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Internal Medicine

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ABSTRACT & COMMENTARY

Improve Diet to Put Out the GERD Fire

By Joseph E. Scherger, MD, MPH

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SYNOPSIS: The authors estimated nearly 40% of gastroesophageal reflux disease symptoms that occur at least weekly can be prevented through a modification of lifestyle factors.

SOURCE: Mehta RS, Nguyen LH, Ma W, et al. Association of diet and lifestyle with the risk of gastroesophageal reflux disease symptoms in US women. *JAMA Intern Med* 2021; Jan 4;e207238. doi: 10.1001/jamainternmed.2020.7238. [Online ahead of print].

Mehta et al searched the Nurses' Health Study II from 2005 to 2017 for five lifestyle factors and the presence of gastroesophageal reflux disease (GERD). The study cohort was 42,955 women age 42 to 62 years. The five factors making up the anti-reflux lifestyle score were: normal body weight; never smoking; moderate to vigorous physical activity for 30 minutes daily; no more than two cups of coffee, tea, or soda daily; and a "prudent" diet.[1] Each factor was independently associated with GERD symptoms, and the risk increased when the factors were combined.

The authors concluded an anti-reflux lifestyle, even among regular users of proton pump inhibitors (PPIs) and histamine receptor antagonists (H2RAs), was associated with fewer GERD symptoms. They estimated nearly 40% of GERD symptoms that occur at least weekly can be prevented through a modification of lifestyle factors.

■ COMMENTARY

Gastric acid serves a purpose — to increase the safety of food humans ingest. Excess gastric acid often causes heartburn in the esophagus, known as acid reflux or GERD. Mechanisms for this include increases in gastroesophageal pressure gradients and mechanical factors such as hiatal hernia. More recently, the role of the gut microbiome and small intestinal bacterial overgrowth (SIBO) have been explored as contributing to GERD.[2,3]

Mehta et al observed that those who engaged in healthy habits (e.g., not smoking, engaging in regular exercise) were less likely to experience GERD. Newer

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recognized dietary risk factors leading to dysbiosis (imbalance of gut bacteria) and SIBO may cause GERD. These include eating inflammatory foods such as grains (except rice), cow's milk, processed vegetable oils, and trans fats.[4] Some patients might experience GERD after eating vegetables that are high in lectins.[5] In my practice, I prescribe an anti-inflammatory diet to help reduce the likelihood of GERD and wean patients off PPIs and H2RAs. ■

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ABSTRACT & COMMENTARY

Air Pollution and Cognitive Decline

By Soroush Nomigolzar, MD, and Nancy Selfridge, MD

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SYNOPSIS: In this large prospective cohort study of subjects in Manhattan, researchers demonstrated an association between exposure to air pollution and decline in cognitive function over time in one cohort, but not the other.

SOURCE: Kulick ER, Wellenius GA, Boehme AK, et al. Long-term exposure to air pollution and trajectories of cognitive decline among older adults. *Neurology* 2020;94:e1782-1792.

Air pollutants are potent oxidants that can lead to oxidative stress and inflammation.[1] Thus, ambient air pollution has been associated with various cardiovascular and respiratory diseases.[2-3] Recently, there has been a growing interest in a potential link between air pollution and neurological damage, especially in the elderly, for whom cognitive decline is a major morbidity.[4] Despite evidence of a pathological central nervous system vascular inflammatory effect of air pollution from animal experiments and human autopsy studies, cohort study results relating longitudinal exposure to air pollution and cognitive decline have been mixed.[5-9]

Kulick et al used data from two prospective cohorts of individuals residing in the northern Manhattan area of New York City to investigate the association between long-term exposure to ambient air pollution and cognitive decline, both cross-sectionally and longitudinally. The data collection was obtained from two ongoing prospective cohort studies of residents in northern Manhattan: the Washington Heights-Inwood Community Aging Project (WHICAP) and the Northern Manhattan Study (NOMAS). WHICAP is a study of aging and dementia. The creators recruited participants in 1992, 1999, and 2010. WHICAP administrators used these inclusion criteria: equal proportion of Hispanic, non-Hispanic Black, and non-Hispanic White participants; and equal proportion of participants age 65-74 years and > 75 years.

