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ABSTRACT & COMMENTARY

Improving Blood Pressure Through Enhanced Sleep

By William C. Haas III, MD, MBA

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

SYNOPSIS: The use of a benzodiazepine hypnotic among hypertensive patients was associated with improvements in both sleep scores and blood pressure.

SOURCE: Li Y, Yang Y, Li Q, et al. The impact of the improvement of insomnia on blood pressure in hypertension. *J Sleep Res* 2016; [Epub ahead of print].

The relationship between disordered sleep patterns and increased cardiovascular morbidity and mortality is widely underappreciated, especially in the primary care setting. Several studies have documented an increased risk for developing hypertension among those with poor sleep patterns.[1,2] Moreover, insomnia has been associated with substantial elevations in blood pressure among those already diagnosed with hypertension.[3] Unfortunately, despite these negative correlations, few studies have evaluated the effect of improving sleep on blood pressure control.

Through a conventional pharmacological intervention, a group of Chinese researchers recently evaluated whether treating insomnia could effectively lower blood pressure in a group of hypertensive patients. Using standard diagnostic criteria established by the World Health Organization for hypertension and insomnia, 566 patients suffering from both disorders were recruited from either an outpatient sleep center or an inpatient geriatric ward. Patients were permitted to participate in the study if currently treated with antihypertensive medications; however, they were excluded if currently taking hypnotics, antipsychotics, or antidepressants. Additional exclusion criteria included diagnosis of sleep apnea, drug/alcohol addiction, chronic renal failure, or a Hamilton Depression score > 16. A total of 403 patients met criteria for participation and 402 completed the study.

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As a part of the intervention, patients were randomized in a double-blind fashion to receive either estazolam or placebo for 28 days. Researchers started patients on estazolam at a dose of 1 mg nightly and adjusted upward to 2 mg on day four based on patient-perceived efficacy — only 21 patients increased to 2 mg per night. The antihypertensive medications patients used during the study were long-acting drugs dosed once-daily in the morning and did not change throughout the study. Blood pressure was measured every seven days for four weeks according to measurement guidelines issued by the World Health Organization.[4] Sleep patterns were assessed along the same time line using the Pittsburgh Sleep Quality Index (PSQI). Patients also were interviewed weekly to follow the use of approved medication (estazolam, placebo, antihypertensives) and restricted medication (antipsychotics, antidepressants, non-issued hypnotics, caffeine).

With regard to sleep outcomes, the global PSQI scores for patients receiving estazolam improved within seven days of treatment and reached nearly 50% improvement by day 28 (18.2 ± 4.9 to 9.3 ± 3.3; $P < 0.001$). Moreover, scores for all individual PSQI components, including sleep latency, sleep efficiency, and sleep duration, improved in the treatment group after four weeks ($P < 0.001$), while the control group only noted improvements in sleep latency. Overall efficacy of insomnia treatment, as determined by ≥ 50% reduction in PSQI global score, occurred in 63.7% of patients in the estazolam group and only 14% of patients in the control group ($P < 0.001$).

Blood pressure demonstrated a similar pattern of improvement. After the third week, the Estazolam group noted significant reductions in blood pressure, and achieved a 10.5 ± 3.9 mmHg and 8.1 ± 3.6 mmHg reduction in systolic and diastolic blood pressure, respectively ($P < 0.001$). The control group did not achieve significant reductions in either systolic or diastolic blood pressure during the intervention.

■ COMMENTARY

Li et al have conducted one of the few studies pertaining to the effect of sleep enhancement on blood pressure control among hypertensive patients. Researchers found that treatment with a benzodiazepine hypnotic (estazolam) resulted in improved sleep patterns, while effectively reducing daytime blood pressure. The study was generally well designed with only minor limitations. The setting of patient recruitment, particularly the inpatient geriatric unit, may have enhanced results due to artificial disturbances in sleep patterns that commonly occur in the inpatient setting and in that age group. Furthermore, recruiting patients from different settings also may have limited the external validity of the study without specifically analyzing the effect of treatment setting. Regardless of these shortcomings, this study highlights the importance of addressing sleep disorders among hypertensive patients.

