

Internal Medicine

Evidence-based summaries of the
latest research in internal medicine

[ALERT]

ABSTRACT & COMMENTARY

Welcome Back, Saturated Fat

By *Joseph E. Scherger, MD, MPH*

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Dr. Scherger reports no financial relationships relevant to this field of study.

SYNOPSIS: The NIH has been conducting systematic review and meta-analysis of randomized controlled trials show that replacing saturated fat with unsaturated vegetable oils rich in linoleic acid does not result in a reduction in atherosclerosis, cardiovascular morbidity, and death.

SOURCE: Ramsden CE, Daisy EZ, Majchirzak-Hong S, et al. Re-evaluation of the traditional diet-heart hypothesis: Analysis of recovered data from the Minnesota Coronary Experiment (1968-73). *BMJ* 2016;353:i1246.

A team of investigators from the National Institutes of Health has been conducting systematic reviews and meta-analyses of previously published and unpublished data from experiments testing the traditional diet-heart hypothesis that saturated fat contributes to cardiovascular disease and death. This hypothesis and subsequent dietary recommendations were based on evidence that replacing saturated fat with unsaturated vegetable oils, particularly with linoleic acid, lowered serum cholesterol.^{1,2} At the same time, observational studies showed that lower serum cholesterol was associated with lower cardiovascular morbidity and mortality.³ The authors reported that no randomized, controlled trials of using

unsaturated fats to lower cardiovascular morbidity have been conducted to prove the hypothesis.

The Minnesota Coronary Experiment was conducted between 1968 and 1973 in one nursing home and six state mental hospitals. Researchers randomized 9,423 women and men ranging in age from 20 to 97 years, with a mean age of 52 years. One-quarter of the subjects were ≥ 65 years of age. Feeding subjects in a cafeteria allowed for more precise assurance of diet adherence than most population diet studies. Both groups ate a similar amount of fat and the average body mass index was 24.5 kg/m². In the intervention group, saturated fat in cooking oils, salad dressings, and

Financial Disclosure: *Internal Medicine Alert's* Editor Stephen Brunton, MD, is a retained consultant for Abbott, Actavis, AstraZeneca, Becton Dickinson, Boehringer Ingelheim, Cemptra, Exact Sciences, Janssen, Lilly, Mylan, Novo Nordisk, and Teva; he serves on the speakers bureau of AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, and Teva. Contributing Editor Louis Kuritzky, MD, is a retained consultant for AbbVie, Allergan, AstraZeneca, Janssen, Lilly, Lundbeck, Medscape, Novo Nordisk, and Sanofi Aventis; he serves on the speakers bureau of Lilly and Lundbeck. Peer Reviewer Gerald Roberts, MD; Executive Editor Leslie Coplin; and Associate Managing Editor Jonathan Springston report no financial relationships relevant to this field of study.

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Internal Medicine Alert, ISSN 0195-315X, is published monthly by AHC Media, LLC
One Atlanta Plaza,
950 East Paces Ferry Road NE, Suite 2850
Atlanta, GA 30326.

GST Registration Number: R128870672.
Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to Internal Medicine Alert, P.O. Box 550669, Atlanta, GA 30355.

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butter was replaced with corn oil products and corn oil polyunsaturated margarine. Autopsy data were available on 149 subjects.

The intervention group with more unsaturated fat intake experienced significant reductions in both total and low-density lipoprotein (LDL) cholesterol, an average of 13.8%. However, there was no difference in mortality among any age or sex cohort. The intervention group actually experienced a higher number of cardiovascular infarcts. Autopsy reports showed no difference in the degree of atherosclerosis among the two groups.

The same authors previously reported a re-analysis of unpublished data from another large randomized, controlled trial, the Sydney Diet Heart Study, conducted during the same period. In this study, the intervention group on the unsaturated fat diet (linoleic acid from vegetable oils) actually showed a higher cardiovascular morbidity and mortality.⁴

■ COMMENTARY

It is becoming clear that saturated fats from natural food sources are not a cause of cardiovascular disease. Indeed, the opposite may be true as discussed by Dr. Mark Hyman in his new book, *Eat Fat, Get Thin*.⁵ The authors in this study noted any food consumed is a substrate that is biochemically processed in the human body. Man has consumed saturated fats for thousands of years, and most commercially available unsaturated fats are processed foods foreign to the body. The fact that LDL particles in the unsaturated fat group may have greater LDL particle oxidation and may be more inflammatory to the cardiovascular system may explain the paradox that lowering total and LDL cholesterol did not result in health benefits.

