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Internal Medicine

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ABSTRACT & COMMENTARY

Risk of New Onset Diabetes When Blood Pressure Becomes Elevated Over the Usual Measurement

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

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

SYNOPSIS: An increase of 20 mmHg in systolic blood pressure was associated with a 58% higher risk of new-onset diabetes mellitus, whereas an increase of 10 mmHg in diastolic blood pressure was associated with a 52% higher risk of developing new-onset diabetes mellitus.

SOURCE: Emdin CA, et al. Usual blood pressure and risk of new-onset diabetes. Evidence from 4.1 million adults and a meta-analysis of prospective studies. *J Am Coll Cardiol* 2015:66;1552-1562.

Type 2 diabetes mellitus (T2DM) is associated with twice the risk of all-cause mortality and three times the risk of cardiovascular mortality relative to age and sex-matched controls.[1] In 2011, 366 million people worldwide had T2DM and that number was expected to increase to 552 million by 2030.[2] Although elevated blood pressure (BP) has been demonstrated to be an independent risk factor for fatal and nonfatal cardiovascular events in the past,[3] it has not been clearly demonstrated that an elevated BP may contribute to new-onset T2DM. Emdin et al analyzed the records of more than 4 million individuals free from T2DM and cardiovascular disease in a contemporary U.K. primary care population and performed a meta-analysis of existing prospective studies in an attempt to accurately determine the association between climbing BP and T2DM.[4]

Researchers analyzed 4,694,120 medical records from the U.K. Clinical Practice Research Datalink. Patients were eligible for inclusion if they had a BP measurement performed between Jan. 1, 1990, and Jan. 1, 2013, and if they were between 30 and 90

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years of age at the time of measurement. All patients with pre-existing vascular disease (i.e., ischemic heart disease, cerebrovascular disease, heart failure, peripheral vascular disease, or renal disease) and T2DM were excluded. To reduce measurement error to which single BP measurements are prone and to diminish the impact of short-term fluctuations in BP on observed associations, the initial measurement was considered to be the "usual blood pressure." In the residual cohort of 4,132,138 individuals, 186,698 new-onset T2DM events were identified. After extensive analysis, the authors concluded that an increase of 20 mmHg in systolic BP was associated with a 58% higher risk of new-onset T2DM, whereas an increase of 10 mmHg diastolic BP was associated with a 52% higher risk of developing T2DM.

■ COMMENTARY

The data analyzed in this study were massive. However, the electronic health records utilized were routinely collected, and significant variations in BP determinations were certainly quite possible. The authors compared their results with their analysis of 30 prospective observational studies involving 285,664 participants who developed 17,388 T2DM associations. The meta-analysis revealed that for each 20 mmHg above usual systolic BP, there was a 77% higher risk of new-onset T2DM and the results were quite similar to the findings of the their study.[4] Of course, large electronic medical records studies have many potential sources of errors, which may have contributed to the final results, but the authors vigorously attempted to prevent any errors from occurring in their careful analysis of the data.

The strengths of the associations between diastolic and systolic BP and the risk for T2DM declined with increasing body mass index and/or age. Because of the many potential data weaknesses in this enormous study, I agree with the authors that further investigation is needed to determine whether the associations observed in this study were causal in nature. ■

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ABSTRACT & COMMENTARY

Using Procalcitonin to Differentiate Bacterial from Viral Meningitis

By Richard R. Watkins, MD, MS, FACP

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Associate Professor of Internal Medicine, Northeast Ohio Medical University, Rootstown, OH

Dr. Watkins reports that he has received research support from Forest Laboratories.

SYNOPSIS: A meta-analysis based on nine studies found an elevated serum procalcitonin to be an accurate test for differentiating bacterial from viral meningitis in adults.

SOURCE: Vikse J, et al. The role of serum procalcitonin in the diagnosis of bacterial meningitis in adults: A systematic review and meta-analysis. *Intern J Infect Dis* 2015;38:68-76.

Differentiating bacterial from viral meningitis is a frequent clinical conundrum. Usually, broad-spectrum antibiotics are administered when meningitis is suspected until cerebrospinal fluid (CSF) cultures are negative for at least 48 hours. This common practice exposes patients

with viral meningitis to antibiotics unnecessarily, which raises costs, increases risk for adverse drug events, and propagates antibiotic resistance. Therefore, rapid non-culture-based testing would be a great benefit in the diagnosis of meningitis.

