Cardiovascular Complications of Dialysis In Children

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Why is this important?

[Diagram showing survival rates for different age groups and causes of death.]


Why is this Important?

Long-Term Survival of Childhood-Onset ESRD

[Graph showing survival rates for different causes of death over age.]
Why is this Important?

**Silent Disease**
- Symptoms can be non-specific or absent
- Early manifestations not detected by our standard investigations
- Pathophysiology still poorly understood

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**Autopsy findings**

Valvular, Coronary & Pericardial Calcification

Microvascular disease

Atherosclerosis, Medial & Intimal Calcification, Stiff Vessels

Left ventricular hypertrophy

Myocardial fibrosis

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**Cardiovascular Risk Factors in CKD**

**Conventional**
- Hypertension
- Hyperlipidemia
- Obesity
- Insulin Resistance

**Uremia-Related**
- Hyperhomocysteinemia
- Increased LDL oxidation
- IV iron induced AOPP
- Hyperparathyroidism
  - Ca/Ph-Product ↑

**Dialysis-Related**
- Fluid Overload
- Infections
- Bioincompatibility
- ACE

Endothelial Dysfunction

Proinflammatory Cytokine Release

Systemic Inflammation

Acute Phase Response

Suppression of Anti-Ca-Precipitants

Atherosclerosis / Calcifying Vasculopathy

Increased Cardiovascular Mortality
Cardiovascular Profiles of Children on Dialysis

CKD Stage 5

- Calcification
  - Coronary & valvular myocardial calcification
  - Intimal and medial calcification
- Blood pressure
- Malnutrition Inflammation Complex Syndrome

Biological Calcification
Histological Evidence of Calcification

Medial Calcification: IMT, "String of Beads"

Peripheral Arteriopathy: "Railroad Tracks"

Coronary Artery Calcifications in Childhood-Onset ESRD

- Goodman et al., NEJM 2000
- Oh et al., Circulation 2002
- Civilibalet al., Pediatr Nephrol 2006
- Eifinger et al., NDT 2000

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Goodman et al.</th>
<th>Oh et al.</th>
<th>Civilibalet al.</th>
<th>Eifinger et al.</th>
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<tbody>
<tr>
<td>15</td>
<td>36%</td>
<td>92%</td>
<td>15%</td>
<td>46%</td>
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Calcification Promoters

- VDR G3
- PTH 1-84
- TGF-α
- LDH 4K

Calcification Inhibitors

- ALP
- PTH 1-84
- TIMP-1
- TIMP-2
- TIMP-3
- TIMP-4
- TIMP-5
- TIMP-6
- TIMP-7
- TIMP-8
Predictors of Coronary Artery Calcification in Young Adults with Childhood-Onset ESRD

<table>
<thead>
<tr>
<th>Effect</th>
<th>Partial R²</th>
<th>Total R²</th>
<th>P</th>
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<tbody>
<tr>
<td>CRP</td>
<td>Positive</td>
<td>0.5</td>
<td>0.50</td>
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<tr>
<td>Mean PTH</td>
<td>Positive</td>
<td>0.15</td>
<td>0.65</td>
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<tr>
<td>Mean (Ca²⁺)ESRD</td>
<td>Positive</td>
<td>0.07</td>
<td>0.72</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>Positive</td>
<td>0.03</td>
<td>0.75</td>
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Oh et al. Circulation 2002;106:100-5

Peripheral Arteriopathy

- The relative risk of having an increased IMT was 3.7 fold greater in those with high PTH levels than in patients with a PTH within 2x ULM
- A bimodal distribution is seen with vitamin D associated increase in IMT

CKD Stage 5

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**Blood Pressure & Dialysis**

- What’s the best approach for measuring BP in pediatric dialysis patients?
  - Pre-, post- or interdialytic BP, ABPM, BP load, nocturnal dip,
- In adults several studies in patients with essential hypertension have described a “J” shaped curve between DBP and mortality
- In adult dialysis patients Foley et al 1996 observed that low, not high, BP was associated with increased mortality

**Systolic BP Post-dialysis And Cardio/Cerebrovascular Mortality in Hemodialysis Patients (1992-1996)**

![Graph showing the relationship between systolic blood pressure and mortality](image)

Systemic blood pressure post-dialysis, mm Hg (ref: 140-149)

**LV Hypertrophy in Children With CKD**

![Bar chart showing the percentage of patients with LV hypertrophy by KDIGO stage](image)

AC Study
LV Geometry in Children with CKD

<table>
<thead>
<tr>
<th>CKiD Cohort</th>
<th>IPPN Cohort</th>
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<tbody>
<tr>
<td>n = 366</td>
<td>n = 507</td>
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</tbody>
</table>

- Calcification
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Ischaemia → Cardiac remodelling → Blood Pressure

CKD Stage 5

- Calcification
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  - Malnutrition Inflammation Complex Syndrome
**Malnutrition Inflammation Complex Signature**

**CONSEQUENCES**
- Leads to a low body mass index
- Hypocholesterolemia
- Hypocreatininemia
- Hypohomocysteinemia

> “Reverse epidemiology” of CVS risks in dialysis patients.

