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C-Reactive Protein Makes It to Center Stage

ABSTRACT & COMMENTARY

Synopsis: *C-reactive protein levels are stronger predictors of first cardiovascular events than low-density lipoprotein cholesterol levels.*

Source: Ridker PM, et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med*. 2002;347:1557-1565.

Using a portion of the database of the Women's Health Study (WHS), Ridker and colleagues previously demonstrated that among a dozen markers of inflammation, C-reactive protein (CRP) was best at identifying women at risk for cardiovascular events.[1] This study finds them tackling the entire database to compare the efficacy of CRP and low-density lipoprotein cholesterol (LDL) as predictors of first cardiovascular events and to define population-based cutoff points for CRP. WHS is an ongoing study of aspirin and vitamin E as primary prevention of cardiovascular events in women 45 years or older (average age 54.7 years at study entry). Twenty-five percent were hypertensive, 12% were current smokers, and 2.5% were diabetic. The average body mass index was 25.9. Blood samples from 27,939 participants were analyzed for CRP and LDL levels. Approximately 400 other samples could not be analyzed. The patients were followed for these end points: nonfatal myocardial infarction, nonfatal ischemic stroke, coronary revascularization, and death from cardiovascular events. Knowing that hormone replacement therapy (HRT) can affect CRP and LDL levels, the total population was divided into those taking (12,139) and those not taking (15,745) HRT at the beginning of the study. The HRT status of 55 women was not known. The CRP and LDL data from both HRT and non-HRT were grouped into quintiles to establish cutoff points and subjected to Kaplan-Meier analysis to construct event-free survival curves.

The relative risks (RR) for first cardiovascular event (after adjusting for age, smoking status, diabetes status, blood pressure, and HRT status) were calculated for each quintile for CRP and LDL, using the first quintile as the reference. The results for CRP

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were 1.0, 1.4, 1.6, 2.0, and 2.3 by increasing quintile. The results for LDL were 1.0, 0.9, 1.1, 1.3, and 1.5. These values were all statistically significant. The data were also analyzed for each end point separately, and CRP continued to be more predictive than LDL. HRT reduced the RR as estimated by CRP but not by LDL. Seventy-seven percent of events occurred in women with LDL < 160 mg/dL and 44% in women with LDL < 130 mg/dL. LDL and CRP levels did not correlate well with each other. To explore the interactions between CRP and LDL, the women were divided into 4 groups, and the relative risks were calculated with the low CRP/low LDL as the reference, using the mean values of CRP (1.52 mg/L) and LDL (123.7 mg/dL). The RRs were 1.0 (low CRP/low LDL), 1.5 (low CRP/high LDL), 1.5 (high CRP/low LDL), and 2.1 (high CRP/high LDL). The age-adjusted event rates per 1000 person-years were 1.3, 2.0, 2.6, and 3.9.

Further analysis of CRP levels and the Framingham risk score showed that CRP levels are independent predictors of risk.

COMMENT BY ALLAN J. WILKE, MD

CRP is the character actor of laboratory tests; it performs very well in bit parts and supporting roles but is still waiting for its shot at the big time. The generally recognized normal value is < 8 mg/dL,[2] which is considerably higher than the mean value in this study. CRP is useful for monitoring the course of inflammatory disorders, detecting and monitoring infection, and staging chronic lymphoid leukemia. It is elevated with tissue injury or necrosis. Is cardiovascular event prediction its starring role? I'm not sure, but I don't think so. As the accompanying editorial notes,[3] there are hundreds of known risk factors for coronary heart disease. Which ones alone are the most predictive? Which ones in combination?

What have we learned from this study? First, CRP levels are stronger predictors of cardiovascular events than LDL levels. Second, CRP and LDL levels are not well correlated and probably predict risk in different populations. Third, the combination of CRP and LDL is better than either test by itself. It is well to remember, however, that the RRs are not great, at best 2-3 times the lowest quintile.

Are the results of this study plausible? Yes. More and more, we are learning that inflammation is central to the development of cardiovascular disease.[4,5] Can we treat an elevated CRP level? Maybe. There are some intriguing hints from a previous study by the same authors that showed that lovastatin might prevent coronary events in patients with a total-to-HDL-cholesterol ratio that was lower than the median and a C-reactive protein level higher than the median.[6]

A weakness of this study is that it is derived from data from the WHS; it may not be wise to extrapolate the results to men. More importantly, WHS was designed to evaluate aspirin and vitamin E as primary prevention for cardiovascular events in women 45 years of age or older, not to look at CRP and LDL as cardiovascular risk factors. Therefore, the possibility of bias exists. I think that the sheer magnitude of the database makes bias unlikely, however.

