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When Should a Carotid Endarterectomy be Considered for Symptomatic Internal Carotid Artery Stenosis in the Elderly?

ABSTRACT & COMMENTARY

Synopsis: *With respect to the prevention of ipsilateral ischemic stroke, elderly patients with 50-99% symptomatic carotid artery stenosis benefited more from carotid endarterectomy than did younger patients, and they were not at increased risk of perioperative stroke or death.*

Source: Alamowitch S, et al. *Lancet.* 2001;357:1154-1160.

Advances in early diagnosis and in effective treatment of multiple illnesses, which commonly occur in the elderly, have resulted in significant recent increases in longevity. Two large randomized, controlled, research trials[1,2] have clearly demonstrated that carotid endarterectomies reduce the risk of stroke in middle-aged and young-elderly (ie, age 60-75 years) patients with severe carotid stenosis. However, relatively few studies have evaluated the benefits of carotid endarterectomy in the old-elderly (ie, > 75 years of age) patient.

Alamowitch and colleagues reported the findings of a study performed by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) group. The results of carotid endarterectomies in patients age 75 years or older were compared with patients who were 65-74 years old and to a third group consisting of patients who were younger than 65 years of age. Among patients with 70-99% carotid artery stenosis, the absolute risk reduction of ipsilateral stroke with carotid endarterectomy was 28.9% for patients aged 75 years or older, 15.1% for those who were 65-74 years old, and 9.7% for the group younger than 65 years of age. Among patients with a 50-69% stenosis, the absolute risk reduction was significant only in those patients who were older than 75. The perioperative risk of stroke and death at any degree of stenosis was only 5.2% for the oldest group, 5.5% for the 65-74-year-old group, and 7.9% for the younger than 65 year old group. In summary, with respect to the pre-

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INSIDE

vention of ipsilateral ischemic stroke, elderly patients with 50-99% symptomatic carotid artery stenosis benefited more from carotid endarterectomy than did younger patients, and they were not at increased risk of perioperative stroke or death simply because of their advanced age.

COMMENT BY HAROLD L. KARPMAN, MD, FACC, FACP

Multiple conferences and meetings have been mounted to ensure that elderly people are afforded the best available methods of care and that they are not denied specific treatment strategies which are known to be effective simply because of their advanced age.[3-5] In an American Heart Association conference held in Washington, DC, in January, 2000, the consensus of the participants was that aggressive treatment can add years of useful life to elderly patients and that age alone should not be a reason for denying therapy that has been demonstrated to be effective.

The data presented by Alamowitch and the NASCET Group in the recent issue of *Lancet* clearly demonstrated that the absolute benefit from endarterectomy in patients with carotid arterial stenosis increases with age and, in fact, is greatest in patients who are older than 75. These findings were confirmed by the Carotid Endarterectomy Trialists' Collaboration (CETC) study, which collated detailed data from individual patients from all available randomized, controlled trials. Analysis of the CETC data also revealed that: 1) the benefits from surgery were greatest among patients who were older than 75 years old, 2) there was no increase in operative risk in the elderly, and 3) the risk of stroke in patients with high-grade internal carotid artery stenosis who were not subjected to surgery was found to be quite significant.

What is most important at this time is to clearly recognize that age alone should not be a deterrent to surgically treating the patient with hemodynamically significant carotid arterial stenosis. The average patient enrolled in the NASCET study was part of a relatively select group of elderly patients with carotid artery disease who differed from most other elderly patients in the community in that they were afflicted with a lower frequency of associated disease, especially cardiac disease. Therefore, carotid endarterectomy in routine clinical practice is statistically most likely to benefit the reasonably fit patient over the age of 75 years who had been subjected to a scrupulous clinical examination in order to exclude those patients who are at increased risk from anesthesia or from developing cardiac complications even when the surgery is performed by skilled surgeons.

There is simply no justification for not investigating symptomatic carotid arterial disease in the older age groups especially in the fit individual who is found to have an appropriate risk profile.[7] Even though symptomatic elderly patients may not wish to undergo a surgical procedure, they should be encouraged to consider the surgical option since trial evidence has now clearly demonstrated that these patients are the ones who are most likely to benefit from the procedure and the operative risks are quite minimal. ❖

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Usefulness of Colonoscopy with Biopsy in the Evaluation of Patients with Chronic Diarrhea

ABSTRACT & COMMENTARY

Synopsis: *Using colonoscopy with biopsy, the diagnoses were Crohn's disease, ulcerative colitis, lymphocytic colitis, ischemic colitis, infectious colitis including CMV, and assorted miscellaneous diseases including such entities as radiation colitis, eosinophilic colitis, and melanosis coli.*

Source: Shah RJ, et al. *Am J Gastroenterol*. 2001;96: 1091-1095.

