DIAGNOSTIC INTERVENTIONS IN NUCLEAR MEDICINE

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PREFACE

The increasing application of "diagnostic interventions" represents one of the most important and fundamental trends in the current practice of nuclear medicine. As late as the 1970s, fewer than 1 percent of nuclear medicine procedures included an interventional maneuver, but there are now many nuclear medicine laboratories in which a third or more of all diagnostic procedures include interventions. Interventions can be as simple and elegant as exposure of a patient's retina to white light to measure activation of cerebral cortical metabolism or as complex as the coadministration of drugs and isotonic exercise to evaluate cardiac functional reserve. The common purpose of all interventions is to extend the diagnostic horizons of nuclear medicine and to address questions that simply do not lend themselves to study under resting or baseline conditions.

The current strength and future growth of nuclear medicine is highly dependent on the interventional concept of diagnostic testing. The growth in importance of "interventions" has paralleled the increasing use of radiotracer techniques to study organ function rather than organ anatomy. In this regard, it is interesting to note that the "mechanism of localization" of radiopharmaceuticals has historically and traditionally been described in functional or physiologic terms, but the information derived from the majority of procedures until the current era has been more frequently anatomical than functional. In this sense, the interventional techniques have allowed the specialty of nuclear medicine to finally achieve its "functional" heritage in clinical practice.

The purposes of this book are several: to develop the general concept of "diagnostic interventions," to provide summaries of current interventional procedures, and to indicate potential avenues of future development. The book also includes a unique discussion of potential drug-induced alterations in radiopharmaceutical localization that may not be desired but that must be recognized for correct study interpretation. A formulary of current nonradioactive drugs used adjunctively as interventional agents in nuclear medicine diagnostic procedures is provided. The editors recognize and acknowledge the difficulty of "capturing" concepts and procedures that are so dynamic and rapidly evolving. It is hoped, therefore, that this book will help focus attention on the concept of "diagnostic interventions" and serve as a core of current knowledge on which the reader can build as new developments are presented in the future.

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1 INTRODUCTION

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IN THE CONTEXT of nuclear medicine studies, an intervention is defined as the coadministration of a drug or the coapplication of a physical maneuver (i.e., leg exercise, blood pressure cuff) to obtain specific diagnostic information or to enhance an existing diagnostic procedure. It should be noted that this is in contrast to "interventional" radiology, wherein the term is used to describe procedures that offer diagnostic and/or therapeutic alternatives to surgery; the term "pharmacoangiography" is probably more synonymous with interventional nuclear medicine procedures. The intent of this book is to describe the "state-of-the-art" of nuclear medicine interventions, to present ongoing research in this area, and to stimulate the reader to recognize the implications and potential of interventional procedures in the future development of nuclear medicine. In this regard, the material has been divided into several broad anatomical sections, which include chapters describing specific organ imaging procedures. These chapters focus on the clinical problem, the purpose of and rationale behind the intervention, the methods for performing the interventional procedure, and the results associated with normal and abnormal studies. Also included for convenience is an "intervention formulary" that specifically outlines the pharmaceutical aspects (i.e., chemistry, mechanism(s) of action, cautions) of commonly used interventional drugs.

It is interesting to note that the first important diagnostic interventions were established early in the history of nuclear medicine. In the late 1940s, sodium iodide I 131 was made available for the widespread medical evaluation of thyroid function. Within five years following the development of the 24-hour radioactive iodine uptake test, it was recognized that the utility of this procedure could be extended by hormonal manipulation, thus giving rise to a series of suppression, stimulation, and discharge tests. Unfortunately, further development of interventional procedures proceeded slowly. As recently as mid-1970, fewer than 1% of routinely performed nuclear medicine clinical studies involved an intervention, still limited primarily to those described in Table 1–1. In the last decade, however, diag-

