Evaluation of Clearance

4

Introduction

All nuclear medicine procedures are fundamentally dependent on the optimal biodistribution of the radiopharmaceutical in question either for obtaining physiologic or metabolic information from images in diagnostic studies or for delivering a maximally tolerated therapeutic dose of radiation to tumor in therapeutic procedures. In turn, in most procedures the biodistribution is primarily dependent on clearance of the radiopharmaceutical from the blood into organs, tissues, or lesions.

The Nuclear Medicine Procedure Manual lists 49 diagnostic studies in the 2012–2014 edition [1]. Thirty-nine of them are included in this book (see Appendix A). Of those 39 studies, 27 involve clearance of the radiopharmaceutical from blood into organs, tissues, or lesions. In all of these studies, images are included that are timed to optimally depict the results of clearance (twenty-six of the 27 studies involve direct injection of the radiopharmaceutical into the blood, and one, the Thyroid Imaging and Uptake Study, involves administration of the I-123 orally followed by absorption into the blood). These 27 studies are listed alphabetically in Table 4.1 within the organ systems plus infection and tumor.

Seven of the 27 studies are entitled perfusion studies but in fact measure clearance (Table 4.2). In these seven studies, the clearance of the radiopharmaceuticals usually parallels blood flow and perfusion, but not always. The graph in Fig. 4.1 shows the correlation between coronary blood flow and the amount of uptake (clearance) of the various radiopharmaceuticals used in myocardial perfusion studies [2]. None of the radiopharmaceuticals that are used to measure myocardial perfusion or blood flow show a one to one correspondence to coronary blood flow.

In five of the 27 nuclear medicine studies that show clearance following an intravenous injection, there is routine imaging of one or more physiologic parameters in addition to clearance such as blood flow, parenchymal transit, and excretion (Table 4.3).

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Table 4.1 Nuclear medicine studies in which the radiopharmaceutical is cleared from the blood

Procedure	Radiopharmaceutical	Cleared by	Other parameters imaged
Cardiovascular system			
Myocardial Perfusion Study	N-13-ammonia	Myocardium	No
Myocardial Perfusion Study	Rb-82 as rubidium chloride	Myocardium	No
Myocardial Perfusion Study	Tc-99m-sestamibi	Myocardium	No
Myocardial Perfusion and Viability Study	Tl-201-thallous chloride	Myocardium	Yes
Myocardial Viability Study	F-18-fluorodeoxyglucose	Myocardium	No
Central nervous system			
Brain Glucose Metabolism Study	F-18-fluorodeoxyglucose	Brain	No
Brain Perfusion Study	Tc-99m-HMPAO	Brain	No
Striatal Dopamine Transporter Study	I-123-ioflupane [DaTscan]	Striatum	No
Endocrine system			
Neuroectodermal Imaging	I-123-MIBG	Neuroectoderm	No
Parathyroid Study	I-123 & Tc-99m-sestamibi	Thyroid and thyroid + adenoma	No
Thyroid Imaging and Uptake Study	I-123	Thyroid	No
Thyroid Metastases Study	I-123/I-131	Thyroid tissue	No
Gastrointestinal system			
Hepatic Artery Perfusion Study	Tc-99m-MAA	Liver	No
Hepatobiliary Study	Tc-99m-trimethylbromo-IDA	Liver	Yes
Liver-Spleen Study	Tc-99m-sulfur colloid	Liver and spleen	No
Meckel's Diverticulum Study	Tc-99m-pertechnetate	Gastric mucosa	No
Genitourinary system			
Renal Glomerular Filtration Study	Tc-99m-DTPA	Kidneys	Yes
Renal Tubular Function Study	Tc-99m-DMSA	Kidneys	No
Renal Tubular Excretion Study	Tc-99m-MAG3	Kidneys	Yes

(continued)

Table 4.1 (continued)

Procedure	Radiopharmaceutical	Cleared by	Other parameters imaged
Infection imaging			
White Blood Cell Activation Study	F-18-fluorodeoxyglucose	Activated WBCs	No
White Blood Cell Migration Study	In-111-white blood cells	WBC localization	No
Pulmonary system			
Lung Perfusion Study	Tc-99m-MAA	Capillary beds	No
Skeletal system			
Bone Mineral Study	F-18 sodium fluoride	Bone mineral hydroxyapatite	No
Bone mineral Study	Tc-MDP/HMDP	Bone mineral	Yes
Tumor imaging			
B-Cell Lymphoma Imaging Study	In-111-ibritumomab tiuxetan	CD 20	No
Neuroendocrine Tumor Study	In-111-pentetreotide	Somatostatin receptors	No
Tumor Glucose Metabolism Study	F-18-fluorodeoxyglucose	Glucose receptors	No

Table 4.2 Nuclear medicine studies that use clearance as a proxy for blood flow

Study	Radiopharmaceutical	Structure
Myocardial Perfusion Study	N-13-ammonia	Myocardium
Myocardial Perfusion Study	Rb-82 as rubidium chloride	Myocardium
Myocardial Perfusion Study	Tc-99m-sestamibi	Myocardium
Myocardial Perfusion Study	Tl-201 as thallous chloride	Myocardium
Brain Perfusion Study	Tc-99m-HMPAO	Brain
Hepatic Artery Perfusion Study	Tc-99m-MAA	Liver
Lung Perfusion Study	Tc-99m-MAA	Lung

These studies are labeled perfusion studies, but the radiopharmaceuticals localize by clearance

