Isolated systolic hypertension in the young: a position paper endorsed by the European Society of Hypertension

Paolo Palatini[a], Enrico Agabiti Rosei[b], Alberto Avolio[c], Gregorz Bilo[d,e], Edoardo Casiglia[a], Lorenzo Ghiadoni[f], Cristina Giannattasio[g], Guido Grassi[h], Bojan Jelakovich[i], Stevo Julius[j], Giuseppe Mancia[k], Carmel M. McEniery[l], Michael F. O'Rourke[m], Gianfranco Parati[d,e], Paolo Pauletto[a], Giacomo Pucci[n,o], Francesca Saladini[a], Pasquale Strazzullo[p], Konstantinos Tsioufis[q], Ian B. Wilkinson[l], and Alberto Zanchetti[r]

Whether isolated systolic hypertension in the young (ISHY) implies a worse outcome and needs antihypertensive treatment is still a matter for dispute. ISHY is thought to have different mechanisms than systolic hypertension in the elderly. However, findings from previous studies have provided inconsistent results. From the analysis of the literature, two main lines of research and conceptualization have emerged. Simultaneous assessment of peripheral and central blood pressure led to the identification of a condition called pseudo or spurious hypertension, which was considered an innocent condition. However, an increase in pulse wave velocity has been found by some authors in about 20% of the individuals with ISHY. In addition, obesity and metabolic disturbances have often been documented to be associated with ISHY both in children and young adults. The first aspect to consider whenever evaluating a person with ISHY is the possible presence of white-coat hypertension, which has been frequently found in this condition. In addition, assessment of central blood pressure is useful for identifying ISHY patients whose central blood pressure is normal. ISHY is infrequently mentioned in the guidelines on diagnosis and treatment of hypertension. According to the 2013 European Guidelines on the management of hypertension, people with ISHY should be followed carefully, modifying risk factors by lifestyle changes and avoiding antihypertensive drugs. Only future clinical trials will elucidate if a benefit can be achieved with pharmacological treatment in some subgroups of ISHY patients with associated risk factors and/or high central blood pressure.

Keywords: arterial stiffness, central blood pressure, stroke volume, systolic hypertension, young

Abbreviations: AIx, augmentation index; aPWV, aortic pulse wave velocity; BP, blood pressure; BPV, blood pressure variability; CARDIA, Coronary Artery Risk Development in Young Adults; HARVEST, Hypertension and Ambulatory Recording VEnetia STudy; ISH, isolated systolic hypertension; ISHY, isolated systolic hypertension of youth; NHANES, National Health and Nutrition Examination Survey; PP, pulse pressure; PWV, pulse wave velocity; WCE, white-coat effect; WCH, white-coat hypertension

INTRODUCTION

There is still debate in the literature about the clinical significance of an isolated increase in SBP detected in the first decades of life. Controversies remain especially about the management of young individuals with isolated systolic hypertension (ISH) because whether ISH in the young (ISHY) implies a worse outcome and needs antihypertensive treatment is increasingly under challenge [1–3]. The lack of a consistent definition of young age for people with ISHY has contributed to the variations in reported outcome. Several issues regarding ISHY were

Journal of Hypertension 2018, 36:1222–1236

[a]Department of Medicine, University of Padova, Padua, [b]Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy, [c]Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia, [d]Department of Cardiovascular, Neural and Metabolic Sciences, S. Luca Hospital, IRCCS, Istituto Auxologico Italiano, Milan, [e]Department of Medicine and Surgery, University of Milano-Bicocca, [f]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, [g]Cardiology IV, 'A. De Gasperis' Department, ASST Niguarda Ca' Granda and Medicine and Surgery Department, Bicocca University, Milan, [h]Clinica Medica, University of Milano-Bicocca, Milan, Italy, [i]University Hospital Center Zagreb, Zagreb, Croatia, [j]Division of Hypertension, University of Michigan, Ann Arbor, Michigan, USA, [k]University of Milano-Bicocca and IRCCS Istituto Auxologico Italiano, Milan, Italy, [l]Division of Experimental Medicine and Immunotherapeutics, University of Cambridge, United Kingdom, [m]St Vincent's Clinic/ University of New South Wales/ VCCRI, Sydney, Australia, [n]Department of Medicine, University of Perugia, Perugia, [o]Unit of Internal Medicine, Terni University Hospital, Terni, [p]Department of Clinical Medicine and Surgery, Federico II University of Naples Medical School, Naples, Italy, [q]First Cardiology Clinic, National and Kapodistrian University of Athens, Hippokration Hospital, Athens. Greece and [r]Istituto Auxologico Italiano and Centro Interuniversitario Fisiologia Clinica e Ipertensione, Università degli Studi di Milano, Milan, Italy

Correspondence to Paolo Palatini, MD, Department of Medicine, University of Padova, via Giustiniani, 2, 35128 Padua, Italy. Tel: +39 49 8212278; fax: +39 49 8754179; e-mail: palatini@unipd.it

Received 16 December 2017 **Revised** 14 February 2018 **Accepted** 16 February 2018

J Hypertens 36:1222–1236

DOI:10.1097/HJH.0000000000001726

reviewed and discussed in a consensus meeting held under the auspices of the European Society of Hypertension, on 18 June 2017, in Padova, Italy. Specific objectives of the panel of experts were to provide an update on ISHY and to discuss a number of open questions on the clinical significance and the management of this condition. Goal of the present document is to provide updated information rather than guidelines because whenever evidence is lacking and opinions of experts are not in full agreement, definitive recommendations cannot be set forth.

TRAJECTORIES OF BLOOD PRESSURE FROM CHILDHOOD TO ADULTHOOD

From puberty to mid-life, brachial blood pressure (BP) changes follow a nonlinear increase and diverging BP trajectories between SBP and DBP: whereas DBP displays a cubic trajectory with a plateau-like behavior, SBP age-related changes are characterized by a steep increase during childhood, a plateau phase between 20 and 40 years [4–7], followed by a subsequent increase (Fig. 1). Therefore, at the population level, pulse pressure (PP) values decrease in the age range between 20 and 40 years. After 50 years of age, PP increases exponentially as the result of further SBP linear increase and a DBP plateau phase is reached around 60 years, followed by a decrease [8]. Changes in adult life have been attributed to progressive stiffening of large arteries [9].

A number of epidemiological observations described the individual patterns of BP change over time and the associated clinical and prognostic significance. However, most of these studies were limited by cross-sectional design and substantial data from large-scale prospective longitudinal BP evaluations, assessing the effective intraindividual time-dependent BP changes, became available only in recent years. It has been observed that higher baseline SBP is predictive for steeper increases in aortic stiffening, BP and the future risk of hypertension, both in adolescence [10,11] and in adulthood [8,12]. Moreover, sex, ethnicity, smoking status, obesity and diabetes mellitus were significant effect-modifiers of an increased annual rate of change in PP [10,11,13]. Changes in body composition also play an important role in determining the rate of BP changes during adolescence. Variations in BMI after puberty have been related to sex differences in BP values from puberty to the age of 50–60 years, and were also shown to be significant determinants of the future risk of hypertension during adulthood [11]. The evidence of a positive relationship between weight gain and increased SBP in early adolescence should form the basis for future interventional research in this field aiming at evaluating the effectiveness of weight control programs during puberty.

There is uncertainty as to whether BP rate of change during childhood before puberty is associated with future risk of hypertension [5,10,14]. Some studies explored the clinical and prognostic significance of different BP trajectories both in early adulthood and in the elderly. In a group of 1169 adults aged 30 years, steeper PP trajectories until the age of 14 years predicted the development of mild chronic kidney disease [15]. Another study described the BP trajectories associated with an increased risk of developing coronary artery calcifications after 25 years, in individuals aged 18–30 years. As compared with individuals with stable BP values, individuals showing increasing values of both SBP and DBP were associated with a nearly doubled risk of coronary atherosclerosis [16]. Steeper increases in SBP and PP during mid-life were also associated with a greater risk of angina [13]. Recently, Tielemans *et al.* [17] exploring data from two prospective and nearly extinct cohorts of individuals aged 50 years at the first evaluation, found that individuals with steeper BP rises were exposed to two-to-four-fold higher risk of cardiovascular and all-cause mortality in the subsequent 10 years, independently of baseline BP. This last observation reinforces the concept that longitudinal changes in BP are of importance in predicting the cardiovascular risk of an individual, and highlights the importance of extending the evaluation not only to baseline BP but also to focus the attention to BP changes over time. Further evidence is needed in order to better characterize the risk associated with increased longitudinal BP trends over life.

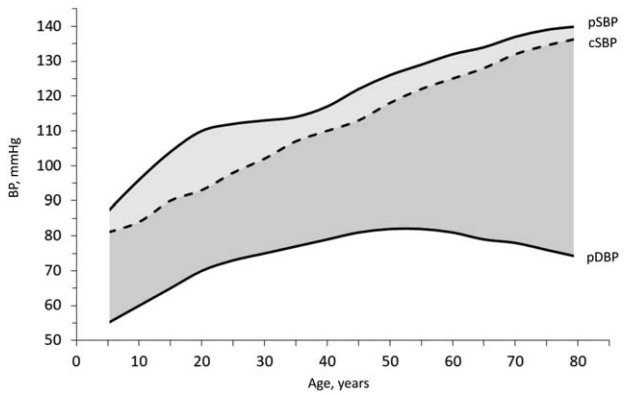

FIGURE 1 Schematic representation of tracking of peripheral SBP and DBP (pSBP, pDBP, black lines), and central systolic pressure (cSBP, gray line) in the general population. The gray area indicates pulse pressure; bright gray area represents pulse pressure amplification. Data are extracted from references [4,7,126,127].

PREVALENCE OF ISOLATED SYSTOLIC HYPERTENSION AND HIGH PULSE PRESSURE IN YOUNG INDIVIDUALS

ISH defined as a SBP at least 140 mmHg and DBP less than 90 mmHg [18] is the most common form of hypertension in the elderly [18,19]. However, ISH can be present also in young and very young individuals, more commonly in men (Table 1).

Prevalence of isolated systolic hypertension in young adults

The prevalence of ISH in the general adult population follows a typical J-shaped pattern, with a nadir in the fifth decade, a steep increase after 70 years of age and an earlier peak, though of lower magnitude, below 30 years of age [19,20]. In the elderly, ISH is more prevalent in women compared with men, whereas in individuals younger than 35 years, the prevalence is higher in men chiefly in the youngest age classes [19,20]. According to data from the National Health and Nutrition Examination Survey

TABLE 1. Prevalence of isolated systolic hypertension in children, adolescents, and in young-to middle-age adults

Authors	Population	Age (years), mean ± SD or age range	Prevalence (%)
Children and adolescents			
Chiolero *et al.* [25]	General Swiss population ($n = 5207$)	12.3 ± 0.5	1.6
Cheung *et al.* [26]	General US Population ($n = 21\,062$)	13.8 ± 1.7	2.5
Karatzi *et al.* [27]	General Greek Population ($n = 2655$)	9–13	11.9
Lurbe *et al.* [29]	Spanish overweight and obese ($n = 593$)	12.2 ± 2.3	4
Young-to-middle age adults			
Staessen *et al.* [19]	General Belgian population ($n = 4202$)	10–30	2.8
		30–40	0.1
		40–50	0.8
Mallion *et al.* [20]	French working population ($n = 27\,783$)	15–19	5.8 (M) <1 (F)
		20–24	9.3 (M) <1 (F)
		25–29	6.8 (M) <1 (F)
		30–34	6.2 (M) <1 (F)
		35–39	6.3 (M) <1 (F)
		40–44	5.8 (M) 2.1 (F)
		45–49	7.8 (M) 3.7 (F)
Liu *et al.* [21]	General US population ($n = 24\,653$)	18–39	3.3 (M) 0.5 (F)
		40–59	6.6 (M) 5.4 (F)
Saladini *et al.* [22]	Italian Stage I hypertensive patients ($n = 1141$)	18–21	48 (M) 13 (F)
		22–25	28 (M) 15 (F)
		26–29	14 (M) 11 (F)
		30–33	15 (M) 4 (F)
		34–37	12 (M) 8 (F)
		38–41	5 (M) 5 (F)
		42–45	1 (M) 0 (F)

F, female; M, male.

