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Internal Medicine

Evidence-based summaries of the latest research in internal medicine [ALERT]

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ABSTRACT & COMMENTARY

Sleep Patterns Predict Diabetes Risk

By Jeff Unger, MD, FACE

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

SYNOPSIS: This study evaluated the sleep patterns of 64,515 women from 2005-2011. Work schedules that interfered with sleep increased the risk of type 2 diabetes.

SOURCE: Vetter C, et al. Mismatch of sleep and work timing and risk of type 2 diabetes. *Diabetes Care* 2015;38:1707-1713.

Patients were queried regarding their chronotype (circadian rhythm most readily defined by sleep timing) pattern using a "morningness-eveningness" questionnaire. Thirty-five percent of women classified themselves as early chronotypes, 54% as intermediates, and 11% as late chronotypes. Overall, moving from early to late chronotypes resulted in lower levels of physical activity, higher body mass indices, and more extreme sleep durations (< 5 hours and > 9 hours). Intermediate chronotype subjects who worked rotating night shifts had a 1.5 times greater risk of developing type 2 diabetes than early chronotypes who were consistent in their shift work schedules. "Circadian misalignment" interferes with sleep-wake cycles. Interestingly, late chronotype subjects who worked day shifts experienced a significant increased risk of developing type 2 diabetes, regardless of how many night shifts they worked. Interference with circadian sleep patterns appears to increase one's risk of diabetes progression.

■ COMMENTARY

Sleep deprivation is a common condition in modern society. U.S. adults sleep on average 6.8 hours per night which, is 1.5 hours less than we did a century ago. Nearly 30% of adults report sleeping less than 6 hours nightly, leading some to suggest that we live in a sleep-deprived society. Adults require on average 6-8 hours of sleep nightly. Short-term sleep deprivation results in striking alterations in metabolic and endocrine function, including carbohydrate tolerance, insulin resistance, increased sympathetic tone, low levels of high-density lipoprotein cholesterol, elevated triglycerides, increased intravascular inflammation, higher risk of breast cancer, and obesity. Darukhanavala et al studied

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sleep pathophysiology over 13 days in 47 healthy volunteers who had a parental history of type 2 diabetes. Individuals who slept on average between 4.5 and 6 hours per night felt more daytime fatigue than those who slept 6 hours a night or longer. The short duration sleepers had more insulin resistance and higher circulating insulin levels, which allowed them to maintain normal glycemia during the study period.

This study suggests that interference with one's normal sleep pattern increases the risk of developing type 2 diabetes. Thus, a person who normally goes to bed at 2 a.m. and gets up at 10 a.m. would develop physiologic stress if he/she must arise at 6 a.m. to work a scheduled day shift. Shift and day workers may be at higher risk of developing type 2 diabetes if they rotate to the night shift at least 3 days per month over a 10-year period.

Finally, sleep deprivation does predict type 2 diabetes onset. A cohort of men from the Massachusetts Male Aging Study who did not have diabetes at baseline were followed for 7 years. Men reporting either 5-6 hours of sleep per night or more than 8 hours of sleep per night were at a two- to three-fold increased risk of developing type 2 diabetes.

High-risk individuals (those who are overweight, physically inactive, have a positive family history, are hypertensive, or have hyperlipidemia) should be informed that the consistency in their sleep and wake cycles might mitigate their progression to diabetes. ■

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ABSTRACT & COMMENTARY

The Mediterranean Diet Plus Extra Virgin Olive Oil May Improve or Maintain Cognitive Function in Mature Adults

By Joseph E. Scherger, MD, MPH

Vice President, Primary Care, Eisenhower Medical Center; Clinical Professor, Keck School of Medicine, University of Southern California

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

SYNOPSIS: A controlled trial of adults 55-80 years of age showed that intake of a Mediterranean diet plus 1 liter of extra virgin olive oil each week improved or maintained cognitive function compared with controls on a low-fat diet who showed cognitive decline.

SOURCE: Valls-Pedret C, et al. Mediterranean diet and age-related cognitive decline: A randomized clinical trial. *JAMA Intern Med* 2015;175:1094-1103.