The main question is whether we add CRP to our list of screening labs. The same editorialist suggests we should not because the "predictive value is markedly diminished when adjusted for other risk factors." CRP will have to wait for its close-up. In the meantime, we need to work to identify our patients at risk for cardio-

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vascular disease and treat or modify known risk factors that improve those risks (hyperlipidemia, hypertension, tobacco abuse, etc). ■

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Fluoroquinolones and Tendinopathies

ABSTRACT & COMMENTARY

Synopsis: *The excess risk of Achilles tendon disorders attributable to fluoroquinolone use was estimated to be 3.2 cases per 1000 patient-years, with most of that increase accounted for by patients 60 years of age and older who concomitantly receive corticosteroids.*

Source: van der Linden PD, et al. Fluoroquinolones and risk of Achilles tendon disorders: Case-control study. *BMJ*. 2002; 324:1306-1307.

The IMS database containing information from UK general practices covering 1 million to 2 million inhabitants was queried in order to perform a nested case control study designed to examine risk factors for the development of Achilles tendon disorders (ATD) related to fluoroquinolone use. The cohort included 47,776 adults who had received a flu-oroquinolone, of whom 704 (1.4%) had Achilles ten-donitis and 38 (.08%) had Achilles tendon rupture. This represented an overall excess risk of 3.2 cases per 1000 patient-years. The adjusted relative risk (RR) of ATD was 1.9 (95% CI, 1.3-2.6) for current fluoroquinolone use; there was no increased risk associated with recent (but not current) or remote past use. While there was no increased risk associated with current use among those younger than 60 years of age, for those 60 years of age or older, the RR was 3.2 (2.1-4.9) and for those in this latter age group who were also receiving corticosteroids, the RR was 6.2 (3.0-12.8). Those with both risk factors, age older than 60 years and corticosteroid use, accounted for 87% of cases of ATD.

■ COMMENT BY STAN DERESINSKI, MD, FACP

A large increase in both fluoroquinolone use and non-traumatic tendon ruptures was observed in The Netherlands between 1991 and 1996.[1] It was concluded, however, that less than 7% of the increase in tendon ruptures could be attributed to the increase in fluoroquinolone use. Nonetheless, the epidemiologic and laboratory evidence demonstrates a strong causal relationship.

Fluoroquinolones are known to cause cartilaginous abnormalities in immature animals, such as beagle pups. Histologic changes in tenocytes of experimental animals exposed to fluoroquinolones include vacuolation of tenocytes and decrease in fibril diameter with an increase in the distance between individual collagenous fibrils. In vitro experiments indicate that fluoroquinolones stimulate matrix-degrading protease activity of fibroblasts while inhibiting fibroblast metabolism.

Much evidence supports the hypothesis that tendinopathy is the consequence of chelation of magnesium ions by fluoroquinolones—a class effect and the reason why simultaneous oral administration of magnesium-containing antacids and fluoroquinolones results in markedly impaired gastrointestinal absorption of the latter. Thus, both magnesium deficiency and ciprofloxacin administration can each cause similar biochemical changes in the Achilles tendons of immature dogs.

Fluoroquinolones remain highly effective antibiotics in most regions. The low incidence of tendon disorders should not preclude their use, especially when only a tiny fraction of these complications involve actual tendon rupture. Nonetheless, the recognition that patients older than age 60, especially those receiving corticosteroids, comprise those at significant risk should alert the clinician. An evaluation in The Netherlands in 1998 found that the median time from initiation of fluoroquinolone use to onset of tendon symptoms was 6 days.[2] It is unfortunate, of course, that these risk factors describe a large number of patients with underlying chronic obstructive lung disease who are at risk of acute bacterial exacerbations and who might benefit, on occasion, from fluoroquinolone therapy. Thus, if a fluoro-

quinolone is the treatment of choice in such a patient, it might be beneficial, albeit unproven, to correct any magnesium deficiency that might be present, with the hope that this would reduce the potential for development of a tendinopathy. ■

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Suspected Pulmonary Embolism in Pregnancy

ABSTRACT & COMMENTARY

Synopsis: *Ventilation/perfusion scanning appears to be safe and effective, at least in ruling out significant clinical pulmonary embolism in pregnant patients. However, prospective studies over longer time periods should be undertaken to validate these conclusions.*

Source: Chan WS, et al. Suspected pulmonary embolism in pregnancy: Clinical presentation, results of lung scanning, and subsequent maternal and pediatric outcomes. *Arch Intern Med*. 2002;162:1170-1175.

