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FROM THE EDITOR

"African Voices" cover research from African countries – a new section of ISH News

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Dear reader,

It is again a pleasure for me to present a new issue of Hypertension News (Opus 69) to you. First, these are terrible times with a war raging in Europe. The International Society of Hypertension (ISH) has taken a strong stand against the Russian invasion of Ukraine. Needless, to say our thoughts go to the people suffering from that war.

Second, as discussed by Dylan Burger, in his report from the Executive Committee on page 2, ISH has changed its Secretariat from January 2022, when "CJ Association Management" (CJAM) in London took over. They will now provide support for membership, governance and communications including Hypertension News. This issue of the ISH Newsletter will be the first together with CJAM, and so far we are impressed by their level of professionalism. We thank the previous Secretariat "In Conference" in Scotland for their help over the past three years. We are also pleased to inform you that the election of a new President of ISH for 2022–24 is now finally under way and we should know the outcome in early May. The new ISH President will be presented to you in a coming issue of the Newsletter.

Moreover, the 2022 ISH Scientific meeting in Kyoto is now getting closer. Abstract submission is open and you can find a link to submit your abstract in Dylan Burger's report. On page 31, there is also an excellent update from the Kyoto secretariat.

Importantly, the burden of hypertension remains one of the major public health concerns in Africa where awareness, treatment, and control levels are low in most countries. This calls for intensification of research on accessible and affordable treatment options, and implementation of context-specific strategies aimed at improving hypertension management. In this issue of Hypertension News, we present for the first time a section on "African Voices", featuring research from two African countries, this time covering basic science and public health topics, elegantly introduced by Lebo Gafane-Matemane (pages 34 to 39). We plan to expand this section in the coming issues.

The emerging public health problem with pre-hypertension and established hypertension in children and adolescents is the focus for a number of papers in this issue of ISH News (pages 8 to 27). There is no doubt that the high prevalence rates of hypertension in many adult populations on a global scale is preceded by similar trends in younger populations. Some factors during fetal life and early childhood may have an impact on the risk of developing hypertension later in life. Other factors of importance are the influence of overweight, obesity, and sedentary lifestyle. Environmental factors such as pollution, chemicals, and exposure to small air-borne particles may also contribute.

Finally, let me thank my talented deputy editor Dylan Burger, all the members of the lovely editorial team, and especially our newcomer Michael Hurcum from CJAM for their dedicated work. Thanks also to all the authors for their valuable contributions.

Have a good read!
Lars H Lindholm

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From the Executive Committee - News highlights

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First, I would like to pass on a happy new year to Hypertension News readers on behalf the ISH executive committee. The early part of 2022 has been extremely active for the executive and I am pleased to provide several updates.

First, as noted in the most recent e-bulletin, the ISH has undergone a transition in administrative support. The ISH has recently appointed Hilary Millroy to the position of ISH Finance Officer. She will provide support for ISH financial operations and report directly to the ISH Treasurer and Finance Committee. In addition, CJ Association Management (CJAM) will now provide support for membership, governance and communications including Hypertension News! This issue marks the first to be prepared with CJAM and I have to say that I have been impressed with the level of support and professionalism of the CJAM team. We thank the InConference team for their support over the past 3 years and wish them the best.

In addition to the changes in administrative support there has also been a transition in leadership of the ISH Asia Pacific Regional Advisory Group and the ISH International Forum. Professor Rafael Castillo has been appointed as ISH International Forum Chair, and Professor Wook Bum Pyun (South Korea) has been appointed to ISH Asia Pacific Regional Advisory Group Chair. We look forward to their leadership.

The ISH Council met as a whole in early February and received updates from committee chairs and discussed key activities.

1. I am pleased to note that the election of the ISH President-elect is now underway and will conclude in early May. We expect to have an interview with the next president-elect in the next issue of Hypertension News.
2. ISH members will note the recent announcement that our membership structure has undergone a restructuring. This is due in part to a revised relationship with the Journal of Hypertension and it has allowed us to restructure our fees to be more accessible. The precise details should be available on the ISH web site shortly and I am confident that our members will see greater value in the revised structure. Stay tuned for an e-mail regarding membership renewals.
3. The dates and location for the 2024 ISH Scientific Meeting have been chosen. We are delighted to join with our Colombian colleagues in the historical city of Cartagena. This will be the first ISH meeting in the Americas in several years and continues the globalization of ISH and its activities that we have seen over the past several years. Please reserve September 18th-24th, 2024 in your calendars.

Before we meet in Colombia however our 2022 Scientific Meeting in Kyoto, Japan promises to be an opportunity to re-engage as a community while discussing cutting edge science. Abstract submission is now open and I encourage all of our members to consider submitting their best work to this exciting meeting. You can submit your abstract here.

Best Regards

Dylan Burger
Chair, ISH Communications Committee

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HOT OFF THE PRESS

Blood pressure increase by paracetamol (acetaminophen)

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Analgesics belonging to the nonsteroidal anti-inflammatory drugs (NSAID) are associated with fluid retention secondary to interactions with renal function, which may increase blood pressure and reduce the efficacy of antihypertensive medications in some patients. Paracetamol (acetaminophen) is also a widely used analgesic, and almost one in ten patients being initiated on antihypertensive medication are also prescribed paracetamol [1]. Some small studies examining the effects of paracetamol on blood pressure may be taken to suggest an increase in blood pressure, but the results have been conflicting [2].

A recent publication by MacIntyre et al [3] provides important new information about this issue. In a double-blind, placebo-controlled crossover study the authors evaluated the effects of paracetamol 1 g qid for 2 weeks on ambulatory blood pressure in 110 patients with untreated or stable treated hypertension (mean daytime ambulatory blood pressure <150/95 mm Hg) and no concomitant major cardiovascular disease, analgesic treatment, or other major confounding conditions. In all, 103 of the 110 randomized patients completed the study. Mean age was 61 years, 76% were male, 68% on antihypertensive medication, and mean daytime ambulatory blood pressure was 133/81 mm Hg (mean office blood pressure 137/86 mm Hg). The primary outcome was a comparison of the change in mean daytime systolic ambulatory blood pressure by treatment. Additional per-protocol analyses were performed in the 90 participants compliant to randomized treatment (as assessed by serum drug levels).

The results [3] show a placebo-adjusted increase in mean daytime systolic ambulatory blood pressure by paracetamol of 4.7 mm Hg (95% confidence interval 2.9–6.6, P <0.0001). Secondary outcomes showed a 4.2 mm Hg (2.4–6.0, P <0.0001) increase in mean 24 h systolic ambulatory blood pressure, and 1.6 mm Hg (0.5–[2.7], P <0.01) and 1.4 mm Hg (0.3–2.5, P =0.017) increases in mean daytime and 24 h diastolic ambulatory blood pressures, respectively. Analyses per-protocol showed similar results, and main findings in untreated and treated patients were similar.

This well designed and conducted, short-term study suggests that paracetamol can increase blood pressure by 4-5/1-2 mm Hg in hypertensive people. The magnitude of blood pressure increase is, if the effects are maintained over prolonged time clinically significant [4-5]. Thus, paracetamol may not be an innocent drug in the context of cardiovascular disease. There are however, important limitations for this study to consider. Thus, it remains to be shown if the observed increase in blood pressure will be maintained over longer periods of treatment with paracetamol. People without hypertension were not evaluated, and the effects in patients with concomitant cardiovascular disease and/or chronic pain were not addressed. This notwithstanding, it may be reassuring to note that a large retrospective cohort study of older hypertensive patients in primary care found no evidence of a sustained rise in blood pressure caused by paracetamol treatment [6]. Also, in another large primary care observational cohort study we have previously confirmed that NSAIDs can increase blood pressure in hypertensive patients. However, concomitant use of NSAIDs did not impair the chance to reach target blood pressure [7]. Thus, it may seem wise to advise regular evaluation of blood pressure in people on extended treatment with paracetamol (in addition, of course, to those on treatment with NSAIDs) and

to initiate or adjust antihypertensive medication accordingly to ascertain adequate blood pressure control.

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HOT OFF THE PRESS

Insight to the cardioprotective effects of GLP-1 (glucagon-like peptide-1) analog liraglutide

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In this study, Helmstadter and colleagues reveal the cardio- and vasoprotective mechanism of the glucagon-like peptide-1 (GLP-1) analog liraglutide at the cellular level in a murine, nondiabetic model of arterial hypertension.[1]

GLP-1 is a peptide hormone with known anti-inflammatory properties, as well as cardiovascular protective effects seen in clinical trials. The authors here demonstrate that the analog liraglutide confers antioxidant and anti-inflammatory effects through mechanisms requiring the endothelial GLP-1R (GLP-1 receptor).

Arterial hypertension was induced in wild-type mice by angiotensin II, resulting in elevated systolic blood pressure and cardiac hypertrophy that were completely normalized by administration of liraglutide. They found that liraglutide reduced ATII-induced oxidative stress and endothelial dysfunction by suppression of inflammation, NADPH oxidase activity and recoupling of eNOS (endothelial NO synthase). Furthermore, administration with liraglutide was able to suppress increased leukocyte infiltration at the inner vascular wall, by reducing expression of pro-inflammatory markers and adhesion molecules responsible for leukocyte adhesion and migration.

Global GLP-1 receptor knockout mice (Glp1r-/-) exhibited impaired endothelial function when infused with ATII, in which treatment with liraglutide did not improve. In addition, liraglutide failed to normalize and even deteriorated levels of aortic Nox2, Nos2, and Tnfa mRNA as well as cardiac Nox2 activity in ATII-infused Glp1r-/- mice. Overall, this suggests that the cardiovascular protection seen in wild-type mice is mediated through activation of canonical GLP-1R.

To further understand the vascular-protective liraglutide signaling through GLP-1R, they generated endothelial cell-specific (Glp1r ec-/-) and myeloid cell-specific (Glp1r my-/-) GLP-1R knock-out mice. Unlike the findings in global Glp1r-/-, ATII-infused vascular dysfunction in Glp1r my-/- was restored by liraglutide. Liraglutide was also able to markedly reduce cardiac hypertrophy and vascular fibrosis in ATII-infused Glp1r my-/-, indicating that GLP-1R expression in myeloid cells is not required for the cardiovascular protective effect of liraglutide.

In contrast to Glp1r my-/- mice, liraglutide failed to improve endothelial function or reduce blood pressure in hypertensive Glp1r ec-/- mice. Vascular fibrosis and cardiac hypertrophy were aggravated by ATII infusion, which was not improved by liraglutide treatment. Furthermore, liraglutide failed to prevent upregulation of inflammatory markers Nox2, Vcam1, and Tnfa mRNA as well as higher nitrate levels. The vessel wall infiltration of Ly6G-Ly6C+ inflammatory monocytes and Ly6G-Ly6C+ neutrophils was not reduced by liraglutide treatment of ATII-infused Glp1r ec-/- mice. Thus, the authors concluded that cardiovascular

protection of liraglutide in mice with ATII-induced vascular dysfunction is predominantly mediated via the endothelial GLP-1R, but not the myeloid cell GLP-1R.

The authors' model of ATII-triggered hypertension provides insight to the cardioprotective effects of GLP-1 analogs and GLP-1R agonists seen in clinical trials. However, cardioprotective mechanisms of liraglutide and its metabolites independent of GLP-1R cannot be fully excluded, representing a limitation in this study. In conclusion, this study supports previous literature highlighting the essential role of GLP-1R signalling by GLP-1 analogs and is consistent with previous findings in mice in the blood pressure reduction produced by GLP-1R agonists. Given the importance of renin-angiotensin-aldosterone system activation for cardiovascular complications, the present data obtained in a model of ATII-triggered hypertension may contribute to a better understanding of the liraglutide-mediated cardioprotective effects reported in clinical trials.

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LEARNING THE ROPES: HIGH BLOOD PRESSURE IN CHILDREN AND ADOLESCENTS

Introduction

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The emerging public health problem with pre-hypertension and established hypertension in children and adolescents is the focus for a number of papers in this issue of ISH News. There is no doubt that the high prevalence rates of hypertension in many adult populations on a global scale is preceded by similar trends in young populations. Some factors during fetal life and early childhood may impact on the risk to develop hypertension later in life, for example in premature or small-for-gestational babies, especially if exposed to a rapid catch-up growth during the first years of life. Other factors of importance, besides genetic traits and a positive family history of hypertension and early onset cardiovascular disease, is the influence of overweight, obesity and sedentary lifestyle. Even environmental factors such as pollution, chemicals, and exposures to small air-born particles may play a role. During the process of migration, now affecting a growing number of children and their parents, a change of diet and lifestyle may cause elevation of blood pressure. Even the stress of war may negatively affect the mental and physical well-being of children, including elevation of blood pressure, as now tragically evident in ongoing conflicts, for example in Ukraine.

Established hypertension in children and adolescents is defined according to guidelines, until now developed mostly in the US and in Europe, but of importance on a much wider scale. Hypertension can also lead to target organ damage such as cardiac remodeling, impaired renal function and increased carotid intima media thickness (cIMT), detectable if the appropriate screening methods are available, which however is not the case in most circumstances on a global scale.

What should then be done to this growing problem? Improved lifestyle based on physical activity, a proper diet, less intake of salt, and avoidance of tobacco are cornerstones of primordial prevention of hypertension, but in some cases also drug treatment has to be considered. In a few cases, not to be missed, there exists secondary hypertension also in children, for example caused by endocrine or renal disturbances, if not by congenital malformations such as coarctatio aorta that may be surgically corrected.

I welcome the reader to this number of informative papers on the topic!

