A 32-YEAR-OLD WOMAN SUDDENLY became aphasic while speaking on the phone. She was fully alert and had no weakness, sensory deficit or headache. The aphasia resolved fully within 15 minutes. She has never had a similar episode. She had no prior history of migraine headache, thromboembolism, palpitations or cardiac disease. An MRI of the brain with diffusion-weighted imaging demonstrated a small acute infarct in the left frontal lobe. Magnetic resonance angiography of the brain and neck was normal. A transesophageal echocardiogram showed a structurally normal heart with the exception of a patent foramen ovale. How should she be managed?

A CONGENITAL CONDITION

During fetal development, the foramen ovale is a physiologic conduit for shunting blood from the right to the left atrium, thereby bypassing pulmonary circulation. At birth, the shift to lower right than left atrial pressure closes a flap valve consisting of overlapping layers of the septae primum and secundum. In most people, these layers then fuse, creating a complete partition between the atria. However, in about one-fourth of the population, this potential interatrial communication persists throughout life—the patent foramen ovale, or PFO.

The vast majority of people with PFO will never have an associated symptom. However, not all PFOs are benign. PFO has clearly been implicated in the pathogenesis of some ischemic strokes and other arterial thromboembolic events. In platypnea-orthodeoxia, a rare syndrome, it produces substantial arterial hypoxemia upon standing. More commonly, right to left atrial shunting through a PFO can potentiate hypoxemia in the setting of pulmonary hypertension. Some data suggest a potential contribution of PFO to migraine headaches and decompression illness in scuba divers.

CRYPTOGENIC STROKE

Three-quarters of a million people in the United States suffer from stroke each year. Even after extensive evaluation, about 16 percent remain unexplained. Among patients with cryptogenic stroke, the prevalence of PFO is about 40 to 50 percent, twice that of the general population. In some of these, the PFO is clearly contributory. In a few patients with acute stroke, echocardiography has demonstrated a large thrombus in transit across the PFO. Based on this observation, researchers hypothesize that many cryptogenic strokes are caused by small emboli that travel across a PFO into the left atrium and then travel to the brain.

A presumption of this hypothesis is that the stroke is preceded by deep vein thrombosis (DVT). Though most...
Innovations in Cardiovascular Care

I CAN’T BELIEVE THIS IS THE FOURTH ISSUE OF The Sanger Report. This will conclude our first year of publication and complete Volume 1. This issue features three clinical articles.

Continuing our focus on adult and congenital heart disease, members of our adult cardiology team, William E. Downey, MD, and Sanjay R. Patel, MD, spotlight a condition known as patent foramen ovale (PFO). They review the high prevalence of PFO and the potential medical complications associated with it. They outline the current therapeutic options available to patients, including the risks and benefits of PFO closure.

Geoffrey A. Rose, MD, director of Sanger Heart & Vascular Institute’s (SHVI’s) Cardiac Ultrasound Laboratory, details the evolution of echocardiography from single plane M-mode to now 3D and 4D imaging. He also details the utility of these advanced images in preoperative assessment of patients and intraoperative assessment of surgical success.

Mark K. Reames Sr., MD, a member of the Department of Cardiothoracic and Vascular Surgery, reviews the history of surgery for lung cancer and thoracoscopy. He also reviews the experience with video-assisted thoracic surgery for lung cancer, which has become the treatment of choice for patients with resectable primary lung cancer at SHVI.

We continue to innovate with better diagnostic tools and less-invasive and improved methods to manage both lung and heart disease. I hope you enjoy reading this issue of The Sanger Report.

Sincerely,

Paul G. Colavita, MD, FACC
President
Sanger Heart & Vascular Institute

SANGER HEART & VASCULAR INSTITUTE AWARDS

- Aetna Institutes of Quality Cardiac Rhythm recently designated Carolinas Medical Center (CMC) as an “Institute of Quality” hospital based upon an evaluation of the clinical performance and overall value of the facility. CMC is now listed as a participating facility in the Aetna Institutes of Quality Cardiac Rhythm online provider directory.

- Sangeev Gulati, MD, recently presented two abstracts at the Heart Failure Society of America meeting in San Diego: “Relationship Between Intrathoracic Impedance, BNP and 6-Minute Hall Walk” and “Timecourse of Weight and Intrathoracic Impedance Changes During Volume Overload.” Dr. Gulati specializes in adult cardiology and heart transplantation for Sanger Heart & Vascular Institute (SHVI) at CMC in Charlotte.

