THE BEAT ™

UNIVERSITY OF OTTAWA HEART INSTITUTE
INSTITUT DE CARDIOLOGIE DE L'UNIVERSITÉ D'OTTAWA

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HIGHLIGHTS

Knowing how estrogen protects arteries might offer a way to capitalize on its benefits while avoiding its well-recognized side effects.

(from Investigating Estrogen's X Factor, pages 1–3)

"This is a great honour. It means that much more knowing it comes from colleagues from around the globe."

– Dr. Robert Roberts, President and CEO, UOHI (from More International Accolades for Heart Institute Leader, page 3)

The Institute has assembled a rare suite of molecular imaging facilities found at only a few locations around the world.

(from Small Animal Imaging: New Tools for Discovery, page 4)

Without widespread clinical adoption of flow quantification, the existing market is too small to attract commercial developers. That's where FlowQuant comes in.

(from Automating the Quantitative Imaging of Cardiac Blood Flow, page 5)

Some tests [for CAD] are more suited to men than women and vice versa.

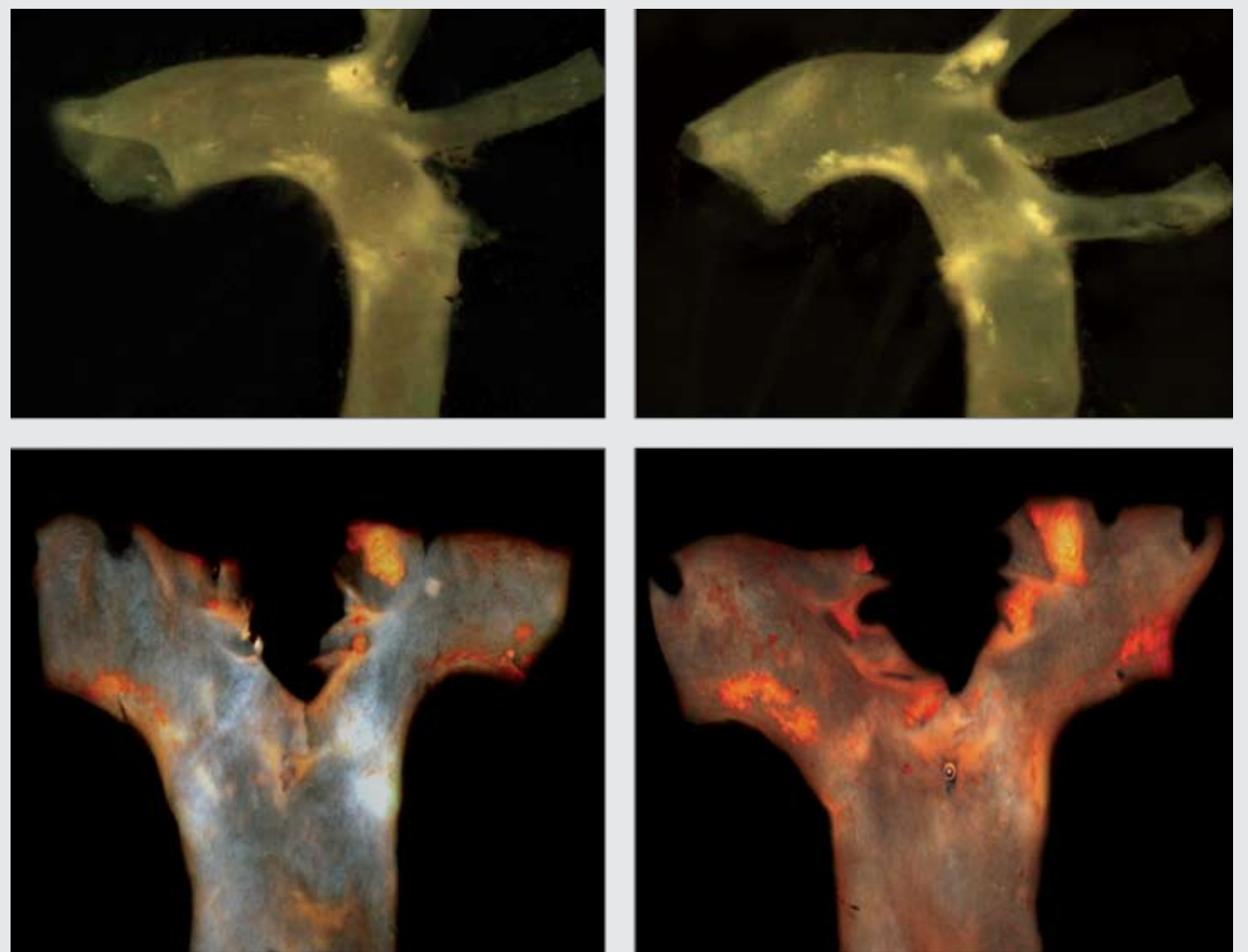*(from Diagnosing Coronary Artery Disease: It's Different for Women, page 6)*

IN THIS ISSUE

Investigating Estrogen's X Factor

Evidence in the aorta: Heart Institute researchers have discovered that a protein triggered by estrogen wards off the development of coronary artery disease. These images of mouse aortas show that, after one month on a high-fat diet, mice genetically engineered to overproduce the protein HSP27 (left, top and bottom) had 35 per cent less atherosclerotic lesion area on the artery wall than did normal mice (right, top and bottom). Lesions are indicated by the light yellow patches in the top row and bright orange patches in the bottom row.

Several years ago, the Vascular Biology Laboratory at the University of Ottawa Heart Institute discovered that a protein known as HSP27 interacts with an estrogen receptor in blood vessels. That initial finding has led to an important new study that may well have uncovered how estrogen protects women against coronary artery disease (CAD).

As a therapeutic tool, estrogen has had something of a rollercoaster ride. Back in the early 1990s, hormone replacement therapy (HRT) was seen by many as a cure-all for the various health risks and conditions that affect women post-menopause. Then, starting in the late 1990s, a series of large clinical trials began to appear that called many of the benefits of HRT into question. In particular, the data showed that the expected reduction in heart disease failed to materialize. Even worse were the increased rates of breast cancer, stroke and blood clots.