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1. Smith and Teitler. Cardiovasc Drugs Ther. 1999 Apr;13(2):123-6

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LEARNING THE ROPES:

Early vascular aging; before-from-after conception and during childhood

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Background

The concept of Early Vascular Aging (EVA) was introduced already in 2008 [1] and describes age-related changes of large elastic arteries with a gradual stiffening of the arterial media, arteriosclerosis. This is different from the well-known development of atherosclerosis that starts in the arterial intima. During the life course, these two processes act in synergy to increase cardiovascular risk and can be measured and quantified in different ways. Most clinicians encounter cardiovascular risk patients among middle-aged or elderly subjects coming to them for a clinical visit and evaluation of cardiovascular risk factors, in some cases even after the first cardiovascular event has occurred. However, it is of importance to realise that these processes damaging the arterial wall and increasing the risk are influenced by factors acting in early life and shaped by genetics, social background, lifestyle and the historical context. Various factors linked to ethnicity, social and living conditions could also influence the development of arterial stiffness (arteriosclerosis) as studied in different populations of children, adolescents and adults around the globe.

The importance of early life programming for adult health and disease has been a research focus of interest ever since the 1970s (Arne Forsdahl, Norway) [2] and 1980s (David Barker, UK, and Gerhard Gennser, Sweden) [3,4] when the first observational studies linking low birth weight with adult risk of hypertension, cardiovascular disease and type 2 diabetes were published. This scientific thinking was further developed by Nick Hales, UK, Peter Gluckman, New Zealand, and Mark Hanson, UK [5], but also in Sweden, with cohort studies from Uppsala and the Swedish Twin Register. In Spain, Empar Lurbe has led a research group on various effects of early life programming such as prematurity and small-for gestational age (SGA) in relation to hypertension and other risk factors during childhood and in adolescence [6]. In Finland, Johan Eriksson has published extensively on long-term outcomes for cardiometabolic health in relation to early life factors in the Helsinki Birth Cohort. Also researchers from a number of other countries have contributed to our understanding in this field, notably from the Netherlands, India and China when widespread famine during historical periods shaped the long-term health of affected birth cohorts.

More recently, the International Society for Developmental Origins of Health and Disease, DoHAD (https://dohadsoc.org/) was set up to promote research into the fetal and developmental origins of adult disease.

The different stages of early life influences

The early life period of interest encompasses not only the late pregnancy (3rd trimester), birth and first year of life, but also the time period from conception and early pregnancy (1-2nd trimesters) when genetic programming starts and embryonic development shapes the origin of organ function, including the cardiovascular system. Also the first years of life are of importance as a mismatch pattern can occur when fetal growth impairment

can lead to SGA birth weight, but later replaced by a rapid catch-up growth pattern. In this way, small babies can become heavier than expected in relation to their weight trajectory. Such mis-match has been associated with adverse effects for cardiometabolic health in a number of studies [5]. Later time periods, for example during pre-puberty, have also been associated with an important impact on growth patterns and organ function of importance to cardiometabolic health and EVA.

During conception, the genetic material from both parents is mixed and the genetic set-up for a new human being is programmed. Epigenetic effects have been described that may affect the genetic programming, for example an unhealthy lifestyle (smoking, obesity) in both the mother and father to be. This shows the importance of pre-conception health advice to young couples planning for parenthood. In India, such programmes have been launched to supplement for folic acid and sufficient caloric intake in young women planning to become pregnant, as directed by Chittaranjan Yajnik in Pune.

Reproductive factors and genetics

A number of reproductive life factors have been documented to influence the cardiovascular health in women, thus strengthening the importance of evaluating the reproductive history for assessing cardiovascular risk[7]. Among such factors are pregnancy hypertension, pre-eclampsia and gestational diabetes; factors that may directly or indirectly influence placental function and fetal growth. Genetic factors that trigger maternal hypertension can also increase the risk of hypertension in the offspring, as well as low birth weight. Protagonists of this genetic programming hypothesis may think that maternal hypertension in pregnancy, placental dysfunction, low birth weight and hypertension in the offspring are just different signs of the same process. On the other hand, researchers that see a wider role for environmental influences rely on both observational studies (historical examples of famine) and experimental feeding studies in lab animals to state that these processes can also be shaped by maternal nutrition, lifestyle and different exposures during pregnancy.

Of special importance is the role of prematurity that could be a primary driving factor for immaturity and organ dysfunction in new-borns, but also a secondary factor when for example pre-eclamptic women have induced labour or cesarean section to prevent harm from pre-eclampsia to both the mother and child. In such cases, prematurity of the new-born child also mirrors the influence of maternal hypertension influencing the blood pressure regulation and vascular architecture of the child. A history of low birth weight in mothers may also influence the same phenotype in her offspring.

Mechanisms involved

The elastic component of the arterial media is elastin that is pre-formed during fetal life and undergoes a gradual depletion during the life course. At the same time the collagen content of the arterial media is relatively increased and forming cross-linkages, even becoming glycosylated; leading to increased arterial stiffness (arteriosclerosis)[8]. This is a mechanism that could be of importance for vascular (arterial) ageing later in life. Also other aspects of the arterial structure can be influenced, for example thinness of the aorta in premature children that may also have less well-developed peripheral microvasculature and small arteries (arteriolae) that may cause an increased total peripheral resistance. All these structural changes could contribute to a relatively increased blood pressure in early life that may be exaggerated by an increased sympathetic nervous system activity and cortisol secretion found in individuals with a background of being SGA or prematurely born.

A new research direction is to understand the importance of gut microbiota for early life maternal-child transmission and later influence on development in offspring, as shown in animal models. In human adults, a link between gut microbiota and arterial stiffness has also been reported.

Early life influences of central hemodynamics - one example

In one population-based study from Malmö, Sweden, our aim was to examine the impact of mismatch patterns reflecting pre- and post-natal growth conditions on markers of arterial stiffness and central hemodynamics in young adults [9]. In all, 1056 participants (484 men and 572 women; age-range 18–44 years), were included. Lower birth weight was associated with higher brachial DBP (bDBP), higher central SBP/DBP, and higher augmentation index (AIx). Lower birth weight in combination with a higher attained BMI in young adult life (the mismatch phenotype) associates with higher bSBP/bDBP and higher central blood pressure. We could therefore suggest an additive hemodynamic programming effect of weight gain during the two first decades of life following low birth weight. Also in Austria, early life factors have been associated with the development of EVA in adolescents [10].

Prevention starts early

The lesson from early life studies of programming for cardiovascular and metabolic health in adults, is that it pays off to implement preventive maternal and child health, as was done in western countries after the Second World War but in many other countries more recently. This strategy is in-line with the WHO´s ambition of safeguarding health conditions of pregnant women, reproductive health and gender equity in health care. It is intriguing to notice that the mean age-adjusted systolic blood pressure has declined in most western populations over 30 years (1980 to 2010), in spite of a documented increase in sedentary lifestyle and obesity. The conventional explanation to this is the effect of better treatment of hypertension, but as such treatment will not reach all in need and is often sub-optimal due to non-compliance, a more realistic explanation is that the improved standards of preventive maternal and child health during the same period have favourably shaped better health conditions for modern children. The introduction of refrigerators in the homes of common families in the 1950s–1960s as a technical innovation reaching the majority in the population, has also meant that food could be preserved cool and fresh without adding too much salt. This has in turn decreased the exposure to salt in early life and thereby lowered blood pressure in salt-sensitive individuals.

Conclusion

In conclusion, the cardiovascular and metabolic health in adults, linked to EVA, is influenced by factors acting early in life against a background of the genetic set-up of each individual. Thus, preventive maternal and child health may be of great importance to shape the health of children growing up. The screening, early detection and treatment of maternal hypertension in pregnancy and pre-eclampsia, as well as gestational diabetes, is a fundamental component of the modern maternal health services. If thereby the incidence of prematurity and SGA births can be reduced, there is hope for less prevalence rates of (age-adjusted) hypertension in coming generations. Conditions for pregnant women cannot be separated from strategies to improve the health and social roles of women in general, especially literacy, working conditions, financial independence and the possibility to make their own informed choices for reproductive and social life.

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LEARNING THE ROPES:

The changing epidemiology of hypertension in children and adolescents

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Background

There are concepts in science that take time to overcome initial disbelief in them before they finally arrive at the moment when they are embraced by the research community. One of these concepts is hypertension (HTN) in children and adolescents. Until the early 1980s, little was known about childhood HTN, mainly because BP was not commonly measured in pediatric clinical practice. Blood pressure levels determined to be abnormal in children, when identified, were considered to be secondary HTN resulting from an underlying condition. Although secondary causes of HTN occur relatively more frequently in hypertensive children than in adults, the prevalence of secondary HTN is only about 1 percent overall, leaving primary HTN as the most frequent type, especially in adolescents [1].

Despite the existence of a large number of studies that have assessed the prevalence of HTN in children and adolescents, this prevalence has been difficult to state for three main reasons. First, blood pressure normally changes with increasing age and body size. This means that establishing a fixed cutoff for values of systolic and diastolic BP elevation is problematic. This difficulty has led to the use of percentiles based on age, sex, and height to define the normal distribution, with a hypertensive level of BP in the 95th percentile or higher. Next, there is a variety of different definitions of HTN employed by the three most recent clinical practice guidelines from Europe [2], the United States [3] and Canada [4]. Finally, considering the beat-to-beat BP variability, the definition of HTN has required that systolic and/or diastolic BP be persistently higher than the established thresholds on three separate occasions. Many cross-sectional studies with only a single measurement of BP have not been able to define the prevalence of HTN.

Prevalence of hypertension

A recent systematic review and meta-analysis provided relevant information about both the global prevalence, as well as the differences according to age, weight status, and methodology. Overall, the prevalence of HTN was 4%, with 9.57% prehypertension. According to age, the prevalence was 4.32% at 6 years of age, increasing to 7.89% at 14 years, and decreasing to 3.28% by 19 years. According to weight status, 15.27% of obese people were hypertensive, 4.99% in overweight people and 1.90% in those with normal weight. Interestingly, the majority were hypertensive by systolic BP [5]. According to the device used, HTN was 7.23% with an aneroid sphygmomanometer, 4.59% with a mercury sphygmomanometer, and 2.94% with an oscillometric sphygmomanometer [5].

Factors related to hypertension

The prevalence of HTN across regions and countries changes according to the unequal distribution of the increment of overweight and obesity, lifestyle, migration and environmental factors. All of them are elements that exert influence over the distribution of BP values in youth.

Overweight and obesity

The relevance of overweight and obesity in the prevalence of HTN is well established. The worldwide childhood obesity epidemic is not only a global phenomenon, but also an important health issue in middle-income and low-income countries, and it has had a profound impact on the prevalence of HTN. Consequently, primary HTN should now be viewed as one of the most common health conditions in young people.

Global obesity rates in girls increased from 0.7% in 1975 to 5.6% in 2016, and from 0.9% to 7.8% in boys, while rates of underweight have decreased for both boys and girls over this time [6]. Body Mass Index (BMI) trajectories of childhood and adolescence, over time and by age, are highly variable across countries, indicating nutritional inequality [7]. In high-income countries, child and adolescent mean BMI has plateaued at high levels since about 2000, but the increase continues to accelerate elsewhere, particularly in parts of Asia [7].

Worldwide, compared to children with normal weight, the odds ratio estimated for the risk of HTN increases progressively from 1.7 in overweight, to 2.6 in obese, 3.7 in severely obese and 4.8 in extremely obese children [8]. A recent study published data coming from Africa showing that the overall prevalence of HTN, elevated BP and combined elevated BP and HTN in children and adolescents was 7.5%, 11.4% and 21.7%, respectively. In the presence of overweight or obesity, HTN was four times more prevalent than in those classified as normal weight [9].

Even though the relationship between obesity and HTN is a well-established one, other factors modulate the association. A study analyzing the secular trend of HTN in children and adolescents from high- and middle-income countries did not mirror the secular overweight and obesity trend [10].

It is fundamental that there be research into the other determinants of BP which includes analyses of their impact on BP at the population level.

Lifestyle

Lifestyle factors that go beyond the relationship between obesity and HTN also need consideration. Beside the well-known impact of an unhealthy diet, sedentarism and limited physical activity, other emerging factors such as screen time and sleep deprivation contribute to BP elevation. Currently, screen time is the most common sedentary behavior, starting even in infants. The risk for high BP associated with screen time is mainly due to the risk of both obesity and sleep restriction. Sleep disturbance is a commonly overlooked risk factor associated with high BP in children and adolescents [1].

Migration

Migration is another factor to be considered. Today, more and more people are migrating to other countries, and international migrants currently account for 3% of the world population. While migration has become an avenue to economic well-being, the resulting variation in population has drastically increased disease rates. An increment in BP is a reliable marker since it responds quickly to migration. In a recent study, the impact of immigration from a region with a relatively calorie-restricted diet to a region of affluent living conditions was analyzed. Israeli-born Ethiopians had a significantly higher risk for hypertensive-range measurements at any BMI level compared with the same age native population. Children and adolescent immigrants are at increased risk for rapid weight gain that correlates directly with the time-lapse since immigration [11]. Therefore, considering the waves of immigration that have occurred over recent years from developing countries to more developed countries, prevention programs are needed for immigrants that begin upon arrival.

