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IN THIS ISSUE

FROM THE EDITOR

ISH Now with Full Speed Ahead!

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Editor

Dear member,

It is again a pleasure for me and my team to present a new issue (Opus 65) of Hypertension News – the electronic newsletter of ISH, this time with three main foci (or focuses, if you like): (i) the 2021 joint meeting of the ESH and the ISH together with the British and Irish Hypertension Society (BIHS), (ii) the 2021 ISH awardees, and (iii) a "Learning the Ropes" section on "Sleep disorders and cardiovascular disease".

The joint meeting on 11–14 April 2021 was a success, despite the fact that it took place exclusively on air due to the Covid-19 pandemic. Almost 5,400 delegates from 128 countries participated with 748 presentations. We owe Anna Dominiczak, the president of the meeting, and her co-workers many thanks for their impressive organisational achievement and for having made three societies work together in a constructive way under very difficult conditions! As pointed out by Thomas Unger in his introduction on page ***3***, the meeting covered just about all thinkable aspects of hypertension. In this issue, we have devoted the "Hot Off the Press" section to the meeting and we have invited a group of eight early-career scientists to report from the meeting. This initiative gave us six short papers covering their recollections of the meeting, which we hope you will enjoy (pages ***4–15***).

The ISH awards represent how our Society celebrates the significant discoveries in hypertension research and the success of its members. In this issue, the Chairman of the Award Committee, Tomasz J Guzik, presents the 2021 awardees on page ***16***, followed by a summary of Ernesto Schiffrin's Franz Volhard Award lecture and two Commentaries honouring him.

Insufficient and inadequate sleep quality is a growing health problem affecting one in three adults, well known to many of us, especially this time of year when we are short of time when completing our grant applications... In general, sleep disorders are associated with obesity, the metabolic syndrome, and with problems related to mental health. Furthermore, sleep disorders and hypertension share several risk factors, although their causal relations remain unclear. Poor sleep quality is associated with impaired quality of life, and an increased risk of coronary artery disease, stroke, and all-cause mortality. Lack of sleep also increases the risk of car accidents and fatal injuries. On pages ***27–35***, you will find three short reviews on sleep disorders covering cardiovascular risk pathophysiology, and the management of obstructive sleep apnea in patients with cardiovascular co-morbidities.

"The Wisdom for Conquering Hypertension" is the theme of the 2022 ISH meeting in Kyoto on 12–16 October, a meeting I am sure many of us are eager to attend. So, save the date and join us! On page ***36***, Hiroshi Itho, the president of the 2022 meeting, gives us more information about the meeting and its innovative programme.

Finally, you will find three reports in this Newsletter: (i) from the Executive Committee, (ii) from the Chair of the ISH Research and Education Committee, and (iii) from the MMM project. Moreover, there is also an interesting "Institute Focus" from the Baker Heart and Diabetes Institute in Melbourne (pages ***39-42***), and two "New Blood" papers (pages ***44–47***).

As always, I would like to close by thanking my Deputy Editor Dylan Burger and our lovely editorial team for their dedicated *pro-bono* work. "Brain storming" over Zoom is far from easy and we are looking forward to better times after the pandemic. Thanks also to Araceli Segreto for her administrative work.

Have a good read!

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Update from the Executive Committee

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Springtime is always a busy time for the ISH with May Measurement Month and World Hypertension Day activities, but it is doubly so when there is overlap with the Scientific Meeting as well.

The 2021 Joint Scientific Meeting of the International Society of Hypertension, European Society of Hypertension, and British and Irish Hypertension Society was attended by more than 5000 registrants and featured outstanding symposia across a range of topics. Several of the most notable presentations are addressed in the **"Hot off"** contributions later in this issue.

The scientific meeting also gives our society the opportunity to recognize the outstanding contributions of our members to the hypertension community and the 2021 slate of awardees, highlighted on pages 16-17 by Awards Committee Chair **Tomasz Guzik**, was highly meritous. Notably, Hypertension News Editor-in-Chief **Lars H. Lindholm** received the ISH Distinguished Fellow Award. Congratulations Lars!

ISH Web Site Redesign Launched

Coinciding with the scientific meeting was the launch of our new web site. This was the culmination of months of work from the web site task force. Early feedback has been overwhelmingly positive and we hope that it will provide a simpler and cleaner interface that better serves our members. Be sure to check out the "President's Blog" which will provide regular updates to membership straight from ISH President **Maciej Tomaszewski**.

Kyoto 2022 Scientific Meeting

With the 2021 Scientific Meeting in the rearview mirror, attention now turns to our next Scientific Meeting (To be held in Kyoto, Japan: 12-16 October 2022). An outstanding program is planned which organizing committee chair (and ISH Vice-President) **Hiroshi Itoh** discusses on page 36. ISH members can help promote the meeting in their networks using meeting's Promotional Toolkit which contains graphics, videos, and simple messaging. This quality of the promotional material is simply outstanding.

May Measurement Month

May represented the launch of ISH's May Measurement Month campaign. With a fresh look and an extended timeline for measurement to accommodate regional health restrictions, the 2021 aims to be our biggest yet. Be sure to catch the report from Neil Poulter on page 49.

World Hypertension Day

World Hypertension Day is a key initiative for raising public awareness about Hypertension. This year, the ISH lent its voice through a new video "8 Simple Rules for Living with Hypertension". The video has been viewed more than 1800 times to date and is a valuable resource for individuals individuals with raised blood pressure across the globe. In addition, a press release highlighted key programs and initiatives targeted to reduce the global burden of hypertension. These activities were supported through heavy social media engagement by membership. Thank you to everyone who helped spread the message that hypertension is a key global health threat.

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HOT OFF THE 2021 ESH/ISH MEETING

Introduction

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The Joint Meeting of the European Hypertension Society (ESH) and ISH together with the British and Irish Hypertension Society (BIHS) in Glasgow on April 11-14, 2021, was an overwhelming success and this despite the fact that it had to be performed exclusively on air due to the Corona Pandemic. Just a few figures to illustrate this: There were almost 5.400 registrations from 128 countries with almost 4.000 connections to the platform. In 118 sessions, 748 live speeches were held, and there were 127 hours of live transmission. An impressive organizational achievement demonstrating that a successful global hypertension congress can be held even under such adverse conditions. Great thanks to the congress president, Professor Anna Dominiczak, and to all those helping to realize this endeavor.

Content wise, the congress covered virtually all thinkable aspects of hypertension. For reasons of actuality with all the fresh impressions and memories, we at HTN News thought that the traditional section "Hot of the Press" in the journal should be devoted this time to some "hot" aspects presented at the Glasgow meeting. We invited some younger scientists to report briefly on their personal recollections of some topics which they thought were of high actuality and of general interest. This initiative granted us six short communication papers which are presented in the following.

Francisco Rios opens the roundelay with an article covering several presentations on immunity and hypertension, demonstrating the complexity of the immune system as a department not only of defense, but also of "internal welfare" and illustrating the tremendous impact of the various immune-regulatory aspects on cardiovascular disease including hypertension.

Thematically not far away, **Nicolas F. Renna** confronts us with a new medico-social-economic entity, called "Syndemic", which has been elicited by the Corona Virus 2 pandemic. He covers questions about a possible role of hypertension as a risk factor for the Covid-19 disease demonstrating, that (in agreement with statements of several hypertension societies) rather old age and comorbidities but not hypertension itself are the culprit. Likewise, antihypertensives such as ACE inhibitors and ARBs, which, on the basis of some mechanistic considerations, have also been accused to be risk factors for the Covid-19 disease, can be dismissed as risk factors as shown in recent clinical trials like BRACE CORONA or REPLACE COVID.

Hypertension in Pregnancy is the next topic, selected with respect to basics by **Nayara Azinheira Nobrega da Cruz** and **Mariane Bertagnolli**, and, relating to clinical aspects, by **Bianca Davidson** and **Erika Jones.** Basic issues discussed were the importance of impaired placental angiogenesis in preeclampsia, the role of mesenchymal stem cells and various aspects of biomarkers such as sFit-1. The clinical paper covers in detail the so-called CALIBER study from the UK characterizing hypertension during pregnancy as an independent cardiovascular risk factor and stressing the fact that women with hypertension during pregnancy ought to be monitored closely after delivery as recommended by the recent ISH Hypertension Guidelines.

Finally the salt issue. Still a matter of controversy after so many years of research, discussions and official recommendations. Basic aspects are dealt with by **Cesar Romero** introducing us to a new regulatory entity called "natriuretic-ureotelic regulation". Another topic he discusses is the role of chloride vs other anions as partners of sodium. In experiments on genetically hypertensive rats, F. Luft and al (Clin Sci 1988;74(6):577-85) have already demonstrated many years ago that drinking a sodium chloride- but not sodium bicarbonate solution can increase blood pressure. New basic data discussed at the Glasgow meeting may shed some light on underlying mechanisms. In addition, exciting new results point to an association of high salt intake and cognitive impairment involving the Tau protein which has long been recognized to be involved in Alzheimer's disease. The last paper of this section by **Neusa Jessen** deals in a very balanced way with several clinical aspects of the salt story discussed at the Glasgow meeting. New data by Franz Messerli and colleagues pointing to a lack of an association between salt intake and premature death are discussed in the light of the large body of evidence accusing a high salt diet to be an important risk factor for hypertension and cardiovascular disease. Recent data suggest that some biomarkers may be able to better distinguish between salt-sensitive and salt-resistant individuals, and there was even a recommendation that salt food "fortification" with nitrate-rich vegetable extracts may be a better solution to the problem than reducing salt in the diet.

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Immunity and Inflammation in Hypertension – A Long Way To Go

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The immune system is often defined as a complex network to protect the body against the invasion of microorganisms. In fact, what we most know about the immune response is derived from studies observing the immune response over a challenge mediated by pathogens or non-self-molecules. This traditional concept is not too far from the truth; however, it is a rather simplistic way to define such a complex system. According to Prof Cohen "The immune system has earned a reputation, justly, for its role as protector of the body against foreign invaders. However, the immune system is not only a department of defence, it also functions as a department of internal welfare"[1]. Following this line of thinking, we should dare to consider that the main function of the immune system is to control the body homeostasis and, in only extreme cases this system faces an infection. This complex network is achieved by a group of circulating and tissue resident cells that patrol vessels and tissues to scavenge cells debris or DAMPS (Danger Associated Molecular Patterns) to avoid unnecessary activation. In stress conditions, the immune system acts to eliminate the stressor agent and ultimately to return the system to the homeostatic state[2]. However, as the old proverb says: "the road to hell is paved with good intentions"; Situations where stressor agents are constantly produced will lead to uncontrolled immune/inflammatory activation, and a response that was primarily induced to eliminate the stressor agent, now can potentially lead to chronic inflammatory diseases and tissue damage.

Given the impact of the immune system in cardiovascular diseases and that patients with high blood pressure exhibit increased plasma inflammatory mediators and immune cells infiltration in the cardiovascular and renal tissues, it comes as no surprise that biomedical research is focused on applying these observations to hypertension research, and this has been under intense investigation in the past 15 years[3,4,5].

At Hypertension 2021, we could witness the presentation of very elegant and high-quality research discussing the importance of the inflammatory and immune response in the pathogenesis of hypertension. Studies were very diverse, as observed in the workshop "Immunity and inflammation in hypertension" chaired by Prof Guzik and Prof Schiffrin. Prof Lembo presented exciting data about how the activation of the CNS (Central Nervous System) can contribute to hypertension development by stimulating spleens to produce and activate the PIGF (Placenta growth factor) - Nrp-1 (neuropilin-1) axis, which induce the activation/maturation of dendritic cells and consequently activate CD8+ T lymphocytes to induce target organ damage. Important innate immunity mechanisms in hypertension development were also well discussed by Prof Drummond, who focused his presentation on inflammasome activation. According to his data, important adaptors of the inflammasome pathway, such as NLRP-3 (NOD-, LRR- and pyrin domain-containing protein 3), ASC (adaptor molecule apoptosis-associated speck-like protein containing a CARD) and IL-18 (interleukin-18), contribute to the major inflammatory response and organ damage in experimental models of hypertension. These two presentations highlight the importance of the two arms of the immune response in the hypertension research: the adaptive immunity, (mediated by lymphocytes) and innate immunity (mediated by monocytes/macrophages, dendritic cells). Of importance, vascular cells also participate actively in the innate immune response, by inflammasome activation and production of inflammatory mediators. An interesting clinical study presented by Dr Crouch in the in the Award Session of the New Investigator Committee showed a negative correlation of urinary potassium concentration and inflammatory mediators observed in hypertensive patients with low salt consumption. Suggesting that potassium may have an anti-inflammatory effect but only in white population and under low salt intake. This clinical study demonstrates how complex are the mechanisms of the inflammation/immune activation and suggests that more causative and temporal studies are necessary to draw a clear understand of the immune system in the pathogenesis of hypertension.

The importance of the inflammation in the CNS was also addressed by Dr Shinohara in the 19th International SHR Symposium, who showed that macrophages depletion in SHRSP (Spontaneously Hypertensive Stroke Prone Rat) reduces the expression of cyclooxygenase-2 in the brain, neuron activity, and blood pressure. Interestingly, in his data, macrophage depletion did not change the plasma levels of IL-1β, thus suggesting the participation of other cells than macrophages in the inflammatory response observed in the SHRSP. Of note, IL-1β is a product of the inflammasome activation, which is also observed in vascular cells. Whether these effects have impact on cognition still needs elucidation. But it certainly opens doors for new research in aging and vascular dementia.

Hypertension is a multifactorial disease, that involves different pressor mediators, oxidative stress, genetic predisposition, and lifestyle. The immune system is educated according to the challenges received over the years, and if individuals with predisposition to hypertension have more pressor mediators and oxidative stress, the low-grade inflammation will be present during life. Therefore, it is expected that the inflammation and immune response observed in these different scenarios are different, at least qualitatively. Current research about the immune system in hypertension models shows the importance of activation of subpopulations of macrophages, dendritic cells presenting modified endogenous molecules, activation of CD4+ and CD8+ T lymphocytes, including subpopulations of CD4+ T cells, such as regulatory T, and more recently gamma-delta T cells in several hypertensive models[5,4]. The activation of granulocytes has also been observed, since NET (Neutrophil Extracellular Traps) formation by activated neutrophils are important mediators of vascular injury[6,7]. Therefore, it is important to determine whether these different arms of the inflammation and immune activation system play an important role according to time and model of hypertension development and organ damage. All these studies are very exciting and bring new paradigms and concepts to the research in hypertension.

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COVID19 and Hypertension: Are We Facing a Syndemic?

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The term "syndemic" refers to synergistic health problems that affect the health of a population in its social and economic context. Coronavirus disease 2019 (COVID-19), indiced severe, acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), has become a global pandemic that is responsible for millions of deaths worldwide. High blood pressure is an important risk factor for cardiovascular disease and causes 7.5 million deaths per year (12.8% of all deaths annually). The global burden of disease study suggests that systolic blood pressure is accountable for the highest proportion of premature death, with 212 million years lost[1].

Early benign case series did not indicate an excess of hypertension in people admitted to hospital with COVID-19[2]. Some later data showed a higher case fatality in patients with hypertension although not related for age[3]. New evidence from medical records in England, suggests that hypertension is not associated with hospital mortality from COVID -19, hazard ratio (HR) 0.95, (95% CI 0.89-1.01). In sensitivity analyses, self-diagnosed hypertension was associated with a slightly higher risk (HR 1.07, 95% CI 1.00-1.15)[4].

Although some studies have concluded that hypertension could be a clinical predictor of severity[5], the mechanism by which hypertension leads to an increased risk of COVID-19 is undoubtedly complex and may well be related to the underlying comorbidity. The prognosis for people with hypertension is markedly worse when COVID-19 infection is complicated by myocardial injury and in the presence of cardiovascular disease[6]. Target organ damage and cardiovascular events associated with poor blood pressure control increase with age. Therefore, it seems plausible that they may explain the observed associations between age, hypertension, and severity of COVID-19 infection[7].

Are antihypertensive medications a serious risk of COVID-19 disease?

From the beginning of the pandemic, many patients wondered whether they should

discontinue these treatments, and inevitably some will have. The concern was fueled by the recognition that coronavirus 2 enters cells by binding to a component of the renin-angiotensin system, particularly ACE2. High-quality, large-scale, case-controlled, observational cohort studies reported that chronic treatment with ACEIs or ARBs was not associated with an increased risk of becoming infected with SARS-CoV-2, or of being hospitalized or dying from COVID-19[8]. However, it is well known that observational studies have important limitations.

