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Internal Medicine

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ABSTRACT & COMMENTARY

Vitamin D and Colon Cancer

By Mercy Kagoda, MD, MPH

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

SYNOPSIS: A self-report of any vitamin D supplementation was associated with a decrease in colorectal polyps.

SOURCE: Sutherland RL, Ormsbee J, Pader J, et al. Vitamin D supplementation reduces the occurrence of colorectal polyps in high-latitude locations. *Preventive Medicine* 2020;135:106072.

Humans obtain vitamin D from diet and through exposing skin to ultraviolet B radiation. Vitamin D3 is metabolized in the skin from 7-dehydrocholesterol. The liver metabolizes vitamin D to 25-hydroxyvitamin D [25(OH)D], which is then metabolized to $1,25(OH)_2D$ in the kidneys. The role of vitamin D in bone health and immune system functioning is accepted and widely studied. More recently, vitamin D supplementation has been investigated for its role in preventing colon cancer. This study helps provide further information on the role of vitamin D supplementation and the presence of colorectal polyps in populations living in high-latitude locations.

Sutherland et al studied data collected from the largest publicly funded center for early detection and screening of colon cancer in Canada: Forzani & MacPhail Colon Cancer Screening Centre (CCSC). Data collection included a colonoscopy report with a histological type of any identified polyps and questionnaires completed before the colonoscopy. Three questionnaires were used: a Canadian Diet History Questionnaire (I or II, depending on when the intake was completed), a Health and Lifestyle Questionnaire, and an International Physical Activity Questionnaire. The Canadian Diet History Questionnaire (DHQ) was used to determine fiber intake, vitamin D dietary intake, and supplement use. The DHQ was developed by the National Cancer Institute Risk Factor Assessment branch and also is used in the United States; the Canadian version includes foods that are specific to Canada.[1]

The primary outcomes of this study included vitamin D supplementation, total vitamin D intake, and their association with any type of colorectal polyps. Participants were recruited from the CCSC. Characteristics of the populations sampled included age, sex, ethnicity, education, marital status, alcohol use, smoking status,

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[INSIDE]

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physical activity, family history of cancer, nonsteroidal anti-inflammatory drug use, vitamin D supplementation, and fiber intake.

The authors analyzed the data using logistic regression models. They used crude and adjusted odds ratios to evaluate the association between vitamin D supplementation and high-risk adenomatous polyps. Likelihood ratio tests helped the authors evaluate effect modifiers. Chi-square tests helped the authors evaluate whether the characteristics were associated with vitamin D use.

For those who reported taking any vitamin D supplementation, the risk for polyps was lower than that of those who reported not taking any vitamin D supplement; OR_{crude} = 0.59 (0.46-0.76). The risk for polyps dropped further for those who reported taking at least the recommended daily intake (RDI) of vitamin D; OR_{crude} = 0.75 (0.65-0.87). These results were adjusted for age, sex, body mass index, smoking status, alcohol use, and fiber intake, since these variables were identified as confounders. Interestingly, there was no significance for meeting vitamin D RDI and high-risk adenomatous polyp (HRAP) detection; OR_{crude} = 0.8 (0.5-1.2).

■ COMMENTARY

This study showed that self-reported vitamin D supplementation was associated with a decrease in the occurrence of any colorectal polyps and, specifically, HRAPs. The main strength of this study was that it avoided outcome bias, since the questionnaire was completed before the colonoscopy and the colonoscopy results. Another advantage of this study is the authors used HRAPs as a primary outcome. HRAPs are considered to be more informative for determining risk for colorectal cancer during screening. Unfortunately, the study was too underpowered to pick up significance for risk reduction regarding vitamin D for HRAPs. This study did not show a significance for meeting vitamin D RDI and HRAPs; OR_{crude} = 0.8 (0.5-1.2).

Serum vitamin D concentration would have clarified the association between serum vitamin D level and HRAPs. Per email communication with the lead author, at the time, they were not collecting blood samples for any biorepository participants and were unable to measure serum vitamin D levels. They have since begun collecting various biological samples. Also, this was not a racially diverse study.

