Cationic Complexes of Technetium for Myocardial Imaging

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Over the past 15 years a major goal of research in cardiovascular nuclear medicine has been the development of ^{99m}Tc complexes that could replace ^{201}Tl and thus enhance the utility of myocardial perfusion imaging. This paper presents an overview of the current state-of-art of the development of cationic ^{99m}Tc complexes for this purpose. Cationic ^{99m}Tc complexes that have been evaluated as myocardial perfusion imaging agents in human volunteers and/or animals are discussed and classified on the basis of the oxidation state of the technetium center.

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From 1973 when it was first produced at Brookhaven National Laboratory (*1,2*), thallium-201 (^{201}Tl) has become more and more important in cardiovascular nuclear medicine. This importance is based primarily on its use in noninvasive stress and rest studies for the evaluation of regional blood flow and the distinction between ischemic and infarcted myocardial muscle. Thallium-201 (an element of group IIIA of the Periodic Table) is analogous to potassium due to its overall ionic charge (+1), ionic radius (1.5 Å), rapid blood clearance (2.9 min), high myocardial extraction (88%), rapid myocardial uptake (5–15 min) and clearance ($T\frac{1}{2}$ = 4.4 hr). However, the extensive use of ^{201}Tl in both planar and SPECT imaging has also revealed that this radiopharmaceutical suffers from several serious deficiencies.

1. Since ^{201}Tl must be produced in an accelerator, it is expensive compared to many other radiopharmaceuticals, and it isn't readily available in every Nuclear Medicine Department.

2. Thallium-201 emits a low-energy photopeak (70–80 keV Hg-201 x-ray) which is significantly attenuated by soft tissues.

3. Thallium-201 has a relatively long physical half-life which increases the dosimetric cost to the patient. In practice, this last deficiency means that only relatively low amounts of ^{201}Tl radioactivity may be injected and the resulting data acquisition times are inconveniently long. Clearly, ^{201}Tl is not the ideal tracer for either planar or single photon emission computed tomography (SPECT) myocardial perfusion imaging studies. For these reasons, the replacement of ^{201}Tl by an agent based on a more suitable isotope has been a longstanding goal of diagnostic nuclear medicine.

An "ideal tracer" for myocardial perfusion must have the following characteristics: (a) rapid blood clearance; (b) rapid and high myocardial uptake; (c) favorable target/nontarget ratios (heart/lung; heart/liver; heart/spleen; heart/blood pool).

In 1980 it was first suggested that cationic complexes of technetium-99m (^{99m}Tc) might provide such ideal agents (*3,4*). Despite the initial skepticism with which the nuclear medicine community greeted this suggestion, a large number of cationic ^{99m}Tc complexes have now been shown to exhibit significant myocardial uptake in animals and humans. From a chemical point of view, these complexes are classified according to the oxidation state of the technetium center, and the reducibility of this center (Table 1).

The first ^{99m}Tc complexes shown to exhibit myocardial uptake in animals belong to the class of reducible Tc(III) cations (*5*). Nineteen trans-octahedral Tc(III) complexes were prepared with "no carrier added" ^{99m}Tc and evaluated in rats and beagle dogs. Of these, only the complexes with halogen and diars ligands exhibited detectable myocardial images, but the absolute myocardial uptake of these complexes was generally poor. Moreover, all of these initial agents exhibited high liver uptake which interfered with the cardiac image. Within this class of reducible Tc(III) cations, the first agent which generated a substantial amount of enthusiasm was $[^{99m}Tc(DMPE)_2Cl_2]^+$ (*4,6–8*). Following favorable results obtained in dogs, this agent become the first ^{99m}Tc cation to be evaluated in human volunteers (*9,*

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TABLE 1
Technetium-99m-Labeled Cationic Complexes

OXIDATION STATE OF TECHNETIUM			
V	III reducible	III non reducible	I
None	DMPE*	Q_2§	DMPE
	DEPE†		TMP††
	DIARS‡		POM-POM¶
			arene‥
			TBI‡‡
			CPI§§
			MIBI¶¶

* DMPE 1,2-bis(dimethylphosphino)ethane.
† DEPE 1,2-bis(diethylphosphino)ethane.
‡ DIARS o-phenylenebis(dimethylarsine).
§ Q_2 N,N′-ethylenebis(acetylacetone iminato).
¶ POM-POM 1,2-bis(dimethoxyphosphino)ethane.
‥ arene 1,3,5-trimethylbenzene and 1,2,3,5-tetramethylbenzene.
†† TMP trimethylphosphite.
‡‡ TBI t-isobutyl isonitrile.
§§ CPI carbomethoxyisopropyl isonitrile.
¶¶ MIBI 2-methoxyisobutyl isonitrile.

