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Short Communication

Heterogeneity of left ventricular perfusion during pulmonary edema and microembolism treated with positive end-expiratory pressure and norepinephrine

M.F. Vidal-Melo[1], R. Schosser[2], C.S. Barcelos[1], B. Zwissler[3] and K. Messmer[3]

[1]*Programa de Engenharia Biomédica, COPPE, Universidade Federal do Rio de Janeiro, 21945-970 Rio de Janeiro, RJ, Brasil*

[2]*Abteilung fuer Experimentelle Chirurgie, Universitaet Heidelberg, W-6900 Heidelberg, Germany*

[3]*Institut fuer Chirurgische Forschung, Universitaet Muenchen, W-8000 Muenchen, Germany*

Regional left ventricular myocardial blood flow was studied in an experimental model of pulmonary edema and microembolization (PEM) ventilated with positive end-expiratory pressure (PEEP). The analysis was based on a 3-dimensional extension of the autocorrelation function used to assess the spatial correlation (r_{spat}) of myocardial perfusion. Experiments were performed on 8 premedicated, anesthetized and mechanically ventilated dogs. PEM was induced with oleic acid (0.01 mg/kg) and glass beads. Successive PEEP values of 10, 15 and 20 cm H_2O (P20) were applied and norepinephrine (NE, 0.2-1.0 $\mu g\ min^{-1}\ kg^{-1}$) was administered after P20. Regional perfusion was measured with radioactive microspheres. The left ventricle (LV) was dissected into 256 samples. r_{spat} was computed as the correlation of regional perfusions of samples p units apart in the apex-to-base, endo-epicardial and angular directions. Analysis was performed after anesthesia and instrumentation (control, C), P20 and NE. Control values of r_{spat} were around 50% in the apex-to-base and angular directions and the sign was inverted in the endo-epicardial direction. A reduction of r_{spat} to values close to zero was observed in all directions for P20 and NE. This is the typical pattern of independent distribution. Thus, the results indicate that, under the experimental conditions used, there is some degree of neighborhood dependence of regional LV myocardial blood flow. This dependence is not observed under PEM, mechanical ventilation with PEEP and NE.

Key words: autocorrelation, perfusion, left ventricle, microspheres, myocardial perfusion, blood flow heterogeneity.

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Correspondence: M.F. Vidal-Melo, Programa de Engenharia Biomédica, COPPE, Universidade Federal do Rio de Janeiro, Caixa Postal 68510, 21945-970 Rio de Janeiro, RJ, Brasil.

The presence of myocardial blood flow heterogeneity (MBFH) under physiological and pathological conditions is an established concept. Several methods have been used to express this heterogeneity as statistical parameters (e.g., coefficient of variation (1)) or by graphic approaches (e.g., histograms (2,3) and density functions (4)).

It has been shown that changes of MBFH occur under different pathophysiological conditions (1,2,5). It might be hypothesized that these changes are accompanied by changes of the 3-dimensional neighborhood dependences or spatial correlation of blood flow. However, none of the usual techniques for quantification of MBFH permits the study of this variable.

In the present report we use an expanded concept of the autocorrelation function, a technique employed in signal processing, to analyze left ventricular myocardial blood flow in an experimental model of pulmonary edema and microembolization (PEM) ventilated with positive end-expiratory pressure (PEEP) and pharmacologically treated with norepinephrine (NE).

Experiments were performed on 8 foxhounds (18 ± 2 kg) premedicated with 1.5-2.0 ml propiomazine, anesthetized with 20 mg/kg pentobarbital sodium, 0.75 mg/kg piritramid and 0.25 mg/kg alcuronium *iv* and maintained by continuous infusion of pentobarbital (5 mg kg^{-1} h^{-1}). Ringer solution was administered at a rate of 5 ml kg^{-1} h^{-1} throughout the experiment. The dogs were intubated and mechanically ventilated (FIO_2 = 100%, 12 cpm). Tidal volumes were adjusted to keep $P_{et}CO_2$ between 35 and 45 mmHg.

