Pulmonary Embolism: Interventional Therapies for Massive and Submassive Emboli

By Eric Thomassée, M.D., and Pete Fong, M.D.

Venous thromboembolism (VTE) accounts for more than 250,000 hospital admissions annually in the United States. The most devastating immediate complication of VTE is acute pulmonary embolism (PE). The great majority of PEs result from deep venous thrombosis (DVT) which dislodge from the lower extremities and travel into the pulmonary circulation. Eighty percent of patients with PE will have a DVT on lower extremity imaging. Fifty percent of patients with proximal DVT will develop PE.2-4

The clinical significance of PE is largely determined by the size of the embolism. Small emboli may cause minimal to no symptoms. Submassive PE is a large PE without hemodynamic compromise but with evidence of right ventricular (RV) dysfunction or myonecrosis. Massive PE is defined as a large PE with hemodynamic compromise (systolic blood pressure <90 mmHg for >15 minutes or requirement of inotropic support).5

Hemodynamic instability occurs when RV afterload increases to the point of decreasing forward flow and LV preload. The result is significant systemic hypotension.

Risk factors for development of pulmonary embolism are largely related to formation of the antecedent venous thrombus. These factors include vein trauma, immobility resulting in venous stasis, acquired factors which increase coagulation and hereditary factors. Acquired factors include cancer, estrogen use, smoking, pregnancy, acute medical illness, obesity and major surgery. Hereditary factors include Factor V Leiden mutation, Protein C deficiency, Protein S deficiency, anti-thrombin deficiency and prothrombin gene mutation, along with others.6

Thromboembolic disease is suspected in the presence of signs and symptoms such as leg pain, unilateral leg swelling, chest pain, dyspnea, hemoptysis, hypoxia, respiratory distress, tachy-arrhythmias, lightheadedness, syncope and hypotension. Diagnosis is confirmed with use of multiple imaging modalities. CT pulmonary angiography can be obtained rapidly and has 83% sensitivity in detecting PEs with a 95% specificity.7 Other imaging modalities include ventilation-perfusion imaging (V/Q scan), magnetic resonance angiography (MRA), echocardiogram and conventional pulmonary angiogram. Detection of lower extremity DVTs with use of ultrasonography or CT venography can also help support the diagnosis of PE.

Treatment options are based on clot destruction/removal with use of anti-coagulants, thrombolytics, catheter-directed therapies (CDT) and/or surgical intervention.

Treatment options are based on clot destruction/removal with use of anti-coagulants, thrombolytics, catheter-directed therapies (CDT) and/or surgical intervention.

At Vanderbilt, we consider emergent surgical embolectomy for massive central PE with (Continued on page 3)
Editorial

By Robert N. Piana, M.D., Editor, Vanderbilt Heart, and Quinn Wells, M.D., Associate Editor

This issue of Vanderbilt Heart is dedicated to Gottlieb C. “Bud” Friesinger II, M.D. Chief of the Division of Cardiovascular Medicine from 1971-1990, Bud remained an incredibly vigorous member of the division up until his death on July 28. We have all benefited from this man of substance with a truly uncanny knack for keen observation, and an unparalleled ability to bridge generations to inspire multiple emerging leaders in cardiology. Bud would certainly revel in the ongoing work of Susan Bell and Jen Giuseffi in the field of geriatric cardiology presented here, as he saw this as one of the new frontiers of clinical medicine. Similarly, he would enjoy providing an objective assessment of proposed innovations to aortic aneurysm surgery and novel approaches to the treatment of pulmonary embolism as presented in this issue. While Bud’s legacy remains very vibrant with all of us, some, like John “Dick” Dixon, M.D., have a unique perspective based on decades of collaboration with Bud.

We hope you will appreciate Dick’s remembrance. Most importantly, Bud would always look forward, and he would be extremely confident in the future of Vanderbilt Heart under the direction of the current inspired leadership that he helped mold.
severe hemodynamic compromise. On the other end of the spectrum, stable patients with small PE may be treated with anticoagulation therapy alone. For many patients with submassive or massive PE we also consider thrombolytic therapy and CDT, an approach addressed in the updated 2011 American Heart Association guidelines as well as a more recent review article by Sobieszczyk in the Oct. 8, 2012, issue of Circulation.5,12 Randomized controlled trials have shown benefit of thrombolytic therapy in both submassive and massive PE with reduction in rates of clinical deterioration with less need to escalate supportive therapies (e.g., intubation, secondary thrombolysis, catecholamine infusion, cardiopulmonary resuscication, or emergent surgical embolectomy/thrombus fragmentation).7-8 Subgroup analysis of a large meta-analysis demonstrates that hemodynamically unstable patients benefit from thrombolytic therapy with a decrease in mortality rate from 12.7% to 6.2%.9