A recent randomized, controlled trial showed patients on a low-carbohydrate/high-fat diet had increased LDL particle size (less inflammatory) than patients eating a traditional American Heart Association low-fat diet with higher complex carbohydrates, whose LDL particles actually shrank and became more inflammatory.⁶ Hence, measuring only

total and LDL cholesterol has limitations in that such measurements do not show how inflammatory these cholesterol particles are.

It has become apparent that clinicians have been giving wrong dietary advice to patients for many decades. The low-fat and non-fat food industry was a mistake because it resulted in higher carbohydrate intake and coincided with the epidemic of overweight, obesity, and type 2 diabetes, major risk factors for cardiovascular disease.

Science has a way of breaking paradigms and keeping medical professionals humble. Greater understanding of the biochemistry of nutrition and the human body gives healthcare providers an opportunity to provide better nutrition recommendations and, hopefully, improved food science. The relative lack of nutrition education in American medicine is most unfortunate, as nutrition is emerging as a major therapeutic tool to prevent and reverse disease. ■

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The Efficacy of Spironolactone for the Treatment of Drug-resistant Hypertension

By Harold L. Karpman, MD, FACC, FACP

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Dr. Karpman reports no financial relationships relevant to this field of study.

SYNOPSIS: Compared to selected other hypotensive drugs, spironolactone was found to be the most effective drug addition for resistant hypertension when added to previous angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, calcium channel blocker, and thiazide therapy.

SOURCE: Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): A randomized, double-blind, crossover trial. *Lancet* 2015;386:2059-2063.

Drug-resistant hypertension is usually defined as blood pressure elevation that is not controlled, even after three recommended blood pressure lowering drugs (i.e., an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) plus a calcium channel blocker (CCB) and a thiazide-like diuretic) are administered at maximum tolerated doses. Because resistant hypertension often is not controlled by drugs from the three categories, an effective fourth-line drug treatment has been sought by many groups.

Since it has been speculated that sodium retention predominantly causes resistant hypertension, Williams et al¹ selected the diuretic spironolactone because of observational and randomized, controlled trial data suggesting good blood pressure lowering efficacy in resistant hypertension.² They conducted a 12-month, double-blind, placebo-controlled crossover trial in which patients were enrolled from 14 sites in the United Kingdom.³ Patients presented with blood pressure readings of ≥ 140 mmHg (or ≥ 135 mmHg for diabetic patients) despite treatment for at least three months with maximally tolerated doses of the three drug groups (ACE or ARB, CCB, and diuretic). Participants rotated through four cycles of once-daily oral therapy with spironolactone, doxazosin, bisoprolol, and placebo. Researchers used home blood pressures rather than clinic blood pressures to eliminate at baseline participants with so-called white coat hypertension or a potential placebo effect. Spironolactone substantially increased the likelihood of achieving blood pressure control when compared to bisoprolol or doxazosin, with almost 60% of participants achieving blood pressure control within three months after starting spironolactone therapy.

■ COMMENTARY

The results of the Williams et al study certainly are encouraging and suggest clinicians should consider using

spironolactone as the fourth drug in a regimen for the treatment of resistant hypertension. Researchers found the drug to be well-tolerated, and the doses of only 25-50 mg daily used in this study were low compared to the 200-400 mg daily that many physicians have used clinically in their practices. Because only 25 mg was the most common daily dose in previous studies, which have shown that the main biochemical effects associated with spironolactone therapy are a reduction in serum sodium and an increase in serum potassium levels, it was important to monitor electrolytes and renal function after initiation of spironolactone therapy.⁴ The Williams et al study was the first randomized, controlled trial directly comparing different active drug treatments in resistant hypertension, and it appears to have produced an unequivocally positive result for spironolactone. Therefore, clinicians should consider adding spironolactone to the standard ACE/ARB, CCB, and diuretic therapeutic regimen in patients with resistant hypertension. ■

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Fitness and Cognition in the Elderly

By William C. Haas III, MD, MBA

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Dr. Haas reports no financial relationships relevant to this field of study.

SYNOPSIS: Peak levels of cardiorespiratory fitness are positively correlated with enhanced cognitive function among older adults.

SOURCE: Freudenberger P, Petrovic K, Sen A, et al. Fitness and cognition in the elderly: The Austrian Stroke Prevention Study. *Neurology* 2016;86:418-424.