Following those outcomes, estrogen in the guise of HRT lost its shine and is no longer widely recommended for the prevention of heart disease in post-menopausal women. And yet, the fact remains that until reaching menopause, women have a lower risk of heart disease than men of equivalent age, while after menopause, their risk equals or exceeds that of men. A protective factor tied to estrogen would explain a

Heart Institute researchers Katey Rayner and Yong-Xiang Chen may well have unmasked estrogen's X factor and opened up a way forward for new modes of prevention and treatment.

great deal about these varying risk levels. But how does it work?

That is the X factor. Knowing how estrogen protects arteries might offer a way to capitalize on its benefits while avoiding its well-recognized side effects. Heart Institute researchers Katey Rayner and Yong-Xiang Chen may well have unmasked that X factor and opened up a way forward for new modes of prevention and treatment.

When the Vascular Biology Lab, funded by both the Heart and Stroke Foundation and the Canadian Institutes of Health Research (CIHR), under the direction of Dr. Ed O'Brien, first discovered the connection between heat shock protein 27 (HSP27) and estrogen, they had no idea what role the protein played. What they soon found out, though, was that the arteries and blood of patients with CAD had far less HSP27 than those of healthy patients. This, and the fact that

similar data was published soon after by another research group, encouraged them to dig deeper. So they tracked down a strain of mouse genetically modified to produce high amounts of HSP27, and they went to work.

The first step was to see if HSP27 really is related to CAD, independent of estrogen. Rayner and Chen put a group of the transgenic mice and a control group on a high-fat diet. After four weeks of eating the mouse equivalent of burgers and fries, all of the mice developed atherosclerotic lesions in their aortas. But the area of those lesions in the females that overexpressed HSP27 was 35 per cent smaller than in the rest of the mice, including the overexpressing males. Rayner and Chen now knew that HSP27 somehow provides protection against atherosclerosis. Because of the gender difference, they also had a good idea that estrogen was involved.

The researchers learned that HSP27 does indeed bind with the scavenger receptor and reduces the uptake of LDL by the macrophages, which inhibits the development of foam cells. They also found that cellular signalling is altered to decrease inflammation.

The researchers then looked at the levels of HSP27 in the blood serum of the mice. HSPs are well known and understood for their role within cells. Referred to as chaperones, they help the body respond to stress. Within the confines of a cell membrane, HSPs make sure other proteins continue to go about their business, fold properly, and maintain their structure in the face of systemic stressors such as increased temperatures. There was no known biological reason for HSP27 to be present in the blood. "Other people had reported finding it there," explained Rayner, "but hadn't asked why or what it was doing."

It turned out that the female mice with low levels of disease had much higher levels of HSP27 in their blood than the other mice. The correlation was too strong to be a coincidence. Something important was definitely going on.

The next step was to figure out how HSP27 ended up in the bloodstream. The research team exposed human macrophage cells – a component of the immune system and a cell type largely responsible for the initiation of atherosclerosis – to both estrogen and LDL cholesterol. They found not only that both the hormone and the "bad" cholesterol triggered the cells to release HSP27, but that introducing the two together had a synergistic effect that increased the secretion rate significantly.

Rayner and Chen had now linked the release of HSP27 to both atherogenic lipids and a high-fat diet, and had identified estrogen as a catalyst. It was time to find out what the suspicious protein actually did once it entered the bloodstream. A good candidate for interaction was the scavenger receptor found on macrophages.

This receptor gets its name from its ability to clear LDL cholesterol from the body. When LDLs accumulate in vessel walls, the scavenger receptor removes that build up by binding with the LDL molecules and carrying them away. While that sounds good, the removal of the lipids can cause an inflammatory response, facilitating the progress of coronary artery disease. The macrophages adhere to vessel walls and become foam cells, which make up the signature fatty streaks that are the hallmark of atherosclerosis.

The researchers learned that HSP27 does indeed bind with the scavenger receptor and reduces the uptake of LDL by the macrophages, which inhibits the development of foam cells. They also found that cellular signalling is altered to decrease inflammation.

The methodical approach that Rayner and Chen took in exploring HSP27's relationship to estrogen established the protein's connection to coronary artery disease, found the method of activation (exposure to estrogen and LDL cholesterol), and illustrated the mechanism by which the protein wards off the development of atherosclerosis.

A strongly collaborative orientation within the lab and throughout the Heart Institute helped move the research forward on a number of fronts. "Our animal models for examining the extent of CAD in the aortas of mice require a lot of time, a lot of devotion, a lot of expertise," said Dr. O'Brien. "A lot of people can't do them, but we have a real mixture of champions that can do it all." Just about everyone in the lab has worked on the HSP27 research at some point.