(NHANES) study [21], it is more common in black than white individuals. ISH is the most common type of hypertension among young men (Table 1). Results from the Hypertension and Ambulatory Recording (HARVEST) study obtained in a population of 18–45 years old grade-1 hypertensive individuals have shown that ISH prevalence was higher in men until 37 years of age and was similar between the two sexes at 38–41 years [23]. A longitudinal analysis from the NHANES Study [21] showed that the prevalence of ISH in 18–39 years old individuals slightly increased 5 years later in men (2.4 versus 3.3%), whereas among women, it slightly decreased (0.9 versus 0.5%), even if these differences did not reach the level of statistical significance.

Prevalence of isolated systolic hypertension in children and adolescents

ISH may be present also in children and adolescents (Table 1). The diagnosis of ISH in individuals less than 16 years conforms with pediatric conventions, and differs from that adopted for adult and elderly patients being defined as a SBP at least 95th percentile and a DBP less than 90th percentile [24]. Among children and adolescents, ISH is the most frequent form of hypertension and is often correlated to overweight and obesity. In a Swiss survey of 5207 children with a mean age of 12.3 years, 2.2% of the study participants were hypertensive (diagnosis confirmed after three separate visits) and among the hypertensive patients, 81% presented ISH [25]. Of note, hypertension was associated with excess body weight, elevated heart rate and parents' history of hypertension. Similar results were observed in a recent BP screening program from a US population [26] in which 21 062 young individuals (mean age 13.8 years) were examined. In this study, sustained hypertension was present in 2.7% of the participants of whom 92% exhibited ISH, 6% systolic–diastolic hypertension and 2% isolated diastolic hypertension. Hypertension was more frequent among boys (3.3%) compared with girls (2.1%), and the prevalence increased with increasing BMI, being 2.6% and 6.6% in overweight and obese individuals, respectively [26]. A higher prevalence of prehypertension (14.2%), stage 1 hypertension (15.7%) and stage 2 hypertension (7.3%) was observed in a sample of 2655 Greek schoolchildren (9–13 years) participating in the Healthy Growth Study [27]. Also in this population, ISH was the most prevalent phenotype (11.9%) and was positively associated with BMI and waist circumference in both sexes and with sedentary behaviors in boys. The relationship between BMI and BP increase was explored in a recent article by Kropa *et al.* [28]. Investigating 2700 middle school and high school physically active children (mean age 15.7 years) the authors observed that BMI accounted for 19.7% of the variability in SBP and for 8.5% of the variability in DBP. Lurbe *et al.* [29] explored the prevalence of hypertension in a group of 593 overweight and obese young chidren (mean age 12.2 years) and observed that 86.2% were normotensive, 8.1% had high–normal SBP, 4% had ISH and 1.7% had systolic–diastolic hypertension. No cases of isolated diastolic hypertension were found.

Distribution of pulse pressure according to age

In the Third NHANES study (1988–1994) [30], in individuals divided into three age classes of 17–44 years, 45–64 years and at least 65 years, an increase in PP was observed from the first to the second age class (from 42.2 to 67.7 mmHg) and then it levelled off (67.0 mmHg in the oldest class). In a recent Chinese population-based study [31], participants were

divided into four age classes (18–30, 30–45, 45–55, and 55–70 years). PP progressively increased with aging being 37.8, 38.7, 42.0 and 48.0 mmHg, respectively, in the four groups. The distribution of PP in adults younger than 45 years was recently explored in 1241 grade 1 hypertensive participants from the HARVEST study divided into seven age classes [22]. Among the men, PP was highest in the youngest age group (61 mmHg), then it gradually decreased with aging and reached the lowest values in the two oldest groups (49 and 50 mmHg, respectively). Among the women, PP decreased from the first to the second age group (from 52 to 45 mmHg) and then it gradually increased to reach the highest value in the oldest group (52 mmHg). Of note, PP in women was lower than in men until 37 years of age, but after that age it was higher in women.

PATHOGENESIS OF ISOLATED SYSTOLIC HYPERTENSION AND ELEVATED PULSE PRESSURE IN THE YOUNG

Hyperkinetic circulation and hemodynamic transition in hypertension of the young

The hyperkinetic state of increased cardiac output, tachycardia and elevated BP has been documented in about one-third of young patients with prehypertension by Julius *et al.* [32] using invasive hemodynamic measurements. The same group of investigators subsequently used a noninvasive measurement method (Echo-Doppler) and found that 14% of 691 study participants (average age 32.6 years) had prehypertension and 37% of them had hyperkinetic circulation [33,34].

Patients with established hypertension characteristically have increased peripheral vascular resistance [32]. It follows that in the evolution from prehypertension to established hypertension, there must be in many young individuals, a hemodynamic transition from high cardiac output to increased vascular resistance. In his unique Bergen study [35], Lund-Johansen followed initially untreated patients with mild hypertension over a period of three decades (1965, 1975, 1982). In the resting state, there was a stepwise increase of BP and vascular resistance together with a decrease of cardiac output and stroke volume. The resting heart rate did not change from the first to the third decade. Thus, in Lund-Johansen study, the reduction of cardiac output was entirely because of a decrease in stroke volume associated with vascular rarefaction. In a hemodynamic study, Julius *et al.* [36] compared prehypertensive individuals with normal resting cardiac output to age-matched normotensive volunteers. There was a marked reduction of stroke volume in the prehypertension group. This decrease was seen at baseline and was even more profound after 'chemical denervation' of the heart with propranolol and atropine. There was no difference in cardiopulmonary blood volume between the prehypertension and normotension groups.

In the evolution of established hypertension, the decrease of stroke volume is associated with increased vascular resistance [33,37]. This rise in resistance is best explained by a BP-induced restructuring of resistance vessels. There are two characteristic elements of restructured resistance vessels; they are less capable of dilating and they contract excessively to various constricting stimuli. The fact that restructuring is a secondary effect of higher BP, and it is already present in early stages of hypertension, supports the notion of early antihypertensive treatment. However, at present, there is no evidence that such an early treatment may be useful. Unfortunately, in the Lund-Johansen [35] and Julius *et al.* [38] studies, there was no information about whether young people with borderline or mild hypertension had ISH, diastolic hypertension or systolic–diastolic hypertension.

Autonomic nervous system regulation in hypertension of the young

In the early 1970s, it was well known that fast heart rate is a strong predictor of hypertension and adverse cardiovascular outcomes [39]. However, there was a considerable disagreement about the pathophysiology of tachycardia. Particularly interesting was the report from the Cleveland Clinic [40] that some patients with tachycardia and elevated BP are hyper-responders to beta adrenergic stimulation. Another possible mechanism was that individuals with tachycardia may have a pacemaker, which inherently induces a faster heart rate. This issue was addressed by Julius *et al.* who used atropine and propranolol to block the cardiac autonomic nervous receptors [41,42]. The basic finding of this study was that in hyperkinetic prehypertension, the sympathetic stimulation is increased whereas the parasympathetic inhibition is decreased. This strongly suggested that the abnormality emanated from the medulla oblongata wherever the sympathetic and parasympathetic tone are regulated in a reciprocal fashion. The autonomic blockade totally abolished the increase of cardiac output and heart rate in the hyperkinetic state thereby proving that the hemodynamic abnormality was neurogenic. Alterations in parasympathetic/sympathetic regulation of the cardiovascular system have also been described in ISHY. The more common finding reported in this clinical condition is the increase in resting heart rate, which may be dependent on the alteration of either vagal or adrenergic control of sinus node activity [43]. Indeed, data collected throughout the years confirm that vagal control of heart rate is impaired in this form of hypertension, the magnitude of the alteration being directly related both to the severity and the duration of the SBP elevation [43,44]. However, it is fair to say that emphasis has been put on sympathetic overdrive and little information exists about the decreased parasympathetic inhibition in hypertension [45]. As mentioned above, data collected in the context of the Tecumseh study have shown that about one-third of the young hypertensive patients display a so-called 'hyperkinectic circulation,' that is, an elevation in both resting heart rate and cardiac output, the latter being the factor majorly responsible for the isolated increase in SBP [34]. Interestingly, in the Tecumseh study, the patients characterized by this specific hypertensive state also displayed an elevation in plasma norepinephrine levels, a finding, which suggests the occurrence of an adrenergic overdrive. This has been later directly documented in young hypertensive patients via the microneurographic as well as the radiolabelled norepinephrine approach [46–48]. The latter technique has shown that in young patients, the

BP elevation is accompanied by a marked increase in systemic but also cardiac and renal norepinephrine secretion, indicating a pronounced adrenergic activation [48,49]. Given the evidence that ISHY may be associated with alterations in arterial compliance and distensibility [50], the observation that sympathetic neural mechanisms exert a tonic inhibition on both compliance and distensibility of large and medium size arteries is of specific interest [51]. This suggests that the abnormalities in sympathetic cardiovascular control detected in ISHY may have adverse effects on vascular structure and function [52].

Arterial stiffness and measurement of SBP in the young

Although one of the most striking features of vascular aging is the progressive increase of arterial stiffness, as measured noninvasively by arterial pulse wave velocity (PWV) [50,53–56], the rate of arterial stiffening with age is not similar in all arterial districts. The largest change in PWV occurs in the aortic trunk (e.g. 0.92 m/s per decade), with much lower rates in the arm (0.48 m/s per decade) and leg (0.56 m/s per decade) [53]. This phenomenon translates to a significant change in stiffness gradient between the central aorta and peripheral arteries. The relative stiffness gradient between the arm and the aorta drops from 118% at age 10 years to 87% at age 20, 64% at age 30 and 46% at age 40 [53]. This large discrepancy in stiffness gradient with age has significant implications in the measurement of BP in the brachial artery in the young and its relationship to central hemodynamics for characterization of central organ damage such as left ventricular hypertrophy.

The relationship between the central aortic PP and the peripheral pulse in the upper limb is described by a transfer function, which depends on the properties of the arteries [57]. As there is a low rate of stiffening in the upper limb arteries [53], this has been approximated to a constant frequency-dependent function after the cessation of body growth (approximate age 18 years) with considerable success in the noninvasive estimation of central aortic pressure [58]. This method has been found useful and reliable down to age 8 years [59,60], presumably because the shorter distance from left ventricle to reflecting sites is offset by lower arterial distensibility. A better method for estimating peak central SBP in youth is from the late systolic shoulder of the radial pressure wave [61]. In the young, the large stiffness gradient is associated with variable effects of wave reflection such that the central and peripheral pressure waveforms differ in spectral power, that is, they have different energy in the harmonic components of heart rate frequency [62,63]. This has pronounced effects on the relationship between central and peripheral SBP. With age, as the stiffness gradient reduces, the differences in energy content of peripheral and pressure wave frequency components also reduce, so that the peripheral and central waves tend to resemble each other. Hence there is less of a difference between central and peripheral SBP, for a relatively constant DBP as occurs in ISH. That is, not only central aortic stiffness but also stiffness gradient between central and peripheral arteries may be a useful measure for evaluating the relevance of ISHY in relation to central organ damage.