Chronic diarrhea is a common problem leading to referral to gastroenterologists, and work-up often includes colonoscopy. Referring physicians need to have some explicit information regarding the use of this approach to their patients, but there is little information available outside the setting of HIV patients. It has been reported that lymphocytic and collagenous colitis may occur in as many as 5-9% of patients evaluated for chronic diarrhea, and these diseases do require colonoscopy and biopsies for diagnosis although biopsy of normal-appearing mucosa otherwise has been discouraged as unhelpful.[1,2]

This study from the University of Cincinnati reviewed 168 patients having colonoscopy with biopsies to evaluate "unexplained" or "chronic" diarrhea of at least 4 weeks duration, with 85% also having ileoscopy performed. Exclusions included prior intestinal surgery, known inflammatory bowel disease, HIV infection, incomplete colonoscopy, and any prior history of colonoscopy for diarrhea. Sixty-eight percent of the patients were women. Diagnoses were Crohn's disease, ulcerative colitis, lymphocytic colitis, ischemic colitis, infectious colitis including CMV, and assorted miscellaneous diseases including such entities as radiation colitis, eosinophilic colitis, and melanosis coli (the last finding assumed to indicate surreptitious laxative use). Shah and colleagues recommended biopsies sampling various areas of the colon and ileum. A total of 31% of patients with normal findings ultimately were diagnosed as having irritable bowel syndrome.

COMMENT BY MALCOLM ROBINSON, MD, FACP, FACG

This paper addresses an important question, and primary care physicians should be aware of the potential advantages of colonoscopic and biopsy evaluations of their patients with unexplained chronic diarrhea. There remains some uncertainty as to the increased yield from complete colonoscopy vs. flexible sigmoidoscopy, but 2 patients would not have been correctly diagnosed had ileoscopy not been done. Many experts would argue with the need to perform colonoscopy in all patients with symptoms that strongly suggest irritable bowel syndrome, but this approach is widely used by gastroenterologists. It is difficult not to believe that the 31% of patients in this series receiving specific diagnoses from endoscopic interventions benefited from these procedures. ❖

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Chronic Fatigue and Vasovagal Faints: Overlapping Syndromes?

ABSTRACT & COMMENTARY

Synopsis: *CFS patients who have undiagnosed syncope should be investigated for vasovagal syncope, and the 2 disorders may share a common mechanism.*

Source: Kenny RA, et al. *Am J Med*. 2001;110:242-243.

Chronic fatigue syndrome (cfs) is characterized by unexplained disabling fatigue. Lightheadedness or syncope reportedly occur in 40-90% of CFS patients, which suggests an overlap of these 2 syndromes.[1]

Kenny and colleagues determined the prevalence of CFS symptoms[2] in consecutive patients with a primary diagnosis of vasovagal syncope confirmed by positive head-up tilt table testing. Patients with at least 2 syncopal episodes in the previous year without a cardiac cause for

Table

Symptoms of CFS in Syncope and Control Subjects

Symptoms	Patients		*P* value
	Syncope (n = 62)	Controls (n = 119)	
	n (%)	n (%)	
Fatigue > 6 months	18 (29)	2 (1)	< 0.001
Postexercise fatigue	15 (24)	7 (6)	< 0.001
Headache	19 (31)	26 (22)	< 0.001
Criteria for CFS	13 (21)	1 (1)	< 0.001
Arthralgia	25 (41)	25 (21)	< 0.006
Sleep disturbance	26 (42)	30 (25)	< 0.02
Myalgia	22 (35)	24 (20)	< 0.02
Impared cognition	6 (26)	19 (16)	< 0.1

syncope and who did not have a diagnosis of CFS were studied. Study patients and age- and sex-matched controls completed a questionnaire for CFS symptoms.

Questionnaires completed by 62 syncope patients (63% women, mean age ± SD = 50 ± 21 years; range 16-83 years) were compared to questionnaires of 119 controls. The symptom criteria for CFS were fulfilled in 13 (21%) of patients but in only 1 control (*see Table*). Twelve of the 13 (92%) patients with CFS were women compared with 13 of the 49 (55%) patients without CFS.