The advent of randomized clinical trials (RCT) was very important. Cohen J et al.[9] report the first results of an RCT (the REPLACE COVID trial) examining the impact of continuing or withdrawing chronic ACEI or ARB treatment in 152 hospitalized COVID-19 patients at 20 international centers. This study showed that the results for patients previously treated with ACEIs or ARBs and hospitalized for COVID-19 were similar, regardless of whether treatment with renin-angiotensin system inhibitors was continued or suspended during their hospital admission. Further reassurance comes from the fact that the conclusions of this REPLACE COVID trial are broadly consistent with the results of an RCT previously presented in the BRACE CORONA study. All hypertensive patients can be confident that continuing their current medications is safe and desirable[10].

Hypertension and COVID-19: What controversies remain?

The relationship between blood pressure level and SARS-CoV-2 susceptibility or outcome in COVID-19 patients has not been sufficiently investigated, and the potential blood pressure target value in these patients is still unknown.

The influence of blood pressure control on COVID-19:

Determining the relationship between BP and COVID-19 outcome is not an easy task due to its high variability and dependence on comorbidities. Another point is chronic hypertension versus new-onset hypertension in COVID-19: One of the main challenges in evaluating the relationship between hypertension and COVID-19 is the lack of data on the proportion of patients with hypertension before the hospitalization. The last controversy, is hypertension after COVID vaccination, although there is a single report of 9 cases of patients who presented post-vaccination hypertension, to date there is no reason for concern or for suspension of vaccination in hypertensive patients[11].

This syndemic needs an immediate health response. Many countries will be facing the worst economic-health crisis in the last 3 centuries. We must seize this opportunity to learn and find solutions. Adequate knowledge and control of blood pressure, an outstanding debt, hand in hand with equal access to health, will surely help improve the health crisis.

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Hypertension and Pregnancy: Basic Aspects

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Hypertensive disorders affect up to 10% of pregnancies worldwide, being a major health problem for women and their infants and causing increased maternal and infant morbidity and mortality.[1, 2] The alarming global number of deaths caused by preeclampsia or due to cardiovascular morbidities following pregnancy with preeclampsia is a result of the current lack of knowledge about its causes and the limited therapies to handle maternal blood pressure (BP) during such insults or in the postpartum period. Improving the identification and follow up of high-risk pregnancies can also significantly contribute to prevent severe outcomes associated with the development of preeclampsia.

The International Hypertension Society (ISH) recognizes these gaps and encourages a wide-ranging discussion of key topics for advancing this field. In the 2021 edition of the ISH and European Society of Hypertension (ESH) joint meeting, international leaders in the field of hypertension in pregnancy presented their most recent contributions in discovering new mechanisms involved in preeclampsia-related placental dysfunction and in the study of emerging biomarkers of preeclampsia.

The early onset of preeclampsia is mainly driven by abnormal trophoblast invasion and impaired arterial remodeling, leading to significant oxidative stress and exacerbated immune responses in the placenta.[3-5] Dr. McClements has studied therapies using mesenchymal stem cells (MSC) originated from placentas of pregnancies with preeclampsia.[6, 7] The potential of this cell therapy is justified by the fact that placentas are rich in MSC. These cells release extracellular vesicles (EV) containing mRNA, miRNAs and proteins that can alter different aspects of placentation,

including immunomodulation, angiogenesis and redox status.[7, 8] At this meeting, Dr. McClements described that MSCs of pregnancy with preeclampsia have impaired angiogenesis capacity compared to MSCs from control pregnancies. They also identified two target miRNAs, mir-183-5p and mir-203a-3p, both related to impaired placental angiogenesis. Their results are supported by others also describing the anti-angiogenic effect of miR-183-5p by suppressing trophoblast invasion and migration through a negative regulation of metalloproteinase (MMP) 9 during preeclampsia.[9] Likewise, miR-203a-3p has also been shown to inhibit angiogenesis by reducing VEGF availability and HIF-1α activity, as previously described in diabetic retinopathy.[10] These findings also open new avenues for testing the use of MSC-derived EVs as new therapeutic targets in preeclampsia.

Soluble vascular endothelial growth factor (VEGF) receptor-1 (sFlt-1), a well-known biomarker of preeclampsia, was also discussed at this meeting, particularly in relation to coagulation disorders in pregnancy. Although sFlt-1 is a soluble protein, it contains a binding site for heparin sulfate, a component of the extracellular matrix, which reduces the bioavailability and signaling of circulating and tissue-present VEGF.[11] During the ISH/ESH meeting, the study presented by Dr. Kurvanov described an increase in the concentration of s-Flt1 as well as thrombocytes aggregation, longer prothrombin time and higher fibrinogen concentration, in pregnancy with preeclampsia compared to controls, suggesting an association between this soluble factor and subclinical disseminated intravascular coagulation and decreased fibrinolytic potential in preeclampsia.

In another presentation, Dr. Moore suggested otherwise that a treatment with a powerful anticoagulant heparin can stimulate the release of s-Flt1 from trophoblasts and placental explants in a dose dependent manner.[12] S-Flt1 was increased in the supernatant of cells treated with heparin while the non-soluble Flt-1 was reduced. In vitro findings were further confirmed by *in vivo* experiments on pregnant rats given a continuous infusion of unfractionated heparin. Treated pregnant rats exhibited increased BP and reduced VEGF bioavailability compared to vehicle-treated animals, indicating that heparin treatment is able to release s-Flt1 and that this soluble factor may contribute to increase maternal BP.

The findings presented during the 2021 ISH/ESH meeting point to important advances in the discovery of potential biomarkers as well as new therapies in preeclampsia. However, as highlighted by Dr. Kotsis in his presentation, the newly discovered biomarkers must still go through a long process of preclinical testing using previous predictive models, in order to consider them effective in predicting preeclampsia, particularly in the early stages of gestation.

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Clinical Aspects of Hypertension in Pregnancy: Complications of Pregnancy as Predictors of Cardiovascular Risk

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Hypertension during pregnancy is an independent risk factor for cardiovascular events. This has clearly been documented in multiple studies[1-3]. Recently, numerous studies have contributed to evidence on the degree of added risk these women experience.

The CALIBER study[4] fills this gap and has reported an excess of cardiovascular complications in women at a younger age. The median age that the complications occur is less than forty years, which is below the age that traditional annual screening for hypertension and other cardiovascular risk factors is initiated. Therefore, to initiate screening at forty is too late. The data from this study were discussed by Lucy Chappell, at the ESH-ISH 2021 Joint Meeting in April 2021. As recommended in the ISH Global Hypertension Guidance[5], it is essential that these women are monitored from a much earlier age.

It has been observed that clinical trials are not a real life setting and the subjects enrolled in these trials are highly selected, excluding the vast majority of patients. The CALIBER data are real world data from a large cohort, with almost 1.9 million pregnancies assessed. Furthermore, the CALIBER population appears to be a realistic representation of pregnant women as demonstrated by similarities to previous populations, with similar risk factors.

A cardiovascular event occurred in 18 624 women within a median follow-up of 9.25 years. The majority (65%) of which occurred in women

under 40 years. The proportion of cardiovascular events in the pre-eclamptic patients was 2.77%, as opposed to half that (1.4%) in non-pre-eclamptic patients. Pre-eclampsia gave a hazards ratio of 1.69 (CI 1.57-1.81) for a first cardiovascular incident and pre-eclampsia resulting in a preterm delivery resulted, in a much higher hazards ratio of 5.63 (5.1-6.26). While the risk was lower in those who had hypertension (but not pre-eclampsia), there remained a strong association with hypertension during pregnancy and the development of chronic hypertension and early cardiovascular events.

Adjusting for persistent hypertension after pre-eclampsia attenuated the risk for cardiovascular events but did not negate it. This means that, independent of the subsequent development of chronic hypertension, pre-eclampsia was associated with an increased risk of cardiovascular events.

Following up on women who have had an episode of hypertension in a pregnancy could improve the lives for not only themselves and their families but the communities in which they live, as they are a young population who contribute to the work force and future generations. Women with hypertension during their pregnancies have a high risk of death at an early age from cardiovascular events. Furthermore, morbidity associated with the maternal hypertensive disorders amounts to 24.2/100 000 DALYs[6].

After a follow up of less than 10 years, women with hypertension during their pregnancy presented with first cardiovascular events, 65% of whom were under 40 years of age. Hypertension during their pregnancy was an independent risk factor, over and above recognised cardiovascular risk factors. Pre-eclampsia, in particular those with a preterm delivery, increases the risk for a cardiovascular event.

These women should be screened for hypertension after any form of hypertension during pregnancy and followed up closely to mitigate the risk for future cardiovascular disease. This policy is promoted in the ISH guidelines and needs to be adopted internationally. Hypertension during pregnancy needs to be recognised as an independent risk factor for cardiovascular events and needs to be included in future risk stratification scores.

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Salt and Hypertension

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A high-salt intake is a pernicious habit, especially for people with hypertension, heart, and kidney diseases. For many years, epidemiological studies have shown negative outcomes of high salt intake. More recently, scientific evidence is elucidating the pathophysiological mechanisms associated with this habit. Some of these concepts have been presented at the 2021 ESH–ISH Joint Meeting. The classical view that high-salt diet increases fluid intake, inducing extracellular space expansion, to later eliminate excess sodium and water has been challenged recently. A new mechanism, named natriuretic-ureotelic regulation, has been proposed, where the kidneys optimize the renal concentration mechanisms to excrete more sodium and less free water, preventing sodium-associated osmotic diuresis[1]. This requires the generation of a massive production of osmolytes (urea) from a catabolic-proteolytic state (mainly in skeletal muscle). The subsequent muscle and liver urea generation ultimately increases plasma urea concentration, expands extracellular space, potentiates the kidney medullary concentration mechanism with less free water excretion, and favors metabolic water generation. Additionally, the muscle's catabolic state is accompanied by a significant energy expenditure of the osmolyte generation. This process has been demonstrated by administering high-salt diets to rodents and a few healthy humans but not in larger population studies. However, during the Glasgow meeting, Giacomo Rossito (Glasgow, UK) presented data exploring the natriuretic-ureotelic regulation hypothesis in a retrospective cohort analysis of essential hypertensive patients. Using metabolomic analysis, he showed that patients with high salt intakes (> 5 gr/day) presented higher urinary sodium excretion with less free water excretion, higher urea levels, and more end products of protein catabolism or the urea cycle than those with low salt intakes. These results support the smaller original studies, proposing a new concept in salt and water homeostasis. It is unclear how much the natriuretic-ureotelic mechanism affects hypertension genesis and hypertensive organ damage. However, this study obligates physicians and researchers to consider this mechanism in the study of salt and water homeostasis. Additionally, the Rossito's research has confirmed that patients on high-salt diets exhibit higher rates of glomerular filtration and glomerular hyperfiltration. Previous studies in animals have shown that a high salt intake could lead to glomerular hyperfiltration. These results may arise from a positive autoregulatory feedback mechanism on the connecting tubule, mediated by the epithelial sodium channel (ENaC), called connecting tubule-glomerular feedback, that may explain these findings[2].

During the ESH–ISH Meeting, chloride has also been discussed, as problems related to a high-salt diet involve not only sodium but also chloride. Thus, previous studies have shown that replacing chloride with other anions, such as citrate, evokes neither the same extracellular space expansion nor the blood pressure changes associated with high-salt diets. Additionally, specific chloride transports, such as the bicarbonate–chloride exchanger Pendrin, are key in sodium reabsorption and blood pressure regulation. In this regard, Dr. Michael Stowasser (Brisbane, Australia) explored the expression of kidney transports through urinary extracellular vesicles (uEVs) analysis coupled with liquid chromatography tandem mass spectrometry. Their results showed for the first time in humans the increased abundance of Pendrin in patients with primary aldosteronism compared with low-renin essential hypertensive patients. However, no changes in the sodium–chloride channel (NCC) or aquaporin 2 (Aqp 2) were observed. Unfortunately, no ENaC subunits were detected in the uEVs. These findings also confirm previous studies in rodents, where

Pendrin abundance was observed in aldosterone-infused animals. Additionally, chloride's role was highlighted during an oral kidney session at the conference. Dr. Puyol (Buenos Aires, Argentina) presented the effect of the anion chloride on the induction of oxidative stress on a high-salt diet. This revealed the chloride anion was associated with more glutathione peroxidase activity than the sodium cation in the kidney cortex, favoring a prooxidative state.

Outside of the kidney, Dr. Constantino Iadecola (NY, USA) revealed the mechanisms associated with high salt intake and cognitive impairment. In animal studies, high salt, independently of blood pressure levels, induces endothelial dysfunction in the brain. This process is mediated by Il-17 generated in TH17 lymphocytes at the intestine, highlighting the role of the gut–brain axis. Thus, Il-17 in cerebral arteries decreases endothelial nitric oxide synthase (eNOS), decreasing cerebral blood flow but also increasing accumulation of the phosphorylated Tau protein. These elegant studies showed that the salt-induced Tau protein, induced by high salt, and not decreased blood flow, induced the cognitive impartment. Thus, future clinical trials should translate these findings to prevent cognitive impairment in patients.

Overall, the ESH–ISH Meeting has contributed new concepts and translational evidence on the role of a high-salt diet in hypertension and hypertension-mediated organ damage.

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Salt and Hypertension – Clinical Aspects

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The clinical importance of high blood pressure has been recognized for almost two centuries now[1] but its etiopathogenesis is still a matter of continuing intense research. Although effective treatment is available, control of blood pressure (BP) remains a global challenge and hypertension continues to be the main risk factor for morbidity and mortality around the world[2]. The simplified and concise 2020 International Society of Hypertension Global Hypertension Practice Guidelines will harmonize the management for worldwide healthcare providers[3] while the search for more effective ways of preventing and controlling hypertension continues. It is well stablished that the onset of hypertension may be prevented, or at least delayed, by healthy lifestyle choices[4], which is also the first line of antihypertensive treatment.

Salt intake is considered the most important dietary risk factor for hypertension, and, in fact, a large body of evidence supports the strong association between high Na intake and raised BP[5]. Nevertheless, the susceptibility to the BP-raising effects of salt, called salt sensitivity of BP (SSBP), is a physiological quantitative trait that varies between individuals and the mechanisms that mediate the pressor effects of salt are not fully explained[6]. Furthermore, although the associations between high sodium intake and increased BP as well as between hypertension and cardiovascular (CV) morbidity and mortality are well stablished and undisputed, the question of impact of dietary salt reduction in hard CV outcomes (stroke, myocardial infarction or death) remains unanswered, with several studies presenting opposed results[5]. As

such, it remains a matter of continued attention and discussion. Recently, Professor Franz Messerli and colleagues analysed the relationship between sodium intake and life expectancy and survival[7]. Global health estimates of 181 countries were used to analyse the relationship between country-specific average sodium consumption with healthy life expectancy (at birth and at 60 years), death due to non-communicable diseases and all-cause mortality for the year of 2010. The authors found a positive correlation between sodium intake and healthy life expectancy (including when the analysis was restricted to 46 high income countries) but not for death due to non-communicable diseases. An inverse correlation with all-cause mortality was also observed. Though such findings suggest that high sodium intake does not shorten life span or increase premature death, a large number of potential confounders and several other limitations of the study, as well acknowledged by the authors, preclude its use as a guide for nutritional interventions. Unfortunately, conducting an adequate trial to evaluate the lifespan effect of high dietary salt in humans, which could raise definitive evidence on hard CV outcomes and mortality, is very difficult, requiring a large sample of the population, followed for a long time, with strict control of several variables. Based in current evidence, the World Health Organization recommends a daily salt intake <5 g[8]. In fact, SSBP is considered an important public health problem, independently of BP[6, 9] but the lack of clear mechanisms and biomarkers for this trait prevents the identification of individuals at higher risk, who could benefit from early intervention.