There are three additional nuclear medicine studies in which the radiopharmaceutical is introduced by a route other than intravenous injection, but clearance is the primary parameter of interest (Table 4.4). In the Lymphoscintigraphy Study, filtered Tc-99m-sulfur colloid is injected into the interstitial space and is carried with the flow of lymph to the sentinel node(s) where it is cleared by phagocytosis into sinusoidal macrophages. In the Lung Aerosol Ventilation Study and the Lung Ventilation Study, Tc-99m-DTPA aerosol and Xe-133 gas, respectively, are inhaled

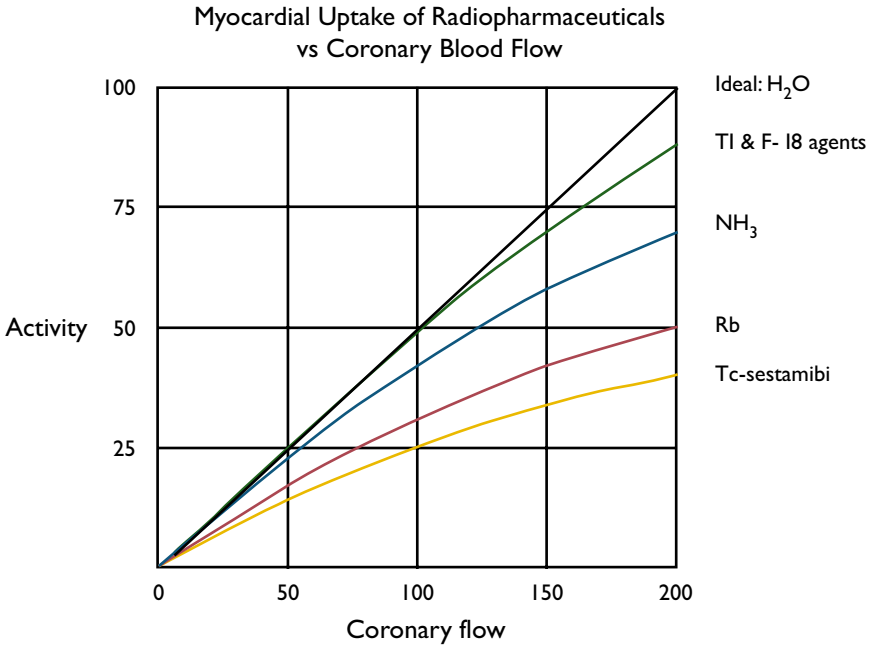

Fig. 4.1 Myocardial uptake (clearance) of radiopharmaceuticals. Clearance of radiopharmaceuticals is often used as a proxy for perfusion, or blood flow, but the correlation between clearance and blood flow is often not one to one [2]

Table 4.3 Nuclear medicine studies with parameters in addition to clearance

Study	Radiopharmaceutical	Structure	Other parameters
Myocardial Perfusion and Viability Study	Tl-201 chloride	Myocardium	Viability
Hepatobiliary Study	Tc-99m-trimethylbromo-IDA	Hepatobiliary tract	Parenchymal transit and excretion
Renal Glomerular Filtration Study	Tc-99m-DTPA	Renal tubules	Blood flow, parenchymal transit, and excretion
Renal Tubular Secretion Study	Tc-99m-MAG3	Renal tubules	Blood flow, parenchymal transit, and excretion
Bone Mineral Study (Three Phase)	Tc-99m-MDP	Bone mineral	Blood flow and extracellular space

and flow through the bronchial tree by the process of ventilation. The Tc-99m-DTPA aerosol is cleared by adherence to mucous in the terminal bronchi and the Xe-133 gas is cleared by confinement in the alveoli.

Table 4.4 Nuclear medicine studies in which the radiopharmaceutical is cleared, but not from blood

Procedure	Radiopharmaceutical	Route of administration
Cardiovascular system		
Lymphoscintigraphy	Filtered Tc-99m-sulfur colloid	Intradermal
Pulmonary system		
Lung Aerosol Ventilation Study	Tc-DTPA aerosol	Inhalation
Lung Ventilation Study	Xe-133 gas	Inhalation

Table 4.5 Nuclear medicine studies with intravenous injection of the radiopharmaceutical, but without clearance from the blood

Procedure	Radiopharmaceutical	Image other parameters
Cardiovascular system		
Cardiac Gated Blood Pool Study	Tc-99m-red blood cells	Yes
Central nervous system		
Brain Death Study	Tc-99m-DTPA	Yes
Gastrointestinal system		
Gastrointestinal Bleeding Study	Tc-99m-red blood cells	Optional
Hemangioma Study	Tc-99m-red blood cells	Yes

There are four other nuclear medicine studies that involve an intravenous injection of the radiopharmaceutical, but there is no clearance of the radiopharmaceutical from the blood in the organ of interest (Table 4.5). The radiopharmaceutical in three of the four studies is Tc-99m-RBCs. The images in these studies depict blood flow and blood volume, but not clearance. The radiopharmaceutical in the fourth study, Tc-99m-DTPA, is cleared in the kidneys by glomerular filtration but not in the brain, the organ that is imaged.