Effects of high heart rate on arterial stiffness

The frequency dependency of the transfer function between the central aorta and peripheral (brachial or radial) pressure pulse determines the relationship between aortic and peripheral SBP for a constant DBP. With changes in heart rate, harmonic components will be amplified or attenuated to different degrees. As the brachial transfer modulus function exhibits a monotonic increase up to a frequency of around 4 Hz in adults and fully grown adolescents (age >18 years) [57,58], a high heart rate implies a higher amplification of the fundamental and first two to three harmonics. That is, a higher PP will be measured in the brachial artery for a similar central aortic PP because of the heart rate-dependent amplification phenomenon [64–66]. The implication for ISHY is that heart rate plays an important role whenever comparing effects of high SBP measured in the brachial artery on central hemodynamics and central organ damage.

Recent studies have elucidated the heart rate dependency of arterial stiffness as measured by arterial PWV and underlying mechanisms [67–69]. This has been quantified as an increase of 0.17 m/s for an increase of 10 beats/minute [68]. A high heart rate has been identified as a significant factor of cardiovascular risk [39,70]. If a high heart rate is associated with ISH where there is also an increase in mean BP, this will also increase the overall arterial stiffness. As arterial stiffness is a significant independent cardiovascular risk factor [71–72], this combined effect will result in a compound increase of overall risk. Specifically, it can also contribute to a preferentially accelerated effect on vascular aging in the young. From the reference values of PWV in the normal population [50] an increase of 10 beats/min, with the associated increase of 0.17 m/s in PWV, would result in additional 2 years of vascular age at a chronological age of 40, but an additional 5 years of vascular age at age 20.

Contribution of stroke volume and arterial stiffness to elevated SBP in isolated systolic hypertension in the young

The arterial BP has two major physiological components, in addition to the simple extremes of SBP and DBP. The static or steady state component, which is represented by the mean arterial pressure is determined, physiologically, by the cardiac output and peripheral vascular resistance. In contrast, the pulsatile component or the PP is determined, physiologically by stroke volume, aortic stiffness and timing of wave reflection. The landmark studies by Lund-Johansen [35] and Julius *et al.* [34,38], described in the previous sections, demonstrated that young patients in the earliest stages of hypertension were characterized by a hyperkinetic circulation, involving elevations of cardiac output and heart rate. However, and somewhat surprisingly, relatively few studies have examined the contribution of stroke volume and aortic stiffness to ISHY per se or whether a hyperkinetic circulation invariably precedes sustained elevation of BP.

In a small study of 32 healthy men aged between 17 and 28 years [73], high brachial PP was positively associated with elevated stroke volume and cardiac output. There was no significant association with heart rate, suggesting that

the stroke volume was probably the major driver of the elevated PPs in these young individuals. The same authors had earlier demonstrated that the contribution of stroke volume to high PP in hypertensive men was mostly marked in younger individuals (those aged <50 years) but became much less important after the fifth decade [74], suggesting that other hemodynamic mechanisms (presumably aortic stiffening and early return of wave reflection) were responsible for the elevated PP observed in older individuals. The Enigma Study [75], which included 1008 young adult university students (mean age 20 years) examined cardiac output and stroke volume using a validated [76,77] noninvasive inert gas rebreathing technique. Carotid–femoral PWV (aortic; aPWV), a robust measure of aortic stiffness, was also assessed. Increased cardiac output and stroke volume were the predominant hemodynamic disturbances in ISHY in the Enigma Study and, in particular, elevated stroke volume was evident in the majority of cases. However, it was also clear that ISHY is a heterogeneous condition, as ~20% of individuals had normal stroke volume, but increased aPWV. Therefore, at least in some individuals, ISHY might be associated with premature aortic stiffening and a trajectory towards sustained ISH in later life.

Blood pressure variability in the young

A number of studies have shown that the cardiovascular risk related to hypertension may not only depend on the magnitude of the BP elevation per se but also on the presence of other associated conditions such as increased BP variability (BPV; either in the short or the long term) [78,79]. Recent data suggest that high BPV may play an important role also in children and young adults. Data from Fujita *et al.* [80] in 198 children and adolescents, from Kotsis *et al.* [81] in 115 young healthy volunteers, and from Boardman *et al.* [82] in 152 young adults (mean age, 31 years) suggest that increased 24 h SBPV is associated with increased arterial stiffness. Also, long-term BPV has been found to be associated with worse outcome in youth. Using data from the Coronary Artery Risk Development in Young Adults (CARDIA), which recruited healthy people aged 18–30 years, Yano *et al.* [83] found that long-term BPV throughout young adulthood was associated with worse cognitive function in midlife. In the Bogalusa Heart Study, Chen *et al.* [84] found that childhood visit-to-visit BPV, measured in 1797 participants, was predictive of adulthood hypertension in addition to the mean levels. Thus, a large body of evidence supports a pathophysiological role for high BPV in determining hypertension and hypertensive complications also in children and young adults.

Some studies have shown that BP and heart rate variabilities were positively correlated to each other, suggesting a primary role of central nervous mechanisms in regulating these hemodynamic parameters [78,79]. In addition, the genetic background may also play an important role in fluctuations of BP over time [85]. Lurbe *et al.* [86] also highlighted the role of low-birth weight as a determinant of future BPV in children and showed that healthy children and adolescents who had lower birth weights tended to have not only the highest BP values but also the highest 24 h SBPV later in life.

The effect of a comprehensive healthy lifestyle on BPV in healthy populations is largely unknown [87]. In a large, population-based study of 1999 young healthy adults, Maseli *et al.* [88] showed that a healthy lifestyle and individual health metrics were significantly associated with a lower BPV. These data suggest (but, of course, do not prove) that a decrease in BPV might contribute to the beneficial effect of a healthy lifestyle regarding the prevention of cardiovascular events.

CHARACTERISTICS OF YOUNG INDIVIDUALS WITH ISOLATED SYSTOLIC HYPERTENSION

As reiterated in this article, ISHY is thought to have different mechanisms than ISH of the elderly. It is, thus, conceivable that also risk factors for ISH may differ between young adults and elderly patients. However, findings from previous studies in patients with ISHY have provided inconsistent results. Long ago, Julius *et al.* [34] documented that young individuals with hyperkinetic circulation had overweight and metabolic disturbances. Among 5685 adults aged 18–39 years from the NHANES study, obesity, male sex, smoking and low-educational level were each associated with higher odds of ISHY [89]. In contrast, studies in smaller samples have found that ISHY was more common in tall men, nonsmokers and active in sports [90,91]. These conflicting data suggest that ISHY is a very heterogeneous condition that may include individuals with totally different genetic background and clinical characteristics.

Association of isolated systolic hypertension in the young with obesity and the metabolic syndrome

As mentioned above, obesity and metabolic disturbances have often been found to be associated with ISHY both in children [25,26] and young adults [34,89]. In the NHANES study [89] and a study by Asgari *et al.* [92], high BMI was a major factor associated with the identification of ISHY. Middlemiss *et al.* [93] found that in young overweight individuals, it was the level of peripheral vascular resistance that distinguished between individuals with elevated versus normal brachial SBP suggesting that the mechanisms underlying elevated SBP in young adults depend on body size. In the Olivetti Heart Study [94], among participants aged less than 50 years ($n = 356$), only 3% had ISHY. Individuals with ISHY had higher values of BMI, waist circumference, fasting blood glucose and HOMA index of insulin resistance compared with normotensive participants. However, none of these differences reached statistical significance, conceivably because of the very small number of individuals with ISHY. Using a lower cut-off (SBP ≥130 mmHg and DBP <85 mmHg) to define ISHY, the prevalence rose to 6% and the differences in blood glucose and HOMA index attained statistical significance ($P < 0.05$). In addition, the prevalence of metabolic syndrome was higher in ISHY than normotensive participants (26 versus 2%, $P < 0.05$). Consistent results were obtained in the MINISAL children program, which was aimed at the assessment of habitual sodium intake in a sample of 1600 Italian children and

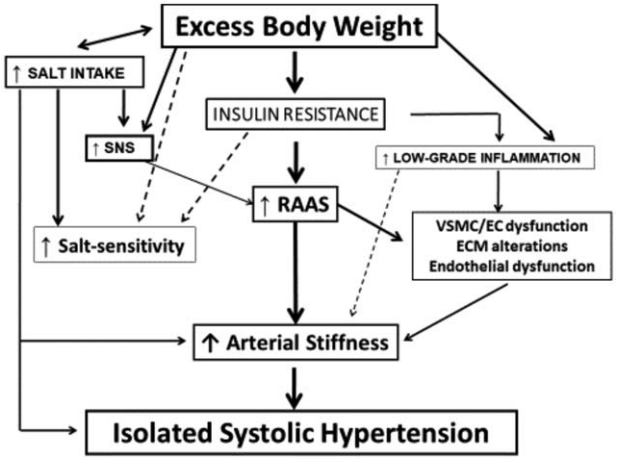

FIGURE 2 Pathophysiological aspects of isolated systolic hypertension in the young. The sketch illustrates the pathogenetic mechanisms that can account for the relationship between obesity and isolated systolic hypertension in young individuals.

adolescents aged 6–18 years [95]. By stratifying the 97 hypertensive patients by hypertensive subtype, the group with ISHY had the highest average BMI z score and the highest habitual sodium intake [95]. Overall, the results of the Olivetti and MINISAL children study, together with the evidence available from other sources [96] suggest that insulin resistance and high salt intake are two important factors in the pathogenesis of ISHY. These two factors may act synergistically as insulin resistance and the accompanying hyperinsulinemia tend to enhance the sympathetic tone, the renin–angiotensin system activity and the sodium and water reabsorption at the renal tubular level [97], thus contributing to increasing BP salt-sensitivity (Fig. 2). Over time, these factors may generate a gradual increase in arterial stiffness that further contributes to the increase in SBP. However, other studies of ISHY patients provided different findings suggesting that ISHY may have different pathophysiologic backgrounds. In the Mahmud and Feely's observational study [91] or the O'Rourke study [90], it was reported that young people with ISH did not have any additional risk factor and that central BP was normal. Indeed, central BP measurement can help to identify the different phenotypes of people with ISHY and the ISHY patients at higher risk [98,99].