CDT for submassive and massive PE is now offered at Vanderbilt University Medical Center. In CDT thrombolytic is delivered directly onto the clot. Certain CDT devices allow for both medication delivery and ultrasound-accelerated thrombolysis. Ultrasound-accelerated thrombolysis utilizes ultrasound waves emanating from a catheter placed into the pulmonary arteries to dissociate fibrin and allow penetration of the thrombolytic agent. This strategy is designed to decrease systemic thrombolytic doses by 50%-70% thereby decreasing major bleeding events. In one small retrospective analysis of patients treated for massive PE, ultrasound-accelerated thrombolysis achieved higher rates of complete thrombus removal when compared to standard CDT thrombolysis.10

Other considerations during treatment of venous thromboembolism include the placement and removal of IVC filters. Indications for IVC filter placement include large lower extremity clot burden with poor cardiopulmonary reserve, contraindication to anticoagulation therapy, and/or recurrent embolic events while on anticoagulation. Once the patient with PE is stabilized and treated, we can extend our therapies to include catheter directed treatment of large ilio-femoral DVT to prevent post thrombotic syndrome, venous claudication, and recurrent PE. Catheter directed therapies for large ilio-femoral DVT include ultrasound-assisted thrombolysis and rheolytic thrombectomy with pulse (Continued on page 12)
Gottlieb C. (Bud) Friesinger II, M.D.

By John “Dick” Dixon, M.D.

A man of many parts – husband, father, grandfather, physician-scientist, mentor, philosopher – Gottlieb C. (Bud) Friesinger II, M.D., is profoundly missed. A gridiron lineman (Muskingum College) and U. S. Marine in his formative years, he exemplified mental and physical toughness as ingredients to unselfish responsibility and teamwork. In his later years, he personified his often-quoted “One-Hoss Shay” (O. W. Holmes) with his ageless determination to bless subsequent generations by helping them reach their intended destinations.

His help on any project exposed his unusual capacity for tenacious concentration. Bud was charismatic, highly intelligent, respectful and engaging, and he was always learning by continuously gathering material by note-taking in presentations and the daily consumption of The New York Times, The Wall Street Journal and The Tennessean. His love for vigorous discussion of timely subjects produced unique relationships with many physicians who eagerly anticipated encountering him at the lunch table.

Cardiovascular Grand Rounds and weekly clinical management sessions will survive, but they may never be the same with that empty seat up front. Speakers found great value in conversing with Bud following their presentation; though sometimes feeling exposed or flabbergasted, they would nevertheless find their message fortified and improved by his candid advice. He was a Jedi of the English language, often using Shakespeare or the Holy Bible like a light sabre to make his point. He was the only one among us using words like “dazzling” and phrases such as “in das Augenblick!” to vividly clarify concepts. His encyclopedic knowledge of contemporary and historical athletic information allowed for fascinating metaphorical parallels between sports figures and medical subjects. For example, he drew similarities between the rhythm of DiMaggio’s hitting streak and proper pharmaceutical usage, and between marathon running and complex left ventricular pressure-volume loops.

Only when directly provoked did he yield and talk about his personal participation in the first successful human defibrillation (1957), or his seminal description with E. Page and R. Ross of the prognostic influence of coronary disease via angiography (1970). He deemed as a privilege the following special commitments to excellence: his formative work in our own division at Vanderbilt, his consultative work with the NIH, his master level fellowships in the American College of Physicians and American College of Cardiology, his service as a Trustee and on the Presidential Council at Johns Hopkins University, his books and individual book chapters, and his participation on significant editorial boards of peer-reviewed journals and more than 100 original publications.

Bud’s roots in tradition provided a strong foundation of knowledge, but a passion for seeking truth allowed for flexibility and room for new ideas. Reared in an era when there were few women and no minorities in academic medicine, he set out to change that
landscape. He also championed the responsibility of resource stewardship, and two of his treatment principles were “a tincture of time,” and “skillful neglect.” A distinct interest of his was the waning art of prognosis (and, in the end, he brushed aside the reassurances of his physicians).

If Bud ever harbored pessimistic thoughts, these were exposed to no one outside a small intimate circle. His were strong political beliefs, and yet still I cannot be sure how he would vote. That was his mystique; he was never ambiguous, rarely indecisive, but always cognizant of the immense shadow he could cast if he were to express a strong opinion. He preferred instead to teach others to think for themselves and carry out their decisions with equanimity. In speaking with other faculty, I am told he was “noble but not proud,” “polite but never excessively so,” “virtuous without severity,” and “completely generous with himself.”

