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Endoscopic Mucosal Resection Provides Less Invasive Treatment Alternative for Patients With Mucosal Esophageal Adenocarcinoma

The Challenge

Esophagectomy has been the standard of care for patients with esophageal adenocarcinoma (EAC). However, this approach has mortality rates of 2% to 10% (depending on hospital volume and patient comorbidities), substantial morbidity (from 30% to 40%), and lengthy postoperative hospital stays (an average of 20 days, on the basis of data from more than 800 patients in the SEER database).

The surgery itself involves alteration of normal anatomy—the loss of the gastroesophageal sphincter. The stomach may no longer empty well, and there is risk of developing gastroesophageal reflux or Barrett esophagus after surgery. Complications such as anastomotic leak in the chest as well as cardiac and pulmonary problems are also possible. In addition, it typically takes weeks for the multiple incisions to heal fully and for patients to begin eating well.

A New Approach

Mayo Clinic is among a handful of medical centers that now offer minimally invasive endoscopic mucosal resection (EMR), alone or in combination with other mucosal ablation techniques such as photodynamic therapy (PDT), to patients with mucosal (T1a) EAC. During EMR, a liquid is injected under the lesion and then an endoscope is used to shave off the lesions (Figure). EMR is typically performed on an outpatient basis. Once the tumor invades the second layer of tissue or when patients present with symptoms such as dysphagia, traditional surgery is typically recommended. For this reason, regular endoscopic surveillance is critical for patients with Barrett esophagus who have been treated endoscopically.

Elimination of hospital stay and reduced mortality and morbidity are the major benefits associated with EMR. Patients typically recover more quickly from EMR than those treated surgically and can resume eating full meals a few days after

the procedure. Possible complications from

EMR include esophageal perforation and a slightly increased risk of bleeding (about 5% of patients treated at Mayo). Delayed possible complications include esophageal stricture (scarring), which typically occurs a few weeks after the procedure, sometimes after multiple procedures. Follow-up endoscopic surveillance, with biopsies and

EMR as indicated, should be performed every 3 months during the first year of follow-up, every 6 months during the second year, and yearly thereafter.

Because the endoscopic approach is new and performed only at select referral centers,

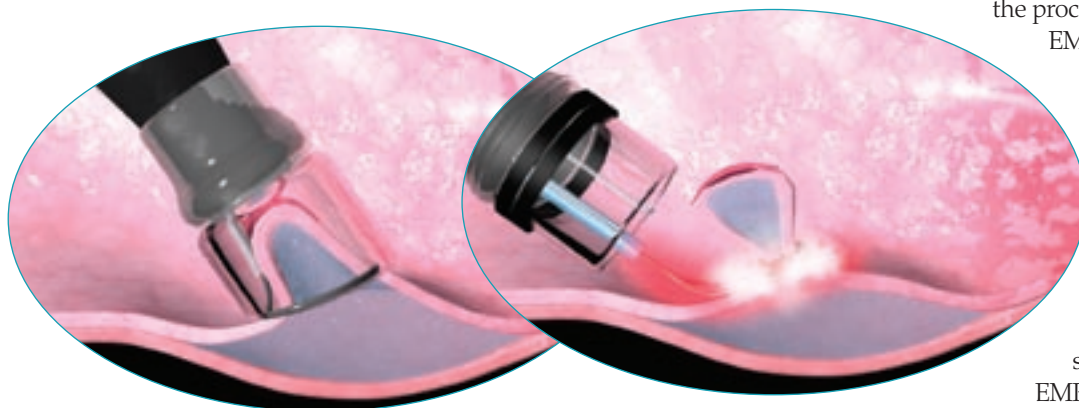


Figure. During EMR, lesions are lifted using submucosal injection with saline epinephrine solution. Mucosal resection is performed by suctioning the lesion into the cap after positioning of a crescent snare. The snare then closes, with application of cautery current removing the tissue. Patients with smaller lesions that are more likely to be removed by a single resection typically undergo EMR using this method.