Subjects with substantial cognitive problems, history of dementia, or who could not speak English or Spanish were excluded. Additional participants were selected from the NOMAS project, established to study stroke risk factors prospectively in multiethnic individuals living in the same community. Participants were recruited between 1993 and 2001 and 2003 and

2008. A subcohort of NOMAS recruits received neuropsychological assessment as a baseline between 2003 and 2008. Inclusion criteria for this group were: age > 50 years, no clinical stroke or clinically identified dementia, and no contraindications to MRI. All individuals from this cohort attended at least one follow-up neuropsychological assessment after five years. The final sample selected by Kulick et al for data analysis (n = 5,330 from WHICAP; n = 1,093 from NOMAS) included those subjects with no baseline dementia, at least one neuropsychological exam during the study, whose primary address was in New York City, and no missing data for the confounding variables.

Satellite and Environmental Protection Agency data for nitrogen dioxide (NO_2), fine particulate matter ($PM_{2.5}$), and respirable particulate matter (PM_{10}) were used in validated, regionalized, universal geostatistical kriging models to estimate the residential air pollution exposure in the calendar year prior to enrollment. Cognitive function, represented by a global cognitive score, was calculated using validated neuropsychological tests assessing three domains of cognitive function (memory, executive function, language) and standardized as *Z*-scores with cohort-specific means and standard deviations. Sociodemographic data for analysis included age at time of cognitive testing, race-ethnicity, and educational level. A summary *Z*-score for socioeconomic status was calculated for each subject based on census information of neighborhood measures of wealth, education, and occupation.

Data from the WHICAP and NOMAS cohorts were analyzed separately. Linear mixed models were used for repeated measures assessing the relationship between exposure to air pollutants and both baseline cognitive function and cognitive decline. The analyses suggest that in the WHICAP cohort, higher levels of ambient air pollution were associated with cognitive decline at baseline as well as a higher rate of cognitive decline over time. However, in NOMAS, there was no significant association between residential ambient air pollution and baseline cognitive decline or rate of decline in cognitive function.

■ COMMENTARY

The populations in WHICAP and NOMAS were similar in most aspects, except the NOMAS cohort was younger, with a median age of 70 years (±9.0) compared to WHICAP's 75.2 years (±6.46), had a lower prevalence of cardiovascular disease, and included a higher percentage of Hispanic individuals (43% in WHICAP, 66% in NOMAS). The mean levels of air pollutants also were similar between the two groups, but there was less variability in pollutant levels in NOMAS. The authors cited these differences between WHICAP and NOMAS as possible explanations for the differences in observed outcomes between the two cohorts. The younger NOMAS cohort could explain the better baseline cognition as well as less decline in cognition upon follow-up for this group. Moreover, individuals in the WHICAP cohort had more cardiovascular diseases, which may have contributed to greater decline in cognition.

Interestingly, the higher percentage of Hispanic individuals in the NOMAS cohort suggests a potential underlying protective factor in Hispanic populations, possibly as the result of genetics or lifestyle factors, such as nutrition, exercise, and alcohol use. Another factor that might have influenced outcomes is that WHICAP was a significantly larger cohort, which increases the power of the data analysis compared to NOMAS. Finally, the NOMAS data excluded individuals with pre-existing dementia and history of stroke or cardiac events, creating a potential selection bias.