This is a post-hoc analysis of a study in Barcelona, Spain, examining antioxidant supplementation in a population of men 55-80 years of age and women 60-80 years of age followed between 2003 and 2009. The authors randomly assigned 447 cognitively healthy volunteers, roughly half men and women, to three groups: a Mediterranean diet plus 1 liter of extra virgin olive oil per week,

a Mediterranean diet plus 30 g/week of mixed nuts (walnuts, hazelnuts, and almonds), and a low-fat diet as the control group. All of the volunteers were at high risk for cardiovascular disease, with 55% presenting with type 2 diabetes and the rest presenting with at least three of the following five risk factors: hypertension, dyslipidemia, overweight, obesity, and a family history of early onset coronary heart disease. None had active cardiovascular disease at the time of the trial.

An experienced neuropsychologist performed a battery of cognitive tests at the beginning of the study and again approximately 4 years later. The dropout rate was similar for all three groups, and 340 volunteers completed the two cognitive screenings.

The 127 volunteers who were on the Mediterranean diet plus extra virgin olive oil showed slight improvement in the cognitive tests, the 112 volunteers on the Mediterranean diet plus nuts showed no significant change, and the 97 on a low-fat diet showed some decline in their cognitive tests.

The authors concluded that in an older population, a Mediterranean diet supplemented with olive oil or nuts is associated with improved cognitive function compared with controls on a low-fat diet.

■ COMMENTARY

This study is small and inconclusive but does suggest two important things. First, eating healthy may preserve cognitive function. The authors did not clearly define the Mediterranean diet but we must assume it is rich in healthy vegetables, fruit, and seafood. What is not clear is the role of pasta. The amount of olive oil consumed in one group may not be practical, and it is not clear how much olive oil and nuts were part of the Mediterranean diet in either group.

The second suggestion is that low fat consumption may be associated with cognitive decline. David Perlmutter, in his well-referenced books *Grain Brain* and *Brain Maker*, underscores the importance of healthy fats in brain health. Our brain is made up of lots of cholesterol, so encourage patients to eat egg yolks.

There is much more work to be done to clarify the role of diet in improving cognitive function. The gut-brain axis is being scientifically illuminated in a way that requires medical professionals to start taking nutrition much more seriously.[2,3] What is clear is that the low-fat diet recommendations of the 1970s, 1980s, and 1990s are obsolete. The Mediterranean diet appears to be one of the best candidates for a nutrition recommendation. ■

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ABSTRACT & COMMENTARY

Botulinum Toxin and Treatment of Spasticity

By Joseph E. Safdieh, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: AbobotulinumtoxinA is effective at reducing spasticity and reducing disability in patients with upper limb spasticity due to stroke or traumatic brain injury.

SOURCE: Gracies JM, et al. Safety and efficacy of abobotulinumtoxinA for hemiparesis in adults with upper limb spasticity after stroke or traumatic brain injury: A double-blind randomized controlled trial. *Lancet Neurol* 2015;14:992-1001.

Assessment of tone is an important part of the neurologic examination. Causes of increased tone include spasticity, rigidity, and paratonia. Spasticity is a common neurologic consequence of upper motor neuron damage, and can occur in the setting of stroke, traumatic brain or spinal cord injury, multiple sclerosis, and other central nervous system conditions. For many patients, spasticity can be quite disabling and may impair functional status more than weakness. Additionally, the care of the patient with spasticity may be difficult due to fixed flexion of upper limb muscles. Upper limb spasticity may impair basic daily activities such as feeding and toileting. Botulinum toxin is an approved therapy for reduction of upper limb spasticity.

These authors report the results of a randomized, controlled trial assessing the effectiveness of

abobotulinumtoxinA 500 units, abobotulinumtoxinA 1000 units, or placebo at reducing muscle tone in patients with upper limb spasticity. The primary endpoint was change in muscle tone using the Modified Ashworth Scale. Secondary endpoints included a Physician Global Assessment score and perceived function using the Disability Assessment Scale in dressing, hygiene, limb position, and pain. Injections were performed into a number of muscles including most hypertonic of the primary target muscle group (flexors of the elbow, wrist, or fingers).