PULMONARY EMBOLISM (PE) IS A PREVENTABLE CAUSE of maternal mortality during pregnancy and the postpartum period. Once PE is suspected, many clinicians begin their evaluation with a ventilation/perfusion scan. Although scanning is assumed to be safe during pregnancy based on low fetal radiation exposure,[1] no clinical data exist to support the notion that there are no adverse outcomes in pregnancy. In addition, little is known about ventilation/perfusion scan interpretation in pregnant women and the safety of withholding anticoagulation in those with normal or nondiagnostic scans.

The purpose of this multicenter, retrospective, observational study was to examine the distribution and safety of ventilation/perfusion scanning in pregnant patients. The safety of withholding anticoagulation therapy in pregnant women with normal or nondiagnostic scans was also examined.

A total of 120 consecutive pregnant patients who presented with suspected PE and had ventilation/perfusion scans were identified through the nuclear medicine departments. Patient demographics, stage of pregnancy, symptomatology, and treatment strategy at the time of original evaluation were recorded. Two independent experts re-interpreted the original ventilation/perfusion scans and categorized them as normal, nondiagnostic, or high probability. Patients were later contacted by telephone to determine postpartum venous thromoembolic events, and pregnancy outcomes.

Scan readings were as follows 87 (72.5%) normal, 29 (24.2%) nondiagnostic, and 4 (3.3%) high probability. Seven were receiving anticoagulation prior to presentation for previously diagnosed PE or deep venous thrombosis; eight women received anticoagulation subsequent to their evaluation. Of the 104 untreated women (1 died secondary to primary pulmonary hypertension), 80 had normal scans and 20 scans were nondiagnostic. In this group, no thromboembolic event was reported after a mean follow-up of 20 months.

Of 110 obstetrical and pediatric outcomes examined over 20 months, 3 spontaneous abortions, 4 congenital, and 4 developmental abnormalities were reported. No childhood cancers or leukemias were reported.

■ COMMENT BY ALAN FEIN, MD, & JONATHAN EDELSON, MD

In this retrospectively examined group of pregnant patients, the prevalence of high probability scans is low (1.8%), compared to the other patients with suspected PE (10%). There were no thromboembolic events reported in those with normal or intermediate probability lung scans, suggesting that ventilation/perfusion scanning in pregant patients has a good negative pedictive value. Importantly, fetal risk was minimal in this population. The percentage of adverse fetal outcomes after ventilation/perfusion scanning was similar to that in the general population, 2.6% compared to 3.6%. These numbers are supported by previous studies that suggested no increase in fetal malformation risk for exposures less than 1 rad; radiation exposure in ventilation/perfusion scans is significantly lower.[2]

In summary ventilation/perfusion scanning appears to be safe and effective, at least in ruling out significant clinical PE in pregnant patients. However, prospective studies over longer time periods should be undertaken to validate these conclusions. ■

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Pharmacology Update

Atomoxetine HCl—New Drug for ADHD

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

THE FDA HAS APPROVED ATOMOXETINE (PREVIOUSLY named tomoxetine), the first nonstimulant/noncontrolled drug to be approved for the treatment of attention-deficit/hyperactivity disorder (ADHD). Unlike previous drugs for this indication, atomoxetine is a selective inhibitor of the presynaptic norepinephrine transporter. Atomoxetine is marketed by Eli Lilly as "Strattera."

Indications

Atomoxetine is indicated for the treatment of ADHD in children, adolescents, and adults.

