The negative U wave in the setting of demand ischemia

(AUGUST 2011)

TO THE EDITOR: We thank Drs. Venkatachalam and Rimmerman[1] for their Clinical Picture article, "Electrocardiography in aortic regurgitation: It's in the details," in the August 2011 issue. This was very interesting, as usual for the *Cleveland Clinic Journal of Medicine*.

The maxim that "a negative U wave is never normal," first noted about 50 years ago, still holds true. However, the authors' statement on page 506—ie, that a negative U wave indicates structural heart disease—is too restrictive, since ischemia is not always due to a structural problem. Functional ischemia from excess demand, such as from tachycardia, sepsis, or gastrointestinal bleeding, can also cause negative U waves.[2,3] The broader comment in the "sidebar" on page 505 could be considered to include demand ischemia, but for clarity, it would be helpful to state this explicitly.

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IN REPLY: We appreciate the comments from Drs. Suksaranjit, Cheungpasitporn, Bischof, and Marx on our recent article on the negative U wave in a patient with chronic aortic regurgitation.[1] The clinical data including electrocardiography, echocardiography, and coronary angiography were presented to emphasize the importance of identifying the negative U wave in the setting of valvular heart disease. We outlined the common differential diagnosis for a negative U wave (page 506). We believe that in the appropriate clinical setting the presence of a negative U wave provides diagnostic utility.

Several published reports to date have described the occurrence of the negative U wave in the setting of obstructive coronary artery disease[2–5] or coronary artery vasospasm.[6] We were unable to find similar data in the setting of demand ischemia in the presence of normal coronary arteries (functional ischemia), but we fully recognize its likely occurrence, and we value the helpful insight.

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Dabigatran

(OCTOBER 2011)

TO THE EDITOR: The article "Dabigatran: Will it change clinical practice"[1] has a dangerous error. In its Key Points, it says "dabigatran is a potent, reversible direct thrombin inhibitor." In fact, it is *not* reversible.[2]

Shamefully poor editing.

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IN REPLY: This is not an error. When we[1] and others[2] said that dabigatran is a reversible direct thrombin inhibitor, we were referring to its effect at the molecular level, the appropriate description of its mechanism of action. However, we suspect that Dr. Smith means that there is no antidote to give in cases of bleeding or overdose. We share his concern and we discussed this in our article.

Unlike heparin, direct thrombin inhibitors act independently of antithrombin and inhibit thrombin bound to fibrin or fibrin degradation products. There are two types of direct thrombin inhibitors: bivalent (eg, hirudin) and univalent (eg, argatroban, ximelagatran, and dabigatran). The bivalent ones block thrombin at its active site and at an exosite and form an irreversible complex with it. The univalent ones interact with only the active site and *reversibly* inhibit thrombin, eventually dissociating from it and leaving a small amount of free, enzymatically active thrombin available for hemostatic interactions. Therefore, in contrast to the hirudins, they produce relatively transient thrombin inhibition.[2–4]

As we pointed out in our article, the lack of an antidote for dabigatran and the lack of experience in treating bleeding complications are major concerns. Fortunately, the drug has a short half-life (12–14 hours) so that the treatment is to withhold the next dose while maintaining adequate diuresis and giving transfusions as indicated. Activated charcoal, given orally to reduce absorption, is under evaluation but must be given within 1 or 2 hours after the dabigatran dose.[1] Dabigatran can be removed by dialysis (in part because it is a reversible inhibitor), a measure that may be necessary in life-threatening cases. Recombinant activated factor VII or prothrombin complex concentrates may be additional treatment options.[1,4] With time will come experience and, we hope, evidence-based guidelines.

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