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EDITORIAL

Is There Additional Useful Information in the Myocardial Washout Characteristics of Teboroxime?

For as long as I can remember one of the central tenets of routine clinical nuclear medicine has been that the ideal radiopharmaceutical should remain in a fixed distribution in the target organ for a considerable period of time. This view, which arose as a result of limitations in the radiopharmaceuticals and imaging systems used has encouraged the neglect of the information that may be present in washout curves. In the past two or three years new technetium-based radiopharmaceuticals coupled with higher sensitivity imaging equipment have sharply reduced the necessary acquisition times. Recently introduced multi-headed devices, of which there are now some 140 installed, can collect sufficient data necessary to reconstruct a clinically useful myocardial image in 2 min or less *(1)*, and we now have developed the ability to use single-headed machines to do the same in 3–8 min (*2,3*). Unless we are operating in the "inject now—image later" scenario, we do not need a radiopharmaceutical with a prolonged retention time in the target organ. Our current abilities to acquire rapid sequential images should cause us to take another look at the washout data of radiopharmaceuticals. If we do have a radiopharmaceutical with a measurable washout from the target organ, can we make use of potential differences in washout rates caused by disease?

The article by Marshall et al. in this issue of the Journal (*4*) reports the use of an isolated perfused heart preparation to examine the effect of flow on extraction and washout of the myocardial imaging agents thallium and teboroxime. They have previously compared thallium and sestamibi (*5*). The use of the isolated perfused heart model is quite common in nuclear medicine, a number of investigations have already been published in which the characteristics of a variety of compounds have been measured and compared (*6–12*).

Thallium, teboroxime and sestamibi have very different pharmacology and pharmacokinetics (*13*) and it would be a mistake if we tried to fit them all into the same mold. In the case of thallium, and to a lesser extent sestamibi, there is significant input, 'redistribution,' to the myocardium from the remainder of the administered dose that is initially distributed throughout the body. Blood levels are not high but as each of these agents is stable in vivo, the blood can act as a conduit for the movement of activity between the body and the myocardium. This is not so for teboroxime whose extraction drops rapidly with time after injection (*14,15*). As teboroxime is closer to the ideal short, sharp input function than the other two agents, it may allow more data to be gleaned from the regional washout rates relative to thallium, whose washout is obscured by continued input, 'redistribution,' and sestamibi, which does not wash out to any appreciable extent. What can the isolated perfused heart model tell us about the kinetics of these processes compared to in vivo models or from clinical data?

The rapid washout of teboroxime prompts a number of questions. The first is: Does the rapid global washout of teboroxime cause an unacceptable loss of signal such that sufficient counts cannot be acquired? Obviously this is more appropriately answered using clinical data of which there is ample evidence to show that the "faster-than-we-are-used-to" washout of teboroxime does not prevent us from collecting high definition images using planar or SPECT techniques (*16*).

Second, Does teboroxime exhibit differential washout related to flow sufficient to cause loss of discrimination? For those who consider only the picture as the final output, the answer is already known in that the interpretation of the images obtained with teboroxime is just as accurate as that obtained from thallium images or from cardiac catheterization, etc. (*16*).

Third, Is there useful information in the rapid washout of teboroxime? If washout is flow-dependent ("differential washout"), then sequential images may provide relative regional

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washout rates that can be related directly or indirectly to flow. This is a question that Marshall and others are attempting to address using the isolated perfused heart model.

Most isolated perfused heart preparations do not recirculate the perfusate contains the radioactivity (contrary to the statement by Marshall, Leppo et al. (*10,11*) recirculate perfusate contains little or no radioactivity but switch to a single-pass mode when the bolus of radioactivity is administered.) Thus these washout rates reflect what Grunwald (*17*) termed the "intrinsic washout," which occurs in the absence of recirculation. As Marshall and others have pointed out, this may be very different to the in vivo situation where recirculation (multiple passes of the initial bolus), or redistribution (in the thallium sense) may occur. Nevertheless, the system can still provide a meaningful comparison of the various agents under standardized conditions. As stated above, of the three myocardial imaging agents, teboroxime alone has a rapid fall in extraction with time after injection and a rapid clearance from the blood, which makes its clinical input function more like the nonrecirculating input function common to most isolated perfused heart preparations.

In relative terms Marshall found that the washout of teboroxime over a 5–40-min time period postinjection was flow-dependent and slower than that of thallium. In contrast, Leppo et al. (*11*) found the washout of teboroxime was faster than that of thallium, but for an earlier 1–6.5-min time period. It has been reported that the washout of radioactivity from the heart after injection of teboroxime in vivo is at least biphasic (*18*), so one may assume that Marshall and Leppo are looking at the two different washout components. As the currently used clinical imaging protocols for teboroxime are completed within 8–10 min the influence of flow on the first component of teboroxime washout, i.e., the time scale studied by Leppo et al. (*11*), may be much more important.

