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INSIDE

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Sleep: The New Heavyweight in Weight Control?

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky; Director, Sleep Disorders Center, Samaritan Hospital, Lexington

Dr. Phillips serves on the speakers bureau for PotomaCME.

Synopsis: *Short (< 7 hours/night) sleep duration is associated with increased BMI and increased genetic influences on BMI. Longer sleep duration may reduce genetic influences on body weight.*

Source: Watson NF, et al. Sleep duration and body mass index in twins: A gene-environment interaction. *Sleep* 2012;35:597-603.

THE AUTHORS OF THIS PAPER SET OUT TO LEARN WHETHER HOW LONG someone sleeps affects his or her body mass index (BMI) as a factor independent from their environment or genetic tendency to put on weight. To do this, they used the University of Washington Twin Registry, which is a community-based sample of twins recruited from the general population of Washington state. All twins were raised together, so environmental and genetic characteristics were matched. The study sample for the current analysis was 2176 individuals from 1088 complete twin pairs (604 monozygotic and 484 dizygotic). Overall, the sample was young (mean 36.6 years), well educated (41% with a college degree or higher), predominantly Caucasian (89%), and female (66%). The most common twin relationship was female monozygotic pairs (38%).

Self-reported usual sleep duration was obtained from responses to the question, "On average, how long do you sleep per night?," reported in hours and minutes. For this study, "normal" sleep duration was considered 7-8.9 hours/night, "short sleep" was < 7 hours/night, and "long sleep" was > 9 hours per night. As a whole, the sample mean sleep duration was 7.2 hours/night (standard deviation = 1.2). In this sample, 317 pairs were short sleepers. The short-sleeping group was 70.0% female, with a mean age of 39 years and a mean sleep duration of 6.06

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hours. The normal sleepers were the largest group, made up of 72 pairs, with a mean age of 35.7 years and a mean sleep duration of 7.53 hours. This group was 70% female. There were 47 pairs of long sleepers, whose mean age was 33.3 years and mean sleep duration was 9.3 hours. This group was 73.4% female.

BMI was calculated from self-reported height and weight and was treated as a continuous variable for analytic purposes.

The authors calculated the twin correlation for BMI, separately by zygosity and sleep group. The twin correlations were used to calculate three different quantities: 1) heritability, 2) shared environmental influences, and 3) nonshared environmental influences. Because the long sleepers were slightly younger and more likely to be female, the investigators calculated the twin pair correlations for BMI stratified by sex and age group.

The investigators then fit a more rigorous biometric genetic model for gene-environment interactions, which I frankly don't understand, and certainly cannot make comprehensible to someone else. But to give you a flavor of this part of the discussion, here is an excerpt: "heritability of BMI at any value for sleep duration (x) can be calculated as:

$$h^2 = \frac{(a_0 + a_x \bullet x)^2}{(a_0 + a_x \bullet x)^2 + (c_0 + c_x \bullet x)^2 + (e_0 + e_x \bullet x)^2}."$$

The point was to estimate the relative influences of genes, environment, age, and gender on the effect of sleep duration on BMI. It is probably worthwhile to note at this juncture that this analysis required a fair bit of estimation and that there are very few truly qualified peer reviewers of this work.

Overall, there was a significant main effect of sleep duration on BMI, with longer sleepers having slightly lower BMIs. The investigators also found that males and older adults reported significantly shorter sleep duration, and older adults were heavier.

With regard to the effect of sleep duration on BMI, the investigators found that for the short-sleeping twin pairs, additive genetic influences accounted for 70% of the variance in BMI, whereas shared environmental factors accounted for just 4%. In contrast, for twin pairs averaging ≥ 9 hours of sleep per night, additive genetic factors accounted for just 32% and shared environmental influences accounted for 51%. In addition, a significant negative interaction between genes and sleep duration was noted, indicating that genetic influences on BMI decrease with increasing sleep duration. At the same time, there was a significant positive interaction between shared environmental influences and sleep duration, indicating that shared environmental influences on BMI increase with increasing sleep duration. These findings suggest that genetic influences on BMI are moderated by habitual sleep duration, with genetic influences predominating in short sleepers and environmental influences predominating in long sleepers.

