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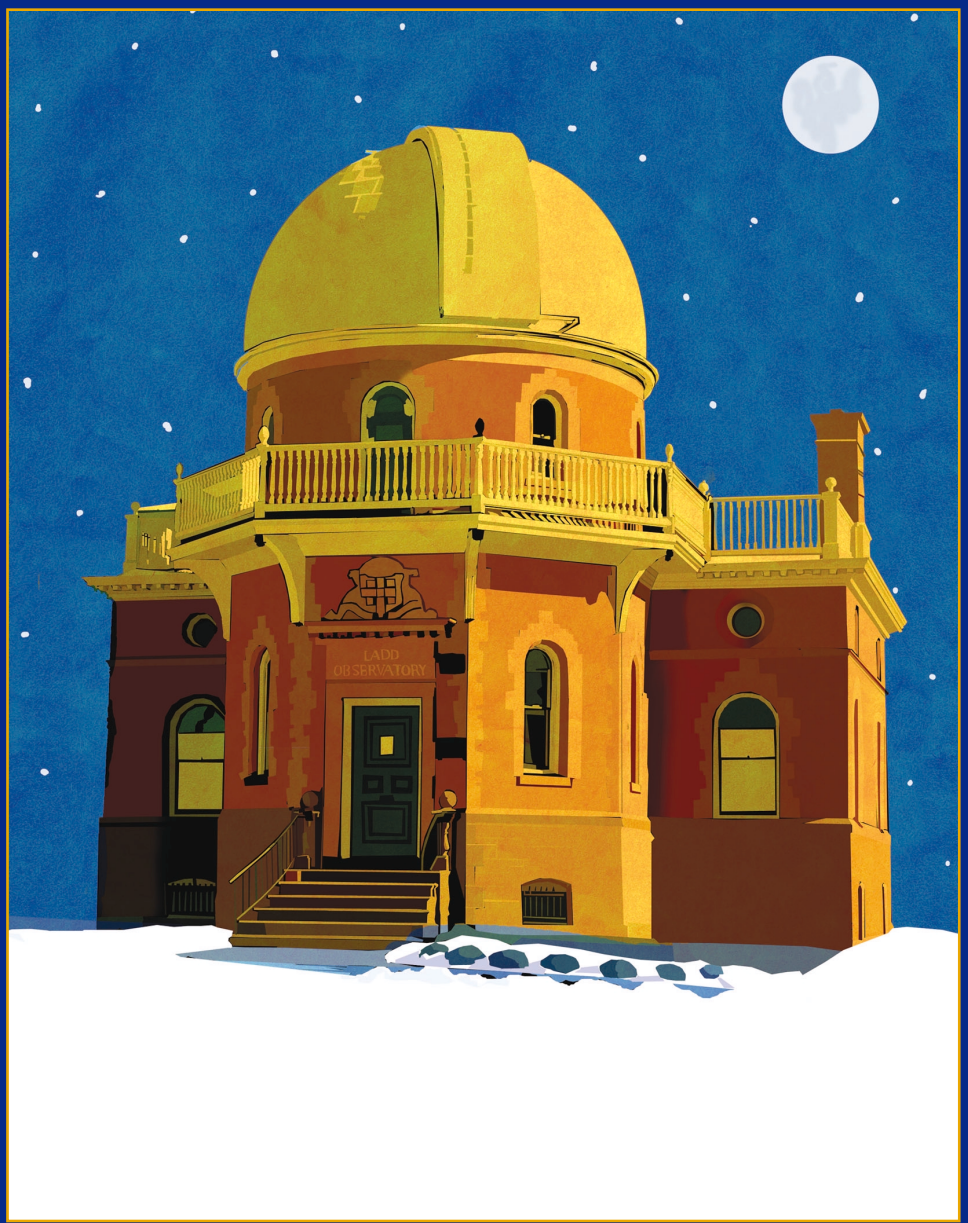

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Commentaries

Dovenning

There is a pejorative term for intellectual time-wasting in Jewish medical circles, called "dovenning," which means "praying while standing and swaying to and fro" in Hebrew. One example would be a protracted discussion on the efficacy of various chemotherapeutic trials on a 95-year old demented person with metastatic cancer. Exercises in verbosity, the showing off of useless knowledge, the recitation of knowledge and the exercise of useless decision-making algorithms when the answer is obvious, without having education as the real motivation.

I read an article recently about an experimental intervention on an animal model of **Huntington's disease (HD)** which made me think that all the seemingly meritorious work that many of us, and I include myself, are involved in trying to develop some treatment for this dread, incurable, inherited disorder represents useless money-wasting, or dovenning. More importantly, this observation applies far and wide, and, to a large degree, we all know it, even if we don't acknowledge it. In this case a drug was given which detoxified the abnormal HD protein. So, instead of figuring out what the protein did, or how to block gene expression, a different approach yielded a great benefit. Will this work in the "real" disease, that is, in humans? It will take time to find out, but the approach is plausible, and could, theoretically prevent disease expression.

The gene for HD has been known for over a decade. It's been expressed in a variety of genetically-engineered rodents who then develop some of the phenotypes of HD along with similar brain pathology. The abnormal protein causes poisoning of the involved brain cells, although how it does so and why it does so only in certain nerve cells and not others, although it is widely expressed, remains unknown. Since the gene abnormality in HD causes a "gain of function" toxic state, rather than a "reduced-function impairment" due to insufficient gene expression, HD can be prevented if the gene expression can be stopped. Through mechanisms related to mRNA interference, chemicals have been developed which stop or reduce expression of the abnormal gene, hence reducing the abnormal gene product, thereby reducing the pathological changes of the disease in the rodent brain. This is clearly how this disease and many, perhaps most, other genetic disorders are going to be halted, hopefully even prevented. Yet we are spending millions of dollars on studies related to incremental advances in disease modification pursuing large, expensive clinical trials testing a drug that may alter mitochondrial function which might be the pathogenetic mechanism but for which there is no direct supportive data. Perhaps we've learned the wrong lesson from cancer trials.

We now devote millions to study how the first symptoms of HD manifest, by studying the children of people with HD; and on studying mitochondrial-boosting drugs (coenzyme Q 10 to be specific) to slow disease progression.

In other neurodegenerative disorders we are making similar investments, often with less scientific rationale, making educated guesses at disease mechanisms to design trials of drugs to alter disease progression, some producing minimal benefits. But we perform other studies of questionable benefit as well. I recently listened to a discussion on weight loss in **Parkinson's disease (PD).** It is common for PD patients to lose weight. For many patients this is not a problem. It becomes easier for them to stand up and walk. It is easier for their spouse to help them get up if they fall. On the other hand it sometimes reinforces a psychological feeling of everything going downhill and it may cause increasing weakness. There are many potential reasons for weight loss: depression, apathy, slowness of chewing and swallowing, dysphagia, dry mouth, loss of olfaction and taste perception, the social difficulties of taking so much longer to eat than others, and likely untold other reasons. Is it important? I think not. In any patient it could be due to any of the explanations, each with a unique profile of the importance of each explanation. I care about my particular patient, because it is important to exclude cancer, diabetes, hyperthyroidism, etc, and to treat depression, but I doubt that figuring out a generic cause for weight loss in PD is of any value. What value will that have?

There is a lot of well done but useless research being published. When reviewers score manuscripts. they grade not only the quality of the work, but also its importance. I think that reviewers are more attuned to grading the quality of the work than its impact. I am not concerned here with reports that have limited relevance. Most doctors are not interested in extremely rare disorders which they will never see or treat, but where the discovery is still relevant. I am more concerned about studies where something is measured that has limited importance. For example, will it matter if weight loss in PD is due to slow eating or early satiety, or reduced interest in food? The bottom line is weight and what can be done to increase it, if it's a problem; and that always calls for more calories unless there is correctable mal-absorption. The increase in intake might occur with richer food, drugs to enhance appetite or foods that are easier to swallow, but we generally approach the problem with all three.

I reported rhinorrhea as a feature of PD. Is it irrelevant, or, as an old college friend would say, "Joseph, Ask me if I care." It does matter, because it is common and patients like to know that it is part of their disease and it saves useless (and expensive) tests and referrals, and is treatable. It also is another, albeit common, premotor sign of PD that may ultimately be used to identify those at risk of developing the motor symptoms of the disease. Although one could argue that, like weight loss, it can be treated without understanding its etiology, it is clear in PD that when neither doctor nor patient recognize it as a part of the disease, it gets neither recognized nor treated. Unless asked about it, the usual inference of a PD doctor to a patient carrying a tissue is that it is used for drooling or tearing, when, in fact, it is for runny nose, unrelated to allergies, in about half the cases. Certainly no one died of rhinorrhea, but quality of life often hinges on non-serious issues, including not being able to eat in public due to a nasal drip.

We need to focus on using our resources wisely. Wasteful clinical projects should not be funded simply to make people with the common diseases feel that they are getting attention. On the other hand the money needs to be used on these diseases, just used more wisely, and not shifted to other areas.

It is good to know things. But some things are more important to know than others, and our exponentially-expanding number of medical papers needs to be contained. There used to be a satirical journal for scientists, *The Journal of Irreproducible Results*. It may be time to establish a number of journals in various medical disciplines, each called, *The Journal of Irrelevant Results.*

– Joseph H. Friedman, MD

Disclosure of Financial Interests

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A Tempered View of Bacteria

The world is a very crowded place. No region is without incredible numbers of living organisms striving to survive, most of them microorganisms such as bacteria. The volume of living matter – the global biomass – amounts to hundreds of billions of tons. And of the countless creature-species constituting this immense mass, the largest contingent is that form of life called the bacteria. Indeed, if all of the global bacteria were gathered in one location and measured, its total biomass would exceed the biomass of any other class of life. Certainly its collective weight would far exceed the gathered weight of all of the world's mammals, including the 6.7 billion humans currently resident in the globe. A conservative estimate argues that over 100 trillion living bacteria reside within the interior of the average adult human being.

The overwhelming majority of those primitive creatures called bacteria eke out a rudimentary existence with neither capacity for, nor thought of, causing disease in humans. There are a rare few bacterial species, pejoratively referred to as germs, that can bestow mortal mischief upon vulnerable humans thus giving a bad name to the entire biological class of bacteria. Most of these one-celled organisms pursue their primordial lives in soil and water; rarely if ever do they interact with humans; and by reducing complex organic chemicals to simpler, more soluble substances, they sustain the world's agriculture with neither ostentation nor complaint. These microbial laborers also populate the human gastrointestinal tract where, in consort with digestive enzymes, they break down ingested foods to more soluble substances such as glucose and amino acids.

Are the majority of bacteria harmless? Perhaps the question should be reworded: Are the majority of bacteria necessary, even vital, for our sustenance, our very survival and indeed, for the survival of the living globe ? The answer is an emphatic yes. (But, of course, that is only a gut reaction.)

Consider now a major form of insect life, the detrivores, those creatures that sustain themselves on a diet of wood and other plant products. There are many in this category including wood lice, earth worms, dung flies, certain beetles, and particularly termites. These invertebrates fulfill a major ecological function in digesting vast amounts of wood and other plant matter and thus contributing materially to the global recycling of organic matter. The social creatures called termites, categorically condemned because of their harm to manmade wooden structures, are nonetheless essential to our global economy. They maintain a symbiotic partnership with anaerobic (oxygen-avoiding) bacteria in their digestive system. They provide an oxygen-poor, protective environment for the bacteria; and these bacteria then generate the enzymes necessary for the termite to decompose wood and other cellulose products into simpler organic nutrients.

A similar synergy exists between the abundant bacteria within the gut of ruminant animals such as cows, deer and camels. Thus an apparently banal diet of hay and grass, with the assistance of this cohort of intestinal bacteria, can be converted into a menu meeting all of the nutrient and micronutrient requirements of these mammalian species.

The human gastrointestinal tract, an uninterrupted thirty foot tube of infinite ingenuity, cannot support the body's dietary needs without the active cooperation of the anaerobic bacteria within its cavity. The gastrointestinal system of the newborn may be free of bacteria, but contact with the exterior soon seeds the small and large intestines with commensal bacteria. By adulthood, the average gut may harbor kilograms of bacteria, most of them sturdily working in behalf of their host-human.

These resident bacteria attack the chemically complex ingredients of the usual human diet, transforming them into simpler and more absorbable food stuffs. And thus, in the words of one physiologist, "Endowing us with functional features that we have not had to evolve ourselves." It is as though these bacteria, laboring as an auxiliary digestive organ, have fulfilled a necessary metabolic function to such a faithful degree that the benefited creatures, from primitive insects to complex mammals, have never bothered to develop certain digestive enzymes through the customary evolutionary process.

These special bacteria have thus given us a gift akin to bestowing upon us such beneficences as hearing aids or eye-glasses. It has been a mutual aid pact since the intestines offer a congenial, warm and oxygen-poor environment for generations of these synergistic bacteria.

What might happen if we were deprived of these supportive bacteria? When experimental mice are raised in a totally germ-free environment, they will require specially pre-digested foods since a normal diet will prove inadequate to sustain them. This happens, too, when humans are medicated with certain antibiotics to sterilize their gut of intrinsic bacteria. Again, the digestive system is out of kilter until the intestinal bacterial flora have been replaced from the exterior.

The world is indeed a complex place, with some species surviving by evolving a variety of protective mechanisms, some by learning to be the predator rather than the prey, and some by entering into complex, mutually advantageous, cooperative enterprises with other creatures in systems called metabolic synergy.

– Stanley M. Aronson, MD

Disclosure of Financial Interests

Stanley M. Aronson, MD, has no financial interests to disclose.

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What Is Interventional Radiology?

Sun H. Ahn, MD, and Mahesh V. Jayaraman, MD

Coined by Dr. Alexander Margulis in 1967, *interventional radiology* is a medical specialty devoted to patients' clinical care in an image-guided, innovative, and minimally invasive manner. Dr. Charles Dotter first introduced interventional radiology to the world in 1964, when he percutaneously dilated a superficial femoral artery stenosis in an 82 year-old woman and averted an amputation. Since then, interventional radiologists have pioneered treatments in many areas of medicine, including balloon angioplasty and stenting in peripheral vascular disease, catheter directed thrombolysis, embolization for cessation of bleeding, needle biopsies and drainages, etc. Many recent and exciting advances have come in the areas of peripheral vascular disease, oncology, uterine fibroid disease, varicose vein management, and dialysis and venous access. In neurointerventional radiology, endovascular therapies for intracranial aneurysms, vascular malformations and atherosclerotic occlusive disease have expanded treatment options for many patients.

Perhaps more important than the technical advances, the field has evolved from a procedure-oriented specialty to a clinical practice with commitment to direct patient care. Interventional radiologists routinely perform inpatient and outpatient consultations, make diagnoses, perform treatments, and longitudinally follow their patients. This issue highlights some of the latest advances in the field of interventional and neurointerventional radiology. For more information please refer to Society of Interventional Radiology (www.sirweb.org) and Society of NeuroInterventional Surgery (www.snisonline.org).

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Disclosure of Financial Interests

The authors have no financial interests to disclose.

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Intracranial Aneurysms: Perspectives On the Disease and Endovascular Therapy

Awais Z. Vance, MD, Mahesh V. Jayaraman, MD, Richard A. Haas, MD, Curtis E. Doberstein, MD

There are approximately 30,000 cases per year in the United States of aneurysmal **subarachnoid hemorrhage** (SAH), leaving 60% of patients dead or disabled. However, improvements in treatment have occurred in the past few decades; a recent meta-analysis shows decreasing case fatality rates from 1973 to 2002.[1]

This article will discuss the epidemiology, natural history, diagnosis and treatment of intracranial aneurysms. We hope that the reader will leave with an understanding of the strengths and limitations of endovascular treatment for intracranial aneurysms.

Epidemiology and Natural History

Intracranial aneurysms are present in 1-5% of the general population;[2] 10 to 30% of patients will have multiple aneurysms.[3] The majority of aneurysms occur in the anterior circulation near the Circle of Willis with the most common locations in descending frequency being the **anterior communicating artery** (**Acomm**), **posterior communicating artery** (**Pcomm**), and **middle cerebral artery** (MCA).

Ruptured aneurysms most often present with subarachnoid hemorrhage. After the initial hemorrhage, the highest risk for rehemorrhage occurs in the first 2 weeks at a rate of 1-2%/ day. If untreated, 50% of patients will re-hemorrhage within 6 months of initial hemorrhage; up to 72% of these patients will suffer death or severe disability.[4,5] While historically, patients were treated 2 to 3 weeks after hemorrhage, the International Cooperative study on timing of Aneurysm surgery[6,7] showed that early treatment was superior. The current standard of care is to treat ruptured intracranial aneurysms as soon as reasonably possible after hemorrhage. Upon presentation, patients are assessed clinically using the Hunt and Hess grading system, from I (minimal headache, no other symptoms) to V (comatose, moribund). As would be expected, the lower the grade at presentation, the better the outcome.

Rupture Risk of Unruptured Aneurysms

Unruptured aneurysms may present with headache, stroke, neurologic deficits related to mass effect or as incidental findings on imaging. The **International Study of Unruptured Intracranial Aneurysms** (**ISUIA**)[8] showed that the risk of rupture was related to the size, location and history of prior SAH. The 5-year rupture rates are summarized in Table 1. To summarize their findings, larger aneurysms, those in the posterior circulation (or Posterior communicating artery), and those in patients with prior history of SAH are all associated with higher rupture rates. In general, most small (<7mm) aneurysms in the anterior

circulation in a patient with no prior personal or family history of SAH can be followed with serial imaging.

Patients with a family history of aneurysm are also at higher risk for rupture for small aneurysms.[9] While these prospective rupture rates are helpful, the ultimate decision to treat or observe an unruptured aneurysm depends on several other factors, including the patient's age, medical status, family history and personal preferences.

Imaging Evaluation

The most appropriate imaging study for evaluation of intracranial aneurysms depends on the clinical presentation. For patients with subarachnoid hemorrhage, the most sensitive examination is required because even very small aneurysms are important to detect. For unruptured aneurysms, a safe (though perhaps less sensitive) imaging modality is preferred because very small aneurysms (<3mm) are unlikely to make a clinical difference. The available imaging modalities include **MR angiography** (**MRA**), **CT angiography** (**CTA**) and catheter-based **digital subtraction angiography** (**DSA**).

MRA is the least sensitive modality, especially for aneurysms < 3mm in size, but uses no ionizing radiation or intravenous contrast. The sensitivity of MRA varies with aneurysm size, with MRA being best for aneuryms 5mm or larger. CTA is more sensitive than MRA, especially for aneurysms <5 mm in size. However, the patient is subjected to the risks of ionizing radiation and iodinated contrast. In aneurysms greater than 5mm in size, the sensitivity for detection is equal to MRA though CTA is superior in characterization of vascular anatomy of adjacent branches.[10,11,12, 13, 14]

Angiography is the most sensitive examination for intracranial aneurysms. It is minimally invasive with a low rate of permanent neurologic morbidity. Recent studies have shown that permanent complication rates at busy neurovascular centers are extremely low,[15] typically much less than 0.1%. Angiography's spatial resolution exceeds that of CTA and MRA by almost an order of magnitude. Newer 3D-DSA technology allows for detailed reconstructions that can allow for examining the aneurysm from a variety of angles and facilitates treatment planning.

For patients previously treated with surgical clips, both MRA and CTA have artifact that precludes adequate evaluation of the treated aneurysm. In those cases, angiography is often necessary. For patients treated with endovascular coils, MRA is an ideal way to follow treated aneurysms, as there is little artifact caused from the coils.

A common question is: who should be screened for aneurysms? The current recommendations are to screen patients in whom at least two immediate relatives have a documented intracranial aneurysm, and all patients with adult polycystic kidney disease.[3,16,17] Familial aneurysms represent approximately 15% of all aneurysm patients.

