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ABSTRACT & COMMENTARY

Is Anxiety a Risk Factor for Cardiovascular Disease?

By Harold L. Karpman, MD, FACC, FACP

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

SYNOPSIS: Anxiety disorders are associated with an elevated risk of a range of different cardiovascular events including stroke, coronary heart disease, heart failure, and cardiovascular deaths, but it is unclear whether these disorders are causal in nature.

SOURCE: Emdin CA, Odutayo A, Wong CX, et al. Meta-analysis of anxiety as a risk factor for cardiovascular disease. *Am J Cardiol* 2016;118:511-519.

Despite the significant amount of published evidence that demonstrates that depression and general psychological stress are associated with incident cardiovascular disease, the association between anxiety and cardiovascular disease is less clear. Previously published studies have demonstrated that anxiety is associated with a high degree of adverse outcomes in heart failure populations.[1] However, these results may be secondary to reverse causality in that patients who suffer from severe cardiovascular disease may develop greater anxiety rather than anxiety causing the illness. A meta-analysis of 20 cohort studies demonstrated that anxiety disorders were associated with a 26% higher risk of coronary artery disease.[2] However, previous studies demonstrated conflicting results on whether anxiety was associated with the risk of stroke, heart failure, or cardiovascular mortality.[3-6]

Because of the possible contribution of anxiety disorders to the development of cardiovascular disease, Emdin et al conducted a comprehensive meta-analysis on the association between anxiety and incident cardiovascular disease and death. Forty-six stud-

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ies comprised of 2,017,126 participants were included in the analysis. A total of 220,253 participants were afflicted with anxiety. The authors had no evidence of interaction between general anxiety and coronary heart disease. However, phobic anxiety was associated with a 41% higher risk of cardiovascular mortality, a 41% higher risk of coronary heart disease, a 71% higher risk of stroke, and a 35% higher risk of heart failure. The authors concluded that their results suggested that, like depression, anxiety should be considered a risk factor for a wide range of cardiovascular diseases.

■ COMMENTARY

A large body of evidence has demonstrated that depression is a risk factor for cardiovascular disease.[5] In a meta-analysis of 21 prospective studies, depression was associated with an 81% higher risk of coronary artery disease.[8] The meta-analysis performed by Emdin et al extends previously published studies demonstrating anxiety to be associated with coronary heart disease.[2] In the study, anxiety was associated with a 41% higher risk of coronary heart disease, a 71% higher risk of stroke, and a 35% higher risk of heart failure. Although there are multiple biologic pathways by which anxiety may increase the risk of cardiovascular disease, it is not clear whether the associations reported in this meta-analysis are causal. However, even if the associations are not causal, the elevated risk of cardiovascular disease in subjects who suffer from anxiety would support greater screening and more aggressive measures to prevent cardiovascular disease developing in anxiety-ridden patients.

The results of this meta-analysis provide additional support for the concept that anxiety disorders are associated with elevated risks of a range of different cardiovascular events, including stroke, coronary disease, heart failure, and cardiovascular death, and it is unclear as to whether the associations are causal; however, the results certainly would support more general screening and more aggressive measures to prevent cardiovascular disease among subjects presenting with anxiety. ■

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ABSTRACT & COMMENTARY

What Influences ICU Admission?

By Eric Walter, MD, MSc

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

SYNOPSIS: There is widespread variability between hospitals in rates of ICU admission. High ICU utilization hospitals were more likely to use invasive procedures and incurred higher costs than low ICU utilization hospitals with no difference in mortality.

SOURCE: Chang DW, Shapiro MF. Association between intensive care unit utilization during hospitalization and costs, use of invasive procedures, and mortality. *JAMA Intern Med* 2016;176:1492-1499.