These authors also examined genetic and environmental influences on sleep duration. Of the total variance in sleep duration, 34% was due to additive genetic influences and the remaining 66% to nonshared environmental influences. When looking at the genetic and environmental influences on BMI, they found significant genetic, shared environmental, and nonshared environmental influences on BMI (all $P < 0.05$) after controlling for the main effects of sleep duration, age, and sex.

■ COMMENTARY

In our overweight, increasingly health-conscious culture, new information about factors influencing weight receives a lot of attention. For example, the *AMA Morning News* (May 2, 2012) included the following blurb, "Extra sleep may help overweight people lose weight. *NBC Nightly News* (5/1, story 11, 0:25, Williams) reported, 'New research out tonight shows that getting a lot of sleep like more than nine hours a night could help overweight people slim down,' while 'sleeping fewer than seven hours a night was associated with higher weight.' Scientists arrived at this conclusion 'by putting sets of twins through different sleep conditions. Researchers think extra rest can work to suppress a gene that is connected to obesity.'"

Let's be clear here. With all due respect to Brian Williams, this was not a randomized, controlled trial, and investigators did not "put sets of twins through different sleep

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Questions & Comments
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conditions." Sleep duration was self-reported, as it almost always is in these kinds of studies. And, as pointed out in this study, sleep duration is under both genetic and environmental control. But, the frenzy in the lay press resulted in a couple of visits to my sleep medicine clinic by patients who wanted to sleep more so they could lose weight.

This study also adds to our understanding of the fascinating association between habitual sleep duration and health in general. The "right" amount of sleep for humans is a topic of fierce debate. Normal humans sleep 7 to 7.9 hours when left alone to do as they wish.[1,2] Sleep duration is both genetically and environmentally influenced, and the heritability of sleep duration is between 31% and 55%.[3-5] However, over the past century, habitual sleep duration has dropped 1.5 hours per night, and since 2001 the percentage of U.S. adults getting at least 8 hours of sleep per night on weeknights has fallen from 38% to 27%.[6,7]

There is evidence that habitual short sleep is associated with obesity.[8,9] But much of the data about sleep duration and health outcomes (from death to hypertension) has indicated a U-shaped relationship between sleep duration and outcomes, with both short (typically ≤ 7 hours per night) and long (typically ≥ 9 hours per night) sleep durations associated with increased risk of adverse outcomes.[10-13] Indeed, several previous studies have demonstrated higher weights for both long and short sleepers.[14,15] However, the population examined in the current study was younger than in many previous studies of this issue, and it is possible that young individuals are more susceptible to the effects of sleep curtailment than are older ones.

What should you tell patients who ask you about this? The main finding of this study is that if you habitually "sleep short" (≤ 7 hours a night) you are likely to have a higher BMI and to have genetic, rather than environmental factors influencing your propensity to gain weight. Conversely, "long sleepers" (≥ 9 hours/night) experience greater influence of environmental factors (which presumably includes diet and exercise, although the authors never say so) on BMI. In addition, sleep duration itself is influenced both by genetics and by environment. One interpretation here is that longer sleep may enhance your environmental efforts (e.g., eat less, move more) to lose weight, but cannot make you lose weight in and of itself. Or, as the authors put it, "…the most parsimonious interpretation of our data is that sleep curtailment activates obesity-related genes." But for an individual who comes from a long line of obese people, longer sleep may help to liberate him or her somewhat from whatever genetic tendency he/she has to put on weight. Sadly, at the end of the day, weight is still determined by calories in and calories out. ■

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Short-term Prescriptions for Analgesics can Lead to Long-term Use

ABSTRACT & COMMENTARY

By Rahul Gupta, MD, MPH, FACP

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

Synopsis: *Elderly patients are often prescribed analgesics after ambulatory and short-stay surgery which may lead to their long-term use.*

Source: Alam A, et al. Long-term analgesic use after low-risk surgery: A retrospective cohort study. *Arch Intern Med* 2012; 172:425-430.

