EDITORIAL COMMENT

You Only Get So Many Heartbeats. . *

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These words, attributed apocryphally to Dr. Sam Levine, have been passed along through several generations of his “offspring.” As happened so many times, Dr. Levine’s vast and encyclopedic clinical experience allowed him to anticipate and accurately predict what subsequently would be proven in well-done and exhaustive clinical trials. In this particular case, Dr. Levine correctly intuited that a low heart rate (HR), no matter the rhythm, would benefit the patient. We now know that a patient’s prognosis after myocardial infarction is closely tied to spontaneous HR. Those with low HRs clearly outlive those with high rates. Low values reflect heightened vagal tone, proven in the experimental laboratory to be cardioprotective, reducing vulnerability to ventricular fibrillation and opposing the pro-fibrillatory effects of heightened sympathetic stimulation. High vagal tone is reflected in a myriad of parameters of HR variability, a highly powerful predictor of outcome that has been poorly embraced by practicing cardiologists. One reason for this lack of acceptance may be that the resting HR itself is hard to outdo as a risk predictor in post-infarction patients and in other forms of heart disease such as heart failure, wherein more moderate heart rhythms auger better than those that are allegro.

It is not surprising that the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) investigators made the efficiency of HR control a primary focus of their research efforts. They and others proved incontrovertibly that rate control using drugs or other interventions is a reasonable treatment option in selected patients with atrial fibrillation (AF) (1–4). So it was only logical that they then would move on to deliver detailed information about rate control in the report in this issue of the Journal (5). They correctly cite a wealth of literature that indicates that high HRs are not good for patients with AF. There have been many case reports and small series in which patients were found to have dramatic improvement of left ventricular function after recovery from what was certainly tachycardia-related cardiomyopathy (6). In fact, there are probably orders of magnitude more cases in which left ventricular function improved, but not as dramatically, not only because of rate control but also because the ventricular response was regularized (7). The exact mechanism by which tachycardia causes deterioration in left ventricular function has not been elucidated, but what is clear is that recovery is independent of the method by which rate control is restored. In fact, medical treatment, even with negatively inotropic medications, works as well as non-pharmacologic approaches.

Dr. Bernard Lown, Dr. Levine’s most famous disciple, emphasized the importance of digitalis in high doses for this indication. The fact is that at the time that Lown and Levine promulgated the notion of rate control as the preferred strategy for AF patients, beta-blockers and nondihydropyridine calcium antagonists, mainstays of current therapy, had not been invented yet. Acetyl-digitoxin was their favorite preparation, which not only slowed but also regularized the ventricular rhythm in chronic AF patients, thus contributing to symptom improvement. Lown also favored this novel preparation of digitalis because it was only partially detectable in commonly used digoxin assays. Thus, physicians who shared the care of Lown’s patients were less likely to reduce the dose of the drug based on a random high blood level. Lown and Levine felt strongly that measurements of digitalis plasma concentrations were not relevant in patients who were receiving the drug for AF. Avoidance of digitalis excess has been facilitated by serum assays in patients with sinus rhythm, but they believed that the ventricular response rate itself was the most appropriate “bioassay” upon which to base dose adjustments. Consequently, they used much larger doses than we use currently, with remarkably good results not only in terms of rate control but also with regard to rhythm smoothing. High doses of digitalis appear to regularize AF, but the mechanism for this interesting phenomenon is not clear and is not necessarily unique to digitalis preparations. Some have thought that digitalis in high concentrations sensitizes the specialized conduction tissue in the atrium or the junction to become the predominant and more regular pacemaker. Whatever the reason, once again clinical experience and acumen antedated trial data. We now know that the smoothing of rhythm and control of rate that is afforded by atrioventricular (AV) node ablation and ventricular pacing is associated with an improvement in ventricular performance and quality of life over and above what might be expected with rhythm control strategies (8).

