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Novel Risk Factors for Predicting Systemic Atherosclerosis

ABSTRACT & COMMENTARY

Synopsis: *The total cholesterol-HDL-cholesterol ratio and the C-reactive protein are strong predictors of peripheral vascular disease.*

Source: Ridker PM, et al. *JAMA.* 2001;285:2481-2485.

Several novel risk factors have been proposed as potential criteria for improved detection of early atherosclerosis. Ridker and colleagues noted that there were no comparative data to guide the clinical use of these potential biomarkers.

The objective of this study was to compare the predictive value of 11 lipid and nonlipid biomarkers as risk factors for the development of symptomatic peripheral arterial disease (PAD).

This was a nested case-control study of 14,916 initially healthy male physicians aged 40-84 years, of whom 140 subsequently developed symptomatic PAD. One hundred forty age- and smoking-matched men who remained free of vascular disease during a 9-year follow-up period were randomly selected as controls.

The main outcome measure was incident PAD, as determined by baseline total cholesterol, high-density cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol-HDL-C ratio, triglycerides, homocysteine, C-reactive protein (CRP), lipoprotein (a), fibrinogen, and apolipoproteins (apo) A-1 and B-100.

In univariate analysis, plasma levels of total cholesterol, LDL-C, triglycerides, apo-B, total cholesterol-HDL-C (all with $P < .001$), fibrinogen ($P < .02$), and CRP ($P < .006$) were significantly higher at baseline among men who subsequently developed PAD while HDL-C and apo A-1 were significantly lower. The total cholesterol-HDL ratio was the strongest lipid predictor of risk (relative risk [RR], 3.9) for those in the highest quartile vs. the lowest quartile. The CRP was the strongest nonlipid predictor for the highest vs. the lowest quartile (RR, 2.8). In assessing joint effects, addition of CRP to standard lipid screening significantly improved risk prediction models based on lipid screening alone ($P < .001$).

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INSIDE

Ridker et al concluded that of the 11 biomarkers assessed at baseline cholesterol HDL-C ratio and CRP were the strongest independent predictors of the development of PAD. CRP provided additive prognostic information over standard lipid measures.

COMMENT BY RALPH R. HALL, MD, FACP

This study provides long awaited answers to our questions about which tests we should be ordering to assist us in estimating our patients' risk for atherosclerosis.

How do we manage the patient with elevated CRP? Studies are now underway to evaluate the effects of statins on patients with elevated CRP.[1] In a subgroup analysis of the Cholesterol and Recurrent Events trial (CARE trial), CRP levels decreased 20% in patients taking pravastatin and increased by 20% in the patients taking placebo over a 5-year period.[2] In the Air Force/Texas Coronary Prevention Study, simvastatin, pravastatin, and atorvastatin in equipotent doses each reduced CRP levels after 6 weeks of treatment.[3] The statins in general then appear to be somewhat effective in reducing CRP levels.

As Maseri has pointed out, "inflammation appears to be a cause and not just a consequence of acute coronary syndromes."[4] We will have to wait for further trials to be completed to be certain that statins are the current best approach for managing patients with elevated CRP. ❖

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Botox Ameliorates Sialorrhea

ABSTRACT & COMMENTARY

Synopsis: *Sialorrhea lessened within 5 days of injection which improved patients an average of 61%, and maintained the benefit an average of 4.7 months.*

Source: Porta M, et al. *J Neurol Neurosurg Psychiatry*. 2001; 70:538-540.

Injection of botulinum toxin has revolutionized the treatment of focal dystonia. Approved by the FDA in 1990, botulinum toxin injection is now the treatment of choice for patients with blepharospasm, torticollis, oromandibular dystonia, spasmodic dysphonia, and hemifacial spasm. The dramatic response to treatment and the safety of the procedure led investigators to apply this technique to a variety of other conditions, including bruxism, lower esophageal and rectal spasms, spasticity, tics, and hyperhidrosis.