After surgical preparation, the animals were isovolemically hemodiluted with 6% dextran 60 to a hematocrit of 28% and allowed to stabilize for 30 min, after which control measurements (C) were performed. Experimental PEM was produced with oleic acid (0.01 ml/kg) and glass beads (100 µm diameter) as previously described (6). After at least 70 min of stabilization, PEEP was increased progressively to 10, 15 and 20 cm H_2O (P20). Finally, norepinephrine (NE) was administered (0.2-1.0 µg kg^{-1} min^{-1}) while PEEP was maintained at 20 cm H_2O.

Organ blood flow was measured with NEN-TRAC microspheres (diameter 16.5 ± 0.1 µm) labeled with ^{141}Ce, ^{51}Cr, ^{103}Ru, ^{114}In, ^{46}Sc or ^{95}Nb, injected into the left atrium (average of 40,000 particles/kg) within a period of 30 s. The arterial reference blood sample was drawn from the right femoral artery over 3 min at a rate of 3.24 ml/min. The regional myocardial blood flow was analyzed after C, P20 and NE.

The dissection scheme for the left ventricle (LV) is shown in Figure 1. After fixing the heart in 6% formaldehyde for 1 week, the atria were removed and the heart was dissected into 10 slices perpendicular to its axis, beginning

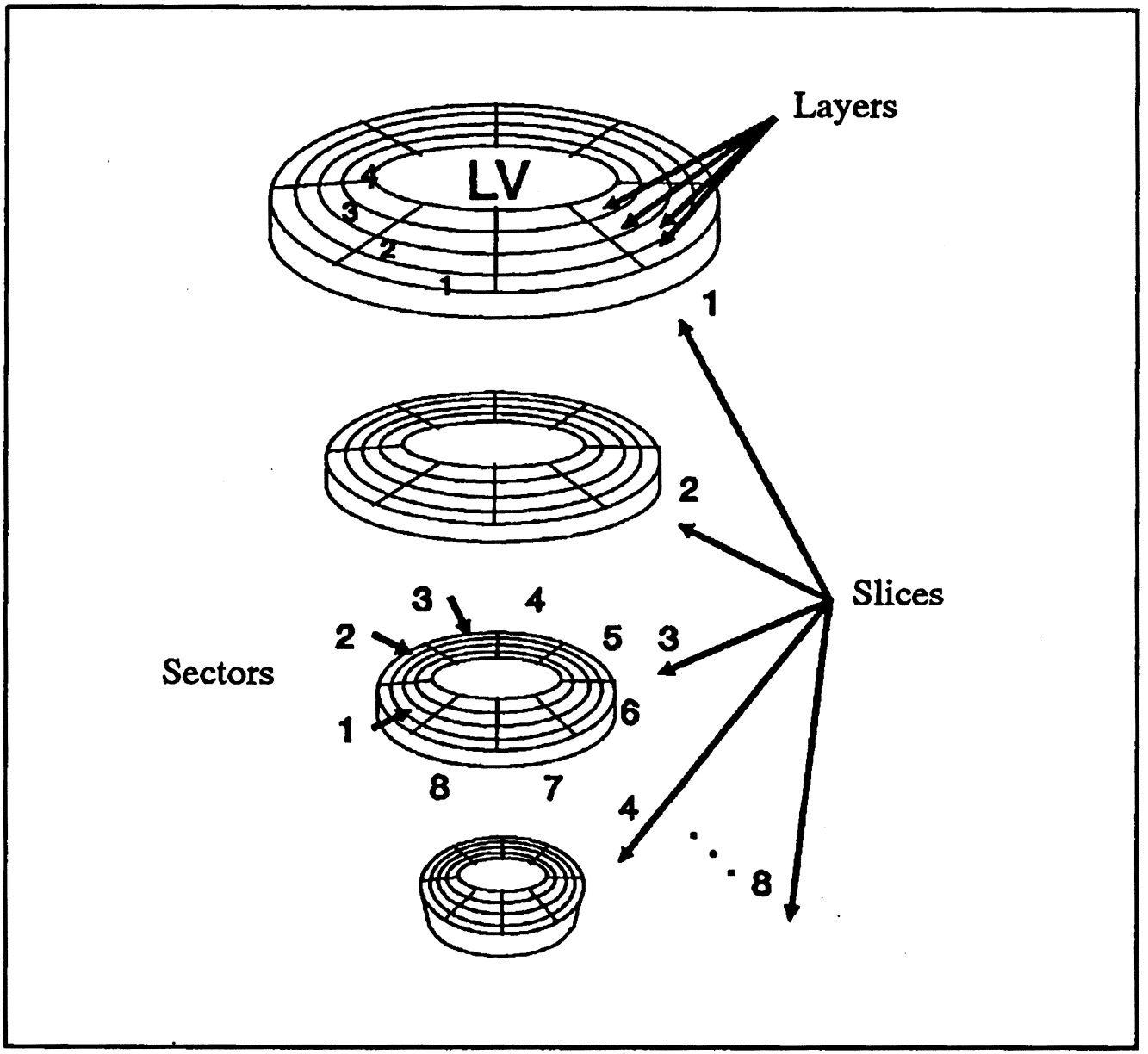

Figure 1 - Dissection scheme of left ventricular myocardium.

at the base. Slices 1-8 were subdivided into LV, right ventricle and septum. LV free wall and septum were considered to constitute the LV. Each LV slice was cut into 8 segments and further subdivided into 4 layers, resulting in 256 samples.

