



Defining myocardial infarction for future care

Joseph Alpert speaks to Adam Born, Assistant Commissioning Editor: Joseph Stephen Alpert is Professor of Medicine and Director of the Coronary Care Unit at University of Arizona Medical Center – University Campus (AZ, USA). A native of CT, USA, Alpert obtained his Bachelor of Arts degree (magna cum laude) from Yale University (CT, USA). He obtained his medical doctorate (cum laude) from Harvard Medical School (MA, USA). Alpert did his internal medicine residency and cardiology training at Peter Bent Brigham Hospital (MA, USA) and was a Research Fellow of the Massachusetts Heart Association (MA, USA) and the National Institutes of Health (MD, USA). Following his fellowship, Alpert became a staff cardiologist and Director of the Coronary Care Unit at the Naval Regional Medical Center in San Diego (CA, USA) and an Assistant Clinical Professor of Medicine at the University of California, San Diego (CA, USA). Following his military service, he returned to Harvard Medical School and was appointed as Assistant Professor of Medicine and Director of the Samuel A Levine Cardiac Unit, Peter Bent Brigham Hospital (MA, USA). In 1978, Alpert joined the faculty of the University of Massachusetts (MA, USA) as Professor and Chief of the Section of Cardiovascular Medicine. In 1992, he was appointed the Robert S and Irene P Flinn Professor of Medicine and Chair, Department of Medicine, University of Arizona College of Medicine, a position that he held until 2006.



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Q Could you tell our readers a little about your career to date & how you came to your current role?

I am currently a Professor of Medicine at the University of Arizona College of Medicine (AZ, USA), I'm a cardiologist and I'm part of the Sarver Heart Center (AZ, USA), which is part of a combined center for both cardiologist and cardiac surgeons. I did my undergraduate work here at Yale University (CT, USA) and then I was at Harvard Medical School (MA, USA) – I spent many years at Harvard training in internal medicine and cardiology. Eventually I became chief of cardiology at the University of Massachusetts Medical School in Worcester (MA, USA), which is a short distance from Boston. I then followed my mentor, James Dalen. When he became the dean of the University of Arizona I came here to be his chief of medicine, which I was for 14 years. That is a very long

time to be chief of medicine here in the USA. Afterwards I did a little time in the dean's office but I wasn't satisfied with that role, I wanted much more clinical involvement, and so I'm back running the coronary care unit and the cardiac rehab. That's half my life; the other half is that I'm the editor-in-chief of the *American Journal of Medicine*, the so-called green journal.

Q What is your research focusing on at present?

When I first started my career I of course followed the research interests of the individuals that I trained with, Lewis Dexter, one of the pioneering cardiologists of the 20th century, and James Dalen, who I've already said was the reason I came to Arizona – he was my other mentor. That laboratory was very interested in pulmonary embolism and right ventricular function, so many of my earlier papers were

in that area, and then subsequently in my career I've become more interested in acute myocardial infarction (MI). I've run coronary care units on both coasts of the USA and have begun now to run a coronary care unit again. Much of what I do these days involves large multicenter trials where I am often on steering committees or data safety and monitoring committees.

Q You recently co-chaired a group of authors that published a new definition of MI, how did this come about?

Part of that had to do with a previous existence. I initially started my career as a marine biologist and spent a substantial amount of time, first on a Fulbright scholarship and then on a NIH scholarship, in Denmark. First studying marine biology and eventually wandering into medicine, I also worked, studied and did research in Bispebjerg Hospital (Copenhagen, Denmark) with a fellow named Nils Lassen who, in the 1960s and 70s, was one of, if not, the leading clinical investigator in cardiac physiology in the world. Through that I developed many friends in the Danish cardiology world and I remain very active in the European Society for Cardiology. Approximately a dozen years ago my good friend Kristian Thygesen and I were having dinner and we were talking about the fact that on that particular day two papers presented at the meeting on MI had contradicted each other. As we talked about it we realized they contradicted each other because they were defining MI differently, they were taking different patients. So we said, 'Well wouldn't it be good if everyone in the world used the same criteria to define a myocardial infarct?' From there we were able to get together the American College of Cardiology and the European Society of Cardiology to fund a first iteration of the international definition, which was published simultaneously in the *Journal of American College of Cardiology* and the *European Heart Journal* in 2000. But of course, as you know, science moves along and there have been papers that have come along that have caused us, each year, to make some modest revisions to the definition. We have published two more papers since 2000, with a large international group, approximately 35–40 people from all over the world, working on the definition. The first revision was published in 2007, the next in 2012 and the group is continuing to meet, with a view towards releasing a fourth revision.

