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ABSTRACT & COMMENTARY

What Should You Tell Your Patients About Sleep Apnea, CPAP, and Heart Disease?

By Barbara Phillips, MD, MSPH

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

SYNOPSIS: In this large, multicenter, randomized, controlled trial, continuous positive airway pressure did not reduce incident cardiovascular events compared with usual care, but did reduce snoring and daytime sleepiness and improved health-related quality of life and mood.

SOURCE: McEvoy RD, Antic NA, Heely E, et al. CPAP for prevention of cardiovascular event in obstructive sleep apnea. *N Engl J Med* 2016;375:919-931.

The long-awaited Sleep Apnea Cardiovascular Endpoints (SAVE) trial was a mammoth undertaking, containing patients from 89 centers in seven countries. It was partly funded by industry (Respironics, makers of continuous positive airway pressure [CPAP] machines) and by the Australian government. The aim was to undertake a randomized, controlled trial of the effect of CPAP vs. usual care on cardiovascular endpoints in patients suffering from moderate-to-severe sleep apnea who already received a cardiovascular or cerebrovascular disease diagnosis. Obstructive sleep apnea was defined as an oxygen desaturation index (ODI) of at least 12 events per hour, which is an ethical and reproducible way to define sleep apnea, since the Apnea-Hypopnea Index (AHI) is a poorly reproducible, frequently changing metric.[1] Of note, very sleepy (Epworth Sleepiness Scale score > 15) or very hypoxemic (SaO_2 < 80% for > 10% of recording time) patients were excluded. Patients were randomized to CPAP or usual care, which was management of cardiovascular risk factors and advice on healthy sleep habits and "lifestyle changes to minimize obstructive sleep apnea," which one would assume means weight loss.

CPAP pressures were set according to an analysis of data from autotitrating (or "smart") CPAP

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machines. After a trial on autoPAP, the pressure on the CPAP machines was set at the 90th percentile (that is, the pressure at or below which the autotitrating or "smart" CPAP machine delivered 90% of the time, when used by the sleeping patient). Patients in both arms were followed at one, three, six, and 12 months and annually thereafter. The primary endpoint was a composite of death from any cardiovascular cause, myocardial infarction (including silent myocardial infarction), stroke, or hospitalization for heart failure, acute coronary syndrome (including unstable angina), or transient ischemic attack. Prespecified secondary cardiovascular endpoints included the individual components of the primary composite endpoint, other composites of cardiovascular events, revascularization procedures, new onset atrial fibrillation, new onset diabetes mellitus, and death from any cause. Other secondary endpoints included symptoms of obstructive sleep apnea, health-related quality of life, and mood.

Ultimately, 2,687 patients were included in the primary analysis. They were fairly typical advanced sleep apneics: 81% men, mean age 61 years, mean body mass index 29 kg/m^2, mean ODI 28/hour, and mean Epworth score 7.4. The mean duration of follow-up was 3.7 years.

Among the participants in the CPAP group, the mean duration of adherence to CPAP therapy in the first month of treatment was 4.4 hours per night, but this fell to 3.5 hours per night by 12 months and remained relatively stable thereafter. The residual AHI during CPAP use, as measured by the CPAP machine (*not* the same thing as measured in a sleep lab, but close enough), averaged 3.7 events per hour, suggesting good control of sleep apnea. (This reviewer was unable to find data about the pressure settings in the paper or the online supplement but suspects that the pressures may have been too low). Of the 1,346 patients in the CPAP group, 566 (42%) demonstrated good adherence to treatment (≥ 4 hours per night) during follow-up.

No significant effect of CPAP was found in the adjusted analysis of data; a primary endpoint was observed in 17% of the CPAP group and 15.4% in the usual-care group (*P* = NS). There did not appear to be a difference in primary endpoints between propensity-matched patients with good CPAP adherence in the CPAP group compared with those in the usual care group, but for secondary endpoints, patients who were adherent to CPAP therapy demonstrated a lower risk of stroke and a lower risk of cerebral events than those in the usual care group.

