Alterations in Regional Pulmonary Blood Flow in Mitral Valve Disease Studied by Radioisotope Scanning

A Simple Nontraumatic Technique for Estimation of Left Atrial Pressure

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A VARIETY of techniques for the determination of the pattern of distribution of pulmonary arterial blood flow are now available. These include pulmonary arteriography,1 differential bronchospirometry,2 and methods employing the external detection of either inhaled or injected radioactive gases.3,4 While considerable useful information has been obtained from the application of these techniques, their widespread clinical use has been limited by either the discomfort and potential hazards of the procedure, or the complex nature of the equipment which is required. The recent development of an external scintillation scanning technique following the intravenous administration of macroaggregates of 131I-labeled human serum albumin (131I-MAA)5-8 affords a new approach to the precise delineation of the pattern of distribution of pulmonary arterial blood flow. This method is technically simple, rapid, painless, without risk, reproducible, and easily applicable to large numbers of patients.

It has become clear from physiological, radiological, and pathological studies that in normal erect subjects blood flow is greater at the dependent zones of the lungs than at the apices and that this pattern may be reversed in patients with mitral valve disease.9,10 The object of the present investigation was to determine whether the external scanning of intravenously injected 131I-MAA might detect the presence or absence of hemodynamically significant mitral valve disease and to ascertain whether the magnitude of the shift of blood toward the apices provides an estimate of the severity of the disease.

Methods

Forty-eight patients ranging in age from 13 to 60 years and averaging 34 years were studied. Thirteen subjects had no cardiovascular disease. Fifteen patients had pure mitral stenosis, five had pure mitral regurgitation, and 15 had combined mitral stenosis and regurgitation. All but one of these 35 patients had rheumatic mitral valvular disease while one had congenital mitral regurgitation. Combined right heart and transseptal left heart catheterizations were carried out with the patients in the supine position in a basal, postabsorptive state within 72 hours of the lung scan. With the possible exception of the patient to be discussed specifically, no detectable change in the patients' clinical conditions occurred during the interval between the two studies.

Pulmonary arterial and left atrial pressures were measured consecutively. Cardiac output was determined either by the Fick method or the indicator-dilution technique, with injection of indocyanine dye into the central circulation.11 Pulmonary vascular resistance (PVR) in dynes sec cm⁻⁵ was calculated from the formula:

\[
PVR = \frac{PAm - LAm \times 1332}{PBF},
\]

where: PAm = pulmonary arterial mean pressure in mm Hg; LAm = left atrial mean pressure in mm Hg; and PBF = pulmonary blood flow in ml/sec.

Scanning Techniques

Thyroidal uptake of 131I was blocked with Lugol's solution for 10 days, starting the evening prior to the injection of 131I-MAA. The latter

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had a concentration of 0.10% and relatively high specific activity (up to 1.5 mc/mg) providing statistically valid count rates averaging approximately 8,000 cpm above background. A dose of 0.1 to 0.5 mg (100 to 300 µc) was injected intravenously during a 5-minute period of quiet breathing in the posture selected for study. The subjects maintained this posture for 5 minutes before the beginning and after the completion of the injection. Every patient was in the erect posture during injections. A number of the patients also had lung scans following injection of \(^{131}I\)-MAA while supine, or tilted head down at an angle of 150°.

The scanning was performed within 1 hour of the \(^{131}I\)-MAA injection with a conventional radioisotope scanner. During the scanning the patients lay prone with the detector mounted above them. A multichannel, 163-hole collimator with a 4%-inch focal point, designed to have a ½-inch wide 50% isoresponse contour at 6%-inch depth, was employed (fig. 1). Horizontal rectilinear scanning was performed at a constant speed of 48 cm/min producing a stepwise sequence of parallel strips spaced 2/18 inch or 3/16 inch apart on photoset and tapper records (fig. 2A). In selected subjects longitudinal scanning over the right lung was also performed.

Under all circumstances the face of the detector was kept equidistant from the skin as it moved down the patient’s back by raising and lowering the probe to the contour of the back, to ensure a constant depth of resolution within the lung (fig. 1). Radiopaque markers placed on the vertebral spinous processes and over the scapula permitted precise delineation of lung apex and base on the photoscan by determining the positions of these markers on a parallax corrected chest roentgenogram exposed in the same projection as the scan (fig. 3).

