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Internal Medicine [ALERT]

Evidence-based summaries of the latest research in internal medicine

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ABSTRACT & COMMENTARY

Late Sunsets, Sleep Deprivation, and Adverse Outcomes

By Alan Z. Segal, MD

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

SYNOPSIS: All living organisms have 24-hour circadian rhythms. A growing body of evidence shows that chronic disruption of this important rhythm may result in poor health outcomes. These negative consequences of disrupted circadian rhythms might be prevented by modifying work and sleep schedules.

SOURCE: Guintella O, Mazzonna F. Sunset time and the economic effects of social jetlag: Evidence from US time zone borders. *J Health Econ* 2019;65:210-226.

Circadian rhythms are present in every living thing. Even simple prokaryotes, such as cyanobacteria, modulate their metabolism based on the wavelength of exposed light. In 2017, the Nobel Prize for Medicine was given to researchers who unlocked the molecular and genetic basis of circadian functions in the drosophila fruit fly. There are multiple determinants of circadian function (known as "zeitgebers," or timekeepers), the most important of which is blue light. The supraoptic nucleus of the hypothalamus is regulated directly by the intensity and timing of exposure to light. Melatonin (the hormone of darkness) is produced by the hypothalamus and is another important circadian regulator. Beyond melatonin, multiple hormones cycle on a circadian basis, the most important of which are cortisol and growth hormone. Hypothalamic temperature regulation also follows a circadian pattern, with a typical body temperature nadir occurring three hours before waking. Appetite and weight are linked to circadian function, including the effects of leptin (which promotes satiety) and ghrelin (which increases hunger). Circadian rhythms affect immune and inflammatory regulation and likely modify the epigenetic modulation of DNA.

Despite these factors, human society has attempted to wrestle control over the circadian clock by creating work schedules (particularly night shifts) that contradict cycles of natural light. While "jet lag" is a transient travel-related disruption in sleep-wake schedules,

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"social jet lag" is a more chronic process, ingrained in the habits of our daily lives.

Although the Earth's rotation takes 24 hours, experiments in humans deprived of natural light or among the blind who cannot detect any light, show that the circadian cycle actually could extend to 24.5 or even 25 hours. Desynchronization between the circadian and "ultradian" cycles results in a disorder known as "hypernychthemeral syndrome" or "non-24," in which small alterations in cycle length add up from day to day, resulting in significant disruptions in sleep-wake cycles. Research in this area is challenging, as subjects in an experimental "free running" paradigm must spend days sequestered in a state of constant dim light exposure, deprived of TV or any other external cue of day or night.

Time zones are one example of a human construct superimposed on the natural variations of day and night. Within any given time zone, sunset times are not constant, but rather get progressively later as one proceeds westward, with the latest sunset being at the utmost western border of each zone. Over this western time zone boundary, sunset shifts an hour earlier as the clock is turned back. Despite these sunset differences, work, school, and social schedules remain fixed, with rigid morning starting times regardless of location within a time zone. Exploiting these variations, Guintella and Mazzonna compared sleep times (using data derived from Fitbit-type devices) across each of the four continental U.S. time zones. They studied sleep geographically at the county level and ZIP code level, and as a continuous variable across the time zone. Data were derived further from the American Time Use Survey (ATUS) and Behavioral Risk Factor and Surveillance Survey (BRFSS).

Living on the "late sunset" (westernmost) side of a time zone resulted in an average of 19 fewer minutes sleep per night compared to living at the easternmost sector of the next time zone. Alternatively, using eight hours as an "optimal" sleep duration, the "late sunset" cohort was 8% less likely to achieve the necessary amount of sleep. The subjects were divided into "employed" (which included students) and "non-employed." Both groups were affected by "social jet lag," but in different ways. Living at the westernmost sections promoted late bedtimes, but this effect was more pronounced in the non-employed. While the employed were 34% more likely to be awake at midnight, the non-employed were 41% more likely to be awake at that hour. For individuals who started work at 7 a.m., their average sleep duration was 36 minutes shorter. Westernmost location promoted late wake-up times, particularly among the non-employed. While employed people were equally likely to be awake at 7:30 a.m. regardless of time zone location, non-employed people in the westernmost locations were 32% more likely to be asleep at that hour.

