



June 2015, Opus 41

Notes from the Editor

- Lars H. Lindholm

Dear member,

As you may be aware, with the move of the ISH Secretariat to The Conference Collective, we have also recently changed the email provider we use to communicate with you, the ISH members.



Unfortunately, it has come to our attention that some organisations and institutes are unintentionally blocking these email communications. As a result, some members may be missing out on key society updates – including membership renewal notices, and Hypertension News!

We assure you that we are taking every action to get this resolved as quickly as possible, to ensure that you stay connected to Society activities.

Some of you will have even received a letter in the post from the Secretariat recently, asking you to confirm if you are receiving the ISH email updates. If you have received one of these letters, we would very much appreciate you taking the time to respond to this using the enclosed postcard.

We ask that you check that your fellow ISH members - friends and colleagues - have received this latest edition, and if they haven't, please advise them to contact the ISH Secretariat at their earliest convenience so that the situation can be resolved.

In the present issue of Hypertension News you will find an interesting presentation of the Centre for Chronic Disease Control in New Delhi, India written by Dorairaj Prabhakaran which I recommend you to read. As usual, there are also several small contributions under the heading "Hot off the Press" from both clinical as well as basic science. Finally, towards the end you will find a fairly comprehensive review of the links between air pollution and vascular health.

Have a good read!

Lars H Lindholm,
Editor

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Have a question about your ISH Membership?

Visit our stand at the
ESH 2015
meeting in Milan



From the ISH President - Rhian Touyz



I am delighted to update you on recent ISH activities. However, I would firstly like to applaud our colleagues at the World Hypertension League (WHL), all our dedicated and dynamic members and affiliated national and regional societies whose excellent work on and around World Hypertension Day (WHD) - 17th May - will ensure that hypertension remains on the global agenda and that we can work together to tackle the challenges presented by this silent killer.



We look forward to continuing to report on your WHD initiatives via the ISH website and / or via New Investigator Committee social medial platforms, in particular Facebook and Twitter. You will also see a report later in the newsletter from the WHL on WHD (see page 20).

The Regional Advisory Groups (RAGs) continue to be busy and we are delighted to have sent multiple teaching faculty members to educational activities and meetings already this year including Beirut (Lebanon), Cape Town (South Africa), Kemerovo (Russia), Tucumán (Argentina).

Reports from Teaching Faculty members can be viewed in the news section of our website and we look forward to keeping you posted on faculty attendance at events including the Russian Antihypertensive League meeting in May in St Petersburg (Russia), CardioAlex, Alexandria (Egypt) in June and the 23rd Congress of the Brazilian Society of Hypertension in Rio de Janeiro in August.

I would like to give my thanks to the organisers of these global meetings who have made, and continue to make, our ISH representatives most welcome!

June Scientific Meetings

We wish our Asian Pacific Society of Hypertension (APSH) and European Society of Hypertension (ESH) colleagues the greatest of success with their Bali and Milan Scientific Meetings this month and the ISH leadership hopes to meet you at these events.

The ISH will have an exhibition booth at the ESH meeting. We welcome you to visit us there and please encourage your friends and colleagues to come to the booth so that they can register their interest in joining the Society.



Visit the ISH Stand

Of note, don't forget that those joining the Society as Research Fellows (new investigators) will benefit from membership at no cost for 3 years!

[Click here](#) to view our new Society brochure for more information or the Society website to view a list of membership benefits.

Hypertension Seoul 2016

Plans are advancing well with the local organizing committee in Korea for the ISH Seoul 2016 Scientific Meeting (24 - 29 September) 2016.

Hypertension Seoul 2016

The 26th Scientific Meeting of the International Society of Hypertension

September 24(Sat) - 29(Thu), 2016
COEX, Seoul, Korea



The theme for the meeting is 'Working Together for Better Blood Pressure Control and Cardiovascular Disease' and we look forward to working closely with Professor Cheol-Ho Kim (Meeting President) and his local organizing committee in helping to create an outstanding scientific program under this banner.

IMPORTANT DATES:

Abstract Submission Deadline:	Feb. 24, 2016
Notification of Acceptance:	Apr. 25, 2016
Online Registration Opens:	Sept. 24, 2015
Early Bird Registration Deadline:	May 16, 2016
Pre-Registration Deadline:	Jul. 31, 2016

I encourage you all to register and submit your abstracts when the Seoul meeting sites open on 1st July!

Annual Council & Committee Meetings

The Society will hold a Council and various committee meetings in June and I am delighted to report that I will chair the inaugural committee meeting on 'women in hypertension research' to focus on developing programs, mentoring schemes, networking systems etc to support and encourage women in hypertension research. I look forward to reporting back on key points of these meetings in the next issue of Hypertension News.

For those of you who will be at the ESH Annual Meeting in Milan, please come by the ISH booth – it would be a pleasure to see you and to share with you the latest ISH news.

- Rhian Touyz

New Investigator Committee (NIC) Update



June ISH New Investigator Committee Networking & Mentorship Event

Young and new investigators are invited to join ISH New Investigator Committee (NIC) for a networking reception in Milan. ISH New Investigator Committee (NIC) and ISH leaders will be on hand as mentors to answer questions that young investigators may have about their research and careers. A list of mentors will be released shortly, so be sure to keep an eye out on our website!

Where, when and how much

The event will start at 8.00pm on **Saturday 13th June** at the **Boscolo Milano Hotel (Milan, Italy)**, a distinctive, contemporary, iconic hotel, full of Italian style and perfectly situated in the heart of the famous fashion shopping district, Quadrilatero della Moda.¹ The beautiful rooftop terrace provides magnificent views of the illuminated Duomo spires making it the perfect place to mingle and make new ISH friends. The event is free of charge.

RSVP

Places are limited.

Please contact secretariat@ish-world.com should you be interested in attending.



Boscolo Milano



Milano Duomo

Institute Focus



Centre for Chronic Disease Control, New Delhi, India

Dorairaj Prabhakaran,
Executive Director



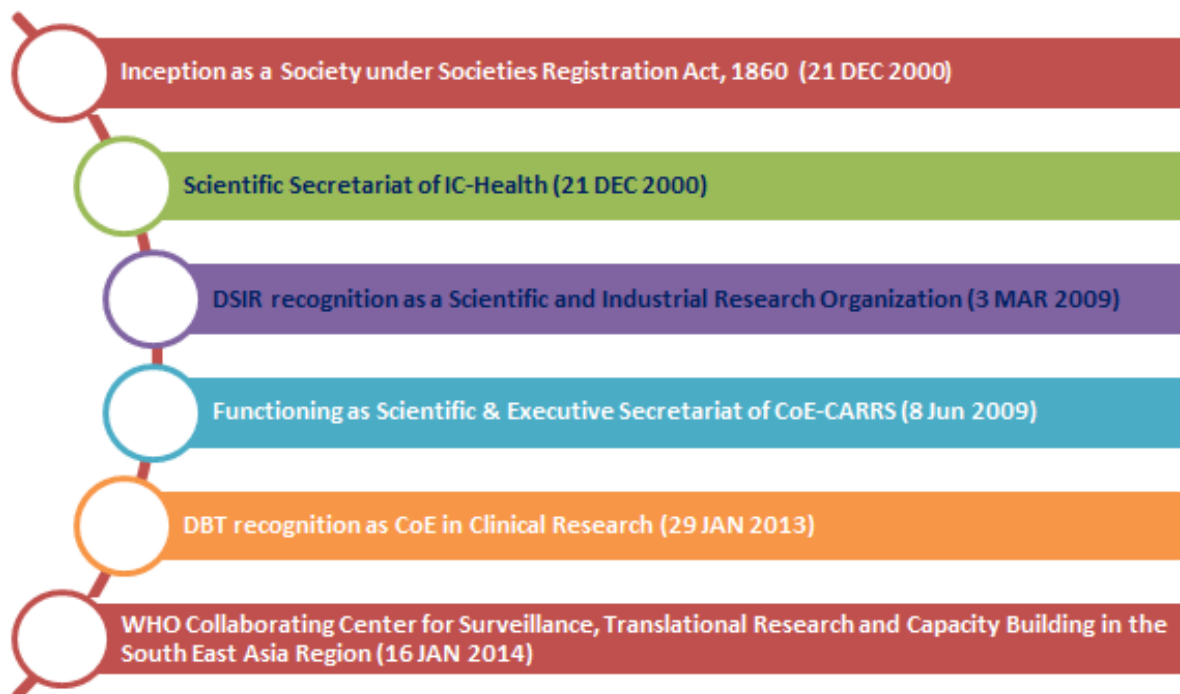
Centre for Chronic Disease Control (CCDC) is an independent and not-for profit biomedical research organization, based in New Delhi, India. CCDC is driven by a passion to promote and protect human health in India and the world at large.