Even though there were some limitations, and findings were not consistent between the two cohorts, the results of WHICAP add to the evidence base linking higher levels of ambient air pollution with accelerated cognitive decline. Further studies on this topic will help solidify the association between ambient air pollution and cognitive decline. In the meantime, the findings can help physicians become more sensitive to the possibility of accelerated cognitive decline in their patients and maintain vigilance for early symptoms and signs. Although many patients may not be able to move away from high pollution, awareness of this modifiable risk

factor can help physicians focus on preventive measures, such as increasing indoor air quality with air purifiers and patient education concerning home cleaning and regular air filter changes. Finally, physicians who are so inclined may use these data to support ongoing public and political advocacy for clean air. ■

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ABSTRACT & COMMENTARY

Does MRSA Nares Colonization Predict Non-Respiratory MRSA Infections?

By Ralph Tayyar, MD

Infectious Disease Fellow, Stanford University

SYNOPSIS: Nares screening for methicillin-resistant *Staphylococcus aureus* (MRSA) carried a high negative predictive value to rule out MRSA infections at various sites.

SOURCE: Mergenhagen KA, Starr KE, Wattengel BA, et al. Determining the utility of methicillin-resistant *Staphylococcus aureus* nares screening in antimicrobial stewardship. *Clin Infect Dis* 2020;71:1142-1148.

Methicillin-resistant *Staphylococcus aureus* (MRSA) nares screening has been a crucial test in antimicrobial stewardship. It has become essential in deciding on de-escalating anti-MRSA coverage in respiratory infections.

Mergenhagen et al studied the significance of MRSA nares testing in ruling out subsequent MRSA infections at various sites. They retrospectively collected data from patients who were screened for MRSA nares colonization between January 2007 and January 2018 across Veterans Administration (VA) medical centers nationwide.

The authors collected 561,325 clinical cultures within seven days of nares swabs from 245,833 unique patients. Out of the MRSA nares screened, 73.7% were performed via PCR and 26.3% were performed via standard culture techniques. MRSA nares screening was positive in 22.9% of the total screened samples, and MRSA was identified in 8.3% of the various clinical cultures.

Researchers classified clinical cultures per source as follows: blood, intra-abdominal, pulmonary, renal, wound, and miscellaneous. For the whole cohort, the negative predictive value (NPV) for isolating MRSA in clinical cultures was 96.9% for MRSA nares screened by PCR and 95.5% for MRSA nares screened by culture. The NPV was lowest in graft cultures at 89.6% and highest in renal system cultures at 99.1%. However, MRSA colonization carried a positive predictive value (PPV) as low as 7.6% in predicting MRSA isolation from renal cultures.

■ COMMENTARY

Mergenhagen et al concluded a negative MRSA nares screen is a helpful tool in ruling out MRSA infection in various clinical cultures. One could argue clinicians might feel less comfortable discontinuing empiric MRSA coverage with NPV lower than 99%.

However, the large number of samples studied would give antimicrobial stewardship programs additional arguments for de-escalating empiric MRSA-targeted therapy when appropriate. The study results should be tailored to individualized cases, and the decision regarding screening nares for MRSA should be based on the clinical likelihood of MRSA infections at the different sites and the risk factors of the screened

patient. Moreover, there was low PPV to the various culture sites and, hence, a positive MRSA nares colonization was not thought to predict the isolation of MRSA. Several other research groups have studied the correlation between MRSA nares testing and non-respiratory infections. In a retrospective, single-centered cohort in Colorado, a group of investigators found a 19.89 odds of developing MRSA bacteremia in MRSA nares-colonized patients compared to non-colonizers.[1] ■

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ABSTRACT & COMMENTARY

Prophylactic PCI for Vulnerable Plaques

By Jeffrey Zimmet, MD, PhD

Associate Professor of Medicine, University of California, San Francisco; Director, Cardiac Catheterization Laboratory, San Francisco VA Medical Center

SYNOPSIS: In this proof-of-concept trial, treatment of non-flow limiting vulnerable plaque by PCI with bioabsorbable stents resulted in no significant difference in lesion-related events compared with optimal medical therapy.