Pain control following surgery is a major priority for both the patient and the physician. It is a common practice to prescribe analgesics to patients undergoing ambulatory and short-stay surgery. From the prescriber's point of view, it is important to keep the patient pain free during the postoperative period. This helps reduce suffering and maintains the patient in a comfortable state during the recovery period. The most common analgesics prescribed in such situations are opioids and nonsteroidal anti-inflammatory drugs (NSAIDs). These medications must be used judiciously since the short- and long-term use of both opioids and NSAIDS is associated with significant adverse effects. In patients undergoing surgery, overprescription of opioids is common and retained surplus medication presents a readily available source of opioid diversion. In one such study, it was reported that more than 40% of the narcotic medication prescribed after ambulatory surgery or hospital discharge remained unused and nearly two-thirds of patients had leftover medication with no disposal instructions for the surplus medication.[1] Not only does this present a risk of opioid diversion but the long-term use, especially among the elderly, can lead to physiologic tolerance, addiction, and other drug-related issues.

In their study, Alam et al aimed to determine whether de novo administration of analgesics to elderly patients after short-stay operations was associated with long-term use of these medications. Researchers conducted a retrospective, nested-cohort study among 391,139 patients from Ontario, Canada, who were 66 years of age and older. During the study period, the subjects included those who were discharged alive after low-pain short-stay surgery hospitalizations such as cataract surgery, laparoscopic cholecystectomy, transurethral resection of the prostate, and varicose vein stripping surgery. Exposure was defined as administration of any opioid prescription within 7 days of hospital discharge. Long-term opioid use was defined as an additional claim for any opioid within 60 days of the 1-year anniversary date of the surgery.

Researchers found that opioids were newly prescribed to 27,636 patients (7.1%) within 7 days of being discharged from the hospital. A total of 30,145 patients (7.7%) were prescribed opioids at 1 year from surgery. Furthermore, patients receiving an opioid prescription within 7 days of surgery were 44% more likely to become long-term opioid users within 1 year compared with those who received no such prescription. The most commonly prescribed opioid was codeine followed by oxycodone. In a secondary analysis, among 383,780 NSAID-naïve patients undergoing short-stay surgery, NSAIDs were prescribed to 1169 patients (0.3%) within 7 days of discharge and to 30,080 patients (7.8%) at 1 year from surgery. Patients who began taking NSAIDs within 7 days of surgery were almost four times more likely to become long-term NSAID users compared to patients with no such prescription. The authors concluded that prescription of analgesics immediately after ambulatory surgery occurs frequently in older adults and is associated with their long-term use.

■ COMMENTARY

While there is both a moral and scientific obligation upon the physician to fully treat pain, the above study illustrates how what is often done to comfort patients in the short term can have longer term consequences. While it is possible that patients undergoing short-stay surgery could have pre-existing untreated pain, it is alarming to see that elderly patients who were prescribed opioids within 7 days of the surgery were much more likely to become long-term opioid users within 1 year when compared to no prescription. Studies have found that the use of opioids among the elderly may be placing them at risk for serious adverse events, including falls, fractures, cardiovascular events, and even death.[2] It is important to note that opioid analgesics are not necessarily safer than non-opioid analgesics such as NSAIDS. However, it is equally disturbing to find in the study that many of those NSAID-naïve elderly patients who were initially prescribed NSAIDs after short-stay surgery continued to use these medications 1 year later. In the elderly, NSAIDS may place patients at especially higher risk for gastrointestinal hemorrhage, cardiovascular events, renal damage, falls, and adverse events from polypharmacy.

While many patients will still need to be treated with analgesics postoperatively, it is important to understand that most analgesics, whether opioids or NSAIDS, place elderly patients at higher safety risks. Therefore, prior to prescribing analgesics, physicians may want to ascertain the need for such. Keeping the patient's medical history and various organ functional status in mind, elderly patients should be started on analgesic medications at low doses, actively monitoring for side effects, while avoiding polypharmacy. Providing patient and caregiver education — including efforts to improve patients' understanding of safe medication taking upon discharge and proper disposal — may prevent many elderly patients from unnecessarily seeking out such analgesics in the long-term. ■

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Pharmacology Update

Peginesatide Injection (Omontys®)

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

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

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

A completely synthetic, once-monthly, erythropoiesis-stimulating agent has been approved for the treatment of anemia in dialysis patients. Peginesatide is a pegylated dimeric peptide that does not share any sequence homology to the endogenous human erythropoietin but shares a similar mechanism of stimulating erythropoiesis.[1] It marketed by Affymax, Inc. and Takeda Pharmaceuticals U.S.A. as Omontys.