In modern practice, MRA is typically used for screening of asymptomatic high risk patients and for follow up of previously detected or previously coiled aneurysms. CTA is often used to characterize a questionable MRA abnormality and oc-

TABLE 1: Prospective 5-year cumulative rupture rates from the International study of unruptured intracranial aneurysms (ISUIA)

Aneurysm Size	< 7mm		7-12mm	13-24mm	>25mm
	Group I (no prior SAH)	Group II (prior SAH)			
Cavernous ICA	0	0	0	3.0%	6.4%
Anterior Circulation	0	1.5%	2.6%	14.5%	40%
Posterior Circulation (incl. PComm)	2.5%	3.4%	14.5%	18.4%	50%

TABLE 2: Typical indications, advantages and disadvantages for available aneurysm imaging modalities:

Modality	Indications	Strengths	Weaknesses
MRA	• Screening of high risk asymptomatic patients • Follow up of previously detected aneurysms • Follow up of previously coiled aneurysms	• No ionizing radiation • No intravenous contrast required • Good for coiled aneurysms	• Limited sensitivity for <5mm aneurysms • Substantial artifact for clipped aneurysms
CTA	• Characterize a questionable MRA abnormality • Occasionally for follow up of aneurysms difficult to visualize by MRA	• Better spatial resolution then MRA • Least time consuming	• Ionizing radiation required • Iodinated contrast required • Less sensitive then DSA for <3mm aneurysms
DSA	• Suspected aneurysmal SAH • Treatment planning when definitive characterization and anatomic definitions necessary	• Highest spatial resolution • Can image and treat in the same setting	• Minimally Invasive • Ionizing radiation required • Iodinated contrast required

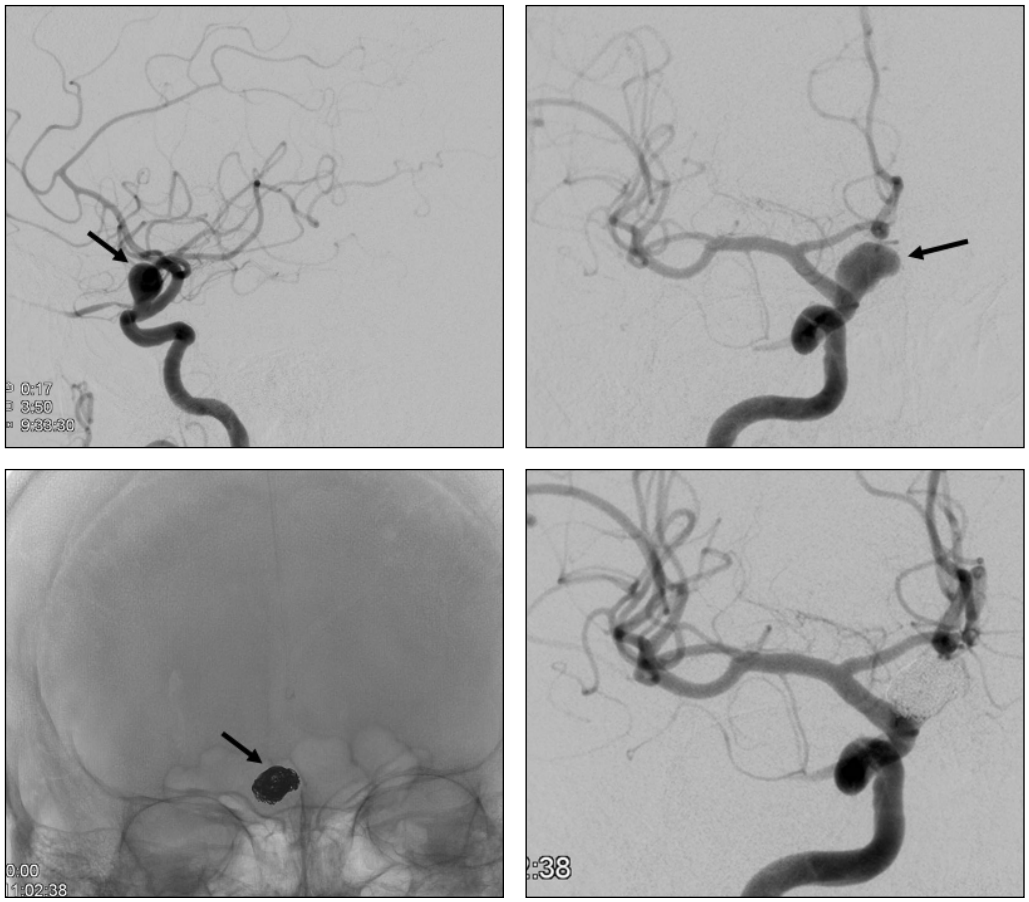

Figure 1. Angiogram images from a 62 year-old male with an unruptured aneurysm. Lateral (upper left) and Frontal (upper right) angiogram images demonstrate a 12mm aneurysm (arrows) arising from the internal carotid artery.

Images after endovascular therapy show coils (arrow, lower left) in the aneurysm. Angiogram following coiling shows no residual filling of the aneurysm (lower right).

casionally for follow up of aneurysms which are difficult to visualize by MRA. DSA is the gold standard and should be performed on all SAH patients since it is important to detect even the smallest of aneurysms in this population. DSA is also used in treatment planning when definitive characterization and anatomic definition is needed. These imaging recommendations are summarized in Table 2.

Treatment Options

The goal of aneurysm treatment is to prevent hemorrhage or re-hemorrhage. Treatment should be safe, effective and durable. The two main options are craniotomy with microsurgical clipping or endovascular coiling. Although neurosurgical clipping is invasive, it has been the traditional treatment with a long track record, with the major advantage of durability. Re-hemorrhage and recurrence rates of surgically clipped aneurysms are extremely low, and routine imaging follow up is typically not necessary.

Endovascular therapy for aneurysms has been performed for several decades, but the Guglielmi Detachable Coil (GDC, Boston Scientific, Natick, MA) in the early 1990s revolutionized the field. In this procedure, a very small microcatheter is placed into the aneurysm sac, and progressively smaller coils are placed to induce thrombosis of the aneurysm, all through a small femoral arterial access. Initially, coil embolization was limited to aneurysms with a narrow opening (neck) to the aneurysm to facilitate coil placement. However, newer balloon and stent-assisted techniques have greatly expanded endovascular treatment horizons. When using balloon-assisted technique, a balloon is inflated at the base of the aneurysm in order to prevent coils from protruding out of the aneurysm and into the parent vessel. For stent-assisted coiling, newer endovascular stents specifically designed for this purpose have been designed. (Figures 1 and 2) One drawback of stents is that the required anti-platelet agents can pose a potential problem in acutely ruptured aneurysms.

Comparative Studies of Clipping and Coiling

When the GDC coil was first introduced, the coiling procedure was typically reserved for poor Hunt & Hess grade patients. Gradually, however, greater use of coiling was applied to patients with better clinical grades. The landmark **International Subarachnoid Hemorrhage Trial (ISAT)** enrolled patients from 1995 onward, mostly in Europe. Patients with good clinical grades who had aneurysms which could reasonably undergo either surgical or endovascular therapy were randomized. The initial data, published in 2003 (after 2143 patients had been randomized), showed a statistically significant reduction in percentage of patients dead or disabled at one year, from 30.9% (surgery) to 23.5% (coiling). Among the initial criticisms of the study were the lack of long term follow-up, and the fact that surgical experience among the European centers may not be comparable to those of major US medical centers. However, more recent long-term data have shown that the coiling treatment is indeed durable, with a statistically lower risk of death at 5 years when compared with clipping.[18] While the risk of re-hemorrhage from a clipped aneurysm was significantly lower than that of a coiled aneurysm, the rates of both were low and did not overwhelm the early benefit of the less invasive procedure. ISAT also established that the rate of recurrent SAH in these pa-

tients was both from treated aneurysms but also from other aneurysms, either those present initially or those which formed in the interim. This stresses the need for long-term follow-up of patients with prior SAH, irrespective of whether they were treated with coiling or clipping. While these results from a landmark study cannot be generalized to every patient, they suggest that if a patient has subarachnoid hemorrhage and an aneurysm that can be treated with either modality, then coiling is associated with a lower rate of death or dependency. A randomized trial at a high volume US neurosurgical center (Barrow Neuroscience Institute, Phoenix, AZ) confirmed these findings, showing a statistically significant benefit to coiling over clipping in patients who could undergo both treatments.[19]

...the current standard of care is to treat ruptured intracranial aneurysms as soon as reasonably possible after hemorrhage.

Unlike ruptured aneurysms, no randomized trial compares surgical and endovascular treatment for unruptured aneurysms. With unruptured aneurysms, the surgical limitations of operating on an acutely injured brain are not present as they are in the setting of SAH, and the goal should be to attempt to give the patient a durable treatment for their aneurysm. The ISUIA study, comparing the outcomes of surgical clipping with endovascular coiling, found that the 1-year morbidity/mortality for endovascular coiling (9.8%/7.1%) was lower than that of surgical clipping (12.6%/10.1%). They study found that poorer surgical outcome was associated with age greater than 50, larger aneurysms, posterior circulation location and in patients with history of ischemic cerebrovascular disease. Poorer prognosis associated with endovascular treatment was less dependent on patient age and aneurysm size though aneurysms >12mm and those lo-

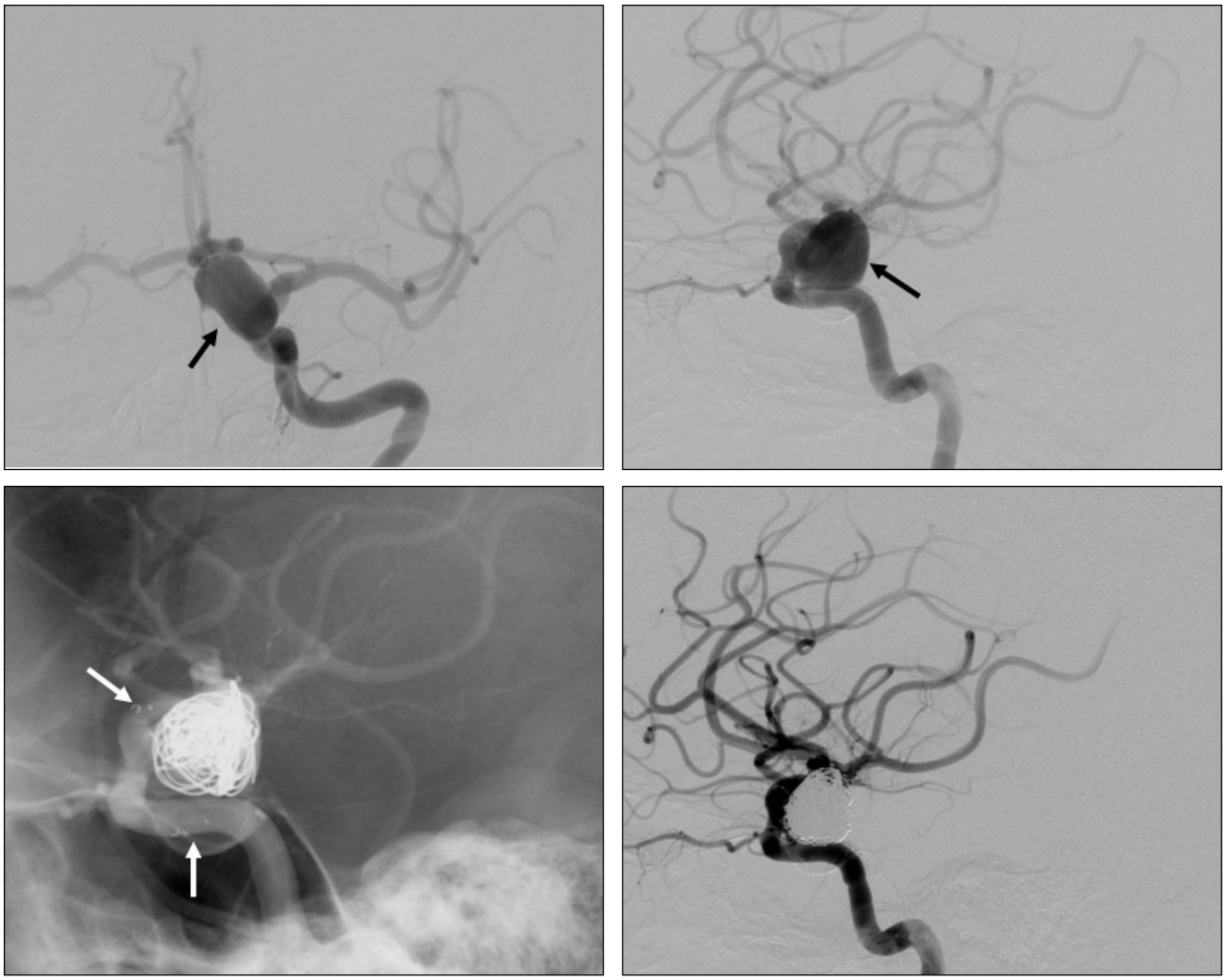

Figure 2. Stent-assisted endovascular therapy of a large aneurysm arising from the left internal carotid artery. Frontal (upper left) and Lateral (upper right) angiograms show the aneurysm (arrows). Note the relatively wide neck (opening) into the aneurysm, as compared with the narrow neck in Figure 1. In this case, treatment was performed using a stent-assisted technique. Post-coiling images (lower left, lower right) show the coils within the aneurysm, without obstructing parent vessel flow. Note the markers indicating the location of the stent within the internal carotid artery (arrows, lower left). Post-treatment angiogram shows patent flow through the parent vessel with only minimal filling of the aneurysm (lower right).

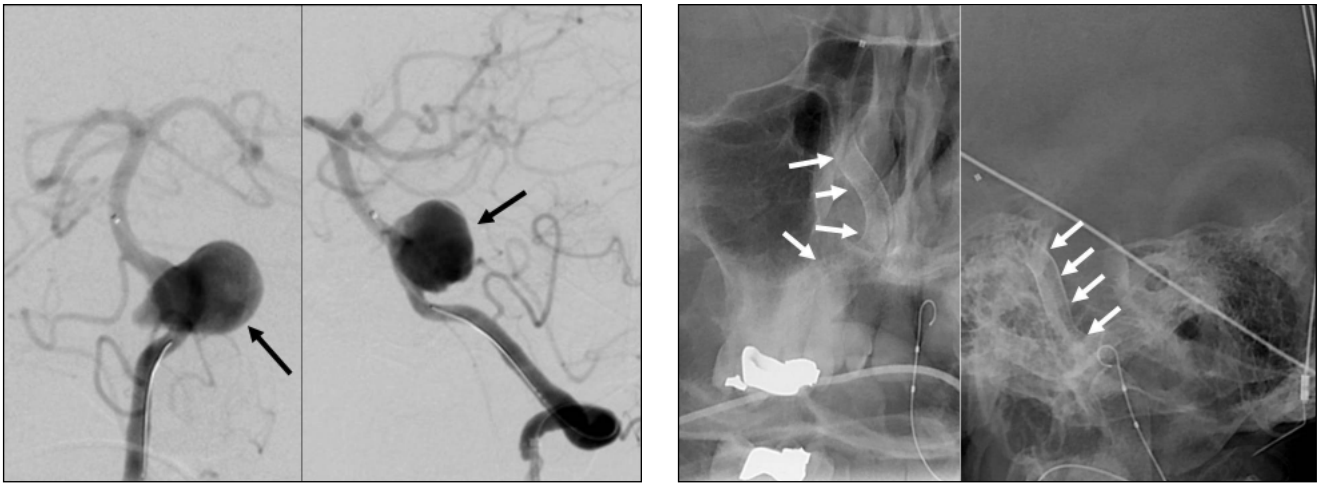

Figure 3. Treatment of a complex, large aneurysm at the vertebro-basilar junction using a flow diverting stent. Initial angiogram images prior to treatment (upper left) show a large aneurysm (arrows) at the confluence of both vertebral arteries to form the basilar artery. Conventional coil embolization or surgery for this lesion would be difficult. Native images (upper right) show a flow diverting stent (arrows) placed from the right vertebral artery to the basilar artery, in order to disrupt flow across the neck of this aneurysm and induce thrombosis. Final post treatment angiogram (lower left) shows stasis of contrast (arrows) well after contrast has washed out of the normal arteries and veins. It is expected this portion of the aneurysm will slowly thrombose and shrink down over time.

cated in the posterior circulation portended a poorer prognosis.[8] Higashida et al performed a retrospective analysis of discharge results in 18 states of 2619 patients treated for unruptured aneurysms at 429 community and academic hospitals. They found that endovascular treatment of unruptured aneurysms was associated with statistically significant reductions in morbidity, mortality and decreased hospital use at discharge.[20] However, both these studies were not randomized, and the data should be interpreted as such, acknowledging the substantial limitation of patient selection bias.

Endovascular Therapy: Limitations and Future Directions

The greatest limitations of endovascular therapy have been the durability of treatment for large and giant aneurysms, and therefore the implicit need for follow-up imaging. ISAT showed that endovascular therapy was indeed durable with respect to preventing re-hemorrhage, but that patient population was mostly small aneurysms.[18] Murayama et al reported aneurysm recurrence rates post coiling from their experience at UCLA from 1991-2002.[21] They found that progressively larger and wider neck aneurysms had progressively higher recurrence rates, ranging from 5.2% for small aneurysms (with a small neck) to 63.2% for giant aneurysms. The mean time to recurrence following treatment was 12 months, with most recurrences by 36 months in a large series.[22] They also found that the major risk factors for recurrence included aneurysm size > 10mm and incomplete initial occlusion. Thus one of the limitations of endovascular treatment remains the durability in large and wide neck aneurysms.

The most exciting future development in endovascular aneurysm therapy is the flow diverting stent (FDS).

The most exciting future development in endovascular aneurysm therapy is the **flow diverting stent (FDS).** Unlike stents used to assist in placing coils into an aneurysm, these devices are designed to be the only therapy used to treat an aneurysm. As such, they have a higher degree of metal coverage than stents currently used. The device is placed in the parent vessel harboring the aneurysm, and by doing so causes marked disruption of the flow vectors leading into the aneurysm. This induces thrombosis of the aneurysm, and animal studies have shown that eventually a neo-intima grows over the previous opening to the aneurysm. This concept is extremely promising, since it ad-

dresses the issues of recurrence of large and giant aneurysm. While none of the devices are FDA-approved, studies outside of the US have shown great promise. The Pipeline Embolization Device (Ev3 neurovascular, Irvine, CA) is the best studied to date, with several hundred human cases performed. (Figure 3) Single center studies have shown very impressive results in treating the large and giant aneurysms endovascularly using that device.[23] Complete thrombosis of the aneurysm can take weeks to months, and eventually the aneurysm sac collapses and restores a normal parent vessel contour. Remarkably, the small perforating arteries which arise from the vessel segment seem to stay patent. Most of the work using FDS has not involved bifurcation aneurysms, so their applicability in that situation is unknown. Much work remains to be done with these devices, and their use in acutely ruptured aneurysms would require the use of antiplatelet agents. All these issues would need to be addressed before they could supplant coils as the major therapy for intracranial aneurysms. If indeed further studies confirm the promising preliminary data, the landscape for aneurysm therapy will change greatly in the coming decade.

What's Best For My Patient?

One of the most common questions is: "what's better: coiling or clipping?" The answer is "it depends..." Certainly the patient's clinical condition and medical co-morbidities should be considered. Depending on their morphology and location, aneurysms may be better suited for one therapy over another. While the trend has been towards a greater percentage of aneurysms treated endovascularly, many aneurysms are still better suited for surgical therapy. For example, MCA aneurysms are often treated surgically owing to their combination of easier surgical exposure than other locations, and their tendency to have wide necks and branch vessel incorporation, anatomic factors which make endovascular treatment more difficult.[24] For patients with an aneurysm that can be treated using either modality, a frank discussion with the patient of the benefits and drawbacks of both options is warranted. In our practice, we discuss the cases jointly whenever possible and frankly discuss the pros and cons of both therapies with our patients.

Conclusion

Intracranial aneurysms are present in 1-5% of the population, most often presenting with subarachnoid hemorrhage. For unruptured aneurysms, larger size (especially >6 mm), posterior circulation location, personal or family history of aneurysm rupture are all associated with higher prospective rates of hemorrhage. Treatment of intracranial aneurysms has evolved over the past two decades, with endovascular coiling offered as primary therapy in a greater percentage of patients. This is primarily based on the results of a large scale randomized trial showing improved outcomes with coiling over surgical clipping in patients with ruptured aneurysms suited for both therapies. Both clipping and coiling are effective at preventing hemorrhage and durable over the long term, with slightly lower rates of re-hemorrhage with clipping compared with coiling. Future endovascular directions may involve the use of flow diverting stents, which induce aneurysm thrombosis over time and show early promise in the most difficult of aneurysms. Aneurysms should be treated at a center that can offer both surgical clipping and coiling in order to result in the best possible patient outcomes.

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Acute Deep Vein Thrombosis (DVT): Evolving Treatment Strategies and Endovascular Therapy

Patrick Conklin, MD, Gregory M. Soares, MD, Gregory J. Dubel, MD, Sun H. Ahn, MD, and Timothy P. Murphy, MD

Deep vein thrombosis (DVT) is a manifestation of **venous thromboembolic (VTE)** disease. VTE encompasses both DVT **and pulmonary embolism (PE).** DVT itself refers to thrombus which has formed in the deep veins of the body which usually parallel an artery of the same or similar name and follow a deep course within an extremity. Formation of thrombus in these vessels frequently results in local and systemic complications leading to significant morbidity and mortality. The Acting Surgeon General Steven K. Galson, MD, MPH, recently released a call to action to reduce the number of cases of DVT and pulmonary embolism in the United States, stressing that collectively DVT and PE contribute to at least 100,000 deaths each year.[1]

An often overlooked yet significant complication of DVT is the **post-thrombotic syndrome** (**PTS** – formerly post-phlebitic syndrome). PTS is characterized by chronic pain and swelling in the affected limb. PTS patients are considered a subset of those with chronic venous insufficiency. They are prone to the skin changes of chronic venous stasis disease, namely hyperpigmentation, lipodermatosclerosis, and atrophie blanche. In the most advanced cases, venous stasis ulcers may occur. Overall, PTS leads to lower quality of life.[2,3]

This article focuses on the epidemiology and treatment of DVT and PTS, including the most recently updated management guidelines from the **American College of Chest Physicians** (**ACCP** 2008) and **the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis** (**ATTRACT**) Trial. The goal is to enable the reader to understand the appropriate management of DVT and recognize the indications for more aggressive treatment of acute symptomatic DVT.

