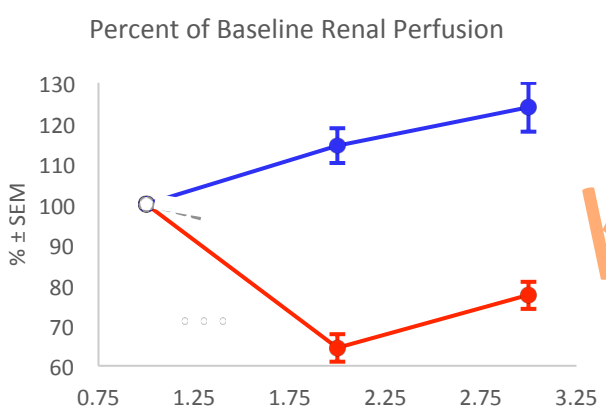


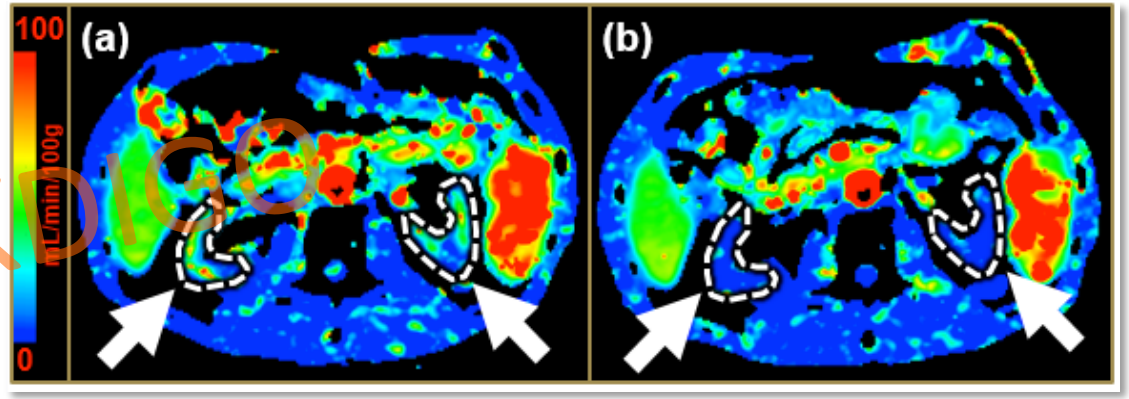




Qirjazi E, Marants R, Li TY, McIntyre CW. TH-PO0355 ASN 2018

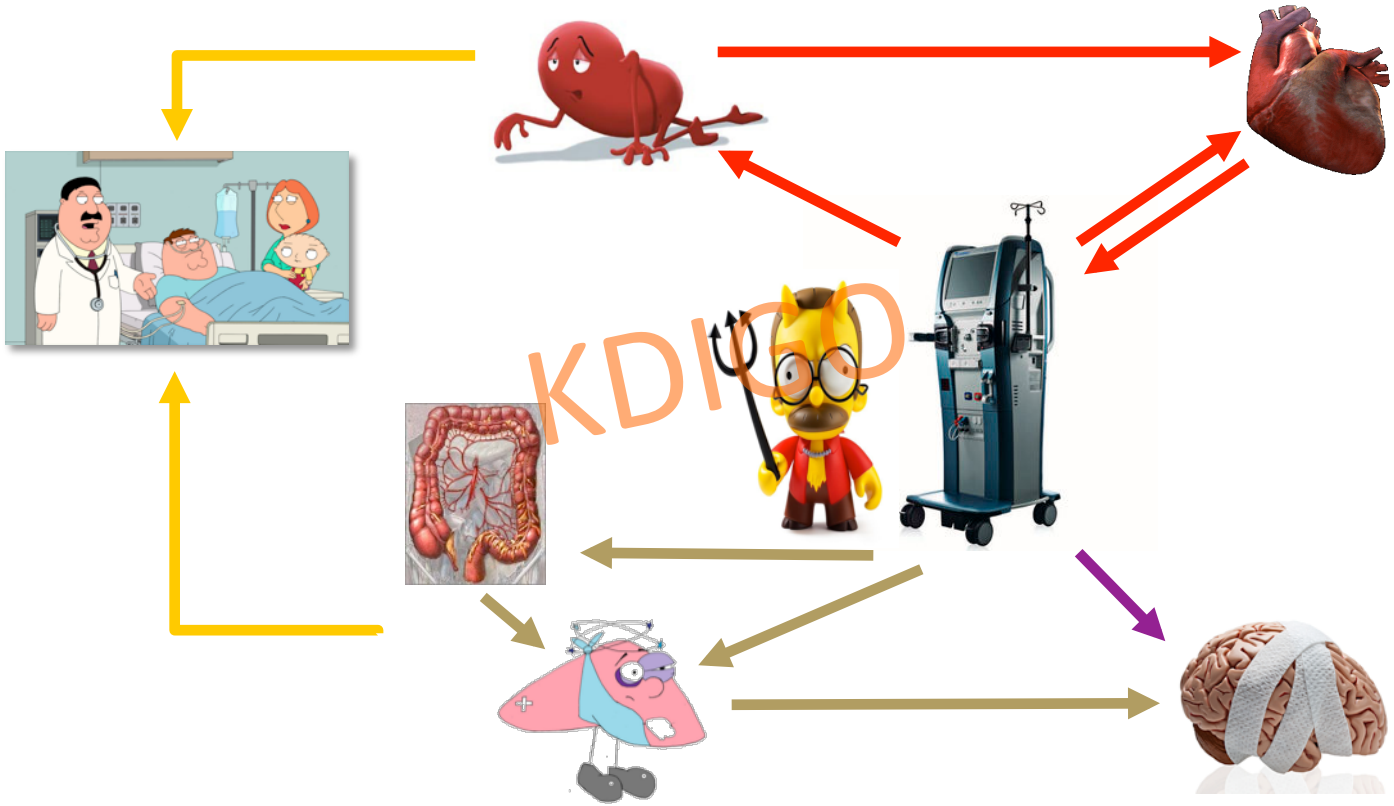
‘Kidney stunning’- recurrent dialysis induced AKI





