



Endothelial Dysfunction and the Preventative Approach to Cardiovascular Disease: An Interview With Mark C.

Houston, MD, MS, ABAARM, FACP, FAHA, FASH

Interview by Karen Burnett

Mark C. Houston, MD, MS, ABAARM, FACP, FAHA, FASH, is associate clinical professor of medicine at Vanderbilt University School of Medicine; director of the Hypertension Institute and Vascular Biology; and medical director of the Division of Human Nutrition at Saint Thomas Medical Group, Saint Thomas Hospital in Nashville, Tennessee. He is also on the faculty of the University of South Florida for the Functional and Metabolic Medicine Fellowship. He is chief medical officer for Destination Medical Centres in the United States, which is part of MVP Holdings, LLC.

He is triple board certified by the American Board of Internal Medicine, the American Society of Hypertension (ASH), and the American Board of Anti-Aging and Regenerative Medicine (ABAARM). He also has a master of science degree in human nutrition.

Dr Houston has presented over 10 000 lectures nationally and internationally and has published more than 200 articles and scientific abstracts in peer reviewed medical journals. He is on the consulting editorial board for many medical journals and is editor-in-chief for JANA (Journal of the American Nutraceutical Association). He is an author and teacher and is active in clinical research.

Integrative Medicine: A Clinician's Journal (IMCJ): Dr Houston, please tell us about your background. Where did you grow up, and did you always want to go into medicine?

Dr Houston: I grew up in Jackson, Tennessee, which is in west Tennessee. I decided at a very early age, about age 6, without any reason whatsoever I can think of, that I wanted to be a physician. I never had anyone in my family who was a physician; I had no one that I knew. So it was almost like I was being called to the profession at an early age. I stuck to that all the way through high school and then decided to do my undergraduate work at Rhodes College. Then, I went to Vanderbilt Medical School.

IMCJ: What led you to decide to go into cardiology?

Dr Houston: When I was doing my training at the University of California in San Francisco, I worked with some of the best cardiovascular people in the world at that time—Dr Kanu Chatterjee, Dr William Parmley, Dr Mel Cheitlin—so I was exposed to cardiovascular medicine very early in my career. From there, I went into a specialty in hypertension and then went on to get a degree in nutrition and antiaging medicine, and now functional medicine and metabolic medicine. I do basically noninvasive, preventive cardiology. Hypertension and lipids are my primary focus now.

IMCJ: Did you have any mentors in the field of functional medicine?

Dr Houston: I did not at the time. I actually got into this field in the mid-1990s, when my father was diagnosed with prostate cancer and I started looking at alternative ways to treat him. In the process, I started to look at cardiovascular medicine from a metabolic and functional point of view, and that's how I really got interested in that to integrate it.

IMCJ: You recently spoke at the Institute for Functional Medicine (IFM) Conference.

Dr Houston: Yes, we did one last year in Phoenix, and we just finished another just a few weeks ago in Tampa.

IMCJ: What did you discuss there?

Dr Houston: The module was advanced cardiovascular medicine and my cospeakers were Dr Mimi Guarneri at Scripps Clinic and Dr Shilpa Saxena in Florida. The module was designed to review all the aspects of cardiovascular medicine from a functional-medicine point of view. My specific topics were hypertension, dyslipidemia, vas-

cular aging, vascular biology, and coronary heart disease risk factors in heart failure and ischemic heart disease.

IMCJ: Tell us about the International Society of Integrative Metabolic and Functional Cardiovascular Medicine and what shape that will take.

Dr Houston: This organization had its beginning at the IFM in Phoenix in June, 2012. My partners in originating this were Dr Mimi Guarneri and Dr Joel Kahn. We have since added ... I think we are up to about 250 to 300 members now. It is an international society. We are just in our infancy as an organization, but it will be one of the first truly functional medicine and metabolic medicine cardiovascular programs with a society to back it up. We will have annual conferences, hopefully at some point a journal, and be able to share our knowledge through websites and interactive questions and answers, through blogs, and through sending out up-to-date medical journals as they come out so everybody is up to date on the latest technologies and the latest information on cardiovascular medicine. At this point, we are still in the process of organizing and getting funding and so forth, but we are very excited that this will probably be one of the premier functional medicine cardiovascular programs internationally.

