Targeting vascular damage (stiffness, calcifications) in CKD: beyond blood pressure
Should we still measure BP in dialysis?
Clinical Problems with cuff BP

Case #1: Variances in Cuff BP vs. Central BP

TWO PATIENTS ... in the periphery, both (red & blue) have identical BP (140/80)
– BUT...... Centrally there is a critical Systolic BP (Sp) difference between patients:
– WHY the different Aortic Sp?... the patients have different Arterial Stiffness!
Clinical Problems with cuff BP

Case #2: Variances in Cuff BP vs. Central BP

SAME PATIENT - before & after drug intervention (GTN for angina)

- There is No change in Cuff Sp ...but .... a Big change Aortic Sp

- Hypertension, Diabetes, Renal, Heart Failure => ALL require CV drug therapies.

Conclusion

Brachial cuff BP is NOT adequate for Systolic BP management
NON-INVASIVE METHODS FOR THE EVALUATION OF VASCULAR FUNCTION

• **ASSESSMENT OF ARTERIAL STIFFNESS:**
  – PWV
  – relating change in diameter/area to distending pressure
  – arterial pressure waveform analysis.

• **ENDOTHELIAL FUNCTION MEASUREMENT:**
  – endothelium-dependent (flow mediated)
  – endothelium-independent (NTG)
  – vascular responses of the brachial artery by high-resolution imaging
i) \[ PWV = \text{distance} / \Delta TA - \Delta TB \]

\[ \Delta TA / \Delta TB = \text{differences between the ECG and tonometer waveforms} \]
ii) The volume – pressure relationship

\[ \frac{\Delta V}{\Delta P} = \text{Compliance} \]

\[ \frac{\Delta P}{\Delta V} = \text{Elastance (Stiffness)} \]

Distensibility = \( 2(\frac{\Delta D}{D})/(\text{SBP} - \text{DBP}) \), where \( D \) is carotid diastolic diameter and \( \Delta D \) is change in artery diameter during systole. The stiffness parameter \( \beta = \ln(\text{SBP} / \text{DBP})]/(D/D) \).
Echotracking is 3 to 10 x more precise than usual image based techniques.

Signal averaging 10-10 000 RF lines

Spatial resolution

- 2 D: 200-400 µm
- TM: 20-40 µm

RF Signal

IMT
The diameter-pressure curve

Diameter (mm)

Local pressure

High-definition echotracking devices
- Wall Track system
- NIUS system

Aplanation Tonometry
- Millar Instruments
Aortic arterial pressure waveform

- $\Delta P$ = augmented pressure
- $PP$ = pulse pressure
- $Augmentation\ index = \Delta P / PP$
- $Tsh$ = time to shoulder
- $LVET = LV\ ejection\ time$

Composite measure – related to:
1) Stiffness
2) Peripheral reflective properties
If the patient’s arteries get stiffer…

- PWV ↑
- the reflected wave arrives sooner back at the heart
- There are three important clinical implications
Pressure Wave Reflection at the Heart

First

- increase in central PP
- \textit{i.e.} increase in (pulsatile) stress on (cerebral) blood vessels

= • increased stroke risk
Pressure Wave Reflection at the Heart

Second

- increase in LV load

= increased LV mass
Arterial stiffening independently increases the risk of all three major cardiovascular outcomes.

- reduced coronary diastolic perfusion
- myocardial ischemia.
EXCELLENT REPRODUCIBILITY WITH PWV AND Alx


**Bland-Altman plot:**
inter-observer variation in Alx (%)

**Day-to-day variation in aortic PWV (m/s)**

Mean=0.9
SD=7.9

Mean=-0.7
SD=1.0

+2SD

-2SD
Brachial-ankle vs carotid-femoral PWV as a determinant of CDV structure and function

Yu et al, JHH 2008

\[ y = 0.90x - 149, \quad r^2 = 0.63, \quad p < 0.0001 \]
**baPWV > cfPWV as a determinant of CDV structure and function?**