Environmental

Extensive industrialization and urbanization have resulted in ambient air pollution rising sharply. Epidemiological studies investigating the effects of short-term and long-term exposure to ambient

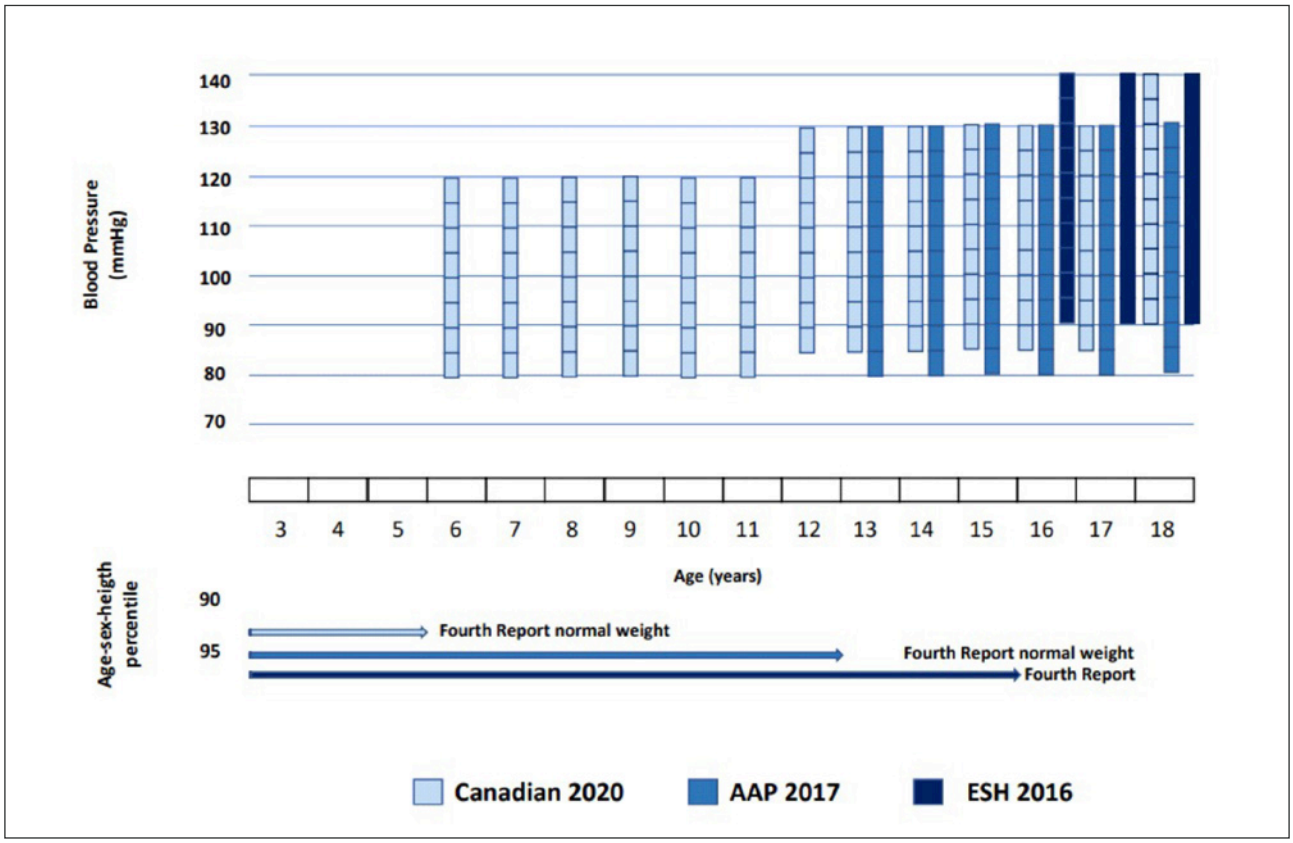
air pollution on HTN and BP among children and adolescents have had controversial results. In a recent meta-analysis, environmental exposure to particulate matter (PMmm) was associated with both, the prevalence of HTN and elevated BP. Whereas HTN was associated with long-term exposure to PM10, elevated BP was affected by exposure to short term PM10, long-term PM2.5, PM10 and nitrogen oxide (NO_2) [12].

Conclusion

The worldwide obesity epidemic is changing the epidemiology of HTN in childhood and adolescence. Hypertension is more prevalent than before, and primary HTN has become the predominant type. The factors of primary HTN can be modified, and childhood is a period in which prevention could be effective. If prevention is sustained throughout childhood, it could contribute to a healthier young adulthood. Therefore, primordial prevention is an opportunity not to be missed.

Legend of figure

Graphic expression of the criteria to define HTN according to Guidelines in Children and Adolescents: European Society of Hypertension (ESH 2016) [2], American Academy of Pediatrics (AAP 2017) (3) and Canadian Guidelines (Canadian 2020) [4].



ESH recommended the approach to percentiles for children up to 16 years old and the adult criteria ≥140/90 mmHg for those 16 years and older. The American Academy of Pediatrics (AAP) recommended the use of percentiles for children up to 13 years of age and ≥130/80 mmHg for those 13 years and older. Canadian Guidelines established different criteria, percentiles until 6 years, between 6-11 ≥120/80 mmHg, 12-17 ≥130/85 mmHg and >18 years ≥140/90 mmHg. Reference tables of percentile distribution used the NHBPEP´s normative tables (Fourth Report) [13], while ESH guidelines did not exclude overweight/obese (BMI ≥85th percentile).

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LEARNING THE ROPES:

Hypertension mediated organ damage in children and adolescents

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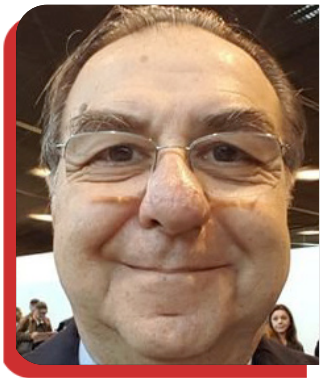

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In the context of a number of new recommendations, the 2017 American Academy of Pediatrics (AAP) guidelines on hypertension in children and adolescents [1], introduced three important novelties regarding evaluation and management of arterial hypertension in youths, compared to previous European and American guidelines [2, 3]:

- Modification of the original normative tables used in the 2004 and 2016 (by ESH), with excluding children and adolescents with overweight/obesity (OW/OB) from normal reference.
- Introduction of a static cutoff of BP ≥130/80 mmHg for adolescents aged ≥13 years, regardless of age, sex and height.
- New recommendation for the definition of left ventricular (LV) hypertrophy (LVH).

These novelties carried important consequences in terms of identification of hypertension mediated organ damage (HMOD), however produced inconsistencies between definition of arterial hypertension and presence of cardiac HMOD.

The exclusion of OW/OB from the normative tables reduced the normal confidence limits of blood pressure, with the consequence of increasing prevalence of arterial hypertension especially in the range of age <13 years [4], theoretically enhancing the chance to identify more HMOD. This effect was even more evident in hypertensive OW/OB, who were easily identified with using the new AAP reduced cut point for diagnosis of hypertension at age 13 or older [5].

LV geometry

LVH is the hallmark of HMOD in adult hypertension and is supposed to be as important in children and adolescents. However, while determining a clear-cut normality limit in adults is easier because of the indications of prospective outcome studies, in children and adolescents, definition of LVH depends on statistical distribution of LV mass values, but also on the way LV mass is normalized for body size. This is a particularly difficult task, given the progressive changes in body size and shape occurring in this range of age, and the recognized interference of obesity [6], a conundrum generating uncertainty.

The AAP guidelines confirmed the recommendation of adopting normalization of LV mass for body height in meters to the allometric power of $^{2.7}$, to avoid underestimation in OW/OB, in line with the choice of excluding OW/OB from normative tables, and consistent with the updated suggestions in literature. However, the adoption of a very high cut-point for the identification of LVH (>51 g/m $^{2.7}$), not based on the distribution of normal values in this range of age, and even higher than the sex-specific cut-points suggested in the 2018 European Adult Guidelines, made identification of LVH in children and adolescents problematic.

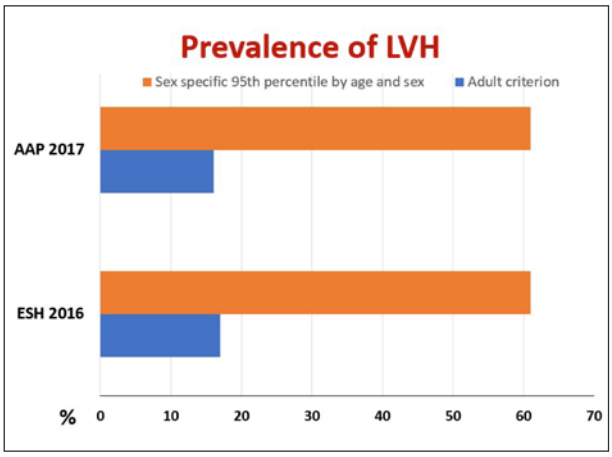

Figure 1: Prevalence of LVH among OW/OB adolescents using ESH or AAP diagnostic criteria for hyertension and definition of LVH by sex-specific age and height criteria or by adult cut point.

When adapting the AAP suggested cut points to real world, the ability to identify hypertensive LVH was poor [5]. In a population sample of OW/OB, including 26-29% of hypertensive youths (depending on definition of hypertension with ESH or AAP guidelines), prevalence of LVH was 4-to-5 fold higher using the 95th percentile of 10 sex-specific and age strata [5, 7] than with the new adult cut point recommended by AAP, maintaining the same criterion of LV mass normalized for m $^{2.7}$ (figure 1, from ref. 5).

Abnormal hypertensive LV structural damage is not only increased LV mass. The most hemodynamically consistent LV geometric pattern in arterial hypertension is in fact concentric. The way to approach LV geometry is the calculation of relative wall thickness (RWT, i.e. wall thickness/LV radius). Consistent with the definition of LVH, AAP recommended using the adult cutoff for concentric LV geometry (RWT>0.42). In contrast, we use a pure statistical approach based on 95th percentile of distribution in normal-weight, normotensive children and adolescents, resulting in a much lower cutoff (RWT≥0.38) [8].

Using 95th percentile of sex and age specific - normative tables [7] to identify LVH, the most frequent LV geometric pattern in hypertensive OW/OB was by far concentric, whereas this association was not found using the adult cutoff from AAP guidelines [5].

Figure 2 displays the probability of being hypertensive, based on the presence of concentric LV geometry with both ESH and AAP definition of hypertension (from ref. n. 5)

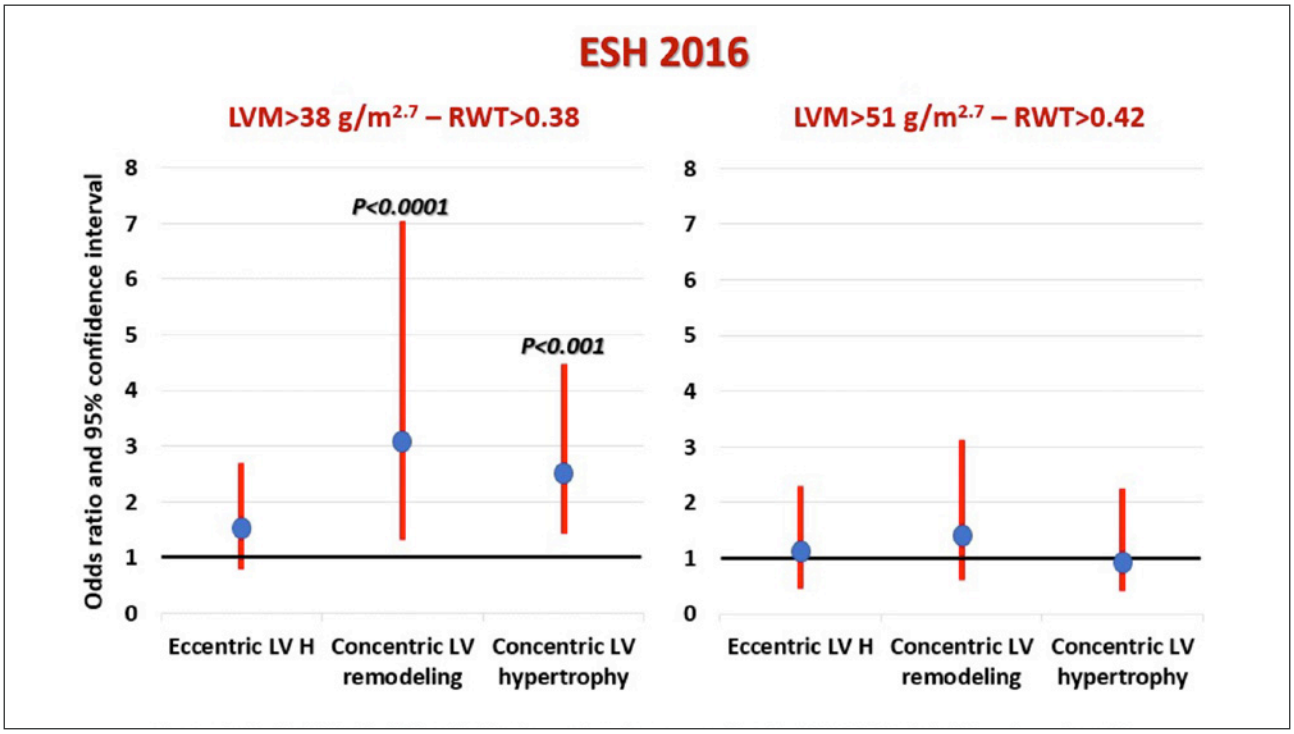

Figure 2: Probability (odds) of being hypertensive, according to ESH 2016 definition, based on LV geometric pattern. In the LEFT panel: LVH and RWT defined by cutoffs based on the 95th percentile of normal distribution. In the RIGHT panel: LVH and RWT defined by adult cutoffs (AAP guidelines).