TABLE 1–1.—EARLY DIAGNOSTIC INTERVENTIONS

1. Thyroid-stimulating hormone (TSH) stimulation (thyroid scan and uptake studies).
2. Triiodothyronine (T_3) suppression (thyroid scan and uptake studies).
3. Perchlorate discharge test (thyroid uptake studies).
4. T_3 suppression (selenomethionine Se 75 parathyroid scan).

nostic interventions have become increasingly important in the clinical practice of nuclear medicine and in research studies involving radiotracers. Currently, interventional procedures may typically constitute up to 30% or more of the total work load of many centers. Table 1–2 illustrates the mix of intervention-based procedures performed at the Nuclear Medicine Division, University of Michigan Medical Center, Ann Arbor, in 1983; and is by no means an exhaustive sample of the total number of such studies reported in the literature.

The discussion of nuclear medicine interventions is usually organized on a respective anatomical basis, as presented in this text. However, the presentation and analysis of this subject as a separate area of past and future development in nuclear medicine probably deserves a classification system based on the nature and/or goal of the interventions themselves (a difficult task to perform due to considerable potential for overlap). Basically, there are two major categories of intervention-based nuclear medicine procedures (Table 1–3). In category 1, the purpose of the pharmaceutical or physical intervention is to modify a parameter of organ function, physiology, or metabolism, which is subsequently evaluated using nuclear medicine techniques. Conversely, in category 2, the purpose of the nuclear medicine study is to directly evaluate the therapeutic benefit of a pharmacologic agent or medical (physical) procedure.

Within Category 1, intervention-induced changes in organ function, physiology, or metabolism may be measured (1) using a radiopharmaceutical that retains its normal distribution characteristics, or (2) by subsequent

TABLE 1–2.—DIAGNOSTIC INTERVENTIONS—1983

Thyroid	TSH stimulation test; T_3 suppression test; perchlorate discharge test
Adrenal	Dexamethasone suppression; ACTH stimulation
Genitourinary	Diuresis renography
Heart	
Myocardial perfusion	Exercise stress; ergonovine
Ventricular function	Exercise stress; cold pressor; dobutamine; nitroglycerin
Peripheral vascular	Ischemia-hyperemia; muscle blood flow
Gastrointestinal	Abdominal compression (gastroesophageal reflux); drug monitoring (e.g., metoclopramide); glucagon (GI tract bleeding)
Hepatobiliary	Gallbladder stimulation (fatty meal, cholecystokinin, or derivatives)

TABLE 1–3.—CLASSIFICATION OF INTERVENTIONS

Category 1	Purpose of intervention is to change parameter of organ physiology or metabolism.
	Intervention-induced changes are measured:
	Using a radiopharmaceutical which retains its normal distribution characteristics.
	By alterations in normal distribution of radiopharmaceuticals.
	Intervention-induced changes are used to enhance evaluation of a different organ system.
Category 2	Purpose of nuclear medicine study is to directly evaluate efficacy of a pharmaceutical or medical procedure.

alterations in the normal distribution of a radiopharmaceutical. Examples of the former subclass include the use of sincalide to induce gallbladder contraction and/or refilling, as monitored by the normal distribution characteristics of technetium Tc 99m disofenin; the furosemide/technetium Tc 99m penetate diuretic renogram for the differentiation of mechanical vs. physiologic ureter obstruction; and the evaluation of leg-exercise–induced alterations in left ventricular wall motion and ejection fraction using various blood pool radiotracers. Examples of the latter subclass include the increase or decrease in thyroid localization of radioiodine induced by thyrotropin or triiodothyronine (T_3), respectively; the diminished or absent localization of thallous chloride Tl 201 in dipyridamole or exercise-induced areas of myocardial ischemia; and the increased localization of carbon 11 (^{11}C) or fluorine 18 (^{18}F) 2-deoxyglucose in regions of increased brain metabolism stimulated by the physical interventions of light or sound.