Dosage

The initial dose in children and adolescents up to 70 kg in body weight is 0.5 mg/kg. The dose may be increased after a minimum of 3 days up to 1.2 mg/kg. It may be given as a single dose in the morning or divided into morning and late-afternoon/early evening doses. Total dose should not exceed 1.4 mg/kg or 100 mg. For patients over 70 kg and adults, the initial dose is 40 mg/d, with increases up to 80 mg/d after a minimum of 3 days. The dose may be increased to 100 mg/d if an optimal response has not been achieved in 2-4 weeks. The maximum dose is 100 mg/d.[1]

Atomoxetine may be taken without regard to meals. Dosage should be reduced for those with hepatic impairment and those taking CYP2D6 isoform inhibitors.[1]

Atomoxetine is available in 10-mg, 18-mg, 25-mg, 40-mg, and 60-mg capsules.

Potential Advantages

Atomoxetine, a nonstimulant, differs from the commonly used drugs for this indication, such as methylphenidate and amphetamines. It does not appear to share the same abuse potential and is not a Scheduled (controlled) drug.[2]

Potential Disadvantages

In short-term studies, weight loss and slower increase in height have been reported in children. About 19% of patients on 1.2 mg/kg/d and 29% on 1.8 mg/kg/d lost at least 3.5% of their body weight. In addition, atomoxetine-treated patients had an average growth of 0.9 cm compared to 1.1 cm for those treated with placebo. In patients treated for at least 18 months, mean weight percentile decreased from 68 to 60 and mean height percentile from 54 to 50.[1] Common side effects include increase in heart rate and blood pressure. The mean increase in heart rate was 5-6 beats/min. The frequencies of tachycardia were 1.5% in the pediatric population and 3% in the adult population compared to 0.5% and 0.8%, respectively, for placebo-treated patients. The frequencies of high systolic BP (vs placebo) in pediatric studies were 6.8% vs 3%, and high diastolic BP were 2.8% vs 0.5%. In adults systolic BP ≥ 150 mm Hg and diastolic BP ≥ 100 mm Hg were 1.9% vs 1.2% and 0.8% vs 0.4%, respectively. Urinary retention or hesitancy has been reported in adults with an incidence of 3% for each compared to 0% for placebo. Erectile disturbance (7% vs 1%), impotence (3% vs 0%), and abnormal orgasm (2% vs 1%) have been reported in placebo-controlled studies. In a small comparative study, atomoxetine appeared to have a higher incidence of vomiting and somnolence than methylphenidate.[3] Atomoxetine is metabolized by CYP2D6. Dose adjustments may be necessary in patients taking drugs that inhibit this enzyme (ie, fluoxetine, paroxetine, quinidine).[1] Atomoxetine is not recommended during pregnancy due to lack of safety data.

Comments

Atomoxetine differs from commonly used drugs for ADHD. It does not release norepinephrine but blocks norepinephrine reuptake by inhibiting the norepinephrine transporter in the brain. It does not appear to have any significant effect on other noradrenergic receptors or neurotransmitters. The effectiveness of atomoxetine has been demonstrated in 4 studies involving pediatric patients (n = 759) and 2 studies involving adults (n = 536). These studies were randomized, double-blind, and placebo-controlled, and 6 to 10 weeks in duration.[1,3,4,5] Patients had ADHD based on DSM-IV criteria, and pediatric patients had inattentive subtypes or hyperactive/inattentive subtypes. Primary effectiveness was based on an investigator-administered and scored

ADHD Rating Scale-IV-Parent Version total score (pediatrics) or Conners Adult ADHD Rating Scale Screening Version (adults). A small percent of patients (7%) are slow metabolizers of atomoxetine, and these patients may achieve therapeutic effect with a lower dose and may be more sensitive to side effects such as increase in heart rate.[1,4] In a small study of pediatric patients who were randomized to atomoxetine (n = 144) or methylphenidate (n = 44), similar effectiveness and tolerability was reported.[3] Most study subjects were males. However, atomoxetine was also reported to be effective and well tolerated involving a subset (n = 51) of girls aged 7-13.[6] The long-term effectiveness and safety is not known as controlled studies were up to 10 weeks in duration.

All strengths of atomoxetine are priced the same, $2.50 per capsule. The cost for a 50-kg child is $2.50 per day and $5.00 for the 100-mg maximum dose.