Spatial correlation (r_{spat}) was determined on the basis of an extension of the digital autocorrelation function estimate (7) to the 3-dimensional case. As used in this study, it provides the correlation of the relative perfusion (RP) of samples p units apart. Thus, when p = 0, r_{spat} = 1. Correlations were computed with p varying in the endo-epicardial (r = 1,4, layers), angular (a = 1,8, sectors) and apex-to-base (h = 1,8, slices) directions.

The r_{spat} estimate for each displacement p in a given direction was computed as:

$$r_{spat}(p) = \frac{V_p^{direction}}{V_{global}} \quad (1)$$

where:

$$RP_{rah} = \frac{Q_{rah}}{W_{rah}} \quad (2)$$

$$\overline{RP} = \frac{1}{N}\sum_{r=1}^{N_r}\sum_{a=1}^{N_a}\sum_{h=1}^{N_h} RP_{rah} \quad (3)$$

$$V_{global} = \sum_{r=1}^{N_r}\sum_{a=1}^{N_a}\sum_{h=1}^{N_h}(RP_{rah} - \overline{RP})^2 \quad (4)$$

$$V_p^r = \frac{N_r}{N_r - p}\sum_{r=1}^{N_r-p}\sum_{a=1}^{N_a}\sum_{h=1}^{N_h}(RP_{rah} - \overline{RP})(RP_{(r+p)ah} - \overline{RP}) \quad (5)$$

$$V_p^a = \sum_{r=1}^{N_r}\sum_{a=1}^{N_a}\sum_{h=1}^{N_h}(RP_{rah} - \overline{RP})(RP_{ra_ph} - \overline{RP}) \quad (6)$$

$$V_p^h = \frac{N_h}{N_h - p}\sum_{r=1}^{N_r}\sum_{a=1}^{N_a}\sum_{h=1}^{N_h-p}(RP_{rah} - \overline{RP})(RP_{ra(h+p)} - \overline{RP}) \quad (7)$$

N = total number of samples; N_r = number of layers; N_a = number of sectors; N_h = number of slices; Q_{rah} = blood flow measured in sample with coordinates rah; W_{rah} = weight of sample with coordinates rah; $a_p = a + p$ for $(a + p) < N_a$; $a_p = a + p - N_a$ for $(a + p) > N_a$; V_{global} = global variance of relative perfusion; V_p^r, V_p^a and V_p^h = covariance of relative perfusions of samples p units apart in the directions r (layers), a (sectors) and h (slices), respectively.