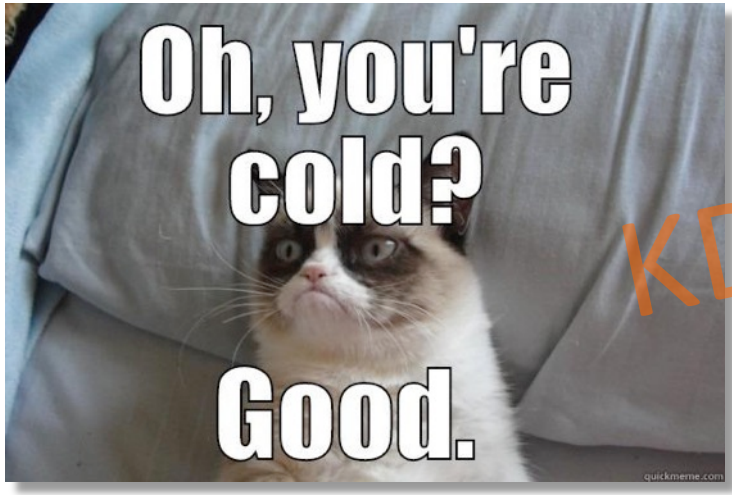
Marants R, Grant CA, Lee T, McIntyre CW. TH-PO341 ASN 2018

HD-induced organ injury- Interconnected and horrible




FIX IT!
KDIGO

Cooled dialysate- application to cardiovascular protection



Randomized Clinical Trial of Dialysate Cooling and Effects on Brain White Matter

Mohamed T. Eldehni, Aghogho Odudu, and Christopher W. McIntyre
Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, University of Nottingham, Nottingham, United Kingdom

ABSTRACT
Hemodialysis is associated with significant circulatory stress that could produce recurrent and cumulative ischemic insults to multiple organs, such as the brain. We aimed to characterize hemodialysis-induced brain injury by longitudinally studying the effects of hemodialysis on brain white matter microstructure and further examine if the use of cooled dialysate could provide protection against hemodialysis-associated brain injury. In total, 73 patients on incident hemodialysis starting within 6 months were randomized to dialyze with a dialysate temperature of either 37°C or 0.5°C below the core body temperature and followed up for 1 year. Brain white matter microstructure was studied by diffusion tensor magnetic resonance imaging at baseline and follow-up (38 patients available for paired analysis). Intradialytic hemodynamic stress was quantified using the extrema points analysis model. Patients on hemodialysis exhibited a pattern of ischemic brain injury (increased fractional anisotropy and reduced radial diffusivity). Cooled dialysate improved hemodynamic tolerability, and changes in brain white matter were associated with hemodynamic instability (higher mean arterial pressure extrema points frequencies were associated with higher fractional anisotropy [peak r=0.443, P<0.03] and lower radial diffusivity [peak r=−0.439, P<0.02]). Patients who dialyzed at 0.5°C below core body temperature exhibited complete protection against white matter changes at 1 year. Our data suggest that hemodialysis results in significant brain injury and that improvement in hemodynamic tolerability achieved by using cooled dialysate is effective at abrogating these effects. This intervention can be delivered without additional cost and is universally applicable.

J Am Soc Nephrol 26: ●●●–●●●, 2015. doi: 10.1681/ASN.2013101086

Blood Purification

Haemodialysis-Induced Myocardial Stunning, without Compromising Tolerability

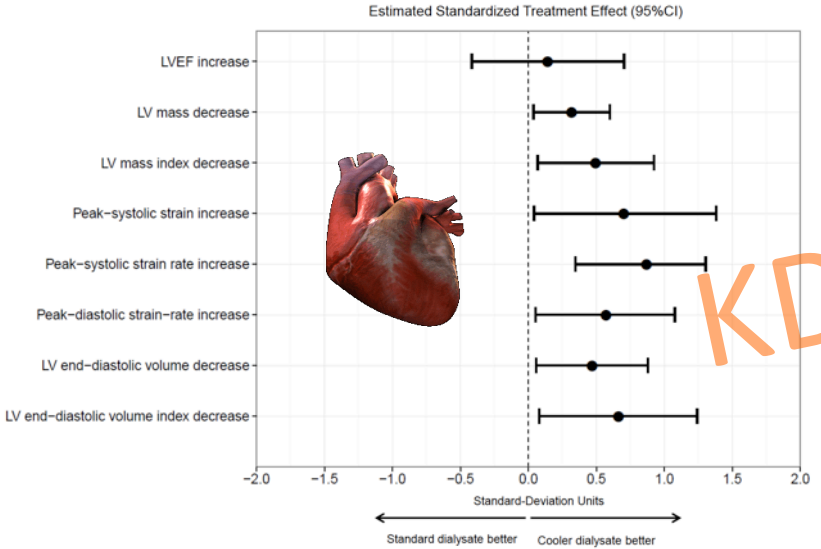
Helen J. Jefferies[a] James O. Burton[a] Christopher W. McIntyre[a, b]
[a]Department of Renal Medicine, Royal Derby Hospital, and [b]School of Graduate Entry Medicine and Health, University of Nottingham, Nottingham, UK