"Our rapid research progress is largely due to the multitude of resources here at
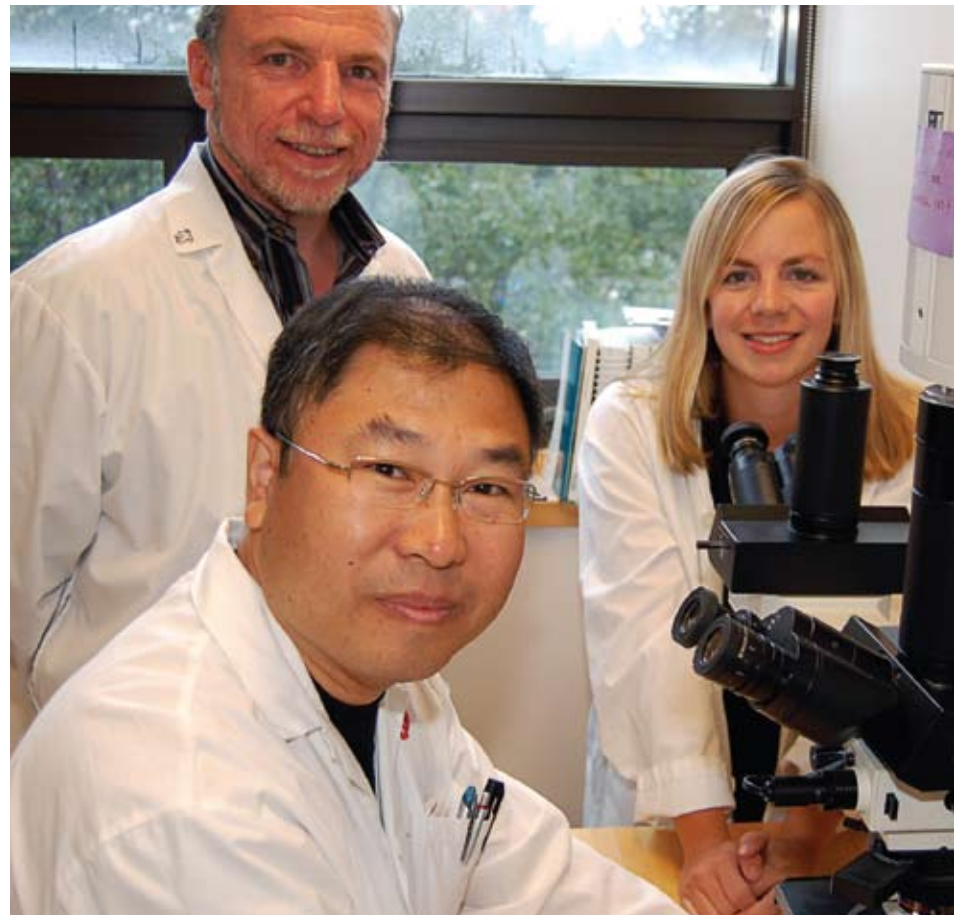

Groundbreaking research: Yong-Xiang Chen, Dr. Ed O'Brien and Katey Rayner (clockwise from front) of the Heart Institute's Vascular Biology Laboratory. Their research has uncovered the mechanism by which estrogen protects women from coronary artery disease.

the Heart Institute," added Rayner. From access to patient blood samples to gene expression (microarray) technology, the lab is studying HSP27 in a multi-dimensional manner that is putting it at the forefront of the field.

Rayner's work on HSP27 won her the American Heart Association's Junior Investigator Award for Women at its Arteriosclerosis, Thrombosis, and Vascular Biology meeting earlier this year, but she is more interested in where the research

goes from here. One area of follow-on study is to find out if HSP27 can repair atherosclerosis as well as prevent it. To do this, the lab plans to partner with the Institute's Molecular Function and Imaging group to use its microPET facility. As Rayner said, "With microPET, the world is our oyster. We can label HSP27 with a radiotracer, then watch where it goes and what it does."

Positron emission tomography (PET) scans will give Rayner and her colleagues
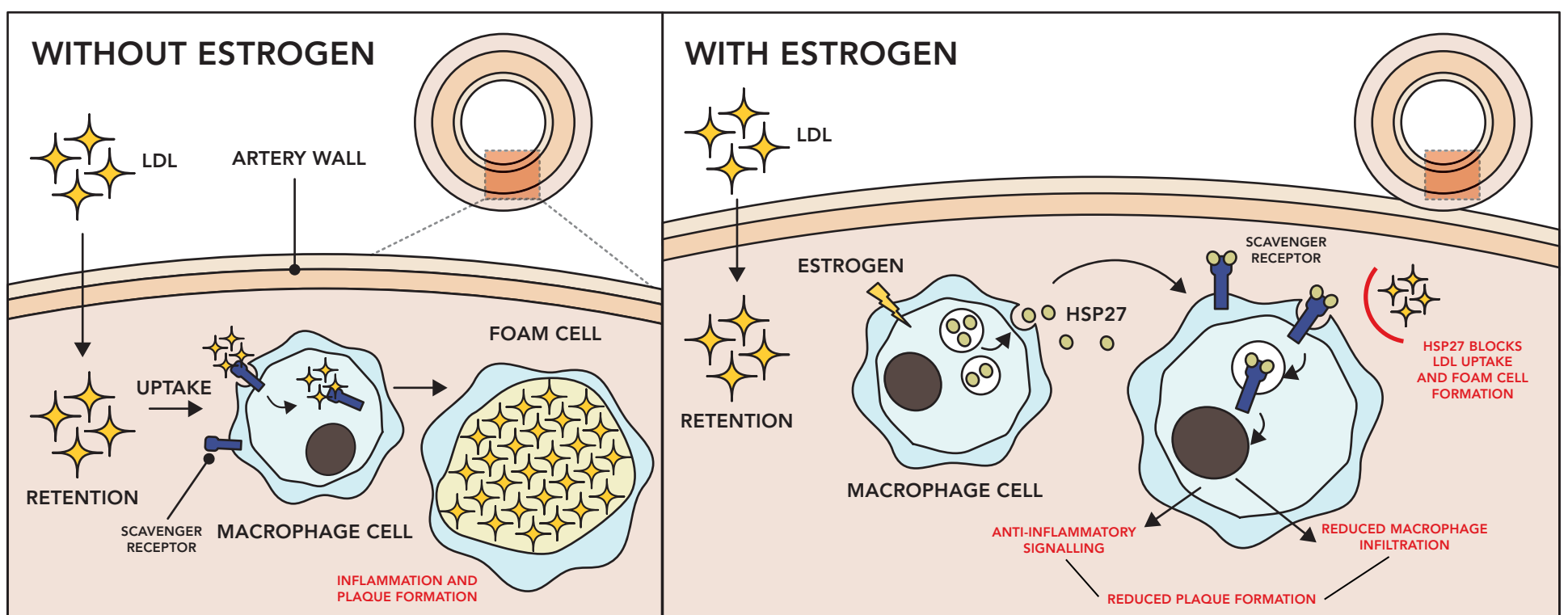
How estrogen protects women's arteries: When you eat a high-fat diet, LDL cholesterol in your bloodstream can collect in artery walls. Without estrogen, macrophage cells from your immune system use their scavenger receptors to clean up the LDLs. Once they have absorbed all they can, the macrophages become foam cells, which make up the plaques indicative of atherosclerosis. In addition, the uptake of LDLs initiates an inflammatory response that increases macrophage presence and, over time, results in coronary artery disease. In pre-menopausal women, the presence of estrogen causes the release of the protein HSP27, which blocks the scavenger receptors and prevents the uptake of LDLs. HSP27 also alters cell signalling to decrease inflammation.

the ability to look at the progression of CAD over time within individual mice and see the extent to which HSP27 alters its course. This is much more powerful for assessing cause and effect than dissecting multiple animals at specific intervals. The microPET, which is designed specifically for small animal research, will also save the time and effort involved in tissue preparation.

