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ABSTRACT & COMMENTARY

Mind-Body Techniques May Enhance Cognitive Fitness in Older Adults

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

SYNOPSIS: A meta-analysis regarding mind-body techniques and cognitive fitness in older adults points to enhanced cognitive performance associated with mind-body interventions in older patients, especially those without preexisting cognitive decline.

SOURCE: Zhang Y, Li C, Zou L, et al. The effects of mind-body exercise on cognitive performance in elderly: A systematic review and meta-analysis. *Int J Environ Res Public Health* 2018;15:2791.

Medical advances are eradicating disease systematically, death rates are falling globally, and life expectation is on the rise. In the United States, by 2050, about 88 million people are likely to be older than 65 years of age, more than double the 2010 record of 40.2 million.[1] With these advances, public health focus must shift to a relatively new area involving the challenge of understanding, preventing, and treating diseases linked with aging (e.g., Alzheimer's disease, hypertension, and arthritis). On the same page, understanding, preventing, and addressing what appears to be normal deterioration associated with aging is equally important in caring for the aging population. Cognitive aging may be defined as the decline in cognitive processing that occurs with aging. Impairments in reasoning, memory, and processing speed develop naturally with age, or so we think.[2] Recognizing that mind-body exercises have shown some efficacy in treating a variety of disorders, such as chronic pain, joint problems, and some mood disorders,[3,4] Zhang et al conducted a comprehensive review of studies about a relationship between (specific) mind-body exercises and cognitive performance. This comprehensive review covered both English and Chinese language literature. The authors searched for randomized trials of at least fair quality in this field involving persons older than 60 years of age with or without known cognitive disorders or deterioration. Additional criteria for inclusion in the meta-analysis were the use of one or more of these mind-body

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interventions: Tai chi, Qigong, yoga, Pilates, and at least one standardized measure of cognitive outcome.

Using these inclusion criteria, Zhang et al identified 19 eligible studies: 15 studies included one control group and the remainder included two or more such groups. Sample sizes ranged from 28 to 456, with 2,539 participants in total across the groups. Other areas of diversity across the studies included type and duration of intervention, time devoted to the intervention, and type of intervention assigned to control group. For example, 15 studies involved Tai chi, four involved yoga, two involved Qigong, and one involved Pilates. Outcome measures involved aspects of cognitive functioning, but the specific outcome measured and tool used varied between the studies. Zhang et al simplified the measures by grouping them into five main categories: global cognition, executive functioning, learning and memory, visual spatial ability, and language.

In addition to organizing data according to outcome measures, the authors analyzed two subgroups. The first looked at respondents with known minimal brain impairment (MCI) vs. non-MCI, and the second looked at total training time. Cognitive improvement was associated with mind-body exercise in all categories of outcome measures (except for language). Significant improvement in cognitive functioning was associated with increase in total training time per day in multiple spheres. Specific training times were not noted.

■ COMMENTARY

At first glance, this meta-analysis of 19 studies regarding mind-body exercise and cognitive fitness in adults 60 years of age and older appears straightforward. A deeper look reveals the complexity inherent in such a study. Zhang et al needed to account for several different mind-body techniques, widely different sample sizes, and several outcome measures. The heterogeneity led the group to temper conclusions regarding the efficacy of mind-body exercise in improving cognitive measures in the elderly and to recommend further investigation. In addition, there was a large gap in that meditation was not included as a mind-body technique. Keeping this in mind, several aspects of this work bear scrutiny and discussion and should generate excitement.

Considering the myriad consequences associated with decline in cognitive functioning and the prospect of growth in the elderly population, any reasonable intervention with an indication for improving cognitive fitness with age is well worth pursuing.

Zhang et al did not attempt to compare the specified mind-body interventions head to head nor was there an attempt to compare or contrast the impact of these mind-body interventions with other forms of exercise. Age-related vulnerability to the effect of the exercises was not explored. Several mind-body interventions, including meditation, were not investigated. Studies regarding these points and other exercise-based interventions deserve ongoing and future investigation. In addition, follow-up and longer-term studies are necessary to determine the longevity of response.