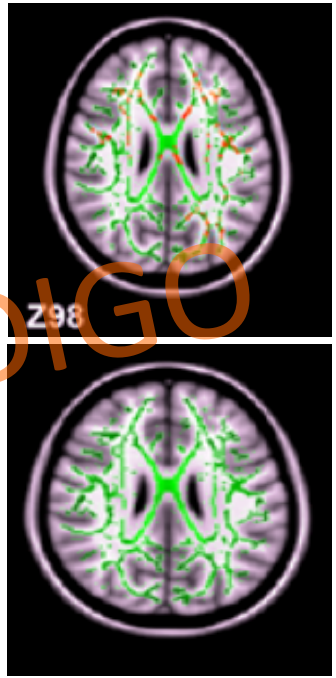
systolic LV function was significantly more impaired during HD_D (P < 0.001). BP was higher during HD_{UF} with fewer episodes of hypotension as a result of a higher peripheral resistance and no difference in stroke volume. The development of thermal symptoms was heterogeneous, with most patients tolerating HD_{UF} well. This study confirms previous findings of reversible LV RWMA that develop during hemodialysis. It also shows that this phenomenon can be ameliorated by reducing dialysate temperature, a simple intervention with no cost implications.

Clin J Am Soc Nephrol ●●: ●●●–●●●, ●●●●. doi: 10.2215/CJN.02010606

Nicholas M. Selby[1] and Christopher W. McIntyre[1,2]

Cardiac and neuro-protection with cooling





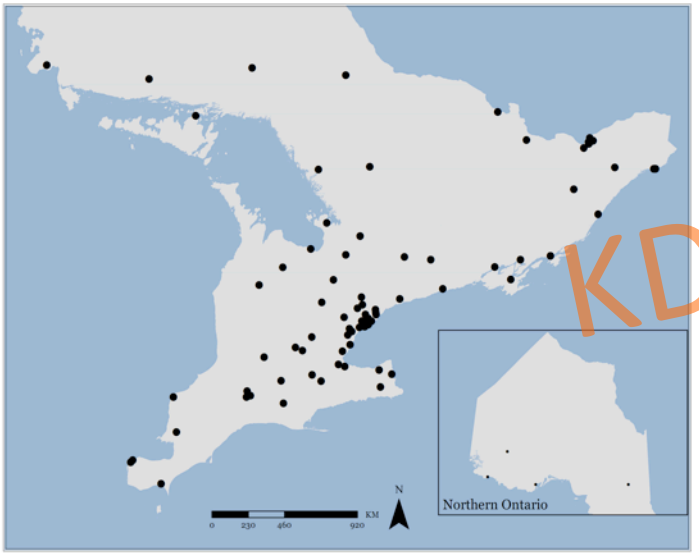
	Group Dialyzed at 0.5°C below Body Temperature (n=19)			Group Dialyzed at 37°C (n=19)		
	Mean FA at Baseline	Mean FA at 1 yr	Significant Voxels (%)	Mean FA at Baseline	Mean FA at 1 yr	Significant Voxels (%)
Anterior thalamic radiation-L				0.335±0.029	0.345±0.029	11.1
Anterior thalamic radiation-R				0.334±0.029	0.343±0.030	10.2
Corticospinal tract-L				0.432±0.024	0.439±0.022	4.4
Corticospinal tract-R				0.417±0.023	0.428±0.018	3.8
Cingulate gyrus-L				0.306±0.025	0.314±0.023	24.3
Cingulate gyrus-R				0.305±0.024	0.312±0.022	1.8
Hippocamups-L				0.261±0.033	0.275±0.032	1.8
Hippocamups-R				0.280±0.033	0.292±0.033	0
Forceps major				0.337±0.025	0.344±0.022	3.9
Forceps minor				0.315±0.030	0.324±0.030	25
Inferior fronto-occipital fasciculus-L				0.310±0.025	0.320±0.024	9.5
Inferior fronto-occipital fasciculus-R				0.321±0.025	0.328±0.024	9.7
Inferior longitudinal fasciculus-L				0.298±0.020	0.306±0.021	13.2
Inferior longitudinal fasciculus-R				0.292±0.020	0.299±0.020	0
Superior longitudinal fasciculus-L				0.288±0.018	0.297±0.018	26.6
Superior longitudinal fasciculus-R				0.273±0.017	0.282±0.013	6.9
Ucinate fasciculus-L				0.301±0.025	0.309±0.026	3.2
Ucinate fasciculus-R				0.305±0.025	0.314±0.027	5.1
Superior longitudinal fasciculus-L (temporal part)				0.318±0.022	0.321±0.024	21.6
Superior longitudinal fasciculus-R (temporal part)				0.350±0.024	0.354±0.021	0.9

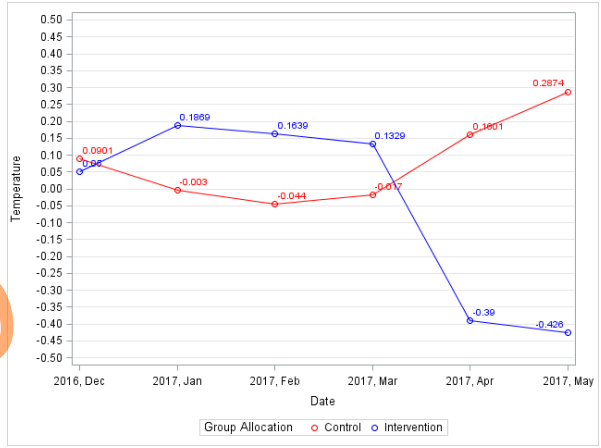
Region-of-interest analysis using John Hopkins University WM labels atlas showing the changes in means of FA at baseline and 1 year of each region stratified by treatment group; percentages of the statistically significant voxels in each region are also presented. L, left; R, right.