To name his many significant disciples would lead to overlooking someone. Many faculty and former fellows could have provided this essay, such as Doug Sawyer, Rose Marie Robertson, Ben Byrd, David Hansen, Francisco Albornoz, and Mike Baker. Asked to comment, Marvin Kronenberg said, “I benefited from watching his extraordinary methods of organization and planning, and from seeing his general approach to life. Bud was a role model in life.” Susan Bell remarked, “Dr. Friesinger took his job as mentor very seriously. There he was, every time I gave a presentation, sitting in the front row with his pen poised to take notes, and days later we would meet over coffee and he would pull out a printed copy of my slides with notes all over them! He was also a personal support. After the birth of my twin sons, the first thing he wanted to do was come to our home and meet them.”

Time will not permit all the stories I have heard from many such as Allen Kaiser who was an Osler intern at Hopkins as Bud materialized during morning rounds to demonstrate echocardiography to him, or Andy Spickard, who told of Bud and Jan’s loving guidance to Andy and Sue when they moved from Vanderbilt to Baltimore in the ’60s. Upon successfully recruiting him to Vanderbilt in 1969, Elliot Newman was quoted by his son, John Newman (then a college student), as gleefully exclaiming, “I’ve just hired the best young cardiologist in America!”

And now, we can still hear our beloved professor quoting Holmes’ “One-Hoss Shay” regarding his favored subject of aging:

In fact, there’s nothing that keeps its youth,
So far as I know, but a tree and the truth.
You see, of course, if you’re not a dunce,
How it went to pieces all at once,
All at once, and nothing first—
Just as bubbles when they burst.

It is in this fashion that a reliable, ever-evolving, self-refining bastion of modern science and medical philosophy suddenly became an honored legacy.

The measure of the greatness of a man is how he is missed. Bud, we miss you.
Management of Aortic Arch Aneurysms: Evolving Approaches to Optimize Clinical Outcomes

By Rashid Ahmad, M.D.

In the Fall 2008 issue of Vanderbilt Heart, John Byrne, M.D., and Michael Petracek, M.D., discussed approaches for management of the dilated aortic root and the ascending aorta. This article will focus on aneurysms involving the ascending aorta and aortic arch with extension into the thoracic descending aorta.

Aneurysms of the thoracic ascending aorta and arch can lead to life-threatening risks of dissection, rupture and death. Both the cumulative and yearly risk of aortic dissection and rupture increase with aneurysm size. The risk of rupture, dissection or death rises from 5% for aortic sizes of 4.0 – 4.9 cm to 14% when the aorta exceeds 6.0 cm.¹ (Figure 1) In asymptomatic patients, current guidelines² recommend evaluation for surgical repair of an ascending aortic aneurysm for:

• Diameter ≥5.5 cm.
• Diameter ≥4-5 cm in the setting of Marfan’s disease, bicuspid valve, Ehlers Danlos, Turner’s syndrome, or familial aortic aneurysm/dissection.
• Aortic growth rate >0.5 cm/year
• Diameter ≥4.5 cm in those undergoing aortic valve replacement.

Surgical options for aneurysms of the ascending aorta include: (A) graft replacement of the ascending aorta beginning above the sinotubular junction, shown with hemi-arch replacement distally; (B) separate valve and graft replacement; (C) composite root replacement with a mechanical prosthesis, although a biological root prosthesis can be substituted; and (D) a valve-sparing David re-implantation procedure. (Figure 2)³

Figure 1. Catastrophic Risk incorporates risk of rupture, dissection or death

Figure 2.
Although an absolute number above 5 cm can be utilized for demarcation of an inflection in risk, it is important to recognize that an indexed approach should also be considered that takes into account the patient's height and weight to provide the personalized therapeutic options for the individual patient. It is sobering to note that in one large series the mean aortic size was found to be 4.8 cm at the time of emergent repair of Type A aortic dissection, which is below the 5-6 cm diameter generally used as an indication for elective operation. Moreover, this type of emergent repair carries an operative mortality of 20%. Clearly, there is an imperative to identify patients earlier in their course to facilitate elective repair of the aneurysm before an emergency strikes.

