EDITORIAL

Adriamycin, Congestive Cardiomyopathy, and Metaiodobenzylguanidine

The untimely death of patients from metastatic breast carcinoma and other malignant neoplasms haunts all medical professionals. The tumoricidal potency of doxorubicin (adriamycin) offers the best possibility of defeating this threat were it not for the mysterious cumulative dose-related cardiotoxicity common to all anthracycline class chemotherapeutic agents. The simplest approach would be to administer less doxorubicin over a given time period. Unfortunately, most tumor types show distinct dose-effects that allow minimal reduction in adriamycin dose without reducing tumoricidal benefits (*1*). Another approach would be to change the manner of therapy: reduce damage by administration of cardiac protectors, develop and administer adriamycin analogues which have the same antitumor efficacy with less relative cardiotoxicity, or alter the schedule of administration. If these protocol adjustments fail, and they have, then a damage control approach is necessary. Invasive or noninvasive tests or markers of individual susceptibility to adriamycin myocardial damage is currently standard clinical practice to avert clinical catastrophy from cardiotoxicity. In order to understand the value of the paper by Wakasugi in this month's *Journal* (*2*), it is necessary to tell the story of two investigative processes, first the study of adriamycin cardiotoxicity and second the study of the neurohumoral axis in heart failure.

The anthracycline chemotherapeutic agents such as doxorubicin and daurorubicin have a well described but poorly understood cardiotoxicity (*3–7*). It is not yet known whether these agents or their metabolites are causative: circulating anthracyclines might trigger release of endogenous substances such as histamine, arachidonic-acid metabolites, platelet-activating factor, calcium, and other compounds injurious to the myocardium (*8*). Another proposed mechanism suggests superoxides from released anthracycline free radicals are causative (*8–10*).

Of these theories, the largest body of experimental data suggests toxicity is a consequence of drug or drug metabolite stimulated reactive oxygen metabolism. In this theory, electrons from formed free radicals are transferred by the quinone moiety of the adriamycin molecule between cardiac flavin dehydrogenases or iron-containing proteins and molecular oxygen. When adriamycin quinones position themselves intracellularly adjacent to mitochondrial complex I and/or sarcoplasmic reticulum calcium pump sites, an augmented reactive oxygen flux can produce histologic damage at these sites typical of adriamycin toxicity. The heart, unlike the lung and liver, is known to have poorer antioxidants (*12*), especially in the young and old (*11,13*). In this way, adriamycin-induced free-radical cascades could overwhelm cardiac endogenous antioxidants such as glutathione peroxidase, leading to oxidation of critical cardiac proteins including membrane components (*12*). This inability is additive or cumulative experimentally. Unfortunately, administration of various exogenous antioxidant free radical quenching agents such as vitamin E or glutathione peroxidase have not been experimentally or clinically successful in averting adriamycin cardiotoxicity (*9,14–17*). Thus, we are no closer today to clinical prevention of adriamycin cardiotoxicity through a direct understanding of its mechanism.

Experimental data could be misleading. Adriamycin dose-response and dose-toxicity discrepancies exist between experimental study and clinical experience of adriamycin toxicity. Acute clinical toxicity is common in experimental animal models of adriamycin toxicity, yet rare in humans. Acute cardiotoxicity in humans following a single poisoning dose appears clinically different than the possibly separate and distinct chronic cardiomyopathy resultant from cumulative effects rather than a single poisoning dose. Acute cardiotoxicity presents within hours to days after as little as a single, large dose of adriamycin as a pancarditis with full-blown biventricular failure. Acute cardiac dilatation and pulmonary congestion occasionally responsive to cardiotonics is associated with electrocardiographic and clinical manifestations of pericardial inflammation. Acute toxicity often is subclinical: acute and reversible electrocardiographic changes without clinical evidence of myocardial dysfunction is reported in as many as 30% of patients within hours after receiving standard adriamycin infusions (*18,19*). Chronic cardiomyopathy is not characterized by electrocardiographic fluctuations nor does it involve the pericardium. It is a congestive cardiomyopathy clinically manifest as a non-dilated tachycardic heart with low output secondary to progressive hypocontractility which is unresponsive to cardiotonics. Heart failure is insidious. Chronic cardiomyopathy, unlike acute cardiomyopathy, often has a delayed clinical expression weeks to even months after the last adriamycin dose. Thus, the different clinical characteristics of acute and chronic adriamycin cardiomyopathy suggest they may be two separate entities with separate patho-

Received Nov. 4, 1991; accepted Nov. 4, 1991.
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genesis rather than a continuum of the same disease with different biologic/physiologic expressions.

