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"…studies suggest that an elevated pulse pressure during the acute stages of stroke is a predictor of subsequent survival and functional outcome."

The current guidelines for the detection and management of high blood pressure depend exclusively on the measurement of systolic and diastolic blood pressure, although these are only two specific points on the arterial pressure wave form [1,2]. However, it may be more appropriate to describe the cardiac cycle as consisting of a pulsatile (pulse pressure) and a steady (mean pressure) component.

Pulse pressure is defined as the difference between systolic and diastolic pressures and primarily reflects the stiffness of large arteries, especially the aorta. Elevated pulse pressure increases the stretch of arteries, induces fatigue and fracture of elastic elements, and accelerates the development of aneurysms, and ultimately their rupture. Similarly, an increased pulse pressure is more likely to contribute to intimal damage, the prelude to atherosclerosis and arterial thrombotic events. Increased pulse pressure has also been associated with thickening of the carotid intima and media [3,4]. Systolic blood pressure increases across all age groups, whereas diastolic blood pressure increases until the sixth decade of life and then declines thereafter. As a result, pulse pressure increases as age rises, especially in older people as systolic and diastolic blood pressure move in opposite directions. Hence, pulse pressure may become the key blood pressure measure in older individuals and increase in importance as a risk factor for cerebrovascular diseases and death [5,6].

Several observational studies have found that pulse pressure is an independent predictor of cardiovascular risk in middle aged and older people, in subjects with high blood pressure, in survivors of myocardial infarction and in patients with left ventricular dysfunction [7–11]. A meta-analysis based on individual patient data from three large trials (Syst-Eur, Syst-China and EWPHE [12–14]) showed that isolated systolic hypertension and pulse pressure were the major determinants of cardiovascular risk in elderly hypertensives [7]. A further meta-analysis of individual patient data in control groups of seven randomized clinical trials (SHEP, Syst-Eur, MRC 1, HEP, MRC 2, EWPHE and STOP) in the INDANA project [8] also reported that pulse pressure, rather than mean pressure, was the major risk factor for adverse cardiovascular events. A 10-mmHg increase in pulse pressure at baseline was associated independently with a 6% rise in total mortality, a 7% rise in cardiovascular mortality and a 7% rise in fatal coronary events. A similar rise in fatal stroke was present, although this was statistically nonsignificant due to the limited number of events. However, the relationship between pulse pressure and fatal stroke became significant ($p = 0.04$) at higher age [8]. Importantly, pulse pressure calculated from 24 h ambulatory blood pressure recordings is a better predictor of adverse events than if derived from office-measured blood pressure in older patients with isolated systolic hypertension [15].

"The role of pulse pressure in acute stroke is becoming increasingly clear."

The role of pulse pressure in acute stroke is becoming increasingly clear. A study with 198 older hypertensive patients with acute stroke, mostly of ischemic type, revealed that for every 10 mmHg increase in 24-h pulse pressure, mortality at 1 year

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increased by 40% (hazard ratio: 1.39; 95% confidence interval [CI]: 1.04–1.86; p = 0.028) [16]. In a second study involving 178 patients with acute ischemic stroke, pulse pressure was higher within the initial hours of acute stroke in those who died versus those who improved (81.9 ± 25.6 mmHg vs 66.9 ± 28.8 mmHg; p < 0.001) [17]. A third study showed that an elevated 24-h pulse pressure (with the measurement starting within 24 h ictus) was associated independently with stroke recurrence at 1 year in 339 patients with first ever acute stroke; the relative risk of recurrence was 1.3 (95% CI: 1.02–1.72; p = 0.036) for every 10 mmHg rise in 24 h pulse pressure [18]. However, the study did not assess the relationship between pulse pressure and earlier events. Analysis of data from the TAIST trial showed that increased pulse pressure was associated with a poor functional outcome at 180 days (odds ratio: 1.14; 95% CI: 1.02–1.26) [19]. However, there was no apparent relationship between pulse pressure and early outcome at 10 days including stroke recurrence, death and neurological deterioration. Together, these studies suggest that an elevated pulse pressure during the acute stages of stroke is a predictor of subsequent survival and functional outcome.

> "...pulse pressure is an understudied cardiovascular risk marker."

If pulse pressure is related to vascular events and outcome after stroke, it is natural to ask whether it should be reduced actively. In general, antihypertensive agents reduce pulse pressure in parallel with their effect on blood pressure, although agents that selectively reduce large artery stiffness may have bigger effects on pulse pressure, for example, angiotensin converting enzyme inhibitors, nitric oxide donors and diuretics. However, there are no clinical trials focusing specifically on the reduction of pulse pressure by antihypertensive treatment and the available data come from secondary analyses of completed trials. For example, the Veterans Affairs Single-Drug Therapy for Hypertension study showed that, after 1 year, pulse pressure was reduced significantly more with hydrochlorothiazide (8.6 mmHg; p < 0.001) than with other antihypertensive agents (atenolol, captopril, clonidine, diltiazem and prazosin) [20]. These results favoring the effect of thiazide diuretics on pulse pressure were also observed in the Treatment of Mild Hypertension Study (TOMHS), which used chlorthalidone [21]. The Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT) demonstrated a better outcome (based on the secondary endpoints of stroke and combined cardiovascular disease) in patients treated with chlorthalidone as compared with doxazosin [22,23]; patients receiving the diuretic had a 2–3 mmHg bigger fall in pulse pressure. In each of these instances, the difference in pulse pressure reduction between treatment groups may have influenced outcome.

Although no comparative trials have been performed in acute stroke, a pooled analysis of three completed randomized trials of glyceryl trinitrate found that it significantly lowered pulse pressure in acute and subacute stroke (weighted mean differnece: -6.1 mmHg; p < 0.001) [24]. Observational studies involving hypertensive patients found that an angiotensin receptor antagonist (eprosartan) reduced pulse pressure (13 mmHg; p < 0.001) and the ratio of pulse pressure to mean arterial pressure (3–4%) [25,26].

In summery, pulse pressure is an understudied cardiovascular risk marker. Elevated pulse pressure is associated with a poor cardiovascular prognosis, especially in older subjects, and reflects the stiffness of large arteries [7,16,27]. Although data on specific cardiovascular protection owing to pulse pressure reduction are lacking, differential effects on pulse pressure versus blood pressure may have influenced cardiovascular outcome in comparative trials of antihypertensive treatments. The relevance of pulse pressure in patients with acute stroke remains unclear; ongoing trials of reducing blood pressure in acute stroke such as ENOS [28] and SCAST will further inform this issue, especially the relationship between lowering pulse pressure and outcome.

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