From an integrative medicine perspective, this study was not chosen in an attempt to promote hypnotics in hypertensive patients with insomnia. Rather, the study was reviewed to draw attention to the importance of sleep in patients with comorbid conditions such as hypertension. Sleep disorders are highly prevalent in the United States, with an estimated 30-40% of the population experiencing inadequate sleep.[5] Unfortunately, primary care providers routinely forget to screen for sleep disorders when conducting a health history.[6] Before sleep disorders can be addressed, they must first be identified.

In addition to raising awareness, hopefully, this study will spur new research regarding integrative treatments for sleep disorders among hypertensive patients. The current body of literature supporting integrative approaches for improving blood pressure through sleep enhancement generally is lacking. One study evaluating prolonged-release melatonin failed to note improvements in blood pressure compared to placebo.[7] On the other hand, another small study implementing twice-daily acupressure for four weeks found significant improvements in PSQI scores as well as systolic and diastolic blood pressure.[8] Additional research demonstrating a connection between integrative treatment modalities and concurrent improvements in sleep and blood pressure are needed.

Until additional research emerges, practitioners should continue to screen

for sleep disorders and review strategies to promote adequate sleep. Safe and effective sleep hygiene recommendations should start with enhancing the sleep environment to ensure the bedroom is cool, quiet, and dark. Encourage patients to reduce excessive "mind noise" through a meditative or journaling practice before bed. Recommend eliminating disrupters of the body's natural circadian rhythm, such as television and/or computers, within the hour before bedtime. These strategies may or may not improve blood pressure as a result of improved sleep, but they certainly will help disordered sleep patterns in a non-habit forming manner. Ultimately, the Li et al study should not be viewed as a nod for benzodiazepines use; rather, it should generate a renewed focus on integrative sleep modalities. ■

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ABSTRACT & COMMENTARY

Predictive Accuracy of the New Risk Equation

By Michael Crawford, MD

Professor of Medicine, Chief of Clinical Cardiology, University of California, San Francisco

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

SYNOPSIS: An evaluation of the predictive accuracy of the new pooled Cohort Risk Equation in > 300,000 subjects without heart disease or diabetes and a low-density lipoprotein cholesterol level between 70-189 mg/dL followed for five years showed that the new equation markedly overestimated the observed risk of cardiovascular events.

SOURCES: Rana JS, Tabada GH, Solomon MD, et al. Accuracy of the atherosclerotic cardiovascular risk equation in a large contemporary, multiethnic population. *J Am Coll Cardiol* 2016;67:2118-2130.

Blaha MJ. The critical importance of risk score calibration: Time for transformative approach to risk score validation? *J Am Coll Cardiol* 2016;67:2131-2134.

The 2013 American College of Cardiology/American Heart Association Pooled Cohort Risk Equation (PRE) has been criticized for its basis in study populations conducted in the 1990s with limited ethnic diversity and age range. Clinicians believe it has limited generalizability to contemporary patients seen in clinical practice. Thus, investigators evaluated the large, contemporary, multiethnic population of Kaiser Permanente Northern California comparing the risk equation-derived five-year risk of atherosclerotic cardiovascular (CV) events with the observed rate. The population selected was > 21 years of age and had a low-density lipoprotein (LDL) cholesterol level between 70 and 189 mg/dL. The study excluded patients with known CV disease, those who had received a statin prescription within five years of enrollment, and those who used statins for primary prevention during the follow-up period. CV events included myocardial infarction, ischemic stroke, and cardiac death. The subjects were subcategorized for diabetes status. More than 941,000 patients met the initial entry criteria and after applying the exclusion criteria, 311,833 patients between the ages of 40-75 years were enrolled — 307,591 without diabetes and 4,242 with diabetes. The main analysis focused on non-diabetics, of which 62% were women, 22,283 were black, 52,917 were Asian/Pacific Islander, and 18,745 were Hispanic. In this study group, there were 2,061 CV events during 1,515,142 person years of follow-up. At all levels of risk predicted, observed CV

events were substantially lower and the difference was greater at higher calculated risk scores. For example, in those with a predicted risk of > 5% in five years, the mean predicted risk was 8.72% vs. an observed rate of 1.85%. The correlation between expected and observed rates was better in diabetics, but researchers observed overestimation, especially at higher predicted risk. In the high-risk group, predicted CV events were 13.38% vs. 5.5% observed. Similar results were noted in the ethnic subgroups. The authors concluded that in a large real-world population, the Pooled Cohort Risk Equation substantially overestimated five-year risk of CV events in adults without diabetes and that ethnicity did not affect this result.

