Modeling the myocardial dilution curve of a pure intravascular indicator


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Modeling the myocardial dilution curve of a pure intravascular indicator. Am. J. Physiol. 273 (Heart Circ. Physiol. 42): H2062–H2071, 1997.—The dispersion and dilution of contrast medium through the myocardial vasculature is examined first with a serial model comprised of arterial, capillary, and venous components in series to determine their time-concentration curves (TCC) and the myocardial dilution curve (MDC). Analysis of general characteristics shows that the first moment of the MDC, adjusted for that of the aortic TCC and mean transit time (MTT) from the aorta to the first intramyocardial artery, is one-half the MTT of the myocardial vasculature and that the ratio of the area of the MDC and aortic TCC is the fractional myocardial blood volume (MBV). The use of known coronary vascular morphometry and a set of transport functions indicates that the temporal change in MDC is primarily controlled by the MTT. An analysis of several models with heterogeneous flow distributions justifies the procedures to calculate MTT and MBV from the measured MDC. Compared with previously described models, the present model is more general and provides a physical basis for the effects of flow dispersion and heterogeneity on the characteristics of the MDC.

myocardial blood flow; blood volume; mean transit time; intravascular indicator

ULTRAFAST X-RAY computerized tomography (CT), magnetic resonance imaging (MRI), and myocardial contrast echocardiography (MCE) measure time-intensity curves for assessing the passage of intravascular contrast medium (or indicator) injected into the aorta through a region of interest (ROI) placed over the myocardium. By Kassab and colleagues (16–18), the arterial tree is composed of 11 orders of blood vessels with the parent vessel (right, left anterior descending, or left circumflex artery) being of the 11th order. The 10th-order artery branches into 18 intramyocardial arteries, whereas the 1st-order arteries terminate into ~3 million arterial
dilution curve (VDC). For a pure intravascular indicator, VDC reflects the TCCs of all vessels in the ROI. Several approximations (3, 8, 10, 28, 34) have been used to calculate from the noninvasively measured MDC the mean transit time (MTT) through the myocardial vasculature, regional myocardial blood flow (MBF), and blood volume (MBV). To justify these calculations, it is important to know whether the approximations adequately simulate the distribution of an indicator in the ROI as it flows through the myocardial vasculature. In this paper, we use a recently described comprehensive morphometric model of the coronary vasculature (16–18) to define a set of TCCs to account for the dispersive nature of blood flow, to simulate the flow heterogeneity in the myocardial vasculature, and to analyze the interrelation between TCC and VDC. The equations derived from this morphometric and heterogeneous model provide a practical procedure to assess perfusion more specific to myocardium.

ANALYSIS

The myocardial vasculature in the ROI is modeled as eight vascular components arranged in series, adapted from the detailed description of the pig coronary vasculature by Kassab et al. (16–18). Each component has its own TCC, such that the summation of the TCCs forms the VDC. Based on the general characteristics of TCC, two equations are derived using parameters of VDC to calculate MBV and the MTT for the indicator to traverse the myocardial vasculature. We assume that the flow is similar among microvessels within a single component and use partitioned transport functions to construct the functional form of VDC and to examine how the VDC is affected by changes in MBF and MBV. Finally, we analyze the VDC of a vasculature formed by many serial models in parallel to assess whether heterogeneous flow distribution in the myocardial vasculature alters the calculated MBV and MTT.

Characteristics of serial model. In the detailed morphometric description of the pig coronary vasculature by Kassab and colleagues (16–18), the arterial tree is composed of 11 orders of blood vessels with the parent vessel (right, left anterior descending, or left circumflex artery) being of the 11th order. The 10th-order artery branches into 18 intramyocardial arteries, whereas the 1st-order arteries terminate into ~3 million arterial
capillaries. The venous system consists of 12 orders with the coronary sinus being of the 12th order. The 11th-order vein has 16 intramyocardial veins, whereas there are ~5 million venous capillaries connected to the 1st-order veins.

