LETTERS TO THE EDITOR

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Myocardial Thallium-201 Kinetics

To the Editor:

We believe that Grunwald et al., in their report of myocardial thallium kinetics in normal and ischemic myocardium, have inaccurately summarized the analysis and interpretation we made of the data we reported in Circulation in 1980. We also believe their assertion that the results of our previous studies1,2 are in total agreement with the results of theirs is not true and is based on erroneous impressions of what we actually reported in our paper.3

The principle observation made by Grunwald et al. concerning thallium kinetics in ischemic myocardium was that the intrinsic washout rate of the isotope was prolonged by a reduction in coronary artery perfusion pressure below 60 mm Hg. Data to support this conclusion were acquired with an external nuclear probe suspended 25 cm over the heart. The authors recognized that "systolic expansion of ischemic myocardium" could spuriously alter their myocardial washout curves, but they apparently could not avoid this problem. Although they state that the results of experiments conducted in five animals in whom simultaneous probe measurements and coronary sinus sampling was performed validate the use of the probe technique, this is obviously incorrect. These experiments only prove that when there is an absence of wall motion abnormalities, there is good agreement between the probe and direct sampling techniques. The authors apparently failed to compare the results of the direct sampling method with that of the probe under precisely those conditions with which they were so concerned — acute ischemia. It is hard to understand why they would think that the results of comparing the two methods under conditions of normal perfusion (when geometric factors are perhaps less of an issue) validate the probe method for use under conditions in which geometric factors are precisely at issue.

It is apparent from their figure 4 and table 1 that the myocardial halftime (t½) for thallium was markedly prolonged only at perfusion pressures close to those seen with complete coronary occlusion (i.e., when blood flow was severely reduced and when bulging of the anterior wall was very likely occurred). With distal coronary pressures ≥ 40 mm Hg, there appears to be no relation between perfusion pressure and myocardial t½. This is especially evident when t½ data from the five animals listed in table 1 are plotted on their figure 4. Finally, after release of a 15-minute coronary occlusion, a rapid increase in the washout slope (i.e., a more negative slope) was not observed (their fig. 3). If, as they maintain, the intrinsic t½ of thallium washout is flow-dependent, then reactive hyperemia after release of a 15-minute occlusion should have caused a marked decrease in the intrinsic t½ and not a return toward control, as they suggest. None of the postocclusion myocardial t½ data were presented for analysis. The authors failed to directly test their hypothesis that the intrinsic washout rate of thallium is directly related to flow when it would have been relatively easy to measure regional blood flow with a coronary flow probe.

The authors claim that we reported no change in coronary venous thallium concentration after coronary artery occlusion and that "this observation gave rise to the apparently contradictory statement that the myocardial washout rate was independent of blood flow." In fact, we did not report the values we obtained for AIV thallium concentration. However, we do have these data. Compared with the value just before occlusion (3.77 × 10⁴ ± 1.46 × 10⁴ μCi/ml [±σ]) that AIV thallium concentration increased to 4.88 × 10⁴ ± 2.11 × 10⁴ μCi/ml (p < 0.02) during the occlusion. In the first paragraph of our discussion we recognized in the limit (i.e., no flow) that washout would of course be prolonged. Under such circumstances, only physical decay of the isotope could remove it from the heart. In this respect, our analysis and that of Grunwald et al. are in accord, notwithstanding the important technical limitations of their study.