Vikse et al sought to determine if procalcitonin (PCT), a serum biomarker that is higher than normal in serious bacterial infections, could accurately differentiate bacterial from viral meningitis. Several studies have been published on the topic, but they produced mixed results. Thus, there is no current consensus on the diagnostic utility of PCT in meningitis. PCT is an attractive test in this setting because it is rapid (i.e., results back in < 24 hours) and has become widely available. Moreover, studies on bacterial meningitis have shown PCT to be elevated even if the blood was drawn following initiation of antibiotic therapy.

A total of nine studies were included in the meta-analysis (n = 725 patients). Of these, two were retrospective and seven were prospective. Different assays were used, and the cutoff for PCT ranged between 0.25 ng/mL to 2.13 ng/mL. Seven of the studies also measured C-reactive protein (CRP) as a biomarker. The sensitivity for PCT for detecting bacterial meningitis was 0.90 (95% confidence interval [CI], 0.84-0.94), specificity was 0.98 (95% CI, 0.97-0.99), and the diagnostic odds ratio was 287.0 (95% CI, 58.5-1409.0). CRP was far less accurate; the sensitivity for bacterial meningitis was 0.82 (95% CI, 0.75-0.88), specificity was 0.81 (95% CI, 0.77-0.84), and diagnostic odds ratio was 22.1 (95% CI, 12.7-38.3). However, significant heterogeneity was found for the diagnostic odds ratio for PCT (I^2 = 66.2%), which the investigators attributed to variation in the types of serum PCT assays used in the studies. Finally, a funnel plot was constructed to detect publication bias, which was asymmetrical, indicating that this type of bias may have been present in the studies included in the meta-analysis.

■ COMMENTARY

The meta-analysis conducted by Vikse et al showed that PCT has a high specificity (i.e., 98%) for bacterial meningitis, making it a highly accurate biomarker for ruling in this serious infection, as well as a high sensitivity (90%). This result is similar to a previous study, which found that PCT had a sensitivity of 95%, a specificity of 100%, a negative predictive value of 100%, and a positive predictive value of 97% at a diagnostic cutoff level of 0.28 ng/mL (AUC, 0.99; 95% CI, 0.99-1) in distinguishing bacterial from viral meningitis in adults.[1] Moreover, using PCT with cutoff value > 2 ng/mL showed sensitivity, specificity, positive predictive value, and negative predictive value of 100%, 66%, 68%, and 100%, respectively, for the diagnosis of bacterial meningitis in children.[2] The use of PCT to rapidly rule out bacterial meningitis has the potential to reduce the costs of unnecessary hospitalization and adverse effects from antibiotics. Another potential benefit is that PCT may provide information about prognosis. In a recent study, children with higher serum levels of PCT were found to have prolonged clinical courses and increased mortality.[3]

[If procalcitonin is elevated, I would wait for the cerebrospinal fluid culture results for at least 48 hours before ending antibiotic therapy.]

One of the limitations to the meta-analysis by Vikse et al is that the overall number of studies included is small. Thus, the risk of publication bias is higher, especially since the funnel plot was asymmetrical. Another limitation is that the investigators excluded studies conducted on children, a group for whom meningitis is a frequent and serious infection. Clearly, the ability to differentiate bacterial from viral meningitis in these patients is highly important.

Should serum PCT be ordered routinely in cases of meningitis? There is good quality evidence that PCT can accurately distinguish bacterial from viral meningitis. When the clinical suspicion for bacterial meningitis is low and the PCT is normal, I would likely stop antibiotics, especially if there is a lymphocyte predominance in the CSF and the Gram stain is negative. However, if the PCT is elevated, I would wait for CSF culture results for at least 48 hours before ending antibiotic therapy. Whether PCT testing will be included in the next Infectious Diseases Society of America clinical guidelines on meningitis is an open question. ■

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ABSTRACT & COMMENTARY

Beta-blocker Dose More Important Than Heart Rate in Systolic Heart Failure

By Van Selby, MD

Assistant Professor of Medicine, UCSF Cardiology Division, Advanced Heart Failure Section, San Francisco

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

SOURCE: Fiuzat M, et al. Heart rate or beta-blocker dose? Association with outcomes in ambulatory heart failure patients with systolic dysfunction: Results from the HF-ACTION trial. *JACC Heart Fail* 2015. doi:10.1016/j.jchf.2015.09.002.