Botulinum toxin exerts its effect by inhibiting the release of acetylcholine at the neuromuscular junction. In the last 2 years, several studies have shown that injection of toxin into the parotid gland is an effective treatment for patients with excess saliva. Excessive drooling or salivation usually accompanies neurologic conditions in which coordination of swallowing is impaired, including ALS, head trauma, cerebral palsy, and Parkinson's disease. Among Parkinson patients followed at the Neurological Institute of New York,

sialorrhea is a common complaint. In 5% of these patients, uncontrolled salivation becomes a major source of hygienic and psychosocial embarrassment. We have found that medical treatments for sialorrhea (typically anticholinergic drugs) are usually ineffective and poorly tolerated by older patients.

In this paper, Porta and colleagues describe their experience injecting botulinum toxin into the parotid and submandibular glands of patients with excessive sialorrhea. Ten patients were enrolled in this open-label study, 4 with ALS, 2 with Parkinson's disease, and 1 each with primary sialorrhea, SSPE, cerebral palsy, and head trauma. Fifteen to 40 units of Botox (botulinum toxin type A) were injected into each parotid gland, and 10-15 units were injected into each submandibular gland. Porta et al defined the anatomy of the parotid and submandibular glands and the trajectory of the facial nerve using ultrasound. Patients rated their improvement using a visual analogue scale. Sialorrhea lessened within 5 days of injection which improved patients an average of 61%, and maintained the benefit an average of 4.7 months. There were no adverse events and side effects were minimal.

COMMENT BY STEVEN FRUCHT, MD

This is a convincing study, showing that Botox is an effective treatment for patients with troubling sialorrhea. Ultrasound guidance is a useful tool to ensure optimal injection of the parotid gland, and it is probably required to inject the submandibular gland, which normally provides up to 70% of daily saliva production. The degree of improvement in sialorrhea is comparable to other studies, and the technique is well tolerated and safe. Fortunately, although the benefit remained only a bit longer than 4 months after injection, repeated injections appeared to sustain the improvement.

Unfortunately, a major limitation to this technique is the cost of the treatment. Botulinum toxin is extremely expensive, between $4 and $5 per unit, or $400 to $500 for an average sialorrhea injection. This does not include the injection fee. At present, Medicare and most managed care plans do not cover this procedure, and it is unclear whether or not physicians will be reimbursed if they perform it. This is unfortunate, as the technique effectively treats an often troubling symptom for which alternative treatments are not adequate. ❖

Dr. Frucht is Assistant Professor of Neurology, Movement Disorders Division, Columbia-Presbyterian Medical Center, New York, NY.

Tubal Ligation Shown to Reduce Incidence of Ovarian Cancer for BRCA1 Carriers

ABSTRACT & COMMENTARY

Synopsis: *Ovarian cancer occurs frequently in women who carry the BRCA1 and BRCA2 gene mutations. In this multinational, retrospective, case-control study, a prior tubal ligation was shown to provide significant protection against subsequent ovarian cancer development. Thus, tubal ligation is a feasible option to reduce risk of ovarian cancer in women with BRCA1 mutations who have completed childbearing.*

Source: Narod SA, et al. *Lancet.* 2001;357:1467-1470.

The lifetime risk for ovarian cancer in women who carry mutations in the BRCA1 or BRCA2 genes is high; estimated to be 40%[1] and 25%[2] respectively. About 10% of all new cases of ovarian cancer in North America are associated with mutations in these genes.[3] In several case control and prospective studies, tubal ligation has been associated with decreased risk of invasive epithelial ovarian cancer, but risk reduction had not previously been demonstrated for those genetically predisposed, such as with BRCA1 or BRCA2 mutations. Thus, the Hereditary Ovarian Cancer Clinical Study Group performed a matched case control study among women who had undergone genetic testing and who carried a pathogenic mutation in BRCA1 or BRCA2. Cases were 232 women with a history of invasive ovarian cancer and controls were 232 women without ovarian cancer. Cases and controls were matched for year of birth, country of residence, and mutation (BRCA1 or BRCA2).