Are these isolated perfused heart data directly applicable to the in vivo situation or does each agent require a different interpretation of the data to apply it to the in vivo situation? For thallium, the short input function used in vitro does not occur in vivo, so that the rapid washout of thallium seen in the isolated perfused heart data is obscured. In the case of teboroxime, Stewart et al. (*19*) have performed in vivo studies in dogs that allow these isolated perfused heart data and in vivo data to be rationalized. Stewart measured washout rates in vivo over a 0–30-min period after an intracoronary injection by using a detector positioned on the myocardium. These washout rates must be considered to be intrinsic washout rates as the intracoronary injection and high extraction do not allow for substantial recirculation of radioactivity, thus they are quite comparable to the isolated perfused heart data. Stewart found that 90% of the radioactivity was extracted and subsequently washed out in a biphasic manner. The first component had a flow-dependent washout half-life of the order of 2 min and the second a flow-independent half-life of about 25 min (Fig. 6). On the other hand, in a closed-chested preparation with an intravenous injection and a 0–30-min data acquisition period after injection, with recirculation, Stewart obtained monophasic washout rates. The washout rate was flow-dependent, since at normal flows it was 21 min while at the higher flows produced by dipyridamole infusion it was reduced to 13 min. This agrees with studies in swine, where a value of 10 min was obtained at elevated flows (*20*). The data also agree very well with clinical data where figures of 22 min at resting flow rates reducing to 15 min on exercise were obtained (*21*). The same large difference in the washout behavior was obtained under comparable conditions using thallium (*17*). Given the similarities in the input function between the isolated perfused heart preparation and the intracoronary injection, the large differences in washout between the intracoronary (2 + 20 min), and intravenous (21 or 13 min), routes of injection in the study by Stewart et al. (*19*) should caution against the over interpretation of isolated perfused heart kinetics. Of course one of the advantages of the isolated perfused heart preparation is that the washout rates can easily be obtained without contamination from surrounding tissue. This is a problem that has certainly plagued in vivo work because of the relatively low spatial and temporal resolution of the imaging systems. One way around this may be to perform the study using technetium-94m which is a positron emitter (*22*).

The data suggest that the washout of teboroxime in vitro and in vivo is flow-related and point to further imaging studies that should be done, for from the clinical point of view this conclusion is not useful unless it can be translated into an ability to detect, using external imaging, differences in regional washout rates (differential washout) that can be ascribed to regional flow differences in the myocardium. The fact that washout appears to be flow-related is not the end of the story for isolated perfused heart work either, as one must presume that washout will not be solely dependent

TABLE 1
Extraction Values for Various Agents

Thallium	Sestamibi	Teboroxime	Comments	Ref.
0.67	—	0.62	Rabbit/RBCs	4
0.83	0.55	—	Rabbit/RBCs	5
0.73	0.39	—	Rabbit/blood	10
0.57	—	0.72	Rabbit/blood	11
0.71	—	—	Rabbit/Buffer	9
0.30	0.15	0.96	Rat/Buffer	12
0.35	—	—	Rat/Buffer	6
0.35	—	—	Guinea pig/Buffer	6

upon flow but may also be affected by metabolic processes. Studies necessary to obtain some of this information in vivo have recently been completed (*20,23*) and it remains to be seen if the isolated perfused heart preparation can be used to generate similar data.

The article by Marshall also reports measurements of the extraction of thallium and teboroxime by the isolated perfused heart. (Extraction must be high to achieve fidelity between counts deposited and flow.) In addition to Marshall et al., other groups (*6,9–12*) have examined the extraction of the three flow agents using the isolated perfused heart model, the results of which are returned below in terms of average peak extraction (*4,5, 9,10,11,*) or extraction at a given flow rate (*6,12*).

As can be seen from Table 1, the extraction values of each of the agents are not entirely reproducible, even when the results emanate from the same laboratories (cf thallium references 4, 5 and 10, 11). Part of this variability is because there are different forms of the model (e.g., recirculating/single pass, whole blood-/ washed RBC-/ buffer-perfused, constant flow/constant pressure, rat/rabbit hearts, effluent counting/online counting, etc).

The average peak extraction for teboroxine of 0.62 that Marshall obtained does not agree with the 90% extraction obtained in vivo by Stewart et al. (*19*). Marshall et al. suggest that the in vitro indicator dilution data are purer than extractions determined in vivo by the 'B/A' method using external counting because the latter includes extravascular radioactivity, which is not strictly extracted, and radioactivity remaining in the vasculature. Stewart used data from 20 to 100 sec to determine the slope of the washout necessary to back-extrapolate the baseline ('B') to peak activity ('A'). Since this was after an intracoronary injection, there should be little contamination of this washout by vascular radioactivity, as even after an intravenous injection of teboroxime, >90% of the radioactivity clears with a half-life of 10–20 sec (*18*). In fact a fast washout phase, which is complete by 10 sec and is presumably vascular radioactivity, can be seen in Stewart's data (Fig. 3). The clinical imaging systems do not differentiate between radioactivity on or in a myocardial cell and extravascular extracellular radioactivity, which may be important as we try to perform compartmental modeling of teboroxime washout.

One must remember that the isolated perfused heart is exactly that and may behave differently to the heart in vivo. Thus, the data generated by the model are as pure as the model is distanced from the in vivo situation. Nevertheless, there is sufficient data to identify a trend, supported by the recent data obtained by Marshall et al., that the extraction of thallium and teboroxime are similar and are higher than sestamibi. This should translate into more of the injected dose in the heart at early times than for sestamibi, a result which seems to occur in humans soon after injection. More importantly, thallium and teboroxime should be more sensitive to flow changes than sestamibi. This has indeed been found in data from first-pass studies of all three compounds performed simultaneously in rats that show that thallium and teboroxime return flows closer to the line of identity than sestamibi (*14*).

If the results obtained with the isolated perfused heart model are physiologically distanced from the clinical situation, why is the model so popular? The model is popular because, as with most models (*24*), it reduces the complexity of the system down to a level that is understandable, yet can still be relevant to the in vivo situation. Thus, we can look at the affinity of a compound for the myocardium, (extraction), in the absence of recirculation; we can also look at the influence of blood components on the extraction. Second, we can change the flow rate or metabolic status of the preparation at will and to greater extremes than is possible in vivo and so exaggerate effects. Third, we can examine the influence of all these manipulations on the retention of compounds by the myocardium. Hopefully, by combining all this information with that from in vivo studies, we can better understand the physiology behind the pictures. We may even be able to use the information contained in regional washout curves to make a better clinical diagnosis.

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