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### [Hypertension Highlights](#)

International Society of Hypertension, World Hypertension, and Three New Classes of Antihypertensive Drugs

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### **Abstract**

Potent new statistics on the true burden of hypertension in the world today -- to be remembered and cited by all those concerned with the dimensions of this healthcare challenge -- were highlighted at the fourth World Hypertension Day. Also this month, important new US guidelines for home blood pressure (BP) monitoring (patients monitor glucose -- why not BP?) were published as well as the latest Blood Pressure Lowering Treatment Trialists Collaborative (BPLTTC) meta-analysis suggesting that it is the BP levels attained, not targeting different classes of drugs for different ages, that matters. And finally, encouraging results for no less than 3 potential new classes of antihypertensive agents, targeting new pathways?

### **International Society of Hypertension Calls for Urgent Action to Reduce Global Burden of Blood Pressure-Related Disease**

A study carried out for the International Society Hypertension (ISH) has estimated that in 2001, blood pressure (BP)-related diseases were the cause of almost 8 million deaths worldwide. Reporting their study in *The Lancet*,<sup>[1]</sup> Carleen M M Lawes, PhD, and other researchers from the University of Auckland, New Zealand, also calculated that approximately half of stroke and ischemic heart disease in that year were attributable to high BP. The study revealed that about 80% of the burden of blood pressure-attributable disease occurred in low- and middle-income economies. Commenting on the study in the same issue of *The Lancet*,<sup>[2]</sup> past and present officers of the ISH criticize international funding agencies and pharmaceutical companies for failing to effectively address the epidemic of BP-related diseases affecting developing countries worldwide, and they call for initiatives to implement BP-control strategies in lower income countries, focusing on providing greater access to primary healthcare services.

Dr. Lawes and colleagues calculated the global burden of disease attributable to high blood pressure (systolic blood pressure [SBP]  $\geq 115$  mm Hg) for groups according to age (30 years or older), sex, and World Bank region in 2001. Data for SBP were obtained from the Global Burden of Disease study for 2000, updated with more recent country-specific data.<sup>[3,4]</sup> World Bank regions included low- and middle-income regions of eastern Asia and the Pacific, Europe and central Asia, Latin America and the Caribbean, the Middle East and north Africa, south Asia, and sub-Saharan Africa, as well as high-income regions globally.

Estimates of disease burden were obtained using data from the World Health Organization (WHO) 2003 *World Health Report*.<sup>[5]</sup> The disease burden related to high blood pressure was defined as population attributable risk; ie, the proportional risk reduction in average disease risk over a specified time that would be achieved by eliminating high BP from the population if other risk factors remained unchanged.

The estimates showed that 7.6 million premature deaths (about 13.5% of the global total) in 2001 could be attributed to high blood pressure. Worldwide elevated blood pressure is responsible for:

Roughly 54% of stroke;

47% of ischemic heart disease;

75% of hypertensive disease (essential hypertension, hypertensive heart disease, and hypertensive renal disease); and

25% of other cardiovascular disease.

About half this burden was in people with SBP greater than 145 mm Hg, but in the remainder it was less than 145 mm Hg. Overall, about 80% of the attributable burden occurred in low- and middle-income economies, with attributable death rates for more diseases 1.5- to 2-fold higher in low- or middle-income regions compared with high-income regions. A greater proportion of the attributable burden of disease occurred in younger people (aged 45 to 49 years) in low- and middle-income regions compared with high-income regions.

The total attributable burden was almost evenly divided between men and women in all regions. The researchers note that in combination with other cardiovascular risk factors -- such as high cholesterol, being overweight or obese, smoking, and lack of physical exercise -- high BP could cause 80% to 90% of ischemic heart disease and 70% to 75% of stroke worldwide.

## **Commentary**

In their commentary,<sup>[2]</sup> Stephen MacMahon, PhD, MPH (George Institute for International Health, University of Sydney, Australia) and co-authors, who include current ISH president Lars H Lindholm, MD, PhD (Umeå University,

Sweden) and immediate past president, Michael H Alderman, MD (Albert Einstein College of Medicine, Yeshiva University, New York), refer to cardiovascular disease as the elephant in the room -- "a massive problem that few want to acknowledge and even fewer want to tackle." They accuse major health-development funds of failing to make "any substantive or sustained effort to address the issue" and the major pharmaceutical companies of failing to offer "material assistance in this global-health crisis, despite gargantuan profits from the sales of BP-lowering drugs in high-income countries." They point out that for those in most low- and middle-income countries, the absence of appropriate primary healthcare services is the major obstacle to the control of blood pressure related diseases.