Compartmental Analysis for Describing the Biodistribution of Radiopharmaceuticals

In the research setting, the biodistribution of radiopharmaceuticals as a function of time, including clearance, is sometimes evaluated mathematically with compartmental analysis [3–7]. However, compartmental analysis requires creation of a relatively accurate model of the system (or systems) under study, designation of rate constants to describe the movement of the radiopharmaceutical between compartments (often bidirectional), measurement of an input function (ideally arterial), measurement of the amount of radiopharmaceutical in tissues as a function of time, and employment of calculus for obtaining the solution in terms of rate constants. Unfortunately, in the clinical setting, the model(s) under study is often unknown and the input data is not available. For these and other practical reasons, compartmental analysis is not applicable in the clinical setting.

A Clearance Equation for Evaluating the Biodistribution of Radiopharmaceuticals

In general, nuclear medicine images are interpreted visually based on image patterns. However, there is an underlying biologic process involving several factors or parameters that determines the initial clearance and biodistribution of the radiopharmaceutical. Here we will construct an equation in physiologic terms that can be used conceptually, without quantitation, to assist in image evaluation, particularly in images without a readily recognizable pattern.

The degree to which an intravenously injected radiopharmaceutical is cleared from blood by a specific organ, tissue, or lesion depends on four factors, which multiplied together determine the amount of radiopharmaceutical that localizes in tissue at a given time after injection [8]. First, there must be a factor accounting for delivery of the radiopharmaceutical from the injection site to the clearance site by blood flow on a per gram basis, F (mL/min-g).

Second, there must be a factor that accounts for the clearance or movement of the radiopharmaceutical from blood into tissue. This factor is the extraction efficiency, EE (no units), of the cells or tissue for the radiopharmaceutical in question. The extraction efficiency will be determined primarily by the extraction mechanism. The extraction mechanism depends on more than the physical and chemical properties of the radiopharmaceutical itself, but also on how the radiopharmaceutical interacts with the components of blood, e.g., whether it binds to protein. The renal imaging radiopharmaceutical Tc-99m-MAG3 is a small molecule that would be easily filtered through the renal glomerulus, but most of it is protein bound so that it is cleared mainly by tubular secretion instead [9].

In addition, the term clearance as applied to radiopharmaceutical clearance must be defined more broadly than the removal of a radiopharmaceutical from blood and the vascular space. In order to encompass all mechanisms of clearance, clearance needs to be defined as clearance from "flowing blood." For example, Tc-99m-macroaggregated albumin is cleared by embolization into arterioles; this process results in the removal of the radiopharmaceutical from flowing blood, but not from the vascular space.

Furthermore, because there are situations in which the radiopharmaceutical may move back out of cells and into the vascular space, extraction efficiency should be thought of as net extraction efficiency. Experience suggests that in most cases disease affects the clearance of radiopharmaceutical into tissue in rough proportion to any effect on the movement from tissue back into blood so that the net change in localization of tracer in tissue will approximately parallel change in severity of disease.

Third, a factor is needed to account for competing substances if the extraction mechanism can be saturated. Any atoms, molecules, or substances that compete for extraction with the radiopharmaceutical are accounted for by including a ratio of the normal concentration or pool of such atoms, molecules, or substances,

P_{Nl} (mole/mL), divided by the actual concentration of such atoms, molecules, or substances, P_{Act} (mole/mL). The units cancel.

The second and third factors multiplied together define the overall extraction efficiency, but it is useful to keep them separate because the effect of competing substances can be evaluated separately from extraction efficiency, which increases the specificity of diagnosis.

The first three factors multiplied together equal the clearance rate for the substance being traced in terms of mL/min per gram of tissue, but they do not determine the amount of radiopharmaceutical that will localize in tissue by a given time after injection.

So, a fourth factor is needed to account for the concentration of the radiopharmaceutical in blood, C (μCi/mL), as a function of time from the time of injection, 0 (min), until the time of the end of acquisition of the clearance or localization image, T (min), $\int_0^T C(t)\,dt\,(\mu\text{Ci-min/mL})$.

These four factors multiplied together give a final equation for clearance of a radiopharmaceutical by an extraction mechanism over a specified amount of time that can or cannot be saturated in terms of radioactivity per gram of tissue, A (μCi/g),

$$A(\mu\text{Ci/g}) = F(\text{mL/min-g}) \times \text{EE} \times P_{Nl}/P_{Act} \times \int_0^T C(t)\,dt\,(\mu\text{Ci-min/mL}) \tag{4.1}$$

Table 4.6 provides some additional analysis of Eq. 4.1 in terms of the biologic meaning of the individual factors and various subsets of factors.

If the extraction mechanism for a radiopharmaceutical is non-saturable, then the extraction efficiency will not be affected by the presence of competing atoms, molecules, or substances and the factor P_{Nl}/P_{Act} can be excluded. Equation 4.1 simplifies to,

$$A(\mu\text{Ci/g}) = F(\text{mL/min-g}) \times \text{EE} \times \int_0^T C(t)\,dt\,(\mu\text{Ci-min/mL}) \tag{4.2}$$

In addition, Eq. 4.1 can be used in ratio form to evaluate the relative clearance or localization in two different sites in one image or in a set of images,

$$\frac{A(\mu\text{Ci/g})}{A(\mu\text{Ci/g})} = \frac{F(\text{mL/min-g}) \times \text{EE} \times P_{Nl}/P_{Act} \times \int_0^T C(t)\,dt\,(\mu\text{Ci-min/mL})}{F(\text{mL/min-g}) \times \text{EE} \times P_{Nl}/P_{Act} \times \int_0^T C(t)\,dt\,(\mu\text{Ci-min/mL})} \tag{4.3}$$