IMCJ: Have you had good feedback on this idea?

Dr Houston: It has been fantastic because most physicians—not only in cardiovascular or cardiology work, but also internists and family practitioners who have an interest in cardiovascular medicine—have not really had an organization where they could go to for collegial evaluations, meetings, and get updated information through e-mails and keep up with this literature.

IMCJ: Cardiovascular disease is still the number one killer in our country, and this is one of the issues that you tackle. You have mentioned in your books and in some of your talks the risk factors for heart disease that are often not given enough attention, like inflammation, oxidative stress, and autoimmune dysfunction of the arteries. Could you talk about some of these factors in cardiology?

Dr Houston: One of the major underpinnings that I am trying to teach people is that our present approach to cardiovascular medicine is a bit obsolete and needs to be totally revamped. We are not achieving an optimal reduction in cardiovascular risk. In fact, most patients who achieve [desired goals for] what we would define as traditional risk factors—hypertension, dyslipidemia, diabetes, obesity, and smoking—even with those controlled by the present definitions, about half the people will still have heart attacks. What that tells you is that we are obvi-

ously missing something. And what I think we're missing is about 395 other coronary heart disease risk factors.

The way I put this in simple terms is that there is infinite numbers of insults to the artery, but there are only three finite responses. Those three finite responses are what you mentioned, which are inflammation, oxidative stress, and autoimmune disease of the vasculature. So the way we are going to try to reapproach cardiovascular medicine is to find biomarkers that identify those three finite responses, and then we backtrack to find the reason—the why. What is the genesis of the inflammation or the other two finite responses? By doing so, you are able to pinpoint one or more causes and reduce the insult to the artery. That then turns off all the downstream effects that end up [initiating] one of those three finite responses, which drive most of the cardiovascular risk from a very basic functional-medicine point of view.

IMCJ: Have you pinpointed some successful tests for this?

Dr Houston: Yes, there are a lot tests you can do, but how I try to get people started is by identifying one or two tests that are really simple to do. They are reimbursable and they have a very high sensitivity and specificity for the finite marker that you are looking at. For example, the best marker for inflammation is high-sensitivity C-reactive protein. For oxidative stress, I primarily use oxidized LDL and myeloperoxidase. And for autoimmune dysfunction, I initially use thyroid antibodies.

If any of these are abnormal, you can get additional supportive information, or if you find all three to be normal, you might want to get into the more sophisticated tests to be sure you haven't missed something.

IMCJ: What were some of the more sophisticated tests?

Dr Houston: For inflammation, you might measure things like the various interleukins—interleukin-1 β , interleukin-6, and TNF- α , and then there is a whole host of other inflammatory markers like serum amyloid A, fibrinogen, and so forth.

If you are looking at oxidative stress, there are a large number of markers there, such as MDA deoxyguanosine. There are both plasma and urinary markers for oxidative stress. You can measure oxidative defense, as well. So you want to try to [determine] the balance of the stress to the defense. There are a lot of labs that measure the defense mechanisms that are inherent to the body like catalase, superoxide dismutase, and glutathione, and then there are the recyclable antioxidants, like vitamins E and C, coenzyme Q10, and so forth.

IMCJ: What is the importance of endothelial dysfunction? What role does this, and vascular muscle dysfunction, play

in cardiovascular disease, and have we underestimated these?

Dr Houston: The endothelium is a very thin monolayer of cells that separates the lumen—the blood and all the white cells, red cells, and platelets—from the vascular smooth muscle. It is the air-traffic control system, basically, for the blood vessel. The communication is bidirectional, and it determines what goes on in the blood, which can be thrombosis, an increase in inflammation, or oxidative stress. It also communicates with the underlying vascular smooth muscle to determine permeability, growth, and other factors. So if the endothelium is healthy, then it sends out good messages to both the blood and also to the vascular smooth muscle.

