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EDITORIAL

The oldest old: does hypertension become essential again?

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This editorial refers to 'Orthostatic hypotension and symptomatic subclinical orthostatic hypotension increase risk of cognitive impairment: an integrated evidence review and analysis of a large older adult hypertensive cohort'[†], by R. Peters *et al.*, on page 3135.

More than a century ago, Erich Frank, a German physician, at that time in Wiesbaden, coined the term 'essentielle Hypertonie' (essential hypertension) by stating 'Ich werde im folgenden dieses Krankheitsbild als essentielle Hypertonie bezeichnen, denn bei dieser Erkrankung ist die zur Blutdrucksteigerung führende Tonuserhöhung der kleinen Arterien des Gesamtkörpers das Primäre. . .' (I will in the following, name this disease essential hypertension because in this disease the increase in tone of the small arteries in the whole body which leads to an increase in blood pressure is the primary event . . .).[1] The concept of hypertension being essential or indispensable (i.e. serving to force blood through sclerotic arteries to the target organs) remained alive and well for decades. Textbook wisdom such as 'May not the elevation of blood pressure be a natural response to guarantee a more normal circulation to the heart, brain and kidneys'[2] continued to spook practising physicians. This concept also instigated fear that, in susceptible patients, blood pressure (BP) could be lowered too much. Hence, the reluctance of many physicians to expose patients to antihypertensive therapy was not surprising, because abrupt lowering of BP paradoxically can increase target organ disease and even directly cause heart attacks, stroke, and death.[3] Gradually, however, the pendulum began to swing toward the other extreme, and 'the lower the better' became the leitmotiv for most physicians treating hypertension. The large, thorough meta-analysis of Lewington *et al.*[4] corroborated and amplified this concept, asserting 'usual BP is strongly and directly related to vascular (and overall) mortality without any evidence of a threshold down to at least 115/75mmHg'. Statements like these unequivocally put an end to the 'essentiality' of essential hypertension.

A whole host of studies and meta-analyses have been put forward documenting that hypertension is a powerful risk factor for cognitive dysfunction and dementia. Scrutiny of these data reveals, however, that predominantly BP elevation during middle age seems to be the culprit and that the older the patient, the less important a risk factor hypertension becomes (*Figure 1*). Indeed, Abell *et al.*[5] most recently showed that a systolic BP ≥130 mmHg at age 50, which is below the traditional ≥140 mmHg threshold used to define hypertension, was associated with increased risk of dementia and that in these patients the excess risk was independent of cardiovascular disease. Data from the Framingham cohort suggest that subtle vascular brain injury with hypertension develops insidiously during life, with discernible effects even in young adults.[6]

Mutatis mutandis in older patients, elevated BP progressively becomes less of a risk factor for dementia and too low a BP increasingly becomes the principle haemodynamic culprit. At age 85 years and older, low systolic BP predicts the onset of dementia[7] and, most importantly, in centenarians, better cognitive and physical performance is associated with higher BP.[8] Streit *et al.*[9] recently showed an association between accelerated cognitive decline and lower BP in the oldest old taking antihypertensives [annual mean change -0.35 points per 10 mmHg lower systolic BP, 95% confidence interval (CI) -0.60 to -0.11, $P = 0.004$].

In the current issue of the *European Heart Journal*, Peters *et al.*[10] examined the relationship between orthostatic hypotension and incident cognitive decline and dementia in 3121 patients aged ≥80 years (the oldest old) from the Hypertension in the Very Elderly Trial (HYVET) cohort. They documented that a baseline orthostatic fall of at least 15 mmHg systolic BP and/or a fall of 7 mmHg diastolic BP, from sitting to standing, was associated with a 36% increased risk of cognitive decline, hazard ratio (HR) 1.36, 95% CI 1.15–1.59. Further examination of the relationship between a subclinical orthostatic drop, defined as any fall in systolic BP exceeding 15 mmHg on standing and any fall in diastolic BP of more than 7 mmHg on standing plus

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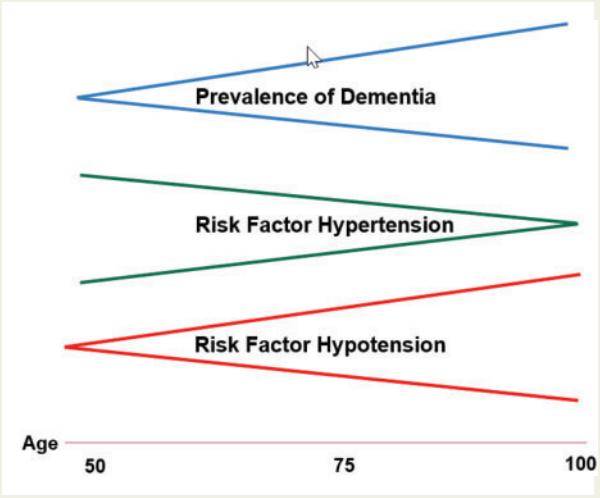