Promising results were presented at the joint meeting ESH-ISH 2021. Chen C. and colleagues, based on bioinformatics approaches, identified several potential biomarkers of SSBP, though pending confirmation in humans[10]. On the other hand, an emerging new scientific view states that the problem in SSBP is not the level of salt in the diet but an abnormal BP response to salt. Opposing to previous knowledge that there is an impairment in renal function, recent studies have shown that the changes in sodium balance and cardiac output in salt-sensitive (SS) individuals are no different from those in salt-resistant normotensives. Instead, there is an abnormal vascular resistance response to high salt intake ("vasodysfunction theory"). In effect, Professor Kurtz and colleagues argued that instead of reducing salt in food, what should be corrected is the mechanism causing such abnormal response. Taking into account previous evidence showing that in SS individuals there is an abnormal reduction of nitric oxide activity that impairs vascular relaxation leading to hypertension, their studies showed that the administration of small amounts of nitrates (in the form of sodium nitrate or beetroot juice) and nitrite (in the form of sodium nitrite) protects against salt induced increases of BP, in Dalh salt sensitive rats and Spontaneously Hypertensive Stroke Prone (SHRSP) rats, respectively[11]. Tiny amounts of nitrate protected against large amounts of salt, with nitrates appearing to be 100 times more potent than potassium for protecting against salt-induced hypertension. Accordingly, salty food fortification with small amounts of nitrate-rich vegetable extracts was proposed as a strategy to prevent salt-induced hypertension without changing the diet.

Though this may be a way forward to protect against the effects of high salt intake in BP, what was not evaluated in these studies and should be considered when designing public health interventions and in future research, is that increasing BP is not the only deleterious health effect of high salt intake. It has been shown that salt can damage target organs by several other pathways, being independently associated to the risk of numerous other important public health problems[12]. In practice, the ideal strategy would require the identification of the SS individuals and the main mechanisms of salt-induced hypertension in their specific settings (accounting for the influence of ethnicity and culture in the BP response to salt), to inform tailored interventions. Presently, no simple, accurate and widely accepted method of estimating dietary sodium intake and no clear guidance as to how to manage the patient are available. Pending further evidence, for the health professional in front of the patient, the use of questionnaires to assess individual salt intake, such as the one presented by Bortolotto L. et al (sodium consumption questionnaire with photographic manual), is an accessible alternative to the 24-hour urinary collection and can guide individualized dietary advice. It could be adapted and validated for specific contexts.

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2021 ISH AWARDS

Celebrating the Success of International Society of Hypertension Community

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International Society of Hypertension Awards are how our Society celebrates the significant discoveries in hypertension research and the successes of its members. A wide range of ISH Awards has been developed to reflect a diverse range of activities and broad, inclusive membership of the Society. Detailed information about the Awards is available at the ISH website: https://ish-world.com/ish-awards-prizes/. When reading lists of previous awardees, one can look back at the long history of the milestones of hypertension research.

The Franz Volhard Award and Lectureship is one of the oldest and most prestigious awards in hypertension research worldwide. It was first awarded in 1972 to commemorate the centenary of the birth of Franz Volhard. This year we celebrate the groundbreaking achievements of Professor Ernesto Schiffrin for his contributions to the understanding of oxidative and inflammatory mechanisms of hypertension.

ISH Robert Tigerstedt Lifetime Achievement Award was created in 1974 to honour work that changed our understanding of aetiology, epidemiology, pathology, or treatment of high blood pressure. This year's recipient, Jan Staessen has been developing our views on epidemiology, pathogenesis, and treatment of hypertension over the years. Other awards include distinguished fellow awards, the recognition of outstanding contributions to research in the field of hypertension, and contributions to ISH as a Society.

Our awardees, Professor Cheol - Ho Kim, Professor Lars H Lindholm, Professor Franz Messerli, and Professor Gianfranco Parati all serve as role models for future generations of hypertension researchers.

The ISH Developing World Award emphasises the global outreach of ISH. Research in understanding and improving cardiovascular outcomes in hypertensive patients in the developing world has become imperative now, increasing prevalence and morbidity from hypertension in these regions. This year we celebrate contributions from Professor Basden Onwubere from the University of Nigeria.

The International Society of Hypertension has always been at the forefront of recognising the importance of women in science and understanding the increasing burden of hypertension in women. This is reflected by the ISH Honour for Senior Women Researchers, through which we celebrate contributions of outstanding hypertension scientists Prof. Catherine Llorens-Cortes, and Professor Empar Lurbe. ISH Award of Excellence for Research in Cardiovascular Health and Disease in Women established in 2018 and awarded this year to Professor Louise Pilote while ISH Mid-Career Award for Women Researchers is awarded to Professor Francine Marques. The latter reflects ISH's focus on women in medicine and an outlook to celebrate the achievement of early and mid-career researchers in hypertension, as their work will decide on the future shape of not only our Society but also the field of hypertension.

A number of awards are devoted to celebrating the successes of our early career researchers linked to the biennial Congress of the Society. This year's recipients include Ashleigh Craig receiving Austin Doyle Award, and Stephanie Cicalese for the ISH New Investigator Oral Presentation Award. Finally, the ISH Paul Korner Award supported by the High

Blood Pressure Research Foundation of Australia has been awarded to Professor Frans Leenen to celebrate his contributions to research on the interface of neuroscience and hypertension.

This year, during the ESH/ISH Hypertension Digital Experience on Air conference awards were awarded based on nominations from 2020 and 2021. The postponement of the conference led to the delay in ISH Awards process. The Awards Committee received several exceptional nominations.; the scientific and society impact of all nominees was truly outstanding, and so were their contributions to our Society. The Awards Committee faced an arduous task. I want to thank Awards Committee Members and assessment panels during the Congress for the time and effort they all devoted to analysing all nominations and in-depth discussions.

I want to use this opportunity to ask all of our members to consider nominating their colleagues for a wide range of ISH Awards. The International Society of Hypertension will award again in Kyoto, 2022. Your nominations ensure that these awards are genuinely reflecting the collegial spirit of our Society. The Committee will be soon advertising the call for Kyoto 2022 awards. The future position of ISH Awards as the most celebrated and distinguished awards in the hypertension community depends on your nominations.

Prof Tom Guzik; ISH Awards Committee Chair, on behalf of the Committee

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2021 ISH AWARDEES

ISH Franz Volhard Award and Lectureship for Outstanding Research

Ernesto Schiffrin

ISH Robert Tigerstedt Lifetime Achievement Award

Jan A. H. Staessen

ISH Paul Korner Award, supported by the High Blood Pressure Research Foundation of Australia

Frans Leenen

ISH Developing World Award

Basden Onwubere

ISH Distinguished Fellow Award

Kim Cheol-Ho
Lars H. Lindholm
Franz Messerli
Gianfranco Parati

ISH Awards of Excellence for Research in Cardiovascular Health and Disease in Women

Louise Pilote

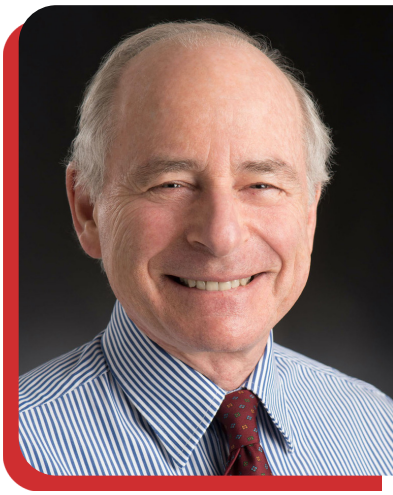
ISH Honour for Senior Women Researchers

Catherine Llorens-Cortes
Empar Lurbe

ISH Mid-Career Award for Women Researchers

Francine Marques

2021 Franz Volhard Award, International Society of Hypertension. From RAAS, Endothelin, Immunity and Genes to Vascular Remodeling in Hypertension



ERNESTO L. SCHIFFRIN

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I felt extremely happy and honored being selected as the 2021 Volhard Award of the International Society of Hypertension, and as well grateful to the ISH Awards Committee. Dr. Franz Volhard (1872-1950) was one of the most prominent nephrologists and academic physicians in Germany in the first half of the 20th Century, having among other achievements classified renal disease in "nephrosis", "nephritis", and renal vascular disease (renovascular hypertension). He also realized that "malignant pale hypertension was accompanied by vessel wall destruction, vasospasm, ischemia, and eventually irreversible organ (renal) damage. ..."[1] distinguishing it from "benign" hypertension. Accordingly, his ideas fed directly into my lecture for the Franz Volhard Award at the virtual 2021 ESH/ISH OnAir joint meeting, on Vascular remodeling in hypertension, the major goal of my research. But I felt also happy to receive this honor named in memory of Franz Volhard, whose courage as Chair of Medicine in Frankfurt University led to his being expelled by the Nazis in 1938 because of his vocal opposition to the regime, only to be reinstated in 1945 after the fall of Naziism.

For many years we have studied with my team of Masters' students, PhD students, postdocs and associate or visiting scientists and collaborators the structure and function of small arteries, and the molecular mechanisms involved in vascular remodeling in hypertension, diabetes and chronic kidney disease. This was following years working on angiotensin and other peptide receptors, on the regulation of aldosterone secretion and on the role of natriuretic peptides. I owe a huge debt of gratitude to all these individuals, many of whom are today highly successful scientists in their own right, as well as to my mentor Jacques Genest Sr.

In the early nineties we were performing studies on small artery structure and function in rodent models of hypertension and hypertensive humans, in the latter dissecting small arteries from biopsies of gluteal subcutaneous tissue.[2,3] Over the next few years we investigated whether antihypertensive treatment reversed remodeling, endothelial dysfunction and stiffness of small arteries.[4-11] More or less in parallel we had become interested in the role of endothelin-1 on blood vessels, and demonstrated its contribution to BP elevation and hypertrophic vascular remodeling and endothelial dysfunction in experimental models of hypertension.[12-15] We also showed using *in situ* hybridization that the expression of preproendothelin-1 was significantly enhanced in the endothelium of small arteries of humans with stage 2 hypertension.[16] To follow-up on these studies and investigate further the pathophysiology of the endothelin system, we generated a transgenic mouse that overexpressed human endothelin-1 targeted to the endothelium by the Tie 2 promoter. This model had only slightly raised blood pressure but presented severe hypertrophic remodeling and endothelial dysfunction in small arteries,[17] associated with vascular inflammation.[18] We then showed that when crossed with ApoE$^{-/-}$ mice and fed a high fat diet these transgenic mice accelerated the progression of atherosclerosis[19]

and enhanced the development of abdominal aortic aneurysms beyond what is found in ApoE$^{-/-}$ mice.[20] We then demonstrated that these effects are mediated via increased oxidative stress through Nox-1 when type 1 diabetes induced by streptozotocin is imposed on the transgenic mice expressing human endothelin-1 already crossed with ApoE$^{-/-}$ mice.[21] In the meantime we had generated an inducible transgenic mouse expressing human endothelin-1 in endothelium using CRE-Lox technology and a modified estrogen receptor triggered by tamoxifen. This mouse exhibited significant BP elevation[22] and over time, vascular remodeling and stiffening, inflammation and endothelial dysfunction and as well reduced renal blood flow.[23] On the basis of our studies of endothelin cited above and especially the evidence in humans with stage 2 hypertension,[16] we have advocated for long that endothelin antagonists be used for treatment of resistant hypertension. Indeed, there is now a trial in resistant hypertension, the PRECISION trial in which we are participating, using Aprocitentan, an ETA and ETB receptor antagonist. We have also shown that endothelin system is activated in chronic kidney disease, and that it can play a role in some of the adverse effects of erythropoietin given to treat the anemia of these patients.[24]

In the late '90s and early 2000s we had gathered evidence in experimental models of hypertension that oxidative stress and inflammation were involved in mechanisms of vascular remodeling and BP elevation. We used a mouse with a mutation in *mCSF* (also known as *CFS1*) which have functionally defective macrophages and infused them with angiotensin II and noted that in the mice homozygous for the mutation BP did not rise, and vascular remodeling and endothelial dysfunction did not develop, suggesting that innate immunity and macrophages played a role in hypertension.[25] Other models of hypertension imposed on these mice yielded similar results in our hands in succeeding publications. We then looked at another immune cell, the T regulatory lymphocyte (Treg), and showed that introgression chromosome 2 from Brown Norway rats that are normotensive, into a hypertensive Dahl salt sensitive rat genetic background was associated with reduced vascular inflammation and enhanced Treg activity in these consomic rats.[26] By performing adoptive transfer of Treg in contrast to T effector lymphocytes into angiotensin II-[27] or aldosterone-infused mice[28] we were able to demonstrate that Treg were anti-hypertensive and anti-inflammatory, and reduced vascular remodeling and endothelial dysfunction, whereas T effector lymphocytes had opposite actions, a ying yang relationship between these two subtypes of immune cells. We then examined the effect of angiotensin II on mice lacking Treg (Scurfy mice, with a mutation in Foxp3, transcription factor responsible for maturation of precursor lymphocytes into Treg). We found that prohypertensive, remodeling, and stiffening vascular actions, endothelial dysfunction, inflammation and oxidative stress were exaggerated in Scurfy mice without Treg, compared to wild type mice.[29] We became interested in gamma/delta T cells, a subtype of innate-like unconventional lymphocyte bearing gamma/delta T cell receptors instead of the much more abundant alpha/beta T cells. Mice lacking gamma/delta T cells responded poorly to angiotensin II with respect to BP elevation, vascular remodeling, endothelial dysfunction. Furthermore, in these mice, activation of alpha/beta T lymphocytes was also impaired. In a cohort of coronary artery disease patients, BP modeled with the expression in whole blood of the constant regions I and II of the gamma subunit of the T cell receptor correlated significantly with the actual BP of the patients, similarly to age and sex, and was additive to the latter, suggesting that gamma/delta T cells played a role in the homeostasis of BP in humans and could become a target for treatment.[30]

More recently we have looked at the participation of microRNAs (miRs) in the modulation of vascular remodeling. We demonstrated that angiotensin II caused microRNA dysregulation with changes in mRNA expression in injured mesenteric arteries. miR-431-5p inhibited *ETS homologous factor (Ehf)*, which in turn inhibited *collagen 1a1* expression. After treatment with an antimiR to miR-431-5p, BP did not rise as much, small artery remodeling, endothelial dysfunction, large artery stiffening, inflammation and superoxide generation were significantly reduced, demonstrating that indeed this microRNA mediated angiotensin II actions through inhibition of Ehf.[31] We have also examined the role of miRs in small arteries from gluteal subcutaneous biopsies from humans with hypertension, diabetes and chronic kidney disease compared to normotensive humans. In that study, the top enriched gene ontology term groups allowed identifying miR-338-3p in small arteries in humans. This miR targets glutathione peroxidase 3 (*GPX3)* and alkaline ceraminidase 2 (*ACER2)* in human aortic endothelial cells, data that was presented at 2021 ESH/ISH meeting.[32]

Finally, in recent work we returned to the model of introgression of Brown Norway chromosome 2 but this time of fragments of chromosome 2 rather than the complete chromosome into the Dahl salt

sensitive background to generate congenic rats.[33] Introgression of the S2^{B}a fragment into Dahl rats was associated with lower vascular inflammation under a normal salt diet, and greater vascular inflammation under a high salt diet. We identified genes encoded in S2^{B}a and S2^{B}b fragments that were expressed differentially uniquely under either the normal or the high salt diet. The Brown Norway Chr 2a fragment encoded differentially expressed genes that were validated by reverse transcription quantitative PCR. This allowed identifying *Enpep* that encodes aminopeptidase A, upregulated under normal salt diet, and *Heparan sulfate 2-O-sulfotransferase* 1, downregulated under high salt diet.[33] Interestingly, aminopeptidase A has being targeted by an antihypertensive agent in development for treatment of primary hypertension in humans.

Although not mentioned during my presentation because of time constraints, I am particularly proud of our discovery of natriuretic peptides as a biomarker of heart failure,[34] the effect of natriuretic peptides to inhibit aldosterone secretion stimulated by angiotensin II, ACTH and potassium,[35] and demonstrating that the association of valsartan and sacubitril has powerful effects on BP, vascular and cardiac remodeling in SHR,[36] which led to the creation of Entrestoâ, that has had extraordinary efficacy in the treatment of heart failure in humans.

None of this work could have been possible without my trainees, technicians, associate scientists and collaborators over more than 40 years, who I thank for their dedication to science, expertise, excellent work and warm friendship, and the granting agencies that have funded our studies, the Medical Research Council of Canada, and its successor, the Canadian Institutes of Health Research (CIHR).

