Case Discussion

Hemodialysis-associated Cardiomyopathy

명지병원

최 혜 민

Case

- 홍OO (M/50)
- P.Hx)
  - ESRD (기저질환?)
    : 2009. 5 미국에서 HD 시작 → 2011년부터 본원 f/u
  - HTN
  - HBV carrier, HCV carrier
  - Multiple drug allergy
    : Bonky(P), Zemplar(P), Venoferrum(P)
  - 2013.4월 Anaphylactic shock (d/t Mircera(P))으로 입원 치료

홍OO (M/50)

- 평소 intractable itching 및 피부 질환
- Medication)
  Levotension 2.5mg(P)
  Sigmart 5mg(P), Lipito 10mg(P)
  Renalmin(P), Calcio(P), Renagel(P), Kashut(P)
  간헐적으로 anti-histamine 및 steroid제
- 2014.8경부터 Pulmonary congestion 및 bilateral pleural effusion 보여 건체중 지속해서 낮추었으나, Intra-dialytic hypotension (IDH) 발생하고 DOE 및 pulmonary congestion도 지속적으로 보임.

홍OO (M/50)

- EKG
  : LVH, T-wave abnormality, consider inferolateral ischemia
- TTE (2013.4)
  : Enlarged LV & LA chambers with normal LV systolic function (EF 63%)
  : Relaxation abnormality, E/E' 12.40
  : No RWMA
  : Eccentric LVH
- Lab
  : CBC 9.7-9300-228K, CRP 4.0, Ca/P 9.3/6.3, PTH 221
  E' 140-4.6-100-23, BUN/Cr 63/10.2, Kt/V 1.4 내외

홍OO (M/50)

- 2014.9.17 CA 컨설트 시행
- Cardiac CT : mLAD critical stenosis
  → CAG 및 PCI 하기로
- 2014.9.29 CAG하였으며 p-m LAD의 stent insertion 시행.
- 이후 조영제 allergy발생하여 Dexamethasone 및 Pheniramine 등의 conservative Tx 후 호전됨.
- f/u EKG상 wide QRS소견 보이고 f/u TTE상 mild pericardial effusion 및 EF 37%소견 보이며 short-term f/u하기로 하고 다음날 퇴원함.

홍OO (M/50)

TTE (2014.9.30)

: enlarged LV & LA & RA chambers with reduced LV systolic function (EF 32% by M-mode, EF 30% by simpson's method)
: Summation of E/A wave d/t tachycardia
: RWMA of LAD territory
: Eccentric LVH
: Moderate pul.HTN with TR GI/GIV
: Hypokinesia of RV (TASP:1.43cm, TAPSE:0.9cm/s)
: Dilated IVC(=2.28cm) without collapse
: Minimal PE
Conclusion)
r/o ICMP d/t LAD stenosis with pul.HTN and RV dysfunction

홍OO (M/50)

- 이후에도 Cardiomegaly, pulmonary congestion, and pleural effusion 지속.
- IDH 지속되고, 환자 general weakness 점점 심해지며 건체중 감량 강력하게 거부하여 체중 조절에 어려움.
  (최근 5개월 사이에 건체중 5kg 정도 낮춘 상태)
- 투석 횟수 늘리면서 건체중 조절하였으나 별다른 호전 없음.
- 투석시 빈맥 소견 (HR 100 정도) → Procolaran(P) 추가
- EKG : LBBB
- Persistent cough (allergic bronchitis?)
- Steroid S/E
- Statin S/E

홍OO (M/50)

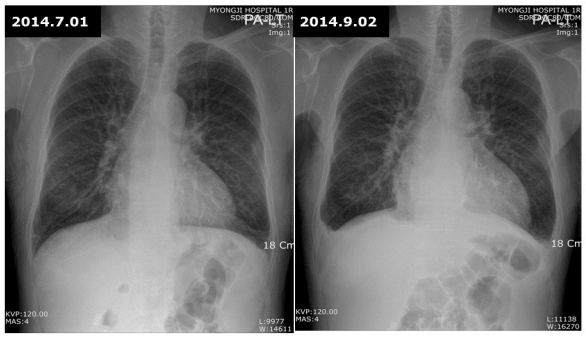
- f/u TTE (2014.12.3) : LVEF 26%
  pulmonary hypertension
- CHF, NYHA Ⅲ-IV, HR >100 (Sinus tachycardia)
- DOE 지속 및 부종 (특히 하지)
- Poor oral intake 및 general weakness
- BP 97/61, HR 108

- 2014.12.04 재입원
  : Daily HD 하면서 보았으나 증상 지속되고 HF 별다른 호전 양상 보이지 않음. IDH도 지속되며 AV access obstruction 발생하는 상태로, PD로 전환할 것을 설득함.

