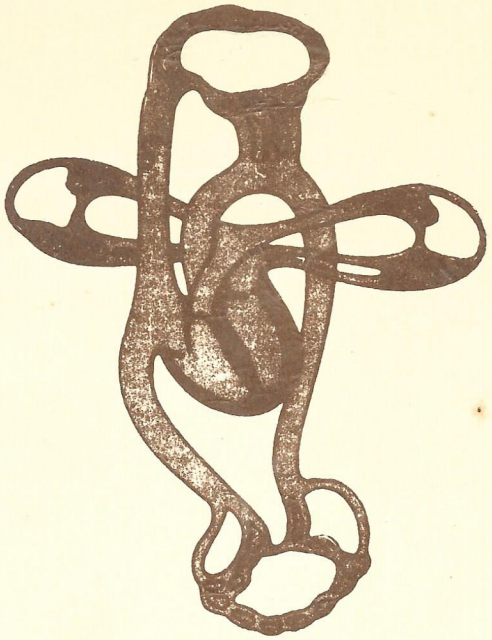

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PREDICTED LEUKOCYTE OCCUPANCY AND POTENTIAL IMPACT IN CORONARY CAPILLARIES

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INTRODUCTION The most frequently identified functions of polymorphonuclear granulocytes (PMN) are related to their antibacterial role and as components of the inflammatory process. This classic view may be too narrow in light of recent evidence and emerging concepts. Data is accumulating to suggest that via a microvascular hemodynamic impact and intrinsic biochemical release processes, hithertofore unsuspected effects may be attributable to the PMN. Of specific relavance to the present report is the fact that available experimental evidence is consistent with a hypothesis, now put foward, that the PMN can produce significant modifications to coronary microcirculation under conditions of reduced perfusion pressure such as may accompany significant large coronary artery disease. A leukocyte-coronary link is suggested by significant, but unexplained, correlations between the occurrence of a myocardial infarction (MI) and the leukocyte count of patients as early as two years before the MI [1-3]. Hemodynamic effects of leukocytes have long been suspected from observations of the living microcirculation. Phenomena which are likely involved include: adherence of activated PMN to venules and resultant flow perturbation with likely elevation in postcapillary resistance; "hold up" of PMN as they pass through small arterioles and capillaries; and physical plugging at arteriole branch points and at strategic sites within capillaries either as a single cell, a PMN aggregate, or as an embolus with the PMN serving as the nucleus for platelet aggregation. Recent quantitative studies are consistent with these concepts [4-8] but their implications to coronary hemodynamics is speculative. Studies of peripheral vascular beds [9,10] show that blood vessel blockage by leukocytes, and subsequent elevations in vascular resistance, are increased when perfusion pressure is decreased. Direct PMN plugging of myocardial capillaries has also been reported [11]. The coronary microvasculature has a unique feature which may render it more susceptible to such PMN effects. We would suggest that the intrinsic capillary flow stoppage/reduction accompanying systole will tend to augment PMN effects in a manner not present in other tissues. During periods of zero or reduced flow, the PMN is more likely to interact with vascular endothelium if appropriate stimuli are present [12-18]. Even if such adherence forces are not present the act of re-starting a stopped PMN is likely more difficult and requires more time than if such flow reductions did not occur. Thus, the coupling of a pathologically associated reduced perfusion pressure with the physiologically related cardiac dynamics and PMN properties [19] may set the stage for dire consequences. The magnitude of the predicted physiological impact of this theory is in part dependent on the extent to which leukocytes are present in capillaries at the onset of systole, thereby enhancing their candidacy for entrapment. In the work now reported a computer simulation was used to estimate the probability of PMN occupancy within a given percentage of capillaries.

MODEL ASSUMPTIONS AND STRUCTURE WBC are assumed to be distributed to a network consisting of N capillaries each with diameter D and length L. The rate of entry of wbc into the network (cells/sec) is assumed to be randomly distributed in time according to a Poisson distribution function. When a wbc enters a capillary it is assumed that no other wbc will enter the same capillary until the initial cell exits. The time a wbc remains in a given capillary is dependent on 1)the cell's unencumbered velocity, Vwbc, and 2)the accumulated time during which the cell experiences unencumbered flow. If,during

the onset of systole, a cell is within a capillary, then this cell is assumed to be halted and experiences a time delay, d, in re-starting and reaching its unencumbered velocity during the diastolic phase.

PARAMETER VALUES All results to be presented are for L=500 μm and D=6.0 μm and for a simulated network which includes N=20 capillaries. Though the computer simulation examines the effect of parameter variation on key variables the following summarizes nominal values of these parameters for reference. Coronary blood flow is taken as 85 ml/min/100gm under basal conditions and the capillary mean blood velocity, Vrbc, is taken as 0.05 cm/sec. If flow homogeneity throughout the myocardium is assumed a nominal value of 1×10^6 capillaries/gm of tissue can be calculated; thus the 20 capillaries of the present simulation represent a tissue mass of the order of 20 μgms. A mean wbc flux of about 1.4 cells/sec would be obtained for a nominal systemic PMN count of 5×10^6 cells/ml, assuming the cells distribute proportionately with flow.