The authors also state that we observed no net change in thallium concentration in the occluded myocardial segment because "as the rate of input of thallium from systemic recirculation is decreased by coronary occlusion, the intrinsic washout rate of thallium is proportionately reduced." However, we were careful to produce acute ischemia only after net accumulation of thallium by the myocardium had ceased. Accordingly, the area rendered ischemic was in negative thallium balance before occlusion. Under such conditions and in face of declining levels of thallium in the blood, whatever isotope is recirculated to the heart effectively is not taken up by it anyway. Furthermore, the capacity for the cell to extract thallium from the blood is finite,4 and cells with normal perfusion at the time of thallium administration (as was the case in our study) attain their maximal concentration gradient compared with levels of isotope in the blood soon after administration of thallium.4,5 In these circumstances, the amount of isotope (μCi/min) emanating from the heart can be thought of as coming from two sources: the effective arterial pass-through component and the so-called intrinsic washout component contributed by the myocardium itself. Since we measured arterial input (actually pass-through after 20 minutes in our study) and venous output, it can be shown that the difference between the two (what we termed net loss) is really what the authors term the intrinsic output rate. Grunwald et al. ignored arterial recirculation of thallium in their study because it was negligible. We accounted for it in our study by subtracting it from the total quantity of isotope leaving the heart per unit time. Furthermore, contrary to what the authors claim, we did not define the intrinsic myocardial washout rate as the product of AIV thallium concentration (tAIV) and AIV flow (fAIV). Indeed, we never used the term "intrinsic washout rate." The product of tAIV and fAIV was defined by us as "thallium output by the myocardium (Tout)." We regret whatever confusion this choice of words may have caused. Nevertheless, since this term was introduced in the context of defining an expression for net thallium uptake/loss by the myocardium, it should be clear that we did not believe that our Tout term represented so-called intrinsic washout. Moreover, in our discussion we specifically focused on the amount of tracer (μCi/MIN) in excess of arterial input released by myocardial cells into the coronary circulation. This variable (i.e., net rate of thallium loss) is what we demonstrated to be unchanged when acute ischemia was produced at a time when the myocardium already was in negative thallium balance. Under conditions of negative thallium balance, our net myocardial clearance rate (fig. 4) is simply the derivative with respect to time of the authors' probe-determined myocardial time-activity curve (what they used to calculate their intrinsic washout rate). Accordingly, the curve they show in their figure 3, which purports to demonstrate very little change in myocardial thallium activity during coronary occlusion and hence a derivative approaching zero, is directly contradicted by our figure 4, which shows that the derivative is distinctly negative during occlusion and, more important, that it is unchanged compared with the preocclusion and succeeding (postocclusion) derivatives. Thus, the author's claim that the results of our studies and theirs are in total agreement simply is not true.

In conclusion, we did not claim then nor do we claim now to have written the last word on this subject. Nevertheless, we feel that our data were properly gathered (albeit with certain limitations recognized in our critique of methods) and logically analyzed. We stand by the results and our own interpretation of our data.

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References

The authors reply:
To the Editor:
In our paper, we assumed the validity of the data obtained by Gewirtz et al., as well as that of our own data, and showed that a basic model of compartmental exchange is in consistent agreement with both sets of data. Gewirtz et al. proposed a different conceptual model, which was inconsistent with our data. Hence, either their assumed model or our experimental data must be incorrect. After due consideration of the questions raised in their letter, we conclude that our data are correct.

The question of geometric changes of the ventricular configuration associated with ischemia is irrelevant to our experimental design. We used direct intracoronary injection of thallium, which results in a localized myocardial source that is free of extramyocardial background. The probe solid angle encompassed the entire myocardial region containing thallium, so the count rates were not dependent upon the myocardial wall thickness or chamber configuration, as would be the case with local sampling. Our experimental design was unusually straightforward: The problem of systemic recirculation was eliminated; there was no background to correct; and there were no solid angle, efficiency corrections or computations to be made from the data. The data are clear and the trend of the data is inescapable.

We did not report blood flow through the proximal coronary artery because only knowledge of perfusion at the capillary level would be meaningful. In ischemic states there is redistribution of capillary perfusion within the proximal arterial distribution, as well as variable and highly significant contribution to the capillary blood flow through collateral vessels. In this type of experiment, coronary flow probe measurements would be misleading. More recently, we have found a direct correlation between intrinsic myocardial thallium-201 washout and microsphere-determined regional blood flow. The suggestion by Gewirtz and colleagues that the myocardial clearance rate should abruptly change in response to transient reactive hyperemia in the blood compartment perhaps reflects a misunderstanding of the compartmental system and its expected behavior. This clearance rate reflects transport from the myocardial compartment into the blood compartment. The rate is slow, with a 1/2 of about 1 hour. We could not expect sudden changes in this clearance in response to transient hyperemia, which lasts a few minutes.