Indications

Peginesatide is indicated for the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis.[2]

Dosage

The initial recommended dose is 0.04 mg/kg body weight given once monthly. The dose may be given as a single intravenous or subcutaneous injection. The subcutaneous and intravenous routes of administration appear similar in effectiveness.[3] For patients already taking epoetin, peginesatide should be started 1 week after the last dose of epoetin. For those on darbepoetin, peginesatide can be started at the next schedule.

Peginesatide is available as 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, and 6 mg single-dose preservative-free vials/syringes and as 10 mg/mL multiple use vials with preservative.

Potential Advantages

Peginesatides is administered once monthly, compared to weekly or every other week with epoetin alfa or darbepoetin alfa. There is no apparent cross reactivity between antierythropoietin antibodies and peginesatides.[4] The drug has been reported to be effective in red-cell aplasia caused by antierythropoietin antibodies.

Potential Disadvantages

An increase in composite cardiovascular safety endpoints (all-cause mortality, myocardial infarction, stroke, or serious cardiovascular adverse events of congestive heart failure, unstable angina, or arrhythmia) compared to darbepoetin has been reported in non-dialysis CKD patients.[2,5] A small percentage of patients develop peginesatides-specific binding antibodies (1.2%).[2] The incidence was higher when the drug was given subcutaneously (1.9%) compared to intravenous administration (0.7%). Peginesatide shares the class warning for erythropoiesis-stimulating agents, namely increased risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence.[1]

Comments

Peginesatide was studied in four Phase 3 studies. Two studies (PEARL 1 and PEARL 2) compared the efficacy and safety to darbepoietin in patients with CKD not on dialysis. Two studies (EMERALD 1 and EMERALD 2) compared the efficacy and safety with epoetin alfa in patients on dialysis. Subgroup analysis of non-dialysis patients in the PEARL trials showed significant increased risk of composite cardiovascular events and all-cause mortality in the peginesatide group.[5] The upper limit of the 90% confidence interval (CI) of the hazard ratio was 1.73, exceeding the acceptable limit of 1.3. Analysis of the EMERALD data (1066 peginesatide, 542 epoetin) showed similar rates of cardiovascular events and mortality.[6] The upper limit of the 90% CI was 1.13. The FDA approval for use in dialysis patients was based on these data. Peginesatide met the criteria for noninferiority in maintaining hemoglobin levels compared to epoetin assessed at week 29-36 of treatment.[2] Peginesatide has not been shown to improve symptoms of anemia or quality of life.

Clinical Implications

Peginesatide is the first synthetic erythropoiesis-stimulating drug approved. Its only advantage appears to be the convenience of once-monthly dosing. However, this advantage may not be truly significant in patients who require dialysis three times a week. Evidence suggests an increased cardiovascular/mortality risk in nondialysis

patients, which raises concern for long-term safety of peginesatide. ■

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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.

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To earn credit for this activity, follow these instructions:

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5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter!

CME Questions

1. **Sleep duration is:**
   a. influenced only minimally by genes.
   b. carefully measured in most studies of its effect on outcomes.
   c. likely to affect genetic influences on BMI.
   d. optimally about 6 hours a night.

2. **In the study by Alam et al, patients receiving an opioid prescription within 7 days of short-stay surgery were how much more likely to become long-term opioid users within 1 year compared with those who received no such prescription?**
   a. 11%
   b. 22%
   c. 44%
   d. 66%

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is an advisor for Endo, Kowa, Pricara, and Takeda.

Statins and Dyslipidemia: Should we be Looking Beyond LDL?

Source: Boekholdt SM, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: A meta-analysis. *JAMA* 2012;307:1302-1309.

Treatment of dyslipidemia with statins produces consistent, durable lowering of low-density lipoprotein cholesterol (LDL-C), which is associated with substantial reductions in myocardial infarction and stroke. Other lipoprotein markers — in particular apolipoprotein B (apoB) and non-high-density lipoprotein cholesterol (non-HDL-C) — are also associated with vasculopathy. Indeed, the putative pathogenetic role of apoB has garnered some enthusiasm from lipidologists who encourage more routine measurement and modulation of apoB as a primary goal.

Risk reduction with statins is imperfect. That is, substantial risk for vascular events and death exists even with excellent LDL-C reduction. Might levels of apoB or non-HDL-C in patients already on a statin help us to discern which ones remain at high risk?