Points to Remember

- The incidence of esophageal adenocarcinoma (EAC) is increasing more rapidly than the incidence of any other form of malignancy in the United States. Current survival following diagnosis of EAC remains poor, with less than 20% of patients surviving more than 5 years.
- Esophagectomy, often combined with pre-operative chemoradiotherapy, is the mainstay of treatment for EAC. But this surgery is associated with considerable mortality and morbidity, including a lengthy hospital stay and lifelong dietary restrictions.
- Endoscopic mucosal resection (EMR) is emerging as a less invasive alternative to surgical therapy in selected patients with mucosal EAC. It can be performed as an outpatient procedure and allows the patient to resume eating full meals.
- Recent Mayo study data show that survival outcomes associated with EMR are comparable to those associated with esophagectomy.

outcome data are just emerging. In a retrospective study of 178 Mayo Clinic patients who received a diagnosis of mucosal EAC between 1998 and 2007, 132 (74%) were treated with EMR and 46 (26%) were treated surgically. Endoscopic therapy consisted of EMR alone or in combination with PDT. Mayo researchers found that overall survival and cumulative mortality in the 2 treatment approaches were comparable at 5 years. Further analysis of the study data suggests that treatment modality was not a significant predictor of survival. In addition, recurrent carcinoma was detected in 12% of the patients treated endoscopically, all of whom were successfully re-treated endoscopically with no impact on overall survival.

In summary, endoscopic therapy with EMR, in conjunction with ablative therapy, appears to be a reasonable alternative to esophagectomy in patients with mucosal EAC. Overall survival appears to be comparable with low recurrence rates. Mayo Clinic's Barrett's Esophagus Unit offers a multidisciplinary approach to evaluate early symptoms, devise a surveillance schedule, and perform all tests and medical and surgical treatments. For more information about EMR and management of EAC or Barrett esophagus or to refer a patient, please call Mayo Clinic Referring Physician Service. See page 8 for contact information.

Valve-Sparing Root Repair in Marfan Syndrome

Composite aortic root replacement has become the gold standard operation for patients with Marfan syndrome and aortic root aneurysms. With an operative risk in the low single digits when performed in high-volume centers under elective circumstances, it is a cornerstone in the prevention of the dreaded complication of acute aortic dissection, which carries a mortality rate of 25% among those who make it to the hospital. But while the results are excellent, this is not an ideal solution.

The Challenge

The long-term results associated with composite root replacement are excellent, and current prosthetic mechanical valves have almost unlimited durability. Reoperations following this procedure principally

Points to Remember

- Cardiovascular disease is the principal cause of mortality and morbidity in patients with Marfan syndrome.
- Aneurysmal dilation of the aortic root is the most common cardiovascular complication of Marfan syndrome and places individuals at risk of catastrophic aortic rupture or dissection. This is in addition to the more insidious effects of aortic valvular insufficiency.
- Valve-sparing root repair frees patients from long-term anticoagulation and has become widely accepted as the preferred surgical approach among experienced surgeons.

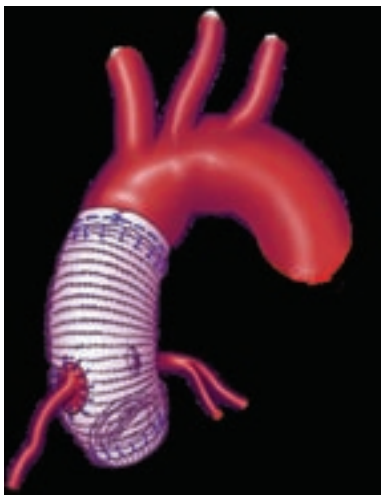


Figure 1. Composite aortic root repair.

occur for the treatment of subsequent aneurysms of the remaining native aorta. The lifetime risk of reoperation on the prosthesis itself is approximately 5%. Reoperation is indicated for infection or for obstruction of the valve orifice or leaflet motion caused by scar tissue. However, because patients with Marfan syndrome undergoing root replacement are typically young, and mechanical valves require anticoagulation with warfarin, which is troublesome over a lifetime, particularly for women of childbearing age, there is a need for a treatment approach that eliminates the requirement for long-term anticoagulation. Bioprosthetic valves have limited durability, and the complexity of a repeat operation after root replacement discourages the use of these valves in young patients.

