

## FROM INNOVATIVE STEMI INTERVENTION TO THE PREVENTION OF HEART DISEASE: 36 YEARS OF BREAKTHROUGHS IN CARDIOVASCULAR MEDICINE

When Virgil Mott agreed to be the first patient at Memorial Hermann-Texas Medical Center (Memorial Hermann - TMC) – and one of the first in the country – to participate in a clinical trial testing the then-experimental thrombolytic drug streptokinase, he was unaware of the impact his decision would have on the countless patients who received the lifesaving therapy following FDA approval. The date was August 3, 1980, and physicians across the country were still uncertain whether opening the occluded arteries of heart attack patients would benefit them in the long run.

Numerous other clinical trials followed, and the experience of thousands of patients proved that hypotheses formulated by affiliated cardiologists at Memorial Hermann-TMC were correct: that the administration of intracoronary fibrinolytics such as streptokinase, urokinase and later, tissue plasminogen activator (tPA) significantly lowered mortality and morbidity rates associated with acute ST-elevation myocardial infarction (STEMI). Thirty years later, Mott was still going strong at the age of 88, and last summer *U.S. News and World Report* ranked the Memorial Hermann Heart & Vascular Institute located at Memorial Hermann Texas Medical Center (“Heart and Vascular Institute”) among the top 50 hospitals in the nation for heart care and heart surgery in its “Best Hospitals 2016-2017” issue.

“Memorial Hermann-TMC and UTHealth have long been home to pioneers in cardiovascular medicine,” says K. Lance Gould, MD, who joined the hospital medical staff

the in 1979 to run the cardiovascular medicine program and is now executive director of the Weatherhead PET Center for Preventing and Reversing Atherosclerosis and the Martin Bucksbaum Distinguished Chair of Cardiovascular Medicine at McGovern Medical School at UTHealth. “Many ideas were generated here 10 to 15 years before they were accepted by the cardiovascular community. Our physicians and scientists discovered fundamental

the largest early series of clot-busting study results in the country and drew conclusions that larger randomized clinical trials later confirmed. In 1980, he began to direct Interventional Cardiovascular Medicine at the hospital, a position he holds today. In a 1981 article that appeared in the *American Journal of Cardiology*,<sup>1</sup> Dr. Smalling, Dr. Gould and other authors at Memorial Hermann-TMC presented their observations about the effects of

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concepts about the pathophysiology of coronary artery stenosis that led to more discoveries and greater innovations – including clinical applications in coronary clot busting, the development of the first heart PET center, new knowledge about reversing coronary heart disease and very advanced work on entirely new ways of analyzing myocardial perfusion images as a guide to decisions about which patients will actually benefit from bypass surgery and stents.

What really makes us stand out from other tertiary heart programs is the environment here, which is very supportive of innovation,” he says. “That support has allowed us to recruit innovative physician scientists recognized worldwide, and over the years they have put us on the map.”

One of those physicians, Richard Smalling, MD, PhD, published

reperfusion on left ventricular performance following intracoronary infusion of streptokinase in patients with acute myocardial infarction (MI). Related articles followed in *American Cardiology*<sup>2</sup> in 1981 and the *American Heart Journal*<sup>3</sup> in 1982. In 1983, a landmark publication in *Circulation*<sup>4</sup> demonstrated dramatic improvements in ventricular function with intracoronary streptokinase.

“We later participated in the first pilot trial of intravenous tPA for the treatment of acute MI and subsequently showed that you could administer IV tPA and achieve similar results to streptokinase, which

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led to the notion that we might be able to begin treating heart attack patients before they arrived in the cath lab,” says Dr. Smalling, who holds the James D. Woods Distinguished Chair in Cardiovascular Medicine at McGovern Medical School. “This hypothesis expanded the possibilities for treating MI significantly and led to the pilot PATCAR\* protocol and further clinical trials that advanced the quality of care we provide.”

Interventional cardiologists at the Heart & Vascular Institute introduced the first Chest Pain Center in Texas in the early 1990s, long before the existence of an accreditation body. “It became obvious to us

that there was a double standard of care in our emergency center,” Dr. Smalling says. “If you came to the ER with a serious traumatic injury, we rushed you to treatment. If you had chest pain, you filled out a medical questionnaire. We changed our approach dramatically and designated a special area of the ER as our heart attack center.”

By 2002, the Heart & Vascular Institute was working with the Houston Fire Department’s EMS units to transmit ECG results from the field. “We developed protocols for transmitting results directly to our emergency center and for ordering paramedics to give thrombolytics to the appropriate patients

with heart attacks,” Dr. Smalling says. “We trained paramedics to interpret 12-lead ECGs. They trained others, and we created a built-in feedback system to report outcomes. The process was formalized into the PATCAR trial, and our door-to-balloon time very quickly went from the former standard established by The Joint Commission of 120 minutes to an average of 42 minutes. Through continual updates and the sharing of data between paramedics, emergency physicians and interventional cardiologists, we created the systems we had to have in place for fast response to heart attack.”

