Cardiac Studies with Metaiodobenzylguanidine: A Critique of Methods and Interpretation of Results

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Metaiodobenzylguanidine (MIBG), a structural analog of norepinephrine, was developed in the early 1980s at the University of Michigan, Ann Arbor, MI, as an imaging agent for pheochromocytoma (*1,2*). It was soon found that MIBG was readily taken up by sympathetic nerves. Because the sympathetic nervous system was believed to play an important role in the manifestation of many types of heart diseases, several groups have used MIBG to study the cardiac sympathetic nervous system in physiologic and pathophysiologic circumstances. Sympathetic nerve destruction by stellate ganglionectomy (*3*), epicardial application of phenol (*3–5*), administration of 6-hydroxydopamine (*6,7*) or transmural myocardial infarction (*8,9*) produces a profound loss of MIBG uptake in the affected myocardium. Sympathetic nerve damage in denervation studies was documented by depletion of myocardial stores of norepinephrine (*3,4,6,7*), decreased radiolabeled NE ([^{3}H]NE) uptake (*7*) and, most specifically, by loss of electrophysiologic responses in denervated myocardium (*5*). Similarly, total cardiac denervation in humans by cardiac transplantation produces marked loss of MIBG uptake (*6,10*). Diseases in which there is well-documented damage to sympathetic neurons, such as symptomatic diabetic autonomic neuropathy and Shy-Drager syndrome, also result in a profound loss of cardiac MIBG uptake (*11*).

The success of MIBG in demonstrating cardiac sympathetic nerve damage in the above situations has resulted in using MIBG to study sympathetic nerve function in other types of heart disease, such as hypertrophic cardiomyopathy (*12,13*) and congestive heart failure (*10,14,15,16*). Changes in the sympathetic nerve functions in these diseases are more complex than in cardiac denervation and are, therefore, harder to interpret. In addition, because cardiac uptake of MIBG is usually less severely affected than in denervation, performing accurate quantitative studies is of greater importance. In this article, two aspects of cardiac MIBG studies will be reviewed: methods for quantifying cardiac MIBG uptake and interpretating the results. The issues involved will be discussed primarily in relation to cardiomyopathy, but the concepts apply to other forms of heart disease and to other tracers that have kinetics similar to MIBG.

CARDIAC NOREPINEPHRINE KINETICS

To properly interpret MIBG cardiac studies, it is important to understand norepinephrine kinetics in sympathetic nerves. Norepinephrine turnover is an accepted method for measuring sympathetic nerve function. The best validated method of measuring norepinephrine turnover involves injecting radiolabeled [^{3}H]NE and measuring its disappearance from the heart over several hours. Studies in animals have shown that, in a variety of physiologic and pathophysiologic situations, [^{3}H]NE disappearance from many organs, including the heart, follows first-order kinetics which are characterized by the fractional turnover rate, k, or the half-time, $T_{1/2}$ of cardiac [^{3}H]NE (*17*). The two constants are related by the equation:

$$k = \frac{0.693}{T_{1/2}}.$$

Norepinephrine turnover is the product of the fractional turnover rate, k, and the endogenous norepinephrine content of the tissue. In most physiologic situations, changes in norepinephrine turnover have only a small effect on the norepinephrine content of a tissue because norepinephrine synthesis changes in parallel with norepinephrine turnover to keep tissue concentrations of norepinephrine relatively constant (*17*).

The Syrian golden hamster is a good animal model for studying norepinephrine kinetics in congestive heart failure. These animals have normal hearts at birth and through

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the first 40 days of development. For approximately the next 30 days, focal cardiac myolysis and cellular infiltration occur followed by healing. Over the next 250 days, the heart hypertrophies and then dilates as congestive heart failure develops. Before heart failure develops, cardiac norepinephrine stores in myopathic hamsters are similar to those in control hamsters (*18*). As heart failure worsens, cardiac NE levels become progressively depleted. A similar situation is seen in human heart failure (*19,20*).

