An Easier Approach to Estimating Risk of Coronary Heart Disease and Stroke

To the Editor:

In their article, Wilson et al provide useful information that allows clinicians to predict coronary heart disease risk in patients without a history of heart disease. This is very much needed because primary care and specialty physicians typically overestimate patients’ absolute heart disease risk and the expected benefits of drug therapy given for primary prevention.2,3

To encourage clinicians to use this type of information, it must be easy to use and incorporate into a busy clinician’s practice.4 In addition, it should facilitate clinicians’ discussion of this information with their patients so that an informed decision about drug therapy or other risk reduction strategies can be made.

We recently developed a simple nomogram for estimating the risk of coronary heart disease and stroke in individual patients using the Framingham data from previous studies by these authors.6,7 Our method allows the clinician and patient to consider the impact of individual risk factors. In addition, it allows them to visualize the interplay between individual risk factors; easily add, remove, or modify risk factors; and observe the impact of changes on risk assessment.

Because modification of risk factors does not necessarily mean that cardiovascular risk will be reduced, we also provided clinicians with a table that provides examples of demonstrated risk reductions that allows the clinician to incorporate the evidence from well-designed clinical trials into the decision-making process.

We encourage the Framingham group to present their risk prediction information in a more visual format rather than as a score sheet. This type of format is faster and easier to use and does not require summation of risk factor points and transfer of this information to tables. It allows the clinician and patient to visualize the potential effects of a combination of risk factors on the chance of coronary heart disease and the expected benefits of drug therapy given for primary prevention.

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Three-Dimensional Imaging of Atrioventricular Node

To the Editor:

In your issue of July 7, 1998, Efimov and Mazgalev describe a very exciting new avenue for study of the AV node. If the new approach is to achieve its full potential, however, it is important that it be assessed in the light of what we already know concerning nodal architecture. Thus, the diagram used by Efimov and Mazgalev (their Figure 1) is simplistic and misleading. On the basis of reconstructions supplemented by microelectrode recordings, we already know that cells comparable to the bundle of His extend posteriorly through the length of the AV node.2 Recognition of this posterior extension of the “lower nodal bundle” is now the more important in the light of its very recent identification by Medkour et al3 as the slow pathway of the AV node. We are also aware that using the sensible criterion proposed by Tawara,4 only the areas upstream of the insulating connective tissue illustrated by Efimov and Mazgalev should properly be described as “node.” We were unaware of this criterion when making our earlier description,2 and it is of interest that Medkour et al3 do not discuss this feature. We now believe that if we are to make full use of techniques similar to those employed by Efimov and Mazgalev, we should follow Tawara’s lead and agree with him that when differentiating node from bundle of His, “I make the border at the place where the system penetrates the atrioventricular fibrous septum, because this place is easily determined anatomically.”5

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Response

It might suffice to stress that the arm-chair drawing shown as an inset in Figure 1 of our article did not imply any morphological fidelity. Its sole purpose was to illustrate the dual-layer AV nodal structure as the proposed source of the multicomponent optical signals recorded in our experiments. Thus, as far as the essence of the discussed study is concerned, we do not feel that the reader would have been misled by the admittedly simplified drawing.

However, Dr Anderson’s criticism is broader and as such deserves special attention. A strict nomenclature related to the AV node and shared by both morphologists and electrophysiologists is clearly missing and needed. Although the fundamental work of Tawara has been available almost from the beginning of this century, it remains puzzling why morphologists were unaware of his simple criterion to divide the complex structure into “node” and “penetrating bundle.” One reason could be the fact that no sharp transitions exist, so that the compact AV node tissue merges gradually with both the posterior nodal extensions (PNEs) and the penetrating bundle. In fact, our drawing was influenced in part by the popular diagram derived from one of Dr Anderson’s coauthored works. This diagram placed the midnodal cells (the compact node) entirely under the collar of fibrous tissue. More recent diagrams, as in the cited work by Medkour et al, continue the trend of rather arbitrary illustrations by locking the egg-shaped compact node between the PNE and what appears to be a new term, the “lower nodal cell bundle.” Notably, Medkour et al reported exact 3-dimensional dimensions of different nodal structures with a 1-μm resolution, while at the same time they concluded that the primary “PNE characteristic was its compact node-like histology and the formation of a continuum without well-defined boundaries with the compact node and the lower nodal cell bundle.”