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Honoring Dr Ernesto Schiffrin with the 2021 ISH Volhard Award

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Dear Members of the International Society of Hypertension,

We extend our heartiest congratulations to Dr. Ernesto L. Schiffrin, the recipient of the 2021 Franz Volhard Award and Lectureship for Outstanding Research of the International Society of Hypertension (ISH). Ernesto is a world leader in hypertension research, cardiovascular medicine, and vascular biology. He is also a role model for young clinician scientists, combining cutting-edge research, clinical service, extraordinary leadership in international scientific organizations as well as his home institution, and mentoring many young scientists who have developed their own outstanding research programs.

Ernesto's pioneering research contributions are too numerous to discuss in detail but a few deserve special attention:

- Discovery of the mechanisms of remodeling of small resistance arteries and the effects of antihypertensive therapy on vascular remodeling in humans, demonstrating that selective antihypertensive agents correct altered structure and function of blood vessels in patients with hypertension[1].
- Demonstration of the role of endothelin in vascular disease and in salt-sensitive and severe hypertension, leading to studies of endothelin antagonists in human resistant hypertension[2].
- Discovery of the role of atrial natriuretic peptide in regulating aldosterone secretion.
- First report on the role of natriuretic peptides as biomarkers of heart failure in humans.
- Demonstration that angiotensin II and aldosterone have important effects on cardiovascular remodeling and elucidation of the mechanisms by which these two hormones interact to cause cardiovascular injury.
- Elucidation of the vascular protective actions of PPARs.
- Exposition of the role of innate immunity, inflammation and T regulatory lymphocytes in vascular remodeling in hypertension[3-5].
- Discovery that combinations of the angiotensin receptor blocker, valsartan, and a neprilysin inhibitor, sacubitril, caused remarkable blood pressure lowering, and vascular and cardiac benefit in spontaneously hypertensive rats. This work facilitated development of Entresto®, now an important agent for treating heart failure.

These achievements, and many more, demonstrate the broad scope of Ernesto's contributions to basic and clinical research and underscore his research leadership in hypertension and cardiovascular disease. The breadth and depth of his research contributions are truly extraordinary and place him among the elite pioneers in the fields of hypertension, vascular biology, and cardiovascular medicine.

In 2011 Ernesto received the American Heart Association (AHA) Excellence in Research Award (formerly the Novartis Award), the highest honor of the AHA in the field of hypertension research. In 2018 he received the Distinguished Fellow Award of ISH and in 2013 he received the Robert Tigerstedt Distinguished Scientist Award of the American Society of Hypertension. Additional high honors from international organizations include the Irvine Page-Alva Bradley Lifetime Achievement Award of the Council for High Blood Pressure Research – AHA, the Björn Folkow Award of the European Society of Hypertension, the Margolese National Heart Disorders Prize from University of British Columbia, and the Queen Elizabeth II Diamond Jubilee Medal. Ernesto was elected Fellow of the Royal Society of Canada in 2006 and appointed Member of the Order of Canada (C.M.) in 2010.

Ernesto's service to scientific journals and professional societies has also been exemplary. He served as Associate Editor of Hypertension for more than 13 years and in 2016 was selected as editor-in-chief of the American Journal of Hypertension. He served as President of the ISH, President of the Inter-American Society of Hypertension, President of the Québec Hypertension Society, President of Hypertension Canada, Chair of the Council on Hypertension - AHA, and has held several other key leadership positions in scientific societies.

Ernesto has trained an impressive list of medical and graduate students as well as post-doctoral fellows, many of whom have assumed important faculty positions at academic institutions and leadership of international professional organizations. For example, Dr. Rhian Touyz, current Director of the Institute of Cardiovascular & Medical Sciences at the BHF Glasgow Cardiovascular Research Centre at the University of Glasgow, United Kingdom and former President of the ISH, was one of Ernesto's protégés.

Ernesto is one of those rare clinician scientists who is innovative, scholarly, and a master of bridging basic and clinical research. His outstanding research contributions have had a major lasting impact on our understanding of the physiology, pathophysiology and therapy of hypertension and cardiovascular disease. We are delighted to congratulate Dr. Ernesto L. Schiffrin as the recipient of the 2021 Franz Volhard Award for Outstanding Research.

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Honoring Dr Ernesto Schiffrin with the 2021 ISH Volhard Award

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The Franz Volhard award of the International Society of Hypertension (ISH) was created in 1972 to honour the outstanding and innovative contributions of Prof Volhard in the field of hypertension and renal pathophysiology. Prof Volhard was a visionary researcher - in the early 1900s, he introduced the concept of pale (renal) hypertension due to a renal-derived pressor substance, later to be identified as the renin angiotensin system, and red (essential) hypertension due to hereditary factors, age, obesity, and severe alcoholism. He emphasized the importance of a rise in cardiac output and a premature reduction of vascular distensibility in the pathogenesis of red hypertension. In recognition of these discoveries, amongst many others, Franz Volhard was described as 'a genius scientist, outstanding physician and brilliant speaker'[1].

It is therefore most fitting that the ISH 2021 Volhard award was bestowed to Professor Ernesto Schiffrin at the virtual ESH/ISH scientific meeting in April 2021. Dr Schiffrin epitomises everything that the award represents - an outstanding physician-scientist who has made major contributions that have advanced the understanding of the pathophysiology of hypertension through seminal discoveries on vasoactive peptides, inflammation and vascular remodeling in hypertension[2-6]. Dr Schiffrin is Distinguished James McGill Professor and Vice-Chair, Department of Medicine, McGill University, Physician-in-Chief, Department of Medicine, Jewish General Hospital, and Director of the Hypertension and Vascular Research Unit, Lady Davis Institute for Medical Research. In recognition of his accomplishments and contributions he was appointed a Member of the Order of Canada, was the recipient of the Bjorn Folkow Award of the European Society of Hypertension and awardee of the Excellence Award for Research in Hypertension of the American Heart Association.

The beauty of Dr Schiffrin's research is that it truly spans discovery science to clinical studies. His earlier work focused on angiotensin and endothelin signaling and molecular pathways leading to generation of oxidative stress in hypertension. He discovered the role of atrial natriuretic peptide in the regulation of aldosterone secretion, the importance of peroxisome proliferator activated receptors (in vascular inflammation and injury and he was amongst the first to study remodelling of resistance arteries in experimental and human hypertension. His work on endothelin-1 clearly defined a role for the endothelin system in hypertension and target organ damage. Together with these discoveries and unique mouse models of endothelin-1-induced hypertension that his group generated, his work has translated to the clinic, where he is a leading investigator in a clinical trial on effects of a novel endothelin antagonist in resistant hypertension. In addition, Dr. Schiffrin is a world leader in the field of inflammation and hypertension. His group was the first to describe an inflammatory response in vessels in hypertension and more recently he identified gamma/delta T lymphocytes as being critically involved in experimental and human hypertension. Among his most impactful contributions are his clinical studies. In particular in the 1980s, Dr Schiffrin reported the utility of natriuretic peptides as a biomarker of heart failure in patients, a concept that is well accepted today. He also reported for the

first time the cardiovascular benefits of associating an angiotensin receptor blocker (valsartan) and a neprilysin inhibitor (sacubitril). He has been at the forefront in phenotyping small vessels in human hypertension and demonstrated differential beneficial effects of some antihypertensive agents. More recently Dr. Schiffrin has led studies of microRNAs in the circulation and small arteries in humans with hypertension, diabetes mellitus and chronic kidney disease using Next Generation Sequencing to understand the potential role of microRNAs in pathophysiology and as biomarkers and therapeutic targets in hypertension.

Dr. Schiffrin has played a major leadership role as President/Chair in the International Society of Hypertension, the Canadian Society of Hypertension and later Hypertension Canada, and the Council on Hypertension (American Heart Association). He has contributed to important collective literary works including major review articles and has edited numerous books. He was associate editor of highest impact hypertension journals including Hypertension, and since 2016 he has held the position of Editor-in-Chief of the American Journal of Hypertension. Beyond his research and academic activities, Dr Schiffrin is an outstanding teacher, mentor and supervisor as evidenced by his many trainees who have gone on to successful independent academic or clinical careers.

Dr Schiffrin's dedication to innovative and impactful hypertension research, his commitment to advancing knowledge that will improve the lives of patients with hypertension and his successes in training future hypertension researchers clearly honour the memory of Franz Volhard. Dr Schiffrin is an outstanding hypertension researcher and the ISH is proud to name him as the 2021 Franz Volhard Awardee.

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LEARNING THE ROPES: SLEEP DISORDERS AND CVD

Focus on Sleep Disorders in Cardiovascular Disease

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Sleep disorders are common in the general population, and are associated with obesity, the metabolic syndrome, hypertension, and with problems related to mental health. Furthermore, sleep disorders and hypertension share several risk factors, although their causal relations remain unclear. Poor sleep quality is associated with impaired quality of life, and an increased risk for coronary artery disease, stroke, and all-cause mortality[1]. Obstructive sleep apnea is the most common form of sleep disordered breathing (which constitute of obstructive sleep apnea, central sleep apnea, and their combination named complex sleep apnea). There are several pathophysiological mechanisms by which obstructive sleep apnea could promote hypertension and cardiovascular disease, including autonomic alterations with sympatho-adrenal activation, endothelial dysfunction, coagulopathy, metabolic disturbances, increased inflammation, and increased oxidative stress [2-5]. Thus, it is not surprising that sleep disordered breathing is a common finding among people with cardiovascular disease, and may be a potential target for reducing cardiovascular risk. Also, studies show improvement in quality of life, and benefits in patients with hypertension and arrhythmias.

Given that sleep disordered breathing is common and may promote cardiovascular disease, this is a condition associated with considerable direct and indirect costs for health care. More important, however, studies suggest that diagnosis and treatment of obstructive sleep apnea is cost effective[6]. There are several useful and simple questionaries to use for screening of obstructive sleep apnea (e.g. STOP-Bang, NoSAS)[7,8]. However, it appears that screening for sleep disorders in general, and sleep disordered breathing such as obstructive sleep apnea in particular, is seldom performed in clinical cardiology. This may be a missed opportunity for diagnosis, potential treatment, and cardiovascular risk reduction in many of the patients we see every day in our practice.

Learning the ropes in this issue of Hypertension News provides you we three short reviews on sleep disorders and cardiovascular risk, covering 1) the risk for cardiovascular disease, 2) the pathophysiology, and 3) the management of obstructive sleep apnea in patients with cardiovascular comorbidities. Focus on sleep disorders in cardiovascular disease is warranted.

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Sleep Disorders and Risk of CVD

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According to Thomas Dekker quote "Sleep is that golden chain that ties health and our bodies together".

Insufficient and inadequate sleep quality is a growing health problem affecting more than one in three adults. Sleep disorders are critical contributors to obesity, diabetes, cardiovascular (CV) disease, heart failure (HF), stroke and depression. Sleep debt increases the risk of motor vehicle crashes, fatal injury, and disability each year.

Sleep can be disrupted by 'sleep and circadian rhythm disorders' (i.e., sleep apnoea, insomnia, narcolepsy, restless leg syndrome, parasomnias, sleep bruxism), work, social or lifestyle behaviours. Unhealthy sleep patterns defined as short (<7 hours) and long sleep (>8 hours), late chronotype, insomnia symptoms, snoring and excessive daytime sleepiness (EDS) have been associated with an increased risk of coronary heart disease (CHD), CV disease, stroke, and all-cause mortality. While patients with a healthy sleep score (Figure 1a) demonstrated a reduced risk of CV disease by 35%, CHD by 34% and stroke by 34% independently of genetic risk score[1], and HF[2] suggesting that treating sleep disorders should be considered for CV prevention.

Obstructive sleep apnoea (OSA) is the most common type of sleep-disordered breathing [3]. Nearly 1 billion of the worldwide adults' population aged 30–69 years have OSA, and the number of people with moderate to severe OSA, for which treatment is generally recommended, is estimated 425 million[4]. Given the already high and increasing prevalence of obesity and aging, the number of people presenting with OSA symptoms continues to grow.

OSA is characterized by recurrent episodes of closure (apnoea) and hypopnea (narrowing) of the upper respiratory airflow resulting in shallow or paused breathing (Figure 1b), intermittent hypoxemia, and arousal associated with maintained or increasing ventilator efforts[3]. Apnoea is defined as at least 90% airflow limitation through the respiratory tract which is maintained for 10 seconds and associated with increased inspiratory efforts from chest and/or abdomen, whereas hypopnea refers to a drop in the airflow of ≥ 30% for ≥ 10 seconds and is associated with a ≥3% oxygen desaturation or arousal. Based on the index denoting average number of apnoeic and hypopneic episodes per hour of sleep (apnoea-hypopnea-index [AHI], OSA is classified as: mild AHI ≥5 and <15 events per hour, moderate AHI ≥15 and ≤30 evets per hour, and severe AHI >30 events per hour.

The most common symptoms, risk factors and OSA associated conditions are summarized in **Table**.

OSA mediated intermittent hypoxia has been suggested as the critical contributor to increased morbidity and mortality. Evidence is emerging on the casual relationship between OSA and development and management of hypertension, diabetes, cardiac arrythmia, HF, sudden cardiac death (SCD), chronic obstructive pulmonary disease, stroke, erectile dysfunction (ED), depression, cognitive impairment, Alzheimer disease (AD) and cancer-related death. Recent data suggests that COVID-19 may adversely affect OSA and that treated OSA patients may be at increased risk of death from COVID-19.

While not all OSA patients are obese, undoubtedly excess weight is as an independent causative factor to the development of OSA, with the severity of disease strongly associated with an increase in body weight[3]. OSA alone can promote obesity related effects further potentiating increased CV morbidity and mortality.

OSA is primarily important in the context of hypertension. Blunted nocturnal BP dipping (defined as a <10% decrease in BP during sleep) is a common feature of sleep disturbances. OSA has been reported in approximately 40% hypertensive patients, increasing to nearly 90% in resistant hypertension patients[5]. OSA should rise the suspicion of secondary hypertension and should be recognized as an important risk modifier increasing CV risk estimated by the SCORE system.

OSA, resulting sleep fragmentation and intermittent hypoxia promotes metabolic disturbances and is highly associated with prevalent and incident type 2 diabetes. The J-curve phenomena on the relationship between daytime napping (i.e., excessive marker of underlying sleep disorder) and the risk of diabetes or metabolic syndrome was found, with no effect of napping below 40 minutes/day.

Severe OSA is associated with significant coronary artery plaque burden independent of traditional CV risk factors. Moderate to severe OSA increases the risk of developing NSTEMI compared to STEMI, with the risk increasing with AHI severity[6]. Patients with moderate to severe OSA demonstrate less severe cardiac injury during an acute non-fatal myocardial infarction (MI) when compared to patients without or with mild OSA, suggesting that OSA may have a cardioprotective effect in the acute phase of MI, likely via ischemic preconditioning.

OSA and AF are strongly associated and may coexist with ED forming a clinical OSAFED syndrome that considerably potentiated the global CV risk. OSA promotes AF via acute apnoea-related arrhythmogenic changes during sleep and long-term atrial remodelling. OSA is highly prevalent in AF patients referred for cardioversion[7]. However, most of AF patients present no symptoms of EDS, indicating that this marker is not a reliable indication for occult OSA. Further relevant findings are related to night-to-night variability in OSA severity (which cannot be detected over one sleep study) demonstrating that OSA severity on a specific night directly corresponds to AF incidence on the same day[8].

Patients with OSA present with a higher prevalence of sleep-related bradycardia and conduction delay, primarily during apnoeic episodes. Undiagnosed OSA is common in patients referred for pacemaker implantation to treat nocturnal bradycardia which in addition to prolong sinus pauses and atrioventricular conduction are substantially reduced following OSA therapy with no need for pacemaker. In this context the 2018 ACC/AHA/HRS Guidelines highlighted OSA evaluation and treatment in patients with documented or suspected bradycardia or conduction delays.

SDB plays a critical role in the development and worsening of HF, and its prognosis[9]. OSA more commonly occurs in HF preserved ejection fraction (EF), whereas central sleep apnoea and cyclic episodes of hypopnea-apnoea breathing (Cheyne-Stokes) increasingly characterize patients with HF reduced EF contributing to arrhythmias and SCD. Thus, screening for SDB in HF patients is urgently required.

OSA is highly prevalent in patients with cerebral infarction, transient ischemic attack (TIA), ischemic stroke or haemorrhagic stroke, reaching 62% in patients with AHI > 10 events per hour and 30% in severe OSA, and is associated with increased poststroke mortality. SDB often precedes acute stroke and TIA. Clinically relevant are findings showing that stroke and TIA patients presents specific phenotype of OSA such as significantly shorter apnoeas and hypopneas[10], suggesting that optimal therapeutic approach requires routine OSA screening in patients with cerebrovascular disease even in the absence of a previous OSA diagnosis.