Epidemiology

Approximately 350,000 individuals are affected by DVT/PE each year in the United States. Many cases are not recognized and the actual number of cases could be twice as high.[1] Studies show that patients with PE demonstrate a 3 month all-cause mortality of 15% to 30%.[1,4,5] As many as 4% of patients with PE will progress to **chronic thromboembolic pulmonary hypertension** (**CTEPH**).[6] PTS will affect nearly 30% of individuals with DVT over a five-year period.[7] It is estimated that the annual direct cost in the United States for PTS is $200 million, with an indirect cost of 2 million lost work days annually due to leg ulcers.[8]

Ultrasound studies have shown that patients with symptomatic venous thromboembolism are most likely to have DVT in the proximal deep veins of the legs; however, only 11% will have upper extremity clot and 15% will have isolated calf DVT.[9] There is general agreement that proximal or iliofemoral distribution DVT is clinically significant and warrants treatment with anticoagulation and or more aggressive measures for severe cases; however, there is with less uniform agreement on the management of calf or infrageniculate DVT.[10] Furthermore, patients with an initial episode of symptomatic DVT are at high risk for recurrent episodes. In a study of 355 patients followed for 8 years after a symptomatic DVT, the cumulative incidence of recurrent VTE was 17.5% after 2 years, 24.6% after 5 years, and 30.3% after 8 years.[11] Recurrence rates are higher if there is residual thrombus in the vessel.[12] Recurrence, particularly of ipsilateral DVT, is a strong risk factor for PTS.[2,7] The cumulative incidence of PTS in these patients increased likewise from 22.8% at 2 years to 29.1% at 8 years.[7]

Risk Factors

There are many risk factors for the development of VTE all of which remain rooted in Virchow's triad of hypercoaguability, stasis and endothelial injury. Hypercoaguability as an etiology for venous thrombosis requires investiga-

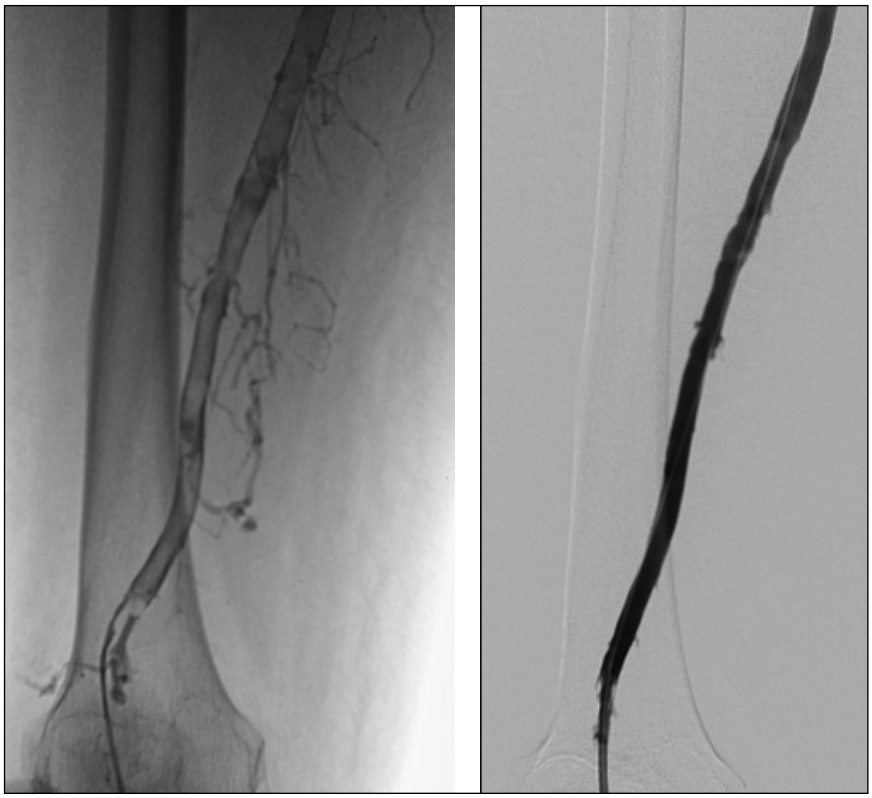

Figure 1: Femoral vein acute DVT pre (left) and post (right) PCDT. Post image reveals >95% thromboreduction.

tion of inherited or acquired thrombophilia. Of the numerous causes for an inherited thrombophilia, the factor V Leiden mutation is the most frequent. Less frequent genetically transmitted thrombophilias include Factor II G20210A mutation, protein C and S deficiencies, and hyperhomocysteinemia.[10] Commonly acquired hypercoaguable states include the presence of known or occult malignancy, recent trauma and other causes of decreased calf-muscle contraction or immobility. Prior DVT may be the greatest risk factor for DVT recurrence with a likelihood of approximately 30% at eight years.[7] The incidence of recurrent DVT is often due to a combination of all three components of Virchow's triad being present following an initial episode of VTE.

Adequacy of Current Treatment Strategies

Aside from the risk of mortality due to PE, early DVT morbidity is directly related to the presence of thrombus. Symptoms of acute proximal DVT include pain and swelling in the extremity and a decreased ability to ambulate. Late complications are primarily related to the development of PTS. The underlying mechanism for long-term venous insufficiency related to PTS involves an inflammatory response followed by recanalization of the acute thrombus, which in turn can causes valvular failure and reflux in the vein.[8] Reflux leads to venous hypertension and may result in edema, venous stasis skin changes and in severe cases to ulceration.[2,6] Once present, PTS can lead to significant limitations in activity, with significant impairment of quality of life. Unfortunately, the treatment options for established PTS are extremely limited, largely palliative and costly.[6]

Since DVT results in both marked early symptomatology and risk of long-term adverse sequelae, comprehensive treatment of acute DVT should address three key therapeutic goals:

1. Decrease risk of mortality due to PE.

2. Decrease early morbidity due to DVT. This may be accomplished through the use of compression, early ambulation, and thromboreduction. Thromboreduction refers to a reduction in thrombus burden by mechanical or pharmacological means.[13]

3. Decrease late morbidity through thromboreduction and valve preservation.[14]

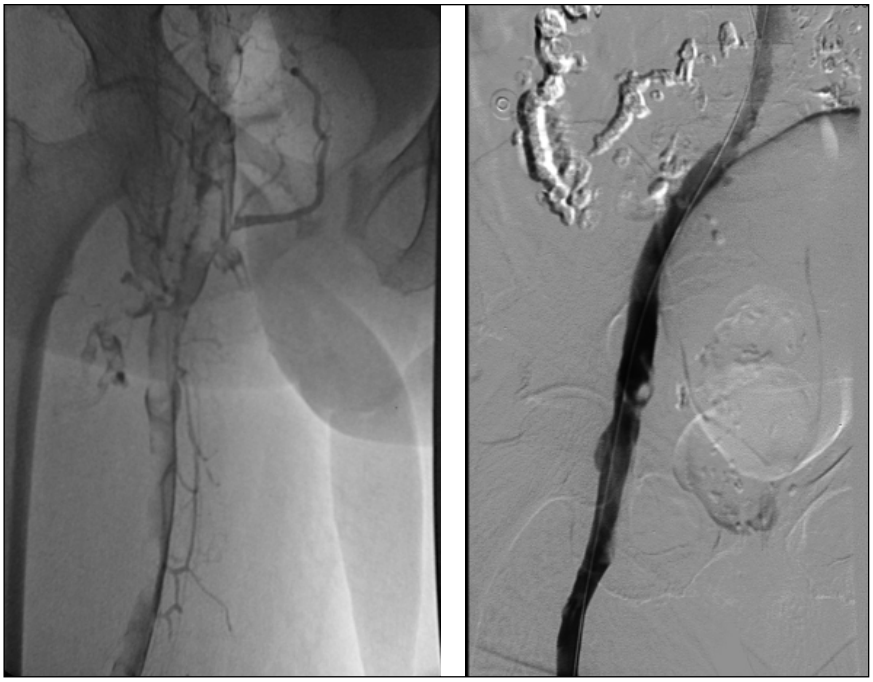

Figure 2: Occlusive common femoral vein DVT (left) and post PCDT (right). Note antegrade flow and lack of collateral veins post PCDT.

Widely accepted and well supported approaches to the prevention of PE through early, effective anticoagulation exist.[15] Less uniformly practiced, but effective guidelines for early graded compression and ambulation have recently become available.[15] Institution of these easily employed means of symptom relief can quickly improve the overall health of those with acute DVT who are also adequately protected from PE. Finally, natural history studies of acute DVT and randomized trial data of the management of iliofemoral DVT offer important observations that the late morbidity of PTS can be prevented or at least mitigated. It is likely that the key to decreasing late sequelae of DVT is valve preservation through early rapid clot removal.[16, 17]

Evolving Treatment Strategies

The treatment of acute DVT remains controversial. The American College of Chest Physicians recommends intravenous anticoagulation as bridge therapy to oral warfarin, along with elevation while at rest, compression of affected limb and early ambulation.[15] Though effective for prevention of clinically significant PE, anticoagulation alone is ineffective for clot removal in the majority of cases, with complete resolution of DVT accomplished in only 10% of patients.[18, 24] The clinical manifestation of anticoagulation's lack of effectiveness for clot dissolution is prolonged acute symptomology of swelling and discomfort. Treatment with anticoagulation alone also does not prevent PTS.[19] Long term follow up data of patients with proximal DVT treated with heparin alone versus heparin and fibrinolysis have shown poorer symptom improvement and worse restoration of venous patency in the heparin alone group.[24]

Finally, Konstantinides and colleagues treated 256 patients who had acute pulmonary embolism with placebo plus heparin or t-PA plus heparin.[20] The incidence of in hospital death or clinical deterioration was significantly higher and the probability of event-free survival was significantly lower in the placebo plus heparin group. In fact, treatment with placebo plus heparin was associated with almost three times the risk of death or treatment escalation compared with t-PA plus heparin. No fatal intracranial hemorrhage occurred in patients who received t-PA plus heparin in that study.

Therefore, heparin treatment alone may carry a higher risk of death or treatment escalation and also falls short in achieving an important long-term goals of DVT management; the minimization of risk of PTS. [20, 21]

Given the fact that anticoagulation alone may be inadequate for acute symptom reduction as well as for PTS prevention, the benefit of thromboreduction has been evaluated. Overall, thromboreduction by surgical thrombectomy has proven beneficial versus anticoagulation alone in randomized trials.[22,23] Unfortunately, surgical thrombectomy is relatively expensive and morbid.[22] Similarly, intravenous systemic thrombolysis (pharmacologic dissolution of thrombus) has shown significant benefit versus anticoagulation alone.[24] Thrombolysis has been shown effective in preservation of valve function, and overall PTS risk may be reduced with thrombolysis.[22,23,25] Systemic thrombolysis for DVT has not been embraced due to fears of significant hemorrhagic complications related to the large doses of thrombolytics required. Studies have suggested a 2-10% risk of major hemorrhagic complication rate when administering systemic anticoagulation.[26] By comparison, **catheter directed thrombolysis (CDT)** can be performed with a lower dose of thrombolytic infused over a longer period of time. The benefits of CDT include improved physical functioning, decreased PTS symptoms, less valvular reflux at 6 months and improved 5-year symptom resolution in a randomized controlled trial.[16,24,27] Significant disadvantages to CDT persist and include long infusions times (48-72 hrs), a necessary ICU stay and the risk for significant bleeding at 11.4% and intracranial hemorrhage at 0.4%.[28] Though CDT offers a promising alternative to surgical thrombectomy and systemic thrombolysis, these drawbacks have tempered wholesale adoption of CDT for thromboreduction.

Contemporary Thromboreduction: Potential For a Paradigm Shift

Pharmacomechanical **Catheter Directed Thrombolysis (PCDT)** may offer a promising solution to the limitations of CDT, systemic thrombolysis and surgical thrombectomy. PCDT combines low-dose thrombolysis with a mechanical device that is placed percutaneously using image guidance via a 2 to 3 millimeter incision to improve and speed thromboreduction. (Figures 1 and 2) The benefits include a decreased level of invasiveness compared to open surgery, as well as, a decreased infusion time and dose of thrombolytic compared with traditional CDT. Moreover, PCDT eliminates the need for a routine ICU stay since it is usually achieved in a single treatment session. The drawbacks include longer initial procedure time and expense than CDT due primarily to the cost of the thrombectomy device. However, since the number of procedures is reduced and the need for post and intraprocedural ICU level monitoring is eliminated, the overall cost-effectiveness of this approach may be greater than that of traditional CDT. Furthermore, any cost-effectiveness analysis must take into consideration both the acute episode of care as well as the potential savings in terms of reduced long-term PTS. This strategy clearly requires further study. Although case series and non-randomized data suggest the possibility of long-term reductions in PTS, there remains a lack of randomized controlled trial data confirming the procedure's efficacy for PTS elimination. To address this paucity of data, the NIH/NHLBI has sponsored the **ATTRACT trial (Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis).** ATTRACT is a Phase III, open-label, multicenter randomized controlled trial which will compare PCDT plus standard anticoagulation versus standard anticoagulation alone. The study seeks to enroll at least 692 patients with proximal DVT in 28 centers and will be multidisciplinary involving Interventionalists, Internal medicine specialists and Emergency room physicians in the US and here in RI (patients may be enrolled at Rhode Island Hospital as well as the Miriam Hospital). The outcomes endpoints include PTS, quality of life, symptom relief, cost, and safety, over a two year follow-up period.

The ATTRACT trial will enroll patients at both Miriam and RI Hospitals

The results of the ATTRACT trial will allow an evidence based appraisal of appropriate indications for PCDT for acute symptomatic DVT. Endovascular intervention and PCDT are currently indicated in "urgent" cases when there is imminent risk to life or limb loss. Typically this involves either extensive inferior vena cava clot with risk to an internal organ's venous drainage and/or phlegmasia cerulea dolens resulting in venous ischemia.[14] The role for PCDT as a first line therapy in the "non-urgent" acute DVT patient is evolving. PCDT has the potential to improve quality of life and reduce long term complications in a minimally invasive fashion, though currently it is often viewed as a 2nd line "salvage" for clinical or anatomic progression while on anticoagulation therapy. The ACCP 2008 guidelines recommend that in addition to appropriate early anticoagulation, DVT patients should ambulate as tolerated and wear 30-40mm Hg compression hose. The College also recommends thrombolysis or CDT in selected patients with extensive acute proximal DVT who have a low hemorrhagic risk, in order to reduce acute symptoms and PTS if the expertise and resources are available.[15]

Summary

DVT and PE contribute to at least 100,000 deaths each year. In addition, 4% of patients with PE will progress to CTEPH[6] and PTS will affect nearly 30%.[11] Anticoagulation alone appears inadequate to prevent PTS in many patients. Newer treatment strategies, includ-

To learn more about CDT and/or PCDT, go to www.sirweb.org.

To learn more about the ATTRACT trial, please contact the Vascular Disease Research Center at (401) 444-7625 or go to www.scvir.org/news/newsPDF/ATTRACT.pdf

ing PCDT, appear to offer the possibility of reducing the pain, suffering and expense of PTS especially in the most severe cases. The NIH/NHLBI sponsored the ATTRACT trial, which will compare PCDT plus standard anticoagulation versus standard anticoagulation alone in patients with proximal DVT. The ATTRACT trial will enroll patients at both Miriam and RI Hospitals and is expected to add significantly to the research in this area. When successfully completed, results from the trial may guide therapy in the years ahead.

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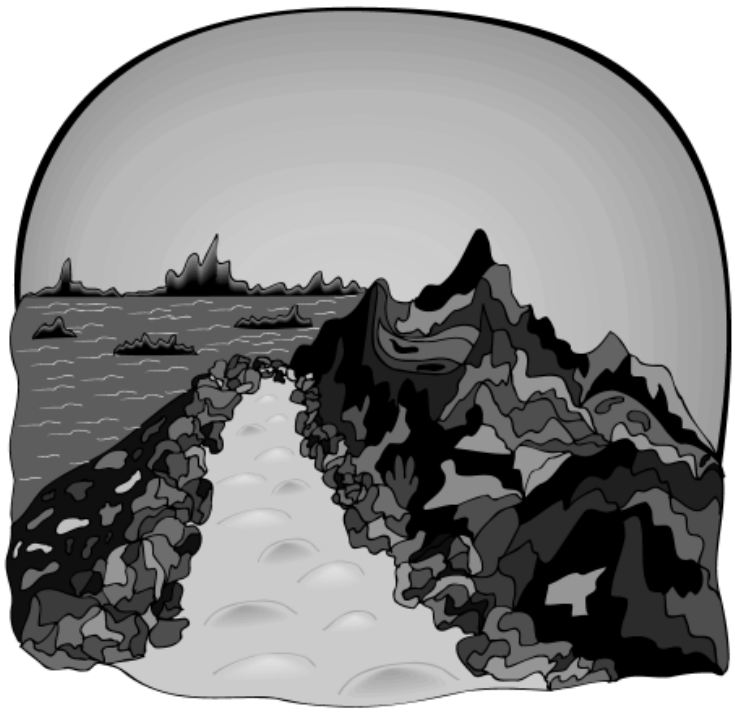

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Peripheral Arterial Disease: Update of Overview and Treatment

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Peripheral arterial disease (PAD) is widely used to describe a common disease process in which blood flow to the lower extremities is impaired as a result of atherosclerotic occlusive disease. PAD, an under-diagnosed and under-treated disorder with substantial morbidity and mortality, affects up to 10 million people in the United States. The pathophysiology of peripheral arterial disease and the risk factors for developing PAD are similar to those for atherosclerotic disease occurring at other sites. Risk factors include cigarette smoking, diabetes, dyslipidemia, hypertension, and hyperhomocysteinemia. Peripheral arterial disease can be diagnosed by performing a directed history and physical examination and using a relatively simple, noninvasive screening test, the ankle-brachial index, which measures the severity of the disease and provides valuable prognostic information. Treatments for PAD include medical therapy and endovascular or surgical revascularization. Optimal medical therapy includes claudication pharmacotherapy, participation in a supervised exercise program, tobacco cessation, and modification of treatable risk factors. Patients with lifestyle-limiting claudication who do not respond to medical management or those with critical limb ischemia should be referred to a vascular specialist for potential revascularization.

Epidemiology

Approximately 10 million Americans are affected by PAD and as many as 3 million experience claudication, its primary lower extremity ischemic symptom.[1] The estimated prevalence of PAD in people older than 70 years is between 14% and 29%.[2,3] In addition, PAD is an important manifestation of systemic atherosclerosis, associated with increased rates of cardiovascular ischemic events and death.[1-3] The prevalence of both PAD and claudication increases with age and exposure to common risk factors, and this prevalence is increasing. In the Framingham Heart Study, the annual incidence of **intermittent claudication (IC)** in people younger than 44 years was 6 cases per 10,000 person-years in men and 3 cases per 10,000 person-years in women. In people older than 65 years, the annual incidence increased 10 fold, to 61 cases per 10,000 person-years in men and 54 cases per 10,000 person-years in women.[4]

Only 10% of patients with PAD have IC, the classic symptom that manifests as a cramping pain in the legs that is induced by exercise and is relieved with rest. Approximately 50% of patients with PAD have atypical lower-extremity symptoms and 40% are asymptomatic.[5] The heterogeneity of clinical presentations may explain why PAD is under-diagnosed and treated in only 25% of affected patients.[6] However, all patients with PAD, whether classic ischemic leg symptoms are present or not, have limited physical activity, impaired walking speed and endurance, and functional decline.[3] Left untreated, PAD can lead to limb amputation.

PAD is a strong predictor of systemic atherosclerosis and is considered a **coronary artery disease (CAD)** risk equivalent.[7,8] PAD is associated with a fivefold increased risk of heart attack and a two- to threefold greater risk of stroke and total mortality.[7] The 10-year risk of death in people diagnosed with PAD is 40% and has remained largely unchanged since 1950.[9] After multivariate adjustment for age, sex, and other risk factors for cardiovascular disease, patients with PAD had a 3-fold higher risk of all cause death and a 6-fold higher risk of cardiovascular-related death than patients without PAD.[10] The international REACH registry recently evaluated cardiovascular outcomes in more than 68,000 individuals and demonstrated that one in five patients with PAD will suffer a heart attack or stroke, be hospitalized, or die due to cardiovascular events within 1 year.[7] In patients with PAD, the combined rates of heart attack, stroke, and hospitalization are equal to or greater than the rates of those with established coronary artery disease.

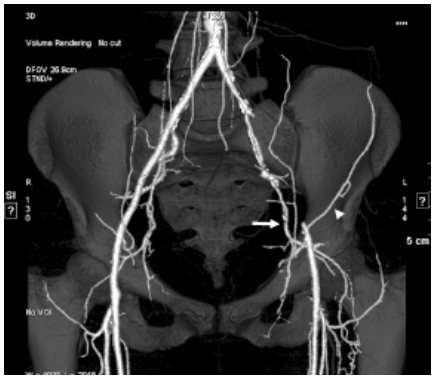
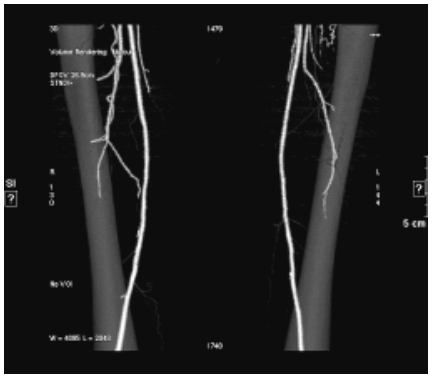


Figure 1a.