Q This third definition focuses more on clinically relevant MI than the universal definition of 2007. Could you explain a little how the definitions differ?

The basic principle of this definition rests on the measurement, by assay, of troponin, which is a component

in the contractile machinery of a myocardial cell. The assays are made by a number of different companies and are extremely accurate at detecting troponin even in tiny amounts, and so we can now diagnose even the smallest myocardial injury from troponin. However, elevation of troponin isn't automatically translated to a MI, you need some clinical criteria as well because other things can injure the heart. For example, if you're in a car accident and you smack your breastbone against the steering wheel you'll get a bruise on your heart that will elevate troponin, but this obviously isn't a heart attack. So there are a lot of clinical criteria, for instance electrocardiographic criteria, that are required to diagnose infarction. However, the fundamental, first component in the definition is elevated troponin.

Q Why was a new definition required? What will it help to achieve & who will benefit?

First of all, with these new very sensitive troponin assays we are picking up people with very small myocardial infarcts and this enables us to treat the patients appropriately. These are people who would not have been noticed in the past to have had a MI – that's one advantage. The other advantage is that many of the big clinical trials are now using the same definition so we are going to be able to make comparisons from one trial to another. That was the goal from the beginning. Trials were comparing apples to oranges and now we want them to be comparing apples to apples.

Q There is some controversy regarding the troponin assays encouraged by the new document & the particular definition of type 2 myocardial infarction. Could you explain some of this controversy? Do you feel it is justified?

Let me just give you a brief rundown. The type 1 MI is what everyone sees on television or in films, a person comes in to the emergency room, clutching their chest, there are clear cut changes on the ECG, and often these patients are taken straight to the catheterization laboratory to have their arteries opened and so forth. This is the standard, everyday MI and represents the majority of MIs – there has been a rupture or an erosion in an atherosclerotic plaque and a clot forms that blocks the artery. That's a type 1, and that's your textbook MI. Type 2 occurs sometimes in people who already have coronary disease and blockages, or in people that don't have disease and blockages but have a sudden huge increase in heart demand, for example they go into arrhythmia where their heart rate goes up to 180 bpm. The blood flow cannot sustain that effort so there is some ischemia in certain zones and some myocardial cells die, elevating the levels of troponin. Alternatively, a patient could have a serious infection that drops their

blood pressure and thus blood flow to the heart is decreased. So, either a marked increase in demand or decreased blood flow into the heart can lead to an infarct even if the person has normal, healthy coronary arteries. That is a type 2 MI, which we call a demand–supply infarct. Type 3 is a rare one, in which a patient comes in and we observe that clinically they have an infarct but before we can collect troponin assays and so forth, the patient dies. You don't need troponin to define that event, but it's a very rare event. Type 4 MI is associated with revascularization procedures, for example angioplasty. Finally, Type 5 is associated with cardiac surgery. In that case, due to suturing and so forth, there is always going to be a slight increase in troponin, so the bar there is set higher – it's ten-times the usual upper limit plus clinical information.

The type 2, as you can see, can be confusing as some patients might have cardiac injury as part of pneumonia syndrome or a bad infection, not as a result of an infarct. So the diagnosis of type 2 can be quite confusing and difficult for the cardiologist.

Q How quickly do you hope the new definition(s) will be adopted? How is this being encouraged?