Investigation is hampered due to species specificity in regard to organ specific anthracycline dose-response side effects. This species confusion is in part responsible for adriamycin reaching human trials prior to general awareness of cardiac side effects. Early studies in canines did not reveal cardiotoxicity as this species is relatively resistant to cardiac side effects. Dogs were peculiarly more likely to develop gastrointestinal hemorrhage, a side effect relatively unknown in humans.

As the clinical experience developed in humans, critical myelosuppression determined interval and maximum dosage for adriamycin therapy protocols. Standard protocols called for 50 to 75 mg/m^2-body surface area adriamycin doses alone or combined with other chemotherapy administered as frequently as at 21-day intervals. Lefrak in 1973 first reported severe cardiomyopathy, which he related to cumulative dose based upon observations that only 1 of 366 patients developed heart failure at cumulative dose less than 550 mg/m^2. Thirty percent (10/33) of patients developed congestive heart failure after receiving progressively more than 550 mg/m^2, of whom 80% (8/10) died from congestive heart failure despite all medical efforts including digitalis and diuretics within 3 wk of onset. ECG and enzymes were useless in distinguishing early congestive heart failure. Postmortem revealed profound myocardial damage. Histology was characterized by myofibrillar dropout and severe sarcoplasmic reticulum and mitochondrial distortion in surviving cells (*3*).

In a retrospective review of 4108 cases, Von Hoff described a progressive dose dependent incidence of clinical cardiotoxicity of 2.2% of all patients treated with adriamycin. The incidence of congestive heart failure increased along a continuum: 3.5% at 400 mg/m^2 cumulative adriamycin dose, 7% at 550 mg/m^2, and 18% at 700 mg/m^2 (*20*).

These observations coupled with a bleak prognosis led to the conventional practice of limiting anthracycline cumulative doses to ~550 mg/m^2 by chemotherapists when standard bolus therapy regimens were used (*21*). Anecdotal reports suggested this threshold was lower in the young and old, those with prior heart disease or hypertension, or in those concurrently receiving other cardiotoxic agents (esp. cyclophosphamide) or mediastinal irradiation. Serial quantitative histologic grading of myocardial change was compared by Tosti et al. (*22*) to multiple regression analyses of risk factors such as age, sex, heart disease, hypertension, previous cardiac irradiation, other cardiotoxic agents, and tumor type. Only prior cardiac irradiation proved to be a significant co-risk factor: 3000 rad cardiac irradiation lowered the cumulative dose threshold by 80 mg/m^2.

Attempts to lessen cardiotoxicity by altering peak adriamycin doses have been made. A similar histopathologic analysis compared cardiac effects of weekly lower peak dose adriamycin infusions to standard 3-wk bolus intervals for the same cumulative doses. Lower, more frequent doses in this way extended the cumulative threshold by 168 mg/m^2 (*22,23*). Thus, cardiotoxicity is related to dose-intensity. Unfortunately, tumoricidal efficacy is similarly effected by dose-intensity, especially in lymphoma and breast carcinoma response (*1,24*). Accordingly, less than 25% of chemotherapy protocols today have incorporated lower dose-intensity adriamycin infusions or more frequent administration than 3-wk high dose boluses for fear of tumoridical compromise.

In the absence of an alteration in dose protocol or an antidote that successfully limits adriamcyin cardiotoxicity, there was a clinical demand to better account for such a wide biologic variation in cardiosensitivity to anthracyclines: the goal was to identify those patients unusually sensitive who would not be protected from congestive heart failure by a ceiling dose threshold of 550 mg/m^2. On the other hand, there was the need to provide equally important maximum tumoricidal benefits by extending adriamycin cumulative doses individually in those patients whose cardiac tolerance would permit this.

Endomyocardial biopsy of the apical portion of the RV septum was shown by Bristow to be the most specific indicator of the degree of adriamycin damage in both animals and humans: quantitation of vacuolar degeneration, cell dropout, and fibrosis of myocardium increased with cumulative adriamycin dose (*25*). Although important observations, the clinically more critical factor was the functional contractility of the tissue rather than its histologic appearance. More worrisome, frequent structural-functional divergence of results has been reported. Biopsy data alone are often insensitive i.e., clinical dysfunction can be present at the time of normal biopsy in many patients, a paradox best explained by scattered sparing of tissue early in toxicity producing biopsy sampling errors (*26*). More physiological approaches were sought for detection of adriamycin cardiomyopathy. When endocardial biopsy was performed, the addition of hemodynamic measurements of function (cardiac output, pulmonary, and systemic pressures) more accurately estimated the individual risk of subsequent development of clinical congestive heart failure (*27*). However, sequential catheterization data is generally impractical due to risk and expense.

