



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

THE BEAT™

A COMPENDIUM OF INFORMATION ABOUT THE UNIVERSITY OF OTTAWA HEART INSTITUTE

HIGHLIGHTS

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— Dr. Michel Le May, Director,
Coronary Care Unit, UOHI
(from *Pioneering Heart Attack Program Becomes Ontario's First Health District-wide Emergency Protocol*, page 2)

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— Alexandre Stewart, Principal
Investigator, UOHI
(from *In Conversation—Alexandre Stewart: The Blueprint of the Mouse Genome*, page 3)

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(from *Two from the Heart Institute Honoured for Top Canadian Achievements in Health Research*, page 4)

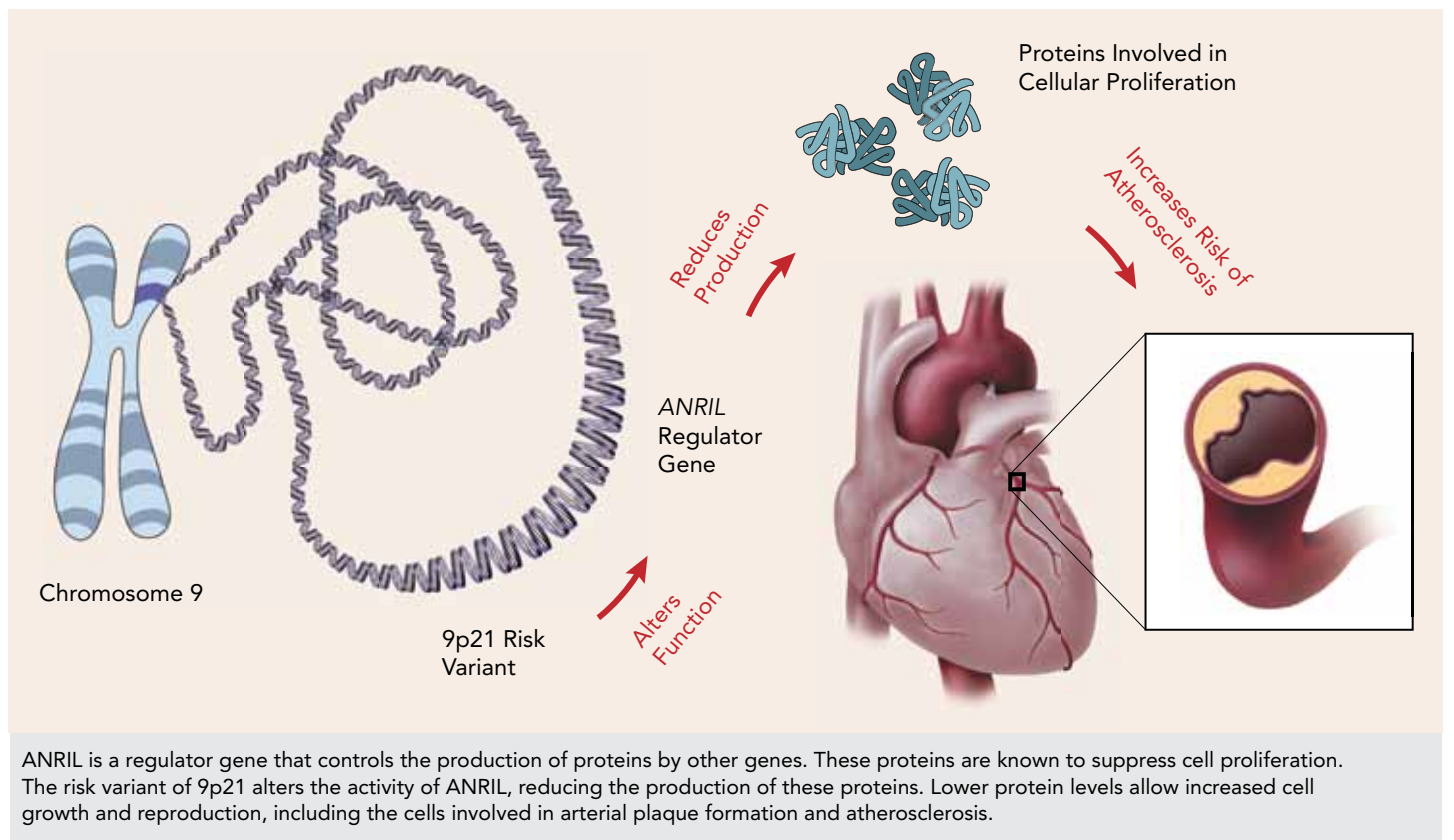
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Learning How a Genetic Risk Factor Influences Heart Disease