- B. Hadley Wilson, MD, presented a lecture at a recent Transcatheter Cardiovascular Therapeutics meeting entitled “Enhancing Outcomes in Acute Myocardial Infarction: The Systems Approach.” Dr. Wilson also co-authored a paper entitled “Improved Late Clinical Safety with Zotarolimus-Eluting Stents Compared with Paclitaxel-Eluting Stents in Patients with De Novo Coronary Lesions: Three Year Follow-up from the ENDEAVOR IV Trial,” which was published in the Journal of the American College of Cardiology: Cardiovascular Interventions.


- Francis Robicsek, MD, and Michael Rinaldi, MD, represented SHVI at the South Atlantic Cardiovascular Society meeting presenting cases related to avoidance of litigation and STEMI, respectively.

- Congratulations to Rohit Mehta, MD, who was selected as a Fellow of the Heart Rhythm Society.
3D and 4D Echocardiography: Further Revolutionizing Cardiac Imaging

Geoffrey A. Rose, MD, FACC, FASE
Director, Cardiac Ultrasound Laboratory

SINCE ITS INTRODUCTION, THE use of cardiac ultrasound (also known as echocardiography) has consistently advanced the care for patients with cardiovascular disease. In the 1950s, Dr. Inge Edler recognized that high frequency sound waves—at the time a new technology harnessed to identify structural defects in the steel of ships—could be applied to study cardiac motion in real time. From this key insight, a cycle of technical and clinical innovation emerged. As newer imaging data were integrated into clinical decision-making, these now more complicated decision pathways spurred development of more sophisticated imaging techniques. The incremental information thus gained in turn served to further advance those clinical care algorithms. This concept can be illustrated by reviewing how mitral valve prolapse (MVP), a common cardiac condition, has been approached over time, leading to its contemporary evaluation using 3D and 4D techniques.

“The ability to obtain images with this degree of anatomic detail has further transformed assessment of patients with mitral valve disease.”

A CHANGING TECHNOLOGY
Displaying a single ultrasound scanline over time created the first echo images. This was known as M-mode imaging (with “M” signifying motion), and it provided the first noninvasive means to identify MVP (see Figure 1) as well as many other cardiac conditions. Although quite simple by today’s standards, M-mode echo nevertheless represented a true breakthrough. It became possible to validate and quantify those clinical impressions formulated from the history and physical examination (soft data) by an external frame of reference (hard data). For clinical medicine, this was nothing short of revolutionary. However, the shortcomings inherent in using a one-dimensional modality to evaluate a 3D object (i.e., the beating heart) were readily apparent. The cycle of innovation began.

Two-dimensional echo was the result of those innovative efforts. Figure 2 demonstrates an example of MVP using 2D echo; this is the same patient as in Figure 1. In the 2D image, cardiac structure is represented in a manner more intuitive than its M-mode counterpart. The image is easier for the clinician to comprehend, thus leading to greater understanding of the nature of the underlying disorder. In the case of MVP, such insights from 2D imaging led to pioneering efforts to repair damaged valves, rather than replacing such valves with a prosthesis. This noninvasive technology enabled clinicians to obtain information about a patient’s heart without use of radiation and at the bedside, which propelled its broader clinical application.

Continued on page 8
FOR DECADES, THE SURGICAL REMOVAL of early stage primary lung cancer has made a substantial improvement in patients’ long-term survival compared to other treatment modalities, including radiation and chemotherapy. To optimize a patient’s survival, surgeons must perform an anatomical resection to prevent clinically significant recurrence of the tumor within the lobe of origin. Simple removal of the nodule and a normal margin of lung parenchyma (wedge resection), while useful in situations of pulmonary function inadequate to tolerate an entire pulmonary lobectomy, creates an environment in which local tumor recurrence may be as high as 20 percent. Therefore the recommended standard of surgical care for early stage lung cancer is pulmonary lobectomy or pneumonectomy in the case of very proximal bronchogenic tumors.

