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Clinical Significance of Iodine-123 Metaiodobenzylguanidine Cardiac Imaging

In a recent issue of the *Journal*, Tamaki et al. (1) found that in their study sample of 106 consecutive patients with stable congestive heart failure (CHF), those experiencing a sudden cardiac death (SCD) had on average a higher washout rate of iodine-123 metaiodobenzylguanidine (MIBG WR) compared with those who survived. Statistically, the cardiac MIBG WR was a powerful predictor of SCD in patients with mild-to-moderate CHF. But how can this best be applied clinically?

The mean (X1) washout rate in those with SCD was 39.9% with a standard deviation (SD1) of 15.2%. For those without SCD, the mean (X2) washout rate was 27.6% with a standard deviation (SD2) of 14.2%. Using this data, we can determine the crossover point below which a patient is more likely than not to fall into the low-risk group (no SCD) and above which a patient is more likely than not to fall into the high-risk group (SCD) (2).

The crossover point (CP) = $(SD1 \cdot X2 + SD2 \cdot X1)/(SD1 + SD2) = 33.5\%$. This CP falls 0.42 SDs above X2 and 0.42 SDs below X1 (i.e., $X2 + 0.42 \cdot SD2 = X1 - 0.42 \cdot SD1$). In normally distributed data, using a *z*-score table, we find that, at best, 34% of the patients will be miscategorized when using the MIBG WR if a fixed threshold value is utilized. If we use a threshold of 27%, as proposed by Ogita et al. (3), then over 50% of the low-risk patients will be miscategorized. Threshold values either above or below the CP will only lead to a miscategorization rate >34%.

In clinical practice, fixed threshold values for continuous data such as the MIBG WR are not rigidly followed. Patients are frequently categorized as "borderline normal" or "borderline abnormal." Are there better ways to make sense of the data so it can be more clinically useful? Simply reporting the means, SDs, and a threshold value does not adequately characterize the data for the clinician caring for an individual patient.

We propose that a more useful way to report continuous variables that impact patient care is to give at least 3 reference values: 1) the point where an individual patient is just as likely as not to belong to group 1 as to group 2; 2) the odds of belonging to group 1 at X1; and 3) the odds of belonging to group 2 at X2. In some situations, additional reference values may be useful. For the MIBG WR data, the CP = 33.5%. This is the point at which the odds are 50/50 in regard to whether the patient is in the high-risk or in the low-risk group. The formula to determine this point is given in the preceding text.

When a patient's MIBG WR is 39.9% or greater, the odds are at least 2.6 to 1 that the patient is in the high-risk group. This is calculated by finding the *z*-score of the absolute value of $(X1 - X2)/SD2$, then dividing 0.5 by the area under the curve to the right of this *z*-score. When a patient's MIBG WR is 27.6% or less, the odds are at least 2.4 to 1 that the patient is in the low-risk group. This is calculated by finding the *z*-score of the absolute value of $(X1 - X2)/SD1$, then dividing 0.5 by the area under the curve to the right of this *z*-score.

This type of numerical summary helps clinicians reasonably apply and explain the MIBG WR to individual patients with stable CHF. When a patient's MIBG WR is around 33%, the test does not help categorize the patient into a low- or high-risk category (a coin flip is just as accurate). However, when the MIBG WR is 27% or less, the odds are greater than 2:1 that the patient is at low risk. When the MIBG WR is 40% or higher, the odds are greater than 2:1 that the patient is at high risk. Basing medical management upon MIBG WR values between 30% and 36% is basically just guessing, and will lead to suboptimal care in a high percentage of patients.

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Reply

We are grateful to Drs. Heston and Wahl for their valuable comments and suggestions to our study (1). They pose a question regarding the use of a fixed threshold value for continuous data, such as a washout rate of iodine-123 metaiodobenzylguanidine (MIBG WR) for the prediction of prognosis, and propose an alternative way to figure out and report such continuous variables. Although the method they propose is indeed intriguing, we think there remain a few important problems to be discussed.

First, the clinical implication of the reference values that they propose would vary depending on the outcome to which the continuous variable is related. For example, in the case where the outcome is sudden cardiac death (SCD) as in our study, the patients with variables near the crossover point would be regarded as life-threatened patients, because they may belong to those with a high risk of SCD, at a rate as high as 50%. Such patients might be regarded as the good candidates for implantable cardioverter-defibrillator therapy in most cases.

In dealing with the issues of life-threatening events like SCD, we think we should put more emphasis on not overlooking the patients at high risk than on not overlooking those at low risk. The threshold of MIBG WR >27% would be appropriate for this purpose, because a negative predictive value as high as 92% could be achieved with this threshold in our study patients (1).

Second, there may be a limitation on the method by Drs. Heston and Wahl, because their calculation is based on the assumption that the results of cardiac MIBG WR exactly follow a normal distribution. In fact, the specificity of abnormal MIBG WR (>27%) for the prediction of SCD was 56% (1), which is different from (higher than) the specificity calculated by Drs. Heston and Wahl.

However, we agree with the suggestion by Drs. Heston and Wahl that there are some borderline cases that require difficult decision making, and that we should not rely only on the fixed MIBG WR value for the identification of the patients at high risk for SCD. The only way to deal with these borderline cases might be to take other clinical indexes that have been shown to be highly predictive of SCD (i.e., left ventricular ejection fraction, electrocardiographic parameters such as T-wave alternans [2], or clinical scores [3]) into account and judge the risk for SCD on a case by case basis.

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