A team of University of Ottawa Heart Institute scientists may have explained one step in the molecular chain of command that controls narrowing of the arteries (atherosclerosis). It appears the function of a regulatory gene known as an ANRIL is altered in the presence of a variant of the 9p21 gene region associated with increased risk of coronary artery disease (CAD). 9p21 is a DNA region with the most significant level of CAD risk found to date.

The buildup of fatty deposits, called plaque, in the inner lining of vessels leading to the heart causes these arteries to narrow and leads to CAD. The resulting blockage cuts blood flow and oxygen to the heart, leading in turn to heart attack, stroke and other debilitating problems related to heart disease. Many people have associated risk

factors such as high cholesterol, diabetes, smoking and high blood pressure that are linked to heart disease. However, physicians and scientists often encounter CAD in patients who have none of these risk factors.

A team of scientists at the Heart Institute, led by Dr. Ruth McPherson, has been trying to find the causes of heart disease by looking into the body's own cells and, deeper still, into their molecular regulation for an explanation.

In 2007, the research team at the Heart Institute's Ruddy Canadian Cardiovascular Genetics Centre identified a common variant in the 9p21 region. The findings showed that 75 per cent of the population has at least one copy of the 9p21 risk variant, which increases the likelihood of CAD independent of other known risk

factors such as smoking, cholesterol, diabetes or high blood pressure. About 25 per cent of the population carries two copies of the 'risk allele,' which doubles their risk. An allele is a form of a gene that is located at a certain position on a specific chromosome—the threadlike structure of DNA molecules.

In research confirmed elsewhere, the Heart Institute scientists also singled out 9p21 as the most significant region of the genome linked to heart attack. The next step was to figure out how 9p21 works. Researchers around the world have been trying to do this very thing. By understanding how it functions, they hope to turn off or at least limit the damage it causes by developing specifically targeted drugs.

(continued on page 2)

The Risk Locus

The genome—the long sequence of DNA that codes for life—is a little like a deck of cards. Some of us hold strong cards and some hold weaker cards. A locus represents a fixed position on a chromosome and could be anywhere in the deck of cards.

When Heart Institute scientists discovered the 9p21 locus, they identified what is essentially a weaker hand of cards for the player holding them because this locus indicates an increased risk for coronary artery disease (CAD). Anyone who draws 9p21 at birth has a 75 per cent increased chance of developing CAD, caused largely by narrowing of the arteries or atherosclerosis. The findings were published in *Science* in 2007 (Vol. 316., no. 5830, pp. 1488–1491).

The identification of 9p21 is regarded as one of the most important discoveries in the genetics of cardiovascular disease. The discovery is significant because 9p21 is an independent risk factor, meaning that it increases risk for CAD separately

from other risk factors such as smoking, diabetes, high blood pressure and high cholesterol.

Its impact is best illustrated by a large exhibit at the annual fall meeting of the American Heart Association where more than 30,000 health professionals meet. For years, free five-minute cholesterol tests and blood pressure measurements were available at the meeting. In 2007, one company began conducting a genetic test that included screening for the 9p21 risk factor. At one point, more than 500 cardiologists were said to have lined up to have the inside of their mouths swabbed for the test.

The story of 9p21 is still unfolding, but someday patients may well be tested for the presence of the risk variant. It might end up being another number, such as cholesterol levels and blood pressure, which people will need to know in order to understand their overall risk profile for heart disease and what they need to do about it. ❁

(Learning How a Genetic Risk Factor Influences Heart Disease, continued)

An analysis of the Heart Institute's investigation into 9p21's molecular function was published in October 2009 in the American Heart Association's journal *Arteriosclerosis, Thrombosis, and Vascular Biology*.