One of the most important messengers in the endothelium is nitric oxide, which is typically counterbalanced by other hormones, but the primary one is angiotensin II in endothelium. What you think of is nitric oxide is doing everything it is supposed to do to prevent hypertension, atherosclerosis, and heart disease, and angiotensin II in endothelium has the opposite effect, where it actually increases atherosclerosis and hypertension in all of the three finite responses we discussed earlier. So when you look at the endothelium, you want to try to balance the nitric oxide bioavailability against the antithesis, which is angiotensin II in endothelium, which through various mechanisms can negate a lot of the effects of nitric oxide.

IMCJ: So, therefore, endothelial dysfunction can influence the effects of nitric oxide?

Dr Houston: Let's step back just a little bit. The endothelium produces a lot of different things; nitric oxide is just one of many. There are a lot of insults that attack the endothelium and damage it. When the damage occurs, it goes into a dysfunctional mode where it starts to produce cytokines and chemokines and other inflammatory markers that cause further damage—not only to the endothelium, but also to the blood elements and also the vascular smooth muscle. So when you look at endothelial dysfunction, it is one of the earliest markers for vascular disease and has a very high predictability of future cardiovascular events—whether it be a myocardial infarction, a stroke, congestive heart failure—or renal dysfunction or failure. There are various tests that we use now that can identify endothelial dysfunction (ED) very early on. Once you identify it, then you try to do either nutrition, nutritional supplements, or medications and drugs to try to reverse the ED and try to increase the production and/or bioavailability of nitric oxide.

IMCJ: What are some of these supplements, vitamins, and medications that you could use to reverse this dysfunction?

Dr Houston: Generally, we try to start out by using a combination of precursors that support not only nitric oxide, but also the enzyme that makes nitric oxide, which is eNOS—endothelial nitric oxide synthase. So arginine, for example, is one of the precursors, along with citrulline, through the eNOS enzyme to make nitric oxide. There is another entire pathway, through the bacteria that are present in the mouth and GI tract, that converts nitrates to nitrites and to nitric oxide. That is what you get through your diet, primarily. Vegetables, [especially] beet-root juices, are very high in nitrate conversion to nitric oxide. So a lot of things that we do to try to convert to a higher nitric oxide level can be done through your diet, but also through supplementation with arginine.

Then, there are a lot of support systems and the cofactors and coenzymes that are part of that system that you need to replace: tetrahydrobiopterin is one of the very important ones, folic acid, glutathione, the reduced form of nicotinic adenine dinucleotide (NADH), and flavin adenine dinucleotide (FAD). All these are precursors in a nutrient resupplementation program.

IMCJ: So endothelial dysfunction is a systemic issue. Is it then true that it could trigger other disease besides hypertension, such as diabetes and others that we do not necessarily think of, like Behcet's disease, as well?

Dr Houston: Because the endothelium is the lining of the artery, and the arterial system is one of the largest organs in the body—in square feet, it is actually the size of six tennis courts—it is probably also the largest endocrine organ in the body, if you look at what it makes. When you get endothelial dysfunction, the primary effect is on the vascular system. Because the vascular system is affected so adversely, however, the downstream effect could be just about anything. I mean, you could have an increased risk of diabetes or insulin resistance. It is also related to dyslipidemia. So there are a lot of different vascular diseases that are termed *vascular*, but there are also things you might not consider as a vascular disease, per se, but are affected by the endothelial dysfunction.

IMCJ: When patients come to you, what do they look like when they have some of these problems? In other words, do they seem to be a typical candidate—perhaps obese, perhaps [with] hypertension? What does the patient look like who may have this situation?

Dr Houston: The diagnosis of endothelial dysfunction is difficult to make just by looking at the patient's phenotype. Even looking at their known risk factors, you can often be fooled. What you can say is that someone who comes in with obvious risk factors like obesity, smoking, diabetes, dyslipidemia, and/or hypertension, are likely to have endothelial dysfunction, but that does not always

count when you do the test because there is a discrepancy.

