Late Sympathetic Reinnervation and Normalization of Canine Myocardial Beta-Adrenergic Receptor Density Following Denervation

TO THE EDITOR: We previously (*1*) reported up-regulation of myocardial beta-adrenergic receptors (β-AR) and the absence of significant sympathetic reinnervation up to 6 mo after intrapericardial denervation. We now report changes in myocardial sympathetic innervation and in β-AR density in the same dogs 2 yr later.

Five female beagle dogs were previously studied, 3–7 wk, 23–28 wk and 2 yr after denervation produced by the intrapericardial technique (*2*). To evaluate the sympathetic reinnervation, dogs underwent [^{123}I]MIBG scintigraphy. The heart-to-lung activity ratio (H/L) was used to quantify myocardial MIBG uptake. For PET determination of myocardial beta-AR density, ^{11}C-CGP 12177 and a graphical method (*3*) were used.

Before surgery, β-AR concentration was 33 ± 4 pmole/ml tissue. The MIBG H/L ratio was 3.1 ± 0.1. As previously reported, β-AR densities increased to 68.9 ± 15.7 pmole/ml tissue and 61.3 ± 7.9 pmole/ml tissue 3–7 wk and 23–28 wk after surgery, respectively. At the same time, MIBG H/L ratios were 1.07 ± 0.1 and 1.06 ± 0.04, respectively. Two years after surgery, MIBG scintigraphy demonstrated a persistant decrease in ventricular sympathetic nerve uptake of the tracer (H/L = 2.11 ± 0.3; $p < 0.05$ versus presurgery). Beta adrenergic receptor density was 29.4 ± 2.2 pmole/ml tissue, a value not different from that observed before surgery.

Following surgical denervation, early (1 mo) and late (6 mo) up-regulation of β-AR was observed (*1,4*), while MIBG myocardial uptake remained low. A partial reinnervation by the sympathetic nervous system usually occurs within the 6 mo to 1 yr following denervation (*5*). Kaye et al. demonstrated that the density of ventricular sympathetic neurons remained too low to restore normal ventricular norepinephrine levels 1 yr after denervation (*5*). Therefore, we did not perform any measurement at that time. Two years after surgery, partial ventricular sympathetic reinnervation occurred, as coarsely assessed by MIBG planar scintigraphy and the relatively insensitive H/L index. Despite this scintigraphic result, it is likely that myocardial norepinephrine content has returned to subnormal value since β-AR density is similar to that measured before surgery.

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Clinically Silent Adrenal Masses

TO THE EDITOR: Some slight arithmetic errors seem to have slipped into the otherwise impressive series of adrenal images presented by Gross et al. (*1*) For instance, the article mentions 44 intra-adrenal neoplasms, whereas only 43 are represented in Table 1 of the original article. Similarly, 14 cases of adenoma with normal patterns are mentioned in Table 2, whereas the text implies that there are only 12. Finally, the number of adenomas is inconsistently given as 185 or 171.

More important, however, an error was made in data analysis. The authors define true-negative as a concordant pattern of imaging in adenoma or a normal pattern in periadrenal or pseudoadrenal masses. This implies that the imaging test is being judged with respect to the diagnosis of destructive adrenal lesions. In that case, however, the 14 adenomas which yielded symmetrical images can not be considered as false-negatives but should be viewed as true-negatives, because the scans in these cases do not raise the suspicion of a destructive lesion. In other words, even if these adenomas are misclassified as normal, their classification as cases without destructive adrenal lesions is correct. Table 1 gives the values for the test parameters that are obtained when these changes are considered.

Alternative analyses can be performed if the aim of the test is to diagnose adenoma or the presence of any adrenal lesion. The corresponding test parameters are also given in Table 1. As can be seen, the negative predictive value is quite different according to the purpose of the test. The absence of a discordant pattern (negative test for destructive lesion) is highly predictive (98%) for the absence of a destructive lesion, whereas the absence of a

TABLE 1
Efficacy of NP-59 Scintigraphy for Different Diagnoses

Diagnosis	Destructive lesion	Adenoma	Any adrenal lesion
Sensitivity	93%	92%	92%
Specificity	100%	100%	100%
Accuracy	99%	94%	93%
Predictive value of a negative test	98%	80%	41%
Predictive value of a positive test	100%	100%	100%

adenoma) is somewhat less predictive (80%) for the absence of an adenoma. A normal pattern (negative test for any lesion), however, does not predict (41%) the absence of disease in the adrenal gland.

REFERENCE

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REPLY: We appreciate the opportunity to correct errors that appeared in our recent article. In Table 1, the number of myelolipomas with discordant patterns of imaging (mass on CT with decreased orabsent NP-59 uptake on the side of the mass) was 2 for a total of 44 as noted in the text. Fourteen adenomas demonstrated nonlocalizing imaging patterns with NP-59 uptake on the side of the mass) was 2 for a total of 44 as noted in the text. Fourteen adenomas demonstrated nonlocalizing imaging patterns with NP-59, for a total of 173 (159 adenomas localized + 14 not identified). There were 12 periadrenal masses identified by CT that were initially classified as "adrenal" (173 + 12 = 185) that demonstrated bilaterally symmetric patterns on NP-59 scintigraphy. Nevertheless, none of these errors have any affect on the efficacy of NP-59 scintigraphy in incidentally discovered adrenal masses as presented in Table 3. We regret these errors and any confusion that they may have caused.

As Dr. De Geeter correctly states, there are multiple ways in which this complex data can be analyzed. Because there are at least three scintigraphic imaging patterns (rather than simple "positive and negative"), calculations of efficacy will depend on how the scintigraphic patterns are defined and ultimately the purpose(s) to which the test is employed. We indeed, defined "true-negative" as a concordant pattern in adenoma or a normal pattern in periadrenal or pseudoadrenal masses, because we believe that the most important diagnosis to make is that of a destructive adrenal lesion. It is this latter group that includes both primary and metastatic malignancies to the adrenal which are lesions requiring further diagnostic attention and/or therapy. We chose to identify the 14 small adenomas that demonstrated symmetrical imaging as false-negative because a small number of destructive, potentially malignant lesions gave an identical imaging pattern. The data analysis presented in De Geeter's table represents an equally valid interpretation given somewhat different criteria on how different groups are defined. These data again demonstrate the highly predictive nature of a discordant imaging pattern for destructive lesions. It is true that a normal pattern of imaging has a lower predictive value for the absence of disease in the adrenal, but this is not important because scintigraphy is not being used as the primary modality to determine the presence of adrenal masses. All our patients had CT imaging, which found an adrenal mass lesion. In this context, NP-59 scintigraphy is used to help characterize the nature of the lesions which were discovered on CT incidentally.

We thank Dr. De Geeter for his comments but we believe that despite differences in the manner in which our data can be manipulated, his analysis and conclusions are, in fact, not all that different from our own.

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