The possibility that is most exciting, though, is that HSP27 could be used as a drug. There are two ways this could work. One would be to use HSP27 itself as a drug. The problem with this approach is that the protein is very costly. Even the amounts required for study are prohibitively expensive. The lab has been working to grow its own, but the process is slow and painstaking. It is exploring possible external collaborations to overcome the supply hurdle.

The other approach would be to find a way to trigger the release of the protein by the body. This dovetails nicely with other research being undertaken in the Vascular Biology Lab. Rayner and Chen's study established that estrogen and LDL cholesterol trigger macrophages to release HSP27, but these are not substances that you want to introduce into people. LDL is a known cause of the condition the researchers are trying to prevent, and estrogen is a powerful, blunt instrument that, as the HRT experience has made clear, can have a variety of negative side effects.

The lab has been working with selective estrogen receptor modulators (SERMs) for some time. (See *The Beat,* Volume 2, Issue 5, "Studying the Link Between Estrogens and Heart Disease.") These compounds can be thought of as tailored estrogens that have differential effects in various tissues. The potential impact of a SERM that could trigger the protective function of HSP27 while avoiding the collateral effects of estrogen would be vast.

Future research looks bright. The lab will be presenting four papers related to this work at the American Heart Association annual Scientific Sessions in November. This latest research addresses topics such as how HSP27 affects gene expression and the use of novel estrogen compounds. ❧

Dr. Edward O'Brien

"We have a real mixture of champions [in our lab] that can do it all."

- Director, Vascular Biology Laboratory, University of Ottawa Heart Institute
- Interventional Cardiologist, University of Ottawa Heart Institute
- Professor, Division of Cardiology, Faculty of Medicine, University of Ottawa
- Canadian Institutes of Health Research Medtronic Research Chair
- Research interests: the biology of atherosclerosis and vessel wall response to interventional procedures ❧

Heart Institute Surgeon Takes Over as Society President

Dr. Paul Hendry

Dr. Paul Hendry, a staff surgeon at the Heart Institute, is the new president of the Canadian Society of Cardiac Surgeons (CSCS).

"One of the problems facing cardiac surgery is human resources, and we have to be to be able to train and appropriately ensure we have enough surgeons in the future. The CSCS will be working to ensure just that – that we have enough surgeons for the future," said Dr. Hendry. The society speaks on behalf of cardiac surgeons across Canada.

Currently, cardiac surgery is not experiencing any shortages. Dr. Hendry would like to see the society work closely with the Royal College of Physicians and Surgeons to maintain uniform training standards in the profession.

Dr. Hendry, who replaces Dr. Christopher Fiendel of the Toronto General Hospital in the two-year term, joined the Heart Institute after research training at Duke University in North Carolina. His areas of specialty include heart assist devices, surgery for heart failure, and heart transplantation. Dr. Hendry has received numerous research grants and has authored and co-authored more than 90 scientific manuscripts. ❧

Correction

In the previous edition of *The Beat* (Volume 3, Issue 2), we inadvertently omitted Dr. Joel Kirsh and the Hospital for Sick Children from our discussion on the development of cardiac autopsy guidelines for the province of Ontario. (See "Canada's First Cardiac Autopsy Guidelines for Unexplained Sudden Deaths.") The involvement of the Hospital for Sick Children was equivalent to that of the other hospitals mentioned in the article.

More International Accolades for Heart Institute Leader

Dr. Robert Roberts, President and CEO of the University of Ottawa Heart Institute and Director of the Ruddy Canadian Cardiovascular Genetics Centre, has been recognized by the International Academy of Cardiology for his achievements in science.

In July at the 14th World Congress on Heart Disease, Dr. Roberts received the Albrecht Fleckenstein Memorial Award for his "distinguished work in the field of basic research." The Fleckenstein Award is presented periodically to recognize outstanding career achievements in basic cardiovascular research. "This is a great honour," said Dr. Roberts. "It means that much more knowing it comes from colleagues from around the globe."

A committee of 130 of the world's top cardiologists and scientists selects recipients from an international pool of nominees. Additional awards were presented in the areas of clinical research, disease pre-vention, research in cardiac function, and education.

Dr. Asher Kimchi was chair of the 14th Congress and is an attending cardiologist at Cedars-Sinai Medical Center and Clinical Professor of Medicine at the UCLA School of Medicine in Los Angeles. As Dr. Kimchi said, "Thousands of scientists and clinicians around the world are committed to the fight against heart disease, and these award recipients are being honoured as the heroes in that fight."

Dr. Roberts is widely recognized in cardiac research, where his original contributions include the molecular biology and genetics of heart disease, groundbreaking work on cardiac creatine kinase (CK-MB) – a key indicator of myocardial infarction – and the discovery of the genetic basis for several inherited cardiac disorders. He has been designated one of the most cited and influential researchers in the world, with more than 700 scientific publications to his credit. Dr. Roberts has served in leadership roles with the National Institutes of Health and the American Heart Association and is the recipient of the American College of Cardiology's Distinguished Scientist Award and the American Heart Association's Merit Award. ❧

Dr. Robert Roberts (left) pictured with Dr. Asher Kimchi, Chairman of the International Academy of Cardiology.