The researchers compared the DNA of men and women who possessed the risk variant to that of people who did not. Olga Jarinova in Dr. McPherson's laboratory found that the expression of ANRIL was different in the two groups. ANRIL is a gene that does not code for a protein. Instead, it regulates the activity of certain other genes, encoding for proteins linked to cell proliferation and atherosclerosis, specifically CDKN2A and CDKN2B.

"When we first noted the relationship between 9p21 and heart disease, we were perplexed because this region was in a 'gene desert,'" said Dr. McPherson, a leading physician-scientist in the area of heart disease. She is Director of the Lipid Clinic and the Atherogenomics Laboratory. "Because no protein coding genes were present in this region, the link with coronary artery disease was initially perplexing."

Her laboratory then demonstrated that the 9p21 region contains a regulatory element which can be activated by the risk allele. This suggests that 9p21 changes the function of the regulatory element, altering the expression of other genes linked to atherosclerosis.

"Our research efforts are aimed at finding the underlying causes of coronary artery disease. We have found one more clue."

– Dr. Ruth McPherson, Director of the Lipid Clinic and Atherogenomics Laboratory, UOHI

"Our research efforts are aimed at finding the underlying causes of coronary artery disease," said Dr. McPherson. "We have found one more clue—the possibility that 9p21 can promote atherosclerosis by regulating

the expression of ANRIL. "The next step will be to further analyze and explain its function. 9p21 is a common variant and we are currently studying many other variations in the gene coding sequence."

Pioneering Heart Attack Program Becomes Ontario's First Health District-wide Emergency Protocol

A program developed at the University of Ottawa Heart Institute to reduce deaths from heart attacks has proven so successful that it is being extended to the entire Champlain Local Health Integration Network (LHIN). The STEMI protocol addresses a serious type of heart attack, ST-elevation myocardial infarction. By ensuring a faster "door-to-balloon" time, the program has cut related deaths in half in

the Ottawa area. Now, people throughout the LHIN can receive the same standard of care, regardless of where they live.

"This means earlier treatment for people in smaller centres and a faster transfer to the Heart Institute," says Dr. Michel Le May, Director of the Institute's Coronary Care Unit. "Every minute counts when the coronary artery is blocked. This program is designed to save time and lives."

The STEMI protocol trains paramedics to diagnose this particularly dangerous and common form of heart attack and route patients directly to the Heart Institute, bypassing local emergency departments. In cases where a patient comes to the emergency department on his or her own and is diagnosed with a STEMI, they are transferred directly to the Heart Institute by ambulance, without treatment or consultation with a cardiologist. When

