Oklahoma Heart Institute

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Hillcrest Medical Center Named "Cardiac Center of Excellence"

United Healthcare recently awarded Hillcrest Medical Center the distinction of being a **"Cardiac Center of Excellence"** for the Tulsa community.

This award recognizes Hillcrest as a leader in providing notable quality cardiac services in comparison to peer facilities in the area.

This national achievement is based upon coordinated services provided by the hospital, physicians and the care team, which result in the best possible outcomes. **Oklahoma Heart Institute at Hillcrest Medical Center** is committed to offering the most comprehensive cardiac services to meet the needs of patients who have complex heart conditions.

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Oklahoma Heart Institute

In this issue

Cover photo of azaleas in Tulsa in late spring by Rick Stiller

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Edition 4

To Our Readers

THE TREATMENT OF cardiovascular disease and its risk factors continues to evolve at a rapid pace.

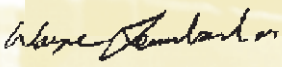
The introduction of balloon angioplasty techniques, followed by the development of coronary stents, revolutionized the management of patients with coronary artery disease. Now drug-eluting stents are producing an equally impressive advancement in this field. Dr. Chandwaney, an interventional cardiologist at Oklahoma Heart Institute, highlights the remarkable story of drug-eluting stents.

Dr. Bresloff, from the division of endocrinology at Oklahoma Heart Institute, discusses the advantages of using TZDs as first-line strategy for the treatment of diabetes mellitus, a major risk factor for coronary artery disease (CAD).

J Thomas, PA from the electrophysiology service at Oklahoma Heart Institute, discusses the current roles for pacemakers. In addition, Dr. Coman, an interventional electrophysiologist, presents the recent extension of pacemaker technology into the realm of heart failure therapy. He addresses the use of biventricular pacemakers for resynchronization therapy in the management of advanced heart failure.

Dr. Sonnenschein takes cardiology to new heights in his article on exercising in higher altitudes.

We hope you enjoy these articles, and welcome any comments or suggestions in regards to the magazine content.



Sincerely,
Wayne N. Leimbach, M.D.

by **Tobie L. Bresloff, MD**

What Is So Great About TZDs?

I prescribe a lot of TZDs (Thiazolidinedione drugs) to diabetic patients. If asked why, the answer is simple. TZDs are better than the alternatives, and our patients deserve the best.

Some of you may know that I spent several years as local Medical Director for one of the large insurance companies. One of my tasks was to try to keep down the soaring pharmacy costs while making sure the patients got the good care they needed. Pharmacy expense had become the fastest increasing area of health care expenditures. I saw that, many times, new drugs were being used which were much more expensive than the older alternatives. At times, these new drugs had few or marginal advantages. This is not the case with TZDs. They are a new class of drugs which treat blood sugar abnormalities in an entirely different way. They also have many non-glycemic effects which help the patient. I will try to describe these effects.

TZDs treat the underlying defect that causes Type 2 diabetes. The underlying problem is the blunted insulin response at the end organ. The pancreas, therefore, needs to make more and more insulin to get the same glycemic response. Eventually, the pancreas cannot increase production any more. At that point, blood sugar elevates and the patient has diabetes. However, TZDs improve the responsiveness of the insulin receptor to the insulin. This improves glucose uptake by muscle and adipose cells. This, in turn, decreases the insulin resistance. TZDs also work on the liver to decrease hepatic glucose output. In the long run, they appear to improve pancreatic beta cell function.

On the other hand, drugs that cause the pancreas to increase insulin production—secretagogues—work by increasing serum insulin levels to try to keep up with the insulin resistance. We now know that having supraphysiologic levels of insulin is bad. High insulin may lead to or expedite the dyslipidemia, hypertension, increased sympathetic activity and the inflammatory response that promotes vascular disease. In addition, even though secretagogues work when first started, we know that their effectiveness eventually wears off and the patient is back to where he started in an average of 3 years. At that point exogenous insulin may be needed.

TZD effects on blood sugar are not immediate. It may take a month or two to see best results. This is because these drugs do not work by increasing production of insulin. Since insulin levels do not go up, and in fact may go down as the cells become more responsive, there is very little hypoglycemia when TZDs are the only drug used, or when used in combination with metformin. We also know that the improvement in HgA1c can last for at least 3 years without a blunted effect.

Now, let me tell you about some of the non-glycemic effects of TZDs. By working to regulate the transcription of genes encoding polypeptides involved in carbohydrate, lipid and protein metabolism TZDs have multiple beneficial effects. Many of these impact the cardiovascular systems. It's important to remember that diabetics primarily die from heart disease and strokes.

Studies have shown that estimates of beta cell function increase significantly when TZDs are used. Tissue cultures and some *in vivo* studies have shown a decrease in beta cell apoptosis, or death. This can, in theory, make a pancreas that is on the brink of failing last longer. Studies are under way to prove this, and early results suggest it is true.

Lipid effects of these drugs are being noticed by cardiologists, as well as endocrinologists. Dyslipidemia in insulin resistance is thought to be a major cause of the increase in heart disease. Diabetics have enhanced VLDL secretion, increased small dense LDL particles, hypertriglyceridemia and decreased HDL-C production. All of

these, of course, are bad. Both of the currently available TZDs have shown that they decrease triglycerides and increase HDL. In addition, they appear to turn the small dense LDL particles into larger less dense ones that are not as atherogenic. All of that is great. We certainly want an antidiabetic drug that positively affects the lipids. The American Diabetes Association recommends that all adult diabetics with total cholesterol over 135 should be on a statin. We are not suggesting TZDs be used as a primary treatment for dyslipidemia; but when choosing an oral hypoglycemic, this class is the only one that favorably impacts lipids.

There is also evidence that TZDs improve blood pressure by decreasing the insulin levels. Hyperinsulinemia raises heart rate and sympathetic activity. This is a gradual effect, and may be fairly subtle. Don't be surprised if your patients who have a TZD started will achieve better blood pressure control after being on the drug for several weeks or months.

In addition, there are studies showing that C-reactive protein decreases after TZD is started. Even if we do not understand exactly why, it is promising that a marker of inflammation and increased risk of heart disease decreases.

TZDs are not for everyone, however. They will not work in patients with absolute insulin deficiency, such as Type 1 diabetes. These patients require insulin in the body in order to work. Nor are TZDs approved for patients with NYHA class 3 or 4 heart failure. The edema that happens in some patients is more likely if they have had diabetes longer, or are on insulin. If edema does occur, look for other causes, such as other drugs that may be adding to the problem: NSAIDs or some calcium channel blockers. The most common cause of edema relates to dietary indiscretion. Also see if the edema is causing any fluid in the lungs. Not all edema is CHF – some is just peripheral edema. The TZD can safely be stopped to see if the edema abates. Often it can be restarted at a lower dose, since the edema is dose dependent.

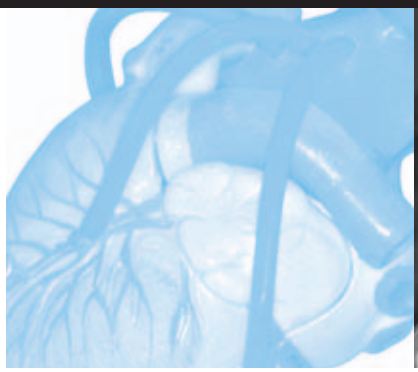
The two current available TZDs have not been seen to cause hepatotoxicity. However, you should also not start TZDs in patients with elevated liver enzymes. Current package inserts state that LFTs should be checked before initiation of the drug, then as needed after. Many of these patients will be on a statin and will be having periodic LFT checks for that reason.

Keep in mind that TZDs also appear to reverse some of the abnormalities seen in patients with polycystic ovarian syndrome. This is not an approved indication. Be aware, however, that some patients may feel that they are unable to become pregnant since they have not done so, and are not having regular menses. You must inquire if these reproductive age females are using some protection if they do not want to be pregnant.

In summary, TZDs can make a huge difference in diabetic control of Type 2 diabetics. They are indicated as first line treatment when used alone, as monotherapy as an adjunct to diet and exercise. They can also be used in combination with a sulfonylurea, metformin, or insulin. I no longer feel that secretagogues should be tried first, since these work by increasing insulin levels, lose their effectiveness and can cause hypoglycemia. The preferred approach would be to use several agents that work at different sites in the body and have complementary and additive actions. Also, remember that TZDs may increase the longevity of pancreatic function. In addition, they work on problems other than hyperglycemia to decrease the risk of cardiac disease in these patients. All of this makes the TZDs a great choice for first line treatment in Type 2 diabetes. The currently available TZDs are Avandia® (Rosiglitazone) and Actos® (Pioglitazone).