The fundamental issue of disagreement is this: In our experiments, recirculation was eliminated so that true myocardial washout could be measured. This washout was observed to occur more slowly in a state of severely reduced blood flow. The experiments reported by Gewirtz et al. were done in the presence of systemic recirculation, because thallium was administered intravenously. When they reduced myocardial blood flow, the net loss rate of thallium from the myocardium did not change. We proposed the explanation that the net loss rate is a balance between continuous uptake from systemic recirculation and intrinsic myocardial washout. In the Gewirtz experiment, the rate of uptake and washout were simultaneously reduced so that little change was observed in the net balance. With this model, both sets of data can be easily understood and accepted as valid. In contrast, Gewirtz et al. assumed that thallium, which recirculates through the heart via systemic recirculation, is not extracted, and this assumption is inconsistent with the data. Rather than alter their previous concepts, they have brought into question the validity of the data. We believe that their assumption that recirculating thallium is not extracted by the myocardium is incorrect, and that the data are valid. Several arguments were presented in support of their assumption, but on mathematically rigorous examination, they are invalid, as indicated below.

Gewirtz et al. first offer new values for the AIV concentration of 3.77 and 4.88 X 10¹⁸ before and after occlusion. These numbers seem reasonable to us. The point we tried to make in our paper was that if the intracellular efflux remained constant as the arterial flow was reduced by a factor of 2 or 3 by arterial occlusion, then the AIV concentration would necessarily increase by a factor of 2 or 3. The value cited by Gewirtz et al. did not increase to anywhere near that amount (the two numbers differ by 1 SD), and that observation is entirely consistent with our data and kinetic interpretation.

They have also offered an interesting mathematical "proof" that their data and ours are contradictory. To do this, as mentioned previously, they first assume that no arterial thallium is extracted by the myocardium, so that the venous effluent consists of the "pass-through" thallium from the arterial perfusion plus the additional thallium contributed from the intracellular compartment. With this assumption, the difference between "arterial input" and "venous output" would represent only the thallium from the intracellular compartment and could be proportional to the derivative of the data we obtained. These data, they correctly point out, are not proportional to the derivative of our data and hence they conclude that their data and our data are in fundamental disagreement. This exercise actually demonstrates that the assumption of no myocardial extraction from recirculation is incorrect. They have assumed the truth of their postulate that no myocardial extraction occurs during the time period of their measurements, and have demonstrated that this assumption leads to a logical conflict with the data. This is a classic technique in elementary geometry, which logically establishes the falsehood of the initial assumption. With our assumption that arterial thallium is continuously extracted, the arteriovenous difference is not proportional to the derivative of our data and no logical inconsistency results. To further support their assumption, they stated that myocardial cells have a finite capacity to extract thallium and so presumably must become saturated with thallium after initial extraction. This seems absurd. Thallium is toxic, and the dose injected is several orders of magnitude less than the amount required to produce physiologic responses. Saturation of binding sites would be demonstrated only with pharmacologic doses.

Finally, the nonspecific comment in their letter concerning concentration gradients was presumably meant to imply that cellular extraction does not occur against a concentration gradient. If that is the implication, it is at odds with all data concerning the relative blood/myocardial concentrations or delayed accumulation of thallium. If that was not the implication, then it has no relevance to the argument.

In summary, the arguments and new data presented by Gewirtz et al. are not only consistent with, but also substantiate, our model. Further experimental work is under way that will bear on the validity of our conceptual hypotheses. As scientific investigators, we must always stand ready to alter our conceptual framework if new data lead to that requirement.

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