Three methods for displaying and recording the output of the scintillation detector were employed: (1) the familiar photoscan provided a visual image of the relative distribution of pulmonary blood flow (figs. 2A top center and 3 center); (2) the output of the detector was also led to a ratemeter which provided continuous graphic recording of radioactivity and was used both with longitudinal and horizontal movement of the detector (fig. 2A top right). With horizontal motion the ratemeter record consisted of a series of spikes as the detector moved from the lateral thoracic wall, a region of low radioactivity, across the lung, where the radioactivity was high, to the spine, another region of low activity and across the other lung. The counting rate profiles can be quantified by planimetric integration of the area beneath the individual peaks. When the detector was moved in a longitudinal direction, the relative height of the ratemeter deflection provided a profile of variations of radioactivity within a vertical segment of lung tissue, from apex to base (see fig. 7). During longitudinal scanning the positions of the reference markers were transcribed to the ratemeter chart record as the center of the detector passed the reference markers on the subject’s back, a maneuver which permitted identification of anatomic landmarks on the ratemeter record. (3) The line-by-line rectilinear sequence was recorded as counts on a digital printer connected to the spectrometer. A system of microswitches attached to the traversing mechanism of the detector was designed to permit the separate selective digital recording of radioactivity from each lung in a line-by-line sequence (fig. 2A top left and B). Actuators placed in the path of the microswitches set the lateral limits of the counting field, ensured that counts from each lung field were recorded from equally spaced distances as the detector moved at constant speed, and permitted background counts arising from the middle mediastinum to be disregarded (fig. 2B). The numerical display of the line-by-line radioactivity was related to the chest roentgenogram by identifying the line in question on the photoscan.

The radioactivity in particular segments of the lung, reflecting the relative contents of \(^{131}I\)-MAA and thus the distribution of pulmonary arterial blood flow, can be expressed as a percentage.
MITRAL VALVE DISEASE

Figure 2
Diagrammatic representation of the detection and recording system. (A) The rectilinear path of the detector is outlined on the back of the patient. The output of the detector provides three types of information. The digital record (top left) displays the number of counts from each horizontal sweep of the detector. The lung scan (top center) provides a visual image of the relative distribution of pulmonary blood flow. A continuous deflection (top right) is recorded on the ratemeter strip chart during longitudinal scanning. The relative height of the deflection is determined by the amount of radioactivity seen by the detector as it moves from apex to base. Also, counting rate profiles are recorded from each lung during rectilinear scanning. (B) Block diagram of the system employed. The adjustable actuators and the system of microswitches attached to the traversing rod of the detector were designed to print selectively the counts from each lung (arising from beneath the areas corresponding to the darker portions of the ruled horizontal lines on the patient’s back).

Figure 3
In order to delimit anatomic boundaries, radiopaque markers are placed on the back of the patient and their positions are transcribed to the photoscan (center) and exposed on the chest roentgenogram (right). As described in the text, the lungs are divided longitudinally into three equal segments (left) from the apex to the top of the right diaphragmatic leaf.
of the total activity of one or both lungs. In order to estimate the pulmonary blood flow per unit of lung tissue, a volume correction is necessary. Since, with rectilinear scanning, the horizontal lines were separated by 2/16 inch or 3/16 inch and the depth of collimation was kept constant, the counts per line divided by the width of lung on the chest roentgenogram at the corresponding level allowed calculation of regional radioactivity per unit of lung volume, that is, the concentration of radioactivity. In order to provide a reproducible, quantitative method for comparing regional blood flows, the right lung was divided into three equal longitudinal segments from the apex to the top of the diaphragmatic leaf (fig. 3). The ratio of concentration of radioactivity between the upper and lower thirds, designated "U/L," was calculated and taken to represent the ratio of blood flow per unit lung tissue in these two regions. Observations made for the left lung were not analyzed in detail since the enlarged left atrium in the patients with mitral valve disease often lay within the counting field, resulting in an apparent decrease in radioactivity.