홍OO (M/50)

- 2015.12.10 CAPD 수술 시행함.
  이후 peritonitis 발생하여 항생제 치료하였으나
  경과 과정에서 Ileus 진행 및 aspiration 발생,
  HF 악화되고 shock condition 지속
  → DNR
  & 2015.1.08 사망

Chest X-ray 경과



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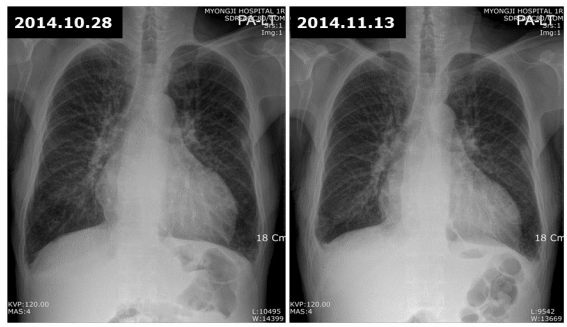

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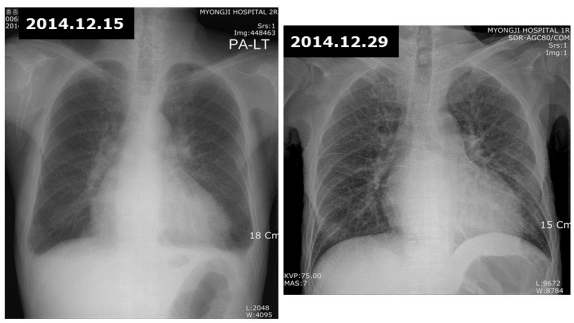


Background (1)

- Cardiovascular mortality ↑ in HD patients

- This is not fully explained by traditional risk factors that are important in the general population.
- Classical complicated atherosclerotic disease appears not to be the predominant mode of death in HD patients.
  KI 2003, 63, 793-808

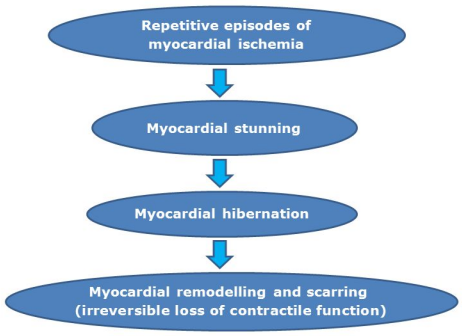
- The increase in cardiovascular mortality is driven by a combination of **sudden cardiac death** and **heart failure** rather than myocardial infarction.
  J Nephrol 1998, 11, 239-245

Background (2)

- It has long been suspected that myocardial ischemia may be precipitated by HD.
- Short intermittent HD treatments exert significant hemodynamic effects, and 20–30% of treatments are additionally complicated by episodes of significant IDH (intra-dialytic hypotension).
- In addition, HD patients are particularly susceptible to myocardial ischemia.
  - myocardial small-vv changes, coronary atheroma, defective vasoregulation, reduced peripheral arterial compliance...

Background (3) : Myocardial stunning

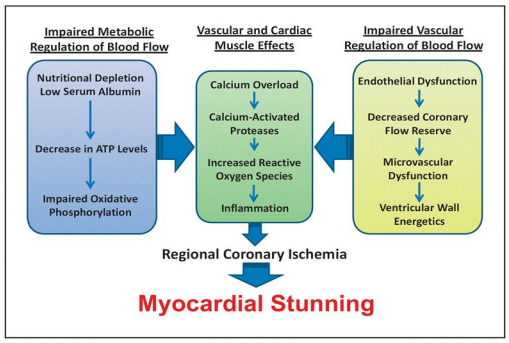
- Myocardial stunning
  : transient myocardial ischemia
  → LV dysfunction that persist after return of normal perfusion
- Repetitive episodes of myocardial ischemia can be cumulative and lead to prolonged LV dysfunction.
- Myocardial stunning has been well described, in the non dialysis pts population, as a causative mechanism for HF.