In addition to sleep times, health outcomes also were affected adversely. Individuals at the western boundary were 11% more likely to be overweight, a difference that reached statistical significance. There were additional nonsignificant trends toward other adverse health outcomes, such as diabetes, cardiovascular disease, and breast cancer. Overall, "self-reported health status" was 2% worse with late sunsets, but this did not reach statistical significance. The authors used "back of the envelope calculations" to estimate economic consequences. They determined that circadian misalignment increases healthcare costs by $2 billion. Productivity losses induced by the extra hour of light in the evening were calculated to total 4.40 million days of work nationwide. There was an estimated 3% decrease in income among those living on the western side of a time zone. Total economic losses were estimated to be $2.35 billion (approximately $82 per capita). The authors calculated that a one-hour increase in daily sleep increases productivity to a greater extent than a one-year increase in education.

■ COMMENTARY

A growing collection of data shows that sleep plays a key physiological role in the "glymphatic" system of the brain, a "dish-washing" mechanism that widens gap junctions and facilitates the removal of toxins. Multiple studies indicate that high-quality sleep, with increased periods of REM and slow-wave sleep, promotes clearance of substances such as amyloid and tau proteins. Although day-to-day deficiencies in sleep duration promote cognitive loss (impairments in vigilance), more chronic cumulative sleep

loss may produce more permanent effects, including possibly Alzheimer's disease.

Seasonal differences in light exposure and sleep times may provide quasi-experimental data similar to this time zone investigation. Although daylight duration varies from 14 hours in summer to only eight hours in winter, humans sleep a fixed amount of time. This effect is strongly driven by latitude and perhaps would be less pronounced closer to the equator. It is possible that bears or other hibernating animals behave in a more physiologically favorable manner, staying active in summer and sleeping for long periods during the winter, allowing for a cumulative clearance of central nervous system toxins. As this study suggests, there would be benefits from more flexibility in work schedules. Although banks or public offices may follow a strict 9 a.m. to 5 p.m. day, retail stores maintain potentially more realistic hours, shifted to 10 a.m. to 6 p.m. or possibly an even later interval. While television schedules are modified to broadcast at appropriate times across Eastern to Pacific time zones, there is no such modification of show times within any given time zone. Modern TV practices, with streaming of content and "binge watching," would provide for more flexibility, but may produce as-yet unrecognized adverse effects on sleep health. ■

ABSTRACT & COMMENTARY

How Safe Are New Medications for Type 2 Diabetes?

By Joseph E. Scherger, MD, MPH

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

SYNOPSIS: In recent years, new medications have been approved for the management of type 2 diabetes, generally after metformin is given. The FDA has reported 55 cases of Fournier's gangrene in patients using SGLT2 inhibitors. These medications may not be worth the risk when lifestyle alternatives are available.

SOURCE: Bersoff-Matcha SJ, Chamberlain C, Cao C, et al. Fournier gangrene associated with sodium-glucose cotransporter-2 inhibitors: A review of spontaneous postmarketing cases. *Ann Intern Med* 2019; May 7. doi: 10.7326/M19-0085. [Epub ahead of print].

The FDA released a report of 55 cases of Fournier's gangrene (FG) in patients who received SGLT2 inhibitors between March 1, 2013, and Jan. 31, 2019. The patients ranged in age from 33 to 87 years. Thirty-nine were men and 16 were women. The time for onset of this serious complication ranged from five days to 49 months. All the patients had surgical debridement and were severely ill. Other complications included sepsis or septic shock (nine patients), diabetic ketoacidosis (eight patients), and acute kidney injury (four patients). Eight patients underwent fecal diversion surgery, two patients developed necrotizing fasciitis of the lower extremity and required an amputation, and three patients died.

For comparison, the FDA identified 19 cases of FG with other antiglycemic medications during a longer period, from 1984 to Jan. 31, 2019. Eight of these patients were on metformin, six were on insulin glargine, two were on short-acting insulin, two were on sitagliptin plus metformin, and one was on dulaglutide. These patients ranged in age from 42 to 79 years. Two patients died.

At the time of this report, the FDA is calling for more awareness among physicians regarding this major complication for patients taking an SGLT2 inhibitor.

■ COMMENTARY

In recent years, many new medications have been approved to treat type 2 diabetes. These have been grouped into several classes based on their mechanism of action. All except metformin and the sulfonylureas are expensive. The FDA report is alarming in that FG is a major complication certain to harm patients, if not lead to their mortality.

