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ABSTRACT & COMMENTARY

Ketogenic Diet Improves Cognition, Daily Function in Alzheimer's Disease Patients

By Joseph E. Scherger, MD, MPH

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SYNOPSIS: In a randomized, crossover trial, patients with Alzheimer's disease on a ketogenic diet for 12 weeks demonstrated improved cognition, daily function, and quality of life.

SOURCE: Phillips MCL, Deprez LM, Mortimer GMN, et al. Randomized crossover trial of a modified ketogenic diet in Alzheimer's disease. *Alzheimers Res Ther* 2021;13:51.

This randomized, crossover trial was conducted at a tertiary care hospital in New Zealand in 2019. The authors enrolled 26 patients (age 50 to 90 years) with Alzheimer's disease (AD). A total of 21 completed the blinded crossover trial. All presented with clinically significant disease at various stages. For 12 weeks, patients ingested either a ketogenic diet or usual diet, supplemented with low-fat, healthy-eating guidelines for two weeks each. A 10-week wash out period separated the two dietary periods. Assessors were blinded as to which diet the patients were on, with measurements taken after each 12-week diet period. The primary outcomes were changes in the AD Cooperative Study – Activities of Daily Living (ADCS-ADL) inventory, the Addenbrooke's Cognitive Examination III (ACE-III) scale, and Quality of Life in AD (QOL-AD) questionnaire. Secondary outcomes considered changes in cardiovascular risk factors and adverse events.

Compared with the usual diet, patients on the ketogenic diet increased their mean within-individual ADCS-ADL score by 3.13 points ($P = 0.0067$) and their QOL-AD by 3.37 points ($P = 0.023$). The ACE-III also increased by 2.12 points, but this did not reach statistical significance. Changes in cardiovascular risk factors were mostly favorable, with decreased body weight and BMI, lower HbA1c, and an increase in HDL cholesterol. LDL and total cholesterol also increased on the ketogenic diet, which, in the short term, was seen with burning fat. Adverse events were mild.

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■ COMMENTARY

Ketones benefit the brain.[1] Before phenytoin, clinicians prescribed a ketogenic diet to help treat epilepsy.[2] Elevated blood sugar levels are harmful to the brain.[3] Thus, it is not surprising that a ketogenic diet would improve function in patients with AD. What is remarkable is these benefits were seen after just two weeks. Although this study size was small and the period brief, this adds to the literature indicating diet may improve cognition in patients with AD.[4] It is time we recognize and act on the data showing that high-sugar, high-carbohydrate diets are harmful, and that low-carbohydrate diets produce major health benefits. ■

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ABSTRACT & COMMENTARY

Intracranial Plaque Rupture and Stroke

By Michael H. Crawford, MD

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SYNOPSIS: An MRI study of cerebral circulation in patients with embolic stroke of undetermined etiology showed evidence of atherosclerotic plaque in most patients.

SOURCE: Lin Tao MM, Li XQ, Hou XW, et al. Intracranial atherosclerotic plaque as a potential cause of embolic stroke of undetermined source. *J Am Coll Cardiol* 2021;77:680-691.

Ruptured non-stenotic intracranial atherosclerotic plaque has been suspected to cause embolic stroke of undetermined source (ESUS), but there are little data to support this hypothesis. Accordingly, Tao et al evaluated the morphology and composition of intracranial plaque in patients with ESUS and small vessel disease (SVD).

They used the 3.0 Tesla MRI to compare the ipsilateral side to the contralateral side of the stroke. Patients with acute ischemic stroke who had undergone a full evaluation for stroke etiology, including intracranial high-resolution MRI and met criteria for ESUS or SVD, were enrolled retrospectively. Patients with bilateral or posterior circulation strokes were excluded, leaving 243 with ESUS and 160 with SVD. Plaque was defined as eccentric focal wall thickening at the point of minimal lumen diameter in the major vessels in the anterior intracranial circulation. Vessel reference sites were adjacent plaque-free areas. The remodeling index (RI) was the ratio of the cross-sectional area of the vessel at the plaque site to the reference vessel area. Plaque burden (PB) was defined as the percent difference between the total vessel area and the luminal area at the plaque site. Among ESUS patients, 69% had any intracranial plaque. Among SVD patients, 40% had any intracranial plaque ($P < 0.001$ for the difference).