Figure 1 Relative risk of hypertension and hypotension for developing dementia throughout a hypertensive patient's late life span.

orthostatic symptoms, showed that it was associated with a 56% increased risk of cognitive decline, and a 79% increased risk of incident dementia. Their meta-analysis combining HYVET with the published literature found orthostatic hypotension to be associated with a 21% increased risk of dementia.

How can we reconcile the observation that both long-standing hypertension and hypotension seem to increase the risk of cognitive dysfunction and dementia? Conceivably, the link between hypertension or hypotension and dementia may be cerebral perfusion *per se* or its regulation.[11,12] Cerebral hypoperfusion assessed by magnetic resonance imaging was associated with accelerated cognitive decline and an increased risk of dementia in 4759 participants of the Rotterdam cohort (median age 61.3 years), with a median follow-up of 6.9 years.[12] Hypertension is a powerful risk factor for atherosclerosis throughout the arterial tree, and long-term middle-age hypertension has been shown to increase the risk of severe atherosclerosis in later life. Not surprisingly, the risk of either Alzheimer's disease or vascular dementia has been found to be three times higher in people with severe atherosclerosis.[13] Conversely, low BP for obvious reasons as well as excessive BP variability can also cause cerebral hypoperfusion. Oishi *et al*., by following a total of 1674 community-dwelling Japanese subjects ≥60 years of age without dementia for 5 years, showed that increased day-to-day home BP variability was, independent of average home BP, a powerful risk factor for the development of all-cause dementia, vascular dementia, and Alzheimer's disease.[14] In this context, the excessive orthostatic BP drop as observed by Peters *et al*. may simply be a marker of periods of hypotension and increased BP variability. As to the pathogenesis of the orthostatic BP drop, it most probably reflects progressively failing autonomic function and other homeostatic mechanisms on the background of a stiff and sclerotic vascular tree in this very old population.

Does this mean that in the oldest old an elevated BP is a *noli me tangere*, in other words that hypertension has become 'essential' again? Although this well may hold true in centenarians, it unfortunately is not quite that simple; even in the very old, hypertension remains a cardiovascular risk factor, and antihypertensive therapy may confer some benefits. Although the recent SPRINT MIND study did not meet its primary endpoint, antihypertensive therapy showed a 19% reduction of mild cognitive impairment.[15] Keeping systolic BP at 120 mmHg or lower for 4 years was just as effective in those older than 75 as in younger patients. However, in the oldest old, antihypertensive therapy is an evidence-free zone. Regrettably this does not prevent those who preach to continue to preach, but restraints those who teach and puts the burden as to what to do and not to do on those who treat.[16]

What is crystal clear, however, is that hypotension in any form, as shown by Streit *et al*. and Peters *et al*., strictly needs to be avoided. This is true not only for prevention of cognitive decline, but also for prevention of depression,[17] falls and hip fractures,[18] and delirium.[19] For practising physicians, this means always recording a standing BP, repeat, record BP sitting and standing, and avoid drugs prone to cause excessive orthostatic BP drops such as beta-blockers, alpha-blockers, diuretics, and blockers of the renin–angiotensin system. In the oldest old, low dose calcium channel blockers, i.e. amlodipine 2.5 mg, once daily or every other day remain the antihypertensive drug class of choice. In addition, a whole host of extra-cardiovascular drugs can cause hypotension, such as some anti-parkinsonian agents, antidepressants, and other psycho-pharmaceuticals. There is never any need for BP cosmetics, there is no evidence of an optimal on-treatment BP target, and, most importantly, in the oldest old, *in dubio*, no treatment may well be more beneficial than any antihypertensive treatment. Unless we make a concerted effort to treat the patient instead of merely treating mmHg, we may well run the risk that the sarcastic dictum of Robert Koch becomes true: 'Wenn ein Arzt hinter dem Sarg seines Patienten geht, folgt manchmal tatsächlich die Ursache der Wirkung.' (When a physician walks behind the coffin of his patient, the cause sometimes literally follows the effect).[20]

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