ICU services comprise 13.4% of total hospital costs and more than 4% of national health expenditures. Yet, the decision as to which patients should be cared for in the ICU largely is subjective. Chang and Shapiro used administrative data to compare ICU use across 94 hospitals in Washington state and Maryland for diabetic ketoacidosis (DKA), pulmonary embolism (PE), upper gastrointestinal bleed (UGIB), and congestive heart failure (CHF). The primary outcomes were risk-adjusted mortality, use of invasive procedures, and hospital costs. Invasive procedures were defined as use of central venous catheters for any of the diagnoses, mechanical ventilation in DKA, thrombolytics in PE, and esophagogastroduodenoscopy in UGIB. Analyses were adjusted for both patient level and hospital level factors. Logistic regression models were used to predict ICU admission rates for each hospital during hospitalizations for each diagnosis. Hospitals also were dichotomized into higher (> 50th percentile for predicted ICU utilization rate) and lower ICU utilization (50th percentile and below) groups.

There was wide variability in rates of ICU admission for each diagnosis (16.3%-81.2% for DKA, 5.0%-42% for PE, 11.5%-51.2% for UGIB, and 3.9%48.8% for CHF). High ICU utilization was associated with increased use of invasive procedures in all four conditions. Increased ICU utilization was associated with higher hospital costs despite comparable lengths of stay. Severity of illness was lower among patients in high ICU utilization hospitals. Hospital mortality did not differ between hospitals with high and low ICU utilization. Correlations between ICU utilization rates for all four conditions were high.

■ COMMENTARY

The ICU is inherently a heterogeneous unit. In the same ICU, we may admit a patient with severe hypotension next to a patient with malignant hypertension. The unit admits a patient presenting with severe bleeding, followed by a patient suffering from portal venous thrombosis. This heterogeneity may explain why so many ICU trials have produced negative results. The variability in admission rates described by Chang and Shapiro highlight another layer of ICU heterogeneity.

In many ways, these results should not be surprising. The decision to admit someone to the ICU is subjective. It will be influenced not only by the patient's severity of illness, but also hospital size, number of ICU beds, bed availability, nurse ratios, physician comfort, reimbursement, and more. Chang and Shapiro found that institutional factors appeared to influence the decision to admit to the ICU more so than patient level factors. High ICU utilization hospitals admitted patients with all four studied conditions frequently to the ICU despite a lower severity of illness. The influence of these institutional factors may be understandable in some circumstances. In this study, smaller hospitals were higher ICU utilizers. It may make sense to admit a patient with DKA to the ICU in a smaller hospital in which floor nurses may not have the time or expertise to manage an insulin drip. However, these results also suggest that many patients may not need ICU care, as there was no difference in mortality between hospitals with high and low utilization. The decision to admit patients to the ICU may expose patients to potential harms, since invasive procedures such as central lines, thrombolytics, intubation, and EGD were used more often by high ICU utilizer hospitals.

These results present significant implications for future studies evaluating ICU outcomes and costs. There may be too much variability from hospital to hospital to compare ICU costs or outcomes directly across hospitals and regions without accounting for both institutional and patient level factors. We simply cannot compare sepsis-related organ failure assessment scores and Charlson comorbidity indices. Future studies must try to better understand the institutional factors that affect the decision to admit a patient to the ICU. At the individual level, ICU physicians and directors must critically consider the reasons why or why not staff chooses ICU level of care for a patient. With a better understanding of the factors that affect the decision to admit to the ICU, clinicians can better determine when ICU level care truly is needed. ■

SHORT REPORT

Is Yoga Effective for Treating Asthma?

By Concepta Merry, MB, BCh, BAO, BA

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

SYNOPSIS: Although the data on yoga in asthma are only of moderate quality, they suggest that yoga may improve quality of life and asthma symptoms.

SOURCE: Yang ZY, Zhong HB, Mao C, et al. Yoga for asthma. *Cochrane Database System Rev* 2016;4:CD010346. DOI: 10.1002/14651858.CD010346.pub2.