Because the myocardial vasculature does not include epicardial vessels, the intramyocardial arteries are taken as the first component of the serial vasculature and the intramyocardial veins as its last component. The remaining orders in the arterial and venous tree are merged into five components under the criterion that their blood volumes are sufficiently small for adequately calculating indicator mass in each component. The capillaries represent the fourth component. The blood volume \( V_{mb} \) of each component derived from Kassab and co-workers (16–18) is listed in Table 1. With \( m \) signifying the definition of a quantity, the total MBV in the myocardial vasculature, therefore, is

\[
MBV = V_{mv} = \sum_{i=1}^{8} V_i
\]

The MTT for the indicator to traverse from the aorta to a point midway in the ith component is identified as \( T_i \). The location subscript \( x \) of \( T_i \), when identified as \( A \) (aortic entrance to the coronary vasculature), \( v \) (venous entrance to the coronary sinus), or \( cs \) (end of coronary sinus where it enters the vena cava), pinpoints the location along the serial myocardial vasculature (Fig. 1) to which the quantity \( T \) is referred.

Based on the indicator dilution theory, the MTT \( (T_i) \) is the volume of vessels situated between the aorta and the ith location divided by the MBF \( (Q) \). Accordingly, we have

\[
T_i = \left[ V_a + \sum_{n=1}^{i} (V_n - 0.5V_i) \right] / Q
\]

Similarly, the MTT from the aorta to the entrance of the first component is \( T_a \), to the end of the eighth component is \( T_8 \), and does not have the

\[
T_x = \int_0^{T_x} th_x(t) \, dt
\]

Vascular dilution curve of serial model. Normally, the injection of an indicator into the aorta does not resemble an instantaneous pulse. If we assume the TCC of aortic blood flowing into the coronary artery to be \( C_A(t) \), then the indicator dilution theory for the serial model yields the TCC at location \( x \) as

\[
C_x(t) = C_A(t) \otimes h_x(t)
\]

where \( \otimes \) symbolizes the convolution integral of the two functions.

The first moment of \( C_x \) is identified as \( t_x \). (Because \( C_x \) is not the TCC of a pulse aortic input, a lower case is used to highlight that \( t_x \) is not \( T_x \) and does not have the physical meaning of MTT defined as blood volume divided by flow). For convolutions in the form of Eq. 5, it can be shown that the area of \( C_x \) is the product of the areas of \( C_A \) and \( h_x \). It can also be shown that the first moment of \( C_x \) is the sum of the first moments of \( C_A \) and \( h_x \) (23). The area of \( h_x \) is unity, and its first moment is
T_x. The application of Eq. 5 to calculate the areas and first moments to all locations along the myocardial vasculature yields the following equalities

\[ \int_0^\infty C_A(t) \, dt = \int_0^\infty C_a(t) \, dt = \int_0^\infty C_i(t) \, dt \]

\[ = \int_0^\infty C_v(t) \, dt = \int_0^\infty C_{cs}(t) \, dt \]

(6)

\[ t_a = T_a + t_i, \quad t_i = T_i + t_A, \quad t_v = T_v + t_A, \quad \text{and } t_{cs} = T_{cs} + t_A \]

(7)

Most components of the serial model either have a small volume or a short vessel length. Thus we can neglect the concentration variations within each component and calculate the mass of indicator in the ith component to be \( V_iC_i(t) \). The VDC can now be identified as the summation of the indicator masses in all components normalized by their blood volume, i.e.

\[ C_{mv}(t) = \left[ \sum_{i=1}^{8} V_iC_i(t) \right] \bigg/ V_{mv} \]

(8)

Based on Eq. 6, the integration of the VDC from 0 to \( \infty \) can be rewritten to

\[ \int_0^\infty C_{mv}(t) \, dt = \sum_{i=1}^{8} \left[ \left( V_i \bigg/ V_{mv} \right) \int_0^\infty C_i(t) \, dt \right] \]

\[ = \int_0^\infty C_A(t) \, dt \]

(9)