10). The resulting images were disappointing because of high pulmonary background, associated with low myocardial uptake, and intense hepatic activity which interferes with imaging of the cardiac apex. These interferences appear to be caused by in vivo reduction of the cationic Tc(III) complexes to its neutral Tc(II) form, $[^{99m}Tc(DMPE)_2Cl_2]^0$ (*11*). A similar discordance between animal and human images was observed for the related reducible Tc(III) agent ^{99m}Tc (DEPE) (*12*). With this agent, the canine heart is readily detected whereas in humans no detectable myocardial uptake is observable in the presence of intense hepatic activity. The fundamental reason underlying the different behavior of reducible Tc(III) cations in animal models and humans is still unknown.

In order to avoid the deleterious effects of in vivo transformation of reducible Tc(III) cations to their neutral Tc(II) forms, a new class of nonreducible Tc(III) cations was developed (*13,14*). Several members of this class were tested in animals, and the best of these, $[^{99m}Tc(acac_2en)(PMe_3)_2]^+$ or Q_2, was evaluated in human volunteers (*15*). While this particular cation gives good results in dogs and rats, it is only a mediocre heart imaging agent in humans because of tight binding to human plasma components. This plasma binding causes both slow blood clearance which prevents myocardial visualization until one hour after injection and also relatively low myocardial uptake. Moreover, with this agent visualization of the heart wall is hindered by the large amount of hepatic uptake which clears only slowly through the hepatobiliary system.

The most recent, and currently most important, class of cationic technetium complexes developed for myocardial perfusion studies is that in which technetium is in the +1 oxidation state (Table 1). For many ligand systems this oxidation state is conveniently accessible as the terminus of the following generic reaction scheme:

$$Tc(VII) \rightarrow Tc(V) \rightarrow Tc(III) \rightarrow Tc(I).$$

The first Tc(I) cationic complex to be evaluated in humans was $[^{99m}Tc(DMPE)_3]^+$ (*16*). Images obtained in both healthy volunteers and infarcted patients were of significantly better quality than those obtained with the related reducible Tc(III) complex $[^{99m}Tc(DMPE)_2Cl_2]^+$ because of higher myocardium/liver uptake ratios. Despite this improvement, $[^{99m}Tc(DMPE)_3]^+$ proved not to be clinically useful because of very slow blood clearance; optimal heart/blood ratios are obtained only 12–14 hr after injection (*16–19*).

In 1984 a new Tc(I) cation containing hydrolyzable ester groups, $[^{99m}Tc(TMP)_6]^+$, was prepared, characterized and shown to have a desirable biodistribution in animal models (*20*). This agent, and the related cation $[^{99m}Tc(POM\text{-}POM)_3]^+$, were then evaluated in healthy human volunteers (*21,22*). Despite the excellent results observed in dogs, in man these compounds exhibit very slow blood clearance, poor myocardial uptake within the first hour after injection, and intense activity in the liver and gallbladder. Images obtained 2–5 hr after administration of the agent were of poor quality. The tight binding of these agents to human plasma proteins, but not to dog plasma proteins, is similar to what was observed for $[^{99m}Tc(DMPE)_3]^+$; the fundamental mechanistic origin of this species specific plasma binding of ^{99m}Tc cations based on phosphorus-containing ligands remains unknown.

In order to reduce binding to human serum proteins, a series of new Tc(I) cations, $[^{99m}Tc(arene)_2]^+$, were prepared, characterized, evaluated in animal models, and subjected to in vitro tests for human plasma binding (*23*). The two agents with the best overall properties were then evaluated in human volunteers (*23,24*). As anticipated from the in vitro plasma binding tests, these agents exhibit rapid blood clearance and heart uptake, giving rise to favorable heart/blood and heart/lung ratios. However, the myocardial uptake is relatively low while the hepatic uptake is very high; the resulting low heart/liver ratio makes interpretation of the cardiac scintigrams very difficult. These clinical deficiencies, combined with the very difficult synthetic procedures used to prepare these organometallic agents, have led to the abandonment of $[^{99m}Tc(arene)_2]^+$ cations as potential myocardial imaging agents. The most important recent development in the search for a ^{201}Tl substitute occurred with the discovery of a new class of Tc(I) cations: the hexakis(isonitrile)technetium(I) complexes. These agents do not bind to human blood plasma, and give good myocardial images in several animal species.

The first isonitrile derivative to be evaluated in humans, $[^{99m}Tc(TBIN)_6]^+$, was developed by Davison and Jones (*25,26*). Preliminary mechanistic studies (*27*) suggest that the cardiac uptake of this agent, and its congeners, is related to lipophilicity and not to participation in the Na^+/K^+ ATPase pump. More extensive studies in normal volunteers (*22*) and infarcted patients (*28*) established the pertinent characteristics of $[^{99m}Tc(TBIN)_6]^+$ as a myocardial perfusion imaging agent. This cation exhibits several favorable characteristics including rapid blood clearance, low binding to plasma proteins, an early redistribution phenomenon which may be useful for distinguishing between ischemia and infarction, minimal myocardial washout, and an acceptable heart/lung ratio at 1 hr after injection. However, the high and persistent liver uptake of $[^{99m}Tc(TBIN)_6]^+$ masks the cardiac apex; this phenomenon is a serious deficiency which bars the routine clinical use of this agent (*22*).

