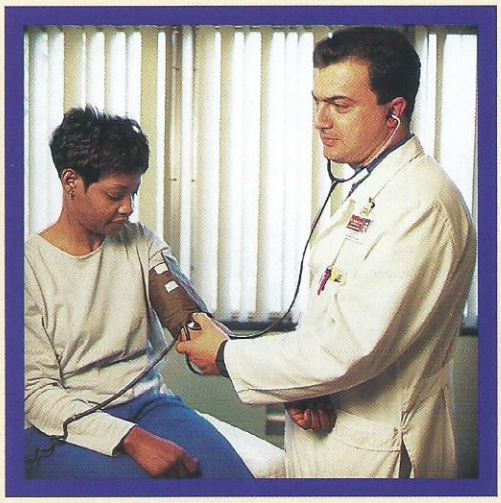
Endothelin and Hypertension

Making the Connection

By Roban Johnson

Researchers at Mercer University School of Medicine, in collaboration with University of Georgia scientists, have uncovered a link between hypertension and plasma endothelin levels — a link that may explain why hypertension is so prevalent among African-Americans and might ultimately lead to better treatment of this disease that affects more than 50 million Americans each year.



Leading the research was Dr. Sitki Ergul, a third-year resident in the Mercer University/Medical Center of Central Georgia internal residency program, who began studying endothelin in 1995. He and his colleagues have now completed the second phase of his study and have clearly shown that a racial difference in plasma endothelin-1 levels does exist in hypertensive individuals. They also have shown that by regulating high blood pressure one can also regulate endothelin levels in African-Americans who have been diagnosed with the disease.

Endothelin first made headlines in the late 1980s when it was discovered by Dr. Masashi Yanagisawa of Japan to be a small peptide that causes blood vessels to constrict. Later studies suggested that endothelin-1 may be involved in a variety of diseases, such as hypertension, atherosclerosis and asthma. However, no studies comparing endothelin levels in different races were reported, and published studies did little to explain why hypertension is so prevalent among the African-American population.

"The majority of clinical endothelin studies were conducted in Japan and England," Dr. Ergul said. "Those studies did not report any significant differences between hypertension and endothelin levels, nor could they show that endothelin is a major part of hypertension."

Although the higher incidence of hypertension and associated complications in African-Americans has been investigated extensively in the past, few explanations have been given to explain the prevalence of the disease among them. With that in mind, Dr. Ergul began noticing how differently African-Americans and Caucasians respond to different anti-hypertensive medications. And with that, his research idea was borne.

With funding from Mercer University School of Medicine, the University of Georgia Research Foundation, the Medical Center of Central Georgia and a grant-in-aid from the Georgia affiliate of the American Heart Association, he and his colleagues went to work. Collaborating on the project were Department Chair John A. Hudson, M.D., and Dr. David C. Parish of Mercer's Internal Medicine Department;

Department Head David Puett, Ph.D., and Dr. Adviye Ergul of the University of Georgia's Department of Biochemistry and Molecular Biology.

Dr. Sitki Ergul located 100 people who met all of the criteria for the study. People with borderline hypertension were excluded, along with individuals who had suffered from renal failure, shock or myocardial infarctions within the past six months. He did include patients whose hypertension was not under control at the time.

Of the 100 people chosen for the study, 50 were hypertensive and 50 normotensive. Each group was then divided into four categories by sex and race, with 12 or 13 subjects in each group. Their blood pressure was taken and blood samples of each patient were put into three different test tubes. Adviye Ergul then measured endothelin levels in each plasma sample during three separate runs. Dr. Parish and Marcus Durham, instructor of medicine and research, then analyzed the data, which showed that a difference in endothelin levels does exist between African-Americans and Caucasians.

"The results were amazing," said Dr. Ergul. "We found that endothelin levels in African-American hypertensives were three to four times higher than in Caucasian hypertensive patients, male and female. And we found endothelin levels in hypertensive African-Americans to be seven to eight times higher than in normotensive African-Americans."

In comparison, Caucasian hypertensive males had only slightly elevated levels of endothelin compared to male Caucasians with normal blood pressure. Although they noted a slight difference in endothelin levels of normotensive Caucasian men and women, they did not observe any significant gender-related differences.

Dr. Ergul presented his findings at the American Heart Association's 69th annual meeting in New Orleans. The results, the first believed published on this subject, appeared in the American Heart Association's October 1996 issue of *Hypertension*.

Dr. Sitki Ergul

By demonstrating that racial differences do exist in plasma endothelin levels of hypertensive people, Dr. Ergul then developed a second study to determine how regulating high blood pressure might effect endothelin levels in African-American hypertensive patients.

In this study, funded by the MedCen Foundation and the National Institutes of Health, 20 hypertensive African-Americans were given conventional anti-hypertensive medications to regulate their blood pressure. To ensure compliance, they were given home blood pressure monitoring kits and were called daily. Within eight days, the blood pressure of all 20 patients was under control. Blood samples were taken on four specific days and endothelin levels checked. The results again were intriguing.

"We found that elevated endothelin levels in African-Americans dropped to normal levels when their high blood pressure was regulated by conventional antihypertensive medications," Dr. Ergul said. These findings were presented at the 12th International Interdisciplinary Conference on Hypertension in Blacks held in London in July 1997.

Dr. Ergul suggests that endothelin may be the key to future discoveries in the treatment of hypertension and its complications in African-Americans. Already, animal studies have found that endothelin levels are impressively high on kidney failure cases — and high endothelin levels have also been linked with heart failure and coronary artery disease.

"In the future, endothelin receptor blockers may be used to help prevent these complications, or they may prove ineffective," Dr. Ergul said. "We don't know yet."

What is known is that for the first time researchers have shown that racial differences do exist in endothelin levels and that a correlation does exist between endothelin levels and hypertension. These discoveries may lead to improved treatment of hypertension in the future. D