Radionuclide angiography offers a safer and less expensive means of monitoring the effect of adriamycin on cardiac function. Alexander, Berger, Zaret et al. in 1979 were able to characterize a wide biologic variation in onset of cardiotoxicity related to cumulative adriamycin dosage utilizing first-pass radionuclide angiography (*28*). Analysis of their LVEF data led them to suggest that a substantial (~15%) absolute LVEF decline from the normal range of function could predict subsequent progressive decline of the adriamycin-treated patient into

clinical ventricular failure at a subclinical point. Patients requiring continued adriamycin beyond this degree of decline into the borderline abnormal resting LVEF range could tolerate an average of 90 mg/m^2 additional adriamycin before clinical congestive failure ensued. Patients with preexistant heart disease were characterized by them as no more predisposed to toxicity but more likely to develop clinical signs of failure due to loss of functional reserve (*29*). Sequential resting LV functional monitoring was championed as a means of preventing subsequent development of clinical heart failure: many patients safely received tumoricidal benefits of anthracycline far exceeding empirical dose thresholds previously advocated, while others particularly sensitive to cardiotoxicity could be detected prior to early congestive heart failure by premature decline in resting contractile function. Nonetheless, resting ejection fraction trends were insensitive to subtle structural histologic changes suggesting that radionuclide ventriculography was insensitive to early adriamycin damage. Strashun (*30*) subsequently showed diastolic dysfunction preceded systolic contractile dysfunction and could provide earlier, more sensitive radionuclide ventriculography indicators of anthracycline related cardiac dysfunction.

More recently, several investigators have shown that some adriamycin-treated patients with normal resting contractile function developed abnormal ejection fraction response to exercise (*31,32*). Although exercise radionuclide angiography appears to be more sensitive than resting functional parameters, knowledge that many normal patients have demonstrated inability to augment function expressed as nonaugmentation of rest LVEF > 5% challenges the specificity of this test (*33*). In addition, fluctuating anemia secondary to myelosuppression by adriamycin contributes a significant variable that must be accounted for in sequential stress studies. Subclinical ASCVD is also more likely to contribute abnormal exercise results if the effect of anemia is not factored into exercise data. Finally, exercise monitoring is impractical as most patients are debilitated and deconditioned. The majority are unable to perform stress testing repeatedly at adequate exercise levels. Therefore, serial rest radionuclide angiography has become standard conventional practice for predicting individual risk of developing clinical cardiotoxicity.

Zaret (*34*) recently presented generally accepted guidelines for serial radionuclide angiography monitoring of chronic doxorubicin cardiotoxicity as follows:

1. Baseline study within first 100 mg/m^2 in all
2. Next follow up studies at ~300 mg/m^2 and 450 mg/m^2 (400 mg/m^2 if high risk of toxicity-cytoxan, heart disease, radiation exposure)
3. Repeat study beyond 450 mg/m^2 prior to each subsequent adriamycin dose
4. Discontinue adriamycin if LVEF decline ≥10% from baseline or final LVEF ≤30% (nl > 50%)

All studies should be performed at least 2 wk after prior adriamycin infusion to avoid contamination of data by occasional acute and reversible cardiodepression (associated with ECG abnormalities) that presumably represent acute dysfunctional toxicity distinctly different from the chronic form.

Adherence to this monitoring regimen in 1500 patients over 7 yr at Yale produced a four-fold reduction in clinical congestive heart failure (*35*). In clinical practice, unusual dedication by the patient and his referring oncologist is required to adhere to such a rigorous monitoring regimen. It is physically and financially difficult for patients to come to the hospital clinic at separate times and places to undergo radionuclide angiography and then chemotherapy. Consequently, noncompliance is all too frequent in many oncology practices.