Also falling under category 1 are intervention-induced changes in organ physiology or function used to enhance the nuclear medicine evaluation of a different organ system. This subclass would include the pentagastrin-stimulated uptake of sodium pertechnetate Tc 99m into gastric mucosa for the enhanced diagnosis of Meckel's diverticula; dexamethasone suppression of the adrenal cortex zona fasciculata to facilitate evaluation of zona glomerulosa or zona reticularis function using ^{131}I-6β-iodomethyl norcholesterol; and, perhaps, the administration of glucagon to reduce peristaltic activity of the gut in the evaluation of gastrointestinal (GI) tract bleeding.

Category 2 represents a relatively unexplored but stimulating offshoot of current nuclear medicine intervention studies: the utilization of radiotracer techniques as noninvasive, in vivo methods for evaluating the pharmacologic effects of new or established drugs, or for monitoring the efficacy of various physical (i.e., surgical) procedures. It may be argued that nuclear medicine studies have historically been used to follow the long-term effects of various interventions on disease processes (i.e., liver scanning to follow the effect of chemotherapeutic agents on liver metastases); however, the intriguing development is the use of radiotracer techniques to directly monitor therapeutic efficacy. Perhaps the best example in this category is

the use of nuclear medicine gastric emptying studies (solid or liquid) to monitor the effect of the drug metoclopramide in promoting gastric emptying rates in patients with diabetic gastroparesis. This rationalization of metoclopramide therapy is important since the drug is only effective in approximately 60% of such patients, and it possesses the potential for significant extrapyramidal side effects. Another common example in this category is the administration of technetium Tc 99m macroaggregated albumin via hepatic artery catheters to monitor the correct placement of regional chemotherapy perfusion systems and/or to evaluate the effects of various interventions (i.e., starch microspheres, epinephrine) on relative hepatic tumor/normal liver perfusion ratios. Although the number of routine intervention studies in this category is limited, review of the recent literature will reveal several preliminary clinical or research studies involving the use of nuclear medicine procedures to evaluate the efficacy of various pharmaceutical agents (Table 1–4) or physical procedures (Table 1–5).

The relatively recent trend toward the utilization of physical and pharmaceutical interventions represents a dramatic development in the practice of clinical nuclear medicine, perhaps equal to or exceeding the more heralded developments in radiopharmaceuticals, instrumentation, and computer applications. Most exciting, the diagnostic horizons of the specialty

TABLE 1–4.—CATEGORY 2.—FUNCTIONAL ASSESSMENT OF DRUG EFFICACY

RADIOPHARMACEUTICAL(S)/ NUCLEAR MEDICINE PROCEDURE	DRUG(S)	THERAPEUTIC EFFECT EVALUATED
Thallous chloride Tl 201; Oxygen 15–labeled water; carbon 11–labeled palmitate, iodine 123–labeled heptadecanoic acid; radionuclide ventriculography	Streptokinase	Thrombolytic revascularization of myocardium
Technetium Tc 99m succimer	Furosemide, inosine, mannitol, phenoxybenzamine	Prevention of warm ischemia during urological surgery
Technetium Tc 99m pentetate	Morphine, metoclopramide	Small intestine transit time
Indium 111 (^{111}In)–labeled platelets	Papaverine, verapamil	Vein graft preservation
^{111}In–labeled platelets	Aspirin, ticlopidine	Platelet accumulation at sites of peripheral artery injury or Dacron grafts
^{111}In–labeled lymphocytes	Cyclosporin-A	Lymphocyte migration
Xenon Xe 133	Methyldopa, propranolol	Cerebral blood flow
Technetium Tc 99m disofenin	Ceruletide	Dose-response curve
Technetium Tc 99m iprofenin	Somatostatin	Gallbladder emptying response to solid meals, bethanecol, sincalide