Odudu A, Eldehni MT, McIntyre CW. Clin J Am Soc Nephrol 2015

Eldehni MT, Odudu A, McIntyre CW. JASN 2014

MY TEMP Trial- cluster RCT





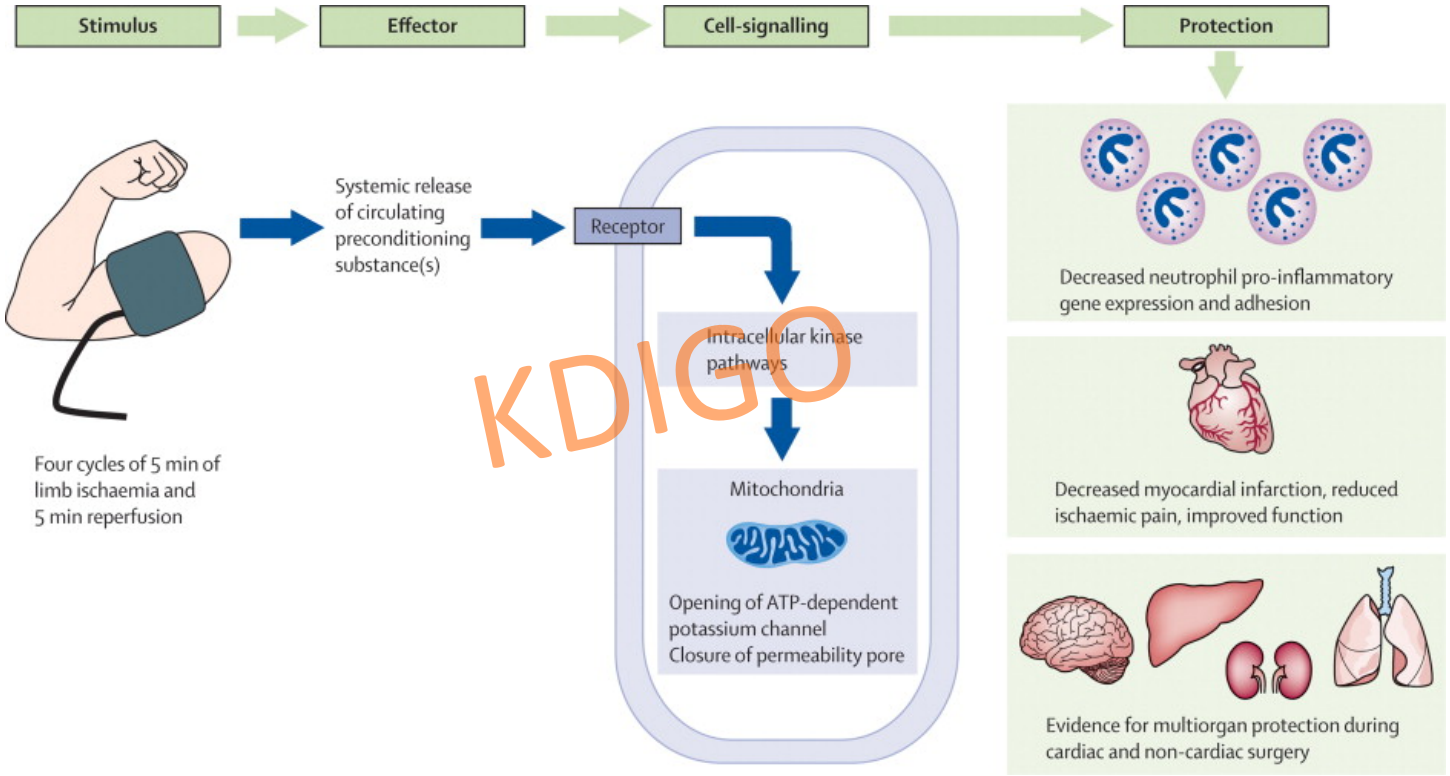
CJASN ePress. Published on February 5, 2019 as doi: 10.2215/CJN.08240718

Article

Associations between Hemodialysis Facility Practices to Manage Fluid Volume and Intradialytic Hypotension and Patient Outcomes

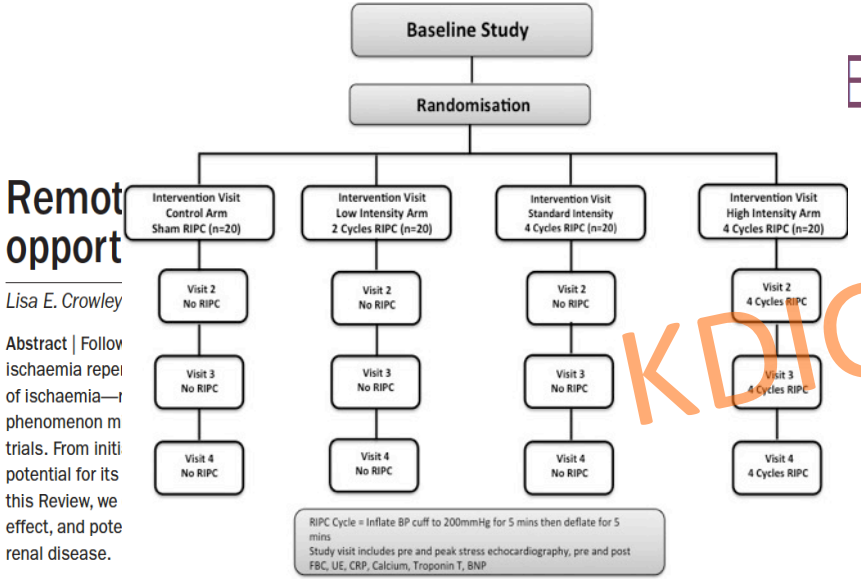
Indranil Dasgupta,[1,2] G. Neil Thomas,[2] Joanne Clarke,[2] Alice Sitch,[2,3] James Martin,[2] Brian Bieber,[4] Manfred Hecking,[5] Angelo Karaboyas,[4] Ronald Pisoni,[4] Friedrich Port,[4] Bruce Robinson,[4] and Hugh Rayner[1]