In the Syrian hamster, the fractional rate loss (or washout) of [^{3}H]NE increases faster than the fall in norepinephrine content, so that norepinephrine turnover is accelerated, demonstrating greater sympathetic tone in heart failure. When normal hamsters and hamsters with heart failure were treated with ganglionic blocking agents for 24 hr, there was little change in cardiac norepinephrine content of normal hamsters, but in myopathic hamsters, cardiac norepinephrine content increased to levels identical to those in normal hamsters. The fractional loss rates decreased to nearly the same value in both groups (*18*). These results indicate that the increased washout rates of [^{3}H]NE in heart failure are due to increased stimulation of sympathetic nerves by preganglionic neurons rather than a primary abnormality in the sympathetic neuron. This increased stimulation is an expected finding because sympathetic outflow is generally increased in heart failure (*21*).

MIBG STUDIES

In in vitro studies, MIBG has been found to qualitatively follow norepinephrine kinetics in terms of its uptake and storage (*22,23*). Only a few studies have attempted to determine the cardiac kinetics of MIBG in vivo. These studies show that MIBG appears to follow first-order kinetics in the heart under several circumstances for the first 24 hr after injection (*7,10*). After initial nonneuronal uptake clears from the heart, cardiac kinetics of MIBG can be characterized by an equation of the form:

$$A(t) = A_0 e^{-0.693\, t/T_{1/2}},$$

where A_0 is the initial cardiac uptake of MIBG and $T_{1/2}$ is the half-time of washout. These two parameters contain all the kinetic information that can be obtained from MIBG imaging studies for processes affecting the whole heart and have physical relevance. The initial uptake is a measure of number and function of norepinephrine transporters, whereas $T_{1/2}$ (or equivalently, k, the fractional loss rate) is a measure of sympathetic nerve activity. As pointed out above, norepinephrine turnover is a more precise measure of sympathetic nerve activity. Fortunately, changes in norepinephrine turnover tend to parallel changes in $T_{1/2}$, and so the washout half-time can be used as a marker of sympathetic nerve activity. To obtain accurate values for these parameters, measurement must be performed after the distribution phase of MIBG is over and the non-neuronal uptake has cleared from the heart. In human hearts, nonneuronal MIBG clears rapidly, as early as 15 min (*6*) and no later than 1 hr after injection (*10*). The clearance is longer in dog hearts (*6*), indicating there are important species differences in cardiac handling of MIBG.

Although MIBG kinetics are qualitatively similar to those of norepinephrine, there are important quantitative differences. In bovine adrenal chromaffin cells, an in vitro model of sympathetic neurons, there is a significantly higher nonspecific uptake of MIBG than norepinephrine (*23*). Similarly, in vivo, drugs that block norepinephrine uptake seem to have less of a blocking effect on MIBG uptake than on [^{3}H]NE (*22*). In rats, cardiac MIBG has nearly twice the washout rate of [^{3}H]NE (*7*). These latter results may reflect the higher nonspecific uptake and washout of MIBG across cell membranes.

Two studies used an exponential model to calculate the MIBG washout rate in the normal human heart. One study which measured heart activity over 24 hr found a washout half-time of 20 hr (*10*). In another study, which measured washout at two time points, the half-time was 25 hr (*13*). Some investigators have measured washout rates as the fractional change between two time points (*12,15*). This method is equivalent to assuming a linear rate loss of MIBG. The problem with this approach is that if MIBG loss from the heart follows first-order kinetics, the fractional loss per hour using a linear model will depend upon the time between images. Shorter imaging times yield higher loss rates. Because investigators have used different time intervals, this lack of uniformity in measuring washout rates makes it difficult to compare results from different studies. Nevertheless, in all studies of cardiomyopathy, cardiac MIBG washout is accelerated compared to normal control subjects (*10,12,13,15,16*).