By using the equalities in Eq. 7, the first moment of \( C_{mv}(t) \) can be expressed as

\[ t_{mv} = \int_0^\infty tC_{mv}(t) \, dt \bigg/ \int_0^\infty C_{mv}(t) \, dt \]

\[ = \left[ \sum_{i=1}^{8} \frac{V_i}{V_{mv}} (T_i - T_a) \right] \bigg/ V_{mv} + T_a + t_A \]

(10)

The terms in braces after the substitution for \( T_i - T_a \) from Eq. 2 will become

\[ \left[ \sum_{i=1}^{8} \frac{V_i}{V_{mv}} (2V_n - V_i) \right] \bigg/ (2QV_{mv}) \]

where \( V_{mv}/(2Q) = T_{mv}/2 \). (Some quantities in this derivation are underlined to show the correspondence.) Thus \( T_{mv} \) relates to \( t_{mv} \) by

\[ T_{mv} = 2(t_{mv} - t_a - T_a) \]

(11)

This MTT is derived without assigning any specific form for TCC. For the purpose of illustration, the functional form of \( C_{mv} \) is calculated with the following \( C_A \) and \( h_{cs} \):

\[ C_A(t) = C_0u(t) \exp (-at) \]

(12)

\[ h_{cs}(t) = b^2(t - t_{sp})u(t - t_{sp}) \exp \left[ -b(t - t_{sp}) \right] \]

(13)

where \( u(t) \) is a unit step function, \( C_0 \) a constant, \( t_{sp} \) the appearance time, and \( a \) and \( b \) are rate constants. The first moment of the aortic TCC is \( 1/a \). The functional form in Eq. 13 is known as the gamma variate, and its first moment is \( 2/b + t_{sp} \), which is \( T_{cs} \). With \( F_1 \text{ as } T_{T_{cs}} \), we set \( h_{cs} \) as \( L^{-1}[h_{cs}]^{\text{th}} \) with \( L \) as the Laplace transform operator and \( L^{-1} \) the inverse Laplace transform operator. Then the TCC at the ith component is

\[ C_i(t) = C_0u(t^*) \exp (-at^*) \times \{(1 - a/b)^F/\Gamma(2F)\} \]

(14)

where \( t^* = t - F_{i,T_{sp}} \) \( \Gamma(\cdot) \) an incomplete gamma function, and \( \Gamma(\cdot) \) the gamma factorial (1, 30). The appearance time for \( C_i \) is \( F_{i,T_{sp}} \) and its first moment is \( T_i + t_a \). In the case that \( x = b \), the terms in braces in of Eq. 14 are simplified to \( (at^*)^2/F/\Gamma(2F + 1) \).

Heterogeneous model. One basic assumption of the serial model is that the flow is similar in microvessels within each component and the lengths of the microvessels are also identical. This uniformity allows the use of one TCC to characterize the transport of indicator from the aorta to the midpoint of each component. In reality, the flows and hence TCCs may differ among microvessels of the same order. Also, the branching orders of vessels of similar size may be different. To account for such heterogeneities, let us assume that the myocardial vasculature has \( k \) branches arranged in parallel (25). Being a serial model, its jth branch has a flow of \( Q_j \) and a blood volume of \( V_j \). The branches and flow subdivide from the coronary artery (location designated as \( a \)) and rejoin at the coronary sinus (location designated as \( v \)).

The diagrammatic sketch in Fig. 2 illustrates a simple heterogeneous model with two branches, each
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where j ranges from 1 to k. The first moment of \(C_{mv}(t)\) computed from Eq. 17 can be expressed as

\[
t_{mv} = \sum_{j=1}^{k} v_j t_{mvj} \quad \text{or}
\]

\[
t_{mv} - t_a - T_a = \sum_{j=1}^{k} v_j (t_{mvj} - t_a - T_a)
\]

(19)

For each branch, \(t_{mvj} - t_a - T_a = 0.5T_{mvj}\). Using Eq. 16, we reexpress Eq. 19 as

\[
2(t_{mv} - t_a - T_a) - T_{mv} = \sum_{j=1}^{k} v_j T_{mvj} - \sum_{j=1}^{k} q_j T_{mvj}
\]

\[
- \sum_{j=1}^{k} (v_j - q_j)T_{mvj} = \sum_{j=1}^{k} (v_j - q_j)(T_{mvj} - T_{mv})
\]