The prevalence of intracranial plaque was higher in the ipsilateral compared to the contralateral side in ESUS patients (64% vs. 43%; OR, 5.25; 95% CI, 2.83-9.73). In SVD patients, this difference was not found (36% vs. 31%; OR, 2.14; 95% CI, 0.87-5.26; $P = 0.13$). Also, ESUS patients exhibited larger PB and RI in the ipsilateral compared to the contralateral plaque (PB: 64% vs. 60%; $P = 0.002$ and RI: 1.17 vs. 1.09; $P < 0.001$). In addition, complicated plaque was ipsilateral more often in ESUS patients (77% vs. 60%; $P = 0.003$). None of these plaque features were associated with

stroke in SVD patients. A multivariate logistic regression analysis excluding overlapping plaque characteristics showed that RI was independently associated with ESUS (OR, 2.30; 95% CI, 1.66-3.17; $P < 0.001$). Using an RI cutoff of 1.162, the area under the curve was 0.74. The authors concluded these data suggest high-risk, non-stenotic intracranial plaque represents a significant underestimated embolic source in patients with ESUS.

■ COMMENTARY

This is an important foundational study. ESUS represents about 20% of ischemic stroke patients,[1] and they are at a high risk of recurrence. Also, there is no established therapy to prevent recurrences. Standard stroke prevention therapies have shown mixed results. In NAVAGATE ESUS, the subgroup with non-stenotic intracranial or generalized atherosclerosis showed no difference in recurrent events between treatment with rivaroxaban or aspirin.[2] By contrast, in COMPASS patients with cryptogenic stroke, reduced recurrence rates were observed on low-dose rivaroxaban and aspirin vs. aspirin alone.[3] Neither study focused exclusively on patients with intracranial atherosclerosis. Techniques for studying intracranial arterial lesions, such as the MRI technique used in the Tao et al study, are relatively new but have shown excellent intra- and interobserver agreement. Thus, now, there are tools to study this issue more carefully. Hopefully, more effective recurrence-preventing therapies will be discovered.

It has been evident for some time that non-stenotic atherosclerotic lesions in extracardiac vessels proximal to the cerebral circulation, such as the proximal aorta, carotids, and vertebral basilar system, could produce emboli to the brain, but evidence of the potential for intracranial vessel plaques to be a source has been limited by technical issues. In the Tao et al study, positive remodeling of ipsilateral arterial plaque sites was shown to be the best independent predictor of ESUS. Thus, intracranial arteries that have enlarged because of the presence of plaque and have a larger RI seem to be the most likely sites of plaque-derived emboli. However, patients with negative remodeling were excluded because they were more likely to be stenotic. Plaque burden was less predictive of ESUS, probably because it can be overestimated thanks to curved vessels and oblique cuts. The authors interpreted images without any clinical knowledge about the patients. This, along with the cutting-edge imaging and sophisticated statistical analysis, made this a compelling investigation.

Still, there were weaknesses. It was retrospective, with a small number of patients, all of whom were Chinese. There were no histologic data to support the analysis of plaque characteristics. Also, there are multiple possible sources of emboli; excluding other causes is imperfect in ESUS. However, one could argue too much attention is paid to patent foramen ovale and occult atrial fibrillation, both of which are unusual causes of ischemic strokes. Finally, the long-suspected-but-not-proven theory that cerebral vessel atherosclerosis and resultant embolization of debris from damaged plaques is getting its due. ■

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ABSTRACT & COMMENTARY

Exercise Intervention for Improving Metabolic-Associated Fatty Liver Disease

By Sebastian Gallego, MD, and Nancy Selfridge, MD

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SYNOPSIS: Researchers assessed the histological appearance of liver biopsies from patients with metabolic-associated fatty liver disease (MAFLD) who completed 12 weeks of structured and supported aerobic exercise. Compared to biopsies from a nonexercising control group, the intervention arm demonstrated some reversal of histopathologic changes caused by MAFLD.

