Stochastic Flow as An Inherent Part of Microcirculation

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Citation

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Abstract

There are two phenomena: (a) a bolus of an intravascular tracer after short period of damped oscillation starts to monotonically decrease toward the level of complete mixing; (b) the pass of erythrocytes through microvessels exhibits an irregular flow. The connection between these phenomena is established by mathematical model based on assumptions: (a) hemodynamic stability, (b) the independence of the future trajectory of any blood particles from a past trajectory.Analysis reveals that stochastic behavior of flow is a property of microcirculation, meaning (a) only a fraction of microvessels is open for flow; (b) the state of microvessels, open or closed, is being governed by a random cause. The rate of reassignment of the openness (R) is a characteristic of microcirculation. Low R is the cause for some capillaries be closed for a long time resulting in impairment of nutrient delivery to the surrounding tissue.

INTRODUCTION

Two phenomena do not appear to be connected: (a) fluctuations of the flow in the microcirculation; (b) a monotonic decrease in concentration of an intravascular tracer (such as erythrocytes-Cr^{51}). Fluctuations can be revealed by observing the red blood cells, and are generated by regular, as well as irregular contractions of smooth muscles, and has been termed as vasomotion [1]. A monotonic decrease in concentration of an intravascular tracer is a well established in the blood volume (BV) measurements [2].

However, mathematical analysis presented in the current manuscript reveals that the only cause for the monotonic decrease is a stochastic flow within the microcirculation. Analysis is based on assumptions: (a) an indicator is in the blood circulation till complete mixing, (b) hemodynamic is stable at time of BV measurement (in other words, the monotonic drop is not due to the leakage of the tracer out of intravascular space and/or the extension of BV during time of measurement) and (c) the independence of any blood particles future trajectory from its past trajectory. Also we assume that the transport of any tracer throughout cardio-vascular system (CVS) is a recurrent process. That is, any particle leaving the left ventricle after passing any of finite chains of artery-arteriole-capillary-venules-vein (systemic as well pulmonary) will return, and times of those various returns will generate a distribution of transit time [3]. Thus, despite the huge number of the paths within vascular system, we assume that the CVS is a finite set of elements. These assumptions lead to the description of the transport of a tracer, as system of differential equations with constant coefficients. It is known that any differential system has as a solution the exponentials series [4] and that is the basis for the connection between stochastic flow and monotonic decrease of a concentration.

Stochastic flow means there is a network of microvessels and: (a) each microvessel from the network is either open for flow or closed; (b) the opening/closing is being governed by a random cause. The probabilities to open and to close are under the central (neuro and hormonal) and local (metabolites) influence.

The recruitment of microvessels, as the mechanism of adaptation to the new level of oxygen demand, has been well established since the research of Krogh [5]. Stochasticity of flow reveals opportunity to change delivery of nutrients without recruitment of microvessels. By changing only reassignment of the openness and keeping fraction of open microvessel constant one could significantly change delivery of nutrients [67]. Thus a stochasticity of flow could be a powerful tool for an adjustment of perfusion to the demand of tissue and the aim of the paper is to reveal that stochastic flow is the inherent property of microcirculation.

MATHEMATICAL MODEL FOR THE PASSAGE OF AN INTRAVASCULAR TRACER

We start with assumptions: (a) the stability of hemodynamic,

and (b) the future trajectory of any particle depends only on the current place of the particle. A model based on the given assumptions is a Markov chain [4] if it includes the following three components: (a) a structure of the CVS, (b) a distribution of a tracer throughout the CVS, and (c) an operator of the transition of an indicator throughout the CVS. In detail:

(a) A structure of the CVS is a set of segments, such as the heart chambers, conductive and micro vessels. The segments are numbered $\{S_k; k=1...N\}$. Three remarks: (i) S_1 is the notation for the right atrium; (ii) subscript m is used for segment S_m corresponding to the aorta, and (iii) S_N is the segment corresponding to the vena cava. Numeration of others segments goes under rule: blood flows from the segments with low subscript to the segments with higher subscript.