Because washout rates require measuring cardiac activity at two or more time points, it is impossible to make any type of quantitative statement about sympathetic nerve activity based on measurements at a single time point. Decreased activity at a single time point could be due to rapid washout of MIBG and a normal initial uptake or decreased initial uptake with normal washout. This does not mean that useful data cannot be obtained from single measurements. It has been shown, for example, that decreased cardiac MIBG activity 4 hr after injection was a better predictor of survival in patients with heart failure than left ventricular ejection fraction, cardiothoracic ratio or left ventricular end-diastolic diameter (*24*).

The other parameter that can be used to evaluate sympathetic nerve function is the initial uptake of MIBG. This parameter is a measure of the number and function of norepinephrine transporters in the heart. This measure of sympathetic nerve function has not been extensively used because more variables affect the initial uptake, making interpretation of results more difficult. Some of these variables include the dose injected, tissue attenuation (in imaging studies) and norepinephrine levels that competitively interfere with MIBG uptake. Allowances can be made for some of the variables involved, and a few studies have measured initial uptake in heart failure. One study found

that the initial uptake of MIBG was similar to normal controls, but the washout was accelerated, indicating that decreased MIBG heart activity in patients with congestive heart failure is due to increased sympathetic nervous system activity (*15*).

Another study, however, found the initial uptake was decreased (*10*). It is possible that initial cardiac MIBG uptake in severe heart failure is decreased since there is decreased cardiac extraction of plasma norepinephrine in heart failure (*20*). A study of experimental right heart failure in dogs showed a marked decrease in [^{3}H]mazindol binding in the right ventricular myocardium (*25*). Mazindol binds specifically to the norepinephrine transporter, the plasma membrane protein responsible for the specific (Type I) uptake of norepinephrine (*26,27*) and MIBG (*28*). Even if there are decreased norepinephrine transporters in heart failure, this finding alone cannot be interpreted as evidence of sympathetic nerve dysfunction. By decreasing the number of norepinephrine transporters, more norepinephrine becomes available in the synaptic cleft, allowing more intense stimulation of cardiac adrenergic receptors. A decrease in transporters, therefore, may be a compensatory rather than a pathologic response. Presently, there are too few data on the initial uptake of MIBG by the heart to draw firm conclusions about its significance in heart failure.

There are also relatively few data on the intraneuronal distribution of MIBG. In a study by Wieland et al. reserpine (a specific blocker of the vesicular monoamine transporter which is responsible for the vesicular uptake of norepinephrine) caused nearly 90% depletion of MIBG in dog adrenal glands suggesting that most intracellular MIBG was in adrenergic vesicles (*29*). Nakajo et al. looked at whole heart activity over 24 hr in control rats and rats treated with a single injection of reserpine (*30*). Differences in heart uptake between the two groups increased until 4 hr after injection when reserpine-treated rats had 50% of the heart activity of control rats, a difference which then persisted to 24 hr. It was concluded that after 4 hr 50% of neuronal MIBG is in a nonvesicular compartment. This conclusion was based on the assumption that reserpine blocks 100% of vesicular MIBG uptake, both specific and nonspecific, and that total blockage of vesicular uptake has no effect on cytoplasmic MIBG kinetics.

These assumptions need to be validated. Another explanation of the data is that reserpine produced only partial blockage of vesicular uptake, and cardiac activity after 4 hr represented residual vesicular uptake. It is noted that residual cardiac activity after 4 hr had the same washout rate as in the untreated rat hearts. Kinetics of cytoplasmic MIBG have been studied in human neuroblastoma cells, which produce norepinephrine but contain very few adrenergic storage vesicles. MIBG in these cells exists as unbound, freely diffusible tracer in the cytoplasm (*31*). When reuptake of MIBG was blocked with imipramine (an inhibitor of the norepinephrine transporter), cytoplasmic MIBG washed out rapidly (60% loss in 3 hr). In intact neurons where vesicular uptake of cytoplasmic MIBG occurs, extravesicular clearance presumably would be even more rapid. More studies need to be done to elucidate the intraneuronal handling of MIBG.