Beta-blockers reduce both morbidity and mortality in chronic heart failure with reduced ejection fraction (HFrEF). More recently, heart rate (HR) reduction has been associated with better outcomes in HFrEF. Fiuzat et al aimed to determine whether higher beta-blocker doses or reduced HR has a greater impact on outcomes in chronic HFrEF.

To compare the relative effects of HR reduction and higher beta-blocker dose, they performed a secondary analysis of the HF-ACTION trial. HF-ACTION randomized 2331 patients with ambulatory NYHA functional class II-IV heart failure and left ventricular ejection fraction < 35% to exercise training vs usual care. Patients were on stable doses of heart failure therapies for at least 6 weeks prior to study enrollment, with 94.5% receiving beta-blockers. Secondary analysis patients were categorized as either high (≥ 25 mg/day of carvedilol equivalent) or low beta-blocker dose and high (≥ 70 bpm) or low HR. The primary endpoint was the composite of death and all-cause hospitalization, and median follow-up was 2.5 years.

In unadjusted analyses, both higher beta-blocker dose and lower HR were associated with reduced risk of death or hospitalization. However, after adjusting for other predictors, only higher beta-blocker dose was significantly associated with the primary outcome (hazard ratio 0.77; $P = 0.03$). Higher beta-blocker dose was associated with improved outcomes regardless of the achieved HR. There was no increased risk of bradycardia among patients on higher doses of beta-blockers. The authors concluded that in HFrEF, titrating beta-blocker doses may confer a greater benefit than reducing HR.

■ COMMENTARY

Multiple large randomized trials have shown that treatment with beta-blockers leads to symptomatic improvement, reduced hospitalization, and increased survival in HFrEF. These trials generally targeted high doses, and as a result current guidelines recommend treatment with moderate to high doses of beta-blockers in HFrEF. However, evidence of a strong dose-response relationship for beta-blockers is somewhat limited, and one meta-analysis found no association between beta-blocker dose and outcome. The findings from the current analysis show that patients with higher beta-blocker doses have a lower risk of hospitalization or death, even after adjusting for other clinical predictors, and support the current recommendations.

Despite clear guideline recommendations, multiple studies have found that most patients with HFrEF are not titrated to target doses. There are many reasons for this, including concern for side effects, health system barriers that prevent easy medication titration, and possibly a lack of clear evidence that outcomes improve at higher doses. With the recent FDA approval of ivabradine, clinicians may be tempted to keep beta-blockers at lower doses and instead initiate ivabradine to achieve HR goals in patients with HFrEF. Ivabradine effectively lowers HR without many of the side effects associated with beta-blockers, and does not affect blood pressure. The findings of Fiuzat and others remind us that such practices are unacceptable for patients with HFrEF. Beta-blockers have beneficial effects in HFrEF beyond lowering HR, and titrating to target doses must be considered the first-line treatment.

This was a post-hoc analysis with several limitations. It is possible that patients on lower doses of beta-blockers were sicker, and therefore unable to tolerate target doses. The authors adjusted for many clinical characteristics, but residual confounders are a possibility. Furthermore, this study did not evaluate the strategy of using a non-beta-blocking medication such as ivabradine to lower HR; rather, it studied the association between baseline HR and outcomes.

Certain strategies can help reach target beta-blocker doses, and there are published guidelines to help increase the chance of successful up-titration. Always start with low doses (i.e., carvedilol 3.125 mg twice per day), and there should be minimal or no evidence of fluid retention when beta-blockers are initiated or

up-titrated. Patients should be instructed to check their weight every morning after every dose increase to identify worsening fluid retention, and they should be advised that any initiation or dose increase may be associated with mild worsening of heart failure symptoms that often resolves after several weeks.

A growing body of literature shows the importance of reaching target doses of beta-blockers in HFrEF. It can be difficult at times, and may require close monitoring. Nevertheless, given the clear benefit this must be the goal for all HFrEF patients. The approval of ivabradine will be a useful addition for a small portion of HFrEF patients, but absolutely cannot substitute for higher beta-blocker doses in those patients who can tolerate it. ■

PHARMACOLOGY UPDATE

Insulin Degludec Injection (Tresiba)

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

Dr. Elliott is Medical Director, Pharmacy, Northern California Kaiser Permanente, 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 a third long-acting basal human insulin analog. Insulin degludec differs from human insulin at position B30, where threonine has been replaced with a side chain consisting of glutamic acid and a C16 fatty acid, which results in an ultra-long duration of action (> 40 hours). Researchers produce it with recombinant technology using yeast cells. It is marketed by Novo Nordisk as Tresiba.