New approaches are needed, these editorialists say, "since the models that have evolved in high-income countries are neither affordable nor practical for the rest of the world, where non-medical healthcare workers often provide the bulk of primary care services and most expenditure on healthcare is out of pocket. The formulation and assessment of new primary-care models of the management of chronic disease in resource-poor settings requires investment in research into healthcare delivery." Unfortunately, the commentators remark, this kind of research is not attractive to most international funding agencies, "many of which still prefer to believe that the world's leading health problems will be resolved by the development of new treatments based on technologies such as genomics, proteomics, or metabolomics." For much of the world's population, however, "any new drugs, however effective, will have little relevance if there is no system in place to deliver treatment to those in need."

This failure to provide primary healthcare "combined with a myopic view of disease targets among those who set international health priorities has contributed to a staggering inequality in access to BP-lowering treatments," Professor MacMahon and colleagues assert. They point out that global expenditure on antihypertensive treatment is about \$50 billion each year, over 90% of which is spent in high-income countries; middle- and low-income regions have a 5-fold greater burden of disease but access to less than 10% of the global treatment resource. "Here the main access issue is whether care can be given to those at the highest risk of fatal or catastrophic events, because most of those for whom blood-pressure lowering is recommended receive no treatment whatsoever." They point out that antihypertensive care available for these populations is not very different from what was available early in the 20th century, before the development of diuretics and beta-blockers. "This travesty cannot continue to be ignored by those most able to bring about change," they declare.

## **World Hypertension Day 2008**

Saturday, May 17, 2008, marked World Hypertension Day, the fourth time this day has been observed since it was initiated by the World Hypertension League (WHL), a division of ISH, in 2005. The purpose of World Hypertension Day is "to promote public awareness of hypertension and its serious medical complications and to encourage citizens of all countries to avoid or control hypertension by providing information on prevention, detection, and treatment."

This year's theme was "Measure Your Blood Pressure -- At Home."<sup>[6]</sup> "By focusing public attention on the benefits of controlling high blood pressure we want to help people better protect themselves against heart attack, stroke, and kidney failure," said Arun Chockalingam, PhD (Simon Fraser University, Vancouver, Canada), secretary-general of the WHL . "We hope World Hypertension Day will motivate people to be screened and to make blood pressure monitoring and management part of their general health management."

According to Professor M Mohsen Ibrahim, MD (University of Cairo, Egypt), an advisor to the WHL, "People often think high blood pressure is only a 'western' disease; but it is not. It is on the rise in developed and developing nations, and if we do not get it under control, it will grow by 50% in the next 15 years. This would leave a lot of people at risk, but World Hypertension Day can help to motivate people and slow this epidemic." World Hypertension Day is supported globally by Novartis, Omron, and sanofi-aventis.

A record-setting number of World Hypertension Day events were set to take place around the world this year. More than 35 countries hosted public events to provide free blood pressure screenings and information about high blood pressure. May 17, 2008 also marked the launch of the largest-ever international survey to draw increased attention to the links between hypertension and heart disease. The "'Do You Know Your Numbers?'" survey is designed to quantify how aware the general public is about high blood pressure, as well as cholesterol and diabetes, and how much importance they place on controlling these contributors to heart disease. The survey is sponsored in part by Novartis. The results of the survey will be released in September 28th, to coincide with World Heart Day 2008, which will focus on better high blood pressure control. "This survey is unique, because it studies how the public views key contributors to heart health." Dr Chockalingam said. "This information is important, because it will help doctors and patients to better communicate about how to improve patients' health by better managing these common, yet devastating, diseases."

Among the many events scheduled worldwide for World Hypertension Day, it is unlikely that any could match the attempt to break the Guinness World Record for the most number of blood pressure readings in 24 hours that was made in Japan on World Hypertension Day 2007. The event, which took place in Chiba Marine Baseball Stadium, was part of the high blood pressure awareness campaign, "Roll Up Your Sleeves, Japan!," organized by the Japanese Society of Hypertension and the Japan Association of Hypertension. It was sponsored by Novartis Pharma KK with special support from Omron. The world record was achieved with a total of 2109 BP readings over 24 hours.<sup>[7]</sup> Chiba Lotte Marines coach Bobby Valentine (formerly manager of the Texas Rangers and the New York Mets in the United States) said that the team, which participated in the event, was proud to have helped achieve the record, "but even better would be to have a stadium full of people that are within the blood pressure success zone!"