By including Chinese studies with the meta-analysis, Zhang et al added important depth to the study and set a bar for further investigations and reviews. The availability of certified providers able to teach and train specific mind-body exercises will vary according to location. Thus, casting a broad net for inclusion helps to account for geographic limitations. Financial barriers may prevent some in the elderly population from participating in mind-body exercises. If future robust studies continue to reveal significant benefit from such interventions, perhaps insurers will take notice and consider coverage.

It is interesting to think about mechanism of action. What do we know about the brain and exercise that can help explain how mind-body exercise may contribute to cognitive improvement? Perhaps one way to approach this question is to consider the elements that the mind-body exercises included in this study had in common. Among other factors, each incorporated breathing, attention, stretching of skeletal muscles (and relaxation of these muscles), and a connection between internal focus and body movement. We know these types of exercises are associated with increased hippocampal volume and possibly with frontal lobe stimulation, two brain regions involved in learning and memory and possible key areas for cognitive health.[5,6] The finding that participants with a

preexisting diagnosis of MCI showed significantly less improvement in a measure of language than those without such a diagnosis is interesting. Further investigation may increase our understanding of an underlying mechanism of action. Equally intriguing and needing further scrutiny is the absence of difference in other areas of cognitive fitness.

Our patients come in all shapes, sizes, and carry with them a true diversity of limitations and strengths. Offering mind-body exercise may be an answer to those who feel intimidated by the prospect of more conventional types of physical activity. With medical evidence in hand, a provider is on safe ground recommending these techniques as part of a comprehensive wellness plan as patients' age. Work remains in this field before definitive answers emerge. However, this study clearly provides evidence of the importance of exercise in maintaining and improving health, and specifically the role of mind-body exercise such as Tai chi, yoga, Qigong, and Pilates in addressing cognitive fitness. ■

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ABSTRACT & COMMENTARY

Early vs. Delayed Cardioversion: A Nonshocking Result

By Joshua Moss, MD

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Dr. Moss reports he is a consultant for Abbott, Boston Scientific, and Medtronic.

SYNOPSIS: For patients presenting to an ED with recent-onset atrial fibrillation, using rate control and outpatient cardioversion only as needed was associated with a high rate of spontaneous conversion within 48 hours of arrhythmia onset and noninferior short-term outcomes compared to immediate cardioversion in the ED.

SOURCE: Pluymaekers NAHA, Dudink EAMP, Luermans JGLM, et al. Early or delayed cardioversion in recent-onset atrial fibrillation. *N Engl J Med* 2019;380:1499-1508.

Symptomatic atrial fibrillation (AF) is a common reason for ED visits and referrals, both for first-time and recurrent episodes. Often, the treatment of choice is immediate pharmacologic or electrical cardioversion. Investigators sought to determine whether such early intervention is superior to a more conservative approach of outpatient observation and delayed cardioversion only as needed.

Pluymaekers et al randomized 437 adult patients from 15 hospitals in the Netherlands at the time of their ED visit to early or delayed cardioversion. Patients had to have hemodynamically stable, symptomatic AF with onset < 36 hours before, with no signs of myocardial ischemia or history of AF lasting > 48 hours. For early cardioversion, a pharmacologic approach was used initially in most patients, with electrical cardioversion as a backup. At enrollment, 40% of patients already were taking oral anticoagulant drugs; otherwise, anticoagulation was initiated before or immediately after cardioversion in patients with high stroke risk. Transesophageal echocardiography was not performed in any patients. For delayed cardioversion, patients were treated in the ED with beta-blockers, calcium channel blockers, or digoxin to achieve symptom relief and a heart rate of ≤ 110 beats per minute. Patients were discharged when stable and returned for an outpatient clinic visit as close as possible to 48 hours after onset of symptoms. If AF still was present on ECG, those patients were referred back to the ED for cardioversion.

The mean age of patients was 65 ± 11 years; 60% of patients were male. Hypertension was common, and most registered a CHA_2DS_2-VASc score of ≥ 2. The predominant symptom of AF was palpitations, although many patients also reported exercise-induced fatigue, dyspnea, and/or chest pain. About 23% of patients already were on an antiarrhythmic drug.