Clinical Implications

ADHD is believed to affect 6-10% of school-aged children and often continues into adulthood. Current therapy includes stimulants such as methylphenidate and amphetamines. Atomoxetine provides a nonstimulant and nonscheduled alternative for treatment both in pediatrics and adults who are not responsive to or are intolerant of current therapy. However, long-term safety of atomoxetine and effectiveness remain to be established. ■

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CME Questions

1. **Which of the following is associated with an increased risk of Achilles tendinopathy related to fluoroquinolone use?**
   a. Age younger than 60 years
   b. Corticosteroid use
   c. Female gender
   d. Past, but not current, use of fluoroquinolones

2. **Which of the following effectively excludes pulmonary embolism in a pregnant patient?**
   a. Negative Doppler ultrasound
   b. Negative homans sign
   c. Normal ventilation perfusion scan
   d. Absence of pleuritic chest pain

3. **Postmenopausal women least likely to suffer a cardiovascular event have:**
   a. low CRP and low LDL levels.
   b. low CRP and high LDL levels.
   c. high CRP and low LDL levels.
   d. high CRP and high LDL levels.

By Louis Kuritzky, MD

Diuretics, Mortality, and Nonrecovery of Renal Function in Acute Renal Failure

DIURETICS ARE COMMONLY USED IN the setting of acute renal failure (ARF), based upon premises that they will reduce volume in extracellular volume overload and may convert oliguric ARF to nonoliguric ARF. To date, no randomized clinical trials have confirmed anticipated benefits in survival or restoration of renal function as a result of diuretic treatment. Mehta and associates postulated that diuretics in ARF would actually increase mortality and forestall recovery of renal function, and they studied critically ill ARF patients (n = 820) at 4 teaching hospitals. ARF was defined as BUN > 40 mg/dL, creatinine > 2.0 mg/dL, or an increase of creatinine > 1 mg/dL over baseline.

Using a covariate-adjusted model, diuretic use was associated with a 68% increase in in-hospital mortality, and a similar (77%) increase in likelihood of death or nonrecovery of renal function. Diuretics used included furosemide, bumetanide, metolazone, and HCTZ, with no demonstrable differences in outcomes dependent on any particular agent, whether used as monotherapy or combination therapy. Patients who were least responsive to diuretics (in terms of urinary output) were disproportionately at risk for adverse outcomes. Mehta et al posit that delay in using dialysis, while medical (diuretic) therapy is used, may indeed by injurious; they further suggest that diuretics, though not yet conclusively proven to be harmful by this single trial, are unlikely to provide benefit in the setting of ARF among critically ill patients. ■

Mehta RL, et al. JAMA. 2002;288: 2547-2553.

Nut and Peanut Butter Consumption and Risk of Type 2 Diabetes in Women

RECENT TRIALS HAVE CONFIRMED that both pharmacologic treatment (acarbose or metformin) and lifestyle intervention (weight loss and exercise) may prevent onset of type 2 diabetes (DM-2) in high-risk individuals. Recent data suggest that it is the type (saturated vs unsaturated) rather than the total fat percentage of diet that better predicts risk of DM-2. Higher intake of saturated fat and transfat negatively affect both glucose metabolism and insulin resistance. Since nuts contain primarily unsaturated fats, as well as fiber, magnesium, vitamins, minerals, and antioxidants, they theoretically provide a dietary substance that could favorably affect likelihood of developing DM-2.

To study the relationship between nuts and DM-2, Jiang and associates evaluated the participants in the Nurses Health Study (n = 121,700 women). Information collected on these women includes family history of diabetes, body weight, smoking, and physical activity; additionally, dietary questionnaires quantitated intake of nuts, dividing inquiry into peanuts, nuts, and peanut butter.

Women in the highest quartile of nut ingestion (at least 5 times weekly) when compared with those who almost never consumed nuts (lowest quartile) demonstrated an age-adjusted 0.55 relative risk (RR) for DM-2. A similar comparison specific to peanut butter showed an RR of 0.79 comparing quartile 1 to quartile 4. Because there has been some concern that increasing nuts in the diet might worsen weight management issues, the fact that this study found that ingestion of nuts in the highest quartile was not associated with significantly greater weight gain than those eating nuts less frequently is reassuring. When coupled with the epidemiologic studies suggesting favorable effects of nuts upon lipids and coronary heart disease, this study provides increasing impetus for clinician endorsement of nut consumption. ■

Jiang R, et al. JAMA. 2002;288: 2554-2560.

Optimal Diets for Prevention of CHD

THE CLASSIC DIET-HEART HYPOTHESIS postulates that dietary saturated fat and cholesterol are causally associated with coronary heart disease (CHD). Though the evidence for this hypothesis is sufficiently compelling that few clinicians debate its veracity, other components of diet, or their effects in concert, may be equally pertinent to the development of CHD.