Remote ischemic preconditioning (RIPC)



Kharbanda KR et al. The Lancet 2009.

RIPC effect on dialysis induced cardiac injury



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Lisa E. Crowley

Abstract | Follov
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renal disease.

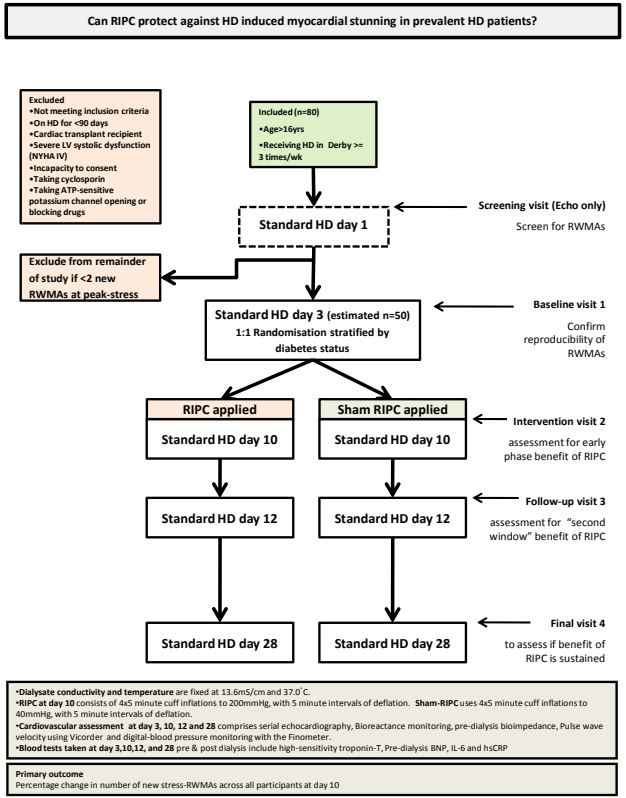
Crowley, L. E. & McIntyre, C. W. *Nat. Rev. Nephrol.* 9, 739–746 (2013); published online 5 November 2013; doi:10.1038/nrneph.2013.226

EWS

KDIGO

Crowley L, Odudu A. McIntyre CW. ASN 2014

Figure 1



Salerno F, Tommassi T Penny J, McIntyre CW. SA-P0858 ASN 2018

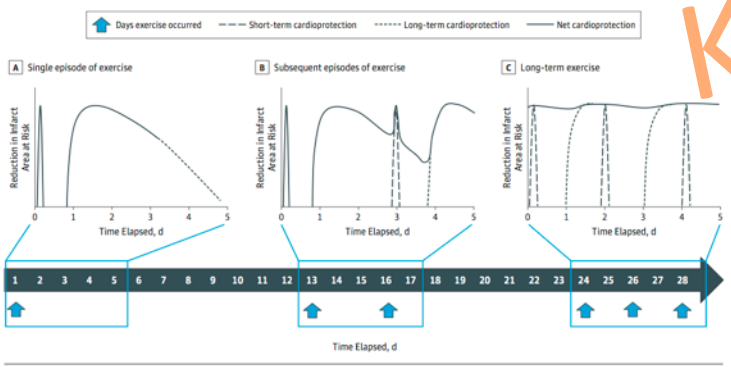
Exercise pre-conditioning to protect against HD-induced cardiac injury

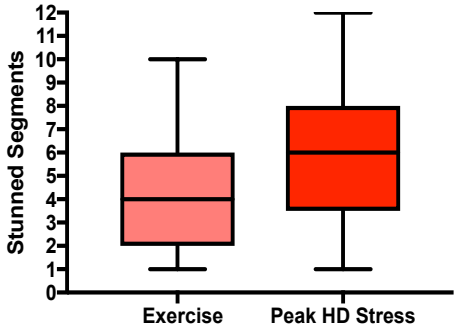
JAMA Cardiology | Review

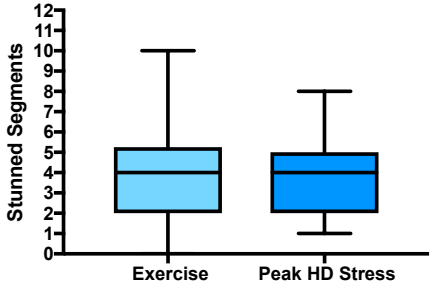
Association of Exercise Preconditioning With Immediate Cardioprotection
A Review

Dick H. J. Thijssen, PhD; Andrew Redington, MD, PhD; Keith P. George, PhD; Maria T. E. Hopman, MD, PhD; Helen Jones, PhD

