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Internal Medicine

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ABSTRACT & COMMENTARY

Healthy or Not: The Controversy Over Egg Consumption Continues

By Joseph E. Scherger, MD, MPH

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SYNOPSIS: A large meta-analysis showed higher consumption of eggs (eating more than one egg daily) was not associated with an increased risk of cardiovascular disease, and was associated with a lower risk of coronary artery disease.

SOURCE: Krittanawong C, Narasimhan B, Wang Z, et al. Association between egg consumption and risk of cardiovascular outcomes: A systematic review and meta-analysis. *Am J Med* 2021;134:76-83.

To help settle the controversy over the relationship between egg consumption and risk of cardiovascular disease, a team of researchers from Baylor, Mount Sinai, the Mayo Clinic, Case Western Reserve, and the Cleveland Clinic conducted a systematic review and meta-analysis of the medical literature published from 1966 through January 2020 for observational studies that reported on the association between egg consumption and cardiovascular events. Controlled trials were unavailable. The authors identified 23 prospective studies with a median of 12.28 years of follow-up. These reflected 1.416 million individuals with 157,324 cardiovascular events. Compared with no eggs/day or one egg/day consumption, higher egg consumption was not associated with an increased risk of cardiovascular disease events. Consuming more than one egg/day was associated with significantly lower risk of coronary artery disease.

■ COMMENTARY

Just as this study was covered in the press, another study from China showed egg consumption was linked to higher mortality from cardiovascular disease and cancer.[1] The controversy continues. My preference is to look at nutrition and human biology. What makes sense based on our current scientific understanding of the causes of disease? Observational studies are based on correlations, and these correlations can be spurious.

Insulin resistance is recognized as the basis of most chronic diseases, especially the risk factors for cardiovascular disease and cancer.[2,3] The excess body fat of

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being overweight and obese comes from eating too many carbohydrates. We all have a carbohydrate threshold that, if exceeded, results in insulin resistance, prediabetes and diabetes, and metabolic syndrome, with its elevated blood pressure and dyslipidemia. Consuming eggs does not cause insulin resistance. In fact, with a low carbohydrate diet, the opposite is true.[4]

There are no carbohydrates in eggs. Like any animal food, how that animal was fed is important. Organic eggs from pasture-raised chickens are different than eggs from grain-fed chickens kept in cages. Mounting evidence from the healthy nutrition literature supports the consumption of quality eggs as part of a healthy diet. One neurologist considers eggs an important food for brain health. Our brains are made largely from cholesterol.[5]

Even though it is limited by its observational nature, the Krittanawong et al study is of better quality than the recent paper from China. It is high time for randomized, controlled trials of nutritional matters of this importance. Meanwhile, I will continue to consume two organic eggs from pasture-raised chickens every day, and recommend such for my patients. ■

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ABSTRACT & COMMENTARY

Time-Restricted Eating, Weight Loss, and Metabolism

By Adelaide Agyepong, MD, and Nancy Selfridge, MD

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Dr. Selfridge is Professor, Clinical Foundations, at Ross University School of Medicine, Barbados, West Indies.

SYNOPSIS: A randomized clinical trial comparing time-restricted eating with a 16-hour fasting interval to a structured three-meal-per-day control group resulted in equivalent weight loss in both groups and no reduction in metabolic markers in either group.

SOURCE: Lowe DA, Wu N, Rohdin-Bibby L, et al. Effects of time-restricted eating on weight loss and other metabolic parameters in women and men with overweight and obesity: The TREAT randomized clinical trial. *JAMA Intern Med* 2020;180:1-9.

Obesity prevalence in U.S. adults is at an alarming age-adjusted 42.4%.[1] Considering even modest weight loss appears to ameliorate insulin resistance and lower cardiovascular risk, identifying effective, simple, and acceptable ways for patients to achieve this goal is desirable. Intermittent fasting has been widely promoted in popular media as a means to lose excess body weight "without dieting." A specific type of intermittent fasting known as time-restricted eating (TRE) refers to eating within a specific period and fasting outside this period. Although TRE's benefits have been demonstrated in animal models, particularly obese mice, the literature regarding the benefits or effects on human populations is limited in quantity and quality.[2]