Three hundred million people worldwide suffer from asthma, and unfortunately this number continues to rise.[1] Pathophysiologically, asthma is a disease of the airways, but in reality the effects of asthma extend far beyond the lungs and negatively affect quality of life.[2]

It is biologically plausible that the ancient Indian practice of yoga could offer some relief for the physical and psychological effects of asthma. It is oversimplistic to refer to yoga as a single entity, given that there are more than 40 different types of yoga. However, common to the many different types of yoga are breathing exercises (pranayama), postures (asanas), and meditation (dhyana), which theoretically could help asthmatics by:

- reducing airway hyper-responsiveness,
- triggering the relaxation response, and/or
- increasing lung capacity.[3,4]

A group of Chinese researchers recently published a Cochrane review of yoga in asthma. Initially, they looked at any study of yoga in asthma, including studies comparing the effects of yoga vs. usual care (or no intervention) or yoga vs. sham intervention. Following detailed review of the available studies, they selected 15 studies, which included 1,048 participants, for review. Most of the studies involved adults only, but two studies included children and adolescents. Understandably, given the origin of yoga in India, most of these studies came from India.

They found some evidence that yoga may improve quality of life in people with asthma (mean difference in Asthma Quality of Life Questionnaire [AQLQ] score per item 0.57 units on a 7-point scale; 95% confidence interval [CI], 0.37-0.77), improve symptoms (standardized mean difference 0.37; 95% CI, 0.09-0.65), and reduce medication use (risk ratio, 5.35; 95% CI, 1.29-22.11) in people with asthma. The mean difference for the AQLQ score exceeded the minimal clinically important difference of 0.5 as per other medical interventions, but this needs to be interpreted with care as the two key studies that included a placebo found no difference. There was no statistically significant impact of yoga on the forced expiratory volume in one second (FEV_1) (mean difference 0.04 L; 95% CI, -0.10 to 0.19). There were no serious adverse events associated with yoga across the studies; however, this was based on a very limited number of data points.

Overall, the authors concluded that there is moderate-quality evidence that yoga may improve quality of life and symptoms in people with asthma. However, they effectively added a disclaimer saying that these findings are preliminary and suggestive rather than conclusive. The authors recommended that large, well-conducted, randomized, controlled trials are needed to fully assess the effect of yoga in asthma. Specifically, the authors recommended the inclusion of a sham yoga intervention group. Ethically designed sub-studies looking at special populations, such as children and people with severe asthma, also need to be considered, if possible.

It is always disappointing when a Cochrane review fails to answer the question at hand because of insufficient quality data. Sometimes, the main contribution a Cochrane review of an integrative therapy is to offer a blueprint for design of future studies needed to fill the existing gaps, just as we have seen in this review. It is interesting to ponder how often funders and principal investigators take these recommendations into consideration when designing new studies. ■

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PHARMACOLOGY UPDATE

Bezlotoxumab Injection (Zinplava)

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 selective, fully human monoclonal antibody directed at *Clostridium difficile* toxin B. Binding of toxin B neutralizes its toxic effect. Bezlotoxumab is marketed as Zinplava.

INDICATIONS

Bezlotoxumab is indicated to reduce recurrence of *C. difficile* infection (CDI) in patients ≥ 18 years of age who are receiving antibacterial treatment of CDI and are at high risk for CDI recurrence.[1]

DOSAGE

The recommended dose is a single dose of 10 mg/kg administered intravenously over 60 minutes during antibacterial treatment.[1] Bezlotoxumab is available as a single-dose vial containing 1 g of bezlotoxumab or 25 mg/mL.

POTENTIAL ADVANTAGES

Bezlotoxumab neutralizes the effect of toxin B and reduces the rate of recurrence of CDI.

POTENTIAL DISADVANTAGES

In subjects with underlying congestive heart failure, the frequency of heart failure was 12.7% in those randomized to bezlotoxumab compared to 4.8% in the placebo group.[1] More deaths were associated with this population (19.5% vs. 12.5%). Bezlotoxumab was associated with infusion-specific adverse reactions in 10% of subjects compared to 8% for placebo. Other adverse events vs. placebo include nausea (7% vs. 5%), pyrexia (5% vs. 3%), and headache (4% vs. 3%).