The median age at which ovarian cancer was diagnosed was 51 years (range, 24-81) and the study was performed at a median of 5 years after diagnosis. Tubal ligation was reported by 39 of the ovarian cancer patients compared to 69 of the controls. Of the participants with BRCA1 mutations, significantly fewer patients than controls had ever had tubal ligation. This association remained significant after adjustment for oral contraceptive (OC) use, parity, personal history of breast cancer, and ethnic group. Among BRCA2 carriers, tubal ligation was not found to reduce risk significantly.

Also demonstrable in this study was a strong protective effect of OCs, and this was evident for carriers of either BRCA1 or BRCA2 mutations. The combination of OC use and tubal ligation offered the greater protec-

tion than either method alone. Among BRCA1 mutation carriers, tubal ligation and a history of OC use, compared with neither exposure, was associated with an odds ratio of 0.28 (0.15-0.52; $P < .0001$).

COMMENT BY WILLIAM B. ERSHLER, MD

Tubal ligation has been associated with a decreased risk of ovarian cancer. For example, after 12 years of follow-up in the Nurses Health Study,[4] a strong inverse relation between tubal ligation and ovarian cancer was seen. There have been several case control studies that were reviewed in a meta-analysis,[5] and again, there appeared to be decreased risk of ovarian cancer in those that had received tubal ligation. The current study adds the important information that the protective effect is evident in those with high risk, those with BRCA1 mutations. The study did not show a significant effect for those carrying BRCA2 mutations, most likely because of the smaller number of participants with this mutation (59 of the 232 cases), and the later onset of ovarian cancer in those with this mutation. The age at tubal ligation was important, with the greatest effect observed in those who had this procedure at a younger age. However, a significant protection was observed even in those who had the procedure at a later age.

This report also confirmed the strong protective effect of prior use of OCs. In fact, the risk reduction for those who had used OCs and had a tubal ligation was 72% when compared to those who had neither interventions.

The mechanism whereby tubal ligation protects against ovarian cancer development is a matter of conjecture at present. A variety of hypotheses have been proposed that implicate an altered hormonal microenvironment or reduced inflammation, but a definitive explanation awaits experimental demonstration.

Methods of preventing ovarian cancer in women with or without these genetic predispositions include prophylactic oophorectomy, chemoprevention with OCs, or regular screening (eg, by ultrasound and serum CA-125). OCs alone have been shown to reduce risk by approximately 50%,[6] but some physicians and patients are concerned about the potential increased risk of breast cancer by such an approach.

Currently, and as clearly supported by this report, tubal ligation offers protection for women at high risk of developing ovarian cancer (particularly those with BRCA1 mutations). In such women who have completed childbearing, tubal ligation with or without continued OCs would seem a logical recommendation. ❖

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Dr. Ershler is Director, Institute for Advanced Studies in Aging, Washington, DC.

But What About Dogs and *E coli*?

ABSTRACT & COMMENTARY

Synopsis: *In England, the first documented case of transmission of E coli 0157:H7 from a dog to a human has been reported.*

Source: ProMED-mail post; www.pro-medmail.org. Accessed May 8, 2001.

The first documented case of transmission of *E coli* 0157:H7 from a dog to a human has been reported in England. The dog was elderly, incontinent of both urine and stool, and described as "largely immobile." He had been kindly taken in by a family 2 months earlier. Their 3-year-old child developed bloody diarrhea and subsequently required hospitalization with hemolytic-uremic syndrome. Fecal samples from the dog were positive for *E coli* 0157. The case probably would not have come to light except that the family is vegetarian, raising suspicions of an atypical source. Although the report did not allude to this, one wonders if the dog's enteric infection contributed to his overall weakened and incontinent condition.

COMMENT BY CAROL A. KEMPER, MD, FACP

How the dog acquired *E coli* 0157 is a matter of speculation. During the 2 months he lived with the family, he was primarily fed a commercially-prepared dry dog food, which according to the manufacturer is heated and sterilized. Whether it was fed raw eggs or table scraps, such as undercooked hamburger meat, before being taken in by the family is not known. Dogs fed table scraps or undercooked meat may be at risk for acquisition of *E coli* 0157. ❖

Dr. Kemper is Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases, Santa Clara Valley Medical Center, Redwood City, Calif.