Mission

To address the growing challenge of chronic diseases, in varied settings of developing countries through:

- Knowledge generation, which can inform policies and empower programmes for the prevention and control of chronic diseases
- Knowledge translation intended to operationalize research results by bridging the critical gaps between relevant research and effective implementation, through analytic work, capacity building, advocacy and development of educational resources for enhancing the health of people and empowerment of public health professionals.

CCDC Mile stones



Clinical Research at CCDC

CCDC undertakes clinical research in various domains of health care with special emphasis on chronic non-communicable diseases. Within the spectrum of chronic diseases, our main focus areas are: cardiovascular disease, diabetes and metabolic disease, cancers and mental health. In addition, basic science research in diet/nutrition and cardiac biochemistry complete the list.

Within these domains CCDC engages in clinical research, scientific writing, health informatics, data analysis, consultancy, training, policy advocacy and scientific secretarial assistance to international research bodies.

Institute Focus



Research at CCDC focuses on

- o Understanding the underlying mechanism of increased risk of cardiovascular disease (CVD) among Indians,
- o Developing a model CVD surveillance program in partnership with Public Health Foundation of India,
- o Research into developing low cost preventive solutions for secondary prevention of CVD, and
- o Innovative use of information technology and traditional methods in the prevention and management of CVD and its risk factors.

CCDC in partnership with Public Health Foundation of India is implementing a cohort modelled surveillance project for cardio-metabolic disease (CMD) and its risk factors which can be adopted for continuing surveillance both within and across countries in South Asia. The first cohort has completed three years of follow up and the second cohort is recruiting participants. Several sub-studies branch out from the surveillance study which includes a wide array of research aspects.

CCDC has led and partnered in many important trials within India and across the globe. Many of them centre on the principle of implementing low-cost, innovative, scalable and sustainable strategies for cardiovascular risk reduction such as the CARRS translation trial, UMPIRE, STITCHES, CORONARY, SIMCARD trial. One of our demonstration projects, the mPOWER heart project involves the use of trained nurses for improving the access to CVD care at primary care and to integrate smartphone-based clinical decision support systems (mDSS) to aid physicians and nurses in practicing evidence based medicine for hypertension/diabetes in order to improve the quality of care.

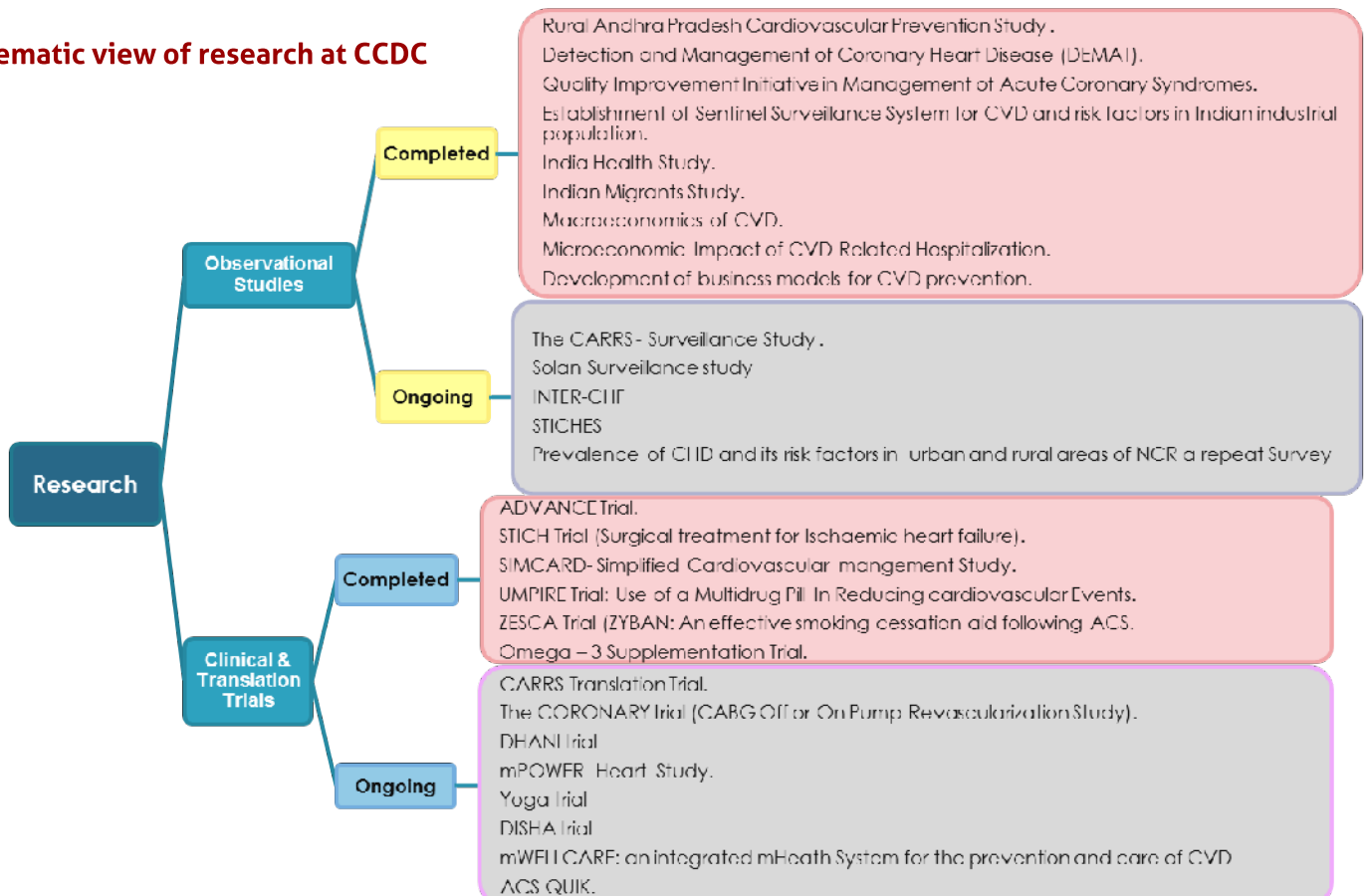
Results from these studies have produced major insights into the epidemiology, developmental origin and biomarkers of CVD and diabetes in India, translation research in CVDs, and development of low-cost combination drugs for CVD prevention in South Asia.