Background (4)

- HD-induced cardiac dysfunction (cardiomyopathy)
  : A newly defined disease entity
  : complex pathophysiology
  : Structural remodelling at macroscopic and cellular level
  → resultant changes in ventricular structure and function

Figure. HD-induced myocardial stunning



Cardiorenal Med 2012;2:125–133

Myocardial ischemic potential in HD patients

- HD pts are particularly susceptible to myocardial ischemia.

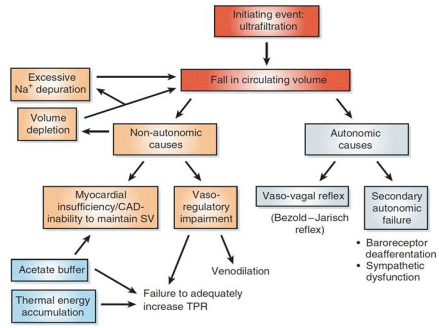
- Large vessel and microcirculatory changes
  → reduced coronary flow reserve
- LV hypertrophy
- Increased peripheral artery stiffness
- Impaired baroreflex sensitivity
  → Defective BP control in the face of UF requirement s

Myocardial ischemic potential in HD patients

- Cardiac physiology of HD

- Short intermittent HD exert significant hemodynamic effect.
- 20~30% are complicated by IDH (intradialytic hypotension).
- Hemodynamic instability and Ultrafiltration
- With intravascular volume shifts,
  LV volume, pr, and morphology are in a load-dependent state, increasing myocardial demand and negatively impacting myocardial mechanics.
  → ↑peak systolic & diastolic wall stress
  (similar to the wall stress in severe CAD)

Figure. Physiological responses to hemodialysis that might be involved in the pathogenesis of IDH



Kidney International 2009, 76, 371–375

Clinical data on
HD-induced myocardial stunning

The first report of silent ST-segment depression during dialysis dates back to 1989.

Nephrol Dial Transplant. 1989;4(7):632-4.

Incidence of arrhythmias and myocardial ischaemia during haemodialysis and haemofiltration.

Zuber M[1], Steinmann E, Huser B, Ritz R, Thiel G, Brunner F.

Author information

Abstract

Thirty-two patients (10 male, 22 female; age 37-82 years) undergoing maintenance haemodialysis or haemofiltration were studied by means of Holter device capable of simultaneously analysing rhythm and ST-changes in three leads. Twenty-five patients were on haemodialysis, seven on haemofiltration, mean duration of haemodialysis/haemofiltration being 3.4 +/- 3 years. Incidence of ventricular tachycardia was low, being detected only in 1 of 32 patients. Ventricular premature beats in excess of 10/h during a period of 2 h were found in 8 of 32 patients and 100 supraventricular premature beats for 2 h or more in 4 of 32 patients. Both ventricular premature beats and supraventricular premature beats were most frequently recorded during the last hour of haemodialysis/haemofiltration. ECG signs of ischaemia were detected in eight patients, four of whom were asymptomatic. Ischaemia also occurred predominantly during the last hour of haemodialysis/haemofiltration. Two symptomatic patients displayed neither arrhythmias nor ST-changes while being monitored. The study shows that silent ischaemia and arrhythmias in patients undergoing chronic haemodialysis/haemofiltration may not be infrequent. Recognition of these events could be of importance in the management of these patients.

PMID: 2510060 [PubMed - indexed for MEDLINE]

HD-induced ischemia

- Dialysis-induced ST depression occurred at rates that vary between 15~40%.
- Cardiac troponins are often elevated in dialysis patients, and that elevated levels predict mortality.
- HD itself is related to an increase in troponin levels.

Clin Chem 2000, 46, 1345-1350

- Higher pre-HD serum cTnT levels in patients prone to IDH as compared with patients without significant hypotensive response to HD.