(Dr. Bresloff is a specialist with Oklahoma Heart Institute in Endocrinology, Metabolism and Hypertension, with expertise in diabetes, lipids, hypertension and thyroid diseases.)

by Robert C. Sonnenschein, MD, FACC



Heart Patients in the Mountains

Many cardiac patients in the Tulsa area travel to mountain regions for fun or work. Physicians in general, and cardiologists in particular, are frequently asked how to instruct and treat these patients.

For the purpose of this brief summary, intermediate altitude represents 5,000 to 8,000 feet, high altitude represents 8,000 to 14,000 feet, very high altitude is 14,000 to 18,000 feet, and extreme altitude is greater than 18,000 feet. We will address the intermediate and high altitude group of travelers in this piece.

Patients who travel to the 5,000 to 14,000 range of elevations experience hypoxia which worsens the higher one climbs. In response to this, pulmonary ventilation increases and PCO2 falls and respiratory alkalosis occurs. Hypoxia also stimulates the sympathetic nervous system, and epinephrine and norepinephrine secretion increase. Epinephrine activity is very transient, but norepinephrine secretion remains elevated for several days. The major circulatory effects are an increase in heart rate, blood pressure, and cardiac contraction velocity. Initially, cardiac output increases by approximately 20%. Venoconstriction causes an increase in central blood volume. The above changes increase cardiac work, with increase in the double product (heart rate X BP systolic pressure). Left ventricular volume is decreased. Increased pulmonary artery pressure may be seen. Prolonged exposure to increased altitude is associated with decrease in sympathetic activity to pre-ascent levels, with decrease in cardiac output and lowering of blood pressure.

Patients with coronary artery disease who have symptoms of angina or CHF before ascent may experience a moderate increase in symptoms during the first few days of increased altitude exposure. This is due to increased cardiac work, and the largest part is due to increased sympathetic output. Alkalosis in the early ascent may increase coronary vasoconstriction. Symptoms improve by 7 to 10 days. Asymptomatic patients pre-ascent may have no symptoms at intermediate or high altitude.

Multiple small studies have been done with patients exercising at altitude or on lower levels of ambient O2 inspiration. Herb Hultgren in High Altitude Medicine speculates that if “a patient with coronary artery disease can reach stage III of the Bruce treadmill protocol, greater than or equal to 6 minutes, without discom-

fort, the patient may also be able to tolerate an altitude of approximately 14,000 feet without discomfort". The acute effects of high altitude probably are due to transient increase in cardiac work for any level of exercise, as compared to sea level, as a function of increased sympathetic output, and not due to myocardial hypoxia directly. Hard cardiac end points such as MI or death associated with going to intermediate or high altitudes are exceptionally rare.

Before going to elevations in altitude, coronary artery disease patients should have a stable clinical pattern. If the patient is in a high-risk group or has more significant symptoms, a more aggressive approach to assessment of cardiac status and then appropriate therapy is probably warranted, though no standards are available. Particularly if a patient is going to a much higher elevation or to a more remote setting where health care may be distant or not available at all, a more complete assessment pre-ascent may be in order.

For patients with valvular heart disease or congenital heart disease, if significantly symptomatic, hypoxic, or significantly pulmonary hypertensive in the pre-ascent state, then travel to high elevations may pose increased risk and should be avoided if at all possible.

Hypertensive patients may exhibit a rise in blood pressure, both systolic and diastolic, with increased elevation. In the first few days at elevation, some increased therapy for blood pressure may be necessary if blood pressure increases significantly, but over a more prolonged period the pressures will return to baseline.

In general for all cardiac patients, symptoms should be well controlled and underlying disease addressed before going to significant altitude elevations. Exercise should be limited during the first 7 to 10 days at elevation, and if necessary, medicine can be increased. If symptoms still occur, oxygen may be administered with significant benefit. Descent of 2,000 to 4,000 feet is often successful in alleviating symptoms.

Acute mountain sickness can affect heart patients, as it can any traveler to increased altitude and does not appear to be associated with age, level of fitness, or underlying disease. However, there is some recent data that acute mountain sickness may be associated with being overweight, recent pulmonary infection prior to ascent, and excessive exercise when first arriving at the elevation. Headache, lassitude, anorexia, and insomnia are frequent symptoms of uncomplicated acute mountain sickness. Change in mentation, cough, shortness of breath, or hemoptysis are signs of much more serious progressive acute mountain illness and usually occur with rapid ascent to the higher elevations. Prevention of acute mountain sickness is helped by gradual ascent to high altitudes, initially sleeping at no higher than 8,000 feet with increases of only 1,000 to 2,000 feet of elevation per night. A high carbohydrate diet started one to two days before ascent may help prevent symptoms. Because of increased fluid loss at higher altitudes, increased hydration is important. Alcohol is not recommended until fully acclimatized.

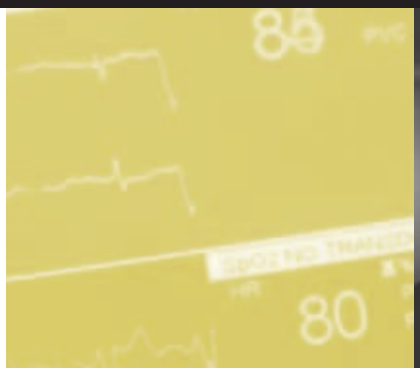
If acute mountain-sickness has occurred during a previous visit to high altitude, The Wilderness Medicine Society recommendations include Acetazolamide 125mg. po twice a day starting the day of or day before ascent and continuing one to two days at altitude. This may significantly alleviate or even prevent the symptoms of acute mountain sickness.

Sleeping medications may increase the chance of acute mountain sickness, and if possible should be avoided. In general, it is best to climb high and sleep low whenever possible.

Once acute mountain sickness occurs, but does not improve, descending 2,000 to 4,000 feet is usually enough to improve symptoms. The patient should never continue to ascend if symptoms continue or worsen. Patients with increasing symptoms or change in mental status should not be left alone and should descend immediately.

(Robert C. Sonnenschein is a cardiologist at Oklahoma Heart Institute who specializes in echocardiography and noninvasive peripheral imaging.)

by James A. Coman, MD, FACC



Congestive Heart Failure:
Restoring Synchrony through Pacing

Over 5 million patients suffer from congestive heart failure (CHF) in the United States. Each year 500,000 people are added to this roster, making CHF the most common DRG, or reason for a Medicare admission annually. Unfortunately, despite aggressive pharmaceutical management with beta-blockers, ACE inhibitors, and aldosterone antagonists, the 5-year mortality from symptomatic CHF remains a startling 50%.

In the past 5 years, several randomized, controlled trials have demonstrated the immense value of cardiac synchrony.

In the past 5 years, several randomized, controlled trials have demonstrated the immense value of cardiac synchrony. The left ventricle, or main pumping chamber, frequently develops dyssynchrony, which is most clearly manifested by the presence of left or right bundle branch block on a regular ECG. These conduction defects represent a slowing of conduction for electricity through the heart's main pumping chambers. In the past, no therapy was available for this problem. Patients with an already impaired left ventricular function (low ejection fraction) from prior heart damage could only suffer further as electricity slowed while moving through the left ventricle. This slowing of electricity prevented the parts of the heart that did still work from working together.

Fortunately, sophisticated pacemakers can now be placed so that the left ventricle can be resynchronized. The technology behind this amazing feat is an extension of standard pacemakers. In the past, both left and right ventricles were paced through a single lead placed in the right ventricular apex. Left ventricular activation occurred in a passive fashion. Now, two leads are placed in the ventricles

with one on the right side, but the second on the surface of the left ventricle. The two leads are then coordinated through complex algorithms and timing cycles within a pacemaker, which is designed, specifically for this problem. A final traditional lead is placed in the right atrium to maintain a coordinated effort between the upper and lower chambers of the heart.

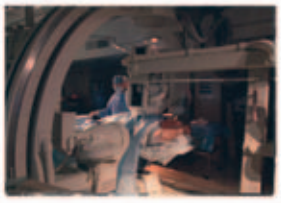
Placing a pacemaker system such as this (called a cardiac resynchronization therapy or CRT system) takes longer than a standard dual chamber pacemaker. Overall, technology has improved so that the entire process takes approximately 60 to 90 minutes. While these devices are available as pacemakers (CRT-P) or as implantable defibrillators (CRT-D), all patients receiving this technology have a significant impairment in left ventricular function and should therefore receive defibrillation therapy simultaneously. In practice, therefore, at Oklahoma Heart Institute, almost all patients receiving CRT devices get the implantable defibrillator version, since studies have shown that death rates are reduced significantly with this type of implant than with the pacemaker alone.