CCDC Quick Facts

- Total Employees: ~100
- Focus Area- Non Communicable Diseases
- Evolved from Coordinator to Initiator
- Established Network: National & International
- Facilities: In-house laboratory



Schematic view of research at CCDC



Institute Focus



Capacity Building at CCDC

CCDC is engaged in a plethora of capacity building activities with several collaborating partners. A network of researchers from across the globe has been established to enhance the research capacity for CVD health.

o CCDC as the scientific secretariat of the Initiative for cardiovascular health research in developing countries (IC-Health), established a network of researchers in 24 developing countries, enhancing the research capacity for CVD health research in these nations.

o Under the Millennium Promise Award, CCDC in collaboration with Emory University provides short-term interdisciplinary training on non-communicable diseases (NCDs) with focus on the epidemiology and prevention of NCDs across the life-course and cross-cutting areas.

o Other capacity building programmes include the ASCEND and SHARE projects for NCDs and mental health respectively. **The Asian Collaboration for Excellence in Non-Communicable Disease (ASCEND)** is a non-communicable disease (NCD) capacity building program of the Asian Non-Communicable Disease Research Network. The **South Asian Hub for Advocacy, Research and Education on Mental Health (SHARE) Study** SHARE is a training and capacity building project. The broad study aims are to establish a collaborative network of institutions in South Asia for reducing treatment gaps for mental disorders in the region through task-shifting and research capacity building and disseminating evidence to partners and collaborating with other Hubs.

o Serves as an implementing partner for the Fogarty International Clinical Research Training Site at PHFI. The outcome of the training has been highly encouraging. There have been over 50 research publications by the fellows and several grant applications have been approved to generated funding support.

o Organised the 42nd and 47th Annual teaching seminar on CVD Epidemiology and Research Methods conducted by the International Society for Cardiovascular Epidemiology and Prevention in the years 2009 and 2014 respectively.

o Instrumental in organising several seminars on CVD epidemiology, INDO-US Advanced Training Seminar on Nutritional Epidemiology.



Policy Advocacy

CCDC has been a key player in advocacy for framing policy guidelines.

- o Assisted the Government of India in developing the National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular diseases and Stroke.
- o Technical assistance to WHO (SEARO) in their capacity strengthening initiative for policy makers and program managers in the SEARO region.
- o Helped develop the regional policy note for the World Bank on NCDs.
- o Helped formulate a set of standards for various primary care and district level hospitals for the India Public Health Standards (IPHS) under Government of India's National Program on Prevention and Control of Cancer, Diabetes, Cardiovascular diseases and Stroke (NPCDCS).
- o Involved in editing journals including a special issue on cardiovascular disease from the Indian Journal of Medical Research, Global Heart and the Disease Control Priorities Network (DCPN); 3rd edition.



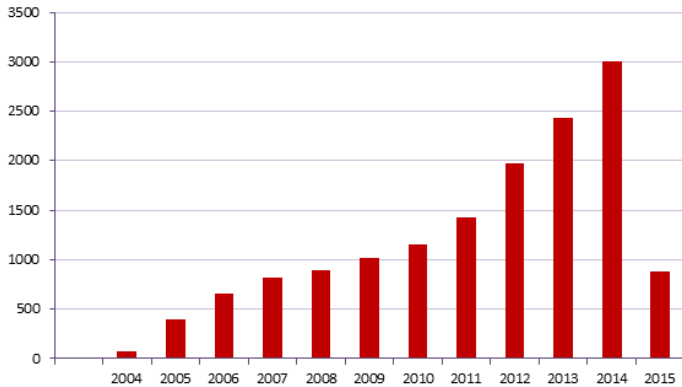
Research from CCDC has produced large number of peer reviewed publications in many high impact journals.

- Average impact factor: 9.72
- Policy briefs to World Bank/ WHO/ Government of India
- Translational potential: The work site program has been cited as an example to emulate by Institute of Medicine (Washington) and the World Economic Forum (WEF)

Institute Focus



Number of citations for CCDC research: 2004- 2015



Visionaries who guided CCDC



Prof. Rajendra Tandon



Prof. Srinath Reddy

- Dorairaj Prabhakaran

Hot off the Press



Thomas Kahan

Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of Cardiovascular Medicine, Stockholm, Sweden; and Department of Cardiology, Danderyd University Hospital Corporation, Stockholm, Sweden

Aortic/brachial pulse wave velocity ratio a better marker of vascular and prognosis stiffness?

The composition of the arterial wall changes from central arteries such as the aorta, where elastin content is high, to peripheral arteries, where collagen content is dominant. Furthermore, the arteries become stiffer with increasing age and with disease. Of note, this increased stiffness with age is more prominent in the central arteries than in the peripheral vessels, and is referred to as aortic-brachial stiffness mismatch. These alterations will enhance the transmission of pulsatile energy into the microcirculation and may increase the risk of microvascular organ damage with increasing age and disease.

An increased arterial stiffness increases pulse wave velocity (PWV), and the carotid-femoral PWV is well recognized as a measure of aortic stiffness. Furthermore, carotid-femoral PWV has been shown to associate independently to cardiovascular morbidity and mortality. This was shown early in patients with end-stage kidney disease and haemodialysis [1], a group of patients attending regular medical care and with progressive atherosclerotic disease and a very high risk of cardiovascular events. Of interest, patients in haemodialysis show no relation between carotid-radial PWV and outcome [2], and an enhanced aortic-brachial stiffness mismatch over time [3], suggesting that

the aortic/brachial PWV ratio may provide valuable prognostic information.

Fortier et al now examined the ratio carotid-femoral PWV to radial-femoral PWV (i.e. aortic/brachial PWV ratio) in relation to mortality in 310 patients in dialysis during a median follow-up of 29 months [3]. Mean age was 67 years and 60% were male; diabetes was present in 43%. Almost half of the patients (146; 47%) died during follow-up. The hazard ratio for aortic/brachial PWV ratio for mortality was 1.43 (95% confidence interval 1.24–1.64; $P < 0.001$) per 1 SD, and this remained significant also after adjustment for confounding factors. The associations for carotid-femoral and carotid-radial PWV, augmentation index, pulse pressure amplification, and other markers of arterial stiffness were weaker and no more significant when adjusted for confounding factors.

This is the first study to show that aortic-brachial mismatch assessed by the aortic/brachial PWV ratio is a stronger marker for mortality than currently used indices of vascular stiffness. Although not unexpected, these novel findings are important as they may suggest a way to improve risk stratification by the use

of aortic/brachial PWV ratio. Also important, it demonstrates that arterial vascular function is heterogeneous. This should, as always, be considered in studies of arterial function. However, some important limitations need to be considered. Most importantly, this study was performed in end-stage kidney disease patients in dialysis, who are at very high risk. Whether these results can be generalized to a broader population warrant further study.

- Thomas Kahan

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Hot off the Press

A place for arterio-venous anastomosis in resistant hypertension?

- Thomas Kahan

Although the efficacy of antihypertensive drug therapy is very well documented, observational studies show that a minority of treated hypertensive patients achieve target blood pressure [1]. There may be several reasons for this and the behaviour of both patients and caregivers may be involved. Some 10-15 % of the adult hypertensive population is considered to have resistant hypertension, as they do not reach target blood pressure despite being offered three or more drug antihypertensive drug classes [2]. Treatment of patients with resistant hypertension has attracted much interest recently as they are at high risk for cardiovascular complications. Several interventional techniques have been introduced, most notably techniques interfering with autonomous nervous vascular control by sympathetic renal denervation [3] and baroreceptor activation therapy [4].

A different interventional approach to treat uncontrolled hypertension was studied by Lobo et al, who evaluated the effects of adding a low resistance high compliance venous segment to the central arterial vasculature by introducing a central arterio-venous femoral-iliac anastomosis [5]. This open study randomized 83 patients with resistant hypertension (office blood pressure 140 mm Hg or more and daytime ambulatory systolic blood pressure 135 mm Hg or more, and on three or more drug classes including a diuretic) to treatment with a novel arterio-venous ROX Coupler device or to a control group with no intervention. By a percutaneous technique a 4 mm in diameter connection between the femoral artery and the iliac vein was created by the interventional device. Mean age was 59 years, one third were female, baseline office blood pressure was 173/100 mm Hg and the participants were on an average of 4.8 antihypertensive medications. The primary outcome was the mean change in systolic office and 24 hour ambulatory blood pressure at 6 months.

