Measurement of Total Myocardial Blood Flow in Dogs with $^{45}$K and the Scintillation Camera

By Yosushi Ishii, William J. MacIntyre, Walter H. Pritchord, and Richard W. Eckstein

ABSTRACT

To establish an innocuous method for evaluating myocardial ischemia, a technique was devised utilizing a scintillation camera to record the distribution of $^{45}$K in the myocardium following an intravenous injection of the tracer. The objective was achieved by determining with the camera the fraction of the total amount of injected material deposited in the myocardium and calculating the total myocardial blood flow as a fraction of cardiac output according to the indicator fractionation principle. Following in vivo measurements in dogs, the entire heart was excised, compared with an aliquot of the injected dose as a standard, and assayed by a well scintillation counter. Reasonable agreement was achieved between estimations determined in vivo and those determined in vitro. Because of difficulties in ascertaining the heart border on the scans, a deconvolution program which used a digital computer was applied to the $40 \times 40$ matrix of digitized scan data to sharpen the transition between counting levels and improve the distributional image of $^{45}$K deposition in the myocardium.

KEY WORDS: indicator fractionation principle, cardiac output, deconvolution program, digital computer, radioisotope scintigraphy.

Because of the high incidence of coronary heart disease and the lack of innocuous methods for evaluating myocardial ischemia or infarction directly, a number of techniques for measuring myocardial blood flow with external counting devices that monitor the radioactivity in the myocardium after a single intravenous injection of $^{42}$K, $^{86}$Rb (1, 2), or $^{85}$Rb (3, 4), have been proposed. These methods, originally suggested by Sapirstein (5), are based on the indicator fractionation principle which postulates that the uptake of tracer by heart muscle equals the fraction of cardiac output perfusing the myocardium during the early stage of recirculation following an intravenous bolus injection of tracer. The principle assumes that the extraction ratio of the myocardium during this stage does not differ significantly from that of the total body. Knowing myocardial uptake, total amount of injected tracer, and cardiac output allows myocardial blood flow to be calculated.

Since individual variability in the depth and the size of the heart precludes an absolute estimate of the myocardial uptake of tracer in relation to the total injected dose in terms of external counting, the determination of absolute flow is quite difficult. Efforts to attain relative independence from the uncertainties of geometry have been made using a coincidence counting system (6) or a twin-probe counting system (7). Nevertheless, either a complex phantom or a system of calibration is required, and the complete delineation of the myocardial region separated from the surrounding regions may still not be attained.

The scintillation camera seems well-suited for this measurement. During the initial circulation of the tracer, radioactivity passing through the central circulatory system represents the equivalence in counting rate of the total injected dose and thus serves as a calibration factor relating the number of microcuries injected to the counting rate observed. During the later stages of circulation, radioactivity deposited in the myocardium is subjected to approximately the same geometrical factors as was radioactivity in the initial flow. Therefore, the fraction of the injected dose localized in the...
myocardium is equal to the ratio of the counting rate recorded at this later time to the peak counting rate recorded from the total dose directly. In addition, since the scintillation camera records spatial information about the deposition of radioactivity, it may be possible not only to estimate absolute myocardial blood flow but also to visualize regional flow distribution.

A similar type of functional imaging of the myocardium has been previously reported by Love et al. (8); they used a rectilinear scanner and $^{42}$K or $^{85}$Rb. These tracers are not suited to application of the scintillation camera because of their high-energy gamma-ray emission. With the availability of $^{42}$K, which has lower energy characteristics and a short half-life, camera visualization of the myocardium is now practical (9).

The primary purpose of the present study was (1) to demonstrate the feasibility of using $^{42}$K with the scintillation camera for measuring total myocardial blood flow and imaging regional distribution and (2) to compare the values of myocardial blood flow obtained from the in vivo method using the scintillation camera with the values obtained from an in vitro method using well-counter assay of heart samples excised immediately after the experiment.