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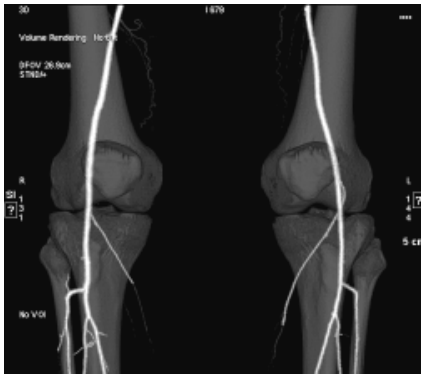


Figure 1c.

Figure 1. 60 year-old female with left thigh and calf claudication. (**a**) Volume-rendered 64–detector row CT angiogram frontal maximum intensity projection (MIP) image at the level of the pelvis shows a chronic long segment occlusion of the left external iliac artery with reconstitution of the left common femoral artery from internal iliac (arrow) and circumflex iliac artery (arrowhead) collaterals. Normal vessels are present on the right. (**b**) Bilateral superficial femoral arteries are normal. (**c**) Bilateral distal arteries in the calves were normal as well.

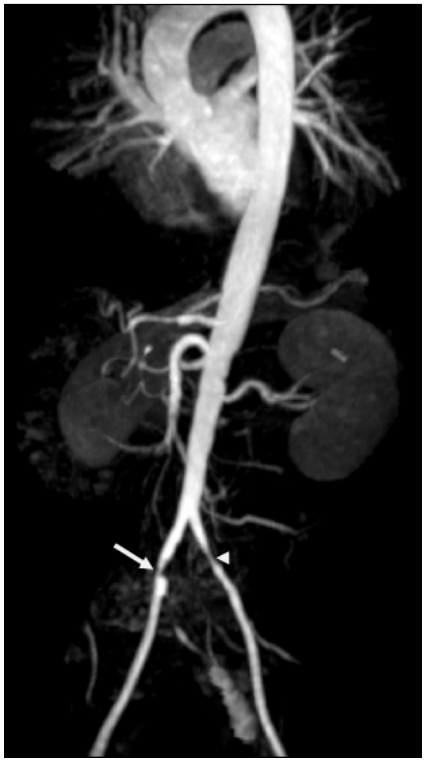


Figure 2. 66 year-old female with bilateral lower extremity claudication. Composite image of coronal oblique maximum intensity projections from a 3D gadolinium-enhanced MR angiogram examination demonstrates short segment stenoses of the right (arrow) and left (arrowhead) common iliac arteries. Internal iliac arteries are not well visualized on this image. Patent aorta, external iliac, renal, celiac, and mesenteric arteries.

Risk Factors

According to the third National Health and Nutrition Examination Survey, the prevalence of PAD increases with tobacco use, African American ethnicity, diminished renal function, diabetes mellitus, and hypercholesterolemia.[2] The risk of PAD progressing **to critical limb ischemia (CLI)** has also been shown to increase under the following conditions: ABI less than 0.7, age greater than 65 years, use of tobacco, and hypercholesterolemia.[3] Several biomarkers, including **C-reactive protein (CRP)**, lipoprotein(a), homocysteine, and D-dimer, have been shown to be associated with the development of systemic atherosclerosis.[11] High levels of some of these inflammatory biomarkers are also predictive of increased short-term mortality.[12]

Clinical Features

A careful history and examination will generally distinguish **intermittent claudication (IC)** from nonvascular causes that may mimic claudication (pseudoclaudication). The patient's lower legs and feet should be examined with shoes and socks off, with attention to pulses, hair loss, skin color, and trophic skin changes.

Clinicians should have a high index of suspicion for PAD, especially in patients who report lower-extremity pain and have diminished pulses, hair loss, or extremity coolness. Although patients with PAD are often asymptomatic, the classic presenting symptom of PAD is IC, a cramping leg pain that is induced by exercise and relieved with rest. Skin pallor occurring after passive elevation of the foot and/or dependent rubor (the onset of erythema after lowering the leg from an elevated position) are also signs suggestive of PAD. A diagnosis of PAD should be considered in patients who report muscular pain in the legs, especially if they belong to known high-risk groups, such as people older than 70 years, African American ethnicity, patients with diabetes or hyperlipidemia, smokers, and those with impaired renal function. The diagnosis can be confirmed in most persons by a noninvasive vascular ultrasound examination, which includes measurement of the ankle-brachial index.

Intermittent Claudication

IC is classically described as fatigue, discomfort, or pain that involves specific limb muscle groups during exertion due to exercise-induced ischemia. The symptom location often indicates the level of arterial involvement, with disease typically occurring at a level above the area of pain. For example buttock or thigh pain is often seen in patients with distal aortic or iliac artery occlusive disease. Health care professionals should be aware that the diagnosis of PAD can often be missed by relying only on clas-

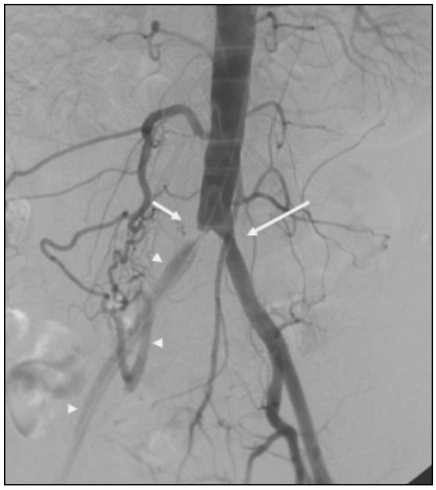
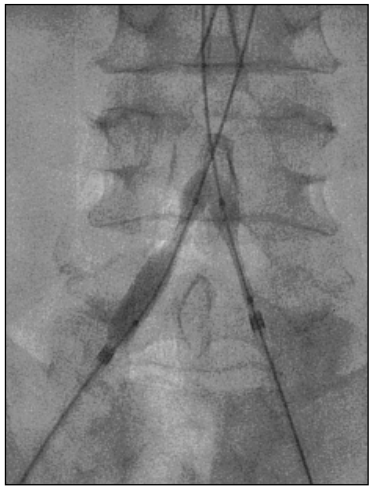


Figure 3a.



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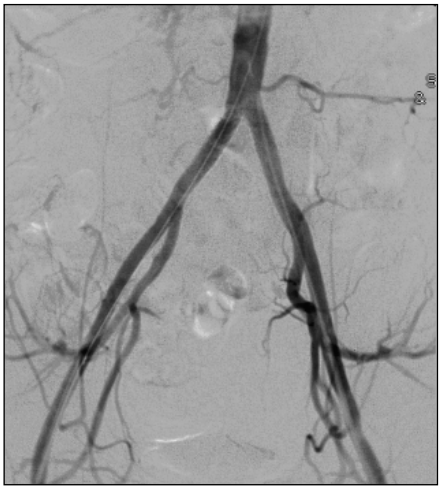


Figure 3c.

Figure 3. 52 year-old male with lifestyle altering right buttock and thigh claudication. His risk factors for PAD include smoking and hyperlipidemia. ABIs measured 0.71 on the right and 0.96 on the left. (**a**) AP image from a pelvic arteriogram shows a severe stenosis of the right common iliac artery origin (short arrow) with a moderate stenosis of the left common iliac artery origin (long arrow). There is delayed filling of the right iliac arteries (arrowheads) compared with the left. (**b**) Fluoroscopic image shows deployment of the bilateral common iliac artery stents. (**c**) Post stent placement arteriogram demonstrates technical success with no residual stenoses. Post procedure ABIs remain normal 4 years post treatment, 1.06 on the right and 1.08 on the left.

sical symptoms of claudication because the majority of patients with PAD are asymptomatic or have atypical symptoms.

Critical Limb Ischemia

When PAD progresses from IC to severe impairment of blood flow to the lower extremity due to arterial stenosis and occlusion, an individual is considered to have **critical limb ischemia (CLI).** CLI manifests clinically as persistent ischemic pain at rest that may lead to non-healing foot ulceration or gangrene. The pain may improve when the leg is in a dependent position and is exacerbated when it is elevated. While more commonly a chronic condition, limb ischemia may also occur acutely, typically as a result of embolism or thrombotic occlusion. A resting ABI value less than 0.4 strongly supports the diagnosis of CLI. CLI can be caused by a number of other disease entities, such as thromboembolism and vasculitis. Because CLI usually requires mechanical revascularization, referral to a vascular specialist is recommended.

Diagnosis

Ankle-Brachial Index

Calculation of the ankle–brachial index is recommended as the initial screening test. This relatively simple, inexpensive, noninvasive test can quantify the severity of PAD and also predict the risk of future cardiovascular events.[2] A recently published meta-analysis suggests that the ABI is a more accurate predictor of an individual's risk of future myocardial infarction or stroke than the traditional predictve method, the Framingham risk score.[13] An abnormal result (0.9 or less) is sufficient to make the diagnosis of PAD in the appropriate clinical setting. When the disease is suspected on the basis of clinical observations but the resting ABI is normal, the ABI should repeated after exercise. Options include toe raises (standing flat-footed and raising the heels off the ground repeatedly) or walking on a treadmill. These patients may have normal resting blood flow, but in the setting of exercise and associated vasodilation, pressure gradients develop across the areas of stenosis, leading to symptoms and an abnormally low value for the ankle–brachial index.

ABI values between 1.0 and 1.4 are normal. Values between 0.9 and 1.0 are borderline, usually occurring in asymptomatic individuals. Patients with claudication typically have ABI values ranging from 0.50 to 0.90, while those with CLI have values of 0.40 or less. An ABI greater than 1.40 suggests poorly compressible, calcified arteries, typically seen in those with diabetes or chronic renal failure. When the resting ABI is combined with exercise treadmill testing, functional capacity can also be assessed. The distance walked can then serve as a baseline functional capacity measure that can assist with future comparisons after either conservative or invasive PAD treatments. If the diagnosis of PAD is uncertain or if revascularization is being planned, imaging with duplex ultrasound, **computed tomographic angiography (CTA),** or **magnetic resonance angiography (MRA)** may be useful.

...the diagnosis of PAD can often be missed by relying only on classical symptoms of claudication because the majority of patients with PAD are asymptomatic or have atypical symptoms.

Computed Tomographic Angiography and Magnetic Resonance Angiography

Both CTA and MRA can localize and quantify arterial stenosis in patients being considered for revascularization. Both CTA and MRA obtain images of vascular structures in cross-section that can be reformatted into three-dimensional angiographic images. (Figure 1) In general, CTA is considered to have better spatial resolution than MRA. (Figure 2) However, with the ongoing development of new MR scanning protocols and as experience with MRA increases, its accuracy may approach that of CTA or contrast angiography.[13] In a randomized trial comparing MRA with CTA for imaging of peripheral arterial disease, the two techniques were found to be roughly similar in terms of diagnostic accuracy, ease of use, and clinical outcome, but total diagnostic costs were lower for CTA.[14]

CTA exposes the patient to iodinated contrast material and radiation, whereas the more expensive MRA does not carry these risks. Because of the possibility of inducing contrast-induced nephrotoxicity, CTA is relatively contraindicated in patients with decreased renal function. In general, MRA cannot be performed in patients with implanted devices such as pacemakers, defibrillators, and metallic aneurysm clips. Gadolinium, the contrast agent used for MR angiography, recently has been linked to development of **nephrogenic systemic fibrosis (NSF)**, especially in patients with a GFR less than 30 mL/min or those receiving long-term dialysis.[15] At our institution, CTA is the preferred noninvasive imaging method; MRA is used when CTA is contraindicated.

Catheter Angiography

The gold standard for diagnosis and evaluation of PAD is catheter-based **digital-subtraction angiography (DSA)**, which can confirm or exclude PAD and can also be used for treatment if appropriate. Angiography can determine the location and severity of stenotic lesions and estimate the degree of calcification. If the stenosis is amenable to percutaneous revascularization, such procedures often can be performed in the same setting. Serious complications of this procedure, which are infrequent, include allergic reactions to the contrast material, bleeding, contrast induced nephropathy, and vessel dissection, thrombosis, or embolization. Alternative contrast agents, such as carbon dioxide, can be used in patients with limited renal function or those with allergies to iodinated contrast material.

Treatment

Risk Factor Modification

Peripheral arterial disease is a strong predictor of systemic atherosclerosis and is considered a CAD risk equivalent.[7,8] Therefore, optimization of cardiovascular risk factors is essential for prevention and management of PAD. Conservative treatment options include cessation of tobacco use, medication therapy, participation in a supervised exercise program, and control of high blood pressure and blood sugar and cholesterol levels.

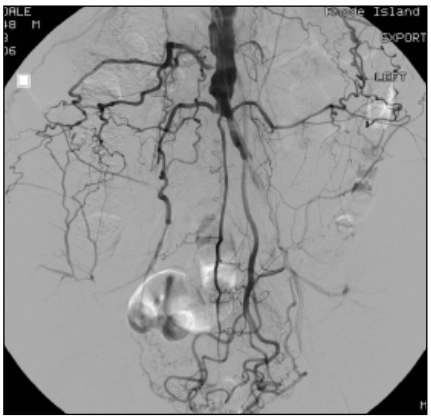
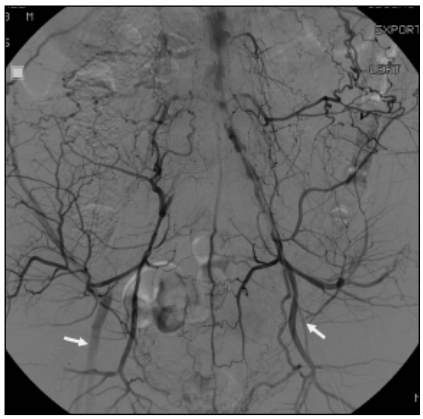


Figure 4a.



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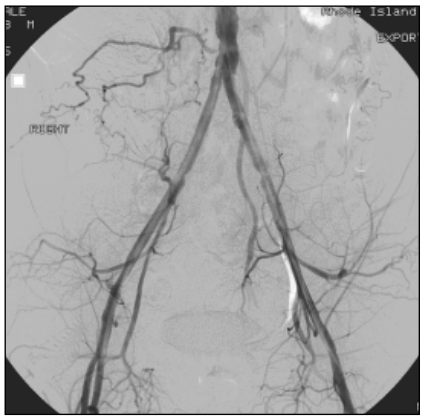

Figure 4c.

Figure 4. 57 year-old male with lifestyle altering buttock and thigh claudication. His risk factors for PAD include smoking and hypertension. ABIs measured 0.56 on the right and 0.68 on the left. (**a**) AP image from a pelvic arteriogram, early phase, shows chronic complete occlusions of both common and external iliac arteries with several collateral vessels present. (**b**) Delayed image from the pelvic arteriogram shows faint opacification of both common femoral arteries (arrows) through several collateral vessels. (**c**) AP pelvic arteriogram following endovascular revascularization with bilateral iliac artery stents shows widely patent iliac arteries without evidence of residual stenoses. Patient remains symptom free three years later and has since returned to work.

Smoking cessation slows the progression of PAD and reduces the risk of death due to vascular causes.[16] A combination approach to smoking cessation, including behavioral therapy, nicotine replacement, and medication, can be more effective than a single modality. Although tobacco cessation has not been shown to significantly improve overall and pain-free walking distance, stopping smoking does reduce the risk of cardiovascular events and progression to CLI.[17] Cholesterol reduction with use of statin medications improves cardiovascular outcomes in patients with PAD[18] and may also improve walking distance and physical activity levels in patients with IC.[19] Proper glycemic control is important to prevent the development of vascular complications. In patients with diabetes, a hemoglobin A_{1c} level of less than 7.0% should be targeted. It is hypothesized that for every 1% increase in hemoglobin A_{1c} level there is approximately a 25% increase in PAD risk .[20] Hypertension, like diabetes, is linked to the development of atherosclerosis and is a major risk factor for PAD. In patients with PAD, the recommended blood pressure goal is less than 140/90 mm Hg. In the diabetic patient, more aggressive blood pressure control is necessary, ideally below 130/80 mm Hg.

Antiplatelet Therapy

Antiplatelet therapy reduces the risk of adverse cardiovascular outcomes and death in patients with cardiovascular disease by approximately 25%.[21] Current recommendations are to use low-dose aspirin (81 mg) daily in patients with PAD to reduce the rate of myocardial infarction, stroke, or vascular death.[22] For patients unable to take aspirin, clopidogrel (Plavix) can be administered at a dose of 75 mg daily. Warfarin has not been shown to have any protective effect in PAD.

FURTHER INFORMATION

- Instructions for patients about PAD and details about the Legs for Life National Screening program for PAD are available through the Society of Interventional Radiology (www.sirweb.org).
- The national nonprofit Peripheral Arterial Disease Coalition provides unbiased, up-to-date information on PAD. The PAD Coalition combines health information from about 62 major national vascular professional societies, health organizations and government agencies. (www.padcoalition.org)
- To learn more about the CLEVER study, visit the following NIH website: http://clinicaltrials.gov/ct2/show/NCT00132743
- For more information about PAD and ongoing clinical trials at the Vascular Disease Research Center (VDRC) at Rhode Island Hospital, visit the following website: http://www.lifespan.org/rih/services/vdrc

Drug Therapy Specific for PAD

The US Food and Drug Administration has approved two prescription medications for intermittent claudication: pentoxifylline (Trental), an oral methylxanthine derivative, and cilostazol (Pletal), a phosphodiesterase III inhibitor. A recent randomized controlled trial comparing the two drugs found cilostazol to be significantly more effective in improving walking distance than pentoxifylline, which was equivalent to placebo.[23] Cilostazol can improve pain-free and peak walking distances in patients with intermittent claudication and is taken orally at a dose of 100 mg BID. Cilostazol is associated with a greater frequency of minor side effects, including headache and diarrhea, and is contraindicated in patients with congestive heart failure.

Exercise Therapy for PAD

Exercise programs are relatively inexpensive, low risk treatment option compared to more invasive therapies. In patients with claudication, multiple randomized controlled trials have shown that supervised exercise programs are more effective at increasing walking distance than unsupervised ones.[24] Supervised exercise programs improve overall and pain-free walking distance and walking time by 50% to 200% from baseline, a level of improvement comparable to that achieved with bypass surgery and potentially better than that achieved with balloon angioplasty.[24-27] Supervised regimens include walking, leg exercises, or treadmill training for 30-60 minutes two to three times

per week. On the basis of findings of randomized controlled trials, the duration of the exercise program should be for 3 to 6 months to improve IC symptoms. Despite proof of the therapeutic benefit of supervised exercise in the PAD population, one of the factors limiting implementation of these programs is the lack of reimbursement by health care payors, so it is important to discuss this with the patient before making a referral.

Revascularization

Mechanical revascularization procedures, which include both endovascular procedures and open surgery (bypass), are used as adjuncts to medical treatment and exercise therapy to restore arterial flow in patients with PAD. Referral for such procedures should be considered in patients with lower extremity pain at rest, those with non-healing ulcers and gangrene, or for individuals with lifestyle-limiting claudication that persists despite risk factor modification, antiplatelet treatment, and participation in a supervised exercise program.

Rapid advances in percutaneous revascularization techniques and equipment have significantly changed the patterns of vascular reconstruction, particularly when lifestyle modifications and drug therapies fail. For purposes of revascularization, PAD is considered in terms of inflow (aortoiliac) and outflow (infrainguinal) occlusive disease. Although surgical bypass has been the traditional therapy for both types, percutaneous endovascular treatment with angioplasty and stents has increasingly become the preferred treatment method to optimize patient outcome while minimizing patient morbidity. (Figure 3) The choice of revascularization procedure depends on several factors, including the location, type, and characteristics of the lesion and co-morbid conditions that affect surgical risks and is best determined after consultation with a vascular specialist.

Endovascular treatment for IC may be more beneficial than exercise in improving symptoms and walking capacity in the short-term, but it is unclear whether this effect is sustained in the long- term.[25] The ongoing **CLEVER study (Claudication: Exercise Versus Endoluminal Revascularization)**, funded by the NIH, is a prospective, multicenter, randomized controlled clinical trial designed to compare the efficacy, safety, and health economic impact of four treatment strategies for patients with PAD and IC: (1) optimal medical care only (claudication pharmacotherapy), (2) optimal medical care plus endovascular stent placement, (3) optimal medical care plus supervised exercise program, and (4) optimal medical care plus endovascular stenting plus supervised exercise. The results should help clarify the role of these various treatment options in PAD and may help physicians identify patients who would benefit from revascularization procedures early in the course of the disease.

Conclusion

PAD is a preventable and treatable disorder with substantial morbidity and mortality, affecting an increasing number of individuals in the United States. The social and economic burden of PAD is expected to increase as the population ages. The mainstay of therapy includes lifestyle adjustment, tobacco cessation, and a supervised exercise program; however, long-term compliance is a challenge and early recognition of PAD is essential to allow implementation of these measures. Optimal treatment of hyperlipidemia, diabetes, and hypertension in conjunction with antiplatelet therapy improves cardiovascular outcomes in these patients. Cilostazol can alleviate the symptoms of IC and improves walking distance. Mechanical revascularization should be reserved for those patients with CLI or lifestyle-limiting claudication. Educational and screening programs directed toward health care professionals and patients with cardiovascular risk factors can help in early diagnosis and proper management of patients with PAD and will ultimately reduce cardiovascular morbidity and mortality.