Newer Approaches

Among the most exciting developments in the surgical treatment of Marfan syndrome in recent years has been the refinement of techniques for valve-sparing root replacement. The late 1970s brought the development of a "valve-sparing root reconstruction" procedure in which the diseased sinuses of Valsalva and ascending aorta were replaced with Dacron grafts, while the native valve leaflets were left intact. The results were excellent, with the anatomy on postoperative echocardiography being almost indistinguishable from normal. Unfortunately, patients with Marfan syndrome appear to be at considerable risk of late aortic insufficiency, probably because of progressive dilation of the aortic annulus.

An alternative "reimplantation" valve-sparing operation was first described in 1992. This procedure involves resuspending the aortic valve apparatus within the Dacron graft (Figure 2). Widely accepted as the preferred approach to valve-sparing procedures, it has become the technique of choice at Mayo Clinic.

Results associated with this valve-sparing approach have been so encouraging that the National Marfan Foundation (NMF) sponsored a multicenter trial to compare the results of the valve-sparing procedure with composite root replacement outcomes. Enrollment in the NMF study began in March 2005, and as of the June 2008 analysis (which included 202 enrolled patients, 32 from Mayo Clinic), 70% of patients had undergone a valve-sparing procedure. Of the remaining patients, most had replacement with a mechanical composite graft.

To date, no early deaths have occurred among study participants. There have been only 3 instances of valve dysfunction, 2 of which were secondary to failed valve-sparing procedures corrected intraoperatively. No late failures of the

valve-sparing procedure have occurred thus far, although follow-up has been brief and is ongoing. Postoperative morbidity, including hospital stay, has been similar for both procedures, although the valve-sparing operation is more complex and requires a longer cross-clamp time.

Cardiovascular surgeons at Mayo Clinic have a long history of aortic repair with excellent morbidity and mortality rates (Figures 3 and 4). They have performed

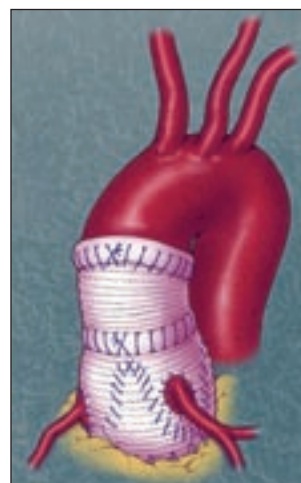


Figure 2. Valve-sparing aortic root repair.



Figure 3. Mortality and perioperative stroke morbidity of aortic root repair procedures at Mayo Clinic in Rochester, Minnesota, 1993-2007.

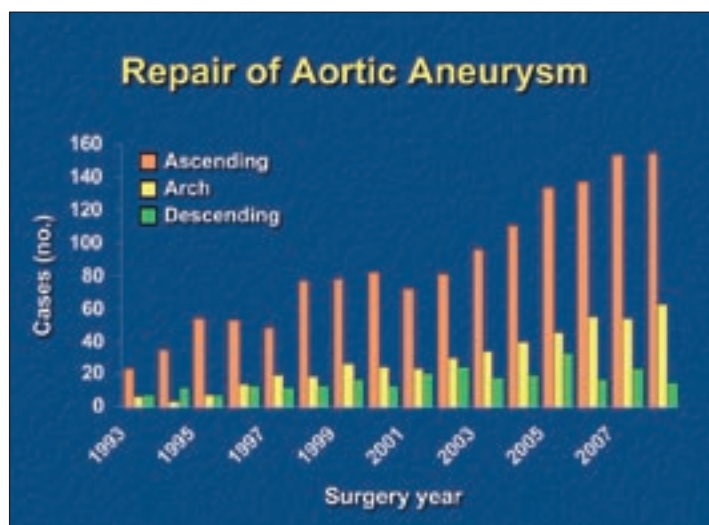


Figure 4. Repair of aortic aneurysms at Mayo Clinic in Rochester, Minnesota, 1993-2008.