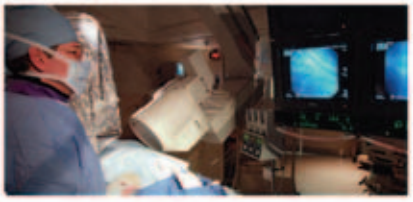
The changes which are usually seen in patients post-procedure are immediate and include improvements in overall well-being, dyspnea, fatigue, pulse pressure, ejection fraction, number of days spent in the hospital each year, and a decrease in the amount of diuretic needed to control volume. Approximately 70-80% of patients respond in this fashion, while the remaining patients fail to respond significantly. Several interventions are available to those patients who fail to respond to this therapy, and revolve around optimizing the atrio-ventricular timing as well as the left to right ventricular timing.

The patients who should be selected for this type of therapy include those who have LVEF < 35%, with class III or IV CHF despite optimal pharmacologic therapy, and a QRS duration over 120 ms on a standard ECG. Several trials are available to determine the best time for placement of such technology. Since many patients demonstrate improved left ventricular remodeling, some investigators have suggested that the optimal timing is prior to progression to class III CHF. An ongoing study at Oklahoma Heart will evaluate this question.

Physicians are frequently asked to improve the quality and quantity of our patients' lives. It is rare in the medical field to achieve both of these goals with a single intervention. The use of CRT-D has clearly allowed us to provide a dramatic leap forward for the quality of our patients' lives who suffer daily from congestive heart failure, while also providing them the cure for ventricular fibrillation. Interventions such as this are also noteworthy for the impressive cost-savings that they bring to the health care system by lowering the frequency of hospitalizations. Together, we can make a dramatic impact in this once overwhelming disease process.

(Dr. Coman is an electrophysiologist with Oklahoma Heart Institute, who subspecializes in cardiac electrophysiology, ablation therapy and pacemakers.)





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THE DOCTORS OF OKLAHOMA HEART INSTITUTE

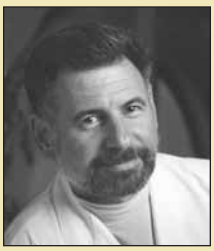
Wayne N. Leimbach, Jr., MD, FACC, FSCAI, FCCP, FAHA

Dr. Leimbach is a subspecialist in interventional cardiology, including cardiac catheterization, coronary angioplasty and related interventional procedures such as stents, atherectomy, laser, intravascular ultrasound imaging and direct PTCA for acute myocardial infarction. He is Director of the Cardiac and Interventional Laboratories at Hillcrest Medical Center. Dr. Leimbach is Co-Director of the Lipid and Wellness Clinic at Oklahoma Heart Institute. He is Director of the James D. Harvey Center for Cardiovascular Research at Hillcrest Medical Center, as well as Director of the Oklahoma Heart Research and Education Foundation. He also serves as Clinical Associate Professor of Medicine at the University of Oklahoma College of Medicine – Tulsa. Dr. Leimbach completed a Clinical Cardiology Fellowship and a Research Fellowship at the University of Iowa Hospitals and Clinics. He also completed his Internal Medicine Internship and Residency programs at Iowa, where he was selected Chief Resident in Medicine. He received his medical degree from Northwestern University in Chicago and his Bachelor of Science degree from the University of Michigan.

Board certified in Internal Medicine, Cardiovascular Disease and Interventional Cardiology

Robert C. Sonnenschein, MD, FACC

Dr. Sonnenschein specializes in echocardiography and noninvasive peripheral vascular imaging. He is Director of Peripheral Vascular Ultrasound Imaging at Hillcrest Medical Center and Oklahoma Heart Institute and serves as Clinical Associate Professor of Medicine at the University of Oklahoma College of Medicine – Tulsa. He completed his Cardiology Fellowship at the State University of New York Upstate Medical Center in Syracuse, where he also completed his Internal Medicine Internship and Residency programs. Dr. Sonnenschein received his medical degree from Rush Medical College in Chicago and his Bachelor of Arts degree from the University of Pennsylvania.



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Registered Vascular Technologist

Robert E. Lynch, MD, FACC

Dr. Lynch is a specialist trained in noninvasive and invasive cardiology. He is former Chief of Cardiology at Hillcrest Medical Center, where he also has served as Chief of Medicine and President of the medical staff. Dr. Lynch is Co-Director of the Lipid and Wellness Clinic at Oklahoma Heart Institute and Director of the Executive Health Program. He is also a Clinical Assistant Professor at the University of Oklahoma College of Medicine – Tulsa. He completed his Cardiology Fellowship, as well as his Internal Medicine Internship and Residency, at the University of Oklahoma Health Sciences Center. Dr. Lynch received his medical degree from the University of Oklahoma School of Medicine and his Bachelor of Science degree from the University of Tulsa. Before establishing his practice in Tulsa, he served as Chief of Medicine at the U.S. Army Hospital, Bangkok, Thailand.

Board certified in Internal Medicine and Cardiovascular Disease

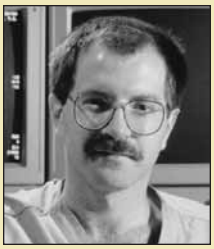
James J. Nemec, MD, FACC

Dr. Nemec is a subspecialist in echocardiography, stress echocardiography and nuclear cardiology. He serves as Director of Nuclear Cardiology for Oklahoma Heart Institute. Dr. Nemec has served as Assistant Professor of Internal Medicine, Division of Cardiology, at Creighton University and as Assistant Professor, Department of Radiology, also at Creighton University. He completed his Clinical Cardiology Fellowship at the Cleveland Clinic Foundation and his Internal Medicine Internship and Residency at Creighton University. Dr. Nemec also completed a year of training in pathology at the University of Missouri, Columbia, MO. He received his medical degree from Creighton University, where he also received his Bachelor of Arts degree.

Board certified in Internal Medicine and Cardiovascular Disease

John G. Ivanoff, MD, FACC, FSCAI

Dr. Ivanoff specializes in interventional cardiology, including cardiac catheterization, coronary angioplasty and related interventional procedures such as stents, atherectomy and direct PTCA for acute myocardial infarction. He is Director of the Catheterization Laboratories at SouthCrest Hospital. Dr. Ivanoff serves as Clinical Associate Professor of Medicine at the University of Oklahoma College of Medicine – Tulsa. He has also served as Assistant Professor of Medicine at the Medical College of Pennsylvania, as well as Associate Director of the Coronary Care Unit and Assistant Professor of Medicine at Hahnemann University Hospital, where he also completed his Cardiology Fellowship. He completed his Internal Medicine Internship and Residency at the Medical College of Pennsylvania, where he served as Chief Resident. Dr. Ivanoff also received his medical degree from the Medical College of Pennsylvania. He completed his Masters degree in biochemistry at Columbia University and received his Bachelor of Arts degree from the University of Pennsylvania.



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Gregory D. Johnsen, MD, FACC

Dr. Johnsen is an interventional cardiologist with expertise in cardiac catheterization, angioplasty and related interventional procedures, such as stents and atherectomy. He is Director of Cardiac Rehabilitation at Hillcrest Medical Center and Director of the Hillcrest Exercise and Lifestyle Programs. He completed his Clinical Cardiology Fellowship at the University of Oklahoma – Oklahoma City, where he then finished an extra year of dedicated training in interventional cardiology. He completed his Internal Medicine Internship and Residency training at the University of Oklahoma – Oklahoma City, where he also received his medical degree. Dr. Johnsen received his Bachelor of Science degree from Oklahoma State University.

Board certified in Internal Medicine, Cardiovascular Disease and Interventional Cardiology

Alan M. Kaneshige, MD, FACC

Dr. Kaneshige is a noninvasive cardiologist with expertise in adult echocardiography, stress echocardiography and transesophageal echocardiography. He is Chief of Cardiology at Hillcrest Medical Center. Dr. Kaneshige is also the Director of the Adolescent and Adult Congenital Heart Clinic at Oklahoma Heart Institute and Director of the Congestive Heart Failure C.A.R.E. Center at Hillcrest

Medical Center. Dr. Kaneshige completed his Internal Medicine Internship and Residency at Creighton University School of Medicine, where he also received his medical degree. He received a Bachelor of Science in chemistry at Creighton University. Dr. Kaneshige completed his Clinical Cardiology Fellowship at Creighton, where he also served as Chief Cardiology Fellow for two years. He completed an additional Cardiac Ultrasound Fellowship at the Mayo Clinic in Rochester, MN. Dr. Kaneshige served as Assistant Professor of Medicine at Creighton University School of Medicine, where he was Director of the Noninvasive Cardiovascular Imaging and Hemodynamic Laboratory.

