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Internal Medicine

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FEATURE

A Review of Updated Guidelines Regarding Bradycardia and Cardiac Conduction Delay

By Joshua D. Moss, MD

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Dr. Moss reports he is a consultant for Biosense Webster and Abbott.

SYNOPSIS: The American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society have established updated guidelines on the evaluation and management of patients with bradycardia and conduction delays. Many key elements remain largely unchanged from prior guideline recommendations on pacemakers published in 2008 and 2012, but there are important new definitions, recommendations, and areas of emphasis.

SOURCES: Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay. *Circulation* 2018. Available at: https://bit.ly/2RKVDrM. Accessed Nov. 9, 2018.

Slotwiner DJ, Raitt MH, Del-Carpio Munoz F, et al. Impact of physiologic pacing versus right ventricular pacing among patients with left ventricular ejection fraction greater than 35%: A systematic review for the 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay. *Circulation* 2018. Available at: https://bit.ly/2QtCKcI. Accessed Nov. 9, 2018.

For patients with sinus node dysfunction (including sinus bradycardia, sinus pauses, and chronotropic incompetence), particularly with nocturnal bradycardia, evaluation should include consideration of screening for sleep apnea. Treatment of sleep apnea can offer cardiovascular benefits beyond reduction in nocturnal bradycardia events. Permanent pacing is not required if nocturnal bradycardia is the only manifestation of sinus node dysfunction. Importantly (and consistent with prior guideline recommendations), observation alone is appropriate in the setting of sinus node dysfunction without any associated symptoms.

The newly emphasized corollary is the absence of any defined minimum heart rate or pause duration that

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should prompt pacemaker implant (even in the absence of symptoms). A pacemaker for minimally symptomatic patients with chronic heart rates < 40 bpm while awake is no longer a Class IIb recommendation.

Appropriate monitoring to establish correlation between bradycardia and symptoms is critical, including via implantable cardiac monitors if symptoms are infrequent (> 30 days between symptoms).

ATRIOVENTRICULAR BLOCK

As in the past, permanent pacemakers are not recommended for patients with atrioventricular (AV) block due to a reversible and nonrecurrent cause (such as Lyme carditis).

Permanent pacemakers also may result in harm to asymptomatic patients with first-degree AV block, second-degree Mobitz type I (Wenckebach) AV block, or 2:1 AV block believed to be at the level of the AV node. However, a permanent pacemaker is recommended now, regardless of symptoms for patients with acquired second-degree Mobitz type II AV block, complete (third-degree) AV block, and high-grade AV block (defined as ≥ 2 consecutive P waves at a constant physiologic rate that do not conduct to the ventricles).

Previously, for asymptomatic patients with these more dangerous types of AV block, a permanent pacemaker was considered a Class IIa recommendation rather than this new Class I recommendation.

CONDUCTION DISORDERS WITH 1:1 AV CONDUCTION

More emphasis is placed on evaluating patients with intact AV nodal conduction but evidence of infranodal conduction disease, particularly left bundle branch block (LBBB). Newly diagnosed LBBB should prompt evaluation for structural heart disease, starting with an echocardiogram, given the strong association between LBBB and left ventricular systolic dysfunction. Ambulatory monitoring for AV block also is recommended for symptomatic patients with LBBB. An electrophysiology study is reasonable if there are intermittent symptoms suggestive of bradycardia, such as lightheadedness or syncope, that cannot be captured on monitoring.

PHYSIOLOGIC PACING

The new guidelines speak more to the increasingly appreciated risks of heart failure and atrial fibrillation associated with chronic right ventricular (RV) pacing. This applies particularly to those patients who do not already suffer from impaired left ventricular function (ejection fraction, ≤ 35%) and would already qualify for cardiac resynchronization therapy (CRT) via biventricular pacing.

[The new guidelines speak more to the increasingly appreciated risks of heart failure and atrial fibrillation associated with chronic right ventricular pacing.]

For patients expected to require ventricular pacing > 40% of the time because of AV block and who have a left ventricular ejection fraction between 36% and 50%, pacing methods that maintain more physiologic ventricular activation are now a Class IIa recommendation based on recent randomized studies.

Such pacing methods include CRT and His bundle pacing (included for the first time in published guidelines). That technique, described for temporary pacing as far back as the 1960s and with permanent pacemaker leads almost 20 years ago, has grown in popularity and garnered research interest in the electrophysiology community recently. A pacing lead is implanted directly into or near the bundle of His using specialized lead delivery tools, depolarizing the ventricles via the His-Purkinje system.