Despite overwhelming evidence supporting the benefits of regular physical activity, relatively few older adults achieve the minimum recommended amount of weekly physical activity.¹ The trend toward increasing physical inactivity among the elderly raises concern, especially in light of research suggesting that physically active adults have a lower risk of cognitive decline and dementia compared to inactive adults.² Efforts to slow cognitive decline and dementia are paramount given the lack of effective treatment options in addition to the associated social and economic burdens.

The precise neuroprotective mechanism resulting from enhanced physical activity remains unclear. One prevailing hypothesis suggests improved cardiovascular fitness reduces cerebrovascular disease.³ Cardiovascular fitness, defined as the body's maximal capacity for oxygen consumption ($VO_2\text{max}$), is an important variable for consideration, as cardiovascular fitness declines with age, but can increase with regular physical activity.

Drawing patients from the original Austrian Stroke Prevention Study, Freudenberger et al conducted a follow-up cohort study to clarify the connection between cardiorespiratory fitness and cognitive function. The primary purpose of the study was to determine the effect of $VO_2\text{max}$ on global and domain-specific cognitive function. Researchers also attempted to determine whether the effect of $VO_2\text{max}$ on cognitive function was mediated by signs of brain aging seen on MRI.

The authors recruited 877 patients from the Austrian Stroke Prevention Study to participate. The original prevention study was a community-based cohort study that evaluated the effects of vascular risk factors on brain structure and function in elderly patients without a history of stroke or dementia. Participants recruited for the follow-up study underwent additional testing, including cognitive testing, exercise ECG, and MRI. Cognitive testing consisted of a battery of validated tests involving memory, motor skills, and executive function. Exercise ECG was

performed to estimate $VO_2\text{max}$ based on the formula: $15 \times (\text{maximum heart rate}/\text{resting heart rate})$. Researchers performed an MRI to quantify lacunar infarct burden, white matter lesions, and atrophy. The authors also assessed vascular risk factors and included cigarette smoking, hypertension, cholesterol, type 2 diabetes mellitus, and body mass index.

With regard to the main outcome, $VO_2\text{max}$ displayed a positive linear trend for enhanced memory, executive function, and global cognition. The differences in effect size between the lowest and highest quartile of $VO_2\text{max}$ were 0.298 for memory ($P = 0.001$), 0.117 for executive function ($P = 0.005$), and 0.260 for global cognition ($P = 0.001$). Interestingly, the differences displayed by individuals in the highest vs. lowest quartile of $VO_2\text{max}$ corresponded to an age difference of four, six, and seven years for global cognition, memory, and executive function, respectively. Finally, with regard to secondary outcomes, the effect of $VO_2\text{max}$ on cognition was not mediated by the presence of lacunar infarcts, white matter lesions, or atrophy.

■ COMMENTARY

Before forming clinical recommendations based on these results, it is important to revisit the purpose of the study. The researchers specifically attempted to determine whether greater cardiorespiratory fitness was associated with better cognitive function based on protection of cortical and subcortical brain structures. Although researchers did not find evidence to support their neuro-structural protection hypothesis, they established a positive correlation between $VO_2\text{max}$ and cognitive performance. In fact, participants with the highest $VO_2\text{max}$ demonstrated a significantly younger cognitive age compared to participants with the lowest $VO_2\text{max}$.

Despite positive correlations between $VO_2\text{max}$ and cognitive performance, advise caution when recommending vigorous physical activity to elderly patients based solely on the results of this study. $VO_2\text{max}$ represents the ability of the cardiopulmonary system to uptake, transport, and use oxygen during bouts

of maximal physical exertion. It is a measure of peak cardiorespiratory fitness and is not synonymous with general physical fitness. Although consistent exercise at sub-maximal exertion levels can improve $VO_2\text{max}$, such vigorous exercise is unlikely advisable for the majority of elderly patients. It is also important to note that up to 65% of $VO_2\text{max}$ may be attributed to non-modifiable genetic factors.⁴

Also consider a few inherent limitations of the study. The cross-sectional nature reflects correlations only at a moment in time. Clinicians can only infer the ability to improve cognitive function with improvements in $VO_2\text{max}$. Additionally, one of the main variables, $VO_2\text{max}$, was estimated and not directly measured, which could alter actual results.