The results of other studies suggest a different mechanism and role for vitamin D in prevention of an *initial* polyp vs. prevention of *recurrent* polyps. A study by Crockett et al on vitamin D supplementation and *recurrent* polyps revealed no effect of either calcium or vitamin D on polyps (sessile serrated adenomas polyps in particular) during the treatment phase, when participants were receiving 1,200 mg/day of calcium and 1,000 IU/day of vitamin D2. However, six to 10 years after supplementation with calcium and vitamin D, there was an increased risk of sessile serrated adenomas polyps; relative risk 3.82 (1.26-11.57).[2] Crockett et al also discussed findings from a chemoprevention trial, which found that "smokers were at higher risk of recurrent conventional adenomas when given a combination of aspirin, calcium, and calcitriol. These results suggest that smokers may be particularly sensitive to calcium-mediated effects that promote colorectal neoplasia."

Further studies are needed to understand the effect of vitamin D supplementation for prevention of a primary polyp vs. recurrent polyps. This may bring to mind the epidemiological studies concerning beta carotene supplementation effects and tobacco smoke in lung cancer — the Alpha-Tocopherol Beta Carotene Cancer Prevention Study and the Carotene and Retinol Efficacy Trial.[3,4] Vitamin supplementation may not always produce the desired effect.

Another interesting consideration Sutherland et al discussed is the vitamin D receptor genotype may influence the effect of vitamin D supplementation. They cited a study by Barry et al that suggests the effect of vitamin D3 supplementation on advanced colorectal cancer risk may be the result of differences in the vitamin D receptor gene.[5] Since genotype frequencies vary by race, the effect of vitamin D supplementation also may vary in different populations.

Sutherland et al found vitamin D supplementation may be beneficial in primary prevention of any colorectal polyps in the population described. However, considering older studies of secondary prevention of colorectal polyps produced contradictory

results, further studies, specifically those that include measurement of serum vitamin D levels, need to be conducted before recommending vitamin D as a means of primary prevention of colorectal polyps. ■

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ABSTRACT & COMMENTARY

Is Isolated Diastolic Hypertension a Disease?

By Michael H. Crawford, MD

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

SYNOPSIS: An analysis of three large prospective databases showed the 2017 American College of Cardiology/American Heart Association revised definition of isolated diastolic hypertension as > 80 mmHg rather than the previous definition of > 90 mmHg resulted in a 5% higher prevalence of diastolic hypertension.

SOURCE: McEvoy JW, Daya N, Rahman F, et al. Association of isolated diastolic hypertension as defined by the 2017 ACC/AHA blood pressure guideline with incident cardiovascular outcomes. *JAMA* 2020;323:329-338.

In 2017, the American College of Cardiology/American Heart Association (ACC/AHA) hypertension guidelines redefined diastolic hypertension (DH) as greater than 80 mmHg based on expert opinion, not trials. McEvoy et al sought to establish the prevalence of DH under these revised guidelines and to assess the association between DH so defined with cardiovascular disease (CVD) outcomes.

To accomplish these goals, they analyzed cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) database from the 2013-2016 survey of U.S. adults and longitudinal data from the Atherosclerosis Risk in Communities (ARIC) study second examination in 1990-1992 with follow-up through 2017. The longitudinal results were validated in NHANES from 1988-1994, NHANES 1999-2014, and the Give Us a Clue to Cancer and Heart Disease (CLUE) II cohort from the 1989 baseline data. In NHANES and ARIC, blood pressure (BP) was measured after five minutes of sitting, and the mean of two to three measurements were used. In ARIC, high-sensitivity troponin and NT-proBNP also were measured. The prespecified cardiovascular disease (CVD) outcomes in ARIC were atherosclerotic (AS) CVD, heart failure (HF), and chronic kidney disease (CKD). ASCVD was a composite of myocardial infarction, ischemic stroke, or CVD death. Sensitivity analyses were performed for age, systolic BP, and antihypertensive treatment.

After excluding patients with missing data and age older than 20 years, 9,590 NHANES patients were available, in whom DH was present in 1.3% by JNC 7 criteria (> 90 mmHg) and 6.5% by 2017 ACC/AHA criteria. Few were recommended for drug therapy by either definition (1.6% and 2.2%, respectively). Among the more than 14,000 ARIC patients ages 46-69 years, after excluding those with systolic hypertension, 2% met JNC 7 criteria for DH and 11% met ACC/AHA criteria. Those with isolated DH were more likely younger, male, Black, overweight, or had lipid abnormalities.