The median duration of the index ED visit was 158 minutes in the early cardioversion group and 120 minutes in the delayed cardioversion group. In the early cardioversion group, conversion to sinus rhythm occurred spontaneously in 16% of patients before the actual cardioversion, and 94% left the ED in sinus rhythm. In the delayed cardioversion group, conversion to sinus rhythm within 48 hours occurred spontaneously in 69% of patients; an additional 28% of patients underwent actual cardioversion.

During four weeks of follow-up, recurrence of AF documented via intermittent monitoring in a subset of patients occurred in 29% of the early cardioversion group and 30% of the delayed cardioversion group, with similar time to recurrence (median, 8 days vs. 12 days). At a four-week visit, 94% of patients in the early cardioversion group and 91% of patients in the delayed cardioversion group were in sinus rhythm, a noninferior outcome for delayed cardioversion per prespecified criteria. One patient in the early cardioversion group suffered a transient ischemic attack (TIA) within four weeks of randomization, and one patient in the delayed cardioversion group experienced an ischemic stroke. Other cardiovascular complications were uncommon and not significantly different between groups. Quality of life (QOL) scores via survey at the four-week visit also were not significantly different between groups. The authors concluded that in patients with recent onset AF, delayed cardioversion was not inferior to early cardioversion in restoring sinus rhythm at four weeks.

■ COMMENTARY

Several conclusions can be drawn from this study. First, episodes of AF starting < 36 hours before evaluation often terminate spontaneously. In this cohort, 16% of patients randomized to the early cardioversion group converted to sinus rhythm before cardioversion, and 69% of patients randomized to the delayed cardioversion group converted to sinus rhythm by 48 hours.

Second, focusing on anticoagulation as well as symptom and rate control at the time of the index ED visit (while deferring cardioversion to the outpatient setting) shortened the time spent in the ED. This obviated the need for cardioversion in more than half of patients, with no rhythm or quality of life disadvantages four weeks later.

Third, regardless of cardioversion approach, AF recurrence in this population is common — at least 30% over four weeks, undoubtedly an underestimate given the use of intermittent monitoring.

Finally, the risk of stroke or TIA, known to be higher after both active and spontaneous cardioversion from AF, is not completely eliminated even when therapeutic anticoagulation is used appropriately. One patient experienced a TIA 10 days after early electrical cardioversion despite rivaroxaban therapy, and one suffered a stroke five days after spontaneous conversion despite dabigatran therapy.

The authors noted another pragmatic difference between the two approaches: Patients in the delayed cardioversion group who went on to convert spontaneously would be classified with "paroxysmal" AF rather than "persistent" AF. This semantic distinction has no particular bearing on an individual patient's symptoms or outcome at four weeks, but it could have important consequences for how future treatment options are considered. For example, catheter ablation is a class IIa recommendation for symptomatic persistent AF refractory to at least one antiarrhythmic drug, but class I for paroxysmal AF.

It is difficult to know what psychological effect an early vs. delayed approach might have on individual patients. On one hand, discharge from the ED in AF could reassure some patients that the arrhythmia is not acutely dangerous and does not necessarily require urgent medical attention. On the other hand, symptoms that originally were mild could be exacerbated after discharge by the new diagnostic knowledge for some patients. Perhaps QOL questionnaires administered after the index ED visit may have revealed a difference that faded by four weeks. Ultimately, the study revealed no clear disadvantage of a wait-and-see approach to recent onset of AF. Whether such an approach has advantages in overall resource use or long-term outcomes remains to be seen. ■

ABSTRACT & COMMENTARY

Mechanism of Persistence of *Moraxella catarrhalis* in Patients With COPD

By Joseph F. John, Jr., MD

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

SYNOPSIS: Investigators examined the mechanism that allows *Moraxella catarrhalis* to persist in some patients with COPD.

SOURCE: Murphy TF, Brauer AL, Pettigrew MM, et al. Persistence of *Moraxella catarrhalis* in chronic obstructive pulmonary disease and regulation of Hag/MID adhesin. *J Infect Dis* 2019;219:1448-1455.

Dr. Tim Murphy in Buffalo has been working on the microbiology of symptomatic pulmonary disease for many years. Here is the latest and greatest installment from a cohort of adults with COPD studied prospectively over the past 20 years. Over the years, Murphy and colleagues have discovered that one of the major bacterial pathogens in COPD, *Moraxella catarrhalis*, has a variability of duration of colonization. What allows this organism to colonize and then persist in some COPD patients and not in others? The reason for the variability has been unknown. In this paper, Murphy et al noted that one of the major adhesins, Hag/MID (in its expression and then disappearance), explains the persistence of *M. catarrhalis*.