The resultant paced QRS complex is narrow and sometimes indistinguishable from the native conducted QRS complex, with an isoelectric segment between the pacing artifact and QRS complex that can be mistaken for lack of pacemaker capture. More research is required before the technique is adopted for more indications, but studies thus far suggest a lower likelihood of deleterious effects compared with traditional RV pacing. ■

ABSTRACT & COMMENTARY

Factors Associated With Urinary Tract Infections Caused by Multidrug-Resistant Gram-Negative Bacteria

By Richard R. Watkins, MD, MS, FACP, FIDSA

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

SYNOPSIS: The authors of a multicenter, retrospective, cohort study from southern and eastern Europe identified predictive factors for multidrug-resistant complicated urinary tract infections.

SOURCE: Gomila A, Shaw E, Carratalà J, et al. Predictive factors for multidrug-resistant gram-negative bacteria among hospitalised patients with complicated urinary tract infections. *Antimicrob Resist Infect Control* 2018;7:111.

Hospitalized patients with suspected complicated urinary tract infection (cUTI) often are treated initially with broad-spectrum antibiotics. Using a model to predict which patients are at high risk for multidrug-resistant (MDR) pathogens would be useful to help make better antibiotic choices, thereby leading to improved antibiotic stewardship.

Gomila et al conducted a retrospective cohort study from hospitals in southern and eastern Europe, Turkey, and Israel. They defined MDR as nonsusceptibility to at least one drug in three or more antimicrobial categories. The investigators obtained data from patients who were admitted for a cUTI and from those who were admitted for other reasons and developed a cUTI during hospitalization. Each hospital contributed 50-60 consecutive patients to reduce selection bias. Inclusion criteria were age > 18 years; patients with a UTI with an indwelling Foley catheter, a neurogenic bladder, urinary retention, renal impairment with a glomerular filtration rate < 60 mL/min, a renal transplant, pyelonephritis, or an ileal loop/pouch; signs or symptoms of a UTI; and a urine culture with > 10^5 colony-forming units of a uropathogen or at least one positive blood culture growing a possible uropathogen and no other evident site of infection (e.g., an intra-abdominal source or pneumonia). Patients were excluded if a polymicrobial urine culture returned positive, a culture revealed *Candida* spp. as the sole isolate, received a diagnosis of prostatitis, or experienced an uncomplicated UTI. The primary outcome was the presence of an MDR cUTI. The secondary outcomes included estimates of the prevalence of MDR in each country, definition of the cUTI microbiology, and assessment of the resistance rates of the uropathogens to different classes of antibiotics.

A total of 948 patients met inclusion criteria, from which investigators obtained 1,074 bacterial isolates. Most patients (56%) were female, and the mean age was 65.8 years. The most frequent isolates were *Escherichia coli* (52%), with 14.5% MDR; *Klebsiella pneumoniae* (15.6%), with 54.2% MDR; *Pseudomonas aeruginosa* (9%), with 38.1% MDR; *Proteus mirabilis* (7%), with 24.1% MDR; and *Enterococcus* spp. (3%), with no MDR rate given. Carbapenem resistance occurred in 2.3% of *E. coli*, 19.6% of *K. pneumoniae*, and 32.6% of *P. aeruginosa*. The MDR rate was < 20% in Hungary and Spain and approximately 60% in Bulgaria and Greece. In a final predictive model, factors that predicted MDR were male sex (odds ratio [OR], 1.66; 95% confidence interval [CI], 1.20-2.29), acquiring a cUTI in a healthcare facility (OR, 2.59; 95% CI, 1.80-3.71), presence of a Foley catheter (OR, 1.44; 95% CI, 0.99-2.10), contracting a UTI during the previous year (OR, 1.89; 95% CI, 1.28-2.79), and receiving an antibiotic in the preceding 30 days (OR, 1.68; 95% CI, 1.13-2.50).

■ COMMENTARY

Antibiotic misuse is the main culprit driving the global spread of antimicrobial resistance. UTIs are diagnosed in hospitalized patients in Europe and North America commonly. Many patients receive inappropriately broad empiric antibiotic therapy. Thus, the Gomila et al study is significant and useful because it helps define which patients are at risk for a cUTI due to an MDR pathogen and inform antibiotic choices. Hospitalized patients at high risk for an MDR pathogen might be started empirically on a broader agent (e.g., a carbapenem, ceftazidime/avibactam, or meropenem/vaborbactam), while those at intermediate or low risk might receive a narrower spectrum drug (e.g., third-generation cephalosporin or a quinolone). De-escalation is appropriate when culture data become available except in a few circumstances, such as septic shock or neutropenic fever. A recent study showed many of the same risk factors also to be associated with MDR in healthy young adults with

community-acquired UTIs.[1] Of note, nitrofurantoin was an effective choice and carried a low risk for inducing MDR.

