Heterogeneity of myocardial blood flow and metabolism: Review of physiologic principles and implications for radionuclide imaging of the heart

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Heterogeneity of myocardial blood flow and metabolism is a known feature of the coronary circulation in laboratory animals[1-9] and has been reported in the normal human coronary circulation as well.[10,11] This review will describe the types of heterogeneity that have been reported, how they relate to one another, and the extent to which physiologic heterogeneity of myocardial blood flow and metabolism may influence the appearance of both positron emission tomography (PET) and single photon emission computed tomography (SPECT) images of the myocardium.

PHYSIOLOGIC PRINCIPLES

Transmural Endocardial/Epicardial Heterogeneity

Spatial heterogeneity of myocardial blood flow was recognized as an issue of physiologic importance when Domenech et al[12] first described a method for measurement of regional myocardial blood flow with radiolabeled microspheres. They noted that flow to the subendocardial (endo) layer of the heart (1- to 2-mm–thick) exceeded flow to the subepicardial (epi) layer in normal dogs. Methodological issues regarding the validity of the observation, however, were apparent at the outset. The authors themselves noted that the endo-epi flow ratio varied with the size of the microsphere used to measure flow.[12] Indeed, with spheres of 50- to 60-μ in diameter, the ratio was 2.5, as compared with 1.3 for spheres of 14-μ in diameter. The difference was said to reflect the tendency for larger spheres to move preferentially in the central axis of the flow stream,[13] which causes them to be underrepresented in proximal intramural vessels supplying epicardial layers of the heart that receive blood from more peripheral portions of the flow stream.[12] Subsequent experiments by other authors[14] confirmed the observation that the endo-epi flow ratio depends on microsphere size and also demonstrated that the ratio measured with a freely diffusible tracer, radiolabeled antipyrine, was very close to 1 and was similar to that observed with 9-μ_spheres. The slight excess in apparent endocardial flow noted with antipyrine was attributed to direct uptake of the tracer from the left ventricular blood pool.[14] The ratio also is known to depend on physical definition of endocardial and epicardial layers, an important issue with regard to imaging considerations. If the normal 10-mm left ventricular free wall is divided in half, the endo-epi flow ratio will be much closer to 1 for standard 15-μ spheres, in comparison with the more usual division into thirds or quarters for physiologic studies in which values of approximately 1.2 typically have been reported[15,16] and recently have been reviewed.[1]

Despite what appears to be at least in part a methodological artifact, a variety of hypotheses have been put forth to account for a relative excess of endocardial blood flow in normal myocardium. Increased vascularity[17] and augmented metabolic work related to greater wall tension are frequently cited explanations.[18] Supporting experimental data have recently been reviewed.[1] In any case the putative excess of endocardial flow is relatively modest (lP515%) and unlikely to be detectable with currently available SPECT or even PET imaging systems (discussed in detail below).

There is no question, however, in the setting of hemodynamically important coronary stenosis that the transmural distribution of flow distal to the lesion is altered such that endocardial flow commonly declines (relative to epicardium) and the endo-epi flow ratio is less than 1.[15,16] In response to stress such as atrial pacing with norepinephrine to simulate exercise or pure vasodilation with adenosine, endocardial flow either fails to increase or even declines versus baseline whereas epicardial flow commonly increases moderately.[15,16,19] Accordingly, transmural flow distal to the stenosis may change little, and the ability of SPECT or PET to register the change in endocardial flow is limited. A transmural decline in flow in response to adenosine or dobutamine

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(ie, coronary steal), however, may be detected with PET and has been reported in human beings with ischemic heart disease.[20,21] The ability of SPECT myocardial perfusion imaging to detect such changes, however, is questionable. It appears more likely that ischemia-induced dilation of the left ventricle accounts for apparent thinning of the left ventricular walls, whether a focal perfusion abnormality is also present or not, rather than endocardial ischemia per se.[22,23] A more detailed consideration of the important radionuclide imaging issues involved has been presented previously[24] and is reviewed below.