During a median follow-up of 25 years, compared to normal BP, there were no statistically significant associations between DH and the composite outcome of ASCVD, HF, or CKD (hazard ratio [HR], 1.03; 95% confidence interval [CI], 0.93-1.15) or any of the individual endpoints. Sensitivity analyses did not change the results. In the NHANES validation cohort, DH was not associated with all-cause or CVD death (HRs, 0.92 and 1.17, respectively). Similar results were seen in the CLUE validation cohort (HR, 1.02 for both endpoints). Also, in ARIC, there were no significant associations between DH and cardiac biomarkers (troponin, BNP). The authors concluded that in this analysis of several populations of U.S. adults, isolated DH by the 2017 ACC/AHA definition was more prevalent than with the JNC 7 definition, but was not significantly associated with CVD outcomes.

■ COMMENTARY

The 2017 ACC/AHA guidelines for the treatment of hypertension caused quite a bit of controversy over the stricter definition of systolic hypertension to greater than 130 mmHg. Such measurements mainly revolved around older individuals in whom systolic BP naturally tends to increase with age and in patients with conditions such as coronary artery disease in whom higher pressures may be required to perfuse the myocardium. At the other end of the spectrum are subjects with isolated DH who more frequently tend to be young men. The new definition of DH raised the prevalence of it several-fold compared to the previous JNC 7 definition. This decision was based largely on older epidemiologic data that showed an increase in the risk of developing CVD at diastolic BPs > 75 mmHg and expert opinion. This carried psychological, social, and financial implications, so it is not a trivial matter.

However, this analysis of NHANES and ARIC data did not demonstrate an increase in CVD events or mortality. Perhaps more importantly, there was no signal of subclinical organ damage, as evidenced by no significant changes in troponin and BNP. Prior studies have shown an association with DH and the development of later systolic hypertension, which was not analyzed in this study.

Despite this possibility, there is no indication for drug treatment of isolated DH. This advice is consistent with the Hypertension Optimal Treatment (HOT) study, which did not show any benefit to reducing diastolic BP from 90 to 80 mmHg. Periodic surveillance for systolic hypertension would seem reasonable.

There were some limitations to the work of McEvoy et al. Although several sensitivity analyses and comparisons to other databases were conducted, there always is the possibility of residual confounding. Also, in ARIC, the lowest age for participation was cut off at 48 years, so these results may not apply to younger individuals. Still, the results were consistent with the NHANES data, where the lowest age was 20 years, and CLUE, where the median age was 42 years.

In addition, the studies used included patients on antihypertensive therapy. In such patients, any intervention would be escalation of therapy to further lower diastolic BP. Sensitivity analyses to adjust for this factor did not change the results. Finally, in ARIC, participants had to self-identify as either Black or white, so the results may not apply to other racial or ethnic groups. On the other hand, NHANES included all ethnicities in proportion to the U.S. population, and the results were the same in this population.

Despite all these potential weaknesses, this was a large study of three population cohorts that all demonstrated the same findings. Isolated DH does not seem to be a pathological entity, yet may represent about one-quarter of U.S. adults who have been recommended for BP therapy since the introduction of the 2017 ACC/AHA guidelines. It is time to re-examine the diastolic component of the controversy over these new guidelines. ■

ABSTRACT & COMMENTARY

Respiratory Syncytial Virus: Effective Prevention Still Needed

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: Prevention of respiratory syncytial virus infection is needed but challenging. New studies show some favorable effectiveness on infant outcomes with both vaccination of healthy pregnant women and passive single-dose immunization of prematurely born babies.

SOURCES: Madhi SA, Polack FP, Piedra PA, et al. Respiratory syncytial virus vaccination during pregnancy and effects in infants. *N Engl J Med* 2020;383:426-439.

Griffin MP, Yuan Y, Takas T, et al. Single-dose nirsevimab for prevention of RSV in preterm infants. *N Engl J Med* 2020;383:415-425.

Respiratory syncytial virus (RSV) is a main cause of seasonal respiratory tract infection and hospitalization in infants. Worldwide, RSV prompts more than 3 million hospitalizations each year, and more than 100,000 children die of RSV infection each year. Young infants, especially those born preterm with chronic lung disease or congenital heart disease, are at particular risk of infection and death. For more than five decades, vaccines have been developed and tested, still with just limited effectiveness. RSV-specific immune globulin is used in monthly injections to reduce severe disease in high-risk premature babies during the winter,

but there is no feasible, useful preventive measure for more widespread use.

Two new studies demonstrate novel techniques to reduce RSV-related morbidity and mortality. First, healthy pregnant women due to deliver near the start of the RSV season were given an RSV vaccine. Second, an extended half-life RSV-specific monoclonal antibody was given to preterm babies.