**Theoretical Background**

Following a single intravenous injection, the tracer, $^{42}$KCl, is homogeneously mixed with arterial blood within the heart chambers without appreciable loss during passage through the pulmonary vascular bed and is distributed, therefore, to the peripheral organs in accordance with blood flow distribution. Thus, the uptake of tracer by the myocardium during a certain period of initial circulation, $U_M(t)$, can be described as the product of the myocardial blood flow, $F_M$, the integrated concentration of the tracer in the arterial blood, $\int_0^{t_1} C_a(t) dt$, and the extraction ratio of the myocardium for the tracer, $E_M$. A similar expression can be employed to describe the uptake of tracer by the remainder of the body circulation. Namely,

$$U_M(t) = F_M \cdot E_M \cdot \int_0^{t_1} C_a(t) dt,$$

and,

$$U_B(t) = F_B \cdot E_B \cdot \int_0^{t_1} C_a(t) dt,$$

where the subscript $B$ refers to body circulation.

The extraction ratio of the myocardium is essentially identical with that of the whole body (5, 10) for at least 3 minutes after injection of the tracer bolus. Furthermore, the distribution pattern of the tracer in the myocardium is believed to be unchanged for at least 10 minutes following injection (11) and to represent the perfusion pattern of myocardial blood flow. Hence, at a certain time, $t$, during this period, the ratio of uptake by the myocardium, $U_M(t)$, to that by the remainder of the body circulation $U_B(t)$, is the same as the myocardium-body circulation ratio for blood flow or proportional to the fractional distribution of cardiac output, $F$. Thus,

$$\frac{U_M(t)}{U_B(t)} = \frac{F_M}{F_B}.$$  

$$\frac{U_M(t)}{[U_M(t) + U_B(t)]} = \frac{F_M}{F_B}.$$  

Observing this process with an external detection system placed over the precordium and simultaneously collecting arterial blood samples shows that...
the tracer in the blood diffuses rapidly into the tissue and accumulates there, resulting in the external counting rate over the precordium reaching a plateau as early as 2 minutes after injection (Fig. 1). During the plateau, the increase in myocardial uptake is compensated for by a decrease in intracavitary blood in the heart. It might then be postulated that with increasing time, when the tracer has nearly completely entered the tissue from the bloodstream, the precordial counting rate would approximate the counting rate for an equivalent amount of tracer taken up by myocardium at an infinite time. In addition, the amount of tracer taken up by the whole body, \( U_M(t) \), would correspond in this case to the total amount of injected tracer, \( I \). Introducing these relations into Eq. 5 permits the myocardial blood flow to be expressed as

\[
F_M = \frac{(U_M(I)/I) \cdot F}{t}
\]

when \( t \) approaches infinity. Thus if the cardiac output, \( F \), is already known, the myocardial blood flow can be calculated merely by determining the amount of the tracer in the myocardium in terms of the response of the external detection system and measuring the amount of the total injected dose in the same way.

**Methods**

A Nuclear Chicago Pho-Gamma II scintillation camera was used for the in vivo measurements; the field of view of the camera was large enough to encompass the heart, the lungs, and a major portion of the liver. Healthy mongrel dogs weighing 15–30 kg were anesthetized with sodium pentobarbital and positioned under the scintillation camera in the left anterior oblique position. A rotation to the right side of 30° was made so that the camera face was perpendicular to the plane of the ventricular septum, thus separating the right heart from the left. An arteriovenous fistula was established between the femoral artery and the femoral vein; the connecting tubing was passed through a side-wall scintillation counter for continuous monitoring of radioactivity in circulating blood during the in vivo measurements with the camera.

With the dog in place under the camera, a dose of \(^{43}\)KCl solution ranging between 0.2 and 1.0 mc was rapidly injected as a bolus into a peripheral vein. The distributions of radioactivity were accumulated by an RIDL 1600 channel analyzer as a digitized 40 × 40 matrix in a pattern corresponding to the isotope location within the body. Hence, each element was represented spatially as a square with sides approximately 3 inch in length.

As the tracer bolus initially passed through the central circulatory system, the rapidly changing sequence of images was recorded at 0.9-second intervals during the first minute after the injection. Similar matrices were then recorded every 60 seconds for the next 10–20 minutes to obtain the slowly changing images of the tracer which deposited peripherally in various organs according to the fractional organ blood flow of the cardiac output. Both the rapid-phase and the slow-phase images in the form of numerical matrices were transferred to an Ampex TM-7291 digital tape recorder for processing by an IBM 360/40 digital computer. The complete details of the data recording system have been described in previous papers (18, 13).

