FETAL CARDIAC BYPASS ANALYSIS BY MEANS OF CORRELATION DIMENSIONS

G. D'Avenio, C. Daniele and M. Grigioni
Dept. of Tecnology and Health, Istituto Superiore di Sanità, Rome, Italy

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Abstract: During in vivo experiments of fetal cardiac surgery performed in sheep, physiological signals were recorded, and subsequently analyzed. In order to characterize their complexity, the fractal dimension was calculated. The adopted model of dimension estimation allowed for a possible multifractal nature of the signals, by considering two distinct fractal dimensions ν_1, ν_2 at different length scales. A comparison was also carried out with an alternative measure of system complexity, Approximate Entropy (ApEn). The results of the analysis suggest that fractal dimension may be a useful indicator of the cardiac stress and, ultimately, of the quality of the support delivered during the operation.

1 INTRODUCTION

Fetal cardiac surgery is actively being studied worldwide, with the favourable prospective of providing the treatment of congenital cardiac malformations as early as possible. In principle, in utero interventions would allow to treat simple primary lesions in order to prevent complex secondary ones. The physiologic fetal low-flow condition and the possibility to use the residual pregnancy as a sort of natural ECMO would allow for the anatomic and functional recovery of the fetus. The final result would be the absolute avoidance of systemic consequences of congenital heart lesions with overall better outcomes compared to those obtained by application of current neonatal and infant repair techniques (Hanley, 1994; Carotti et al., 2003).

However, although the technical feasibility of fetal cardiac or cardiopulmonary bypass has already been demonstrated (Sakata et al., 1998; Reddy et al., 1996a; Reddy et al., 1996b), its main drawback remains the progressive deterioration of the fetoplacental unit function, occurring especially during the post-bypass recovery phase. Hence, a relevant research effort is ongoing, based on methods to improve the fetoplacental tolerance and to monitor the fetoplacental unit function during extracorporeal circulation (Carotti et al., 2003).

In our study we sought to investigate the effectiveness of new methods for monitoring left ventricular contractility during experimental fetal cardiac surgery procedures, based on a nonlinear analysis of the left ventricular pressure, according to the concept of fractal dimension.

The aim of the study was to provide useful insights on fetal monitoring with regards also to the topic phase of post-operative recovery.

2 MATERIALS AND METHODS

The experimental model used for fetal surgery procedures was the fetal lamb at 110 to 130 days of gestation (delivery term is approximately 145 days). Two animals were selected and managed according to the anaesthesiological and surgical protocols already described (Grigioni et al., 2000), in compliance with the Guide for Care and Use of Laboratory Animals of the Italian Ministry of Health.

Prolonged extracorporeal circulation (ECC) was run under steady-flow assistance without the use of an oxygenator, using a miniaturized bypass circuit to minimize the autologous priming volume (Carotti et al., 2003).

Left ventricular pressure was measured with a Millar pressure transducer (Millar Instruments, Inc., Houston, Texas. USA), mounted on a catheter tip. A 12-bit A/D board (AT-MIO16F, National Instruments, USA) was used to sample the signal at the output of the pressure amplifier, under control of

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an original software developed in the LabView (National Instruments Corp., USA) environment. The analysis of the signals was carried out by means of original Matlab (The MathWorks, Natick, MA, USA) programs.

After instrumentation of the animal, the baseline signals were recorded. Subsequently, atrial venous and pulmonary arterial cannulation were performed and a 60-min. cardiac bypass was run at a flow rate of 300 ml/Kg/min. At the end of the circulatory assistance the cannulae were removed, blood priming volume was reinfused, and a 90-minute observation period followed (recordings at 30, 60, 90 min. after ECC) before animals were sacrificed.

Correlation dimension. The left ventricular pressure was analyzed using the estimation of the fractal dimension, according to the method of (Grassberger and Procaccia, 1983).

Denoting by x the signal whose fractal dimension is to be calculated (in this case, the left ventricular pressure), the set of points defined as

$$\xi_i = \{x(t_i), x(t_i + \tau), ..x(t_i + (m-1)\tau)\}, \; i = 1,2,..N \quad (1)$$

where τ is an appropriate delay, constitute a geometrical object (usually denoted as an attractor) which is embedded in the m-dimensional phase space.

The dimension of this object, then, will be smaller than m, for sufficiently high values of m. Denoting the correlation integral as

$$C(l) = \lim_{N \to \infty} \frac{1}{N^2} \sum_{i,k=1}^{N} \theta\left(l - |\xi_i - \xi_k|\right), \qquad (2)$$

where $\theta(x) = 1$ for x>0 and $\theta(x) = 0$ otherwise, ξ_i and ξ_k being two noncoincident points in the phase space, defined by (1),it can be demonstrated that, for small values of the distance l, $C(l) \propto l^{\nu}$. The exponent ν can be considered as the fractal dimension of the constructed set of points in the phase space.

In the current study, the delay τ was chosen equal to $\tau_{1/2}$, i.e., the value at which the autocorrelation function $f(\tau)$ of the original pressure signal falls at half its maximum value, $f(0)$. Thus, an excessive degree of correlation between components of the vectors ξ_i was avoided. In fact, setting τ at a very low value has the consequence that the attractor is stretched along the diagonal of the phase space, as shown in Fig. 1; this renders more difficult to compute the correlation dimension. It is convenient, instead, to choose τ equal to $\tau_{1/2}$, yielding a more expanded structure in the phase space, and at the same time not having too much decorrelation between the components of ξ_i, which would be characteristic of a purely noisy signal.