Of the 44 patients randomised to intervention 1 withdrew consent before the procedure was performed and 1 did not receive a device due to anatomical reasons. At 6 months there was a 27/20 mm Hg reduction in office blood pressure and a 14/14 mm Hg reduction in 24 h ambulatory blood pressure in the intervention group, as compared to 4/2 and 0/0 mm Hg reductions in the control group, respectively. These differences between the groups (23/18 and 13/13 mm Hg, respectively) were all significant. Furthermore, antihypertensive medications were more often reduced in the intervention group (reduced in 11, increased

in 4), and more often increased in the control group (reduced in 2, increased in 10) during follow up. The results were similar in the 17 patients with a previous renal denervation procedure. The authors report 25 (58 %) complications. There were 13 procedure related complications, of which 2 were considered serious. Another 12 (29 %) were device related and were all lower limb oedema due to iliac vein stenosis proximal to the anastomosis, which required treatment with venoplasty and stenting.

This is an important study for several reasons. There is an unmet need for new therapeutic interventions for patients with resistant hypertension. This is the first prospective controlled study on antihypertensive treatment by an arterio-venous coupler device. The interventional procedure is relatively simple to perform, and the haemodynamic results can be viewed immediately, whereas the confirmation of a successful procedure with sympathetic renal denervation or baroreceptor activation therapy at present remains difficult. The blood pressure reduction was substantial, which was to be expected, as the interventional procedure will reduce arterial resistance through increased arterial compliance. The effects of the intervention may actually be greater, as the results may have been attenuated by the changes in drug use during the course of the study.

However, there is still a way to go until this novel approach to treating resistant hypertension is ready for implementation in clinical practice. First, Lobo et al did not assess drug adherence to ascertain the blood pressure effects are not confounded by other factors than the arterio-venous coupler device, which may be particularly important when there was no sham treated control group [6]. Second, there were several complications related to the procedure and the device. Of note, almost one third of the patients required an intervention for iliac vein stenosis, and we have yet to see the long-term risk of local vascular complications. Third, the arterio-venous femoral-iliac anastomosis may have hemodynamic consequences on the heart and circulation with untoward effects, such as impaired coronary artery circulation due to the marked reduction in diastolic blood pressure, which may be important caveats in diseased patients [7,8].

- Thomas Kahan

See references overleaf

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Hot off the Press



Bo Carlberg (shown Left)
and **Mattias Brunström**

Department of Public Health and Clinical Medicine,
Umeå University
Sweden

Benefit against risk with thrombolysis in acute ischemic stroke

Intravenous thrombolysis with alteplase is the standard treatment for acute ischemic stroke. The time window for which treatment is approved, however, differs between countries. In the U.S., the license for alteplase is only valid up to 3.0 hours after first symptom, whereas in Europe the licence extends up to 4.5 hours. Also, guidelines disagree on whether treatment should be given at all. In most emergency medicine guidelines, treatment is not recommended, whereas in guidelines issued by stroke associations, treatment is strongly recommended.¹

In The Lancet, Emberson and colleagues present results from an individual patient data meta-analysis of alteplase treatment for acute ischemic stroke.² This meta-analysis shows significant improvement in the overall likelihood of a good stroke outcome, up to 4.5 hours after first symptom in the stratified analysis, and up to 5.0 hours in the regression model. We argue, in a letter to the Lancet, that the relative risks are misleading, and that results should be presented as absolute risks, together with data on intracranial bleeding and all-cause mortality.³

Using the crude numbers presented in the original paper, we calculated absolute risk reductions (ARR), and numbers needed to treat (NNT), for a good stroke outcome depending on treatment delay. If treatment was given ≤ 3.0 hours after first symptom, the ARR was 9.8 % and NNT was 10. If treatment was given > 3.0 but ≤ 4.5 hours after first symptom, the ARR was 5.2 % and the NNT was 19. The absolute risk increase (ARI) for symptomatic intracranial bleedings at 7 days was 5.5 %, and the number needed to harm (NNH) was 18. In addition, the authors present a borderline significant ARI of 1.4 % for 90-day mortality, giving a NNH of 71. Neither the risk of intracranial bleeding or all-cause death interacted with treatment delay.

In the present situation, with discordant recommendations, the decision to use alteplase to treat ischemic stroke is ultimately up to each clinician. When facing the patient, it is helpful to know what to expect from the potential treatment. In this

meta-analysis, the best available evidence to date, the beneficial effects of thrombolysis seems to outweigh the risks, if treatment is given ≤ 3.0 hours after first symptom. In the time window 3.0-4.5 hours after first symptom, however, the chance of a good stroke outcome is approximately the same as the risk of an intracranial bleeding.

- Bo Carlberg
- Mattias Brunström

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Hot off the Press



Ooneb Mian, Montreal, Canada (left)
and Dylan Burger, Ottawa, Canada (right)
ISH New Investigator Committee members,
Media Working Group

Vascular Type 1A Angiotensin II Receptors Control BP by Regulating Renal Blood Flow and Urinary Sodium Excretion.

The systemic vasoconstrictor effect of angiotensin II by activating AT1 receptors on vascular smooth muscle cells (VSMCs) has been argued as an integral component in the pathogenesis of hypertension since cardiac output and peripheral vascular resistance are the main determinants of blood pressure. On the other hand, Guyton first proposed that sodium excretion by the kidneys provides a compensatory system with infinite gain to counter mechanisms of blood pressure elevation (1). In this regard, Coffman lab previously demonstrated a critical role for kidney AT1A receptors in the development of angiotensin II-induced hypertension by transplanting kidneys from AT1A-knockout mice into wild-type mice and showing blunted blood pressure responses (2). However, the kidney consist of a heterogeneous population of cells, and in that study the exact cell type within the kidney responsible for this effect was not elucidated.

Recently, the Coffman lab sought to examine the role of vascular AT1A receptors in blood pressure regulation and development of hypertension. In an article recently published in the Journal of the American Society of Nephrology, Sparks and colleagues generated mice with a specific deletion of AT1A receptors in VSMCs of both conduit and resistance vessels using Cre-LoxP technology (3). VSMC knockout of AT1A receptors caused a small but significant reduction in baseline blood pressure, and enhanced sodium sensitivity in mice. Additionally, these mice were resistant to angiotensin II-induced hypertension; protection which was attributable to enhanced urinary sodium excretion. Vasoconstrictor responses to angiotensin II in the renal circulation were almost completely abrogated in the VSMC-knockout mice although angiotensin II-dependent responses in the systemic vasculature were largely preserved, possibly due to enhanced

sympathetic outflow.

One experiment that may have added value is to the present study is to transplant the VSMC-AT1A-deficient kidneys into healthy mice. Such experiments would leave systemic AT1A receptors in place and eliminate any indirect contributions of the systemic circulation.

Nevertheless, when viewed in the context of their previous work, the authors provide compelling evidence that renal AT1A receptors in VSMCs play a critical role in the development of angiotensin II-dependent hypertension. Importantly, by highlighting the impact of angiotensin II-dependent vascular responses in the kidney on natriuresis and blood pressure control this study bridges the concepts of vascular actions of angiotensin II and altered renal sodium handling in the pathogenesis of hypertension.

- Ooneb Mian
- Dylan Burger

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TIME -Is dosing time important for treating hypertension?



Amy Rogers , TIME Study Doctor (shown left)

Medicines Monitoring Unit (MEMO)
Minewells Hospital and Medical School
University of Dundee, Dundee, UK



It is known that there are differences in the blood pressure lowering efficacy and duration of action when antihypertensive medications are administered at different times of day.

Additionally, night-time BP has been shown to be a better predictor of cardiovascular outcomes than day-time BP[1]. The MAPEC study suggested that bedtime administration of one or more antihypertensive medication was better for ambulatory blood pressure control and cardiovascular risk reduction[2]. It has also been postulated that the positive results of the HOPE study could be partly explained by night-time dosing of Ramipril[3].

The question then remains: Does it matter what time people take their antihypertensive medication?

The TIME (Treatment In Morning vs Evening) study is recruiting patients taking once daily antihypertensive medication. The aim is to establish whether night time dosing is better (or worse) than morning in preventing myocardial infarction, stroke, and vascular deaths. Recruitment to the study is open to anyone in the UK who takes antihypertensive treatment once daily. The aim is to recruit at least 10,000 treated hypertensive participants and follow them up until sufficient end-points have occurred to analyse the study.