TABLE 1–5.—CATEGORY 2—FUNCTIONAL ASSESSMENT OF PROCEDURE EFFICACY

RADIOPHARMACEUTICALS/ NUCLEAR MEDICINE PROCEDURE	PROCEDURE	PARAMETER(S) EVALUATION
Thallous chloride Tl 201	Tr. sluminal coronary angioplasty	Reperfusion
Technetium Tc 99m macroaggregated albumin	Hepatic or carotid artery catherization	Catheter placement, extrahepatic flow, tumor vs. normal perfusion ratios
Technetium Tc 99m pentetate; ^{99m}Tc–labeled resin	Gastroplasty	Gastric emptying rate
^{111}In–labeled platelets	Percutaneous transluminal coronary angioplasty	Platelet accumulation at dilatation site
MUGA	Artificial heart	Cardiovascular dynamics
^{15}O–labeled H_2O; ^{15}O–labeled carbon monoxide	Superficial temporal artery–middle cerebral artery anastomosis	Pre- and Post-operative regional CBF and CBV

have been widened; whole categories of diagnoses that would be outside the limits of this specialty without the use of interventions now fall under the purview of nuclear medicine. The best example is the diagnosis of occult coronary artery disease, which is essentially always performed in conjunction with a physical or pharmacologic intervention due to the low diagnostic yield from studies performed under basal conditions. Furthermore, the development of interventional procedures has required nuclear medicine to live up to its functional promise. It has often been observed that conventional diagnostic radiology is primarily an "anatomical" or "morphological" specialty, whereas nuclear medicine is capable of providing functional information. In the past, however, elegant functional mechanisms have often been used to no greater purpose than to achieve radiotracer localization for subsequent static, anatomical imaging. On the other hand, the majority of interventional procedures are specifically designed around measurements of function, the critical diagnostic parameter being the functional response to the intervention.

A major implication arising from the trend to intervention-based procedures centers around educational requirements. Interventional procedures are generally more complex than standard imaging studies. Drugs are administered, patients are physically stressed and organ function is transiently altered. Nuclear medicine physicians and allied personnel involved in these procedures must understand not only the rationale of the techniques with respect to tracers and imaging, but also the rationale, means of assessment, and potential complications of the intervention. Substantial new knowledge and skills must be acquired and stronger affiliations with referring clinicians, emergency specialists, and pharmacists must be developed.

It is interesting to observe that residents in training who have the

benefit of learning from the staff physicians in the respective clinical disciplines such as cardiology and endocrinology as well as their own mentors in nuclear medicine have an excellent and unique opportunity to acquire the tools for correct and safe application of these new intervention studies. In a real sense, they are growing up with them. For the rest of nuclear medicine practitioners, the education and re-education process is substantially more difficult, even painful; and one of the major challenges facing organized nuclear medicine will be in helping its members acquire the necessary new knowledge and skills. Indeed, if physicians in nuclear medicine do not respond to the educational and collaborative challenges posed by intervention studies, the potential for improved diagnosis will not be realized; there is also a real potential that radionuclide procedures will become fragmented among the various clinical disciplines.

It is becoming recognized that a thorough knowledge of interventional procedures is required even if the nuclear medicine laboratory is not routinely involved with such procedures in its clinical practice. For example, a patient may present to nuclear medicine with a drug history that includes one of the described interventional agents. In this case the interventional drug may interfere with the normal, expected biodistribution of radiotracer. Several other interfering drug-radiopharmaceutical interactions have been reported and are excellently summarized in the chapter by Hladik, et al, found within this text. As noted within this chapter, any suspected drug- or procedure-induced alteration of radiotracer biodistribution should be thoroughly investigated as a potential beneficial interventional procedure. Excellent examples of this "serendipitous" development of new procedures are the evolvement of the in vivo red blood cell labeling procedure and the use of nuclear cardiology studies to monitor the toxic response of Adriamyacin.

In summary, interventional procedures represent an important aspect of current clinical nuclear medicine practice and an exciting direction in the forefront of the specialty. Over the past five years, these studies have clearly accounted for the majority of growth and have widened the diagnostic horizons of nuclear medicine. However, they have brought with them substantially increased educational requirements and the need for closer coordination between the nuclear medicine physician, physicians in the respective clinical disciplines, and pharmacists. It seems likely that this trend will continue. The "fundamentals" underlying the practice of modern nuclear medicine must now be expanded conceptually to include "physiologic and pharmacologic interventions."