Since the arch gives rise to the carotid arteries, one of the most critical aspects of complex aortic arch surgery is preservation of cerebral perfusion to minimize stroke risk. Historically, the approach was deep hypothermic circulatory arrest with patients being cooled to 18°C for approximately one hour of cerebral protection. Although cooling protected the brain by reducing neural metabolism, the consequences included troublesome coagulopathic bleeding at the end of the case. The next evolution to deep cooling was perfusing retrograde through the superior vena cava, which presumably allowed backward blood flow into the cerebral circulation via veins across capillaries and then into the arteries. Although this approach may help prevent particulate matter and air emboli to the cerebral vessels, there is no data supporting that there is metabolic exchange of oxygen and nutrients by neural tissue.

Further evolution has now led to selective cerebral perfusion of both carotid arteries with special cannulas and monitoring of oxygen levels in both hemispheres of the brain. This strategy requires only moderate hypothermia and the patient is cooled to 25°C. Specialized grafts are available that allow for replacement of the ascending aorta, each of the arch vessels as well as the descending aorta in reduced time.

With improvements in recent technical strategies, this open surgical approach leads to better outcomes, fewer strokes and better survival. At Vanderbilt Heart, patients with minor comorbidities requiring total arch replacement have had successful operations and were discharged to home in less than a week. In well selected patients, the mortality from arch replacement can be as low as 5% - 8%.

When aneurysms involve the aortic arch as well as the descending aorta, arch replacement is done with an "elephant trunk." (Figure 3). The "elephant trunk" is an extension of the arch graft and floats in the descending aorta. The floating graft provides a landing zone for future endovascular stenting or surgical replacement of the descending aorta as a staged operation. (Continued on page 8)
Management of Aortic Arch Aneurysms

(Continued from page 7)

For patients with major co-morbidities an alternative option is hybrid surgery that involves a combination of open debranching of the arch vessels and endovascular exclusion, which eliminates the need for going on cardiopulmonary bypass. This is done by partially clamping the ascending aorta and sewing a specialized patch graft that has limbs for individually replacing the innominate, carotid and subclavian arteries as end-to-end anastomoses. Once this is done, endovascular stenting of the diseased arch/descending aorta is performed through another limb in the patch graft.

In this evolving and complex arena of aortic arch surgery, we recommend referring patients for evaluation in the following circumstances:

- Ascending aorta size ≥ 4.5 cm
- Ascending aorta size ≥ 4.0 cm in patients with connective tissue disorders such as Marfan’s, Loey-Dietz syndrome or bicuspid aortic valve:

Personalized treatment of these patients will include determination of the aortic size index, rate of growth of the aneurysm and timely surgical intervention to avoid the catastrophic outcome of rupture, dissection or death.

REFERENCES
Understanding Cognitive Effects of HMG CoA Reductase Inhibitors

By Jennifer Giuseffi, M.D., and Susan Bell, M.D.

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, commonly referred to as “statins,” are the most frequently prescribed and efficacious agents for the treatment of dyslipidemia.\(^1\) Statins lower low density lipoprotein (LDL) cholesterol and triglycerides (TG’s), while elevating protective high density lipoprotein (HDL), thus retarding the development and progression of coronary artery disease, ischemic cerebrovascular disease and peripheral vascular disease. In general, statins are well tolerated with minimal side effects.\(^3\) The most commonly reported adverse effects include transaminitis, gastrointestinal upset, hepatotoxicity and myopathies. With an aging population, the potential benefits and adverse effects of statin therapy on cognitive function must also be considered. This controversial area has been a focus of media attention in recent years, and merits careful evaluation by clinicians.

Recent observational and retrospective case-control data have suggested a possible benefit of statin therapy on cognitive function. The potential impact of statin use on the development of Alzheimer’s disease was evaluated in the Rotterdam Study. In this prospective, observational study of nearly 7,000 patients in the Netherlands, statin use was associated with a significantly lower incidence of the development of Alzheimer’s disease (HR 0.57 95% CI 0.37 to 0.90), while no benefit was seen with other cholesterol lowering agents.\(^4\) Another small randomized trial has shown benefit of atorvastatin on neurocognitive testing compared to placebo.\(^5\)

Several mechanisms for a cognitive benefit of statins have been suggested. The first is a direct effect of reducing the levels of neurotoxic amyloid proteins whose processing is believed to be, at least in part, cholesterol dependent.\(^6\) The second is an indirect effect of statins related to reduced vascular injury yielding less cerebral hypoperfusion and fewer cerebrovascular events,\(^7\) which is thought to lessen the symptoms of Alzheimer’s disease.\(^8\) It is important to note that the association of statin therapy with a cognitive benefit could also represent an indication bias, in that patients without symptoms of advanced Alzheimer’s disease may be more likely to receive preventive therapies such as statins and antihypertensive medications.