Patients are invited by General Practitioners and Hypertension clinics writing to their treated hypertensive patients and by advertising and social media. It is hoped that the pre-consented database, UK Biobank, will also play a part in study recruitment. A centralised mailing to all GP practices in the UK was undertaken at the end of 2014 which resulted in 200 practices to date inviting their patients to take part. These are currently being followed up with the assistance of the UK research networks who are providing support to the study. Once patients have been invited by their GP no further input is required from practices. We have also asked hospitals and practices to put up posters in their practices even if they do not want to actively invite patients. To date, 2,900 patients have been recruited.

Patients register themselves directly for the study at www.timestudy.co.uk, where they can read more detailed information. Consent for the study is completed by the patient online before inputting their study data directly via the web portal. Study participants need to have regular access to the internet, as this study is done entirely through a secure website and all contact is via the website and email. Although this excludes a certain proportion of patients, for practical and financial reasons it would be difficult to do a study of this size in the conventional way. Previous studies that have used this method found it to yield high quality and cost-effective data. Participants are asked periodically by email to complete online follow-up forms designed to collect data on the acceptability of the drug administration time and potential side effects.

The primary end point of this study is determined by record-linkage. All UK hospitalisations and deaths and all potential endpoints undergo adjudication by a committee blinded to the treatment time allocation.

If this study shows that the time of day patients take their medication does influence their risk of major cardiovascular events, it could provide very cost-effective health benefits. Given the prevalence of hypertension in the population, even a modest effect could translate into important benefits.

TIME is a British Hypertension Society Research Network Study. It is led by Professor Tom MacDonald with a team based at the University of Dundee. The study is funded by a British Heart Foundation research grant.

As the study is a British Hypertension Society Research Network study, members of this network have already been asked if they can directly invite suitable patients from their clinics. We hope that consultants who are not members of the network will also do the same. Anyone who is interested in finding out more about this can contact the co-ordinating centre in Dundee via www.timestudy.co.uk.

- Amy Rogers

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Guido Grassi

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Sympathetic Activation in Hypertension: pathophysiological role and target for treatment

Over the past 30 years a growing amount of information has been collected on the importance of adrenergic neural factors in the development and progression of high blood pressure and related target organ damage. The interest for the sympathetic overdrive in the pathogenesis of hypertension has been recently renewed with the investigations showing the potential sympathoinhibitory and blood pressure lowering effects of renal nerves ablation in the so-called "resistant hypertension" state.

Evidence collected throughout the years has shown that essential hypertension is characterized by a reduction in the inhibitory influence exerted by the vagus on the heart, with a resulting increase in resting heart rate. The sympathetic nervous system also participates in this heart rate increase, due to the tachycardic effects adrenergic neurotransmitters have on sinus node activity [1]. Both vagal and sympathetic cardiovascular influences appear to be already altered in the pre-hypertensive stage and in borderline hypertension, i.e., in conditions in which blood pressure may be still in the normal or in the high-normal range [1]. Indeed, evidence exists that in both these two conditions sympathetic nerve traffic, as assessed via the microneurographic technique, appears to be already elevated [1]. Conversely, in these pre-hypertensive stages baro-reflex control of cardiac vagal drive, when assessed by evaluating the tachycardic and the bradycardic responses to arterial baroreceptor stimulation and deactivation (vasoactive drug infusion technique) shows a clear-cut reduction. The two above mentioned autonomic alterations appear to be a hallmark of established hypertension [1,2]. However, while the parasympathetic dysfunction remains stable in magnitude in conditions characterized by more severe increases in blood pressure values, the sympathetic activation undergoes a progressive potentiation from the mild to the more severe hypertensive state [1,2].

Two further issues related to the autonomic alterations in hypertension deserve to be mentioned. First, a state of sympathetic hyperactivity is detectable not only in young and middle-aged hypertensives, but also in the elderly, even when the blood pressure increase selectively affects systolic blood pressure values [1]. Second, the hypertension-related increase in adrenergic drive appears to be (i) specific for some cardiovascular districts, such as the heart, the kidneys and the skeletal muscle vasculature [6]; and (ii) peculiar to the hypertensive state of essential nature [1]. This latter feature is in sharp contrast with the parasympathetic control of heart rate, which appears to be markedly deranged both in essential and in secondary hypertension, such as in primary hyperaldosteronism and in

renovascular hypertension [1]. Recently, the information on the sympathetic derangements occurring in the high blood pressure state have been expanded with the evidence that a marked adrenergic overdrive (greater than the one characterizing essential hypertension) characterizes drug resistant hypertension (3), thereby becoming a potential target for new therapeutic interventions, as it will be briefly mentioned in the last part of this report.

Given the relevance of adrenergic overdrive in the development/progression of the hypertensive state as well as to the hypertension-related end-organ damage (left ventricular hypertrophy, vascular hypertrophy, endothelial dysfunction, etc) [1], sympathetic deactivation represents an important goal of the non-pharmacological as well as pharmacological interventions aimed at lowering elevated blood pressure values.

As far as non-pharmacological interventions are concerned, there is overwhelming evidence demonstrating the sympathomodulatory effects of low-calorie dietary interventions and regular physical exercise programs. Since both the two procedures trigger clear-cut blood pressure lowering effects of magnitude often related to the degree of the sympathoinhibition, the hypothesis has been advanced that the antihypertensive effects of the two interventions are related to their sympathoinhibitory effects [1]. Recently, two invasive procedures, i.e., implantation of a device capable of stimulating the carotid baroreceptor (and thus inhibiting sympathetic activity and enhancing barore-flex control of cardiac vagal drive) and renal sympathetic denervation throughout a catheter positioned in a renal artery and connected to a radiofrequency generator, have been successfully developed. Initial promising and exciting results have been reported in resistant hypertension, with documented evidence of a marked sympathoinhibitory effect which presumably plays a major role in the blood pressure lowering effects of the two interventions [2,4].

As far as the effects of antihypertensive drug treatment on autonomic cardiovascular function is concerned, there is evidence that some pharmacologic classes of antihypertensive drugs (such as beta-blockers, ace-inhibitors and angiotensin II receptor blockers) may elicit profound sympathoinhibitory effects, while other classes may leave unchanged (long-acting calcium antagonists), or even further increase (diuretics, short-acting calcium antagonists) the adrenergic cardiovascular drive [1]. Information on the effects of different antihypertensive drug combinations on autonomic

Council's Corner: Hypertension Issues - a personal view

cardiovascular function is scarce at present. This will certainly represent one of the major areas of research in the next few years in the field of the sympathetic dysfunction in hypertension.

- Guido Grassi

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Report on the Celebration of World Hypertension Day



Mark Niebylski

CEO, The World Hypertension League

Congratulations and Thank You to all those who participated and shared in the celebration of World Hypertension Day (WHD) held on May 17, 2015.

This year, the World Hypertension League (WHL), in close partnership with the International Society of Hypertension (ISH), promoted the theme of 'Know Your Numbers' with the goal of increasing awareness of high blood pressure and the risk for hypertension-related non-communicable diseases (NCDs). To help achieve this, WHL and ISH members and partners were outreached to participate via blood pressure screenings, calls to actions, community events, media releases, and awareness campaigns worldwide. The planned effort is detailed in a report published by Dr. Norm Campbell and colleagues.¹

One of the most noteworthy achievements was the blood pressure screening effort with a goal on 1 Million screenings for WHD 2015. It is with great joy to report that we not only attained this lofty goal but far surpassed it by reaching a current tally of 2,446,193. Amongst the many nations reporting were Argentina, Brazil, Canada, China, India, Indonesia, Malaysia, Nigeria, Vietnam, and the US with likely some still to report. Alongside the screenings, many provided awareness on lifestyle modification and dietary salt reduction to help reduce the risk for stroke, cardiovascular disease, and kidney disease.