There were some limitations to this study. First, it included hospitals in several countries that reported higher rates of MDR pathogens compared to the United States. Therefore, further validation of the results for different regions is needed. Second, not all important risk factors, such as history of an MDR pathogen, were included in the analysis. Finally, because of the retrospective observational design, the study may have been influenced by unmeasured confounding variables. The predictive factors Gomila et al identified could serve as the basis for developing a score to identify patients at high risk for MDR cUTIs. Deciding about empiric antibiotic therapy requires balancing the need for an active drug with the risks associated with coverage that is too broad, such as promoting antimicrobial resistance and *Clostridioides difficile* infection. This study is a significant contribution to the evidence for treating cUTIs and should help clinicians choose appropriate empiric antibiotic therapy. ■

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ABSTRACT & COMMENTARY

Healthcare-Associated Infections: Better, But Not There Yet

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: One-day prevalence studies demonstrated that there was a 16% reduction in the risk of healthcare-associated infections from 2011 to 2015.

SOURCE: Magill SS, O'Leary E, Janelle SJ, et al. Changes in prevalence of health care-associated infections in U.S. hospitals. *N Engl J Med* 2018;379:1732-1744.

Using the Emerging Infections Program, researchers at 10 participating sites recruited as many as 25 hospitals (general, women's, and children's) in their areas to participate in a one-day prevalence of healthcare-associated infections (HCAI). Each hospital selected a study date from May 1, 2015, through Sept. 30, 2015. The survey included 12,299 patients in 199 hospitals. The results were compared to a 2011 survey involving a similar number of hospitals and patients. The patients in the two surveys were similar regarding the proportion in critical care units (15%), the median interval from hospital admission to the survey (three days), and the proportion with an HCAI who died (approximately 11%). However, in 2015, the percentages with a urinary catheter were lower (18.7% vs. 23.6% in 2011), as were those with a central venous catheter (16.9% vs. 18.8%).

In 2011, 452 of 11,282 patients (95% confidence interval [CI], 3.7-4.4) contracted one or more HCAI. In 2015, using the same definition, this was true of only 394 of 12,299 patients (95% CI, 2.9-3.5), a difference that was significant ($P < 0.001$). Pneumonia was the most frequently identified infection, followed by gastrointestinal (mostly due to *Clostridioides difficile*) and surgical site infections. A little more than three-fourths of the latter were deep incisional or organ-space infections.

The most frequently isolated pathogens were *C. difficile*, *Staphylococcus aureus*, and *Escherichia coli*. Of the 47 isolates of *S. aureus* for which susceptibility test results were available, 21 were methicillin-resistant. Carbapenem resistance was detected in only three of 66 isolates of *E. coli*, *Klebsiella* spp., and *Enterobacter* spp. After multiple adjustments, investigators determined that the risk of acquiring an HCAI was 16% lower in 2015 than it had been in 2011 (risk ratio, 0.84; 95% CI, 0.74-0.95; $P = 0.005$). Without adjustment for the presence of a ventilator, central venous catheter, or urinary catheter, there was a 24% reduction in HCAI during the interval.

■ COMMENTARY

This study demonstrates that national activities, locally applied, have reduced the prevalence of HCAI in the United States significantly. The investigators estimated that in 2015, there were 633,300 patients (95% CI, 216,000-1,912,700) with an HCAI, a number that translates into a reduced prevalence since 2011.The largest improvement was seen in surgical site and urinary tract infections. The authors suggested that the former may be related to improved surgical antibiotic practices and, possibly, MRSA decolonization procedures. The decreased use of bladder catheters may have been responsible, at least in part, for a corresponding decrease

in urinary tract infections despite adjustments in the multivariate analysis. In contrast, there was no evidence of a decrease in the prevalence of healthcare-associated pneumonia cases, most of which were not associated with mechanical ventilation, or of *C. difficile* infection. The latter presents some difficult issues in interpretation because of the introduction of PCR testing for the presence of the *toxinB* gene, which, if used alone, may overestimate the frequency of infection by this organism, possibly by a factor of 2. Although the diagnostic methods were not examined, such confounding may have masked an actual decrease in *C. difficile* infection. Overall, these results point to the remarkable progress that has been made in reducing HCAI in the United States, but they also demonstrate that there is a long way to go. ■

BRIEF REPORT

Patients Need to Rethink the 'Quality' in Healthcare

By Carol A. Kemper, MD, FACP

Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases, Santa Clara Valley Medical Center

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

SOURCE: Fenton JJ, Jerant AF, Bertakis KD, Franks P. The cost of satisfaction: A national study of patient satisfaction, health care utilization, expenditures, and mortality. *Arch Intern Med* 2012;172:405-411.