We call it *vascular translational medicine*. What that means is two things. One, you can have a lot of risk factors and have normal endothelial function, or someone can walk in and he looks totally normal without any obvious risk factors and have very bad endothelial dysfunction. The only way you can sort this out is to actually measure the endothelial dysfunction noninvasively. There are several machines that do it, but the one that has probably got the best sensitivity and specificity in the outcomes data is EndoPAT. EndoPAT is extremely accurate in defining ED, but also in predicting future cardiovascular events.

To perform the EndoPAT test, calipers are put on both index fingers and a blood pressure cuff is placed over the arm. You occlude the brachial artery for 5 minutes, release it, and you get what is called a *hyperemic response*—hyperemic response to reclusion of the blood flow. That produces endogenous nitric oxide, and the artery will dilate dramatically if it is healthy. You compare the occluded arm with the control arm to see what the difference is. The more dilation you get, the healthier the artery is, but if you get a ratio that is below a certain level—we use 1.68 as a cutoff point between normal and abnormal—then you can find someone that is having endothelial dysfunction.

IMCJ: So in addition to improved diet and exercise, do you recommend certain vitamins and supplements to patients with hypertension?

Dr Houston: Yes, we have published extensively on how to control hypertension using a nonpharmacologic approach. We start with the DASH-2 diet, which is basically a lot of fruits, vegetables and fiber, and also very high in antioxidants and very high in electrolytes like potassium and magnesium. It is very low in sodium. That DASH diet, DASH-1, and DASH-2 generally will lower blood pressure about 12 over 6 to 7 millimeters of mercury—just that one thing.

Then we put them on an aggressive aerobic and resistance exercise program after screening carefully to be sure they do not have underlying heart disease. Once they are trained [and begin the program], within usually probably 3 to 4 months, their blood pressure will fall dramatically because exercise increases the activity of eNOS, which is the enzyme that makes nitric oxide. We get them to lose visceral fat, particularly, but also total body fat, and increase their lean muscle mass. Using weight as a criteria for success is not as accurate, obviously, as using visceral and total body fat to determine whether or not you are achieving a reduction in inflammatory adipocytes, which are part of this inflammatory process from being overweight.

The final thing we do is start a group of nutraceuti-

cal supplements. There is a whole list of these that are effective—not just for blood pressure reduction, but also for prevention of cardiovascular disease—things like coenzyme Q10, lycopene, and whey protein. All of these things are very good in vasodilatation and hypertension reduction.

IMCJ: Do you have any patients whose bodies seem to show resistance to this treatment, and then what do you do?

Dr Houston: There are a few people who would fall into what is called the *resistant weight-loss group*. We do have a very specific program that we use for those patients, but with regard to just following the rest of the program, if you do everything correctly, there are very few people who are really resistant to that. The main thing you run into are people who have extremes of blood pressure. If they have very high blood pressure and you start this type of program, you may not be able to get them completely off medication. But the ones who are in the milder form, if they follow all these suggestions over a period of 6 months to a year, most of them typically improve. In fact, we published the studies showing that 62% of those patients were able to discontinue blood pressure medications within about a year.

IMCJ: Could you please tell us about your research into treatment for dyslipidemia?

Dr Houston: We take a totally different approach to the management of lipids. Most people in the lipid world have been very involved with trying to get just the LDL cholesterol under control, and LDL is not the total story here. When you measure [only the total LDL], you are missing what the components of the LDL consist of. The real driving force for heart disease, particularly coronary heart disease, is the LDL particle number and secondarily the LDL particle size. The only way to accurately measure those is with an advanced lipid profile. This is really the state of the art for lipid management: to define the problem exactly with an advanced profile, as opposed to the old obsolete measurements of total levels.

The other part of the lipid profile that is part of this advanced evaluation is also measuring the size and particle number of HDL and the particle numbers for VLDL, which is triglyceride. And in that, we also look at what is called *dysfunctional HDL*. One of the brand new stories about dyslipidemia is that just because your HDL is elevated does not mean you have protection from heart disease. Unless the HDL is functioning properly, it not only may be unable to do its job, but in fact, could actually be peroxidative and inflammatory in and of itself if it is altered through various mechanisms.