■ COMMENTARY

Other investigators have evaluated the PRE in several research populations that were not used in the creation of the PRE and found conflicting results. Interestingly, in cohorts gathered in the 1990s, the correlation between observed and predicted CV events by the PRE was better than in more contemporary populations. Some have argued that more contemporary populations include more patients on aspirin and statins, less smoking, and generally better lifestyles. Consequently, for this study, investigators excluded patients on statins before or during the study period. One could argue that this removed the higher-risk patients, but sensitivity analyses did not support this idea. Also, this study enrolled patients and followed them from 2008 until 2013, so it was not influenced by the new PRE. Other strengths included the large population (> 300,000) and the inclusion of reasonable numbers of all four major ethnic or racial groups in the United States. In addition, the patients were part of an integrated health system in which clinical data collection was of high quality.

One potential weakness of this study was the assumption that patients with health insurance are of higher socio-economic status and probably engage in better health habits than other populations. This may be true, but these are the majority of patients practitioners see. Additionally, data on diabetics were inadequate because researchers excluded diabetics from the main analysis. This was necessary because in their system, most diabetics were receiving statins. However, researchers' analysis of a diabetic subgroup that was not on statins confirmed overestimation of events by the PRE, but less so than observed in non-diabetics. An accompanying editorial noted that event rates were very low in this study in part because softer endpoints, such as revascularization, were not included.

Even though this study seems like a step in the direction of adjusting the risk equation to reflect contemporary practice, this issue remains highly controversial because of the treatment implication of a "high" risk score. Using the PRE will probably result in over-treatment with statins, which will lead to high costs for any health system. Using other considerations, such as a CT calcium score, family history, or high-sensitivity C-reactive protein, have their proponents, but these practices have not been well validated. It would be nice to use this study to calibrate the PRE, but this study evaluated five-year risk, and the PRE predicts 10-year risk. At this time, we are back to using physicians' judgment considering all the data we have at our disposal, including the PRE and perhaps even the old LDL-cholesterol targets. ■

BRIEF REPORT

Which Patients with TIA Are at High Risk for Recurrent Cerebral Vascular Events?

By Matthew E. Fink, MD

Professor and Chairman, Department of Neurology, Weill Cornell Medical College; Neurologist-in-Chief, New York Presbyterian Hospital

Dr. Fink reports he is a retained consultant for Proctor & Gamble and Pfizer.

SOURCE: Yaghi S, Rostanski SK, Boehme AK, et al. Imaging parameters and recurrent cerebral vascular events in patients with minor stroke or transient ischemic attack. *JAMA Neurol* 2016;73:572-578.

Recurrent cerebral vascular events (RCVEs) are one of the main determinants of outcome in patients after minor strokes and transient ischemic attacks (TIAs). The risk of recurrence is highest within 90 days and is particularly high in the first 48 hours. A number of scoring systems have been developed to attempt a prediction and stratify high-risk from low-risk patients. However, the scores have been limited because they were derived from mostly non-neurologist diagnosed TIA samples and their applicability to patients seen by current neurology stroke teams is questionable. The objective of this study was to determine predictors of early recurrent cerebral vascular events among patients with TIA or minor stroke, defined as an NIHSS of 0 to 3. This retrospective cohort study was conducted at two tertiary care centers, Columbia University in New York, and Tulane University in New Orleans, from

2010 until 2014. All patients were diagnosed with a TIA or minor stroke by a neurologist when they presented to the ED. The primary outcome was a recurrent neurological event unexplained by any other medical condition. Of 1,258 total patients, 71 experienced recurrent events. In a multivariate model of prediction for recurrent infarct, the significance predictors were 1) infarcts on neuroimaging (CT or diffusion-weighted MRI), with an odds ratio of 1.75, and 2) large vessel disease etiology, with an odds ratio of 6.69. When both predictors were present, there was a further increase in the risk of patients experiencing recurrent cerebral vascular events. When neither predictor was present, the rate of recurring events was extremely low (up to 2%). Patients who experienced recurrent events were less likely to be discharged. ■

PHARMACOLOGY UPDATE

Lifitegrast Ophthalmic Solution (Xiidra)

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

Dr. Elliott is Medical Director, Pharmacy, Northern California Kaiser Permanente, and Assistant Clinical 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.