Increasingly, healthcare professionals recognize that the major cause of type 2 diabetes is insulin resistance resulting from a diet high in processed carbohydrates.[1] A growing number of clinics and academic health centers are reversing type 2 diabetes using a very low carbohydrate diet and intermittent fasting.[1-3] In *The Diabetes Code* by Jason Fung, part four of the book is titled, "How Not to Treat Type 2 Diabetes."[1] Here, Fung details each medication and cites why they are counterproductive in managing the underlying disease.

While the medications may make the numbers look better, such as blood sugar and HbA1c, they generally make disease characteristics such as body weight, insulin resistance, and fatty liver disease worse, or do not reduce the complications of diabetes (e.g.,

heart disease). SGLT2 inhibitors are not the only medications for type 2 diabetes that can produce major side effects. Insulin causes hypoglycemia, increases weight gain, worsens metabolic syndrome, increases overall mortality, and increases the risk of cancer.[4-6] Similar side effects occur with taking sulfonylureas.[1] Thiazolidinediones fell out of use because of increased heart disease and cancer risk.[7,8] Taking DPP-4 inhibitors does not lead to weight gain and can be effective against diabetes, but using these inhibitors does not lower heart disease risk.[9]

Since studying this new material on reversing type 2 diabetes through diet and other lifestyle measures such as daily exercise, I only treat this disease with diet and metformin, usually at the lower dose of 500 mg twice daily. I have seen patients lower their HbA1c from very high levels (over 12) to normal. Motivational counseling and lifestyle education are the key skills my team and I use to reverse this disease. Most patients are not aware that their diabetes is reversible. American medicine and medical education are centered on prescribing medications and performing procedures at great cost to society. My team manages chronic diseases that are reversible through lifestyle changes.

There is an exciting paradigm shift underway that all primary care physicians should be embracing. We can restore health in ways we never thought possible. Not all patients are willing to change, and we will still have to provide disease management (what I call palliative care) to some patients with type 2 diabetes and other reversible chronic health problems. ■

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ABSTRACT & COMMENTARY

The Promise and Perils of the Apple Heart Study

By Joshua D. Moss, MD

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Dr. Moss reports he is a consultant for Abbott, Boston Scientific, and Medtronic.

SYNOPSIS: A large study with virtual enrollment of Apple Watch users helped illustrate the positive predictive value of wearable, pulse-based atrial fibrillation detection technology, as well as the ability to enroll and follow huge numbers of research subjects in a short period.

SOURCE: Turakhia M, Perez M. Results of a large-scale, app-based study to identify atrial fibrillation using a smartwatch: The Apple Heart Study. Presented March 16, 2019, at the 2019 American College of Cardiology Scientific Sessions, New Orleans.

The Apple Watch can measure heart rate and regularity via photo plethysmography, which uses changing absorption of green or infrared light to detect the pulse in the wrist. The goal of the Apple Heart Study was to evaluate the ability of this watch to identify subjects with atrial fibrillation (AF) and help guide subsequent clinical evaluation.

U.S. residents who were at least 22 years of age, did not already have a diagnosis of AF or atrial flutter, and were not using anticoagulation were given the opportunity to enroll virtually via their Apple Watch and iPhone. Over eight months, 419,297 subjects enrolled. Once enrolled, the watch would take periodic, opportunistic measurements of the pulse rate and regularity via generation of a tachogram. A positive finding, suggestive of AF, would trigger more frequent passive measurements. Then, five confirmations would generate a notification to the subject of an irregular pulse. Those subjects were connected to a telehealth

doctor who could refer them for additional care or mail them an ECG patch. The primary endpoints were AF confirmed by the ECG patch in subjects ≥ 65 years of age and simultaneous AF noted on the ECG patch and via the watch.

The mean age of enrolled subjects was 41 ± 13 years. Eighty-four percent of subjects were younger than 55 years of age. A majority of subjects were younger than 40 years of age. About 6% of the enrolled population were ≥ 65 years of age. Over the course of the study, 2,161 subjects (mean age, 57 years) received an irregular pulse notification. The notification rate was about 3% in subjects ≥ 65 years of age, about 0.37% in subjects 40-54 years of age, and about 0.16% in subjects 22-39 years of age.