Effect of regular physical activity on arterial distensibility and isolated systolic hypertension in the young

A large number of epidemiologic studies have shown an association between regular physical activity and decline in the risk of cardiovascular and all-cause mortality [100,101]. It is possible that regular exercise training may attenuate cardiovascular disease through a variety of factors, including lower BP, reduced BMI, better lipid profile, and so forth [101,102]. In addition, it has been shown that aerobic physical activity can limit the age-related decline in arterial elasticity as measured from carotid–femoral PWV [103] and improve small artery compliance in young adults [104] as well as in children [105]. However, the long-term effect of regular endurance exercise training on central BP and augmentation index (AIx) is still controversial, because of contrasting findings between different studies [106–109]. Training-induced bradycardia together with the improvement of cardiovascular risk factors can account for the better indexes of arterial distensibility observed in trained individuals compared with their sedentary counterparts [110–112]. However, there is ample evidence that heart rate has a negative relationship with the AIx and central SBP [113,114], because of the delayed return of the reflected wave and the increase in stroke volume at low heart rates. These bradycardia-related mechanisms may account for the conflicting results on central hemodynamics found in athletes [106,107,109,115]. In particular, equivocal data have been published for central BP because in some studies, athletes exhibited lower central BP than sedentary controls [27], in other studies, no difference was found between athletes and controls [106,107,116] and in some other, athletes even showed an increased central BP [108,109]. In summary, training-induced bradycardia may have an apparently unfavourable effect on central hemodynamics because of the prolongation of ejection duration so that the reflected wave may return in systole. On the other hand, improved small artery compliance and reduced peripheral resistance can decrease the magnitude of the reflected wave in athletes [117]. Long distance and Olympic marathon runners usually have low body height and attain success at a later age than other athletes. In these persons, a higher degree of aortic stiffness may assist in developing and maintaining an optimal entrainment between heart rate and stride rate [118], so that upward as well as forward motion increases perfusion of the heart [118], and the legs [119] for hours at a time.

The increased stroke volume, secondary to bradycardia may explain why peripheral PP is higher and ISHY is more common in athletes than sedentary people [22,75]. High elasticity of the vascular tree may also contribute to the elevation of SBP in trained individuals. So-called spurious systolic hypertension was first described by Mahmud and Freely [91] and O'Rourke *et al.* [90] in small groups of apparently healthy young men who were often participating in sports activities. ISH in these individuals has been attributed by these authors to exaggerated amplification of the arterial pressure wave travelling to the periphery [2,90,91].

CLINICAL SIGNIFICANCE OF ISOLATED SYSTOLIC HYPERTENSION IN THE YOUNG

Although noninvasive measurement of central hemodynamics has provided new insights to ISHY, whether this condition implies a worse outcome and needs antihypertensive treatment remains unclear. Only did a few studies assess the association of SBP, PP or ISH with future risk of adverse outcome in young individuals providing inconsistent results. From the analysis of the literature two main lines of research and conceptualization have emerged for ISHY. Simultaneous assessment of peripheral and central BP led to the identification of the above-mentioned

condition called pseudo or spurious ISH, first described by O'Rourke *et al.* [90], which was considered an innocent condition. However, an increase in vascular stiffness, assessed by PWV has been documented by some authors in individuals with ISHY [75]. History and evidence in favour of these two different views, whose apparent differences may be a result of categorization, are reported here in the following.

The 'innocent condition' view

Study of wave reflection phenomena show changes in pattern in children during growth and maturation up to the time that maximal height is reached (around 17–20 years of age) [120], then further changes from 30 years onward that can only be attributed to fatigue and fracture of elastin fibres, with degeneration, dilation and stiffening of the proximal, predominantly elastic thoracic aorta [121–123]. The adverse process of arterial aging in human adults has been widely studied, and is the cause of ISH in adults, and the most common cause of cardiac failure and stroke in the elderly [123,124]. This is entirely different to ISHY [120], wherever elevation of SBP and PP is caused in many individuals by high amplification of the arterial pulse in the upper limb, and is not associated with high SBP or PP in the aorta, or to high left ventricular SBP [120,122]. Attention was first directed by findings of elevation of SBP in the brachial and radial arteries of young tall men with normal DBP and mean BP in the brachial artery and normal SBP in the proximal aorta. As mentioned above, this was described as 'Spurious Systolic Hypertension' [90,120] – whenever high SBP and DBP were confined to the upper limbs, and not apparent in other arteries or in the central aorta. A good prognosis for such individuals has been shown over a 31 and 12-year period by Yano *et al.* [1] and by Saladini *et al.* [22], respectively.

The Australian Group in Sydney in a long series of studies has shown progressive increase in aPWV in normal individuals aged 18–80 years [53], progressive increase in SBP and PP with age, which was greater in central than in peripheral (brachial and radial) arteries, progressive increase in augmentation (height of the second systolic peak) of both central and peripheral pulses and progressive decrease in amplification of the pulse (ratio of radial PP divided by aortic PP) with age [120]. They explained these changes on the basis of differences in aortic stiffness, and hence timing of reflected waves as the aorta stiffens with age. This work concentrated on adults, and was linked with interpretations of brachial arterial pressures with age, typified by the Framingham study [7,8]. This covered a normal population from 25 to over 80 years of age. Initially, no children were studied. In Framingham, there was little increase in SBP with age in the 20s or 30s, but progressive increase beyond, up to the 80s. The 'plateau' of the 20–40-year-olds was most obvious in men. Data on change in BP with age in the pediatric group was obtained from the US National report on high BP in children and adolescents [125], and linked up with the adult Framingham data to show low SBP of around 60 mmHg around 2 years of age increasing progressively to 80 mmHg at 5 years of age, and linking with the adult Framingham data to confirm presence of a relative plateau of brachial SBP between the pediatric and adult populations (Fig. 1). A single study linking pediatric and adult populations, and running from neonates to 35 years gave further support for the presence of a plateau of brachial SBP around 20 years of age [14]. The Sydney Group published a longitudinal study from 2 to 19-year-old children [126], and then combined the Framingham with central SBP data of McEniery *et al.* [127] in adults to estimate central SBP from brachial pressure. All are presented in Fig. 1. These data combined suggest that the 'plateau' in change in brachial SBP of the young adult population is because of maximal amplification of the aortic pressure wave to the upper limb at this age. The rise in central SBP with age appears to be linear from age 10 to 80 years as is the increase in PWV with age [53,122,127] and the progressive increase in augmentation of pressure waves [and (reverse) amplification of the pulse waves] throughout life [120,123]. The relative plateau of increase in brachial SBP from age 10 to 80 years is seen in all the large studies of arterial SBP that cover this age range; it has not previously been explained, but can be on the basis of variable timing of wave reflection. The same explanation can be applied to the apparently paradoxical finding that, the neonatal invasively recorded radial artery pressure wave shows a prominent 'tidal wave' as seen in elderly and hypertensive adults [128]. This is attributable in infants to early return of wave reflection caused by short body length [128]. In fully grown older adults, the same pattern is caused by high aortic PWV.

According to this concept, there would not necessarily be any abnormality in elevated brachial SBP in childhood, adolescence or young adulthood whenever this elevated SBP is confined to upper limb arteries. It can be explained by physiological mechanisms, and it reverts to the normal range in adult life [1,2,22,129]. This is supported by studies showing that ISH in young male individuals does not carry greater risk than those without [1,2,22], and that the vast majority of persons with this condition revert into the normal range of SBP in later life ('Young Finns' study [129]), and their aortic PWV remains within normal limits with aging.

The current review concentrates on changes in the radial pressure waveforms with age. But changes in central BP can be synthesized from the radial artery pulse, using a Generalized Transfer Function, or a Second Systolic Shoulder method [59,60]. The 'benign view' was proposed also by other authors [2] who recognized the limitation of numbers derived exclusively from the cuff sphygmomanometer.

The 'true hypertension' view

According to other authors, ISHY should be considered a condition of true hypertension associated with increased future cardiovascular risk [75] because data from four separate studies, containing six [90], 174 [91], 750 [130] and 1008 [131] healthy young participants, respectively, challenge the view that the condition is spurious. These studies have examined the phenomenon of spurious ISHY with regard to brachial and central pressure, and PP amplification. The SphygmoCor device was used in all studies. Mahmud and Feely [91] observed a greater difference between central and brachial SBP in those with spurious ISHY versus those with normal BP (brachial-central difference of 31 versus 20 mmHg). However, pressure

amplification was actually lower in the individuals with spurious ISHY compared with sex-matched controls, whenever amplification was expressed in the conventional manner as the ratio of peripheral to central PP. In the study by Hulsen *et al.* [130], amplification was significantly higher in the participants with spurious ISHY, denoted as those individuals with high brachial SBP and 'normal' central SBP, defined arbitrarily as less than 90th percentile. However, in the Enigma Study, the largest cohort studied to date [75,131], there was no difference in amplification between individuals with ISHY and matched normotensive controls.

It is widely accepted that PP amplification varies between individuals, depending on a number of factors, including height and heart rate [131], and amplification may well be abnormally high in some young individuals with ISHY. However, in contrast to the notion that spurious ISHY arises from exaggerated amplification of normal central BP, the proponents of the 'true hypertension' view [131,132] contend that further examination of the data from the studies described above reveals that central SBP is actually higher in individuals with ISHY versus controls: 116 versus 100 mmHg [91], 120 versus 98 mmHg [130] and 117 versus 105 mmHg [131], for brachial and central SBP, respectively. In the study by O'Rourke *et al.* [90], central SBP was 119 mmHg. Therefore, according to the Cambridge investigators [3,131,132], these data suggest that individuals with ISHY are simply amplifying an already elevated central BP and that such individuals may be at significantly increased cardiovascular risk.

As discussed in an earlier section of this document, the majority of participants with ISHY in The Enigma Study were also characterized by higher levels of stroke volume and cardiac output compared with normotensives [75]. Moreover, further data from the Anglo-Cardiff Collaborative Trial in over 4700 individuals demonstrate clearly that although PP amplification is only moderately higher in participants with ISHY compared with normotensives, stroke volume is markedly higher [132] and is the predominant driver of the elevated PPs observed in young participants with ISHY. This has important clinical significance, based on the studies by Lund-Johansen [35] and Julius *et al.* [32–34], which showed that elevations in stroke volume and cardiac output in young individuals represent the earliest phase of essential hypertension and are likely to transform over time into sustained and irreversible essential hypertension. In at least some of the individuals with ISHY in The Enigma Study, aPWV was also elevated, suggesting that ISHY might also be associated with premature aortic stiffening [75]. Thus, the Enigma Study investigators concluded that these individuals appear to have the same pathophysiological mechanism underlying their hypertension as older ISH patients, although it is unlikely that such stiffening is because of age-related elastin degeneration. As discussed in more detail in other sections of this document, we know that BP and PP track throughout life. As such, individuals with ISHY with elevated PP and aortic stiffening may be predisposed to sustained ISH and an excess of cardiovascular risk, in later life. Clearly, further long-term, observational studies are required to accurately determine the fate of individuals with ISHY. According to the 'true hypertension' view, a large body of evidence indicates that ISHY is associated with increased brachial and central BP suggesting that the majority of individuals with ISHY are likely to be at increased future cardiovascular risk.