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**CKD Stage 5**

- **Calcification**
  - Coronary & valvular myocardial calcification
  - Intimal and medial calcification
- Blood pressure: ischemia, cardiac remodelling
- Malnutrition Inflammation Complex Syndrome

> Myocardial fibrosis
> Maladaptive arterial tone
Myocardial Fibrosis

- 1943 Rossle: interstitial widening and fibrosis is common in the hearts of patients dying from uremia
- Severity of fibrosis increases with
  - the stage of CKD
  - time on maintenance HD
- Potential reversibility: reduction of fibrosis post transplantation

Important Players in Myocardial Fibrosis

Factors that operate from the initial stages of CKD
- renin-angiotensin-aldosterone system
- oxidative stress
- excess of cytokines (cardiotrophin-1, transforming growth factor-b1)

Factors that act preferentially in more advanced stages of CKD
- hyperphosphatemia
- excess PTH
- cardiac calcification
- ischemia
- anemia

Hypothetical factors
- cardiotonic steroids
- cellular senescence
- anti-cardiotropin antibodies
- relaxin

Myocardial Fibrosis

CONSEQUENCES
- Predisposition to re-entry type atrial and ventricular arrhythmia
  - Sudden cardiac death
- Poor LV compliance impacts LV filling
  - With increasing LV volume risk of pulmonary congestion
  - Volume depletion may critically lower LV filling pressures
- Myocardial dysfunction
  - Diastolic heart failure primarily the result of cardiac fibrosis
  - Prognosis worse in CKD patients with diastolic heart failure compared with systolic heart failure
Maladaptive Arteriolar Tone
• Arterial calcification
• Endothelial dysfunction
• Neuro-humoral factors

Throughout A Single HD Session We Undertook Non-invasive, Continuous Haemodynamic Monitoring Using The Finometer
• Finger cuff provides continuous pulse-wave analysis at the digital artery
• An arm cuff is wrapped around the same arm as the finger cuff to undertake a “Return-to-flow” calibration of finger cuff pressure against brachial readings
• Wrist device houses software to calculate hemodynamic variables

Group trend
• Cardiac output more dependent on chronotropic than ionotropic response
• Whilst the intradialytic BP fall changes in TPR were small
Maladaptive Vascular Tone

Arterial stiffness and remodelling
- increases afterload
- reduced coronary perfusion during diastole
  ➢ Myocardial demand supply mismatch

CKD Stage 5

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  - Intimal and medial calcification
- Blood pressure: ischemia, cardiac remodelling
- Malnutrition Inflammation Complex Syndrome
  ➢ Myocardial fibrosis
  ➢ Maladaptive arterial tone
  ➢ Maladaptive cardiovascular response

Peritoneal Dialysis

- PD considered hemodynamically less challenging compared with HD
- However increasing volume overload with PD vintage

Kramer et al. Kidney Int 2011
Peritoneal Dialysis

- Metabolic insults drive the cardiovascular morbidity
- Short-term hemodynamic responses:
  - Glucose stimulates insulin = ↑ cardiac output
  - Intraperitoneal fluid instillation increases preload or pulse wave reflection = ↑ diastolic BP
  - Biocompatible/ bicarbonate fluid = baroreflex sensitivity
  - APD causes cooling = ↑ TPR, ↓ CO & SV
- Increased endotoxin levels, from gut oedema, intraperitoneal pressure...but less than HD

Advanced Glycation End Products (AGEs)

Extracellular Volume
PD vs. HD
Plum et al NDT 16:2378, 2001

PD pts are overloaded
Peritoneal Dialysis:
Chronic Volume Overload

Hemodialysis
Hemodialysis is a hemodynamic stress
- Intradialytic hypotension
- Reduced or absent tachycardic response or bradycardia

Kaplan-Meier Survival Curves with Frequent, Occasional and no IDH
Intradialytic Hypotension

- Non-osmotic causes
  - Volume depletion
  - Myocardial Ischemia (AVO, mobility to maintain flow)
- Osmotic causes
  - Vasovagal reflex (Bradycardia, shock reflex)
  - Baroreceptor desensitization

Ultrafiltration

Rate more important than actual volume

Myocardial Stunning

- **Myocardial stunning - transient** post-ischemic myocardial dysfunction with relatively normal blood flow
- The resultant LV dysfunction is global or discrete to parts of the LV
- Repeated episodes of ischemia and stunning are cumulative resulting in 'myocardial functional hibernation' - non-infarcted
Fall in cardiac output and global MBF at 15 minutes in the absence of UF