Since the ratio of the normal and actual pools of atoms, molecules, or substances that behave the same relative to the extraction mechanism, P_{Nl}/P_{Act}, and the ratio of

Table 4.6 Analysis of clearance equation

Factors	Mathematical equivalent	Biologic description
$F\ (\mathrm{mL/min\text{-}g}) \times \mathrm{EE} \times P_{\mathrm{Nl}}/P_{\mathrm{Act}} \times \int_0^T C(t)\,\mathrm{d}t\ (\mu\mathrm{Ci-min/mL})$	A (μCi/g)	Radiopharmaceutical cleared per gram of tissue through time "T"
F (mL/min-gm)	Same	Blood flow per gram of tissue
EE	Same	Extraction efficiency for substance being traced
$P_{\mathrm{Nl}}/P_{\mathrm{Act}}$	Same	Normal concentration of traced substance/actual concentration of traced substance
$\int_0^T C(t)\ \mathrm{d}t\ (\mu\mathrm{Ci\text{-}min/mL})$	Same	Concentration of radiopharmaceutical per mL of blood integrated from time of injection to end of image acquisition, T
EE * $P_{\mathrm{Nl}}/P_{\mathrm{Act}}$	Same	Overall extraction efficiency
F (mL/min-g) * EE * $P_{\mathrm{Nl}}/P_{\mathrm{Act}}$	Cl (mL/min-g)	Clearance rate per gram of tissue
$F\ (\mathrm{mL/min\text{-}g}) \times \int_0^T C(t)\,\mathrm{d}t\ (\mu\mathrm{Ci\text{-}min/mL})$	A_{A} (μCi/g)	Radiopharmaceutical available to be cleared per gram of tissue, A_{A}, through time "T"

the concentration of radiopharmaceutical in the blood, $\int_0^T C(t)\,\mathrm{d}t\ (\mu\mathrm{Ci\text{-}min/mL})$, are almost always the same at a given time in any two sites within one study, they will cancel giving,

$$\frac{A\ (\mu\mathrm{Ci/gm})}{A\ (\mu\mathrm{Ci/gm})} = \frac{F\ (\mathrm{mL/min\text{-}gm}) \times \mathrm{EE}}{F\ (\mathrm{mL/min\text{-}gm}) \times \mathrm{EE}} \tag{4.4}$$

Thus, in most cases the relative biodistribution of the radiopharmaceutical, saturable or non-saturable, following initial clearance will depend on only two factors or parameters, blood flow and net extraction efficiency.

The diagnostic procedures listed in the Nuclear Medicine Procedure Manual [1] were used to construct tables of studies according to whether clearance of the radiopharmaceutical requires all four factors, Eq. 4.1, or just three factors, Eq. 4.2. In creating the tables, studies in which the radiopharmaceutical is not cleared from blood, e.g., Lymphoscintigraphy with filtered Tc-99m-sulfur colloid, Gastric Emptying Study with Tc-99m-sulfur colloid-labeled instant oatmeal, and Lung Aerosol Ventilation Study with Tc-99m-DTPA aerosol, or are injected intravenously but are not extracted or cleared, e.g., Cardiac Gated Blood Pool Study with Tc-99m-RBCs and Gastrointestinal Bleeding Study with Tc-99m-RBCs, were not considered.

Table 4.7 Nuclear medicine studies that require the full clearance equation (the extraction mechanism is saturable)

Myocardial Viability Study (F-18-fluorodeoxyglucose)	Thyroid Metastases Imaging Study (I-123 as sodium iodide, I-131 as sodium iodide)
Brain Glucose Metabolism Study (F-18-fluorodeoxyglucose)	Thyroid Uptake Measurement (I-123 as sodium iodide)
Striatal Dopamine Transporter Study (I-123-ioflupane [DatScan])	Hepatobiliary Imaging Study (Tc-99m-trimethylbromo-IDA)
Neuroectodermal Imaging Study (I-123-MIBG)	Tumor Glucose Metabolism Study (F-18-fluorodeoxyglucose)
Thyroid Imaging Study (I-123 as sodium iodide)	

The tables of examples of studies that fall into various clearance categories must be viewed as tentative because the extraction mechanism and the factors that affect the extraction mechanism are not fully understood for many radiopharmaceuticals.

Table 4.7 lists nuclear medicine studies in which the radiopharmaceutical is thought to clear by an extraction mechanism that is saturable. This phenomenon is well recognized for radioiodide radiopharmaceuticals, e.g., I-123 and I-131. The most common competing atom or molecule is nonradioactive iodide from recently administered intravenous CT contrast material. The effect of an increased blood glucose concentration on the extraction efficiency of F-18-fluorodeoxyglucose (FDG) is probably more complicated [10]. Change in the blood glucose concentration may affect the expression of glucose receptors, which would affect the extraction efficiency. Tc-99m-trimethylbromo-IDA binds to the same hepatocyte receptor that extracts bilirubin so elevated blood levels of bilirubin will compete with Tc-99m-trimethylbromo-IDA and decrease its extraction efficiency [11].