(20)

Note that the term in braces is zero. For a parallel model with identical branches, \(v_j\) equals \(q_j\), \(T_{mvj}\) equals \(T_{mv}\), and Eq. 20, therefore, reduces to Eq. 11, which is that of a serial model. Within the ROI, the heterogeneity may be characterized by small differences between \(v_j\) and \(q_j\), and between \(T_{mvj}\) and \(T_{mv}\). Then the term on the right-hand side of Eq. 20, two orders of magnitude smaller, is used as an accuracy assessment of the following approximation

\[
T_{mv} = 2(t_{mv} - t_a - T_a)
\]

(21)

Because \(T_{mv}\) is \(V_{my}/Q\), we have

\[
Q/V_{my} = (V_{mv}/V_{my})/[2(t_{mv} - t_a - T_a)]
\]

(22)

where \(V_{my}\) is myocardial tissue volume.

One can calculate from the following definition the second moment of \(C_{x}\) as

\[
\sigma_x^2 = \int_0^\infty (t - t_a)^2 C_{x}(t) \, dt / \left[ \int_0^\infty C_{x}(t) \, dt \right]
\]

(23)

The transport function of the coronary sinus, which is the gamma variate in Eq. 13, has \(2b^2\) as its second moment. It can be calculated that 74% of the indicator in a bolus injected at time 0 passes through the coronary sinus within the period of \(T_{cs} - \sigma_{cs}\) to \(T_{cs} + \sigma_{cs}\). Because Gaussian normal distributions also have such a characteristic, we refer to \(\sigma_{cs}\) here also as the standard deviation. The area, \(t_a\), and \(\sigma_{x}\) of \(C_{x}\) serve as parameters to compare the functional characteristics of TCC.

Myocardial blood volume and calculation procedure. The MDC \(C_{my}(t)\) is an indicator concentration curve normalized by the myocardial tissue volume \((V_{my})\). Accordingly, the mass of the indicator in the myocardium is \(V_{my}C_{my}(t)\). Based on the definition of VDC, the mass of indicator in the myocardial vasculature is \(V_{mv}C_{mv}(t)\). With no indicator destruction or leakage from the myocardial vasculature, the equality of these two masses at any given time yields

\[
V_{mv}C_{mv}(t) = V_{my}C_{my}(t)
\]

(24)
By using the equalities in Eq. 18 of the heterogeneous model, the integration of Eq. 24 can be rewritten as

\[ \frac{V_{\text{mv}}}{V_{\text{my}}} = \left[ \int_0^t C_{\text{my}} \, dt \right] / \left[ \int_0^t C_A \, dt \right] \] (25)

If we assume that the signals \( C_{\text{my}} \) and \( C_A \) could be derived from the intensities of contrast medium being assessed by CT, MRI, or MCE from the myocardium and aorta, then Eq. 25 allows us to calculate the fractional blood volume in the myocardial tissue \( V_{\text{mv}}/V_{\text{my}} \). Similar substitutions in Eq. 10 lead to the determination of \( t_{\text{mv}} \) and \( t_A \). The velocity distribution in a Poiseuille flow has an average velocity of one-half the maximum velocity. The length of the tube divided by the maximum velocity is the appearance time, and the length divided by the average velocity is the MTT. As a result, the MTT of the TCC of a Poiseuille flow is twice its appearance time. If we consider that the blood flow from the aortic ROI to the intramyocardial artery (T_a) has the Poiseuille velocity distribution, we can then estimate T_a to be twice the time taken between the appearance of indicator from the aorta to the intramyocardial artery, i.e., twice the time between the appearance of signals \( C_A \) and \( C_{\text{my}} \). The substitution of \( t_{\text{mv}}, t_A, \) and \( V_{\text{mv}}/V_{\text{my}} \) so assessed into Eq. 22 yields MBF per unit myocardial tissue volume \( Q/V_{\text{my}} \).