The CPAP group also experienced greater reductions in sleepiness, other symptoms of obstructive sleep apnea (snoring and witnessed apneas), anxiety, and depression than the usual care group; the percentage of patients with clinically relevant depression scores was 25-30% lower in the CPAP group than in the usual care group by the end of follow-up. In addition, the CPAP group demonstrated greater improvement in scores on the physical and mental subscales of the 36-item Short Form Survey, as well as fewer days off from work because of poor health. The number of serious adverse events and the rate of traffic accidents and accidents causing injury did not differ significantly between the two groups.

■ COMMENTARY

This paper surprised and disappointed those of us who regularly manage sleep apnea, but perhaps it shouldn't. Three other randomized trials have investigated the effect of CPAP on cardiovascular endpoints in patients presenting with obstructive sleep apnea.[2-4] Two studies — a multicenter study conducted in Spain that compared CPAP with usual care in 725 patients with obstructive sleep apnea who did not have prior cardiovascular disease[2] and a single-center study involving 224 patients with obstructive sleep apnea and coronary artery disease who had just undergone revascularization[4] — did not find a difference in incident cardiovascular endpoints over several years of follow-up, although in adjusted analyses, both studies reported better outcomes among patients who used CPAP at least four hours per night than among patients who did not receive CPAP or who used CPAP less than four hours per night. The third study, which included 140 patients with

recent ischemic stroke, showed no effect of CPAP on event-free survival over two years.[3] In other words, CPAP appears to "work," but the patient needs to use it. In the SAVE study, patients who were assigned to CPAP used the treatment for a mean of 3.3 hours per night over several years. Several studies, including those mentioned above, have indicated that this level of CPAP use is probably not enough to prevent or reduce cardiovascular damage. There are several other possible explanations for the disappointing findings of this study, including that controlling sleep-disordered breathing 90% of the time is not good enough, that 3.5 years is not long enough to see a difference in outcomes due to CPAP, and that excluding very sick (hypoxemic and sleepy) patients reduces the effect of therapy. There are randomized, controlled trials that demonstrate significant cardiac benefits of CPAP, including the ORBIT trial, which showed reduced likelihood of recurrent atrial fibrillation in sleep apnea patients who used CPAP.[5]

[Although this relatively short-term study of selected, poorly adherent patients did not show a benefit of CPAP in reducing cardiovascular disease, it most definitely demonstrated ... a benefit of CPAP in improving symptoms that matter to patients.]

In the accompanying editorial, Mokhlesi and Ayas argued that the poor CPAP adherence in this trial likely contributed to the negative results.[6] They noted that it would be "prudent to offer CPAP to patients with obstructive sleep apnea and severe hypoxemia during sleep regardless of symptoms — these patients were excluded from the SAVE trial. However, on the basis of the results from the SAVE trial, prescribing CPAP with the sole purpose of reducing future cardiovascular events in asymptomatic patients with obstructive sleep apnea and established cardiovascular disease cannot be recommended."

Although this relatively short-term study of selected, poorly adherent patients did not show a benefit of CPAP in reducing cardiovascular disease, it most definitely demonstrated, as have many previous studies, a benefit of CPAP in improving symptoms that matter to patients, such as sleepiness, depression, anxiety, snoring, and time off work,[7] without significant adverse events. Frankly, this is better than antidepressants and many other efforts we make to help improve such symptoms in patients. Sleepiness in particular is an important symptom since it predicts the likelihood of crash and death.[8]

Here's what I tell my patients: "You have significant sleep apnea, which is a risk for heart attacks, heart failure, cardiac arrhythmias (especially atrial fibrillation), hypertension (especially medication-resistant hypertension), stroke, car crash, depression, cognitive depression, and death. The safest, cheapest, best-studied treatment for this is CPAP, a breathing mask you wear during sleep. CPAP has been shown to reduce or prevent some of these conditions, as well as improving sleepiness. So far, there essentially are no significant side effects reported for CPAP, but there are some follow-ups required. And it doesn't work if you don't use it. I would recommend that we give it a try." ■

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ABSTRACT & COMMENTARY

Optimal Blood Pressure in Patients Presenting with Aortic Stenosis

By Michael Crawford, MD

Professor of Medicine, Chief of Clinical Cardiology, University of California, San Francisco

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

SYNOPSIS: A post-hoc analysis of patients suffering from mild to moderate aortic stenosis in a study of low-density lipoprotein cholesterol lowering showed that the optimal blood pressure for the best survival was 130-139/70-90 mmHg.