The link of arterial hypertension with LV geometric pattern of pressure overload helps when identifying LVH mostly due to arterial hypertension from LVH that might be present just because of obesity, aiding decision-making. The ESH 2016 guidelines with the adopted definition of hypertension and LV geometry help achieve this clarification. Using adult cut points for LV geometry might be confounding.

Kidney

In adult hypertension, microalbuminuria, assessed on spot urine specimens as microalbumin/creatinine ratio of >30 mg/g, is a potent marker of HMOD, easily obtainable and cheap. Unfortunately, a specific pediatric definition of microalbuminuria is not yet available, due to lack of consistent data and, conventionally, the adult cutoff is used, with some risk of misclassification especially at the youngest age and in the presence of obesity, both conditions associated with increased values. Among many contradictory studies, in an interventional study on 55 adolescents undergoing antihypertensive treatment [9], microalbuminuria was associated with both severity of hypertension and LVH. After one year of therapy, together with the reduction of BP values and regression of LVH, also microalbuminuria was significantly reduced. Despite the uncertainty of detection in this range of age, assessment of microalbuminuria might be useful namely to follow the evolution of therapy.

In addition to microalbuminuria, in the adult population, hypertension can be associated with increasing risk of chronic kidney failure (CKD). There is little data in children and adolescents, and most studies are performed in the presence of overt CKD. Thus, the question of whether identification of hypertensive kids with mildly reduced glomerular filtrate (GFR) is useful does not have yet a clear answer. However, identification of association between mild reduced GFR and hypertension can be important for both risk stratification and decision making also in this range of age, especially considering that there is a significant relation between mildly reduced GFR (≥60 <90 mL/min/1.73 m2) and increase in mean blood pressure [10]. In addition to microalbuminuria, also a mild reduction of GFR should be considered as a marker of kidney damage in children and adolescents with hypertension.

Hypertension and vascular damage

The association between high BP and vascular damage was originally observed by many authors, especially in the Bogalusa Heart Study. However, it must be taken into account that the relationship between high BP and vascular damage is not specific.

The damage can be anatomical or functional. The anatomical one is commonly identified as increased carotid intimal-medial thickness (cIMT), and the functional one is linked to measures of vascular stiffness (namely the pulse wave velocity).

A recent meta-analysis confirmed that hypertension is correlated with increased cIMT. This study, however, also found that this relation between hypertension and high cIMT tended to disappear after adjustments for other cardiovascular risk factors. Unfortunately, there are not normative tables relating cIMT to age and sex. Thus, the relationship between hypertension and vascular damage in this range of age is still a matter of research.

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LEARNING THE ROPES:

Sorting Through the Guidelines: Diagnosis of hypertension in children and adolescents in the US and Europe

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Following identification of childhood hypertension as a clinical entity in the mid-1970s, the first set of clinical practice guidelines for the identification and management of high blood pressure in the young was issued in the United States by the National High Blood Pressure Education Program (NHBPEP) in 1977 [1]. This was followed by a series of revised American guidelines from the NHBPEP through the "Fourth Report" in 2004 [2]. In 2009, the European Society of Hypertension (ESH) issued the first set of Europe-specific pediatric guidelines, which was followed by a revision in 2016 [3]. By this time, the NHBPEP had turned over guideline development to professional societies, which led to the pediatric guideline being updated and reissued by the American Academy of Pediatrics (AAP) in 2017 [4].

Two important components of these guidelines have been inclusion of normative blood pressure (BP) data and definitions of hypertension. Hypertension in adults is defined based on the BP level above which there is an increased rate of adverse cardiovascular (CV) events such as heart attack or stroke; these data are usually derived from large-scale clinical trials. Since these events essentially do not occur during childhood, a different approach to defining normal and abnormal BP levels in children and adolescents is required. Given this, the NHBPEP committee that wrote the first guideline decided to adopt a statistical definition of pediatric hypertension based upon the distribution of BP values in healthy children [1]. BP percentiles were constructed from BP measurements obtained by auscultation in several large screening studies, and the 95th percentile was denoted as "hypertensive". In order to prevent over-diagnosis, and because the true prevalence of childhood hypertension was unknown at the time (previously adult hypertension criteria had been used to define childhood hypertension), it was further decided that at least 3 BP readings above the 95th percentile would be required before a diagnosis of hypertension could be made.

Subsequently, both the normative data used to generate childhood BP percentiles and the definitions of pediatric BP categories have been refined by successive iterations of pediatric guidelines. The most current AAP and ESH recommendations for classification of BP levels in childhood are summarized in Table 1. There are many similarities between the AAP and ESH guidelines – both carry forward the 90th percentile as the definition of normal BP and the 95th percentile as the definition hypertension for younger children. Both also adopt the same static cut-points used in their respective national adult guidelines to define the categories of BP for adolescents. Additionally, both guidelines endorse the routine use of ambulatory BP monitoring (ABPM), and contain similar recommendations for the diagnostic evaluation of children and adolescents with confirmed hypertension.

Where the AAP and ESH guidelines differ is in the age at which use of the static cut-points begin. For the AAP guideline it is 13 years of age, and for the ESH guideline it is 16. The rationales for these decisions are interesting and highlight one

area that would benefit from improved alignment in future iterations of the guidelines. The AAP chose the age of 13 years because at that age, the 90th percentile of BP in its normative tables (see below) for boys and girls with heights at the 50th percentile was almost exactly 120/80; the adult BP level denoting normal BP. The ESH chose 16 years of age because according to their normative tables [3], some taller children had "normal" BPs higher than the adult level of BP in the adult ESH hypertension guideline, and it was felt that these children should not be considered normotensive if their BP was actually higher than the level considered abnormal in an adult.

The other major difference in this aspect of the AAP and ESH guidelines is the normative data used to generate BP percentiles. For the new 2017 guidelines, the AAP commissioned new tables of normative BP values based only upon BP readings obtained in children of healthy weight. This was done because the tables in the previous guideline (the 2004 Fourth Report from the NHBPEP) were generated from a database of BPs that contained nearly 30% children with overweight or obesity, and it had previously been shown that inclusion of so many children of unhealthy weight actually biased the "normal" values upward [5]. The new normative data in the 2017 AAP guideline resulted in values that were, on average, 2-4 mmHg lower for each age/sex/height group than the previous values. Of note, these BP values were remarkably similar to those in a 2016 international analysis of cross-sectional BP surveys in China, India, Iran, Korea, Poland, Tunisia, and the United States that also included only children of healthy weight [6]. The ESH guideline on the other hand, carried forward the normative data from the 2004 NHBPEP Fourth Report [2], which shows that for children (especially boys) 16 years of age and older, the 95th percentile values actually exceed the BP level used to define adult hypertension by the ESH.

One other slight difference between the guidelines with respect to diagnosis of hypertension, relates to interpretation of ABPM. The AAP guideline endorses use of interpretation criteria published by the American Heart Association (AHA) in 2014 [7]. These incorporate both mean BP and BP load, leading to six possible BP phenotypes: normotension, white coat hypertension, pre-hypertension, ambulatory hypertension, masked hypertension and severe ambulatory hypertension. The ESH guideline on the other hand, incorporates only mean BP into its interpretation criteria, resulting in the usual four BP phenotypes (normotension plus white coat, ambulatory and masked hypertension). Both guidelines recommend the same pediatric normative data for ABPM, although the ESH guideline recommends adoption of the adult threshold value for tall adolescents, again because in the normative ABPM data the tallest boys have 95th percentile values for wake mean systolic BP that exceed the adult ABPM threshold. The AHA pediatric ABPM recommendations are likely to change in mid-2022 [8], thereby creating another opportunity for future alignment of the AAP and ESH guidelines.

The final notable differences between the two guidelines relates to treatment goals and monitoring for target-organ effects of high BP. The ESH guideline is more forceful in its recommendations to screen every child with confirmed hypertension for target organ damage with echocardiography, and the AAP guideline contains a lower treatment goal (90th percentile) for treatment of children and adolescents with uncomplicated primary hypertension. This latter difference is likely explained by the more enthusiastic uptake in the United States than in Europe of data from the Systolic Blood Pressure Intervention Trial (SPRINT), which demonstrated significant reductions in the rates of CV events in adults randomized to a systolic BP goal of <120 mmHg [9]. The guidelines otherwise align on their emphasis on achieving ideal CV health during childhood, so that over the life course there will be reductions in morbidity and mortality attributable to CV disease.

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Table 1. Comparison of AAP and ESH pediatric hypertension guidelines

Blood Pressure Stage/Level	AAP Guideline[†]	ESH Guideline[‡]
Normal BP	<90th percentile up to age 13*; <120/80 starting at age 13	<90th percentile through age 15, <130/85 starting at age 16
Elevated/High-normal BP	≥90th to <95th percentile up to age 13*; 120-129/80 starting at age 13	≥90th to <95th percentile through age 15; 130–139/85–90 starting at age 16
Stage/Grade 1 hypertension	≥ 95th percentile to < 95th percentile +12 mmHg up to age 13*; 130-139/80-89 starting at age 13	≥95th percentile to 99th percentile +5 mmHg through age 15; 140–159/90–99 starting at age 16
Stage/Grade 2 hypertension	≥95th percentile +12 mmHg up to age 13*; ≥140/90 starting at age 13	> percentile +5 mmHg through age 15; 160–179/100–109 starting at age 16

[†]The AAP guideline also recommends immediate/urgent referral if BP is >30 mmHg above the 95th percentile; the ESH guideline contains no specific numerical value for a level of BP warranting immediate evaluation

[‡]The ESH guideline also contains a definition of isolated systolic hypertension as a specific sub-type of hypertension; the AAP guideline does not

*or the corresponding value for children ≥13, whichever is lower

AAP, American Academy of Pediatrics; BP, blood pressure; ESH, European Society of Hypertension

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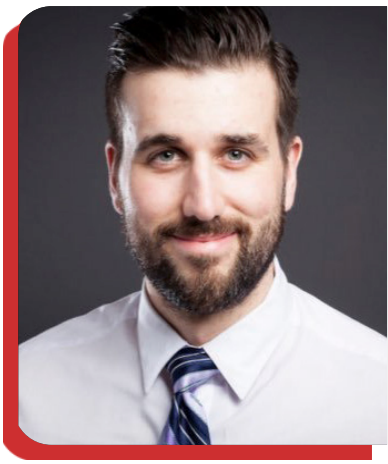
LEARNING THE ROPES:
Pediatric antihypertensives: a short overview



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DOI: 10.30824/2204-9

Pediatric hypertension (pHTN) is a complex and multifactorial disorder with a rising prevalence. Current guidelines originating from Canada [1], the United States [2], and Europe [3], among others, have published criteria aimed at identifying and diagnosing pHTN. However, due to the challenges with obtaining an accurate blood pressure (BP) in children, as well as some of the complexities with diagnosis (the use of Z-scores), many children will go undiagnosed with pHTN. Risk factors for pHTN include obesity [1], sleep disordered breathing [4], both proteinuric [5] and non-proteinuric renal disease, and cardiac disease, among others. Importantly, untreated pHTN is directly related to end organ damage including left ventricular hypertrophy, hypertensive retinopathy, and early vascular aging [6]. When left unopposed, pHTN trajectories will continue into adulthood [7]. As such, much research in the field of both adult and pHTN is directed at diagnosing hypertension early and initiating treatment to prevent the development of end organ damage and legacy hypertension.

Initially, confirmation of pHTN is required with several independent measurements, or the preferred gold standard ambulatory BP monitoring. Once confirmed, a detailed work-up ensues to determine whether pHTN is primary or secondary in nature. If deemed primary, and related to poor lifestyle choices, or obesity, then interventions are targeted at balanced weight loss, increasing activity, and dietary modification. When secondary causes are identified, interventions are targeted at the disease in an attempt to improve the BP. However, it is quite common for children with both primary and secondary pHTN to require pharmacological intervention. Complicating this is the lack of studies and dosing regimens for children [8]. However, the last 10-15 years has seen a marked improvement in the management of pHTN, and several therapeutics are available.

Calcium channel blockers (CCBs) are approved for use in pediatric patients and are commonly prescribed in pHTN. Their BP lowering effect largely comes from dilatation of peripheral arteries [9]. Amlodipine is commonly first line and is prescribed as once daily dosing (OD). Nifedipine can be used in some pHTN urgencies as a rapid acting, sublingual, or oral agent.

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) modulate the renin-angiotensin-aldosterone system (RAAS), are antiproteinuric, and have blood pressure reducing properties. They are one of the most extensively studied classes of antihypertensives in children [9]. Commonly used ACEi agents include Fosinopril, Enalapril, and Captopril. Dosing varies but is typically OD or twice daily (BID). In children, the ARBs losartan, and candesartan are used most often, with dosing on a per-day basis. Lastly, there are the aldosterone receptor antagonists, which includes eplerenone and spironolactone, both of which are used OD and BID.

Diuretics are typically used in specific circumstances where fluid overload is leading to an increased BP, or respiratory compromise. Furosemide is the most commonly used and leads to an increase in urine volume. Thiazide diuretics are also used in pHTN, typically OD [10]. Beta blockers (BB), or beta-adrenergic antagonists are used in pHTN. They reduce BP in patients by reducing cardiac output, sympathetic output, and through reduction of renin release. BB are typically prescribed OD or BID.