A MEDLINE search produced 147 trials assessing diverse dietary factors, which indicated that omega-3-fatty acids, trans-fatty acids, carbohydrates, glycemic index, fiber, folate, individual foods (eg, nuts), and specific dietary patterns demonstrate a relationship with cardiovascular disease. From these data, several strategies, in addition to cholesterol reduction, are well substantiated to be associated with lesser risk of CHD: substitution of unsaturated fat (especially polyunsaturated) for saturated fat, reduction of transfatty acids, increases of omega-3 fatty acids (ie, from fish oil or plant sources), and a diversified diet which includes high intake of fruits, vegetables, nuts, and whole grains (low in refined grains). Despite the fact that common practice for management of obesity, an important contributor to CHD, suggests restriction of dietary fat to < 30% of total energy intake, the data to support such intervention are lacking. Rather, it may be more prudent to focus upon the favorable dietary characteristics detailed above, contained within a moderately hypocaloric diet. ■

Hu FB, Willett WC. JAMA. 2002;288:2569-2578.

Best Obtainable Tracing

By Ken Grauer, MD

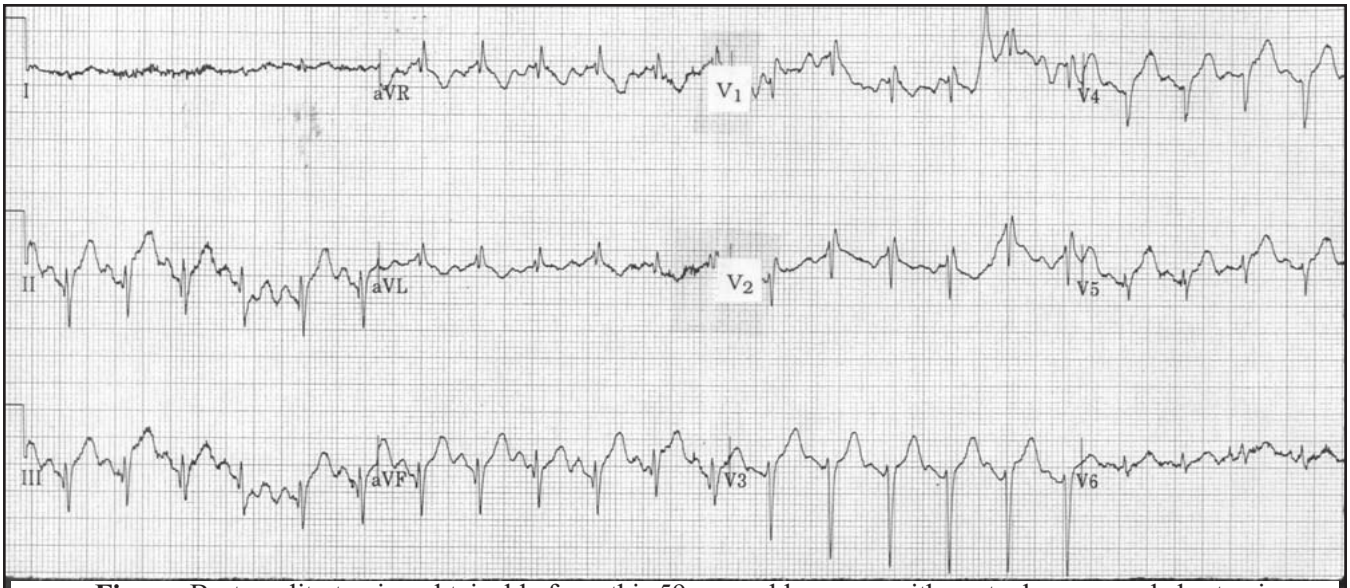

Figure. Best quality tracing obtainable from this 59-year-old woman with acute dyspnea and chest pain.

Clinical Scenario: The tracing in the Figure was obtained from a 59-year-old woman with a long history of smoking. She presented with acute dyspnea and atypical chest pain. Because of moderate respiratory difficulty, this was "the best quality tracing obtainable." In full acknowledgment of its suboptimal technical quality, how would you interpret this ECG? What findings may be of potential concern?

Interpretation/Answer: As stated, the technical shortcomings of this tracing make accurate interpretation problematic. The clinical reality, however, is that optimal quality tracings may not always be obtainable in acutely ill patients, especially when there is respiratory distress.