SOURCES: Nielsen OW, Sajadieh A, Sabbah M, et al. Assessing optimal blood pressure in patients with asymptomatic aortic valve stenosis: The Simvastatin Ezetimibe in Aortic Stenosis Study (SEAS). *Circulation* 2016;134:455-468.

O'Gara PT. Management of hypertension in patients with mild to moderate aortic stenosis: Navigating the SEAS. *Circulation* 2016;134: 469-471.

Systemic hypertension is common in aortic stenosis patients and is associated with worse outcomes. However, little is known about what the optimal blood pressure is in these patients in whom relative hypotension may not be tolerated well. Investigators from the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) trial sought to answer this question using the data from this otherwise negative study. The SEAS study excluded patients with heart failure, diabetes, or known atherosclerosis and enrolled patients with aortic flow velocities between 2.5 m/s and 4 m/s with normal ejection fraction and no symptoms.

This report is a post-hoc analysis of the data to correlate blood pressure (BP) with outcomes in 1,767 patients who had adequate measurements of aortic velocity and BP. The primary endpoint for this analysis was all-cause mortality. BP was defined as an average of all measurements during the first four years of follow-up (median 4.3 years). A U-shaped association between systolic BP (SBP) and all-cause mortality was identified with values from 130-139 associated with the best survival with diastolic (DBP) in the range of 60-90 mmHg. SBP > 139 increased the risk of death (hazard ratio [HR] = 1.7 for SBP > 160; $P = 0.033$) as did lower SBPs (HR = 1.6 for SBP 120-129, $P = 0.039$). Low SBP remained harmful in patients suffering from mild and moderate aortic stenosis. A high SBP was associated with myocardial infarction and cardiovascular death in patients with mild but not moderate aortic stenosis. These data were not changed by adjustment for a history of hypertension or antihypertensive treatment. The authors concluded that in patients with asymptomatic aortic stenosis without heart failure, diabetes, and overt atherosclerotic vascular disease, the optimal SBP is 130-139 and the optimal DBP is 70-90 mmHg.

■ COMMENTARY

Guidelines recommend treatment of hypertension in patients presenting with aortic stenosis, but target BPs are not given. This post-hoc observational analysis of the SEAS trial provides some useful information in this regard. SBPs > 160 and < 130 were associated with increased mortality, but mild systolic hypertension was not (140-159 mmHg). However, the authors suggested that it is reasonable to treat SBP > 140 based on their previous analysis of the SEAS data, which showed that hypertension was associated with worse outcomes in these patients. Interestingly, both the authors and the accompanying editorial provided no explanation for the reason elevated SBP is detrimental in aortic stenosis. Thus, it may be acceptable to tolerate SBPs in the 140-159 range if relative hypotension has been an issue with treatment.

The adverse effect of low DBP is easier to explain, since reducing myocardial perfusion pressure in diastole in patients who probably have high diastolic left ventricular pressures would clearly reduce myocardial oxygen supply, even if the patient had normal coronary arteries. Similar results have been observed in patients with acute coronary syndromes and acute heart failure. The higher mortality risk with high DBPs is harder to explain, but is observed in all studies of BP and outcome. Since BP levels did not influence the time to aortic valve replacement, the effect probably is mediated by augmenting coronary artery disease or other comorbidities.

In SEAS, antihypertension treatment was not regulated, but a previous analysis of this database showed that renin angiotensin aldosterone system blockers generally were safe in aortic stenosis patients. This prompted the editorialist to state that no drugs were off limits if used carefully in these patients. This is probably true for drugs we commonly use now, but may not be for some drugs such as powerful direct vasodilators (e.g., hydralazine). Also, most aortic stenosis patients are elderly and often present with

multiple comorbidities that have to be taken into account with drug choice for hypertension. In aortic stenosis in particular, drugs with potent effects on AV conduction may be relatively contraindicated if there are signs of conduction disturbances, such as first-degree AV block.