Small Animal Imaging: New Tools for Discovery

Imaging technologies like positron emission tomography (PET) or single photon emission computed tomography (SPECT) offer doctors a non-invasive window inside their patients to look for physical and functional abnormalities. Until recently, research scientists haven't had access to this same window when observing their much smaller animal subjects. The newly expanded suite of small animal imaging technologies at the University of Ottawa Heart Institute offers scientists a unique set of tools for cardiac research and the ability to more quickly translate new research findings into therapies and improved patient care.

Non-invasive imaging has been a boon to the diagnosis of heart disease. Doctors can now see a patient's internal anatomy and the state of the cardiac function, both in three dimensions. This ability to visualize form and function from the outside has improved the speed and precision of diagnoses without the risks inherent with invasive procedures, such as catheterization.

With the acquisition of a microSPECT/CT (computed tomography) scanner earlier this year through a collaboration with MDS Nordion, the Heart Institute now has the full spectrum of technologies available for cardiac imaging in both humans and small animals. Along with the microPET scanner installed last year and an onsite cyclotron for producing the radioactive tracers integral to the imaging process, the Institute has assembled a rare suite of molecular imaging facilities found at only a few locations around the world.

"The whole package that the Heart Institute has is not common. Perhaps only one other site in Canada has this level of small animal imaging capability," said Glenn Wells, a scientist with the Cardiac Imaging group who specializes in SPECT research. "When you consider our strong integration of clinical and research expertise and the focus on heart disease, it puts us in a unique situation."

The advantages of using non-invasive imaging for animal research are significant. With traditional laboratory methods, animals must be dissected and the tissues prepared and stained to observe the results of an experiment protocol. Doing so can be laborious and painstaking, requiring a great deal of time and a variety of specialized technical skills. Non-invasive imaging can reduce or eliminate the need for hands-on processing of specimens, and because the rats and mice can be imaged repeatedly over time, the number of animals required for a given study can be greatly reduced.

As Wells explained, "Previously, you would take a large group of animals, divide them into treatment and controls groups, and proceed with the study protocol. You would sacrifice a portion of the animals on day 1, do all your dissections, preparations and analysis, sacrifice another portion of animals on day 3, and so on. To study the time course of how a therapy was altering aspects of disease progression, you would need tens or even hundreds of animals. Now you can treat a single animal, let the disease progress and image it again."

The ability to serially image individual animals also enhances the internal

Glenn Wells, PhD, FCCPM

"Non-invasive small animal imaging facilitates the research we are already doing and opens the door to things that were never possible before."

- Research Investigator, Department of Nuclear Cardiology, University of Ottawa Heart Institute

- Assistant Professor, Department of Medicine (Cardiology), University of Ottawa

- Adjunct Professor, Department of Physics, Carleton University

- Research interests: the integration of CT with PET and SPECT for both human and small animal imaging; image reconstruction, correction and quality enhancement
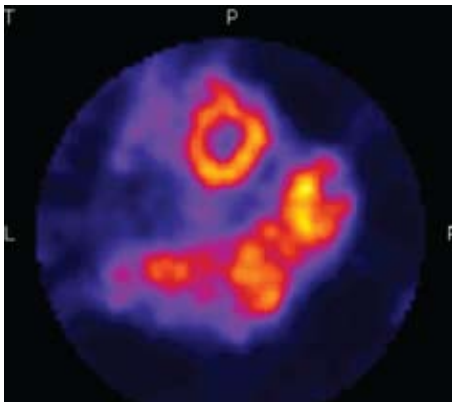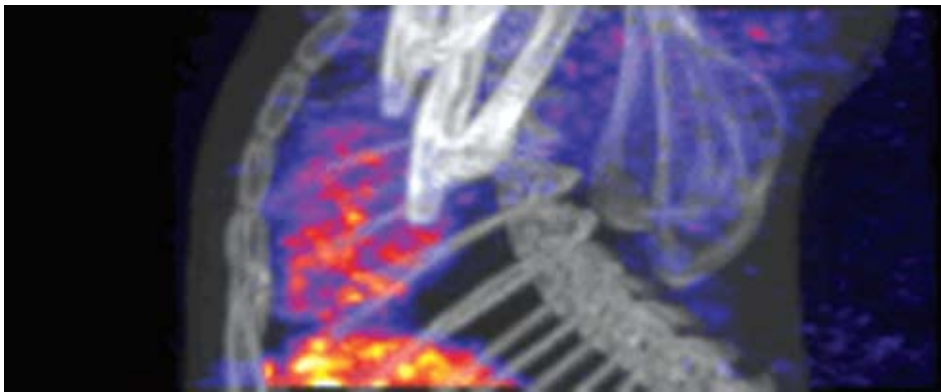
The benefits of non-invasive animal imaging: This capability allows researchers to follow the course of disease and treatment in the same animal, providing data with great statistical power and reducing the number of animals needed to conduct research. These SPECT images of mice show a cross-sectional view of cardiac blood flow (left), with the classic doughnut shape of the heart, and a side view of bone metabolism (above).
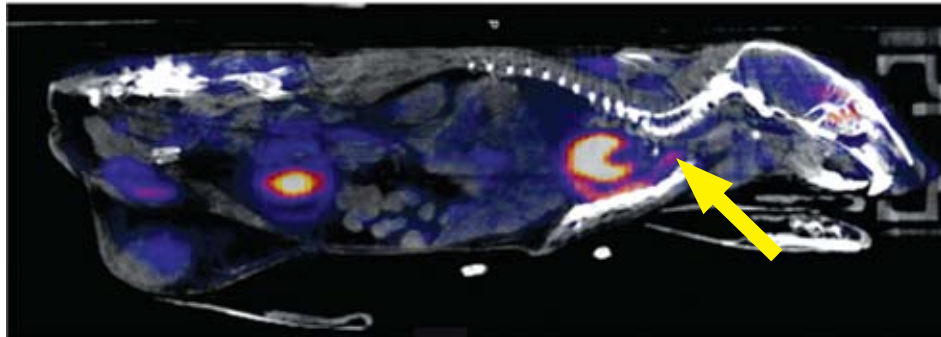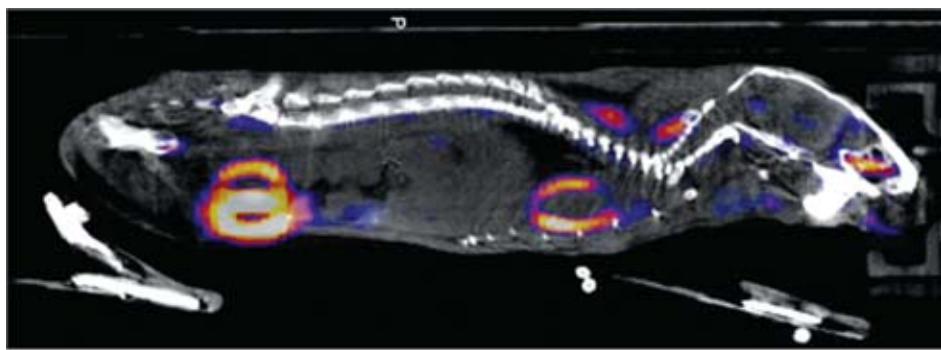
Imaging form and function in small animals: These microPET/CT scans confirm that the technology can image atherosclerotic lesions in the very small aorta of a mouse. The pink area indicated by the arrow (bottom) represents lesions that are absent in the healthy mouse (top). Non-invasive imaging will support research efforts throughout the Heart Institute.