What can be said about this tracing is that the QRS complex is narrow and that the rhythm is regular at a rate of approximately 150 beats/minute. Upright (sinus) P waves appear to precede each QRS complex in lead II, suggesting that the rhythm is probably sinus tachycardia. There is marked left axis deviation. An rSR' pattern is seen in several of the complexes in lead V_1. Precision beyond this point is difficult to attain.

The overall pattern of this ECG is most suggestive of pulmonary disease. If new, these findings could be consistent with acute pulmonary embolism, although they more often reflect the long-standing existence of chronic obstructive pulmonary disease. A rightward or axis deviation may also be seen as occurs in this case. The finding of a "null vector" (flat complex) in lead I is an interesting manifestation that when seen supports the ECG diagnosis of a pulmonary pattern. Additional findings that further support this impression are the incomplete right bundle branch block (rSR') pattern in lead V_1, the relatively tall and somewhat peaked P waves in the inferior leads, and the drop off in QRS amplitude with minimal R waves and persistent S waves in the lateral precordial leads. Findings of potential concern (especially in view of the history of chest pain on presentation) are apparent small q waves that occur in association with a difficult-to-assess ST segment appearance in each of the inferior leads. The possibility of acute ST segment elevation also exists in leads V_3 through V_5. Clearly, the patient needs to be monitored, acute serum markers (troponin, CK-MB) should be obtained, and a follow-up ECG should be done as soon as the patient's clinical condition allows to confirm sinus tachycardia and rule out the possibility of acute infarction. ■

In Future Issues:

NSAIDs and GI Bleeding

PHARMACOLOGY WATCH

FDA Approves Claritin For OTC Use For Seasonal Rhinitis

After years of legal wrangling, the FDA has approved loratadine (Claritin, Schering-Plough) as an over-the-counter (OTC) product for the treatment of seasonal rhinitis. Loratadine is considered a nonsedating antihistamine, and its OTC approval was linked with the FDA's work with the National Transportation Safety Board to improve public awareness about the concerns of drowsiness while driving associated with older antihistamines. The OTC switch also comes within months of loss of patent protection for loratadine and the entry into the market of generic equivalents. The OTC switch applies to all 5 formulations of Claritin, and at least 1 generic house plans to market "Reditabs." Meanwhile, Schering-Plough continues to aggressively market desloratadine, the active metabolite of loratadine under the trade name Clarinex, in an attempt to protect its $3 billion Claritin market.

Simpler Atrial Fibrillation Management

Management of atrial fibrillation (AF) may be simpler in the future based on the results of 2 studies published in the December 5, 2002, *N Engl J Med*. The larger of the 2 studies (AFFIRM) enrolled more than 4000 patients in the United States and Canada with AF and at least 1 other risk factor for stroke such as hypertension, coronary artery disease, diabetes, congestive heart failure, or age older than 65. Patients were randomized to a rhythm control strategy with cardioversion followed by amiodarone, sotalol, propafenone, or older antiarrhythmics such as procainamide or quinidine; or a rate control strategy with digoxin, beta-blockers, and/or calcium channel antagonists. All patients in both groups were anticoagulated with warfarin. The primary end point was overall mortality. The 5-year death rate was 23.8% in the rhythm control group and 21.3% in the rate control group (P = 0.08). Rhythm control was associated with more hospitalizations and more adverse drug effects. In the second study from The Netherlands, 522 patients with persistent AF after electrical cardioversion were randomized to treatment aimed at rate control or rhythm control. Both groups received oral anticoagulation, and the composite end point was death from cardiovascular causes as well as bleeding, implantation of a pacemaker, or severe adverse effects of drugs. After a mean duration of nearly 2.5 years, the primary end point occurred in 44 patients in the rate control group (17.2%) and 60 patients in the rhythm control group (22.6%) (P = 0.11). Although both studies showed trends toward adverse outcomes with rhythm control, neither study reached statistical significance. The authors of both studies suggest that a rate control strategy for the treatment of AF is at least as good as the rhythm control strategy. In an accompanying editorial, Michael D. Cain, MD, states that "on the basis of these data, rate control can now be considered a primary approach to the treatment of atrial fibrillation." He also suggests that nonpharmacologic treatments for AF will still be pursued with the goal toward maintaining

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sinus rhythm (*N Engl J Med*. 2002;347:1825-1833; 1834-1840; 1883-1884).