## **New US Guidelines for Blood Pressure Monitoring at Home**

People with hypertension should routinely monitor their blood pressure at home to help manage the disease, according to a new joint scientific statement from the American Heart Association (AHA), the American Society of Hypertension (ASH), and the Preventive Cardiovascular Nurses' Association. Use of a home monitor can confirm suspected or newly diagnosed hypertension and rule out the diagnosis for patients whose readings at the doctor's office do not reflect their actual pressures over time. Home monitoring can also be used to evaluate the response to antihypertensive treatment, and to motivate patients to take their medications regularly. The full statement is published online in *Hypertension*,<sup>[8]</sup> along with an executive summary<sup>[9]</sup> that also appears in the May issue of the *Journal of the American Society of Hypertension*,<sup>[10]</sup> and is scheduled for publication in the *Journal of Cardiovascular Nursing*.

Lead author Thomas G. Pickering, MD, DPhil (Columbia Presbyterian Medical Center, New York), who was chair of the statement writing group, stressed that high blood pressure is notoriously difficult to treat to goal and that home monitoring can help the many patients who fail to reach target levels despite treatment. "BP measurement and tracking could be improved with home monitoring by the patients themselves, in much the way people with diabetes monitor their blood sugar levels with home glucose monitors," he proposed. He said that there is strong evidence that the traditional way of measuring blood pressure in adults can be misleading. Studies indicate that between 10% and 20% of people diagnosed with high BP in the doctor's office show the white coat effect. "It is also believed that some people with normal blood pressures in their doctors' offices have pressures that spike to potentially dangerous levels in other situations," Dr. Pickering added.

The statement says that home monitoring is particularly useful in the elderly, who show both increased BP variability and white coat effect, as well as in patients with diabetes, patients with kidney disease, and in pregnant women. Dr Pickering noted that because everyone's BP is highly variable during the day, taking 1 reading at a doctor's office every few months does not give a complete picture of a patient's condition. Home monitors can take multiple measurements during each session, and can be used at different times of day. Many monitors also store and average blood pressure readings over time, providing crucial data for patients to take to their physicians so they can work as a team to diagnose and treat the condition.

Many types of home monitors are relatively inexpensive, costing less than \$100. The statement recommends that patients be reimbursed for the purchase of a monitor as prescribed by their healthcare provider (physician and/or nurse practitioner) and that providers be reimbursed for services related to initial patient education regarding correct technique; yearly or as-needed assessments to validate that individuals' technique; interpretation of BP readings stored in the monitor memory; and personal, telephone, and/or e-mail consultation to deliver medical advice-based on analysis of home BP readings. Monitors should be renewable after 5 years or if they are shown to be inaccurate.

"Home blood pressure monitoring also gives patients the physiologic feedback they need to see regarding blood pressure," says Nancy Houston Miller, RN, co-author and former president of the Preventive Cardiovascular Nurses Association. "Rather than 3 to 4 office blood pressure checks per year, if they measure blood pressure at home in addition to following up with their healthcare provider, patients are likely to achieve goals more quickly and be confident that medicines are working for them." She believes that nurses and nurse practitioners have a significant role to play in interpreting data from BP devices and educating patients about needed lifestyle interventions and medications.

Suzanne Oparil, MD, immediate past president of ASH, said that the society is "encouraged by this joint statement on the value of home blood pressure monitoring and confident it will be helpful in reducing the incidence of heart attack, stroke and kidney disease." The statement writing group said home BP monitoring is evidence-based healthcare that can improve the quality and lower the cost of caring for the 73 million people with hypertension.

Although earlier AHA guidelines have included home monitors, this is the first statement to have detailed recommendations on their use. They advise patients to purchase oscillometric monitors that measure BP in the brachial artery with a cuff that fits around the upper arm. Wrist monitors are not recommended. The statement notes that only a few of the home BP devices on the market have been subjected to proper validation tests such as the Association for the Advancement of Medical Instrumentation (AAMI) and British Hypertension Society (BHS) protocols, and that several devices have failed the tests. Current lists of validated monitors are available on the Web sites of the dabl® [sic] Educational Trust and the British Hypertension Society (see Resource list).