This study shines light on the important topic of preserving cognitive function with aging. Cardiorespiratory fitness appears to function as a protective

factor against cognitive decline. However, the study falls short of establishing a connection between improvements in cardiorespiratory fitness and improvements in cognitive function. Until additional studies are performed with regard to optimizing cognitive function, clinicians should continue counseling their patients on age-appropriate exercise given the many other well-known health benefits. ■

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PHARMACOLOGY UPDATE

Pimavanserin Tablets (Nuplazid)

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

Dr. Elliott is Medical Director, Pharmacy, Northern California Kaiser Permanente, and Assistant Clinical Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved the first drug to treat hallucinations and delusions associated with Parkinson's disease (PD). Pimavanserin, an atypical antipsychotic agent, is an inverse agonist and antagonist at serotonin 5-HT_{2A} receptors and to a lesser extent the serotonin 5-HT_{2C} receptors.¹ The drug was granted breakthrough designation and given a priority review.² Pimavanserin is marketed as Nuplazid.

INDICATION

Pimavanserin is indicated for the treatment of hallucination and delusions associated with PD psychosis.¹

DOSAGE

The recommended dose is 34 mg taken as two 17 mg tablets once daily with or without food.¹ Dose titration is not recommended.

POTENTIAL ADVANTAGES

Pimavanserin is currently the only drug approved for this indication.

POTENTIAL DISADVANTAGES

Pimavanserin carries the same boxed warning for increased mortality in elderly patients with dementia-

related psychosis as other atypical antipsychotics. Pimavanserin prolongs QT interval. Do not give it to patients with known QT prolongation, history of cardiac arrhythmias, or with other drugs known to prolong QT interval.¹ Adverse events reported, compared to placebo, during placebo-controlled studies were nausea (7% vs. 4%), peripheral edema (7% vs. 2%), and confusion state (6% vs. 3%).¹ Eight percent of patients discontinued treatment due to adverse events compared to 4% on placebo.

COMMENTS

The efficacy of pimavanserin was demonstrated in a six-week, randomized, placebo-controlled, parallel-group study (n = 199).^{1,2} These subjects received a PD diagnosis at least one year prior to study entry (Mini-Mental State Examination [MMSE] score ≥ 21) and exhibited psychotic symptoms that were severe enough to require antipsychotic treatment. Subjects were randomized (1:1) to pimavanserin 34 mg or placebo. Efficacy was assessed using the PD-adapted Scale for the Assessment of Positive Symptoms (SAPS-PD). This is a nine-item scale for the hallucination and delusions domain of SAPS, with each item scored between 0 and 5, with 0 representing no symptoms and 5 severe and frequent

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symptoms. Pimavanserin treatment showed a mean change from a mean baseline of 15.9 of -5.79 vs. a mean change with placebo of -2.73 from a mean baseline of 14.7 (a difference of -3.06; 95% confidence interval, -4.91 to -1.20). This represented a 36.4% and 18.6% reduction, respectively, and a medium effect size (Cohen's d, 0.50). The magnitude of change was similar for both hallucinations and delusions. Placebo-subtracted changes were approximately -20% for both total and subgroups. A pooled analysis of four randomized trials also found pimavanserin to be beneficial.³

CLINICAL IMPLICATIONS

A complication of PD, psychotic symptoms can occur in up to 50% of patients and may be associated with medications used to treat the disease, particularly those that elevate dopamine levels. Current treatment options include a reduction of anti-Parkinson drugs as well as off-label clozapine and quetiapine.⁴⁻⁶ Reduction of drugs may worsen motor problems; clozapine has been associated with agranulocytosis, while

the efficacy of quetiapine is uncertain. Pimavanserin is the first FDA-approved treatment. The wholesale cost for pimavanserin is \$1,950 for a 30-day supply. ■

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CME QUESTIONS

1. Analysis of current data and prior randomized, controlled trial data suggests which of the following diets would show reduced cardiovascular morbidity and mortality?
 - a. A diet low in saturated fats and high in vegetable oils.
 - b. A diet high in saturated fats from natural food sources.
 - c. A diet low in fats from all sources.
 - d. None of the above
2. In patients suffering from drug-resistant hypertension, spironolactone added to previous maximal angiotensin converting enzyme or angiotensin II receptor blocker, calcium channel blocker, and thiazide-like diuretic therapies:
 - a. had no substantial effect upon the blood pressure.
 - b. was not well-tolerated.
 - c. substantially increased the likelihood of achieving blood pressure control.
 - d. None of the above
3. VO₂max displayed a positive linear trend for all of the domains of cognitive function except:
 - a. memory.
 - b. executive function.
 - c. motor skills.
 - d. None of the above

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

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Glucose Variability in T2DM: Ready for Prime Time?