The FDA has approved the first eye drop for the treatment of dry eye disease. Lifitegrast is a selective lymphocyte-function-associated antigen-1 (LFA-1) antagonist. It is marketed as Xiidra.

INDICATIONS

Lifitegrast is approved for the treatment of the signs and symptoms of dry eye disease.[1]

DOSAGE

The recommended dose is one drop in each eye twice daily approximately 12 hours apart.[1] Lifitegrast is available in a 5% solution in single-use preservative-free units.

POTENTIAL ADVANTAGES

Lifitegrast is the first drug and the first in class approved for this indication.

POTENTIAL DISADVANTAGES

Most frequently reported adverse events (vs. vehicle) were instillation site irritation (15% vs. 3%), dysgeusia (15% vs. 0.3%), and decreased visual acuity (5% vs. 4%).[1,2]

COMMENTS

Lifitegrast is believed to inhibit ocular inflammation in dry eye disease.[3] Efficacy and safety of lifitegrast was evaluated in four randomized, double-masked, vehicle-controlled, 12-week studies in adult subjects with dry eye disease.[1-4] The four studies were similar in design. Two included both signs and symptoms as primary endpoints and the other two used signs or symptoms as the primary endpoint. Symptoms were assessed with the eye dryness score (EDS) using a visual analogy scale from 0 to 100 (0 = no discomfort and 100 = maximal discomfort) or 4-point visual-related function subscale score of the Ocular Surface Disease Index. Signs of dry eye disease were assessed with the inferior fluorescein corneal staining score (ICSS) with 0 = no staining, 1 = few/rare punctate lesions, 2 = discrete and countable lesion, 3 = lesions too numerous to count but not coalescent, 4 = coalescent. Results were assessed at days 14, 42, and 84. In the two studies with both signs and symptoms as endpoints, lifitegrast showed significant improvement for signs or symptoms over the vehicle, but not both. In the other two studies with a single endpoint, lifitegrast was better than vehicle in each study. In the most effective studies, the difference observed between lifitegrast and vehicle was 18% for symptoms and 13% for signs.

CLINICAL IMPLICATIONS

Dry eye disease affects about 20 million people in the United States.[5] It is characterized by ocular discomfort, decreased tear quality or quantity, and chronic ocular inflammation. This condition frequently is associated with increasing age and most common in postmenopausal women.[2] The most common treatment is artificial tears. Cyclosporine increases tear production and is approved for the treatment of keratoconjunctivitis sicca. Lifitegrast is the first drug approved specifically for dry eyes. The wholesale cost of lifitegrast is $426.73 for 60 single-use units. ■

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Clinical Briefs

By Louis Kuritzky, MD

Many Treatment Choices for Type 2 Diabetes

SOURCE: Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: A meta-analysis. *JAMA* 2016;316:313-324.

The real goals of diabetes treatment are reduction in microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (myocardial infarction and stroke) endpoints. With that in mind, it should be sobering to review current FDA-approved labeling for antidiabetic meds: "There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with [insert drug name] or any other anti-diabetic drug."

A recent large meta-analysis (301 clinical trials) addressed cardiovascular mortality as well as all-cause mortality for the most commonly used antidiabetic drugs (metformin, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, insulin, DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists) seeking to discern any differences in cardiovascular events or mortality, as well as safety.

Despite an impressive amount of data, no particular class of agents — as monotherapy or in combination — provided distinct advantages for risk reduction of cardiovascular events or mortality.

Recent cardiovascular safety trials featuring two agents (empagliflozin and liraglutide) challenge the concept that diabetes treatment is ineffectual for cardiovascular risk reduction, but if clinicians believe in "class effects" of medications, it appears dubious that any clear winners will emerge any time soon in the quest for cardiovascular risk reduction. ■

Antiretroviral Therapy for HIV Patients

SOURCE: Rodger AJ, Cambiano V, Bruun T, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner Is using suppressive antiretroviral therapy. *JAMA* 2016;316:171-181.