In this randomized, controlled trial by Lowe et al, TRE was compared to consistent meal timing (CMT). Participants of the TRE group were asked to restrict eating for a 16-hour period and eat ad libitum during an eight-hour window (noon to 8 p.m.). The CMT group consumed three structured

meals per day and was permitted to eat snacks between meals. The TRE group was permitted only noncaloric drinks outside the eating window. Neither groups were given a daily caloric restriction. The primary outcome assessed was weight loss for all participants. Secondary outcomes assessed for the in-person cohort included changes in weight, fat mass, lean mass, fasting insulin, fasting glucose, insulin resistance (HOMA-IR), hemoglobin A1c (HbA1c) levels, lipids (triglycerides, total cholesterol, low-density lipoproteins [LDL], and high-density lipoproteins [HDL]), estimated energy intake, total energy expenditure, and resting energy expenditure from an in-person cohort. Participants were recruited from across the United States between August 2018 and June 2019, and data collection was completed in October 2019. The total length of the study was 12 weeks.

Out of 1,975 potential candidates, 141 met inclusion criteria and were randomized to CMT or TRE intervention groups. Data were collected from 116 participants age 18 to 64 years with a body mass index (BMI) range of 27 kg/m^2 to 43 kg/m^2. However, only 105 participants completed the study. Of the 11 participants who did not complete the study, eight were lost to follow-up and three discontinued the intervention. An in-person cohort of 50 participants who lived within a 60-mile radius of the University of California, San Francisco (UCSF) was randomized and enrolled for metabolic testing, with 46 participants completing the four in-person visits. Data were collected via a mobile app created for the study, and patients received a Bluetooth scale that connected to the study app. The TRE group received daily reminders of their eating window through the app. All participants were instructed to use the scale daily in the morning before eating or drinking and before structured physical activity.

Looking at the weight change in the total cohort, there was a significant decrease in weight in the TRE group ($P = 0.01$) and a decrease in weight in the CMT group that was not statistically significant. Weight change between groups also was not statistically significant. Percentage decrease in weight from baseline was statistically significant in both the TRE group (-1.17%; 95% confidence interval [CI], -1.89% to -0.45%; $P = 0.002$) and the CMT group (-0.75%; 95% CI, -1.47% to -0.04%; $P = -0.04$), with no significant differences in results between these groups (-0.41%; 95% CI, -1.43% to 0.60%; $P = 0.43$).

In the in-person cohort, there were no statistically significant within-group or between-group differences in metabolic measurements (fasting glucose, fasting insulin, HOMA-IR, HbA1c, triglycerides, total cholesterol, LDL, or HDL levels). A significant decrease in appendicular lean mass was reported in the TRE group ($P < 0.001$) and between groups ($P = 0.009$), but not in the CMT group. There also was a significant decrease in appendicular lean mass index among TRE participants ($P < 0.001$) and between groups ($P = 0.005$), but not in the CMT group. Various other body composition measurements (e.g., fat mass, lean mass, waist and hip circumference) were assessed with no significant difference found between the groups. Finally, no adverse effects of either intervention were reported.

■ COMMENTARY

Although the simplicity of TRE eating may make it easy to implement, Lowe et al showed there was no statistically significant difference in weight changes or cardiometabolic markers for those who fast for an extended period during the day (TRE) compared to those eating three consistent meals per day (CMT). The strengths of this study include its randomized control design, the recruitment of participants from across the United States, and inclusion of an in-person cohort to assess metabolic marker measurements. This study was conducted for a period of three months, and there was a large percentage of participants who could be analyzed at the end of the study period.

However, there were some limitations. Although the primary objective was to assess the effects of TRE on weight loss and various metabolic markers, only one eating/fasting regimen (eight hours/16 hours) was assessed. The reasoning the authors offered for the chosen TRE interval was to mimic skipping breakfast for the participants, making it easier to adopt. Thus, results from this study may not be generalizable to all TRE regimens.

In a similar study by Chow et al, TRE was compared to an ad libitum diet, and participants randomized to the TRE group were allowed to self-select an eight-hour eating window.[3] In this study, the earliest end of the eating period chosen was 5 p.m. Although this was a small study population of 20 participants and did not address the contribution of TRE timing to the weight loss and metabolic improvements observed in study participants, it is reasonable to question whether alternative eating windows might affect results. Comparison of TRE to a single CMT structure of three meals daily also is a limitation of this study. Considering additional CMT eating schedules, such as six smaller, evenly distributed meals daily, would be a valuable enhancement.