Prognostic value of elevated pulse pressure in the young

The clinical significance of elevated PP in young individuals remained unexplored for long because of the obvious necessity of a long-term follow-up to collect a sufficient number of events. The first authors that highlighted a different prognostic value of PP according to age were Sesso *et al.* [133] who examined 11 150 men during a mean follow-up of 10.8 years. These authors compared the predictive role of mean BP and PP for the development of cardiovascular disease among adult-to-elderly versus young-to-middle age men. In individuals aged at least 60 years, multivariate Cox analysis demonstrated a graded increase in risk of cardiovascular disease from the first to fourth quartile for both PP and mean BP. In contrast, among younger men (<60 years of age), mean BP preserved its predictive role for unfavourable outcome, whereas PP only showed a marginal and not significant predictive value. Further evidence in young individuals came from the study by Sundström *et al.* [134] who examined 1 207 141 18-year-old conscripts (mean age 18.4 years) followed for 24 years. These authors observed that only DBP and not SBP was significantly associated with all-cause mortality. More recently, the above-mentioned study by Yano *et al.* [1] compared the risk of cardiovascular mortality in different hypertension subtypes. Among men with ISHY, the risk of unfavourable outcome was similar to that observed in patients with high-normal BP and lower than that observed in diastolic or systolic–diastolic hypertensive patients. A different trend was observed among the women. In the female sex, ISHY was associated with a greater increase in risk of cardiovascular mortality, only lower than that observed for systolic–diastolic hypertension and higher than that in women with diastolic hypertension. The prognostic significance of PP and mean BP for development of hypertension needing treatment and cardiovascular events was recently tested in 1241 young to middle-aged participants from the HARVEST study (mean age 33.1 years, mean follow-up 12.1 years) [22]. Participants in the highest PP tertile had a reduced risk of incident hypertension-needing treatment and of cardiovascular events compared with those in the bottom tertile. In contrast, participants in the top mean BP tertile had an increase in risk for both outcomes. In summary, the data from the literature indicate that PP has a different prognostic significance in young and elderly individuals. In the elderly, PP is a well established predictor of risk whereas in young men, high PP may even have a protective role. More data are needed to better understand the clinical significance of elevated peripheral PP among young women.

ASSESSMENT OF YOUNG INDIVIDUALS WITH ISOLATED SYSTOLIC HYPERTENSION AND ROLE OF CENTRAL BLOOD PRESSURE

The first aspect to consider whenever evaluating a person with ISHY is the possible presence of white-coat

hypertension (WCH) because one of the strongest determinants of high PP in these individuals is a pronounced white-coat effect (WCE) [22,29,34]. The role of the WCE in young patients with elevated SBP was first described by Julius *et al.* [34] in the Tecumseh study. These authors observed that young borderline hypertensive patients with hyperkinetic circulation had a marked WCE assessed with home BP measurement, whereas those with normokinetic hypertension and the normotensive participants had a very small difference between office and home BP. Similar findings were obtained by Lurbe *et al.* [29] in 593 overweight and obese children (mean age 12.2 years), 24% of whom had ISH. In the ISH group, 75% of the children had WCH versus 10% among the systolic–diastolic hypertension group. Saladini *et al.* [22] in a cohort of young to middle-aged grade-1 hypertensive participants (mean age 33.1 years) observed that the strongest predictor of high PP in these participants was the systolic WCE. These data suggest that a pronounced alarm reaction to the doctor's visit is a strong determinant of increased office SBP in ISHY and suggest that all participants with ISHY should be assessed with out-of-office measurement to exclude WCH. Detection of sustained hypertension should prompt investigation of whether the patient has other risk factors or target organ damage [2,18] in order to decide whether antihypertensive treatment is needed (Fig. 3). If ISHY is confirmed by out-of-office measurement, assessment of central hemodynamics and arterial distensibility may provide additional useful information.

Central (aortic) BP represents the direct load determining target organ damage [135,136]. Indeed, a meta-analysis of clinical studies showed that central BP is related to left ventricular hypertrophy, carotid intima–media thickness and albuminuria, independently of peripheral BP [137]. This has been also shown in a cohort of 300 young to middle-aged patients, being central mean BP associated with end-organ damage, even when adjusted for ambulatory 24-h BP [138]. In the HARVEST study [99], ISHY participants with low central SBP had a risk of development of hypertension requiring antihypertensive treatment similar to that in the normotensive participants of control whereas those with high central SBP had a risk comparable with that observed in participants with systolic–diastolic hypertension.

It should be pointed out, however, that measurement of central BP has to be calibrated with BP values normally obtained by conventional (usually oscillometric) brachial measurements [139]. Another important limitation to the use of central BP in ISHY is the lack of official threshold values that differentiate normal from high central BP [140,141]. A possible approach is to calculate central BP value corresponding to the current brachial 140/90 mmHg cut-off, on the basis of BP amplification. Analysis of cross-sectional data in healthy men ($n = 3603$) and women ($n = 3176$) from the Anglo-Cardiff Collaborative Trial, suggested a cut-off value of central BP approximately of 125/90 mmHg [131]. A subsequent study, specifically aimed to derive and validate outcome-driven thresholds of central BP, determined the values of 110/80 mmHg for optimal central BP and 130/90 mmHg for hypertension in a derivation cohort (1272 individuals and a median follow-up of 15 years) [142]. Regarding central PP, a value greater than 50 mmHg predicted adverse cardiovascular outcomes in over 2400 participants without cardiovascular disease from the Strong Heart Study [143]. Reference values for central SBP and PP have been published by Herbert *et al.* [66] in healthy populations and patients with cardiovascular risk factors, providing age-specific and sex-specific reference ranges.

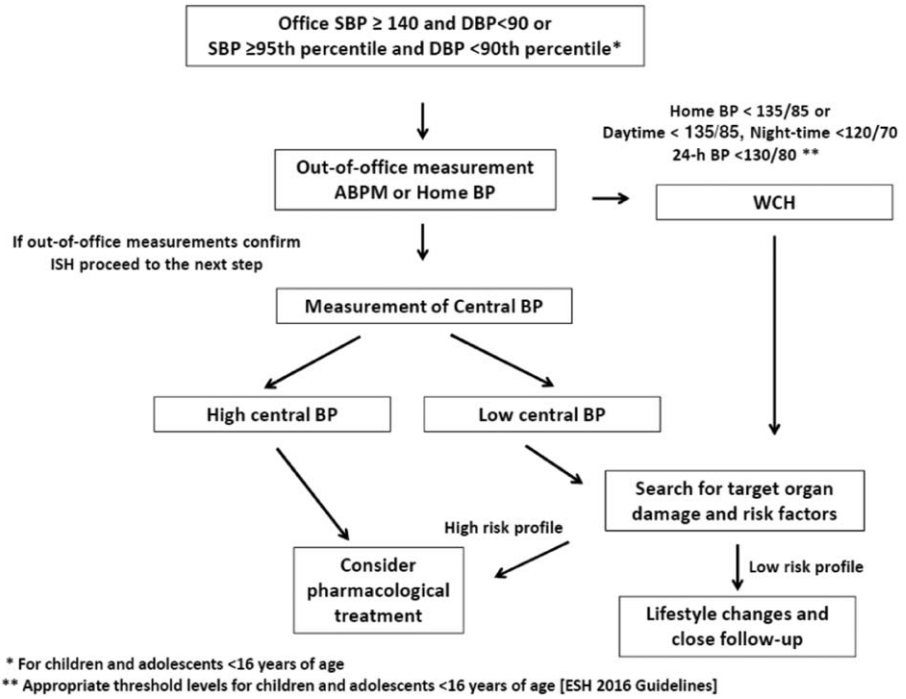

FIGURE 3 Proposal for a diagnostic flow-chart for young individuals with isolated systolic hypertension.

For each decade of age, they provided the 10th, 25th, 75th and 90th percentile for central BP values. Although this approach has never been applied to peripheral BP, it may be of help for distinguishing between individuals with spurious hypertension (normal central BP) and those with ISH (central BP in the high-normal range or higher) with possible implications for treatment. Nevertheless, it might be of particular relevance in young participants to quantify the phenomenon of pressure amplification by comparing measured central and peripheral BP values versus reference PP amplification in the normal population [66]. The reduction of PP amplification or the increase of its reciprocal PP ratio, which has been associated with risk factors or disease [136], will allow the clinician to detect early vascular aging process, possibly providing prognostic information on ISHY. This hypothesis should be supported by future studies evaluating fixed threshold versus age-specific and sex-specific reference ranges of central BP for the estimation of cardiovascular risk in the young beyond traditional brachial cuff measurement. At any rate, central BP appears as a promising tool for evaluating the overall cardiovascular risk of ISHY participants and for deciding whether they may need antihypertensive treatment. It is, thus, the opinion of this panel that central BP should always be included in the assessment of ISHY as summarized in Fig. 3.

MANAGEMENT OF ISOLATED SYSTOLIC HYPERTENSION IN THE YOUNG ACCORDING TO PRESENT GUIDELINES

ISHY is infrequently mentioned in the guidelines on diagnosis and treatment of hypertension, whose focus remains almost invariably confined to treatment of hypertension in middle-aged and elderly people. Little attention is somewhat surprisingly devoted to this condition also in guidelines dealing with the mechanistic aspects, the clinical significance and the need for treatment of hypertension in adolescents and children, an example, being the recent guidelines issued by the American Academy of Pediatrics [144] as well as a position paper of two recognized experts in this area [145]. An exception is the guidelines on hypertension in children and adolescents of the European Society of Hypertension published in 2016 [24] which, as mentioned above, included ISHY in a Table classifying the hypertension phenotypes in these age categories. The European guidelines on children and adolescents mention the case of young individuals in whom an isolated brachial SBP elevation is accompanied by a normal central SBP. Although recognizing the peculiarity of this condition, they refrain from reaching any firm conclusion on its clinical significance because of the limitation of available prognostic data and the uncertain prognostic superiority of central versus brachial BP in general, and even more in younger population strata. This is in line with the position taken by the 2013 guidelines of the European Society of Hypertension and the European Society of Cardiology [18] on hypertension in the adulthood in which specific mention was made of the possibility that this condition reflects mechanistically regional discrepancies of arterial distensibility and has no adverse prognostic significance, as argued and reported by the pioneer studies of O'Rourke *et al.* [90,120]. However, given the large number of studies currently devoted to ISHY and the growing evidence on its mechanistic and clinical aspects, it is the opinion of this panel that these young individuals should receive recommendations on lifestyle modification (particularly cessation of smoking), and that they require long-term follow-up as some will develop sustained hypertension. In individuals who present with other risk factors and/or have high central BP, pharmacological treatment may be considered.

FUTURE RESEARCH DIRECTIONS

Given the present lack of data on the prognostic significance of ISHY and the consequent uncertainty about whether this condition should also be managed with drug treatment, there is a need for a placebo-controlled clinical trial in the near future to elucidate if a benefit can be achieved with treatment at least in some subgroups at higher risk. Because of the young age of the participants and the consequent long time necessary to accumulate a sufficient number of hard events, organ damage might be used as an intermediate endpoint for assessing the benefits of antihypertensive therapy. Particular emphasis should be put on the prognostic role of central BP.

CONCLUSION

Epidemiological, pathophysiological and clinical research has removed ISHY from being one of the Cinderellas of the hypertension world. Epidemiological research has shown that in childhood, adolescence and young adult life, an elevation of SBP with no concomitant increase of diastolic values is by no means rare, and that this is particularly the case in the male sex and in overweight or obese individuals. Mechanistic research has additionally documented that in these people, an isolated SBP elevation may be associated with, and caused by, not just one but, to a variable quantitative degree, multiple factors that can operate in isolation or interact to determine this BP phenotype: a hyperkinetic heart (as demonstrated decades ago by the pioneer work by Julius *et al.*) [32–34], a selective increase in heart rate or stroke volume, and an increase in arterial stiffness above the values regarded as normal for young age ranges.