SOURCE: O'Gorman P, Naimimohasses S, Monaghan A, et al. Improvement in histological endpoints of MAFLD following a 12-week aerobic exercise intervention. *Aliment Pharmocol Ther* 2020;52:1387-1398.

Metabolic dysfunction caused by insulin resistance, type 2 diabetes mellitus, and obesity is associated with an increased risk of cardiovascular disease and metabolic-associated fatty liver disease (MAFLD), previously referred to as non-alcoholic fatty liver disease (NAFLD).

MAFLD has a global prevalence estimated at 25% and is a major contributor to morbidity and mortality from chronic liver disease worldwide.[1] The natural history of MAFLD includes potential progression of this chronic liver inflammation to non-alcoholic steatohepatitis (NASH), liver cirrhosis, and hepatocellular carcinoma. There is no known pharmacologic treatment or cure for MAFLD, although both aerobic and resistance exercise have shown histological benefits in MAFLD patients when associated with 7% to 10% weight loss. These tactics comprise the current evidence-based recommendations for management of this condition.

Exercise has been associated with a reduction in morbidity and mortality for several inflammatory conditions, such as cancer, type 2 diabetes mellitus, arthritis, and atherosclerotic cardiovascular disease. Therefore, it makes sense that it might be a helpful intervention for MAFLD. A recent meta-analysis of the effect of exercise interventions without weight loss on MAFLD demonstrated significant improvement in liver steatosis, measured noninvasively, after both aerobic and resistance exercise training interventions.[2] However, other recent studies have shown no histologic improvement in MAFLD after exercise interventions.[3,4] Thus, O'Gorman et al investigated the effect of a 12-week aerobic exercise program without dietary intervention or weight loss on improving MAFLD histological endpoints and explored the optimal dose, frequency, and type of exercise necessary for that outcome. The authors further determined the effect of the prescribed exercise intervention on participant cardiorespiratory fitness, physical activity levels, and measures of cardiometabolic health, including body composition, vascular health, glucose metabolism, lipid metabolism, and circulating inflammatory markers. Sustainability of the exercise intervention was determined at 12 weeks and 52 weeks post-exercise intervention.

Twenty-eight participants with biopsy-confirmed MAFLD, all of whom attended an outpatient hepatology clinic, were divided into a treatment group (n = 18) and a control group (n = 10), based on participant preference. Of these, four participants dropped out before the completion of the first follow-up assessment in week 13, two in the treatment group and two in the control group, leaving 16 in the intervention group and eight in the control group for the week 13 data analysis. The age range of the participants was 46 to 77 years (mean 61), the male-to-female ratio was 7:17, and the average BMI was 35.7 kg/m^2.

All participants were assessed at baseline and at week 13 for dietary intake using a four-day diet diary, hepatic elastography (a noninvasive assessment of hepatic steatosis and fibrosis), and cardiorespiratory fitness using a modified Bruce protocol and estimates of VO_2 max. Cardiometabolic analysis measures included fat mass, skeletal muscle mass, waist and hip circumference, liver function tests (LFTs), lipid profile, fasting glucose, hemoglobin A1c, and circulating inflammatory markers (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], tumor necrosis factor alpha [TNF-alpha], interleukin 6 [IL-6], and interleukin 1 beta [IL-1 beta]). Additionally, the treatment group underwent follow-up liver biopsies at 13 weeks to assess changes in liver histological architecture. Statistical analysis using independent *T* tests and Mann-Whitney *U* tests found no differences in means for baseline measures for the control and treatment groups nor differences in baseline liver histology measures. Standard tests for multivariate analysis were applied to assess within-group differences in repeated measures for both continuous and categorical data. Effect size was calculated using eta squared,

and statistical significance was set at $P < 0.05$. The treatment intervention consisted of a 12-week moderate-to-intense aerobic exercise program, three to five sessions/week (two supervised by an exercise specialist and one to three unsupervised sessions). The exercise program was individualized and graduated in duration and intensity. Supervised group sessions consisted of five to seven minutes of warm-up, 21-42 minutes of moderate-intensity aerobic exercise (increasing over the 12-week study period), followed by a five- to seven-minute cool-down. For unsupervised sessions, participants were sent text messages to encourage them to repeat the same format of the supervised sessions and reminding them of the specific duration and intensity of the exercise prescription for the week. Unsupervised sessions were prompted once weekly for the first three weeks, and prompts increased to three per week in weeks 8-12.