Kenny et al recommend that CFS patients who have undiagnosed syncope should be investigated for vasovagal syncope and suggest that the 2 disorders may share a common mechanism.

COMMENT BY JOHN J. CARONNA, MD

Most people have fainted once or seen someone faint. The Framingham Study[3] recorded information on fainting. In the entire 26 years of surveillance of more than 5000 subjects, at least 1 syncopal episode was reported by 3% of the men and 3.5% of the women. More than 75% of the subjects had only a single faint. Isolated syncope in the absence of overt neurological and cardiovascular disease was not associated with increased morbidity or mortality and was not a frequent indicator of undiagnosed cerebrovascular disease.

Recurrent vasovagal syncope, in contrast, is a clinical problem that often is unresponsive to treatment, but symptoms may be improved by the use of selective serotonin reuptake inhibitors (SSRIs).Therefore, recurrent fainting resembles CFS. Like CFS, recurrent syncope also can be a disabling disorder, and quality of life deteriorates as a function of the recurrence of episodes. Syncopal episodes not only can produce physical trauma but also can create serious psychological discomfort. Employment, education, and social interactions may be severely restricted. SSRIs can improve clinical outcome in patients with refractory syncope (ie, those who are unresponsive to beta-blocking, vagolytic, negative inotropic, and mineralocorticoid therapy). Perhaps this is because SSRIs cause postsynaptic serotonin receptors to down-regulate in the brainstem, thereby blunting the brain response to rapid shifts in cerebral serotonin levels.[5]

The causes of recurrent syncope are legion.[6] Clinicians should add CFS to the list. ❖

Dr. Caronna is Vice-Chairman, Department of Neurology, Cornell University Medical Center, Professor of Clinical Neurology, New York Presbyterian Hospital, New York, NY.

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Runners Rejoice!

ABSTRACT & COMMENTARY

Synopsis: *Former Olympic runners were not at increased risk of either hip or knee arthritis as compared to former team sports athletes or controls.*

Source: Kettunen JA, et al. *Am J Sports Med.* 2001;29:2-8.

This is a retrospective review to investigate lower extremity disability of former elite athletes. In 1995, a questionnaire was sent to 1321 former Finland Olympic track and field, power, and team sport athletes from 1920 through 1965. The athletes were grouped by activity level and by sport played. The control group was age-matched individuals determined to be healthy at the time of their military physical at age 20. The questionnaire was returned by 75% of the athletes and 71% of

the controls. All participants were grouped by occupation to determine if an association between occupation and disability existed. The purpose of the study was to determine if an elite running athlete is at greater risk of developing lower extremity disability later in life than other athletes or the general population.

The results showed that hip and knee disability were more common in the elderly than in the young, and those with greater body mass were at greater risk for knee disability. Additionally, those with a history of prior knee ligament injury, meniscus injury, or with an occupation like a farmer or a skilled worker had greater lower extremity disability than controls. Based on the questionnaire, all age-adjusted former athletes had less hip disability than the controls, but former team sport athletes had greater knee disability than all others. Physician diagnosed knee arthritis was higher in team sport athletes, but hip arthritis was diagnosed similarly in all groups.

COMMENT BY JAMES R. SLAUTERBECK, MD

So is the running athlete at greater risk for lower extremity disability? I often get asked this question in one form or another in my sports medicine clinic. I traditionally have responded by saying, "If your knee has never been seriously injured, or if you have not had knee surgery, you can probably run guilt free. However, if your knee swells or is painful, you should be suspicious of internal damage and consider cross training on a bike or in the swimming pool."

Several strengths are present in this article. The study defines a specific group of elite athletes and stratifies the athletes by sport, injury, and disability. Additionally, age, body mass index, and occupation were recorded and adjusted because these contribute to lower extremity disability. Finally, the questionnaire was returned by a high number of the athletes and controls (75% of the athletes and 71% of the controls).

Some shortcomings are present in addition to those inherent to a retrospective study. Although the control group was healthy at the time of their military physical, I am unsure if they participated in running or team sports later in life. Possibly a better control group would be nonsmoking, normal weight, nonathletic males and females determined by a questionnaire. Additionally, I am unsure if the questionnaire was validated.