The data from AFFIRM presented by Olshansky et al. (5) is very interesting with this historical perspective. They found a number of interesting things that deserve emphasis. First, objective measures of rate control are important in assessing the worth of any intervention. Unfortunately, there is no universally agreed-upon parameter for effective rate control. It is clear that HR should be assessed at rest as well as during effort, but what the target HR should be and during what level of exertion has never been standardized. The authors chose a simple,
office-based clinical assessment (or the option of a Holter-based measurement) that appears to have been reliable and fairly reproducible. The authors also found that rate control is not as easy as many have assumed. Single-drug therapy failed frequently, multiple drugs failed sometimes, and frequent dose titration to achieve optimal rate control was critical. All of this “affirms” that rate control, although conceptually simple, should not be taken lightly. Nevertheless, the strategy worked fairly well, with a good percentage of patients achieving the end point. This may help to explain why the rate control strategy worked so well compared with rhythm control in AFFIRM and in the other three trials in which it was tested. It was not surprising that beta-blockers were the most effective drugs in the study and that they were highly useful in patients at rest or with activity. What was surprising, but in agreement with the experience of Lown and Levine, was how well digitalis performed, either as a single drug or when used in combination. Digitalis works better in the sedentary, elderly population than in young active patients in whom its vagomimetic effects can be overcome by the increases in sympathetic tone that accompany high activity levels. Because the elderly were well represented in AFFIRM, the good performance of digitalis is interpretable. But these comparative data must be put into context: the selection of rate-control therapy was not randomized or blinded, and comparisons of efficacy are therefore difficult, especially given the great inequalities among groups with regard to clinical characteristics. Prior treatment was also diverse, but interesting, in that patients who were treated with a particular rate control drug before study entry tended to continue using that drug in the study itself, a self-fulfilling prophecy of efficacy. As one would have expected, certain drugs were used much more frequently in specific clinical syndromes, based on tolerance or efficacy for reasons other than rate control itself. For example, digitalis was used more frequently than beta-blockers or calcium channel blockers in cardiomyopathy but not in hypertension. Atroventricular node ablation was not used as a parallel strategy but as a last resort intervention in drug non-responders, which is its appropriate niche. Notably, AV node modification, now appropriately abandoned as a dangerous rate-control strategy, was not used in the study. As valuable as the data from this study are, there is much we still do not know. We really do not know whether a rate control strategy can be applied to the most symptomatic patients with AF. The AFFIRM study and its cousins recruited a large number of patients who were selected because they were already fairly comfortable with their arrhythmia. In addition, although we think that well-controlled HRs are good for patients, we do not have hard outcome data from any trial that show this incontrovertibly. For example, we don’t know whether drug-induced rate slowing is as beneficial prognostically as having slow HRs from high vagal tone. Neither AFFIRM nor any other trial has shown that patients live longer, are hospitalized less, or have a higher quality of life as a function of HR control. It would be good to know if there should be a preferred order of rate control therapy and whether any one approach is superior in terms of these hard endpoints. Whether or not those data can be mined from the AFFIRM database, or from the results of any other trial(s), remains to be seen. The fact is that further refinement is unlikely. However, there is at least the hope that we will have drugs available that effect AV nodal conduction in a more specific way than present-day therapy. For example, there is much interest both in purine agonists that are more cardioselective and AV-node selective than adenosine and in the possibility that these new compounds may have a long enough half-life and sufficient bioavailability to be used orally.

Until new drugs and new data are available, it seems logical and reasonable to pursue rate control aggressively in patients with AF no matter what long-term strategy is ultimately pursued, and this approach is reflected in current guidelines (10). Such conservatism is based on a wealth of positive clinical experience, now buttressed by a series of well-executed clinical trials for which we owe our fellow clinical scientists a debt of gratitude. Clearly, the old clinical saw “You only get so many heart beats. . .you should save some for later in life” has more meaning than most of us (maybe even Levine and Lown) could have imagined.

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REFERENCES