Madhi et al vaccinated healthy women at 28 to 36 weeks of gestation with a single-dose intramuscular, RSV fusion protein nanoparticle vaccine in a randomized trial comparing offspring of vaccine-vaccinated and placebo-vaccinated (2:1 ratio) women. A total of 4,636 women were randomized, most in South Africa and the United States. Injection-site reactions were more common with vaccine than placebo injection, but other side effects were not detected with vaccine use.

During the first 90 days of life, medically significant RSV infection was seen in 1.5% of offspring of vaccinated women and 2.4% of offspring of women who received placebo injections. Infection requiring hospitalization (2.1% vs. 3.7%) and infection requiring oxygen use (0.5% vs. 1.0%) were similarly lower in offspring of women who received the true vaccine. The differences were statistically significant but did not reach the pre-determined criterion to be considered "successful." Nonetheless, severe RSV illness was less likely in offspring of mothers who were vaccinated.

Griffin et al evaluated nirsevimab, an extended half-life monoclonal antibody, in 1,453 infants born following gestations of 29 through 34 weeks. They, too, used a 2:1 ratio of vaccine recipients to placebo recipients. The vaccine consisted of 50 mg of nirsevimab given intramuscularly at the beginning of an RSV season. There were no notable hypersensitivity-type reactions. Infection requiring medical care was less common with vaccine than with placebo (2.6% vs. 9.5%), as was RSV-related hospitalization (0.8% vs. 4.1%).

■ COMMENTARY

RSV is an RNA virus with two surface proteins responsible for much of its pathogenesis and infectivity.[1] The fusion protein accounts for viral entry into the host cell and is the target of natural neutralizing antibodies.[1] This protein was the basis of the vaccine tested in pregnant women in the Madhi et al study and of the monoclonal antibody used in the Griffin et al study. These preventive efforts are more likely to be useful than the attempted 1960s vaccine that prompted formation of non-neutralizing antibodies and, sadly, enhanced T cell responses with worsened disease.[1] Although each new trial demonstrated statistically significant favorable effects compared to placebo, each intervention was only about 70% effective in preventing serious RSV illness. Prevention efforts will continue. So far, efforts have failed to prevent actual infection to a significant degree. But vaccination still can be useful, since it reduces the risk of being sick enough with infection to require medical care, hospitalization, or oxygen supplementation. Illness prevention, even if not preventing all infection, could be effective in saving many of the 100,000-plus lives of children currently dying each year with RSV bronchiolitis.

Concurrently, treatment of RSV infection has evolved. While supportive care (e.g., fluids, nutrition, comfort measures, oxygen as needed) has proven efficacy, various disproven treatments, such as bronchodilators, hypertonic saline, steroids, antibiotics, and high-technology oxygen delivery systems, have been used widely (albeit ineffectively).[2-5] Quality improvement efforts can be effective in reducing unnecessary treatments.[6-8]

All around the planet, there is eager expectation of a vaccine for SARS-CoV-2. However, one hopes not to see too many correlates with COVID-19 and RSV bronchiolitis. Each is caused by an RNA virus with important surface proteins that can serve as vaccine targets. Further, each illness has prompted the widespread use of costly, unproven, and potentially dangerous treatments. Hopefully, it will not take decades to find a SARS-CoV-2 vaccine that works. In the meantime, the widespread isolation, masking, and social distancing implemented to reduce COVID-19 also likely will reduce the incidence of RSV bronchiolitis this coming fall and winter. ■

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PHARMACOLOGY UPDATE

Clascoterone Cream 1% (Winlevi)

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

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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 a first-in-class topical androgen receptor inhibitor for the treatment of acne vulgaris. Clascoterone cream works by binding to the androgen receptors in the sebaceous gland, thereby limiting binding of androgens, such as testosterone and dihydrotestosterone.[1,2] Clascoterone is marketed as Winlevi.

INDICATIONS

Clascoterone should be prescribed to treat acne vulgaris in patients age 12 years and older.[3]

DOSAGE

The recommended dose is application of approximately 1 g twice daily to affected areas.[3] Clascoterone is available as a 1% cream (60-g tube).

POTENTIAL ADVANTAGES

Clascoterone provides a new mechanism of action directed at one of the pathogenesis pathways of acne. There is limited systemic exposure as opposed to oral anti-androgens (e.g., oral contraceptives, spironolactone).[3]

POTENTIAL DISADVANTAGES

In 44 clascoterone-treated subjects (20 adults, 22 adolescents) who were evaluated after treatment for two weeks, hypothalamic-pituitary-adrenal axis suppression was observed in one adult and two adolescents at day 14.[3] Elevation of potassium levels has been observed in 5% of clascoterone-treated subjects with normal levels vs. 4% of vehicle-treated subjects.[3] Clinical experience was limited mainly to white study participants.