SOURCE: Stone GW, Maehara A, Ali ZA, et al. Percutaneous coronary intervention for vulnerable coronary atherosclerotic plaque. *J Am Coll Cardiol* 2020; Sep 22;S0735-1097(20)37240-5. doi: 10.1016/j.jacc.2020.09.547. [Online ahead of print].

Plaque rupture events leading to myocardial infarction (MI) do not necessarily occur in areas with significant stenosis and flow limitation. Instead, the theory goes, areas of significant plaque burden containing a necrotic lipid core and covered with a thin cap of tissue represent "vulnerable" plaques that lead to acute coronary syndromes. The study of vulnerable plaque has been hampered by the dual problems of how to identify them and what to do about them once identified. First, intravascular imaging with a combination of intravascular ultrasound (IVUS) and near infrared spectroscopy (NIRS) has demonstrated a track record of recognizing and categorizing such plaque, with the obvious caveat that it requires an invasive procedure to do so. Indeed, the 2019 Lipid Rich Plaque study showed this technology can help identify both patients and plaques that are at significantly elevated risk for subsequent events.[1]

The PROSPECT ABSORB trial was designed to examine the results of treating such vulnerable plaques by stenting, specifically with the Absorb bioresorbable vascular scaffold (BVS). To this end, patients who presented with MI and had undergone successful percutaneous coronary intervention (PCI) of all ischemic lesions underwent imaging with a combined NIRS-IVUS catheter (Infraredx, Bedford, MA). Those who met a prespecified threshold for vulnerable plaque in angiographically non-obstructive lesions were eligible for participation. The authors examined 902 patients with MI, leading to the identification of 182 patients at 15 sites who were randomized to treatment with Absorb BVS or to medical therapy alone. Of 93 patients randomized to treatment with the Absorb, 92 underwent successful BVS implantation. One patient was found to have a vessel larger than the Absorb allows and was treated with a metallic drug-eluting stent. All patients were treated with guideline-directed medical therapy, including dual antiplatelet therapy, for six to 12 months and high-intensity statins. Overall adherence rates were high.

All but one patient had clinical follow-up available at 24 months, and 167 underwent follow-up angiography and IVUS at a median of 25 months. Unsurprisingly, minimum lumen area measured by IVUS was significantly wider in patients treated with the scaffold compared with those treated with medical therapy alone (6.9 ± 2.6 mm^2 in BVS-treated lesions compared to 3.0 ± 1.0 mm^2 in medical therapy alone-treated lesions). Binary restenosis, defined as diameter stenosis > 50% within the scaffolded segment, was present at follow-up in four of 86 BVS-treated lesions. Stenoses > 50% were seen in 12 of 80 lesions in the medical therapy arm ($P = 0.02$). Regarding clinical outcomes, the primary safety outcome of target lesion failure was not different between the two groups (4.3% vs. 4.5%). A nonsignificant trend was seen toward fewer "lesion-related MACE" in the BVS-treated arm (4.3% vs. 10.7%; OR, 0.38; 95% CI, 0.11-1.28; $P = 0.12$). The absolute difference here was caused primarily by fewer episodes of angina-driven revascularization, not by MI. The authors concluded interventional treatment of non-flow-limiting lesions with high plaque burden was safe and resulted in larger lumen size at follow-up. They argued this justifies a larger randomized trial powered to detect clinical outcomes.

■ COMMENTARY

Can stenting of non-obstructive coronary lesions, identified by intravascular imaging as vulnerable plaques,

prevent downstream events such as MI? Or, alternatively, does the risk of the stenting procedure itself, or that of restenosis, outweigh the potential benefits of mechanical stabilization? How reliable is the combination of IVUS and NIRS at identifying troublesome lesions? From a scientific standpoint, these are interesting questions. For the most part, answers remain elusive.