Accuracy of CPT Evaluation and Management Coding

ABSTRACT & COMMENTARY

Synopsis: *The error rate for physician coding of patient visits is substantial and appears to occur more frequently for new patient visits than for established patient visits. The complexity of the CPT coding guidelines and a lack of physician training in CPT coding probably accounts for the error rate.*

Source: King MS, et al. *J Am Board Fam Pract.* 2001;14: 184-192.

Current procedural terminology (cpt) coding is designed to reflect the resources used when providing care. Clinicians use CPT codes to bill Medicare and other payers for their services. Proper coding has important legal and financial implications. Clearly the level of coding translates into practice reimbursement. Also, accurate coding documents the level of services and helps protect physicians from the legal ramifications of a Medicare audit.

This study examined how accurately a sample of family physicians code outpatient visits. A group of 600 randomly selected family physician members of the Illinois Academy of Family Physicians were sent the progress notes of 6 patients to code. The 6 cases represented both new and established visits and different levels of services. The physicians were asked to code the level of service for each of the visits. In addition, they completed a brief demographic survey to elicit coding practices and characteristics that might be associated with coding ability. The physicians' coding was then compared to a gold standard which represented the consensus code of 5 expert billing coders.

The response rate to the survey was 42%. For established patient visits, physicians agreed with the experts' consensus codes in 52% of the cases, overcoded in 16% of the cases, and undercoded in 33% of the cases. For new patients, physicians agree in only 17% of the cases, with overcoding in 82% of the cases and undercoding in 1% of the cases. No statistically significant relationships were found between physician accuracy in coding and variables such as years in practice, coding training, patient care time, and charges for office visits.

COMMENT BY MARTIN LIPSKY, MD

King and colleagues conclude that physicians have difficulty in accurately applying the current CPT guidelines. Given the recent concern regarding coding fraud, the study's format removed any financial incentives for coding, strongly supporting natural error rather than an attempt to defraud as a cause for coding errors. Although this study was done with family physicians, there is no reason to believe that internists would also experience a similar error rate. Certainly when I discuss coding with my internal medicine colleagues they relate the same frustrations and uncertainty that I do about CPT coding. However, future studies looking at coding across specialties would be interesting.

This study also notes that the pattern of error differs between new and established patients. The physicians tended to overcode new visits more than old visits. It is possible that many physicians did not recognize that new patient visits require more documentation to establish a higher service level. Another possiblity is the sense physicians have that new patients require more effort and their coding levels could reflect this assumption.

Although no financial analysis was done, it appears that overcoding was balanced by undercoding suggesting that the overall financial impact of coding errors was neutral. For many of us faced with coding our visits, this study supports the contention that there might be a simpler set of guidelines in the future. To their credit, the CMS (the new acronym for HCFA) is trying to develop their guidelines. In the meantime, this study provides evidence that a certain amount of error in coding is inherent with the current guidelines. ❖

Pharmacology Update

Almotriptan (Axert—Pharmacia Corporation) For Migraine

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

The fda has approved pharmacia's almotriptan malate for the treatment of migraine with or without aura in adults. The drug is touted as being as effective as other triptans, but with a favorable side effect profile, especially cardiovascular side effects. Almotriptan will be marketed by Pharmacia under the trade name "Axert."

Indications

Almotriptan is indicated for the acute treatment of migraine with or without aura in adults.

Dosage

The recommended dose of almotriptan is 6.25 mg or

12.5 mg initially. If the headache returns, the dose may be repeated after 2 hours. No more than 2 doses should be taken within a 24-hour period. The safety of using almotriptan for more than 4 headaches in a 30-day period has not been established. Patients with impaired renal or hepatic function should take an initial dose of 6.25 mg.[1]

Almotriptan is supplied as 6.25 mg and 12.5 mg tablets.