Yu et al, JHH 2008

<table>
<thead>
<tr>
<th></th>
<th>ba-PWV</th>
<th>cf-PWV</th>
<th>P-value</th>
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<td>LVM</td>
<td>0.29**</td>
<td>0.22**</td>
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<td>Peak E</td>
<td>−0.12</td>
<td>−0.13*</td>
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<td>Peak A</td>
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<td>E/A ratio</td>
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<td><strong>Arterial structure</strong></td>
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<td>Incr-M</td>
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<td>Al</td>
<td>0.38**</td>
<td>0.32**</td>
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</table>
Endothelial function testing

Pulse waveforms from a hemodialysis patient before (left panel, “stiff” pattern) and after (right panel, “normal” pattern) nitroglycerin administration.

AIx improved from +24% to –11%

Changes in AIx – may test EDD-vasodilatation and EID-vasodilatation
Methods of stimulating increased blood flow

A

Pneumatic cuff

L-NMMA

B

Doppler or Millar probe?

L-NMMA

C

ACH

L-NMMA

D

ACH

Schematic representation of reactive hyperemic response in the human forearm after five minutes of ischemia

- **A** = Flow debt mL/100 mL
- **B** = Excess hyperemic flow ml/100ml
- Flow debt repayment = B/A
- **Peak flow**
- **Duration of hyperemia**

---

**Legend:**
- **Baseline**
- **Occlusion**
- **Postocclusion**
- **Time, min**

---

**Graph:**
- X-axis: Time, min
- Y-axis: Forearm blood flow ml/100 ml/min
- Various data points and markers indicating flow changes during ischemia and hyperemia.
Controls ESRD
Time to debt repayment (s)

Flow debt repayment (%)

BA diameter (Δ%) FMD GTN

- control subjects
- CKD patients
- HD patients

Pannier B et al. Kidney Int 2001
Uraemia – stiffness - endothelial dysfunction - microparticles

Apoptosis, Activation

Endothelial Injury

Endothelial MPs Release

NO Synthesis Inhibition

ENDOTHELIAL DYSFUNCTION

AGE
LPS
Uremic toxins
Oxidized LDL
Inflammatory cytokines
Oxidative Stress
Low/oscillatory Shear Stress
Unknown in vivo stimuli?

Philosophy and pathophysiology

- **Central arteries**
  - “lower” stiffness
  - High sensitivity to ageing (VC?) and BP
- **Peripheral arteries**
  - “higher” stiffness
  - Sensitive mainly to vasoactive substances of endothelial origin
- **PWA + baPWV + cfPWV = best approach?**
  to be continued...
Virtual Histology of Atherosclerotic Plaques Using Intravascular Ultrasound
Schwarz et al., NDT 2000;15:218-23

IMT

INTIMA

MEDIA

Non-CRF

CRF
WHICH ONE IS THE MOST RELEVANT

Criteria:
- Age: AUC 72 ± 5%
- Pulse Pressure: AUC 72 ± 5%
- Carotid IMT: AUC 68 ± 6%
- LVmassix: AUC 72 ± 5%
- Calcification score: AUC 82 ± 4%
- Aortic PWV: AUC 82 ± 4%

Calcification score: cut-off 390; sensitivity 83%; specificity 69%; PPV 41%; NPV 94%
Aortic PWV: cut-off 10.75 m/s; sensitivity 84%; specificity 73%; PPV 72%; NPV 93%

G. London 2006
CAC and PWV in CKD
AA Haydar, A. Covic, S. Colhoun et al
Kidney Int. 2004

VC and PWV
P Raggi et al
Kidney Int. 2007
Scatter plot of change in CaSc against change in PWV

at 12 mo \( (r = 0.52, \ P < 0.001) \)

and

at 24 mo \( (r = 0.33, \ P = 0.003) \)

Sigrist, M. K. et al. CJASN
PWV, Aix, etc are they useful?