Oral Anticoagulation Vs Aspirin in AF

In a related study, oral anticoagulation was found to be superior to aspirin in preventing stroke in patients with atrial fibrillation (AF) or paroxysmal AF. The study was a pooled analysis of 6 trials of more than 4000 patients who were randomized to receive therapeutic doses of oral anticoagulant or aspirin with or without low-dose oral anticoagulants. Patients receiving oral anticoagulation were significantly less likely to experience stroke (2.4 vs 4.5 events per 100 patient years; hazard ratio [HR], 0.55), ischemic stroke (HR, 0.48), or cardiovascular events (HR, 0.71) but were more likely to experience major bleeding (2.2 vs 1.3 events per 100 patient years; HR, 1.71). Anticoagulant therapy also showed benefit on all-cause mortality but only after 3 years of therapy. Interestingly, more benefit was seen for anticoagulation vs aspirin in patients younger than 75 compared to those 75 years or older. A lesser benefit was also seen for women compared to men. The authors suggest that oral anticoagulation is more effective than aspirin in decreasing the risk of stroke and other cardiovascular events in patients with nonvalvular AF (*JAMA*. 2002;288:2441-2448).

Immunization Does Not Cause Autism

A new study should put an end to concern regarding the MMR (measles, mumps, and rubella) vaccine and its possible link to autism. Researchers in Denmark looked at the records of all children born between January 1991 and December 1998, representing a cohort of almost 540,000 children. Of those, 82% (440,655) received the MMR vaccine. In the cohort, 316 children were diagnosed with autism and 422 were diagnosed with other artistic spectrum disorders. After adjustment for potential confounders, the relative risk for artistic disorder in the vaccinated children compared to the unvaccinated was 0.92 (95% CI, 0.68 to 1.24). The relative risk for other artistic spectrum disorders was 0.83 (95% CI, 0.65 to 1.24). The authors also looked for a possible association between age at the time of vaccination, the time since vaccination or the date of vaccination, and development of artistic disorder and found no relationship. They also found no temporal clustering of cases of autism at any time after immunization (*N Engl J Med*. 2002;347:1477-1482).

Statins May Lower CRP Levels

C-reactive protein (CRP), an inflammatory marker, has shown to be a strong predictor of cardiovascular events, perhaps even more predictive then LDL cholesterol levels (*N Engl J Med*. 2002; 347:1557-1565). Most physicians have looked at these studies with interest but have been unsure what to do with an elevated CRP level in an individual patient. Perhaps even more importantly, it is unclear whether lowering CRP affects cardiovascular outcomes. Until an answer is found to this important question, an increasing body of evidence is suggesting that statins may lower CRP levels.

Simvastatin Reduced CRP Plasma Levels

A recent study reviewed the use of simvastatin in 130 patients with mixed hyperlipidemia and 195 patients with hypertriglyceridemia in a placebo-controlled, double-blind trial. After 6 weeks of treatment with simvastatin 20, 40, and 80 mg, significant reductions in CRP plasma levels were noted vs placebo ($P < 0.05$) (*Am J Cardiol*. 2002;90:942-946). CRP lowering by statins appears to be a class effect with multiple reports of benefit with various statins in the last 2 years.

FDA Actions

Roche's pegelated interferon alfa-2a (Pegasys) has been approved for use in combination with a ribavirin for the treatment of hepatitis C. The drug was approved in October 2002, but Roche has been eagerly awaiting the approval for combination treatment in order to compete with Schering-Plough's Peg-Intron/ribavirin combination for the same indication.

Eli Lilly has received approval to market atomoxetine (Strattera) for the treatment of attention deficit hyperactivity disorder (ADHD). Unlike other drugs for this indication, atomoxetine is not a stimulant and is not listed as a controlled substance. Rather, the drug is a selective norepinephrine reuptake inhibitor, which seems to play a role in regulating attention, impulsivity, and activity levels. Strattera is approved for treatment of ADHD in children, adolescents, and adults.

Eli Lilly has also received approval to market teriparatide injection (Forteo) for the treatment of osteoporosis in postmenopausal women who are at high risk for fracture. Teriparatide is a portion of human parathyroid hormone, which stimulates new bone formation in the spine and hip. The drug is given by daily injection in the thigh or abdomen. ■