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CLINICAL REVIEW

Is obstructive sleep apnoea causally related to arterial stiffness? A critical review of the experimental evidence

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SUMMARY

Large elastic arteries and smaller muscular conduit arteries become stiffer with ageing, a process that is accelerated in the presence of cardiovascular disease (CVD). In recent years, numerous techniques have been developed to measure arterial stiffness, either in single vessels or in entire muscular arterial trees. These techniques have increasingly been shown to improve stratification of cardiovascular risk and risk reduction beyond that provided by conventional risk factors.

Obstructive sleep apnoea (OSA) has been increasingly linked with excess cardiovascular morbidity and mortality however the mechanisms are still not well understood. Robustly designed studies have shown that treatment of OSA with nasal continuous positive airway pressure improves important intermediate risk factors for CVD including hypertension and endothelial function. More recently, there has been increased exploration of arterial stiffness in both cross-sectional and interventional studies in OSA patients.

This review aims to give the reader a better understanding of the measurement and pathophysiology of arterial stiffness as well as providing an indication of how well a prognostic indicator are the various measures of arterial stiffness for hard cardiovascular endpoints. A critical appraisal is then provided of cross-sectional and interventional studies that have explored these same techniques in OSA populations.

Introduction

Obstructive sleep apnoea (OSA) is increasingly being linked to excess cardiovascular disease (CVD). Longitudinal community cohort studies have shown both an increased risk for all-cause and cardiovascular mortality[1,2] as well as an increase in the incidence of coronary artery disease, heart failure[3] and stroke.[4] In the latter sleep heart health study (SHHS), the increased risk for developing these adverse outcomes that was attributable to OSA was independent of age, obesity, cholesterol and blood pressure levels.[3,4] However, whilst these cohort studies provide strong evidence of a causal link between OSA and CVD, there are still no prospective randomised trials of sufficient duration to demonstrate that treating OSA with continuous positive airway pressure (CPAP) reduces cardiovascular death or events. In reality, the vast majority of cardiovascular focussed studies in OSA has tended to examine intermediate markers of CVD risk, either in cross-sectional or interventional studies.

Arterial stiffness is increasingly being linked with poorer cardiovascular outcome and many studies now support its utility as an early independent predictor of cardiovascular mortality and morbidity. This review provides an overview of arterial stiffness in terms of its definition and measurement and what determinants and risk factors are linked to it. Also included is an overview of studies from the general cardiovascular literature that give a prognostic indication of arterial stiffness independent of traditional risk factors. This will enhance understanding of the OSA studies that have assessed arterial stiffness which follow.

Definitions of arterial stiffness

The stiffness of the artery wall can be calculated by applying a stress to the artery and measuring the resultant strain. The ratio of stress to strain (Young's modulus) gives the stiffness of the material. Due to the complexities in accurately measuring the stress and strain in arteries both *in-vivo* and *ex-vivo*, there have been many different indices developed that relate experimental measurements

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of parameters of vascular function to arterial wall stiffness. The definitions of these indices have been compiled in the literature previously.[5,6] Whilst many of these stiffness parameters have existed for some time, new parameters are constantly being developed, for example the cardio-ankle vascular index (CAVI).[7] Some of the existing and more recent arterial stiffness indices are summarized in Table 1.

Physiological determinants of arterial stiffness

Pressure dependency

All measures of arterial stiffness are pressure, or stress dependent as the arterial wall has a curvilinear stress/strain relationship, such that the wall stiffness increases with increasing distending pressure.[8] Therefore comparisons must relate to the same distending pressure, or in population studies, account for blood pressure as a factor that influences arterial stiffness.

Various indices have been developed to correct for pressure, or to adjust for the exponential relationship between stiffness indices and pressure. The main indices are the beta stiffness index (β, Table 1 [9]) and the CAVI (Table 1 [7]).

Heart rate dependency

The effect of heart rate on arterial stiffness has been investigated in terms of the dependency on arterial pressure.[10] Pacing studies have shown measurable differences in carotid–femoral pulse wave velocity of up to 12% between heart rates of 60 and 100 beats per minute independent of any changes in arterial pressure.[11] Thus a difference of 3% for a change of 10 beats per minute would be relatively small.