Although sleep activity was recorded for participants, Lowe et al did not consider the circadian system in the intervention design. In previous animal models, researchers hypothesized the circadian system's role in regulating glucose, lipid, and energy metabolism throughout the day requires an appropriate alignment of feeding interval to result in improvement in these outcomes.[4-6] Indeed, in prior TRE trials in humans, results do appear to depend on the timing of the chosen eating window.[6]

Other studies of humans show eating a larger breakfast and a smaller dinner improves glycemic control, weight loss, lipid levels, and reduces hunger.[4] In human studies, the association between BMI and the timing of food intake strengthens substantially when considering food intake in relation to the internal circadian time, best aligned with sleep/wake cycles as opposed to time of day.[6]

The in-person cohort was derived from a select population near the UCSF campus. This population most likely is exposed to similar environmental, social, and economic factors, which may contribute to dietary choices.[7] It is possible that with a larger and more varied selection for the in-person cohort, results may have differed. The authors observed a significant decrease in appendicular lean mass and lean mass index in the TRE group, an observation that adds to findings from the current literature that have resulted in recommendations for protein supplementation for individuals using TRE for weight management.[3]

Ultimately, additional high-quality studies in human subjects are required to determine if this method of eating, or any of its variations, are safe to help with weight loss, especially those with weight- and diet-related health risks. The true test of a successful weight loss diet is long-term weight loss maintenance, and most studies to date have been conducted over a short period, often less than six months.[2-6] Because of the limited effect on weight reduction over a short period, no effect on cardiometabolic markers, and potentially significant reduction in measures of lean body mass, intermittent fasting currently cannot be recommended to patients as an alternative to calorie reduction and regular exercise for weight control. Longer-term studies of intermittent fasting regimens that account for circadian rhythms, employ food diaries to assess dietary quality, and track lean body mass changes are required to determine if sustained and meaningful weight loss or metabolic improvements can result from time-restricted eating. ■

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ABSTRACT & COMMENTARY

Is There an Ideal Time to Administer Antihypertension Medications?

By Michael H. Crawford, MD

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SYNOPSIS: Taking all antihypertensive agents before bed vs. upon awakening in hypertensive patients showed there was less hypertension during sleep and few cardiovascular events over a six-year follow-up.

SOURCE: Hermida RC, Crespo JJ, Domínguez-Sardiña M, et al. Bedtime hypertension treatment improves cardiovascular risk reduction: The Hygia Chronotherapy Trial. *Eur Heart J* 2020;41:4565-4576.

Although known to reduce sleeping blood pressure (BP), there are few data on the effect of bedtime administration of the entire daily dose of antihypertensive medications vs. administration upon awakening in the morning on BP control and cardiovascular (CV) outcomes. The Hygia Chronotherapy Trial was a randomized, multicenter, controlled, open-label, blinded, endpoint study of whether bedtime administration is superior. Hermida et al conducted this work in 40 primary care practices in Northern Spain, using 24-hour ambulatory BP (ABP) measurements to diagnose and manage hypertension. They recruited more than 22,000 patients with hypertension. Each participant underwent confirmatory 48-hour ABP measurements. After excluding those with an invalid study or normotension in untreated subjects, the authors randomized 19,168 subjects to all antihypertensive pharmacologic treatment at awakening or at bedtime. Pregnant patients, rotating shift workers, those with secondary hypertension, those

with known CV disease, and those with renal failure all were excluded. A minimum follow-up of one year was required, with a target of five years. Eighty-four subjects were excluded for failing to follow up at one year. In the final study population (19,084), the mean age was 61 years, and 56% were men. Each of the 292 physicians involved chose the antihypertensive drugs. At each outpatient visit (at least annually), 48-hour ABP was performed, with the subject noting in a diary when he or she retired and awakened. The primary outcome was a combination of myocardial infarction, coronary revascularization, heart failure, ischemic stroke, or CV death.

The bedtime group achieved lower sleeping BP readings than the morning group, but there was no difference in awake BP measurements. Sleep hypotension was rare (0.3% of participants), and there was no difference between groups. Poor drug compliance was about 3% for both groups. CV events occurred in 1,752 subjects over the median six-year follow-up. The adjusted hazard ratio (HR) for the combined primary endpoint in the bedtime group vs. the morning group was 0.55 (95% CI, 0.50-0.61; $P < 0.001$). The HR for CV death was 0.44 (95% CI, 0.34-0.56; $P < 0.001$). The HR for hemorrhagic stroke was 0.39 (95% CI, 0.23-0.65; $P < 0.001$). The HR for heart failure was 0.58 (95% CI, 0.49-0.70; $P < 0.001$). Total adverse events were not significantly different between groups (6.7% morning, 6% bedtime). No subgroup demonstrated better outcomes with morning drug administration.