EFFECT OF NOREPINEPHRINE LEVELS ON MIBG STUDIES

Another issue is the role of plasma norepinephrine in MIBG studies. In in vitro systems, norepinephrine has been shown to competitively block MIBG uptake (*23,28*). The human norepinephrine transporter showed 24% inhibition of MIBG uptake at 100 n*M* norepinephrine (17,000 pg/ml) and 87% inhibition at 1000 n*M* norepinephrine (170,000 pg/ml) (*28*). Normal plasma values of norepinephrine are in the range of <1 to 3 n*M* (up to 500 pg/ml). Plasma levels of norepinephrine rarely, if ever, exceed 10 n*M* in heart disease and, thus, do not reach levels that can inhibit MIBG uptake. Plasma levels of norepinephrine, however, do not represent norepinephrine levels at the uptake site of MIBG, i.e., sympathetic nerve synapse. When sympathetic nerve activity is increased, more norepinephrine is released at the synapse, increasing synaptic norepinephrine levels, and causing increased spillover of norepinephrine into the circulation. Increased plasma levels of norepinephrine are, therefore, a marker of sympathetic nerve activity (except in pheochromocytoma and other catecholamine producing tumors where plasma levels of norepinephrine are due to tumor production). The level in the synapse is unknown but is probably in the range of .1 to 10 μM. Increased plasma levels of norepinephrine are routinely found in congestive heart failure but correlate only approximately with the degree of failure (*32–34*). If plasma norepinephrine values are a marker of cardiac sympathetic nerve activity, then there should be a correlation between cardiac uptake of MIBG (i.e., initial uptake, Ao) and plasma levels of norepinephrine. When these correlation are sought, they have not been found (*10,14–16*); an explanation is certainly needed.

Plasma levels of norepinephrine represent the integrated outflow of all sympathetic neurons, not just those of the heart. Since sympathetic tone is controlled at the central level (i.e., brainstem, basal ganglia and cerebral cortex) activation of the sympathetic nervous system tends to be a general phenomenon. Direct measurement of peripheral sympathetic nerve electrical activity in heart failure correlates with the degree of failure (*21*). Despite these correlations, these findings cannot provide direct information about cardiac sympathetic nerve function. Reflex and integrative mechanisms exist at the synaptic, sympathetic ganglion and spinal cord levels that can modulate sympathetic nerve activity locally. It is reasonable to assume that in congestive heart failure, sympathetic neurons may be more strongly activated than the rest of the sympathetic system.

There are some quantitative data to support this concept. In the Syrian golden hamster, there is no correlation between the degree of cardiac and splenic sympathetic nerve activity (*18*) (the spleen has a high density of sympathetic

innervation). In a study of congestive heart failure in humans (*35*), 1.9% of plasma norepinephrine was derived from cardiac sympathetic neurons in normal subjects compared to 10.8% in patients with congestive heart failure. This indicated that cardiac sympathetic neurons were more strongly activated than the rest of the sympathetic nervous system in congestive heart failure. If cardiac sympathetic neurons can be activated independently from the rest of the sympathetic nervous system, cardiac MIBG uptake should correlate poorly with plasma norepinephrine levels. Although plasma norepinephrine levels are undoubtedly useful in studying sympathetic nervous activity, the exact role they play in the interpretation of cardiac MIBG studies is limited. It should be pointed out that a study often cited to indicate that elevated plasma levels of norepinephrine depress cardiac uptake of MIBG was performed in patients with pheochromocytomas (*36*), the majority of whom had extremely elevated plasma levels of norepinephrine (above 1500 pg/ml, the exact values were not given). These levels are rarely achieved in heart failure. Interestingly, in that study 75% of patients with pheochromocytomas who had values less than 1500 pg/ml had nonvisualization of their hearts compared to 6.8% of patients without pheochromocytoma. Since the mechanism for the elevation of plasma catecholamines is different in heart failure, the results of this study may not be applicable for the range of plasma catecholamines seen in heart failure.