Prevention of seroconversion in HIV serodiscordant couples (in which one partner is HIV positive and the other is not) is reduced by using barrier methods, especially when the HIV-positive partner is receiving antiretroviral therapy (ART). ART provides sustained reductions in HIV viral load and reduced infectivity, but would it be safe for serodiscordant couples to omit barrier methods entirely?

Rodger et al performed a prospective observational study (n = 888) of serodiscordant sexually active heterosexuals, men who have sex with men (MSM), and gay couples. The HIV-positive partners all were receiving ART, and > 80% presented with undetectable levels of HIV virus (some subjects on ART did not report viral load status, but are presumed to be similarly undetectable). Couples agreed to abstain from barriers during intravaginal or intra-anal intromission.

During 1.3 years (mean) of follow-up, there were no confirmed HIV conversions; any new HIV conversions were found to be from HIV strains not harbored by the HIV-positive partner and must have occurred from another external HIV-positive source.

Since intra-anal transmission is more common than intravaginal transmission, it is particularly welcome that the rate of conversion was zero among all participants, including the 340 MSM. ■

Ticagrelor vs. Aspirin in Post-TIA and Stroke Patients

SOURCE: Johnston SC, Amarenco P, Albers GW, et al. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. *N Engl J Med* 2016;375:35-43.

The first 90 days after a transient ischemic attack (TIA) or ischemic stroke is a high-risk period for recurrence of cardiovascular thrombotic events. Even with aspirin treatment, recurrences occur in as many as 10-15% of patients. Ticagrelor is an inhibitor of the P2Y12 receptor on platelets, similar in mechanism to clopidogrel. Ticagrelor is indicated for reduction of thrombotic events in persons with acute coronary syndromes or ST-elevation myocardial infarction. Might a different mechanism of action than aspirin treatment, as provided by ticagrelor, reduce thrombotic events in patients who experience a TIA?

The SOCRATES trial enrolled patients (n = 13,199) who had suffered an ischemic stroke or TIA within 24 hours of the event. Study subjects were randomized to ticagrelor (180 mg loading dose, then 90 mg twice per day) or aspirin (300 mg loading, then 100 mg once per day) for 90 days. The primary outcome was a composite of stroke, myocardial infarction, or death.

Although results trended favorably in the ticagrelor treatment arm (hazard ratio = 0.89), they were not statistically significant. Since the treatment costs of aspirin are substantially less than ticagrelor, and the adverse bleeding effect profile is similar, aspirin should remain the drug of choice, except for patients who are aspirin intolerant. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. **In a large, multiethnic, primary prevention population, the new Pooled Cohort Risk Equation:**
   a. accurately predicted observed risks in diabetics.
   b. accurately predicted observed risk in non-white subjects.
   c. overestimated observed risk in all subgroups.
   d. underestimated observed risk in white subgroups.

2. **In patients who present with transient ischemic attack or minor stroke, the period of time with the highest risk of recurrence is the first 48 hours following the initial event.**
   a. True
   b. False

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]

The Zoster Vaccine Rapidly Loses Effectiveness in Adults Over 60

Integrative Treatment for Restless Legs Syndrome: What Does the Evidence Say?

Internal Medicine [ALERT]