Well, it is being encouraged because now we have not just the American College of Cardiology and the European Society of Cardiology on side, the American Heart Association also endorses it and has people on the task force, and the World Heart Federation supports it. So the four biggest international cardiology groups are in favor of this. The US FDA is adopting this definition and so it's going to be forced on all future clinical trials here in the USA. Also, when we ask at various meetings how many people are using the new definition I would say that 80% of cardiologists in the USA, Europe, Japan, Australia, New Zealand and so forth are using the new definition. Also, every month articles come out on MI that are using the new definition, so we are progressing well.

There are areas of controversy, as you pointed out, the type 2 and type 4 MI. There's no question that that is going to need further research and further refinement. But certainly for type 1, which is most of the patients that end up in my clinical trials where the drugs and devices are used, most physicians and trials are now using the new definition.

Q Finally, what do you think will be the hot topics in cardiovascular care over the next few years?

Well, there's a number of things. I'm sure that in the UK, just as in the rest of Europe, North America and all developed countries, there's a rising mean age of the

population. So we're seeing a marked growth in elderly individuals and with that there is a change in the kinds of heart disease that we're seeing. Just to give you one example, in the USA today, in this 24-h period, more people will turn 85 years of age than will be born. If you think about that for a minute, you realize there is a changing demographic of what we're seeing in the hospital – so there's a lot of elderly individuals, some in pretty good shape and some in not so good shape. One of the things changing in that environment is that we used to have rheumatic heart disease with mitral stenosis, aortic regurgitation and so forth; we see almost no or very little rheumatic disease in the industrialized countries, both in the west and in the east. We see a lot of atherosclerotic calcific aortic stenosis and there are all these percutaneous valves that are being implanted now. I think that's going to be a huge area; there's going to be fewer patients going for valve surgery and more patients going to the catheterization laboratory for procedures.

Number two, with this elderly population there is huge growth in two areas: atrial fibrillation and heart failure. Both of these are what I would call growth industries. We're not terribly good at taking care of heart failure, we are much better at taking care of atrial fibrillation but there is a lot of clinical research that needs to be done in that area with respect to questions like: should we control the arrhythmia with antiarrhythmic drug and push people to stay in sinus rhythm or should we just control the heart rate? There are new anticoagulants that prevent stroke, which is a high risk in atrial fibrillation patients, which also need to be considered. But heart failure shouldn't have a similar prognosis to many terrible metastatic cancers – half the patients of either are dead within 3 or 4 years. So that's an area that is also getting intense investigation.

Recently more attention is being paid to the fact that for patients who are arriving with serious end-stage heart failure that qualify for heart transplants there just aren't enough hearts to go around. There's a lot of work, therefore, on artificial hearts. Already in Europe and North America there are people walking around with backpacks that are powerpacks for totally artificial hearts.

Of course, finally, is the whole area of prevention. In Asia 100 years ago a heart attack was a rare event. Right now, in India, China, Taiwan and so on the number one reason for admittance to hospital is MI. There's a huge epidemic of MI going on in Asia, and that's why the number cause of death worldwide is no longer infectious disease, it's ischemic heart disease.

Q Is there anything else you wish to add?

For me, as someone who has been almost as much involved in European cardiology as North Ameri-

can cardiology, I really see cardiology as a field where we all, throughout the world, relate to one another. Because, yes, there are regional differences in disease but by and large we're all dealing with the same kind of problems, countries are dealing with the same sort of health issues. The National Health Service in the UK is dealing with the same issues we see here – a wave of elderly patients with a lot of heart failure, atrial fibrillation and so forth. So when cardiologists meet they almost immediately understand each other and each other's problems, and even though there are differences in healthcare systems, when you take the 'airplane view' from 30,000 ft the differences are really not that great. To me, it's a wonderful experience going to international conferences, meeting with my colleagues and realizing that we are all dealing with the same issues and problems. It creates a feeling of

fellowship and camaraderie among cardiologists all around the world.

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