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Picture This-Medical Imaging and IT

Dr. Daniel S. Berman, Director of Cardiac Imaging at Cedars-Sinai Medical Center and President Elect of the Society of Cardiovascular CT, speaks to EHM about the evolution of nuclear cardiac imaging.

With a reputation as one of the top hospitals in the US, along with one of the best heart and heart surgery departments in the annual guide to the 'America's Best Hospitals' edition of *U.S. News and World Report*, Cedars-Sinai Medical Center is at the forefront of innovation in cardiac imaging.

In his role as Director of Cardiac Imaging at the center, Daniel S. Berman is responsible for seeing patients; reading, interpreting and reporting examinations; and running a large research section in cardiac imaging. One of the projects with which he is currently involved is extending the current environment to include a research imaging core that will have MRI, CT, and possibly SPECT-CT and PET/CT for both micro and small animal imaging, as well as large animal and human volunteer patient studies.

Berman is considered one of the principal developers of the techniques and applications of nuclear cardiology. Speaking about his field and how it has developed over the last few years, he says: "Nuclear cardiology involves examining the heart through the use of radioactive tracers: injections of small amounts of radioactivity intravenously that localize in the cardiovascular structure, usually in the heart."

He recalls that when he started working in the field, nuclear medicine did not even have a proper name, and only about 100 studies were being done throughout the world in patients with a variety of different experimental radioisotope-based agents. These days, the number of studies has ballooned to around 10 million per year in the United States alone.

"I was fortunate to be one of the first people to see the potential of this new approach for cardiac disease," says Berman. "I was a nuclear medicine resident at Sacramento Medical Center, and 50 miles away at Travis Air Force Base were Barry Zaret and Bill Strauss. They were the first people to do exercise myocardial perfusion imaging, and it was this that really started the field. At this time it was carried out with potassium-43. In fact, that was the first kind of scan I did with exercise using a rectilinear scanner. Quite quickly this turned to another agent called rubidium-81. This agent is what I wrote my initial manuscript in myocardial perfusion imaging on."

A growing field

By 1976, thallium was made available and Berman describes how there was a marked growth in the field. He recalls that by 1980, he had already recognized multiple opportunities for the use of this approach for the diagnosis of patients who had an intermediate likelihood of coronary artery disease. Shortly thereafter, it became used as a method for risk stratification, and the early data regarding the ability of nuclear testing to define patients as high risk and separate them from low risk came from Cedars-Sinai Medical Center.

Working with leading figures in the application of Bayes' Theorem in cardiac practice in the field, including George Diamond, Jim Forrester, Berman and his team established a database which allowed them to follow all of the patients who had come through for stress testing. "It was this database that enabled us to look at the patients over time and see the degree to which risk stratification was possible with this tracer.

"After those early studies performed with exercise, pharmacologic stress methods became common, first with dipyridamole, then with adenosine..With dipyridamole becoming available, this opened up the opportunity to study myocardial perfusion at rest and stress, even in people who couldn't exercise.

"Around 1990, an agent became commercially available which allowed us a technetium-99m tracer for examining myocardial perfusion. With better imaging properties than thallium-201, we could actually look at ventricular function at the same time."

Berman and his group got involved in establishing methods for computer-based automatic assessment of ventricular function from myocardial perfusion images and the automatic assessment of myocardial perfusion; the quantitative analysis of myocardial perfusion scans methods developed at Cedars-Sinai have become the most widely used approaches in the world used to interpret the scans.

In the 1990s, the American Society of Nuclear Cardiology, of which Berman was a founding member, had swelled to a membership of close to 6000. This society is dedicated to standardization and bringing nuclear cardiology to its full potential. This includes setting standards for how studies should be done and for the qualifications needed in order to be doing it appropriately.

According to Berman, “It was the bringing of standardization to the field that really helped its broad growth around the country. What then ensued, particularly in the late 1990s and early 2000s, is that many cardiologists in their own private offices began to obtain cameras and perform nuclear cardiology studies. The expansion of these systems into offices has led to the nuclear stress tests becoming one of the most commonly used methods for assessment of the patient with known or suspected coronary artery disease.”

Cardiac nuclear scans

As with all noninvasive testing, there are very few complications associated with nuclear scans, as Berman describes: “As such a small amount of the agent is used, I haven’t heard of any chemical reactions being reported.”

However, Berman notes that they do use a small amount of radioactivity, and there is a possibility that the radioactivity could lead to mutation that could potentially be involved in the generation of cancer many years later, although this is theoretical. “We do not know whether these small amounts of radioactivity given with the cardiology studies results in cancer 20 or 30 years later, but on a theoretical basis, given what we know about the relationship between the radiation and late cancer development, it is a possibility. Because of this, we keep our doses as low as possible and we recommend using the tests only when they are needed.”

“The process behind the nuclear scan involves the intravenous injection of a small amount of tracer that gets taken up in the myocardium in proportion to the heart muscle blood flow. By seeing whether or not there is a uniform distribution of the tracer throughout the left ventricle, we’re able to see the degree to which the blood flow is normal at rest and stress. If a patient has a blockage obstructing flow in a coronary artery, during stress, when the blood flow to the normal heart muscle is increased three to fourfold, the blood flow through the artery with the blockage will not be able to increase as much as through the normal coronary arteries, and this produces a reduction in the uptake of radioactivity in that region of the heart.”