(b) Distribution of a tracer throughout the CVS is a vector $z(t) = \{z_k(t), k=1,..,N\}$, where the k^{th} component of z(t) is the fraction of a tracer within the S_k at time t. In particular, the $z_m(t)$ is the tracer recorded in aorta. An initial distribution of an indicator, z(0), is $z_1(0)=1$, and for all $k>1$ $z_k(0)=0$, meaning that a tracer is injected into the right atrium at time t=0,

(c) An operator $A= \{a_{ij}\}$ provides the transition of a tracer during one cardio cycle, where a_{ij} is the fraction of a tracer within S_i that passes during one cardio-cycle into S_j : as result the distribution of the tracer at time t, z(t), transforms to the distribution at time t+1: $z(t+1) = z(t)A$, and, recursively: $z(t) = z(0)A^t$. (2.1)

The standard approach to deal with (2.1) is based on the decomposition of matrices [4] and the dilution curve in the aorta, $z_m(t)$, is given by (2.2);

Figure 1

$$z_m(t) = b_{m1} + \sum b_{mi} s_i^{-t-1} + \sum \left|b_{mj}\right| \cdot \left|s_j\right|^{-t-1} \cos(\omega_j t) \qquad (2.2)$$

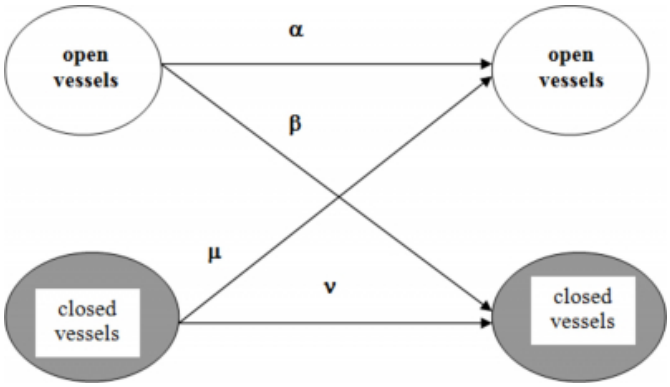
where $\{s_i\}$ are the roots of the equation Det(sA-E)=0; b_{m1}, $\{b_{mi}\}$, and $\{b_{mj}\}$ are constants and can be obtained from a combination of eigenvectors of A [4].

The right side of (2.2) is the sum of three sequential terms: the constant, the steadily decreasing term, and the damped oscillating term.

A stochastic flow necessary to produce the monotone decrease of a tracer is generated by vasomotion presented on Figure 1. It is a network of microvessels in which every microvessel is either open or closed. Blood passes through open microvessels and is sequestered in closed microvessels. Greek letters, Figure 1, represent the probabilities for microvessels to change their state during one cardio-cycle: □ is the probability to be open and remain open, □ is the probability to be open and become closed, v is the probability to be closed and remain closed, and μ is the probability to be closed and become open. There are two characteristics of flow: the fraction of open microvessels, $n_o=\mu/(\mu+$□$)$, and the rate of reassignment of the openness (or the rate of switching between open and closed microvessels [8]), R=□+μ. To insert such a scheme into the mathematical model, let introduce two segments of the microcirculation: S_{j-1} (the segment of open microvessels), S_j, (the segment of closed microvessels). The exchange between S_{j-1} and S_j is as on Figure 1. Additionally, let introduce segment S_{j+1}, this is the segment receiving blood from microcirculation given by the segments S_{j-1} and S_j. This implies the following equalities for the elements of matrix A $a_{jj} = v$; $a_{j-1j} =$ □. $a_{j-1j+1} =$ □ and $a_{jj+1} = \mu$□□.

Figure 2

Figure 1. Microcirculation as stochastic system White circles are for open vessels; dark circles are for closed vessels



RESULTS

We start with the analysis of diagonal elements of matrix A, these are the elements $\{a_{ii}\ i=1,\ldots,N\}$. The a_{ii} is the probability of a tracer in segment S_i to spend next cardio-cycle in the same segment. There are four segments, heart chambers, with non-zero a_{ii}, since during cardio-cycle part of blood remains in each chamber. As established in the following statements only the presence of non heart and non zero $\{a_{ii}\}$ leads to the existence of a steadily decreasing term in (2.2).

First statement: If all non-heart a_{ii} are zero, then $s_1=1$ is the only real characteristic number, in other words the dilution

curve (2.2) contains only damped oscillation around the level of complete mixing. The frequencies of oscillations are:

Figure 3

$$\Delta = 2\pi k / T \quad k = 1; 2; K$$

with T as the mean time to pass the whole CVS.

Second statement: If some of a non-heart a_{jj} is non-zero (a_{jj}=v=1-μ, and a_{j-1j} = .) then real positive characteristic number, s_2, exists, and 1+ μ< s_2<1++μ. In other words, random flow leads to the monotone decrease in a tracer concentration.

The proof for these statements is given in Appendix.

DISCUSSION

Having proof of the existence of a stochastic flow, two questions remain: (1) is the given proof acceptable, (2) what is the significance of a stochastic flow.