consistency of the data letting each animal be its own control. This dramatically increases the statistical power of the results. By not disturbing the system that you are observing, you are less likely to introduce unintended variability across subjects. In addition, microSPECT and microPET can provide researchers with an image of the whole mouse or rat body,

allowing them to view the entire organism and making it easier to detect unexpected effects.

The other great advantage to these technologies is their ability to facilitate translational research – the evolution of new knowledge from the laboratory to clinical care. "The imaging elements are the

same for human and rodent hearts," said Rob deKemp, the head imaging physicist at the Heart Institute and Canada's leading expert in the physics of cardiac PET imaging. "In fact, if you put same-sized PET [or SPECT] images side by side of a human heart and a mouse heart, you wouldn't be able to tell the difference, even though the mouse heart is a thousand times smaller."

The radiotracers and image analysis methods are also identical for human and animal imaging, making the results of animal studies directly translatable to humans. There are still differences, for example, between how a mouse and a person will respond to a certain drug, but the chemistry of the tracer does not change from one to the other. This decreases the amount of variability when moving from the bench to the bedside.

Translatability of PET and SPECT is also enhanced because human cardiac imaging has been around longer than the micro technology. Animal imaging is a more recent development and poses unique challenges in terms of small sizes and heart rates ranging from 300 to 600 beats per minute. Our experience with human imaging is guiding the implementation of animal imaging techniques, such as procedures, analytical software and image correction. These techniques will, in turn, be applied to the understanding and treatment of human disease.

With the increasing importance of genomics, Heart Institute scientists will have the ability to explore a new wealth of possibilities much more quickly than they could have done previously. A researcher will be able to give a mouse a new compound or activate a certain gene; inject a tracer that will illuminate the physiological or disease process in question; image the location and magnitude of the effects, not only in specific tissues but also throughout the organism; and then follow the progress of the disease or intervention in that same mouse into the future. As Wells put it, "Non-invasive small animal imaging facilitates the research we are already doing and opens the door to things that were never possible before."

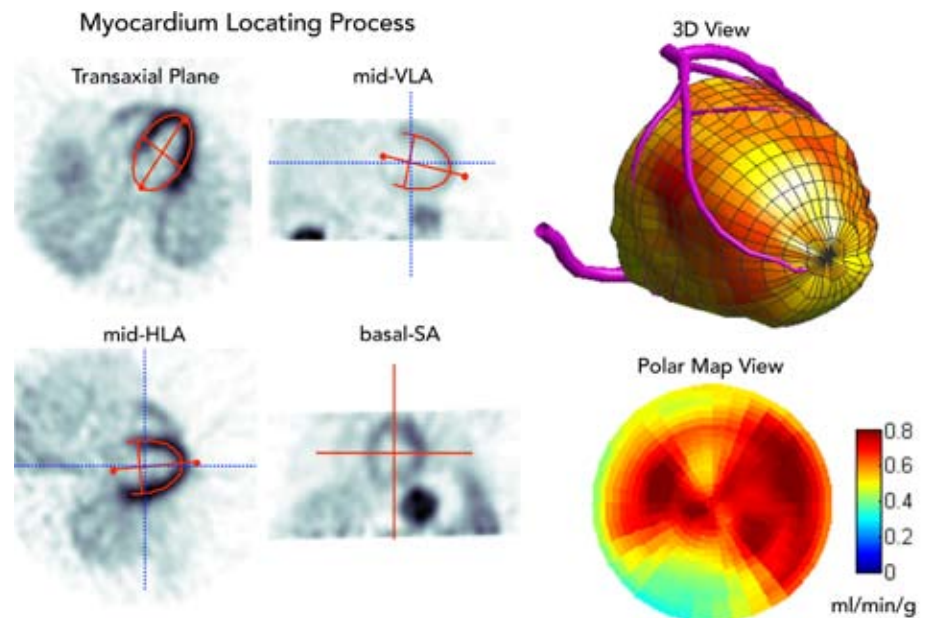# Automating the Quantitative Imaging of Cardiac Blood Flow

You can't use it on your PlayStation or Wii, but FlowQuant is the latest must-have for your PET or SPECT system. Take note, because it's sure to be high on the wish list of your favourite cardiac imaging researcher. Designed to help generate flow quantification data for myocardial perfusion imaging (MPI), the software package developed at the University of Ottawa Heart Institute is nearing commercial release.

MPI is an important tool for diagnosing coronary artery disease. It measures the ratio of the heart's peak capacity under stress to its normal resting capacity by detecting how quickly a radioactive tracer is extracted from the blood by the heart muscle tissue, or myocardium. These rest-versus-stress uptake levels, as well as relative measures across areas of the heart, indicate the extent to which blood flow to the tissue is compromised.

perfusion is compromised evenly across the myocardium.

