Abstract

Arterial events in developing countries frequently occur over a young adult age, starting as early as the third decade of life. Atherosclerosis (atheroma formation) is the vascular alteration that ultimately occludes arteries causing coronary artery disease (CAD), stroke or peripheral arterial disease (PAD). In contrast, arteriosclerosis is a process that is thought to in-part be caused by atherosclerosis, but which may also occur independently thereof, and contribute toward the development of vascular damage that leads to occlusion or rupture of the artery. Little is known about the pathogenesis of premature arterial events (events occurring in men < 50 years of age or women < 55 years of age). As arteriosclerosis, which enhances pulse pressure (PP) and hence blood pressure (BP) by increasing aortic stiffness, is presently perceived as largely a disorder of ageing, conventional thought is that it is unlikely to contribute. Arteriosclerosis may even occur at a young age, but the impact may not be detected from BP measures. In the present thesis I therefore evaluated the contribution across the adult age range of arteriosclerotic aortic dysfunction to arterial disease in groups of African ancestry living in South Africa.

Through the impact of conventional risk factors on arteries, several arteriosclerotic arterial functional changes contribute to cardiovascular events. It is nevertheless uncertain whether these effects are accurately reflected by changes in PP in either central (PPc) or peripheral arteries. I therefore, aimed to determine the extent to which relations between modifiable risk factors and arterial function translate into increases in PP in 1232 black South Africans from the South Western Township (SOWETO) of Johannesburg. With adjustments for confounders, diabetes mellitus was associated with an increased carotid-femoral pulse wave velocity (PWV) and forward travelling wave pressures (Pf) but neither brachial PP, PPc, nor backward travelling pressure waves (Pb). Independent of confounders, uncontrolled hypertension was associated with an increased Pf, but not with changes in brachial PP, PPc or Pb. Thus, neither brachial nor central arterial PP are adequate indexes of relations between modifiable conventional risk factors and risk-related arteriosclerotic aortic functional changes.

As the age at which arteriosclerosis begins to contribute to events is uncertain, I subsequently determined, across the full adult lifespan, the extent to which arteriosclerosis-related changes in arterial function occur in those with precipitous arterial events (stroke and critical limb ischaemia [CLI]). Despite similar brachial PP and BP levels, as compared to 726 age, sex and ethnicity-matched randomly selected controls, over 10-year increments in age from 20 to 60years, multivariate-adjusted aortic PWV, characteristic impedance (Zc), Pf, and early systolic pulse pressure amplification (PPamp) were consistently and markedly altered in 356

participants with either CLI or stroke (35.4% premature). Of the patients with stroke, 10.7% were haemorrhagic in origin, 22.1% had a cardio-embolic cause; 17.6% were classified as small artery occlusion and 2.5% as large artery occlusion (atherosclerotic), 31.9% were indeterminate in origin and 15.2% were from alternative aetiology. Aortic stiffness accounted for Zc increases (no differences in aortic diameter), and Pf was accounted for by changes in Zc and not aortic flow or wave re-reflection. Compared to age- and sex-matched controls, independent of risk factors, PWV and Zc were more strongly associated with premature events than events in older persons and Pf and early systolic PPamp were at least as strongly associated with premature events as events in older persons. Despite similar BP levels, arteriosclerosis-related changes in arterial function are consistently associated with arterial events beyond risk factors from as early as 20 years of age.

The extent to which arteriosclerotic aortic dysfunction mediates arterial damage through effects beyond not only peripheral, but also central arterial BP, is uncertain. I therefore aimed to determine whether the impact of aortic stiffness on atherosclerotic or small vessel end-organ damage beyond brachial BP depends in part on stiffness-induced increases in central arterial pressures produced by an enhanced Zc. In 1021 participants, 287 with stroke or CLI, and 734 from a community sample with atherosclerotic or small vessel end-organ measures although Zc and carotid-femoral PWV were correlated, these relations were not independent of confounders. Both Zc and hence central arterial pressures generated by the product of Zc and aortic flow (Q) (P_{QxZc}), as well as PWV were independently associated with carotid intima-media thickness, estimated glomerular filtration rate (eGFR), endothelial activation markers (V-CAM-1) and events. With further adjustments for brachial PP or systolic BP (SBP), PWV and P_{QxZc} were both associated with eGFR, V-CAM-1 and events. Relationships between PWV and eGFR, V-CAM-1 or events were independent of P_{QxZc} and relationships between P_{QxZc} and eGFR, V-CAM-1 or events were independent of PWV. Thus, beyond brachial BP, the impact of aortic stiffness on arterial damage involves effects that are both dependent (proximal aortic Zc and hence P_{QxZc}) and independent (PWV indexes stiffness across the full length of the aorta) of central arterial pulsatile load. Hence, PWV and brachial PP may be insufficient to account for all of the damage mediated by increases in aortic stiffness.

In conclusion, I provide evidence published in the high impact journals *Art Thromb Vasc Biol (ATVB)*, *J Hypertension* and *Am J Hypertens* to advance our understanding of arteriosclerosis as a possible cause of arterial disease. In this regard, I show that in contrast to what has previously been thought, that arteriosclerotic aortic dysfunction is as strongly associated with arterial events over a younger as over an older adult age. Moreover, I demonstrate that these effects go undetected because the impact on arterial function produced by risk factors is

largely on central arterial forward wave pressures with little impact on brachial or peak central arterial pressures. Further, I show that the impact of arteriosclerosis on arterial damage may occur through both forward wave pressure (P_{QxZc}) effects and pressure-independent effects (as indexed by aortic PWV).