Board certified in Internal Medicine and Cardiovascular Disease
Board certified in Adult and Transesophogeal Echocardiography

Ernest Pickering, DO, FACOI

Dr. Pickering is a cardiology specialist trained in noninvasive and invasive cardiology with subspecialty expertise in cardiac catheterization and angioplasty. He is Chief of Cardiology at SouthCrest Hospital and past Chief of Cardiology at Tulsa Regional Medical Center. He completed a Cardiovascular Disease Fellowship at Baylor College of Medicine in Houston, TX. Dr. Pickering's Internal Medicine Residency was completed at Oklahoma Osteopathic Hospital in Tulsa. He received his medical degree from Philadelphia College of Osteopathic Medicine and his Bachelor of Science degree from Shelton College, Ringwood, NJ.

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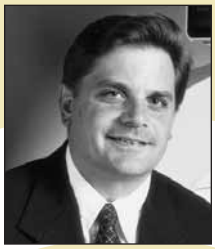
James A. Coman, MD, FACC

Dr. Coman is a subspecialist in cardiac electrophysiology, ablation therapy and pacemakers. He is Director of Electrophysiology at Hillcrest Medical Center. Dr. Coman also serves as Clinical Associate Professor of Medicine at the University of Oklahoma College of Medicine – Tulsa. He completed an Electrophysiology Fellowship at the Cleveland Clinic Foundation, where he was Chief Fellow. His Cardiology Fellowship was also performed at the Cleveland Clinic Foundation. Dr. Coman's Internal Medicine Internship and Residency training were completed at the University of Alabama, Birmingham, AL. He received his medical degree from the University of Alabama School of Medicine and his Bachelor of Science degree in biomedical engineering from Vanderbilt University, Nashville, TN.

Board certified in Internal Medicine, Cardiovascular Disease and Electrophysiology

Edward T. Martin, MS, MD, FACC, FACP, FAHA

Dr. Martin is a noninvasive cardiologist with subspecialty expertise in non-invasive imaging. He is Director of Cardiovascular Magnetic Resonance Imaging at Oklahoma Heart Institute, SouthCrest Hospital and Hillcrest Medical Center. Dr. Martin is also Director of Nuclear Cardiology at SouthCrest Hospital. In addition, he is a Clinical Associate Professor of Medicine at the University of Oklahoma College of Medicine – Tulsa. Dr. Martin has specialty training in Nuclear Medicine, as well as additional training dedicated to Cardiovascular Magnetic Resonance Imaging. He completed his Cardiology Fellowship at the University of Alabama. Dr. Martin's Internal Medicine Internship and Residency training were performed at Temple University Hospital in Philadelphia. He received his medical degree from the Medical College of Ohio. Dr. Martin completed his Master of Science degree in mechanical engineering at the University of Cincinnati and his Bachelor of Science degree in physics at Xavier University. Dr. Martin is a founding member of the Society of Cardiovascular Magnetic Resonance and is an editorial board member of the Journal of Cardiovascular Magnetic Resonance.



Board certified in Internal Medicine and Cardiovascular Disease

Roger D. Des Prez, MD, FACC

Dr. Des Prez is a noninvasive cardiologist with subspecialty expertise in echocardiography, nuclear cardiology and transesophageal echocardiography. He is Director of Echocardiography and Peripheral Vascular Ultrasound Imaging at SouthCrest Hospital. Dr. Des Prez received his medical degree and Bachelor of Arts degree from Vanderbilt University. He completed his Residency in Internal Medicine and Pediatrics at University Hospital of Cleveland. Dr. Des Prez practiced for six years as an internist with the Indian Health Services in Gallup, NM. He returned to Vanderbilt University as a member of the Internal Medicine Faculty, at which time he also completed his cardiology training. In addition to noninvasive cardiology, Dr. Des Prez is interested in outcomes research and computers in medicine.

Board certified in Internal Medicine, Pediatrics, Critical Care and Cardiovascular Disease

Board certified in Adult and Transesophageal Echocardiography

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Board certified in Internal Medicine
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Board certified in Internal Medicine

Board eligible in Cardiovascular Disease

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Dr. Chandwaney is an interventional cardiologist with expertise in cardiac catheterization, coronary angioplasty and related interventional procedures such as coronary stents, atherectomy, intravascular ultrasound and peripheral vascular interventional procedures. He completed his Clinical Cardiology Fellowship at Northwestern University Medical School in Chicago, IL., where he also completed an Interventional Cardiology Fellowship. Dr. Chandwaney's Internal Medicine Internship and Residency were performed at Baylor College of Medicine in Houston, TX. He received his medical degree from the University of Illinois at Chicago. Dr. Chandwaney completed his Master of Science degree at the University of Illinois at Urbana Champaign, where he also received his Bachelor of Science degree.

Board certified in Internal Medicine and Cardiovascular Disease
Board certified in Interventional Cardiology

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Board certified in Internal Medicine
Board certified in Endocrinology and Metabolic Diseases

Frank J. Gaffney, MD

Dr. Gaffney is an invasive and noninvasive cardiologist with subspecialty expertise in transesophageal echocardiography. He completed his Cardiovascular Medicine Fellowship at Scott & White Memorial Hospital in Temple, Texas. Dr. Gaffney completed his Internal Medicine Internship and Residency at Brooke Army Medical Center in San Antonio. He then remained on staff at Scott & White Memorial Hospital for several years, before entering his Fellowship in Cardiovascular Medicine. Dr. Gaffney earned his medical degree from New York Medical College, Valhalla, New York, and he received his Bachelor of Arts degree at Hofstra University in Hempstead, New York.

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Board certified in Cardiovascular Disease

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Dr. Moosa is an interventional cardiologist with expertise in cardiac catheterization, coronary angioplasty and related interventional procedures such as coronary stents, atherectomy, intravascular ultrasound and peripheral vascular interventional procedures. He is Director of Peripheral Vascular Services at SouthCrest Hospital. Dr. Moosa completed his Clinical Cardiology Fellowship at Howard University in Washington, DC, where he also completed his Internal Medicine Internship and Residency. Dr. Moosa received his medical degree from the University of Ibadan, Nigeria. He obtained his Bachelor of Science degree at the University of Durban-Westville, South Africa.

Board certified in Internal Medicine and Cardiovascular Disease
Board certified in Interventional Cardiology

Obesity has become a major epidemic in the United States. It is associated with the development of diabetes mellitus, hypertension, and hyperlipidemia, all of which are major risk factors for the development of atherosclerotic cardiovascular disease. The Nurses' Health Study recently showed a significant increase in risk of coronary heart disease for a basic metabolic index (BMI) of greater than 23.

We also know that abdominal obesity increases coronary artery disease risk independently of basic metabolic index (BMI). Abdominal obesity is one of the major markers of the dysmetabolic syndrome, a major independent risk factor for coronary artery disease. Persons having three or more of the following five characteristics have the dysmetabolic syndrome. These characteristics include:

Waist circumference greater than 40 inches for men and greater than 35 inches for women.

Triglycerides greater than 150.

HDL cholesterol less than 40 for men and less than 50 for woman.

Blood pressure greater than or equal to 130/85.

Fasting blood sugar greater than or equal to 110mg/dl.

47 million U.S. adults (24%of the entire population) have the dysmetabolic syndrome and are at risk of coronary heart disease.

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Effective therapies for treating the obesity epidemic have remained elusive. Diet therapy has produced modest weight loss but rarely do the patients maintain the weight loss. Surgical therapies have been effective but are expensive and associated with definite risk.

A new target for multi-risk management involves selective cannabinoid receptor antagonism. Recently, results of the Rio-lipid study and the Rio-Europe studies have been presented showing impressive sustained weight loss with the use of the drug rimonabant, a selective cannabinoid receptor antagonist.

The Rio-lipid study showed that 72.9% of patients on rimonabant 20mg per day lost greater than 5% of their baseline body weight at one year. In addition, 44.3% of the patients lost greater than 10% of their baseline body weight in one year with the 20mg dose of rimonabant. In addition, therapy produced decreases in triglycerides, hsCRP, and small atherogenic LDL particles.