SOURCE: Kovatchev B, Cobelli C. *Diabetes Care* 2016;39:502-510.

The benefits of glycemic control in type 2 diabetes (T2DM) include improved microvascular status (retinopathy, neuropathy, nephropathy) and better quality of life. Striving for progressively better control of hyperglycemia is typically associated with an increased incidence of hypoglycemia, consequences of which can range from transient unpleasant central nervous system dysfunctions and signs of autonomic activation to coma and death.

While A1c is an accurate measure of mean glucose levels, two individuals with the same A1c level can present markedly different excursions of glucose above and below the mean, which generates A1c. Typically, higher glucose variability above and below the mean reflects more episodes of greater hyperglycemia as well as hypoglycemia, which may not be readily discerned through just examining A1c. Continuous glucose monitoring, as well as frequent self-monitoring of blood glucose, have created a window of observation to detect glucose variability.

What's the practical yield of attending to glucose variability? There is still some disagreement about the best way to measure variability, since hyperglycemic excursions typically are much less concerning than similar excursions toward hypoglycemia, so it may be necessary to use separate metrics for hypo- vs. hyperglycemic variability. Additionally, computations to assess glucose variability are not paper-and-pencil simple — they require computational tools. However, it has been shown that, as an example, at the same A1c level, glucose variability was substantially less in patients taking oral agents who added

a GLP1-RA (e.g., exenatide) vs. those who added insulin glargine. While not yet a tool for routine practice, analysis of glucose variability appears to hold promise for the future. ■

Improvements in Pain and Physical Function After Bariatric Surgery

SOURCE: King WC, Chen JY, Belle SH, et al. *JAMA* 2016;315:1362-1371.

The metabolic benefits of bariatric surgery are prompt, significant, and — for the most part — durable. Many patients who suffer from severe obesity also experience joint pain (especially knee and hip) and limited mobility. What kind of effect does bariatric surgery have on those endpoints?

King et al reported on outcomes among patients with severe obesity (median body mass index = 49.5 kg/m²) who underwent bariatric surgery (n = 2,221). The outcomes of interest were bodily pain and physical function, as measured by SF-36. To be considered “improved,” patients had to meet the threshold for minimal meaningful increment of change, rather than just achieve statistical significance alone.

At one year, the majority of surgical subjects demonstrated clinically meaningful improvements in pain and physical function. Specifically addressing those already experiencing disability due to knee (n = 633) or hip (n = 500) pain at baseline, more than 75% of each group reported symptomatic improvement at one year, which was durable through three years of observation.

In addition to the favorable metabolic changes (e.g., remission of diabetes, prevention of diabetes) associated with bariatric surgery, meaningful improvements in physical function and disability due to joint pain occur promptly and are durable through at

least three years of follow-up. ■

Two Thumbs Down for COPD Screening

SOURCE: U.S. Preventive Services Task Force. *JAMA* 2016;315:1372-1377.

Since none of the currently available pharmacologic treatments for COPD can be considered disease modifying (that is, alters the course of progression or reduces mortality), even if we were to identify COPD early, why would we have any confidence that treatment would be beneficial? Despite numerous clinical trials demonstrating improvements in lung function, activity, frequency of exacerbations, and symptoms in COPD patients, none of the medications have been able to achieve the lofty threshold of disease modifying. Only smoking cessation and oxygen at late-stage disease have been found to be disease modifying.

Upon review of the currently available evidence, the U.S. Preventive Services Task Force (USPSTF) assigned a level “D” recommendation to the issue of screening asymptomatic adults for COPD, which means, “the USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.” Within its Recommendation Statement, the USPSTF included recognition of one potentially valuable role of screening with spirometry: enhancing quit rates among smokers. But even then, results of clinical trials are mixed. Only one study that presented pulmonary status using the technique of lung age had an effect on smoking cessation rates; other studies presenting spirometry results in traditional methodology did not improve smoking cessation outcomes.