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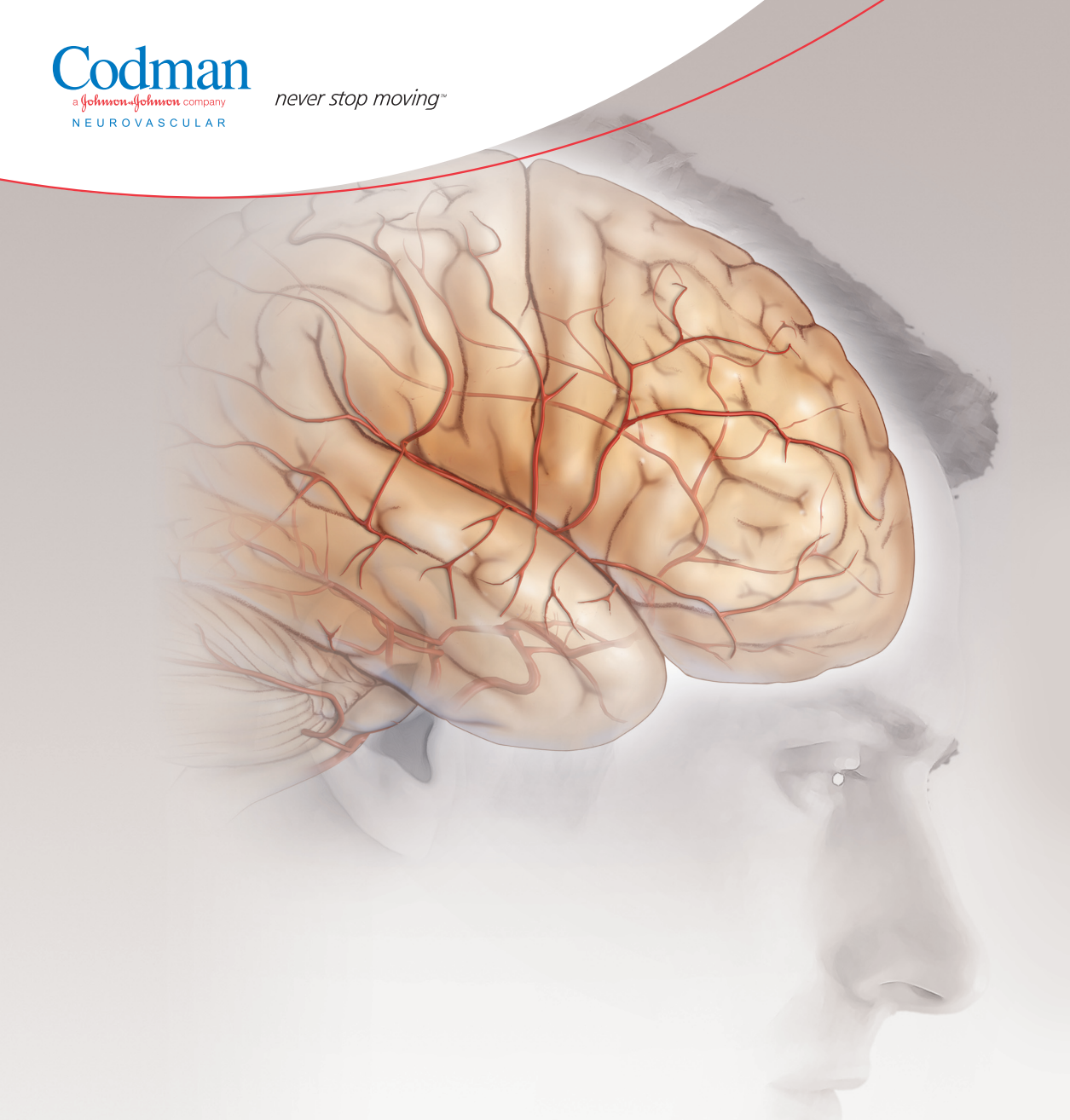

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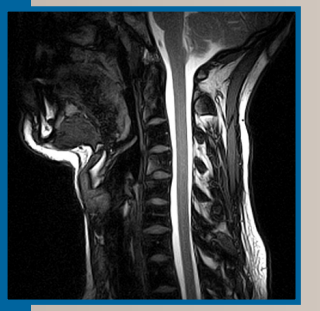

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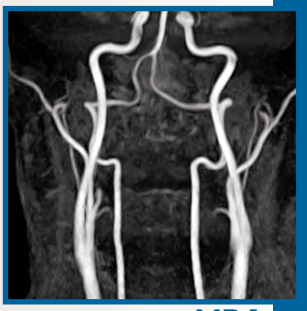

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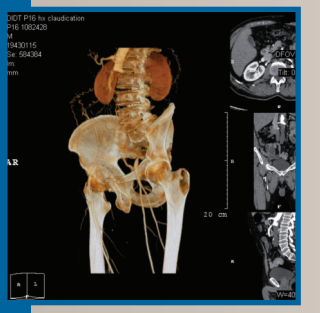

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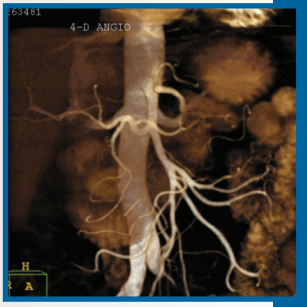

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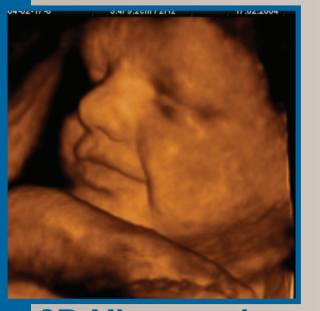

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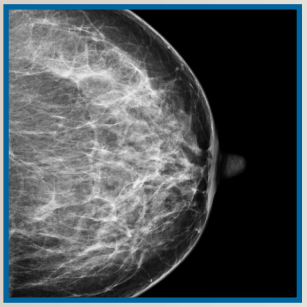

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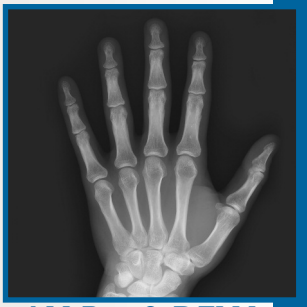

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Thermal Ablation: Clinical Applications, Safety, and Efficacy

Farrah J. Wolf, MD, and Michael D. Beland, MD

In the past decade, the role of radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation in interventional oncology has undergone rapid growth. Treatment is based upon the principle that precise alterations in tissue temperature induce irreversible changes at the molecular level resulting in cellular death accomplished by the application of cytotoxic levels of heat or tissue freezing.

Radiofrequency Ablation

RFA transforms radiofrequency energy into heat. A percutaneous radiofrequency electrode is powered by a generator capable of producing up to 200 watts of power. After a grounding pad has been placed on the patient, the unit is powered on, and pulses of radiofrequency energy are delivered by means of an intralesionally placed electrode. An oscillating current of electrons is created and flows in a circuit between the conducting electrode and grounding source resulting in ionic agitation and frictional heating.

Microwave Ablation

Unlike radiofrequency technology, MWA does not require the use of grounding pads because an electrical current does not flow through the patient. A microwave antenna is percutaneously placed into the tumor under image guidance and powered by a microwave generator. An oscillating electromagnetic waveform radiates from the antenna active-tip, creating a rapidly alternating electric field which polar water molecules strive to align with by spinning back and forth. The resultant rise in kinetic energy induces the development of cytotoxic temperatures within the target lesion and surrounding tissues.

Cryoablation

Cryoablation induces cellular death by producing subfreezing temperatures of -80°C to -160°C as an iceball forms intraprocedurally within the ablation zone. Current cryoapplicators are loaded with a single refrigerant, high pressure argon gas, as well as helium for active thawing so that consecutive freeze-thaw cycles may be used during ablation treatments.

The Patient Experience

As a percutaneous procedure requiring only conscious sedation in the majority of patients, thermal ablation is performed on an outpatient basis. In our practice, patients are seen in consultation before scheduling their procedure, to select the most suitable modality based on tumor location, biology, and treatment goals. Any additional pre-procedural imaging studies needed to ensure sufficient planning of the percutaneous approach to the target lesion are ordered at this time as well as coagulation studies.

Ablations are performed in the Radiology Department under ultrasound- or CT-fluoroscopic guidance. Patients are generally discharged home several hours following ablation with instructions to contact the on-call radiologist with any questions or concerns. If overnight observation is needed, the patient is admitted to the interventional radiology service. A follow-up visit at the ablation clinic is scheduled for all patients within 1 week. At this visit, plans for follow-up care and imaging are arranged at 3-, 6-, and 12-month intervals or as clinically indicated.

Ablation in Practice

With continued research and increasing clinical experience, minimally invasive thermal ablation has become a viable option for many patients, whether curative or palliative, and an integral component of multidisciplinary oncologic treatment plans.

Liver Ablation

Patient Selection

Only 10-20% of **hepatocellular carcinomas (HCCs)** are amenable to surgical resection at the time of diagnosis due to disease staging, poor hepatic reserve,

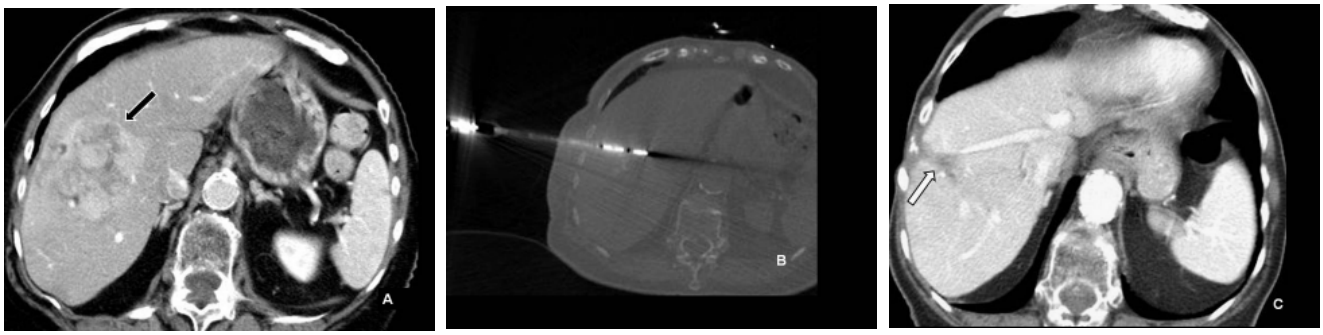

Figure 1. An 86 year-old female is shown on CT (left) to have a 6.6x6.0cm hypervascular lesion with an epicenter in hepatic segment VIII, extending to segment V (black arrow) consistent with hepatocellular carcinoma status post chemoembolization. Prior to ablation the patient underwent a second chemoembolization procedure to further reduce the size of this lesion. One month later the patient presented for MWA (center) and on 4-month post-ablation follow-up portal venous phase CT (right) the treatment zone shows post-ablation changes within segment VIII with no evidence of enhancement to suggest residual or recurrent disease within the ablation cavity (white arrow) now measuring 2.0x1.2cm.

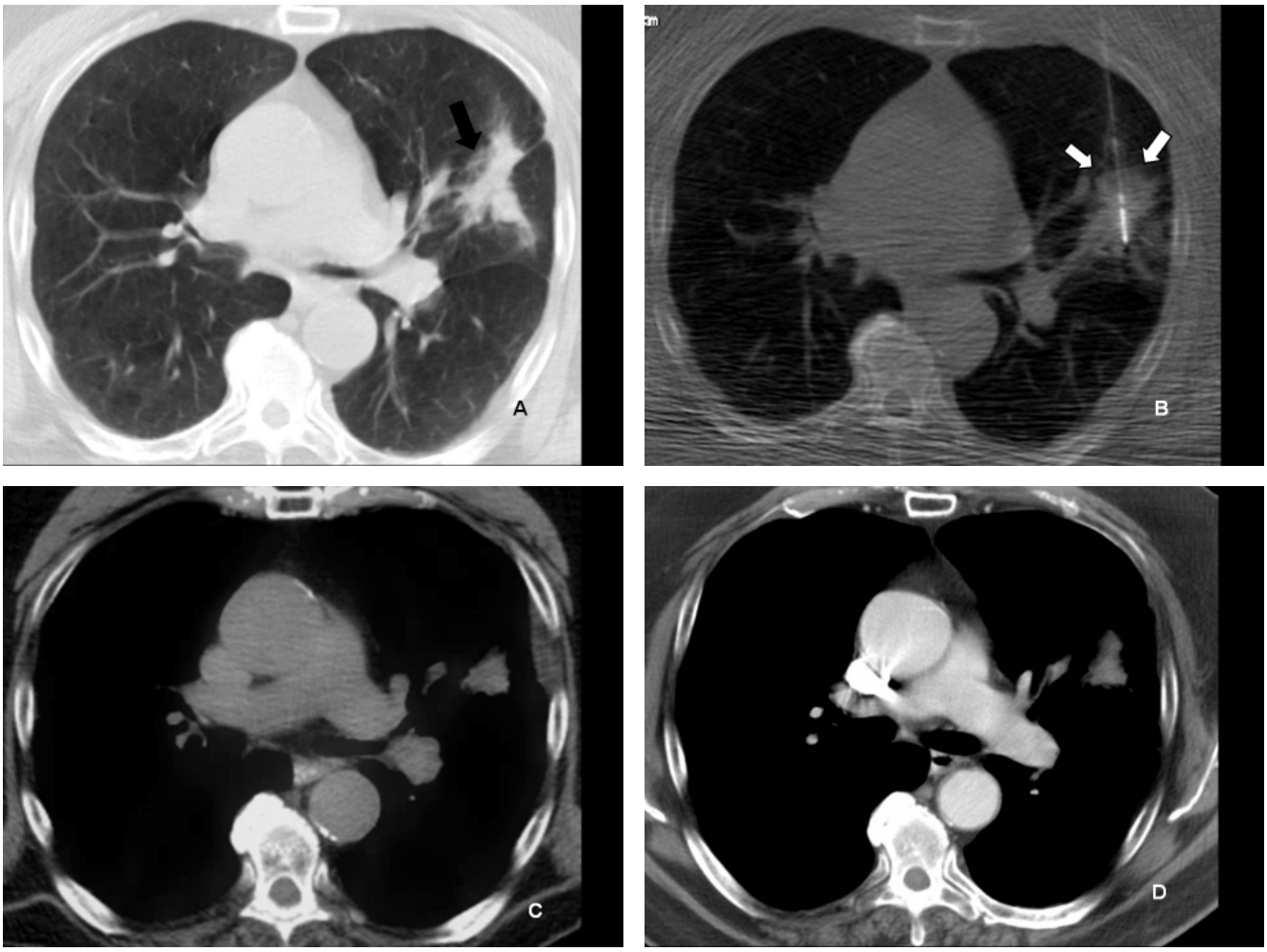

Figure 2. A 78 year old male presented with a 5cm, stage 1B, left upper lobe (LUL) adenocarcinoma (upper left, black arrow) and underwent RFA with a deployable tine electrode visualized intraprocedurally (upper right, white arrows indicate 2 tines). Follow-up PET-CT (lower left) 8 months post-ablation shows thermal scarring at the ablation site within the LUL with no uptake. One-year follow-up chest CT (lower right) also shows no signs of residual nor recurrent disease at the LUL ablation site.

or medical comorbidities.[1] Although chemotherapy and external beam radiation offer limited success in the treatment of HCC, surgical resection is shown to increase both 5-year and disease-free survival rates.[2] Because only a small number of these patients are surgical candidates, minimally invasive thermal ablation has increased in popularity with results comparable to those reported in surgical literature.

Analogous to the cytoreductive capabilities of chemotherapy, percutaneous ablation is used to lessen tumor burden and provide palliative care. [3] Thermal ablation is used as a bridging treatment for future liver transplantation. If a wait-listed patient develops small HCCs (3 lesions <3cm or 1 lesion <5cm) expected to grow in size threatening their standing or eligibility for future transplant, they may undergo ablation to stop the growth of tumor cells.

Resection of isolated colorectal hepatic metastases has been shown to increase 5-year survival from 2 to 37%.[4] As anatomic location of the lesion, hepatic reserve, and medical comorbidities determine resectability, only 10-25% of patients are surgical candidates.[4] Thus, for the majority of patients with hepatic metastases percutaneous thermal ablation is a viable option as a focused ablation can maximize preservation of functional parenchyma and lesions may be re-treated at a later date if clinically indicated.

Clinical Practice & Outcomes

RFA, cryoablation, and alcohol injection have been shown to be safe and effective means of treating unresectable primary and metastatic hepatic lesions. From 1998 to 2001, 123 patients with unresectable hepatic malignancies, including those with significantly impaired liver function (Child's C), underwent 168 RFA sessions at our institution confirming the efficacy of this technique. [5] Meta-analysis of such studies concluded that lesions measuring <2.5cm in diameter had a greater than 90% likelihood of being successfully ablated, and lesions 3.5-5.0cm 50-70%, with no evidence of residual disease or local recurrence.[6] Target lesion location also emerged as a significant factor in determining treatment success. A deleterious "heat sink" effect due to perfusion-mediated cooling is harmful to the generation and maintenance of cytotoxic temperatures throughout the ablation zone. High local recurrence rates were seen when lesions >3cm in well-vascularized hepatic tissue were treated with RFA.

Compared to radiofrequency, MWA offers numerous advantages including an improved convection profile enabling generation of consistently higher intratumoral temperatures. With a significantly deceased vulnerability to "heat sink", sizeable vessels (>3mm diameter) in close proximity to target lesions are not contraindications to treatment. Additionally, the unique flexibility of using multiple antennae simultaneously allows for the creation of bigger ablation zones and successful treatment of larger lesions in shorter sessions.[7,8]

Another series from our institution details the treatment of 118 hepatic lesions, either primary HCCs or metastases from distant primaries, and is the largest reported clinical MWA series to date in the liver.[9] Lesions ranged in size from 0.3-12.0cm and 84 MWA sessions were performed with a technical success rate of 96%. Index tumor size was not significantly predictive of recurrence at the ablation site until lesions reached sizes >4.5cm (P=0.02), with a mean 13±1 months to first recurrence.[9]

Complications

Post-procedural discomfort is controlled with acetaminophen/hydrocodone, and patients resume normal activities within 24 hours. A common complication unique to RFA is minor skin burning at the site(s) of grounding pad placement. Additional complications include post-ablation syndrome, a flu-like illness lasting for 4-5 days following ablation, and pneumothorax and/or pleural effusion when treating lesions in close proximity to the diaphragm.[5] Rarely, post-procedural bleeding, pseudoaneurysm or arteriovenous fistula formation and hepatic or portal vein thrombosis occur.[4]

Lung Ablation

Patient Selection

More than 15% of patients diagnosed with stage I or II **non-small cell lung cancer (NSCLC)** have tumors deemed surgically unresectable. This figure increases to 30% for those over 75 years of age or older due to tumor staging or medical inoperability.[10] Significant cardiorespiratory comorbidities are also present in patients with oligonodular metastatic disease to the lungs for which surgical resection has been shown to increase survival making percutaneous ablation a practical treatment option.[10]

Patients with recurrent disease after surgical intervention are also candidates for ablative therapy. Indications for palliative ablation include dyspnea, cough, hemoptysis, or pain due to advanced disease.

Clinical Practice & Outcomes

With early success demonstrated in animal models, our institution was first to report the use of RFA in the clinical treatment of pulmonary malignancies.[11] Much data now document the use of RFA in the treatment on NSCLC and pulmonary metastases with a synergistic effect observed when RFA is performed prior to treatment with conventional external beam radiation.[12]

Thermoablative procedures for primary and metastatic pulmonary malignancies will exceed 150,000 per year by 2010, an increasing proportion of which may utilize microwave energy which is capable of producing ablation zones 25% larger in diameter, 50% larger in cross-sectional area, and 133% larger in volume compared to RFA.[13,14] A study of 50 patients who underwent MWA of 82 intraparenchymal pulmonary lesions at our institution, both NSCLCs and metastatic lesions, showed 1-, 2-, and 3-year cancer-specific mortality rates to not be significantly affected by index tumor size >3cm or <3cm.[10] The mean diameter of treated lesions was 3.5±1.6cm, double that of tumors treated with RFA. Conversely, the data generated by 153 patients who underwent RFA at our institution for 189 pulmonary malignancies showed a statistically significant improved survival rate in patients with index tumors <3cm in diameter (P<0.002).[15] Thus, MWA emerges as the modality of choice when treating more sizeable pulmonary lesions.

Complications

The most common complication is pneumothorax, occurring in 12.5-16% of patients following RFA, comparable to the rates seen secondary to percutaneous lung needle biopsy.[12] Additional complications include pleural effusions, chest wall hematomas, post-procedure pleurisy, and pneumonia.

Kidney Ablation

Patient Selection

Current indications for percutaneous renal ablation include the presence of primary **renal cell carcinoma (RCC)** in patients deemed to be non-surgical candidates and recurrence of RCC after surgical intervention.