RESULTS

Figure 3 illustrates the TCCs at the aorta, the second and fourth components of the serial microvascular model, and the exit of the coronary sinus calculated from Eq. 14 with a \( T_{\text{cs}} \) of 8 s, \( t_{\text{ap}} \) of 4 s, a of 0.5 s\(^{-1}\), and the values listed in Table 1. These TCCs depict the progressive dispersion of an intravascular indicator that remains solely within the myocardial vasculature. The closer the site of TCC measurement is to the venous exit, the longer the appearance time, the smaller the peak concentration, and the larger the second moment (or the width of the TCC). These features are comparable to the TCC used by Dawson and colleagues (7) for the pulmonary microvascular network.

The VDC for this serial model is depicted in Fig. 4 together with the TCCs of the aorta and coronary sinus. The short appearance time of the VDC is a consequence of the TCC in the first component, and the jaggedness of VDC results from the use of only eight components to simulate the myocardial vasculature. Although the first moment of the VDC (5.65 s) is smaller than that of the TCC of the coronary sinus (10 s), their standard deviations (VDC, 3.17 s; TCC, 3.46 s) are comparable. The characteristics of the VDC in relation to the aortic TCC are similar to those previously reported (34).

One can apply this myocardial model to examine how various changes in flow and volume alter the form of VDC. The case presented in Fig. 4 serves as control and is reproduced as the solid curve in Fig. 5. The second case has a flow of 0.5Q with no change in volume. The \( T_{\text{cs}} \) is shortened to 4 s, and the new VDC is the curve with the dotted line in the same figure. The third case has the VDC and venous TCC represented by curves with the dashed lines, which correspond to a flow of 0.5Q and a \( T_{\text{cs}} \) of 16 s.

During microvascular vasodilation, changes in blood volume are coupled with changes in flow. Suppose that MBF is increased to 4Q and MBV is increased to 2V_{\text{mv}}. The \( T_{\text{cs}} \) of this case is shortened to 4 s. Also assume that the blood volume change of each component is proportional to the total MBV change, i.e., they have the \( F_i \) values listed in Table 1. Then the VDC is found to be similar to the curve with the dotted line in Fig. 5, which has the same 4-s \( T_{\text{cs}} \). Conversely, if vasoconstriction results in a decrease in MBV to 0.5V_{\text{mv}} and flow to 0.25Q, then \( T_{\text{cs}} \) is lengthened to 16 s. This time we find that the VDC is identical to the curve with the dashed line in Fig. 5, whose \( T_{\text{cs}} \) is 16 s.

Specific vasoactive agents could produce a doubling of flow by dilation of small arteries and arterioles (e.g., a doubling of volumes of 2nd and 3rd components of serial model in Table 1). These internal volume adjustments lead to a new set of \( F_i \) values and a new VDC, which is depicted in Fig. 6 as the curve with a solid line. The 4-component vasodilation is 4.45 s. The curve with the
dashed line in Fig. 6A is the VDC with a flow increase that results in a change of $T_{cs}$ to 4.45 s. As another example, the flow may be doubled because of a doubling in the capillary blood volume caused by recruitment. $T_{cs}$ flow increases to 5.26 s, and VDC is represented by the solid curve in Fig. 6B. The curve with the dashed line in the same figure shows the VDC with a flow decrease that is proportional to the increase in $T_{cs}$. A comparison of these case studies over these wide blood volume changes indicates that the functional form of VDC is mainly controlled by the value of $T_{cs}$. Because the VDC is composed of the convolutions of the aortic TCC and transport functions, the functional form of VDC is also affected by the form representing the aortic TCC.

Equation 16 relates the actual MTT of a heterogeneous model to the MTT values of its branches. Without the latter information, Eq. 21 becomes a more practical procedure to calculate the MTT. Can Eq. 21 provide a reasonable estimate of the actual MTT? To address this question, four cases of heterogeneity are considered under the condition that the blood volume of and blood flow to the entire vasculature remain unchanged. The first case is composed of two branches with equal flow but different MTT (7 and 9 s, respectively). These MTT values are chosen so that their flow-weighted average remains 8 s. Because the product of MTT and flow of an individual branch is its volume, we have the corresponding blood volumes of the branches as 0.4375 $V_{mv}$ and 0.5625 $V_{mv}$, which add up to the same total blood volume. The substitution of these fractional values into Eq. 20 yields an approximate $T_{mv}$ for this microvascular system based on Eq. 20 is longer than the actual one by 0.25 s, or 3.1%.