In order to decrease the hepatic activity associated with $[^{99m}Tc(TBIN)_6]^+$, Jones and Davison developed a closely related derivative, $[^{99m}Tc(CPI)_6]^+$, which contains a hydrolyzable ester functionality (*29,30*). This derivative exhibits the rapid blood clearance characteristic of the isonitrile complexes, and also undergoes relatively rapid clearance from the lung and liver (at 1 hr after injection the heart/lung ratio is 2.4 and the heart/liver ratio is 0.6). However, there are two ways in which the biodistribution of this agent differs significantly from that of the TBIN analog: (a) there is no early myocardial redistribution after stress; (b) there is a relatively rapid myocardial washout, presumably due to cardiac metabolism of the hydrolyzable ester functionalities, which allows repeat injections to be performed within ~3–4 hr. This CPI agent would appear to be potentially useful for routine clinical applications, but the hydrolyzable ester groups of the CPI ligand may make it difficult to formulate an acceptably stable radiopharmaceutical kit.

An alternate chemical approach to decreasing the hepatic uptake associated with $[^{99m}Tc(TBIN)_6]^+$ has led to the development of $[^{99m}Tc(MIBI)_6]^+$, an ether substituted analog which exhibits such superior myocardial imaging properties that it is being marketed commercially (*31,32*). (This new agent has been referred to in the literature by a variety of designations, including ^{99m}Tc methoxy isobutyl isonitrile (MIBI); ^{99m}Tc HEXAMIBI, ^{99m}Tc 2-methoxy-2-methylpropyl-isonitrile (MMI); ^{99m}Tc isonitrile (ISO); RP-30; RP-30A; and Cardiolite). It should be stressed that this agent is clearly not a ^{201}Tl analog; both its mechanism of uptake, and its properties as a myocardial perfusion imaging agent, are significantly different from those of ^{201}Tl. For example, preliminary mechanistic studies have shown that, similarly to $[^{99m}Tc(TBIN)_6]^+$, the uptake of $[^{99m}Tc(MIBI)_6]^+$ by myocytes is not inhibited by ouabain and thus is independent of the Na^+/K^+ ATPase pump (*32*). Moreover, even though the MIBI complex does not undergo metabolism, it appears to be tightly bound to a cystosolic protein of low molecular weight (~10,000 D) by a mechanism which is sensitive to extreme conditions of hypoxia (*32*). This tight binding within myocytes appears to be the factor which underlies the most important clinical property of $[^{99m}Tc(MIBI)_6]^+$, i.e., the lack of significant myocardial washout or redistribution. The fact that $[^{99m}Tc(MIBI)_6]^+$ does not undergo significant myocardial washout or redistribution means that this agent possibly functions as a chemical microsphere. Scintigrams obtained even several hours after injection represent the distribution of myocardial blood flow at the time of injection (*33*). This is an especially valuable property when dealing with emergency or unstable patients; the agent can be injected at the time of admission, and then scintigraphic imaging can be accomplished after the patient has been treated and/or stabilized. However, the lack of redistribution also means that the traditional stress/rest study for differentiating ischemia from scar must be accomplished by means of two separate injections, rather than the single injection procedure used with ^{201}Tl (*34*). The properties of $[^{99m}Tc(MIBI)_6]^+$ also allow for other new myocardial imaging protocols. For instance, because of the superior nuclear properties of ^{99m}Tc, high quality tomographic (SPECT) images can be obtained in ~30 min. This time period is the same as is required for acquisition of the three classic planar images (anterior, LAO 45, LAO 70), but the information about regional myocardial blood flow that is obtained from SPECT is more complete and better delineates the extent and location of the lesions in three dimensional space. The advantages of this protocol could lead to the routine use of SPECT in cardiovascular nuclear medicine, and this in turn could have significant repercussions on the rotating gamma camera market. In addition, the properties of $[^{99m}Tc(MIBI)_6]^+$ allow for evaluation of left ventricular ejection fraction and wall motility (in a first pass or gated study) at the beginning of the session in which SPECT imaging will be performed.

It is clear that the isonitrile Tc(I) derivate $[^{99m}Tc(MIBI)_6]^+$, has opened up new possibilities and new vistas for cardiovascular nuclear medicine. At least 30 papers on the clinical or mechanistic aspects of this agent were presented at the June, 1988 meeting of the Society of Nuclear Medicine (*35*). However, it is also clear that this agent is just the first of what eventually will be a series of clinically useful cationic technetium complexes (*36,37*). The properties of $[^{99m}Tc(MIBI)_6]^+$ are not ideal (for instance, its myocardial extraction efficiency is less than that of ^{201}Tl), and it is anticipated that the next generation of cationic ^{99m}Tc agents will both improve on these properties, and will also incorporate properties that are optimized for specific clinical situations.

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