For supervised sessions, participants were provided heart rate monitors to gauge exercise intensity, starting at 40% to 59% of heart rate reserve (HRR) and increasing to 55% to 75% HRR by week 9. Participants were trained to use the Borg scale to rate perceived exertion to duplicate the same intensity exercise for their unsupervised sessions. The control group was provided standard care. Diet was not changed during the study period in either group.

An assessment at week 13 showed statistically significant increased cardiorespiratory fitness in the treatment group, with the mean VO_2 max increasing by 17% compared to the control group ($P = 0.027$). VO_2 max also improved between baseline and week 13 within the treatment group. The treatment group also demonstrated improved cardiometabolic markers, including body mass (2.1% mean reduction, $P = 0.038$), waist circumference (4.0% mean reduction, $P = 0.015$), and fat mass (4.9% mean reduction, $P = 0.007$) vs. controls. Additional improvements were noted within the treatment group vs. baseline measures for waist-to-hip ratio (2.4% mean reduction, $P = 0.008$) and increased skeletal muscle mass (3.8% mean increase, $P = 0.034$), weight loss, and BMI. No patient achieved 7% to 10% weight loss, although 19% of participants in the treatment group achieved 5% weight loss by the end of the intervention period. Histological changes in liver biopsy specimens were assessed for 12 of 16 patients from the treatment group (four participants declined repeat liver biopsy). Those changes included improvement in liver fibrosis by one stage in 58% ($P = 0.034$) of patients and decreased hepatocyte ballooning (a characteristic histopathologic finding of steatohepatitis) by one stage in 67% ($P = 0.020$) of patients. Improvements in liver fibrosis and hepatocyte ballooning were associated with increases in estimated VO_2 max by 25% ($P = 0.020$) and 26% ($P = 0.010$), respectively. Treatment group participants demonstrated no changes in hepatic steatosis ($P = 1.000$), lobular inflammation ($P = 0.739$), or NAFLD activity score ($P = 0.172$). Furthermore, there were no significant changes in LFTs, nor changes in measured circulatory inflammatory markers (CRP, ESR, TNF-alpha, IL-6, IL-1 beta), lipid profiles, or measures of glycemic control. Although participants were encouraged to continue exercising after the 12-week prescribed and supervised exercise intervention, none of these beneficial changes were sustained at a one-year follow-up.

■ COMMENTARY

The results from this study supported existing evidence indicating exercise alone may improve pathologic liver changes characteristic of the metabolic dysfunction associated with obesity, insulin resistance, and type 2 diabetes. The limitations of the study methodology included a small sample size, nonrandomization of study participants, and an invasive and potentially risky biopsy procedure as part of the baseline and post-intervention assessment that likely limited recruitment. The control group was not subjected to liver biopsy after 12 weeks, and medication checks were not performed for either group after study participants were recruited. Thus, there was no control for changes in biopsy findings caused by non-exercise-related variables. Both conditions introduce a possibility of type II statistical error. Despite histologic improvement in hepatic fibrosis and hepatocyte ballooning noted in the treatment group, no other histologic changes met statistical significance; therefore, it is difficult to judge the clinical significance of the improvement without a longer study period.