ECG Review

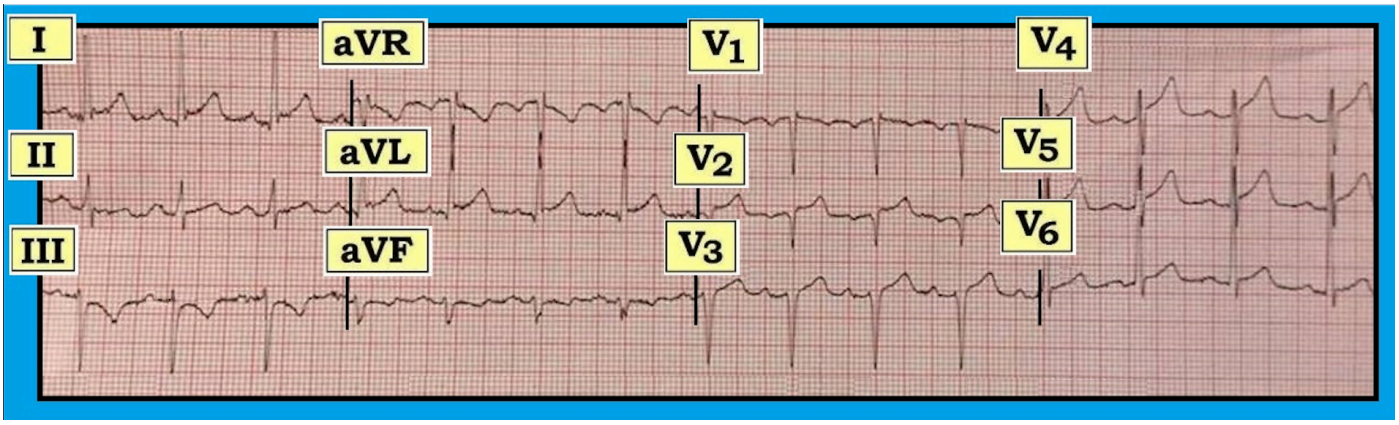
By Ken Grauer, MD

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.

Acute STEMI or False Alarm?

The ECG in the figure below was obtained from a 61-year-old man whom paramedics treated for new onset chest discomfort. How would you interpret this ECG? Is there evidence of acute ST elevation myocardial infarction (STEMI)?



There are a number of findings on this ECG that strongly suggest acute STEMI. Note the following:

• The rhythm is sinus. Intervals are normal. The axis is slightly leftward (at about -15 degrees). Voltage for left ventricular hypertrophy (LVH) is satisfied by an R wave in lead aVL that clearly exceeds 12 mm in amplitude.

• There is a Q wave in lead V1, a QS in V2, and no more than the tiniest of R waves in lead V3. Thus, R wave amplitude is clearly reduced in the anterior leads, and Q waves in V1, V2 could be consistent with septal infarction.

• The T wave in leads V2-V5 looks like it may be hyperacute. T wave amplitude in lead V2 seems disproportionately tall compared to the QRS complex in this lead. Additionally, the amount of J-point elevation in leads V4 and V5 seems more than is normally expected in these leads, especially given relatively small R waves in V4 and V5.

• There is ST elevation in lead aVL that looks to be the mirror image of lead III. There appears to be reciprocal change in the inferior leads.

Considering the above findings together, one must be concerned about the possibility of acute left anterior descending coronary artery occlusion in this 61-year-old man with new onset symptoms. That said, there are a number of features against this being an acute anterior STEMI. These include:

• **Probable Lead Malposition —** It is surprising how frequently leads V1 and V2 are placed too high on the chest. Doing so may give the false impression of anterior infarction. Clues in this tracing that precordial leads were probably placed one (or even two) interspaces too high include: 1) a significant negative component to the P wave in both lead V1 and V2 and 2) the finding of an r' deflection in lead V1. Perhaps lead V3 also is malpositioned? So maybe there is not loss of R wave (and development of Q waves) after all in the anterior leads?

• **Other Factors —** The leftward axis might account for normal T wave inversion in predominantly negative limb leads III and aVF. Shape of the J-point ST elevation in limb leads I and aVL is concave up (i.e., "smiley"-configuration) with small, narrow septal Q waves and J-point notching. This has the appearance of early repolarization. Finally, LVH is present not only by meeting voltage criteria in lead aVL but also by the presence of a surprisingly tall R wave in lead V6, which partially is masked by overlap of QRS complexes from V5. LVH is notorious for producing a reciprocal "strain" pattern in anterior leads, and this could account for at least some of the suspicious T wave appearance in leads V2 and V3.

It is difficult to be certain from this single tracing if acute STEMI is evolving. One simply cannot always tell from the initial ECG. Depending on clinical circumstances one might either decide to repeat the ECG with an echocardiogram in the ED (looking for wall motion abnormality) or simply proceed to cardiac catheterization for definitive diagnosis. It turned out that this patient did not have acute infarction.