Potential Advantages

The incidence of chest pain associated with almotriptan in preclinical studies was lower than that reported for sumatriptan in premarketing studies.[2] Single doses from 12.5 mg to 50 mg did not have a significant effect on the electrocardiography of healthy volunteers while doses of 25 mg and 50 mg had a small dose-related increase in systolic and diastolic blood pressure up to 4 hours postdose (2.78 and 4.17 mg Hg and 3.77 and 6.11 mg Hg, respectively).[3] Animal studies also suggest a more favorable cardiovascular safety profile than sumatriptan.[4] In a comparative assessment of almotriptan and sumatriptan, patients reported they were more satisfied with the side effects profile of almotriptan.[5] Subjects were asked "how bothered" they were by any side effects of the study medication. No differences were reported in terms of pain relief, functional status, or health-related quality of life. Almotriptan, as with naratriptan, does not appear to interact with propranolol as some patients may be taking the latter for migraine prophylaxis.[6]

Potential Disadvantages

As with other 5-HT 1B/1D agonists, almotriptan is contraindicated in patients with documented ischemic heart disease or symptoms consistent with ischemic heart disease.[1] Cerebrovascular (eg, stroke), vasospastic-related events (eg, colonic ischemia), and increases in blood pressure have been reported with 5-HT1 agonists.

Almotriptan is metabolized by monamine oxidase and, to a lesser degree, cytochrome P450 3A4 and 2D6. Inhibitors of MAO and CYP 3A4 are expected to reduce the elimination of almotriptan. Coadministration with SSRIs has been reported, albeit rarely, to cause weakness, hyperflexia, and incoordination.[1]

Comments

Almotriptan is a 5-HT 1B/1D receptor agonist similar to other triptans such as sumatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. These drugs are thought to act on the receptors in meningeal arteries and trigeminovascular nerve endings.[7] The newer agents have better oral bioavailability compared to sumatriptan. Their efficacy and recurrence rates appear to be similar with the possible exception of a lower efficacy with naratriptan and a lower recurrence rate and a faster onset with rizatriptan.[8] Almotriptan is priced the same for either strength, about $11 per tablet.

Clinical Implications

Almotriptan provides another alternative for the oral management of migraine. While differences among the triptans appear small, there may be a greater interpatient difference in response and tolerance.[7] Premarketing clinical studies suggest that almotriptan may have a low incidence of chest symptoms compared to what has been reported with sumatriptan. Chest symptoms have been reported as a frequent occurrence with sumatriptan, but are rarely significant.[9] There are no comparative studies among the triptans specifically assessing differences in chest pain. Some difference may be attributed to variations in subject inclusion and a wider definition of chest pain. Until there are data to clearly differentiate among the triptans, they are all contraindicated in patients with suspected or documented ischemic heart disease. ❖

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CME Questions

1. Which one of the following statements is *false*?

a. Pravastatin is the only effective statin for lowering the CRP.
b. Inflammation appears to be a cause and not just a consequence of acute coronary syndromes.
c. The total cholesterol/HDL-c ratio appears to be the strongest predictor of PAD among the lipid biomarkers tested.
d. Atorvastatin, simvastatin, and pravastatin all appear to be equally effective in lowering plasma CRP.

2. Which of the following interventions has *not* been demonstrated to reduce ovarian cancer development in women with BRCA1 mutations?

a. Oophorectomy
b. Tubal ligation
c. Oral contraceptives
d. Regular screening by ultrasound and serum CA-125

By Louis Kuritzky, MD

Smoking Cessation in Patients with Chronic Obstructive Pulmonary Disease

Smoking cessation for patients with COPD is the most important single step for reducing risk of disease progression. Although there are numerous reports of smoking cessation that use a variety of tools and techniques, none has specifically addressed the efficacy of buproprion SR (BUP) for patients with existing COPD. This report provides specific focus on a population (n = 404) of mild-to-moderate COPD patients treated with traditional dosing BUP in a placebo-controlled trial for 12 weeks. In addition to BUP (or placebo), all participants received counseling about smoking cessation.