Increasingly, patient satisfaction is an important and commonly used surrogate marker for healthcare quality. Further, reimbursement to physicians may be based on patient satisfaction as a "quality" metric. But the evidence linking a patient's subjective sense of satisfaction and the actual delivery of quality care remains tenuous, at best.

Fenton et al conducted a prospective cohort study of 51,946 adults participating in the national Medical Expenditure Panel Survey from 2000-2007. The researchers compared patient satisfaction (based on five items from the Consumer Assessment of Health Plans Survey) at one year with healthcare expenditures (total cost, prescription drug cost) and healthcare use (ED visits, hospitalization) at two years, and mortality. Mortality figures were assessed at an average of 3.9 years of follow-up. The data were adjusted for demographics, health status, chronic illness, insurance status, and socioeconomic status. The authors found that those with the highest level of satisfaction paid the highest healthcare costs and demonstrated the highest rates of mortality. Patients in the highest quartile for year 1 patient satisfaction paid an adjusted 8.8% greater healthcare expenditure at year 2, and 9.1% higher prescription drug costs at year 2. They also exhibited a 12% greater risk of hospitalization (adjusted odds ratio, 1.12; $P = 0.02$) and a 26% greater risk of mortality (adjusted hazard ratio, 1.267; $P = 0.02$). The risk of mortality remained significantly higher even when researchers eliminated patients with three or more diseases or the worst self-rated health scores from the analysis. Only the risk of going to the ED appeared lower in those more satisfied.

How does one make sense of this? I suggest that the wrong questions are asked. Perhaps we have trained patients to think about their healthcare in the wrong way. How many times have I heard patients complain that their surgeon was not warm? I have had to explain to patients that they do not want a warm and fuzzy surgeon; you want him or her to excel at surgery.

Our large, multispecialty clinic randomly contacts 10 of patients per month with a lengthy questionnaire, detailing their satisfaction with their visit. This includes a few questions about their actual visit with the doctor (e.g., Did the doctor listen to your concerns?), but also questions such as "Were the chairs in the waiting room comfortable?" and "Was the parking adequate?" As best I can tell, all it takes is one in 10 patients who hated their experience, for whatever reason, to skew the results. Aside from the cost of generating all these data, how relevant is it? I do not know, but when I go to a movie and reflect on the experience, I do not think about the parking lot or fault the acting because the popcorn did not contain enough butter. The most demanding patients may not be the most satisfied, unless they get everything they want, which simply cannot translate into the best healthcare. I see a patient who loves her plastic surgeon. He is attractive and friendly, gave the patient a discount for her last surgery, and she raves that the facility is so gorgeous — there are wait staff who take her drink orders; it is like going to the spa. Never mind the nasty infection she contracted for a routine tummy tuck. She still loves the surgeon.

My male partner has read that patients trust their male doctors more when their shoes are polished, they wear

a nice watch, and their shirt is ironed, so he makes sure to polish his shoes every day he is on call, wears a conspicuous gold watch, and presses his shirts. Patients believe male doctors should look like successful salesmen because they do not know what else to think.

Although access to parking is important, I am concerned we are training patients to rate their subjective "experience" as a measure of healthcare quality, rather than educating them on how to assess the actual appropriateness and quality of their care. We need to train patients to understand what is important for their healthcare. If one wants quality, look at physicians' evaluations of each other, their referral base, and other hard indicators, like surgical outcomes and infection rates, not the color of the chairs in the waiting room. ■

PHARMACOLOGY UPDATE

Rifamycin Delayed-Release Tablets (Aemcolo)

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

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

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

The FDA has approved a new drug for the treatment of traveler's diarrhea (TD). Rifamycin sodium is the second in the class of rifamycin antibacterials (rifamixin) to be approved for this indication. The FDA granted qualified infectious disease product, priority review, and fast track designations. Rifamycin will be marketed as Aemcolo.