The strengths of this study included intervention and control groups with no significant baseline differences despite nonrandomization and a superbly structured group exercise intervention that included a supervised component, with a high level of reported adherence (93%) during the 12-week implementation period. In fact, it is likely the structure of the intervention program (graduated moderate- to vigorous-intensity aerobic exercise, a supervised group setting, and text message prompts for unsupervised sessions) influenced the positive liver histology endpoints noted in this study that were not apparent in previous exercise intervention studies.[3,4]

Clinicians can capitalize on the findings from this study in clinical practice, citing an additional possible salubrious effect of a committed exercise program. First, this study suggests adherence to exercise is easier and more likely in a set of patients with metabolic disorder and associated conditions when the exercise program includes a group setting, supervision, and structured encouragement. These are conditions for clinicians to promote when creating exercise prescriptions for patients. Although exercise with moderate weight loss remains the goal and foundation of lifestyle-change counseling for patients with metabolic disorder and MAFLD, patients who have struggled repeatedly with

weight loss can be encouraged that exercise alone, performed with sufficient consistency and at least moderate intensity, can improve cardiometabolic risk profile and appears to improve associated fatty liver changes. ■

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PHARMACOLOGY UPDATE

Viloxazine Extended-Release Capsules (Qelbree)

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

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The FDA has approved a new nonstimulant, nonscheduled drug to treat attention-deficit/hyperactivity disorder (ADHD) in children and adolescents. Viloxazine is categorized as a selective norepinephrine reuptake inhibitor.[1] However, in contrast to other similar agents (e.g., atomoxetine), it produces a more moderate inhibitory effect on norepinephrine uptake, selective antagonistic activity toward 5-HT2B receptors, and agonistic activity toward 5-HT2c receptors. Its psychopharmacological profile is as a serotonin norepinephrine modulating agent.[2] Viloxazine is distributed as Qelbree. The drug has been marketed in Europe for more than 40 years to treat depression.

INDICATIONS

Viloxazine should be prescribed to treat ADHD in patients age 6 to 17 years.[1]

DOSAGE

The recommended starting dose for ages 6 to 11 years is 100 mg once daily.[1] Clinicians can titrate the dose in 100-mg increments weekly up to a maximum of 400 mg once daily. For patients age 12 to 17 years, the recommended starting dose is 200 mg, and may be titrated similarly up to 400 mg once daily. The dose should be lower for patients with severe renal impairment. The capsules may be swallowed whole or the contents may be sprinkled onto applesauce. Viloxazine is available as 100 mg, 150 mg, and 200 mg extended-release capsules.

POTENTIAL ADVANTAGES

Viloxazine provides a potentially different mechanism of action for treating ADHD. Viloxazine is not classified as a controlled substance.

POTENTIAL DISADVANTAGES

The more common adverse effects compared to placebo are somnolence (16% vs. 4%) and headache (11% vs. 7%).[1] Other adverse reactions include nausea, irritability, tachycardia, fatigue, and suppressed appetite.[1] Slower weight gain or slight weight loss vs. placebo-treated subjects have been observed in clinical trials.[1] This may be caused by drug-induced appetite suppression. There is a dose-dependent increase in heart rate and diastolic blood pressure.[1] Suicidal thoughts and behavior have been reported; therefore, patients should be monitored for clinical worsening and emergence of suicidal thoughts.[1] Viloxazine may activate mania or hypomania.[1] Viloxazine is a strong CYP1A2 inhibitor; avoid substrates of the isoenzyme (e.g. duloxetine, ramelteon).

COMMENTS

The efficacy of viloxazine was evaluated in three randomized, three-arm, placebo-controlled, monotherapy trials.[1,3,4] Two studies (Studies 1 and 2) included subjects age 6 to 11 years and one (Study 3) included subjects age 12 to 17 years. Study 1 was a six-week study (one week titration, five weeks maintenance). Subjects (n = 477) were randomized to 100 mg, 200 mg, or placebo. The primary endpoint was the change from baseline to the end of study on the total score on the ADHD Rating Scale (ADHD-RS-5). This is an 18-question document that assesses hyperactivity, impulsivity, and inattentive symptoms, with higher score representing more severe symptoms. Study 2 was an eight-week investigation (three weeks titration, five weeks maintenance). Subjects (n = 313) were randomized to 200 mg, 400 mg, or placebo. Study 3 was a six-week examination (one week titration, five weeks maintenance). Subjects (n = 301) were randomized to 200 mg, 400 mg, or placebo. All