INDICATIONS

Insulin degludec is indicated for use as a long-acting insulin to improve glycemic control in adults with diabetes mellitus.[1]

DOSAGE

Insulin degludec is given subcutaneously once daily and the dose is individualized. It is available as 100 units/mL and 200 units/mL at 3 mL in prefilled pens (FlexTouch). It also will be available in combination with insulin aspart in a 70/30 ratio (Ryzodeg) in other parts of the world and perhaps eventually in the United States.

POTENTIAL ADVANTAGES

Insulin degludec provides an alternative to insulin glargine and insulin detemir as long-acting human insulin analogs. It may be administered at different times of the day without loss of efficacy.

POTENTIAL DISADVANTAGES

Increase in body weight was greater with insulin degludec compared to insulin detemir.[3]

COMMENTS

Insulin degludec forms a stable depot of multihexamers upon injection.[2] There is a gradual dissociation of these hexamers into readily absorbed monomers. Three studies evaluated the efficacy of insulin degludec in type 1 diabetic subjects and in six studies in type 2 diabetic subjects.[1] In type 1 subjects, insulin degludec was compared to insulin glargine and insulin detemir using a noninferiority design with a pre-specified noninferiority margin of 0.4%. In type 2 subjects, insulin degludec was compared to insulin glargine when added to oral antidiabetic agents and, in one study, compared to sitagliptin when added to oral agents. In two 52-week studies in type 1 diabetics, insulin degludec was noninferior to insulin glargine and insulin detemir when administered with the evening meal and insulin aspart administered before each meal. The difference in HbA1c reduction from baseline compared to insulin glargine was -0.01% (95% confidence interval [CI], -0.14% to 0.11%). The difference compared to insulin detemir was -0.09% (95% CI, -0.23% to 0.05%).

In a 26-week study, insulin degludec, when administered any time each day, was also noninferior compared to insulin glargine administered at the main evening meal. Type 2 insulin-naïve diabetics who were inadequately controlled on one or more oral agents were randomized to insulin degludec or insulin glargine. At week 52, noninferiority was shown with a treatment difference of -0.09% (95% CI, -0.04 to 0.22). In subjects who were inadequately controlled on various insulin regimens, oral agents, or any combination, noninferiority was shown for insulin degludec and insulin glargine. The results were similar when administering insulin degludec at alternate times.

In a 26-week study, insulin degludec was noninferior to insulin glargine when added to metformin with or without a DPP-4 inhibitor. Insulin degludec, plus one

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Clinical Briefs

By Louis Kuritzky, MD

Leaving the Annual Physical Behind

SOURCE: Mehrotra A, Prochazka A. *N Engl J Med* 2015;373;16:1485-1487.

Commentary that should have led us away from participating in the annual physical has been in front of us for more than 35 years. In 1979, a Canadian task force suggested that the practice of the annual physical, quite simply, be abandoned. Echoing this sentiment, the Choosing Wisely campaign (2013) voted thumbs down to annual preventive examinations in otherwise asymptomatic individuals.

Jane and John Q. Public, however, seem determined to keep the annual physical alive. Approximately one-third of adults sign up for an annual physical each year in the United States, with no sign of abatement over the last 8 years. As clinician-scientists, we must somehow evolve into one of two primary camps. First, embrace what expert reviewers have concluded based on evaluation of outcomes data — that the annual physical does not improve outcomes and expends billions of dollars that otherwise could be spent for greater benefit — and eschew further endorsement of the annual physical. Or second, admit that the annual physical (though perhaps lacking merit on the basis of measurably improved health outcomes) provides fertile ground for germination of difficult-to-quantify elements, such as improved clinician-patient relationships, while acknowledging the recognized outcome limitations.

Mehrotra and Prochazka go so far as to suggest that if the fundamental benefit of the annual physical is relationship building, then we might consider establishing contact visits with the specific agenda of relationship building, rather than anticipating relationship growth as a "sidestream benefit." To date, the annual physical has shown minimal, if any, benefit or potential for harm. The busy clinical setting has little room for spending time frivolously. Each of us will have to balance the absence of concrete benefits from the annual physical with the rewards measured by ourselves and our patients, accrued by the acutely well patients seeking the reassurance of the annual physical. ■

Is Breakfast the Most Important Meal of the Day?

SOURCE: Jakubowicz K, et al. *Diabetes Care* 2015;38:1820-1826.