(1) Acceptance of the proof. Validity of conclusions of mathematic model is based on used assumptions. We made three main assumptions: (i) hemodynamic is stable, (ii) a tracer is intravascular, and (iii) the number of the segments of CVS is finite. Let analyze the assumptions. (i) Most elusive is suggestion about stability of hemodynamic. However, for time of 10 min, with some precautions at time of BV measurement, hypothesis of stability is plausible. (ii) The CVS contains enormous number of segments, however, the huge amount of elements is due to the parallelness of the paths from heart to heart. Mathematically it means that the range of A is relatively low (about 50 at most), and there are only few singularities of the function F(s), (A.3). (iii) Any real indicator is leaking from vascular system. However, erythrocytes ^{51} Cr remains in vascular system for days and could be considered as strictly intravascular, even albumin ^{131} I with possible leakage in hours is considered as intravascular if correction for the leakage is done [9]

(2) Significance of stochastic flow. Let assume that stochastic flow is the inherent part of microcirculation. (a) Since the recruitment of microvessels is the main mechanism for increasing blood flow through any tissue [510], then the variation of flow is due to variation of the fraction of open capillaries, n_o (n_o=μ/(μ+)). This can be done by two different ways: (i) by variation of probability for close microvessels become open (it is μ), (ii) by variation of probability of open microvessels become close (it is). Both probabilities are under neural control, but metabolic influences are different. Open microvessels are a target of delivered metabolites and hormones; close microvessels are a target of local metabolites, thus the regulation of flow could be a complicated process. (b) The tissue around closed capillaries could experience a lack of delivery/removal of substrates/products of metabolism, if the R (rate of vasomotion) is low. The increase of the R could be a tool to improve microcirculation having low fraction of open microvessels. It has been shown [6] that without changes in blood flow through the tissue, just changes in R, one can change oxygen consumption 3-8 fold.

Thus stochastic flow could be a powerful tool in the regulation of a quality of microcirculation.

CONCLUSION

There are regions of microcirculation with stochastic flow as an immanent property.

APPENDIX

In sequel a_{ii} of the heart chambers will be denoted as a_j, j=1, 2, 3, 4.

Statement 1. If non-heart a_{ii}=0, then the equation Det(sA-E)=0 can be written as

Figure 4

$$(-1)^{N-k-1}\sum_{k>1}^{M}(-1)^{k+1}a_{1i_1}\cdot a_{i_1i_2}\cdot K\cdot a_{i_kN}\cdot a_{N1}s^{k+1}-(-1)^{N-4}\prod_{j=1}^{4}(1-a_j s)=0 \qquad (A.1)$$

where a_j stays for the residual fraction of the j-heart chamber and the factor $a_{1i_1}\cdot K\cdot a_{(i_kN)}$ is the probability to pass through the vascular system in (k+1) cardio-cycles.

Equation (A.1) can be rewritten as the equation for generating function [4] to pass whole CVS:

Figure 5

$$F(s)=\prod_{j=1}^{4}\frac{1}{1-a_j s}\sum_{k>1}^{M}a_{1i_1}\cdot K\cdot a_{i_kN}\cdot a_{N1}s^{k+1}=H(s)\cdot VS(s)=1, \qquad (A.2)$$

where H(s) and VS(s) are the generating functions for distribution of transit time to pass heart and vascular system, respectively. Since VS(s) is a polynomial with positive coefficients, the direct calculations show that minimum of F(s) outside singular points of H(s) is higher then 1 under condition that the heart volume is less then the volume of vascular system (formally H'(1) < VS'(1)). That means the only damped oscillations around level of complete mixing

could be observed. The estimation of frequencies follows from a Taylor decomposition of lnF(s):

Figure 6

$\ln F(1+\Delta) = 2\pi ki \Rightarrow F'(1)\Delta \approx 2\pi ki \quad \Delta = 2\pi ki / T \quad k = 1; 2; K$, with T as the mean transit time to pass the whole CVS (T=F'(1), [3]).

Statement 2. If some of the non-heart a_{jj} is non-zero then (A.2) becomes:

Figure 7

$$F(s) = \prod_{i=1}^{4} \frac{(1-a_i)s}{1-a_i s} \sum_j \left(\alpha \cdot P_{j1}(s) + \beta \cdot \frac{P_{j2}(s)}{1-s \cdot v} \right) = 1 \qquad (A.3)$$

$P_{j1}(s)$ and $P_{j2}(s)$ are polynomials. The decomposion of (A.3) in vicinity of 1/v reveals the presence of a real characteristic number:

Figure 8

$$s_2 \approx 1 + \mu + \beta \cdot T_m / T_{open} \cdot$$

where T_m is the mean time for the tracer to pass the microcirculation, and T_{open} is the mean time for the tracer to pass the heart, conductive vessels, and open for circulation microvessels.

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