Eighty-one patients were randomized to each of the three groups: 500 units, 1000 units, and placebo. Outcome measures were recorded at weeks 1, 4, 12, 16, and 20 after treatment. Reduction in Modified Ashworth Score was 0.3 in the placebo group, 1.2 in the 500 unit group, and 1.4 in the 1000 unit group at 4 weeks. Of note, benefits were seen as early as 1 week and persisted even at 16-20 weeks. The Physician Global Assessment score was also improved in the treatment group in a dose-dependent manner as compared to placebo. Disability Assessment Scale scores were better in the treatment group (no difference between low and high dose) compared to placebo. There were two deaths (one in the placebo group) that were not related to treatment effect. The most common adverse events in the treatment groups included muscle weakness and fatigue.

■ COMMENTARY

This study adds to the literature on the use of botulinum toxins in treating upper limb spasticity after stroke or traumatic brain injury. It demonstrates some interesting findings, including evidence of a benefit even 1 week after treatment as well as a sustained benefit from a single treatment even after 12 weeks. This is important to note because if treatment can be spaced out further than every 3 months, there would be less burden on patients and caregivers to return for frequent follow-up treatment visits. Additionally, the study demonstrated not only reduction in passive tone but also improvement in active range of motion of the affected limb. This potentially could lead to significant improvement in the quality of life of the patient and caregivers, as patients can use the affected limb in a more useful way. ■

BRIEF REPORT

Delay in Performing Endovascular Reperfusion Results in Worse Disability Outcomes

By Matthew E. Fink, MD

Louis and Gertrude Feil Professor in Clinical Neurology and Chairman, Department of Neurology, Weill Cornell Medical College; Neurologist-in-Chief, New York Presbyterian Hospital

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

SOURCE: Sheth SA, et al. Time to endovascular reperfusion and degree of disability in acute stroke. *Ann Neurol* 2015;78:584-593.

In the past year, multiple clinical trials have reported that intra-arterial endovascular reperfusion with mechanical clot extraction, using the SOLITAIRE stent retriever device and others, results in better neurological outcomes than treating patients with intravenous thrombolysis alone with TPA. There is still uncertainty regarding the maximum time window, and how important early intervention is as related to neurological recovery and long-term outcomes. The investigators used the combined databases of the SWIFT (*Lancet* 2012) and STAR (*Stroke* 2013) trials to identify patients treated with the SOLITAIRE device who achieved substantial reperfusion. They then ranked the 90-day modified Rankin scale outcomes for "time of onset to recanalization" (OTR) time intervals ranging from 180 min to 480 min.

Analysis of these data showed substantial time-related reductions in disability for the entire range of outcomes. A shorter OTR time was associated with an improved 90-day Rankin Scale outcome in all groups. The mean Rankin scores were 1.4 for the 120-240 min OTR group, 2.40 for the 241-360 min group, and 3.3 for the 361-660 min group ($P < 0.001$). There were no significant differences between the groups in the incidence of intracerebral hemorrhage, mortality, or length of hospitalization. The predicted probability and confidence interval of good neurological outcome (mRS 0-2) at 90 days was a continuous variable inversely related to the time from symptom onset to

recanalization. For every 15-min acceleration in the time to reperfusion, 34 per 1000 patients treated will have improved disability outcomes, which translates to 1 out of 100 patients improved, for every 5 minutes of reduced OTR time. ■

PHARMACOLOGY UPDATE

Daclatasvir Tablets (Daklinza)

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

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

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

The FDA has approved the first drug for the treatment of hepatitis C (HCV) genotype 3 infection that does not require the co-administration of interferon or ribavirin. Daclatasvir is a nonstructural 5A (NS5A) protein inhibitor that is marketed by Bristol-Myers Squibb as Daklinza.

INDICATIONS

Daclatasvir is indicated for use in combination with sofosbuvir for the treatment of chronic HCV genotype 3 infection.[1]

DOSAGE

The recommended dose is 60 mg once daily in combination with sofosbuvir (400 mg) with or without food.[1] The duration of treatment is 12 weeks. Daclatasvir is available as 30 mg and 60 mg tablets.

POTENTIAL ADVANTAGES

Daclatasvir plus sofosbuvir is the first interferon and ribavirin-free regimen for the treatment of HCV genotype 3.