There are several other antihypertensives for which there is even scarcer data, and thus their use in children requires further studies. These include alpha blockers, clonidine, and vasodilators like hydralazine. Alpha blockade is most often used as an adjunct when first- and second-line agents are not effective. Doxazosin is an example of an alpha-1 selective blocker and is often dosed OD. Careful attention must be paid to the common side effect of orthostatic hypotension. Clonidine, which is a central-acting agent, is used more often in pediatrics for treatment of attention deficit hyperactivity disorder and drug withdrawal; however, it does have a modest antihypertensive effect [9]. It should not be used as monotherapy, or initial therapy, and there is a significant side effect profile which limits its use. Vasodilators like hydralazine are commonly used in cases of pHTN urgency and emergency via intravenous administration.

As seen above, several antihypertensive classes exist, but prescribing practises are non-uniform and it is unclear which antihypertensive to start first in children with pHTN [8]. Canadian guidelines [1] suggest starting CCBs, ACEi or ARBs first, as monotherapy. BB may be used but are less preferred due to side effects. Similarly, American guidelines [2] suggest initiating monotherapy with ACEi, ARB, CCB or thiazide diuretic. These guidelines do not suggest the use of BB in children as a first line agent. Lastly, European guideline [3] recommendations are more tailored to the patient who requires treatment. They advocate for use of ACEi or ARB in patients with diabetes and microalbuminuria, or CKD and proteinuria [3], which mechanistically makes sense. They additionally go on to recommend BB or CCB in children with pHTN and migraine, for example.

Thus, it is clear that pHTN is a complex condition from a patho-mechanistic, diagnostic, and therapeutic standpoint. There are several textbooks, journal articles and symposia (ESH-ISH, IPNA, ESPN) dedicated to this very topic. As such, this review only scrapes the surface of a vast body of literature. Ongoing challenges include the need for more robust trials in pHTN to better identify medications that are pediatric-specific, safe, and effective. Ultimately, given the risk of end organ damage, and persistence of pHTN into adulthood, there is a need for rapid diagnosis, and initiation of treatment to prevent poor outcomes in our pediatric patients.

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INVITED PAPER

Institute Focus
Center for Molecular Cardiology, University of Zurich

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DOI: 10.30824/2204-10

The Center for Molecular Cardiology (CMC), originally known as the "cardiovascular research" laboratory was first founded by Thomas F. Lüscher (www.tomluescher.ch, Figure 1) in the early nineties, at the University & University Hospital of Basel in Switzerland. In those days, he had just returned from an intensive training period in cardiovascular research at the Mayo Clinic and Mayo Foundation, Rochester, Mn., U.S.A., under the supervision of Professor Paul M. Vanhoutte (Figure 1), a life-long colleague and mentor of his.

After a rather short intermediate period at the University of Bern in 1996, the cardiovascular research laboratory moved to the University of Zurich where Thomas F. Lüscher became Director of Cardiology. Here, the laboratory was setup at the Institute of Physiology situated in the University Campus of Irchel. During these years, the laboratory of cardiovascular research became an internationally recognised reference institution in the field of basic and translational cardiovascular research and accordingly, was awarded several prestigious national and international research grants and awards, among them by the Swiss National Research Foundation, the European Union, the Fondation Leducq among others. These were essential to further increase the scientific production and to offer diverse career opportunities to many of its members. Indeed, numerous members of the laboratory went on to becoming professors in prominent Universities across the globe in Japan, India, Europe, the United States and Switzerland.

In 2014, the laboratory of cardiovascular research made an important leap forward by moving out of the Institute of Physiology and becoming an independent research center of the University of Zurich named "Center for Molecular Cardiology" (CMC, www.cmc.uzh.ch). The CMC was established at the newly built University of Zurich's campus in Schlieren (Figure 2) and during this phase, Professor Giovanni G. Camici (Figure 1) took

Figure 1: The leaders of the Center for Molecular Cardiology Giovanni G. Camici (left) and Thomas F. Lüscher (middle) with their mentor and visiting professor, the late Paul M. Vanhoutte, a pioneer in vascular biology.

Figure 2: The Center for Molecular Cardiology at the Schlieren Campus of the University of Zurich with its young PhD students and Postdocs involved in vascular research.

over the directorship of the center with Thomas F. Lüscher as Chairman. Here the CMC quickly established itself as a "state of the art" research facility with modern equipment for basic and translational cardiovascular research.

Currently, the CMC led by Giovanni G. Camici and Thomas F. Lüscher (Figure 1) stands on a research ground of over 600 m2 and counts well over 30 international scientists organized in eleven research groups, with specific focuses spanning across the wide spectrum of key topics from endothelial dysfunction, atherosclerosis, thrombosis, aortic valve disease to dementia and stroke (Figure 3). Since the early nineties, the CMC contributed over 1,000 scientific publications and obtained over 40,000 citations. Owing to the outstanding contribution made by the scientists from all over the world working at the CMC over the last decades, knowledge of the mechanisms underlying cardiovascular disorders has increased considerably and quality of health care in the field has improved.

The central concept underlying the research activities carried out at the Center for Molecular Cardiology (CMC), stems from the notion that blood vessels represent a key link between our organism and the surrounding environment.

Figure 3: The Center for Molecular Cardiology with its MD and PhD students, post docs and visiting scientists (back row) and its research group leaders (front row).

Indeed, dysfunction of blood vessels irrigating all vital organs is a crucial early step in the development of cardiovascular disease (CVD). In line with the above, CVD is usually referred to as a set of conditions where the wall of blood vessels thickens as the result of an accumulation of fatty materials. This condition is known as atherosclerosis and its lethal complications include stroke and heart attack.

Thomas F. Lüscher has been involved in research on vascular structure and function and in particular the endothelium for several decades, with seminal contributions to the field spanning from cellular biology and the regulation of endothelial vasoactive

substances (Figure 4), to the effects of aging, hypertension, lipids and diabetes, up to clinical studies in the forearm using plethysmography and ultrasound technology, as well as coronary angiography confirming the findings of basic science in the human circulation of healthy volunteers and patients with cardiovascular disease. The role of aging and longevity genes was a major topic in the past years, demonstrating that vascular and in particular endothelial aging is the common final pathway of cardiovascular disease. More recently, the interest has shifted to the role of inflammation in patients with plaque rupture and acute coronary syndromes, as well as those with Takotsubo syndrome and acute myocarditis and the role of micro RNAs and MRI in its diagnosis.

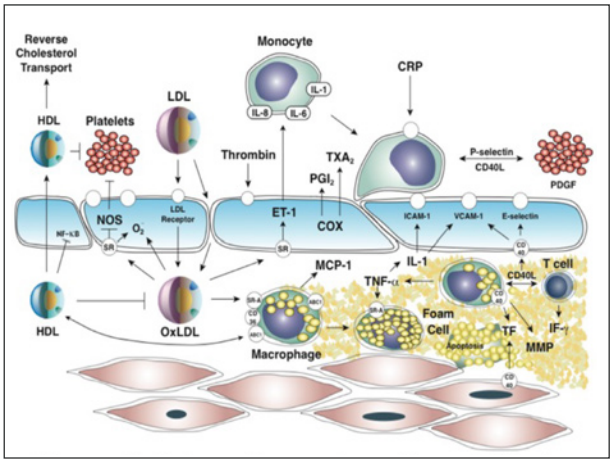

Figure 4: Schematic overview of crutial factors and pathways involved in the pathophysiology of cardiovascular disease.

In line with the research focus of the CMC, its director Giovanni G Camici who is an internationally renowned cardiovascular biologist, focused the early phase of his career on investigating molecular mechanisms underlying arterial thrombosis with a specific focus on tissue factor (TF). Among many findings, he showed that drugs eluted by drug eluting stents (DES) induce TF activity and thus, may be paradoxically involved in stent-thrombosis, a rare complication associated with high mortality (Circ Res. 2006, Eur Heart J. 2010). Here he also investigated novel compounds as potential candidates to be eluted by DES (e.g., DMSO and Pik75) and demonstrated that they do not induce TF and specifically inhibit smooth muscle cell proliferation while sparing that of endothelial cells (Circulation. 2006, Eur Heart J. 2014).

Later in his career, Prof. Camici focused on studying aging and age-dependent cardio and cerebrovascular disease (CVD and CBVD). Here, his team showed that several lifespan regulating genes not only determine life span as such, but also play a crucial role in the pathogenesis of age-dependent diseases such as arterial thrombosis, arterial stiffness, myocardial infarction, and stroke (J Am Coll Cardiol. 2017, Eur Heart J. 2015, Gerontology. 2011). Initially he unexpectedly found that in mice, aging "per se" does not affect arterial thrombosis, the key event in major adverse cardiovascular events (MACE) thus, underscoring the importance of controlling risk factors and their effect on inflammation and ROS (Arterioscler Thromb Vasc Biol., 2010). Next, he showed that the longevity factor JunD delays onset of age-related endothelial dysfunction and mediates myocardial infarction via regulation of ROS (Circulation. 2013, Thromb Haemost. 2020) while also determining stroke outcome through the pro-inflammatory cytokine Interleukin-1β. In this context, he also assessed levels of JunD in stroke patients and found them to be decreased as compared to healthy controls (Stroke, 2019). Finally, Prof Camici, became interested in investigating the role of inflammation in aging, which was recently termed inflamm-aging (Eur Heart J, 2020, J Am Coll Cardiol. 2022). Here, to deepen his understanding about the role of the IL-1 family in aging and age-related CVD, his team assessed the effect of postischemic administration of Interleukin-1b neutralizing antibody and found that it reduces brain damage and neurological deficit in experimental stroke. This effect was mediated by a decreased post-ischemic endothelial activation and MMP-9 expression (Circulation, 2020). Similarly, he also showed that antibody-based inhibition of TNF-a in aged mice, improves the outcome in the latter to levels similar of young animals (Eur J Clin Invest, 2021). Additionally, he demonstrated that SiRNA mediated inhibition of MMP-2 blunts the progression of age-related vascular stiffness via a preserved NO bioavailability and a decreased elastin degradation (Cardiovascular Research, 2021).

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ISH2022 KYOTO:
Abstract submission is now open

HIROSHI ITOH
President, ISH2022 Kyoto scientific meeting
Vice President, ISH

The 29th Scientific Meeting of the International Society of Hypertension (ISH2022) will be held from October 12 to 16, 2022 at the Kyoto International Conference Center with the theme of "The Wisdom for Conquering Hypertension". The local organizing committee is divided into the Finance, Scientific Program, Public Relations, and Award Committees which are intensively preparing for the meeting. We hope that hypertension researchers from around the world will meet in person and share scientific progress in Kyoto. However, as the COVID-19 pandemic continues, we will hold the meeting on-site in a hybrid format that will also provide online contents. With this, we hope to include participants who are not able to join the meeting in person.

Like many other countries, Japan is beginning to ease border restrictions, which started with business travelers in March. We believe that the situation in Japan will have improved enough in October to be able to welcome overseas participants to Japan. October is one of the best months to visit the beautiful city of Kyoto because of the mild climate: little rain, neither too hot, nor too cold.

Local Organizing Commitee


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Vice Chair Hiromi Rakugi


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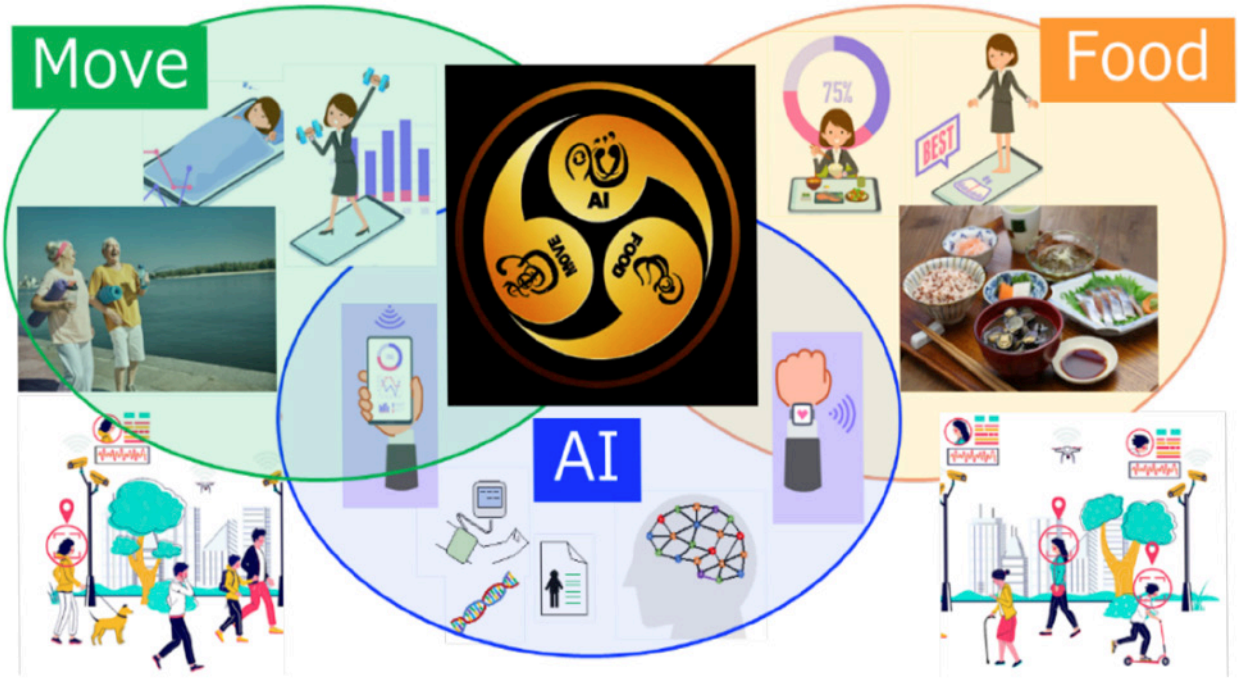

ISH2022 is focusing on three main topics: Food (food and nutrition), Move (exercise and fitness) and AI (artificial intelligence and digital health), that are related to hypertension. There are almost 60 sessions covering 13 themes that are based on the three main topics of ISH2022; Food, Move, and AI. Additionally, the planning of 15-30 minute Mini Presentation and Debate sessions is in progress. Joint sessions based on proposals from ISH Committees and RAG have been secured.