COMMENTS

The efficacy and safety of bezlotoxumab was assessed in two similar randomized, double-blind, placebo-controlled studies in subjects receiving standard of care (SoC) antibacterial treatment (metronidazole, vancomycin, or fidaxomicin) for a confirmed diagnosis of CDI.[1] Subjects were randomized to a single-dose of bezlotoxumab or placebo. In study one, 403 patients were randomized to bezlotoxumab and 404 to placebo. Study two randomized 407 and 399, respectively. The median time for the single-dose bezlotoxumab infusion was three days after the start of SoC (range -1 to 14). The efficacy endpoint was clinical cure, and those who achieved cure were assessed for recurrence through 12 weeks after infusion. Clinical cure was defined as no diarrhea for two consecutive days following the completion of ≤ 14 days of treatment. Recurrence was defined as development of a new episode of diarrhea and positive stool test of toxigenic *C. difficile*. Sustained clinical response was defined as clinical cure and no recurrence through 12 weeks after infusion. Sustained clinical response was 60.1% for bezlotoxumab vs. 55.2% for placebo in study one, and 66.8% vs. 52.1%, respectively, for study two. Statistical significance was achieved in study two only. Recurrence was significantly lower with bezlotoxumab (17.4% vs. 27.6% and 15.7% vs. 25.7%, respectively).

CLINICAL IMPLICATIONS

C. difficile is the leading cause of antibiotic-associated diarrhea. Two endotoxins (A and B) are secreted by the disease-causing strains.[2] The original Phase III studies included bezlotoxumab, actoxumab (antibody to toxin A), or the combination. Treatment with actoxumab or the combination provided no benefit; therefore, only bezlotoxumab was marketed.[3] Toxin B is thought to be primarily responsible for disease symptoms.[2] The drug appears to have marginal effect in producing sustained clinical effect but appears to reduce recurrence. The effect may be greater in those with high risk of CDI recurrence. These include ≥ 65 years of age, history of CDI in the past six months, immunocompromised state, severe CDI at presentation, or *C. difficile* ribotype 027. In patients with a history of congestive heart failure, risk vs. benefit must be assessed before treatment.[1] The cost for bezlotoxumab was not available at the time of this review. It is expected to be available in the first quarter of 2017. ■

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Clinical Briefs

By Louis Kuritzky, MD

Low-dose OTC Proton Pump Inhibitor for GERD Relief

SOURCE: Peura D, Le Moigne A, Pollack C, et al. A 14-day regimen of esomeprazole 20 mg/day for frequent heartburn: Durability of effects, symptomatic rebound, and treatment satisfaction. *Postgrad Med* 2016;128:577-583.

Esomeprazole is available over the counter as Nexium 24 (20 mg) and by prescription as Nexium 40 mg. More than 75% of patients with uncomplicated gastroesophageal reflux disease (GERD) enjoy symptomatic relief with a four- to eight-week course of prescription esomeprazole 40 mg daily, and many of the remainder find improvement with twice-daily dosing.

Might even a lower esomeprazole dose over the short term be effective? To test this hypothesis, Peura et al performed two clinical trials in which they randomized subjects to 20 mg esomeprazole or placebo daily for two weeks. The remarkable thing about the patient population is that subjects were excluded if they received a confirmed diagnosis of GERD or erosive esophagitis or were on a prescription for GERD medications. One might perceive such patients as those with insufficiently burdensome symptoms to seek clinician care for relief. Study subjects reported frequent heartburn at least two days/week for the past month.

Daily low-dose esomeprazole (20 mg) was statistically significantly superior to placebo for symptom relief during 14 days of administration and the week following discontinuation, without evidence of rebound. When patients do not achieve satisfactory symptomatic relief from GERD with low-dose treatment, appropriate courses of action include increasing the dose, switching to another proton pump inhibitor, adding an H_2 antagonists, or adding an alginate. ■

Home BP Monitoring Associated with Better BP Control

SOURCE: Erden S, Mefkure Ozkaya H, Banu Denizeri S, Karabacak E. The effects of home blood pressure monitoring on blood pressure control and treatment planning. *Postgrad Med* 2016;128:584-590.