The present review has addressed an aspect of ISHY, which can be legitimately defined as a clinical dilemma regarding ISHY pathophysiology and appropriate patient's management. The ISHY condition identified by O'Rourke *et al.* [90,120] is characterized by an isolated SBP elevation at the level of the brachial artery with normal central BP. These individuals did not exhibit a greater cardiovascular risk or progression to systolic–diastolic hypertension, which made this condition appear as clinically innocent, a conclusion favored by its attribution to an excessive peripheral pulse wave amplification attributable to higher harmonic content of aortic waves at the generalized transfer function frequencies of greatest amplification (about 4 Hz), and where aortic impedance modulus is very low [122]. However, the clinical innocence of ISHY with a normal central SBP has not been unequivocally supported by the results of other investigations [131,132], and it is also

somewhat weakened by the persistent uncertainty on whether central BP is prognostically superior and overcomes the predictive value of peripheral BP. In addition, ISHY is often associated with sympathetic activation, which may play a mechanistic role because of its ability to increase arterial stiffness by increasing heart rate [67–69,112] but also by acting directly on the elastic modulus of the vessel wall [110,146–148] as well as by determining and supporting a hyperkinetic performance of the heart.

The most appropriate conclusion seems, thus, that the issue remains open to future research and to additional mechanistic and epidemiological contributions that might clarify the clinical nature of an ISHY that presents a high brachial but normal central SBP, that is, with spurious systolic hypertension. Although the above-mentioned findings suggest that ISHY may not be clinically innocent, all major prospective studies now available [1,22,133,134] are substantially negative. Cross-sectional studies have shown that in ISHY patients, concomitant metabolic risk factors (insulin resistance, metabolic syndrome, overweight, diabetes, etc.) may be more frequent than in the control population. For this reason, the 2013 European guidelines on arterial hypertension [18] recommended to only follow these people closely, modifying risk factors by lifestyle changes and avoiding antihypertensive drugs. Hopefully, future studies will clarify whether a benefit can be achieved with pharmacological treatment in ISHY patients who present with other risk factors and/or have high central BP.

ACKNOWLEDGEMENTS

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Yano Y, Stamler J, Garside DB, Daviglus ML, Franklin SS, Carnethon MR, *et al.* Isolated systolic hypertension in young and middle-aged adults and 31-year risk of cardiovascular mortality: the Chicago Heart Association Detection Project in Industry Study. *J Am Coll Cardiol* 2015; 65:327–335.
2. Lurbe E, Redon J. Isolated systolic hypertension in young people is not spurious and should be treated: con side of the argument. *Hypertension* 2016; 68:276–280.
3. McEniery CM, Franklin SS, Cockcroft JR, Wilkinson IB. Isolated systolic hypertension in young people is not spurious and should be treated: pro side of the argument. *Hypertension* 2016; 68:269–275.
4. Shen W, Zhang T, Li S, Zhang H, Xi B, Shen H, *et al.* Race and sex differences of long-term blood pressure profiles from childhood and adult hypertension: the Bogalusa Heart Study. *Hypertension* 2017; 70:66–74.
5. Wills AK, Lawlor DA, Matthews FE, Sayer AA, Bakra E, Ben-Shlomo Y, *et al.* Life course trajectories of systolic blood pressure using longitudinal data from eight UK cohorts. *PLoS Med* 2011; 8:e1000440.
6. Cheng S, Xanthakis V, Sullivan LM, Vasan RS. Blood pressure tracking over the adult life course: patterns and correlates in the Framingham Heart Study. *Hypertension* 2012; 60:1393–1399.
7. Franklin SS, Gustin W 4th, Wong ND, Larson MG, Weber MA, Kannel WB, *et al.* Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation* 1997; 96: 308–315.
8. Franklin SS, Wong ND. Hypertension and cardiovascular disease: contributions of the Framingham Heart Study. *Glob Heart* 2013; 8: 49–57.
9. Bazzano LA, Whelton PK, He J. Blood pressure in westernized and isolated populations. In: Lip GYH, Hall JE, editors. *Comprehensive, hypertension*. Philadelphia: Mosby, Elsevier; 2007. pp. 21–30.
10. Theodore RF, Broadbent J, Nagin D, Ambler A, Hogan S, Ramrakha S, *et al.* Childhood to early-midlife systolic blood pressure trajectories: early-life predictors, effect modifiers, and adult cardiovascular outcomes. *Hypertension* 2015; 66:1108–1115.
11. Wills AK, Lawlor DA, Muniz-Terrera G, Matthews F, Cooper R, Ghosh AK, *et al.*, FALCon Study Team. Population heterogeneity in trajectories of midlife blood pressure. *Epidemiology* 2012; 23:203–211.
12. Butler KR Jr, Penman AD, Minor DS, Mosley TH Jr. Determinants of pulse pressure and annual rates of change in the Atherosclerosis Risk in Communities study. *J Hypertens* 2015; 33:2463–2470.
13. Syme C, Abrahamowicz M, Leonard GT, Perron M, Richer L, Veillette S, *et al.* Sex differences in blood pressure and its relationship to body composition and metabolism in adolescence. *Arch Pediatr Adolesc Med* 2009; 163:818–825.
14. O'Rourke MF, Adji A. Pressure paradox: high pulse pressure and low mean pressure are favorable features in young adults. *Hypertension* 2017; [Epub ahead of print].
15. Das SK, McIntyre HD, Mamun AA. An early life course association of pulse pressure with adulthood estimated glomerular filtration rate: evidence from a large community-based birth cohort study. *J Hypertens* 2017; 35:392–400.
16. Allen NB, Siddique J, Wilkins JT, Shay C, Lewis CE, Goff DC, *et al.* Blood pressure trajectories in early adulthood and subclinical atherosclerosis in middle age. *JAMA* 2014; 311:490–497.
17. Tielemans SM, Geleijnse JM, Menotti A, Boshuizen HC, Soedamah-Muthu SS, Jacobs DR Jr, *et al.* Ten-year blood pressure trajectories, cardiovascular mortality, and life years lost in 2 extinction cohorts: the Minnesota Business and Professional Men Study and the Zutphen Study. *J Am Heart Assoc* 2015; 4:e001378.
18. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, *et al.* 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31:1281–1357.
19. Staessen J, Amery A, Fagard R. Isolated systolic hypertension in the elderly. *J Hypertens* 1990; 8:393–405.
20. Mallion JM, Hamici L, Chatellier G, Lang T, Plouin PF, De Gaudemaris R. Isolated systolic hypertension: data on a cohort of young subjects from a French working population (IHPAF). *J Hum Hypertens* 2003; 17:93–100.
21. Liu X, Rodriguez CJ, Wang K. Prevalence and trends of isolated systolic hypertension among untreated adults in the United States. *J Am Soc Hypertens* 2015; 9:197–205.
22. Saladini F, Fania C, Mos L, Mazzer A, Casiglia E, Palatini P. Office pulse pressure is a predictor of favourable outcome in young-to-middle-aged subjects with stage 1 hypertension. *Hypertension* 2017; [Epub ahead of print].
23. Saladini F, Dorigatti F, Santonastaso M, Mos L, Ragazzo F, Bortolazzi A, *et al.*, HARVEST Study Group. Natural history of hypertension subtypes in young and middle-age adults. *Am J Hypertens* 2009; 22:531–537.
24. Lurbe E, Agabiti-Rosei E, Cruickshank JK, Dominiczak A, Erdine S, Hirth A, *et al.* 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. *J Hypertens* 2016; 34:1887–1920.
25. Chiolero A, Cachat F, Burnier M, Paccaud F, Bovet P. Prevalence of hypertension in schoolchildren based on repeated measurements and association with overweight. *J Hypertens* 2007; 25: 2209–2217.
26. Cheung EL, Bell CS, Samuel JP, Poffenbarger T, Redwine KM, Samuels JA. Race and obesity in adolescent hypertension. *Pediatrics* 2017; 139: pii: e20161433.
27. Karatzi K, Protogerou AD, Moschonis G, Tsirimiagou C, Androutsos O, Chrousos GP, *et al.* Prevalence of hypertension and hypertension phenotypes by age and gender among schoolchildren in Greece: the Healthy Growth Study. *Atherosclerosis* 2017; 259:128–133.
28. Kropa J, Close J, Shipon D, Hufnagel E, Terry C, Oliver J, Johnson B. High prevalence of obesity and high blood pressure in urban student-athletes. *J Pediatr* 2016; 178:194–199.
29. Lurbe E, Torro MI, Alvarez-Pitti J, Redon P, Redon J. Central blood pressure and pulse wave amplification across the spectrum of peripheral blood pressure in overweight and obese youth. *J Hypertens* 2016; 34:1389–1395.