THORACOTOMY

Historically, these procedures have been performed through a thoracotomy incision. This type of incision causes a great deal of trauma to the chest wall, secondary to division of the latissimus dorsi and serratus anterior muscles, and retraction with or without resection of one of the ribs to achieve exposure to the lung and its vascular and bronchogenic structures. Thoracotomy creates a great deal of patient discomfort, making proper pulmonary toilet, including coughing and deep breathing with clearing of pulmonary secretions, quite difficult in the postoperative period. In these situations, the risk of respiratory failure requiring reintubation, pneumonia and even death may be substantial. Mortality associated with a thoracotomy and lobectomy is approximately 3 to 4 percent. The respiratory failure rate requiring reintubation is between 10 and 15 percent.

THORACOSCOPY

Fortunately, thoracoscopy or video-assisted thoracic surgery (VATS) has progressed to a point where lobectomy can be performed as a reasonable treatment for early stage lung cancer. Thoracoscopy was developed by Swedish internist Hans Christian Jacobaeus, MD, in 1910, to treat tuberculosis. It was used extensively in Europe for the treatment of mycobacterial infections. However, its use diminished quite sharply with the development of antituberculous drugs and antibiotic therapy in the 1950s.

There was a resurgence of the technique in the 1970s when the need for pleural biopsy made the technique more popular. More complex surgeries using the thoracoscope began around 2000, including anatomical lung cancer resections as well as esophagogastrectomies. The thoracoscopic lobectomy was performed first by Robert J. McKenna Jr., MD, in 1996 and was popularized by Ralph J. Lewis, MD, and Robert J. Caccavale, MD, with the advancement of thoracoscopic stapling devices.

IMPROVED SURVIVAL

Currently, approximately 5 percent of the lung cancer programs in the United States and Europe use VATS lobectomy as a significant treatment modality for lung cancer. The data show that anatomical VATS resections have an improved survival over that of anatomical resections done via thoracotomy. It’s important to recognize, however, that in order to achieve these results, true anatomical resections, which remove the entire parenchymal basin of the involved pulmonary lobe and thus require individual division of the bronchus, pulmonary vein and pulmonary arteries at their origins, must be performed in order to achieve the lower rates of cancer recurrence that are seen with complete lobectomy. This is in contradistinction to a generous wedge resection, which includes mass ligature or stapling of the pulmonary parenchyma, bronchus, arteries and vein using more advanced stapling devices. Wedge resection leaves pulmonary parenchyma and node-bearing tissue behind, increasing the probability of cancer recurrence.

“Currently, approximately 5 percent of the lung cancer programs in the United States and Europe use VATS lobectomy as a significant treatment modality for lung cancer.”

Surgical Options for Patients Who Have Lung Cancer

Mark K. Reames Sr., MD, FACS
Cardiothoracic Surgeon

For decades, the surgical removal of early stage primary lung cancer has made a substantial improvement in patients’ long-term survival compared to other treatment modalities, including radiation and chemotherapy. To optimize a patient’s survival, surgeons must perform an anatomical resection to prevent clinically significant recurrence of the tumor within the lobe of origin. Simple removal of the nodule and a normal margin of lung parenchyma (wedge resection), while useful in situations of pulmonary function inadequate to tolerate an entire pulmonary lobectomy, creates an environment in which local tumor recurrence may be as high as 20 percent. Therefore the recommended standard of surgical care for early stage lung cancer is pulmonary lobectomy or pneumonectomy in the case of very proximal bronchogenic tumors.

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Physicians at Sanger Heart & Vascular Institute have extensive experience with pulmonary lobectomy using VATS. We use a thoracoscopic approach in more than 95 percent of patients who are considered to be candidates for lung cancer resection. Currently, we have performed 180 VATS procedures in a three-and-a-half-year period, achieving a mortality rate of 0.55 percent. Our respiratory failure requiring reintubation rate is 1.1 percent.