Figure 2. Cardioprotection Through Exercise Preconditioning

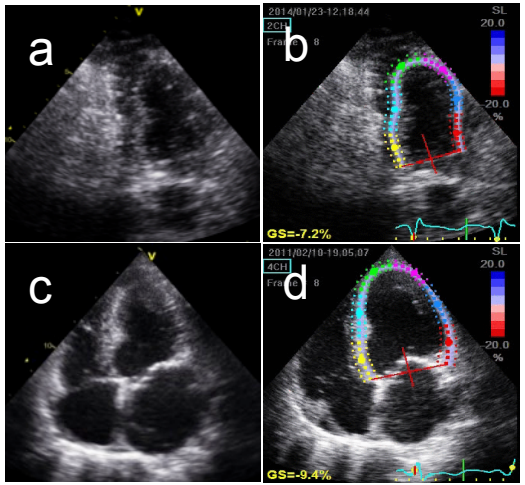




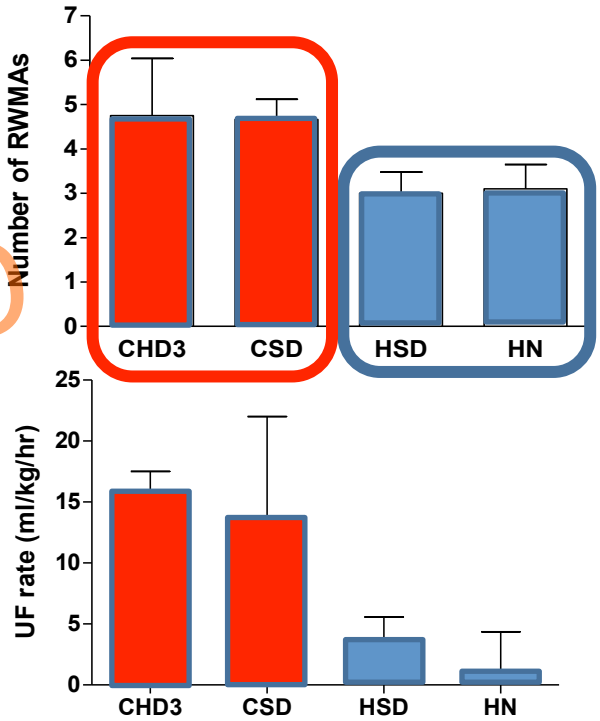


Penny J, Bohm C, McIntyre CW. Nephrol Dialysis and Transplant 2019

Impact of daily dialysis on HD-induced cardiac injury



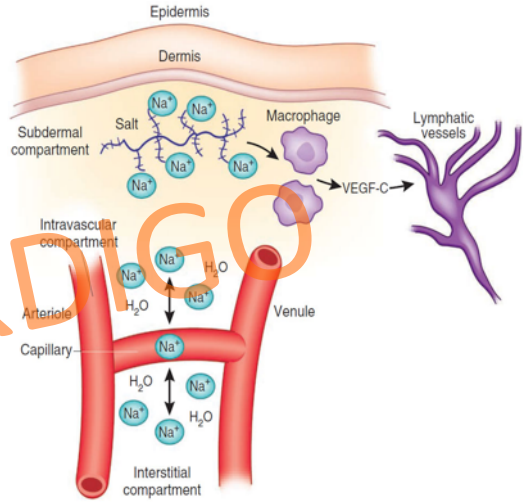
KDIGO

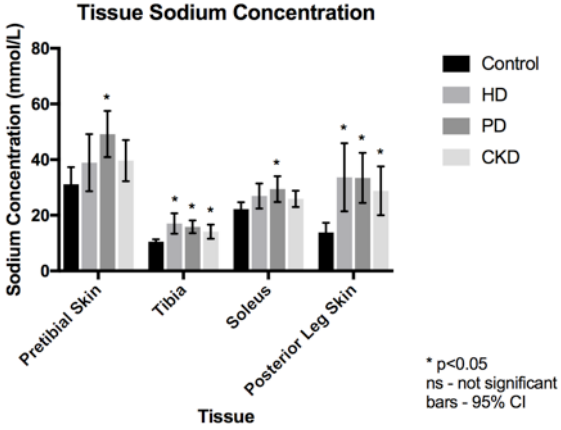


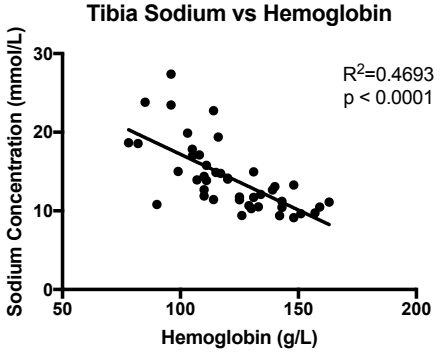
Jefferies HJ, Schiller B, Moran J, McIntyre CW. CJASN 2011