The regulation of coronary microvascular tone, which plays an essential role in determining regional as well as transmural distribution of myocardial blood flow, is complex and also has been shown to be heterogeneous in nature.[25-28] Whereas the great majority of resistance to flow in the coronary circulation occurs in microvessels (small arteries and arterioles) that are less than approximately 200-μ in diameter, differences in relative responsiveness to various stimuli among different sized vessels of this class have been reported by Chilian and colleagues.[25-28] Thus small arterioles appear to be more responsive both to metabolic signals and to changes in perfusion pressure than larger arterioles or small arteries.[28,29] In contrast, responsiveness to endothelium-dependent flow-mediated dilation appears to be greater in large arterioles than in smaller arterioles, which in turn are more responsive than small arteries.[28,29] The coordination of these responses potentially is complex. In fact, it is possible for constriction in one class of microvessels (eg, larger arterioles) to be offset by dilation of others (eg, smaller arterioles) with varying effects on both overall vasodilator reserve and responses to commonly used coronary vasodilator drugs such as adenosine and dipyridamole.[30,31] For example, diminished flow responsiveness to adenosine of myocardial segments perfused by coronary vessels without significant stenosis in patients with ischemic heart disease[21,32] may in part reflect redistribution of microvascular resistance with baseline dilation of smaller arterioles compensating for impaired flow-mediated dilation of larger atherosclerotic arterioles.

Transmural Fractal Heterogeneity

Flow heterogeneity on a more local scale (sample size <1% of left ventricular mass) was first reported in the early 1970s[14,33] and has since been studied extensively by Bassingthwaighte and colleagues,[3,6,8,34] as well as other authors.[1,2] The observed spatial heterogeneity of myocardial blood flow reflects the sum of temporal variation, method variation, and true spatial variation.[8] Experiments by King et al[8] with 15-μ microspheres demonstrated that method variation and temporal variation were 10% or less each and that true spatial variation (SD/mean) was on the order of 25% for the left ventricle.

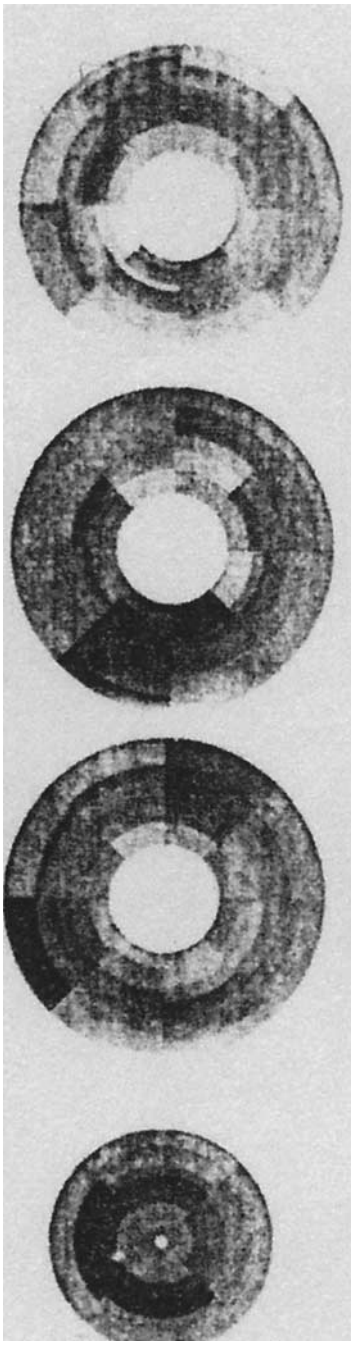

Figure 1 . Myocardial flow maps (base to apex, with septum at 9 o'clock and anterior at 12 o'clock) from normal baboon heart. Darker bands indicate higher flows (maximum, 2 mL/min/g), and lighter bands indicate lower flows (minimum, 0 mL/min/g). Considerable variation in flow both within and between endocardial and epicardial layers at all levels of the left ventricle is apparent. (Used with permission from King et al. Circ Res 1985;57:285-95.)

More detailed mathematical analysis of the spatial distribution of flow has shown that flows in nearby neighbors at a spatial resolution of 0.5% of left ventricular mass (|P50.5 g) are highly correlated, are stable over time, and are fractal in nature.[3,6] The range of flows even within myocardial layers of the normal heart may be wide, ranging from as low as 20% to as high as 250% of mean global flow[1] (Figure 1). It is interesting, nonetheless, that normal endocardial flow on average exceeds epicardial flow by 10% to 20% despite the fractal nature of flow distribution and the associated variation throughout the left ventricle.