In my opinion, thoracoscopic lobectomy versus thoracotomy is the treatment of choice for patients with resectable primary lung cancer. Some of the major benefits include:

- a shorter hospital stay (an average of 3 days with thoracoscopy vs. an average of 8 days with thoracotomy)
- lower respiratory failure rates and mortality rates (0.55 percent with thoracoscopy vs. 3 to 4 percent with thoracotomy)
- faster convalescence (4 to 5 weeks with thoracoscopy vs. 2 to 3 months with thoracotomy)

For more information, to refer a patient or for clinical questions, call 877-999-SHVI (7484).
patients with cryptogenic stroke don’t have an obvious venous thrombus, we may not look hard enough. When venography was used to systematically investigate the legs of 42 patients with arterial embolism and PFO, DVT was found in 24 patients. In 13 of these patients, DVT was found only in the calf veins and would likely have been missed with conventional investigation.\(^1\) In another study using MR venography, pelvic vein thrombi were found in 20 percent of patients with cryptogenic stroke and PFO.\(^2\)

So what’s the risk of a recurrent neurologic event, and how can we reduce it? No data exist on the risk of recurrence without any therapy. Among 943 patients treated with aspirin or warfarin after cryptogenic stroke in the presence of PFO, the annual risk of stroke was 2 percent; death 0.9 percent; and transient ischemic attack (TIA) 2.2 percent.\(^3\) In another study of 581 patients with PFO and cryptogenic stroke, the risk of recurrent stroke or TIA at four years was 4 percent in patients with no PFO; 2 percent in patients with PFO alone; and 15 percent in patients with PFO and atrial septal aneurysm.\(^4\) However, not all PFOs are the same. Some appear to cause a higher risk of first and subsequent stroke than others. In addition to the prominently increased risk conferred by atrial septal aneurysm, other potential factors increasing the risk of a recurrent neurologic event include:

- larger PFOs
- spontaneous right-to-left shunting
- prominent eustachian valves
- a hypercoagulable state

It’s unclear whether warfarin has any therapeutic benefit over aspirin. Several studies have suggested trends toward benefit with warfarin, but no strong conclusions can be drawn.

Though no devices are currently approved for PFO closure in the United States, percutaneous device closure of PFO has risen in prominence as an alternative to medical therapy after cryptogenic stroke. The two most commonly used devices are the AMPLATZER\textsuperscript{c} cribriform and the GORE HELEX\textsuperscript{TM} septal occluders. These devices use a metallic scaffold to position fabric on both sides of the atrial septum to occlude the PFO. They are effective in closing the defect, with more than 95 percent of newer devices achieving complete closure. This can be done safely: In a report of 1,970 closures, there were no strokes and TIA occurred in 0.2 percent; tamponade in 0.3 percent; and access-site problems in 1.5 percent.

However, it’s far from clear that device closure reduces the risk of recurrent stroke. Observational studies have suggested some therapeutic benefit. Among 1,430 patients undergoing closure, the annual risk of recurrent stroke was 0.19 percent and TIA was 1.5 percent, comparing favorably with 2 percent for each with medical therapy.\(^1\) While these data are promising, they’re potentially confounded by placebo effects, selection bias and the absence of independently adjudicated outcomes. Results of the first randomized trial in the field were presented at the American Heart Association meeting in November. The CLOSURE-I trial randomized 909 patients with cryptogenic stroke...
or TIA in the setting of PFO to medical therapy (aspirin or warfarin) or PFO closure using the STARFlex device plus medical therapy. Seventy-two percent of patients were enrolled on the basis of a stroke. Closure of the PFO did not reduce the primary endpoint of recurrent stroke or TIA at 2 years with recurrent strokes occurring in 3.1 percent of the closure patients and 3.4 percent of the medically treated patients. Similarly, recurrent TIA occurred in 3.3 percent of the STARFlex patients and 4.6 percent of the medically treated patients. These results were substantially affected by device- and procedure-related events with three of the 12 strokes in the closure arm being directly related to the procedure and another two being due to late atrial fibrillation that was likely due to the device.

Whether these data apply to other closure devices isn’t known. Prior data has suggested a substantially higher incidence of device-related thrombus with the STARFlex device than with the AMPLATZER and GORE HELEX devices. Thus, it’s not clear that this negative trial applies beyond this device. In an effort to clarify the field, three randomized trials are ongoing:

- **RESPECT (AMPLATZER PFO Occluder)**
- **PC-Trial (AMPLATZER PFO Occluder)**
- **REDUCE (GORE HELEX)**

### MIGRAINE HEADACHES

Migraine headaches affect approximately 27 million people in the United States. Observational studies have demonstrated PFO in about 50 percent of patients who have migraines with aura. This led to the theory that substances such as serotonin and micro-emboli bypass the pulmonary circulation and reach the central nervous system via the PFO. Several non-randomized studies have suggested significant improvement in migraine frequency in patients undergoing PFO or atrial septal defect closure for cryptogenic stroke. In contrast, the only prospective randomized control trial, Migraine Intervention with STARFlex Technology (MIST), found no benefit of PFO device closure in patients who have migraines. Several industry-sponsored studies of PFO closure to treat migraine are ongoing. In the interim, current evidence doesn’t support closing PFOs as a treatment for migraine.