Blood Purif 2004, 22, 338-343

Hemodialysis-Induced Cardiac Injury: Determinants and Associated Outcomes

James O. Burton,* Helen J. Jefferies,* Nicholas M. Selby,* and Christopher W. McIntyre*†

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- 70 HD patients
- Serial intradialytic echo로 RWMA의 development와 recovery 측정
- HD-induced myocardial stunning occurred in around 2/3 of pts.
- In multivariate analysis,
  IDH, UF volume, patient age, and cardiac TnT (pre-dialysis)
  independently determined the propensity to suffer HD-induced cardiac injury.

Myocardial stunning was associated with increased relative mortality at 12 mo ($P = 0.019$). Cox regression analysis showed increased hazard of death in patients with myocardial stunning and elevated cTnT than in patients with elevated cTnT alone ($P < 0.02$). Patients with myocardial stunning who survived 12 mo had significantly lower LV ejection fractions at rest and on HD ($P < 0.001$).

Conclusions: HD-induced myocardial stunning is common, and may contribute to the development of heart failure and increased mortality in HD patients. Enhanced understanding of dialysis-induced cardiac injury may provide novel therapeutic targets to reduce currently excessive rates of cardiovascular morbidity and mortality.

CJASN 2009, 4, 914-920

HD-induced ischemia에서 중요한 dialysis-related factor는?

- Data on Modification of Dialysis method

  1) **Hemodynamic stability**

  2) **UF volume and Rate**

HD-induced ischemia : Hemodynamic stability

- Modification of dialysis technique to assist in the maintenance of BP without the alteration of UF volume removal.

- **Standard bicarbonate** vs **Biofeedback technique (BFD)** HD
  [BFD : respond to significant declines in relative blood volume by temporarily UF rate↓& dialysate conductivity↑]

- **Standard dialysis** with dialysate temperatures of 37°C and **cooled dialysate** at 35°C .

Occurrence of Regional Left Ventricular Dysfunction in Patients Undergoing Standard and Biofeedback Dialysis

Nicholas M. Selby, MD, Stewart H. Lambie, MD, Paolo G. Camici, MD, Christopher S. Baker, MD, and Christopher W. McIntyre, MD

• ***Background:*** **Cardiac failure and cardiovascular death are extremely prevalent in dialysis patients. Recurrent subclinical myocardial ischemia is important in the genesis of heart failure in nondialysis patients. We examined whether this phenomenon occurs in response to the stress of hemodialysis (HD).** ***Methods:*** **Eight patients prone to intradialytic hypotension were recruited for a randomized crossover study to compare the development of left ventricular regional wall motion abnormalities during standard (HD) and biofeedback dialysis. Patients underwent serial echocardiography with quantitative analysis to assess ejection fraction and regional left ventricular systolic function during both types of dialysis. Blood pressure and hemodynamic variables also were measured by using continuous pulse wave analysis.** ***Results:*** **Forty-two new regional wall motion abnormalities developed in all 8 patients during HD compared with 23 regional wall motion abnormalities that developed in 7 patients during biofeedback dialysis (odds ratio, 1.8; 95% confidence interval, 1.1 to 3.0). The majority of regional wall motion abnormalities showed improvement in function by 30 minutes postdialysis. Overall mean regional function was significantly more impaired during HD ($P = 0.022$). At peak stress, ejection fraction (measured by percentage of change from baseline) was significantly lower during HD ($P = 0.043$). Blood pressure was higher during biofeedback dialysis, with significantly fewer episodes of hypotension (odds ratio, 2.0; 95% confidence interval, 1.01 to 4.4). Significantly smaller decreases in stroke volume and cardiac output and a greater increment in pulse rate were observed during biofeedback dialysis.** ***Conclusion:*** **This study shows that reversible left ventricular wall motion abnormalities develop during dialysis with ultrafiltration. We also show that this phenomenon can be ameliorated by the improved hemodynamic stability of biofeedback dialysis and therefore is a potential target for intervention.**

Am J Kidney Dis **47:830-841.**

Dialysis-Induced Regional Left Ventricular Dysfunction Is Ameliorated by Cooling the Dialysate