Of these 2,161 subjects, 945 completed a first telehealth visit, and 658 went on to receive an ECG patch. A total of 450 subjects wore the patches and returned them for analysis (0.1% of the original cohort and 21% of those who received irregular pulse notifications). The CHA_2DS_2-VASc score was ≥ 2 in 13% of the original cohort, 33% of the cohort who received an irregular pulse notification, and 38% of those who wore and returned an ECG patch. The patch yielded a diagnosis of AF for 34% of subjects. The longest episode was one hour or longer in 89% of subjects with AF on the patch. A 90-day survey of subjects who received an irregular pulse notification revealed that 15% of those subjects had received an AF diagnosis prior to study enrollment. While wearing the patch and the watch, an irregular tachogram carried a positive predictive value of 0.71 for true AF (0.60 in patients ≥ 65 years of age). An irregular pulse notification carried a positive predictive value of 0.84 for true AF (0.78 in patients ≥ 65 years of age).

■ COMMENTARY

The Apple Heart Study received a great deal of attention both at the American College of Cardiology Scientific Sessions and in the media — and for good reason. It was remarkable in its size and scope, particularly considering that enrollment and data collection occurred over only about eight months. The data accrued add valuable information about the demographics of AF in the United States, although limited to a small subset of the population with the means and desire to purchase and wear an Apple Watch, as well as the willingness to complete the less passive portions of the study (only 21% of the enrolled subjects who received an irregular pulse notification went on to wear and return an ECG patch for analysis).

It is safe to say that the study confirmed the ability of the watch to detect AF via background monitoring. Virtually all cardiologists who treat AF commonly have now met patients who discovered their arrhythmia via a watch notification. However, the actual sensitivity of the algorithm is unknown, considering the lack of gold-standard diagnostic information (or almost any information) about the vast majority of patients who never received an irregular pulse notification. How many of them actually had AF while wearing the watch? A basic analysis of the available data from the tiny subset (0.1% of the overall cohort) who simultaneously wore an ECG patch and the watch suggests that 81 of the 450 must have had true AF on the patch yet received no irregular pulse notification, compared with 72 who had AF and did receive a notification. The calculated "instantaneous" sensitivity is only 47%, although the watch had generated an irregular pulse notification for every one of those patients at some point. False-positive pulse notifications were less common, but about 5% of patients without AF on the ECG patch still received a notification from their watch.

It is interesting that the positive predictive value for watch notifications was slightly *lower* in older patients compared with the rest of the population. A similar analysis of the cohort of ECG patch wearers who were ≥ 65 years of age suggests an "instantaneous" sensitivity of only 40% and specificity of 94%. While chance could play a role, I suspect older patients simply experience more frequent atrial and ventricular ectopy, the irregularity of which could result in a false-positive tachogram. In a large population, even a relatively small rate of false-positive indications (which will be amplified with longer periods of wearing the watch) may generate a tremendous amount of unnecessary anxiety, testing, and treatment. Therein lies one potential peril. Treatment of AF and anticoagulation for stroke prevention both carry risks, and confirmatory monitoring will undoubtedly reveal other abnormalities that may or may not have become clinically significant. On the other hand, if the true sensitivity of the watch is less than 50%, there also is risk of false reassurance and undertreatment of true disease.

That said, I find it difficult to argue that patients should not be empowered to monitor themselves for conditions that potentially put them at risk. Any motivated patient can check their own pulse many times per day; the watch simply makes that process easier. The added burden to clinicians will come largely from the need for much more discussion with patients about the relative merits and risks of all the potential downstream tests, medications, and procedures.

The healthcare community will need to learn how to build an infrastructure to handle this added burden, which will undoubtedly extend to more disease processes going forward. In the meantime, we will need to use the opportunity and technology to conduct more rigorous studies, even if on a smaller scale, to test the true benefit and risk of continuous pulse screening so that patients can be advised accurately. ■

PHARMACOLOGY UPDATE

Erdafitinib Tablets (Balversa)

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.

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

The FDA has approved the first targeted therapy for metastatic bladder cancer. Erdafitinib is a kinase inhibitor that targets genetic alterations of certain fibroblast growth factor receptors (FGFRs). These regulate biological processes, including cell growth and division.[1] Erdafitinib received breakthrough therapy status and accelerated approval based on tumor response rate. Further clinical trial data are required to confirm the clinical benefit of erdafitinib. It is marketed as Balversa.

INDICATIONS

Erdafitinib should be used to treat locally advanced or metastatic urothelial (transitional cell) carcinoma with susceptible FGFR3 or FGFR2 genetic alterations in patients who progressed during or following at least one course of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.[1] Patient selection should be based on an FDA-approved companion diagnostic device (therascreen FGFR RGQ RT-PCR Kit).