ADDITIONAL ISSUES

Another problem arises in using the results of in vitro studies to interpret in vivo observations. In vitro systems for studying norepinephrine and MIBG kinetics are useful since they isolate uptake and storage components from the reflex, hormonal, vascular and other activities that influence sympathetic nerve function in vivo. Sympathetic neurons, however, are structurally and functionally quite different from adrenal chromaffin cells, the most commonly used model for sympathetic neurons. Although the qualitative kinetics of MIBG and norepinephrine may be similar in these systems, it is impossible to tell if they are quantitatively alike. This is even more apparent when nonphysiologic systems are studied: pheochromocytoma (PC-12) and neuroblastoma (SK-N-SH) cells (*37*).

Lastly, the issue of species specificity arises. As previously stated, there appears to a large difference in nonspecific uptake and washout of MIBG between dog and human hearts (*6*). Although animal studies give useful information which may be difficult or impossible to obtain in humans, care must be taken in extrapolating the results to human studies.

CONCLUSION

MIBG appears to be reliably detect sympathetic nerve damage in myocardial infarction, surgical denervation and autonomic neuropathies. In diseases such as hypertrophic cardiomyopathy and congestive heart failure, MIBG washout is increased and initial uptake is variably suppressed, indicating changes in sympathetic nerve function that may have important pathophysiologic implications.

Studies of cardiac sympathetic nerve function with [^{3}H]NE and MIBG suggest that these agents follow exponential loss from the heart after intravenous injection. More studies with MIBG need to be performed to determine if these kinetics pertain to the various different physiologic and pathologic situations that are being studied with MIBG. If MIBG does follow first-order kinetics in the heart, the most meaningful way of reporting MIBG kinetics would be in terms of initial uptake and half-time of washout (or equivalently the fractional loss rate).

It has become commonplace in the literature to describe changes in MIBG kinetics in congestive heart failure and other cardiac diseases as a result of sympathetic denervation or dysfunction. This terminology is imprecise and implies that there is sympathetic nerve damage or dysregulation. Decreased cardiac output of any etiology, from acute blood loss to chronic myocardial disease, will cause activation of the sympathetic nervous system. One would therefore expect to see increased cardiac washout of MIBG in heart failure. MIBG imaging studies alone cannot distinguish between compensatory changes versus damage/dysfunction of sympathetic neurons in these disease states.

Another mistake is equating MIBG uptake with neuronal norepinephrine stores (*38*). Whereas cardiac norepinephrine levels and [^{3}H]NE uptake decrease in parallel in congestive heart failure (*18*), these two parameters of sympathetic nerve function are distinct, though interrelated, processes and can become dissociated. In dogs, section of cardiac sympathetic nerves causes marked decreases in both [^{3}H]NE uptake and tissue levels of norepinephrine. As reinnervation of the heart occurs over several months, [^{3}H]NE uptake improves much more rapidly than tissue levels of norepinephrine (*38*). Whether MIBG can be used as a marker of tissue norepinephrine levels, and under what circumstances, requires further study.

Because of the complex nature of sympathetic nervous system regulation, it is difficult to determine if a given change in sympathetic function represents a pathologic or compensatory event. In fact, it may represent either. An example of this occurs in congestive heart failure. When cardiac output falls, volume retaining reflexes are activated. Expanded intravascular volume increases end-diastolic volume, which improves cardiac output by the Frank-Starling mechanism. Increasing end-diastolic volume elevates cardiac output only up to a certain point, however, beyond which cardiac output falls. When myocardial disease progresses to the point that optimal diastolic volume cannot return cardiac output to normal, symptomatic heart failure ensues. Volume retaining reflexes remain active and further volume retention worsens failure. A similar situation may be operative in sympathetic nerve activation. Norepinephrine may initially support the failing heart, but overstimulation may exacerbate failure. Evidence for this effect is found in studies that have demonstrated improvement in

failure after treatment with beta-adrenergic blocking drugs (*40,41*). It would be interesting to see if there is correlation between improvement with beta-blocking and the degree of sympathetic activation as determined by MIBG studies.

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