Not to be outdone, Regional WHL India Office under the Director Dr. Venkata Ram in Hyderabad, India, Regional WHL Sub-Saharan Africa – Director Dr. Daniel Lemogoum in Cameroon, and Regional WHL South America Office – Director Dr. Marcelo Orias in Argentina were all launched on WHD 2015. Meanwhile, the Regional WHL China Office – Director Dr. Xin-Hua Zhang in Beijing, China celebrated their 1 year anniversary on WHD 2015.



Images of World Hypertension Day events

To further the promotion of and celebration of the event, the WHL announced the recipients of the 2015 Excellence and Notable Achievement Awards on WHD 2015. It is with honour and enthusiasm to confer Excellence Awards to Professor Liu Lisheng, MD in Beijing (Distinguished Service & Hypertension Prevention and Control at the Population Level), Dr. Larry Appel, MD, MPH at Johns Hopkins University in Maryland (Dietary Salt Reduction at the Population Level), and Hypertension Canada (Hypertension Prevention and Control at the Population Level). We also announced 18 Notable Achievement Awardees in three categories, namely dietary salt reduction, hypertension prevention and control, and rising star. A full report on the awardees will be released in the coming months. We salute each and every one of you.

The WHL and ISH are certain there are many more successes from WHD too numerous to report at this time. Photographs, stories, and future plans continue to pour into. For example, we applaud the American Society of Hypertension and Hypertension Canada in joining

together to have the Niagara Falls, an international landmark at the border the two countries share, lit at night for WHD 2015. Last but not least, we extend our congratulations and heartfelt thanks to Juliet Regine in Kensington, Maryland, USA who was named the Grand Champion of the WHD Inaugural student art competition. Well done!

This year's event was truly memorable and we are currently planning to draft more detailed reports for posting on our websites, in newsletters, and perhaps for publication in the Journal of Clinical Hypertension. These successes and stories have provided us with many 'lessons learned' that will serve as the platform for WHD 2016. We are already looking forward to it!

For more information on WHD 2015, Please e-mail either kimbree.redburn@gmail.com or CEO@whleague.org.

- Mark Niebylski

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An Update on Hypertension Prevention & Control in Sub-Saharan Africa 2015 (Fact Sheet & Infographic)

Hypertension is a driving force in the global epidemic of non-communicable diseases (NCDs) and is the leading risk factor for death and disability globally. The global burden of hypertension is greatest where resources are the lowest, with developing countries disproportionately impacted by hypertension. By 2025, almost three-quarters of people with hypertension will be living in developing countries. Over 14 million deaths from NCDs occur between the ages of 30 and 70, of which 85% are in developing countries. The World Economic Forum describes NCDs as the greatest threat to economic development, predicting a cumulative loss in global economic output of \$47 trillion USD, or 5% of gross domestic product, by 2030.

For these and many other reasons, the World Hypertension League (WHL) in partnership with ISH initiated an effort to assess hypertension prevention and control in Sub-Saharan Africa and better illustrate why it is so urgent and important.¹ Based on existing resources,^{2,3} the WHL and ISH developed a new fact sheet with 14 supporting Sub-Saharan Africa organizations and found that: In Sub-Saharan Africa in 2010, hypertension was the leading risk for death increasing by 67% since 1990. Hypertension was estimated to cause over 500,000 deaths and 10 million years of life lost in 2010 in Sub-Saharan Africa. It was also the 6th leading risk for disability (contributing more than 11 million disability adjusted life years). Further, in Sub-Saharan Africa, stroke, the major clinical outcome of uncontrolled hypertension, has increased 46% since 1990 to become the 5th leading risk for death. **The new fact sheet is scheduled to be released within the coming weeks on 'Early View' in the Journal of Clinical Hypertension, the home journal of WHL with Free Access.**

To coincide with the release of the fact sheet, the WHL and ISH created two separate Sub-Saharan Africa hypertension infographics (see overleaf) that will also be published and disseminated. These one-page instruments, also adopted from the global hypertension WHL/ISH fact sheet², were designed to target individuals, professionals, providers and hypertension societies. The easy to read infographics capture hypertension morbidity & mortality, United Nations' health goals, economic impact, and recommended integrated management treatment protocol (based on the World Health Organization).



- Mark Niebylski,
CEO, World Hypertension League

Based on these new resources, the magnitude of the issues at hand can be clearly understood and evidence based recommendations put forth. But the 'best next steps' and calls to action remained a concern. To best address this and implement a consistent process and approach, a needs assessment was recently performed with the assistance of supporting organizations.⁴ Some of the insightful findings include the need to: 1) enhance partnerships with and engage additional African national hypertension organizations, 2) expand procurement and distribution of quality, affordable, generic antihypertensive medications, 3) develop comprehensive, multi-tiered national hypertension programs reproducible in low-resource settings, and 4) enhance education initiatives for the public and healthcare professionals and extends to strategic planning and advocacy at the national policy level. To help spearhead this effort, the WHL just announced the launch of the WHL Regional Sub-Saharan Africa Office – Director Dr. Daniel Lemogoum in Cameroon who, along with Dr. Norm Campbell – WHL President, were invaluable in engaging supporting organizations and promoting awareness.

- Mark Niebylski

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Hypertension Prevention & Control in Sub-Saharan Africa 2015

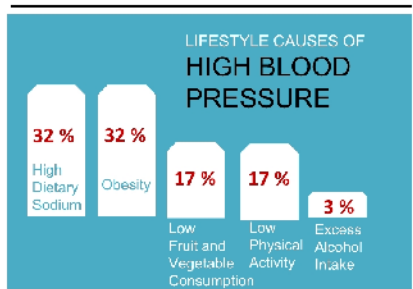
- Infographic for prevention and control

Hypertension in Sub-Saharan Africa

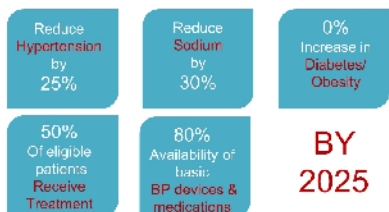
WHY PREVENTION AND CONTROL ARE IMPORTANT

67% INCREASE
IN HYPERTENSION
Between 1990 and 2010

4 IN 10
PEOPLE GLOBALLY
HAVE HYPERTENSION



United Nations Goals



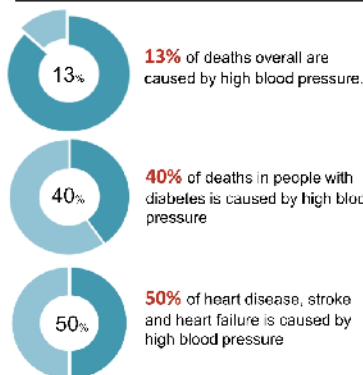
#1 Risk for Death in 2010

Estimated to Cause
500,000
DEATHS



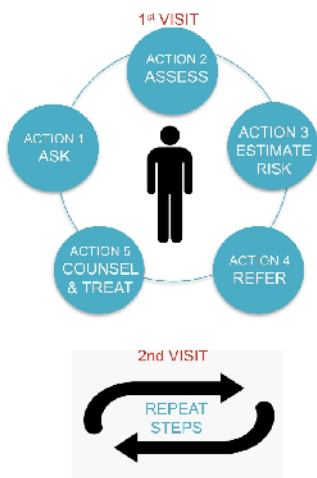
AND

10 MILLION
YEARS OF LIFE
LOST



ECONOMIC IMPACT OF HYPERTENSION **7.3%** TOTAL HEALTH CARE SPENDING IN SUB-SAHARAN AFRICA
AT A COST OF OVER **\$2,000,000,000** USD IN 2011

PREVENTION OF HEART ATTACKS, STROKES AND KIDNEY DISEASE THROUGH INTEGRATED MANAGEMENT OF DIABETES AND HYPERTENSION : WHO PEN PROTOCOL 1



- Measure blood pressure at all relevant clinical encounters.
- Diagnose new cases of hypertension based on a series of blood pressure checks performed on several days or immediately in patients presenting with symptoms or signs of an acute condition related to hypertension (e.g. stroke, heart attack).
- Use an adequate cuff size in relation to arm circumference (i.e. a large cuff for large arms).
- Assess cardiovascular risk in those diagnosed with hypertension, and manage treatment in accordance.
- Treat those at high total cardiovascular risk to controlled blood pressure levels.
- Treat hypertensive persons at moderate total cardiovascular risk according to resources.
- Assess and manage hypertensive disorders in pregnancy.
- Advocate for healthy public policy and for a comprehensive national program for hypertension prevention and control.
- Encourage and assist community blood pressure screening programs, provided accessible and affordable treatment is available for long term treatment of those found to have hypertension.