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## THE MORE YOU DO IT, THE BETTER YOU ARE

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Close collaboration with the fire department’s EMS teams and advances in the science of EMS have shortened the response time for the 50 percent of Houston heart attack patients who dial 911. “From the EMS standpoint, the care we provide cardiac patients today is dramatically different from the treatment we provided 15 years ago,” says David Persse, M.D., who has served as the physician director of the City of Houston’s Emergency Medical Services since 1996. “The science behind EMS is rapidly maturing. We’ve learned much more about disease processes and how to improve treatment in the field, and we’re also learning how to be more efficient in transporting patients.”

Dr. Persse’s predecessor, Paul Pepe, M.D., implemented a tiered system in which some ambulances were staffed with EMTs while others carried paramedics. “It pays off in outcomes if you can dispatch the

more highly trained paramedics for serious cases like cardiac arrest,” Dr. Persse says. “If we send paramedics for what turns out to be a broken leg, they’re not available to respond to the next heart attack. What we did is make them more

but when we dispatch the paramedic squad, we also send an ambulance with EMTs,” Dr. Persse says. “The squad program reduced response time by 2.7 minutes in the areas where we’re focused. The patient goes to the hospital in the ambu-

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available, reduce response time and make them more proficient at handling cardiac arrest. The more you do it, the better you are.”

In high-volume areas inside the 610 Loop, the Houston Fire Department implemented a paramedic squad program, which has since been expanded to outlying areas. “Our paramedics ride in vehicles unequipped to transport patients,

and instead of being tied up for an hour or more, the paramedic is freed up within 15 to 20 minutes to move on to the next case.”

With the implementation of the squad program, Dr. Persse says EMS saw a doubling of the number of cardiac arrests in ventricular fibrillation when paramedics arrived on the scene. “In the old days, when it took us longer to respond to 911

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calls, we saw more patients in asystole. If we can increase the number of patients we reach while they're still in ventricular fibrillation, we're saving lives. When we initiated the paramedic squad concept, the percentage of patients we reached in ventricular fibrillation increased from 65 percent to 78 percent."

Dr. Persse says his EMS team has been accused of favoring Memorial Hermann over other hospitals. "The data does not support that hypothesis," he says. "It's true that Memorial Hermann developed a very sophisticated system. We did the PATCAR research project with Dr. Smalling's group, which tied us more closely to Memorial Hermann -TMC, but patients can choose the

hospital they want to go to and we honor that choice. Our paramedics are committed to saving lives, and if they know a hospital can get their patients from the back of the ambulance straight to the cath lab, they tend to choose that hospital. What Memorial Hermann had in place needed to be routine at every hospital in town that has interventional cath capability - and now it is, in hospitals from Kingwood to Clear Lake - which is good news for patients in every neighborhood."

Since then, data from the PATCAR trial and several European trials have provided evidence of the feasibility and potential benefits of pre-hospital and early in-hospital administration of thrombolytic ther-

apy following the onset of symptoms of acute MI. "Outcomes data have shown that patients treated with thrombolytics by paramedics fare better in terms of morbidity and mortality than those who go straight to the cath lab," Dr. Persse says. "If you administer thrombolytics early, more downstream tissue is saved. Some tissue will die when you have a heart attack, regardless of the treatment you receive. Some tissue will be injured and totally recover. Thrombolytics given in the field can mean the difference between a man who survives a heart attack but is no longer able to walk upstairs versus a man who recovers and can engage in active play with his grandkids."

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## THE MAGIC OF NEW IDEAS

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**W**hile Dr. Smalling was developing the interventional cardiology program and working with the Houston Fire Department's EMS teams, Dr. Gould turned his attention to building the world's first cardiac PET center. "The PET scanners available at that time had the capability to image only slices of the heart," he says. "Working with physicists, we designed and built the first full-heart PET scanner. It was later propagated into four more generations of scanners, one of which we have today at the Weatherhead PET Center."

With better imaging quality and whole-heart capability, Dr. Gould's team suddenly found themselves identifying patients with coronary artery disease who were asymptomatic. In response, they developed a vigorous dietary and medication treatment regimen that relieved

pain, partly reversing existing disease and preventing additional vascular conditions, heart attacks, sudden cardiac death and the need for balloon dilation or coronary bypass surgery. In 1994, Dr. Gould's

team published the first paper demonstrating improved coronary flow reserve capacity than by determining percent stenosis on arteriogram," he says. Research led by Dr. Gould at the Weatherhead PET Center has been featured on

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team published the first paper demonstrating improved coronary blood flow by quantitative PET measurements with intense short-term treatment.<sup>5</sup> A separate study was published in the *Journal of the American Medical Association* the following year.<sup>6</sup>

"I focused on PET imaging because I knew that if we did it right, we could select candidates for sur-

gery much more accurately based on coronary flow reserve capacity than by determining percent stenosis on arteriogram," he says. Research led by Dr. Gould at the Weatherhead PET Center has been featured on the covers of four medical journals: the *Journal of the American College of Cardiology* in 2003, *The Journal of Nuclear Medicine* in 2007, *JACC Cardiovascular Imaging* in 2009 and *Molecular Imaging* in 2010.