Figure 5. Valve-sparing and composite root reconstruction performed at Mayo Clinic in Rochester, Minnesota, 1993-2008.

valve-sparing procedures since 1993, with numbers increasing over recent years as confidence in the long-term durability of the procedure builds. The valve-sparing operation has become the preferred procedure in patients with Marfan syndrome, and currently 80% to 90% of native valves are spared in patients who have favorable anatomic characteristics (Figure 5). This group includes patients with Marfan syndrome as well as other causes of aortic root enlargement, such as familial thoracic aortic aneurysmal disease and bicuspid aortic valve disease. Valve-sparing surgery has thus become an important part of the aortic surgery program at Mayo Clinic. To refer a patient, contact Mayo Clinic Referring Physician Service. See page 8 for information.

Diabetic Retinopathy

The Challenge

Diabetic retinopathy affects more than 5.3 million persons aged 18 years or older in the United States. Most patients with diabetes mellitus for 20 years have some degree of diabetic retinopathy. Diabetic retinopathy is classified into 2 types: nonproliferative and proliferative. Proliferative retinopathy (Figure 1) refers to retinal neovascularization from ischemia. Nonproliferative changes (Figure 2) occur before the onset of neovascularization due to increased capillary permeability and ischemia. The typical funduscopic findings are microaneurysms and hemorrhages.

Retinal hemorrhages, depending on their location, have a dot-blot or flame-shaped appearance. As vascular permeability increases, retinal edema may ensue. Lipoproteins may precipitate out, giving the appearance of hard exudates. Infarctions of the nerve fiber layer may also occur, producing the appearance of cotton-wool spots. As background retinopathy increases in severity, more numerous retinal hemorrhages are seen, along with irregularity of the veins or venous beading.

In patients with background diabetic retinopathy, the leading cause of decreased visual acuity is macular edema. Diabetic macular edema can be categorized as focal or diffuse. Focal diabetic macular edema refers to leakage

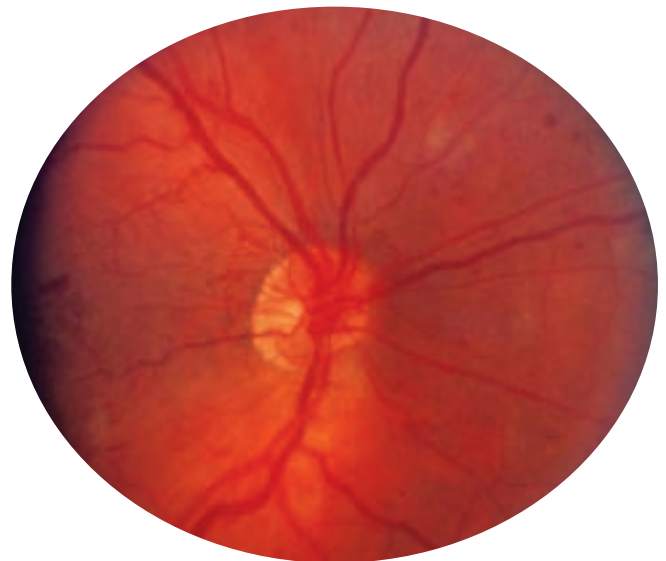


Figure 1. Color fundus photograph of proliferative diabetic retinopathy shows neovascularization.

primarily from microaneurysms. Diffuse diabetic macular edema is due to increased widespread leakage from the capillary bed.

As retinal ischemia increases, vascular endothelial growth factor is upregulated, which promotes retinal neovascularization. Although neovascularization may occur in the iris or the trabecular meshwork and thus result in neovascular glaucoma, the primary location of the neovascularization is on the retinal surface.

The natural history of retinal neovascularization is for continued growth and fibrosis. As the vitreous contracts, it may cause the sites of neovascularization to bleed. Typically, the hemorrhage occurs in the vitreous, causing such symptoms as floaters and the appearance of cobwebs. As the neovascularization progresses, fibrosis develops. The increasing retinal neovascularization and fibrosis may exert tractional forces on the retina. When this traction overcomes the adhesive force of the retina to the retinal pigment epithelium, a traction retinal detachment occurs. Once the macula is detached, visual acuity is poor.