In order to test the specificity of the detecting system, a phantom experiment was carried out in which five Vynilite boxes containing known and increasing concentrations of Na$^{131}$I were placed in a row adjacent to one another and scanned in a manner analogous to that employed clinically. The specificity of the counting field is demonstrated by the linear relationship between the concentrations of Na$^{131}$I and the counts recorded. The diagonal line represents the line of identity.

**Figure 4**

A phantom of Vynilite boxes containing increasing concentrations of Na$^{131}$I was scanned in a manner analogous to that employed clinically. The specificity of the counting field is demonstrated by the linear relationship between the concentrations of Na$^{131}$I and the counts recorded. The diagonal line represents the line of identity.

**Figure 5**

The reproducibility of the method is demonstrated by the relationship between the results obtained from the scans of 11 patients performed under identical conditions on two separate occasions. The diagonal line represents the line of identity.

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lized during the period of observation, and if none of it leaves the region, then $Q_m/dt = 0$, $Q_e/dt = 0$, and $Q/dt$ will be directly proportional to the regional blood flow. It has been shown by Wagner and co-workers\(^8\) that the metabolism of MAA is negligible during the first hour following injection. Tow and associates\(^3\) have also shown that the pulmonary extraction efficiency in animals and man exceeds 80%, the particles of MAA being trapped in the first capillary bed they encounter. Thus, although $Q_e/dt$ is not zero, an appreciable error is not introduced because the particles not trapped by the lung are extracted from the blood in the systemic capillary bed and do not recirculate to a significant extent. Following intravenous injection, mixing of the particles in the bloodstream has been shown to be uniform prior to their arrival in the lungs.\(^3\)

Further evidence that regional pulmonary arterial flow distribution may be assessed accurately with \(^{131}\)I-MAA injection was provided by Lopez-Majano and associates\(^4\) who correlated simultaneous measurements of the partition of flow between the two lungs by the \(^{131}\)I-MAA technique, and by differential spirometry, a method based on the principle that the oxygen uptake of a lung is a direct function of the pulmonary arterial flow to that lung. Excellent agreement between the methods was noted, with a correlation coefficient of +0.96.

Less than 5% of the \(^{131}\)I-MAA used in this study contained aggregates smaller than 10 \(\mu\)m or larger than 150 \(\mu\)m in diameter. When diluted in saline at pH 5.5, the aggregates become spherical and assume a nearly uniform particle size between 10 and 15 \(\mu\)m in diameter.\(^3\) The density of the MAA used was found to be within 5% of that of whole blood. It has been shown that in the doses employed in this study the MAA itself will not create hemodynamic alterations.\(^8\) More than 80% of the injected \(^{131}\)I can be recovered from the urine in 48 hours, and extensive toxicity studies in animals and man have demonstrated the wide margin of safety of the dose and preparation.\(^8\) A 300 \(\mu\)c dose of \(^{131}\)I-MAA results in total body radiation of 0.1 rads and total lung radiation of 1.2 to 1.8 rads.\(^3\)

**Results**

In 13 normal subjects in whom \(^{131}\)I-MAA was infused in the erect position, the ratio of \(^{131}\)I-MAA distribution per unit of lung volume in the upper third of the right lung to that in the lower third (U/L) averaged 0.43 ± 0.08 (SD) (fig. 6). When the same subjects were given \(^{131}\)I-MAA while in the supine position, U/L averaged 0.92 ± 0.05,
The influence of gravity on pulmonary blood flow is illustrated by the ratemeter records obtained from longitudinal scans in a normal subject. When $^{131}$I-MAA was injected with the subject in the erect position (left) there was a linear increase in blood flow from apex to base. Uniform perfusion was present after an injection in the supine position (center). When the indicator was injected with the subject tilted headdown at an angle of 150°, there was a marked increase in blood flow to the dependent apex of the lung (right).

indicating essentially uniform distribution. $^{131}$I-MAA was administered to two normal subjects tilted to the headdown position, and U/L was 1.47 and 1.69, respectively. The effects of posture on the distribution of pulmonary blood flow are illustrated in the ratemeter records of a normal subject, scanned longitudinally, who was erect, supine, and tilted headdown at the times of the administration of $^{131}$I-MAA (fig. 7). Two normal erect subjects were rapidly infused with $^{131}$I-MAA during a prolonged maximal inspiration maintained with an open glottis. U/L values of 0.13 and 0.14 resulted, and the photoscans showed an absence of activity in the topmost zones of the lung (fig. 8).