Patients are advised to consult their healthcare providers about the accuracy of their home monitor as well as their technique in using it. After 5 minutes of rest and while seated, they should take 2 to 3 readings at a time, 1 minute apart, on the nondominant arm. The arm should be supported, with the upper arm at heart level, and feet on the floor (back supported, legs uncrossed). The patient should have abstained from exercising, smoking, or drinking coffee or tea over the 30 minutes before taking the blood pressure measurement. To get a reliable estimate of the true BP, the statement recommends following the latest European Society of Hypertension guidelines on home BP measurement,<sup>[11]</sup> which suggest taking at least 2 readings in the morning and 2 in the evening every day for 1 week, but discarding the readings for the first day, so that there are 12 readings on which to make clinical decisions.

The statement notes that the number of hypertensive patients monitoring their BP at home has been rising in past years, going from 38% in 2000 to 55% in 2005. "I think this is a very healthy trend," Dr Pickering said, although he stressed that "with a condition like high blood pressure, it really does depend on the patients remembering to change their lifestyles or remembering to take their pills."

## **No Evidence for Selection of Specific Blood Pressure-Lowering Regimens in People of Different Ages**

Some national hypertension guidelines, such as those for the United Kingdom<sup>[12]</sup> and Canada,<sup>[13]</sup> recommend treatment with particular BP lowering drug classes according to age, based on possible differences in cardiovascular effects. However, according to the results of the latest meta-analysis by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC), published in the *British Medical Journal*,<sup>[14]</sup> there is no strong evidence that specific classes of antihypertensive drugs are more beneficial in terms of preventing cardiovascular events in people of different ages. The BPLTTC members say that their findings "should greatly simplify decision making for millions of clinicians around the world."

For this meta-analysis, trials were eligible for inclusion if they randomized 1000 patients or more to either (a) medication to lower BP vs control (placebo or less intensive treatment), or (b) different classes of BP-lowering drugs. All trials included were completed between 1995 and 2006. The investigators compared total major cardiovascular events (stroke, coronary heart disease [CHD], and heart failure) as primary outcome in patients aged < 65 years ("younger") vs aged ≥65 years ("older"). Of 37 eligible trials, 31, including 96,466 younger individuals and 94,140 older individuals (mean age 57 and 72 years, 58% and 51% men, respectively), were included in the meta-analysis.

### **Results of BPLTTC Meta-analysis**

Mean BP at baseline was higher in the older group in the trials and more events occurred overall in the older patients. There was no difference in reduction in primary outcome events between the 2 age groups in the trials that compared BP-lowering trials with placebo or that compared different antihypertensive drug classes, despite differences in BP reductions between the groups with some of the randomized treatments. Similarly there was no difference when secondary outcomes -- stroke, CHD, heart failure, cardiovascular death, and total mortality were compared in the 2 age groups, or in analyses of the trials for which individual patient data were available or who included only patients in 1 age group. A subsidiary analysis comparing the effects of regimens based on diuretics or beta-blockers with other drug classes (angiotensin converting enzyme [ACE] inhibitors and calcium channel blockers combined), showed no difference in proportional reduction in major cardiovascular events in the younger vs older patients.

### **Limitations, Implications, and Comment**

These results do not completely exclude the possibility of differences in the proportional effects of blood pressure lowering regimens between age groups, but they do suggest that any such differences are likely to be small, the investigators conclude. Thus, they suggest that factors such as tolerability and cost are probably reasonable bases for choice of drug as long as an effective blood pressure reduction is achieved. They add that among the older age group there was, in almost every analysis and for almost every outcome, an estimate

of effect suggesting benefit from BP lowering, with no evidence of harm and the absolute benefits of treatment in terms of serious vascular events prevented are likely to be particularly large among older individuals because of their higher average risk. "These data also provide considerable reassurance that current approaches to the use of blood pressure lowering treatments based on absolute risk, that assume constant proportional risk reductions across age groups, are an appropriate means of quantifying the likely absolute benefit to be gained from lowering blood pressure," they conclude.