Table 4.8 lists nuclear medicine studies in which the radiopharmaceutical is thought to clear by an extraction mechanism that is non-saturable under most circumstances. Examples include radiopharmaceuticals that do not bind to a receptor and whose extraction depend on mechanical mechanisms such as the extraction of Tc-99m-macroaggregated albumin by embolization into arterioles (normally an extraction efficiency of 100 %) and the extraction of Tc-99m-DTPA in the kidneys by glomerular filtration (normally an extraction efficiency of 20 %). The technetium-99m bone mineral radiopharmaceuticals also do not bind to a receptor, but are chemisorbed onto hydroxyapatite with little evidence that the extraction efficiency is easily affected by most other atoms, molecules, or substances [12]. The extraction mechanism for Tc-99m-MAG3 can be saturated under experimental conditions, but it is uncertain whether this happens clinically [9].

Table 4.9 lists the four factors that make up the clearance equation across the top and three parameters related to those four factors in the first column. The idea is to explore the role that each of the four factors plays in determining the initial biodistribution or localization of an intravenously injected radiopharmaceutical. The first parameter, "approximate range encountered clinically," estimates the range of the values that may be encountered clinically relative to normal, N, for each of the four

Table 4.8 Nuclear medicine studies that require only the simplified clearance equation (the extraction mechanism is non-saturable)

Myocardial Perfusion Study (N-13-ammonia)	Renal Glomerular Filtration Study (Tc-99m-DTPA)
Myocardial Perfusion Study (Rb-82 as sodium chloride)	Renal Tubular Excretion Study (Tc-99m-MAG3)
Myocardial Perfusion Study (Tc-99m-sestamibi)	White Blood Cell Activation Study (F-18-fluorodeoxyglucose)
Myocardial Perfusion & Viability Study (Tl-201 as thallous chloride)	White Blood Cell Migration Study (In-111-WBCs, Tc-99m-WBCs)
Brain Perfusion Study (Tc-99m-HMPAO, Tc-99m-ECD)	Lung Perfusion Study (Tc-99m-macroaggregated albumin)
Parathyroid Imaging Study (Tc-99m-sestamibi)	Bone Mineral Study (F-18 as sodium fluoride)
Hepatic Artery Perfusion Study (Tc-99m-macroaggregated albumin)	Bone Mineral Study (Tc-99m-methylene diphosphonate)
Liver-Spleen Study (Tc-99m-sulfur colloid)	

Table 4.9 Conditions that affect the four clearance factors

Parameter	F	EE	P_{Nl}/P_{Act}	$\int_0^T C(t)\,dt$
Approximate range encountered clinically	0 to >10 N	0–10 N	~0 to 1.3 N	N to >10 N
Example of a condition at lower end of range	Necrosis, distal to arterial occlusion	FDG: Down regulation of GLUTs from hyperglycemia	l-123: Recent CT contrast material	–
Example of a condition at upper end of range	Arteriovenous malformation (AVM)	FDG: Upgrade regulation of GLUTs in high-grade tumor	l-123: Low-iodine diet	Embolus from injection site

N Normal value, *F* Flow (mL/min-g), *EE* extraction efficiency, P_{Nl}/P_{Act} pool (normal)/pool (actual), $\int_0^T C(t)\,dt$ integral of concentration of radiopharmaceutical in the blood from time of injection until the end of the time of image acquisition (μCi-min/mL)

factors. The second and third parameters "Example of a condition at lower end of range" and "Example of a condition at upper end of range" give examples of conditions that may result in changes toward the lower and upper ends of the ranges listed in the first row for each factor. Notice that the clinical range for blood flow, F, ranges from zero in the case of an arterial occlusion to greater than 10 times normal with an arteriovenous malformation. The estimated range for extraction efficiency, EE, is similar. The competing substance correction ratio, P_{Nl}/P_{Act}, again ranges as low as zero but does not extend much above normal. In general, it is difficult to

markedly reduce the level of a normally circulating molecule or substance, P_{Act}. Finally, the amount of radiopharmaceutical per milliliter that is available for clearance, $\int_0^T C(t)\,\mathrm{d}t$, is usually unaffected by pathologic conditions, but a thrombus that forms at the injection site, is impregnated with concentrated radiopharmaceutical, and then embolizes to the lungs will result in a focus of intense increased activity in the lung. The cause is that the flowing blood that contained the embolus has a much higher concentration of activity than other blood.

Equivalence of the Traditional Physiologic Clearance Equation and the Nuclear Medicine Clearance Equation (as Presented in This Chapter)

The traditional non-nuclear medicine clearance equation specifies the physiologic capacity of an organ to clear a substance from the blood. We will use the creatinine clearance equation as an example of a traditional clearance equation,

$$\mathrm{Cl}(\mathrm{mL/min}) = \frac{U(\mathrm{mg/min})}{P(\mathrm{mg/mL})} \tag{4.5}$$

Here "Cl" is clearance in traditional physiologic terms with units of mL/min, "U" is the amount of creatinine in a 24 h urine collection on a per minute basis with units of mg/min, and "P" is the plasma concentration of creatinine with units of mg/mL. The initial step of multiplying the concentration of creatinine in the 24 h urine collection times the urine volume has been omitted. Also, the factor that normalizes the result for body surface area has been left out for simplification. Notice that the traditional physiologic clearance equation determines a rate that describes the capacity of the kidneys to clear creatinine from the blood. The clearance rate, Cl, does not give any specific information about the plasma creatinine concentration or the amount of creatinine in the urine, only the ratio of the two.

In the nuclear medicine setting, the goal is to understand the factors that determine the biodistribution of the radiopharmaceutical, which is reflected in the images. We will start with the nuclear medicine equation for the amount of cleared substance as developed above (see Eq. 4.1).