Two photoscans of the same patient are spliced together (right) to show the absence of blood flow at the apex when $^{131}$I-MAA was rapidly injected during a maximal inspiration while the patient was erect, compared to the relatively uniform perfusion when the indicator was injected with the patient supine. The chest roentgenogram (left) provides anatomic landmarks.
In the 35 patients with mitral valve disease, U/L after injection of $^{131}$I-MAA in the erect posture averaged 1.01 ± 0.34, a value which was significantly greater than normal ($P < 0.001$) (table 1, fig. 6); the photoscan, chest roentgenogram, and ratemeter record of a patient with severe mitral stenosis are shown in figure 9. The differences in U/L resulting from injections in the supine and erect postures tended to be minimal in patients in whom U/L following injection in the upright position was already elevated.

Thus, in seven patients with mitral valve disease in whom the U/L ratio following injection in the upright position exceeded 0.90, no significant difference was observed when the lung scan was repeated following injection of $^{131}$I-MAA in the supine position.

There was an excellent correlation between U/L and the mean left atrial pressure in the 35 patients with mitral valve disease, $r = +0.91, P < 0.001$ (fig. 10). U/L was less than 0.65 in all patients in whom the mean left atrial pressure was less than 15 mm Hg, with the exception of patient 1 (S.C.) who was treated for heart failure during the 3 days between her lung scan and cardiac catheterization. In all patients in whom U/L exceeded 1.00, the mean left atrial pressure was considerably elevated and exceeded 18 mm Hg. The regression equation relating mean left atrial pressure in mm Hg (MLAP) to U/L was: $MLAP = 14.10 \times U/L + 5.32$. The regression analysis allowed estimation of the mean left atrial pressure from U/L within 5.3 mm Hg at the 95% confidence level.

Although U/L also showed a significant correlation with a number of other hemodynamic variables, in no instance was this correlation as close as with the mean left atrial pressure. The correlation coefficient ($r$) relating U/L to the mean pulmonary arterial pressure...
Table 1

<table>
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<th>Patient</th>
<th>Age, sex</th>
<th>U/L</th>
<th>MLAP (mm Hg)</th>
<th>MPAP (mm Hg)</th>
<th>MPAP-MLAP (mm Hg)</th>
<th>CI (L/min/m²)</th>
<th>PVR (dynes sec cm⁻²)</th>
<th>LA-LV (mm Hg)</th>
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Abbreviations: U/L = upper/lower zone; ¹³¹I-MAA distribution per unit of lung volume; MLAP = mean left atrial pressure; MPAP = mean pulmonary arterial pressure; CI = cardiac index; PVR = pulmonary vascular resistance; LA-LV = left atrial to left ventricular mean diastolic pressure gradient; MS = mitral stenosis; and MR = mitral regurgitation.
pressure was +0.68, P < 0.001 (fig. 11A), relating U/L to the mean pressure gradient between the pulmonary artery and left atrium it was +0.53, P < 0.01 (fig. 11B), to the pulmonary vascular resistance it was +0.57, P < 0.001 (fig. 11D), and to the cardiac index it was −0.61, P < 0.001 (fig. 12A). When the five patients with pure mitral regurgitation were excluded from consideration, the correlation coefficient relating U/L to the mean diastolic gradient across the mitral valve was +0.55, P < 0.01 (fig. 11C).

The pulmonary arterial and left atrial pressures are closely interrelated variables (fig. 12B), and it was of interest to determine whether U/L was more dependent upon the pulmonary arterial or the left atrial pressures. Accordingly, the partial correlation coefficient relating U/L and the mean pulmonary arterial pressure, correcting for mean left atrial pressure, was calculated and found not to be significant, r = +0.09. On the other hand, the partial correlation coefficient relating U/L to the mean left atrial pressure, correcting for mean pulmonary arterial pressure was +0.81, P < 0.001. These calculations suggest that the mean left atrial pressure is a primary determinant of U/L.