KDIGO

Tissue sodium deposition- ^{23}Na MRI in CKD patients

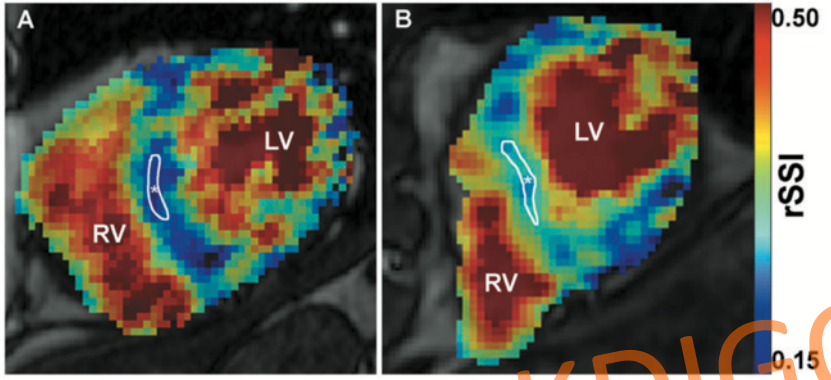


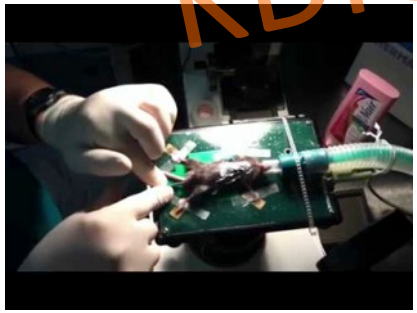




Qirjazi E, Akbari A, Scholl T, McIntyre CW. SA-OR033 ASN 2018

Myocardial Na deposition- <u>cardiotoxic</u>





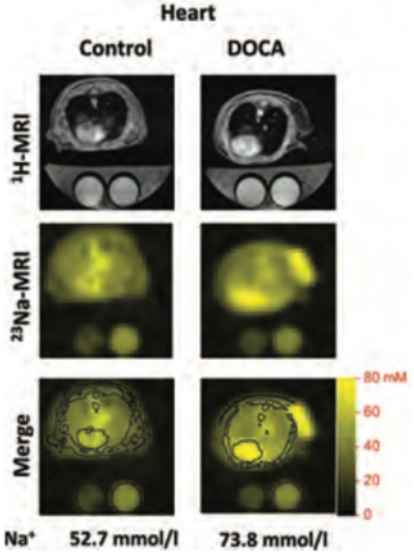
TH-PO512

Detection of Na+ Stores in the Myocardium and Skeletal Muscle of DOCA Treated Mice Using 23Na-MRI

ESC European Society of Cardiology
European Heart Journal - Cardiovascular Imaging (2018) 00, 1–8
doi:10.1093/ehjci/jey134

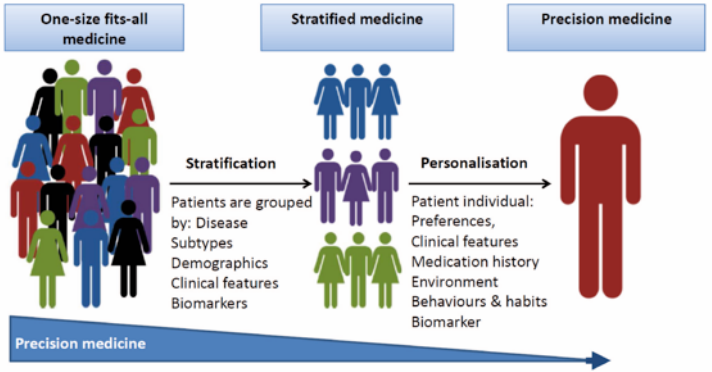
Increased myocardial sodium signal intensity in Conn's syndrome detected by ^{23}Na magnetic resonance imaging

Martin Christa [1,2†], Andreas M. Weng [3†], Bettina Geier[1], Caroline Wörmann[1], Anne Scheffler[4], Leane Lehmann[4], Johannes Oberberger[1,2], Bettina J. Kraus[1,2], Stefanie Hahner [2], Stefan Störk [1,2], Thorsten Klink[3], Wolfgang R. Bauer[1,2*], Fabian Hammer[1,5*†], and Herbert Köstler [1,3†]

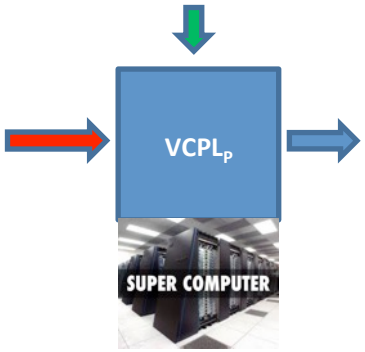


We need to do better- Precise and timely

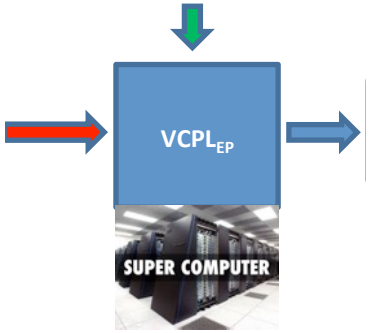
- Can only detect when harm has been evidenced
- No adequate biomarkers
- No feasible epidemiologically based approach
- No window for intervention or refinement before irreversible harm (HF or SCD)



Virtual cardiac physiology laboratory- VCPL



KDIGO

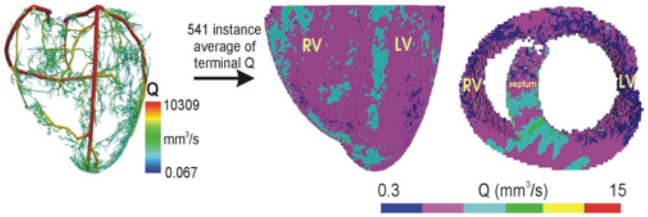


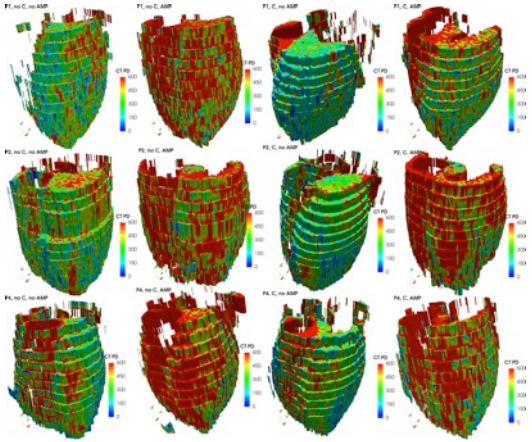
MYOCARDIAL PERFUSION

EP ACTIVITY

Virtual cardiac physiology laboratory- Patient specific simulation of uremic heart