Eye-Directed Treatment

The mainstay of treatment for diabetic macular edema and proliferative diabetic retinopathy is laser photocoagulation. Prompt treatment is recommended when eyes have high-risk characteristics of proliferative disease. Panretinal photocoagulation in eyes with high-risk characteristics decreases the risk of severe visual loss by approximately 60%.

For an eye that does not have high-risk characteristics, panretinal photocoagulation may still be recommended, depending on the condition of the other eye, as well as the documented progression of the retinopathy. Focal laser photocoagulation for clinically significant diabetic macular edema decreases the risk of moderate visual loss by 50%. Such photocoagulation is most effective in patients with focal or multifocal leakage primarily from microaneurysms.

Diffuse macular edema, due to leaking primarily from parafoveal capillaries, may suggest an underlying systemic condition. Often, patients with this type of edema have hypertension, congestive heart failure, or renal disease as a contributing factor. Normalization of blood pressure or diuresis may improve diabetic macular edema.

Control of Systemic Factors

There is strong evidence that lowering hemoglobin A1c levels to approximately 7% is advantageous in reducing the onset and progression of diabetic retinopathy. Similarly, research shows

Points to Remember

- Major risk factors for diabetic retinopathy include duration of diabetes mellitus, degree of hyperglycemia, and presence of hypertension, hyperlipidemia, pregnancy, and renal disease. Less consistent risk factors are obesity, cigarette smoking, moderate alcohol consumption (more than 1 beverage per day), and lack of physical activity.
- Diabetic retinopathy is classified as nonproliferative and proliferative.
- The mainstay of treatment for proliferative diabetic retinopathy and diabetic macular edema is laser photocoagulation.

that a decrease in systolic or diastolic blood pressure, or both, can help reduce the development and progression of diabetic retinopathy. Aggressive lowering of total cholesterol and triglyceride levels may cause regression of the exudates.

Mayo Clinic ophthalmologists treat thousands of patients with retinal diseases each year. To refer a patient or consult with an ophthalmologist, call the Mayo Clinic Referring Physician Service. See page 8 for contact information.

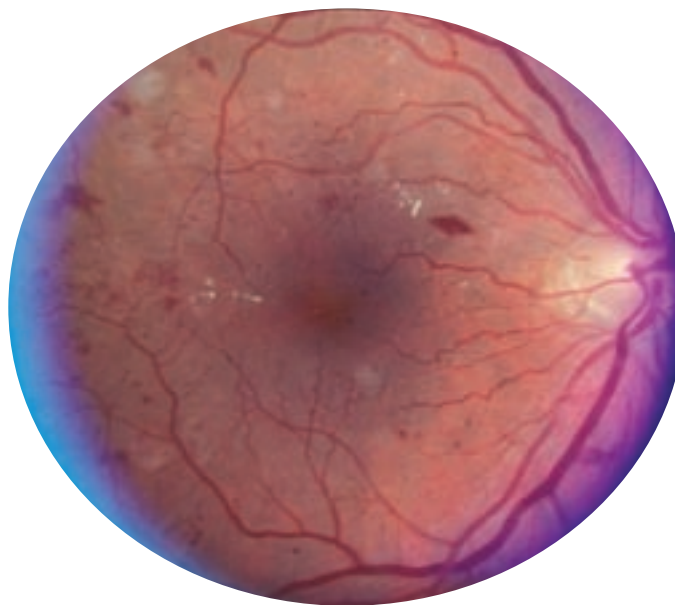


Figure 2. Color fundus photograph of nonproliferative diabetic retinopathy shows retinal hemorrhages, yellow lipid exudates, and cotton-wool spots.

The Utility of Autonomic Testing

Autonomic testing can distinguish primary from secondary autonomic disorders, true autonomic neuropathy from conditions that mimic it, and psychogenic from organic conditions. It can also help to differentiate progressive diseases and serve as a means of monitoring disease progression and response to treatment. Referrals to Mayo Clinic for autonomic evaluation are increasingly coming from both within and outside the field of neurology, as physicians develop a wider appreciation for the role of autonomic testing in differential diagnosis and management.