Finally, consider a heterogeneous vascular tree formed by 11 branches in parallel. In this fourth case, the distribution of flows among the branches classified according to $T_{mv}$ is depicted in Fig. 7A. The only constraint in constructing this distribution is that the
MBF and MBV that are limited to very specific settings and are based on specific assumptions, the present model is more general. It shows that the first moment of VDC, adjusted for that of the aortic TCC and MTT from the aorta to the first intramyocardial artery, is one-half of the MTT of the myocardial vasculature and that the ratio of the area of the MDC and aortic TCC is the fractional MBV. The use of recently described, detailed coronary vascular morphometry and a set of transport functions to characterize the indicator dispersion along the myocardial vasculature indicates that the temporal change in VDC is primarily controlled by the MTT.

We have used 8 vascular components in our model rather than the 22 generations of the entire coronary tree. Because of the manner in which Eqs. 16 and 22 are derived, the same equations could still be deduced if the serial vasculature were divided into more components. In determining the effect of heterogeneities in regional flow and microvascular anatomy, several branch models are used. The small difference between the MTT estimated for a 2-branch model and an 11-branch model from the actual MTT indicates that Eq. 21 will yield an adequate estimation of MTT for a vasculature with more branches on the distributions of flow and volume. The primary effect of these simplifications (merging generations into components or taking a finite number of branches) is on the form of the VDC. When we expand the 8-component model to one with 16 components, the only modification is to smooth out the initial portion of the VDC with jaggedness. For the 2-branch model, the VDC exhibits two peaks, which are smoothed out when the 11-branch model is used.

The gamma variate function has been shown to be a good analytic representation for the venous TCC. The partition scheme to obtain $C_i(t)$ from $C_i(t)$ accurately reflects the distribution of MTT along the myocardial vasculature. It also gives a specific distribution for the standard deviations of TCC. The VDC is a sum of TCCs. Thus the redistribution of standard deviation among the TCCs, because of the nature of flow (laminar or turbulent) or the anatomy of the vasculature while $T_{cs}$ and $\sigma_{cs}$ are kept constant, may not change the functional forms of VDC significantly from those shown in Fig. 8.

The equalities in Eqs. 6, 18, and 25 for calculating the areas of TCC and MBV are derived for a complete vascular network with a blood flow of Q. Because the approach selected to account for flow heterogeneity can be readily expanded to cover actual vascular flows, Eq. 25 is valid whether or not the vasculature within the ROI has homogeneous flow among the branches. When a thin section of myocardium is selected for placement of the ROI, the myocardial vasculature will have some vessels directing flow out and others bringing flow into it. The equalities may still be applicable to the partial myocardial vasculature in the thin section, because the blood flow and blood volume of the section as calculated by Eqs. 22 and 25 with CT correlated well with those measured by the radiolabeled microspheres and direct morphometry (34). The correlations reported in that study have a slope close to unity and a positive inter-
cept that may result from setting their \( T_a \) to zero in their calculation of MBF (34).

Physical nature of vascular flow. The serial model presented here is comparable to the one-dimensional dispersion analysis carried out by Harris and Newman (12). The approach of expanding the serial model into a parallel model provides the basis to fully simulate heterogeneous branching flows while accounting for the flow dispersion within the branch. Vascular flow has been modeled as one through a set of parallel branches (22, 25). The analysis of Knopp et al. (22) aims to establish the fit to the measured venous TCC, whereas our analysis and that of Lee (25) aim to describe the physical nature of the VDC.