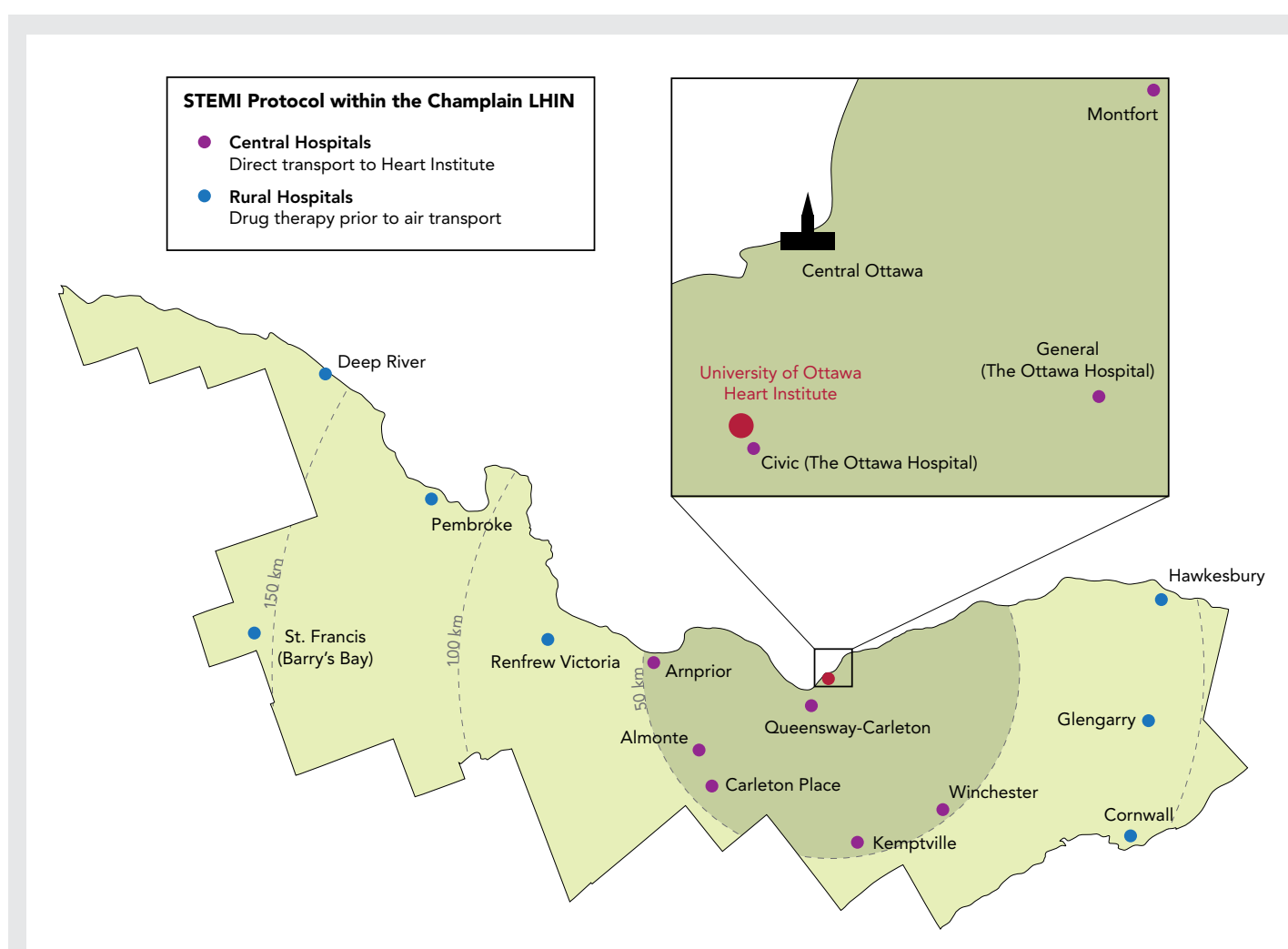
either of these situations arises, a Code STEMI is triggered in the Heart Institute. An emergency STEMI team, available 24/7, is alerted to administer optimal care—usually a percutaneous coronary intervention (PCI), also known as angioplasty—as quickly as possible.

An evaluation of the protocol carried out in 2004–05 and published in the *New England Journal of Medicine* found that it reduced the chances of dying of a heart attack by 50 per cent. Fewer than 5 per cent of Heart Institute patients treated through the protocol died, compared to 10 per cent receiving conventional treatment of clot-busting drugs and monitoring. The protocol also cut emergency room congestion, reducing paramedic traffic volume by about 40 per cent, and reducing wait times for all patients.

The protocol began as a pilot project in 2001, initiated by Dr. Le May, together with Dr. Justin Maloney, Medical Director of the Ottawa Base Hospital Paramedic Program, and Dr. Richard Dionne, Assistant Medical Director of the paramedic program. Since then, the protocol has been a model for similar programs in other urban areas, including Kingston, Hamilton, Quebec City and Vancouver.

"Canada is acknowledged as a leader in developing approaches to the treatment of STEMI," says Dr. Le May. "This protocol is one of the reasons why."