While this potential salutary effect of statins is encouraging, concerns have also been raised that these agents may adversely impact neurocognitive function in some patients. A five-year review of adverse events submitted to the U.S. Food and Drug Administration identified 60 patients who reported short-term memory loss, amnesia and nonspecific memory loss in the setting of statin therapy.\(^9\) This analysis was based on self-reported symptoms without objective neuropsychiatric testing, and the majority of the symptoms resolved with discontinuation of the medication. The majority of these cases were related to therapy with the most lipophilic statin agents, simvastatin and atorvastatin. Following this review,

(Continued on page 10)
two randomized trials looked specifically at the effect of lipophilic statins, simvastatin and lovastatin, on cognitive function. Both of these studies showed only minor decrements in cognitive function.\textsuperscript{10, 11} Perioperative statin therapy has also been implicated as a risk factor for increased postoperative delirium.\textsuperscript{12} However, the presence of atherosclerotic disease in treated individuals may be a confounder in this study.

Potential mechanisms for statin-related cognitive dysfunction could include effects on myelination and oxidative stress. Myelin is composed of cholesterol, and statin therapy may impair myelin formation and function.\textsuperscript{13} Statin therapy also decreases levels of coenzyme-Q10, which is essential for mitochondrial function,\textsuperscript{14} and this may have an indirect effect on cognition.

Randomized control trials now show a neutral effect of statins on cognition. The DALI (Diabetes Atorvastatin Lipid Intervention) study found improvements in verbal memory without any additional effects on cognition.\textsuperscript{15} In the PROSPER study of pravastatin in an elderly population (aged 70 to 82 years), no significant effect of statin therapy on cognitive function was noted.\textsuperscript{16} In the LEADe (Lipitor's Effect in Alzheimer's Dementia) study patients actively being treated for Alzheimer's dementia were randomized to atorvastatin versus placebo for 72 weeks with co-primary endpoint of cognition and general function.\textsuperscript{17} No significant benefit or detriment was noted with statin therapy. A meta-analysis combining patients from PROSPER and those >70 years of age from the Heart Protection Study found no significant effect on the development of Alzheimer's disease or dementia with statin therapy.\textsuperscript{18}

Randomized control trials now show a neutral effect of statins on cognition. The DALI (Diabetes Atorvastatin Lipid Intervention) study found improvements in verbal memory without any additional effects on cognition.\textsuperscript{15} In the PROSPER study of pravastatin in an elderly population (aged 70 to 82 years), no significant effect of statin therapy on cognitive function was noted.\textsuperscript{16} In the LEADe (Lipitor's Effect in Alzheimer's Dementia) study patients actively being treated for Alzheimer's dementia were randomized to atorvastatin versus placebo for 72 weeks with co-primary endpoint of cognition and general function.\textsuperscript{17} No significant benefit or detriment was noted with statin therapy. A meta-analysis combining patients from PROSPER and those >70 years of age from the Heart Protection Study found no significant effect on the development of Alzheimer's disease or dementia with statin therapy.\textsuperscript{18}

In conclusion, the evidence regarding statins' effect on cognition is inconsistent. The reported incidence of cognitive dysfunction related to statin therapy is rare. In contrast, the benefits of statin therapy are potent and clear, reducing adverse cardiovascular events and death. Therefore, statins should not be withheld from elderly patients with potential benefit from this therapy. In treated patients with suspected statin-related memory loss or cognitive dysfunction, the medication should be discontinued. If the drug is implicated based on resolution of symptoms after discontinuation, the level of indication for statin therapy must be considered. If the potential benefit of statin therapy is strong, one could consider changing to a less lipophilic agent, such as pravastatin.\textsuperscript{19} In the event that the memory loss does not resolve with discontinuation, an alternative diagnosis should be pursued and formal neurocognitive testing considered. The current body of evidence is not sufficient to change practice, but should provoke a discussion with patients regarding the risks and benefits of statin therapy to facilitate informed decision making.
REFERENCES


Pulmonary Embolism

(Continued from page 3)

spray technology. The latter therapy uses pressurized saline to inject thrombolytics into the clot and suction the lysed clot particles in the same setting. Finally, stenting of venous lesions has proven beneficial in maintaining venous patency such as is seen in May-Thurner syndrome. 11

Vanderbilt Heart and Vascular Institute has developed a “Level 1” cardiovascular system to facilitate the transfer of massive and submassive PEs from referring hospitals for acute management including systemic thrombolytics, catheter directed therapies and/or surgical thrombectomy. By utilizing the full spectrum of available technologies and working as a multidisciplinary team comprised of cardiothoracic surgery, interventional cardiology and critical care medicine we hope to optimize outcomes in venous thromboembolic disease.

REFERENCES