In my opinion, the strengths exceed the shortcomings. This article reports on team and individual Olympic athletes from one country to determine if athletes differ in risk for lower extremity disability when compared to controls. The conclusions will be of great interest to many concerned athletes. We can comfortably tell our runners that they may run and remain at low risk for knee and hip disability as long as they remain uninjured. Additionally, we can counsel team sport participants that they are at greater risk for knee disability when compared to individual sport participants.

So does this study affect my patient care? I believe so. Runners are often a well-read group of athletes and can be difficult to treat and counsel. This paper is readable by athletes and physicians and supports ones' desire to run but warns of the risk of running after significant knee injury. ❖

Dr. Slauterbeck is Associate Professor, Department of Orthopedic Surgery, Texas Tech University Health Sciences Center, Lubbock, Tex.

Pharmacology Update

Diclofenac Gel for the Treatment of Actinic Keratosis

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Diclofenac gel for the treatment of actinic keratosis (AK) is reaching the market several months after it received FDA approval. The gel combines the anti-inflamatory diclofenac with hyaluronate sodium for the topical treatment of these common skin lesions. SkyePharma has licensed the marketing rights for the United States, Canada, and Mexico to Bioglan Pharma. Diclofenac gel will be marketed under the trade name Solaraze.

Indications

Diclofenac gel is indicated for the topical treatment of AK.

Dosage

Diclofenac gel is applied to lesion areas twice daily. The amount should be enough to cover each lesion adequately. The recommended duration of therapy is from 60 to 90 days. One-half gram of gel will cover about 25 cm^2 of lesion. Diclofenac gel is supplied in tubes of 25 g and 50 g at a strength of 30 mg/g (3% w/w). Patients should avoid exposure to sunlight or sunlamps.

Potential Advantages

Diclofenac gel provides an alternative to other topi-

cal treatments such as masoprocol and 5-fluorouracil and may be better tolerated in terms of local adverse events.

Potential Disadvantages

Common side effects compared to vehicle are contact dermatitis (19% vs 4%), rash (35% vs 20%), and dry skin (27% vs 12%). About 18% of patients discontinue treatment due to side effects compared to 4% for the vehicle.[1] Optimal therapeutic effect may not be evident for up to 30 days. Due to some systemic absorption, albeit low, diclofenac gel should be used with caution in patients with active gastrointestinal ulcers, or bleeding, or severe renal or hepatic impairment. Also, concomitant administration of NSAIDs should be minimized.[1]

Comments

Diclofenac is a cyclooxygenase inhibitor used widely in the oral from for the treatment of pain and inflammation. It is also used as a topical ophthalmic drop for post cataract surgery and prior to corneal refractive surgery. In the topical formulation, diclofenac is formulated with hyaluronate sodium. Hyaluronate has been reported to enhance drug delivery to pathogical sites.[2] The mechanism of action of diclofenac in AK is not known, but it has been proposed that the inhibition of antiangiogensis may be a mechanism of action.[2] In clinical trials reported by the manufacturer, diclofenac gel had a success rate of 18-47% compared to 10-20% for the vehicle.[1] Success was defined as complete clearance of AK lesions 30 days after a treatment regimen. Statistical differences were demonstrated for lesions on the forehead and face but not on the scalp, arm/forearm, and the back of the hand, although numerical advantage was reported for these body locations.

Diclofenac may be better tolerated but currently there are no comparative studies with 5-fluorouracil or masoprocol. Cost is currently not available.

Clinical Implications

AK is a common premalignant inflammatory skin lesion involving areas of the body exposed to the sun. The prevalence of the disease is believed to be about 25% in the Western Hemisphere and more prevalent in individuals with fair complexion and older than the age of 50 years.[3,4] Left untreated, AK may progress to squamous cell carcinoma. Treatment ranges from topical application of 5-fluorouracil or masoprocol to excisional surgery, Mohs surgery, cyrosurgery, or radiotherapy, but each has its limitations. Diclofenac gel offers another, perhaps better-tolerated option for treatment of these common skin lesions. ❖

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Attention CME Subscribers

CME question No. 32 in the May 15 issue of *Internal Medicine Alert* contained an error. The question will be omitted from the CME test. Please leave the space blank on your answer sheet. A reminder will also be sent with your CME Scantron. We regret any confusion this may have caused. ❖

CME Questions

38. Colonoscopy in chronic or unexplained diarrhea might be expected to provide a specific diagnosis in what percent of patients?

a. 90%
b. 75%
c. 30%
d. less than 5%

39. Melanosis coli found in the setting of chronic diarrhea is most likely to indicate:

a. previous history of diverticulosis.
b. viral infection, such as Herpes simplex or CMV.
c. surreptitious laxative use accounting for diarrhea.
d. error in interpretation of histopathology.