The above apparent imprecisions reflect the fact that the work on defining AV nodal morphology is still ongoing and that the correlation (or its absence) between the morphological structures and their electrophysiological importance is far from well understood. While the importance of striving for precision even in hand-drawn diagrams should not be underestimated, the task of comprehensively updating current knowledge of the AV node should not be postponed until the 100th anniversary of Tawara’s work.

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Is the Antiarrhythmic Effects of PA Related to Wavelength?

To the Editor:

In their excellent article, Kwan et al found that (1) the antiarrhythmic effect of procainamide (PA) could not be attributed to the alteration in wavelength because it did not significantly affect wavelength during ventricular fibrillation (VF), and (2) the ability of PA to decrease the number of wavelets by preventing spontaneous wave breaks can represent a novel mechanism of antiarrhythmic drug action. Because PA antiarrhythmic and defibrillating effects in rats and guinea pigs cannot be explained by prolongation of wavelength, and the mechanisms of preventing wave break are not clear, let us discuss briefly the features required for antiarrhythmic defibrillating compounds.

In an attempt to clarify the mechanisms underlying the maintenance of VF, we examined the factors involved in transient VF (TVF) versus sustained VF (SVF). No differences were found between cardiac muscle mass, heart rate, action potential duration, and effective refractory period of animals that exhibited TVF versus SVF. Similar to Kwan et al (Figure 8), TVF exhibited slow and synchronized electrical fibrillating activity, with a large part of ventricular mass acting in synchrony, whereas SVF exhibited unorganized, less synchronized electrical activity at a higher rate, with small local fibrillating areas. Untreated VF starts as an organized electrical activity resembling TVF, which becomes faster, less organized, and unsynchronized within a few seconds owing to “spontaneous wave break.” “Synchronized” fibrillation may occur only in hearts with good functional cell-to-cell coupling, ensuring continuous propagation of electrical signals through the myocardium in a manner that brings the viable cardiomyocytes to act almost in unison. Attenuation of spatial and transmural inhomogeneity of gap junctional alteration by enhancement of intercellular coupling can facilitate conversion of SVF into TVF by preventing spontaneous wave break and decreasing the number of reentry circles via synchronization of small local circles into bigger ones. Spontaneous defibrillation occurs when the viable myocardium acts as a functional syncytium and the majority of myoccardial cells are simultaneously in the refractory period.

Fast (fibrillating) cellular activity associated with temporary hypoxia or ischemia increases junctional resistance, decreases gap junctional conduction, and causes intercellular uncoupling, most likely owing to an increase in cytoplasmic free Ca2+ concentration ([Ca2+]i) and/or alteration in intercellular cAMP gradient. An excess of diastolic [Ca2+]i downregulates intercellular communication, impairs intercellular coupling, and thus increases the number of fibrillating microareas by spontaneous wave break.

Following this assumption, we hypothesized that an antiarrhythmic defibrillating drug should prevent intercellular desynchronization. It should decrease the number of fibrillating circles and thereby slow down the fibrillating rate. It should prevent or attenuate [Ca2+], overload-induced electrical uncoupling and thereby enhance or reestablish intercellular coupling and synchronization. It should increase gap junctional conductance, should not decrease conduction velocity, and should preserve excitation-contraction coupling.

Finally, it was found that PA possesses 1 of the main antiarrhythmic effects: it prevents Ca overload and decreases previously enhanced [Ca2+], toward its normal level. In this way,
PA prevents spontaneous wave break, decreases the number of reentrant waves, and synchronizes fibrillating activity, thereby exhibiting antiarrhythmic effects unrelated, at least directly, to wavelength.