30. Rogers RG, Onge JM. Race/ethnic and sex differentials in pulse pressure among US adults. *Ethn Dis* 2005; 15:601–606.
31. Attard SM, Herring AH, Zhang B, Du S, Popkin BM, Gordon-Larsen P. Associations between age, cohort, and urbanization with systolic and diastolic blood pressure in China: a population-based study across 18 years. *J Hypertens* 2015; 33:948–956.
32. Julius S. Neurogenic component in borderline hypertension. In: Julius S, Esler MD, editors. *The nervous system in arterial hypertension*. Springfield, IL: Charles C Thomas; 1974. pp. 301–330.
33. Julius S, Jamerson K, Mejia A, Krause L, Schork N, Jones K. The Association of borderline hypertension with target organ damage and higher coronary risk. *JAMA* 1990; 264:354–358.
34. Julius S, Krause L, Schork NJ, Mejia A, Jones KA, Van den Ven C, *et al*. Hyperkinetic borderline hypertension in Tecumseh, Michigan. *J Hypertens* 1991; 9:77–84.
35. Lund-Johansen P. Twenty-year follow-up of hemodynamics in essential hypertension during rest and exercise. *Hypertension* 1991; 18 (5 Suppl):III54–III61.
36. Julius S, Randall OS, Esler MD, Kashima T, Ellis T, Bennet J. Altered cardiac responsiveness and regulation in the normal cardiac output type of borderline hypertension. *Circ Res* 1975; 36 (6 Suppl 1):199–207.
37. Egan B, Panis R, Schork N, Julius S. Mechanism of increased alpha adrenergic vasoconstriction in human essential hypertension. *J Clin Invest* 1987; 80:812–817.
38. Julius S, Quadir H, Gajendragadska K. Hyperkinetic stage: a precursor of hypertension? A longitudinal study of borderline hypertension. In: Gross F, Strasser S, editors. *Mild hypertension: natural history and management*. Japan: T. Pitman Medical; 1979. pp. 116–126.
39. Palatini P, Julius S. Review article: heart rate and the cardiovascular risk. *J Hypertens* 1997; 15:3–17.
40. Frohlich ED, Tarazi RC, Dustan HP. Hyperdynamic (-adrenergic circulatory state: Increased (-receptor responsiveness. *Arch Intern Med* 1969; 123:1–7.
41. Jose AD, Taylor RR. Autonomic blockade by propranolol and atropine to study intrinsic myocardial function in man. *J Clin Invest* 1969; 48:2019–2031.
42. Julius S, Pascual. London R. Role of parasympathetic inhibition in the hyperkinetic type of borderline hypertension. *Circulation* 1971; 44:413–418.
43. Mancia G, Grassi G. The autonomic nervous system and hypertension. *Circ Res* 2014; 114:1804–1814.
44. Pavlov AV, Tracey KJ. The vagus nerve and the inflammatory reflex-linking immunity and metabolism. *Nat Rev Endocrinol* 2012; 8:743–754.
45. Grassi G, Mark AL, Esler M. The sympathetic nervous system alterations in human hypertension. *Circ Res* 2015; 116:976–990.
46. Anderson EA, Sinkey CA, Lawton WJ, Mark AL. Elevated sympathetic nerve activity in borderline hypertensive humans. Evidences from direct intraneural recordings. *Hypertension* 1989; 14:177–183.
47. Floras JS, Hara K. Sympathoneural and haemodynamic characteristics of young subjects with mild essential hypertension. *J Hypertens* 1993; 11:647–655.
48. Esler M, Lambert G, Jennings G. Regional norepinephrine turnover in human hypertension. *Clin Exp Hypertens* 1989; 11 (Suppl 1):75–89.
49. Esler M, Jennings G, Lambert G, Meredith I, Horne M, Eisenhofer G. Overflow of catecholamine neurotransmitters to the circulation: source, fate and function. *Physiol Rev* 1990; 70:963–985.
50. Mattace-Raso F, Hofman A, Verwoert GC, Wittemana JC, Wilkinson I, Cockcroft J, *et al*. Reference values for arterial stiffness collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: establishing normal and reference values. *Eur Heart J* 2010; 31:2338–2350.
51. Grassi G, Giannattasio C, Failla M, Pesenti A, Peretti G, Marinoni E, *et al*. Sympathetic modulation of radial artery compliance in congestive heart failure. *Hypertension* 1995; 26:348–354.
52. Bruno RM, Ghiadoni L, Seravalle G, Dell'oro R, Taddei S, Grassi G. Sympathetic regulation of vascular function in health and disease. *Front Physiol* 2012; 3:284.
53. Avolio AP, Chen SG, Wang RP, Zhang CL, Li MF, O'Rourke MF. Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community. *Circulation* 1983; 68:50–58.
54. Avolio AP, Deng FQ, Li WQ, Luo YF, Huang ZD, Xing LF, *et al*. Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China. *Circulation* 1985; 71:202–210.
55. Engelen L, Bossuyt J, Ferreira I, van Bortel LM, Reesink KD, Segers P, *et al*. Reference values for local arterial stiffness. Part A: carotid artery. *J Hypertens* 2015; 33:1981–1996.
56. Bossuyt J, Engelen L, Ferreira I, Stehouwer CD, Boutouyrie P, Laurent S, *et al*. Reference values for local arterial stiffness. Part B: femoral artery. *J Hypertens* 2015; 33:1997–2009.
57. Karamanoglu M, O'Rourke MF, Avolio AP, Kelly RP. An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. *Eur Heart J* 1993; 14:160–167.
58. Chen CH, Nevo E, Fetics B, Pak PH, Yin FC, Maughan WL, *et al*. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. *Circulation* 1997; 95:1827–1836.
59. Lowenthal A, Evans JM, Punn R, Nourse SE, Vu CN, Popat RA, Selamet Tierney ES. Arterial applanation tonometry: feasibility and reproducibility in children and adolescents. *Am J Hypertens* 2014; 27:1218–1224.
60. Milne L, Keehn L, Guildher A, Reidy JF, Karunanithy N, Rosenthal E, *et al*. Central aortic blood pressure form ultrasound wall-tracking of the carotid artery in children: comparison with invasive measurements and radial tonometry. *Hypertension* 2015; 65: 1141–1147.
61. Pauca AL, Kon ND, O'Rourke MF. The second peak of the radial artery pressure wave represents aortic systolic pressure in hypertensive and elderly patients. *Br J Anaesth* 2004; 92:651–657.
62. Latham RD, Westerhof N, Sipkema P, Rubal BJ, Reuderink P, Murgo JP. Regional wave travel and reflections along the human aorta: a study with six simultaneous micromanometric pressures. *Circulation* 1985; 72:1257–1269.
63. O'Rourke MF. Wave travel and reflection in the arterial system. *J Hypertens Suppl* 1999; 17:S45–S47.
64. Avolio A, Butlin M, Tan I. Importance of pressure pulse amplification in the association of resting heart rate and arterial stiffness. *Hypertension* 2013; 62:e46.
65. Williams B, Lacy PS, CAFÉ and the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) Investigators. Impact of heart rate on central aortic pressures and hemodynamics: analysis from the CAFE (Conduit Artery Function Evaluation) study: CAFE-Heart Rate. *J Am Coll Cardiol* 2009; 54:705–713.
66. Herbert A, Cruickshank K, Laurent S, Boutouyrie P, on behalf of The Reference Values for Arterial Measurements Collaboration. Establishing reference values for central blood pressure and its amplification in a general healthy population and according to cardiovascular risk factors. *Eur Heart J* 2014; 35:3122–3133.
67. Lantelme P, Mestre C, Lievre M, Gressard A, Milon H. Heart rate: an important confounder of pulse wave velocity assessment. *Hypertension* 2002; 39:1083–1087.
68. Tan I, Spronck B, Kiat H, Barin E, Reesink KD, Delhaas T, *et al*. Heart rate dependency of large artery stiffness. *Hypertension* 2016; 68: 236–242.
69. Xiao H, Tan I, Butlin M, Li D, Avolio AP. Arterial viscoelasticity: role in the dependency of pulse wave velocity on heart rate in conduit arteries. *Am J Physiol Heart Circ Physiol* 2017; 312:H1185–H1194.
70. Custodis F, Shirmer SH, Baumhäkel M, Heusch G, Böhm M, Laufs U. Vascular pathophysiology in response to increased heart rate. *J Am Coll Cardiol* 2010; 56:1973–1983.
71. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, *et al*. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; 37: 1236–1241.
72. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010; 55: 1318–1327.
73. Alfie J, Majul C, Paez O, Galarza C, Waisman G. Hemodynamic significance of high brachial pulse pressure in young men. *Clin Exp Hypertens* 2004; 26:199–207.
74. Alfie J, Waisman GD, Galarza CR, Cámera MI. Contribution of stroke volume to the change in pulse pressure pattern with age. *Hypertension* 1999; 34 (4 Pt 2):808–812.
75. McEniery CM, Yasmin. Wallace S, Maki-Petaja K, McDonnell B, Sharman JE, *et al*., ENIGMA Study Investigators. Increased stroke volume and aortic stiffness contribute to isolated systolic hypertension in young adults. *Hypertension* 2005; 46:221–226.

76. Gabrielsen A, Videbaek R, Schou M, Damgaard M, Kastrup J, Norsk P. Noninvasive measurement of cardiac output in heart failure patients using a new foreign gas rebreathing technique. *Clin Sci (Lond)* 2002; 102:247–252.
77. Peyton PJ, Thompson B. Agreement of an inert gas rebreathing device with thermodilution and the direct oxygen Fick method in measurement of pulmonary blood flow. *J Clin Monit Comput* 2004; 18:373–378.
78. Parati G, Ochoa JE, Lombardi C, Bilo G. Blood pressure variability: assessment, predictive value, and potential as a therapeutic target. *Curr Hypertens Rep* 2015; 17:537.
79. Parati G, Liu X, Ochoa JE, Bilo G. Prognostic relevance of blood pressure variability: role of long-term and very long-term blood pressure changes. *Hypertension* 2013; 62:682–684.
80. Fujita H, Matsuoka S, Awazu M. White-coat and reverse white-coat effects correlate with 24-h pulse pressure and systolic blood pressure variability in children and young adults. *Pediatr Cardiol* 2016; 37:345–352.
81. Kotsis V, Stabouli S, Karafillis I, Papakatsika S, Rizos Z, Miyakis S, *et al.* Arterial stiffness and 24 h ambulatory blood pressure monitoring in young healthy volunteers: the early vascular ageing Aristotle University Thessaloniki Study (EVA-ARIS Study). *Atherosclerosis* 2011; 219:194–199.
82. Boardman H, Lewandowski AJ, Lazdam M, Kenworthy Y, Whitworth P, Zwager CL, *et al.* Aortic stiffness and blood pressure variability in young people: a multimodality investigation of central and peripheral vasculature. *J Hypertens* 2017; 35:513–522.
83. Yano Y, Ning H, Allen N, Reis JP, Launer LJ, Liu K, *et al.* Long-term blood pressure variability throughout young adulthood and cognitive function in midlife: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Hypertension* 2014; 64:983–988.
84. Chen W, Srinivasan SR, Ruan L, Mei H, Berenson GS. Adult hypertension is associated with blood pressure variability in childhood in blacks and whites: the bogalusa heart study. *Am J Hypertens* 2011; 24:77–82.
85. Berg K. Molecular genetics and genetic epidemiology of cardiovascular diseases and diabetes. Introductory remarks: risk factor levels and variability. *Ann Med* 1992; 24:343–347.
86. Lurbe E, Torro I, Rodríguez C, Alvarez V, Redón J. Birth weight influences blood pressure values and variability in children and adolescents. *Hypertension* 2001; 38:389–393.
87. White WB. Importance of blood pressure control over a 24-h period. *J Manag Care Pharm* 2007; 13 (Suppl S-b):S34–S39.
88. Maseli A, Aeschbacher S, Schoen T, Fischer A, Jung M, Risch M, *et al.* Healthy lifestyle and blood pressure variability in young adults. *Am J Hypertens* 2017; 30:690–699.
89. Grebla RC, Rodriguez CJ, Borrell LN, Pickering TG. Prevalence and determinants of isolated systolic hypertension among young adults: the 1999-2004 US National Health And Nutrition Examination Survey. *J Hypertens* 2010; 28:15–23.
90. O'Rourke MF, Vlachopoulos C, Graham RM. Spurious systolic hypertension in youth. *Vasc Med* 2000; 5:141–145.
91. Mahmud A, Feely J. Spurious systolic hypertension of youth: fit young men with elastic arteries. *Am J Hypertens* 2003; 16:229–232.
92. Asgari S, Khalili D, Mehrabi Y, Kazempour-Ardebili S, Azizi F, Hadaegh F. Incidence and risk factors of isolated systolic and diastolic hypertension: a 10 year follow-up of the Tehran Lipids and Glucose Study. *Blood Press* 2016; 25:177–183.
93. Middlemiss JE, Miles KL, McDonnell BJ, Yasmin. Maki-Petaja KM, Cockcroft JR, *et al.* Mechanisms underlying elevated SBP differ with adiposity in young adults: the Enigma study. *J Hypertens* 2016; 34:290–297.
94. Strazzullo P, Barba G, Cappuccio FP, Siani A, Trevisan M, Farinaro E, *et al.* Altered renal sodium handling in men with abdominal adiposity. A link to hypertension. *J Hypertens* 2001; 19:2157–2164.
95. Campanozzi A, Avallone S, Barbato A, Iacone R, Russo O, De Filippo G, *et al.*, MINISAL-GIRCSI Program Study Group. High sodium and low potassium intake among Italian children: relationship with age, body mass and blood pressure. *PLoS One* 2015; 10:e0121183.
96. Rocchini AP, Key J, Bondie D, Chico R, Moorehead C, Katch V, *et al.* The effect of weight loss on the sensitivity of blood pressure to sodium in obese adolescents. *N Engl J Med* 1989; 321:580–585.
97. Strazzullo P, Barbato A, Galletti F, Barba G, Siani A, Iacone R, *et al.* Abnormalities of renal sodium handling in the metabolic syndrome. Results of the Olivetti Heart Study. *J Hypertens* 2006; 24:1633–1639.
98. Radchenko GD, Torbas OO, Sirenko YM. Predictors of high central blood pressure in young with isolated systolic hypertension. *Vasc Health Risk Manag* 2016; 12:321–328.
99. Saladini F, Santonastaso M, Mos L, Benetti E, Zanatta N, Maraglino G, Palatini P, HARVEST Study Group. Isolated systolic hypertension of young-to-middle-age individuals implies a relatively low risk of developing hypertension needing treatment when central blood pressure is low. *J Hypertens* 2011; 29:1311–1319.
100. Franco OH, de Laet C, Peeters A, Jonker J, Mackenbach J, Nusselder W. Effects of physical activity on life expectancy with cardiovascular disease. *Arch Intern Med* 2005; 165:2355–2360.
101. Palatini P, Graniero G, Mormino P, Nicolosi L, Mos L, Visentin P, *et al.* Relation between physical training and ambulatory blood pressure in stage I hypertensive subjects. Results of the HARVEST trial. *Circulation* 1994; 90:2870–2876.
102. Fagard RH. Exercise therapy in hypertensive cardiovascular disease. *Prog Cardiovasc Dis* 2011; 53:404–411.
103. Hayashi K, Sugawara J, Komine H, Maeda S, Yokoi T. Effects of aerobic exercise training on the stiffness of central and peripheral arteries in middle-aged sedentary men. *Jpn J Physiol* 2005; 55: 235–239.
104. Saladini F, Benetti E, Mos L, Mazzer A, Casiglia E, Palatini P. Regular physical activity is associated with improved small artery distensibility in young to middle-age stage 1 hypertensives. *Vasc Med* 2014; 19:458–464.
105. Nettlefold L, McKay HA, Naylor PJ, Bredin SS, Warburton DE. The relationship between objectively measured physical activity, sedentary time, and vascular health in children. *Am J Hypertens* 2012; 25:914–919.
106. Taylor BA, Zaleski AL, Capizzi JA, Ballard KD, Troyanos C, Baggish AL, *et al.* Influence of chronic exercise on carotid atherosclerosis in marathon runners. *BMJ Open* 2014; 4:e004498.
107. Edwards DG, Lang JT. Augmentation index and systolic load are lower in competitive endurance athletes. *Am J Hypertens* 2005; 18 (5 Pt 1):679–683.
108. Vlachopoulos C, Kardara D, Anastasakis A, Baou K, Terentes-Printzios D, Tousoulis D, *et al.* Arterial stiffness and wave reflections in marathon runners. *Am J Hypertens* 2010; 23:974–979.
109. Laurent P, Marenco P, Castagna O, Smulyan H, Blacher J, Safar ME. Differences in central systolic blood pressure and aortic stiffness between aerobically trained and sedentary individuals. *J Am Soc Hypertens* 2011; 5:85–93.
110. Mangoni AA, Mircoli L, Giannattasio C, Ferrari AU, Mancia G. Heart rate-dependence of arterial distensibility in vivo. *J Hypertens* 1996; 14:897–901.
111. Giannattasio C, Vincenti A, Failla M, Capra A, Cirò A, De Ceglia S, *et al.* Effects of heart rate changes on arterial distensibility in humans. *Hypertension* 2003; 42:253–256.
112. Tomiyama H, Hashimoto H, Tanaka H, Matsumoto C, Odaira M, Yamada J, *et al.*, baPWV/cfPWV Collaboration Group. Synergistic relationship between changes in the pulse wave velocity and changes in the heart rate in middle-aged Japanese adults: a prospective study. *J Hypertens* 2010; 28:687–694.
113. Messerli FH, Rimoldi SF, Bangalore S, Bavishi C, Laurent S. When an increase in central systolic pressure overrides the benefits of heart rate lowering. *J Am Coll Cardiol* 2016; 68:754–762.
114. Wilkinson IB, Mohammad NH, Tyrrell S, Hall IR, Webb DJ, Paul VE, *et al.* Heart rate dependency of pulse pressure amplification and arterial stiffness. *Am J Hypertens* 2002; 15:24–30.
115. Knez WL, Sharman JE, Jenkins DG, Coombes JS. Central hemodynamics in ultra-endurance athletes. *J Sci Med Sport* 2008; 11:390–395.
116. Nualnim N, Barnes JN, Tarumi T, Renzi CP, Tanaka H. Comparison of central artery elasticity in swimmers, runners, and the sedentary. *Am J Cardiol* 2011; 107:783–787.
117. Wilenius M, Tikkakoski AJ, Tahvanainen AM, Haring A, Koskela J, Huhtala H, *et al.* Central wave reflection is associated with peripheral arterial resistance in addition to arterial stiffness in subjects without antihypertensive medication. *BMC Cardiovasc Disord* 2016; 16:131.
118. O'Rourke M, Avolio A, Stelliou V, Young J, Gallagher DE. The rhythm of running: can the heart join in? *Aust N Z J Med* 1993; 23:708–710.
119. Folkow B, Haglund U, Jodal M, Lundgren O. Blood flow in the calf muscle of man during heavy rhythmic exercise. *Acta Physiol Scand* 1971; 81:157–163.