Flow quantification, as the name suggests, is a technique that provides quantitative data and offers a more detailed picture than relative measures. Due to the high sensitivity and accurate image correction of PET scanners and the latest SPECT systems, it is now possible to quantify the flow of blood to the myocardium in terms of ml/minute/gram of tissue. This is done by applying an analytical model to the data derived from a dynamic imaging sequence. The more detailed quantitative information may also make it possible to use PET and SPECT to diagnose microvascular disease.

The clinical value of flow quantification is still being evaluated, but the technique is a focus of research for Rob deKemp's group in the Heart Institute's Molecular

Measuring the rush of blood to the heart: FlowQuant eliminates the need for specialized expertise by automating quantitative measures of blood flow in myocardial perfusion imaging. This information is of great interest to researchers and may aid in diagnosing coronary artery disease and determining treatment options.

"The advantage of FlowQuant is that all the phases of image generation are automated, including selection of the myocardium."

– Jennifer Renaud, master's student

Whether imaged using positron emission tomography (PET) or single photon emission computed tomography (SPECT), MPI is the best non-invasive method for determining the presence and extent of atherosclerosis and resulting diseased areas of heart muscle in symptomatic patients. But while MPI works well in detecting more advanced conditions, clinicians would like to have a way to detect coronary artery disease at earlier stages so that preventive measures can keep the situation from progressing. MPI may also fail to provide useful diagnostic data if

Function and Imaging Program, as well as for other institutions around the world. For example, the program is currently conducting a clinical study to assess the incremental diagnostic benefits of flow quantification over relative MPI and to determine which patients see the most benefit. The technique also offers a method for acquiring more sensitive data in animal studies.

The problem is that only academic training centres have the resident technical expertise necessary for generating flow

quantification images. While there is a need out there, without widespread clinical adoption of flow quantification, the existing market is too small to attract commercial developers. That's where FlowQuant comes in. The software package processes the images so the user, whether a cardiologist or biologist, can gather flow quantification data without the need for technical processing skills. Any site with the necessary PET or SPECT equipment for human studies and microPET or microSPECT for animal studies could take advantage of this expanded data set.

DeKemp's group focuses on the development of image analysis tools, the validation of tools and methods, and the assessment of the clinical value of flow quantification. "FlowQuant was initially developed for the analysis of human hearts. Now we've scaled it down for the analysis of rat and mouse hearts. This will let us do more collaborative work with researchers throughout the Heart Institute that have specific mouse disease models," he said. "The software has evolved from my research over the years and the contributions of many students."

One of those is Jennifer Renaud, a master's student who has added a reference database to the package. This database lets users compare imaging results with those of normal clinical scans to help identify areas of impaired flow. "The advantage of FlowQuant," Renaud explained, "is that all the phases of image generation are automated, including selection of the myocardium." If done manually, this selection of the myocardium within the overall scan can require an expert eye. "Once you have identified the myocardium,

FlowQuant samples that area to obtain the activity values for the tracer. These values are then input to the analytical model, which generates the quantitative data." The user picks the files to process and which tracer-specific analytical model to apply, and the software does the rest.

FlowQuant can be used for a variety of cardiac medical imaging processes in addition to MPI, including imaging of glucose metabolism and the sympathetic nervous system. The radiotracers are specific to the physiological parameter being imaged, and each tracer requires its own analytical model to process the data. The package also supports dynamic (quantified), static, and gated images, and can process files individually or in batch mode.

FlowQuant is currently available directly through the Molecular Function and Imaging group by contacting deKemp. An agreement for commercial distribution is in process. As with all software, the development cycle never ends. Specific features for future releases include models for additional SPECT tracers and physiological parameters and the incorporation of CT analysis.

In the meantime, deKemp is involved in a number of other projects. He is working with the Institute's Chief of Cardiology, Dr. Terrence Ruddy, on a study comparing the latest SPECT image correction technology with that of PET. He is also part of a Heart Institute team assessing the image quality of exercise versus drug-induced stress in rubidium versus ammonia tracers. How about the stress induced by editing thousands of lines of software code? ❧

Robert deKemp, PhD, PEng, PPhys

- Head Imaging Physicist, Department of Cardiac Imaging, University of Ottawa Heart Institute
- Director, Animal PET Research Imaging Laboratory, University of Ottawa Heart Institute
- Associate Professor of Medicine (Cardiology) and Engineering, University of Ottawa
- Adjunct Professor of Physics, Carleton University
- Research interests: medical imaging physics and engineering, PET, SPECT, X-ray computed tomography (CT), X-ray angiography, and 3D fusion imaging of coronary angiography and myocardial perfusion ❧

Diagnosing Coronary Artery Disease: It's Different for Women

Clinicians strive to treat men and women equally, but in many diagnostic situations gender differences are real and need to be taken into account. This is true for coronary artery disease (CAD), where some tests are more suited to men than women and vice versa.

The classic symptoms of obstructive coronary artery disease involve chest heaviness behind the breastbone that radiates to the throat, jaw, shoulders and arms. The sensation occurs with exercise or emotional stress and is quickly alleviated with rest. Though both men and women can experience classic symptoms, women may exhibit atypical symptoms or may present with variations. These can include shortness of breath, or chest pain in a different location that lasts longer or that occurs at rest. Women may also suffer from unrelated chest pain syndromes that confuse the issue or from disease in smaller vessels or the microvasculature.

Younger women have an innate protection against the development of CAD that is lost after menopause. This explains the roughly 10-year time lag between the onset of symptomatic CAD in women as compared with men. "We understand that the likelihood of a patient having CAD is primarily influenced by age, gender and symptoms," explained Dr. Rob Beanlands, Chief of Cardiac Imaging and Director of the National PET Centre at the University of Ottawa Heart Institute. "However, other factors such as genetics – family history and ethnic background – and environmental factors play a role but are not fully understood."