In its first year of full operation, from May 2005 to May 2006, 344 STEMI patients were transported to the Heart Institute, including 209 patients transferred from city hospitals and 135 transported by advanced care paramedics. The median "door-to-balloon" time in that first year was 63 minutes, well below the 90 minutes recommended by the Canadian Cardiovascular Society



The Heart Institute's STEMI heart attack program has been extended across the entire Champlain Local Health Integration Network (LHIN), encompassing 16 hospitals. Those that are centrally located transport STEMI patients directly to the Heart Institute for interventional treatment. More distant, rural sites administer clot-busting drugs prior to helicopter transport.



Dr. Michel Le May pioneered the Heart Institute STEMI protocol with leading colleagues in the Ottawa paramedic community. The protocol has proven so effective for saving lives that it has served as the model for similar programs across Canada. Dr. Le May's work in this area has been named a Top Canadian Achievement in Health Research (see p. 4).

What is a STEMI?

A heart attack, or myocardial infarction, occurs when a coronary artery becomes suddenly blocked by a blood clot or by plaque that has broken away from an artery wall. This blockage causes at least some of the heart muscle being supplied by that artery to become infarcted, or die. There are two kinds of heart attacks, mild and more severe. STEMI, or ST-Elevation myocardial infarction, is the more severe kind. In a STEMI, the coronary artery is completely blocked by the blood clot. As a result, virtually all the heart muscle being supplied by the affected artery starts to die.

STEMIs are diagnosed through electrocardiograms (ECGs). The ECG shows an elevation in what is called the "ST segment," indicating that a large amount of damage is taking place. STEMI's are most often treated with percutaneous coronary intervention, or angioplasty, which involves, using a balloon catheter to clear blocked arteries and insert a stent to keep the artery open after surgery. 🌀

and American College of Cardiology/
American Heart Association.

As a result of its success, the protocol has now been extended to 16 hospitals in the Champlain LHIN—the first such in Ontario

to be applied across an entire regional health district. Coverage includes the original four Ottawa-area hospitals, as well as others as far away as Barry's Bay (183 km). Those close at hand follow the STEMI protocol, sending patients directly to the Heart

Institute once STEMI is diagnosed. Those further away follow a slightly adapted protocol calling for the administration of fibrinolytic, or clot-busting, drugs before the patient is transferred to the Heart Institute via helicopter.

"The whole point of this approach is to reduce deaths by providing needed treatment faster," said Dr. Le May. "Now patients throughout eastern Ontario will have the same access to improved care as their urban counterparts." 🌀

In Conversation



Alexandre Stewart: The Blueprint of the Mouse Genome

In May 2009, researchers from the Mouse Genome Sequencing Consortium published the first complete mouse genome sequence in the journal *PLoS Biology*. This is a significant milestone because the mouse is the most widely used experimental model for human diseases and disorders.

Alexandre Stewart is a principal investigator at the University of Ottawa Heart Institute in the Ruddy Canadian Cardiovascular Genetics Centre. Research at the Ruddy Centre focuses on the search for genetic risk factors of coronary artery

disease and other cardiac conditions, such as sudden cardiac death, cardiomyopathy, and heart failure. The work of identifying relevant genes and understanding their function often involves developing mouse models.

Stewart uses transgenic mouse models, strains of mice that contain insertions of human DNA, to explore cardiac and skeletal muscle biology. He first became interested in the mouse genome as a postdoctoral researcher looking at worldwide distribution of the mouse mammary tumor virus.

The Beat: What makes the mouse such a popular model organism for genetics research?

Stewart: As a model system, mice are ideal because we can manipulate the mouse genome fairly easily. We can introduce genes, we can remove genes, we can ask questions about functionality and how specific genes affect the process of disease progression. There are many things we can learn from the mouse because the genome of the mouse is so similar to the human genome.

The Beat: Publication of the complete mouse genome indicates that there are more differences between it and the human genome than previously thought. Is this a problem for research using mice as a genetic model for humans?

Stewart: No, not for important genes. The more important a gene is, the more conserved it is across species—meaning that that piece of genetic coding remains the same despite other evolutionary changes. The basic physiology of mammals has not changed that much. If you have a gene controlling a fundamental process, that almost guarantees it will be conserved in any mammal you look at. Even the fact that certain genes can reside on different chromosomes in mice and in humans doesn't greatly affect their function.