INDICATIONS

Rifamycin is indicated for the treatment of TD caused by noninvasive strains of *Escherichia coli* in adults.[1]

DOSAGE

The recommended dose is 388 mg (two tablets) orally twice daily for three days.[1] It should be taken with a glass of fluid (not alcohol) and can be taken with or without food. Rifamycin is available as 194 mg of rifamycin in a delayed-release formulation.

POTENTIAL ADVANTAGES

Rifamycin is formulated using a Multi Matrix (MMX) technology. The enteric-coated, pH-dependent polymer film allows the drug to be released in the distal small bowel and colon.[2] In addition to minimal systemic absorption, this targeted release reduces the risk of disturbing the microflora in the upper gastrointestinal tract.[3]

POTENTIAL DISADVANTAGES

It is not recommended for use in patients with diarrhea complicated by fever and/or bloody stool or caused by other (e.g., invasive) bacteria.[1]

COMMENTS

The approval of rifamycin was based on two randomized, Phase III trials. The authors of one trial compared the drug to placebo. In the second trial, the authors compared rifamycin to ciprofloxacin in subjects with TD.[1,4,5,6] In trial 1, subjects were randomized to rifamycin (two tablets twice daily for three days; n = 199) or matching placebo (n = 65). The primary endpoint was time to last unformed stool (TLUS) between the first dose of the study drug and the last unformed stool passed before the start of clinical cure.[5] Clinical cure was defined as passage of two or fewer soft stools or no watery stools, no fever, and no sign or symptoms of enteric infection during a 24-hour interval or no stools or only formed stools during a 48-hour interval. The median TLUS was 46 hours for rifamycin vs. 68 hours for placebo. Percent clinical cures were 81.4% compared to 56.9%, respectively.

In trial 2, the authors compared rifamycin (n = 420) to ciprofloxacin (500 mg twice daily) for three days (n = 415).[4,6] TLUS was 44.3 hours for rifamycin compared to 40.3 hours for ciprofloxacin, demonstrating noninferiority. Clinical cure rates were 85.0% compared to 84.8%. The risk of colonization by extended spectrum beta-lactamase-producing *E. coli* was more likely with ciprofloxacin than rifamycin. Adverse reactions associated with rifamycin in these trials were constipation (3.5%) and headache (3.3%).[1]

CLINICAL IMPLICATIONS

TD is the most common travel-related illness, affecting 10-40% of travelers.[7] High-risk areas are Asia, Africa, the Middle East, Mexico, and Central and South America. The most common bacterial pathogens are enterotoxigenic and enteroaggregative *E. coli*. Less common pathogens include mucosa-invasive *Campylobacter jejuni*, *Shigella* spp, and *Salmonella* spp.[8] The International Society of Travel Medicine recommends azithromycin, ciprofloxacin, and rifaximin as options for moderate to

severe TD, with azithromycin as the preferred agent to treat severe TD.[9] A fluoroquinolone (e.g., ciprofloxacin) and rifaximin are options if fluoroquinolone-resistant *E. coli* or invasive bacteria are not suspected.[9]

Rifamycin provides another potential option for noninvasive TD due to *E. coli*. Rifamycin has been shown to be noninferior to ciprofloxacin, but comparative efficacy to rifaximin has not been published. Azithromycin and ciprofloxacin can be given as a single dose (unless symptoms have not resolved in 24 hours) compared to a three-day course for rifaximin and rifamyin.[9] Rifamycin is expected to be available the first quarter of 2019. ■

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CME QUESTIONS

1. Under newly published guidelines, a permanent pacemaker is indicated if:
a. there are overnight heart rates in the 30s with pauses up to four seconds.
b. there is asymptomatic Mobitz type I block (Wenckebach).
c. there is asymptomatic Mobitz type II block.
d. a patient is minimally symptomatic, with a chronic heart rate < 40 bpm.

2. Which of the following is correct regarding a comparison of the adjusted risk of acquiring a healthcare-associated infection in the United States in 2011 vs. 2015?
a. The risk was 16% lower in 2015 compared to 2011.
b. The risk was 16% higher in 2015 compared to 2011.
c. The risk did not change between 2015 and 2011.
d. The risk could not be calculated because of changes in reporting.

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.