In an accompanying editorial,<sup>[15]</sup> Jan A Staessen, MD, PhD, Study Coordinating Centre, Hypertension Unit, Department of Molecular and Cardiovascular Research, University of Leuven, Belgium, and colleagues say that they understand the appeal of an age-oriented strategy in the choice of first line antihypertensive drugs because it would translate certain physiologic and pharmacologic principles, such as the decrease in plasma renin with age, into clinical practice. They suggest that although the BPLTTC analysis strongly supports the early and aggressive management of hypertension, irrespective of age, it did not exclude the possibility that ACE inhibitors and other inhibitors of the renin system given as first line treatment in older people might be less efficacious than diuretics or calcium channel blockers.

### **Orally Active Aminopeptidase A Inhibitor -- a Prototype for a New Antihypertensive Drug Class**

Scientists in France have developed what may prove to be a prototype of a new class of centrally acting antihypertensive drugs. Their research showing that RB150, an orally active prodrug that inhibits brain but not systemic renin-angiotensin system (RAS) activity, reducing blood pressure in an experimental animal model, is reported in *Hypertension*.<sup>[16]</sup> For a number of years Catherine Llorens-Cortes, PhD, and colleagues at Inserm (Institut national de la santé et de la recherche médicale) U 691, Collège de France, and Université Pierre et Marie Curie-Paris VI, Paris, France, have been researching the brain's RAS and its role in hypertension. Among the main bioactive peptides of the brain RAS, angiotensin (Ang) II and Ang III exhibit the same affinity for type 1 and type 2 angiotensin receptors. Both peptides, injected intracerebroventricularly, cause a similar increase in BP.

Previous research by Dr. Llorens-Cortes' group indicated that in the brain, conversion of AngII to AngIII, which is catalyzed by aminopeptidase A (APA), is a necessary step in increasing blood pressure.<sup>[17,18]</sup> They used specific and selective APA inhibitors to show that AngIII is one of the main effector peptides of the brain RAS, exerting tonic stimulatory control over BP in hypertensive rats.<sup>[19]</sup> APA, therefore, is a potential therapeutic target for the treatment of hypertension. Their work in this field is being done in partnership with Quantum Genomics Corp (Jersey City, New Jersey and Massy, France).

After developing a specific, selective APA inhibitor, EC33 [(S)-3-amino-4-mercaptobutyl sulfonic acid] that did not cross the blood-brain barrier, Dr. Llorens-Cortes' group modified it chemically to create a systemically active prodrug, RB150 (4,4'-dithiobis{bis[(3S)-3-aminobutyl sulfonic acid]}). Having



previously shown that RB150 administered intravenously blocked RAS activity and reduced blood pressure markedly in conscious, hypertensive deoxycorticosterone acetate (DOCA)-salt rats,<sup>[20]</sup> they investigated oral administration of RB150 in the same animal model. Doses of RB150 7.5 to 50 mg/kg administered in saline progressively inhibited brain APA activity after 3.5 hours. Doses of 15 to 50 mg/kg reduced APA activity to approximately 54% of that in DOCA-salt rats given saline only and reached levels measured in normotensive rats. Oral administration of RB150 at doses of 0.1 to 30.0 mg/kg reduced mean BP in a dose-dependent manner in conscious DOCA-salt rats, with an 50% effective dose (ED<sub>50</sub>) of 0.84 mg/kg. Heart rate was not decreased significantly.

The hypotensive effect began 2 hours after administration, was maximal at 5 hours, and remained significant after 7 hours. After 24 hours, there was still a nonsignificant hypotensive effect, but this had disappeared at 48 hours. No effect of RB150 was seen on BP or heart rate in normotensive rats. This treatment also significantly decreased plasma arginine-vasopressin levels and increased diuresis in the DOCA-salt rats, which contribute to the BP decrease, the researchers suggest. Also, since the brain RAS is known to be involved in drinking behavior, water intake was monitored after oral administration of RB150, but no change in water intake was observed in these animals.

Dr. Llorens-Cortes and her colleagues believe that this treatment could be particularly beneficial in hypertensive patients with low plasma renin and high levels of arginine-vasopressin, who are resistant to the antihypertensive medications usually prescribed.