More recently, at the American College of Cardiology meetings in New Orleans in March 2005, the results of the Rio-Europe study were presented. They confirm the findings of the North American Rio-lipid study. Weight loss at one year was 8.6 kilograms (about 19 pounds) for the rimonabant 20mg daily versus 3.6 kilograms for the diet therapy group. Two-year follow up data showed the weight loss was maintained in the rimonabant-treated patients.

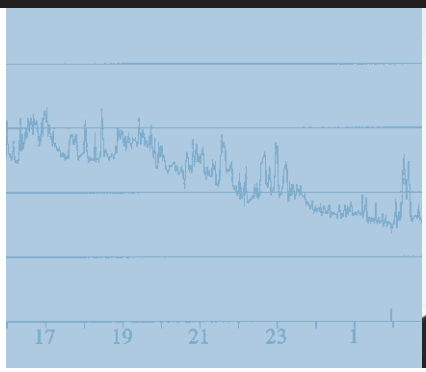
Currently, Oklahoma Heart Institute is involved in the Stradivarius Trial looking at the use of rimonabant 20mg daily for inhibition of atherosclerosis progression assessed by IVUS (intravascular ultrasound) in overweight patients. The trial clinical coordinating center is the Cleveland Clinic.

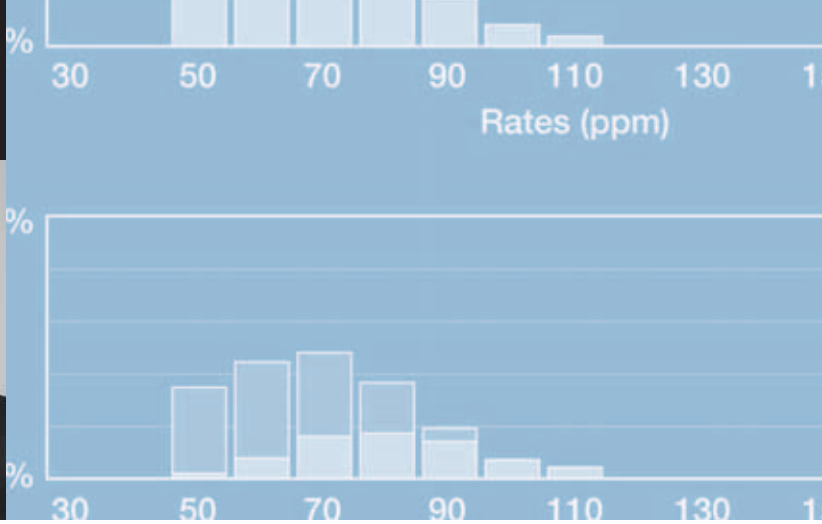
Since rimonabant produces weight loss which reduces major risk factors for coronary artery disease and, since rimonabant use helps to correct several abnormal metabolic parameters, it is postulated that rimonabant may stop progression of atherosclerotic plaque in coronary arteries within two years of therapy. The trial design is similar to that of the REVERSAL trial, which showed a halting of plaque progression within 18 months of initiation of intensive lipid-lowering therapy with Atorvastatin 80mg daily. Patients with significant obesity and evidence of dysmetabolic syndrome, who also have evidence of atherosclerotic vascular disease either manifested as coronary artery disease or peripheral vascular disease, would be considered for this study. For more information, call 592-0999 and ask to speak with one of the Research Nurses.

Recently, results of studies have been presented showing impressive sustained weight loss with the use of the drug rimonabant, a selective cannabinoid receptor antagonist.

Oklahoma Heart Institute

by J Thomas, MHS, PA-C





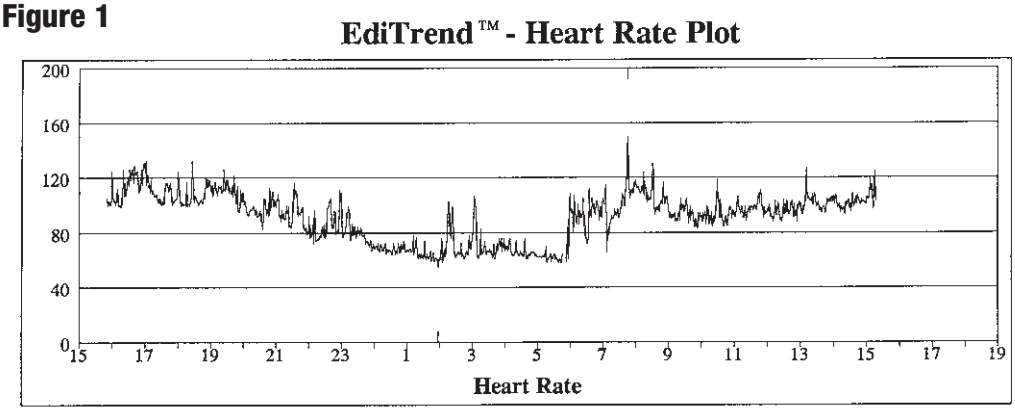
The Evolution of Pacing:
Chronotropic Incompetence

Every year more than 400,000 pacemakers are implanted worldwide. The first permanent pacemaker implanted in 1958 was a simple, single chamber device that delivered asynchronous (continuous) impulses. Since that time, the indications and technology of cardiac pacing have continued to evolve. Pacemakers today are equipped with complex algorithms and sensors to manage and monitor a patient's heart rhythm.

Early pacemakers were primarily implanted to prevent death in patients with bradyarrhythmias (slow heart rates). Today, the majority of pacemakers are implanted to improve patients' quality of life. The function of a pacemaker is to correct bradycardia, generally accepted to be rates less than 40 beats per minute during waking hours.

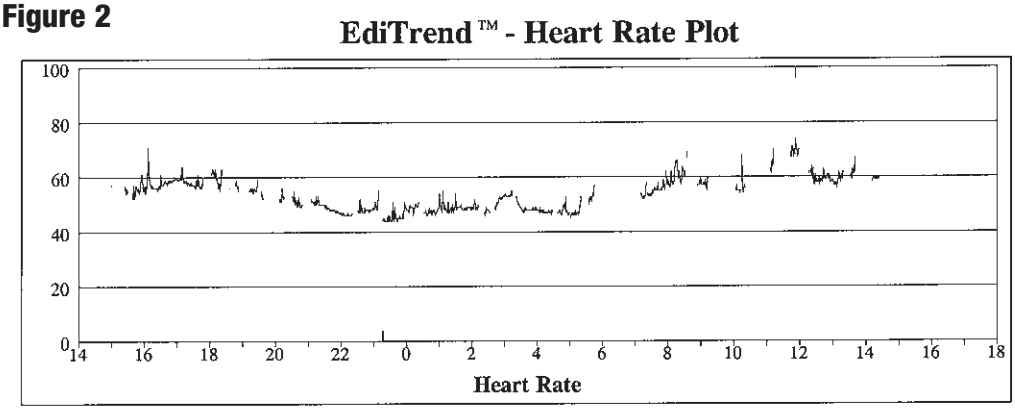
There are two main types of bradyarrhythmias. Atrioventricular conduction disturbances (heart block) occur when there is alteration of the normal communication between the upper and lower chambers. Heart block is usually caused by idiopathic fibrosis of the heart's conduction system but can also be caused by medications, heart attacks, and structural heart disease. It is well described that advanced types of heart block (2:1 AV block, complete heart block) warrant pacing. Sinus node dysfunction encompasses any dysfunction of the

Figure 1



Normal heart rate response during activities of daily living

Figure 2



Abnormal heart rate response during activities of daily living, demonstrating severe chronotropic incompetence

heart's natural pacemaker, the sinus node, and includes sinus exit block, sinus arrest, tachycardia-bradycardia syndrome, and chronotropic incompetence.

Chronotropic incompetence represents a shift in the traditional definition of bradycardia. Chronotropic incompetence is the inability of the heart to regulate its rate appropriately in response to physiologic stress. For example, a heart rate of 60, while entirely appropriate at rest, is insufficient during moderate to heavy exertion. Patients with chronotropic incompetence typically experience symptoms of exertional fatigue, dyspnea, and lightheadedness. Symptoms of chronotropic incompetence can easily be mistaken for aging as patients frequently report feeling as if they have aged 5-10 years over the past 6-12 months.