Now we will show how the nuclear medicine clearance equation, initially expressed in terms of an amount rather than a rate, is equivalent to the traditional physiologic clearance equation. It will be assumed that the nuclear medicine study is the Renal Glomerular Filtration Study with Tc-99m-DTPA since Tc-99m-DTPA is primarily restricted to plasma and interacts with the kidney in a manner similar to creatinine.

It is useful to explain the reason why the two equations are equivalent in words and then, secondarily, in mathematical steps. The left-hand side of the nuclear medicine clearance equation is the amount of test substance that has been cleared from the blood in the allotted time, A (μCi/g), and is, therefore, equivalent to the amount of creatinine that is cleared by the kidney in 24 h, U (mg/min), in the traditional physiologic clearance equation. In addition, in the nuclear medicine clearance equation, the amount of tracer available for clearance is the integral of blood concentration of the tracer from the time of injection to the time of image acquisition, $\int_0^T C(t)\,\mathrm{d}t\,(\mu\mathrm{Ci\text{-}min/mL})$, and is, therefore, equivalent to "P (mg/mL)" in the traditional physiologic clearance equation. Then, if we divide both sides of the nuclear medicine clearance equation by "$\int_0^T C(t)\,\mathrm{d}t\,(\mu\mathrm{Ci\text{-}min/mL})$" and reverse the left- and right-hand sides of the equation, we get,

$$F\,(\mathrm{mL/min\text{-}g}) \times \mathrm{EE} \times P_{\mathrm{NI}}/P_{\mathrm{Act}} = \frac{A\,(\mu\mathrm{Ci/g})}{\int_0^T C(t)\,\mathrm{d}t\,(\mu\mathrm{Ci\text{-}min/mL})} \tag{4.6}$$

The factors "EE" and "$P_{\mathrm{NI}}/P_{\mathrm{Act}}$" together determine the full extraction efficiency. However, when the extraction mechanism cannot be saturated as is the case with glomerular filtration, the factor "$P_{\mathrm{NI}}/P_{\mathrm{Act}}$" can be deleted. In addition, initially the nuclear medicine clearance equation was expressed on a per gram basis and the creatinine clearance equation is implied to be on a per kidneys basis. The "per gram" in the nuclear medicine equation can be replaced by an understood "per kidney" to give,

$$F\,(\mathrm{mL/min}) \times \mathrm{EE} = \frac{A\,(\mu\mathrm{Ci})}{\int_0^T C(t)\,\mathrm{d}t\,(\mu\mathrm{Ci\text{-}min/mL})} \tag{4.7}$$

In the case of the creatinine clearance equation, it is assumed that the concentration of creatinine in plasma, and therefore blood, is constant so that the units can be expressed on a per minute basis rather than a 24 h basis. In addition, "EE" for Tc-99m-DTPA and glomerular filtration will be 20 %, which converts blood flow to the lesser amount of blood volume that would be completely cleared of test substance in the same time, i.e., the same value as "Cl (mL/min)" in the creatinine clearance equation. Thus, the traditional physiologic clearance equation and the nuclear medicine clearance equation are essentially equivalent.

The factor for normalizing the creatinine clearance equation for body surface area could have been carried along with no effect on the mathematical argument. Despite the mathematical equivalence between the creatinine clearance equation and the nuclear medicine clearance equation, there is a significant difference. The creatinine clearance equation is designed to be evaluated and to produce a numerical answer. But the nuclear medicine clearance equation discussed above is meant

to be used on a conceptual basis only and, in particular, to evaluate relative clearance or uptake in images.

However, there are two other nuclear medicine clearance equations for renal clearance with either Tc-99m-DTPA or Tc-99m-MAG3 that are clearance rates in absolute terms, i.e., the amount of cleared radiopharmaceutical is compared to the amount injected into the blood. These absolute nuclear medicine clearance equations yield a quantitative clearance result in terms of a rate of clearance, mL/min, and are discussed in Chap. 9, Quantitation of Function: Absolute Measurements.

Clinical Applications of the Nuclear Medicine Equation for Clearance

In this section we give examples of how Eqs. 4.1, 4.2, and 4.4 can be used to analyze clearance conceptually and in physiologic and molecular biologic terms. Table 4.10 lists a variety of conditions that affect one or more of the four factors that comprise the general clearance or uptake equation that in turn determines the initial biodistribution of an intravenously injected radiopharmaceutical, A (μCi/gm). The conditions are listed in column one, the radiopharmaceuticals in column two, and the various components of the clearance equation in the remaining columns.

In the first example, infection results in increased localization of F-18-fluorodeoxyglucose (FDG) from both increased blood flow and increased extraction efficiency by activated white blood cells [12] with no change in the competing substance pool or local blood concentration of the radiopharmaceutical. In the second example, a pulmonary anatomic arteriovenous malformation results in markedly decreased clearance of Tc-99m-macroaggregated albumin because, even though the

Table 4.10 Conditions and their effect on factors affecting radiopharmaceutical biodistribution

Condition	Radiopharmaceutical	A	F	EE	P_{NI}/P_{Act}	$\int_0^T C(t)\,dt$
Infection	F-18-FDG	↑↑	↑↑↑	↑↑	–	–
Lung AVM	Tc-99m-MAA	↓↓	↑↑	↓↓	–	–
Subacute viral thyroiditis	1-123, 1-131	↓	↑	↓↓	–	–
Graves disease	1-123	↑↑	↑	↑	–	–
Recent CT contrast	1-123, 1-131	↓↓	–	–	↓↓	–
Low iodine diet	1-131	↑	–	–	↑	–
Injection embolus	Tc-99m-MAA	↑↑	–	–	–	↑↑
Injection embolus	F-18-FDG	↑↑	–	–	–	↑↑
Tumor, diabetic, glucose ↑↑	F-18-FDG	↓↓	↑	↓↓	↓↓	–