Another implication of this study is that if patients are on antihypertensive therapy with an SBP < 120 or a DBP < 70 mmHg, one should consider reducing the therapy. In those with BPs in these ranges who are not on antihypertensive medication, seek other causes of relative hypotension and correct them.

The results of this study fit in with the general theme that BP targets for antihypertension treatment likely are different for different patient populations, and one size does not fit all. ■

PHARMACOLOGY UPDATE

Adalimumab-atto Injection (Amjevita)

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 a biosimilar to adalimumab (Humira), a recombinant IgGI monoclonal antibody specific for human tumor necrosis factor (TNF). Biosimilars are biological products that are highly similar to the reference product with no clinically meaningful differences in terms of the safety, purity, and potency of the product.[1] This is the fourth FDA-approved biosimilar. Adalimumab-atto is marketed as Amjevita.

INDICATIONS

Adalimumab-atto is indicated for the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), adult Crohn's disease (CD), ulcerative colitis (UC), and plaque psoriasis (Ps).[1]

DOSAGE

The recommended dose for RA, PsA, and AS is 40 mg every other week subcutaneously. Some patients not receiving methotrexate may benefit from 40 mg every week.[1] For JIA, the dose is 20 mg every other week (15 kg to < 30 kg) and 40 mg every other week for those 30 kg or heavier. For CD and UC, the dose is 160 mg on day one (or 80 mg daily for two consecutive days), 80 mg two weeks later, and a maintenance dose of 40 mg every other week beginning two weeks later. For Ps, the initial dose is 80 mg followed by 40 mg every other week. Adalimumab-atto is available as 20 mg and 40 mg single-use prefilled glass syringes and 40 mg single-use prefilled SureClick autoinjector.

POTENTIAL ADVANTAGES

Adalimumab-atto provides an alternative to adalimumab for multiple chronic inflammatory conditions.

POTENTIAL DISADVANTAGES

Adalimumab-atto is not designated as interchangeable with Humira, which means it cannot be substituted without provider approval.

COMMENTS

Adalimumab-atto is approved based on evidence of biosimilarity that includes structural and functional characterization, animal data, human pharmacokinetic and pharmcodynamic data, clinical immunogenicity data, and clinical effectiveness and safety data.[2] There were sufficient data for the clinical studies section of the prescribing information for adalimumab-atto to be the same as that for adalimumab, with the exception of pediatric Crohn's disease, hidradenitis suppurativa, and uveitis.

CLINICAL IMPLICATIONS

Adalimumab-atto is the third biosimilar that targets tumor necrosis factor alpha. Based on FDA criteria, it is highly similar to the reference product (Humira) and has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically inactive components are allowable in biosimilar products. The drug is not interchangeable with the reference product without provider approval. The marketing of adalimumab-atto may be delayed until at least March 2017 because of potential patent litigation and the 180-day Notice of Commercial Marketing provision of the Biologics Price Competition and Innovation Act.[3] ■

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Clinical Briefs

By Louis Kuritzky, MD

Early Response to Exercise in Depressed Patients

SOURCE: Suterwala A, Rethorst CD, Carmody TJ, et al. Affect following first exercise session as a predictor of treatment response in depression. *J Clin Psychiatry* 2016;77:1036-1042.

Although most depressed patients treated with antidepressants note favorable symptom improvement, only about one-third achieve full remission. Selective serotonin reuptake inhibitors are the most common first-line antidepressants used in the United States and, although generally well tolerated, may induce problematic adversities such as sexual dysfunction. Additionally, the response to pharmacotherapy may take several weeks or longer to manifest, during which time clinicians cannot be confident whether any particular antidepressant ultimately will be effective. If the response to a chosen antidepressant treatment turns out to be insufficient, the clinician will have wasted the patient's time and money, and potentially exposed the patient to unwanted adverse effects.

Exercise has been noted to produce favorable outcomes in depressed patients. Might the early response to exercise predict who would respond favorably over the long term?

