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Transcript of Dr. Zipes's lecture at the 2nd Vulnerable Patient Symposium held by AEHA
on March 6th in conjunction with
the Annual Conference of American College of Cardiology 2004
New Orleans, LA

I have approached this very differently and with a great deal of frustration as an electrophysiologist, because there are some sobering statistics. 30 to 50% of sudden cardiac death due to coronary disease occurs the first cardiac event. One-third of sudden cardiac death occur in patients with known coronary disease or risk markers but power is sufficient to be a useful marker of sudden death and only a small percent have well established risk markers. Therefore, in two-thirds or so, we're unable to predict the individual at risk for sudden death. The risk factors lack specificity, sensitivity and predictive accuracy. We can identify populations at risk, but not the individuals with sufficient degree that I would put an ICD in the these individuals, and these are major problems. The standard risk factors on the left that we're all aware of and some exciting new ones that are being explored from CRP to others as well, but if you look at some data, for example, in MADIT II, this shows time vs mortalityin the conventionally treated and the ICD treated group and one sees that the mortality continues to increase after the initial event. If you look at another study, this is from Maastricht, the medium time for myocardial infarction to sudden cardiac arrest was nine years. How do you predict that? And if the myocardium is remodeling, as I indicated in an editorial that I wrote for

an article that Gene (Eugene Braunwald) and Mark Pfeffer published, what triggers sudden cardiac death? Why did the patient die on Tuesday and not on Monday, or on Wednesday? What was the change? And I would submit to you that the CRP data, though did predict groups at risk for sudden death, is not specific enough because I think there's an interaction between an anatomic or functional substrate, transient initiating event and then the basic arrhythmia mechanism that lead to sudden death. And to illustrate this, I pulled out a case report we published 20 years ago. This is a 40 year old man who developed an incessant supraventricular tachycardia after his second infarct and the development of right bundle branch block. Now, if you look on the left, this was a scalar ECG, he's got sinus rhythm and then as the rate increases seven beats a minute, he developed a supra ventricular tachycardia and that was more or less incessant. We studied this individual and it turned out he had a concealed accessory pathway. Now, he was born with that, but he never had the first episode of tachycardia until he developed an infarct with a right bundle. He had the substrate all this time but never developed tachycardia. So, what happened? You see on the top prior to the infarct, the sinus-initiated conduction traveled down the AV node and His-Purkinje system rapidly and every time it attempted to turn around –and enter the accessory pathway, the accessory pathway was found to be refractory and it always met with block. Now, after the infarct with the right bundle, His-Purkinje conduction prolonged 40 milliseconds. During a rate of 74, the impulse still gets down quickly enough and it can't turn around to re-enter and initiate tachycardia, but when the rate increased a little bit more, there was further slowing of conduction and now he could re-enter the accessory pathway and start SVT. My point is that remodeling that alters conduction by a few milliseconds can start a tachycardia in a substrate that was present for 40 years, but was never used -- it took the development of a bundle branch block for this to happen and this can make that individual 9 years after his infarct (e.g., the Maastricht study) a candidate for sudden death.

Now, there's some speculative data here, but I want to show you one study which we published about different sites of origin of premature ventricular beats that could determine whether or not they could start a tachycardia. This is the use of optical

mapping in an isolated wedge preparation, but the guts of the data are here. Dr Jiashin Wu created ischemia in this model. Now, the epicardium is more sensitive to the effects of ischemia than is the endocardium, for unknown reasons. Prior to ischemia, conduction, when we stimulate the epicardium here, travels to the endocardium without any problem. Stimulating the endocardium travels to the epicardium without any problem. Now, with 390 seconds of ischemia, there's lateral epicardial conduction delay but still transmural conduction. The endocardium is more resistant to ischemia, so there's good propagation. Now, after 500 seconds of ischemia, there's lateral epicardial block, the impulse travels to the endocardium and re-enters to the epicardium. The impulse initiated in the endocardium travels normally. What does this mean? Well, if you had a PVC arising in the endocardium, it would propagate without delay/block or re-entering, but a PVC starting in the epicardium would produce lateral block and re-entry and could precipitate VT or VF. And let me show you the images -- this is now after 500 seconds of ischemia we're pacing the epicardium and you see the re-entry classic figure of eight, but we pace the endocardium and there's propagation transmurally with no conduction delay or block. So, depending on where a PVC arose, it could initiate or not initiate VT or VF. We call these "windows of opportunity" and timing and a substrate are very critical for the development of re-entrant arrhythmias.