Intuitively, incorporation of home blood pressure monitoring (HBPM) into the regimen of BP control interventions should improve outcomes. Encouraging patients to take ownership of their BP management, elimination of white-coat hypertension, and the ability to detect overtreatment by identification of episodes of hypotension at home could improve outcomes of hypertensive patients. But does HBPM improve outcomes?

Erden et al retrospectively evaluated charts of 1,006 hypertensive Turkish adults, of which 40% participated in HBPM. They compared several outcomes: office BP, percent achieving BP control (defined as < 135/85 mmHg), and vascular health (cardiovascular [CV] events and retinopathy).

The HBPM group was statistically significantly more likely to achieve BP control (85% vs. 56%). More difficult to explain is the polarity of vascular results: CV events actually were statistically significantly *more* common in the HBPM group, whereas retinopathy was *less* common. While the HBPM group, on average, had been treated for hypertension for a substantially longer duration (nine years vs. seven years), this would not reconcile why one vascular compartment (retina) showed favorable effect, whereas CV events did not, especially since a ponderous amount of clinical trial data shows a consistent relationship between office BP lowering and CV outcomes. ■

A Link Between Obesity and Asthma Severity

SOURCE: Bhatt NA, Lazarus A. Obesity-related asthma in adults. *Postgrad Med* 2016;128:563-566.

Asthma, like hypertension, may be more than one entity. That is, more than one underlying pathophysiology may lead to similar phenotypic expression. Just as hyperaldosteronism may present with hypertension that is otherwise indistinguishable from "essential hypertension," might the clinical presentation of asthma reflect various underpinnings?

It perhaps has been underappreciated that risk for development of asthma increases as body mass index increases over 25 kg/m^2, that obese asthmatics may be more treatment resistant, and that obese asthmatics experience higher rates of asthma-related hospitalizations (with worse outcomes).

Mechanistically, obesity-related asthma (ORA) is characterized by less occurrence of atopy and eosinophilia. Perhaps this helps explain the observation that steroid responsiveness is lower in ORA patients. Other features of inflammation differ in ORA vs. atopic asthma, such as interleukin levels.

Determining which aberrant inflammation circuitry in ORA deserves intervention to improve ORA outcomes is not yet clear. On the other hand, there are very encouraging prospective randomized trial data confirming improvements in asthma achieved through weight loss in obese patients. Clinicians should be aware that individualization of treatment for ORA may need to include attention to weight reduction to optimize outcomes. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. **Phobic anxiety:**
   a. is associated with no increase in the risk of cardiovascular events.
   b. is associated with an elevated risk of a range of a range of different cardiovascular events, including stroke, coronary heart disease, heart failure, and cardiovascular death.
   c. always occurs in patients who develop cardiovascular disease.
   d. is always the cause and not just the result of cardiovascular disease.

2. **In the study of ICU admission rates by Chang and Shapiro:**
   a. wide variability in rates of ICU admission for each diagnosis suggests that institutional factors influence the decision to admit a patient to the ICU.
   b. the decision to admit a patient to the ICU is made on objective criteria alone.
   c. smaller hospitals were less likely to admit a patient with one of the studied conditions to the ICU.
   d. the rate of admission to the ICU for patients with diabetic ketoacidosis was very similar across all studied hospitals.
   e. ICU admission rates across hospitals in California were studied.

3. **Which of the following is true regarding the use of yoga for people with asthma?**
   a. It is associated with significant serious adverse effects.
   b. It results in a statistically significant improvement in FEV_1.
   c. The mechanism of action is clearly understood.
   d. It improves the quality of life.

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]

Diastolic Blood Pressure Goals

Cranberry Capsules Are Not Effective in Preventing Bacteriuria with Pyuria in Elderly Women in Nursing Homes

How Safe Is Your Honey?