The relatively wide variation in flow, particularly in small regions that are well below the mean, raises the question of whether these areas are ischemic. Alternatively, low-flow regions could reflect low workload and oxygen consumption with balanced oxygen supply and demand. Detailed metabolic analyses of substrates such as fatty acids and glucose, energy stores (adenosine triphosphate [ATP] or phosphocreatine), various mitochondrial enzymes, and adenosine and lactate have been carried out by many investigators,[1,4,5,9] though not always with consistent results. Thus, although ATP levels do not appear to vary with local flow, consistent with the hypothesis that metabolic balance is maintained regardless of flow, measurements of local PO_2 do vary with local flow[35]; this is an unexpected observation given the presumption of close matching of myocardial oxygen supply and demand.[1] Nonetheless, a substantial body of data indicates that low-flow areas on balance are not ischemic, as demonstrated by normal, rather than depleted, ATP or phosphocreatine content and absence of indicators of acute ischemia such as increased adenosine and lactate content.[5,36] Local areas with low flow, therefore, tend to have reduced uptake of metabolic substrates such as fatty acids and glucose in association with reduced oxygen consumption and vice versa.[1] Finally, contrary to expectation, vulnerability to ischemia does not appear to be related to the absolute level of resting blood flow but, rather, to the relative decline from baseline.[37] Stated another way, high-flow and low-flow regions of the stenosed porcine coronary circulation have been shown to be equally vulnerable to ischemia,[37] an observation of considerable importance in the interpretation of quantitative PET studies of myocardial blood flow and metabolism in human beings with ischemic heart disease. In particular, the data suggest that chronic low-flow regions may be no more vulnerable to ischemia than those regions with normal or even high basal flow. It is possible that stress-induced myocardial hibernation[16] may play a role in this regard, although further studies are required to test this hypothesis.

CARDIAC RADIONUCLIDE IMAGING PRINCIPLES

PET or SPECT could in principle be used to determine patterns of physiologic heterogeneity in myocardial blood flow or metabolism. However, there are several potential methodological limitations of each technique, primarily caused by the finite resolution of the imaging devices. These limitations can both induce artifactual heterogeneity and mask true physiologic heterogeneity. It is necessary to understand these limitations in order to interpret properly the flow or metabolism heterogeneities seen (or not seen) with PET and SPECT.

Current-generation PET and SPECT scanners, when used in realistic cardiac imaging situations, have in-plane resolutions that are, at best, about 6-mm full width at half maximum (FWHM) and 12-mm FWHM, respectively. High-energy SPECT (ie, fluorodeoxyglucose SPECT with a high-energy collimator) is at best 15- to 20-mm FWHM. These resolutions are often further degraded by the user in an attempt to compensate for noise. Resolution itself is not influenced by noise. However, one tends to "smooth" noisy images (eg, reconstruct with a filter that cuts off at a lower frequency) more heavily than high-count images in order to make them more clinically interpretable.

Slice thickness and axial resolution are also important. Typically, PET scanners might have 2- to 10-mm–thick slices with an effective resolution of about 6-mm FWHM. In SPECT, on the other hand, slice thickness can be made identical to the in-plane pixel separation—typically 4 to 6 mm. Axial resolution, however, is usually the same as in-plane resolution, at best around 12 mm (depending on the collimator used and the collimator-to-patient imaging distance). The effects of limited resolution and heterogeneity on measurements of metabolism and flow depend on whether the index of metabolism or flow is derived from a static uptake image or from a model that uses the kinetics of tracer uptake and clearance.

Effects of Limited Resolution on "Uptake" Images

The effects of limited resolution on "uptake" images comprise the simplest case. Examples of such images are thallium or technetium sestamibi SPECT scans, fluorodeoxyglucose uptake images (with either PET or high-energy SPECT), and static ammonia uptake images.