### **Editorial Comment**

In an accompanying editorial,<sup>[20]</sup> Anderson J Ferreira, PhD (Federal University of Minas Gerais, Belo Horizonte, Brazil) and Mohan K Raizada, PhD (University of Gainesville, Florida) say that the study by Dr Llorens-Cortes' group strengthens the AngIII hypothesis and the role of APA in central control of BP and shows that brain APA can be influenced by simple oral administration of RB150. Thus, "it is an important first step in the development of oral drug-based therapeutics for neurogenic hypertension." They raise some points and questions that they believe should be addressed before APA inhibitors can function as therapeutic agents. For example, the roles of AngII and AngIII in various cardioregulatory brain regions in the control of cardiovascular functions, including BP control, should be delineated. Another issue is whether global inhibition of APA is necessary for maximal effects on blood pressure and vasopressin release. Targeting selective brain regions such as the paraventricular nucleus, rostral ventrolateral medulla, and nucleus tractus solitarius might be more effective, they suggest. They believe it would also be critical to extend the findings from the DOCA-salt rat to other models of hypertension, "particularly those that are not brain RAS dependent, to further validate the therapeutic potential of the APA targeting." Nonetheless, they believe that this study "may turn out to be the key for the therapy of neurogenic/angiotensin-dependent hypertension."

## Identification of Angiotensin-Converting Enzyme-2 Activators as Potential Antihypertensive Drugs

Activation of angiotensin-converting enzyme 2 (ACE 2) could lead to a new class of antihypertensive drugs that would also be effective in reversing cardiac and renal fibrosis, say University of Florida (Gainesville) researchers in the May 1, 2008 issue of *Hypertension*.<sup>[21]</sup> ACE 2, a homolog of ACE, is a key RAS enzyme involved in balancing the adverse effects of angiotensin II on the cardiovascular system. It is known to degrade angiotensin II (AngII) to generate angiotension<sup>[1-7]</sup> which has vasodilatory and antiproliferative effects. Blocking AngII with ACE inhibitors or angiotensin receptor blockers (ARBs) has been shown to increase cardiac ACE2 expression. Altered expression of ACE2 is associated with cardiac, renal, and vascular dysfunction.

Previous studies have suggested that pharmacologic enhancement of ACE2 activity may have beneficial effects on the cardiovascular system and protect against hypertension-induced pathophysiology. As part of research funded by the National Institutes of Health (NIH), José A Hernández Prada, PhD (Physiology and Functional Genomics, University of Florida College of Medicine, Gainesville, Florida) and colleagues have used a structure-based drug-discovery approach to identify a compound that<sup>[21]</sup>:

Enhances ACE 2 activity;

Causes "considerable" reductions in BP; and

Reverses cardiac and renal fibrosis in spontaneously hypertensive rats (SHRs).

"This observation is remarkable, because rational drug design is traditionally directed at the discovery of enzyme inhibitors or receptor blockers that compete with the natural ligand," the researchers explain. They believe that the new approach will enable rational development of enzyme activators.

Dr Hernández Prada and colleagues used a novel rapid molecular docking approach to computationally screen approximately 140,000 small molecules, a small number of which were selected for in vitro testing for their ability to modulate ACE2 activity. The new screening approach involved rotating the molecules in thousands of different orientations to determine how they would bind to certain pockets on the enzyme's surface. After a small number of potentially active compounds had been identified, in vitro assays revealed 2 (xanthenone and resorcinolnaphthalein) that enhanced ACE2 activity by 1.8 to 2.2-3 fold. ACE2 activity was enhanced in a dose-dependent manner by the 2 compounds, with median effective concentration (EC<sub>50</sub>) values of 20.1 and 19.5 μmol/L, respectively. Both were selective for ACE2, showing no significant effects on ACE activity. Xanthenone was selected for large-scale synthesis and in vivo testing because it was more soluble than resorcinol naphthalein.

## Results With in vivo Experiments

Acute in vivo administration of xanthenone resulted in a rapid, dose-dependent transient and robust decrease in BP in SHRs and normotensive Wistar-Kyoto (WKY) rats. The antihypertensive effect was significantly greater in SHRs compared with WKY rats. At a dose of 10 mg/kg, BP sure decreased by a mean of  $71 \pm 9$  mm Hg in SHRs compared with only  $21 \pm 8$  mm Hg in WKY rats ( $P < .05$ ). Chronic infusion of xanthenone (120 mcg/day) resulted in a significant decrease in BP in SHRs (17 mm Hg,  $P < .05$ ), whereas it had no effect in WKY rats. The decrease in blood pressure was also associated with improvement in cardiac function and change of pressure over time in SHRs, but no significant changes in left ventricular (LV) systolic pressure, LV end diastolic pressure, perfusion pressure, or heart rate. Chronic infusion of xanthenone also caused a significant reversal of myocardial, perivascular, and renal interstitial fibrosis in SHRs.