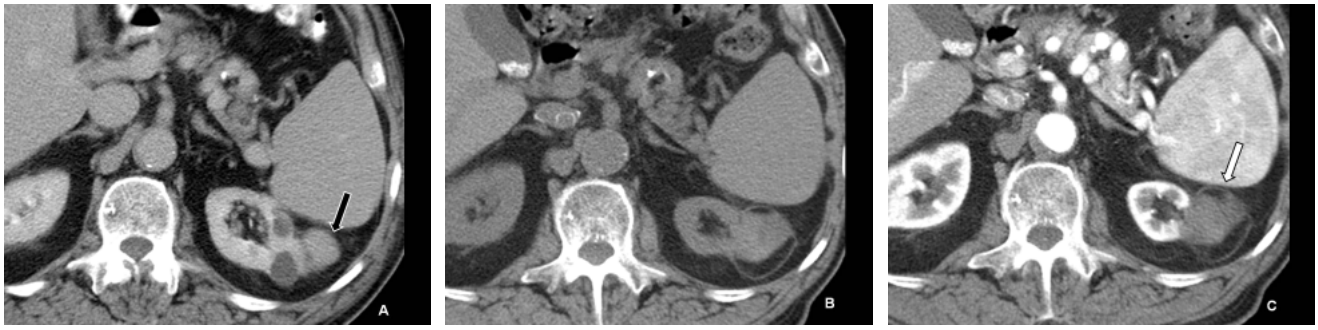

Figure 3. A 79 year-old male was found on CT (left) to have a 3.3x2.5x2.3cm exophytic enhancing soft tissue mass (black arrow) extending from the left kidney highly suspicious for renal cell carcinoma (RCC). He presented 3 months later for percutaneous biopsy and RFA. Twenty-six month post-ablation follow-up abdominal CT shows no evidence of residual nor recurrent disease within the ablation zone on pre- (center) or post-contrast (right) images. The ablation zone demonstrates retraction with a surrounding halo (C, white arrow), a characteristic appearance of ablated RCC.

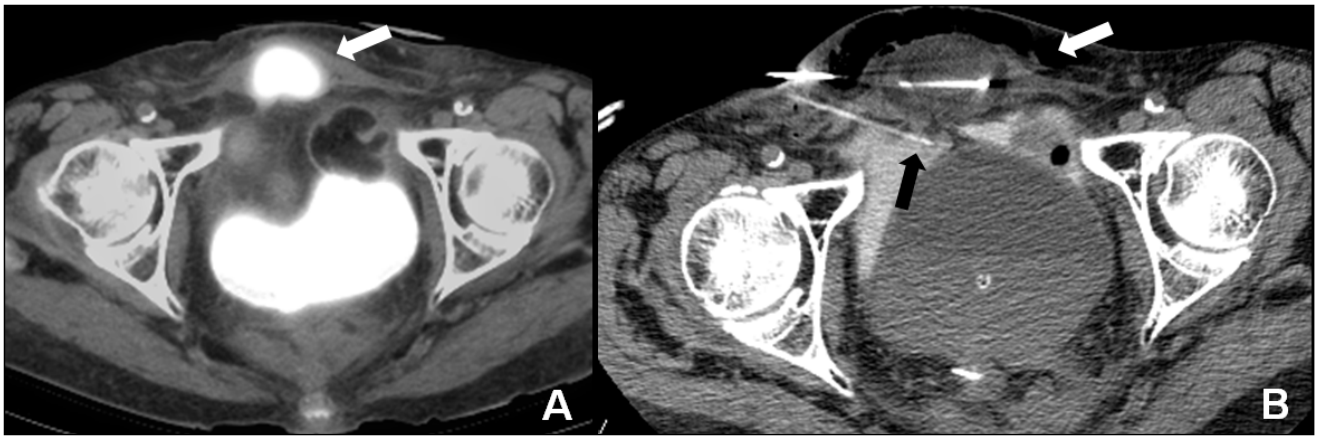

Figure 4. A 75 year old female with endometrial cancer status post radiation presented with complaints of a painful nodule on her lower abdominal wall. PET-CT revealed a highly FDG-avid 5x2.7cm anterior pelvic wall mass (left, white arrow). Two months later, the patient presented for cryoablation of this superficial metastasis. Intraprocedurally (right), hydrodissection was used to displace the bladder and colon inferiorly by instilling warmed saline mixed with contrast by means of a percutaneously placed catheter (black arrow). To protect the overlying skin, air insufflation (white arrow) was used to raise the skin and subcutaneous tissues superiorly. In clinical post-ablation follow-up the patient was noted to no longer have pain at this site.

Clinical Practice & Outcomes

With clinical studies demonstrating short- and intermediate-term post-ablative outcomes on par with those seen following surgical intervention, RFA is commonly used in the treatment of RCC. Early data evaluating the oncologic efficacy of RFA in the treatment of RCC reports a local control rate of 97.2% at a mean 18 months post ablation.[4] Hegarty et al. show that of 72 patients who underwent RFA for 81 lesions all were alive at a median follow-up of 13 months with evidence of complete tumor ablation after a single treatment in approximately 90% of cases.[16] Overall, cancer-free survival rates for RFA at 1 and 2 years compare favorably to those generated by partial nephrectomy of T1a lesions. [4]

Massachusetts General reports on RFA of 100 renal neoplasms over 6 years.[4] All lesions either <3cm or exophytic in growth underwent complete necrosis, and larger lesions >3cm were more likely to require re-treatment in a second session.[4] Likewise, successful treatment of all exophytic lesions was demonstrated by McDougal et al. who followed 16 patients for 4 years after percutaneous RFA of RCCs and report outcomes comparable to those documented after surgical intervention at 4 years follow-up.[17]

This patient population may also benefit from the advantages of MWA including shorter procedural times and the ability to treat larger lesions by using multiple antennae simultaneously. Lesions ranging in size from 3.9-13.0cm have been ablated with MW energy in ablate and resect clinical trials. [4] Reproducible and sizeable ablation zones are created in single 10-minute treatments with uniform tissue necrosis on pathologic examination. [4]

With promising short-term results, cryoablation is emerging as an effective treatment modality for RCC. Features unique to cryoablation include decreased risk of thermally-induced ureteral strictures and the ability to watch intraprocedural iceball formation, indicative of real-time treatment progress. This technology, similar to MWA, allows for the use of multiple probes simultaneously. A series of 41 patients underwent cryoablation for 48 RCCs with up to 4 probes used simultaneously creating iceballs as large as 6.5cm in diameter allowing the treatment of sizeable lesions.[4]

Complications

Multi-institutional review documents that percutaneous RF and cryoablation are safe treatment options with low associated complication rates.[4] Self-limited, asymptomatic, microscopic hematuria has been reported following MWA. Thermally-induced ureteral strictures are rarely documented, however, precautions including hydrodissection and ureteral stent placement may be used to protect the ureters from thermal injury.

Adrenal Ablation

Adrenal neoplasms, for which surgical resection is traditionally recommended, may be effectively treated with RFA. Cytotoxic effects are demonstrated in recurrent primary adrenal cortical carcinomas, adrenal metastases from a variety of systemic primaries, and in biochemically functioning adenomas.[18] Aldosteronomas and pheochromocytomas have been successfully ablated with resultant normalization in laboratory values and elimination of the need for long-term pharmacologic management.[19]

Palliative Ablation

Percutaneous thermal ablation has a documented role in the treatment of osteoid osteoma with clinical success demonstrated in up to 94% of patients following RFA.[4] The palliative treatment of painful osseus metastases is also emerging as an indication for RFA. A multicenter study recently reports a clinically significant reduction in pain in 95% of patients and decreasing opioid requirement at 8-12 weeks after RFA.[4]

Patients who pursue ablation as palliative therapy are followed longitudinally for resolution of symptoms. We reported on one of the first groups of patients with painful extra-abdominal metastatic disease to be treated with cryoablation in the US.[20] The response parallels European reports of successful palliation of local symptoms following cryoablation of recurrent pelvic malignancies including

rectal cancer.

With continued investigation, indications for use of radiofrequency, microwave, and cryoablation will continue to expand. Thermal ablation is, and will continue to be, an integral component of oncology treatment plans as the fourth arm of cancer therapy.

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Intracranial Atherosclerotic Disease:
Epidemiology, Imaging and Treatment

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Over the past decade, there has been a marked awareness of the epidemiology, clinical severity and treatment options for patients with **Intracranial Atherosclerotic disease (ICAD)**. Once thought to be uncommon, it is now known that ICAD is almost as common as extracranial (cervical) carotid atherosclerotic disease. In addition, it is known which subgroups that are at the highest risk of subsequent stroke. While the optimal treatment paradigm for ICAD is unknown, endovascular techniques (angioplasty and stenting) can be safely done that may reduce stroke rates in appropriately selected patients. In this article, we review the epidemiology, natural history, imaging, and treatment of ICAD.

Epidemiology

ICAD accounts for approximately 5 to 10% of all strokes and **transient ischemic attacks (TIAs).**[1] Among the more specific studies, the German Stroke Study Collaboration prospectively identified 4157 patients over 20 months at 11 different centers who were admitted within 24 hours of, new acute ischemic symptoms. [2] They found isolated symptomatic intracranial stenosis >50% in 6.5% of patients, proximal middle cerebral artery occlusion in 3.7% and basilar artery occlusion in 1.2%. Mortality rates at 100 days for these 3 groups were dismal at 10.1%, 21.4%, and 44.7%, respectively. There was a higher rate of intracranial disease in African-American, Japanese, Chinese, and Hispanic patients, [3, 4] and conversely higher rates of extracranial disease in Caucasians. [5, 6]

In the US annually, there are approximately 750,000 strokes and an additional 250,000 TIAs. Extrapolation of these prevalence rates to the multi-cultural population of Rhode Island, leads to an estimated 200 to 300 strokes and TIAs every year from symptomatic intracranial atherosclerosis.

Natural History and Stroke Rates

Subsequent stroke rates in patients with symptomatic intracranial stenosis are high, especially in patients with >70% stenosis. Initial reports from medical subgroups in trials in the 1980s had suggested annual stroke rates of 7-8%, [7] but these trials suffered from poor follow-up and selection bias. There is a general paucity of natural history data among symptomatic, untreated patients. Among the more recent studies, Wong et et al. reported follow-up in 705 patients presenting with acute stroke.[8] One-year stroke rates for patients with intracranial atherosclerosis only and for patients with intracranial and extracranial atherosclerosis were 17.1% and 24.3%, despite medical therapy. In another series, 47 patients with >50% stenosis were evaluated and 38 patients completed 6 months of follow-up.[9] Thirteen patients (38%) suffered a stroke at 6 months. Medical therapy over this time was not reported.

The **GESICA (Groupe d'Etude des Stenoses Inta-Cranieenes Atheromateuses symptomatiques)** study prospectively evaluated symptomatic ICAD in 122 patients with a single stenosis of at least 50%. [10] During a mean follow-up period of 23.4 months, 38.2% of patients had a cerebrovascular event in the territory at risk, including stroke in 13.7% and TIA in 24.5%, despite antiplatelet or antithrombotic therapy.

Imaging

Four imaging modalities can be used to diagnose and characterize ICAD: conventional angiography, **Magnetic resonance angiography (MRA), Computed tomography angiography (CTA),** and **transcranial Doppler (TCD).** The latter 3 modalities are non-invasive while conventional angiography is minimally invasive.

Advantages of MRA are that the brain parenchyma can be characterized at the time of the exam and that no radiation or intravenous contrast is required (vessel imaging employs flow physics alone). Although CTA requires contrast and radiation, the spatial resolution is improved over MRA.

The purported advantages of TCD imaging is that it is non-invasive, a bedside examination, and less expensive. However, it is highly dependent on the experience of the operator and not all patients have acoustic windows.

The **Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA)** trial compared TCD and MRA with conventional angiography for the detection of >50% stenosis.[11] TCD and MRA had negative predictive values of 86% and 91%, respectively. Positive predictive values were less impressive (possibly due to low disease prevalence) at 36% and 59%, respectively.

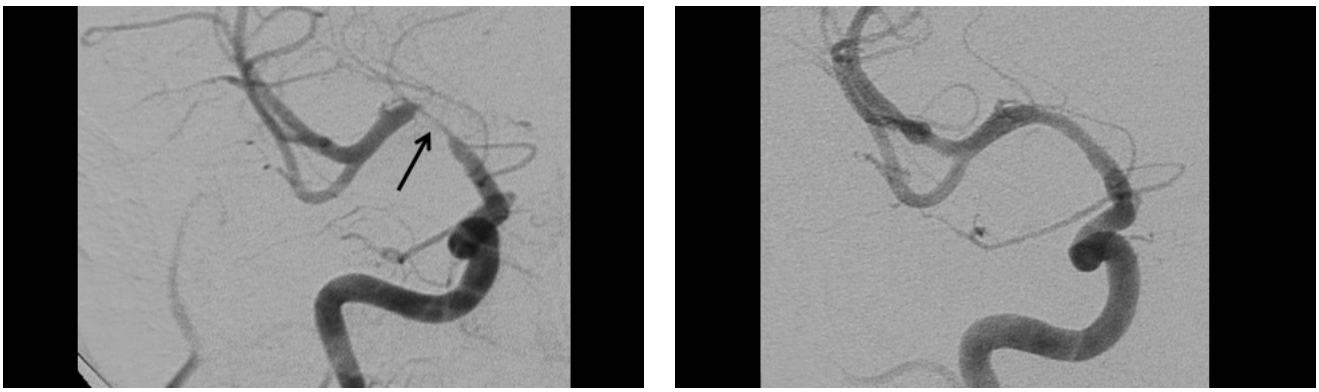

Figure 1. Images from intracranial angioplasty and stent placement in a 49 year old male who presented with crescendo TIAs in the right hemisphere, occurring despite antiplatelet agents. Initial angiogram shows a high grade stenosis of the right middle cerebral artery (MCA) (arrows, left). After angioplasty and stent placement, the vessel caliber is markedly improved and flow through this segment is greatly increased (right). The stent was placed in this case because of elastic recoil that occurred after the angioplasty (not shown).

Given the reasonably high negative predictive values of MRA and TCD, they can be used as initial imaging in patients. However, an abnormal MRA or TCD requires a confirmatory test. CTA is the best non-invasive test for intracranial atherosclerosis given its superior spatial resolution over MRA. Catheter angiography remains the best test for diagnostic purposes (Figure 1) because of its ability to accurately quantify the degree of stenosis and assess vessel morphology, but is usually reserved for patients who are considered for treatment with endovascular therapy.

Medical Therapy

The prospective, randomized **Warfarin-Aspirin Symptomatic Intracranial Disease (WASID)** trial showed that warfarin was of no benefit over aspirin in preventing recurrent stroke, and patients on warfarin had significantly higher rates of hemorrhage.[12] WASID was a multicenter, double-blinded trial of patients with symptomatic ICAD and lesions with >50% narrowing. Patients were randomized to ASA or warfarin, with primary endpoints being ischemic stroke, brain hemorrhage, and death from vascular causes. Although criticized for its non-standard ASA regimen and high rate of dropout for both medications (28.4% in warfarin group), the study was terminated prematurely as there were significantly higher rates of hemorrhage in warfarin group and warfarin provided no benefit over aspirin for the prevention of stroke. The primary endpoints were reached in 21% of patients at 2 years in the aspirin group and 22% of the warfarin group.

Subgroup analysis of the WASID data [2] pinpointed certain high risk subgroups: patients with severe stenoses (>70%), and those enrolled less than 17 days after the initial event. Patients with a >70% stenosis had a 23% chance of stroke at 1 year and 25% at 2 years, despite medical therapy. Even more sobering than the likelihood of stroke in patients with ICAD are the clinical consequences. Of the 106 strokes which occurred in the WASID study group, 73% were within the same territory as the stenotic lesion and 44% were disabling.

Cilostazol is the only other anti-platelet agent to be studied specifically in patients with symptomatic ICAD. Although no strokes were seen in either treatment group (cilostazol and aspirin vs. placebo and aspirin at 6 months, progression of ICAD as measured by MRA was less common in the cilostazol group (6.7% versus 28.8%; p=0.008). The TOSS-II trial is now ongoing and compares cilostazol and aspirin vs. clopidogrel and aspirin in patients with symptomatic ICAD.

Certainly optimal medical therapy for ICAD would include aggressive management of hypertension, smoking cessation, control of diabetes and hyperlipidemia. While no trials have directly compared more potent anti-platelet agents such as Clopidogrel (Plavix) or Asprin/Dipyridamole (Aggrenox), both of those agents are commonly used in ICAD patients.

Endovascular Therapy

Angioplasty

Given the dismal natural history of intracranial stenosis despite medical therapy, there has been great interest in using endovascular techniques to improve stroke-free survival. In 1980, Thoralf Sundt reported the first successful intracranial angioplasty. Early investigators reported highly disparate and, in some cases, dismal results. Among the first studies specifically looking at ICAD patients was the study by Higashida et al, showing a 38% major complication rate in treatment of 8 patients with symptoms refractory to medical management.[13] However, over the ensuing decade, significant technical refinements have resulted in a marked reduction in procedural complications.

Connors et al introduced the concept of "sub-maximal" angioplasty.[14] They showed that technical factors affected outcome. By using a balloon smaller than the native vessel (which differs from coronary and peripheral angioplasty where the balloon chosen is *the same size or larger* than the target vessel), and inflating slowly, the trauma to the vessel wall was markedly reduced, and with it, the procedural complication rate dropped substantially. Several recent groups have reported their results, and 30-day major complication rates have been reduced to between 4 and 6%. (Table 1)

While procedural success is key, the ultimate goal is prevention of further stroke. Many of the same groups have followed patients for a long term and have shown impressively low stroke rates. (Table 2) Clark documented no subsequent neurological events in 17 treated patients who were followed for a mean of 22 months.[15] Yoon reported similarly impressive results: only 1 TIA event in 32 patients followed for 20 months.[16] In their series of 120 patients with a mean follow-up of 42 months, Marks et al. reported a 3.2% stroke rate in the territory of treatment which included perioprocedural strokes and deaths.[17] Finally, Wojak reported an annual stroke rate of 1.8% in 60 patients with a mean follow-up of 45 months.[18] Considering that most of the patients in these series had >70% stenosis, these rates appear to be substantially lower than the natural history on medical therapy.

These same groups[17, 18] also provide data on restenosis in these patients. Symptomatic and angiographic restenosis occurred in approximately 5-10% and 10-30%, respectively, with a mean time to restenosis of 6 months.

All of these studies combine to show that intracranial angioplasty has matured to be a treatment that is safe, durable and effective at preventing recurrent stroke. What is lacking is randomized data comparing angioplasty with medical management alone, or with stenting.

Stenting

Many centers have taken a leap of faith and extrapolated data from coronary and peripheral artery disease, choosing to perform stent placement in addition to angioplasty. However, no data show a superiority of in-

Table 1

Series	N	Complication rate	Technical Success
Higashida et al. 1993	8	38%	
Clark et al. 1995	17	9.1%	
Marks et al. 1999	23	4.3%	
Connors et al. 1999	50	6.0%	98%
Yoon et al. 2005	32	6%	91%
Marks et al. 2006	120	5.8%	93%
Wojak et al. 2006	60	4.8%	91%

Table 2

Series	N	Mean Follow-up	Annual Stroke Rate
Clark et al. 1996	17	22	0%
Yoon et al. 2005	32	20	0%
Marks et al. 2006	120	42	3.2%
Wojak et al. 2006	60	45	1.8%

Table 3: Complication rates of intracranial stent placement for ICAD using balloon mounted stents.

Series	(n)	Complication Rate	Technical success
Gomez et al. 2000	12	5.3%	
Levy et al. 2001	11	36%	100%
SSYLIA 2004	43	6.6%	90%
Yu et al. 2005	18	16.7%	
Lylyk et al. 2005	104	9.5%	98%
Mazighi et al. 2006	28	14.2%	
Jiang et al. 2007	213	4.3%	92%

tracranial stenting over angioplasty alone in most patients with ICAD.

One of the early studies evaluating dedicated intracranial stent, the **Stenting of Symptomatic atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA)** trial[19] was a nonrandomized phase I study to evaluate the frequency of subsequent stroke in ICAD patients with >50% stenosis. Although successful stent deployment was seen in 95%, the frequency of stroke at 30 days and 1 yr was 7.2% and 10.9% - which do not appear to be substantially different from the WASID natural history data.[12] Several other studies evaluated the use of balloon mounted stents for ICAD patients (Table 3), with most of these demonstrating higher complication rates than those of angioplasty alone.[10, 19-24]

Combining the lessons learned from submaximal angioplasty with the enhanced navigability of a self-expanding stent design, the Wingspan stent (Boston Scientific, Natick, MA) was introduced with the intent of being placed after angioplasty, to reduce restenosis and improve stroke free survival. A phase I study reported a 30-day death and ipsilateral stroke rate of 4.5%, confirming safety, with a 1-year stroke rate of 9.3%.[23] One concern about the Wingspan stent, however, is what appears to be a higher than expected restenosis rate. Despite this, the Winsgpan stent is helpful in the management of flow limiting dissections occurring during angioplasty, elastic recoil, or some patients with recurrent stenoses. Further data will be needed to determine if stenting offers any advantage over simple angioplasty alone in ICAD patients.

Future Directions

Perhaps the biggest area of interest in ICAD therapy is the recently started, NIH-funded, randomized study comparing maximal medical management alone with medical therapy and stent placement, the **Stenting vs. Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS)** trial (http://clinicaltrials.gov/ct2/show/NCT00576693). The goal is to enroll 640 patients, with the medical treatment group being monitored for blood pressure targets, cholesterol levels and anti-platelet therapy. Patients in the endovascular treatment arm will all be treated with Wingspan stent placement, in addition to maximal medical therapy. All patients will have greater than 70% stenosis of the target artery and have strokes or TIAs referable to that lesion. We eagerly await the results of this landmark trial.