Data From: High Blood Pressure: Why Prevention and Control Are Urgent and Important - A 2014 Fact Sheet from the World Hypertension League and the International Society of Hypertension. Published in "The Journal of Clinical Hypertension" (2014); DOI: 10.1111/jch.12372



Dedicated to the Prevention and Control of Hypertension Globally

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Air Pollution Exposure and Vascular Health



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Air Pollution Exposure and Vascular Health

Introduction

Since the 1950s, and the well documented and studied "Great Smog" in London, a myriad of epidemiological studies from around the world have demonstrated important robust associations between exposure to air pollution and adverse effects on human health. Indeed, the Global Burden of Disease study demonstrated exposure to indoor air pollution (predominantly from the burning of biomass for cooking) to be the 4th leading population risk factor for morbidity and mortality behind poor diet, cigarette smoking, and hypertension, with exposure to urban ambient air pollution also within the top 10.¹ The authors attributed approximately 7 million deaths worldwide each year to exposure to indoor and urban ambient outdoor air pollution. The ubiquitous nature of exposure makes this a major public health concern, and one that has often been overlooked by the public, physicians, and politicians. However, high profile air pollution episodes and the recent successful legal challenge against the United Kingdom government by an environmental lobby group for the exceedances of air quality standards² have renewed interest in this issue, and the need to improve air quality is now moving towards the top of the agenda.

What is air pollution?

Air pollution is a complex mixture of particulate matter, gases, metals and volatile organic compounds produced from a wide range of sources, ranging from environmental tobacco smoke, to coal burning power stations and traffic fleets.³ Determining which components of the air pollution mixture are responsible for the adverse health effects has been one of the major challenges in the field, especially as there is often considerable overlap in emission profiles. It has been argued that the gaseous components may simply be a marker of exposure to particulate matter⁴, although adverse health effects have been demonstrated after exposure to ozone, nitrogen dioxide, sulphur dioxide, carbon monoxide, and particulate matter.⁵ However, the strongest relationship has been demonstrated with fine and ultrafine particulate matter resulting from the combustion of fossil fuels, especially those derived from traffic sources.⁶

What are the adverse health effects of exposure to air pollution?

The observation that air pollution might be detrimental to health is not new, but the interest of the scientific community was piqued following the Great Smog in London in 1952. From 5th to 8th December 1952, a temperature inversion, still air and large amounts of coal burning from industry as well as home heating resulted in a well documented smog episode; with a large spike in airborne particulate matter, black carbon and sulphur dioxide. This episode was associated with an additional 3,000 deaths over the week of the exposure, and an estimated 9,000 further deaths in the following 3 months from respiratory and cardiovascular diseases.⁷ Since then there have been a large number of epidemiological studies that have further investigated this link.

It is perhaps intuitive to think that air pollutants inhaled into the lung might be associated with respiratory diseases, and indeed there is a robust and strong association with the development of lung cancer, with around an 8% increase in incidence with each 10 µg/m³ increase in background concentrations of PM_{2.5} (particulate matter with a mean aerodynamic diameter <2.5 µm).⁸ Indeed, this may be a conservative estimate, with current data from the European ESCAPE study demonstrating an 18% increase in risk for each 5 µg/m³ increase in concentration, despite exposures being largely below current air quality standard guideline levels.⁹ As well as the association with lung cancer, exposure to air pollution is also linked to the development of asthma and chronic obstructive pulmonary disease, acute exacerbations and respiratory tract infections, as well as lung function decline and reduced lung development.¹⁰⁻¹³

The association with cardiovascular diseases, however, is substantial and perhaps more surprising at first glance. Recent meta-analyses of large numbers of epidemiological studies have demonstrated that each 10 µg/m³ increase in PM_{2.5} is associated with a 2.5% increase in risk of acute myocardial infarction,¹⁴ a 2.1% increase in the risk of hospitalization or death from heart failure,¹⁵ and a 1.1% increase in the risk of admission to hospital with acute stroke.¹⁶

Underlying vascular mechanisms and clinical implications

The epidemiological evidence of adverse health effects of exposure to air pollutants is compelling and robust, nevertheless these studies by their nature are limited to describing associations, and not the underlying mechanisms that might provide biological plausibility for the observations. Over the past few years there have been numerous studies addressing these mechanisms using in vitro and in vivo toxicology studies as well as human clinical studies, leading to well described underlying pathophysiological mechanisms.

As myocardial infarction and stroke are complications of atherosclerosis, it would thus be expected that increased exposure might

Air Pollution Exposure and Vascular Health

influence the development and progression of atheroma. In the longitudinal German Heinz Nixdorf Recall Study it was demonstrated that individuals living near major roads (and by inference having a higher background exposure to traffic-derived air pollution) had increased coronary artery calcification as measured by electron-beam computed tomography than those living further away from a major road.¹⁷ In another cohort of people living in Los Angeles, residential background PM_{2.5} concentrations was associated with an increase in carotid intima-medial thickness (CIMT; a validated surrogate of atheroma) measured by B-mode ultrasonography after correction for confounders.¹⁸ The same investigators later demonstrated that in addition to increased CIMT, higher background PM_{2.5} concentrations are also associated with accelerated progression of CIMT.¹⁹ These observations are strengthened by in vivo rodent studies performed by our group which have demonstrated that in apolipoprotein E^{-/-} mice (an animal model of atherosclerosis) fed on a western high fat diet had increased development of atherosclerotic plaque of a more advanced phenotype after intra-tracheal instillation of diesel exhaust particles²⁰ (an important component of urban ambient air pollution²¹).

Clinically, atherosclerosis may lead to both myocardial ischaemia, due to flow restriction in epicardial coronary vessels, and plaque rupture resulting in formation of thrombus, subsequent vessel closure and myocardial infarction.²² In patients with asymptomatic coronary heart disease (but with a history of prior myocardial infarction) on maximal medical therapy including aspirin, statins, and betablockers, ST segment depression on the electrocardiogram (a marker of myocardial ischaemia) and overall ischaemic burden was increased when subjects exercised in an exposure chamber filled with controlled levels of diesel exhaust as compared to when they exercised in the presence of pure filtered air, suggesting that acute exposure to air pollution has a pro-ischaemic effect.²³

Atherosclerotic plaque rupture and erosion is due to a combination of systemic and local inflammation as well as changes in haemodynamics and arterial wall stress.²² Inhalation of PM air pollution (concentrated ambient particles and dilute diesel exhaust) has been shown to cause a local inflammatory response in the lung, with increased release of proinflammatory cytokines and changes in the antioxidant response.³ Indeed, local and systemic oxidative stress is thought to be the central principal underlying the adverse health effects of exposure to air pollutants, either through a secondary inflammatory mechanism, or by particles exerting a direct oxidative insult.⁵ There is also evidence that exposure to PM air pollution results in an acute change in haemodynamics. Acute exposure to concentrated ambient particles results in an early increase in diastolic blood pressure²⁴ (closely correlated to the black carbon content of the aerosol, suggesting this effect to be due to combustion-derived PM) and acute vasoconstriction.²⁵ Inhalation of diesel exhaust similarly results in acute vasoconstriction²⁶ and increases in central arterial stiffness.²⁷