To encourage young people and those from emerging countries to attend the ISH2022 Kyoto meeting, there will be ten types of awards and grants which will be given by ISH2022 Kyoto, the International Society of Hypertension (ISH), or the Asian Pacific Society of Hypertension (APSH).

Lineup of Awards and Grants

Supported by the ISH2022 Kyoto

1) Presenter Travel Grant

The applicants shall give a presentation at the ISH2022 Kyoto and must be younger than 35 years old (born after October 1, 1987). The Travel Grant will be given to a maximum of 250 participants with full coverage of the registration fee, accommodation fee, and travel expenses.

2) Global Talent Complimentary Registration

The Registration grant will be awarded to a maximum of 100 participants from Low- or Lower-Middle-Income Countries (LMICs) as defined according to the World Bank Country Classification. The grant can be requested by presenting authors at all ages.

3) Young Investigator Award

This award will be offered to encourage Young Investigators who are younger than 35 years old (born after October 1, 1987) and recognize excellence in scientific contribution at the ISH Kyoto 2022.

4) Best Oral Presentation Award

5) Best Poster Presentation Award

For Best Oral (4) and Poster (5) presentation, all presenters regardless of age and country will have a chance to win the award. Candidates will be selected from all presenters based on the scores of abstracts. Awardees will be judged at an award session of the meeting with consideration for live performance.

Supported by the ISH

6) Austin Doyle Award

This award was established to recognize the contribution of Austin Doyle, Past President of the ISH and Founding Chairman of the High Blood Pressure Research Council of Australia. It will be awarded to a graduate who is within 5 years of postgraduate qualification. Finalists will be judged to have submitted the best original presentation relevant to clinical medicine at the ISH Biennial Scientific Meeting.

7) ISH New Investigator Oral Presentation Award

This award was established in 2012 to encourage New Investigators and recognize excellence in scientific contribution. It will be awarded at the ISH Biennial Scientific Meetings to a New Investigator judged to have given the best oral presentation among finalists. Finalists will be selected from eligible presenters on the basis of the scores of their abstracts.

Supported by the APSH

8) APSH Young Investigator Award

This award can be requested by presenting authors who are younger than 35 years old (born after October 1, 1987) from the APSH Member Societies include APAC region: Australia, Mainland China, Hong Kong, China, India, Indonesia, Bangladesh, Pakistan, Japan, Korea, Sri Lanka, Malaysia, Nepal, New Zealand, Philippines, Singapore, Taiwan, Province of China and Thailand. Awardees will be decided according to the APSH policy and APSH has full responsibility for this award.

Organized by the ISH New Investigator Committee (NIC)

9) ISH New Investigator Travel Grant

These awards will be given to the finalists of both the Austin Doyle and ISH New Investigator Oral Award.

10) ISH and NIC International Forum Awardees

The NIC will be hosting a pre-meeting New Investigator event, with top-rated abstracts from each of the ISH Regional Advisory Groups selected as awardees.

The details of grants and awards will be explained on the ISH2022 Kyoto official website - **www.ish2022.org**

To be considered for these grants and awards, please submit your abstracts to ISH2022 Kyoto. We extend our warmest welcome to your participation.

We are happy to announce the following important dates for the ISH2022 KYOTO:

Call for Abstracts:
Open now until May 17, 2022

Registration:
Early Bird Registration will start in April, 2022

We look forward to receiving abstracts from many of you.

Counting down to the ISH2022!

We have supporters from all over the world promoting ISH2022, and they will serve as ambassadors in their regions. We will start counting down with video messages from ISH Council members, ambassadors, and supporters from various regions. We will be counting down and letting the excitement build for the ISH2022. You will find the videos on the ISH2022 official website and social media.

Please visit our website, Facebook, Twitter and Instagram to find out the latest information and keep yourself in the loop! We are looking forward to seeing you all in October. In the meantime, please stay healthy.

AFRICAN VOICES

Introduction

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DOI: 10.30824/2204-11

The burden of hypertension remains one of the major public health concerns in Africa [1]. Awareness, treatment and control levels are low in most countries [2-4]. This calls for intensified research on accessible and affordable treatment options, and implementation of context-specific strategies aimed at improving hypertension management. In this issue of Hypertension News, we present for the first time a section on African Voices, featuring research from two African countries covering basic science and public health topics.

The first paper is by Elvine Pami Nguelefack-Mbuyo, from the University of Dschang, Cameroon. In this paper, she focuses on the roles of two medicinal plants used in Cameroonian folk medicine for the treatment of hypertension, *M. africana* and *C. zeylanicum*. The antihypertensive effects of these plants were investigated using male Wistar rats. She presents evidence and potential mechanisms of action by which the plant extracts lower blood pressure. From the observations, she concludes that medicinal plants may offer an alternative therapeutic intervention for hypertension management, though caution should be taken with some plant species.

Continuing with ways to improve hypertension management in Africa, the second paper is by Solomon Nyame, from the Kintampo Health Research Centre, Ghana. He discusses the importance of community-based strategies in the management of hypertension, highlighting the need for adequate training of community health workers (CHWs). This paper shows how task-shifting, particularly the involvement of CHWs and nurses in providing hypertension care, can improve hypertension control. He concludes that multicomponent approaches, involvement of multiple stakeholders and cooperation are essential for the successful implementation of evidence-based task-shifting interventions for management of hypertension in Ghana.

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AFRICAN VOICES

Evidence-based cardiovascular effects of two medicinal plants used in the management of hypertension in Cameroon

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DOI: 10.30824/2204-12

Hypertension is a serious health threat that considerably reduces life expectancy if not handled early and properly. It is particularly severe in black populations as it affects populations at a younger age with an early onset of complications [1]. Increased peripheral resistance is the common feature found in both human and animal hypertension as a result of decreased NO bioavailability and/or increased secretion of vasoconstrictive factors. Despite the panoply of antihypertensive drugs on the market, the management of hypertension is still a great challenge, especially for people in low-and middle-income countries. In these areas, hypertension is poorly controlled due to limited health care facilities, the incapacity of most patients to scrupulously adhere to medical prescriptions because of their indigence, and resistance to pharmacological interventions. Therefore, plant-based medicine remains their sole therapeutic alternative. Screening of the efficacy, safety, and mechanisms of action of such excerpts is of paramount importance and is a prosperous way for the discovery of new and effective drugs.

Mammea africana Sabine (Clusiaceae) and *Crinum zeylanicum* (L.) L. (Amaryllidaceae) are two medicinal plants used in Cameroonian folk medicine for the treatment of hypertension. Nω-Nitro-L-Arginine Methyl Esther (L-NAME) is a nitric oxide synthesis inhibitor which is used experimentally to induce hypertension. The antihypertensive effects of *M. africana* and *C. zeylanicum* were assessed on male Wistar rats chronically administered with L-NAME, and it was observed that the aqueous extract from the stem bark of *M. africana* partially reversed L-NAME-induced hypertension after 2 weeks of oral administration (Fig. 1A), while the leaf methanolic extract of *Crinum zeylanicum* completely reversed it after 3 consecutive weeks (Fig. 1C) [2,3].

Diuretics are a class of antihypertensive drugs recommended as first-line pharmacological therapy in black hypertensive patients [4]. We wanted to know if the antihypertensive effect observed could result from a diuretic effect. The results revealed that *M. africana* had no effect on water, Na+, or K+ excretion, implying that this plant has no diuretic properties [2]. Whether *C. zeylanicum* acts as a diuretic is still to be investigated. However, it was found that *C. zeylanicum* was able to prevent L-NAME-induced functional renal damage [3].

One of the main therapeutic strategies in the management of hypertension is to reduce peripheral resistance. Using rat aorta rings, we demonstrated that *M. africana* successfully relaxed aortic rings precontracted by KCl (60 mM) or noradrenaline (1 µM) with respective EC50 values of 197.60 µg/mL and 0.36 µg/mL [2]. Removal of the endothelium and pretreatment of aortic rings with L-NAME or L-NAME + glybenclamide (an ATP-activated potassium channel blocker) significantly ($p < 0.001$ and $p < 0.05$) inhibited the vasorelaxant effect of *M. africana* (Fig. 1B). This result shows that *M. africana* exhibits both endothelium and

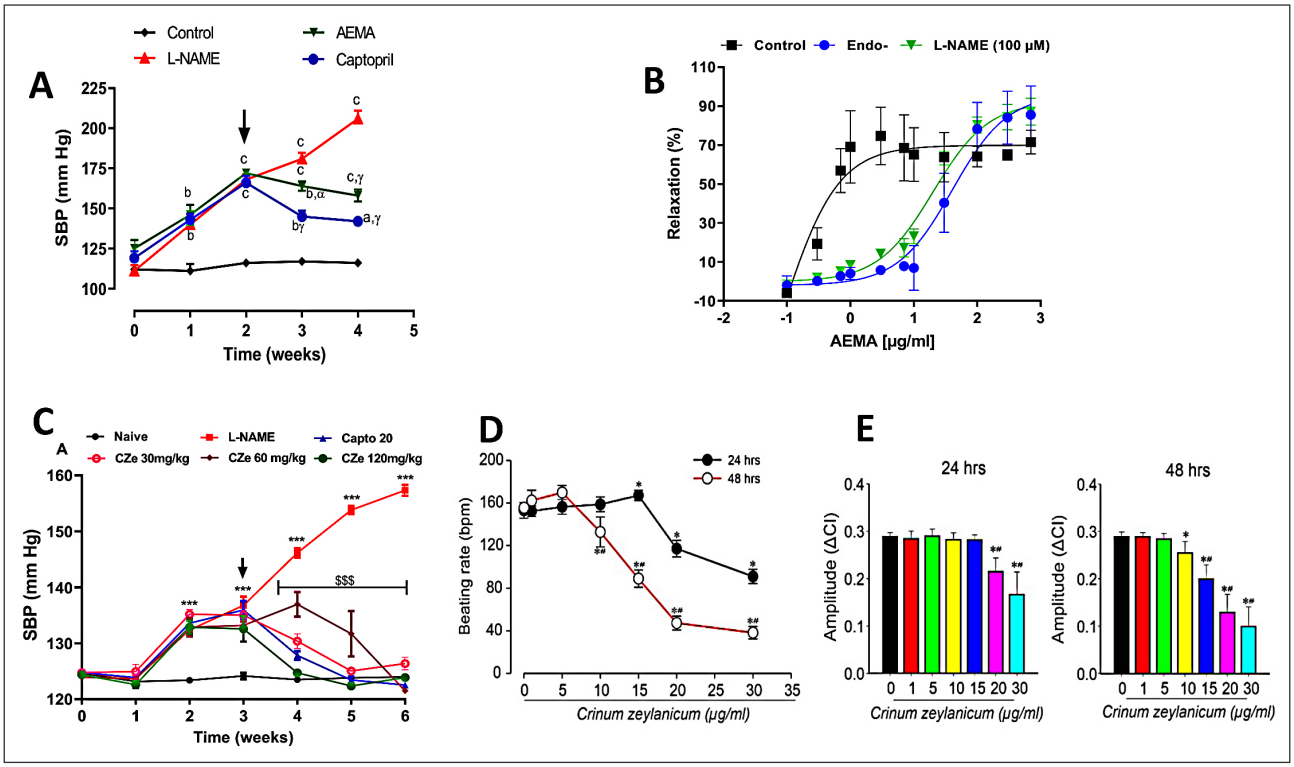

Figure 1: Cardiovascular effects of the aqueous extract from the stem bark of Mammea Africana (EAMA) and leaf methanolic extract of Crinum zeylanicum (CZe). Panel A: Effect of M. africana (200 mg/kg/d) on systolic blood pressure (SBP) of L-NAME hypertensive rats. $^{a}P < 0.05$; $^{b}P < 0.01$; $^{c}P < 0.001$ compared to control. $^{\beta}P < 0.01$; $^{\gamma}P < 0.001$ compared to L-NAME. Panel B : Vasorelaxant effects of M. africana on intact aorta (control), endothelium denuded aorta (endo-), or on intact aorta pretreated with L-NAME. Panel C: Effect of C. zeylanicum against L-NAME-induced hypertension. $^{***}p < 0.001$ compared to the naive group. $^{\$\$\$}p < 0.001$ compared to L-NAME. Panel D: effect of C. zeylanicum on the beating rats of cardiomyocytes. Panel E: effect of C. zeylanicum on the amplitude of beating signal of cardiomyocytes. * and # ($p < 0.05$, Student's t-test) indicate results that show significant difference from control (untreated) and from previous concentrations, respectively. Data represent the mean ± SEM and the arrow indicates the time when the plant extract was administered. Figures are from references 2,3, and 5.

non-endothelium vasorelaxation. The endothelium dependent vasorelaxant effect is achieved through the NO-cGMP-KATP signaling pathway.