To these points, this trial provided some valuable insight. Among patients who had recently suffered an MI, identification of nonobstructive vulnerable plaque by the study definition was made in only one in five patients. The primary safety endpoint, target-lesion failure at two years, occurred in fewer than 5% of patients, regardless of treatment assignment. Although the more inclusive endpoint of lesion-related MACE appeared to show a trend favoring the scaffold group, even this trend was driven primarily by angina requiring revascularization, not by MI or cardiac death. Even if this trend were borne out to be statistically significant in a larger trial, the benefit would be of treating the lesion now rather than treating it later, at a cost of unnecessarily scaffolding many more vessels. A larger trial is, by all accounts, in the works. For now, identification and interventional treatment of vulnerable plaque remains a goal. ■

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PHARMACOLOGY UPDATE

Relugolix Tablets (Orgovyx)

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.

The FDA approved the first oral, nonpeptide, gonadotropin-releasing hormone (GnRH), also known as luteinizing hormone release hormone (LHRH), antagonist to treat advanced prostate cancer. Relugolix is a small molecule antagonist that suppresses the production and secretion of testosterone by blocking GnRH receptors in the anterior pituitary gland.[1] The FDA gave the drug priority review and orphan status. Relugolix is manufactured by Bushu Pharmaceuticals in Japan and distributed by Myovant Sciences as Orgovyx.

INDICATIONS

Relugolix should be prescribed to adults with advanced prostate cancer.[1]

DOSAGE

Administer a loading dose of 360 mg on the first day, followed by 120 mg daily at approximately the same time each day without regard to meals.[1] Usually, relugolix is continued upon development of nonmetastatic or metastatic, castration-resistant prostate cancer.[1] Relugolix is available as 120 mg tablets.

POTENTIAL ADVANTAGES

Relugolix is the first oral drug in this therapeutic class, as current therapies (e.g., GnRH agonists and antagonists) are injectables. GnRH antagonists do not produce the transient increase in serum testosterone and accompanying worsening of symptoms or new signs and symptoms associated with GnRH agonists. There are more patients with testosterone recovery on relugolix after discontinuation of treatment. In contrast to leuprolide, relugolix does not carry a warning in the prescribing information for higher risk of cardiovascular events.

POTENTIAL DISADVANTAGES

Androgen deprivation, such as with relugolix, may prolong the QT/QTc interval.[1] Animal studies suggest relugolix may cause embryo-fetal toxicity. Female partners of reproductive potential should use effective contraception during and for two weeks after the last dose of relugolix. Avoid coadministration of relugolix and combined P-gp and strong CYP3A inducers, since the combination may hinder efficacy.[1] Concomitant administration of P-gp inhibitor may increase the risk of adverse reactions.[1] Some patients may not properly adhere to the schedule with an oral medication vs. periodic injections.

COMMENTS

Researchers evaluated the efficacy and safety of relugolix in a randomized, open-label study of men with advanced prostate cancer requiring at least one year of androgen deprivation.[1,2] These subjects experienced biochemical or clinical relapse following local primary intervention, newly diagnosed castration-sensitive metastatic disease, or advanced localized disease.[1] Subjects were randomized in a 2:1 ratio to relugolix (n = 622) or leuprolide acetate 22.5 mg or 11.25 mg (Japan and Taiwan; n = 308) administered subcutaneously every three months for 48 weeks. The median baseline testosterone level was recorded at 408 ng/dL. The primary efficacy endpoint was achieving and maintaining serum testosterone to castrate levels (< 50 ng/dL) by day 29 through 48 weeks. Results were 96.7% for relugolix compared to 88.8%