Between 1994 and 2014, patients with COPD were seen every month. An exacerbation caused by *M. catarrhalis* was considered to be the onset of new clinical symptoms and the acquisition of a new strain of *M. catarrhalis*. Investigators studied the genetic characteristics of the Hag/MID gene in persistent and cleared strains. Researchers also studied adherence to human epithelial cells and expression of the Hag/MID protein for the persistent and cleared strains. Earlier studies had shown that Hag/MID mediates adherence of the bacterium to respiratory epithelial cells, one of the virulence phenotypes. When Hag/MID is expressed, the bacterium shows aggregation when grown in brain heart infusion broth, a second virulence phenotype.

The major finding of the study was that most strains that expressed Hag/MID on acquisition in COPD patients ultimately lost that expression during persistence. The authors went on to study the mechanism of the loss of Hag/MID expression. In five persistent strains, the Hag/MID gene had one of two different genetic changes. One was an out-of-frame mutation; thus, the protein was not expressed. Another mode of dysregulation was caused by slipped-strand mispairing through changes in a polynucleotide repeat near the start codon in the open reading frame. The impact of the loss of Hag/MID was studied further with regard to virulence phenotypes. Loss of the protein resulted in decreased adherence to respiratory epithelial cells and loss of aggregation.

■ COMMENTARY

An adhesion molecule aids a bacterium to inhabit an abnormal respiratory tract initially, perhaps causing a frank exacerbation of bronchitis. Then, for it to persist, it loses the very adhesin that aided its initial colonization. Why does the bacterium even care to make this small genetic change that results in a radical change in protein expression (in this case, a protein that is related to virulence)? The paradox may reside mainly in the concept that pathogens in COPD do not want to kill the host. In the case of the COPD patient, the host houses an immense surface area of respiratory epithelium that offers a sanctuary if the bacterium can reside relatively peacefully. Entry is the first order for *M. catarrhalis*, but guaranteed survival in a demanding environment is paramount. Indeed, in this study, Hag/MID continued to be expressed in 28 of 30 strains that were cleared, whereas only 17 of 30 strains that were persistent continued to express the protein. The longer the persistence, the less likely it was that Hag/MID would be expressed. Hag/MID is a multifunctional autotransporter. Why would its persistence be facilitated by its absence?

Hag/MID elicits an immune response, both mucosal and systemic. Perhaps these responses select the Hag/MID-negative phenotype, allowing the organism to escape some immune control. Analogously, there are prospects for immunization with Hag/MID. Vaccines may reduce initial colonization with *M. catarrhalis*, an apparent advantage for the COPD patient. Enter the airway microbiome, the last consideration in this paper. Clearly, compared to the airway microbiome in healthy people, the airway microbiome in COPD patients contains several pathogens, including *M. catarrhalis*. Even the COPD airway has to come to some equilibrium. In that sense, the downregulation of Hag/MID serves an equilibrium of the microbiome even in the altered pulmonary airway. This work by Murphy et al shows the complexity of the bacterial pathogens' flux into

and out of the pulmonary environment. One of these pathogens, *M. catarrhalis*, is well armed to invade this environment, but once there, is happy to downregulate its virulence.

This research group may have discovered a trait of some pathogens to invade but, once established in a milieu, to use genetic mechanisms to modify its protein expression to become part of the microbial background. ■

PHARMACOLOGY UPDATE

Dupilumab Injection (Dupixent)

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 the first treatment for chronic rhinosinusitis with nasal polyposis (CRSwNP). Dupilumab is a human monoclonal IgG4 antibody that inhibits the actions of interleukin-4 (IL-4) and interleukin-13 (IL-13) by binding to the alpha subunit of the IL-4 receptor (IL-4R alpha). Previously, dupilumab was approved to treat moderate-to-severe asthma with an eosinophilic phenotype and moderate-to-severe atopic dermatitis. The FDA granted priority review and fast-track breakthrough designation. The drug is distributed as Dupixent.