The Beat: What are the implications for research of having a complete mouse genome sequence?

Stewart: This is a great first step, and it took a long time to get to this point. We now know precisely what we're dealing with in terms of the genetic sequence, but there's going to be an enormous amount of work to figure out how it all works.

Our understanding of genome biology is really at its beginning. Right now, we're still figuring out how this blueprint works in mice and in humans, in parallel. And each is teaching us something about the other. We're learning from both plans, both genomes. Mice get very similar diseases to what humans get, in many respects. So completely understanding the mouse genome will shed a lot of light on human diseases.

The Beat: What do we need to know about differences in mouse and human genetics that we don't yet?

Stewart: We need to understand what makes a mouse a mouse and a human a human, why we're different, why certain genes behave a certain way in the mouse and don't do quite the same thing in humans. You can knock out a gene in a mouse, get rid of it completely, and the mouse is fine. And

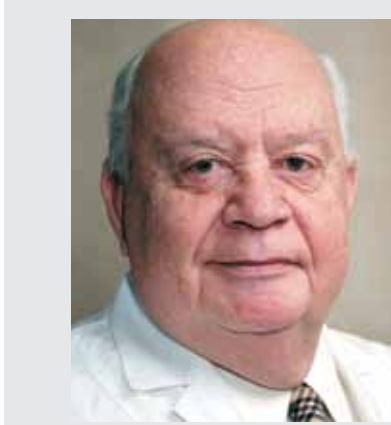
you can have a mutation in the corresponding human gene and it causes a very severe effect. That's very important for drug development, for understanding defects in metabolism.

The Beat: How will genetic variability in mice influence future research in this area?

Stewart: We now have the full sequence of one strain of mouse. Just as it is for humans, 99.9 per cent of this information will be valid for other strains of mice, but you will also find regions of divergence or difference. We now have several individual human genomes sequenced, and the goal is to sequence a thousand different human genomes to determine what the level of diversity is among humans. We're still finding genes we didn't even know existed among humans.

I think the need to understand the genetic diversity of mice is just as compelling because not every mouse is susceptible to disease in the same way, just as not every human is susceptible to disease in the same way. And if we understood the genetic reasons for these variations in mice, it might shed light on the same phenomena in humans. 🌀

Two from the Heart Institute Honoured for Top Canadian Achievements in Health Research



Adolfo de Bold



Dr. Michel Le May

Adolfo de Bold, PhD, and Dr. Michel Le May are among eight Canadians whose work is being honoured as Top Canadian Achievements in Health Research. The new award, given jointly by the Canadian Institutes of Health Research (CIHR) and the Canadian Medical Association Journal (CMAJ), represents the first ever such recognition and celebration of Canadian health research and innovation excellence.

The award winners were selected by a blue-ribbon, peer-review panel of Canadian

and international experts. The goal of the panel was to identify the discoveries and innovations with the most significant impact on the health of people in Canada and around the world.

Adolfo de Bold is Director of the Cardiovascular Endocrinology Laboratory at the University of Ottawa Heart Institute. Through years of dedicated laboratory work, he made one of the landmark discoveries in cardiovascular physiology and established the area of research for which his lab is named.

In 1981, de Bold discovered atrial natriuretic factor (ANF), a hormone produced in the heart. He found that, through ANF, the heart is able to regulate blood pressure, blood volume, and the growth of cardiovascular tissue. This groundbreaking work revealed that the heart has a previously unknown endocrine function and led to the discovery of additional related hormones.

Since then, the number of scientific papers stemming from his discovery has run to the tens of thousands. Associated diagnostic and therapeutic tools in use today include a widely employed biomarker for cardiac hypertrophy and heart failure and drugs to treat congestive heart failure.

“This discovery has received a great deal of international recognition over the years. But this award is special,” said de Bold. “It is recognition from your close peers here in Canada. In many ways, it is that recognition that is most difficult to attain and most pleasing to receive.”