Routine autonomic tests of sudomotor, cardiovagal, and adrenergic function are non-invasive. Because test results are quantifiable, responses from the 3 systems can be compared to determine selective and/or relative autonomic dysfunction. For example, a patient might have moderate involvement of the cardiovagal system and severe involvement of adrenergic function without impacting sudomotor function. Or both the cardiovagal and adrenergic systems may be normal in the face of isolated anhidrosis, suggesting the possibility of chronic idiopathic anhidrosis, a more benign disorder that does not progress to widespread autonomic failure and for which symptomatic and sometimes specific treatment is available. Only by testing all 3 systems can such diagnostically informative patterns emerge.

Routine Tests of Autonomic Function

Sudomotor Tests

The quantitative sudomotor axon reflex test (QSART) is used to evaluate postganglionic sudomotor function. The thermoregulatory sweat test (TST) is used to evaluate both preganglionic and postganglionic function over the entire anterior body surface. When evaluated together in the same patient, TST and QSART can differentiate

Points to Remember

- Autonomic testing helps to determine the presence, severity, distribution, and localization of autonomic dysfunction.
- Symptoms and conditions that can benefit from autonomic testing include syncope, flushing, bladder and bowel dysfunction, dizziness, endocrine dysfunction, Parkinson-like symptoms, gastrointestinal tract distress, painful feet, orthostatic intolerance, extreme fatigue, tachycardia, cognitive dysfunction, anhidrosis, and hyperhidrosis.
- Routine reimbursable autonomic evaluation includes tests of sudomotor, cardiovagal, and adrenergic function.

preganglionic from postganglionic lesions.

The distribution of abnormal sweat responses measured by QSART and TST is of diagnostic importance for a number of conditions such as peripheral neuropathy. For example, small-fiber neuropathy with the symptom of burning feet can be associated with idiopathic disease and also with diabetes. In such cases, the most distal sites may have abnormal QSART and TST responses with more proximal sites becoming involved as the disease progresses. Using a 10-point composite autonomic severity score that they developed, Mayo physicians found that sudomotor testing is highly sensitive in identifying clinical distal small-fiber neuropathy in patients who have normal or unrelated

Physician Update

Mayo Clinic has online options for medical professionals

An e-mail newsletter and a physician video blog. Visit www.mayoclinic.org/medicalprofs for more details.