Analysis of Regional LV Wall Motion In An Adult Patient during Standard HD

Stunned myocardial segments exhibit significantly greater reduction in MBF
Ischaemia
Reduced blood flow
Reversible regional LV dysfunction
Myocardial stunning

Patient K, 2 yr old

Time Strain Curve in HD patient at peak stress (end of HD)

Asynchronous regional LV contraction
Reduced peak segmental area
Factors associated with Regional LV Dysfunction

<table>
<thead>
<tr>
<th></th>
<th>Pearson's Correlation</th>
<th>R²</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Absolute systolic BP</td>
<td>-0.26</td>
<td>0.07</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Intradialytic systolic BP change</td>
<td>0.32</td>
<td>0.10</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>UF [mls/kg]</td>
<td>0.30</td>
<td>0.09</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Months on HD</td>
<td>0.05</td>
<td>0.002</td>
<td>&lt;0.71</td>
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Cardiac Reflexes

Mechanoreceptors within the LV wall respond to an increase in end-diastolic pressure
- reflex bradycardia and vasodilation (Bezold–Jarisch reflex)
- Low-pressure stretch receptors in A, V & pulmonary vessels form the cardiopulmonary reflex.
- Sympathetic response activated by cardiac distension from increase venous return
- Baroreflex arc under autonomic control, regulates BP
- Impaired baroreflex sensitivity (BRS) is an accepted marker of autonomic dysfunction

Impact......Baroreflex sensitivity

IDH-resistant with impaired BRS exhibit the greatest increase in TPR during HD.
A strong correlation between volume and CO at the end of HD in unstable patients with impaired BRS, rendering their CV response to HD highly volume dependent.
Treatment

Preventative/modulatory

- CKD-MBD
- Salt and water balance
- Cardio-protective measures
- Residual renal function
- PD: biocompatible solutions
- HD: hemodynamic stability

Coronary Calcification Score in Incident Dialysis Patients

Block et al. Kidney Int 2005

RIND Trial: Improved Survival of Dialysis Patients by Calcium-Free Phosphate Binders

Block et al. Kidney Int 2007
**cIMT Covaries with Phosphate Binder Intake and Ca*P Product in Dialyzed Children**

- R=0.41; p<0.05
- R=0.42; p<0.05

**Calcimimetic Prevents Vascular Calcifications in Uremic Rats**


**Vitamin D Supplementation On Arterial Morphology And Function**

- PWV SDS
- *<0.0001
- IMT SDS
- *<0.008
Kaplan-Meier survival curves in patients who started PD and were treated or not with ACEi and/or ARBs
Kaplan Meier survival curves in patients who started HD

Prognostic Benefits of Carvedilol, Bisoprolol, and Metoprolol Controlled Release/Extended Release in Hemodialysis Patients with Heart Failure: A 10-Year Cohort

RRF Better Preserved in PD vs. HD

Peritoneal Dialysis

Diuretic Use May Preserve Urine Output in Children on PD

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Glomerulopathy</td>
<td>4.14</td>
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<tr>
<td>Urine output at PD initiation</td>
<td>0.55</td>
</tr>
<tr>
<td>Daily ultrafiltration (L/m²/d)</td>
<td>1.53</td>
</tr>
<tr>
<td>Dialytic glucose exposure (g/kg/d)</td>
<td>1.27</td>
</tr>
<tr>
<td>Icodextrin use</td>
<td>2.10</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>1.21</td>
</tr>
<tr>
<td>Diuretic use</td>
<td>0.31</td>
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<tr>
<td>ACE inhibitor use</td>
<td>1.37</td>
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</table>

Na/Fluid Removal and Mortality in PD Pts

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RR</th>
<th>p Value</th>
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<tbody>
<tr>
<td>RRF 1 mL/min</td>
<td>0.53</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Na removal (10 mmol/kg)</td>
<td>0.90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total fluid removal (100 mL/d)</td>
<td>0.90</td>
<td>&lt;0.01</td>
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Biocompatible Dialysate Solution

Summary of Evidence to date

Hemodialysis
Increased Hemodynamic Stability

Cooled Dialysate & Intradialytic Hypotension
Carnitine & Intradialytic hypotension

No Real Benefit

Hemodialysis Plasma Electrolytes

Hemodialysis Dialysis Modality
Hemodialysis
Dialysis Modality

Conclusion

• Cardiovascular disease is important in paediatrics and modifiable
• The profile for PD and HD patients is different
• In PD patient respond our attention should be focused on the metabolic effects of dialysis
• In HD patients our attention should be focused on improving hemodynamic stability