The authors concluded bedtime administration of all antihypertensive medications resulted in lower sleeping BP control and markedly reduced CV events compared to taking all BP medications upon awakening.

■ COMMENTARY

Prior studies have shown ABP is superior for predicting outcomes in hypertensive patients, especially if blunted nocturnal BP reduction is detected (non-dipper pattern). Also, studies have demonstrated that bedtime administration of at least one antihypertensive medication abrogates the non-dipper pattern of sleep BP and lowers CV disease risk, but these studies did not include a control arm. In a randomized, controlled study, the authors observed 2,000 patients who experienced fewer CV events with bedtime drug administration compared to awakening.[1]

The strengths of the Hygia trial include its large size (almost 20,000 patients) and the use of primary care centers. Asking patients to keep diaries to establish the circadian pattern of sleep and awake periods was helpful. The 48-hour ABP tactic improved reproducibility. In addition, there was a long follow-up period, with a robust number of CV events. The Hygia study showed there was better sleeping BP control with bedtime drug administration without loss of awake BP control. There was less non-dipping observed in the bedtime group and markedly fewer CV events. Finally, bedtime administration was safe, and patient adherence was excellent.

But there were some weaknesses. First, the subjects were all Spanish Caucasians. Transferability to other ethnic groups is unknown. Second, the medication regimens used were not prescribed by the study protocol; rather, each participating physician devised his or her own treatment program. They were given the Spanish government's documents on selecting drugs for BP control, but how much they applied these recommendations is unknown. Third, the authors could not separate the effects of bedtime administration in dippers and non-dippers. Interestingly, there were other positive results of bedtime administration. Serum creatine and LDL cholesterol levels were lower, and HDL cholesterol levels were higher in the bedtime group.

How do clinicians translate these finding into practice? Not all medications may be well-tolerated when taken at bedtime (e.g., diuretics). In the Hygia study, there was less diuretic use in the bedtime group. However, there are studies that showed changing one medication to bedtime produced similar results as Hygia, and the medications shifted usually were calcium blockers or ACEI/ARBs. Culling one medication would thwart the triple-drug combination pills that are so popular with patients, but would solve the diuretic-before-bed issue.

The authors of other studies have suggested ACEI/ARBs would work best if taken at bedtime since the renin-angiotensin-aldosterone system is more active during sleep. The asleep mean SBP was 115 mmHg in the Hygia study, and hypotension during sleep was rare (0.3%). Still, the medications used here were calibrated by ABP, which usually would not be the case in U.S. clinical practice.

Finally, splitting the antihypertensive agents might reduce compliance if no other medication were taken twice a day. Thus, there are advantages to taking all the BP medications at once. I have moved at least one medication to the evening when patients note early morning hypertension, but may have to rethink my usual all-in-the-morning routine advice. Further trials that include more diverse populations would help me change my practice. ■

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PHARMACOLOGY UPDATE

Vericiguat Tablets (Verquvo)

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 has approved a treatment for patients with severe heart failure (HF) with reduced ejection fraction. Vericiguat is a soluble guanylate cyclase stimulator that relaxes smooth muscle and promotes vasodilation.[1] The FDA granted priority review. It is distributed as Verquvo.

INDICATIONS

Vericiguat is indicated to lower the risk of cardiovascular death and HF hospitalization in adults with symptomatic chronic HF and an ejection fraction less than 45%. The drug should be prescribed for these patients who also have been hospitalized recently for HF or need outpatient intravenous diuretics.[1]

DOSAGE

The patient should take 2.5 mg orally every day with a meal.[1] Double the dose about every two weeks to a target dose of 10 mg once daily, as tolerated. Vericiguat is sold as 2.5-mg, 5-mg, and 10-mg tablets.

POTENTIAL ADVANTAGES

Vericiguat provides a treatment option with a different mode of action to reduce the composite risk of death from cardiovascular causes or first hospitalization in patients with high-risk HF.