The link between OSA and increased risk of dementia and AD is of clinical importance. OSA may impair amyloid-β clearance and affect the link between slow wave activity and amyloid-β.

Awareness of OSA has increased over time but still remains low. Early detection and identification of patients with SDB is integral to curb the disease burden as its CV consequences impose a large economic burden on the global healthcare system. OSA and CV disease commonly coexist sharing multiple risk factors. Thus, the implementation of the AHA Life's Simple 7 recommendations (i.e., not smoking, having a healthy diet habits, being physically active, losing excess weight, controlling cholesterol, glucose and BP levels) are vital for ideal CV health and can prevent from OSA mediated CV disease.

Figure 1a

Figure 1a. Healthy sleep pattern.

Figure 1b

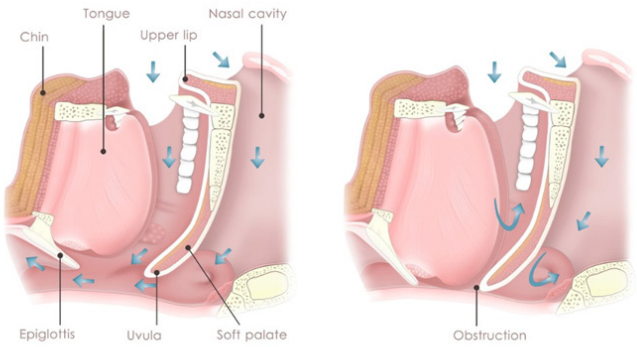

Figure 1b. Airway during normal sleep and obstructive sleep apnoea (republished with permission

Table

Pay attention to the risk factors for OSA

- ✓ Waist circumference of >94 cm for men, >80 cm for women
  Alarming: >102 cm for men, >88 cm for women
- ✓ Neck circumference ≥ 43 cm in men, ≥ 41 cm in women
- ✓ Male gender
- ✓ Postmenopausal state
- ✓ Smoking
- ✓ Alcohol / Sedative use
- ✓ Craniofacial bony abnormalities

OSA attributable to high-risk population

- ✓ Hypertension
- ✓ Pre-diabetes / Diabetes type 2
- ✓ Coronary artery disease (acute coronary syndrome)
- ✓ Cardiac arrhythmia (atrial fibrillation, nocturnal bradycardia, sinus pauses)
- ✓ Transient ischemic attack / Stroke
- ✓ Heart failure
- ✓ Dementia / Alzheimer disease

OSA nighttime symptoms

- ✓ Loud snoring
- ✓ Often insomnia
- ✓ Abrupt awakenings / gasping / choking
- ✓ Witnessed apneas
- ✓ Nocturia
- ✓ Reflux symptoms

OSA daytime symptoms

- ✓ Excessive daytime sleepiness
- ✓ Dry mouth
- ✓ Morning headache
- ✓ Elevated blood pressure
- ✓ Difficulty concentrating
- ✓ Depression, irritability
- ✓ Decreased libido / Erectile dysfunction
- ✓ Cognitive dysfunction

Table. Common symptoms, risk factors and high-risk population associated with obstructive sleep apnoea (OSA).

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Pathophysiology of Sleep Disordered Breathing

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Introduction

Twenty years ago, it would have been easy to summarise the pathophysiology of sleep disordered breathing as repetitive nocturnal apnoea in obese persons causing sympathetic nerve system activation, hypertension and over time general cardiovascular disease, heart failure and stroke. The continuing studies in the field have added considerable knowledge but also many exceptions to this simplified description. Furthermore, despite the wealth of physiological understanding, the evidence for best treatment beyond weight loss and life-style modifications is limited. Part of the explanation for this is that most trials have excluded symptomatic patients, as it has been considered unethical not to offer them treatment. Nonetheless the strong association between sleep disordered breathing and obstructive sleep apnoea (OSA) in particular,

and cardiovascular disease is well established.[1, 2] The term sleep disordered breathing include OSA, central sleep apnoea (CSA) and the combination of these (complex sleep apnoea). This short review will focus on the pathophysiology of OSA. For a complete account of sleep apnoea and cardiovascular disease the author recommend an excellent review by professor John Floras (the author's post-doc mentor).[2]

Acute physiological effects of OSA

Obstructive apnoea or hypopnea occur when the upper airway collapses completely or partially during sleep impeding inspiration. The cause of loss of airway-patency is extremely complex but is more common in overweight individuals, detailed in a review by Dempsey *et al*.[3] Each obstruction triggers a cascade of events.[3] The repetitive but failed inspiratory efforts markedly reduce the intrathoracic pressure, up to -60 mmHg. This increases the transmural pressure difference over the large vessels including the aortic arch and the heart with the equivalent amount, since these are hydraulically connected with the extra-thoracic circulation and increase cardiac afterload. Ventricular interdependence impedes right ventricular filling despite an increased systemic venous return. Pulmonary and aortic baroreceptors (stretch receptors) sense the increased transmural pressure gradient and misinterpret this as an increase in blood pressure, and at the brain stem level inhibit sympathetic efferent discharge to the heart, kidneys, and resistance vessels. These combined effects lead to a reduction in heart rate and cardiac output, and temporarily reduce peripheral resistance and a drop in arterial blood pressure. This makes the circulatory system poorly prepared to handle the subsequent arterial oxygen desaturation and CO2 accumulation that now takes over and elicit sympathetic excitation and vasoconstriction, at the same time as the hypoxia increase efferent vagal tone. The desaturations may reach 60% SaO2 or lower. The apnoea usually terminates after 30-90 seconds due to arousal, that further stimulate sympathetic activation. In many patients this is, after a few deep breaths, repeated again and again, 30 to 60 times an hour. These effects do not occur to the same degree in all patients but represent the classical pathophysiology behind OSA (Table 1).[3] It is important to note that the apnoea-induced sympathetic excitation carry-over also to an increased daytime activation, and that patients with heart failure handle these challenges less well.[4]

Table 1. Obstructive apnea: consequences of negative intrathoracic pressure

Acute: atrial, ventricular, pulmonary, and thoracic vessel distension, increased afterload, increased myocardial O_2 demand, decreased coronary flow, reduced stroke volume, reflexive sympathetic nerve firing and noradrenaline release
Chronic: increased risk for atrial fibrillation, atrial and ventricular hypertrophy or dilatation, thoracic aortic dilatation
Not detected by brachial blood pressure measurements
Not affected by antihypertensive treatment

Based on Floras, 2018.[2]

OSA in hypertension

It has been shown that the apnoea-induced sympathetic activation and mechanical effects over time cause endothelial dysfunction, and contribute to aortic stiffness.[5] Concordant increases in efferent renal sympathetic nerve traffic stimulate both noradrenergic and renin-aldosterone mediated sodium and water retention.[6] At the same time the disrupted sleep pattern have negative effects on glucose homeostasis and contribute to systemic inflammation.[7] Over time these combined effects contribute to the development of hypertension.[2]

In line with this, the prevalence of hypertension in individuals with at least moderate OSA is higher even after adjustments for common comorbidities. For instance, the large HypnoLaus population survey (n=2,121), after multivariable adjustment, demonstrated an odds ratio for hypertension prevalence of 1.6 for moderate-severe OSA (apnoea-hypopnea index >20/h).[1] In one small cohort of patients with therapy-resistant hypertension the prevalence was as high as 83%.[8]

Despite this strong association, treatment of OSA with continuous positive airway pressure

(CPAP) only reduce blood pressure on average 2/2 mmHg.[9] Part of the explanation may be that our techniques to measure blood pressure, such as ambulatory blood pressure monitoring, fails to capture the transient blood pressure swings associated with repeated apnoea. Each intermittent measurement may trigger an arousal terminating any apnoea. Indeed, one study utilising continuous blood pressure measurements by digital photoplethysmography showed that therapeutic continuous positive airway pressure lowered average night-time and daytime blood pressure by 13/11 and 10/11 mm Hg, respectively, in 36 randomized (58% hypertensive) participants.[10] Further support for a causative association is given in a recent meta-analysis including 5,550 participants showing a pooled prevalence of left ventricular hypertrophy (LVH) of 45% in the OSA population, with an odds ratio 1.70 for LVH in subjects with OSA as compared to controls.[11] Still, it is an unanswered question why some patients with OSA appears to be protected and do not develop hypertension.

OSA and cardiovascular diseases

The association between OSA and several cardiovascular diagnoses is well established in population studies, but it is hard to elucidate the exact relationship since OSA often is recognised in relation to an event, and it is difficult to separate the effects of confounders and mediators, such as obesity and blood pressure.[1] In brief, it may be advisable to consider OSA in all patients experiencing nocturnal cardiovascular events, such as stroke, angina, acute coronary syndrome or sudden cardiac death.[2] The acute haemodynamic effects may also contribute to aortic strain and OSA should be considered in patients with aortic aneurysm.[2] Atrial fibrillation is common in OSA patients, and is associated with increased risk for relapse after cardioversion or ablation.[12] Anatomically the pulmonary vein area is responsible for the majority of atrial fibrillation, and is located just outside the stiff pericardium and hence susceptible to stretch during OSA induced pressure swings. In pulmonary hypertension, OSA, in the absence of any alternative cause, can be detected in 20-40% of individuals and is potentially directly caused by the von Euler-Liljestrand mechanism.[13]

OSA in heart failure is complex and deserve its own review article. The shared pathophysiology with increased neurohumoral activation and hypertension in addition to peripheral oedema and nocturnal rostral fluid shift contributes to a high prevalence of OSA in heart failure.[6] In patients hospitalised with decompensated hear failure, 80% have CSA or OSA.[14] In stable patients with heart failure with both reduced and preserved ejection fraction, the prevalence is about 50%.[2, 15] As heart failure progress, CSA and complex sleep disorders becomes more prevalent, and likely contribute to the poor diagnosis.[2]

In conclusion, nocturnal sleep disturbances are common in all cardiovascular patients and cause a range of acute and chronic physiological effects that likely contribute to an increased morbidity and mortality. We can expect an increased prevalence of OSA in the future with an ageing and more overweight population. In elderly, the symptoms are often less apparent though OSA is also associated with cognitive impairment.[16] Despite ample physiological understandings many questions remain, and more evidence particularly on treatment effects is needed before the concept of sleep apnoea as a modifiable risk factor may enter the guidelines. Unfortunately, few such trials are ongoing.

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FULL REFERENCE LIST

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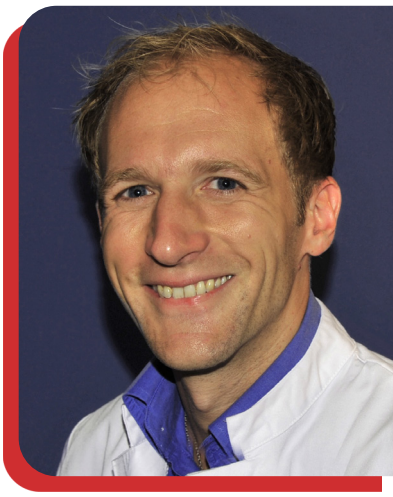
Obstructive Sleep Apnea Management in Patients with Cardiovascular Comorbidities



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Obstructive sleep apnea (OSA) is highly prevalent in patients with cardiovascular (CV) comorbidities such as hypertension or atrial fibrillation and is associated with increased risk of mortality, CV events and arrhythmias.[1] Continuous positive airway pressure (CPAP) is established as first line therapy in OSA patients with moderate or severe OSA due to its impact on both symptoms and quality of life. In clinical care, CPAP is recommended to be combined with lifestyle changes and weight loss.

Up to 50% of OSA patients may have hypertension, and 30% of hypertensive patients will likely have OSA.[2] Patients with untreated OSA followed over 4 years have a 2-3 fold increased risk of developing incident hypertension, independent of the usual risk factors for hypertension.[2] Meta-analyses of randomized trials of CPAP in patients with hypertension have reported modest blood pressure decreases of between 2 to 3 mmHg.[3] In patients with atrial fibrillation, the prevalence of OSA in patients with AF is higher (21-74%) than in controls without AF (3-49%).[4] In a meta-analyses of several non-randomized studies, the use of CPAP was associated with a 42% decreased risk of AF-recurrence.[5] Randomized studies in the field of atrial fibrillation management are currently ongoing.

Three randomized controlled trials assessed the effects of CPAP on secondary prevention of CV events (**Table**). The Sleep Apnea Cardiovascular Endpoints (SAVE) trial randomised over 2000

patients with established CV disease or cerebrovascular disease to CPAP plus usual care, or usual care alone.[6] The use of CPAP (over a mean follow-up of 43 months) did not significantly reduce the primary composite endpoint of major adverse cardiac events, although sleepiness did improve. In a pre-specified subgroup analysis, those with CPAP adherence >4 hrs/night had a lower risk of stroke (HR 0.56 CI 95% 0.32-1.00) and total cerebrovascular events (HR 0.52 95% CI 0.30-0.90).

In the RICCADSA trial, patients with moderate or severe OSA (but with no daytime sleepiness) were randomised to CPAP or control after coronary revascularisation, and followed up for a mean of 57 months.[7] The CPAP group showed no change in CV endpoints including repeat revascularisation, although the subgroup using CPAP > 4 hrs/night had a lower CV risk (HR 0.29 95% CI 0.10-0.86).

A further study (ISAACC trial) examined patients with acute coronary syndrome and moderate or severe OSA.[8] CPAP had no significant effect on the primary composite endpoint of CVD events or death. In this trial there was no relationship between hours of CPAP use and outcomes, but the adherence to CPAP was low at 2.78 hrs/night.

The reasons for these randomised trials failing to demonstrate CV benefit has been debated. The consensus was, that a better phenotyping of sleep apnea is required. Patients with a similar apnea hypopnea index have widely different combinations of abnormalities in airways anatomy, neuromuscular responsiveness, respiratory chemosensitivity and loop gain. Poor compliance with airways pressure support in patients with no excessive daytime sleepiness may also bias randomised trials to find no effect of intervention. Another limitation in carrying out randomized controlled trials with cardiac endpoints in OSA is that patients with severe sleepiness or hypoxemia -the groups who might benefit the most from treatment – were often excluded because of ethical reasons. Additionally, CPAP tolerance remains a key issue in interpreting results.

Despite the absence of a clear evidence that OSA treatment prevents CV events in secondary prevention, current guidelines for the management of hypertension and atrial fibrillation recommend testing for and treating OSA to improve hypertension and rhythm control.[8,9] Attended in-hospital polysomnography is the gold standard test for OSA. However, as shown by a recent survey by the European Heart Rhythm Association (EHRA) and the Association of Cardiovascular Nurses and Allied Professions (ACNAP), structured testing for OSA only occurs in the minority of patients due to the fact that access to polysomnography in a sleep laboratory as well as the reference method for OSA diagnosis is limited due to long waiting lists, high labor intensity and high costs.[10]

Home Sleep Apnea Test (HSAT) with oxygen saturation and other respiratory measures is more widely available, can be set-up by the patient at home and have shown to be an inexpensive, reliable and sensitive alternative technologies to polysomnography in a sleep laboratory. To prevent fragmentation of care, a structured OSA testing and management pathway can be implemented in a specialized hypertension or AF clinic with a holistic approach. An integrated pathway for OSA testing and management has been proposed previously and could be embedded in a specialized outpatient clinic. Interdisciplinary collaboration between the sleep specialist, cardiologist/nephrologist and specialized nurses is crucial to coordinate the care and to assure that patients will be tested for OSA (Figure) . In the case of a positive test result showing moderate-to-severe obstructive OSA (apnea-hypopnea index ≥15/h with predominant obstructive respiratory events), the referral to the sleep clinic for CPAP initiation and titration as well as the structured long-term follow-up should be integrated in the usual care pathways in AF-clinics. First, CPAP treatment should always be combined with weight loss interventions if needed and lifestyle modification (e.g. alcohol avoidance, sleep hygiene, etc.) as important components of risk factor management programs, which have been shown to improve both, OSA severity as well as blood pressure and symptoms in patients with atrial fibrillation. Additionally, interrogation of CPAP efficacy, adherence and side effects should be implemented in the regular assessment of patients treated with CPAP.