The coefficients of variation of RP for the C, P20 and NE experimental points were 25.2 ± 5.2%, 20.5 ± 3.3% and 18.4 ± 3.8% ($P<0.05$ for pairwise comparisons). Plots of spatial correlation (r_{spat}) against p in angular direction are shown in Figure 2A for C, P20 and NE. Curves are symmetrical in relation to p = 4. Note that the NE curves fall to values closer to 0 than C curves as p increases. P20 assumes intermediate values. This reduction to 0 of P20 and mainly NE can also be observed in Figure 2B for the apex-to-base direction.

Figure 2C shows plots of r_{spat} for radial direction. For p = 1 no distinction between C, P20 and NE is observed. At p = 2 and more clearly for p = 3 there is a separation between C values, which become negative, and P20 and NE values, which remain close to 0.

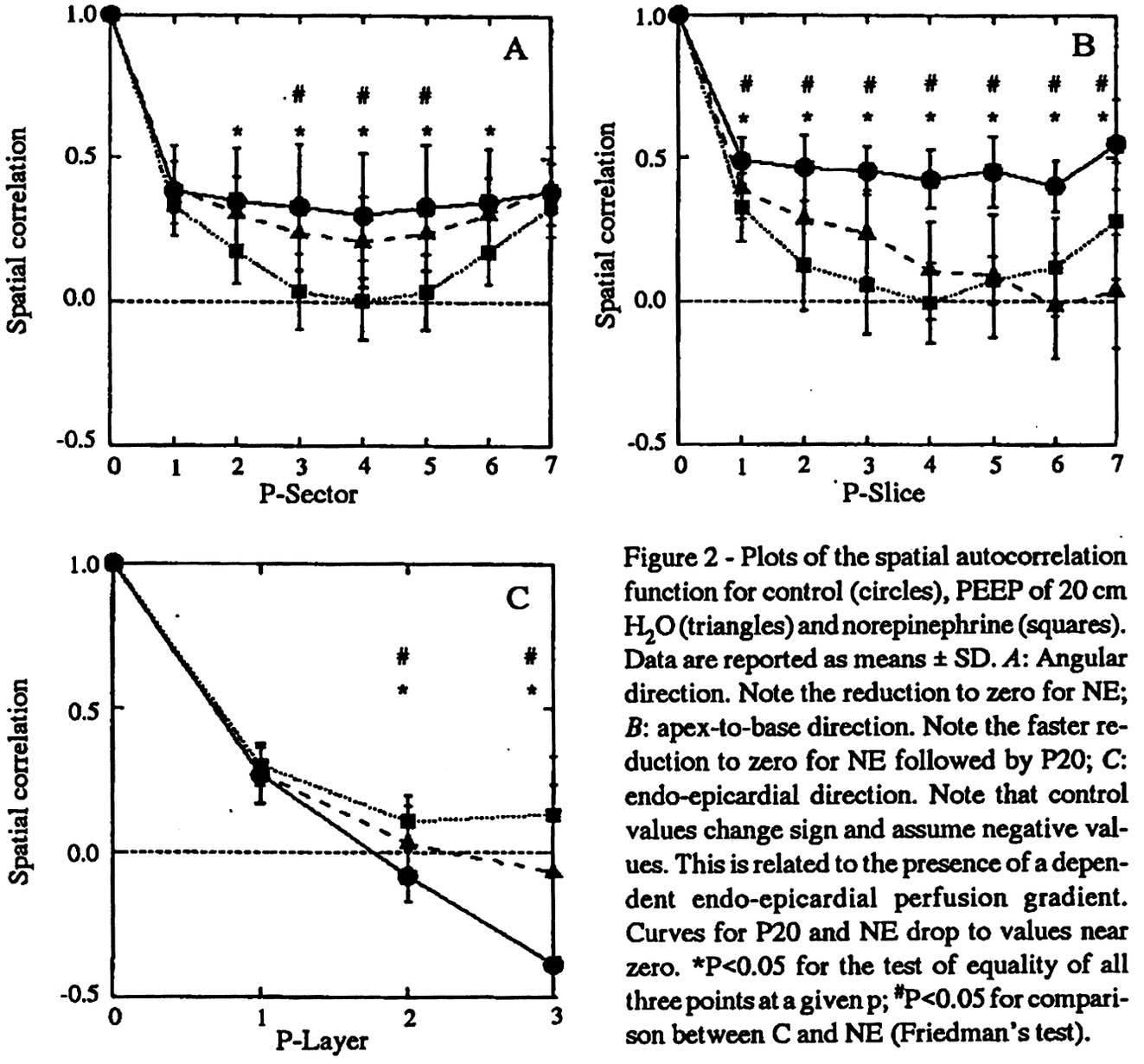

Figure 2 - Plots of the spatial autocorrelation function for control (circles), PEEP of 20 cm H_2O (triangles) and norepinephrine (squares). Data are reported as means ± SD. *A*: Angular direction. Note the reduction to zero for NE; *B*: apex-to-base direction. Note the faster reduction to zero for NE followed by P20; *C*: endo-epicardial direction. Note that control values change sign and assume negative values. This is related to the presence of a dependent endo-epicardial perfusion gradient. Curves for P20 and NE drop to values near zero. *$P<0.05$ for the test of equality of all three points at a given p; #$P<0.05$ for comparison between C and NE (Friedman's test).

Recently, van Beek et al. (8) proposed a method for estimating spatial correlation using fractal dimension. Austin Jr. et al. (5) used auto-correlation in a 2-dimensional approach, without considering direction, to assess local continuity. In the present study we present a method based on autocorrelation which considers direction and permits direct computation of the degree of 3-dimensional neighborhood dependence of LV myocardial perfusion.