POTENTIAL DISADVANTAGES

Vericiguat may cause embryo-fetal toxicity. It should not be prescribed to pregnant women. Patients with reproductive potential should use an effective method of contraception.[1] Concomitant administration of a phosphodiesterase type 5 inhibitor is not recommended because of a higher risk of hypotension.[1] The most common adverse reactions vs. placebo are hypotension (16% vs. 15%) and anemia (10% vs. 7%).[1]

COMMENTS

Soluble guanylate cyclase is a key enzyme of the nitric oxide signaling pathway.[2] Impairment or dysregulation of this pathway has been implicated in the development and progression of HF. Vericiguat stimulates guanylate cyclase, resulting in smooth muscle relaxation and vasodilatation. Researchers evaluated efficacy in a randomized, placebo-controlled, double-blind study of subjects with symptomatic chronic HF and left ventricular ejection fraction less than 45% following a worsening HF event, the Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA).[1,3] An HF event was defined as HF hospitalization within six months before randomization or use of outpatient intravenous diuretics within three months before randomization. Subjects mainly were white (64%) and male (76%). A total of 22.4% were Asian. Fifty-nine percent were New York Heart Association (NYHA) class II and 40% were class III. The mean left ventricular ejection fraction was 29%, and 67% had been hospitalized for HF in the previous three months. The median biomarker, N-terminal prohormone B-type natriuretic peptide (NT-proBNP), level was 2,816 pg/mL. Ninety-three percent were on two or more standard drugs for HF. Subjects were randomized to vericiguat (n = 2,526) or placebo (n = 2,524). The primary endpoint was a composite of time to first event of cardiovascular death or hospitalization for HF.

The median follow-up was 11 months. The median dose of trial medication was 9.2 mg. The event rate percentage of patients/year was 33.6 for vericiguat vs. 37.8 for placebo, a 10% reduction in risk (HR, 0.90; 95% CI, 0.82-0.96; $P = 0.019$), an absolute rate reduction of 4.2 per 100 patient years. A reduction in hospitalization for HF, rather than death from cardiovascular causes, was the primary driver. Subjects in the highest baseline NT-proBNP quartile, compared to the other three quartiles, did not respond favorably to vericiguat. The benefit of vericiguat, relative to placebo, tended to be greater with longer duration since hospitalization, with less benefit in the subgroup randomized within three months of HF hospitalization when the risk for primary outcome was the highest.[4]

CLINICAL IMPLICATIONS

HF affects about 6.5 million adults, with approximately 1 million hospitalizations annually.[5] Approximately 50% of these are caused by HF with reduced ejection fraction. There are numerous pharmacological treatment options, including sodium-glucose cotransporter 2 inhibitors, angiotensin-converting enzyme inhibitors, beta-blockers, vasodilators, angiotensin receptor blockers, mineralocortisone receptor antagonists, and angiotensin receptor-neprilysin inhibitors.[5,6] Vericiguat provides a vasodilator with a different mode of action, producing benefit mainly in reducing HF hospitalization. The benefit appears to be modest; however, VICTORIA included sicker patients, with a higher percent with NYHA class III and higher median levels of NT-proBNP compared to previous HF studies with sacubitril/valsartan and dapagliflozin that showed a lower risk of

cardiovascular death and HF hospitalization or HF worsening.[7,8] The role of vericiguat remains to be determined, particularly when it comes to identifying which patients are more likely to benefit. The cost for vericiguat 10 mg is $583 for a 30-day supply. ■

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CME QUESTIONS

1. What level of egg consumption is associated with a lower risk of coronary artery disease?
a. No eggs
b. One egg/day
c. More than one egg/day
d. One egg three times per week

2. Time-restricted eating is best defined as:
a. alternating periods of fasting and eating every 24 hours.
b. consistent fasting and eating periods within a 24-hour cycle.
c. consistent fasting and eating periods within a 48-hour cycle.
d. cessation of the eating period by a set evening time.

3. A study of antihypertension medication administration at bedtime vs. at awakening showed:
a. less blood pressure reduction during sleep.
b. fewer cardiovascular events.
c. more early morning hypotension.
d. reduced control of awake blood pressure.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

Internal Medicine [ALERT]