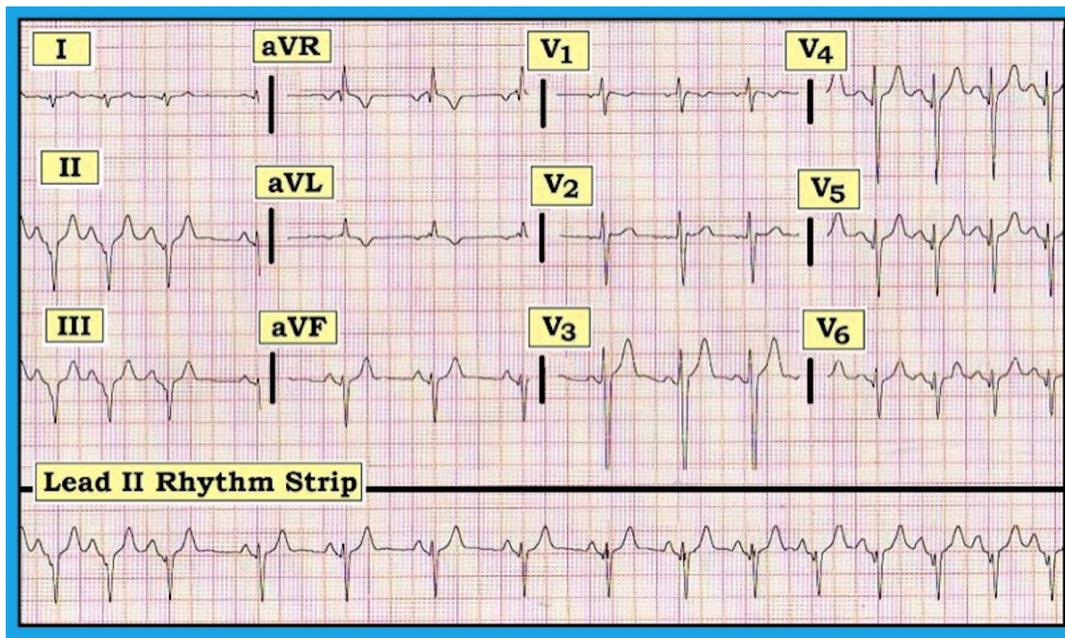
These USPSTF recommendations should not be misconstrued to reflect on the utility of spirometry for symptomatic individuals. ■

Professor Emeritus in Family Medicine, College of Medicine, University of Florida

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Why is This Young Athlete's ECG Abnormal?

The ECG in the figure below was obtained from a previously healthy 19-year-old man, presumably as part of a vigorous pre-exercise evaluation. There are no symptoms. How should one interpret this tracing? In view of this presentation, what clinical entities should be considered in the differential diagnosis? How might one proceed in his or her evaluation?



This ECG is markedly abnormal for a 19-year-old man. The long lead II rhythm strip at the bottom shows a phasic arrhythmia, with upright P waves with a fixed PR interval preceding each QRS complex. This is most likely marked sinus arrhythmia, though it is hard to rule out the possibility that the slight reduction in P wave amplitude that seems to occur with slower rates might be due to a wandering atrial pacemaker. In either case, the rhythm is benign in a 19-year-old man.

It is the remainder of the ECG that is of most interest. The PR, QRS, and QT intervals are normal. The mean QRS axis is indeterminate (predominantly negative in both leads I and aVF). There is no chamber enlargement. What is distinctly unusual is inferior negativity of the QRS and an almost reverse R wave progression in the chest leads with small Q waves in leads V4, V5, and V6. There is T wave inversion in lead aVL, with T waves otherwise upright (albeit a bit peaked). In summary, this is not a “normal” ECG for an otherwise healthy 19-year-old.

Diagnostic considerations include undetected congenital

heart disease, some type of cardiomyopathy, a prior episode of myocarditis that spontaneously resolved, or some other unusual form of electrical conduction. Surprisingly, an echocardiogram was unremarkable. This essentially ruled out underlying structural heart disease, leaving an abnormal conduction pathway as the most likely explanation.

Close inspection of the terminal portion of the PR segment in leads II and III reveals subtle downsloping at the point of transition with the QRS complex. Consultation with an electrophysiology cardiologist confirmed suspicion that this ECG represents a pseudo-infarction pattern in a patient with Wolff-Parkinson-White syndrome.

Depending on the relative amount of preexcitation and the location of the accessory pathway, the appearance of Wolff-Parkinson-White syndrome on ECG may be varied and subtle. The inferior pseudo-infarction pattern seen here is due to negative delta waves in leads II and III. Delta waves are otherwise not readily recognizable on this tracing.