Suterwala et al performed a randomized, controlled trial of exercise in depressed patients (n = 126). High-dose exercise (180 minutes/week moderate-vigorous activity) was compared with low-dose activity (45 minutes/week). Exercise was supervised during one session each week for the entire 12-week duration of the trial.

The Positive and Negative Affect Scale (PANAS) was administered to both groups immediately after the very first supervised session in the study's first week. A favorable PANAS score after the first exercise session proved to be a good predictor of improvement at 12 weeks, as well as likelihood of remission, but only in the high-dose exercise group. We may be better able to capture the potential for beneficial effects of exercise in depression by early identification of responders. ■

COPD Patients Who May Need Intensified Smoking Cessation

SOURCE: Tottenborg SS, Thomsen RW, Johnsen SP, et al. Determinants of smoking cessation in patients with COPD treated in the outpatient setting. *Chest* 2016;150:554-562.

Like most other endeavors in medicine, the road to successful smoking cessation is not one-size-fits-all. Prior to end-stage disease for patients with COPD, the only intervention that has been shown to be truly disease-modifying is smoking cessation. How can we best target our efforts to ensure best smoking cessation outcomes? Tottenborg et al studied a large population of smokers suffering from COPD in Denmark (n = 3,233) to see which demographic factors were associated with likelihood of smoking cessation. In this population (in contrast to other data from the United States), clinician encouragement to cease smoking was not statistically significantly associated with likelihood of cessation.

Over a five-year period of observation, factors that were identified as associated with lesser likelihood of smoking cessation included younger age (30-39 years compared to ≥ 70 years), lower income, unemployment, and low severity of COPD. Although we can't change our patients' age, income, job status, or COPD severity, Tottenborg et al suggested identifying the characteristics that predict less success with smoking cessation may allow clinicians an opportunity to redouble efforts in these same individuals. ■

USPSTF Endorses TB Screening for High-risk Individuals

SOURCE: USPSTF. Screening for latent tuberculosis infection in adults: US Preventive Services Task Force recommendation statement. *JAMA* 2016;316:962-969.

The U.S. Preventive Services Task Force (USPSTF) recently issued a Level B recommendation endorsing screening for latent TB in high-risk populations, meaning, "there is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial."

Based on screening using either the Mantoux tuberculin skin test or the interferon-gamma release assay, the USPSTF concluded that both are sufficiently sensitive and specific to be considered accurate. Despite the absence of TB screening trials that confirm benefits, since treatment of latent TB prevents progression to active TB, a moderate degree of benefit should be achieved through screening.

However, TB screening is not advocated on a population-wide basis. Instead, USPSTF recommends screening in high-risk populations. Such individuals include persons who have lived in countries of high TB prevalence (e.g., Mexico, Philippines, Vietnam, India, China, Haiti, or Guatemala), have lived in high-risk congregate settings (e.g., homeless/correctional facilities), are immunosuppressed (e.g., HIV or on immunosuppressive meds), or have been in contact with persons suffering from active TB. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. **The symptom/outcome that continuous positive airway pressure most reliably improves in patients presenting with obstructive sleep apnea is:**
   a. cardiovascular risk.
   b. glucose control.
   c. cognitive impairment.
   d. sleepiness.

2. **The optimal systolic blood pressure in patients with mild to moderate aortic stenosis is:**
   a. 130-139 mmHg.
   b. > 140 mmHg.
   c. 140-159 mmHg.
   d. < 130 mmHg.

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.

[IN FUTURE ISSUES]

Reactivation of Hepatitis B Virus Coinfection During Treatment of Chronic Hepatitis C Virus Infection

What Influences ICU Admission?