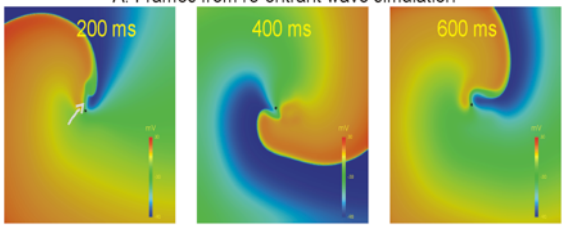
$VCPL_P$



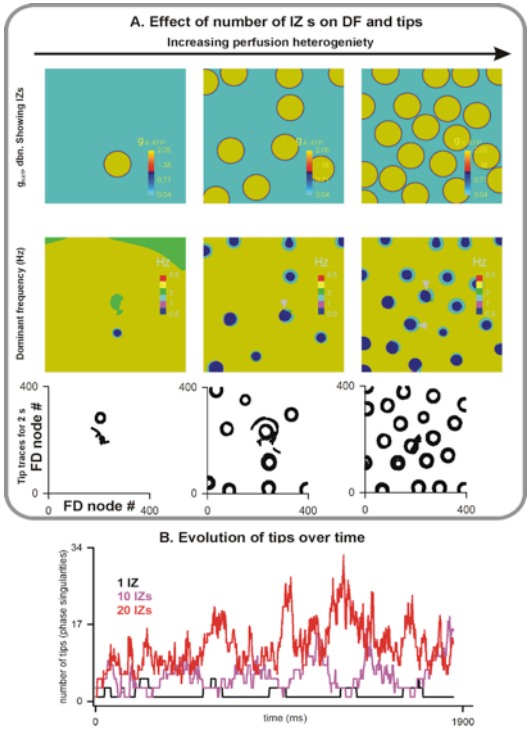


Patient specific data

KDIGO



$VCPL_{EP}$

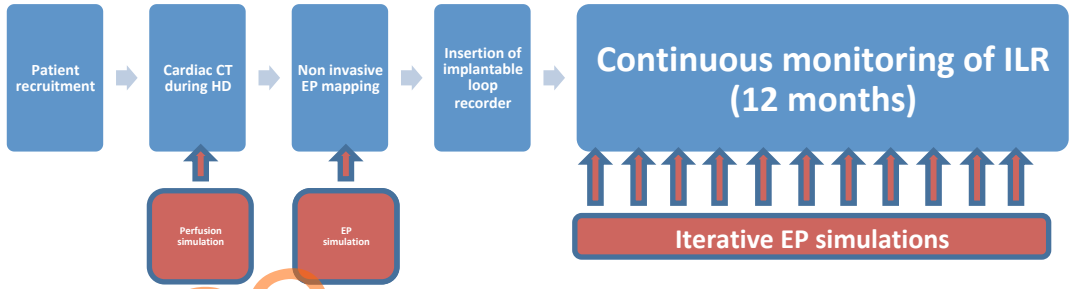


Kharche S, McIntyre CW. Frontiers in Physiol. 2018

Kharche SR et al. PLOS ONE 2017

So what does this all actually look like?

Current VCPL validation



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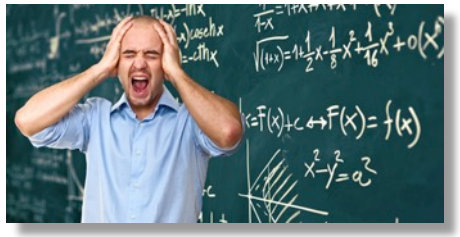
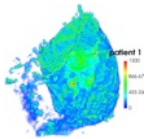
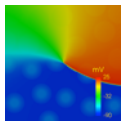
Patient Specific data

VCPL



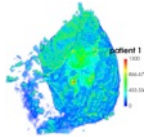
Simulated CV HD response

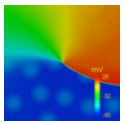




MODIFY VIRTUAL TREATMENT

Simulated CV HD response





Conclusion and Controversy

The New England
Journal of Medicine

Volume 290 MARCH 28, 1974 Number 13

ACCELERATED ATHEROSCLEROSIS IN PROLONGED MAINTENANCE HEMODIALYSIS

ARMANDO LINDNER, M.D., BERNARD CHARRA, M.D., DONALD J. SHERRARD, M.D., AND BELDING H. SCRIBNER, M.D.

Abstract The survival experience of 39 patients receiving long-term regular hemodialysis in Seattle since 1960 was studied with particular reference to mortality and morbidity from arteriosclerotic cardiovascular complications. Mean age (± 1 S.D.) was 37.0 ± 9.5 years for the group at the start of dialysis. Mean duration of treatment was 6.5 years (range, one to 13). Overall mortality was 56.4 per cent at the end of the 13-year follow-up period, and 14 of 23 deaths could be attributed to arteriosclerotic complications: myocardial infarction was responsible for eight, strokes for three, and refractory congestive heart failure for three deaths.

The incidence of these complications was many times higher than for normal and hypertensive groups of comparable age, and similar to rates found in Type 2 hyperlipoproteinemia. These results indicate that accelerated atherosclerosis is a major risk to long-term survivors on maintenance hemodialysis. (N Engl J Med 290:697-701, 1974)

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LAWSON HEALTH RESEARCH INSTITUTE