Internal Medicine [ALERT]

ECG Review

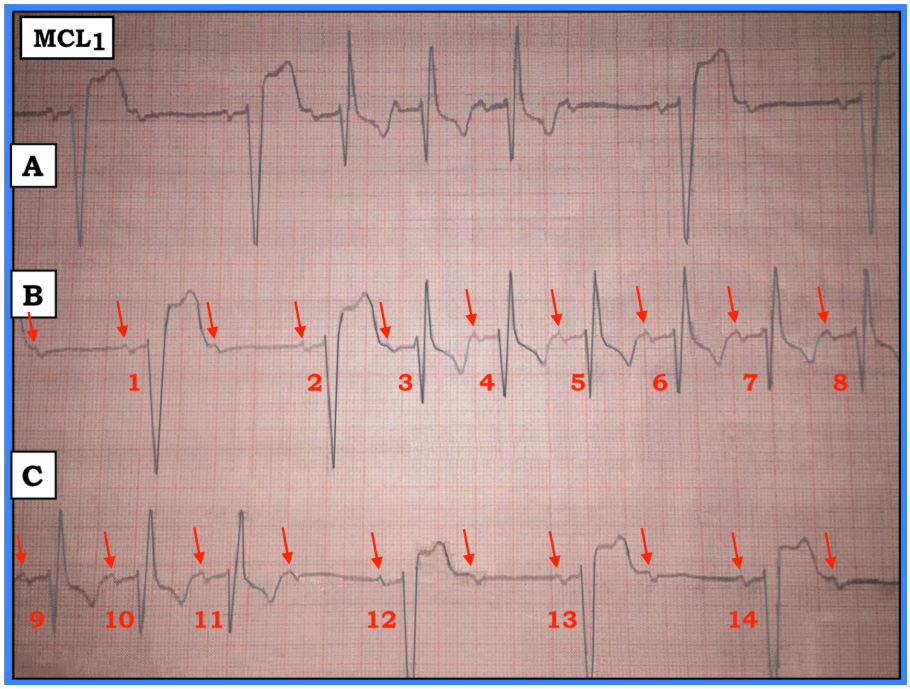
By Ken Grauer, MD

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.

An Alternating QRS with AV Block?

How would you interpret the three successive lead MCL-1 rhythm strips shown in the figure below?



This is a fascinating tracing. P waves march out through the entire tracing (red arrows). There is some conduction. That said, there are two different QRS complexes, and the PR interval is not the same in front of all conducting beats.

Start with what you know. Focus on the middle and lower tracings (Panels B and C). Beats 1, 2, 12, 13, and 14 are all preceded by a similar-looking P wave with a constant PR interval. This tells us that these beats clearly are conducted.

There is no 12-lead ECG on this patient, which means that our assessment of QRS morphology is limited to this single right-sided MCL-1 monitoring lead. That said, the QRS complex for all beats on this tracing looks to be widened. The predominantly negative rS configuration of beats 1, 2, 12, 13, and 14 is consistent with left bundle branch block (LBBB).

Beats 3, 4, 5, 6, 7, 8, 9, 10, and 11 also appear to be conducted as the PR interval preceding these beats looks to be constant. However, QRS morphology of these beats suggests a change to right bundle branch block (RBBB) conduction. If confirmed on a 12-lead, this would mean there is alternating bundle branch block (ABBB).

There is also 2:1 AV block in some parts of this tracing. Interestingly, second-degree AV block with 2:1 AV conduction occurs in association with the QRS complexes manifesting LBBB (i.e., beats 1, 2, 12, 13, and 14). In contrast, 1:1 AV conduction occurs in association with the QRS complexes manifesting RBBB (i.e., beats 3, 4, 5, 6, 7, 8, 9, 10, and 11).

There are some additional confounding findings on this tracing. These relate to a highly unusual pattern of variation in the PR interval in which the PR interval preceding LBBB beats is different from the PR interval preceding RBBB beats. In short, we cannot explain all findings on this tracing. That said, what is apparent is that there is second-degree AV block with significant bradycardia and intermittent 2:1 AV conduction. Also, there is a pattern of ABBB, which almost always indicates severe His-Purkinje disease. A pacemaker almost certainly will be needed.

Additional information about this case can be found at: http://bit.ly/2gd1HbG.