The TCC at the exit of a well-mixed chamber is characterized by Eq. 12. The transport function of a plug flow is a delta function with a time delay. The convolution of TCCs of two well-mixed chambers and a plug flow produces a gamma variate with a delay in the appearance of the indicator. Because the gamma variate fits well with the TCC of many organs (4, 6) and the VDC obtained by MCE (14, 19), it has been suggested that the indicator transport in a vasculature be compartmentalized as a chambers-plug-flow series. Such a modeling of the central circulation is physically appropriate, because a beating heart mixes the blood in the heart chamber like that of a well-mixed chamber. In contrast, flow through a complex vascular network is very different from such a compartmentalized model. Thus a good fit of the gamma variate to the venous TCC of an organ does not necessarily trivialize the disparate nature between vascular flow and compartmental model.

The transport function of Poiseuille flow (a tube flow with a parabolic velocity profile) has a concentration jump at the appearance time and then a decay in the form of \( 1/t^3 \). Take the volume contained in a well-mixed chamber or plug flow as one-half of the Poiseuille flow. Although the gamma variate of this chamber-plug-flow model shows an indicator appearance and a decay similar to that of the Poiseuille flow, their physical nature to transport the indicator is different. Because of the minute diameter of the capillary, the rapid diffusion of indicator in the radial direction makes its transport along the capillary like that of a plug flow with minimal longitudinal dispersion. However, indicator transport across the pulmonary capillary network is significantly dispersed because of flow heterogeneity among the capillaries (2). Simulation of blood flow in the myocardial vasculature as a chambers-plug-flow model may delineate the connection between TCC and dispersive indicator transport produced by nonuniformities in velocities and path lengths within a vascular network. Consequently, the use of an analytic function to represent a TCC should be viewed only as a mathematical means for solving convoluted integrals or partitioning TCC.

Comparison with previous studies. Many procedures have been developed to calculate from the VDC measured by CT, MRI, and MCE for MBV, MBF, and MTT. For a comparison with our model, these approaches could be divided into three categories. For the sake of simplicity, we will deal with all TCCs and VDC that have been deconvoluted and a myocardial vasculature that is simplified to the case where \( T_a \) and \( t_a \) are zero. By assuming that the standard deviation is proportional to the MTT with a proportional constant \( \alpha \), the equation obtained by Gobbel et al. (10) through a center of gravity analysis could be generalized to

\[
T_{mv} = \frac{1}{2/(1 + \alpha^2)}(t_{ROI} - t_a - T_a)
\]

Depending on the vascular system (4, 7), the value of \( \alpha \) ranges between 0 and 1. For the current analysis with the myocardial vasculature as the ROI (i.e., \( t_{ROI} = t_{mv} \)), Eq. 21 indicates that the value for \( \alpha \) is 0.

One category of studies operates under the assumption that the VDC is a selected combination of TCCs. In several studies (3, 10, 31), the indicator concentration in the vasculature within the ROI is assumed to be constant or well mixed. With this assumption, the VDC becomes the venous TCC and the first moment of VDC equals the MTT, i.e., \( \alpha = 1 \). We note from Fig. 8 that the form of VDC looks quite similar to the venous TCC; however, the VDC has a much longer appearance time than the VDC. In treating the VDC as a multiple-point measurement, the analysis done by Mor-Avi et al. (28) also yields an \( \alpha \) of unity. Equation 26 with a unity \( \alpha \) and an assessed MBV were used to calculate the MBF (38).

Wang et al. (34) approximated the MDC as \( f_a C_a(t) + f_v C_v(t) \) (where \( f_a \) and \( f_v \) are the fractional blood volume in the arteries and veins in the ROI) and provided several approximations (Eqs. 5 and 6 in the appendix of their paper) to relate \( C_a(t) \), \( C_v(t) \), \( C_{mv}(t) \), and \( C_v(t) \). Although the approximations relating the areas of these TCCs are different from Eqs. 6 and 9, they also deduced Eq. 25 relating MBV with the area of MDC. Despite the graphic nature in the determination of \( T_{mv} \), it can be shown mathematically that these approximations lead to Eq. 26 with \( \alpha \) as 0. The procedures so derived have been used to assess the coronary microvascular site of autoregulation and the relation between MBV and MBF (27, 39).