Primary education (grades K-6) teachers have parroted the mantra "breakfast is the most important meal of the day" to children and parents alike for at least 60 years. Although I'm not quite sure whether our grandparents' teachers also had the same party line, it wouldn't surprise me in the least. Before continuing further I must confess to my own breakfast pathology: Since my teens, I have happily consumed a 12-ounce Mountain Dew and a Chunky candy bar for breakfast every morning, eschewing coffee or anything that required more preparation than tearing open the single-layer silvery Chunky wrapper. After ingesting this carbohydrate/caffeine concert, I am happy to abstain from further calories until noon or later, after which I employ what you would call "normal" food.

It's a good thing I don't have type 2 diabetes (T2DM), because apparently the omission of breakfast wreaks havoc on carbohydrate metabolism later in the day in diabetics. To elucidate the phenomenon further, Jakubowicz et al compared glucose, fatty acid, and glucagon metrics in a population of T2DM patients, half of whom consumed breakfast and the other half did not. All meals were provided to subjects and standardized for caloric content. Subjects were randomly assigned to a crossover-design methodology. Omission of breakfast was associated with less secretion of insulin and glucagon-like peptide and higher levels of free fatty acids, glucose, and glucagon. In an era where the expanding tools for management of T2DM are accompanied by a comparably expanded price, it's nice to know that some simple lifestyle measures may enhance the opportunity for glucose control. ■

Confirming the Value of Total Knee Replacement

SOURCE: Skou ST, et al. *N Eng J Med* 2015;373:1597-1606.

Since more than 500,000 total knee replacements are performed annually in the United States, it is heartening to review a clinical trial confirming efficacy. After all, it was not so long ago that a clinical trial of knee lavage — an equally well-respected, time-honored, and commonplace orthopedic intervention — failed to show benefit when compared to sham lavage in patients with knee pain and osteoarthritis.

This prospective, controlled trial included 95 patients who were randomized to medical treatment (physical therapy, analgesia, and anti-inflammatory agents) or total knee replacement, which was also followed by medical therapy. Outcomes were measured at 12 months. As measured by the Knee Injury and Osteoarthritis Outcome Score, total knee replacement patients enjoyed significantly greater improvements than medical therapy, although both groups did improve significantly over 12 months. Additionally, because of symptom progression, 26% of subjects originally assigned to medical therapy ultimately underwent surgical intervention during the 12-month interval.

Total knee replacement provides better outcomes for pain, symptoms, activities of daily living, and quality of life than medical therapy alone. ■

Continued from page 181

or more oral agents, was superior to add-on sitagliptin. In type 1 subjects, the overall rate of confirmed hypoglycemia and severe hypoglycemia was not significantly different between insulin degludec and detemir.[3] However, the rate of nocturnal confirmed hypoglycemia was lower with insulin degludec. Similarly, the rates of nocturnal confirmed hypoglycemia were numerically or significantly lower with insulin degludec compared to insulin glargine.[4]

CLINICAL IMPLICATIONS

Insulin degludec is noninferior to insulin glargine and insulin detemir in terms of glycemic control but may offer a lower risk of nocturnal hypoglycemia. The clinical relevance remains to be determined as the absolute difference, while statistically significant in some studies, is quite low — about 1.5 episodes per patient years of exposure for type 1 subjects and 0.4 for type 2 subjects.[4,5] Insulin degludec is slightly more expensive — $29.60 per 100 units for insulin degludec compared to $26.90 for insulin detemir and $24.90 for insulin glargine. Insulin degludec is expected to be available in the first quarter of 2016. ■

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CME QUESTIONS

1. **A higher incidence of new-onset diabetes mellitus:**
   a. was not found to be associated with a higher than usual systolic or diastolic blood pressure.
   b. was related to a higher than usual systolic blood pressure but not to a higher than usual diastolic blood pressure.
   c. was associated with either a higher than usual systolic and/or diastolic blood pres-sure.
   d. None of the above

2. **A secondary analysis of a recent trial of beta-blockers for heart failure with reduced ejection fraction showed that adjusted mortality and re-hospitalization were least when:**
   a. beta-blockers were titrated to heart rates < 70 bpm.
   b. high doses of beta-blockers were used.
   c. when heart rates < 55 bpm were avoided.
   d. vasodilator beta-blockers were used.

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]

Is it Normal Aging or Chronic Kidney Disease?