SIMULATION The principal objective was to estimate the probability of PMN occupancy within the simulated coronary capillary network. Let X be a discrete random variable denoting the number of capillaries containing a wbc at any instant. The estimation of the density function, p(X), was obtained as follows. Each capillary was sampled at 0.01 second intervals for 200 consecutive seconds, yielding 20,000 total samples. During each sampling interval the number of capillaries containing a wbc was determined. With n_k equal to the number of times that k capillaries were occupied by a wbc, the determined relative frequency, $n_k/20,000$ for k=0,1,2....20 was used to estimate p(X). From p(X), which denotes the probability of occupancy of exactly k capillaries at any instant, a cumulative probability distribution function, F(X), denoting the probability that at least k capillaries contain a wbc is then easily obtained. The effect on F(X) of variations in the following parameters were then investigated: 1)arteriolar wbc concentration, [WBC]; 2)wbc cell velocity in capillaries, Vwbc; and 3)wbc re-start delay time, d, following entrapment during systole. Results here presented are for a diastolic time, T, of 0.45 seconds and for convenience the percentage of occupied capillaries, %CAP = k/20 x 100 is used.

RESULTS Illustrative data is shown in Tables 1 & 2. Table 1 lists the probabilities, F(X),(in %), that at least X % of the capillaries (%CAP) are occupied by a wbc for concentrations of 5000 and 20,000 cells/μl, and for wbc delays of 0.0, 0.1, and 0.2 seconds. All data in this table is for Vwbc=350μm/sec. Table 2 illustrates the variation in F(X) with Vwbc for the fixed conditions of [WBC] = 20,000 and a delay to diastolic time, d/T = 0.222.

TABLE 1

	d/T = 0		d/T = 0.222		d/T = 0.444	
[WBC]=	5000	20,000	5000	20,000	5000	20,000
%CAP						
00	100.0	100.0	100.0	100.0	100.0	100.0
10	47.3	99.3	58.3	99.8	75.1	99.8
20	7.9	83.8	12.6	93.5	25.6	99.3
30	0.2	49.6	0.9	68.0	5.4	93.3
40	0.0	19.9	0.0	39.2	0.0	72.8
50	0.0	6.0	0.0	14.2	0.0	47.9
60	0.0	0.4	0.0	3.8	0.0	23.2
70	0.0	0.0	0.0	0.2	0.0	9.7
80	0.0	0.0	0.0	0.0	0.0	2.5

TABLE 2

%CAP	Vwbc (μm/sec) 350	272	175	088
00	100.0	100.0	100.0	100.0
10	99.8	98.9	99.1	99.6
20	93.5	93.0	93.2	94.6
30	68.0	77.7	75.5	80.4
40	39.2	46.0	43.7	50.9
50	14.2	19.8	20.5	22.3
60	3.8	4.7	8.9	8.8
70	0.2	1.1	2.5	5.0
80	0.0	0.0	0.7	0.2

DISCUSSION From theoretical considerations one might predict that the probability of capillary occupancy by a wbc will tend to increase with increasing wbc count. This tendency is borne out by the simulation results in quantitative terms. For conditions of no assumed wbc delay, we find for example that the probability of at least 30% of the capillaries being occupied increases from 0.2 to 49.6% as the [WBC] increases from 5000 to 20,000. The fractional increase in F(X) from its value at [WBC] = 5000 depends on the X level of interest and on the magnitude of F(X) at this level. For example, at the X=20% level, F(X) increases from 7.9 to 83.8% for d/T = 0, but at the same level it increases from 25.6 to 99.3% for d/T = 0.444. The smaller fractional increase in the latter case is attributable to the greater value for F(X) associated with the longer delay time. This tendency for F(X) to increase with very moderate assumed delay times, is quite apparent from the data. For example, the probability that at least 40% of the capillaries are occupied for a [WBC] = 20,000, increases from 19.9 to 39.2 to 72.8% for progressive 0.1 sec increments in delay. The effect of Vwbc on F(X) is much less dramatic.

Variations in velocity over the four-fold range from 350 to 88 μm/sec produced only marginal effects on F(X). Similar results were obtained for greater velocities as well. From a conceptual point of view the relationship between Vwbc and F(X) is somewhat complex. If the systemic wbc count is assumed constant, then a decrease in Vwbc is associated with a decrease in the mean wbc flux entering the capillary network; this will decrease F(X). On the other hand, the velocity decrease will cause an increase in the wbc residency time within the capillary, thereby tending to increase F(X). The simulation results suggest that these two oppositely directed affects tend to balance. The balance however is not complete as may be noted from the data summarized in table 2. Though there is a trend toward a greater value of F(X) with decreasing velocity, the trend is not monotonic as there appear to be velocity ranges for which F(X) has local extremum.

CONCLUSION The simulation results suggest that wbc occupancy within capillaries of the coronary microvasculature can be sufficiently large so as to be consistent with the concept of an augmentation of their hemodynamic impact. Though it is not apriori possible to set a threshold value for the required occupancy rate, the quantitative data herein obtained clearly establishes the range of effects; the importance of systemic and quite probably local vascular wbc count; and the significance of even small delays in recovery of wbc transiently trapped within capillaries.

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