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Addressing Vascular Plaque Ruptures

### PLAQUE RUPTURE IN THE CORONARY VESSELS

You are listening to ReachMD, The Channel for Medical Professionals. Welcome to Medical Breakthroughs from the University of Pennsylvania Health Systems with your host, Northwestern University Internist, Dr. Lee Freedman.

A ruptured vascular plaque with subsequent thrombus. The cause of the sudden heart attack that occurs without warning. How can we approach this devastating condition? With me today is Dr. Emile Mohler, III, Director of Vascular Medicine and Director of the Vascular Diagnostic Center at Penn Presbyterian Medical Center in Philadelphia.

**DR. LEE FREEDMAN:**

Thank so much for being with us, Dr. Mohler.

**DR. EMILE MOHLER:**

Hello, pleasure to be with you.

**DR. LEE FREEDMAN:**

Well, plaque rupture we have come to understand seems to be the cause of many, if not the majority, of heart attacks. Tell us a little bit about plaques and the difference between stable and unstable plaques.

**DR. EMILE MOHLER:**

Well, one of the things that of course no later we have learned is that the patient's first presentation is not always a chest pain, but actually frequently a heart attack itself. So, there has been a lot of research done to try to identify those individuals, who are at risk for developing heart attack before it occurs. Because patients of course do not always read the textbook and have the classic symptoms. The first thing that can happen is, as you point out, a plaque rupture. So, there are several different types or ways that a clot can form in the artery and that is for example the classic way where we have rupture of the plaque itself. The overlying coating, if you will, of tissue ruptures and exposes tissue factor and other procoagulant proteins that then can result in platelet activation and aggregation and

ultimately a thrombus formation that occlude the vessel. We do know that there are other ways that a thrombus can form and that's for example with plaques that just ulcerate. For example, ulceration like you would have in the stomach for example, where just the overlying tissue is not so much ruptured, but the endothelium is no longer present and you have a prothrombotic situation on the surface of that plaque. The next potential way that actually plaques can become unstable is in rare circumstances. It is reported although I think the research is relatively weak about it and that's a calcified nodule can appear on the surface of the plaque, which can act kind of like a lugging rod for thrombus formation.

**DR. LEE FREEDMAN:**

Is that something that is felt to occur commonly or this is a more unusual cause for thrombus?

**DR. EMILE MOHLER:**

I think that's much more unusual cause and then the fourth way that you can actually have a problem with instability; the plaque is actually rupturing or hemorrhaging into the plaque. Thus, rather than exposing outside, you can actually bleed into the plaque because of the friable tissue when the lot of plaques have angiogenesis and small capillaries that form in the plaque itself and they can rupture and you can have expansion of the plaque itself in unstable variety, if you will, by bleeding into the plaque. You may or may not get a thrombus in that situation, but you could certainly advance the plaque to a point that it's hemodynamically significant and causing ischemia.

**DR. LEE FREEDMAN:**

Has there been research in terms of risk factors for the formation of thrombus or increasing plaque by one of this four mechanisms. Is it genetic, is it blood pressure related, smoking?

**DR. EMILE MOHLER:**

Well, unfortunately all of the above. So, what happens of course is the genetics and environment? All play a significant role in development of plaque and also in the formation of thrombus and heart attack. There are actually now genes that have been described, so called heart attack gene that is involved in predisposition, increased predisposition to develop a heart attack at 9p21 is what it's called. The function unfortunately is completely unknown, but it is associated with heart attack, we do know that the plaques that are eccentric. Another is the ones that are of the plaque models outward and of to the side rather than circumferential are the most dangerous plaques and most prone to rupture. Do know also that the plaques that have heavy amount of inflammatory cells, macrophages, T cells for example. Those are plaques where that ulceration or hemorrhage is more likely to occur and rupture especially with thinning of the cap on the plaque.

**DR. LEE FREEDMAN:**

So, genetic components, some morphologic characteristics of the plaque, and then inflammatory predispositions?

**DR. EMILE MOHLER:**

Which in is inflammatory predisposition of course can be fueled by the classic risk factors like smoking, hypertension, diabetes, and hypercholesterolemia.

**DR. LEE FREEDMAN:**

From a clinical standpoint, are there ways that we in the office can pickup, who might be more likely to have an unstable plaque versus a stable plaque?

**DR. EMILE MOHLER:**

Well, we would like to able to pick out the patient that is at risk and that has been the focus of looking at the high-risk patient. So, of course, those patients who have risk factors like diabetes or smokers are probably, you know, in that category if they do have coronary disease unless they have addressed those risk factors or at the higher risk. So, just phenotyping the patient so to speak from a risk factor standpoint, but we don't unfortunately have a test that could be ordered in the office that's an imaging test to look at the plaque. Intravascular ultrasound is one way that has been determined to look at that. PET imaging may become potentially a way to look at this, but unfortunately the PET imaging and MR imaging of the coronary arteries has not advanced to that point yet. The best we have though to look at whether there is a pro-inflammatory state are biomarkers such as high-sensitivity C-reactive protein and the one we are talking about today lipoprotein-associated phospholipase A2 or Lp-PLA2.

**DR. LEE FREEDMAN:**

Before we get to the markers, if I could ask in terms of imaging modalities of the Ultrafast CT, it would seem to me because we are talking about calcium, those might be better at identifying stable plaque or is that not the case.