POTENTIAL DISADVANTAGES

Daclatasvir is a substrate of CYP3A isoenzymes, and the plasma levels/therapeutic effect may be affected by strong CYP3A inhibitors, as well as moderate and strong inducers.[1] Strong inducers are contraindicated. Serious symptomatic bradycardia has been reported with the concomitant administration of sofosbuvir and amiodarone.[1]

COMMENTS

The safety and efficacy of daclatasvir were evaluated in one Phase 3, open-label, 12-week clinical trial involving 152 subjects with compensated liver disease.[1,2] The majority of these were treatment-naïve (n = 101) and the remainder were treatment-experienced (n = 51). Most treatment-experienced subjects failed with prior peginterferon/ribavirin regimens and a few were treated with sofosbuvir and ribavirin. Those with previous exposure to NS5A inhibitors were excluded. Subjects were mainly males (59%), white (90%), and many (76%) had a viral load ≥ 800,000 IU/mL. One-quarter of subjects had cirrhosis. Subjects received daclatasvir/sofosbuvir (60 mg/400 mg) for 12 weeks. Sustained viral response was defined as HCV RNA below 25 IU/mL (SVR12). Overall, treatment response was 89% (96% of those without cirrhosis and 63% in those with cirrhosis). Response in treatment-naïve subjects was numerically slightly higher, 90% vs 86%. Of the subjects without SVR12, 94% were the result of post-treatment relapse."[3] Sixty-nine percent of these subject had cirrhosis at baseline. Other potential factors contributing to relapse were very high baseline viral load and NS5A-Y93H RAV mutation. Most frequently reported adverse events were headache (14%), fatigue (14%), and nausea (12%).

CLINICAL IMPLICATIONS

Genotype 3 is a less common HCV genotype in the United States but is the most difficult genotype to treat with available direct acting agents.[3] Current treatment is sofosbuvir with weight-based ribavirin plus weekly peginterferon for 12 weeks. For patients in whom interferon is not an option, previously available treatment was sofosbuvir and weight-based ribavirin for 24 weeks. Daclatasvir, when used in combination with sofosbuvir, provides an effective treatment for HCV genotype 3 infections, particularly in noncirrhotic patients. The drug is significantly less effective in patients with cirrhosis. An open-label, randomized study of daclatasvir, sofosbuvir, and ribavirin for 12 vs 16 weeks in treatment-naïve and treatment-experienced patients with genotype 3 subjects with compensated advanced fibrosis/cirrhosis (F3/F4) is scheduled for completion in December 2015.[4] The cost for the combination is $49,000 for 4 weeks. ■

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Clinical Briefs

By Louis Kuritzky, MD

Fixing Intractable Pruritus: Azathioprine

SOURCE: Maley A, Swerlick RA. *J Am Acad Dermatol* 2015;73:439-443.

When we can identify and remove the source of pruritus, we would like to do so. Unfortunately, sometimes the cause cannot be identified, as in recurrent urticaria, for which an inciting agent remains unconfirmed as often as half of the time. Additionally, there are times when a necessary or preferred treatment must be continued despite pruritus, as is sometimes the case with opioid analgesics. While traditional antihistamines often effectively relieve pruritus, the tricyclic antidepressant doxepin is actually many times more potent than other antihistamines and also effectively treats pruritus. However, since it is highly sedating at doses effective for pruritus, it generally is not used as a first line-treatment. Although systemic steroids are often effective, their side effect profile limits chronic use.

Based on the theory that pruritus may be an immunologically mediated phenomenon — corroborated by the frequency of pruritus relief through systemic steroid administration — Maley and Swerlick administered azathioprine to patients (n = 96) with intractable pruritus. Azathioprine inhibits T-cell and B-cell proliferation, leading to its role in prevention of organ transplantation rejection. Each of these patients had suffered long-term pruritus (mean = 53 months), and the mean pruritus score was 9.25 on a 10 point scale. Azathioprine was found to be highly effective: The post-treatment pruritus score came down from 9.25/10 to 1.63/10. Advantages of azathioprine include that it is once daily, inexpensive, and drug levels can be monitored. Disadvantages include consequences of immune suppression, including malignancy. While probably not a treatment to be commonly employed in the primary care setting, this retrospective study supports consideration of azathioprine when other efficacious treatments have been exhausted. ■

Dextromethorphan-Quinidine Combo for Alzheimer's Patients with Agitation

SOURCE: Cummings J, et al. *JAMA* 2015;314:1242-1254.