General population

CKD population
# Expert consensus document on arterial stiffness: methodological issues and clinical applications

Laurent et al European Heart J. 2006

<table>
<thead>
<tr>
<th>Measurement site</th>
<th>First author (year, country)</th>
<th>Events</th>
<th>Follow-up (years)</th>
<th>Type of patient (number)</th>
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<tr>
<td>Aortic PWV</td>
<td>Blacher (1999, Fr)</td>
<td>CV mortality</td>
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<td>ESRD (241)</td>
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<td>General population (1678)</td>
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<td>Ascending aorta (invasive)</td>
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<td>CV events</td>
<td>3.4</td>
<td>HT, ASCCT study (2073)</td>
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<td>Severe CV events</td>
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<td>CV events</td>
<td>3.4</td>
<td>HT, ASCCT study (2073)</td>
</tr>
</tbody>
</table>

IGT, impaired glucose tolerance; CHD, coronary heart disease. Countries: Dk, Denmark; Fr, France; GB, Great Britain; Ge, Germany; Gr, Greece; Jp, Japan; Ne,
PWV, Aix, etc - are they also useful in CKD / dialysis populations?

Aortic Stiffness and Mortality in ESRD: PWV and Alx

![Graph showing probability of overall survival with different PWV categories]

- PWV < 9.4 m/s
- 9.4 ≤ PWV ≤ 12.0 m/s
- PWV > 12.0 m/s

Duration of Follow-Up (Months)

- N = 241, F/U = 72+/−41 months
- N = 189, F/U = 52+/−36 months

Blacher Circulation, 1999 (99): 2434
London et al, Hypertension, 2001, 38: 434
In younger dialysis pts. impact might be different
VC Increases Mortality Risk – EBCT evaluation, or even simpler...

Presence of Abdominal Aortic Calcification Is Significantly Associated With All-Cause and Cardiovascular Mortality in Maintenance Hemodialysis Patients

Senji Okuno, MD,1 Eiji Ishimura, MD,2 Kayoko Katozani, MD,1 Yoko Fujino, MD,1 Kaori Kohn, MD,1 Yoshifumi Maeno, MD,1 Kiyoshi Maeoawa, MD,1 Tomoyuki Yamakawa, MD,1 Yasuo Imanishi, MD,2 Masaaki Inaba, MD,3 and Yoshiki Nishizawa, MD3

CS>400 adds 15-28 yrs of age
CS<10 lowers age by 8-10 yrs

Probability of survival in ESRD patients according to postischemic forearm flow debt repayment (FDR)

Survivorship

\[ \chi^2 = 17.9 \]

\[ P < 0.001 \]

Causes and Consequences of Increased Arterial Stiffness in Chronic Kidney Disease Patients

Paul Gusbeth-Tatomir  Adrian Covic
Dialysis and Renal Transplantation Center, Parhon University Hospital, Iasi, Romania

Arterial Stiffness in Renal Patients: An Update
Adrian Covic, MD, PhD, Paul Gusbeth-Tatomir, MD, and David J.A. Goldsmith, MA, FRCP
How can we treat?

Treatment is important! Impact of change in PWV on survival

Guerin, *Circulation* 2001
SIMPLE THINGS: CONTROL BP

Annual PWV progression
(adjusted for initial PWV, age, HR, and sex)
in treated hypertensive subjects as a function of MAP control
(Benetos, *Circulation* 2002)
Control BP, but all antihypertensives are equal?


CONCLUSION: In hemodialysis patients, trandolapril is as effective as losartan in decreasing PWV independent of its depressor effect and in suppressing elevated IDL-C levels.
Vascular compliance changes under ACE-I in non-diabetic CKD
Mimura et al *JHH* 2008
**Volume overload** is related to arterial stiffness

Targeting VC and stiffness with the same strategies – is it possible?