doses produced statistically significant reduction in ADHR-RS-5 total scores vs. placebo, with a placebo-subtracted difference ranging from -12% to -14.3% (-16- to -17.7-point reduction vs. -10.9- to -11.7-point reduction for placebo). Baseline mean scores ranged from 40 to 44. Improvement was observed in inattention and hyperactivity/impulsivity subscales.[3] Significant reduction was observed in the first week of treatment.[3] Approximately 3% of subjects in the clinical trials discontinued treatment because of adverse reactions.[1]

CLINICAL IMPLICATIONS

ADHD is a common diagnosis in U.S. children, with an estimated incidence of 6.1 million in 2016, of whom 62% were taking ADHD medication.[5] Of affected children, 60% had at least one other mental, emotional, or behavioral disorder, most commonly behavioral or conduct problems. Stimulants (e.g., methylphenidate, amphetamines) generally are first-line treatment for ADHD. Three nonstimulants are FDA-approved (atomoxetine, clonidine, and guanfacine). These are options for patients who cannot tolerate stimulants (e.g., agitation or sleeplessness) or who experience inadequate response. There are no published comparative studies between viloxazine and stimulants or other nonstimulants. The authors of a systematic review and network meta-analysis estimated the comparative efficacy and tolerability of oral medications (both stimulants and nonstimulants) for ADHD in children, adolescents, and adults.[6] They concluded that in children and adolescents, amphetamines were superior to atomoxetine and guanfacine, and methylphenidate was superior to atomoxetine in terms of reducing ADHD core symptoms as rated by clinicians. Viloxazine offers another option with a different psychopharmacological, side effect, and drug-drug interaction profiles. The cost for viloxazine is $299 for a 30-day supply (100 mg, 150 mg, or 200 mg once daily). ■

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CME QUESTIONS

1. **What dietary factor has been shown to improve function in patients with Alzheimer's disease?**
   a. Protein
   b. Fat
   c. Complex carbohydrates
   d. Ketones

2. **A sophisticated MRI study of the intracranial circulation showed atherosclerotic plaques in what percentage of patients with embolic stroke of undetermined source?**
   a. 24%
   b. 43%
   c. 69%
   d. 78%

3. **Which histological endpoints of metabolic-associated fatty liver disease were observed in liver biopsies after 12 weeks of aerobic exercise intervention?**
   a. Decreased hepatic steatosis, hepatocyte ballooning, and liver fibrosis
   b. Decreased hepatic steatosis only
   c. Decreased liver fibrosis and hepatocyte ballooning
   d. Decreased hepatic steatosis, hepatocyte ballooning, liver fibrosis, and lobular inflammation

Internal Medicine [ALERT]

