Effects of Renin-Angiotensin System blockade on arterial stiffness and function

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Determinants of vascular overload (afterload) on the heart

Peripheral Resistance

Arterial Stiffness

Wave reflection

Inertance
Flow-Pressure relationship - influence of the frequency
(Resistance = slope of the relationship)

\[ R = 8 \eta \frac{L}{\pi r^4} \] (\( \eta \)-viscosity; \( L \)-length; \( r \)-radius - number of vessels)

\[ R = \text{Mean Blood Pressure/Cardiac output} \]
Diagrammatic representation of volume-pressure relationship

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

\[ \Delta P / \Delta V = \text{Elastance (Stiffness)} \]
The arterial wall is a heterogeneous material

- Distensible balloon (rubber=elastin)
- Rigid/stiff net (steel=collagen)
- Ballon souple
- Filet inextensible
The arterial wall is a heterogeneous material

A. Tedgui and B. Levy, 1994
Diagrammatic representation of pressure-volume relationships

Pressure vs. Volume graph with two curves labeled Einc=1 and Einc=2. The curve Einc=1 has a higher pressure at a given volume compared to Einc=2. The change in pressure with respect to volume, $dP/dV$, is indicated by a dashed line between the curves.
Arterial function and blood pressure

Pure Conduit Function

Conduit and Cushioning Function

Blood pressure

Systole  Diastole

Mean pressure

Blood pressure

Systole  Diastole

Mean pressure
Correlation between common carotid artery (CCA) distensibility and aortic pulse wave velocity (PWV) in human population

\[ r = -0.825 \]
\[ p < 0.0001 \]
Pressure wave analysis

- measured pressure wave
- forward/incident pressure wave
- reflected pressure wave
- pulse wave velocity

Young subjects

Old subjects
Increasing Wave Reflection
Aortic arterial pressure waveform

$\Delta P = \text{augmented pressure}$

$PP = \text{pulse pressure}$

Augmentation index = $\Delta P / PP$

$Tsh = \text{time to shoulder}$

$LVET = \text{left ventricular ejection time}$
Relationship between the time of appearance of reflected wave on the pressure wave in central artery (time to shoulder - TSh) and aortic pulse wave velocity (PWV)

\[ R = -0.671 \]

\[ p < 0.0001 \]
Relationship between the time of appearance of reflected wave on the pressure wave in central artery (time to shoulder - TSh) and body height

R = 0.585
p < 0.0001
Influence of Left ventricular ejection time (heart rate) on the timing of forward and reflected Waves and on Systolic Augmentation Pressure (Aix)

Positive Aix

Negative Aix

T - traveling time of pressure wave to reflecting sites and back

LVET

Forward-traveling wave

Backward-traveling reflected wave

Actual (composite) wave
Aortic stiffness and all-cause mortality in general population (Laurent et al Hypertension 2001)

Kaplan-Meier  P<0.0001

Follow-up (years)

Survival

Low PWV tertile
Medium PWV tertile
High PWV tertile
Wave reflection (Aix) and cardiovascular survival

- Log rank test for cardiovascular mortality. Chi square =23.11 ; P<0.0001.
Pressure Waves Recorded Along the Arterial Tree

Maximum Early Wave Reflection

Maximum Amplification

Age 68 years

Age 54 years

Age 24 years

Arterial Pressure Waves Recorded in Young Subjects

Normotensive Subjects

Pseudo-Hypertension

Essential Hypertension

Cross-over: 3x 4 weeks, n=20

AUC: p=0.001 vs baseline, vs atenolol

B Pannier et al., Clin Exp Pharmacol Physiol, 2001
Mean values and SEM in group 1 (no baseline AII inhibition) for aortic systolic blood pressure and augmentation index in relation to ingestion at 8:00 AM on different study days of placebo, 600 mg eprosartan, 25 mg captopril, and 60 mg ISMN.
BRACHIAL BLOOD PRESSURES at 1 year

AORTIC SBP (At 1 year)

Δ SBP (mmHg)

Per/Ind (n=65)  Aténolol (n=65)

-22.5  -8.0

p<0.001  p<0.001

AORTIC PP (At 1 year)

\[ \Delta PP \text{ (mmHg)} \]

Per/Ind (n=65)  Aténolol (n=65)

-9.3  2.3

\[ p<0.001 \]
\[ p<0.001* \]

PWV (carotido-femoral)

\[ \Delta \text{PWV (m/s)} \]

\begin{align*}
\text{Per/Ind} & : -0.79 & \text{p}<0.001 \\
\text{atenolol} & : -0.99 & \text{p}<0.001 \\
\end{align*}

AUGMENTATION INDEX (aortic)

LEFT VENTRICULAR HYPERTROPHY

Comparative effect of perindopril and nitrendipine on left ventricular mass index (g/m²)

Left ventricular mass index (g/m²)

- **Perindopril**
- **Nitrendipine**

- * p<0.01 vs base
- § p<0.01 vs nitrendipine

London et al Circulation 1994
Approach to reduction of blood pressure and aortic stiffness with antihypertensive treatment

Control of overhydration

BP>160/90

perindopril

Nitrendipine

Perindopril + atenolol

Nitrendipine + atenolol

Perindopril-atenolol-nitrendipine

Nitrendipine-atenolol-perindopril

Guérin et al Circulation 2001
All cause survival according to changes in aortic pulse wave velocity (Δ PWV) in response to BP decrease

\[ \chi^2 = 28.01 \]
\[ P < 0.00001 \]

Δ Mean blood pressure (mm Hg)

Δ Aortic PWV (m/s)

ACEi

β-

Ca-
Probability of all-cause survival according to prescription (alone or in combination) of perindopril (+ yes ; - no). $\chi^2 = 23.3; p < 0.0001$

From Guérin et al. Circulation 2001
Serum CRP levels in ESRD patients with treatment including or not ACE inhibitor (Perindopril)

Without Perindopril (11.8±11.1)
With Perindopril (7.3±9.7)

P=0.009

London et al Kidney Int 2003
The Conduit Artery Functional Evaluation (CAFE) Study in ASCOT

Peripheral And Central Pulse Pressure (PP) on Amlodipine/Perindopril and Atenolol-based Therapy

Brachial PP
Diff Mean (AUC) = -0.9 (-1.9, 0) mm Hg

Central PP
Diff Mean (AUC) = 3 (2.1, 3.9) mm Hg

The CAFE investigators; Circulation 2005 in press
Peripheral And Central SBP on Amlodipine/perindopril and Atenolol-based Therapy

Brachial SBP
Diff Mean (AUC) = 0.7 (-0.4, 1.7) mm Hg

Central SBP
Diff Mean (AUC) = 4.3 (3.3, 5.4) mm Hg

Atenolol
Amlodipine/perind.

The CAFE investigators; Circulation 2005 in press
The Conduit Artery Functional Evaluation (CAFE) Study in ASCOT

Total CV Events and Procedures + Development of Renal Impairment

The CAFE investigators; Circulation 2005 in press