Passive wall structure

The stiffness of the artery wall is due to the mechanical properties of the wall material. The extensibility due to a change in distending pressure is essentially determined by the load-bearing components, mainly elastin and collagen and to a lesser extent by the wall matrix constituents which can be affected by mineral deposits such as calcium.[12]

Over longer periods of time, spanning months or years, the artery undergoes changes in the structural arrangement and quantities of collagen and elastin, altering vessel wall stiffness, vessel wall thickness, and luminal diameter.[13] This arterial remodelling is in response to chronic applied forces such as pulse pressures[14] and endothelial shear stress.[15,16] Arterial remodelling can also be induced by genetic predisposition to changes in elastin and collagen networks, and by environmental factors such as diet.[17,18]

Endothelial derived factors

The distribution of the transluminal pressure load on elastin and collagen structural elements in the arterial wall can be actively changed by the vascular smooth muscle component of the media.[19] The smooth muscle, and therefore vascular stiffness itself, can be modulated by endogenous vasoactive mediators. These mediators may be vascular endothelium dependent (nitric oxide, endothelin,

Table 1
Definition and units of the various indices of arterial stiffness.

Index	Definition	Equation
Augmentation index (AIx)	The % increase in pressure after the peak of blood flow in the vessel. Units: % of pulse pressure	$(P_s - P_i)/(P_s - P_d)$
Capacitive compliance; large artery elasticity index	Ratio of volume and pressure decrease in the arterial tree during diastolic pressure decay. Units: $m^3\,mmHg^{-1}$	$\Delta V/\Delta P$
Cardio-ankle vascular index (CAVI)	The pressure independent β stiffness index obtained without diameter measurements. Units: non-dimensional	$(2\rho \cdot PWV^2/\Delta P)\cdot \ln(P_s/P_d)$
Characteristic impedance (Z_c)	Ratio of pressure and flow velocity in the absence of wave reflections. Units: $mmHg\,m^{-1}\,s^{-1}$	$\Delta P/\Delta v$
Compliance (C)	Diameter or area change for a change in pressure with fixed vessel length. Units: $m\,mmHg^{-1}$ or $m^2\,mmHg^{-1}$	$\Delta D/\Delta P$
Distensibility or compressibility	Diameter or area change for a small change in pressure; the inverse of Peterson's elastic modulus. Units: $mmHg^{-1}$	$\Delta D/(\Delta P \cdot D)$
Input impedance (Z_{in})	Ratio of measured pressure to measured flow. Units: $mmHg\,min\,ml^{-1}$	P/Q
Oscillatory compliance; small artery elasticity index	Ratio of oscillating pressure change and oscillating volume change during the pressure decay of diastole. Units: $m^3\,mmHg^{-1}$	$\Delta V/\Delta P$
Peterson's modulus (E_p)	Pressure step required for a theoretical 100% stretch from resting diameter at a fixed vessel length. Units: mmHg	$(\Delta P \cdot D)/\Delta D$
Pulse wave velocity (PWV)	Velocity of the pressure pulse along an arterial segment. Units: $m\,s^{-1}$	Distance/transit time
PWV, aortic (carotid–femoral)	Velocity assumed to represent aortic PWV using non-invasive measurements of the carotid and femoral arterial pulses. Units: $m\,s^{-1}$	$(d_f - d_c)$/transit time d_f = suprasternal notch to femoral distance d_c = suprasternal notch to carotid distance
PWV, brachial–ankle (baPWV)	Velocity calculated using the pulses detected at the brachium and ankle. Distance from suprasternal notch to brachium (d_b) and ankle (d_a) is conventially calculated proportional to height rather than measured. Units: $m\,s^{-1}$	$(d_a - d_b)$/transit time $d_a = 0.8129 \cdot \text{height (m)} + 0.12328$ $d_b = 0.2195 \cdot \text{height (m)} - 0.020734$
Stiffness index (β)	Logarithm of the ratio of systolic and diastolic pressures, divided by the relative change in diameter. This is a pressure independent index. Units: non-dimensional	$\ln(P_s/P_d)/((D_s - D_d)/D_d)$
Volume elastic modulus; bulk modulus (B)	Pressure change required for a theoretical 100% increase in volume at constant arterial length. Units: mmHg	$(\Delta P \cdot V)/\Delta V = (\Delta P \cdot D)/(2 \cdot \Delta D)$
Young's modulus (E)	Pressure change per unit area required for a theoretical 100% stretch from the original length. Units: $mmHg\,m^{-1}$	$(\Delta P \cdot D)/(h \cdot \Delta D)$
Static incremental modulus (E_{inc})	The ratio of a small pressure change over the resulting small change in dimension. Units: $mmHg\,m^{-1}$	$(\Delta P \cdot D^2)/(2h \cdot \Delta D)$

where D: diameter; d: diastolic; i: augmentation inflection point; P: pressure; V: volume; v: flow velocity; Q: flow; s: systolic; ρ: density.