40. All the following are significantly more prevalent in patients with recurrent vasovagal syncope than in controls *except*:

a. chronic fatigue.
b. fatigue post exercise.
c. headaches.
d. impaired cognition.
e. arthralgias.

41. Endurance running athletes have:

a. a similar chance of developing knee disability as prior team sports athletes.
b. an increased chance of developing hip disability compared to the general population.
c. a similar chance of developing knee disability as the general population.
d. an increased chance of developing knee disability compared to the general population.

42. If left untreated, AK may progress to squamous cell carcinoma.

a. True
b. False

By Louis Kuritzky, MD

Parathyroid Hormone (1-34) in Postmenopausal Women with Osteoporosis

Though numerous agents for prevention and treatment of osteoporosis (OSPS) are available, none is ideal for all women, and each has a distinct limitation. The dominant function of most agents is to inhibit bone resorption, thereby reducing bone loss, but doing little to increase, or stimulate, new bone formation. Hence, the idea of using a therapy that stimulates bone formation is appealing.

Neer and associates point out that parathyroid hormone (PTH) has various effects upon bone, depending upon administration method. To test the hypothesis generated by successful animal studies, Neer et al studied PTH (vs. placebo) in postmenopausal women (n = 1637) with prior vertebral fractures. PTH was self-administered by injection daily for 24 months. All subjects also received vitamin D and calcium supplementation.

There were statistically fewer new nonvertebral fractures in the PTH treatment group than placebo (RR = 0.47); similarly, bone mineral density increased 9-13% more than placebo recipients. The medication was well tolerated, with no serious side effects. PTH has been shown to be effective in preventing fractures and stimulating bone formation. ❖

Neer RM, et al. N Engl J Med. 2001; 344:1434-1441.

Biochemical Markers of Liver Fibrosis in Patients with Hepatitis C Virus Infection

It is common practice to perform liver biopsy for definition and prognostication of hepatitis C (HEPC). This process is not without consequence: although mortality is rare (0.03%), other serious complications are significantly more common (0.3%), not to mention the pain at the time of biopsy, and in 30%, postbiopsy pain. Imbert-Bismut and colleagues sought to evaluate the predictive value of basic serum biochemical markers for the diagnosis of liver fibrosis, (early as well as advanced). If indeed such markers had valuable predictive capacity, some liver biopsies might be avoided.

Imbert-Bismut et al studied 11 different serum markers, including traditional transaminases, alpha-2 macroglobulin, haptoglobin, gamma-globulin, apolipoprotein A-1, gamma-glutamyltranspeptidase, and total bilirubin. The study group included 205 HEPC patients who had undergone liver biopsy. Serum markers were assayed in years 1 and 2.

Twelve percent of patients had sufficiently low scores using multiple serum markers that liver biopsy could have been avoided with 100% certainty that no significant fibrosis was present. Imbert-Bismut et al suggest that use of serum markers may substantially reduce unnecessary liver biopsy in patients with HEPC. ❖

Imbert-Bismut F, et al. Lancet. 2001; 357:1069-1075.

Management of Chronic Tension Type Headache

Chronic tension type headache (CTH) is defined by the International Headache Society criteria as occurring 15 or more days/month for at least 6 months. Since this disorder is not infrequent (1.5% of men, 3% of women) and results in decrements in quality of life, as well as decreased work performance, choosing the most efficacious management is of great clinical relevance.

The current study was a randomized placebo-controlled trial (n = 203) comparing tricyclics (TCA) with stress management, or the combination. TCA therapy used amitriptyline or nortriptyline, titrated from a low starting dose, to maximize tolerability, up to 100 mg/d of amitriptyline or 75 mg/d nortriptyline.

Stress management techniques (SMT) included deep muscle relaxation, instruction in cognitive coping skills, and guidance in stress management. Treatments (or placebo) were administered for 6 months.

Each active treatment arm was significantly more effective than placebo. TCA therapy had the greatest number of individuals with improved headache score (38%), followed by stress management (35%). The combination of treatments was most effective, producing a favorable response in 64% of subjects. Holroyd and colleagues conclude that a combined approach to CTH results in the most favorable outcome. ❖

Holroyd KA, et al. JAMA. 2001;285: 2208-2215.