Summary

Intracranial atherosclerosis accounts for 5 to 10% of all strokes. The natural history is poor, especially among patients with a greater than 70% stenosis. Studies of medical therapy have shown no benefit to warfarin over aspirin in these patients. In fact, patients with a greater than 70% stenosis who present with a stroke in the territory at risk have a 25% risk of stroke in the subsequent 24 months, despite medical therapy. First line therapy for these patients is aggressive risk factor management, including smoking cessation, blood pressure control, management of diabetes and correction of dyslipidemia. Intracranial angioplasty has a low complication rate between 4-6%, and low post-treatment annual stroke rate between 2-4%. What was once considered a very high risk procedure has now shown to be as safe as carotid endarterectomy for symptomatic patients. Stent placement can be performed in select cases as an adjunct to primary angioplasty. While we await the results of the SAMMPRIS trial, we can still offer aggressive medical and endovascular options for patients with this lethal disease.

From a management standpoint, we believe that intracranial imaging (TCD, MRA or CTA) should be performed in patients with stroke or TIA. Consultation with a neurologist would be helpful, as would consultation with a neurointerventional radiologist to help identify patients who may benefit from more aggressive endovascular therapy in conjunction with medical therapy.

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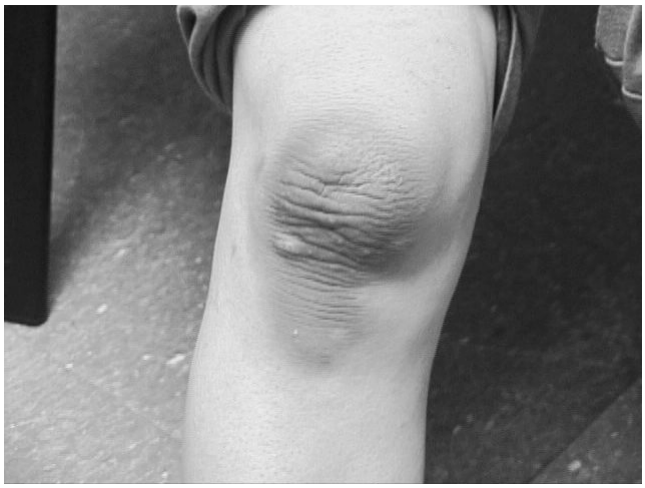
Images In Medicine

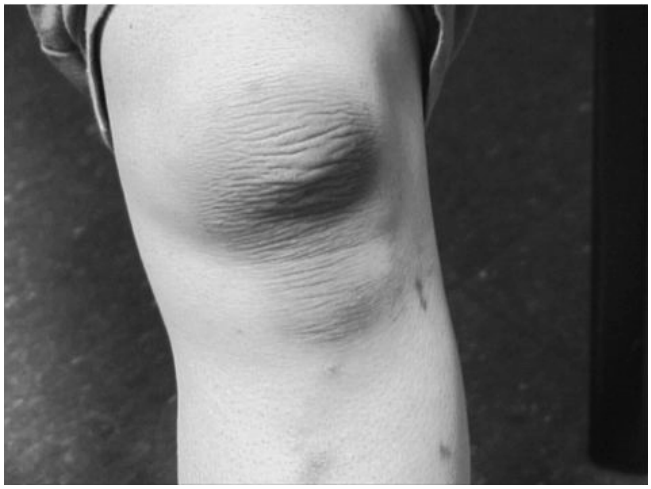
Knee Lichenification In Parkinson's Disease: "Parkinson Knees"

Joseph H. Friedman, MD, and Stephen Glinick, MD

Lichenification describes a leathery pattern of response of the predisposed skin to repeated rubbing or scratching, which once established may become self perpetuating even after the etiology has been removed.[1] This is a well described syndrome in people who spend time on their knees or other body parts, including, for example, Muslims who pray several times each day.[2] We could find no references to its occurrence in **Parkinson's disease (PD).**

The photos are the knees of a 54 year-old man who had been diagnosed with PD 21 years before and suffered from severe fluctuations in response to his medications. He had had a unilateral pallidotomy before **deep brain stimulation (DBS)** was developed but was not a candidate for DBS due to psychiatric problems. At the time of the photos he was taking carbidopa-levodopa 10/100 2 tablets every two hours, entacapone 200 mg three times daily and pramipexole 1.0 mg three times daily. He was "on" with dyskinesias half the day and "off", unable to walk, the other half. When unable to walk he crawled, resulting in the skin changes over his knees.





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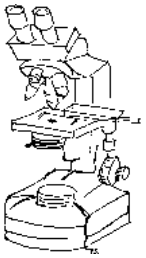
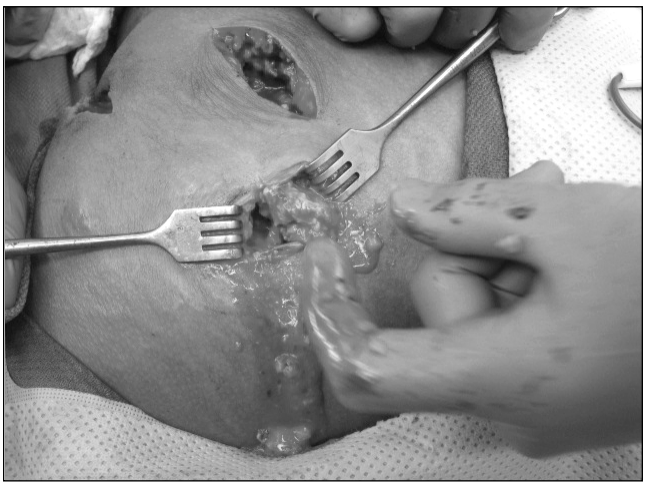


The Creative Clinican

X Marks the Spot: Cosmetic Surgery Gone Awry

Dalila Zachary, MD, Donovan Rosas, MD, Florence Chan, MD, and Karen Tashima, MD

A healthy 21 year-old woman presented to Rhode Island Hospital Emergency Department with intermittent fever for the previous 48 hours. Four days before presentation she received hydrogel buttock injections in a beauty salon in Florida. The majority of the injections were to the right buttock. She stopped the injections to the left buttock due to pain. She was evaluated for a near syncopal event at a hospital in Florida where they attributed her symptoms to a vasovagal episode. She was also diagnosed with cellulitis of both buttocks and given a prescription for cephalexin. Upon arrival home, the patient noticed night sweats and fevers. She also experienced chest pain, shortness of breath, headache, and photophobia. Her past medical history was significant for a remote methicillin susceptible *Staphylococcus aureus* abscess in the groin. On physical examination she had a temperature of 103.4, pulse 113, blood pressure 109/55. The examination was remarkable for "X" markings on both buttocks, more on the right than left. The right buttock was indurated and swollen with some tenderness to palpation. There was no erythema, fluctuance or drainage. The left buttock was less indurated and swollen. The remainder of her examination was normal. Her white blood cell count was 11.4, hemoglobin 8.9, platelet count 155,000. A chest CT-scan did not reveal a pulmonary embolus. Abdomen and pelvis CT-scans and pelvis revealed asymmetric fullness of the right gluteus maximus and medius muscles, with no evidence of organized collection to suggest abscess formation. There was also diffuse subcutaneous stranding. With concern for a possible right buttock infection, the patient was started on intravenous vancomycin and piperacillin-tazobactam. She declined surgical exploration for probable infection, so she was continued on intravenous antibiotics and closely observed. After five days of antibiotics, an area in the right buttock started to spontaneously drain pus. She was then taken to the operating room for incision, drainage and debridement. During the washout, multiple cavities of gross purulence and necrotic fat were found in both buttocks. No organism was ever isolated from the operative specimens. She was continued on vancomycin and piperacillin-tazobactam during her 12-day hospitalization, then changed to ciprofloxacin and trimethoprim-sulfamethoxazole on discharge for 7 days. Her follow-up outpatient appointments with plastic surgery revealed slowly healing bilateral buttock wounds.



Photograph taken during operative washout. Gross purulence was noted.

Discussion

A number of biological and synthetic injectable fillers have been developed for and used in soft-tissue augmentation and facial contouring since the first attempts at fat transplantation in 1893. Cross-linked polyacrylamide hydrogel, a nondegradable filler, has been approved for facial contouring in Europe, Australia, and Asian countries. The hydrogel itself produces the filling effect. The foreign-body reaction is minimal and transient, and fibrosis is seen only as thin strands of a vascularized network of connective tissue fibers, which anchor the gel in place and prevent migration.[1] The Food and Drug Administration in the United States has not approved it, because of concerns about its efficacy and safety.

Within the past three years, more reports of buttock enhancements using hydrogel, silicone or other similar thick liquids have surfaced from the Northeast to Miami. Across the internet, people are discussing injections of black-market, medical-grade silicone, industrial-grade silicone, or hydrogel as a cheap, fast and easily accessible way to plump up breasts, buttocks, thighs, even wrinkles. These reports raise concerns over the potential administration of unknown chemicals as well as the possibility of organ failure and even death following these injections. A 46-year-old California woman in 2005 died of multiple organ failure after receiving buttock injections of what had been billed as "French polymer" but were actually cooking oil. The beautician who delivered the injections was sentenced to 15 years in prison.[2] Just this year, a 43 year-old woman in New York died from a silicone pulmonary embolism after receiving injections to her thighs and buttocks,[3] and two women in Florida landed in the Intensive Care Unit with or-

gan failure after receiving the so-called hydrogel injections in the buttocks. Investigations revealed they were injected with industrial silicone.[4]

With the potential for irreparable injury and even death befalling those who seek this type of cosmetic surgery, it is imperative that the medical community be aware of this problem and be vigilant in the treatment of possible bacterial infections.

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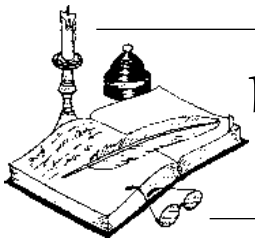


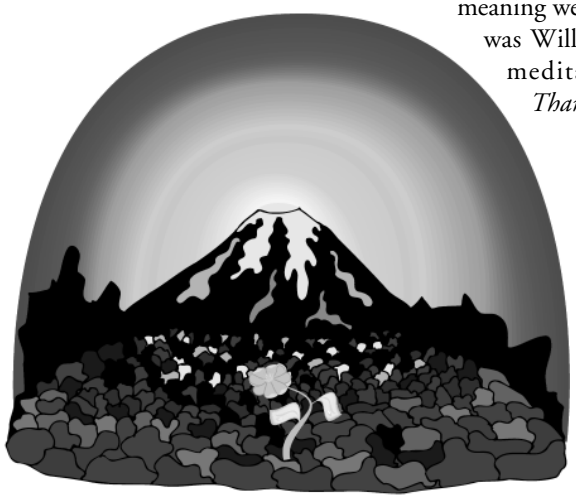
Physician's Lexicon

A Graveyard of Words

December is an inopportune time to explore words pertaining to death, interment and cremation. But these words pertaining to the inevitable departure of humans need to be understood as readily as the terminology that defines births and new human beginnings. The art of medicine, dedicated to the preservation of life, understandably refrains from excessive discussion of the technical features accompanying death. Yet, except for those whose existence is based on denial of reality, the substance of death is there; and it is accompanied by a small vocabulary of its own. Some are of classical Greco-Latin origin; some Anglo-Saxon and a small number are eponyms.

The word, death, is from the Saxon and Teutonic word, *doth.* Cemetery, stems from the Latin, *coemeterium*, meaning a room to sleep, and is derived earlier from a Greek word meaning 'a place to lie down' which, in turn, is related to a Latin word, *coitus*, meaning a coming together, as in the word coition, or even a sexual union.

The Greek root for death (or that which is extinguished) is *thanato-*, appearing in words such as thanatology (the study of death) and euthanasia (a painless death; using the Greek prefix, *eu-*, meaning well or good.) And then there was William Cullen Bryant's poetic meditation on death called *Thanatopsis*, written at age 17.



Mausolus, was the king of Caria. When he died, he was interred in a magnificent sepulchral monument constructed by his wife, Artemisia, giving rise to the word, mausoleum. A sepulcher descends directly from the Latin, *sepulcrum,* meaning a tomb. The word, tomb, is also from the Greek, *tumbos*, meaning a mound and is cognate with the Latin, *tumulus*, meaning a raised heap of earth.

A sarcophagus—a stone coffin of ancient Greece—literally means that which eats flesh. The Greek root, *sarco-* (as in words such as sarcoidosis, sarcomere and sarcoma) means flesh; and the Greek root, *phagos* (as in words such as phagocyte) means to eat, to consume. A casket is not a diminutive of cask but rather a corruption of the French, *cassette*, meaning a box or a chest.

Cremation derives from the Latin, *cremare,* meaning to burn or consume by fire. It has been occasionally pointed out that only the letter 'm' separates the word creation from cremation.

– Stanley M. Aronson, MD

THE WARREN ALPERT MEDICAL SCHOOL OF BROWN UNIVERSITY
Brown
Division of Geriatrics
Department of Medicine

GERIATRICS FOR THE PRACTICING PHYSICIAN

QUALITY PARTNERS OF RHODE ISLAND
Quality Partners of RI

EDITED BY ANA TUYA FULTON, MD

Medication and Non-Adherence In the Older Adult

Syed Latif, MD, and Lynn McNicoll, MD

Ms. D, a 65-year-old woman with hypertension and diabetes, presented to your office for a routine appointment. Her most recent hemoglobin A1C was 9.0. On examination, her vital signs were normal with the exception of blood pressure which was 165/85. Her medications included zestoretic and pioglitazone. On questioning, she revealed that she has not been able to buy her medications because they are too expensive: she had reached the 'donut hole' in her prescription coverage plan.

Definition and Impact of Medication Adherence

The term "non-adherence" is preferred to "non-compliance" because non-compliance implies an element of fault or blame on the part of the patient.[1] Non-adherence has been defined in the literature as a patient's passive failure to follow a prescribed therapeutic regimen. The same principle applies to dietary regimens, screening tests, and lifestyle modifications. Non- adherence to medication has profound implications on the patient as well as on doctor-patient relationships and interactions, plans of care, and the healthcare system.

Without taking medications as prescribed, the patient will not benefit from the medication, adequate drug serum levels will not be achieved, and the medication will not be an effective therapeutic intervention. For example, if a patient with diabetes mellitus is prescribed an oral agent but is not consistently adhering to the regimen, only suboptimal intermittent glucose control will be achieved instead of the continuous control required for optimal prevention of the long-term consequences of diabetes. In addition, physicians may erroneously interpret the inadequate glucose control as indicating a need for more medication and thus potentially over-prescribe, putting the patient at risk for hypoglycemia.

Ultimately, non-adherence leads to increased healthcare utilization through undertreatment of chronic and acute problems. It has been estimated that the yearly cost of non-adherence in America ranges from $396 to $792 million,[2] and that approximately 1/3 to 1/2 of all medication-related hospital admissions are attributed to non-adherence.[2] Continuing with the example above, the patient with uncontrolled diabetes will have elevated serum glucose levels that impair immunity, rendering her susceptible to infections, and predispose her to developing a diabetes-related syndrome, such as hyperosmolar hyperglycemic non-ketotic state, either of which can result in a costly hospital admission.

Table 1. Potential Etiologies for Non-Adherence

- Complex medication regimens (HIV and HAART)
- Convenience factors (eg, dosing frequency)
- Behavioral factors
- Treatment of asymptomatic conditions
- Affordability
- Side effect profiles of medications
- Severity of the problem (VA hypertensive study)
- Patient disagreeing with therapeutic plan

Reasons for Non-Adherence

An estimated 33 to 50% of patients do not adhere to their medication regimens as prescribed.[3] In a study aimed at adherence in the elderly population, it was demonstrated that when prescribed statin therapy, there was only 40% compliance.[4] Also, the highest rate of non-adherence tends to occur within the first few months of therapy.[3] Explanations include the sudden added financial burden of a new prescription or the appearance of side effects soon after initiation. These possibilities should be explored with every patient in the months following the addition of new medications.

A multitude of reasons contribute to non-adherence. (Table 1).[3] For example, the elderly patient with multiple medical problems requiring complex drug regimens may find it difficult to take numerous medications multiple times each day. The rate of adherence is inversely proportional to the number of medications a patient takes. Complex regimens of multiple drugs are commonly a problem for older adults, who take the highest number of medications of all age groups.[1]

Another common reason for is cost. Although older Americans are no longer the poorest, they are still overrepresented in the poverty range. With Medicare Part D prescription programs, older adults are required to pay 100% for their medications costs once their costs reach the "donut-hole" at $2700 (their co-payment plus their insurers' payments). Patients leave the hole, after paying up to $4350 out-of-pocket for medications. As a result, many elderly patients on limited incomes begin rationing their medications or stop taking them altogether.[5]

Patients are often not forthcoming about non-adherence because of guilt, lack of education or understanding about the importance of adherence, embarrassment about their inability to manage an overwhelmingly complex drug regimen or about their financial limitations, or fear of angering their physicians.

Table 2. Solutions for Non-Adherence

Patient Education
Helping Patients Improve Their Organization Skills
Mailed Communications
Manual Telephone Follow-up
Self-Monitoring
Obtain help from family members
Simplifying the Medication Regimen
- Recommend Pillboxes
- Using generic medications if cost is an issue
- Combination drug regimens
- Once a day dosing if possible
- Ask patients to bring in pill bottles at every visit
- Provide written instructions

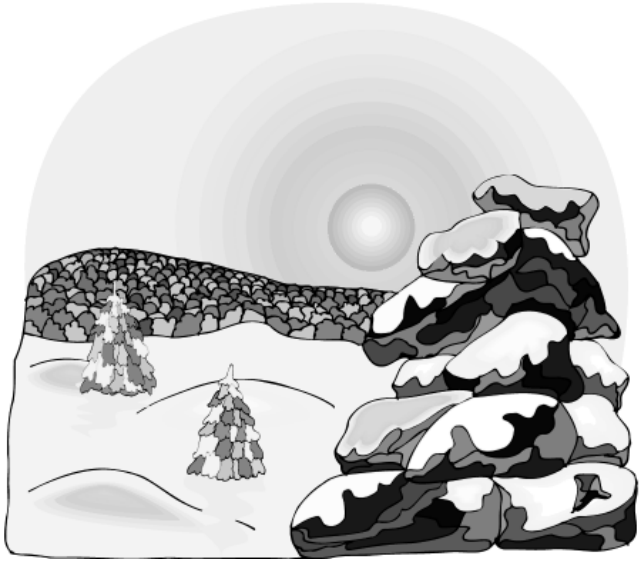
Solutions

Health care providers can employ numerous interventions to improve adherence in the older adult. (Table 2). Simplifying a patient's medication list as much as possible can increase adherence as well as save the patient money. For example, when **Highly Active Anti-Retroviral Therapy (HAART)** was introduced, the complex regimens required patients to take multiple medicines throughout the day. As a result, many patients could not adhere to these regimens because of the time and effort that was required. However, as therapies have improved and regimens became streamlined, adherence improved. In one study, HIV patients reported a 94% improvement in adherence with simplification of the regimen, as well as with directly observed therapy. [6]

Another simple intervention is to ask patients to bring their pill bottles at each visit. This lets the physician quickly assess whether or not the medications are being taken as prescribed.

Pre-loaded pillboxes can provide reminders and improve adherence. When the list of medications is long and the regimen complex, the risk of non-adherence grows. The boxes divide the medications into daily doses. Alternatives include using charts to track medication administration as well as a reminder system, available with electronic systems like personal digital assistants. For patients with cognitive impairment, the physician might ask family members to keep track of medication usage.

If cost is as an important reason for non-adherence, switching brand name medications to generic or cheaper alternatives is helpful. Reviewing the regimen for medications that may no longer be necessary can streamline the regimen for ease and cost purposes. If the side effects are troubling for the patient, alternative medications in the same class but with better side effect profiles can be identified.



Back to the Case

Ms. D was advised to use pharmacy retailers with low cost prescriptions, and her antihypertensive and diabetic medications were changed to generics. She was counseled about the long-term consequences of not appropriately managing her hypertension and diabetes. She agreed to the plan as described and was asked to return for a follow-up visit in one month. At that visit, her blood pressure was better controlled at 130/70 and she reported no difficulty in obtaining her medicines.

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Patterns of Obesity Among Men and Women In Rhode Island In 2007

Patricia Markham Risica, DrPH, RD, Jana Hesser, PhD, Yongwen Jiang, PhD,and Kathleen Taylor

The proportion of adults who are overweight or obese has increased markedly in the past two decades,[1] both nationally and in Rhode Island.[2] These increases are alarming due to the anticipated increases in associated diseases [3,4] and in the associated health care costs and loss of productivity.[5] This report presents survey data on the differing patterns of obesity among Rhode Island adult men and women, and associated risk factors.

Methods

Overweight is defined as having a **body mass index (BMI)** (BMI = weight divided by the square of height measured in Kg/m^2) of 25 or greater but less than 30; obesity is defined as having a BMI at or above 30. This analysis is focused primarily on obesity although any degree of overweight or obesity is associated with increased health risks. Obesity rates were calculated using heights and weights reported by respondents to the Rhode Island **Behavioral Risk Factor Surveillance System (BRFSS)** during 2007. The BRFSS is a telephone survey of randomly selected Rhode Island adults aged 18 or older.[6] Survey data are weighted to be representative of the Rhode Island adult population. During 2007, there were 4,499 respondents to the BRFSS. Data presented here are for adults ages 20 and older.

Results

In 1998, 46% of RI men and 27% of women were overweight, while 18% and 15%, respectively, were obese. By 2007 the proportion of overweight had increased to 51% for men and 29% for women, and to 23% and 22% obese. Because many respondents under-reported their weight, or over-reported their height, the actual proportions are likely to be higher.[7]

Which Adults are at Risk?