Recently in this *Journal,* Estorch showed abnormal ^{111}In-antimyosin myocardial uptake in 85% of patients with no other risk factors for myocardial necrosis than advanced cumulative adriamycin dosage (500 mg/m^2) (*36*). The majority of these patients' rest and exercise function measured by radionuclide angiography was normal. This diverging structural-functional relationship is not surprising. Several large series have demonstrated histologic changes of cardiotoxicity in the absence of rest or stress dysfunction or subsequent development of even the mildest clinical signs of myocardial toxicity (*37,38*). On the contrary many patients in theses studies developed congestive heart failure without abnormal histologic changes (*26*). *The advantage of a more sensitive measure of adriamycin cardiotoxicity would be two-fold. First, the detection of early damage is valuable for understanding the adriamycin pathophysiology as it pertains to variable dose-response characteristics and to disease progression. Second, an early noninvasive monitor is valuable if the disease represents a continuum in which early subclinical manifestation are reversible or at least progression at early stages is preventable prior to the development of irreversible contractile abnormalities. The detection of subtle, early changes would be most useful in studying the efficacy of newer approaches to limiting or, preferably, preventing cardiotoxicity either through new dosage schedules, less toxic analogues, or addition of ameliorating agents.* Attempts to reverse the pathogenesis of this lethal side effect have met to date with failure, possibly because tests of contractile function as endpoints are too crude reflecting later degrees of irreversible cardiac damage.

The clinical presentation of adriamycin cardiotoxicity suggests the need to examine the neuroendocrine physiology of the failing heart. Most congestive cardiomyopathies, of which adriamycin is so classified, typically reveal a decrease in β-adrenergic responsiveness associated with decreased in situ myocardial catechol-

amine stores and increased circulating plasma catecholamines with progressive adrenergic unresponsiveness (*39–41*). Clinical adriamycin cardiotoxicity presents with minimal dilatation at onset. Cardiac output is characteristically preserved at early clinical stages by a disproportionate increase in heart rate and afterload to counter the declining inotropy and lusitropy. This tachycardia has recently been explained by Shenasa et al. (*42*) as a peculiar preservation or even augmentation in norepinephrine responsiveness of atrial sinus receptors, a mechanism that could be distinctly separate from myofibrillar adrenergic receptors.

In this month's edition of *The Journal of Nuclear Medicine*, Wakasugi and colleagues have attempted to demonstrate abnormal cardiac adrenergic activity following induction of histologically confirmed adriamycin cardiotoxicity (*2*). They have shown an adriamycin dose-dependent decline in rat myocardial adrenergic receptor meta-iodobenzylguanidine (MIBG). MIBG is an analog of guanethidine and was initially synthesized as a potential antihypertension agent (*43*). It shares the so-called type I neuroreceptor uptake, storage, and release mechanism throughout the body with norepinephrine (*44*). Unlike norepinephrine, MIBG is not metabolized by catechol-o-methyl transferase and monoamine oxidase and thus has longer-lived residence in adrenergic receptors. Type I receptor sites were first targeted scintigraphically with ^{123}I- and [^{131}I]MIBG by Wieland et al. in studies designed to identify abnormal adrenal medullary tissue as well as various neuroectodermal tumors. In the process of these oncologic studies, normal myocardial visualization with MIBG was first observed (*45*). A semiquantitative note was inferred in cases of β adrenergic hyperfunction due to excess circulating catecholamines from these tumors (esp. pheochromocytomas). Absence of myocardial visualization was seen in such cases as a soft sign of systemic adrenergic dysfunction (*46*). In this way, an inverse relationship between plasma catecholamine concentrations and myocardial MIBG activity was demonstrated. Subsequent studies by Sisson et al. have shown that various perturbations of adrenergic nerves produce analogous MIBG and norepinephrine rat myocardial movement. Direct injury to nerves with 6-hydroxydopamine reduced uptake of both. Sympathomimetic drugs stimulate discharge or washout of both. However, the concentration of norepinephrine flux paralleled but always exceeded concentrations of MIBG. This concentration difference was ascribed to another (Type II) diffusion mechanism and potentially compromised MIBG as a less-than-perfect analog of norepinephrine. Nonetheless, MIBG kinetics did directly reflect norepinephrine flux in myocardium (*47*). As such, it has been accepted as at least a semiquantitative indicator of adrenergic norepinephrine movement suitable for study of myocardial neuron injury: uptake of regional MIBG reflects neuron integrity and release of MIBG reflects adrenergic function (*48*).