The initial dilution curve and the subsequent decrease in radioactivity in the arterial blood were recorded from the blood passing through the well counter via the arteriovenous shunt tubing. After the in vivo measurements, a known aliquot of the injected dose was then passed through the tube to calibrate the dilution curve and to calculate the cardiac output.

After the in vivo measurements by the camera were completed, the dogs were immediately killed by bleeding through the arteriovenous fistula, and the entire heart was excised from each dog. With the excised heart in place under the camera, the counting rate from the heart was compared with that from an aliquot of the injected dose placed in a phantom at known volume. Finally the total content of \(^{43}\)K in the myocardium was assayed in multiple samples by a well scintillation counter and compared with that in the aliquot of the injected dose. No attempt was made at this time to identify variations in regional flow by isolating specific segments of the myocardium.

Because of the high energy of the gamma rays of \(^{43}\)K, considerable penetration of the septa was observed with the conventional 3-inch thick scintillation camera collimator. The first three determinations were made with a 3-inch collimator, but in all subsequent measurements a 4-inch collimator was used. Even with this improvement, considerable scatter and penetration were noted and tended to obscure the myocardium from surrounding organs. For this reason a deconvolution program by iteration, as proposed by Nagai et al. (14, 15), was used in the complete processing to more closely approximate the original unscattered distribution.

**Calculations and Data Handling**

According to the indicator fractionation principle as stated in Eq. 6, the total myocardial blood flow was calculated by multiplying the cardiac output, \( F \), by the ratio of the myocardial uptake, \( U_M \), to the entire injected dose, \( I \). For the in vivo measurements by the camera, this objective was achieved by using each heart as its own standard or phantom; the response of the camera to the total injected dose was measured while the dose was contained within the heart during its first passage through the central circulation. This value was then compared with the response of the camera to the radioactive material in the myocardium alone by delineating the outline of the heart border on the scintillation camera field and integrating the counting rate recorded from that region.

The total dose, \( I \), can be approximated in terms of counting rate per minute by observation of the plateau value (Fig. 2) exhibited by the camera during the
interval in which all of the injected material is in the field of view of the camera but none has yet left the thoracic aorta. The response of the camera in terms of total counts collected during the 0.6-second collection time of each frame can be averaged over several frames during the first passage—the rapid phase—and converted to the units of counts per minute. The result of summing the total activity recorded by the camera during the first 9 seconds shown in the determination in Figure 2 is illustrated by the matrix in Figure 3 with the various contour lines delineating percent of maximum count.

To determine the uptake by the myocardium, the total counts falling within the region of the heart borders as delineated on the camera recording were summed for a specific period of time during the slow phase. The onset and the duration of this period varied, depending on the time of passage of the material through the central circulatory system and the clearance of the activity from the circulating blood. This summation was usually accomplished by integrating the frames from the third to the seventh minute after injection. Since there was no deposition of the tracer through the pulmonary circulation, the borders of the heart were fairly obvious on the matrix during this period, except on the lower border where some uncertainty was caused by the proximity of the high activity in the liver. The summation of the myocardial counting rate from the third through the seventh minute following injection is shown by the matrix of Figure 4A. According to the indicator fractionation principle, this image of the matrix approximately corresponds to the distribution pattern of regional blood flow. In spite of the difficult delineation between heart and liver, superposition of the rapid-phase contour line (40% level) on the slow phase as shown in Figure 4B allowed this border to be reasonably well delineated. Three-dimensional views (12, 16) of this matrix from both the right and the left sides are illustrated in Figure 5. This figure demonstrates that the maximum activity was in the liver but that the deposition in the myocardium was still readily discernible. As would be expected, the deposition in the right heart was obviously lower than that in the left heart.

Results

In the present study, the total myocardial blood flow was calculated as the fractional blood flow of the cardiac output, which was determined as the ratio of the myocardial uptake of $^{43}$K to the total injected dose of $^{43}$K in terms of the various measuring conditions: (1) in vitro measurement by a well scintillation counter, (2) in vitro measurement by a scintillation camera, (3) in vivo measurement by a scintillation camera yielding unprocessed matrices, and (4) in vivo measurement by a scintillation camera yielding deconvoluted matrices (Table 1).