In 2009, Dr. Gould began the Century Health Study, which is now a repository for data on outcomes in 4,000 patients. The researchers have enrolled patients in the study

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through 2016 and hope to extend it for another decade.

“Heart disease does not have to progress. We can stop it in 90 percent of patients,” he says. “Through the Century study, we’re working to enhance the medical community’s overall approach to cardiovascular disease by prevention through patient education. Our long-range goal is to reduce the cost of cardiovascular care through

data into a simple package, providing a 3-D image of the heart and allowing for better interpretation of imaging results.

“Blood flow in the heart is quite complex and not easy to interpret, even for experts,” he says. “Now when we see blue on the PET scan, we know it indicates low flow potential and the need for a stent.”

Data analysis has also evolved. Dr. Gould and his team have devel-

oped a statistical methodology that excludes the effect of crossovers in randomized clinical trials, for instance, participants who are highly motivated and engage in exercise outside of the parameters of the trial, or those who are assigned to take a drug as part of a study but fail to follow the protocol.

serve capacity. Other centers are trying to duplicate the Century study, but it remains the longest running randomized trial that includes lifestyle management, intensive drug management and the use of PET to guide elective heart procedures for assessing heart attack damage and selecting patients for procedures based on flow measurements rather than percent stenosis, which is what most cardiologists use.

“These are rolling innovations that are changing the way we practice cardiovascular medicine,” he says. “No heart center in the world has this documented range of innovation in a comprehensive approach to coronary artery disease. Advances like these are rooted in the magic of new ideas, an enormous amount of public and private grant support and the drive to advance and improve care. I’m still amazed at what we’ve accomplished. It’s like you’re driving in a race in unknown territory and see the next hill and wonder what’s over it. When you reach the other side, you find more ways to save hearts and more knowledge that changes the way physicians practice cardiovascular medicine – if they can keep up with you.”

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more accurate diagnosis and a focus on prevention, as well as providing physicians with quantitative coronary blood flow as the best guide for invasive procedures.”

Since the initiation of the Century Health Study, interventional techniques for the treatment of STEMI have dramatically improved, with more advanced instrumentation, better timing and more effective medications. Advances in PET imaging led Dr. Gould and his team to develop software that integrates

oped a statistical methodology that excludes the effect of crossovers in randomized clinical trials, for instance, participants who are highly motivated and engage in exercise outside of the parameters of the trial, or those who are assigned to take a drug as part of a study but fail to follow the protocol.

“We couldn’t do what we’ve done here anywhere else in the country,” Dr. Gould says. “Right now, we have the largest database in the world measuring coronary flow re-

## ENDNOTES

\*Pre-hospital Administration of Thrombolytic Therapy with Urgent Culprit Artery Revascularization (PATCAR) speeds up the time in which heart attack victims receive lifesaving thrombolytics. Using wireless technology, EMS teams relay ECG results and other vital signs to waiting cardiologists. By the time patients arrive at the emergency center, they have been diagnosed and received preliminary treatment.

<sup>1</sup> Reduto LA, Smalling RW, Freund GC, Gould KL. Intracoronary Infusion of Streptokinase in Patients with Acute Myocardial Infarction: Effects of Reperfusion upon Left Ventricular Performance. *AJC* 1981;48:403-409.

<sup>2</sup> Reduto LA, Freund GC, Gaeta JM, Smalling RW, Lewis B, Gould KL. Coronary artery Reperfusion in Acute Myocardial Infarction: Beneficial Effects of Intracoronary Streptokinase upon Left Ventricular Performance. *Amer J Cardio* 1981; 48:403-409.

<sup>3</sup> Smalling RW, Fuentes F, Freund GC, Reduto LA, Wanta-Matthews M, Gaeta J, Walker W, Sterling R, Gould KL. Beneficial Effect of Intracoronary Thrombolysis Up to 18 Hours After Onset of Pain in Evolving Myocardial Infarction. *Am Heart J* 1982;104:912-920.

<sup>4</sup> Smalling RW, Fuentes F, Matthews MW, Freund GC, Hicks CH, Reduto LA, Walker WE, Sterling RP, Gould KL. Sustained Improvement in Left Ventricular Function and Mortality by Intracoronary Streptokinase Administration During Evolving Myocardial Infarction. *Circulation* 1983;68:131-138.

<sup>5</sup> Gould KL, Martucci JP, Goldberg DI, Hess MJ, Edens RP, Latifi R, Dudrick SJ. Short-term cholesterol lowering decreases size and severity of perfusion abnormalities by Positron Emission Tomography after dipyridamole in patients with coronary artery disease. *Circulation* 1994;89:1530-1538.

<sup>6</sup> Gould K, Ornish D, Scherwitz L, Brown S, Edens RP, Hess MJ, Mullani N, Bolomey L, Dobbs F, Armstrong WT, Merritt T, Ports T, Sparler S, Billings J. Changes in myocardial perfusion abnormalities by positron emission tomography after long term, intense risk factor modification. *JAMA* 1995;274:894-901.

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