Now, Wakasugi et al. have turned to the cardiac MIBG uptake mechanism to better understand the contribution of abnormal adrenergic function in the pathogenesis of adriamycin cardiotoxicity. They have compared "gold standard," albeit insensitive, histologic signs of adriamycin toxicity to MIBG tissue concentrations in progressively adriamycin poisoned rat myocardium. They site histologic evidence of neuronal vacuolar damage in rat myocardium exposed experimentally to adriamycin and similar damage to human myocardial neurons in routine clinical trials with adriamycin derivative daurorubicin as a pathogeneic rationale. Unfortunately, they were unable to monitor more sensitive functional parameters. Had they done so, earlier physiologic signs of adriamycin toxicity might have been detected as in current clinical practice.

The Wakasugi et al. study was designed to eliminate nonspecific alteration of myocardial MIBG concentrations. Ischemia and ischemic infarction have been demonstrated to reduce myocardial MIBG uptake (*49*). By demonstrating similar quantitative thallium uptake patterns throughout the right and left ventricles in both adriamycin poisoned and control rat myocardium, they have dispelled the suggestion that declining MIBG uptake may be an epiphenomenon due to decreased myocardial blood flow.

They compared regional myocardial ratios of tissue-bound norepinephrine levels and [^{125}I]MIBG uptake in chronically adriamycin poisoned and control rats. Adriamycin-exposed myocardium revealed significant total reductions in both tissue bound norepinephrine and MIBG. However, MIBG tissue uptake was twice as retarded and, unlike norepinephrine, revealed a dose-dependent decline. They allude to the failure of numerous studies to consistently identify adriamycin myocardial neurotoxicity histologically. The authors suggest that MIBG uptake could more sensitively monitor adriamycin cardiac neurotoxicity than physiologic assays of tissue norepinephrine levels, much less cruder anatomic examination of histologic changes.

They have offered only two possible explanations for their findings: either a secondary phenomenon due to exaggerated compensatory hyperadrenergic release (washout) from failing myocardium or direct cardiac adrenergic neuron damage. They conclude that hyperadrenergism is less likely because myocardial norepinephrine levels did not decline as plasma norepinephrine levels rose with progressive failure in an inverse dose-related relationship. Nor did either the tissue norepinephrine or the MIBG concentration decline follow known right versus left ventricular ratio of adrenergic tissue: left ventricular activity decline should have been exceeded by right ventricular activity decline, reflecting greater RV adrenergic density. It did not. Finally, they invoke indirect histologic evidence of typical progressive myonecrosis as suggestive evi-

dence of wider spread necrosis of cardiac neuroadrenergic tissue.

One other major possibility remains to explain Wakasugi's results of progressive depletion of both MIBG and norepinephrine myocardial stores with cumulative adriamycin exposure: progressive extra-cardiac hyperadrenergism could increasingly displace cardiac MIBG synthesized stores (i.e., displacement washout) rather than reduced synthesis or neurogenic retention from receptor damage as the explanation for adriamycin dose-dependent decline in myocardial MIBG. This washout, in fact, would be more likely to occur by alternate Type II diffusion uptake pathways in high catecholamine states. Thus, it is incumbent that future studies be directed to selectively block central and peripheral synthesis of catecholamines to distinguish direct neuron damage from hyperadrenergic factors which would promote accelerated cardiac receptor washout and secretion with resultant depletion of adrenergic receptor stores.

If Wakasugi can ultimately prove adriamycin functionally damages myocardial adrenergic neurons, this data helps to explain long standing clinical observations since Lefrak that adriamycin toxicity is refractory to inotropic agents including catecholamines. Those clinical observations were confirmed by Weinberg who experimentally showed a depressed contractile response of previously adriamycin-treated isolated rat heart muscle to norepinephrine (*66*). That the adrenergic receptor was at fault has been implied by the elegant work of Bristow in the general field of congestive cardiomyopathy where the failing human myocardium is demonstrated to have a decreased total population of functioning beta adrenergic receptors (*39,40*). Increased levels of catecholamine in plasma of patients with congestive heart failure suggest there may be beta receptor down regulation (*41*). Finally, diminished agonist binding affinity of myocardial beta receptors in adriamycin induced cardiomyopathy is also reported (*50*).