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Dialysis patients who develop cardiac failure have a poor prognosis. Recurrent subclinical myocardial ischemia is important in the genesis of heart failure in nondialysis patients. It has previously been demonstrated that subclinical ischemia occurs during hemodialysis; therefore, this study examined whether the improved stability of cool-temperature dialysis lessens this phenomenon. Ten patients who were prone to intradialytic hypotension entered a randomized, crossover study to compare the development of dialysis-induced left ventricular (LV) regional wall motion abnormalities (RWMA) at dialysate temperatures of 37 and 35°C. Serial echocardiography with quantitative analysis was used to assess ejection fraction and regional systolic LV function. BP and hemodynamic variables were measured using continuous pulse wave analysis. The severity of thermal symptoms was scored using a simple questionnaire. Forty-nine new RWMA developed in nine patients during hemodialysis with dialysate at 37°C (HD_{37}), compared with thirteen RWMA that developed in four patients during HD_{35} (odds ratio 3.8; 95% confidence interval 2.1 to 6.9). The majority of RWMA displayed improved function by 30 min after dialysis. Overall, regional systolic LV function was significantly more impaired during HD_{37} ($P < 0.001$). BP was higher during HD_{35}, 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_{35} 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 1: 1216–1225, 2006. doi: 10.2215/CJN.02010606

HD-induced ischemia : Hemodynamic stability

- In both studies, a significant number of new RWMAs occurred during standard dialysis.

- By improving mean BP and reducing IDH episodes with either biofeedback dialysis (BFD) or reduced-temperature dialysis,
  → significant reduction in the number of new RWMAs was observed.

- They also observed a higher overall LV ejection fraction, with both BFD and cool dialysis.

HD-induced ischemia : UF volume and Rate

- UF volume/rate and dialysis-induced cardiac injury

- The effects of more regular and longer HD schedules

Frequent Hemodialysis Schedules Are Associated with Reduced Levels of Dialysis-induced Cardiac Injury (Myocardial Stunning)

Helen J. Jefferies,* Bhupinder Virk,†‡ Brigitte Schiller,†‡ John Moran,†‡ and Christopher W. McIntyre*§

1) Conventional in-centre HD 3 times per wk (**CHD3**, n=12),
2) Short daily in-centre HD 5–6 times per wk (**CSD**, n=12),
3) Short daily home HD 5–6 times per wk (**HSD**, n=12),
4) Nocturnal home 5–6 times per wk HD (**HN**, n=10)

would abrogate dialysis-induced myocardial stunning.

- UF vol. and IDH were both significantly lower in home-based frequent Tx.
- HD-induced myocardial stunning was ubiquitous in CHD3 patients.
- The proportion of patients exhibiting dialysis-induced RWMAs was reduced significantly with increasing dialysis intensity (CHD3>CSD>HSD>HN).
- More frequent HD was associated with fewer RWMAs.
- The UF rate correlated strongly with the number of RWMAs.

Conclusions Frequent HD regimes are associated with less dialysis-induced myocardial stunning compared with conventional HD. This may contribute to improved outcomes associated with frequent HD therapies.

Clin J Am Soc Nephrol 6: 1326–1332, 2011. doi: 10.2215/CJN.05200610

Role of large vv CAD in HD-induced myocardial stunning

- Myocardial stunning can occur in HD population even in the absence of conventional epicardial CAD.
- Study on pediatric patients group
  [: with uremic cardiovascular disturbances, but in the absence of conventional cardiovascular risk factors]

Pediatric Myocardial Stunning Underscores the Cardiac Toxicity of Conventional Hemodialysis Treatments

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*Departments of *Nephro-urology and †Pediatric Cardiology, Great Ormond Street Hospital for Children, London, ‡Department of Renal Medicine, Derby City General Hospital, Derby, and §School of Graduate Entry Medicine and Health, University of Nottingham, Nottingham, United Kingdom*

Background and objective: In adults, hemodialysis (HD)-induced ischemia causes reversible myocardial dysfunction (myocardial stunning) that is progressive with raised attendant mortality. Children share an increased risk for death from a spectrum of uremia-related cardiovascular abnormalities but in the absence of significant classical atheromatous coronary artery disease; therefore, we elected to assess children who were on HD for the occurrence of myocardial stunning to investigate the relative importance of characteristic uremic cardiovascular abnormalities in the development of ischemic cardiac injury.