120. O'Rourke MF, Adji A. Guidelines on Guidelines: focus on isolated systolic hypertension in youth. *J Hypertens* 2013; 31:649–654.
121. Dawber TR, Thomas HE Jr, McNamara PM. Characteristics of the dicrotic notch of the arterial pulse wave in coronary heart disease. *Angiology* 1973; 24:244–255.
122. Nichols WW, O'Rourke MF, Vlachopoulos C. *McDonald's blood flow in arteries*. 6th ed. London: Hodder Arnold; 2011.
123. O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. *J Am Coll Cardiol* 2007; 50:1–13.
124. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA* 1996; 275: 1557–1562.
125. Uiterwaal CS, Anthony S, Launer LJ, Witteman JC, Trouwborst AM, Hofman A, Grobbee DE. Birth weight, growth, and blood pressure: an annual follow-up study of children aged 5 through 21 years. *Hypertension* 1997; 30 (2 Pt 1):267–271.
126. Ayer JG, Harmer JA, Marks GB, Avolio A, Celermajer DS. Central arterial pulse wave augmentation is greater in girls than boys, independent of height. *J Hypertens* 2010; 28:306–313.
127. McEniery CM, Yasmin. McDonnell B, Munnery M, Wallace SM, Rowe CV, *et al.*, Anglo-Cardiff Collaborative Trial Investigators. Central pressure: variability and impact of cardiovascular risk factors: the Anglo-Cardiff Collaborative Trial II. *Hypertension* 2008; 51: 1476–1482.
128. Gevers M, van Genderingen HR, Lafeber HN, Hack WWM. Radial artery blood pressure measurement in neonates: an accurate and convenient technique in clinical practice. *J Perinat Med* 1995; 23:467–475.
129. Aatola H, Koivistoinen T, Tuominen H, Juonala M, Lehtimäki T, Viikari JSA, *et al.* Influence of child and adult elevated blood pressure on adult arterial stiffness: The Cardiovascular Risk in Young Finns Study. *Hypertension* 2017; 70:531–536.
130. Hulsen HT, Nijdam ME, Bos WJ, Uiterwaal CS, Oren A, Grobbee DE, Bots M. Spurious systolic hypertension in young adults; prevalence of high brachial systolic blood pressure and low central pressure and its determinants. *J Hypertens* 2006; 24:1027–1032.
131. McEniery CM, Yasmin. Maki-Petaja KM, McDonnell BJ, Munnery M, Hickson SS, *et al.*, Anglo-Cardiff Collaboration Trial Investigators. The impact of cardiovascular risk factors on aortic stiffness and wave reflections depends on age: the Anglo-Cardiff Collaborative Trial (ACCT III). *Hypertension* 2010; 56:591–597.
132. McEniery CM, Franklin SS, Wilkinson IB, Cockcroft JR. Isolated systolic hypertension in the young: a need for clarity. *J Hypertens* 2013; 31:1911–1913.
133. Sesso HD, Stampfer MJ, Rosner B, Hennekens CH, Gaziano JM, Manson JE, Glynn RJ. Systolic and diastolic blood pressure, pulse pressure, and mean arterial pressure as predictors of cardiovascular disease risk in men. *Hypertension* 2000; 36:801–807.
134. Sundström J, Neovius M, Tynelius P, Rasmussen F. Association of blood pressure in late adolescence with subsequent mortality: cohort study of Swedish male conscripts. *BMJ* 2011; 342:d643.
135. Pauca AL, Wallenhaupt SL, Kon ND, Tucker WY. Does radial artery pressure accurately reflect aortic pressure? *Chest* 1992; 102:1193–1198.
136. McEniery CM, Cockcroft JR, Roman MJ, Franklin SS, Wilkinson IB. Central blood pressure: current evidence and clinical importance. *Eur Heart J* 2014; 35:1719–1725.
137. Kollias A, Lagou S, Zeniodi ME, Boubouchairopoulou N, Stergiou GS. Association of central versus brachial blood pressure with target-organ damage: systematic review and meta-analysis. *Hypertension* 2016; 67:183–190.
138. Saladini F, Mos L, Casiglia E, Malipiero G, Mazzer A, Palatini P. Central blood pressure is an independent predictor of future hypertension in young to middle-aged stage 1 hypertensives. *Blood Press* 2013; 22:9–16.
139. Hope SA, Meredith IT, Cameron JD. Effect of noninvasive calibration of radial waveforms on error in transfer-function-derived central aortic waveform characteristics. *Clin Sci (Lond)* 2004; 107:205–211.
140. Papaioannou TG, Karageorgopoulou TD, Sergentanis TN, Protogerou AD, Psaltopoulou T, Sharman JE, *et al.* Accuracy of commercial devices and methods for noninvasive estimation of aortic systolic blood pressure a systematic review and meta-analysis of invasive validation studies. *J Hypertens* 2017; 35:894–896.
141. Sharman JE, Avolio AP, Baulmann J, Benetos A, Blacher J, Blizzard CL, *et al.* Validation of noninvasive central blood pressure devices: ARTERY Society task force consensus statement on protocol standardization. *Eur Heart J* 2017; 38:2805–2812.
142. Cheng HM, Chuang SY, Sung SH, Yu WC, Pearson A, Lakatta EG, *et al.* Derivation and validation of diagnostic thresholds for central blood pressure measurements based on long-term cardiovascular risks. *J Am Coll Cardiol* 2013; 62:1780–1787.
143. Roman MJ, Devereux RB, Kizer JR, Okin PM, Lee ET, Wang W, *et al.* High central pulse pressure is independently associated with adverse cardiovascular outcome the strong heart study. *J Am Coll Cardiol* 2009; 54:1730–1734.
144. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, *et al.*, Subcommittee on screening and management of high blood pressure in children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics* 2017; 140; pii: e20171904.
145. Flynn JT, Falkner BE. New clinical practice guideline for the management of high blood pressure in children and adolescents. *Hypertension* 2017; 70:683–686.
146. Mangoni AA, Mircoli L, Giannattasio C, Mancia G, Ferrari AU. Effect of sympathectomy on mechanical properties of common carotid and femoral arteries. *Hypertension* 1997; 30:1085–1088.
147. Failla M, Grappiolo A, Emanuelli G, Vitale G, Fraschini N, Bigoni M, *et al.* Sympathetic tone restrains arterial distensibility of healthy and atherosclerotic subjects. *J Hypertens* 1999; 17:1117–1123.
148. Giannattasio C, Failla M, Lucchina S, Zazzeron C, Scotti V, Capra A, *et al.* Arterial stiffening influence of sympathetic nerve activity: evidence from hand transplantation in humans. *Hypertension* 2005; 45:608–611.