DOSAGE

The recommended initial dose is 8 mg (2 × 4 mg) orally once daily with a dose increase to 9 mg (3 × 3 mg) once daily based on serum phosphate levels and tolerability at 14 to 21 days.[2] Treatment should be continued until disease progression or unacceptable toxicity. Dose modification/reduction is recommended because of adverse reactions (e.g., hyperphosphatemia, ocular disorders).[2] Erdafitinib is available as 3 mg, 4 mg, and 5 mg tablets.

POTENTIAL ADVANTAGES

Erdafitinib offers the first targeted therapy for bladder cancer patients with susceptible FGFR mutations.

POTENTIAL DISADVANTAGES

Erdafitinib can cause central serous retinopathy/retinal pigment epithelial detachment, resulting in visual field defect.[2] This was reported in 25% of treated patients. Regular ophthalmological examination is recommended. Hyperphosphatemia was reported in 76% of patients.[2] Thirty-two percent of patients received phosphate binders during treatment. Erdafitinib may cause embryo-fetal toxicity. Erdafitinib causes a wide variety of adverse events involving numerous organ systems and laboratory abnormalities.[2] Grade 3 or higher adverse events include stomatitis (9%), hand-foot syndrome (6%), hyponatremia (16%), and onycholysis (10%). Erdafitinib can produce significant drug-drug interactions with strong/moderate CYP2C9 and CYP3A4 inhibitors and inducers as well as drugs that are substrates for these isoenzymes and transporters such as organic anion transporter 2 and P-glycoprotein.

COMMENTS

The efficacy and safety of erdafitinib were evaluated in an open-label, single-arm study that included 87 subjects with locally advanced or metastatic urothelial carcinoma.[2] Subjects were screened for FGFR3 gene mutations or FGFR gene fusions. Dosing started at 8 mg daily and increased to 9 mg once daily in subjects with serum phosphate levels below the target of 6.5 mg/dL between days 14 and 17. Erdafitinib was continued until disease progression or unacceptable toxicity. The primary efficacy endpoint was objective response rate (ORR) and duration of response (DoR) based on the RECIST v1.1 criteria determined by a blinded independent review committee. RECIST is a standardized measurement of solid tumor burden assessed primarily by imaging (e.g., MRI, CT).[3] Ninety-seven percent of subjects received at least one course of cisplatin or carboplatin previously. Twenty-four percent had been treated with an anti-PDL1/PD-1 agent (i.e., checkpoint inhibitors). The ORR rate was 32.2%, with 29.9% as partial response. Results were better with FGFR3 mutations (40.6% vs. 11.1% for FGFR3 fusion).

CLINICAL IMPLICATIONS

Bladder cancer is the sixth most common cancer in the United States.[1] Up to 21% of locally advanced or metastatic urothelial carcinomas have FGFR alterations, which is considered the third highest mutated cancer.[1,4] Platinum-based chemotherapy has been the standard of care for advanced or metastatic bladder cancer. Checkpoint inhibitors (e.g., atezolizumab, pembrolizumab), which act by "releasing the brakes" on the immune system, have been approved for patients who have progressed during or after platinum-based chemotherapy, who are not eligible for cisplatin-containing chemotherapy, and whose tumors expressed PD-L1 or are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. Erdafitinib offers a potential option for those with susceptible mutations who have progressed on platinum therapy or on a checkpoint

inhibitor or when the latter is not an option. A clinical trial is currently in progress that compares erdafitinib with docetaxel or vinflunine (not available in the United States) or pembrolizumab in participants with advanced urothelial cancer and selected FGFR mutatons.[5] The estimated completion date is November 2020. The cost of therapy is $20,160 for a 28-day supply of 8 mg, $22,680 for a 28-day supply of 9 mg. ■

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CME QUESTIONS

1. **Why are circadian rhythms important?**
   a. Circadian rhythms determine when we wake up and when we go to sleep.
   b. Circadian rhythms regulate vital metabolic and hormonal functions.
   c. Circadian rhythms are tightly linked to times of sunrise and sunset.
   d. Circadian rhythms do not affect brain health.

2. **What treatments are most effective at reversing type 2 diabetes?**
   a. Metformin
   b. Dipeptidyl peptidase-4 inhibitors
   c. A low-fat diet
   d. A low carbohydrate diet with exercise and intermittent fasting

3. **The Apple Watch study for detecting atrial fibrillation showed that:**
   a. investigators could enroll many patients quickly.
   b. 25% of subjects received an irregular pulse notification.
   c. 90% of those notified responded.
   d. the positive predictive value for finding true atrial fibrillation was 0.50.