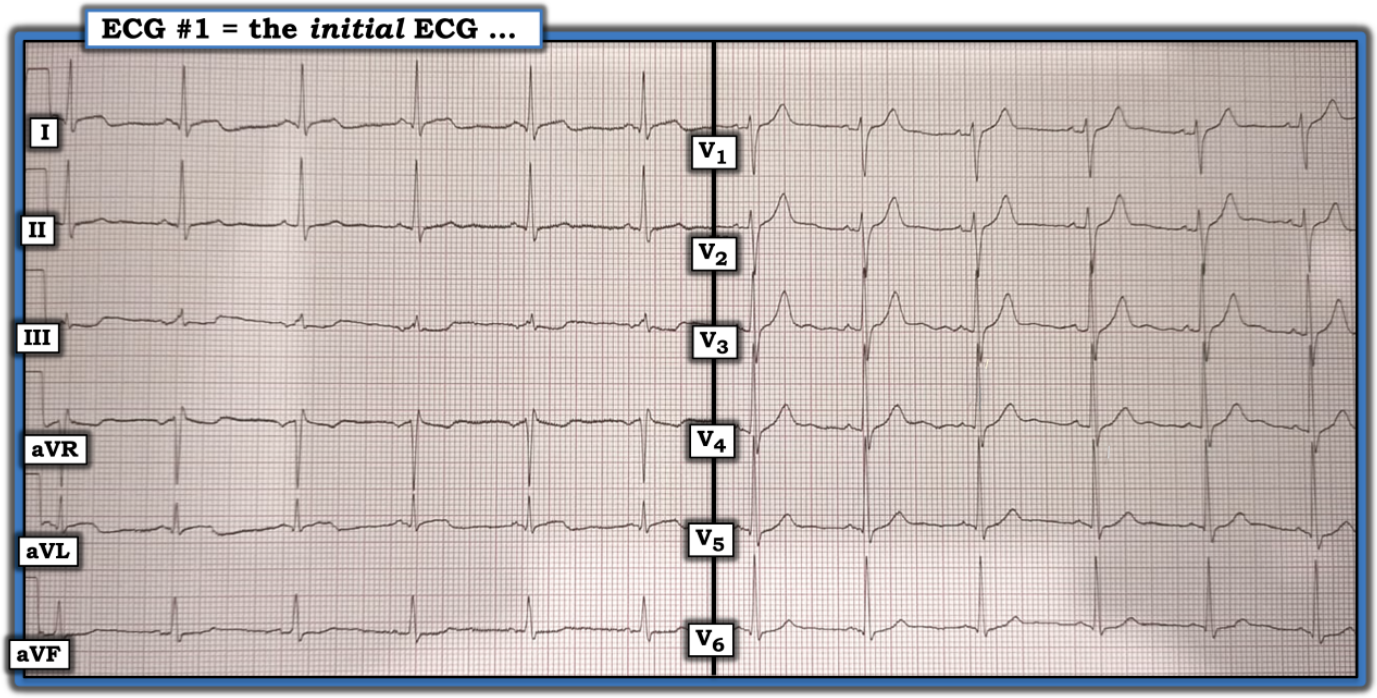
ECG Review

By Ken Grauer, MD

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

Acute Myocardial Infarction, or Related to COVID-19?

The ECG in the figure below was obtained from a man in his 30s. How would one interpret this tracing if told the patient's only symptom was recent shortness of breath on exertion that he had not experienced?



Notably, the patient's spouse has tested positive for COVID-19. Would one's interpretation of this ECG be different if told this patient reported new-onset chest pain instead of dyspnea? The ECG in the figure shows sinus rhythm with normal intervals and axis. There is no chamber enlargement. There are small septal q waves, and reasonable R wave progression. The remarkable findings relate to ST-T wave abnormalities in several leads.

There is subtle-but-real ST segment coving with slight elevation in high lateral leads I and aVL. Reciprocal ST-T wave depression is seen in leads III and aVF, with slight ST segment flattening in the remaining inferior lead (lead II). In a patient with new chest pain, these findings should suggest recent or acute infarction.

An additional abnormal finding in this ECG relates to the relative amplitude of the upright T waves in the six chest leads. In the absence of left ventricular hypertrophy, it is uncommon for an upright T wave in lead V1 to be taller than the upright T wave in lead V6. In a patient with new chest pain, the clearly more voluminous (i.e., taller in height and wider at its base) T wave in lead V1 compared to the T wave in lead V6 suggests there may be an ongoing ischemic process.

It turns out the history in this case was exactly as described in the opening paragraph. That is, this patient reported dyspnea on exertion of recent onset — and close exposure to a COVID-19-positive individual. This patient experienced no chest pain.

Unfortunately, a full evaluation was not performed at the time the patient was seen initially, so diagnostic considerations are presumptive. That said, the combination of a clearly abnormal ECG in this otherwise-healthy younger adult with COVID-19 exposure and recent dyspnea on exertion should suggest COVID-19-related myocarditis as the most likely explanation. Subsequent follow-up supported this presumption.

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