Now, you also need to consider the site of the infarct and the areas of re-entry that may or may not produce a tachyrhythmia. This is from another study in a canine heart by Dr. Jianyi Wu.. This is the border zone next to the infarct over here, using optical mapping and I just want to make a couple of points. The anatomic location of the re-entrant circuit in VT involves the ischemic or the infarct area and the re-entrant loop is as depicted here. These are four beats, this is the first one… the second one… the third one… now you see progressive conduction delay over here and the fourth beat produces conduction delay and now re-entry. This is how VT starts. This could be sudden death if the timing were very critical and there can be clockwise re-entry, as you see on this side or counterclockwise re-entry in the same model. But if the timing is not exquisitely accurate, one gets non-sustained VT. Here for example. is the premature beat which re-enters a couple of times, blocks here and stops and then there's no VT

and no sudden death. And if there is no area of conduction delay and block, for example, over here the propagation, though not uniform, does not create the area of block for re-entry to occur, and therefore this animal did not have inducible ventricular tachycardia. So, how do we pick any of this up by looking at risk factors? Yet these are the electrophysiologic parameters that determine whether or not a tachyrhythmia is sustained and whether sudden death occurs; therefore, timing and activating sequence determine whether or not VT or VF will occur after an infarct and I don't know how to evaluate that with risk factor analysis.

I want to share with you one other piece of data that Dr. Norihiro Ueda is actually presenting in a couple of days at the ACC and raise the potential issue whether a period of ischemia can pre-dispose to ventricular tachycardia or fibrillation by other mechanisms. This is again the same animal model. This is the canine ventricular wedge used to create a model of Long QT3. This is due to prolonged sodium inactivation which can be replicated with ATX-II. The purpose of this study was to determine whether an episode of ischemia sensitized the myocardium to the effects of this Long QT prolonging drug– in the isolated ventricular wedge. This wedge had 40 minutes of ischemia and then re-perfusion before application of the drug and at this point, the electrophysiology had returned totally to normal. So, 40 minutes of ischemia, complete recovery and then drug given in one group,while this group of wedges just had perfusion with no ischemia and then drug.

What I'll show you over here is that the exposure to 40 minutes of ischemia made this myocardium very vulnerable with significant QT prolongation compared to control. – These are the images that correspond to the tracings below. So, this is the first beat that's over here -- this is the second beat -- and then there's a repetitive response, that was spontaneous, this is a fourth paced beat over here and then the fifth and then spontaneous tachyrhythmia. Now, initially, this is focal activity that's rather haphazard and then you'll see a very nice re-entry develop and here's the re-entry now. This did not happen in the other wedges that did not have an episode of ischemia. So, we raise

the issue that a prior episode of ischemia, even after apparent complete recovery, can make the myocardium vulnerable to an intervention to which it was not vulnerable prior to the episode of ischemia. And this may have relevance in patients with Long QT or in individuals who are taking drugs that prolong the QT that have a much greater effect on QT after an episode of ischemia than prior.

Therefore in this model, a prior episode of ischemia, even after an apparant electrophysiologic recovery, enhances the arrhythmogenicityin this Long QT 3 model through the development of early after deplorizations and re-entry raising the issue whether ischemia can sensitize patients with Long QT and possibly, other situations as well.

So, the problems from the electrophysiology standpoint are very great. The triggers are myocardial EP processes that probably determine the onset or lack of VT VF or sudden death, which is difficult to measure clinically and the indirect EP surrogates, i.e., risk factors, don't really measure these phenomena and obviously give us no clue about mechanism.We must continue to rely to on other indirect risk factors for now -- I agree absolutely with what Dr. Braunwald presented, that's the state-of-the-art, but we don't understand the EP as to why the patient fibrillated on Tuesday and not on Monday or Wednesday.

At the present time, the way to approach the SCD dilemma is to have rapid automated external defibrillator (AED) deployment. An initiative we started in Indianapolis I call the "Neighborhood Heart Watch." We deploy these large "mailboxes" in which an AED is placed. We've only put five up so far -- this one's on my lawn in Indianapolis and all 38 houses that live around this area have keys to this box and have access to the AED. We must never forget that eight out of ten sudden cardiac deaths occur in the home. So, you can have AED's in all the airports and athletic events you want, you only get accesss to one out of five SCD candidates. And this is an attempt then to get the AED out into the home, into the community and allow rapid access while we're still trying to unravel the basic electrophysiology. Thank you very much.