COMMENTS

Inhibition of lipids and inflammatory cytokines were observed with clascoterone in human sebocytes in vitro.[4] The safety and efficacy of clascoterone were evaluated in two international, randomized, double-blind, vehicle-controlled, 12-week trials that included subjects with moderate to severe facial acne vulgaris.[3,5] Subjects were mainly white (91%) and female (62%), with 45% age 12-17 years and 55% age 18 years or older. Most had moderate disease (83%), and 17% had severe disease based on Investigator's Global Assessment (IGA) of acne severity at baseline. IGA is a five-point scale: clear (0), almost clear (1), mild (2), moderate (3), and severe (4). Subjects also presented with a mean inflammatory lesion count of 42.4 and a mean noninflammatory lesion count of 61.4. Subjects were randomized to clascoterone (342 in study 1 and 367 in study 2) or vehicle (350 in study 1 and 362 in study 2). The primary efficacy endpoint was the proportion of subjects with at least a two-point reduction in IGA compared to baseline and an IGA score of 0 or 1, absolute change, and percent change from baseline in acne lesion counts (inflammatory and non-inflammatory) after 12 weeks of treatment.

IGA response rates compared to the vehicle were 18.8% for clascoterone vs. 8.7% for study 1 and 20.9% vs. 6.6%, respectively for study 2. The overall mean reductions in inflammatory lesions were 46% vs. 33% and 31% vs. 19%, respectively, for noninflammatory lesions. Long-term safety was evaluated in an open-label study in which subjects (n = 607) who completed one of the two Phase III trials were administered clascoterone up to nine months.[6] Those with an IGA score ≥ 2 continued the drug, and those with an IGA score ≤ 2 were taken off treatment. Subjects were permitted to apply the cream to acne on the trunk as well as the face. The most common adverse events were local erythema and scaling/dryness (9.8% and 4.7% at month 9). No accumulation or increase in adverse events were observed. No corticosteroid-like topical effects (i.e., skin atrophy, telangiectasia, or striae) were observed.

CLINICAL IMPLICATIONS

Acne vulgaris is a common cutaneous chronic inflammatory disorder affecting 85% of teenagers.[7] Four factors are believed to play vital roles in the pathogenesis, including hyperseborrhea and dysseborrhea, altered keratinization of the pilosebaceous duct, *Cutibacterium acnes*, and inflammation.[2] Androgens play a role in hyperseborrhea and hyperkeratosis as well as alteration in composition of sebum.[2] Clascoterone is the first topical androgen receptor inhibitor for moderate acne. The current guideline from the American Academy of Dermatology recommends topical combination of benzoyl peroxide (BP) and antibiotic or retinoid + BP or retinoid + BP + antibiotic.[7]

Currently, there are no comparative studies of clascoterone to other topical agents. Clascoterone cream provides another option with a different mechanism of

action. It is expected to launch in early 2021. Cost information is not yet available. ■

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CME QUESTIONS

1. **An analysis of two large study databases has shown that moving to the new guideline definition of isolated diastolic hypertension as > 80 mmHg would result in:**
   a. a strong association with cardiovascular events.
   b. a strong association with cardiovascular mortality.
   c. a strong association with elevated cardiac biomarkers.
   d. a substantial increase in the number of individuals with this diagnosis.

2. **Which is true regarding respiratory syncytial virus?**
   a. Infection is preventable now by vaccination of pregnant women.
   b. Infection is preventable now by passive immunization of newborns.
   c. Illness (bronchiolitis) is effectively treated by bronchodilators, steroids, and high-flow nasal cannula oxygen.
   d. Illness (bronchiolitis) is a cause of more than 100,000 childhood deaths worldwide each year.

3. **Based on the study by Sutherland et al, which statement is true?**
   a. A randomized clinical trial concluded that the benefits from vitamin D3 or vitamin D2 supplementation for the prevention of recurrent colorectal adenomas are independent of the vitamin D receptor genotype and phenotype.
   b. Self-reported vitamin D supplementation in people living at high latitudes and with no history of colorectal polyps or adenomas was associated with a decrease in the occurrence of colorectal polyps.
   c. In people with an adenoma, calcium and vitamin D supplementation were associated with a lower risk of sessile serrated adenomas or polyps six to 10 years after supplementation began.
   d. The risk of colorectal adenoma is directly related with serum vitamin D (25[OH]D) concentrations.