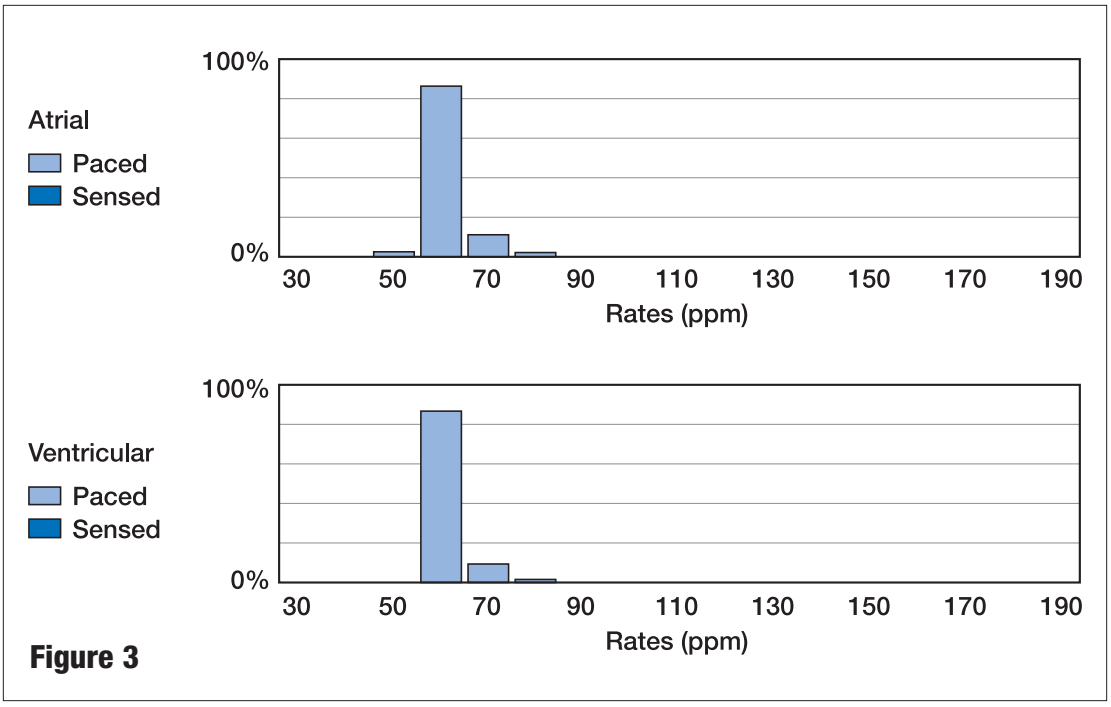


Figure 3

Ventricular histogram showing severe chronotropic incompetence

Chronotropic incompetence can easily be identified with simple diagnostic testing. A simple walk test in the office can identify the relative bradycardia present during exertion. This evaluation is performed by having the patient walk up and down a flight of stairs at a brisk rate and measuring their radial pulse upon return. A normal person should reach heart rates near 100 beats per minute with this test. In fact, a normal heart rate response to activities of daily living consists of reaching the 100 beat per minute mark 70-80 times per day, regardless of age. An abnormal walk test can be confirmed by placing a Holter monitor to record the heart rate plot over 24 hours (Fig. 1 & 2). Many people mistakenly use the peak exercise heart rate as a marker for this

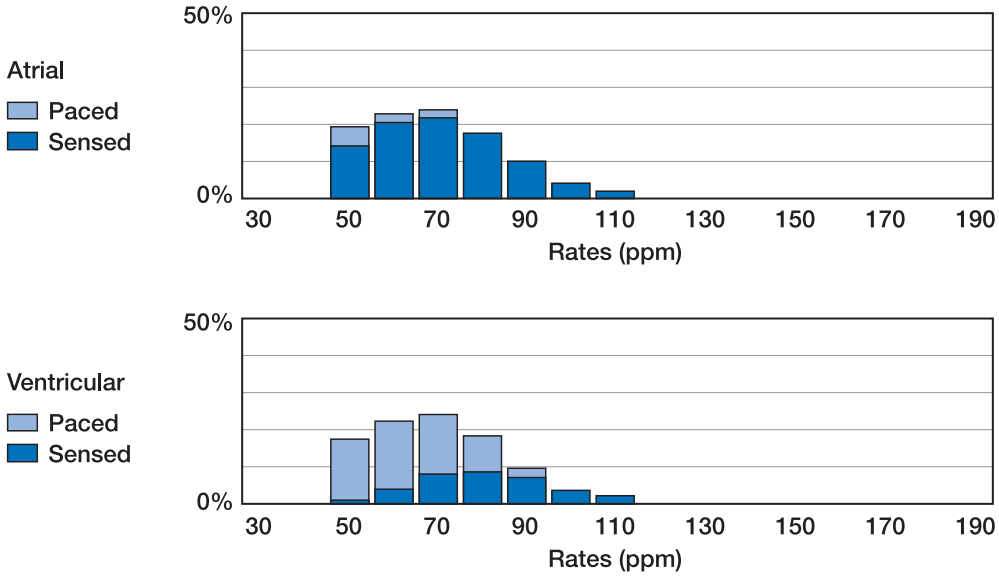


Figure 4

Ventricular histogram showing normalization of heart rate response by pacemaker

form of bradycardia. In fact, over two-thirds of patients with chronotropic incompetence can reach their age predicted peak heart rate. Caution should therefore be used when looking at exercise stress tests for this diagnosis.

Fortunately, the evolution of pacing technology has provided an excellent solution for this population. Many pacemakers today are equipped with advanced sensors, which allow mimicry of normal sinus node behavior. These sensors are usually set to evaluate both motion of the body during activity as well as respiratory rate. By combining these two complex pieces of information, the heart rate response is appropriate during most forms of physical activity (Fig. 3 & 4). The scientific data, which supports the use of this type of technology, was limited in the past. Currently, Oklahoma Heart Institute is the national coordinating center for the LIFE study, which is designed to evaluate the utility of these sensors in this population. This project has enrolled 1500 patients around the nation and reached enrollment completion during the month of April. We are proud of our leadership in this area and are thrilled that our patients have access to advanced technology through research such as this.

(J Thomas is Director of Physician Extenders at Oklahoma Heart Institute and serves as Clinical Adjunct Faculty for the University of Oklahoma Physician Assistant Program. J has special interest and dedication in cardiac pacing and electrophysiology.)

■ *by* **Raj H. Chandwaney, MD, FACC, FSCAI**

Restenosis in Percutaneous Coronary Intervention:

The Path to Drug Eluting Stents and Beyond

Percutaneous coronary intervention (PCI) has evolved as an important element of the standard of care in managing patients with coronary artery disease. Andreas Gruentzig performed the first successful human percutaneous transluminal coronary angioplasty (PTCA) on September 16, 1977.[1] Impressive acute and long-term success have been documented in that initial patient (see figure 1).[2] Unfortunately, despite the sustained benefit Andreas Gruentzig achieved in the initial patient treated with PTCA, such durable long-term outcomes could not be repeated reliably. Coronary restenosis became the Achilles heel of PCI (see figure 2).

The classically described pathophysiologic mechanisms of coronary restenosis include elastic recoil, negative remodeling, and intimal hyperplasia. In fact, the processes that occur after vascular injury caused by PTCA are complex (see figure 3). These complex processes include mechanical stretch, endothelial denudation, vasoactive hormones, growth factors, circulating cells, lipids, extracellular matrix synthesis, and smooth muscle cell activation, migration, and oncogenesis.[4]

Coronary stents were the first armament that proved to be valuable in the battle against coronary restenosis. The European BENESTENT trial[5] and its American equivalent STRESS trial[6] were the two landmark studies published in the same issue of the New England Journal of Medicine in 1994 that documented a significant reduction in coronary restenosis using the Palmaz-Schatz stent compared to PTCA alone. Since the publication of these trials, the

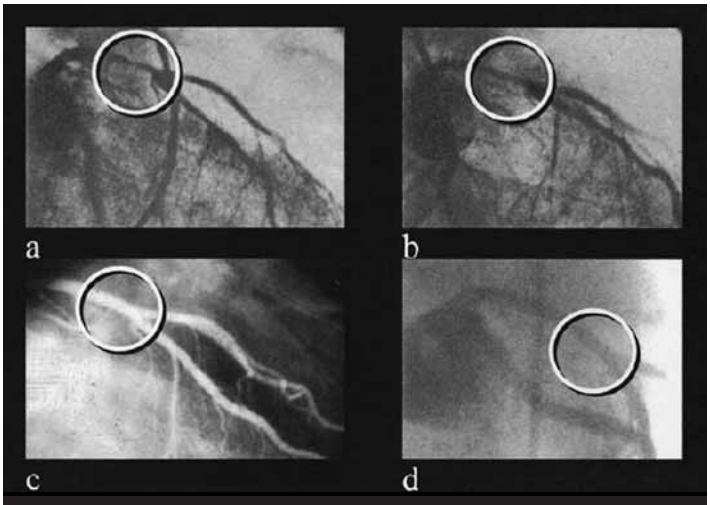


Figure 1 Coronary angiograms of the first patient to undergo PTCA by Andreas Gruentzig. Panel A demonstrates the lesion before PTCA. Panel B demonstrates the lesion immediately post PTCA. Panels C and D demonstrate durable long-term outcome at the lesion site 10 and 23 years post PTCA, respectively.[2]

