resemble clinical observations of concealed retrograde conduction from the atria to the SA node described by Langendorf et al. and by myself. It was concluded that in these instances the retrogradely conducted impulses produced a refractory period in the approaches to the sinus node, with the consequence of a slowing of the subsequent antegrade conducted sinus impulse; the postectopic cycle was therefore prolonged. Some critical conditions must be realized for these phenomena to occur, and the opportunity for a clinical documentation and analysis arises very rarely. It is to be hoped that the experimental technic will permit the speculations on a firm basis. However, the final answers must await a method for direct recording from the human sinus node, whose behavior cannot be deduced with certainty from the evidence of atrial derivations.

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References


The author replies:

To the Editor:

Dr. Fleischmann's comments are appreciated. We fully recognize that our interpretation of the atrial cycle lengths observed following atrial depolarizations evoked progressively earlier in the sinus cycle is only one of several possible. As has been suggested, the plateau sections of the curves, shown in figures 2 and 4 of our manuscript, might represent only the ascent time of the premature depolarization, plus one normal sinus cycle, plus its descent time to the atrium. This is unlikely, however, for the following reasons: (1) ample in vitro evidence exists demonstrating that premature depolarization of cells with spontaneous phase-four depolarization results in a diminished slope of phase four of the action potential for several beats; (2) if there were no sinus node depression conduction times into, plus those out of the node, would equal 17–32% of the sinus cycle lengths observed in our patients, which seems extremely long; (3) the sinus cycle lengths following A2-A3 should, if this hypothesis were correct, equal 100%—in fact, they were always prolonged. It is possible, but unlikely, that the conduction of several successive sinus beats was delayed by the single atrial premature depolarization.

Dr. Fleischmann is correct concerning the tail of the curves, however. Very late premature depolarizations (90–100%) obviously collide with impulses leaving the sinus node, but this does not account for the entire tail of the curves. If that were the case, the shortest A1-A2 interval first entering the sinus node would be the 70% or “critical value” shown in Dr. Fleischmann's figure. Retrograde conduction into the sinus node would be prodigiously prolonged. There would be no “step up” in the A2-A3 interval when the sinus node pacemaker was first passively depolarized, because its depression would be very slight at that point, and only then progressively lengthen. The curves, like ours, would be continuous.

With regard to the use of the term “entrance block,” we were very careful to state: “In our patients who demonstrated block into the sinus node, the refractoriness of tissues responsible for transmitting impulses between the atrial myocardium and the sinus node is greater than that of the atrium itself.” “Entrance block” is a shorthand way of making this statement, and the technic merely defines this refractory period. These patients had normal sinus node function.

We, too, were intrigued with the points which fell between the plateau and entrance block sections of our curves, but because of space limitations did not refer to them in the manuscript. We interpreted them to represent partial sinus node entrance block. The dominant pacemaker was passively depolarized but the entire sinus node was not penetrated. A shift in the dominant pacemaker to a slower one within the sinus node resulted. We feel this is a more likely explanation than the one suggested, because these A2-A3 intervals were followed by extremely long atrial cycles with a different P-wave morphology for several successive beats, and a gradual return to baseline intervals.

Lastly, we quite agree, and stated clearly, that there is no indirect method which will “obviate the need for some direct measurement of conduction time from sinus node to atrium.” Until that is achieved, however, refinements of the technics suggested may yield clinically important information regarding sinus node function.

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Of Toads and Flowers

To the Editor:

I read Dr. Daniel S. Lukas' editorial (Circulation 46: 1, 1972) with great interest and respect for his views as a clinician and a clinical pharmacologist.

His reasoned appeal for the use of digitoxin rather than digoxin, however, appears to be flavored by some omissions and interpretations which I do not think are quite fair or appropriate to views of other cardiologists and pharmacologists. I feel an obligation to state some of my views on his remarks.

A citation referring to his own work reveals digoxin to be 23% protein-bound. Findings in our laboratory of in vivo human serum protein binding of digoxin after oral administration (permitting passage through the portal circulation and providing an ample opportunity for optimal binding with protein) reveal less than 5% of H-digoxin to be protein-bound. This finding, I believe, is of more import than suggested in the discussion. A reference cited in the editorial reports a
LETTERS TO THE EDITOR

significant correlation between the total serum protein concentration and the dose-corrected serum digitoxin activity. Here we really strike at the heart of the 10-fold (or more) differences in serum concentration between digitoxin and digoxin. This explains the 10-fold (or more) differences in serum concentration between digitoxin and digoxin and further strengthens the feeling, so eloquently stated by George Okita, that this difference is related to the polar structure of digitoxin compared to nonpolar digoxin.

The omission of the influence of drug interaction in digitoxin metabolism, also related to protein binding and polarity of the compound, deserves comment. Solomon et al., and Jelliffe and Blankenhorn, indicate there is alteration of digitoxin metabolism that may occur with concomitant administration of such frequently used drugs as phenobarbital, phenylbutazone, diphenylhydantoin, and spironolactone. Some interactions are due to stimulation of metabolizing enzymes, and others to competition for protein-binding sites (in serum as well as tissue). Since multiple drug administration is so common (often the rule in the elderly patient), I believe this aspect of digitalis metabolism should have been mentioned. Digoxin, being neither extensively metabolized nor protein-bound should escape these problems.

Digitoxin may indeed be a more useful drug in the cardiac patient with renal insufficiency than we previously supposed. However, the mean dominant half-time of digoxin in 11 anephric subjects studied in our laboratories was 98.88 hours (4.12 days). This figure is not quite as long as that observed for the T½ of digitoxin in patients with normal renal function, and I fail to appreciate much advantage gained through the use of digitoxin for these patients. Sufficient experience has accumulated regarding the use of digoxin in patients with renal insufficiency, nephrectomy, transplant, dialysis, etc. for me to feel comfortable and confident with the drug in the presence of these problems. We do not really know the reasons for differences in serum concentrations of digitoxin in renal failure and normal renal function, as well as what happens to digitoxin metabolism in hepatic dysfunction, thyroid disease, obesity, the elderly patient, the renal transplant, the unilaterally nephrectomized patient, infants, etc.

Two- to fivefold differences in digitoxin serum levels were noted by Gjerdrum18 in patients receiving the same loading and maintenance doses suggesting somewhat less predictable response than was outlined by the editorial. Interestingly, he also reports a significant correlation between the T½ of digitoxin and the serum concentration of creatinine and only a “small” correlation between serum concentration and body weight. Dr. Lukas’ arguments regarding his preference for digitoxin are not very convincing to me.

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References

Of Toads and Flowers
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