Internal Medicine [ALERT]

ECG Review

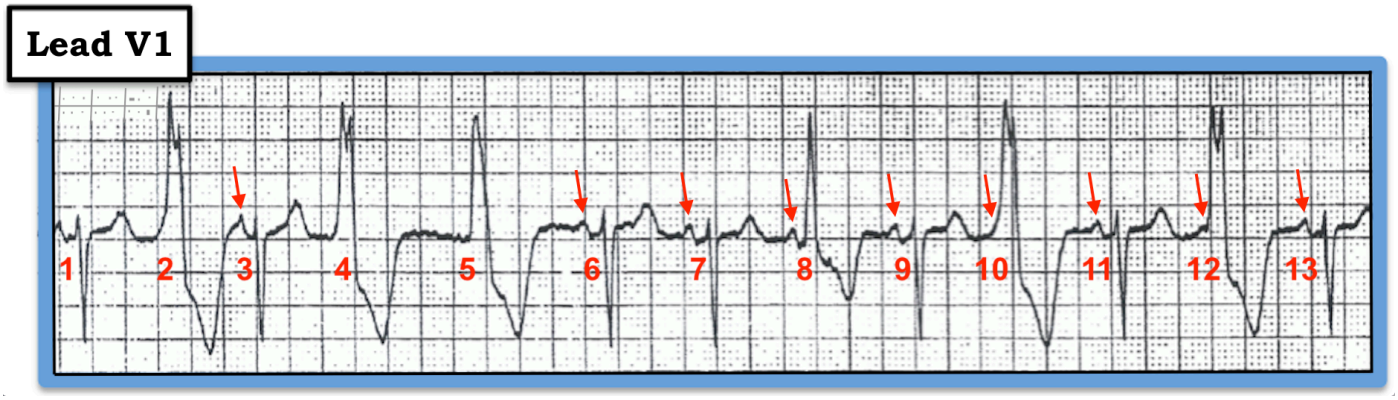
By Ken Grauer, MD

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

Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.

Why Do the Beats Keep Changing?

How would you interpret the rhythm in the figure below? How certain are you of your diagnosis? Why does beat 8 look so different from all other beats in this tracing? What clinical situation commonly is associated with arrhythmias such as the one shown here?



Unfortunately, no clinical information is provided for the rhythm strip shown in the figure. Nevertheless, to facilitate interpretation, we number the beats and highlight with red arrows the atrial activity that clearly is present.

The easiest way to begin interpretation of a complex arrhythmia, such as the one shown here, is by looking to see if there is an underlying rhythm. The key lies with recognition of the two consecutively conducted sinus beats in the middle of the tracing (beats 6 and 7). Additional sinus beats manifest a similarly shaped, narrow QRS complex and similar P wave shape with constant PR interval preceding beats 1, 3, 9, 11, and 13. Thus, the underlying rhythm is sinus.

Beats 2, 4, 5, 10, and 12 are wide. These beats are either not preceded by any P wave or preceded by an on-time P wave that notches the very beginning of the QRS complex with a PR interval that is too short to conduct. Therefore, these beats must be ventricular in etiology. We call these beats premature ventricular contractions (PVCs), even though they occur relatively late in the cycle (usually just before the next on-time sinus P wave would be able to conduct).

Clinically, this late-cycle feature of these PVCs is similar to the phenomenon of accelerated idioventricular rhythm (AIVR), in which a ventricular rhythm at a slightly accelerated rate (usually between 60-110 beats/minute) is seen in patients with recent acute infarction who have just reperfused the infarct-related artery. Note that this is the picture we see for ventricular beats 4 and 5, which, if they were followed by additional ventricular beats at similar R-R interval spacing, would constitute AIVR at a rate of ~75 beats/minute. Even though we are not given any clinical information about this patient, the finding of a bigeminal pattern of late-cycle PVCs with two consecutive ventricular beats at a rate consistent with AIVR is characteristic enough to strongly suggest consideration that the rhythm in the figure might represent a reperfusion rhythm.

We save assessment of beat 8 for last. Note that this beat is preceded by an on-time P wave with a PR interval that is too short for normal conduction. Note also that both QRS and T wave morphology of beat 8 is intermediate between morphology of the pure ventricular beats on this tracing and the sinus-conducted beats. Beat 8 is a fusion beat, and it proves beyond doubt that widened beats in this tracing are ventricular in etiology.

Additional discussion of this case is available at: http://tinyurl.com/KG-Blog-129. Please also see the ECG Review in the October 15 issue of *Internal Medicine Alert* for further review on recognition and the clinical significance of fusion beats: http://bit.ly/2dpfhZ6.