- The case of vit D
- The case of P binder
- The case of statins
Effects of Vitamin D on Arterial Stiffness and VC

New strategy to attenuate pulse wave velocity in haemodialysis patients

Tsuneo Takenaka\textsuperscript{1} and Hiromichi Suzuki\textsuperscript{2}
Statin therapy and VC

Quinibi, *Kidney Int.*, 2005, 67 (suppl 95), S43-S50
Statins have a favorable effect on:

PWV, inflammation (CRP), oxidized lipids

Changes in PWV and over 6 months in patients treated with placebo (open circles) and fluvastatin (closed circles).

Other strategies

Glycemic control is always mandatory
Tomyiama, *Hypertension* 2006

The persistence of raised fasting plasma glucose during the study period

![Graph showing estimated annual rate of increase of the brachial-ankle pulse wave velocity (cm/sec/year).](image)
Weight Change Is Associated With Change in Arterial Stiffness Among Healthy Young Adults


N = 152 white and black adults aged 20-to 40 years
mean annual PWV changes = 29.9 cm/s/year (regression) for those with 4.5 kg annual weight loss and 18.2 cm/s/year (progression) for those with 4.5 kg annual weight gain
OSA – non-dipping – autonomic neuropathy

Drager LF et al. Chest 2007; 131(5) :1379

- Severe OSA - associated with arterial stiffness and heart structure abnormalities,
- Additive effects with HTA.


- A reverse-dipper pattern associated with increased PWV and with less day: night variability in heart rate
Other strategies

Impact of an Exercise Program on Arterial Stiffness in Hemodialysis Patients

![Graph showing the impact of an exercise program on arterial stiffness over different months of exercise.](image)
• N = 405 young men and women

• Findings suggest that arterial stiffness-related benefits of exercise are most likely to accrue if exercise prescription in young adults targets improvements in cardiorespiratory fitness.
Effects of anemia correction on FMD and brachial artery compliance

Verbeke et al. JASN 2007
Choice of RRT

Does it matter?
THE INFLUENCE OF DIALYTIC MODALITY ON ARTERIAL STIFFNESS, PULSE WAVE REFLECTIONS, AND VASOMOTOR FUNCTION

Adrian Covic,¹ David J.A. Goldsmith,² Laura Florea,¹ Paul Gusbeth–Tatomir,¹ and Maria Covic¹
Successful Renal Transplantation Decreases Aortic Stiffness And Increases Vascular Reactivity In Dialysis Patients.
A. Covic et al., *Transplantation*, 2003, 76:1573)

- 21 HD patients studied 1/12 pre and 3/12 post live-related renal transplantation
  – compared to a group with essential HT
- Echo, PWA and PWV pre and post RTx
- PWV fell significantly after RTx (**)  
- Similar to age, gender and BP matched EHT controls (*)
AIx

Pre-RTx, on dialysis  Post successful RTx

Heart rate adjusted AIx, %

P = 0.012

Covic, Transplantation 2003
Zoungas, KI 2004
Arterial stiffness and wave reflections in renal transplant recipients

Francis Verbeke¹, Wim Van Biesen¹, Patrick Peeters¹, Luc M. Van Bortel² and Raymond C. Vanholder¹

- After correction for age, BP and anthropometry, Al and PWV remained 7.4% and 0.7 m/s higher in RTR than controls

- = difference in vascular age of >10 years.

WHY SUCH A DIFFERENCE –
LESSONS TO BE LEARNED?
(multivariate analysis) - independent factors: GFR and CRP

Differences RTR vs controls
- in GFR = 2/3 of the ↑
- in CRP = 1/3 of the ↑
in PWV and AI
Summary and Conclusions

- Alterations in large artery structure, and function, are fundamental to hemodynamic changes in chronic kidney disease

- Calcification, Sodium-RAAS, inflammation and AGE’s are likely to be major explanations of the changes

- Targets to prevent / retard vascular stiffening
  - Ovehydration / salt / renin-angiotensin-aldosterone \( Y \)
  - Inflammation / lipids \( Y \)
  - Wave reflections \( Y \)
  - Calcification \( Y \)
  - AGE’s \((Y)\)