The mean myocardial blood flow value for the in vitro measurements by well counter was $4.6 \pm 0.6\%$ of the cardiac output and that for the scintillation camera was $5.5 \pm 0.3\%$. The mean myocardial blood flow value for the in vivo measurements for the unprocessed matrices was $6.3 \pm 0.6\%$ of the cardiac output and that for the deconvoluted matrices was $5.9 \pm 0.8\%$. The in vitro measurements by the well counter would be expected to show the lowest absolute value and also to be the most reliable, since only the activity actually in the myocardium was measured. The in vivo measurement for the deconvoluted matrices resulted in a smaller value than that for the unprocessed matrices and approached the in vitro value, which indicates that the activity due to surrounding tissue had been largely compensated for by the computer processing.

In the last four experiments, the cardiac outputs were determined and the absolute myocardial blood flow was calculated. The mean cardiac output was $3.08 \pm 0.35$ liters/min. The mean absolute myocardial blood flow was calculated to be $150 \pm 23$ ml/min by the in vitro data and $180 \pm 35$ ml/min by the in vivo data. In vivo value of myocardial blood flow was $21\%$ higher than the in vitro value with a little scatter amounting to $\pm 5\%$ SD.

In general, a reasonable agreement was achieved between the estimation of the fractional dose of tracer in the myocardium determined by in vivo methods and the measurement of the myocardial uptake in the excised heart. Furthermore, the average fractional value of cardiac output determined by the in vivo method appeared to be well within accepted values determined by other methods (17, 18).
### TABLE 1

**Ratio of Myocardial Blood Flow to Cardiac Output**

<table>
<thead>
<tr>
<th>Dog</th>
<th>In vitro measurement</th>
<th>In vivo measurement by scintillation camera</th>
<th>Cardiac output (liters/min)</th>
<th>Ratio: deconvolved matrices to well counter data (× 100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well counter (%)</td>
<td>Scintillation camera (%)</td>
<td>Unprocessed matrices (%)</td>
<td>Deconvolved matrices (%)</td>
</tr>
<tr>
<td>1*</td>
<td>4.2</td>
<td>5.4</td>
<td>6.5</td>
<td>4.6</td>
</tr>
<tr>
<td>2*</td>
<td>4.2</td>
<td>5.4</td>
<td>6.5</td>
<td>4.6</td>
</tr>
<tr>
<td>3*</td>
<td>3.7</td>
<td>5.4</td>
<td>6.5</td>
<td>4.6</td>
</tr>
<tr>
<td>4</td>
<td>5.1</td>
<td>5.8</td>
<td>6.5</td>
<td>4.6</td>
</tr>
<tr>
<td>5</td>
<td>4.2</td>
<td>5.0</td>
<td>6.8</td>
<td>6.2</td>
</tr>
<tr>
<td>6</td>
<td>5.0</td>
<td>5.4</td>
<td>6.8</td>
<td>6.2</td>
</tr>
<tr>
<td>7</td>
<td>5.3</td>
<td>5.8</td>
<td>7.3</td>
<td>6.1</td>
</tr>
<tr>
<td>8</td>
<td>4.9</td>
<td>5.8</td>
<td>6.3</td>
<td>6.3</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td>6.3 ± 0.3</td>
<td>5.9 ± 0.8</td>
</tr>
</tbody>
</table>

*Scintillation camera was equipped with a 3-inch collimator for the measurements in these dogs.

### Discussion

The two basic assumptions of this application of the Sapirstein method are, first, that the extraction ratio for the heart is equal to the extraction ratio for the whole body and, second, that the amount of indicator taken up by the whole body is equal to the amount of indicator injected. If these assumptions are valid, then the fraction of the injected indicator, such as potassium or rubidium, taken up by the myocardium early after injection equals the fraction of the cardiac output perfusing the myocardium (Eq. 6).

The validity of the first assumption in rats and dogs was originally shown by Sapirstein (5); he concluded that the extraction ratio for the heart is the same as that for the whole body during the measurement. Since the total body uptake and the organ uptake as utilized by Sapirstein cannot be determined by direct means in man, other investigators (7, 10) have shown that the concentration of the indicator in the mixed venous blood is in effect equivalent to the integrated concentration in the coronary sinus, so that recirculation of the indicator during this time would not cause significant redistribution of the indicator either in the heart or the body.