In the apex-to-base and angular directions, the results show higher correlations of relative perfusion among regions for the control situation than for conditions of PEM, mechanical ventilation with PEEP 20 cm H_2O and use of NE. In these cases, values closer to 0 were observed with increasing p. In the radial direction (Figure 2C), the change in r_{spat} signal with increasing p shows the dependence of relative perfusion for the epi-endocardial region of each sector in addition to the well-known global epi-endocardial perfusion gradient. After P20 and NE, a trend toward zero, similar to the other directions, was observed.

A rapid drop to 0 in r_{spat} with increasing p is the typical pattern of independence (strictly, no linear dependence) (7). Thus, the observations based on 3-dimensional autocorrelation function demonstrate that, under the experimental conditions used, there was some degree of neighborhood dependence of regional LV myocardial blood flow. Under conditions of PEM, mechanical ventilation with PEEP of 20 cm H_2O and use of NE, in addition to more homogeneous distribution of relative perfusion, there was a significant decrease of neighborhood dependence.

References

1. Sestier FJ, Mildenberger RR & Klassen GA (1978). *American Journal of Physiology*, 235: H64-H71. 2. Schanzenbacher P & Klocke FJ (1980). *Circulation*, 61: 590-595. 3. Marcus ML, Kerber RE, Ehrhardt J & Abboud FM (1975). *Circulation*, 52: 254-263. 4. King RB, Bassingthwaighte JB, Hales JRS & Rowell LB (1985). *Circulation Research*, 57: 285-295. 5. Austin Jr RE, Aldea GS, Coggins DL, Flynn AE & Hoffman JIE (1990). *Circulation Research*, 67: 319-331. 6. Zwissler B, Forst H, Ishii K & Messmer K (1989). *Research in Experimental Medicine*, 189: 427-438. 7. Bendat JS & Piersol AG (1971). *Random Data: Analysis and Measurement Procedures*. Wiley- Interscience, New York, 18-22, 181-184, 311-314. 8. van Beek JHG, Roger SA & Bassingthwaighte JB (1989). *American Journal of Physiology*, 257: H1670-H1680.

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