INDICATIONS

Dupilumab should be prescribed as an add-on maintenance treatment for adults with inadequately controlled CRSwNP.[1] Dupilumab also can be prescribed to treat inadequately controlled moderate-to-severe asthma with eosinophilic phenotype or oral corticosteroid-dependent asthma as well as moderate-to-severe atopic dermatitis.

DOSAGE

The recommended dose for CRSwNP is 300 mg administered subcutaneously every other week.[1] Dupilumab is available in 200 mg and 300 mg prefilled syringes.

POTENTIAL ADVANTAGES

The is the first FDA-approved treatment for inadequately controlled CRSwNP.

POTENTIAL DISADVANTAGES

Adverse outcomes, compared to placebo, include injection site reactions (6% vs. 4%), conjunctivitis (2% vs. 1%), arthralgia (3% vs. 2%), and gastritis (2% vs. 1%).[1] Approximately 5% of patients taking the drug developed antibodies to dupilumab, with approximately 2% neutralizing antibodies.[1]

COMMENTS

The efficacy of dupilumab was evaluated in two randomized, double-blind, placebo-controlled studies.[1-3] The trials included subjects with CRSwNP on background intranasal corticosteroid, despite prior sinonasal surgery (63%) or treatment with systemic corticosteroid (74%) in the past two years. Those who were ineligible or intolerant to corticosteroids also were included. At the investigators' discretion, surgery or rescue corticosteroids were allowed during the studies. All subjects showed evidence of sinus opacity based on CT scans (73-90% exhibited opacification of all sinuses).

In trial 1, subjects were randomized to either dupilumab (n = 143) or placebo (n = 133) every other week for 24 weeks. In trial 2 (three arms), subjects were randomized to dupilumab every other week for 52 weeks (n = 150), dupilumab every other week for 24 weeks and then every four weeks until week 52 (n = 145), or placebo for 52 weeks (n = 153). The co-primary efficacy endpoints were mean change from baseline to week 24 in bilateral endoscopic nasal polyps score (NPS; 0-8 scale) and change in nasal congestion (NC)/obstruction score (averaged over 28 days; 0-3 scale) assessed by the subjects' daily diary. Polyps on each side of the nose were graded as such: 0 = no polys; 1 = small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2 = polyps reaching the lower border of the middle turbinate; 3 = large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate; 4 = large polyps causing complete obstruction of the inferior nasal cavity. Total NPS was the sum of both sides of the nose. NC was graded by severity category (0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms).

Dupilumab showed a significant mean difference from placebo in NPS of -2.06 (95% confidence interval [CI], -2.42 to -1.69) for trial 1 and -1.89 (95% CI, -2.10 to -1.51) for trial 2. The overall mean reduction across both studies was 32% from an overall baseline score of 5.96. NC showed a 37% mean reduction vs. placebo from an overall baseline mean of 2.40. In trial 2, improvement continued at week 52 with every-other-week dosing. However, mean NPS improvement diminished in trial 1 after discontinuation of the drug and moved toward baseline. NC improved with dupilumab as

early as week 4 and maintained at week 52. Dupilumab also improved the ability to smell and alleviated sinonasal symptoms. The drug reduced the use of systemic corticosteroids and/or the need for sinonasal surgery by 76%. The benefit seems to be consistent in patients with or without prior sinonasal surgery.[1]

CLINICAL IMPLICATIONS

Chronic rhinosinusitis is a heterogenous inflammatory condition characterized by worse sense of smell, facial pain-pressure fullness, nasal obstruction, or mucopurulent drainage.[4] It is divided into two phenotypes: with and without polyps. The condition is estimated to affect about 12% of the U.S. population.[5] CRSwNP patients tend to exhibit elevated levels of eosinophils and interleukins 4, 5, 10, and 13.[6] Atopy and asthma are common comorbidities and seem to share pathophysiology with CRS, which can result in significant healthcare costs and diminished quality of life.[4] The recommendation by the American Academy of Otolaryngology-Head and Neck Surgery Foundation for initial treatment is saline nasal irrigation and/or intranasal corticosteroids.[4] For those with persistent symptoms, medical treatment (systemic corticosteroids, anti-inflammatory antibiotics) and sinonasal surgery are options.[4,7] However, there are patients who are refractory to medical treatment and are candidates for surgery; some patients still suffer after surgery (recalcitrant).[7] Several biologics are under investigation for CRS.