CME OBJECTIVES

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

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

[IN FUTURE ISSUES]

Sacubitril-Valsartan Reduces Functional Mitral Regurgitation

Physicians Cannot Agree on Who Benefits From ICU Care

Neuropathy in Systemic Lupus Erythematosus

Internal Medicine [ALERT]

ECG Review

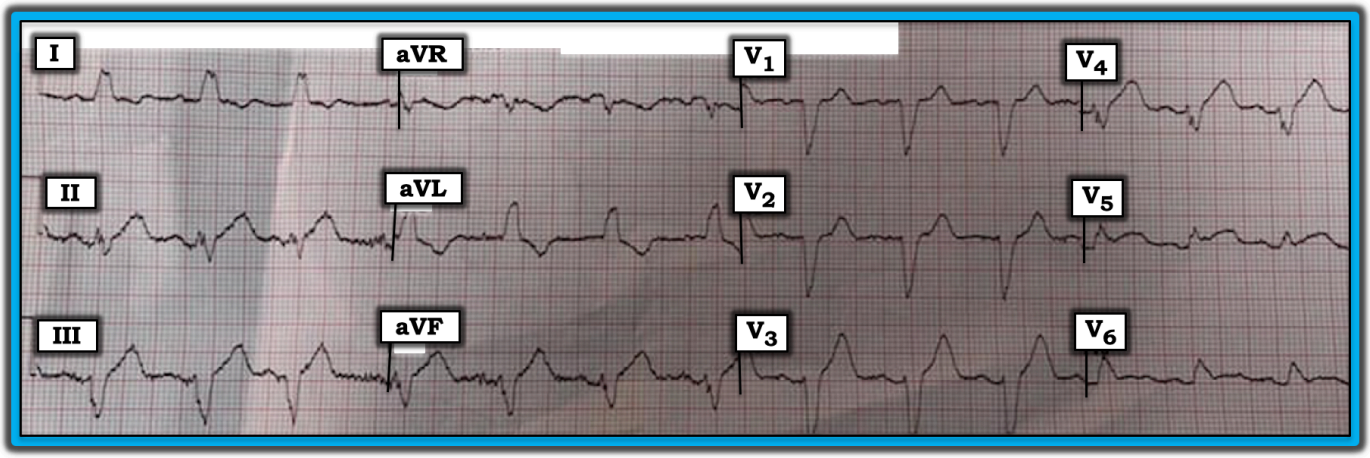
By Ken Grauer, MD

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

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

Why Is the QRS Wide?

The ECG in the figure below belongs to an older woman who called EMS because of new-onset chest pain. How might one interpret the tracing? Why is the QRS complex wide?



The rhythm is sinus at ~85 beats/minute. The QRS complex is wide. QRS morphology is consistent with complete left bundle branch block (LBBB) in that there is a monophasic R wave in left-sided leads I and V6 and a predominantly negative QRS complex in right-sided lead V1.

Much of the time, a diagnosis of acute myocardial infarction (MI) will be more difficult in the setting of complete LBBB. That said, there are instances in which definitive diagnosis of an acute ST-segment elevation MI (STEMI) is possible. The ECG in the figure is one of those instances. Typically, with either left or right bundle branch block, the direction of the ST-T waves in the three key leads (I, V1, and V6) will be opposite the last QRS deflection. For example, since the QRS complex in left-sided leads I and V6 is all upright when there is complete LBBB, we expect the ST-T wave to be oppositely directed, or negative. Instead, there is subtle-but-real ST elevation in lead V6. Leads V4 and V5 exhibit an even more abnormal appearance. That is, there is frank ST elevation in lead V5, which should not be there, and the T wave in lead V4 is hyperacute (disproportionately tall, fatter than expected at its peak, and unusually wide at its base). Similar hyperacute changes can be observed for the ST-T waves in each inferior lead. Although more subtle in leads III and aVF, there is little doubt that the ST-T wave in lead II is disproportionately tall, fatter than expected at its peak, and much wider than expected at its base.

This patient was in process of evolving a large acute inferoposterolateral STEMI, with development of this new LBBB just minutes after the initial ECG was recorded. The patient was taken to the cardiac catheterization lab soon after arrival at the hospital. The "culprit" artery was the obtuse marginal branch of the left circumflex artery.

For more information and further discussion on this case, please visit: http://bit.ly/2Zheqjh.