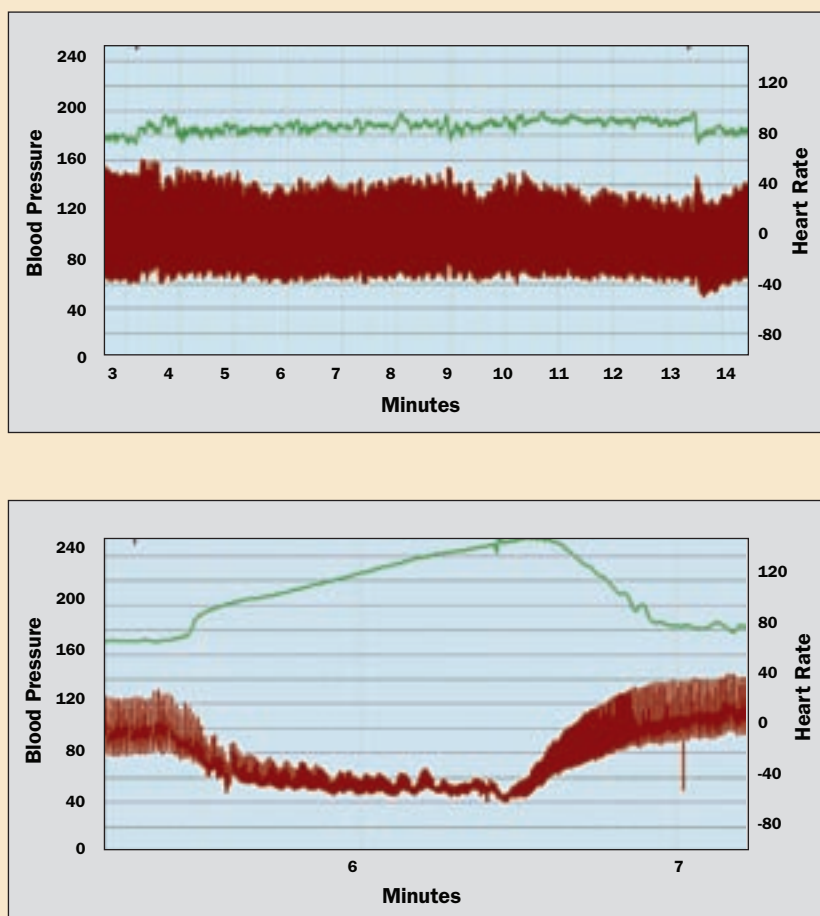


Figure. A graphic display of changes in blood pressure and heart rate (green line) over time in response to head-up tilt in a normal subject (top) and a patient with orthostatic hypotension (bottom).

abnormalities on electromyographic testing.

Cardiovagal and Adrenergic Function Tests

The 2 main tests of cardiovagal function in the autonomic test sequence are heart rate response to deep breathing and the Valsalva ratio, which involves several calculations and up to 4 maneuvers. The measure used for Valsalva ratio is beat-to-beat blood pressure. Once an invasive technique, measurement of beat-to-beat blood pressure can now be done with a recording device placed on the patient's finger.

Beat-to-beat blood pressure under various laboratory conditions is a proven method of testing adrenergic function for many conditions, including orthostatic hypotension (OH) (Figure). OH is well recognized as a potential consequence of Parkinson disease and diabetes and is increasingly recognized as a common disorder among the elderly. Symptoms of OH such as fatigue and impaired concentration can be subtle and difficult to diagnose. Even when

mild, symptoms of OH can be debilitating and markedly affect activities of daily living. Severe and sustained OH can induce syncope, with resultant falls and injury. In younger patients, symptoms may include palpitations, anxiety, and nausea and may be indicative of autonomic neuropathy. Adrenergic testing helps distinguish OH syncope from psychogenic disorders and from other conditions that induce loss of consciousness such as seizures and transient ischemic attacks. Autonomic tests can also determine severity of OH, an important factor when considering behavioral, pharmacologic, and nonpharmacologic treatments.

Mayo's autonomic testing laboratory highlights the complexity of the autonomic system. Although physicians cannot dissect all aspects of autonomic function, autonomic testing helps detect deficits that may not have been undiagnosed, determine if the problems are benign or represent a true autonomic failure, and, if so, quantify its severity and distribution.

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www.mayoclinic.org/medicalprofs

CME Opportunities

Psychiatric Genomics: Applications for Clinical Practice

August 9-13, 2010

Rochester, MN

This course offers a broad array of lecture topics beginning with a review of basic genomics and progressing to clinical applications. It is designed for individuals with an interest in understanding the ways in which genes affect mental illness and impact disease course and prognosis. Pharmacogenomic principles that guide the treatment of psychiatric illness will be specifically highlighted.

Contact: 800-323-2688.

Pediatric Days 2010

September 13-14, 2010

Chicago, IL

This course is designed to provide general pediatricians, pediatric subspecialists, family physicians, physician assistants, nurses, nurse practitioners, and resident physicians with current information on medical and surgical conditions affecting children and adolescents. Contact: 800-323-2688.

13th Annual Mayo Clinic Internal Medicine Update: Sedona 2010

October 7-10, 2010

Sedona, AZ

This 4-day course offers primary care physicians, nurse practitioners, and physician assistants a practical update on various subspecialty topics, including cardiovascular diseases, dermatology, endocrinology, gastroenterology, hematology, hepatology, integrative medicine, neurology, pulmonary, rheumatology, women's health issues, and others.

Due to the popularity of this course, it is offered twice: October 7-10, 2010, and October 21-24, 2010. Early registration is encouraged to ensure enrollment in your preferred session. \$75 discount for online registration no later than September 1 (www.mayo.edu/cme). Contact: 480-301-4580.

To view all Mayo Clinic CME offerings visit www.mayo.edu/cme/



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