for leuprolide. The decline in levels were more rapid with relugolix (99% achieved < 50 ng/dL by day 15 vs. 95% at day 29 for leuprolide). This happened because of initial upregulation of GnRH agonists, such as leuprolide, resulting in a sharp rise in hormones released by the pituitary, including follicular-stimulating hormone (FSH) and luteinizing hormones (LH) and resultant transient increase in testosterone levels. Continual administration results in suppression of FSH and LH and testosterone suppression. The sponsor reported noninferiority and superiority of relugolix over leuprolide, but the FDA reviewer did not accept this.[2,3] Overall, the adverse reaction profiles were similar between the two groups (e.g., hot flush, musculoskeletal pain, fatigue, and laboratory abnormalities such as glucose, triglyceride, ALT/AST increases, and hemoglobin decreases).[1] Diarrhea, mainly mild or moderate, was more common with relugolix (12% vs. 7%). The risk for major adverse cardiovascular events (MACE) appears to be lower with relugolix (2.8% vs. 6.2%), particularly in those with a history of MACE (3/84 [3.6%] vs. 8/45 [17.8%]).[2] There was a 54% reduction in cumulative incidence at the end week 48. In this trial, more than 92% of subjects presented with cardiovascular risk factors.

CLINICAL IMPLICATIONS

There were an estimated 190,000 cases of prostate cancer and 33,000 deaths in the United States in 2020.[3,4] Androgens (i.e., testosterone) have been shown to stimulate prostate cancer growth.[3,4] Therefore, castration (orchiectomy) or chemical castration with GnRH agonists or antagonist are standard therapies for advanced prostate cancer.[3] The National Comprehensive Cancer Network Guidelines (Version 3.2020) consider GnRH agonists or antagonists to be equally effective. The benefit of no initial increase in serum testosterone and perhaps lower risk of MACE may be potential benefits with an antagonist such as relugolix. The latter may be particularly relevant for those with cardiovascular risk factors, which is common in this population. Most deaths among prostate cancer patients happen because of cardiovascular disease rather than from index-cancer mortality.[5] The cost for relugolix was unavailable at the time of this review. ■

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CME QUESTIONS

1. **What is one way to reduce the likelihood of experiencing gastroesophageal reflux disease?**
   a. Drink three or more cups of tea each day.
   b. Eat only vegetables.
   c. Engage in moderate to vigorous physical activity for 30 minutes daily.
   d. Eat only grains.

2. **In the study by Kulick et al, which reason was suggested for the lack of association between higher levels of air pollution and cognitive decline in the Northern Manhattan Study cohort?**
   a. The subjects were from a different urban area.
   b. The cohort's mean age was younger.
   c. The mean ambient air pollutant levels were lower.
   d. The cohort included fewer Hispanic subjects.

3. **A small trial of prophylactic stenting of vulnerable but non-stenotic coronary plaques vs. medical therapy at 25 months showed:**
   a. larger minimum lumen area.
   b. lower target lesion failure.
   c. fewer cardiovascular events.
   d. improved survival rates.

Internal Medicine [ALERT]