Internal Medicine [ALERT]

ECG Review

By Ken Grauer, MD

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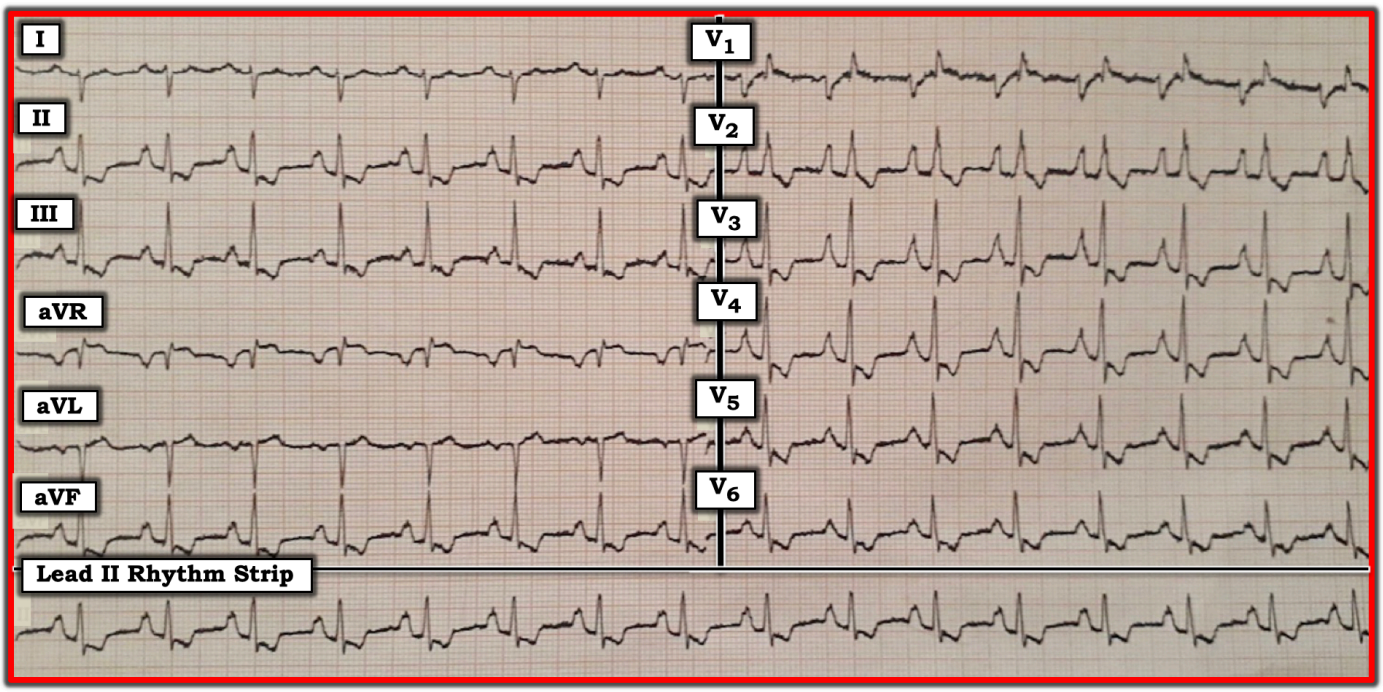
Dr. Grauer reports no financial relationships relevant to this field of study.

A 'Detective' Diagnosis

The ECG in the figure below was obtained from a 40-year-old man. Without the benefit of any history, how might one interpret this tracing? Is there evidence of an acute coronary syndrome? Is there a common diagnosis that potentially explains all the findings?



There is baseline artifact that is most marked in lead V1. The rhythm is sinus at a rate just under 100/minute. The PR, QRS, and QT intervals are normal. Additional relevant findings include marked right axis deviation (RAD), marked right atrial abnormality (RAA), a small Q wave and predominant R wave in lead V1, persistence of S waves across the precordium, and ST-T wave depression in multiple leads.

Although one might be tempted to ascribe the diffuse ST-T wave depression in the figure to ischemia, it is far more likely to reflect marked right ventricular hypertrophy (RVH) with pulmonary hypertension. That is because this unifying diagnosis potentially could explain all the important ECG findings noted so far. One might find it easiest to think of the ECG diagnosis of RVH as a "detective diagnosis." This is because no single finding reveals the diagnosis. Instead, just like a detective, the provider must evaluate a combination of findings occurring in the right clinical context to make a diagnosis.

This 40-year-old man has uncorrected Tetralogy of Fallot. This explains the findings of right atrial and right ventricular enlargement with pulmonary shunting and pulmonary hypertension.

For more information about and further discussion on this case, please visit: https://bit.ly/2zVt04D.