First-line management of agitation in persons with dementia is supposed to be non-pharmacologic. When this is insufficient to adequately manage agitation, atypical antipsychotics have been often used, but the recognition that such agents are associated with increased mortality has dampened enthusiasm for their use. A trial of citalopram was promising, but the adverse effect of potential QT prolongation remains a concern. The idea to use a combination of dextromethorphan and quinidine for agitation stems from the approval of this same combination for treatment of pseudobulbar affect. Pseudobulbar affect, which is sometimes colloquially called "emotional hyperlability syndrome," is typified by outbursts of exaggerated or inappropriate positive (e.g., laughing) or negative (e.g., crying) emotions. A patient might burst into uncontrolled sobbing because he or she discovered his or her shirt was not buttoned properly. Since agitation syndromes are also emotion-laden, might the combination of dextromethorphan and quinidine work here?

Cummings et al randomized patients assessed to have probable Alzheimer's disease and a history of agitation to the combination of quinidine and dextromethorphan or placebo for 10 weeks. Aggression scores were substantially improved compared to placebo. Adverse events leading to discontinuation were infrequent (5.3% on the quinidine-dextromethorphan combination, 3.1% on placebo). The combination of dextromethorphan and quinidine appears promising for management of aggression in Alzheimer's patients. ■

Between-arm Differences in BP Predict Peripheral Arterial Disease

SOURCE: Singh S, et al. *J Am Soc Hypertens* 2015;9:640-650.

Although there is little evidence to support this practice, it has been suggested that when there is a measureable difference in blood pressure (BP) between arms, the arm with the higher BP should be considered the reference or actual BP. A number of different authors have pointed to a relationship between interarm BP discrepancy and adverse cardiovascular events, but the methods with which BP was obtained in many studies call into question whether any such relationship is valid. Specifically, it has been demonstrated that when BP is obtained simultaneously in both arms, the results often differ from BP obtained sequentially in both arms, with the former being more accurate. Unfortunately, much of the literature on inter-arm BP difference has been generated using sequential arm BP measurement.

Singh et al reviewed data from trials that only examined studies performed with simultaneous inter-arm BP measurement. They determined that an inter-arm systolic BP difference of as little as 10 mmHg was associated with a doubling of the risk for peripheral arterial disease. Although a trend for increased mortality and cardiovascular disease was noted when inter-arm systolic BP difference was > 10 mmHg, the results were not statistically significant. ■

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CME QUESTIONS

1. **Which individual is at highest risk for developing type 2 diabetes?**
   a. A 32-year-old female. Her bedtime is 10 p.m. She awakens at 6 a.m. daily. She works from 7-3 p.m. She is overweight.
   b. A 44-year-old female. Her bedtime is 2 a.m. She awakens between 9 and 10 a.m. She prefers to work the night shift. She works the day shift (7 a.m.-3 p.m.) seven times a month.
   c. A 40-year-old mother of three. Her bedtime is 10 p.m. She awakens at 6 a.m. She works 3 p.m.-10 p.m. 5 days a week. No shift work.
   d. A 55-year-old female. She is not overweight, exercising 3-5 days weekly. Her bedtime midnight. She awakens at 7 a.m. Work begins at 9 a.m. 5 days per week. Occasional overtime requires her to work 12-hour shifts.
2. **Which diet showed the highest amount of preservation of cognitive function?**
   a. Mediterranean diet plus 1 liter of extra virgin olive oil/week
   b. Mediterranean diet plus extra tree nuts
   c. Low-fat diet
   d. Both a and b
3. **Botulinum toxins are effective and approved for use in treating spasticity associated with all of the following conditions *except*:**
   a. stroke.
   b. traumatic brain injury.
   c. cerebral palsy.
   d. multiple sclerosis.

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]

Antibiotic Use and Diabetes

Eat Right, Preserve Your Memory, and Stay Happy

Procalcitonin in Differentiating Bacterial from Viral Meningitis

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.