Dr. Michel Le May, a Heart Institute cardiologist, has developed an acclaimed program that insures standardized treatment for a type of heart attack called

ST-elevation myocardial infarction (STEMI) (see “Pioneering Heart Attack Program,” p. 2).

“A distinguished national award, such as this, is an honour, but not just for me,” said Dr. Le May. “I am part of a very large team of dedicated professionals who go to work everyday with the goal of saving lives. They have made a supreme effort to develop a creative, more efficient means of delivering emergency medical services.”

The Heart Institute’s STEMI program, which reduces related deaths by 50 per cent, evolved from trials led by Dr. Le May. His research and protocol are acclaimed in Canada, the U.S. and Europe. Elements of the program have been adopted in several cities across Canada as the standard in emergency heart attack treatment. 🌸

Correction

In Volume 4, Issue 3, we incorrectly identified Dr. Ross Davies as an associate professor at the University of Ottawa. He is, in fact, a full professor.

New Real-Time Imaging Technology for Treatment of Arrhythmia Patients

Patients with irregular heart beat, or arrhythmia, benefit from new technology for visualizing cardiac anatomy. The new DynaCT at the University of Ottawa Heart Institute combines the advantages of conventional three-dimensional CT imaging with live X-ray imaging to produce a digital image of the beating heart.

The large instrument, shaped like the letter “C,” rotates around the patient for 180°, taking pictures over a 4-second period and, in less than a minute, provides physicians with a composite 3-D image. With this real-time image in hand, physicians can correct the arrhythmia right away, potentially saving patients separate visits for diagnosis and treatment.

“The Heart Institute is at the forefront of applying technology to improve patient outcomes,” said Dr. Robert Lemery, Medical Director of the Electrophysiology Laboratories. “Earlier this year, we became the first medical facility in North America to implement dual-axis rotational cardiac X-ray technology for clinical use. Now, with the addition of DynaCT, we’re building on our commitment to provide our patients with the best possible care.”

Bob Scherer, charge technologist for Radiology, leads the technical implementation of the new system. He likens the electrophysiology team to electricians, trying to find a short circuit and fix it. Normally, electricity flows



The new DynaCT system generates real-time 3-D images that help Heart Institute physicians diagnose and target treatment of dangerous arrhythmias. The technology makes it possible to conduct the diagnostic imaging and ablation treatment in a single procedure, reducing the need for multiple patient visits and likely reducing the overall radiation dose.

through the heart in a regular, measured pattern, causing the heart muscle to contract and expand on a regular basis. Thus, the heart beat. When the electricity flow is disrupted or blocked, the result is an arrhythmia, which can include a heart beat that is too fast or too slow. These are common disorders that may have minimal consequences, but they can

also indicate a serious problem leading to stroke or heart attack.

Arrhythmias are diagnosed through electrophysiology (EP) studies, which allow the collection of data that document the flow of electricity, including any areas of “short circuit.” They are treated in the EP Lab using a procedure called ablation,

which eliminates the tissue housing the short circuit. In an ablation procedure, a catheter, which is a narrow, flexible wire, is inserted into a blood vessel and is advanced up to the heart. Once the catheter reaches the heart, electrodes at its tip gather data that pinpoint the faulty electrical wiring. Energy—generally either intense heat or intense cold—is then used to destroy the tissue, restoring normal electrical flows.

“Right now, patients have a cardiac CT prior to their EP study and possible ablation,” Scherer explained. “Having to make two separate visits is inconvenient for them. Plus, it could expose them to more radiation, as the imaging needs to be done again in order to correct the problem. And often, when they come for the second appointment, their hydration level may not be the same, which means their heart isn’t exactly the same size. That could make it more difficult and time-consuming to carry out ablation.”

DynaCT itself isn’t new—it’s been around since 2004, used primarily for imaging the brain. What’s new is the ability to capture a beating heart as it contracts and expands with each beat.

“It’s kind of like doing a 1,000 piece jigsaw puzzle on a large piece of cardboard,” explained Scherer. “Imaging the brain is like trying to fit one piece in at a time. Imaging a beating heart is like trying to do it while someone is shaking the cardboard.” 🌸