A activity (μCi/g), F flow (mL/min-g), EE extraction efficiency, P_{NI}/P_{Act} pool (normal)/pool (actual), $\int_0^T C(t)\,dt$ integral of concentration of radiopharmaceutical in the blood from time of injection until the end of the time of image acquisition (μCi-min/mL)

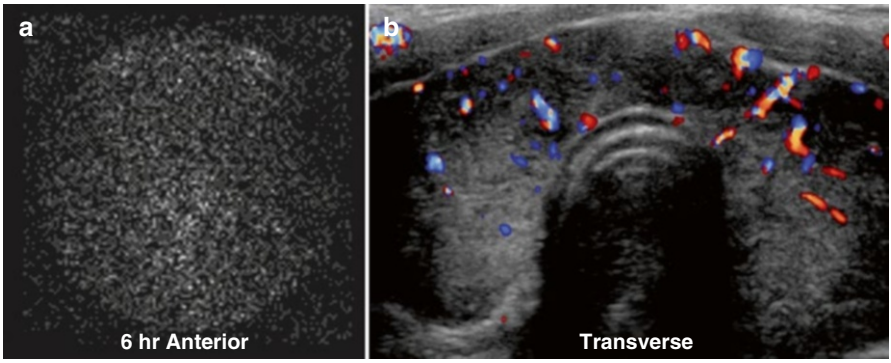

Fig. 4.2 Subacute viral thyroiditis. A 38-year-old female with symptoms of hyperthyroidism, depressed blood thyroid-stimulating hormone level, and a history of a recent pharyngitis. (**a**) Pinhole nuclear medicine image shows very little I-123 in the thyroid gland. The 6 h I-123 thyroid uptake value was markedly decreased at 2.1 % (normal range: 7–20 %). (**b**) Transverse ultrasound image of the neck shows a moderately enlarged thyroid gland with a nonhomogenous echo pattern and moderately increased blood flow by color Doppler

blood flow will be markedly increased, the extraction efficiency will be essentially zero and, thus, clearance will be essentially zero. Of interest, this example demonstrates that most nuclear medicine procedures that are labeled as depicting blood flow or perfusion actually reflect clearance.

In the third example, subacute viral thyroiditis results in significantly decreased uptake of I-123 despite an increase in blood flow because of a markedly decreased extraction efficiency secondary to depressed blood levels of thyroid-stimulating hormone (Fig. 4.2).

In the fourth example, Graves disease results in increased uptake of I-123 in the thyroid from increased blood flow and extraction efficiency. In the fifth example, the recent intravenous administration of CT contrast causes a marked decrease in thyroid uptake of I-123 secondary to a marked increase in competing atoms, i.e., nonradioactive iodine. In the sixth example, a low-iodine diet causes a small increase in thyroid uptake of I-123 secondary to a small decrease in the nonradioactive iodine blood pool.

In the seventh and eighth examples, Tc-99m-macroaggregated albumin or FDG, respectively, adheres to a small thrombus at the injection site, which then embolizes to the lungs resulting in a focus of significantly increased radiopharmaceutical secondary to a significantly increased concentration of radiopharmaceutical in the blood containing the embolus that flowed to the particular area of lung in question (Fig. 4.3). Interestingly, in the case of FDG, the adherence of FDG to the thrombus changes the extraction mechanism from binding to glucose receptors on cell membranes to microembolization.

In the ninth example, a patient with lung cancer demonstrates widespread metastases in a baseline study (Fig. 4.4a). Post therapy the metastases appear to have resolved, but there is also no uptake in the brain (Fig. 4.4b). The patient was determined to have unrecognized diabetes with an elevated blood glucose level.