After the injections are made, sophisticated cameras are used to take pictures from 180 degrees around the patient. With this kind of angular sampling, it’s possible to take the data sets and reconstruct them into slices corresponding to all the different portions of the heart muscle. When this procedure is done using tracers like thallium or technetium sestamibi, it is known as single photon emission computed tomography (SPECT).

Another procedure that is used for nuclear scanning of the heart is positron emission tomography (PET). This approach is based on tracers that emit positrons, a different kind of radioactive decay. When positrons decay, two packets of energy are emitted in opposite directions 180 degrees apart from one another. Detection of positrons uses a PET scanner, with a ring of detectors surrounding the patient. In recent years, PET has begun to grow at a rate that is greater than that observed with SPECT imaging. SPECT imaging has reached a plateau in recent years, after having approximately 20 years of double-digit growth on an annual basis.

“What nuclear cardiology offers in general is an optimal opportunity to perform molecular imaging so that tracers can be labeled with either positron agents or single photon agents,” Berman explains. “They can be labeled to examine various biological processes in the body or various molecular processes, so that we can get an image related to that specific process. Examples of these are imaging the neuronal uptake of a tracer so that we can take an image of the cardiac nervous system. The heart actually has a small amount of nervous innervation that comes from the autonomic nervous system, and its activity can be imaged.

“Another example is to use fluorodeoxyglucose, a measurement of glucose metabolism, to measure the degree to which glucose metabolism is occurring within the heart to indicate that the heart muscle is alive. This study is done with PET scanning. We could also potentially have a tracer that specifically targets the process called apoptosis, which may become a marker for activity of cardiac disease. This very specific cellular process, apoptosis, or programmed cell death, has the potential to be imaged with either PET or SPECT methods, as examples of how molecular imaging is likely to come to the fore in nuclear cardiology.”

Excellent tools

Berman continues to lead the specialty of cardiac imaging in generating outcome data for cost-effective analysis of cardiac imaging tests. According to him, if you consider the use of cardiac imaging in patient management, then there are excellent tools available in cardiology to combat heart disease. “We have certain drugs that are used to prevent a disease from occurring in the first place,” he says. “There are drugs that we use to reduce the risk of patients who have heart disease by reducing ischemia – too little blood flow to the heart. We have more invasive techniques such as angioplasty or bypass surgery that are used to revascularize the heart in situations where medical therapy doesn’t seem to be adequate.

An important question facing the physician is does the patient with suspected or known cardiac disease fit into this spectrum? Do they just need to be treated with medicine? Do they not need anything at all? Do they need to be considered for an invasive study? (An invasive study is coronary angiography performed by putting a catheter up through the femoral artery to the region of the heart and taking selective coronary angiograms, a procedure that is associated with a small risk. It often leads to angioplasty or bypass surgery.)

“The cardiac imaging studies I’ve been describing are noninvasive,” Berman points out. “I’ve only talked about nuclear cardiology, but cardiac echocardiography, cardiac CT, and cardiac magnetic resonance imaging all deserve to be put in this basket. So the question that increasingly needs to be answered is, given the fact that there’s a limited pool of resources, how can we best utilize these resources in taking care of cardiac patients? And then a secondary question related to imaging is, can the imaging tests that I’ve described, including the nuclear cardiology exam and the other exams, provide a more cost-effective way of taking care of patients compared to other approaches that might be available, such as sending everybody for the invasive catheterization procedure and then deciding how to manage them?

“And the answer is that we are finding that this is a big area for exploration. We have a need for more information regarding outcomes and the degree to which the imaging is or is not effective in the various cardiac situations. And if it is effective, what pathway is the most cost effective? Is it best to start, for example, with a nuclear scan in a person who has chest pain or with a CT coronary angiogram in an evaluation as to whether or not this patient actually has disease and how that disease should be treated? These are questions that will be worked out over time as we begin to study outcomes more extensively than we have in the past. They require large registries or randomized clinical trials, quite a bit of time and large numbers of patients for these kinds of questions to be answered.

“This will take a combination of work with cardiologists, imaging specialists, epidemiologists, outcome specialists and statisticians. It’s a very complex field with complex analyses, but will provide important answers as to how we should allocate funds in the future to best take care of patients.”

New frontiers

According to Berman, cardiac imaging is on the verge of an important new frontier, which is how to best apply the new developments in molecular imaging to the practical care of patients. One of the areas he is most interested in and that he feeels has a great deal of promise is imaging not only the anatomic presence of disease and the functional consequence of the degree of obstruction of the coronary arteries, but also the activity of the plaques blocking the artery in order to best characterize patient risk.

“What has happened until this point is that we have acted more like plumbers. If we see high-grade obstructions in the pipes, we open the pipes. We need to recognize that while obstructed vessels are predictive of adverse outcomes, the majority of patients with obstructed vessels would live quite well on medical therapy alone over a long period of time, because knowing that there’s an obstruction present does not tell us anything about the disease activity.

“The potential is for us to be able to image the coronary plaques using coronary CT angiography and to image the plaque activity using something like fluorodeoxy glucose or labeled apoptosis imaging agents or labeled integrin or some other molecule that exists within the active inflamed plaque, so as to separate the patients who need the most aggressive interventions from those who can be safely treated medically. I consider that a large and important new frontier.

“And the other thing I would say is that imaging is intrinsically expensive, with its often very large machines. What we have to do is continue to do everything possible to encourage the development of the outcomes information that will allow us to understand the strengths and weaknesses of the imaging approaches and develop the most cost effective approaches to the use of imaging, toward the ultimate goal of eradicating heart disease.”