The mechanism of the effect on cardiac function remains to be elucidated. It may be an indirect effect as a result of the decrease in BP, but the researchers believe that effects of xanthenone in reversing myocardial and perivascular fibrosis indicate that the improvement in heart function is more likely due to the marked reduction in collagen deposition in cardiac tissue.

## Implications for New Treatments

"The clinical ramifications of this study are directly significant for cardiovascular disease and diseases associated with hypertension, such as obesity and diabetes," the researchers say. The study provides evidence suggesting that development of a new class of antihypertensive drugs (specific for ACE2) may serve as a complementary strategy in the treatment of cardiovascular disease. Study co-author David A Ostrov, PhD (Assistant Professor, Department of Pathology, Immunology and Laboratory Medicine, University of Florida, Gainesville) added that early results also show xanthenone inhibits inflammation, which has significant implications for a number of human diseases, including autoimmune disorders such as type 1 diabetes and rheumatoid arthritis as well as other diseases involving fibrosis, such as Alzheimer's. Additional research will continue to explore the compound's effectiveness in animals and humans.

## Slow-Releasing Hydrogen Sulfide Compound With Potential as Antihypertensive Therapy

Hydrogen sulfide ( $H_2S$ ) is known to have cardiovascular effects such as the ability to dilate human blood vessels and protect the heart against ischemia/perfusion injury, and it also plays a role in hypertension, although to date this has been undefined. Now a team of researchers from Singapore and the UK has identified a slow-releasing  $H_2S$  compound that mimics the generation of  $H_2S$  in vivo and has revealed more about the biologic properties of the gas. In addition, the blood pressure lowering effect of the compound in SHRs without affecting heart rate and without weight loss or other signs of toxicity, suggests that it, or a compound like it, may be of a therapeutic benefit

in cardiovascular disease, the researchers believe. Their study, which was supported by the National University of Singapore and King's College University of London, is published in the May 6, 2008 issue of *Circulation*.<sup>[22]</sup>

The research team was attempting to find a new molecule to replace the H<sub>2</sub>S-releasing compounds previously used in experiments in the cardiovascular system. They believe that the old compounds did not mimic the biologic effects of endogenously produced H<sub>2</sub>S. A new compound was needed that released H<sub>2</sub>S into the body in a more controlled and regulated manner, over extended periods of time. They identified morpholin-4-ium 4-methoxyphenyl (morpholino) phosphinodithioate (GYY4137) from a series of compounds based on a commercially available agent that releases H<sub>2</sub>S in organic solvents (Lawesson's reagent). GYY4137 was found to release H<sub>2</sub>S slowly both in aqueous solution in vitro and after intravenous or intraperitoneal administration in anesthetized rats in vivo. This compound was described about 50 years ago as an accelerant for rubber, but that its biologic activity has never previously been reported.

In cultured rat vascular muscle cells GYY4137 had no significant cytotoxic effects or effects on the cell cycle profile or p53 expression. It caused a slow relaxation of precontracted rat aortic rings and dilated the perfused rat renal vasculature by opening vascular smooth muscle adenosine triphosphate-sensitive potassium (K<sub>ATP</sub>) channels. Bolus injection of GYY4137 in the rat kidney did not consistently affect perfusion pressure and it did not affect heart rate or contractility in isolated rat hearts.

The chronic effect of GYY4137 on blood pressure in normotensive WKY rats and SHRs was determined by tail-cuff plethysmography. GYY4137 lowered blood pressure in both WKY rats and SHRs with an effect that was apparent after 2 days and still present after 14 days of treatment. The effect was significantly greater in SHR than normotensive rats. When treatment stopped, BP returned to pretreatment levels in WKY rats within 7 days, whereas blood pressure in SHR was still significantly reduced at that time. BP was normalized in both WKY and SHR after 14 days without treatment. Daily treatment with GYY4137 had no effect on weight gain and did not produce any noticeable signs of toxicity. The clear antihypertensive effect of GYY4137 raises the possibility that this compound, or a like slow-releasing H<sub>2</sub>S donor, may be of therapeutic benefit in clinical conditions associated with excessive vasoconstriction, the researchers believe. GYY4137 may also serve as a useful tool to probe the biologic significance of H<sub>2</sub>S in cardiovascular and other systems, they suggest.

## Resources

The dabl[R] Educational Trust

British Hypertension Society

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