Digoxin Use in this 81-Year-Old Man?

By Ken Grauer, MD

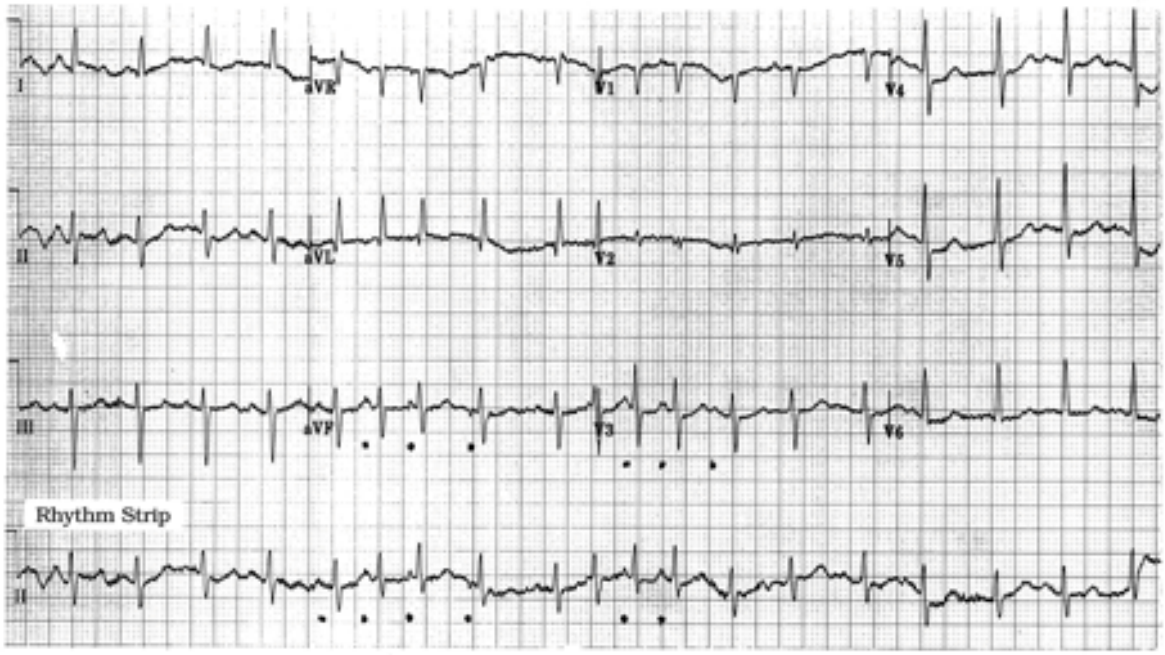

Figure. 12-lead ECG obtained from an 81-year-old man on digoxin.

Clinical Scenario: The ECG shown in the Figure was obtained from an 81-year-old man who presented with heart failure and pneumonia. Digoxin was among his many medications. Why do you suppose he was on digoxin?

Interpretation: Interpretation of the ECG in the Figure is made difficult by the presence of artifact in the baseline. One might be tempted to assume that the irregularly irregular rhythm seen in the lead II rhythm strip at the bottom of this tracing reflects atrial fibrillation. However, close inspection of the rhythm strip suggests that despite baseline wander and artifactual markings, there probably *is* atrial activity in this lead II rhythm strip. Directing one's attention to the deflections occurring just above the dots in the rhythm strip suggests the presence of *different* shaped P waves with varying PR intervals. That these deflections are likely to be real and true manifestations of atrial activity rather than artifact is suggested by confirmation in other simultaneously recorded leads of the presence of P waves (*see dots in leads aVF and V_3*).

Thus, this is an irregularly irregular supraventricular (narrow-complex) rhythm with multiple differently shaped P waves—a description that strongly suggests multifocal atrial tachycardia (MAT) as the etiology of the rhythm.

MAT most often occurs in the setting of chronic pulmonary disease. It is also sometimes seen in the presence of multisystem disease (such as pneumonia, sepsis, acid-base disturbance, or electrolyte disorders). The treatment of choice is to identify and correct the underlying medical cause(s) of the rhythm. Although digoxin may help with rate control, caution is urged with use of digoxin for MAT because of the predisposition for developing digoxin toxicity. One wonders if this 81-year-old man with heart failure may have mistakenly been placed on digoxin for heart failure and misdiagnosis of his irregular rhythm as atrial fibrillation. ❖

In Future Issues: Novel Cardiovascular Risk Factors