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Response
We appreciate the comments of Drs Tribulova and Manoach. Very interestingly, the authors found that similar to its effects on canine ventricular fibrillation (VF), procainamide also decreases the complexities of VF in smaller hearts (rat and guinea pig) by a mechanism that is also independent of wavelength prolongation. The proposed mechanism(s) of procainamide-induced increase of cell-to-cell coupling as a basis for the prevention of spontaneous wave break is interesting, but we do not think that this is a unique mechanism for the prevention of wave break. We have shown in an in vitro swine model of stable VF (ie, perfusion maintained during the VF through the coronary artery) that in spite of good perfusion, procainamide reversibly regularized VF by preventing spontaneous wave break. We think that active regenerative cellular properties, including dynamic action potential duration (APD) restitution, may be involved. Although the wavelength (product of APD and conduction velocity) remains unchanged after procainamide, the drug tends to flatten the APD restitution curve and prevents the generation of action potentials with short duration during VF. Our working hypothesis is that activation with short APD is intrinsically a weak stimulus that undergoes block (wave break). By preventing the initiation of activation with shorter APD, procainamide might prevent spontaneous wave break. We therefore think that in addition to the possible passive mechanism (increased intercellular coupling resistance) of wave-front breakups, as proposed by Drs Tribulova and Manoach, there also exists the distinct possibility of active cellular properties (APD restitution properties during VF) that act in concert to either prevent or promote spontaneous wave breaks.

Evidence for a Link Between Adipose Tissue Interleukin-6 Content and Serum C-Reactive Protein Concentrations in Obese Subjects
To the Editor:
We read with interest the editorial by Tracy1 on inflammation in cardiovascular disease (CVD). Serum concentrations of C-reactive protein (CRP) were demonstrated to be related to increased risk of CVD, which underlines the potential inflammatory nature of human atherosclerosis.2,3 Interestingly, an unexpected association between CRP and body mass index (BMI) was found in several population studies2–4 without any explanation. The production of CRP is regulated by cytokines, principally interleukin-6 (IL-6), and serum CRP levels reflect IL-6 activity in humans. It was demonstrated that IL-6 is released in vivo by subcutaneous adipose tissue and is thereby able to have systemic effects, particularly in obese subjects.5 Thus, we hypothesized that adipose tissue may play a role in the regulation of serum CRP concentrations via IL-6 production.
To test this hypothesis, we measured CRP and IL-6 in both blood and adipose tissue from 13 fasting obese subjects (2 men, 11 women) aged 44 ± 24 years (BMI, 39.1 ± 1.3 kg/m²; percent fat mass, 44.3 ± 2.4%). CRP concentrations were determined with a BNII nephelometry analyser (Behring). IL-6 concentrations were determined by ELISA (QuantiKine, R&D Systems). Body composition analysis was carried out by dual x-ray absorptiometry (QDR 1000, Hologic).
Serum CRP and IL-6 concentrations were 4.49 ± 0.07 mg/L and 2.77 ± 0.31 pg/mL, respectively. In adipose tissue, IL-6 concentrations were 12.81 ± 1.28 pg/g fat, whereas CRP was undetectable. Serum CRP concentrations were significantly correlated with BMI (r = 0.633, P < 0.05), body fat mass (r = 0.718, P < 0.05), and percent fat mass (r = 0.872, P < 0.005) but not with lean body mass (r = −0.435, P = 0.13). A strong correlation was found between serum CRP concentrations and adipose tissue IL-6 content when expressed as picogram per total fat mass (r = −0.757, P < 0.01) but not as picogram per gram of fat (r = 0.446, P = 0.12).

These data are consistent with the role of human adipose tissue in the regulation of blood circulating CRP concentrations via IL-6 production in obesity. In addition, the higher IL-6 production from adipose tissue
seems to be more related to the increase of total fat mass than an overexpression of IL-6 in adipose tissue. Because CRP was proposed as a predictive marker of CVD risk, whether slightly elevated concentrations of CRP are the consequence of adipose tissue secretion, an inflammatory process, or both remains to be established.

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