Design, setting, participants, & measurements: We included all single-center long-term HD patients (n = 12; range 2 to 17 yr), excluding those with structural cardiac disease. Patients underwent conventional thrice-weekly HD for 4 h using high-flux membranes. We measured regional left ventricle wall motion using serial echocardiography (before HD, during HD, and 15 min after HD). Significant stunning was defined as a 20% reduction in regional wall motion (RRWM) in two or more segments and hyperkinesis as an either >20 or >50% increase in shortening fraction (SF).

Results: Eleven of 12 patients developed myocardial stunning with varying degrees of compensatory hyperkinesis in unaffected segments, maintaining left ventricular ejection fraction throughout HD. The mean segmental $\%SF_{[Overall]}$ and $\%SF_{[RRWM]}$ fell during HD (2.19 to 1.77 and 2.72 to 1.37, respectively). Intradialytic BP reduction was significantly associated with mean segmental $\%SF_{[RRWM]}$.

Conclusions: Children who receive conventional HD experience myocardial stunning. These data, in combination with previous adult studies of intradialytic myocardial blood flow, suggest a characteristic cardiovascular phenotype in HD patients that predisposes to significant demand ischemia.

Clin J Am Soc Nephrol 2009, 4, 790-797

Long-term consequences of recurrent HD-induced ischemic injury

- **Continuum of myocardial stunning and hibernation**
  : repetitive episodes of ischemia
  myocardial stunning
  Myocardial hibernation
  Myocardial remodeling and scarring,
  irreversible loss of contractile function
- **Interaction with HD treatment**
- **Propagation of cycles of injury**

Hemodialysis-Induced Cardiac Injury: Determinants and Associated Outcomes

James O. Burton,* Helen J. Jefferies,* Nicholas M. Selby,* and Christopher W. McIntyre*†

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- **1yr f/u**
- Those pts who did not develop HD-induced myocardial stunning
  : only one significant cardiac event,
  no change in segmental shortening fraction,
  no reduction in overall LV ejection fraction
  100% survival.
- Dialysis-induced myocardial stunning,
  : 28% of the patients had died.
  In those pts who survived to the 1-yr f/u,
  rough halving of shortening fraction
  reduced overall LV ejection fraction

Clin J Am Soc Nephrol 4: 914–920, 2009. doi: 10.2215/CJN.03900808

Renal Failure, 30:701–709, 2008

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DOI: 10.1080/08860220802212908

CLINICAL STUDY

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

- Dialysis-induced myocardial stunning was associated with an increased rate of intra-dialytic and post-dialytic ventricular arrhythmias.
- Interlinked major identifiable causes of cardiovascular mortality in HD patients

Potential effects of hemodynamic perturbation on other vascular beds

- The possibility of other critical vascular beds being potentially affected by systemic perturbation of BP and volume status during dialysis resulting in reduced perfusion
- **Brain**
  : sequential cerebrovascular insults &
  progressive development of ischemia-based white matter lesions
  → progressive loss of cognitive function in dialysis patients(?)
- **Gut stunning**

Therapeutic options
: more questions than answers

- PD vs HD
- Antioxidants/anti-inflammatory agents
- Remote preconditioning
- HD protocol
  - Dialysate temperature (37°C vs. cooled)
  - Dialysis frequency (daily vs. thrice/week)
  - Volume removed per session (i.e. decreasing UF)
  - Session duration of dialysis (long vs. short)
  - Location/vessel of AVF/catheter
  - Central venous catheter vs AVF vs AVG
  - Flow rate during HD (lower vs. higher)

Summary (1)

- HD procedure exerts significant acute stress upon the cardiovascular system.
- Subclinical ischemia is precipitated by dialysis.
- Dialysis-related cardiac injury is common, cumulative and directly involved in the poor outcomes characteristic in this patient group.
- Episodes of ischemia may potentially have a role in the development of cardiac failure and as a trigger for arrhythmias.

Summary (2)

- The same process of dysregulated blood flow under the stress of HD to a variety of vascular beds may be an important element in the development of such poor outcomes in HD patients manifested in a variety of body systems.
- Reducing the acute impact of dialysis on the cardiovascular system would seem to be a desirable therapeutic target.