IMCJ: I think that is something people are generally unaware of.

Dr Houston: There are a lot of good studies in the literature showing that if you have an HDL that is over 85, a large amount of that HDL, or a large number of people who have that level, have dysfunctional HDL.

IMCJ: Changing the topic, when you look at functional medicine, where do you see spiritual wellness in the scheme of things?

Dr Houston: I truly believe that the human body has to be balanced with mind, body, and spirit. Otherwise, the interconnections become totally misconnected, fouled up, and you get disease. If you just look at cardiology in and of itself, there are enormous amounts of literature that talk about psychoneural immunology and how it affects the heart and the blood vessels. So how you think [affects you]: are you depressed, are you anxious, are you hopeful, are you pessimistic? All these things have a direct effect on heart-rate variability, heart-rate recovery time, blood-pressure vasoconstriction, immune dysfunction, inflammation, and oxidative stress. So you really cannot separate any of these three things. You have to treat them in total. Otherwise, you will not have the success that you really want to have.

IMCJ: Can the placebo effect offer an explanation of the medical importance of spiritual wellness? If you believe your treatment is working and you have confidence and are feeling positive, then that belief can sometimes equal success.

Dr Houston: I think you are exactly right. The placebo effect, having faith in the program, a belief in a higher power, a spirit, that connection in people who meditate [or] do prayer—they heal better. They have better outcomes, and this is shown in anything. It is shown in not just cardiovascular disease, but also in cancer and cancer recovery.

IMCJ: Do you discuss this aspect with your patients or do you incorporate it into your program?

Dr Houston: Absolutely. It is incorporated into every program. We try to allow people to pick and choose what they are comfortable with based on their background, their spirituality, their religious preferences, and organize a program that will be beneficial to them and not try to impose something that they are not comfortable with, which could in itself create more stress. But the bottom line is if you talk to people about the mind-body-spirit connection and you offer support in that, they will do better than those who do not follow that program.

IMCJ: What are you working on right now? What are you interested in researching or investigating?

Dr Houston: We have ongoing research projects. Most of these are related to hypertension, dyslipidemia, and cardiovascular disease—endothelial dysfunction. We presently have a couple of studies where we are looking at some natural compounds that are high in nitrites and nitrates that improve blood pressure in endothelial dysfunction. We are looking at several nutritional supplements that are good for blood-pressure control, developing a whole new line of cardiovascular supplements for not only endothelial dysfunction, but also for plaque regression, for coronary heart disease, for congestive heart failure, ischemic heart disease, and new compounds for dyslipidemia. All these will be done through a very sophisticated approach, using metabolomics in the identification of very specific targeted nutrients—not only in supplements, but also in herbals.

IMCJ: Do you think attitudes are changing about functional medicine?

Dr Houston: Absolutely. I really think that the populists, the patients, are going to demand a different type of medicine. People are really coming to functional medicine physicians because they get to the root of the causes, and they are not just treating a symptom.

It is not like “my chest hurts,” so here, take an anti-inflammatory. Or, “I have gastroesophageal reflux,” so here, take a PPI (proton-pump inhibitor). Functional medicine [assesses] the symptom then goes back and asks the reason [why] you got it and treats [the cause] from a very basic level, as opposed to the typical A to B approach, which is: disease, drug. That is not the way we need to be practicing medicine. It has not worked very well. We do really well in acute medicine in the United States; we are probably the best in the world. But when it comes to managing chronic diseases and getting to the root of problems, we have unfortunately taken more of a pharmacologic approach without really thinking about what we are doing. So functional medicine is, in my opinion, the wave of the future. It is really taking over traditional medicine very, very quickly. I think in the next 3 to 5 years, this will be the way that most medicine will be practiced in the United States. If you are not on board with understanding functional medicine, I suspect that the number of patients who come to see you will start to dwindle dramatically.

There are a lot of great articles and books out there that get into this in more detail. Obviously, the IFM symposium and others address these problems. So people who are interested should read those articles, read those books, and try to attend some of these symposia.