The knowledge of cardiac adrenergic activity in adriamycin cardiomyopathy might also prove beneficial in the broader understanding of other congestive cardiomyopathies. Virtually all vasodilator and positive inotropic drugs introduced in the last decade to reverse congestive heart failure acutely decrease cardiac filling pressures or increase cardiac output. Initial clinical and commercial excitement for over 100 such agents has disappeared. Long term clinical efficacy in virtually all cases has not been shown (*51*). Although cardiac contractility is depressed in most patients, positive inotropes do not produce consistent benefits. Although systemic vessels are excessively constricted in heart failure, drugs reversing vasoconstriction do not make patients feel better or live longer. In fact, traditional therapeutic efforts to augment contractility in the face of clinical congestive heart failure are widely held as counterproductive to long-term survival. There is a growing appreciation that positive inotropic agents and vasodilators unmask chronic reflex neurohormonal responses that could hasten death through cardiac dilatation and arrythmias.

The failing myocardium has a plasticity in regard to mechanical contractility and energy expenditure (*52*). The mature cardiocyte is a terminally differentiated cell and responds to growth stimuli with cell growth only, and not additional replication. The myocyte can alter protein expression with a tendency to re-express fetal proteins. Biochemical changes are both trophic and destructive: energy conservation is balanced by contractile function depression.

Changes in the expression of myosin heavy chains determines myosin ATPase activity and muscle shortening velocity. In failure, adult myocardial cells must change or accelerate protein synthesis as part of a reparative process. It is speculated that fetal expression of protein synthesis is expressed with production of "slow" myosin to replace "fast" myosin. Slow myosin is more mechanically energy efficient. Stretch sensitive ion channels may mediate these changes, possibly in response to tension mediated subendocardial hypoperfusion. Growth factors such as proto-oncogenes, heat-shock-protein and other early mediators might effect these protein changes i.e., a feedback link between hemodynamic/mechanical stimuli and biochemical signals. Sarcoplasmic reticulum down regulates by reducing the concentration of Ca-ATPase pumps.

Neurohumoral responses to congestive heart failure primarily augment renin-angiotensin and sympathetic adrenergics to preserve organ perfusion. Vasoconstriction increases afterload and further lowers cardiac output. Second messenger response is depressed. Beta adrenergic receptors are blunted, adenylate cyclase is depressed, and chronotropy, inotropy, and lusitropy response to norepinephrine is depressed. This is important. Long-term norepinephrine-mediated inotropic augmentation increases cardiac energy expenditure which accelerates the rate of cell death in the failing heart (*53–56*). It does so via second messengers like cyAMP and inositol-1,4,5 triphosphate, which increase calcium entry into myocardial cells. Cellular calcium overload increases cytosolic calcium concentrations, producing cardiac relaxation abnormalities by preventing necessary pumping of calcium out of the cells during diastole. Inotropic drugs augment intracellular calcium and in some circumstances this might be deleterious, especially in adriamycin induced congestive cardiomyopathy which is characterized by a glut of cytoplasmic and intra-mitochondrial calcium.

The study of beta receptors in congestive heart failure have divergent theories or models depending upon pathogenesis (*39,40,41*). One model, left ventricular hypertrophy, reveals increased β receptors. Another, left ventricular dilatation, reveals decreased beta receptors. Receptor desensitization and resensitization is

poorly understood in the multifactorial aspects of human congestive heart failure. Beta receptor regulation is dependent upon circulating norepinephrine levels, neuron-released norepinephrine, local metabolism, and presynaptic uptake mechanisms. Apparently, the failing heart loses its ability to respond to sympathetic neurotransmitters as an adaptive process. Pharmacologically, this tachyphylaxis or tolerance to norepinephrine is a second step in congestive heart failure. The first step is an increase in circulating catecholamines (*57*). Plasma norepinephrine generally correlates directly with severity of failure. This response is measurable in plasma and urinary catecholamines levels. Chronic stimulation of the heart in failure by beta adrenergic agonists such as norepinephrine leads to a decrease in number of the receptor molecules in the sarcolemma of cardiac muscle cells (*58*). Biochemically, this down regulation of norepinephrine responsiveness is due in part to phosphorylation of receptor proteins in reactions catalyzed by both cyclic AMP-dependent and cyclic-AMP independent protein kinetics (*53,58*). Other inotropes such as cardiac glycosides and calcium do not seem to undergo desensitization in this manner (*59*).