The assessment of a patient for CAD begins with determining his or her pre-test probability of having the disease. Based on this likelihood, further diagnostic investigations may be warranted. Physicians will only perform further testing when they have insufficient information to make a diagnosis or determine the risk of future heart attack or death. When requesting a test, it's important that the physician understand what additional information the test will provide and how it will guide patient therapy. "Many available tests tend not to provide sufficient information in lower-risk patients who have a low pre-test likelihood of CAD," said Dr. Beanlands. "Likewise, in patients with high pre-test likelihood of disease, testing adds little to the diagnostic certainty but may be helpful in determining risk and directing therapy."

The likelihood of having CAD for a 49-year-old man presenting with classic symptoms is over 85 per cent. For a 49-year-old woman, the likelihood is only 55 per cent. Because of his high pre-test probability, the male patient may not require a test for diagnosis, but additional testing may be required to guide therapy. The diagnosis for the woman, though, is uncertain. Testing would assist in both her diagnosis and her treatment.

Current guidelines recommend that, in the absence of contraindications, exercise (treadmill) stress testing (EST) be the first line of investigation for both men and women. This recommendation is made based on the fact that treadmill testing is reasonably accurate, relatively inexpensive and readily available. However, EST is not appropriate for all patients. Age, fitness level, musculoskeletal or vascular disease, instability and other contraindications can prevent some patients from undergoing EST. Of those who are able to exercise, some may be unable to reach a target heart rate.

The overall accuracy of EST is approximately 70 to 75 per cent, leaving a 25 to 30 per cent chance that the results may be incorrect. For women, the accuracy rates are worse because treadmill tests are more likely to produce a false positive result. This is because, in the absence of disease, women are more likely than men to exhibit ST depression, an alteration in the ST segment of the ECG readout that can be an indicator of CAD. Some suggest that this "abnormal" response is related to catecholamine surges associated with exercise and physical stress (i.e., the fight-or-flight response) or with hormones; the upshot being that exercise may produce different physiological responses in women.

However, EST does provide valuable information such as blood pressure response and exercise capacity, and it remains a very strong predictor of patient prognosis. More accurate technology is available at many centres, and ongoing studies will give us greater detail about the utility of these tools as first-line investigations in women. Recent research suggests that it may be more cost-effective to forgo EST altogether for women and pursue other testing options (see sidebar).

Similar to EST, SPECT is a commonly used test for first-line investigation of women. Though accurate, breast tissue attenuation can occasionally lead to uncertainty of diagnosis. Similar to looking at a light bulb through a piece of paper, the penetration of the light is dependent on the thickness of the paper. Since women have more chest wall tissue overlying the heart, they are more prone to breast attenuation than men. This same phenomenon may be an issue with obese patients. Attenuation can compromise image quality and result in visual defects, which can be interpreted as disease. Technological advances minimize the artifacts associated with attenuation and are an advantage of newer SPECT cameras and all PET cameras.

PET also has the potential added benefit of quantifying blood flow as an absolute measurement, determining more precisely the amount of blood delivered to the tissue. This may improve diagnostic accuracy. CAD is common in women, but some may suffer chest pain syndromes that result not from large vessel diseases but from small vessel or microvascular conditions, which in turn can cause symptoms that would be interpreted as normal with many tests. The unique ability of PET to quantify blood flow may help in the diagnosis of these conditions. The added value of this quantification approach is the subject of ongoing research.

Cardiac CT, a new technology, appears to be very accurate and holds promise, but expertise is not readily available at all centres. The University of Ottawa Heart Institute and other centres are conducting studies to better understand its true accuracy, impact on other services and potential benefit to patients. "Currently, cardiac CT may best be used as a tiebreaker," said Dr. Benjamin Chow, Cardiologist and Co-director of Cardiac Radiology at the Heart Institute, "if there is discordance between symptoms and routine testing or if a test is equivocal or non-diagnostic in a woman or a man."

These various tests have different levels of accuracy, but accuracy is dependent on correct test selection for each patient and for each setting. In many situations, the physician will decide which test is most appropriate based on accuracy, patient factors (e.g., ability to exercise and physique), and additional information required. EST is only appropriate for patients who can exercise adequately. SPECT and PET can be performed on most patients where CAD is suspected, so long as the technology is available. CT is highly accurate, but some patients may have significant coronary calcification, which may limit diagnostic accuracy. Because of the delay in the onset of CAD in women, this may be less of a consideration until a woman is much older.

Though some centres may not have ready access to all these modalities, it is important that they are available to patients, if required. The most important factors influencing test selection should be pre-test likelihood and other patient factors, test accessibility, and local expertise, as well as an understanding that heart disease may present differently in women. ❦

Cardiac Imaging Technologies

SPECT
Single photon emission computed tomography (SPECT) is a nuclear imaging technique that employs radiotracers and gamma rays to assess coronary blood flow. A tiny amount of radioactive substance is injected into the patient and gives off energy that is "traced" to reveal areas of the heart that are not receiving sufficient blood flow.

Positron Emission Tomography
Similar to SPECT, cardiac PET assesses the coronary blood flow to the heart by using radiotracers that emit positrons. PET has the added benefit of having superior spatial resolution and accuracy. It is also the most sensitive method for assessing heart tissue viability, which is relevant for patients with more severe CAD and heart failure.

Cardiac CT and CT Angiography
In CT imaging, a high-resolution multi-slice scanner uses X-rays to obtain 3D data to create cross-sectional images of the heart. The University of Ottawa Heart Institute has a dedicated cardiac CT to assess structures such as the coronary arteries. CT angiography has a high negative predictive value, meaning that it rarely produces a false negative result. If a CT angiogram is normal, it is extremely unlikely that a patient of either gender has CAD.

Stress Echocardiogram
The stress echo uses ultrasound to provide selected views of the motion of the heart before exercise, immediately post-exercise and about five minutes after exercise to identify abnormalities induced by lack of blood flow.

Invasive Coronary Angiography
Invasive coronary angiography is an invasive test, whereby dye is injected directly into the coronary arteries, which are then X-rayed. ❦