There may still be some circumstances in which this equality does not hold or holds for a limited time only. In that case the accumulation of the \(^{42}\text{K}\) deposition should be recorded only during that period of time when the extraction ratios are equal. If this time is quite short, statistical limitations may limit the accuracy of measurement. In addition measurement in this early phase would necessitate correction for blood activity in the heart chambers as discussed by Donato et al. (1, 7).

The criterion of the second assumption—complete uptake—is, of course, never met. The relatively small correction of precordial activity due to radioactivity in the blood (Fig. 1), however, indicates that this phenomenon accounts for only a small error if measurement is made after 2-3 minutes for relatively complete blood clearance of the radioactive material.

It should be pointed out that satisfying this second assumption may be, in some instances, in conflict with satisfying the first assumption. Because of the first assumption, the measurement should be made within the first 3 minutes when extraction of potassium by the myocardium and the whole body is believed to be equal. Therefore, it cannot be assumed that these techniques can be extrapolated directly to clinical measurements. It may be necessary, especially with abnormal subjects, to restrict the measurement to the time (3 minutes or less) when extraction ratios of \(^{42}\text{K}\) for the myocardium and the whole body are equal and then to use other relationships to correlate injected dose with body uptake or to correct for intracavitary radioactivity as referred to above.

Concerning transport into the myocardial muscle cell, it has been suggested that the limiting barrier to exchange of radiopotassium is at the cell wall and that a relatively passive barrier exists at the capillary wall (19, 20). Hence the problem of whether tracer clearance truly reflects quantitative change in blood flow needs to be scrutinized. Experimentally, Moir (21) has found that myocardial blood flow, according to the rubidium-clearance method, underestimates actual flow, for example, at a higher flow rate. Meanwhile Friedman (22) has pointed out that the extraction ratio...
of the tracer is inversely related to blood flow. To account for this finding, he has proposed a system consisting of nutritive and shunt pathways in parallel. It is assumed that flow-limited exchange of
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The tracer with all compartments occurs in the nutritive pathways and that no exchange occurs along the shunt pathways. Although the degree to which the potassium-uptake method is a measure of flow under various circumstances is at present unknown, it might safely be concluded that the present measurement reflects that portion of total coronary blood flow involved in the nutritional fraction of heart muscle, namely nutritional blood flow.

The justification for summatng matrices during the third to the seventh minute after injection for the myocardial uptake requires some discussion. The fact that there is an early significant intracavitary contribution to the external counting rate renders the measurement of exact myocardial uptake difficult. This fact may partially account for the observation that the in vivo values were consistently higher than the in vitro values. Correction for this effect could be made with a nondiffusible tracer such as 99mTc albumin utilizing the technique of Donato et al. (1). This material would also aid in the identification of the heart border, since individual chambers can be actually identified (13). However, when comparing a series of matrix frames of the slow phase, the recorded counts within the heart border appear to reach a steady state as early as 2 minutes. This steady state is actually the result of a declining intracavitary count rate and a concomitant continued myocardial uptake resulting from continuing arterial recirculation and myocardial extraction. Considering these reciprocal effects, both of blood and myocardium, on the total average counting rate made during the measurement indicates that the intracavitary effect might not be serious and that the contribution from the surrounding tissue might be much more important.

The surrounding tissues included in the field of the view of the camera are essentially lung, skeletal muscle, and liver. Since the transcapillary diffusion of tracer across the pulmonary capillaries is negligible and the fractional flow of cardiac output to the bronchial circulation or that of related skeletal muscle is quite small, the contribution of lung and skeletal muscle should not be serious. As to the liver, however, since its flow per gram is of the order of myocardial flow, the extent of its inclusion in the counting area might well result in an appreciable error.

With scintillation probes, the contribution from unwanted areas, such as the liver, has been excluded by collimation, but individual variability in terms of the region of interest poses a difficulty in accurately delineating the heart border from the liver. However, since the scintillation camera is able to visualize quite well the uptake of radiopotassium by the myocardium, only those regions identified as being within the heart borders during the rapid phase were selected to be summated.