The most common adverse drug effects were insomnia, headache, anxiety, and dry mouth. The discontinuation rate for BUP was not different from placebo, and there were no serious adverse events.

At 7 weeks, 28% of subjects remained smoking abstinent (placebo = 16%). This number decreased to 16% (placebo = 9%) 14 weeks after cessation of pharmacotherapy.

Though these rates are a bit less than those demonstrated in some previous trials, the potential for success in even a small subgroup of COPD patients has important individual and public health implications. ❖

Tashkin D, et al. Lancet. 2001;357: 1571-1575.

Is the Placebo Powerless?

The word placebo in medical usage is derived from the Latin word which means "to please." The intent of current parlance is that a placebo is any concrete intervention that possesses no demonstrable inherent therapeutic effect. Hence, any effect occurring in placebo recipients, favorable or untoward, is attributed to other secondary effects, such as the personal belief system of the patient, positive thinking, etc. Your reviewer prefers to think of placebo as the channel of forces that can be marshaled (for positive or negative outcomes) in persons given appropriate stimuli. For instance, mothers confronted with their child trapped beneath a heavy vehicle call upon untapped strength to free their child, yet when strength-tested under less stimulating situations, are unable to repeat such acts.

Quantification of the effect of placebo has perhaps been overestimated, since most trials compare placebo with an active therapy. During such a trial, regression to the mean and natural history of the disease over time might be misinterpreted as favorable placebo effects. Hence, the best comparison trial for placebo effect would be placebo vs. no treatment. To this end, Hrobjartsson and Gotzsche performed a meta-analysis on 114 trials (n = 3795).

Hrobjartsson and Gotzsche comment that there were no significant placebo effects on objective outcomes. Subjective outcomes and pain demonstrated some small possible benefit, but since their review also shows that increasing sample size was associated with lesser magnitude of effect, the possibility of bias related to trial size is evident. Hrobjartsson and Gotzsche posit, based upon this review, that use of placebos is unjustified outside the setting of clinical trials. ❖

Hrobjartsson A, Gotzsche PC. N Engl J Med. 2001;344:1594-1602.

Understanding the Experience of Pain in Terminally Ill Patients

At least 20% of terminal patients experience moderate to severe pain, and the proportion may be as high as 75%, specifically among seriously ill cancer patients. Because of concerns about the veracity of data referable to pain in terminally ill patients, Weiss and colleagues surveyed by personal interview almost 1000 terminally ill patients. The line of inquiry was specifically: 1) In the past 4 weeks, did you desire more pain medicine than you received from your PCP/pain specialist? 2) Why did you not want more?

Half of these patients reported moderate-to-severe pain in the previous 4 weeks, the majority of whom had seen their PCP during this period. Most PCP patients (62%) were satisfied with their level of analgesia, but almost one-third did desire increased analgesia, and 9% wanted a decrease or cessation of analgesia.

Patients who did not desire more analgesia mentioned fear of addiction, adverse drug effects, and desire to avoid medication as their rationale.

Since the demographics of this report include a diversity of US communities and ethnicities, it may well be representative of clinical practice in a variety of settings. It is encouraging that the background level of moderate-severe pain in this group is not as high as previously described in some studies, yet the 30% of individuals reporting a desire for increased analgesia highlights the need for continued vigilance to analgesic adequacy. ❖

Weiss SC, et al. Lancet. 2001;357: 1311-1315.