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

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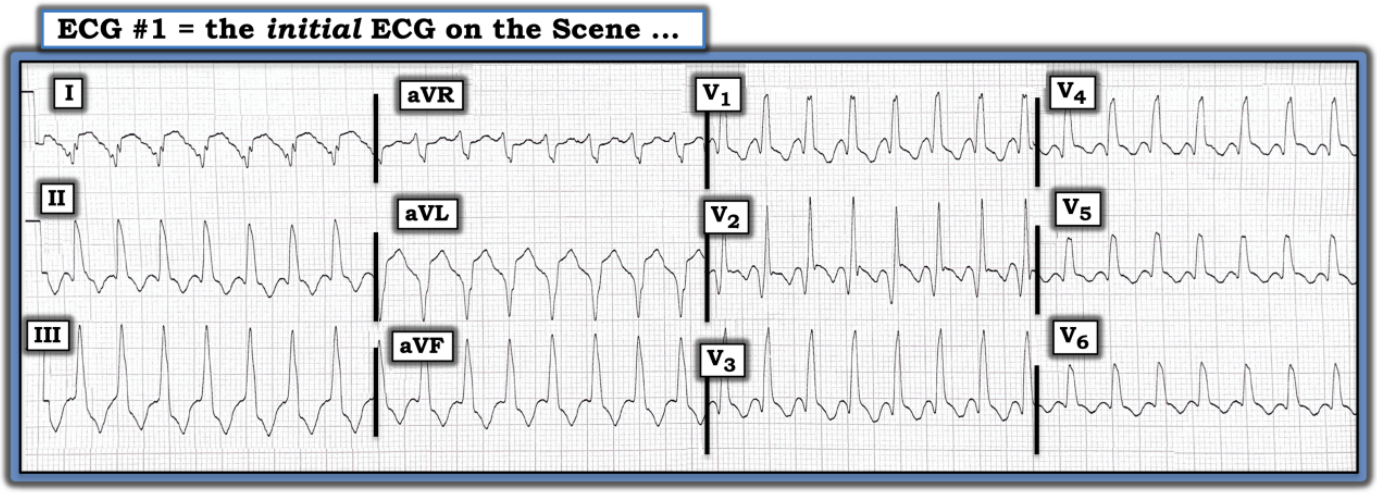
Dr. Grauer reports no financial relationships relevant to this field of study.

What Is the Cause of This Regular WCT?

The ECG in the figure below was obtained from an older woman who presented with hypotension. What is the rhythm?



The rhythm in the figure is a regular, wide complex tachycardia (WCT). The heart rate is approximately 220 beats/minute, and there is no clear sign of P waves. The principal differential diagnosis is between ventricular tachycardia (VT) and a supraventricular tachycardia (SVT) in which the reason for QRS widening is either pre-existing bundle branch block or aberrant conduction because of the rapid heart rate.

That said, there are several clues on this ECG that should allow one to rapidly arrive at the diagnosis of this tachyarrhythmia with near certainty. The odds in favor of VT when an older adult presents with a regular WCT rhythm, without clear sign of P waves, exceed 90%, even before one considers specific ECG features in the tracing. It is for this reason that the emphasis always should be on assuming the rhythm is VT (and treating the patient accordingly) until one can prove otherwise.

VT may be even likelier because the QRS complex is all negative in lead I. This means there is "extreme" axis deviation, which I define as complete negativity of the QRS complex in either lead I or lead aVF.

QRS morphology during the WCT rhythm does not resemble any known form of conduction disturbance. Whereas the QR pattern with predominant positivity in lead V1 resembles right bundle branch block (RBBB) conduction, the lack of any R wave at all in lead I and the lack of any S wave at all in lead V6 rules out RBBB conduction. The all-negative QRS complex in lead I, and the predominantly positive QRS in lead V1, rule out left BBB conduction.

There are wide and deep Q waves in virtually all chest leads. This suggests delay in the initial vector of ventricular depolarization. In contrast, the initial vector of ventricular depolarization tends to be more rapid when the rhythm is supraventricular (and traveling through organized conduction pathways). The rhythm in the figure almost is certain to be VT. The patient was treated accordingly. She responded to synchronized cardioversion by return to a sinus rhythm in which QRS morphology looked completely different to that seen during the WCT.

For more information about and further discussion of this case, please visit: https://bit.ly/3bFfQKJ.