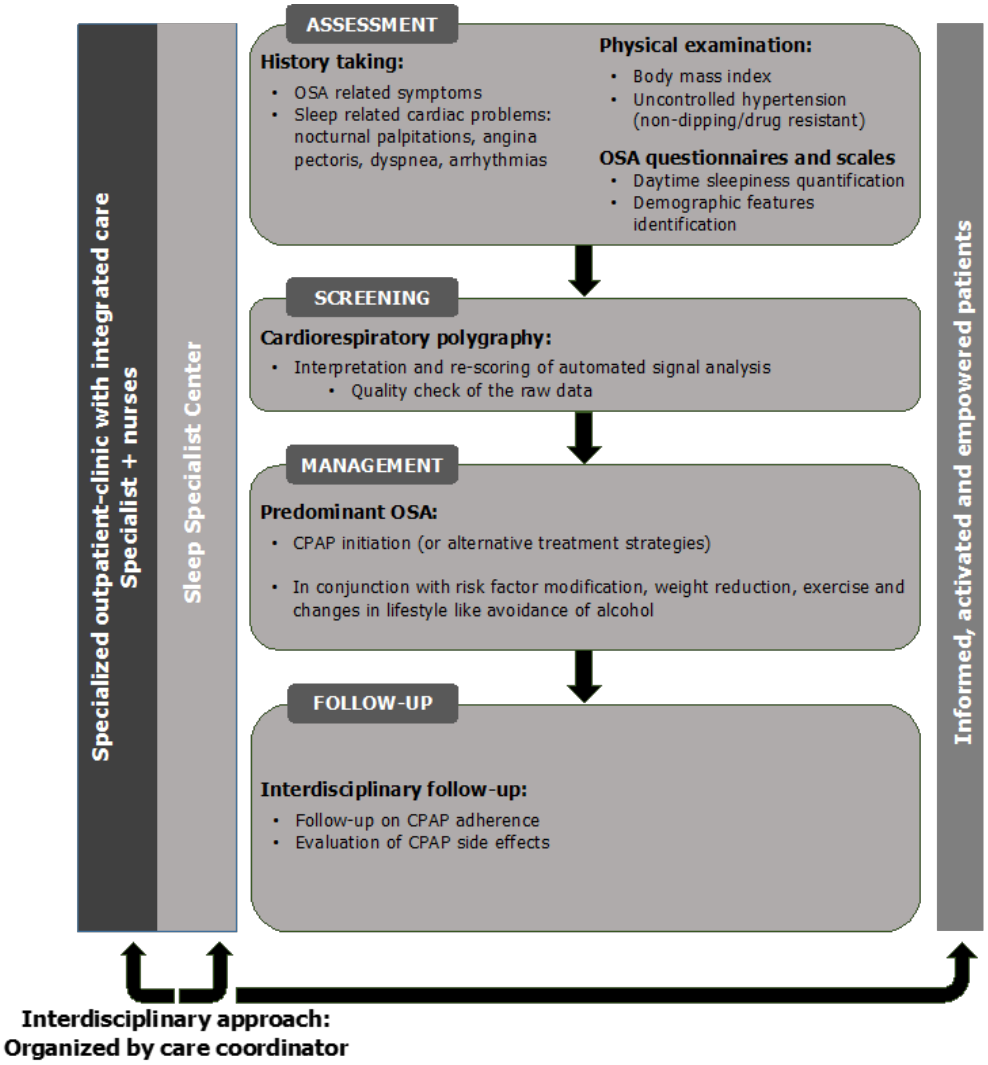
In conclusion, OSA is highly prevalent in patients with CV comorbidities. Despite the absence of a clear evidence that systematic treatment of OSA can prevent secondary CV events, OSA management is recommended to control blood pressure and sinus rhythm. Testing for and treatment of OSA can be best organized within an integrated care pathway with a close and interdisciplinary collaboration between the sleep specialist, cardiologist/nephrologist and specialized nurses.

Table Randomised trials of OSA treatment with CPAP therapy in patients with cardiovascular disease: entry criteria, number of patients, mean follow-up, primary results, and results of subgroup analysis of higher adherence subgroup.

Trial	Patient group	OSA diagnosis	Intervention (patient numbers)	Follow-up (mean)	Primary outcome (MACE)	Daytime sleepiness at baseline
SAVE	Prevalent CVD	ODI>12/h	CPAP v control (1346/1341)	43 months	HR 1.10 (95% CI 0.91-1.32)	ESS <15 Severe sleepiness excluded
RICCADSA	Revascularised CVD	AHI>15/h	CPAP v control (122/122)	57 months	HR 0.80 (95% CI 0.46-1.41)	ESS <10 Non sleepy
ISAAC	Acute coronary syndrome	AHI>15/h	CPAP v control (631/631)	40 months	HR 0.89 (95% CI 0.68-1.17)	ESS<10 Non sleepy

AHI: apnea-hypopnea index; CPAP: continuous positive airway pressure; CVD: cardiovascular disease; ESS: Epworth Sleepiness Scale; MACE: major adverse cardiovascular events; ODI: oxygen desaturation index; OSA: obstructive sleep apnea

Figure



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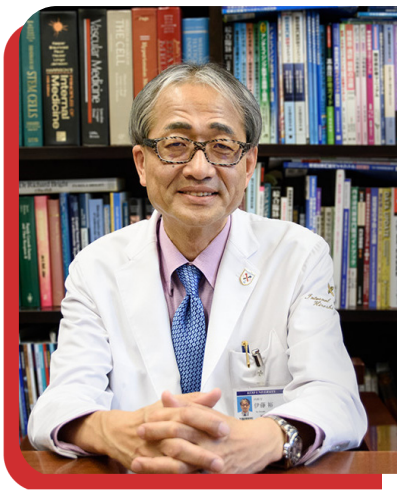
INVITED PAPER

ISH2022: New Normal ISH Meeting Born in Kyoto



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Keio University School of Medicine Tokyo, Japan
President, The Japanese Society of Hypertension, Vice president of ISH

DOI:10.30824/2106-16

ISH2022 will be held from October 12 to 16 2022 in the City of Kyoto at Kyoto International Conference Center with the theme of "The Wisdom for Conquering Hypertension". Please save the date!

Although COVID-19 forced us to meet virtually for a while, we hope ISH2022 Kyoto will be a chance for many of our colleagues and friends from all over the world to gather in together in person and share our wisdom on conquering hypertension to ensure a better quality of life for people.

We will also provide ISH2022 programs in a virtual format for those who have limited access, to offer expanded opportunities.

Why should you attend ISH2022 in Kyoto?

It's because we:

1. Provide cutting-edge innovative scientific programs
2. Offer the opportunity to explore the old capital of Japan and knowledge-centered city, Kyoto
3. Provide a variety of interesting, informative and interactive sessions for many young and enthusiastic clinicians and researchers

Innovative scientific programs

We are honored to have the 2012 Nobel Prize Laureate for the discovery of iPS cells, Shinya Yamanaka for the keynote lecture at ISH2022! Not only that, ISH2022 covers the following categories;

1. **Three Main Topics: AI/Dx, FOOD/ Nutrition, Physical Fitness with the view of correlations with hypertension**

We believe that these three topics have inter-disciplinary impacts correlations and will lead to the realization of well-being of all the people in the world.

2. **Hypertension for SDGs Toward 2030 World (Climate, Disaster, Isolation/Mental health etc.)**

Hypertension and hypertension-related diseases are relevant to many of sustainable development goals including the problems of poverty and hunger, education, gender, disaster, and climate change. We discuss and share the information about hypertension and hypertension-related diseases from the perspectives of SDGs

3. **Global Health and Hypertension with Diversity (Racial, Economical difference, Medical resources etc.)**

Considering racial and social differences of the environment in terms of education and lifestyle, pathogenesis and epidemiology of hypertension are diverse. Therefore, prevention and treatment of hypertension to achieve a better quality of life need to be approached with their diversities.

4. **Life-course and Hypertension (Preconception, DOHaD, cancer etc. and hypertension)**

The significance of hypertension differs at each stage of life. At each stage, a multifaceted approach is required. Hypertension control and research need a seamless transition from one stage to another.

5. **Super-aged Society and Hypertension (Sarcopenia, Dementia, Social Capitals etc.)**

Japan is now a super-aged society and coping with the increase of aging population is an urgent issue. The number 1 cause of death from non-communicable diseases is hypertension. In super-aged societies, prevention and control of hypertension is essential for healthy and happy longevity.

6. **Hypertension Next Generation therapy (Renal Denervation, Single compound pills, Applications etc.)**

Since many target molecules for antihypertensive therapy are being identified, new antihypertensive drugs are expected to be developed. Furthermore, challenging antihypertensive therapies such as device therapy, vaccines or apps. are being developed. We will discuss the current status of the development of next-generation hypertension treatment methods and their future directions.

7. **Convergence of Communicable Diseases and NCDs**

Hypertension has been categorized as a lifestyle-related disease, i.e., non-communicable diseases (NCDs), but the COVID-19 pandemic has opened our eyes for the need to restructure our understanding of it and its relations with communicable diseases.

8. **Japan Method for conquering hypertension ("Hypertension Zero Town" etc.)**

We will introduce JSH achievements aiming at the creation of "Hypertension Zero Town" in cooperation with more than ten Japanese cities and towns nationwide with the aid of Japanese Government by various innovative methods.

9. **Pathophysiology of Hypertension: Chronicle to the Future**

We will review the past and future prospects of hypertension research, which aims at the deep understanding of pathophysiology.

10. **Blood Pressure Measurement: Conventional and Future**

The history of clinical research and medical practice of hypertension began nearly 100 years ago, with the first development of blood pressure measurement. Now, wearable devices enable us to monitor blood pressure for 24 hours, real time. We will discuss how such methods have changed and will change the future of hypertension, its direction, possibilities and challenges.

11. **Imaging and Biomarker for Hypertension Management**

Imaging and biomarkers play an important role in the evaluation of the degree and evolution of various organ damages caused by hypertension. The establishment of more accurate testing methods with non-invasive approaches is essential for the realization of preemptive medicine and personalized medicine for hypertension.

12. **Hypertension Reigning Over Systemic Diseases**

By understanding the dynamic link between hypertension and systemic diseases such as stroke, cardiovascular diseases, heart failure, diabetes, and metabolic syndrome etc., we can expect to develop new medicine for hypertension.

Kyoto: Old capital of Japan and Knowledge-centered city

Kyoto, the ancient capital of Japan, is famous for its long history and unique culture.

Kyoto has 17 UNESCO World Cultural Heritage Sites and is brimming with unique culture and atmosphere. Kyoto is also renowned as one of the most academic cities in Japan. Including Kyoto University, one of the most prestigious universities in Japan, Kyoto has 50 universities and colleges that provide higher and specialized education to Japanese as well as overseas students. Kyoto University is the birthplace of Spontaneously Hypertensive Rats (SHR), which were first

established and introduced into the academic field in 1963 by Professor Kozo Okamoto. Moreover, CiRA, the Center for iPS Cell Research and Application headed by Nobel laureate Professor Shinya Yamanaka, was founded in Kyoto University in 2010. It is also the home to high-tech companies, such as Nintendo, Kyocera, and Omron. You will discover the coexistence of old and new, tradition and modernity.

For many young and enthusiastic clinicians and researchers

ISH2022 warmly welcomes young clinicians and researchers by offering a discounted registration fee for the young and participants from developing countries. We will have the young investigator's sessions hosted by and for young researchers.

We will prepare attractive educational sessions with bi-directional talks between speakers and audience.

We hope that ISH2022 in Kyoto will be a NEW NORMAL meeting and offer you the opportunity to discover the latest knowledge and expertise on treatments and cures for hypertension and related diseases.

Please visit our official website for details

We are looking forward to meeting you in Kyoto in 2022.

Hiroshi Itoh - hiito@keio.jp

INSTITUTE FOCUS
Baker Heart and Diabetes Institute

MORAG YOUNG
Baker Heart and Diabetes Institute,
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Assoc. Prof. Morag Young heads the Cardiovascular Endocrinology Laboratory at the Baker Heart and Diabetes Institute in Melbourne, Australia, where she was awarded the Alice Baker and Eleanor Shaw Gender Equity Fellowship. This fellowship is supported by the Baker Foundation, a philanthropic supporter of the Baker Institute since its establishment in 1926. The five-year fellowship reflects both the Institute and the Baker Foundation's commitment to addressing the limited number of female scientists at senior levels, and acknowledges the significant challenges faced by researchers with career interruptions and family/carer commitments. She has also been a member of the International Aldosterone Society, and the US and Australian Endocrine Societies for many years and in 2019 chaired the International Aldosterone Meeting in New Orleans and served on the POC for US Endo from 2017-2019.

Her laboratory had the unenviable task of moving from the Hudson Institute of Medical Research to the Baker Institute as Melbourne commenced the first of several waves of lockdowns of workplaces, schools etc. in response to the COVID-19 pandemic. This relocation brings her research group back to the Institute where she undertook her undergraduate and postgraduate research with Professor John Funder and post-doctoral training with Assoc. Prof. Tim Cole. Long standing collaborations with Professor Peter Fuller and Dr Jun Yang at the Hudson Institute, where her laboratory was located for 18 years, continue to form a network of research groups that investigate the mineralocorticoid receptor (MR) - from the molecular interactions within the MR through to establishing the true incidence of primary aldosteronism (PA) in newly diagnosed hypertension and other key patient cohorts. The move by the Young Lab to the Baker Institute has opened new opportunities and collaborations with cardiac specialists and clinics to translate novel outcomes of her discovery science program.

From physiology to the molecular endocrinology of the MR

Morag Young began her PhD studies investigating the pathophysiology of mineralocorticoid receptor (MR) signalling in the heart and vasculature using whole animal models; her work now incorporates over 18 years of experience in molecular endocrinology to understand MR actions in both "classic" target tissues and in "non-classic" (i.e., non-epithelial) tissues. Post-doctoral training in the laboratory of the late Prof Keith Parker (UTSW, Dallas TX) focused on understanding the role of Steroidogenic Factor-1 in the development of the hypothalamo-pituitary adrenal (HPA)-axis and obesity, and more importantly laid the foundations for developing novel transgenic mouse models, while working at the Hudson Institute. To do this Morag employed transgenic animal technologies, established disease models and identified non-renal pathways for MR activation in cardiomyocytes, monocytes/macrophages and endothelial cells. Her molecular studies were advanced during a sabbatical with Prof Donald McDonnell (Duke University, Durham, NC) during which she used phage display technology to probe liganded MR binding surfaces. Work with AProf Colin Clyne and Dr Jun Yang, a graduate student at the time, resulted in a series of new cell- and potentially ligand-selective MR coregulator proteins for the MR. The unique ligand-dependent or cell-specific profile of coregulatory proteins that associate with the MR is key for understanding the mechanisms underlying variable MR actions across tissues and whether these actions will allow for selective actions of new MR antagonists.

Morag's current research now seeks to identify and understand non-genomic actions of the MR that are cell-type selective and that underpin the development of cardiovascular disease. It is well known that steroid hormone receptors not only serve as ligand-activated transcription factors but can also modulate cell transduction pathways or tether other transcription factors. This diversity of signalling mechanisms offers new therapeutic options for heart failure and other forms of cardiovascular disease. This work is a long way from her undergraduate studies with Professor Funder, which challenged the belief at the time that MR acted predominantly in the kidney to regulate electrolyte, blood volume and hence blood pressure. Cardiac fibrosis/hypertrophy was proposed to be secondary to these actions of the MR in the kidney or driven by angiotensin II, another key effector hormone of the renin-angiotensin-aldosterone-system (RAAS). However, the importance of these early studies, and those from other groups, is evident by the success of the RALES, EPHASUS and EMPHASIS trials of MR antagonists and the development of newer, more receptor-selective MR antagonists

Photo: Left to right, Morag Young, Tim Cole, Peter Fuller and Jun Yang.