ST Elevation in Lead aVL

By Ken Grauer, MD

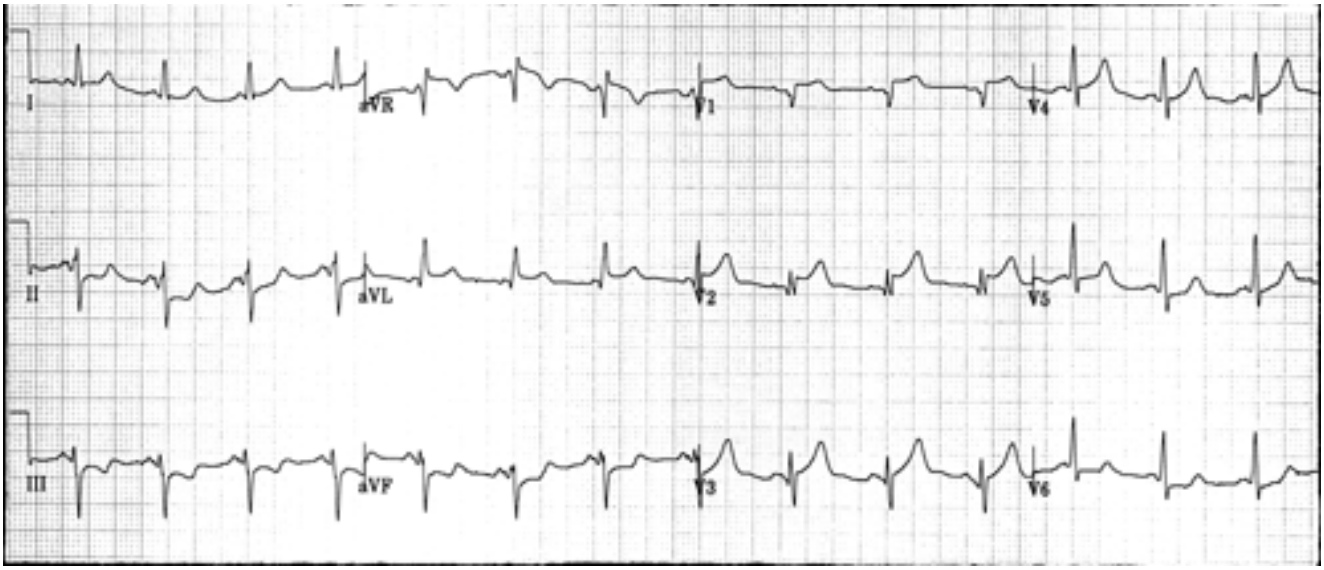

Figure. 12-lead ECG obtained from a 50-year-old man with new-onset chest pain.

Clinical Scenario: The 12-lead ECG shown in the Figure was obtained from a 50-year-old man with new-onset chest pain. In view of a negative prior history of coronary disease, what might cardiac catheterization show?

Interpretation: The rhythm in this tracing is sinus, albeit with a shortened PR interval. The mean QRS axis is leftward (about -40°), consistent with a left anterior hemiblock pattern. There is no sign of chamber enlargement. Small q waves are seen in leads I and aVL, as in leads V_2 and V_3. A QS complex is seen in lead V_1. Obvious ST segment elevation is seen in the anterior precordial leads, with reciprocal ST segment depression in most other leads on this tracing. As suggested in the title of this ECG Review, ST segment elevation is also seen in lead aVL. In the setting of new-onset chest pain, the overall ECG picture seen here is strongly suggestive of acute anteroseptal infarction.

ST segment elevation in lead aVL has been shown to provide insight into the *anatomic* site of acute coronary occlusion. In an interesting correlative study by Birnbaum et al, patients with ST segment elevation in lead aVL that occurred in association with ST segment elevation in several other anterior precordial leads (V_1, V_3, V_4, and/or V_5) most often were found at cardiac catheterization to have acute occlusion of the left anterior descending (LAD) coronary artery *proximal* to the first diagonal branch.[1] This was precisely what was found at catheterization for the patient whose ECG is shown in the Figure. In contrast, patients with ST segment elevation in lead aVL and V_2, but ST segment *depression* in other precordial leads most commonly had acute occlusion of *only* the diagonal branch of the LAD. Those in the study with ST segment elevation in lead aVL but ST segment *depression* in lead V_2 were more likely to have a culprit lesion in the obtuse marginal branch of the circumflex artery. ❖

Reference

1. Birnbaum Y, et al. *Am Heart J*. 1996;131:38-42.

In Future Issues:

Pioglitazone Improves Lipid Profiles More Effectively Than Rosiglitazone