Another advantageous aspect of the camera method is the ability to attain independence from the individual geometrical variability in terms of depth and volume. To compare the myocardial uptake with the total injected dose with the same geometry, isoefficiency counting conditions, such as those attained by using positron coincidence counting (6) or a twin counting system (7), are necessary. However, with the present method of using the scintillation camera, measurement of the injected dose while it is within the heart chambers means that absorption, scatter, and volume corrections are almost exactly duplicated for the determination of the ratio of injected dose to myocardial uptake.

It is the problem of heart border identification that has provided the greatest uncertainty and to which considerable effort has been applied. With the conventional 3-inch collimator, visualization of the heart border was quite indefinite due to both septal penetration and scatter. Although the longer collimator of 4½ inches improved the situation, it was still necessary, as shown in Table 1, to correct for the spread function of the collimator by deconvolution of the matrices. In addition this correction is increasingly important when the energy of the radionuclide is such that the point-spread function of the detector exhibits a long trailing edge.

FIGURE 3
A: Summation of counts in each element of the 40 X 40 matrix collected by the camera during 9 seconds of the rapid phase of 13K dilution obtained by integrating from frame 3 through frame 9 shown in Figure 2. B: Contour lines are expressed as percents in relation to maximum counts in matrix. Because of low counts collected in A, the 40% contour has been selected as best delineating the limits of the heart border in this example.
SLOW PHASE

K43. SLOW PHASE 4 1/2 IN. COLLIMATION.

SYMBOLS REPRESENT CONTOURS AT LEVEL LISTED

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Three-dimensional view of the matrix from Figure 4A from two angles. The x and y dimensions coincide with the spatial distribution of the 40 x 40 matrix. The height of the z-axis is proportional to the number of counts accumulated in that matrix element. Orientation of the top drawing is that of the observer viewing the matrix of Figure 4 from the lower right corner projecting toward the upper left. The dotted and the shaded areas show the region falling within the solid contour line in Figure 4B and thus represent the elements corresponding to the myocardium. The elements corresponding to the right heart are dotted, and the left heart elements are shaded. The higher peaks in extracardiac regions correspond to the elements in the camera field over the liver. The highest elements occur at the top edge of the camera field and probably represent kidney deposition. The bottom view shows the projection from the lower left of the matrix in Figure 4 looking toward the upper right. This orientation enables a greater separation to be seen between the myocardial deposition and the liver deposition.

Actually, integration of the selected area on the unprocessed scans showed an abnormally high accumulation, presumably due to the high deposition of material in the liver which contributed by penetration and scatter a considerable counting rate to the area of the myocardium. Using the iterative program proposed by Nagai et al. (14, 15) and a point-spread function of 40K for the scintillation camera caused the counting rate within the heart borders to decrease consistently (Table 1), and the rate fell within a reasonable range of agreement compared with values from the in vitro assay of myocardial content.

As suggested earlier, this methodology lends itself very well to measurement of regional differences as well as to determination of an integrated estimation for total myocardial blood flow. Numerical values of matrices, contour lines, and three-dimensional displays all reflect differences in deposition. For example, Figures 4 and 5 show that the counting rate in the right heart is lower than that in the left. Although the ultimate size of the minimum region that can be identified has not yet been determined, it must be expected that when such regions are visualized the variations in deposition may be due to either less flow per unit mass (e.g., myocardial ischemia) or less mass (e.g., necrosis of the myocardium).

Even with the several limitations described above, the feasibility of determining alterations in regional myocardial blood flow by a procedure no more traumatic than a peripheral vein injection seems to well merit further investigation especially for clinical evaluation of coronary heart disease.

Acknowledgment

This work would not have been possible without the help of Dr. J. K. Poggenburg and the Oak Ridge National Laboratories who provided us with the 40K. The iteration program for deconvolution was written by Mr. Thomas S. Houser, who together with Miss Elaine Rohr, Mr. William P. Drescher, and Mr. S. Tucker Taft performed the computer analysis. Dr. Nobuo Ohya, Mr. John Dattilo, Mrs. Jacqueline Rutkowski, and Mr. Richard L. Williams aided technically in the animal experimentation.

References


Correction
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The twelfth line from the bottom of the left column should read preliminary results (70). In addition to the
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