2 PHYSIOLOGIC STRESS INTERVENTIONS IN CARDIAC IMAGING

ANDREW J. BUDA, M.D.

PHYSIOLOGIC STRESS interventions are designed to assess the reserve capability of coronary flow and myocardial function. In the normal individual, a sufficiently intense physiologic stress may increase coronary flow and cardiac output by 500% to 600%. However, in patients with cardiac disease, these reserve responses may be absent, or considerably blunted. Thus, physiologic stress testing has proved extremely helpful in detecting cardiac abnormalities when resting cardiac function appears normal.

Feil and Seigel[1] first reported the potential of exercise stress testing in patients with angina pectoris more than half a century ago. Subsequently, physiologic stress testing with ECG monitoring has become a traditional part of cardiovascular assessment. With the rapid development of cardiac radionuclide imaging in the late 1960s and early 1970s, the addition of exercise stress testing and other stress maneuvers has added a new dimension to the evaluation of myocardial ischemia and cardiac dysfunction. Zaret et al.,[2] in 1973, first reported the administration of potassium-43 at peak exercise to detect exercise-induced perfusion defects. Thereafter, beginning in 1976, several investigators demonstrated the use of thallous chloride Tl 201 imaging with exercise as a noninvasive technique for detecting myocardial ischemia related to underlying coronary artery disease. Following the development of gated equilibrium radionuclide angiography by Zaret and collaborators,[3] Borer et al.,[4] in 1976, described the use of supine exercise equilibrium radionuclide angiography for the detection of coronary disease. They demonstrated that patients with coronary disease were unable to increase their ejection fraction response with maximal exercise, and also exhibited new regional wall motion abnormalities with exercise.

Although dynamic exercise remains the standard approach to physiologic stress testing, a number of other interventions have been used, including: (1) isometric exercise, (2) atrial pacing, (3) cold pressor testing, (4)

TABLE 2–1.—APPROACHES TO PHYSIOLOGIC STRESS TESTING

Dynamic exercise
Isometric exercise
Atrial pacing
Cold pressor testing
Postextrasystolic potentiation
Volume loading
Negative intrathoracic pressure

postextrasystolic potentiation, (5) volume loading, and (6) negative intrathoracic pressure (Table 2–1). Each of these may be considered an alternative physiologic intervention whenever dynamic exercise is not feasible. These alternative approaches are important since, in our experience, 20% to 30% of subjects are unable to perform dynamic exercise, or exercise inadequately to produce a sufficiently intense cardiac stress.

This chapter reviews physiologic considerations, indications, contraindications, protocols, and results of these physiologic stress interventions when used in combination with cardiac radionuclide procedures.

PHYSIOLOGIC CONSIDERATIONS

Coronary Vascular Reserve

A physiologic stress procedure tests coronary vascular reserve. Coronary vascular reserve relates to the ability of coronary vessels to increase blood flow in response to oxygen demands, and/or as compensation for decreased oxygen carrying capacity of blood. In the normal individual, sufficient physiologic stress increases coronary blood flow threefold to fivefold. On the other hand, in a patient with coronary disease, coronary flow in the myocardial bed supplied by a stenotic vessel will fail to increase appropriately. This may lead to malperfusion of regional coronary flow, mismatch of myocardial oxygen supply and demand, and resultant stress-induced ischemia. This stress-induced ischemia will result in decreased uptake of thallous chloride Tl 201, producing regional perfusion defects, and will result in wall motion abnormalities and abnormalities in left ventricular volumes and ejection fraction on radionuclide ventriculography.

The in vivo studies of Gould et al.[5, 6] on artificial stenosis in the canine model have provided important data concerning relationships of flow and degree of stenosis at rest and following physiologic stress. They found that greater than 80% stenosis was necessary before a significant decrease in coronary blood flow occurred at rest. However, following a physiologic stress (in their case, temporary coronary occlusion), coronary maximal hyperemic response was impaired with a 40% to 60% stenosis. To produce a