Effects that mask real inhomogeneities. Finite resolution blurs high-count areas into adjacent low-count areas. For example, consider a 10-mm–thick myocardial wall at end diastole in which the epicardial half of the wall takes up twice as much tracer as the endocardial half of the wall. Figure 2 illustrates the count profile through a gated end-diastolic short-axis slice of the wall for a

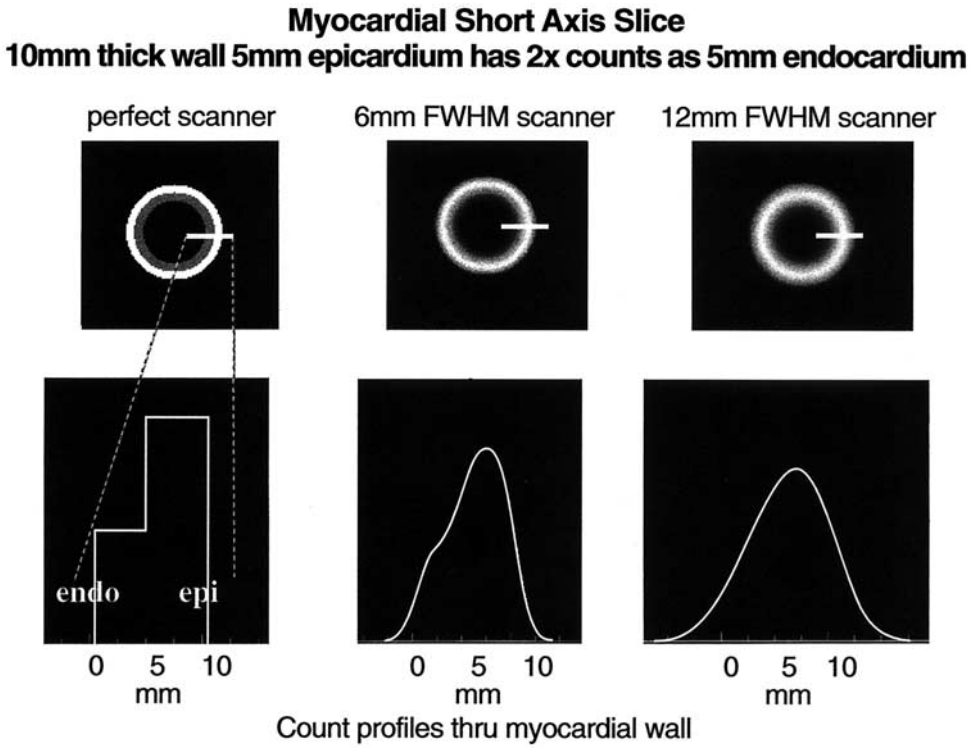

Figure 2 . Simulated slices *(top row)* and slice profiles *(bottom row)* obtained with scanners having perfect *(left column)*, 6-mm *(middle column)*, and 12-mm *(right column)* spatial resolution. In the model, epicardial activity (outer 5 mm of nominal 10-mm–thick wall) is twice that of endocardial activity. The ability to clearly distinguish endocardial from epicardial activity is extremely limited for the 6-mm scanner and non-existent for the 12-mm scanner.

"perfect" scanner, a scanner with 6-mm resolution, and a scanner with 12-mm resolution. Clearly, even at 6-mm resolution, it is very difficult to perceive this large endocardial-to-epicardial difference in tracer uptake (although there is a definitely observable asymmetry in the profile), and at SPECT resolutions, it is nearly impossible. The situation at end systole or with a thicker wall is a little better. Similar effects occur circumferentially around the myocardium. Defects in uptake, surrounded by regions of normal uptake, will be difficult to perceive (and even more difficult to quantify) unless the defect size is larger than the resolution of the scanner. Clearly, small heterogeneities will be even more difficult to visualize.

Effects that produce artificial inhomogeneities. When the myocardial wall is approximately the same thickness as the resolution of the scanner used to image it, the maximum intensity in that region of the wall can be artificially reduced. This is known as the partial-volume effect. If a particular short-axis slice has varying wall thicknesses around its circumference, some of which are comparable to or smaller than the resolution of the imaging device, then the thinner regions will appear less bright than the thicker regions, even though both regions have the same uptake (and therefore the same perfusion or metabolism). This effect has been described in detail for both PET and SPECT resolutions, along with illustrations of the artifactual heterogeneities that might be produced.[24] To understand the magnitude of the effect, imagine an end-diastolic slice that had a uniform uptake of 100. When imaged with a 7-mm–FWHM PET scanner, this slice would have an apparent uptake of 98 at a 15-mm–thick region of the wall, 90 for a 10-mm–thick region, and only 65 over a 5-mm–thick wall.[38] Clearly, the effects of varying wall thickness on apparent homogeneity of uptake can be important.