If exposure to air pollution can trigger coronary artery plaque rupture or erosion, then one would expect to see an association between acute exposure and the triggering of acute myocardial infarction. In a landmark study, patients in the Augsburg Myocardial Infarction Registry in Germany who had survived more than 24 hours after acute myocardial infarction were asked in a standardized interview their activities in the preceding 4 days. The authors found that subjects were almost 3 times more likely to have been in traffic (and therefore exposed to traffic-derived air pollutants) in the hour preceding the onset of their symptoms, suggesting acute exposure may be a trigger for myocardial infarction.²⁸ Indeed, it has since been estimated that due to the ubiquitous nature of exposure to air pollution, on a population level, that exposure to air pollution and especially that resulting from traffic sources is the leading risk factor for the triggering of acute myocardial infarction.²⁹

After plaque rupture within the coronary (and cerebral) circulation, circulating platelets are recruited to the site of injury and activated, resulting in thrombus formation. Exposure to dilute diesel exhaust has been shown to increase thrombus generation in human controlled exposure studies using an ex vivo model of thrombosis in healthy volunteers, a finding accompanied by increased activation of platelets and formation of platelet monocyte aggregates.³⁰ Following the development of thrombus, the normal vascular endothelial response is to release stores of the endogenous fibrinolytic mediator tissue plasminogen activator (t-PA) in order to balance thrombus formation and break-down, and to prevent vessel closure. Diesel exhaust has been shown to impair the release of t-PA from the vascular endothelium after acute exposure of healthy volunteers and patients with coronary heart disease to dilute diesel exhaust.^{23, 31}

In addition to effects on vascular endothelial endogenous fibrinolytic function, we have also demonstrated that acute exposure to diesel exhaust results in impairment of vascular vasomotor function. Thirty healthy volunteers were exposed to dilute diesel exhaust and filtered air for one hour during intermittent exercise in a randomized double-blind controlled crossover study. Vascular endothelial function was assessed in the arterial bed of the forearm at 2 and 6 hours after exposure by means of venous occlusion plethysmography with the infusion of vasodilators. The vasodilation response was reduced to endothelial dependent mediators following exposure to diesel exhaust, but not to endothelium independent mediators.³¹ This effect appears to be due largely to the reduced bioavailability of nitric oxide within the vasculature,^{32, 33} that in turn may be due to systemic oxidative stress. The presence of vascular endothelial function may limit the ability of the coronary circulation to vasodilate in response to impending vessel closure, but is also the initiating step in the development of atherosclerosis³⁴ – perhaps explaining, along with the presence of systemic inflammation and oxidative stress, the association with increased atherosclerosis in people with higher exposure to traffic-derived PM.

One of the most widely studied effects of air pollution exposure is the effect on heart rate variability (HRV) and cardiac autonomic control. Epidemiological and panel studies have demonstrated effects of exposure on measures of HRV, and a recent meta-analysis demonstrates an inverse relationship between increasing exposure to PM air pollution and reductions in HRV.³⁵ However, these findings have not always been seen in controlled exposure studies.³⁶ Reduced HRV is associated with worse cardiac prognosis

Air Pollution Exposure and Vascular Health

following myocardial infarction, as well as in patients with diabetes and those with heart failure.³⁷ It is proposed that alterations in cardiac autonomic tone might result in an increase in arrhythmia, although the association between cardiac arrhythmia and PM air pollution exposure is inconsistent. We have not demonstrated an acute effect of exposure to air pollutants on arrhythmia in controlled human exposure studies,³⁸ but there are some reports of both atrial and ventricular arrhythmia in at risk populations in epidemiological and panel studies.³⁹

An increase in arrhythmia may underlie an increase in mortality in acute myocardial infarction, but this may be even more important in other conditions such as heart failure. We have recently demonstrated in a meta-analysis an association between exposure to air pollution and hospitalization and mortality from heart failure.¹⁵ The pathophysiological mechanisms underlying this observation remain the subject of ongoing investigation, but may be related to development of arrhythmia, changes in myocardial performance, or myocardial ischaemia.

These observations have demonstrated that air pollution exposure results in critical effects on the cardiovascular system and systemic circulation, thus giving credence and biological plausibility to the strong epidemiological associations seen between exposure and cardiovascular morbidity and mortality.

Exposure to air pollution results in cardiovascular morbidity and mortality: what can we do to mitigate this risk?

Epidemiology studies have demonstrated that the adverse effects associated with exposure to air pollution are dose dependent, with increasing exposure leading to greater effect, and that there is no apparent minimal threshold.⁴⁰ Strategies to reduce exposure to the population therefore have the potential to result in major improvements in public health. The improvement in air quality in the United States from the 1970s to 2000s is estimated to have increased the average life expectancy by 7 months for each 10 µg/m³ reduction in background PM_{2.5} concentration.⁴¹

The introduction of clean air policies have led to major improvements in air quality over the years. The 1990 banning of bituminous coal in Dublin, Ireland resulted in a 70% reduction in ambient black smoke concentrations with a corresponding 10% reduction in cardiovascular deaths and 15% reduction in respiratory mortality.⁴² Modern strategies to improve air quality have involved the introduction of stringent air quality standards, controls on emissions from new vehicles, low emission zones, and industry regulations. Given the ubiquitous nature of exposure to air pollutants, policy level interventions are really the only practical way to result in major public health gains. We should remember that in addition the burning of fossil fuels results in the emission of potent greenhouse gases, and therefore interventions to improve air quality will have further important environmental benefits and will help to mitigate climate change. Whilst this is clearly achievable and enforceable in the developed world, it should be noted that the majority of the world's most polluted cities lie in the developing world, the Middle East, India, China and South America. In these countries, there is a difficult equation to balance between economic development, rapid urbanization and industrialization with regulatory controls on emissions, and indeed in many of these parts of the world the air quality continues to deteriorate.

There are also smaller scale interventions that have been shown to be of benefit in reducing the impact of individuals exposure to air pollutants. Some studies have demonstrated important improvements in respiratory health and vascular function after introducing HEPA (high-efficiency particle arrestance) filters into domestic homes to reduce exposure to residents living in urban areas and areas with high exposure to ambient woodsmoke.⁴³ We have demonstrated that the addition of efficient filters into the air inlet of modern vehicles effectively reduces exposure to individuals travelling within the vehicle, that is associated with an improvement in self-reported respiratory symptoms.⁴⁴ The filtration of diesel exhaust by means of a highly efficient retrofit particle trap fitted in-line with the exhaust of a commercial diesel engine, or by formal HEPA filtration, results in improvements in vascular endothelial function, platelet activation and thrombus formation.^{45, 46} We have also demonstrated in both healthy volunteers and patients with coronary heart disease living and working in the very highly polluted city of Beijing, China, that wearing a close-fitting and efficient facemask to reduce exposure to urban ambient PM air pollution results in an improvement in respiratory symptoms, and objective improvements in blood pressure, heart rate variability, and myocardial ischaemia.^{47, 48} It remains to be seen if this use of such small-scale interventions might have an impact on public health, but there may be a role for those at very high risk on highly polluted days, and we eagerly await further evidence.

Perhaps the most important interventions we could address on a personal level are related behavioural. Increasing the use of public mass transport to reduce the number of vehicles on the roads, choosing active transport over the car (walking, cycling, etc.), and reducing our own exposure by walking/cycling along smaller roads away from major highways. Education is also vital – informing the scientific community, public, and patients of this important public health risk factor, as it only when such issues are in the public eye that there is a drive to improve things.

In Summary

Air pollution is a major public health concern, and is estimated to result in around 7 million deaths worldwide each year, predominantly from cardiovascular diseases. There is a robust epidemiological evidence base demonstrating the importance of exposure to air pollution as a risk factor for disease, and the mechanistic studies have demonstrated important underlying mechanisms that provide

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biological plausibility for these observations. Furthermore, studies have also demonstrated the potential impact of strategies to reduce air pollution on public health, and the wider implementation or tightening of these control measures are also likely to have major environmental benefits in mitigating climate change.

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- Jeremy P. Langrish

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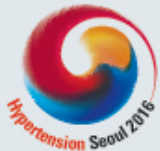
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