### HYPOXIA SYNDROMES

Usually, interatrial communications do not produce hypoxia because left atrial pressure is greater than right. However, in the setting of pulmonary hypertension, right atrial pressure may exceed left, driving some desaturated blood from the venous system into the left atrium and thereby exacerbating hypoxia. Usually, this exacerbation is minimal. However, occasionally it can be substantial and improved with PFO closure.

More rarely, hypoxia due to right to left interatrial shunting can occur despite normal atrial pressures. The platypnea-orthodeoxia syndrome is dyspnea and arterial desaturation that occur in the upright position but improve with recumbency. In this rare syndrome, some anatomic abnormality (commonly a persistent eustachian valve) directs flow across the septum in a manner that is exacerbated by standing. Physicians can diagnose this condition by performing echocardiography on a tilt table and thereby demonstrating postural augmentation of an interatrial shunt in the upright position. In these cases, closure of the PFO or atrial septal defect is curative.

### SO, HOW SHOULD WE MANAGE OUR PATIENT?

The patient has had a single cryptogenic stroke in which the PFO may be contributory. Further studies should include an evaluation for hypercoagulability. Transesophageal echocardiography should be done to assess for atrial septal aneurysm and atrial pathology and exclude other potential sources of cardioembolic events. Therapy should include aspirin with consideration given to three months of warfarin, even if the hypercoagulability evaluation is unrevealing. The optimal strategy for prevention of recurrent neurologic events is unknown and requires completion of randomized control trials.

Physicians should tell the patient that they don’t know whether the risks of closing her PFO outweigh the benefits. She should be informed of the ongoing randomized trials of PFO closure and be offered the opportunity to participate. If she isn’t interested in participating in one of the trials, medical therapy should be recommended.

For more information or to schedule an appointment, call 877-999-SHVI (7484) or visit www.sangerheart.org.

### REFERENCES:


3D and 4D Echocardiography

Continued from page 3

A SUPERIOR DIAGNOSTIC TOOL

Despite the advantage of 2D imaging beyond that achieved by M-mode imaging, there remain clinical questions that are only best understood through examination of 3D images. (As mentioned, the heart is a complex 3D object.) Consider mitral valve repair. Figure 3 demonstrates a 3D image of the mitral valve (same patient as in Figures 1 and 2). The mitral valve is presented from the surgical perspective, i.e., it’s oriented to correspond to the view of the valve that the surgeon has during open-heart surgery. The ability to obtain images with this degree of anatomic detail has further transformed assessment of patients with mitral valve disease. At Sanger Heart & Vascular Institute (SHVI), preoperative determination of the feasibility of percutaneous or surgical repair using 3D echo and 4D echo (3D imaging in real time) has become our standard approach. The ability to have cardiologists and surgeons “speak the same language” by having image data displayed in an easily recognizable format has been a key driver of our highly successful mitral surgical repair rate of more than 90 percent.

Nationally, the estimated rate of mitral valve repair is less than 70 percent; higher rates of valve repair denote greater programmatic expertise.

In addition to providing exquisite but nevertheless qualitative anatomic information, the capability to derive detailed quantitative 3D data has become available (see Figure 4). Mitral leaflet height and length can be precisely measured, as well as sizing of the annular dimensions. This provides for greater operative planning, which promises to further shorten operative times and improve repair results.

THE FUTURE OF IMAGING

Where do we go from here? 3D/4D echo techniques are just beginning to enter the clinical arena of day-to-day care. The ability of these approaches to provide quantifiable data is just developing. Many other conditions, such as hypertrophic cardiomyopathy (see Figure 5), are best evaluated in the 3D/4D domain. But just as 2D imaging supplanted our reliance on M-mode, it appears to be a matter of time before 3D/4D imaging moves to the forefront of noninvasive imaging. The Imaging Group at SHVI is working to lead this advance.

For more information about our cardiac imaging services, call 704-373-0212.