Reducing heart rate and cardiac inotropy can lead to a reduction in blood pressure. Exposure of cardiomyocytes to ranged concentrations of *C. zeylanicum* (1, 5, 10, 15, 20, and 30 µg/mL) induced a time-and concentration-dependent decrease in the beating rate of cardiomyocytes. Besides, this plant reduced the beating signal amplitude of cardiomyocytes (Fig. 1E). This result suggests that the plant extract displays a negative chronotropic and inotropic effect that may account for its antihypertensive effect.

The cytotoxic effect of *C. zeylanicum* was examined using undifferentiated mouse-induced pluripotent stem cells (miPSCs) and cardiomyocytes. It was found that *C. zeylanicum* exhibited a detrimental effect on the proliferation and viability of miPSCs, reduced the embryoid body size and down-regulated the gene expression of sarcomeric markers such as Myh6, Myl2, and cTnT. In addition, exposure to high concentrations of *C. zeylanicum* caused a disruption in sarcomere organization, which is consistent with the down-regulation of cardiac sarcomeric genes. In contrast, *C. zeylanicum* did not affect the proliferation nor the viability of cardiomyocytes [5] after 150 hours. These results indicate that *C. zeylanicum* has a cytotoxic effect only on undifferentiated stem cells and not on differentiated cardiomyocytes.

Taken together, these studies provide evidence of the antihypertensive potential of *M. africana* and *C. zeylanicum*. These plants could be an interesting therapeutic alternative in the management of hypertension and a potential source of new antihypertensive drugs. However, the use of *C. zeylanicum* during pregnancy may be harmful to the fetus.

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AFRICAN VOICES

Using concept mapping to prioritize strategies for hypertension care at the Community Health Planning Services Setup in Ghana: evidence from a task strengthening initiative

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To implement community-based strategies, there is the need to understand context. Evaluation of the Ghanaian context revealed that training on hypertension was low among community health workers, thus there was limited knowledge regarding hypertension management at community level [1]. Studies have demonstrated the effectiveness of using evidence-based task strengthening strategy for the high blood pressure control (TASSH) model tailored to the needs of community health nurses to deliver hypertension care [2,3]. In 2015, our current collaborators established in a cluster RCT in 32 district hospitals and community health centers in Ashanti Region, Ghana, that an evidence-based Task-Shifting Strategy for HTN Control (TASSH) based on the WHO Cardiovascular Risk Package and the provision of health insurance coverage (HIC) to patients, delivered by community health nurses (CHNs) led to a 20.4 mmHg mean reduction in systolic blood pressure (SBP) for TASSH + HIC group and 16.8 mmHg mean reduction in SBP for HIC group at 12 months [3].

Our efforts to systematically implement an evidence-based task-strengthening strategy for hypertension control (TASSH) in Ghana necessitated that we engage stakeholders to identify strategies for enhancing intervention uptake and sustainability. This study sought to describe national, regional, and district health stakeholders' perspectives and characterize the array of strategies needed to enhance the uptake of evidence-based TASSH within Ghana's Community-based Health and Planning Services (CHPS) zones. The CHPS initiative is Ghana's flagship strategy for achieving universal health coverage [4,5].

A mixed-method study was conducted among national, regional, and district health stakeholders within GHS, serving patients who utilize CHPS zones to understand what strategy will be useful to implement across the CHPS zones.

About 68% of participants were male with a mean age of 40 years and mean years of experience providing hypertension-related care within GHS of 9 years. As shown in Figure 1, a conceptual map emerged, consisting of 46 strategies needed for implementing evidence-based TASSH, organized into 6 clusters: 1) Referral Systems; 2) Availability of Equipment; 3) Protocols and Guidelines; 4) Capacity Building/Training; 5) Policy Reform, and 6) Technical Support and Supervision. Availability of equipment was rated as the most important strategy (mean 4.80 out of 5) needed to implement evidence-based TASSH, while Capacity Building/ Training was rated as the most feasible strategy (mean 4.20 out of 5) to address. Although important (mean 4.40 out of 5), policy reform was rated as the least important and feasible strategy to address.

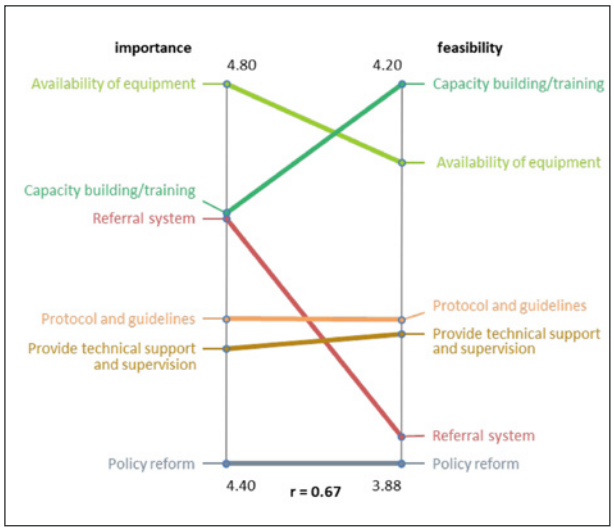

Figure 1: Pattern matching graph for average cluster ratings between importance and feasibility of each cluster.

There are two key outcomes from this formative phase of activity seeking to design strategies to address hypertension at the peripheral health facilities. To begin with, successful implementation of a community-based hypertension control programme requires multicomponent, multi-stakeholder action and cooperation. Outputs from this study signal 6 broad areas for interventions as well as specific requirements for action across the various level of care. Secondly, our work underscores the importance of incorporating the perspectives of healthcare leadership (different stakeholder groups) in highlighting strategies that will be useful for the implementation processes of community-based task-shifting strategies for hypertension management and control. Encouragingly, some of the identified strategies mimic the Ministry of Health strategies set out to prevent, control and manage non-communicable diseases (NCDs) including hypertension. For example, the policy document as part of its strategic areas of implementation specifies health system strengthening; particularly in terms of capacity building and provision of logistics as a priority for preventing and managing NCDs at community level. These findings demonstrate strategies that can help inform future interventions on the adoption and sustainability of evidence-based TASSH within Ghana's CHPS zones. Also, national, regional and district health stakeholders can support healthcare workers by facilitating access to equipment and strategies for enhancing capacity and training by implementing evidence-based task-shifting hypertension interventions in Ghana.

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EARLY CAREER RESEARCHERS

Introduction

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I am delighted that in this edition we have four fantastic and diverse articles from the ISH new investigator community, clearly demonstrating the breadth of research being driven by early career researchers. The articles cover both clinical and basic science perspectives, and feature research investigating the role of the kidneys in blood pressure management and trying to understand mechanisms that could be exploited in the future of blood pressure control. There is also discussion of the implications of poorly managed blood pressure and the impact that this can have, from the cellular level to organ damage.

Cesar A. Romero is an Assistant Professor at Emory University, USA, where he has research interests in hypertension and renal physiology. He offers an interesting summary of his research into the renal function reserve (RFR). Despite its commonplace in clinical practice, the mechanisms controlling RFR and the role it plays in homeostasis are unclear. Cesar's article addresses mechanistic insights into RFR and offers a fresh perspective on the potential role that RFR plays in renal vasodilation, sodium homeostasis and resultant blood pressure regulation. His work could lead to novel clinical approaches.

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Sticking with the kidneys, Ana Paula de Oliveira Leite, a Postdoctoral Researcher at Tulane University, USA, continues to address mechanisms for controlling blood pressure and hypertension; specifically discussing the roles of angiotensin II in proximal tubules. Ana summarises findings from her research using proximal tubule-specific mouse models, in which she has tested the roles of intratubular angiotensin II and its AT1 (AT1a) receptors and the key role in sodium reabsorption.

Next, Emily Waigi, a PhD Student at University of South Carolina, USA, highlights the relationship between high blood pressure and cognitive function and vascular Alzheimer's disease. She presents consideration of a therapeutic approach for managing the disease progression involving the advanced glycation receptor and the role in soluble protein oligomer-related disease progression.

Finally, Joanne O'Donnell, a Research Fellow at Monash University in Australia, reminds us of the importance of cell death in hypertension, and details the consequences of different cell death pathways. She pays particular attention to apoptosis and describes a related phenomenon that results in the onset or accelerated hypertension.

EARLY CAREER RESEARCHERS

Cell death in hypertension

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There are many mechanisms known to contribute to hypertension. A growing body of evidence supports that the immune system, acting via inflammation, may influence vascular remodelling and tissue damage during hypertension [1]. Cell death has also been implicated as a factor impacting vascular remodelling. Apoptosis, the classical form of cell death, is the most explored form of cell death in hypertension [2]. However, there are many different types of cell death, each with different biological consequences that could impact hypertension via different mechanisms.

Apoptosis was first observed in the 1970s, and the molecular pathways involved have since been very well characterized [3]. Apoptosis occurs constantly as a mechanism of cell maintenance and clearance, and it is therefore essential that these dying and dead cells remain undetected by the immune system. Apoptosis can be triggered by extrinsic ligands (such as FasL or TNFα) or from within the cell (intrinsic; triggered by events such as DNA damage or hypoxia). Both extrinsic and intrinsic apoptosis culminate by the effector proteins Bak and Bax forming pores in the mitochondria, resulting in cell death. Caspases-3 and 7, which are activated by Bak and Bax, were once considered the effectors of apoptosis, however their roles were recently revised. Caspases-3 and 7 were found to degrade the mitochondrial contents released during apoptosis to prevent their recognition by the immune system [4]. Therefore, when caspases-3 and 7 are inhibited during apoptosis, the mitochondrial contents are released causing the dying cells to produce and secrete type-I interferons. The biological consequences of such an event are not yet known. Apoptosis has been heavily studied in hypertension and has been implicated to have a role in arterial stiffening and vascular remodelling in hypertension [2], as well as roles in pulmonary arterial hypertension and preeclampsia [5,6]. However, this new role for the apoptosis caspases, caspases-3 and 7, as gatekeepers of apoptosis-induced inflammation, highlights the possibility that apoptosis may play more than one role in this disease. There is the possibility that if apoptosis goes awry, such as when caspases-3 and 7 are ineffective or inhibited, the immune system is activated and contributes to the onset or acceleration of hypertension. This potential new mechanism may allow for a different perspective of the role of apoptosis in hypertension – from a consequence to a contributor. Exploring this possibility may allow for targeted approaches to treat the patients who are impacted by this phenomenon.

Unlike apoptosis, whose primary role is to induce cell death without alerting the immune system, other cell death pathways such as necroptosis and pyroptosis, promote inflammation. Necroptosis is triggered by external ligands including TNFα, FasL and some toll-like receptors (TLRs). It occurs when certain apoptosis machinery (such as caspase-8 and the Inhibitors of Apoptosis (IAPs)) are inhibited. [3] Whilst the necroptosis pathway utilises some components of the apoptosis pathway, it also uses unique components such as RIPK3 and MLKL. During necroptosis, the cellular membranes are permeabilized by MLKL and the cellular contents are released. These are recognized as Danger Associated Molecular Patterns (DAMPs) by neighbouring cells through TLRs to elicit inflammation. Necroptosis is often

considered a back-up form of cell death. For example, necroptosis occurs during some viral infections when the virus blocks apoptosis to ensure the survival of virus-containing cells. However, other biologically-relevant roles for necroptosis are emerging, and one could speculate that necroptosis may contribute to the inflammation observed in hypertension.

Pyroptosis is another form of proinflammatory cell death, resulting in inflammation primarily through IL-1β. Pyroptosis requires multiple cellular signals to occur: firstly TLR signalling leads to NF-κB activation and inflammasome activation [3]. The inflammasomes are then involved in caspase-1 activation and cell death, often resulting in IL-1βand/or IL-18 release. The pyroptosis pathway is a strong inducer of inflammation, and IL-1β is often associated with hypertension. While much work has been completed highlighting roles for IL-1β in different murine models of hypertension,[7] its role is still unclear.

Hypertension is a multi-faceted disease, affecting different organs and cell-types, and different factors may contribute to the disease of patients. Whilst apoptosis-associated inflammation, necroptosis and pyroptosis may play a significant role in promoting hypertension in some patients, the magnitude of these effects will likely differ between individuals. Identifying which subsets of patients may be impacted by these and the specific mechanisms involved will be key to improving their blood pressure control.

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EARLY CAREER RESEARCHERS

Angiotensin II and NHE3 in the proximal tubules of the kidney are two key players in blood pressure control and hypertension

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Hypertension is steadily developing into an epidemic and crisis in public health worldwide. More than 25% of the world's adult population and 46% of the United States' adults develop hypertension and require antihypertensive treatments. Although hypertension is a very common medical condition involving genetics, hormonal disorders, increased neural sympathetic activities, high salt diets, and lifestyles, the underlying mechanisms remain incompletely understood. Moreover, although different classes of antihypertensive drugs are currently available to treat hypertension, only about 50% of hypertensive patients have their blood pressure (BP) adequately controlled. Some patients develop resistant hypertension, even treated with more than 3 different antihypertensive drugs, and advanced to hypertension target tissue damages, including stroke, cardiovascular diseases, and kidney failure1. Therefore, it remains imperative to further study and uncover new and additional mechanisms and therapeutic targets of hypertension.

Recently, we have focused our research efforts on studying the roles of angiotensin II (AngII) and its AT_1 (AT_{1a}) receptors, which is the most important effector for the endocrine, paracrine, and intracrine renin-angiotensin system (RAS) in the proximal tubules of the kidney [2]. The proximal tubule has a higher concentration of angiotensin II (AngII) than the circulation or other tissues, and plays a crucial role in regulating body salt and fluid balance, basal BP regulation, and the development of hypertension.