**DR. EMILE MOHLER:**

Well, Ultrafast CT scan is a useful modality to evaluate plaque burden, if you will. So, calcium accumulates with cholesterol on the plaque, but unfortunately what it doesn't tell you is the ratio between the amount of calcium and the amount of cholesterol present in the inflammatory situation of the plaque. So, for example, you could have let's say 2 patients with a calcium score of 100 or 1 patient may have just a lot of calcium for each of those plaques that you score, but another patient may have a lot of cholesterol and a lot of inflammatory cells that overwhelm that 100 score on the calcium scale. So, you don't really know just from the Ultrafast CT scan what is happening at the plaque level and whether there is a stable or unstable plaque. It just tells you, yes or no, whether there is plaque present and then of course what level of risk compared to patients with similar age that are seen.

**DR. LEE FREEDMAN:**

If you have just tuned in, you are listening to medical breakthroughs from the University of Pennsylvania. I am Dr. Lee Freedman and I am discussing plaque rupture in the coronary vessels with Dr. Emile Mohler, III, Director of the Vascular Diagnostic Center and Director of Vascular Medicine at Penn Presbyterian Medical Center.

**DR. LEE FREEDMAN:**

Dr. Mohler, tell us more than about the biomarkers that can give us some indication of vulnerable plaque.

**DR. EMILE MOHLER:**

Sure, as I mentioned earlier, there is 2 main biomarkers that we are using in Clinical Medicine today. One is high-sensitivity C-reactive protein and a level greater than 3 is thought to be very high risk, greater than 2 is considered abnormal and you really need in clinical practice to repeat that twice because the variability that can occur in the setting of a virus or other disease state that may elevate that. The newer biomarker on the scene, which is generated and has been in fair amount of research data generated to look at this biomarker, is lipoprotein-associated phospholipase A2 or Lp-PLA2. It is marketed as the plaque test by a company called diaDexus to evaluate the risk of the patient as a biomarker.

**DR. LEE FREEDMAN:**

Is it just a marker of inflammation or does it have a specific activity within the plaque?

**DR. EMILE MOHLER:**

Well, it's a unique biomarker, in that it's carried along with low-density lipoprotein. So what's interesting is as LDL accumulates in the plaque, phospholipase enzyme can go to work and release substances such as lysoPC and oxidized fatty acids that are proatherogenic, the pro-inflammatory and can increase the amount of inflammation in the plaque leading to plaque instability and therefore, promoting potentially plaque rupture hemorrhage, etc. and myocardial infarction.

**DR. LEE FREEDMAN:**

I noticed also on your study that you also looked at interleukin-6. Is that something that's commonly looked at?

**DR. EMILE MOHLER:**

Interleukin-6 is a pro-inflammatory cytokine that is not typically looked at in clinical practice. I think because of variation lab to lab and non-standardization, but certainly is a marker that's been reported to be elevated in patients who have an increased inflammatory situation.

**DR. LEE FREEDMAN:**

And we certainly have our patients at risk on aspirin in case there is rupture and thrombus formation, but might there be some other ways to get it stabilizing the plaque?

**DR. EMILE MOHLER:**

Well, yeah, one of the big ways, which I think is very effective and I think the data is extremely strong is the HMG-CoA reductase

inhibitors, statins. Statin drugs in multiple studies have shown to reduce heart attack and stroke rate and it is thought that one of the primary ways this occurs is due to plaque stability and usually we know that in the early studies where we injected contrast dye in the coronary arteries with angiograms, we didn't see a big regression with statins, but within a year, we started to see reduction in heart attack and stroke rate and then we began to understand that the statin drugs are actually stabilizing the plaque, reducing inflammation and actually promoting plaque stability.

**DR. LEE FREEDMAN:**

With your article in the recent Journal of the American College of Cardiology, you looked at another molecule that might be helpful. Can you tell us about that?

**DR. EMILE MOHLER:**

Yes, the study design that we used where we randomized patients to either receive a statin drug, in this case atorvastatin, has background treatment. After the patients received either 20 mg or 80 mg of atorvastatin, they then were randomized to receive a novel Lp-PLA2 inhibitor called darapladib and with varying doses 40, 80, and 160 mg compared to placebo once daily for 12 weeks. So, we looked and evaluated whether patients would have a reduction in the levels of activity of this enzyme in the bloodstream after treatment according to protocol.

**DR. LEE FREEDMAN:**

Do we know the mechanism that darapladib works by?

**DR. EMILE MOHLER:**

Yes, it is thought to inhibit the enzyme itself. So, the small molecule is thought to prevent activity, not completely, but to reduce the activity of the enzyme especially hopefully that the amount in the plaque and we have done some previous preclinical work with animals with pig model that showed the amount of Lp-PLA2 activity is reduced in the plaque itself after giving this drug.

**DR. LEE FREEDMAN:**

Can you tell us in this particular study how it worked and what the outcomes were?

**DR. EMILE MOHLER:**

Yeah, the outcomes were interesting. First of all, we wanted to see with background treatment of atorvastatin whether we would have any further reduction of Lp-PLA2 activity because statin drugs themselves reduce activity of this enzyme and we did see a significant reduction in activity even up to the high dose level, which was encouraging. We also looked at of course safety and the drug was very well tolerated with few side effects and a few dropouts due to any of the side effects.

DR. LEE FREEDMAN:

Also, it had some good effects on C-reactive protein and this interleukin-6.

DR. EMILE MOHLER:

Yes it did. In a kind of preliminary way so to speak, we looked at these cytokines in patients that were enrolled in this study and found a significant reduction as you point out. So, we were encouraged that our hypothesis that this would reduce inflammatory activity is consistent with those results.

DR. LEE FREEDMAN:

Well, I want to thank Dr. Emile Mohler, who has been with us discussing the difference between stable and unstable or vulnerable plaques in the coronary arteries. He reviewed several of the characteristics of these plaques including the biomarkers that can help to tell us if a patient has an increased risk from unstable plaque and then he reviewed how statins and now perhaps darapladib, a new agent, may help to stabilize plaques and prevent the sudden heart attack that occurs without warning.

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