Boekholdt et al performed a meta-analyis of statin trials (n = 62,154) that included data on apoB and non-HDL-C, examining the relationship between on-treatment levels of LDL-C, apoB, non-HDL-C, and cardiovascular outcomes. For each increase of one standard deviation in the level of any of these three markers, the risk for a cardiovascular event increased, and to a very similar degree (13%-16% increase per standard deviation). However, when comparing the three markers with one another, non-HDL-C showed a statistically significantly greater association with increased risk than the other two markers. The authors suggest that based on this and other data, stronger consideration should be given to promoting non-HDL-C as an important target for reduction in subjects with dyslipidemia. ■

Broadening Perspectives on Maintaining Healthy Erectile Function

Source: Meldrum DR, et al. Lifestyle and metabolic approaches to maximizing erectile and vascular health. *Int J Impot Res* 2012;24:61-68.

For more than a decade, it has been recognized that nitric oxide (NO) is critical in the attainment and maintenance of an erection. Accordingly, pathology that induces endothelial dysfunction, and hence impaired generation of NO, is consistently associated with erectile dysfunction (ED). Traditional cardiovascular risk factors such as hypertension, dyslipidemia, diabetes, and cigarette smoking are each associated with increased prevalence and incidence of ED. Increases in oxidative stress appear to be a common denominator for many of the paths that lead to endothelial dysfunction.

Additional lifestyle factors that have been associated with endothelial dysfunction include insufficient exercise, obesity, and specific dietary components (e.g., high carbohydrate diet).

Many of the risk factors associated with endothelial dysfunction are modifiable. For instance, obesity is associated with insulin resistance, which lowers vascular NO. Exercise improves NO levels systemically. A high-fat intake may increase oxidative vascular wall stress.

There is some literature support for multifactorial intervention in men with ED to help restore sexual function. Meldrum et al suggest a list of factors that might favorably impact endothelial health (and hence, sexual functionality), including: 1) maintenance of healthy weight; 2) regular aerobic exercise; 3) low-fat, low glycemic-index diet; 4) smoking cessation; 5) alcohol moderation; 6) folate and omega-3 fatty acid supplementation; and 7) ARB rather than ACE treatment of hypertension. ■

When Thiazides are Associated with Hyponatremia

Source: Rastogi D, et al. Evaluations of hospitalizations associated with thiazide-associated hyponatremia. *J Clin Hypertens* 2012;14:158-164.

Control of hypertension is rewarded with important reductions in myocardial infarction, stroke, and cardiovascular death. Yet, the job of hypertension control is daunting, since on a worldwide basis it is estimated that more than one-fourth of all adults have hypertension! It has been known for more than 5 decades that thiazides can produce electrolyte disarray, including hypokalemia, hyponatremia, and hypomagnesemia, any of which can result in serious adverse effects and/or hospitalization. Rastogi et al performed a retrospective case-control study to elucidate risk factors for hyponatremic hospital admission while on a thiazide diuretic. They compared 1802 cases of hospitalized thiazide-associated hyponatremia with controls (n = 9003).

Risk for hyponatremic hospitalization doubled with each 10-year increase in age. The only other statistically significant associations were coadministration of an ACE inhibitor and concomitant hypokalemia. The coadministration of an ARB had a strong trend toward increased risk, but was marginally non-significant. Patients with comorbid diabetes, dyslipidemia, and gastroesophageal reflux disease were also more likely to be admitted for hyponatremia. Hopefully, recognition of these associations will assist clinicians to prevent hyponatremia, or at least detect its presence earlier. ■

Any Acute Changes?

By Ken Grauer, MD, *Professor Emeritus in Family Medicine, College of Medicine, University of Florida*

Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.