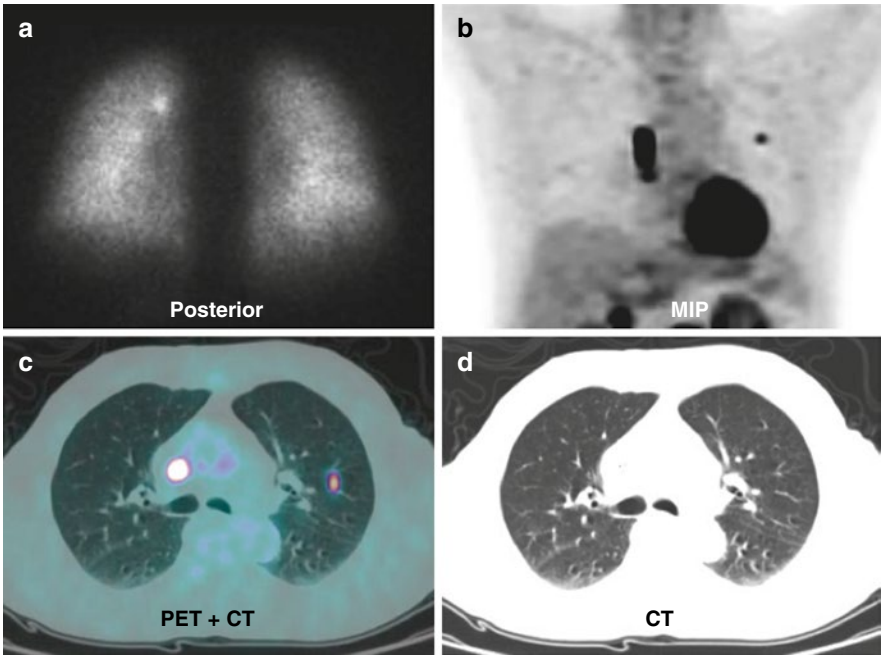

Fig. 4.3 Injection-related microembolus. (**a**) Posterior image from a Tc-99m-macroaggregated albumin lung perfusion study for possible pulmonary embolus shows a focus of increased activity in the medial superior left lung. This finding is most likely secondary to Tc-99m-macroaggregated albumin that adhered to a microthrombus that formed at the injection site and then embolized to the lung. (**b**–**d**) Maximum intensity projection (*MIP*) and tomographic images from a FDG PET-CT study show a focus of increased FDG in the left lung without a CT correlate. This finding is most likely secondary to FDG that adhered to a microthrombus that formed at the end of the superior vena caval catheter and then embolized to the lung

A few days later, after the hyperglycemia had been treated, a repeat study demonstrated progressive metastatic disease and normal brain uptake (Fig. 4.4c). The absent uptake in the first post-therapy study probably cannot be fully explained by the increased nonradioactive glucose pool and suggests a possible downregulation of cell membrane glucose receptors resulting in a decreased extraction efficiency [10].

Many other examples of common or unusual areas of increased or decreased localization or clearance of radiopharmaceutical could be analyzed in this same fashion. However, these nine examples illustrate how the clearance equation can be used conceptually to help clarify the pathophysiology, and in some cases the etiology, of image findings.

Again, the clearance equation is meant to be used conceptually, without quantitation, to assist in the evaluation of nuclear medicine images, particularly those that do not demonstrate a readily recognizable pattern. The equation is in physiologic terms and is designed to describe the initial clearance and biodistribution of an intravenously injected radiopharmaceutical from the blood into organs, tissues, and lesions. Because

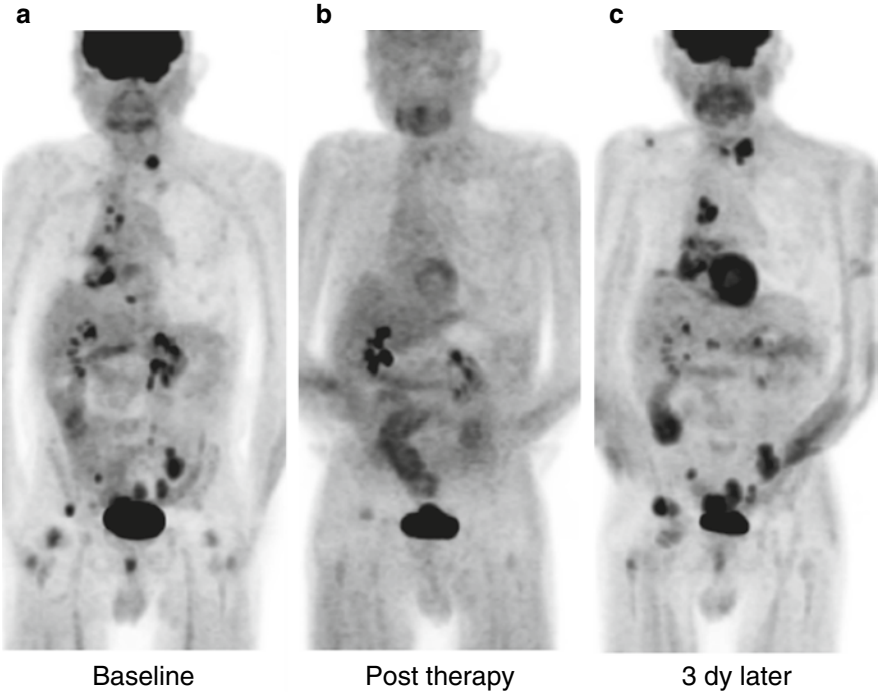

Fig. 4.4 A 76-year-old male with lung cancer. Anterior MIP (maximum intensity projection) images from sequential FDG PET-CT studies. (**a**) The baseline study shows widespread metastases. The blood glucose was 105 mg/dL. (**b**) Post therapy (11 weeks later), the metastases appear to have resolved. Of note, there is very little FDG uptake in the brain. The patient was not known to be a diabetic, but the blood glucose was 260 mg/dL. (**c**) The patient was sent to his physician for treatment of newly diagnosed diabetes. Three days later the blood glucose was 76 mg/dL and the study was repeated. The repeat study demonstrates progressive metastatic disease and normal brain uptake. The elevated blood glucose level at the time of the initial post-therapy study is probably insufficient to fully explain the essentially complete lack of uptake in the metastases and brain. It is postulated that, in addition to a possible competitive effect, the elevated glucose level caused a downregulation of the glucose receptors

of the wide applicability of this nuclear medicine clearance equation, it is a relatively fundamental equation from the point of view of the initial biodistribution of radiopharmaceuticals and image interpretation. In Part III, Quantitative Evaluation in Nuclear Medicine Studies, the use of the clearance equation will be evaluated more fully in all of the nuclear medicine studies in which it is applicable.

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