To study the roles of intratubular Ang II and AT_1 (AT_{1a}) receptors in the proximal tubules, our laboratory has used the gold standard proximal tubule-specific iL1-Sglt2-Cre/LoxP approach to generate mutant mouse models with deletion of AT_1 (AT_{1a}) receptors or the Na+/H+ exchanger3 (NHE3) selectively in the proximal tubules. Our proximal tubule-specific mutant mouse models are somewhat different from those of Gurley et al [3], who used the PEPCK-Cre/Agtr1a-flox approach, while Li et al [4] used the KAP2-iCre/Agtr1a flox approach. The differences may be due to the specificity of the promoters used to overexpress the Cre enzyme, with PEPCK and KAP2 reportedly being expressed not only in the proximal tubule but also in other segments of the nephron or other organs. In comparison, our lab used the mouse model that expresses the Cre only in Sglt2-expressing proximal tubules [2].

Using the iL1-SGLT2-Cre/Agtr1a flox approach [2], we demonstrated that under basal conditions, systolic, diastolic, and mean BP was significantly lower in males and females, proximal tubule-specific knockout of Agtr1a-/- mice, PT-Agtr1a-/- mice [5]. The lower BP phenotype was associated with significant inhibition of proximal tubule Na+ reabsorption, increased glomerular filtration rate, and augmented pressure-natriuresis response. Moreover, AngII-induced hypertension was significantly attenuated by about 50% in male and female PT-Agtr1a-/- mice without revealing any significant sex differences [2,5,6].

In further studies, we determined the downstream target of AngII in the proximal tubules of the kidney. We focused on the major Na+/H+ exchanger 3 (NHE3) as it is responsible for reabsorbing >50% of filtered Na+ and fluid, and AngII is well-recognized to act to increase the expression and activity of NHE3 in the proximal tubules. We therefore used the same iL-Sglt2-Cre/Nhe3-flox approach to generate a mutant mouse model with deletion of NHE3 selectively in the proximal tubules, PT-Nhe3$^{-/-}$. Interestingly, the basal BP and proximal tubule reabsorptive phenotypes were quite similar between PT-Agtr1a-/- mice and PT-Nhe3$^{-/-}$ mice. Indeed, basal systolic, diastolic, and mean arterial BP was about ~12 ± 3 mmHg lower in adult male and female PT-Nhe3$^{-/-}$ mice, with significant natriuretic and/or augmented pressure-natriuresis response [7]. Deletion of NHE3 selectively in the proximal tubules of the kidney also significantly attenuated AngII-induced hypertension by 50% [8]. These studies provided strong evidence for an important role of intratubular AT_{1a} receptor-mediated effects of AngII and NHE3 in the proximal tubules in basal BP control and the development of AngII-dependent hypertension, without any significant sex differences [5,6,7,8].

In summary, our recent studies using new proximal tubule-specific mutant mouse models have demonstrated that the AngII/AT_{1a}/NHE3 signaling pathway in the proximal tubules of the kidney, plays a critical role in the regulation of basal BP as well as the development of hypertension. This AngII/AT_{1a}/NHE3 signaling pathway may be a new therapeutic target to prevent and treat hypertension associated with activation of the intratubular renin-angiotensin system and significant Na+ and fluid retention. In our next steps, we will study the roles of proximal tubule mitochondrial NAD-dependent deacetylase sirtuin-3 in the development of AngII-dependent hypertension and kidney injury. Sirtuin3 is closely involved in energy metabolism, oxidative stress responses, and mitochondrial homeostasis during hypertension and kidney diseases.

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EARLY CAREER RESEARCHERS

Scientific communication: The link between hypertension and the accumulation of soluble protein oligomers

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The brain is an intricate organ, composed of a dense network of capillary beds that form primary sites for oxygen and nutrient exchange. In the brain, microcirculation is regulated by resistance arteries and arterioles whose density and location varies based on energy requirements to maintain neuronal homeostasis. With this in mind, any pathological, physiological, or environmental interference that promotes changes in the cerebral circulation, leads to cerebrovascular dysfunction and affects cognitive function as is observed in aging [1]. In addition to aging, chronic arterial hypertension is one of the most important cardiovascular risk factors that poses a major challenge on the onset and progression of cognitive decline and dementia in mid and late life, and particularly in Alzheimer's disease (AD), the most common cause of dementia in the elderly [2]. AD pathology is augmented by the accumulation of small, neurotoxic, and soluble Aβ oligomers (SPOs) in the brain. Although the blood brain barrier (BBB) maintains the right balance of the intracerebral pool of SPOs concentration to that in the bloodstream, there are specialized receptors that shuttle SPOs into and out of the brain [3]. Furthermore, the deposition of these toxic SPOs in the brain leads to complex cerebromicrovascular impairment and microhemorrhages by inflicting structural damage in the arterioles.

In spite of this, chronic arterial hypertension also plays a critical role in exerting synergistic deleterious effects by disrupting the structural integrity and function of the aging cerebral microcirculation, which in turn contributes to the exacerbation of cognitive decline and progression of AD. For instance, in hypertension, angiotensin II is implicated in the progression of atherosclerosis, and interestingly, intracranial atherosclerosis has also been linked to AD [4]. It is postulated that the hypoperfusion caused by arterial stenosis may lead to reduced SPOs clearance and their increased production, which subsequently promotes atherosclerosis by inducing inflammation, endothelial dysfunction, and oxidative stress [4]. Further, Angiotensin II promotes the production of SPOs and aggravates their effects on vascular dysfunction. Although a myriad of harmful effects of chronic arterial hypertension on AD pathology exist, those that stand out in this context include promoting BBB disruption, leading to microglia activation hence amyloid plaque formation and neurotoxicity, promoting neurovascular uncoupling and increasing capillary atrophy leading to formation of ghost vessels and impaired cerebral blood flow, and contributing to microvascular damage by promoting microvascular rarefaction, and causing small vessel disease and white matter hyperintensities [5,4].

Despite the substantial evidence that hypertension leads to cognitive decline, the underlying cellular and molecular mechanisms remain to be fully elucidated. However, a study by Daniela et al.,[2] showed that in transverse aortic coarctation (TAC) mice, cerebral amyloid deposition was observed as early as four weeks. However, ablation of the receptor for advanced glycation end products (RAGE) in these mice protected them against hypertension-induced AD pathology and cognitive impairment. It prevented the transport of SPOs into the central nervous system, plaque formation and SPOs deposition around blood vessels. If translated in humans, this could be a promising targeted therapeutic strategy to control vascular-related AD. In addition, clinical trials have shown that hypertension is a treatable risk factor for cognitive decline and AD. Experimental studies have identified some antihypertensive therapies like ACE inhibitors, angiotensin receptor blockers and diuretics that play a role in delaying the progression of cognitive decline[6]. However, there are many shared risk factors for hypertension and AD that need to be considered like comorbidities, sex differences, ethnic backgrounds, genetic and lifestyle factors, and metabolic traits. With this in mind, perhaps venturing into personalized treatment of hypertension and AD can be a promising and attainable approach to safeguard vascular and brain health[7].

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EARLY CAREER RESEARCHERS

Reserve vasodilation in the kidney: more than a backup for glomerular loss?

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It is well known that the kidney has the capacity to increase its blood flow after a protein meal or an amino-acid vein infusion. Classically known as renal functional reserve (RFR), this vasodilation was first described almost 80 years ago [1]. However, the mechanisms behind it and its homeostatic significance are still not fully understood. Clinicians have been using RFR as a way to predict residual renal function in kidney donors, or as a predictor of CKD in patients with AKI or other renal disorders for several decades now.

RFR seems a rapid way to increase excretion of excessive salt, glutamate, and other waste products after a significant protein meal. After a protein/amino-acid load, the glomerular filtration rate (GFR) increases by ~20%. According to some, despite glomerulotubular balance, a 10% increase in GFR would increase salt excretion by 22% [2]. Therefore, a 20% increase in renal vasodilation induced by proteins may increase sodium excretion by ~40%, which could be very significant in a hypertensive patient. Absence of this mechanism, especially in a high-salt diet, may induce a positive sodium balance and consequent blood-pressure increase to reach sodium homeostasis, based on the pressure-natriuresis curve described by Guyton. In this context, RFR may have an important role in sodium homeostasis and blood-pressure regulation.

Mechanisms behind RFR

Research has shown that intratubular infusion of amino acids is enough to induce vasodilation and that the N-methyl-D-aspartate (NMDA) receptors are related to this phenomenon [3], dismissing previous hypotheses related to endocrine (glucagon/insulin) or the central nervous system as mediators. Preliminary work in our lab has shown that epithelial NMDA-receptor activation in the connecting tubule, is sufficient to induce activation of a vasodilator response in the afferent arteriole [4]. This is dependent on an autoregulatory mechanism—connecting tubuloglomerular feedback (CNTGF). CNTGF is a vasodilator mechanism that increases sodium excretion when excess salt reaches the distal nephron [5]. We have found that NMDA-receptor activation by amino acids sensitizes CNTGF, increasing afferent-arteriole vasodilation. All these data suggest that the vasodilator response induced by CNTGF is the common mechanism behind the vasodilation induced by salt and protein/amino-acid load [4].

According to the pressure-natriuresis curve, when sodium is not adequately excreted (positive balance) blood pressure increases, which induces forced natriuresis (pressure natriuresis) to reach sodium balance. Following this principle, we can speculate that an absence or alteration of CNTGF

may at least intermittently induce increased blood-pressure to force sodium excretion and eventually cause hypertension.

In animal models of hypertension, such as spontaneous hypertensive rats, CNTGF is almost absent [5]. Our preliminary results demonstrate that CNTGF/NMDA inhibition increases blood pressure4. In humans, RFR absence is more prevalent in hypertensive patients and their offspring [6,7] and has been linked to a nondipper pattern, a phenotype that may explain the longer time needed to excrete a nocturnal sodium load [8].

These data suggest that RFR is not only a backup for glomerular number (capillary surface) decrease in a compensatory way, but also a quick salt homeostasis regulator that prevents blood-pressure fluctuations. Further work is needed to confirm the role of RFR in blood-pressure regulation and hypertension.

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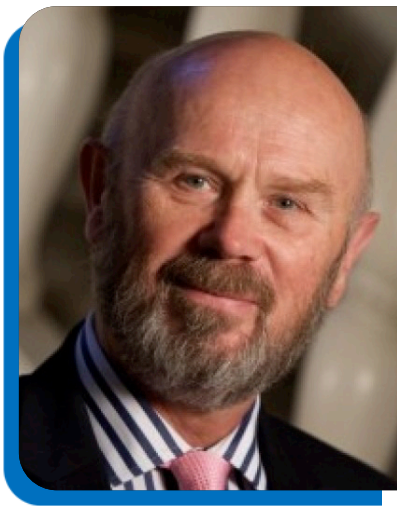
MMM REPORT

May Measurement Month gears up to achieve its biggest year yet!



NEIL POULTER

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Preparations for May Measurement Month (MMM), the annual global screening campaign that helps people to get their blood pressure (BP) checked, are in full swing ready to launch on 1st May 2022.

With a new refreshed brand look and feel, to coincide with its new independent charity status, and an exciting new campaign to attract participants, MMM is looking ahead to its fifth year of screenings and collaborations.

Over 650,000 people participated in 2021, the results of which will be published in May 2022 to coincide with the launch of this year's screenings. This year, MMM is also working with the European Heart Journal on a study from smaller countries who have collectively secured over 2000 participants across their MMM campaigns.

80 countries have already signed up for MMM 2022. With COVID-19 restrictions having been eased in most territories, the global MMM team is looking forward to being able to reach many more people this year. Home screening options will also be carried forward into 2022, building awareness of the accessibility of home monitoring as well as increasing the participant base.

MMM is also collaborating with AF-SCREEN this year to begin atrial fibrillation screenings in a selected number of countries. As such, the participant questionnaire now includes questions on whether atrial fibrillation had been detected, diagnosed or treated in the past. The broader questionnaire has also been extended to include information on how participants usually access BP monitoring,

and how that is funded. It also includes questions on whether they have ever experienced heart failure or an irregular heartbeat, and if they've had COVID-19, how long their symptoms persisted.

Prof. Neil Poulter, CI of the MMM Campaign said: "Despite COVID-19, the MMM campaign in 2021 has generated several novel and exciting results, shortly to be published. Meanwhile, it is with increased enthusiasm that MMM 2022 is being set up around the world to expand not only screening activities, but also the associated research platform and collaborations".

Raised BP remains the number one cause of preventable death worldwide. Therefore, it is vital that MMM continues to increase public understanding of the importance of BP measurement, and helps to save lives that need not be lost.

For more information about how you can support, visit **www.maymeasure.org**

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DDD REPORT

Dylan's Distribution Data

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Despite a release close to the holiday season and vacation periods for many of our members, the December release of Hypertension News remained highly successful. It has been downloaded more than 5000 times in the 2 months for which we have data and remains on track to achieve strong readership levels. Notably, there was significant attention on our "Learning the Ropes" feature on RAAS measurement as well as contributions from our new investigators. Interestingly, the October "learning the ropes" feature on aspects of sex and gender in hypertension continues to receive significant attention as well with over 100 downloads in the month of January alone. We thank our readers for their continued support of Hypertension News.

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MEANWHILE IN 'HYPERTENSION MEWS'...

Restrictions are gone in Sweden, so it is time to tour the world!

Photos by Li Winther from the Lindholm family.

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