A new biology for the MR

Given that the risk of hyperkalemia and reduced renal function remains high for patients with heart failure taking MR antagonists, a key goal of the lab is to identify new mechanisms of action of the MR that modulate pathogenic actions of the MR, but not physiological (i.e. electrolyte homeostasis) actions. This has led to the development of a series of transgenic animal models in which the MR was selectively deleted in macrophages, cardiomyocytes and endothelial cells and resulted in the identification of new MR-regulated pathways. Of note MR signalling in macrophages is key for the induction of the proinflammatory response and which has expanded our understanding of corticosteroids and their receptors in inflammatory cells. In endothelial cells the MR regulates cell adhesion pathways and nitric oxide signalling, whereas in the cardiomyocyte the MR regulates ion handling proteins, and thus cell excitability, in a sex-specific manner. Another new biological role of the MR identified in cardiac cells in particular, was regulation of time keeping for the molecular clock. This led to new collaborations with leading circadian biologists Prof David Kennaway (Adelaide) and Prof David Ray (Oxford, UK). The molecular clock is instrumental for generating the circadian rhythms that drive many biological functions including blood pressure, metabolism, immune regulation and cell repair mechanisms; while glucocorticoids acting via their receptor (the GR) are established regulators of cellular clock timing, evidence from studies published by her laboratory show that the MR also plays a role that links to MR-dependent cardiovascular disease. Linking MR-mediated cardiac tissue dysfunction to circadian rhythmicity represents a significant advance in our understanding of the biology of MR signalling and has specific relevance for the MR in non-renal tissues where cortisol, and not aldosterone, is the primary ligand. Understanding the interaction between the molecular clock and the MR represents a new biology for the receptor and new direction for the laboratory.

Clinical studies – translating new findings to the clinic

Studies are underway to determine if outcomes from the preclinical and basic science studies can be translated to the clinic to enhance diagnosis or therapies. This work is being done in collaboration with Monash Heart and Dr Jun Yang. Other studies seeking to link MR activation and internal circadian rhythms investigated 24hr ambulatory blood pressure profiles in patients with either essential hypertension or PA and demonstrated that the increased blood pressure load in patients with PA was associated with loss of the normal 24hr blood pressure profile. Further studies are underway to investigate an intersection between the MR and circadian stress at the Baker Institute.

Primary aldosteronism

Other key studies investigating inappropriate MR activation in patients include collaborative work with Dr Jun Yang, who leads the Endocrine Hypertension Group at the Hudson Institute and Prof Peter Fuller. Studies led by Dr Yang also seek to translate and verify preclinical findings in patients and to determine if new MR regulated pathways can assist with diagnosis of patients with PA at an earlier stage to allow patients to start target therapy much earlier. This is important because patients with PA have a much higher risk of cardiovascular disease than for patients with equivalent high blood pressure but with essential hypertension. Ongoing studies include evaluation of the effectiveness of different treatment options for PA in clinical trials.

MR versus GR, aldosterone versus cortisol

Assoc. Prof Tim Cole Biochemistry Department at Monash University was the first to generate both an MR and a GR knockout mouse. Collaborative work between the laboratories of AProf Cole, AProf Young and Prof Fuller seeks to understand the actions of adrenal steroid hormones, which includes studies on steroid hormone nuclear receptors as well as the short-chain alcohol dehydrogenase-reductase enzyme family, specifically 11 beta hydroxysteroid dehydrogenase types 1 and 2 (11bHSD 1 and 2). Glucocorticoids exert their effects by binding to the intracellular GR and MR respectively. 11bHSD1/2 are responsible for the interconversion of active cortisol to cortisone and control ligand access to the receptors; 11bHSD1 is widely expressed but at high levels in tissues where GR signalling is critical (adipose, liver). 11bHSD2 is expressed predominantly in renal epithelial cells and as determined in the laboratory of Prof Funder, metabolised cortisol to inactive corticosterone thus allowing aldosterone to access the MR and control salt and water. Prof Fuller has led studies investigating the evolutionary role of MR in development and has identified fundamental structure-function relationships critical for ligand binding and MR signalling. Given the importance of the endocrine system for control of cell-cell communication and coordination of almost all our daily activities, understanding the actions of these two important corticosteroids is essential for all aspects of systemic physiology and homeostasis, in humans and other mammals.

New collaborations

AProf Cristian Carvajal from Santiago Chile is also interested in understanding the role of the MR in hypertension and elevated risk of cardiovascular disease. Following a visit to AProf Young's laboratory in 2017 and 2019 they established collaborative studies to pursue common interests in identifying new biomarkers of MR-dependent hypertension and renal injury in the cargo exosomes isolated from urine of patients and have published data on alpha-1-acid glycoprotein 1 (AGP1) thus far. They have been successful in obtaining funding to continue these studies and between laboratory exchanges may hopefully resume one day.

Photo: Cristian Carvajal, Morag Young and Jun Yang

Conclusions

Now located at the Baker Heart and Diabetes Institute, located on the grounds of The Alfred Hospital in Melbourne, the Young Lab has worked through the restrictions of the pandemic and set up novel collaborative studies with new colleagues in diabetes and cardiac dysfunction while maneuvering through COVID-related delays in delivery of supplies and equipment. Research at the Baker focuses on diabetes, cardiovascular disease, obesity, and their complications at the basic, clinical and population health levels and has close ties with clinical departments within the Alfred hospital.

The Institute overlooks the beautiful Falkner Park and the Melbourne City skyline and is in walking distance of many excellent coffee shops, which will thankfully continue running as we enter yet another lockdown.

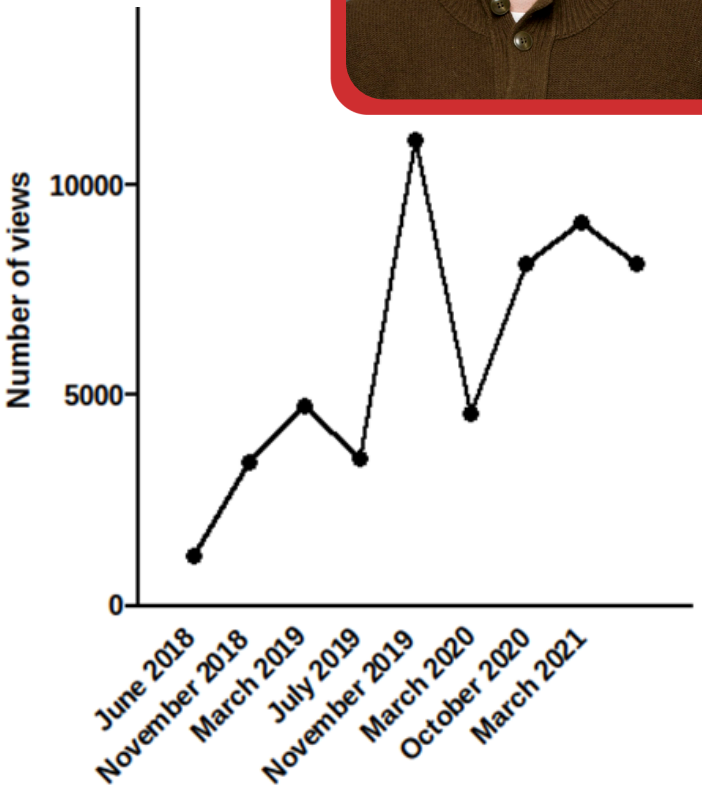
Photo: in the new lab with students Monica Kanki and Nikshay Karthigan

Morag Young - morag.young@baker.edu.au

"DDD" DYLAN'S DISTRIBUTION DATA

DYLAN BURGER
Ottawa Hospital Research Institute,
Ottawa, Canada.

Our March edition of Hypertension News was well received by the community and continued a trend of high readership. In total we had 8157 downloads which represents our third highest readership to date and the highest total that we have seen for a March issue. Highly read sections included the Hot Off the Press Basic Science feature from Dr. Quynh Nhu Dinh "Let's AIM2 find treatments for vascular dementia" and our Learning the Ropes features on pulmonary hypertension. There was also significant interest in our "New Blood" articles which were introduced for the March issue.



Dylan Burger - dburger@uottawa.ca

Be careful of your drink! clip from Lancet 1901

THE LANCET.] [FEB. 9, 1901.

Annotations.

"Ne quid nimis."

THE ROYAL COMMISSION ON THE BEER-POISONING EPIDEMIC.

THE Royal Commission which was appointed to inquire into the "recent exceptional sickness and death attributable to poisoning by arsenic in beer" met for the first time on Feb. 5th, under the presidency of Lord Kelvin, to consider the course of procedure. We believe that a preliminary course of procedure was decided upon, and we hope that the Commissioners have elected to direct their attention in the first instance exclusively to the question of poisonous beer. As we have pointed out, "exceptional sickness and death" have been traced indubitably to arsenic in beer, and this matter needs no further discussion. We hope the Commissioners will at once decide upon a recommendation that legislative measures be immediately taken to stop effectually the introduction of arsenic into beer.

MEANWHILE IN 'HYPERTENSION MEWS'...

all is well and cosy now when more than half of the adult Swedes have been Covid-19- vaccinated

The New Normal: Blood Pressure Monitoring and Cardiovascular Risk Assessment in the Era of Remote Care Delivery

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DOI:10.30824/2106-18

The time has come for telehealth to become usual care.

Telehealth has played a major role in the public health response to the COVID-19 pandemic and facilitated remote healthcare delivery. A key function of telehealth is to support the remote delivery of healthcare while maintaining a link between patient and physician.

To capitalise on the full potential of telehealth, the approach should include a broad range of digital technologies that integrate information communication technology alongside care delivery to support patient consultation, transfer data between multidisciplinary teams and remotely monitor physical measurements[1]. Telehealth presents an opportunity to improve ongoing care delivery for hypertension management and cardiovascular disease CVD prevention.

Remote blood pressure monitoring.

There are numerous, well-known challenges that limit accurate clinic blood pressure (BP) measurement, such a whitecoat hypertension and poor adherence to BP measurement protocols[2]. Given known challenges and the sustained need to reduce face-to-face clinical consultations due to COVID-19, it may be argued that there is little need nor justification for in-person clinic BP measurement. In fact, telehealth presents an opportunity to improve BP management (Figure 1). With the use of validated devices, home and ambulatory BP monitoring are alternatives that support accurate, remote BP measurement and may be superior to usual care for BP management[3]. There is strong rationale for widespread use of home and ambulatory BP monitoring as both are more reproducible than office BP and more predictive of target organ damage[4].

Out-of-office blood pressure measurement for absolute CVD risk assessment.

CVD primary prevention guidelines typically recommend the use of absolute CVD risk assessment to identify those at increased risk that require intervention. Most absolute CVD risk equations were derived using clinic BP measurements obtained either in a research or clinical setting. Despite the strengths of home and ambulatory BP monitoring, neither measurement method is currently recommended for use in absolute CVD risk assessment. This is in part due to a lack of evidence on the utility of such measurement methods for absolute CVD risk assessment. However, one study has demonstrated that the use of home or ambulatory BP had little effect on CVD risk assessment when compared to clinic BP[5]yet existing cardiovascular risk scores were developed for use with measurements obtained in clinics. With a shift to telemedicine, further work is needed to understand the role of remote BP measurement for absolute CVD risk assessment to identify individuals at increased risk and support guideline-recommended CVD prevention interventions.

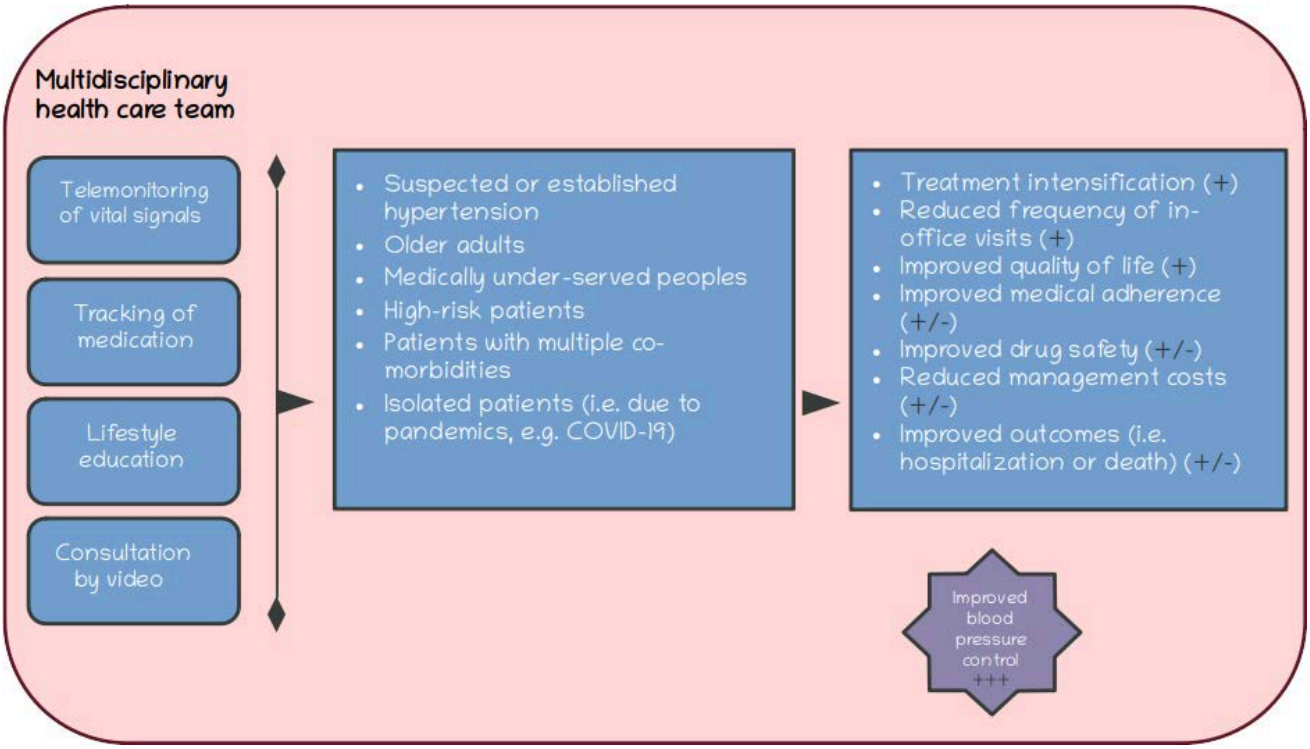
Next steps to support telehealth for BP management and CVD prevention.

The major challenges impeding the use of telehealth for BP management and CVD prevention include: 1) obtaining accurate home BP readings; 2) integrating digital technologies, including BP devices, to support data transfer to healthcare providers; and 3) confirming the

validation of using home BP measurements for absolute CVD risk assessment. Patients need to be supported to obtain a validated BP device with appropriate instructions provided to measure and record BP accurately. Ideally, home BP devices need to be fully integrated with existing healthcare information communications technology so that data can be automatically recorded from devices and transferred to the patient's health record to support healthcare providers to make informed decisions about patient management. However, so far there is no consistency in approaches to achieve this in practice. Finally, given the superiority and accessibility of home BP monitoring, further research is urgently needed to investigate the use of home BP for absolute CVD risk assessment.

In summary, the new normal of remote healthcare delivery presents an opportunity to address the known challenges to BP measurement and improve patient outcomes.

Figure 1. The use of telemedicine in the management of hypertension. Adapted from Omboni et al[1]



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Autophagy and Hypertension-Associated Premature Vascular Aging

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DOI:10.30824/2106-19

Many of the pathophysiological changes that occur in hypertension are the result of an accelerated deterioration in organ function, similar to what is observed in aging. While the increased incidence of cardiovascular events as we age is generally attributable to the natural decline in organ function, in hypertension, organ dysfunction is premature in its onset and particularly pronounced, especially in the vasculature[1]. In fact, arteries from hypertensive patients and animals present a range of phenotypes including, hypercontractility, stiffening and remodeling, inflammation, and oxidative stress, that a relatively early in there onset compared to age-matched normotensive controls. As a result, vascular age determination, as opposed to chronological age *per se*, has now been introduced into clinical guidelines for cardiovascular disease prevention. Nonetheless, a critical barrier to our progress in reducing the morbidity and mortality of hypertensive patients is our lack of understanding of the precise mechanisms that underlie premature vascular aging.

The aged phenotype is classically viewed as the accumulation of damaged cellular debris and dysfunctional organelles. Although waste products are an inevitable consequence of normal cellular metabolism, multiple systems are devoted to its repair, clearance, or recycling. Autophagy is the evolutionarily conserved catabolic process essential for both maintaining homeostasis via the recycling and removal of damaged cellular debris and dysfunctional organelles, as well as to provide micronutrients during times of starvation and stress.

Autophagy has long been associated with longevity, including the lengthening of lifespan[2]. Therefore, it is plausible that a decline in autophagy contributes to premature vascular aging in hypertension. This notion is supported by studies that showed that an upregulation of autophagy reversed several phenotypes of vascular aging in old mice, including endothelial function[3]. Moreover, our own previous data have reported that autophagic activity is reduced in resistance and conduit arteries from spontaneously hypertensive rats (SHR), and that reconstitution of autophagy ameliorated endothelial function and arterial stiffness in SHR[4].