Three of the patients with mitral valve disease were studied both before and after surgical correction. In patient M.L. (table 1, no. 13), who showed considerable clinical improvement following mitral valve replacement, U/L fell from a preoperative value of 1.15 to 0.98 2 weeks postoperatively and declined further to 0.80 8 weeks postoperatively. In contrast, in patient T.E. (table 1, no. 32), U/L showed relatively little change, from 1.26 preoperatively to 1.06 6 months after
mitral valve replacement. Cardiac catheterization revealed left ventriculo-atrial regurgitation around the mitral valve prosthesis and only a minor decline in the mean left atrial pressure, from 23 to 20 mm Hg. In patient A.S. (table 1, no. 10) U/L declined from a preoperative value to 0.63 to 0.45 3 months after mitral valvotomy.

Discussion

It has long been suspected that the pulmonary blood flow is not distributed evenly throughout the lungs in man but that it is lower at the apices than at the bases when subjects are in the erect or sitting positions. Indeed, in 1887, Orth attributed the predilection of tuberculosis to the apices to this uneven distribution of blood flow and suggested that the effects of gravity were responsible for the relative ischemia of these regions. Strong support for the latter concept was provided by the studies of Martin and associates who found that the concentrations of O₂ and CO₂ in expired air differed significantly in the erect subject, and by Mattson and Carlens, who demonstrated by lobar bronchopneumography that a substantial decrease occurs in oxygen uptake by the upper lobe when the erect posture is assumed. Subsequently, West and Dollery, and Ball and co-workers, utilizing radioactive gas techniques, demonstrated marked differences in regional lung perfusion depending on body
position which were also in accord with the concept that gravity profoundly influences the distribution of pulmonary blood flow.

The findings of the present study, utilizing the technically simpler $^{131}$I-MAA technique, are in general accord with the results of the investigations utilizing radioactive gases. Thus, it was observed in normal subjects that when injections were made with the subjects in the erect position, the blood flow per unit lung volume in the upper third of the lung was approximately 40% of that in the lower third. When the subjects were in the supine position at the time of injection, the distribution was essentially uniform throughout the lung, and when they were placed in the headdown position, the injected $^{131}$I-MAA accumulated predominantly at the apices (fig. 7). A detailed comparison of the results utilizing the radioactive gas and $^{131}$I-MAA techniques does, however, reveal a small, though systematic difference. In the erect position the former method yields lower values of U/L than does the latter. It is likely that the maximum inspiratory position utilized with the radioactive gas method exaggerates the relative ischemia at the apices. This view is supported by the finding in the two normal subjects studied by the $^{131}$I-MAA technique in a fashion comparable to that employed with the gas technique in whom the values for U/L were much lower than during quiet breathing (fig. 8). In addition, in order to avoid the complex geometric problems involved in the corrections for lung volume below the top of the diaphragm, we do not assess perfusion at the very bottom of the lung, a factor which may account in part for differences in the values of U/L in normal subjects derived from the application of the two methods.

It is widely appreciated that mitral valve disease is frequently accompanied by elevations of the pulmonary vascular resistance as well as by intimal and medial thickening of the pulmonary vessels. In 1936, Parker and Weiss demonstrated that these anatomic changes are not uniform throughout

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Figure 12

(A) Relationship between U/L and cardiac index. (B) Relationship between pulmonary arterial and left atrial pressures. Note the departure from relative linearity at the higher levels of left atrial pressure.
the pulmonary vascular bed but that they show a predilection for the vessels perfusing the lung bases. A similar distribution of changes was shown during life by angiocardiograms which revealed dilatation of the pulmonary vesselsperfusing the apices and attenuation of the vessels leading to the lung bases.24

Both the inhaled and injected radioactive gas methods have shown reductions in perfusion of the lung bases in patients with mitral valve disease and pulmonary hypertension, and in general the perfusion abnormality has correlated with the severity of the disease.9, 10 One of the major findings of the present investigation is the linear relationship between the extent of the redistribution of pulmonary blood flow and the level of the mean left atrial pressure (fig. 10). No detectable differences in the relationship between U/L and atrial pressure were observed among the patients with mitral stenosis, mitral regurgitation, and combined stenosis and regurgitation. Although the correlations between U/L and other hemodynamic variables, such as the pulmonary artery pressure, pulmonary vascular resistance, the pressure gradient across the pulmonary vascular bed, the gradient across the mitral valve, and the cardiac index were also statistically significant, in no instance was the correlation coefficient as high as it was with the mean left atrial pressure. This finding, as well as the observation that the correlation between U/L and the pulmonary arterial pressure was not significant when corrected for variations in left atrial pressure suggests that pulmonary venous hypertension plays the dominant role in the alteration in the distribution of pulmonary blood flow that occurs in mitral valve disease.