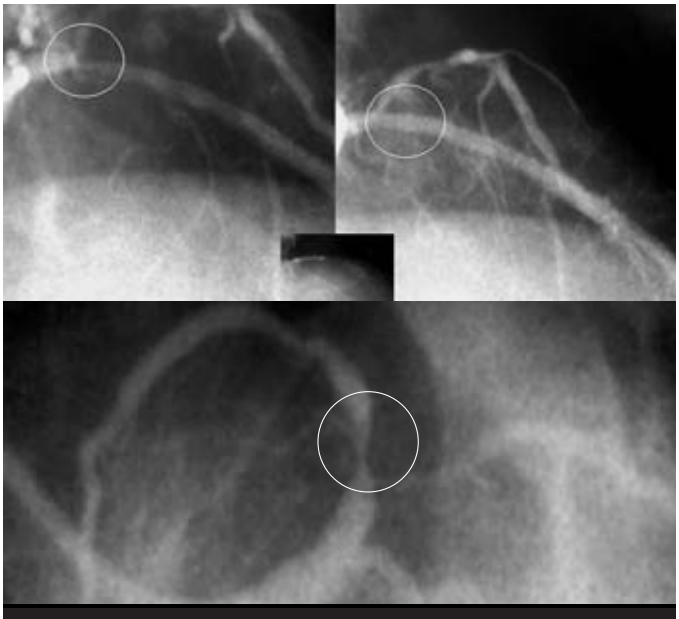


Figure 2 Restenosis in PCI. Upper left image demonstrates severe stenosis pre PTCA. Upper right image demonstrates excellent result immediately post PTCA. Lower image demonstrates severe restenotic lesion 3 months post PTCA.[3]

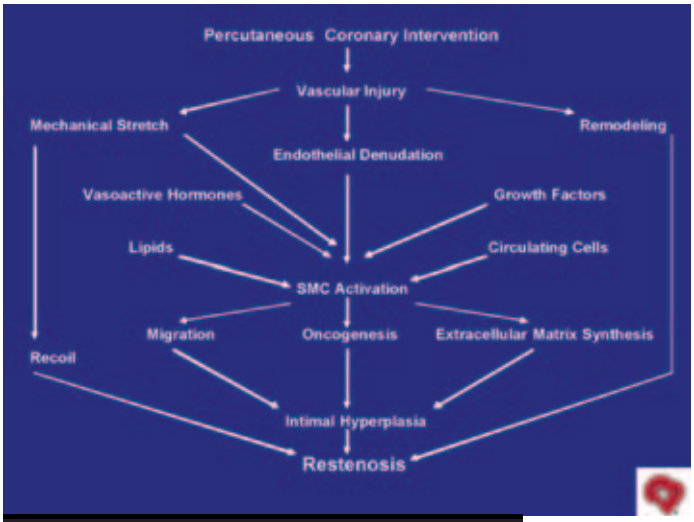


Figure 3 Mechanisms of coronary restenosis.[4]

worldwide use of coronary stents has grown exponentially. Coronary stents reduce restenosis by creating a scaffold to prevent elastic recoil and negative remodeling thus eliminating two of the three classical pathophysiologic mechanisms of restenosis. Ironically, coronary stents cause the third mechanism of restenosis (intimal hyperplasia) to amplify (see figure 4). This concept has been well demonstrated in numerous stent trials which demonstrate that late loss (a surrogate for intimal hyperplasia) is greater in coronary arteries treated with stenting rather than those treated with PTCA alone. Nevertheless, improved net gain is achieved due to the greater acute gain that can be achieved with stenting (see figure 5).[8]

Well defined clinical risk factors for coronary restenosis include diabetes mellitus and previously treated restenotic lesions.[9,10,11] Angiographic predictors for coronary restenosis include small vessels, ostial lesions, long lesions, and bifurcation lesions.

Many strategies such as PTCA, directional coronary atherectomy, high speed rotational atherectomy, "Stent Sandwiches" (placing a stent within a restenosed stent), excimer laser coronary angioplasty, and cutting balloon PTCA have been examined as potential solutions to treat coronary restenosis. Although each of these techniques continues to play a valuable role in PCI, none of these has provided a worthy approach in the treatment of coronary restenosis.[12-18]

Intravascular brachytherapy proved to be the first technique to demonstrate significant benefit in the treatment of coronary restenosis. This technique involves temporarily placing devices that emit radiation into areas of the coronary artery that have just been treated for coronary restenosis with techniques such as PTCA. The radiation inhibits cellular proliferation by disrupting DNA most profoundly during mitosis and the G2 phases of the cell cycle. Both gamma emitting (Checkmate by Cordis), and beta emitting (Beta-Cath by Novoste, and Galileo by Guidant) radiation devices were validated in clinical trials and became commercially available.[19] Unfortunately, due to decreased market penetration since the release of drug eluting stents, each of the intravascular brachytherapy systems will be discontinued and no longer available. Long-term five year follow-up for the GAMMA 1 trial were recently presented and revealed a delayed catch-up phenomenon that led to equivalent rates of target vessel failure in those patients treated with the gamma emitting radiation devices compared to those treated with PTCA alone.[20] Five year data for either of the beta emitting radiation devices are yet to be presented.

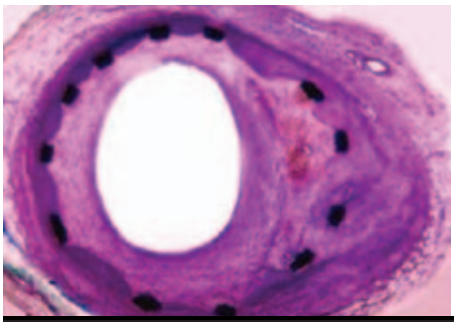


Figure 4 Histological cross-sectional slide of a stented artery demonstrating adequately apposed stent struts with aggressive intimal hyperplasia causing restenosis.[7]

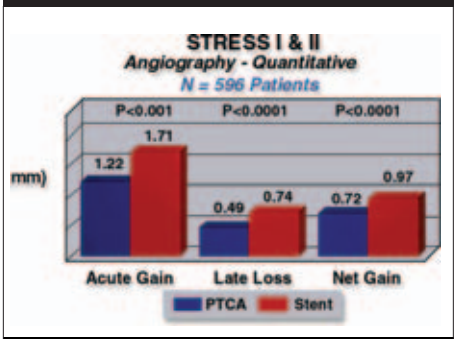


Figure 5 Acute gain, late loss, and net gain in the STRESS I and II trials. This graph demonstrates that despite the increased intimal hyperplasia (late loss) observed with stenting, a net gain is achieved due to the greater acute gain that can be achieved at the time of the PCI.[8]

Numerous pharmacologic approaches that might prevent coronary restenosis have been studied. A noteworthy approach involved tranilast, a smooth muscle cell growth inhibiting drug. Early animal studies demonstrated markedly significant reductions in neointimal hyperplasia.[21] The PRESTO trial was a large multicenter randomized trial designed to study the effect of tranilast on coronary restenosis in humans of which Oklahoma Heart Institute was a major participating study site. Unfortunately, the drug proved to be of no benefit in humans.[22] Another remarkable approach studied involves the use of vitamins B6, B12, and folic acid to reduce coronary restenosis. A preliminary study published in the New England Journal of Medicine revealed a significant reduction in coronary restenosis with the use of the combined vitamins.[23] The study was criticized for its small sample size and post-hoc analysis which revealed a significant benefit only in those patients treated with PTCA alone, and no significant benefit in those patients treated with stents. The FACIT trial, a larger follow-up study published more recently in the New England Journal of Medicine showed no significant benefit with the vitamin combination and actually showed a trend towards increased coronary restenosis in those patients treated with the vitamin combination leading to controversy regarding the use of this approach.[24] Finally, a paradoxical observation is that although HMG coenzyme reductase inhibitors are a critical part of the management of patients with coronary artery disease because of their well proven benefit in reducing major adverse cardiac events, the "statin" drugs do not reduce coronary restenosis.[25]

Drug eluting stents are now recognized as our most dominant weapon in the battle against coronary restenosis. After overcoming the obstacles of conducting a large amount of research with many drugs and polymer coating combinations, two drug eluting stent systems have been approved for clinical use.