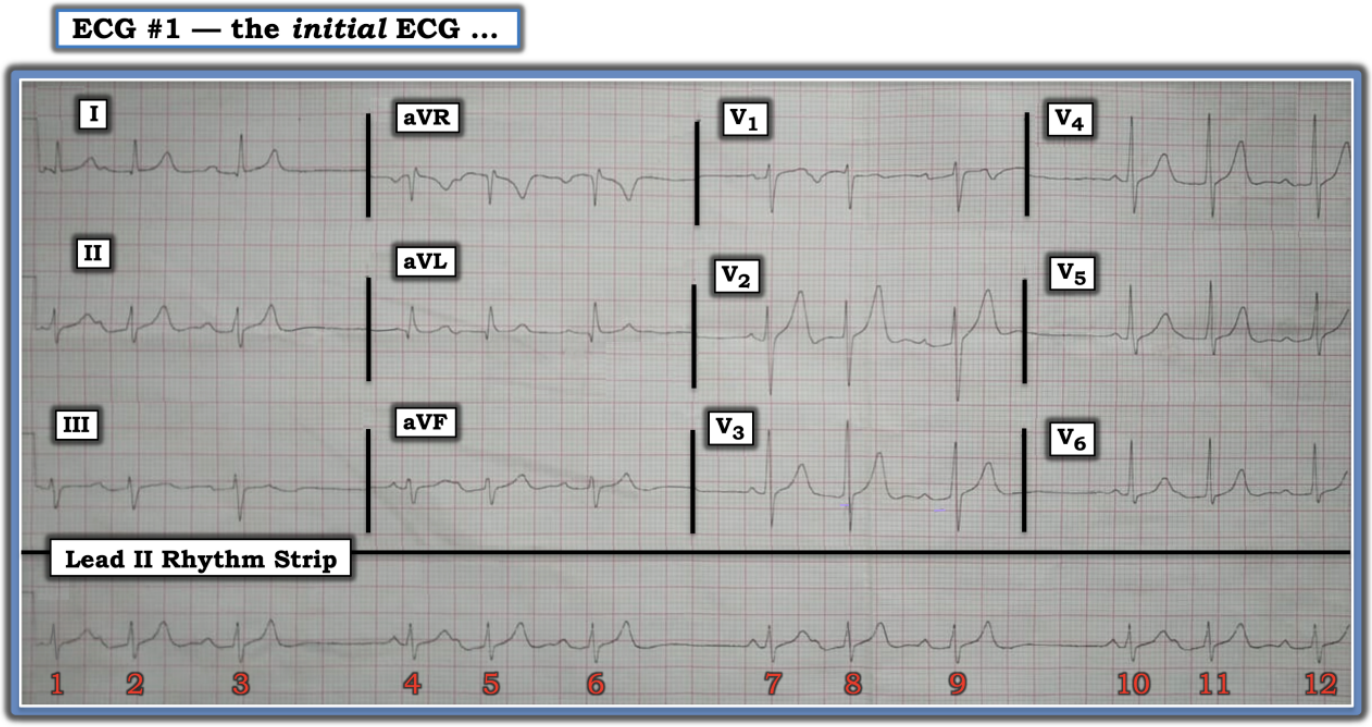
ECG Review

By Ken Grauer, MD

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

Why Is There Group Beating?

The ECG in the figure below was obtained from a 40-year-old man with an irregular heartbeat. How would one interpret this rhythm?



This is a difficult tracing. The QRS complex is narrow in all 12 leads. This tells us that the rhythm is supraventricular. Although the rhythm is irregular, there is group beating — that is, a definite pattern of three-beat groups can be seen. The sequence and relative duration of the R-R intervals between beats is similar in each of the four groups. A short pause of similar duration separates each of the three-beat groups. Some P waves also are visible. The fact that the PR interval preceding beats 4, 7, and 10 is the same suggests an underlying sinus rhythm is present.

The complex part of this tracing is the realization that a number of additional P waves are present. The difficulty is trying to figure out how many additional P waves are present and what this means. Definite P waves precede beats 3, 6, 9, and 12, each with a similar PR interval that is longer than the PR interval of sinus beats 4, 7, and 10. In addition, it appears P waves also are present, notching the terminal part of the T waves of beats 1, 4, 7, and 10. The PR interval of these four P waves is similar and prolonged. Note the T waves of beats 2-3, 5-6, 8-9, and 11 all appear to be taller and more peaked than the T wave of beats 1, 4, 7, and 10. The reason for this could be the P waves are hidden within each peaked T wave. Because these P waves occur so early in the refractory period, they are not conducted to the ventricles. Thus, the reason for the short pause that follows each of the three-beat groups is there is a non-conducted PAC that peaks the T waves of beats 3, 6, and 9.

Sometimes, it is simply not possible to be certain of the etiology of a rhythm from a single tracing. This ECG illustrates one of those times. What can be said is the rhythm is not AV Wenckebach, because the atrial rhythm is clearly not regular (as it should be for second- or third-degree AV block). Therefore, no pacemaker is needed. Instead, my hunch is repetitive PACs are visible, or perhaps short runs of atrial tachycardia with intermittent PR interval prolongation or non-conduction of atrial activity arising when P waves occur early in the cardiac cycle.

For more information about and further discussion on this case, please visit: http://bit.ly/3nAGtpt.