A Middle-aged Man with Palpitations

The lead II rhythm strip in the figure below was obtained from a middle-aged man with new-onset palpitations. He is hemodynamically stable.

- What is this rhythm most likely to be?
- What might be done diagnostically to confirm your suspicion?

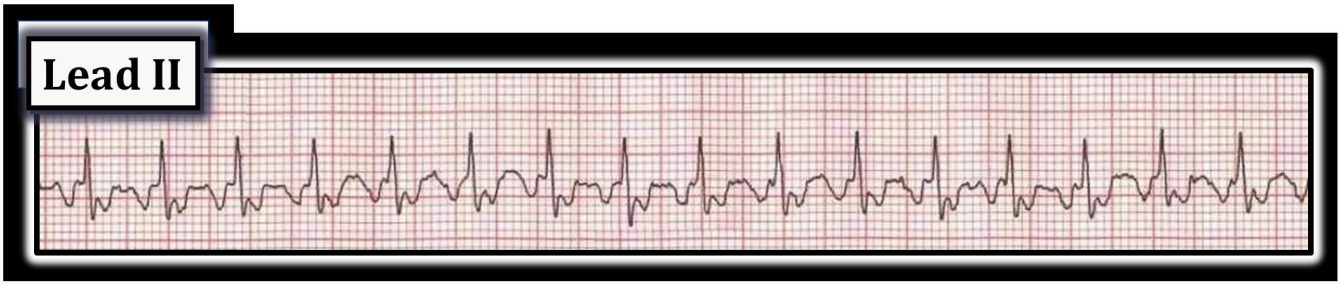

Figure: Lead II rhythm strip from a middle-aged man with palpitations.

Interpretation: Since the patient is hemodynamically stable, there is time to systematically assess the rhythm. We favor use of the, "Ps, Qs, 3R" approach to remind of us of the five key parameters to assess. It does not matter in what sequence we address these parameters. What counts is that we include in our approach a search for *P* waves (presence of atrial activity), QRS width, and the 3 Rs (rate of the rhythm, regularity, and if atrial activity is present — whether such atrial activity is related to neighboring QRS complexes).

Normal sinus *P* waves are not present because there is no upright *P* wave in lead II. However, atrial activity does appear to be present, as we see one (if not two) negative deflections within each R-R interval. One of these negative deflections occurs just before the QRS complex. The other appears just after the QRS within the middle of the ST segment. If these negative deflections do represent atrial activity, then there is a consistent relationship between each QRS complex and the negative deflection that precedes it.

The QRS complex looks to be narrow. That said, it is impossible to be certain of this from inspection of this single monitoring lead. A 12-lead ECG obtained during tachycardia confirmed that the QRS complex was indeed narrow and that the first negative deflection in each R-R interval was not part of the QRS complex). The ventricular rhythm is regular. Each R-R interval is just over two large boxes in duration, so the ventricular rate is just over 150/min.

Impression: Putting together the above findings, we have described a regular supraventricular tachycardia (SVT). The three most common causes of a regular SVT rhythm are: 1) sinus tachycardia (in which sinus *P* waves sometimes may be hiding within the previous ST segment), 2) paroxysmal supraventricular tachycardia (PSVT), and 3) atrial flutter.

We have already ruled out sinus tachycardia because there are no upright *P* waves in lead II. We suspect this rhythm is atrial flutter because: 1) Atrial flutter is by far the most commonly overlooked SVT rhythm, since flutter waves are often not overly evident when the ventricular rate is fast, 2) The ventricular rate is very close to 150/min, which is consistent with the most common ventricular rate for untreated atrial flutter, and 3) The negative deflections we describe above are perfectly spaced at a rate of approximately 300/min (precisely twice the ventricular rate.

Application of a vagal maneuver temporarily reduced the ventricular response. This allowed diagnostic atrial activity at a regular rate of 300/min to be seen. The only rhythm that does this is atrial flutter.

NOTE: For a complete illustrated discussion of this tracing, fast forward to the 1:22 point in my ECG Video #12 at the following link: ***https://youtu.be/PnHIzDh4BZ8?t=1m22s*** (The case is reviewed over the next 11 minutes). ■