The first drug eluting stent to be approved for clinical use was the Cypher sirolimus drug eluting stent manufactured by Cordis. Sirolimus is a natural macrocyclic lactone, derived from the streptomyces fungus. It is a potent immunosuppressive agent that was developed by Wyeth-Ayerst Laboratories and approved by the Food and Drug Administration for the prophylaxis of renal transplant rejection in 1999. Sirolimus binds to an intracellular

receptor protein and elevates p27 levels, which leads to the inhibition of cyclin/cyclin-dependent kinase complexes and, ultimately, induces cell-cycle arrest in the late G1 phase (see figure 6).[26] The SIRIUS trial was the landmark multicenter, randomized trial that enrolled over 1100 patients and documented reductions in coronary restenosis with the use of the sirolimus eluting stent. Nine month in-segment restenosis was significantly reduced from 36.3% in the bare metal stent group to 8.9% in the sirolimus eluting stent group.[28]

The second drug eluting stent system that was approved for clinical use was the Taxus paclitaxel drug eluting stent system manufactured by Boston Scientific. Paclitaxel is a naturally occurring compound derived from the Pacific yew tree with potent antiproliferative effects, thought to be due to inhibition of microtubule formation during the mitotic phase of the cell cycle (see figure 6). The TAXUS IV trial was the landmark multicenter, randomized trial that enrolled over 1300 patients and documented reductions in coronary restenosis with the use of the paclitaxel eluting stent. Nine month in-segment restenosis was significantly reduced from 26.6% in the bare metal stent group to 7.9% in the paclitaxel eluting stent group.[29]

Several new drug eluting stents are undergoing clinical investigation and are expected to be approved for clinical use in the near future. Most noteworthy are the ABT-578 eluting stent which will be manufactured by Medtronic, and the everolimus eluting stent which will be manufactured by Guidant. Both of these drug eluting stents will be available on a more flexible (and hence more deliverable) cobalt-chromium platform. Both ABT-578 and everolimus disrupt the cell cycle at the G1 phase, similar to sirolimus (see figure 6).

Recently, direct comparisons of the sirolimus eluting stent versus the paclitaxel eluting stent have been presented. The REALITY trial randomized 1386 patients with relatively simple coronary lesions from 90 centers in Europe, Asia, and Latin America to either the Cypher sirolimus eluting stent or the Taxus paclitaxel eluting stent. Clinical outcomes were not statistically different between the Cypher- and Taxus-treated patients.[30] The independently funded SIRTAX trial randomized 1005 patients with coronary lesions of varying degrees of complexity to either a Cypher or Taxus stent. Target lesion revascularization was significantly reduced from 8.3% using the Taxus drug eluting stent compared to 4.8% using the Cypher drug eluting stent.[31] ISAR-

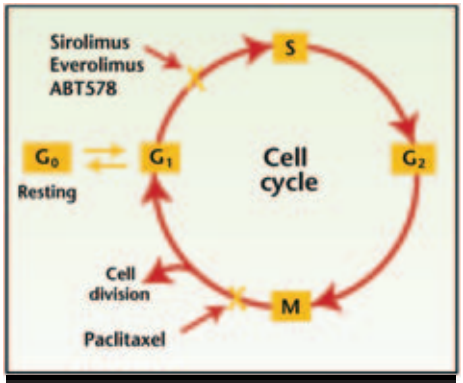


Figure 6 Diagram of the cell cycle and locations that various drugs used in drug eluting stent systems have their inhibitory effects.[27]

DIABETES examined a total of 250 diabetic patients randomized equally to the Cypher or Taxus stent, using a primary end point of angiographic late lumen loss and secondary end points of angiographic restenosis at six months and TLR at nine months. At six months, patients in the Cypher arm of the study had significantly lower rates of angiographic restenosis (16.5% vs. 6.9%).[32] The results of these comparative trials lead this author to conclude that with relatively routine coronary lesions both the Cypher and Taxus drug eluting stents are equally effective. However, in patients with more challenging coronary lesions or a greater clinical risk for coronary restenosis (i.e. patients with diabetes mellitus), the Cypher drug eluting stent may have a small advantage over the Taxus drug eluting stent.

The more durable results achieved with drug eluting stents have prompted investigators to question whether the outcomes achieved with multivessel PCI can rival those observed with coronary artery bypass graft surgery (CABG). The ARTS I trial compared the outcomes of multivessel stenting to CABG in the pre drug eluting stent era. ARTS I showed no significant difference in mortality between the two groups, although there were a significantly greater number of repeat procedures required in the patients undergoing PCI due to restenosis. ARTS II compared a series of patients who underwent multivessel PCI with drug eluting stents to the historical CABG group in ARTS I. ARTS II revealed no significant difference in repeat procedures between the two groups and a trend toward a higher rate of major adverse cardiac events in the CABG group. These data are motivating interventional cardiologists to recommend multivessel PCI with drug eluting stents rather than CABG in patients who are appropriate candidates for either approach.[33]

As of yet, limited data exist for the more challenging lesion subsets encountered in PCI. These challenging categories include unprotected left main disease, saphenous vein bypass grafts, bifurcation lesions, chronic total occlusions, restenotic lesions, and acute ST elevation myocardial infarctions. Small, and in some cases non-randomized data collected in these types of patients are intriguing. Oklahoma Heart Institute is committed to playing an active role in this area by participating in multicenter trials designed to acquire the data needed to better understand how to best manage such complex patients. As drug eluting stent technology advances, and the interventional cardiologist's experience with these difficult lesions broadens, we may be able to achieve a sustained, and universal benefit in a broad variety of challenging lesions.

(Dr. Chandwaney is an interventional cardiologist with Oklahoma Heart Institute, with expertise in cardiac catheterization, coronary angioplasty and related interventional procedures such as coronary stents, atherectomy, intravascular ultrasound and peripheral vascular interventional procedures.)

References

1. Gruentzig A. Am Heart J. 1982;103:779–783.
2. King SB, III, Meier B. Circulation 2000; 102: IV81-86.
3. Image from slide collection at HYPERLINK "http://www.tctmd.com" www.tctmd.com.
4. Bailey SR. Cathet Cardiovasc Intervent. 55:265-271, 2002.
5. Serruys P, et al. NEJM. 1994: 331:489-95.
6. Fischman DL, et al. NEJM. 1994. 331:496-501.
7. Image from slide collection at HYPERLINK "http://www.tctmd.com" www.tctmd.com.
8. Wong SC, et al. Circ. 1995. 92: 1-281.
9. Carozza JP, et al. Ann Intern Med. 1993; 118: 344-349.
10. Abizaid A, et al. JACC. 1998; 32: 584-9.
11. Mittal S, et al. Am J Cardiol. 1997; 80:711-5.
12. Mahdi NA, et al. Am J Cardiol. 1998; 82(11):1345-51.
13. Shiran A, et al. Circulation. 1998; 98(3):200-3.
14. Vom Dahl J, et al. Circ. 105(5):583-8, 2002.
15. Giri S, et al. Cathet Cardiovasc Intervent. 2001; 52: 24-34.
16. Mehran R, et al. Amer Heart J. 2001; 141: 610-4.
17. Suzuki T. TCT 2003, September 15-19, 2003; Washington, DC.
18. Albiero R. RESCUT. Transcatheter Cardiovascular Therapeutics 2002.
19. Lowe, et al. JACC. 2002; 39: 183-93.
20. Leon M. TCT 2004 meeting; September 30, 2004; Washington, DC.
21. Ishiwata S, et al. JACC. 2000; 35: 1331-37.
22. Holmes D et al. Presented at the American Heart Association Scientific Sessions. November 12, 2001.
23. Schnyder G, et al. N Engl J Med 2001;345:1593-600.
24. Lange H et al. N Engl J Med 2004; 350:2673-81.
25. Serruys PW, et al. Eur Heart J. 1999; 20: 58-69.
26. Sousa JE, et al. Circulation. 2001;103:192.
27. Rogers CDK. Rev Cardiovasc Med. 2005; 6:S3-S12.
28. Moses JW et al. N Engl J Med 2003; 349:1315-23.
29. Stone GW et al. N Engl J Med 2004; 350:221-231.
30. Morice CM. Presented at ACC 2005, April 2005; Orlando FL.
31. Windecker S. Presented at ACC 2005, April 2005; Orlando FL.
32. Kastrati A. Presented at ACC 2005, April 2005; Orlando FL.
33. Serruys P. TCT 2004 meeting; September 27, 2004; Washington, DC.

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