Dupilumab is the first biologic treatment to be approved for CRSwNP and is effective in reducing nasal polyp size, improving symptoms (e.g., nasal congestion, loss of smell), and reducing the need for oral steroids and surgery. The cost is $3,019.50 for a four-week supply or $39,253 for a one-year supply. ■

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CME QUESTIONS

1. In a study of new-onset atrial fibrillation (AF) comparing early ED cardioversion to delayed outpatient cardioversion, most of the early group demonstrated:
a. a shorter ED stay.
b. spontaneous cardioversion.
c. sinus rhythm upon discharge.
d. recurrent AF within four weeks.

2. Once *Moraxella catarrhalis* has exacerbated COPD, what usually happens to permit its persistence?
a. It continues to cause inflammation.
b. It changes genetically.
c. It becomes resistant to antibiotics.
d. It proceeds to colonize the intestinal tract.

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

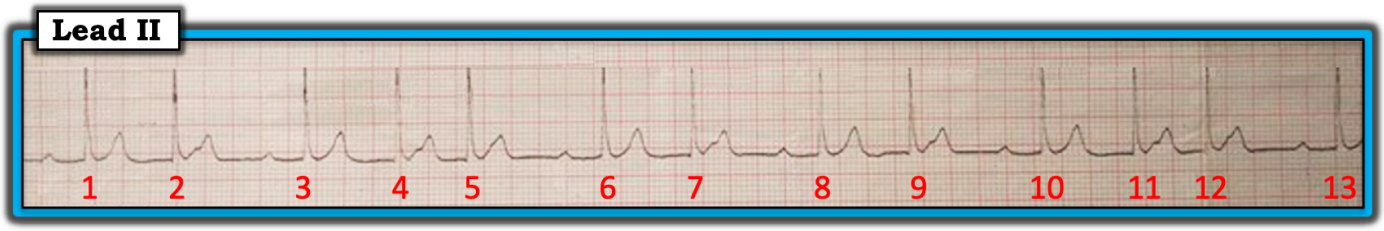
By Ken Grauer, MD

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

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

Is There Group Beating?

Unfortunately, no history is provided with the rhythm in the figure below. How should one proceed in analyzing this challenging rhythm strip?



Unless there are calipers readily available, it is unlikely one could be certain of the rhythm diagnosis. That said, what observations can one make that should greatly limit diagnostic possibilities? The rhythm in the figure is supraventricular because all QRS complexes are narrow.

First, it is important to recognize the group beating in the figure because it immediately suggests that some form of Wenckebach conduction may be present. Specifically, there are three groups of two beats each (beats 1-2, 6-7, and 8-9) and two groups of three beats each (beats 3, 4, and beats 5 and 10, 11, and 12). Further, there are five short pauses (the R-R intervals between beats 2-3, 5-6, 7-8, 9-10, and 12-13). Each pause is terminated by a sinus-conducted P wave with an identical (and slightly prolonged) PR interval. Thus, each group in this tracing begins with a sinus-conducted P wave that manifests the same PR interval

In addition to the sinus P waves that precede beats 1, 3, 6, 8, 10, and 13, there are other signs of regularly occurring atrial activity. For example, there is notching at approximately the same point in the upslope of the ST segment of beats 2, 4, 7, 9, and 11. This is not due to chance. Also, there appears to be extra peaking of the T waves of beats 1, 3, 6, 8, and 10. Even more subtly, there appears to be angulation in the upslope of the remaining two T waves (the T waves of beats 5 and 12). While impossible to rule out frequent premature atrial contractions, the regularity of the above-described deflections should suggest the possibility of an underlying regular atrial rhythm. (This could be confirmed easily if calipers were available for precise measurement.)

Still, even without calipers, a final observation should suggest second-degree AV block, Mobitz Type I (AV Wenckebach) as the most likely diagnosis. This observation is the presence of Wenckebach "periodicity." In addition to group beating and an underlying regular (or at least almost regular) atrial rhythm, progressively decreasing R-R intervals within the two three-beat groups and the finding that duration of each of the short pauses is less than twice the shortest R-R interval are highly characteristic features of AV Wenckebach.

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