It is currently unclear whether such desensitization of the myocardium to beta adrenergic receptors is beneficial or deleterious. As in other long term compensatory mechanisms, benefits might be derived by lowering energy use in the energy-starved failing heart. On the other hand, down regulation clearly lowers cardiac output. Use of beta agonists, once standard therapeutic dogma in congestive heart failure, is now controversial. On the other hand, equally controversial use of beta antagonists such as receptor blockers and converting enzyme (second messenger) inhibitors is advocated by some. Indeed, controlled trials of the beta blocker metoprolol have improved the ejection fraction and other hemodynamics in patients with congestive heart failure, presumably by increasing beta adrenergic-receptor density and catecholamine responsiveness (*60*).

The next neurohumoral arm, the cardiac sympathetic effectors, are the guanine nucleotide binding proteins ("G proteins") which link beta receptors to the biochemical effectors. Their metabolism is another intermediary messenger system with separable stimulatory (Gs) and inhibitory (Gi) moieties which can be imbalanced in congestive heart failure as well. Gi catalyzes cyAMP production and Gs inhibits cyAMP production. Both are, in other words, signalling proteins or second messengers. Depending upon the balance of Gs and Gi, cyAMP and inositol 1,4,5, trisphosphate (IP_3) increase entry of calcium into myocardial cells in cytosolic sarcoplasmic reticulum, thereby mediating augmentation of contractility and relaxation while increasing cardiac energy expenditure. It has recently been demonstrated that Gi levels are increased in heart failure (*61*). Possibly as critical, Gs levels have been shown to be decreased in failure (*62*). The net result is a reduced Gs to Gi ratio. Gs will augment myocardial cyAMP at the same level of circulating norepinephrine, Gi will blunt cyAMP at these same levels. This relative preponderance of Gi might play a critical role in the pathophysiology of heart failure.

Peripherally, threats to cerebral blood flow from central myocardial failure activate high pressure receptors in the heart (atria) and great vessels (arteries) which normally send tonic inhibitory impulses to two vasoconstrictors (*63*). These central baroreceptors turn off inhibitory signals to the central nervous system to release increased neurohormones and to the pituitary to release vasopresson. In this way altered cardiac performance does not threaten cerebral perfusion due to compensatory intravascular volume expansion and heightened tone. Threatened renal blood flow triggers renal baroreceptors to release renin with subsequent angiotensin II release which maintains glomerular hydraulic filtration pressure by efferent glomular arteriolar constriction to expand volume. Angiotensin II alters baroreceptor responsiveness directly as well. Thus, there is a tendency in congestive heart failure to over-secrete renin-angiotensin II (sustained activation). As a result, baroreflex mechanisms normally used to maintain cerebral and renal flow are imbalanced in chronic heart failure (*64*). Angiotensin II within the kidney also stimulates renal release of prostacyclin and prostaglandin E2 which antagonize angiotension II contraction peripherally. PE 2 dilates afferent glomerular arterioles, but peripherally blocks Ang II vasoconstriction. These second messengers or effectors temporarily vasodilate to limit effects of destructive vasoconstrictor systems, but ultimately lose out to constrictors (*65*). Chronic effects in failure and the interaction of renal and cardiac effects are to be characterized. The goal to therapy is to maintain a delicate balance. MIBG could unlock the door to the understanding of this complex biochemical mediation or effector of β adrenergic mechanisms that are central to this altered neurohumoral balance in congestive heart failure.

In conclusion, MIBG is a marker of both central and peripheral cardiovascular adrenergic mechanisms, which together with the renin-angiotensin system, vasopressin, and serotonin contribute to the downward hemodynamic spiral of congestive heart failure. MIBG offers a new tool in understanding the altered balance in feedback loops between local sarcolemmal energy demands and systemic nutrient demands driving this progressively more complex cardiomyopathy. It is more likely that therapeutic success will follow by first understanding and then modifying the neurohumoral interactions and pathophysiologic adaptations in congestive heart failure rather than crudely correcting hemodynamic abnormalities. The study of MIBG in adriamycin cardiotoxicity might prove key to this understanding and thereby advance the treatment of congestive heart failure in the future.

Similarly, this new tracer might provide critical insight into the pathophysiology of anthracycline cardiotoxicity. Oncologic patients receiving adriamycin are ravaged by their medical infirmities reflecting extent of disease and by iatrogenic disease produced by chemotherapy damage. We must not add to their physical and psychic agony by a battery of suboptimal diagnostic studies that only serve to temporarily avoid functional cardiotoxicity. Instead, we must dissect the biochemical complexity of the myocardial pump mechanism and its multi-level responses to insults such as adriamycin. We must utilize tracers such as MIBG to provide the humane solution to adriamycin cardiotoxicity.

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