In ungated images, myocardial motion and thickening can produce similar partial-volume effects.[38,39] Regions that thicken normally tend to have a larger average thickness than regions that do not thicken appreciably. This can make poorly contracting regions appear to have lower uptake than is really the case.[22,23] Current gated SPECT myocardial perfusion scans routinely take advantage of this by using color-coded image sequences to depict increased wall thickening as an increase in brightness from end diastole to end systole. It is important to be aware, however, that the converse is not necessarily true. Walls that are already considerably thicker than the

resolution at end diastole will not increase in brightness with further thickening, as the partial-volume effect is greatly minimized in such cases. Fortunately, such cases are uncommon in clinical practice, especially given that patients with severe aortic stenosis or hypertrophic cardiomyopathy, who are likely to have very thick walls, generally are not subjected to stress testing for safety reasons and thus do not commonly undergo myocardial perfusion scanning.

Effects of Limited Resolution and Heterogeneity on Flow and Metabolism Measurements Using Models

Absolute flow and absolute metabolic rates can be measured by means of PET data. In general, such measurements are rarely, if ever, attempted with SPECT. Two common tracers used for absolute flow measurements in PET are nitrogen 13–ammonia and oxygen 15–water, whereas fluorine 18 deoxyglucose is the most common metabolic tracer. Compartmental models are used to convert the dynamic data acquired with these tracers into flow or metabolic values. A region of interest (ROI) is drawn and a time-activity curve created from the ROI. If there is heterogeneity of flow in the ROI, then the data may not be properly described by the models. For example, consider an ROI that contains tissue with 2 different flow values. When O-15–water is used to measure flow, a simple 1-compartment model is used. This model assumes a monoexponential washout convolved with the input function. However, if tissues with 2 or more different flow values are present in the ROI, the washout will not be monoexponential. Accordingly, the model will no longer describe the data and will give a poor fit such that flow values obtained will not accurately reflect average flow to the ROI. This effect is the reason why the "perfused tissue index"[40] may be unreliable when used as an indicator for determining myocardial viability.[41]

A similar situation arises for blood flow measurements with N-13–ammonia. Again, if the tissue of interest contains a mixture of flow values, the model may no longer be appropriate for the data and poor fits and erroneous flow values may result. One approach to minimizing this problem is to compute parametric images—that is, pixel-by-pixel fits to the models.[11] By computing flow pixel by pixel, rather than in an ROI, there will be less of a chance of averaging together regions of disparate flow. Even in this case, however, the finite resolution of the scanner may blur together pixels with disparate flow (eg, from small scale heterogeneities), again causing the pixel-by-pixel models to give inappropriate fits to the data.

A similar problem arises with computations of FDG-18 metabolic rates. However, the most common approach, the Patlak plot, has the advantage of being based on a model that continues to fit the data even when heterogeneities in metabolism exist.[42,43] This is because the Patlak approach produces data that can be fit to a straight line (the slope of which is related to the metabolic rate). Because the sum of 2 or more straight lines with different slopes is also a straight line, metabolic heterogeneity at least still results in good fits of the data to the model. The resulting slope of the line then represents an average metabolic value within the region (or of the pixel).

INTEGRATION OF IMAGING AND PHYSIOLOGIC CONSIDERATIONS

It is useful to consider the sample volume size that can be resolved by current-generation SPECT and PET scanners when relating the above noted imaging principles to laboratory experiments, which typically have involved myocardial tissue samples of 0.5 g or less. There are a number of complexities, including the extent to which images are smoothed after acquisition, as well as "real-life" practical limitations such as cardiac motion and image acquisition time, to name but a few, which preclude an exact answer. Nonetheless, with a few simplifying assumptions, it is possible to develop a reasonable estimate. For SPECT imaging systems, spatial resolution on the order of 1.4- to 1.5-cm FWHM is possible if limited smoothing is applied to the images. Resolution in the axial direction is similar. Thus sample resolution cubes of approximately 3.0 cm^3 are possible with limited smoothing and $(1.7\text{-}1.8\ cm)^3$, or about 5.4 cm^3, with more liberal smoothing. Given a myocardial tissue density of 1.05 g/cm^3, such cubes correspond to samples of 3.2 to 5.7 g. Much of the spatial heterogeneity of myocardial blood flow and metabolism reported, which is based on measurements of tissue samples of 0.5 g or less, will be smoothed over at this level of spatial resolution, as will endocardial/epicardial flow heterogeneity of normal myocardium.