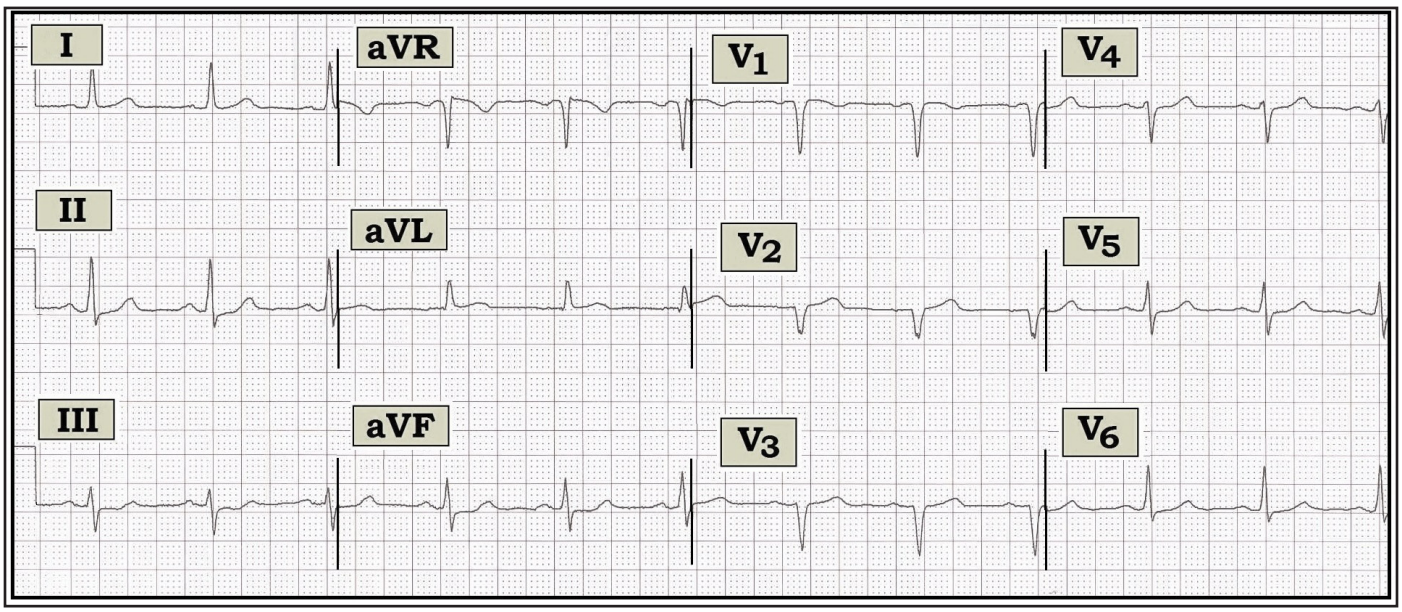

Figure — 12-lead ECG obtained from a 72-year-old woman with new-onset chest discomfort. Do you agree that there are "no acute changes?"

Scenario: The 12-lead ECG shown above was obtained from a 72-year-old woman seen in the emergency department (ED) with new-onset chest discomfort. No prior ECGs were available for comparison. The tracing was interpreted as "showing no acute changes." Do you agree? What else do you see?

Interpretation: The rhythm is sinus at a rate of ~75/minute. All intervals and the axis are normal. There is no chamber enlargement. With regard to Q-R-S-T changes, there are several findings of note:

1) There are Q waves (QS complexes) in anteroseptal leads V1-through-V3. A small positive deflection (r wave) finally develops by lead V4. Thus, transition is delayed (only occurring between leads V4-to-V5).

2) There is subtle (but real) ST segment elevation in lead aVL.

3) Support that the subtle ST elevation in aVL is truly a real finding is forthcoming from the ST segment flattening and subtle (but real) ST depression seen in each of the inferior leads (II, III, aVF).

It is important to remember that the shape of ST elevation is more important than the amount of elevation. Acute myocardial infarction (MI) may sometimes occur with only minimal ST elevation. We judge ST segment deviations (elevation or depression) with respect to the PR segment baseline. Of the five lateral leads (I, aVL, V4, V5, V6), lead aVL views the heart from the highest and most peripheral perspective (looking down at the heart from the left shoulder). As a result, lead aVL may sometimes be the only lateral lead to show acute changes (as may be the case here).

Given the clinical history of a 72-year-old woman presenting to the ED with new-onset chest discomfort and no prior tracing available for comparison, the findings in the ECG shown are clearly of concern. Lack of any r wave at all until lead V4 suggests prior anteroseptal infarction. The subtle (but real) ST elevation in lead aVL with equally subtle (but real) "reciprocal changes" in leads II, III, and aVF suggest that the patient may be in the process of evolving an acute high lateral MI. ECG changes of acute MI may evolve quickly — sometimes in less than an hour. Careful observation, presumptive initial treatment measures, serum troponins, and repeating the ECG in short order should clarify the clinical picture. ■

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