Internal Medicine [ALERT]

ECG Review

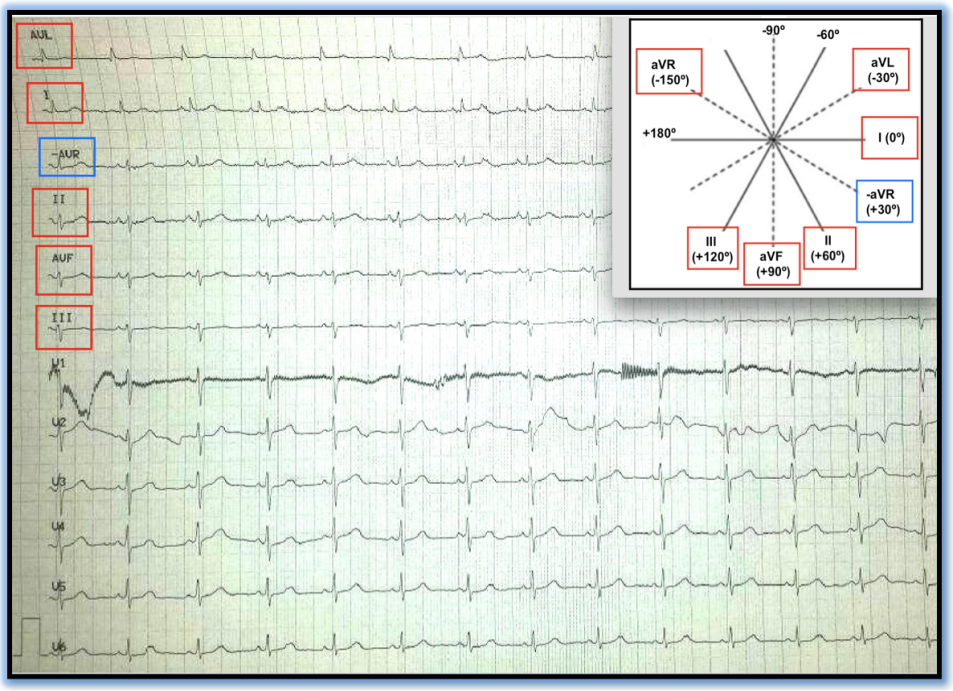
By Ken Grauer, MD

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.

Why are aVR Waveforms Positive?

The 12-lead ECG in the figure was obtained from a previously healthy middle-aged woman who presented with back pain over the previous month. Does her ECG provide any clue to the etiology of her symptoms? Can you explain why the QRS complex in lead aVR shows global positivity (i.e., positive P wave, QRS complex, and T wave)?



The ECG in the figure provides no clue to the etiology of this patient's symptoms. The reason the P wave, QRS complex, and T wave are all positive in aVR is that instead of the usual 12-lead format (to which interpreters in the United States are accustomed), the Cabrera format has been used instead.

The 12-lead ECGs that are recorded in the United States typically display simultaneous recording of four sets of three leads (leads I, II, III; aVR, aVL, aVF; V1, 2, 3; and V4, 5, 6). One or more long lead rhythm strips are typically displayed immediately below the 12-lead. In contrast, note that a simultaneously recorded long lead rhythm strip for each of the 12 leads is displayed in the figure and that the vertical sequence used for the limb leads is markedly different from the usual format. That is, rather than lead I, the first lead displayed is lead aVL.

Note also that a minus sign appears before the designation aVR. This is because the polarity of lead aVR is reversed when using the Cabrera format. As a result, the mirror image picture (i.e., global positivity rather than negativity) is displayed for aVR (within the blue rectangle in the figure). With ever expanding utilization of the Internet for international medical correspondence, it is increasingly important for medical providers to recognize ECG formats used elsewhere in the world. The Cabrera format has been in general use in Sweden since 1977. It is also used in a number of other countries. Although unlikely to displace the non-sequential standard format used in the United States, the Cabrera format offers the advantage of a more logical, equally spaced (30 degrees apart) sequential lead organization (see insert in the top right corner of the figure). Once accustomed to this format, determination of axis, frontal plane ST-T wave vector calculation, and serial ECG comparisons are all facilitated.

As to interpretation of the ECG in the figure, the rhythm is sinus, left axis deviation is present, and there are nonspecific ST-T wave changes but nothing that looks to be acute. These findings are unrelated to this patient's back pain.

NOTE: Please see ***http://tinyurl.com/KG-Blog-114*** for additional information on the Cabrera format.