The situation with PET myocardial perfusion imaging is potentially different, as spatial resolution under clinical conditions is roughly twice as great as that of SPECT and thus $(0.7\ cm)^3$, or 0.36 g, cubes are possible. Although resolution of endocardial/epicardial flow distribution for normal wall thickness (nominally 1 cm) may not be possible, transmural heterogeneities would be expected to approach that seen with microsphere experiments. Indeed, a coefficient of variation of spatial heterogeneity of myocardial blood flow on the order of 25% has been reported in normal human beings.[10,11] The heterogeneity reported in PET studies of normal volunteers, however, appears to have a more regional nature

than that reported for microspheres. Thus, when N-13–ammonia is used, flow in the distal third of the left ventricle was noted to be reduced in comparison with that of the mid and proximal thirds in a 24-segment model of the left ventricle (8 regions at each of 3 slice levels: apex, mid, and base).[11] Anteroseptal flow in that study also was modestly but significantly reduced compared with that of the septum but not other segments.[11] In comparison, the inferior segment was reported to have systematically reduced flow versus the anterior and lateral segments when O-15–water was used in a 48-segment model of the left ventricle (4 regions on each of 12 slice planes).[10] The reason for differences between the two studies is unclear and may reflect a variety of methodological issues, as different tracers and acquisition and analysis techniques were used.

It is noteworthy, however, that heterogeneity of myocardial blood flow can be explained at least in part by differences in the electrical activation sequence, which in turn leads to differences in regional systolic strain and therefore differences in the oxygen requirement.[34,44] Early activation results in contraction against a lower afterload and hence reduces the oxygen requirement and therefore myocardial blood flow.[34] Reduced basal flow in the anteroseptal segment of the left ventricle is consistent with this hypothesis, as electrical activation of the left ventricle normally begins across the anterior septum.

It is also true that electrical activation spreads from the endocardium to the epicardium, and thus if activation sequence were the only factor involved, one might also expect endocardial flow on average to be less than that of the epicardium. However, wall stress in the endocardium exceeds that in the epicardium, notwithstanding early activation of the endocardium, and as noted above, is a commonly advanced explanation for relative excess of endocardial blood flow in normal myocardium.[18] Figure 1, reproduced from King et al,[8] displays maps of regional myocardial blood flow (15-μ microsphere technique) from base to apex in 4 left ventricular rings. The spatial resolution of the microsphere data reflects a sample size of 15 × 10 × 1 mm with an average weight of 0.17 g. It is apparent that the flow map differs in many respects from published records of electrical activation sequences for the normal left ventricle. Normal activation first begins across the anterior septum from the endocardium to the epicardium and then spreads in an organized wave-like fashion to the free wall and then, finally, to the base of the left ventricle (Figure 3). [45] It is clear, therefore, that notwithstanding a reasonable correspondence between regional flows observed on a small scale and other indices of myocardial aerobic metabolism, the basis for such heterogeneity remains to be determined. The electrical activation sequence certainly appears to be capable of influencing flow distribution[44]; however, other factors such as local differences in contractile state, relaxation, and perhaps efficiency of oxygen utilization may all play a role and merit additional consideration.