Precisely how autophagy induction reduces the aged vascular phenotype (both chronological vascular aging and premature vascular aging associated with hypertension) is the focus of intense and rigorous research[5]. Until now, many of the important discoveries are centered on the premise that reduced autophagy leads to the accumulation of damaged cellular debris and dysfunctional organelles that causes inflammation and oxidative stress. Subsequently, this pro-inflammatory/pro-oxidative milieu quenches nitric oxide bioavailability. Therefore, upregulation/reconstitution of autophagy decreases these vascular dysfunctions. While these rigorous investigations have provided an important phenotypic understanding of how autophagy can ameliorate vascular function and structure in aging and hypertension, most of these studies have attempted to upregulate autophagy in the vasculature directly by using systemic interventions (e.g., lifestyle modifications, pharmacological agents administered orally, or transgenic overexpression). Therefore, these studies cannot rule out the contribution of multiple organ systems contributing to the vascular phenotypes measured.

Given the close association of autophagy with metabolic homeostasis, it is plausible that upregulation of autophagy imparts influence on metabolic pathways in diverse organs such as the liver and adipose tissue, as well as in endothelial and vascular smooth muscle cells. Catabolism of metabolic substrates via autophagy would therefore lead to the generation of novel

metabolites that can elicit anti-hypertensive and anti-vascular aging effects.

In summary, the generation of autophagy-dependent metabolites, especially from extravascular depots, proposes both a physiological mechanism by which autophagy can prevent vascular aging, and a pathogenic mechanism of decreased autophagy in hypertension. Moreover, these mechanisms incorporate the known anti-hypertensive and vasculoprotecitve effects of intermittent fasting and exercise, given that both lifestyle interventions are known stimulators of autophagy.

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COMMITTEE REPORT

Research and Education Committee Goes Global

NADIA KHAN

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British Columbia, Canada.

With the pandemic, the world has undergone a seismic shift in research and education. Research programs, work in scientific labs and clinical trials came to a halt and educational opportunities such as conferences were deferred or cancelled. Despite these impacts on research and education, new opportunities and lessons emerged. First, we bore witness to unprecedented, ultra-rapid development of vaccines and the development and testing of novel clinical treatments for COVID-19 infections made possible through advanced technologies and concentrated global efforts on a singular issue. In our first virtual ESH/ISH conference, over 5000 attendees and speakers from all over the world were able to access high quality educational sessions without leaving their homes and offices.

Harnessing global, diverse talent and leveraging the now commonplace technologies for communication, can multiply the Society's impact and reach on hypertension research and education. In developing our committee's aims and mandate to encourage the advancement of scientific research and knowledge globally, we aimed to use virtual platforms and partner with diverse, talented researchers and hypertension leaders globally. The committee also listened to the ISH member's input asking to help promote member's research and provide greater opportunities to participate in impactful knowledge outputs from the Society.

Prior to my role as chair of the Committee, I served as a council member and on the Women

in Hypertension Research Committee for 4 years and co led the Americas Regional Advisory Group. I am a health services researcher at the University of British Columbia in Canada investigating ethnicity and sex impacts on cardiovascular disease and management; and hypertension management including use of digital health tools. I am Professor and Head of General Internal Medicine, director of St. Paul's Hospital Hypertension Clinic and immediate past President of Hypertension Canada. I was appointed in October 2020 to chair the Research and Education committee. The committee comprises leaders in hypertension including Professor Tazeen Jafar from the University of Singapore, Professor George Stergiou from Athens University, Professor Claudio Borghi from the University of Bologna, Professor Yoshihiro Kokubo from Osaka University and our New Investigator liaison, Dr. Manja Zec from the University of Arizona. The committee developed the following initiatives:

1. **College of Experts:** (Lead, Professor Tazeen Jafar) The committee is assembling a cadre of diverse hypertension experts from around the world from clinical hypertension, research, policy and public health to provide the Society with expert guidance on various initiatives and issues including development of position papers, implementation and knowledge dissemination.

2. **Position Papers:** (Lead, Professor George Stergiou) The Committee is planning to develop 4 position papers on several important and timely issues including Night-time dosing of antihypertensive agents, the Virtual Management of Hypertension, Exercise and Hypertension as well as Single-Pill Combinations. Given that the papers are intended to be applicable to a diverse, global audience, we selected women and men leading experts on each topic from the regions represented by our Society. This initiative also gives an opportunity for early career investigators and clinicians to co-author and work with senior coauthors to build capacity within the Society.

3. **Café ISH:** (Leads, Professor Nadia Khan, Dr. Manja Zec) The goal of the ISH Café series is to share knowledge and viewpoints in hypertension in short, widely accessible videos delivered by experts around the world. This initiative helps promote ISH member's expertise and research. Highlights of some of the topics in the video series include:

Professor Ernesto Schiffrin (Canada) "Viewpoint: Top 3 Basic Science Must-Read Papers in Hypertension from 2020"

Professor Rhian M. Touyz (UK/Canada) "Novel and Emerging Drug therapies in Hypertension"

Professor George Stergiou (Greece): "Is Night-time dosing beneficial for managing blood pressure?"

Dr. Lyudmila Korostovtceva (Russia): "The Effects of Shift-Work on Blood Pressure"

The Café ISH series is expected to launch at the end of June.

4. **ISH Academy**: (Leads Professor Nadia Khan, Professor Yoshihiro Kokubo) The ISH Academy is a new online hypertension school. Anytime, anywhere, online education on hypertension taught by the world's leading experts on hypertension. This multi-day program will be uniquely designed for researchers or care practitioners to provide a comprehensive, education covering all essential and advanced subjects within hypertension from blood pressure regulation to management of endocrine hypertension. The course is expected to be ready for launch in early 2022.

5. **ISH Research Library:** (Lead, Professor Nadia Khan) The ISH research library is a curated collection of information on hypertensive research databases to improve access for hypertension research for ISH members. We plan to include information on the study design, key variables, and access application information for each of the hypertension research databases. Datasets will include for example, May Measurement Month and clinical trial data sets.

6. **ISH Endorsements:** (Lead, Professor Claudio Borghi) The committee is responsible for vetting endorsement opportunities for the society including education events, conferences, and other initiatives.

The committee would like to thank the President of ISH, Professor Tomaszewski, Dr. Brandi Wynne (lead for the New Investigator Committee), Dr. Vikas Kapil (Young Blood group), all of the Regional Advisory Group chairs, Dr. Dylan Burger lead from Communications Committee and Professor Muscha Steckelings lead for the Women in Hypertension Research Committee, for collaborating with the committee on these important initiatives and helping assemble our global teams.

Committee Leads:

Nadia Khan (Chair)

Tazeen Jafar (lead for College of Experts)

George Stergiou (lead for Position Papers)

Claudio Borghi (lead for Endorsement)

Yoshihiro (lead for Education section)

Manja Zec (NIC liason)

Full list of committee members

Nadia Khan - nakhanubc@gmail.com

Biggest Ever May Measurement Month Campaign Gets Underway

NEIL POULTER

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May Measurement Month (MMM), the global campaign initiated by the International Society of Hypertension (ISH) in 2017, that raises awareness of the need for people to get their blood pressure (BP) checked, has now officially started its extended programme of screenings in 2021, with more countries than ever before taking part.

In the first three years of the campaign (2017, 2018 and 2019) over 4.2 million people were screened globally, and almost 1 million people identified with untreated or inadequately treated hypertension. This year the fourth campaign is running from May to November, to allow for countries to be flexible within their COVID-19 restrictions.

MMM is thrilled to welcome Gambia, Kazakhstan, Norway, Tanzania, and Thailand, who are joining the campaign for the first time this year, bringing the number of participating countries to 92 in total. Each country is supported if required with a supply of blood pressure monitors (provided by our partners Omron), marketing assets and educational, easy to digest information around BP, what it means, the associated risks and optimal management, to share with participants.

In the event of COVID-19 preventing the usual face to face BP screening, in order to help as many people as possible access BP measurement, MMM have also introduced the possibility of home screening this year, with online guides and advice supported by an easy to complete questionnaire to submit their results. These are featured on a newly launched MMM website, maymeasure.org, and a newly designed MMM app – which we hope will encourage more people to record their results digitally which reduces the load of data cleaning.

In further efforts to work with the current pandemic challenges, MMM have teamed up with vaccination centres in the UK, Philippines and Georgia to screen participants whilst they attend for their COVID-19 vaccinations. This setting potentially could involve a huge number of people, albeit under different circumstances of measurement.

MMM is also partnering with the ZOE COVID Symptom Study app in 2021. The ZOE initiative was launched in March 2020 to support vital COVID-19 research by health science company ZOE (with scientific analysis provided by King's College London) and has over 4 million contributors albeit mainly in the UK. MMM is discussing the inclusion of some BP specific questions and to provide another platform for participants to input their home BP results, all data from which will be shared.

The short participant questionnaire that sits alongside the usual MMM BP screening has been updated this year to include questions on COVID-19, use of oral contraceptives and hormone replacement therapy, birthweight, adherence to therapy, usual consultation costs and exercise, as a move to increase the width of the data collected, and outputs of the campaign.

Raised BP remains the biggest single contributing risk factor to global death causing about 30,000 deaths per day. It is therefore vital that MMM continues to increase public understanding of the importance of BP measurement, and helps to save lives that need not be lost despite the variably difficult conditions imposed by COVID-19.

Interest in linking with MMM as a platform for research has arisen from several groups including, The Global Burden of Disease (joint analyses are in progress), Centre for Disease Control in the US (significant funding and research on pollution is being negotiated), Resolve to Save Lives (follow-up in Bangladesh, Philippines and Vietnam of those detected with raised BP by MMM).

MMM held an excellent one-hour session at the 2021 ESH-ISH Virtual meeting in April. The session included a brief summary of the 2017 and 2018 campaigns but featured the main 2019 results, followed by a review of the 12 abstracts and posters based on MMM data included in the main meeting programme, with four brief regional presentations from China, India, Argentina and Kenya. Finally, the exciting prospects and plans for MMM21 were outlined.

Meanwhile, the third MMM supplement, including 47 national publications from 2019 in the European Heart Journal Supplements is now available online at via the Oxford University Press website. With the publication of these new papers, we are very proud to say that we now have over 140 publications arising from MMM.

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

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The election as a Fellow honors members of the Society who have distinguished themselves through excellence in clinical practice or research in the field of Hypertension.

https://ish-world.com/membership/join.htm

LET'S REDUCE DISPARITIES IN THE MANAGEMENT OF HYPERTENSION.

Hypertension remains the leading global cause of cardiovascular disease and preventable death.[1] Low- and middle-income countries have more people with hypertension than high-income countries and lower rates of blood pressure control.[2]

These disparities vary significantly according to ethnicity and genetic differences, and are accompanied by lower levels of awareness, treatment, and control.[3]

Read the **2020 International Society of Hypertension Global Hypertension Practice Guidelines** to learn how to start addressing the needs of hypertensive patients worldwide.

ish-world.com

References

[1] Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; 396:1223-1249.

[2] Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol.* 2020 Apr;16(4):223-237. doi: 10.1038/s41581-019-0244-2. Epub 2020 Feb 5. PMID: 32024986.

[3] Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension global hypertension practice guidelines. *J Hypertens.* 2020 Jun;38(6):982-1004. doi: 10.1097/HJH.0000000000002453. PMID: 32371787.

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In collaboration with
the 17th Congress of the Asian Pacific Society of Hypertension (APSH)
the 45th Annual Meeting of the Japanese Society of Hypertension
The Wisdom for Conquering Hypertension

ISH 2022 Kyoto will highlight

① Innovative Hypertension Research Programs
② Sophisticated & Attractive Events in Kyoto
③ Highly-cooperative System for Young People

Program focused on 1. Food 2. Moving 3. AI

Your proposal is always welcome at " www.ish2022.org "!!

Activity of the Japanese Society of Hypertension (JSH)

JSH Plan for the Future
Good Blood Pressure for Lively 100 Years

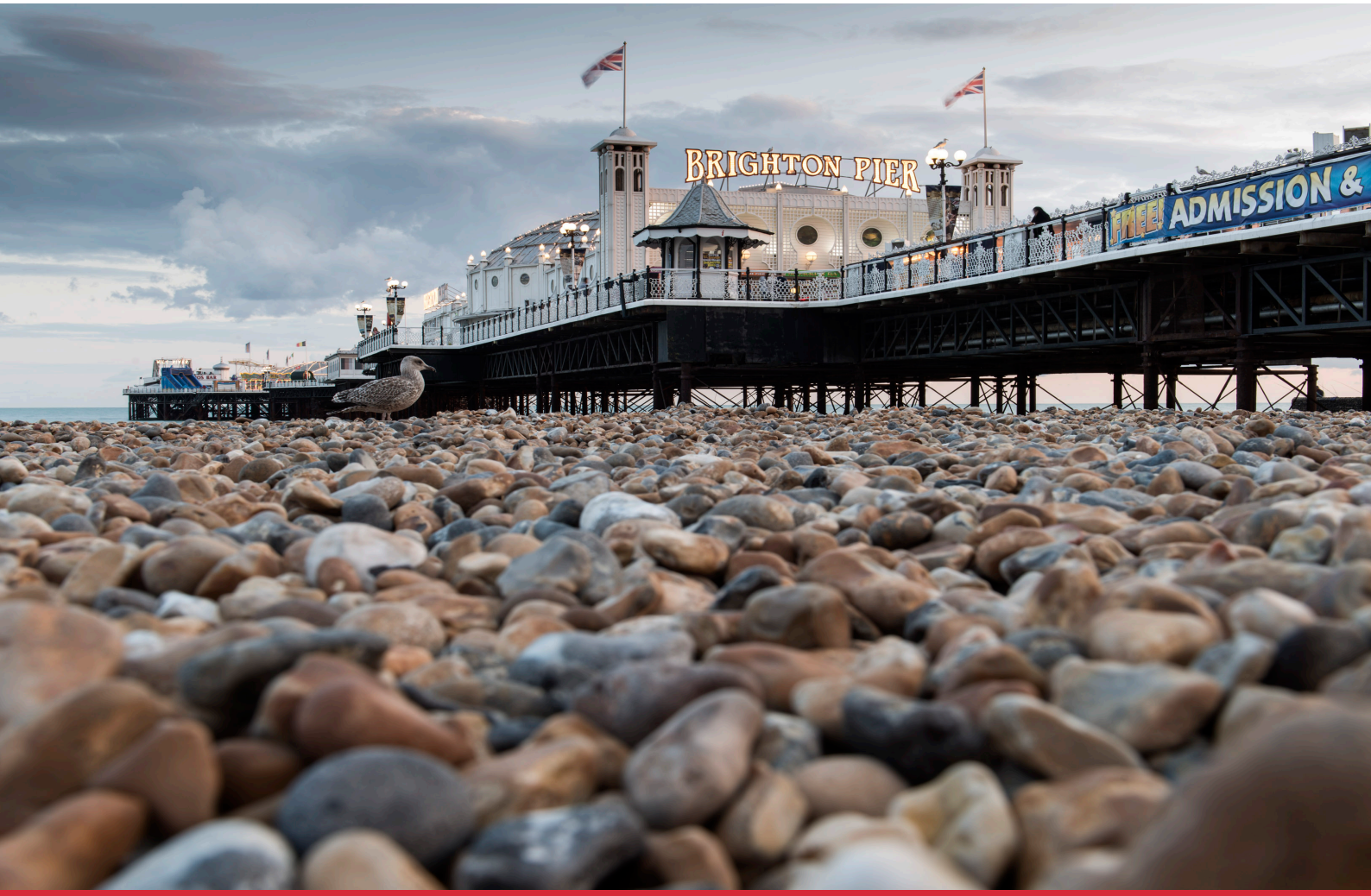
Reduce hypertensive patients by 7 million in 10 years, and Expand the healthy life expectancy
Through…

1 Medical System — Establish a lifetime-care system for individuals with hypertension
2 Academic Research — Promote research in hypertension and embody "Future Medicine"
3 Social Edification — Develop a social model for self-controlled blood pressure

BIHS

British and Irish Hypertension Society

Committed to preventing cardiovascular disease



British and Irish Hypertension Society Annual Scientific Meeting 2021

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