In 2007, Rhode Island men exceeded the national sample of men in the proportion who were overweight (51% vs. 43%), although they were less likely to be obese (23% vs. 27%).[8] In 2007 women in Rhode Island were less likely to be either overweight (29% vs. 30%) or obese (22% vs. 26%) compared to women nationally.[8]

Demographic disparities for obesity differ markedly between men and women in 2007. (Table 1) For men, small differences in obesity were not significant among racial and ethnic groups (23.9% of White non-Hispanic, 16.4% of Hispanic and 15.5% of Black non-Hispanic men were obese). On the other hand, White non-Hispanic women (20.7%) were significantly *less* likely to be obese than either Black non-Hispanic (37.5%) or Hispanic (29.0%) women.

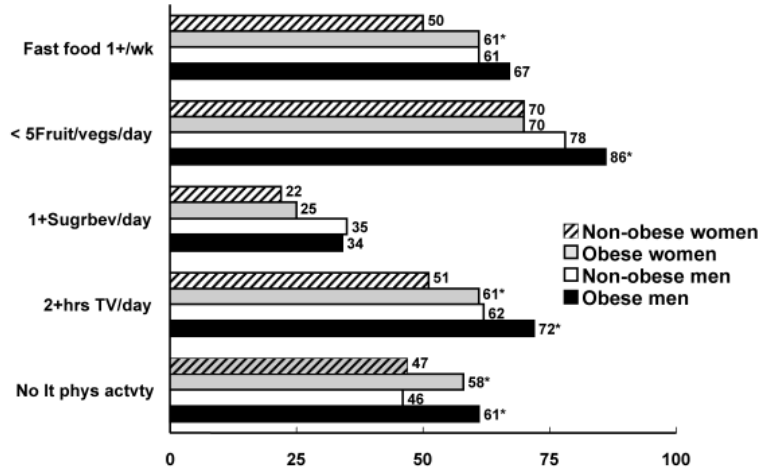
Similarly, differences in obesity by educational level or income status were noted for women, but not for men. The prevalence of obesity was lower for women of higher education, and for women of higher income. Women who are college graduates reported the lowest obesity proportion (16.7%) while women with less than a high school education have the highest obesity proportion (32.4%). The proportion of obese women with household incomes of $75,000 or more is 18%, compared to 30.2% for women with annual household incomes less than $25,000. In contrast, there is no significant difference in the rate of obesity for men by differing levels of education, or levels of income, but men did differ in risk of obesity by age group. Men from 45-64 years of age were at highest risk for obesity compared with other age groups, but for women, no differences in risk were found between age groups. (Table 1)

Table 1. Obesity Disparities by Gender

	Percent Obese	
	Men	Women
White NH	23.8	20.7*
Black NH	15.5	37.5
Hispanic	16.4	29
20-29	15.7*	20.4
30-44	20.9	20.3
45-64	29.4	25.3
<HS	26.8	32.4*
HS Grad	25.1	28.8
Some College	21.8	19.5
College Grad	20.9	16.7
<$25,000	26.6	30.2*
$25-74,999	20.5	26.2
$75,000+	24.4	18

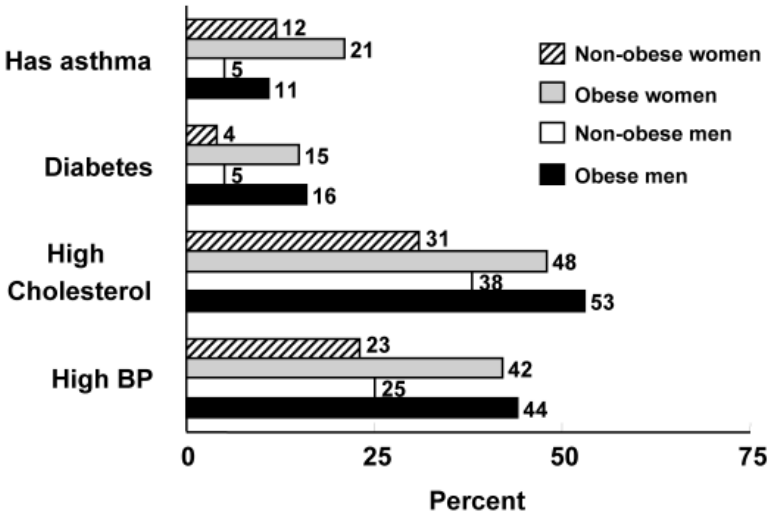
* differences statistically significant at p <.01

Figure 1. Behavioral risks among obese and non-obese adult men and women, ages 20+, RI 2007.



* differences between obese and non-obese women or men are statistically significant at p <.01

Figure 2. Health conditions among obese and non-obese adult men and women, ages 20+, RI 2007.



All obese/non-obese differences for both men and women are statistically significant at p<.01

Behavioral Risk Factors for Obesity

Several indicators of nutrition and physical activity were assessed comparing Rhode Islanders who are obese or not obese, and making those comparisons separately for men and women. These likely risk factors included: fruit and vegetable consumption, fast food consumption, sugar-sweetened beverage consumption, hours of TV viewing, and participation in non-work related regular physical activity. (Figure 1)

Obese men are significantly more likely to eat less than the recommended 5 or more servings of fruits and vegetables a day (86%) than non-obese men (78%). There were no differences in fruit and vegetable intake for obese and non-obese women (both about 70%). In contrast, obese women (61%) were significantly more likely than non-obese women (50%) to eat fast food one or more days each week, while the proportion of men eating fast food were roughly the same for obese (67%) and non-obese men (61%). About 34% of men and 22% of women reported consuming one or more sugar-sweetened beverages per day, but no differences in consumption of sugar-sweetened beverages were found between obese and non-obese individuals for either men or women.

For men and women, the proportion of individuals watching two or more hours of television a day was significantly higher for obese women (61%) and men (72%) compared with non-obese women (51%), and non-obese men (62%). Also, the proportion of individuals who did not engage in regular physical activity (less than 30 minutes of moderate, or 20 minutes of vigorous activity per day, five days or more per week) was significantly higher among obese women (58%) and men (61%) than among their non-obese counterparts (47% and 46% respectively).

For both genders, obesity was significantly related to an increased risk of asthma, diabetes, high cholesterol and high blood pressure. (Figure 2)

Discussion

All adults in Rhode Island are at high risk of overweight or obesity. For men, risk differs by age group, but otherwise men of all racial/ethnic, income or educational levels are at similarly high risk. For women, Black and Hispanic women, low-income women, and women with lower educational attainment are at higher risk of obesity than White women, higher-income and more highly educated women.

Inadequate fruit and vegetable consumption increases the risk of obesity for men as does frequent fast food consumption for women. Both men and women who watch television and those who are not physically active in their leisure time are at higher risk of obesity than those who turn off the TV and/or are more physically active. The lack of association of consumption of sugar sweetened beverages by obesity status is perplexing, but a recent study in California documented a risk of obesity with soda consumption among adults.[9] To a lesser extent, a study in New York documented the same risk.[10] The risk has been consistently reported among children.[11, 12]

An unhealthy diet and sedentary life styles are concerns for all adults. But identifying demographic and behavioral differences between men and women might stimulate the creation of gender-specific strategies to promote an active lifestyle and healthy diet.

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The authors have no financial interests to disclose.

Point of View

America's Multi-Tiered Healthcare System: Is Organ Transplantation Fair?

Peter Than and Paul Morrissey, MD

Two high profile surgical cases recently demonstrated that even for citizens with health insurance, America has a multi-tiered health care system. The champion of universal health care, Senator Edward Kennedy, chose to have his brain tumor surgery at Duke rather than accept the consensus recommendation from a panel at the Massachusetts General Hospital. Similarly Steve Jobs, CEO of Apple computer, traveled from northern California to Tennessee, for a liver transplant to treat a metastatic neuro-endocrine tumor. The *New York Times* opined, "Whenever someone rich and famous receives a transplant, suspicions inevitably arise about whether that person managed to jump to the head of the waiting list and take an organ that might have saved the life of somebody just as desperate but less glamorous."

When celebrities obtain organs quickly, it heightens awareness that inequities may exist and compels people to question the process. In 1995, baseball's Mickey Mantle presented with a chief complaint of stomach pain. He was diagnosed with cirrhosis and liver cancer. Nine days later, he was placed on a waiting list for a liver transplant; two days, later he was transplanted.

We know that wealthy patients have greater access to care than poor patients; white patients receive better care than black patients; the insured receive better care than the uninsured; and celebrities receive greater care than the average person. These disparities assume greater importance in organ transplantation because of the limited supply of organs. These observations drive at the heart of the debate between balancing equity and utility.

Given the complexities of the organ allocation system, the public might understandably feel that the playing field is not level. Nonetheless, organs are allocated through a computer-generated list that is based on objective criteria (laboratory data, HLA matching and waiting time). Deviations from the list are investigated and the few cases that have been identified resulted in harsh penalties for transplant centers. Why is it then that the Mickey Mantles of the world receive transplants expeditiously while other patients are relegated to long waiting times? The possibility is that personal resources allow them access to a nation-wide system whereby they are able to make use of super-specialized physicians and services or, in the case of organ allocation, to gain admission to centers with shorter waiting times.

Recently, Steve Jobs received a liver transplant in Memphis. The median waiting time for a liver in Tennessee was 143 days in 2007 compared to 1851 days in California for the commonest blood group. Organs procured from deceased donors are kept within designated regions in the United States. Patients may be listed

in one or more region, but must travel to each center for the complex medical evaluation and the transplant procedure when an organ becomes available. Listing in regions with shorter waiting times increases the chances of obtaining an organ more quickly. This, of course, is more readily available to people able to pay for transportation and lodging.

The average waiting time between each of the eleven US organ allocation regions varies with respect to organ. Not much regional variation exists in kidney waiting time, likely reflecting the disproportionately large demand relative to the supply, the **United Network for Organ Sharing** (**UNOS**) criteria that place priority on waiting time over medical illness and the universal availability of dialysis. On the other hand, there is significant regional variation in waiting times for liver transplantation, reflecting varying donor potential (number of deceased donors per million population) and families' consent rates (35-60% of potential donors actually donate). In 2005 the median time spent on a waiting list for a liver in Region 1 (CT, ME, MA, NH, RI) was 1347 days. Compare this to 75 days for Region 3 (AL, AK, FL, GA, LA, MS).

The liver model of end-stage liver disease (MELD) places wait-listed patients on a continuum of medical illness based on renal function (creatinine), coagulopathy (PT INR) and liver function (bilirubin).

One study showed that geographic variation in organ availability was the greatest reason that Hispanics are less likely to receive a liver transplant. This difference likely reflects the clustering of certain ethnic and income groups. Proximity to a transplant center and socioeconomic factors influence one's access to transplantation. One study from California found lesser rates of transplant referral for Medicaid patients compared with age-matched Medicare recipients. Notably, however, once in the system, insurance status did not influence receipt of a deceased donor kidney.

The process from organ failure to obtaining a transplant has many steps, each a potential source of inequity. From the onset of symptoms not all patients have equal access to primary care. Once a diagnosis is established, physicians have different personal attitudes and biases toward placing patients on waiting lists. There is often delayed referral to transplant centers and a protracted pre-transplant work-up, most often related to logistic challenges for individual patients. The required lifelong regimen of expensive immunosuppressive drugs exacerbate the vulnerability within groups.

The allocation of kidneys is largely based on wait time and HLA matching. Since dialysis is available as a lifesaving therapy, little of the allocation is based on the burden of medical disease. Conversely, livers are allocated based on the severity of medical illness with time waiting serving only as a tie-breaker. Also, the inevitability of death without liver transplantation lessens the impact of cultural beliefs and patient understanding. Access to the health care system is important, but even patients presenting to Emergency Departments with end-stage cirrhosis undergo rapid evaluation and listing for transplantation, and when sick enough by objective medical criteria often receive prompt transplantation with minimal waiting time. Availability of an organ for transplantation becomes paramount and geographic disparities can be exploited for the recipient's benefit.

UNOS continually reviews the fairness of organ allocation and revises policies. In 2006 it noted that the sickest heart failure patients were dying on the wait list as healthier patients received organs in some regions. The geographic boundaries for each allocation were expanded, resulting in the shipping of more hearts to sicker patients and a dramatic decrease in deaths on the waiting list. The development of objective scoring systems for liver and lung allocation and a kidney allocation system with reduced weight on HLA all improved the fairness of organ allocation.

Technologically we have made great strides in organ transplantation. However, the scientific advances have paved the path to perhaps the greatest moral challenge in medicine—the necessity to allocate scarce resources to needy patients. An unbiased system is evolving but disparities in race, socioeconomic status, gender, and regional variation remain and demand attention. In today's environment, uninsured patients are less likely to gain transplant listing; those with kidney failure are relegated to dialysis and those with other end-organ failure cling to the hope of access to transplant wait lists through emergent hospitalization.

Conversely, those with financial resources take advantage of shorter waiting times in certain regions or unique therapies at specialized centers. It is a very American concept for patients to make personal choices and individualize treatment. However, this requires a system that provides unique opportunities and a patient with resources to exploit them. Variability in organ allocation is diminishing, but until a completely level playing field is established prominent patients will take advantage of the benefits inherent in the system.

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The authors have no financial interests to disclose.

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Fifty Years Ago, December 1959

In "Athletic Injuries to the Upper Extremity," A.A. Savastano, MD, focused on injuries to the hand, wrist, forearm, elbow, upper arm, and shoulder.

In "Transient T-Wave Inversion after Paroxysmal Ventricular Tachycardia in Normal Adult Hearts," Joseph B. Karas, MD, and Frank B. Cutts, MD, described the case of a 28 year-old woman, who smoked two packs of cigarettes a day, and the case of a 26 year-old man. The authors found the prognosis "usually excellent" in such cases.

Robert M. Lord, Jr, MD, and Lester L. Vargas, MD, described the uncommon but urgent problem" of "Tension Pneumothorax in a Newborn Infant." The full-term baby boy, born to a 28 year-old gravida I para I mother by cesarean section because of cephalopelvic disproportion at the Providence Lying-In Hospital, was later transferred to Rhode Island Hospital for a closed thoractomy. The baby was discharged on the 18th hospital day.

Lieutenant Ralph L. Nachman, MC, described "Unilateral Renal Disease with Hypertension," the case of a 42 year-old man admitted with a cough, headache, and pulmonary infiltrate to the US Naval Hospital. After diagnosis, he had a left nephrectomy.

Edward S. Cameron, MD, and Warren W. Francis, MD, in "Total Glossectomy for Carcinoma, describe the case of a 89 year-old patient at the Rhode Island Tumor Clinic. The authors reported that, post-procedure, the patient's "difficulty with eating and speech has been moderate."

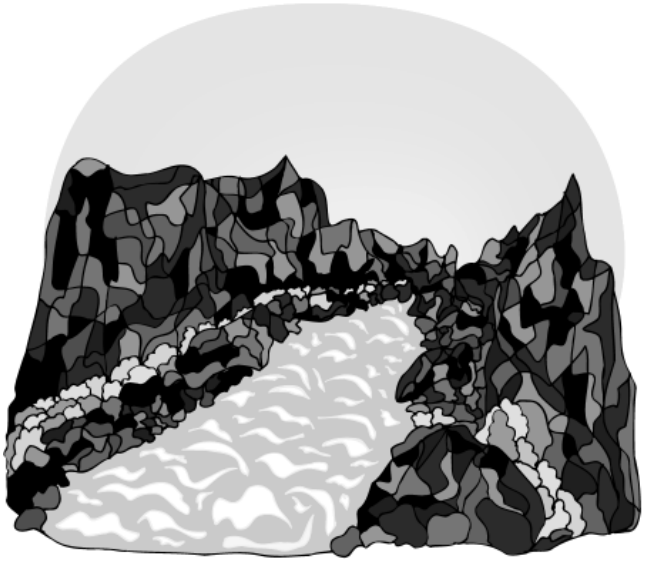
Twenty-Five Years Ago, December 1984

Seebert J. Goldowsky, MD, in "Extracorporeal Shock Wave Lithotripsy," discussed a recent presentation by Dr. George Pfister, radiologist at the Massachusetts General Hospital, on the new procedure. "The equipment {currently availably only from Philips) costs about $1.25 million. Preparing the room and…the necessary support systems brings the cost to about $2 million. Considering the limited number of cases for which this new modality will be indicated, we wonder how the health planning groups in RI will respond ….for a Certificate of Need…"

John I. Sandson, MD, Dean of Boston University School of Medicine," presented "Medical Education: Past, Present and Future" at the Oration of Medical Education at The Miriam Hospital. The Journal reprinted the talk. He noted: "Medical education must be adequately funded to provide efficient high quality health services to all."

Stephen R. Smith, MD, in "An Analysis of the Fourth Year of Medical School," reported: "Medical students appear to choose their elective courses reasonably and generally avoid premature specialization."

H. Denman Scott, MD, Director, Rhode Island Department of Health, in "Should We Welcome for-Profit Hospitals to Rhode Island?" answered No.



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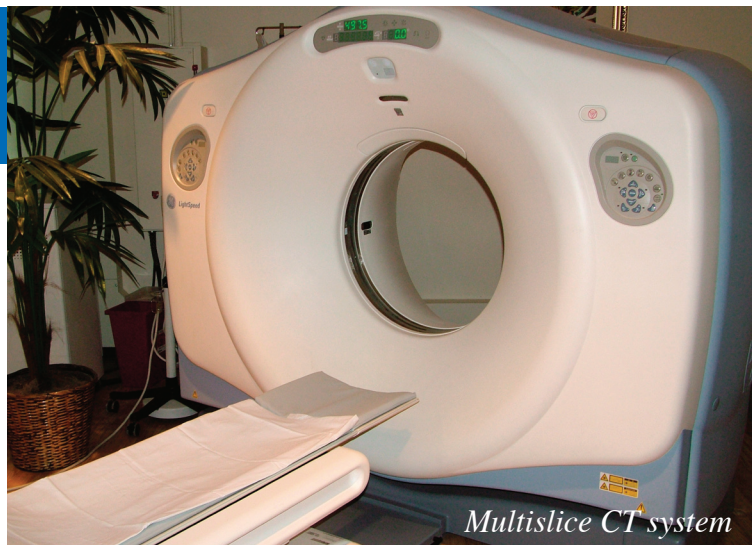
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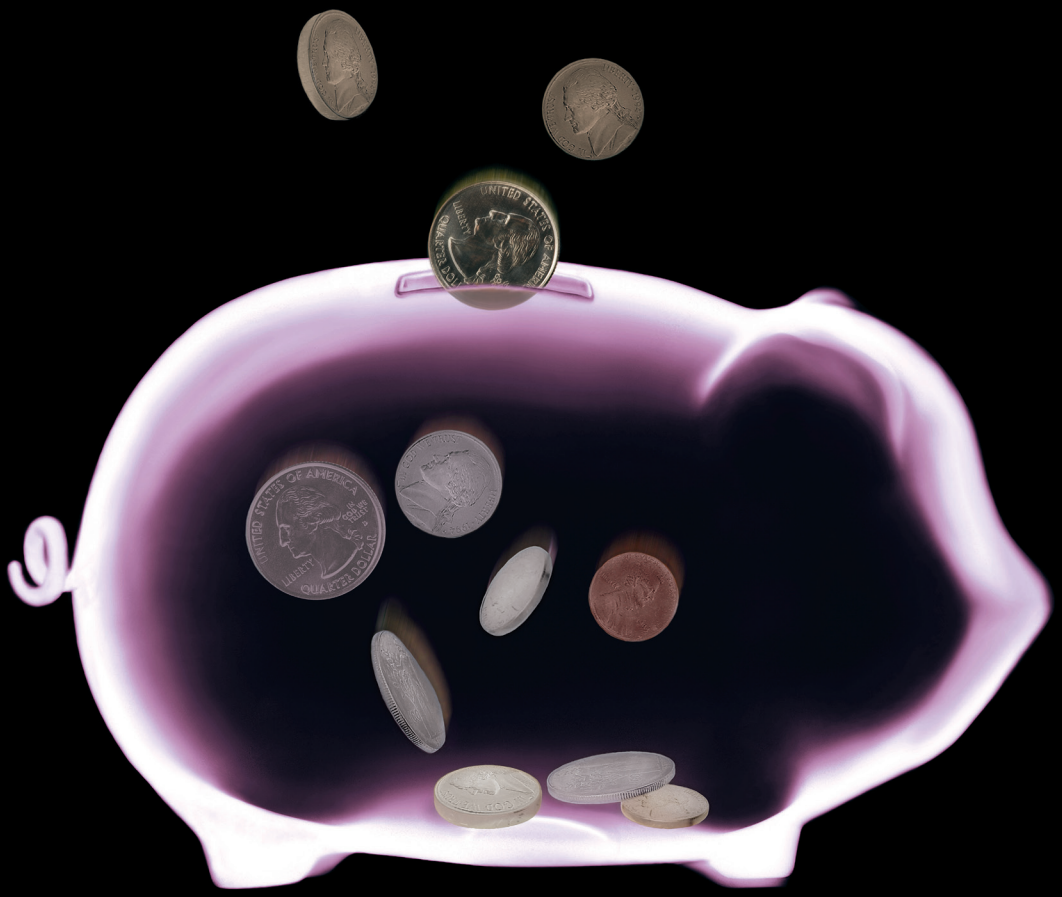

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