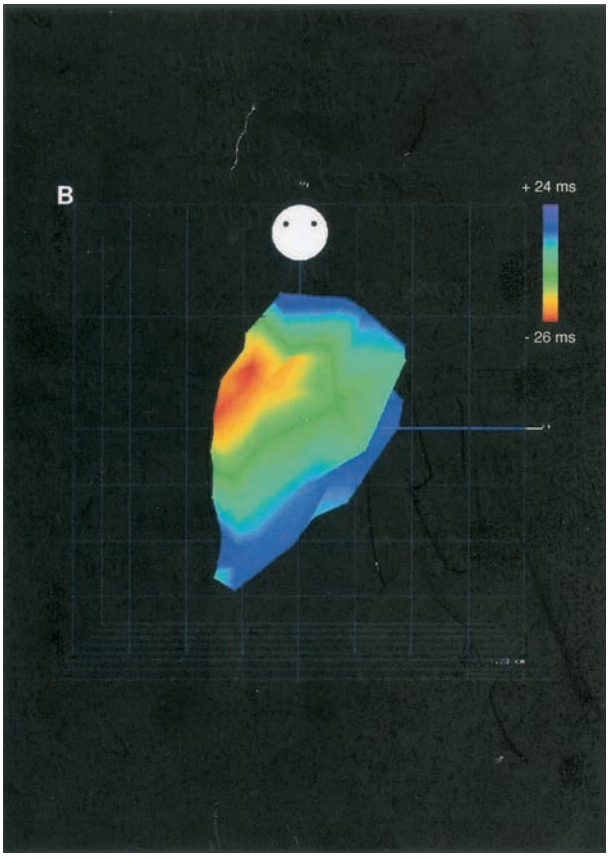

Figure 3 . An electrical activation map of a normal swine left ventricle obtained during sinus rhythm. The map shows earliest activation *(red)* in the region of the anterior septum with organized wave-like spread to the free wall (*yellow* to *green* to *light blue*) and then to the base of the ventricle near the atrioventricular groove *(dark blue)*. Data were obtained from an intracavitary electrode catheter that sampled 60 endocardial locations at a spatial resolution of approximately 2 to 4 mm. As compared with Figure 1, myocardial flow maps complied from base to apex of the left ventricle based on a sample size of 15 × 10 × 1 mm (average, 0.17 g). (Used with permission from Gepstein L, Hayam G, Ben-Haim SA. Circulation 1997;95: 1611-22.)

SUMMARY AND CONCLUSIONS

Physiologic heterogeneity of myocardial blood flow and metabolism is as an established feature of the normal coronary circulation. Heterogeneity is seen at the level of endocardial and epicardial layers of the heart, and more local heterogeneity is seen within and across these layers. When the left ventricular myocardium is considered on a spatial scale of tissue samples of 0.5 g or less, the degree

of flow heterogeneity may be striking, with values ranging from as low as 20% of the overall mean to as high as 250%. Two of the most remarkable features of this heterogeneity are (1) its stability over time in any given heart and (2) the unexpectedly comparable vulnerability to ischemia of myocardial regions exhibiting very different levels of baseline flow, including those with values well below the overall mean. The mechanisms involved, though clearly related to myocardial contractile function and oxygen demand, are still not well understood and require additional research, particularly to better understand why and how relatively large differences in flow and metabolism occur over quite small and scattered regions of myocardium (Figure 1).

The implications for myocardial flow and metabolic imaging depend principally on the type of imaging modality used. For current SPECT systems, the small-scale heterogeneities of flow and metabolism for the most part will be averaged away by spatial resolution, FWHM, of 14 to 17 mm. As noted above for normal-thickness left ventricular walls, this fact has at least one positive feature in that it makes possible assessment of regional wall thickening as well as global systolic function.[38,39,46,47] Smoothing away of flow heterogeneities under basal conditions also facilitates image interpretation for the most common indication for which SPECT is used in clinical cardiology, namely, the evaluation of patients with known or suspected ischemic heart disease.

For PET imaging of the heart, particularly quantitative studies of myocardial blood flow and metabolism, physiologic heterogeneity is more of an issue. The fact that flow heterogeneity in clinical PET images appears to be more segmental in nature[10,11] than that reported in experimental animals (Figure 1) raises the possibility that although the degree of heterogeneity is similar (lP525%), the underlying mechanisms may not be entirely the same. Nonetheless, the fact of spatial heterogeneity of myocardial blood flow in clinical PET images is real and must be considered when the results of studies of patients with known or suspected ischemic or other heart disease are interpreted. Finally, the situation appears to be different for PET metabolic imaging. Under conditions of euglycemic, hyperinsulinemic clamp, PET scans of FDG-18 have been described as "homogeneous" in appearance in normal subjects.[48] Similarly, PET images of carbon 11–palmitate have been reported to show "homogeneous" tracer uptake and washout in normal subjects.[49] Correlation, therefore, of PET myocardial blood flow and "metabolism" images must take into account the potential for regional mismatch, even in normal individuals.

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