ECG Review

By Ken Grauer, MD

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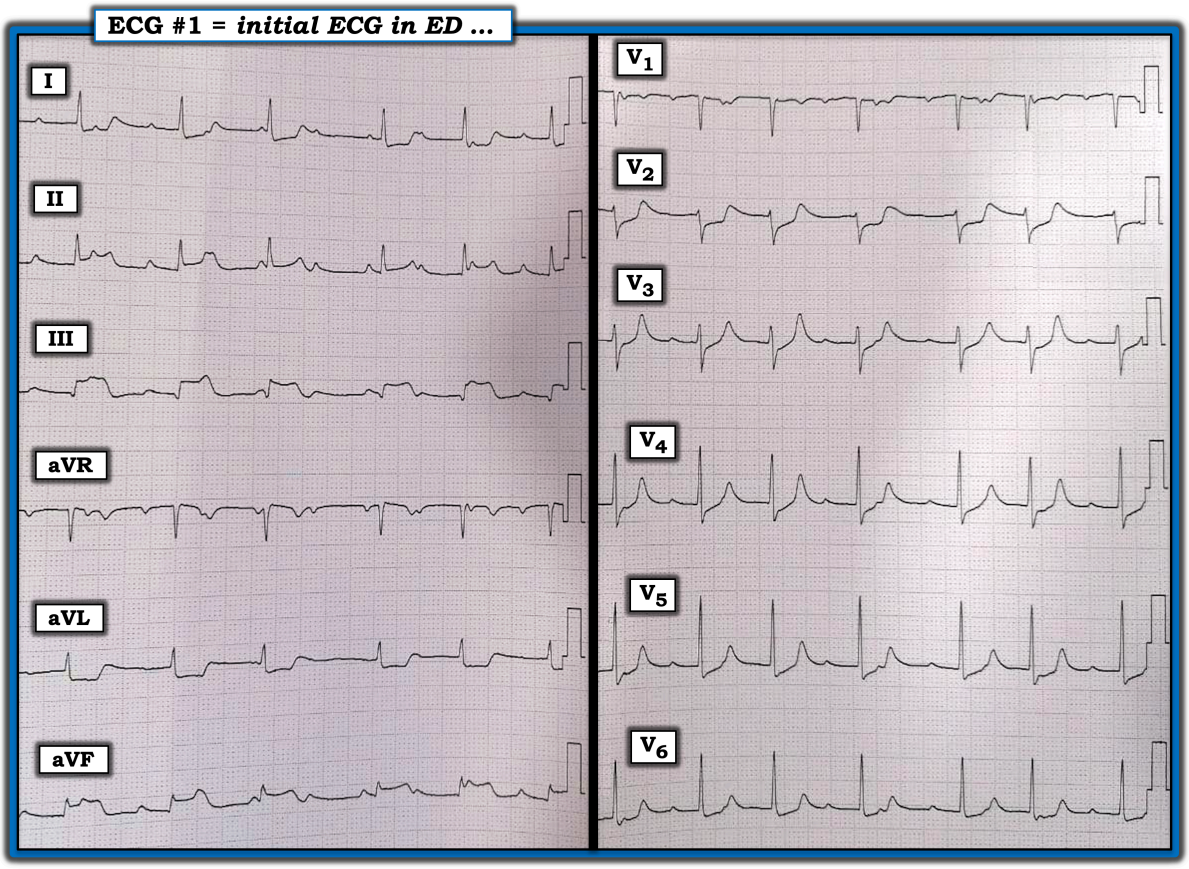
What Is the Rhythm? What Is the Culprit Artery?

The ECG in the figure below was obtained from a middle-aged man with chest pain. What can one say about the cardiac rhythm? How can one determine the "culprit" artery?



Although definitive diagnosis of the cardiac rhythm is not possible from the limited period of monitoring seen in the figure, the rhythm is supraventricular, as all QRS complexes are narrow. It looks like the atrial rhythm is regular at an increased rate, and it looks as if some form of group beating is present. Some P waves appear to be conducting, as judged by the repetition of similar PR intervals (best seen in lead V6). But some P waves are not conducted. This suggests there is some type of second-degree AV block.

Regarding the rest of the 12-lead ECG, there is ST segment elevation in leads II, III, and aVF. Considering the tiny size of the QRS complex in lead III, a relatively large Q wave is seen in this lead. Reciprocal ST depression is seen in leads I and aVL. The ST segment in lead V1 is flat. Peaked T waves with significant ST depression are seen in the other five chest leads. Considering the history of new chest pain, the ECG findings are diagnostic of recent or acute infero-postero occlusion-based myocardial infarction (OMI). The anterior lead ST depression (that is maximal in leads V2 through V4) indicates acute posterior involvement. The fact that the ST segment in lead V1 is flat rather than depressed (as it is in other chest leads) suggests there is associated acute right ventricular involvement. This localizes the acute occlusion to the proximal right coronary artery because neither the left circumflex nor the left anterior descending artery supplies the right ventricular wall. Additionally, the fact that the QRS complex is narrow and the rest of the 12-lead ECG is diagnostic of acute inferior MI strongly suggests the conduction disturbance is a type of AV Wenckebach (Mobitz I), second-degree AV block.

For more information about and further discussion on this case, please visit: https://bit.ly/39BnMNz.