The recent observations made by West and associates25 are of interest in attempting to explain the relation between left atrial pressure and the redistribution of pulmonary blood flow which occurs in mitral valve disease. When the pulmonary venous pressure in the isolated suspended dog lung was elevated, the blood flow at the base of the lung declined as a consequence of the development of perivascular edema which resulted in local elevations of pulmonary vascular resistance. It is possible that this mechanism may play a role in initiating the redistribution of pulmonary blood flow associated with mitral valve disease, but the relatively slow return of the pattern of distribution toward normal following the lowering of the left atrial pressure at operation indicates that factors other than acute perivascular edema must also play a significant role. We have observed that U/L generally exceeds normal values in patients with the Eisenmenger syndrome and with primary pulmonary hypertension who have elevated pulmonary arterial pressures and pulmonary vascular resistance but normal left atrial pressures. This finding indicates that disease in the pulmonary arterial bed may alter the distribution of pulmonary blood flow. However, it is of interest that at any given level of pulmonary arterial pressure U/L is significantly higher in patients with mitral valve disease than in those with pulmonary hypertension alone and that U/L has never exceeded 1.00 in the absence of pulmonary venous hypertension, regardless of the pulmonary arterial pressure.

The 131I-MAA technique may prove to be of considerable practical value in the clinical assessment of patients with mitral valve disease. Certainly, it is far safer, produces less discomfort, and provides more quantitative data concerning the distribution of pulmonary blood flow than either pulmonary arteriography or differential bronchspirometry. The necessary equipment for the application of the 131I-MAA method is readily available and is far simpler than that required for the radioactive gas techniques. Indeed, lung scanning is already used routinely in the detection of pulmonary emboli in many institutions. The close correlation between U/L and mean left atrial pressure indicates that it is possible to predict the latter quite closely in patients with mitral valve disease by means of simple lung scanning. Since the 131I-MAA method appears to be a reasonably accurate technique for estimating the level of the left
atrial pressure in such patients, the technique has been found useful in the screening of patients with the clinical findings of mitral valve disease who were not considered symptomatic enough to warrant cardiac catheterization. Lung scanning has been similarly employed in the preoperative study of patients so ill that left heart catheterization was considered unusually hazardous. The method also appears to be useful in determining whether the pulmonary venous pressure is elevated in patients with known severe pulmonary arterial hypertension. In such patients it is often difficult to measure pulmonary arterial wedge pressure reliably and the more extensive manipulations necessary for left heart catheterization may be poorly tolerated. In these patients, assessment of the distribution of pulmonary arterial blood flow by lung scanning affords a means for determining the existence of pulmonary venous hypertension, which suggests the presence of potentially correctable lesions such as mitral stenosis or cor triatriatum.

Summary

The distribution of pulmonary blood flow was studied by external scintillation scanning of intravenously injected 131I-labeled macroaggregates of human serum albumin. The technique, its validation, and the underlying considerations are discussed in detail.

In 13 normal subjects, in whom the indicator was injected while they were in the erect position, the ratio of concentration of radioactivity per unit of lung volume in the upper third of the right lung to that in the lower third (U/L) averaged 0.43 ± 0.08 SD. When 131I-MAA was injected with the subjects in the supine position, this ratio averaged 0.92 ± 0.05.

In 35 patients with mitral valve disease in whom the injections were made while they were in the erect position, varying abnormalities of the distribution of the pulmonary arterial blood flow were observed, U/L averaging 1.01 ± 0.34. The extent of the abnormality of distribution was found to be a function of the hemodynamic severity of the mitral valve disease, and U/L correlated more closely with the mean left atrial pressure than with any other hemodynamic variable. The potential applicability of the 131I-MAA technique in the detection and assessment of mitral valve disease was discussed.

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References


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