The reasons why Wang et al. (34) derived a value for \( \alpha \) similar to ours may be serendipitous and empirical. If \( C_a(t) \) and \( C_v(t) \) are selected from the family of TCCs (see Fig. 3) to construct the VDC and MDC, they will exhibit two peak concentrations, because of different peak times in \( C_a(t) \) and \( C_v(t) \), instead of being smooth as in Fig. 4. As tabulated in Table 1, the fractional blood volume in the capillaries (45% of MBV) is larger than that in the three arterial components (26%) or the four venous components (29%). Furthermore, a myocardial vasculature composed of arterial and venous compartments may be too simplistic to assess the dispersive and heterogeneous factors relating the TCCs and VDC.

In the second category of studies, the MDC and the blood flows through several coronary arteries were measured (8, 31, 33), from which rate constants such as \( 1/t_{a}^{MBF} \) and \( a \), or \( b \) in Eqs. 12 and 13 were determined. These rate constants have a linear correlation with the measured MBF, which is expected using a compartmental analysis. If the inverse of the rate constant is taken...
as the MTT, then a blood volume can be calculated from the measurements (38). Our modeling of VDC provides a better physical understanding of the correlation between $t_{mv}$ and flow. It also yields a procedure to compute quantitatively MBV and MBF from the measured MDC and aortic TCC.

The third category of studies is based on residual analysis. The work of Clough et al. (6) exemplifies this approach, which is conceptually similar to ours. Flow dispersion and flow heterogeneity (2-branch model) are considered in their analysis. Using the morphometry of pulmonary circulation for the calculation, they examined how the ROI kinematics and input dispersion affect the use of the height-to-area ratio of the mass of indicator resident within the ROI (similar to the MDC) as the MTT. In this study, we analyze the relation between VDC and TCC to obtain Eq. 21 for estimating $t_{mv}$ from $t_{mv}$.

Limitations of Model. This model assumes that the indicator remains entirely within the intravascular space and that the intensity measurement from a ROI can be converted to the indicator concentration. Of the three imaging techniques mentioned, this assumption of intravascular indicator is strictly true only for MCE. Sonicated albumin microbubbles remain entirely within the intravascular space, and their rheology is similar to that of red blood cells both in microcirculatory preparations (21) and in the beating heart (14, 24). Contrast agents used for CT leave the intravascular space to briefly enter the interstitial space, thus significantly lengthening the calculated MTT (5). Mathematical manipulations have been proposed to correct for this effect (39). In the case of MRI, paramagnetic agents enter the interstitial space and this effect is prolonged if there is microvascular damage (24, 37). Newer agents are currently being studied whose extravascular effect is minimal (36).

Despite being true intravascular indicators, however, microbubbles used for MCE have their own limitations. The relation between measured video intensity signal and actual microbubble concentration is nonlinear for two reasons, microbubble shielding and logarithmic compression of the signal (33). Low doses of microbubbles are used to circumvent the first problem (33). The second problem is currently being addressed by developing procedures to measure acoustic intensity before applying compression and postprocessing (15).

Another potential issue relates to microbubble destruction by ultrasound (35). The concentration of microbubbles used for aortic injection, however, is high enough not to be significantly affected by this phenomenon (35, 9). Reducing acoustic power is also helpful in this regard. Sonicated albumin microbubbles behave like red blood cells only when the endothelium is functionally normal. They adhere to abnormal damaged endothelium, prolonging the MTT (20, 29). Finally, newer microbubbles have a small proportion of larger bubbles that can become lodged within the microcirculation. When injected intravenously, these bubbles are trapped by the pulmonary circulation and do not enter the myocardium (32). When injected into the arterial system, however, they can be trapped in the myocardial microvasculature, producing a long first moment or MTT (32).

In summary, analysis of indicator transport through the myocardial vasculature with flow heterogeneity indicates that the areas, first moments, and a timing comparison of time-concentration curves of contrast agents in aortic blood and myocardium have the potential to provide accurate estimations of MBV, MTT, and MBF.

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