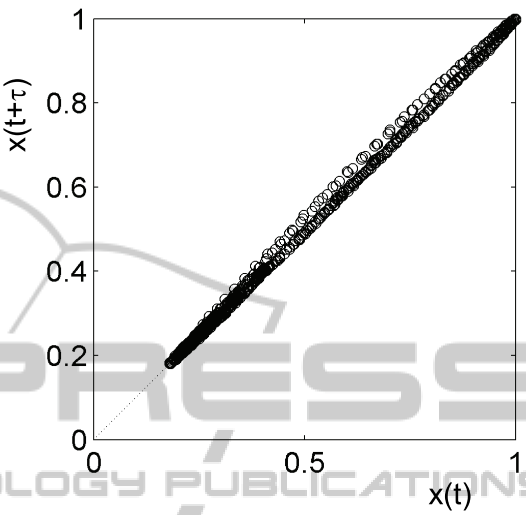

Figure 1: Two-dimensional section of the attractor composed of the points ξ_i, according to (1), when τ =1 ms. The time series x(t) is the left ventricular pressure recorded during the experiments described in the text. In this limit case, the attractor is stretched along the diagonal of the phase space, rendering more difficult the extraction of the correlation dimension.

In this study, we adopted a slight modification of the correlation integral, proposed by (Theiler, 1986). This procedure is aimed at minimizing the effect of the degree of autocorrelation present in the original signal, in that the linear range (in the log-log plane) of the correlation integral is not restricted, as happens with the original Grassberger-Procaccia algorithm. In the following, a Theiler window of T=5 sampling points was employed in the calculation of the modified form of the correlation integral.

The dimension of phase space was set to m=5. As shown in the Results section, this is higher than what is strictly required for the calculation of a fractal dimension ν (i.e., m>2ν, according to the Takens criterion (Takens, 1980)). In order to have a more general estimation scheme, we considered more than a single fractal dimension. Thus, a pair (ν_1, ν_2) of fractal dimensions was calculated, ν_1 (ν_2) being the slope of the regression line relative to lower (higher) distances *l* in the phase space. The cut-off distance marking the separation between the low- and high-distance regions was found as the one warranting a good quality of the $C(l)$ data fit: considering, for each regression line, the correlation between the $C(l)$ points and the relative approximating line, in terms of the Pearson correlation coefficient r, the cut-off distance l' between the two regions was yielded by the maximization of the sum of the coefficients r relative to the low and high distances l in the phase space.

The usefulness of calculating two correlation dimensions was verified with the analysis of a monodimensional signal, whose values were given by the abscissae of the Cantor set (Mandelbrot 1982), with noise added to investigate about the efficiency of the proposed scheme for correlation dimension estimation.

The Cantor set is a fractal object, built with an iterative procedure. In the first step, the interval [0, 1] is split in three equal parts, and only the intervals [0, 1/3] and [2/3, 1] are retained. For the n-th iteration, each of the intervals retained after the n-1-th iteration is subjected to the same procedure, discarding the central third. The Cantor set is comprised of the extrema of the retained intervals, in the limit $n \to \infty$. For such a fractal set, the Hausdorff-Besicovich dimension is $D_{HB} = \log(2)/\log(3)$.

Since it has been demonstrated that $D_2 \le D_{HB}$, D_2 denoting the correlation dimension (Grassberger and Procaccia, 1983), we compared the result of the correlation dimension calculation with the theoretical value, $\log(2)/\log(3)$. This is particularly well-grounded, in this case, since the strict inequality $D_2 < D_{HB}$ can be expected only for the case of a dynamical system not spanning uniformly the phase space, whereas the uniform coverage of the attractor implies that $D_2 = D_{HB}$ (see section 3 of (Grassberger and Procaccia, 1983)). In our example the data points were taken once and only once from the Cantor set, so that it can be excluded that some regions of the phase space were covered more often than others. Therefore, we expect that $D_2 = D_{HB}$ $= \log(2)/\log(3)$.

We added to the series $x_c(k)$, generated after 13 iterations of the procedure previously described, a noise with a flat probability density function, of zero mean and range equal to 2^{-11}. The embedding dimension was set to m=1. As shown in Fig. 2, where the value $(1/2)2^{-11}$ is marked by a vertical line, the determination of two fractal dimensions correctly highlights the presence of additive noise: at the lower values of l, the fractal dimension ν_1 was found to be 0.9434, as a result of the "space-filling" property of stochastic data (Grassberger and Procaccia, 1983), i.e., the noise added to the Cantor set data. Instead, the calculated value of n2 was 0.6277, very close to the theoretical value 0.6309.

Had a unique correlation dimension been carried out, it would have been biased by the noisy data, and overestimated (in this example, n=0.6614). Thus, the proposed procedure can be used to automatically identify a noise level, and calculate the appropriate correlation dimension above that noise level, making use efficiently of the available data. It must be underlined that this is a parameter-free procedure.

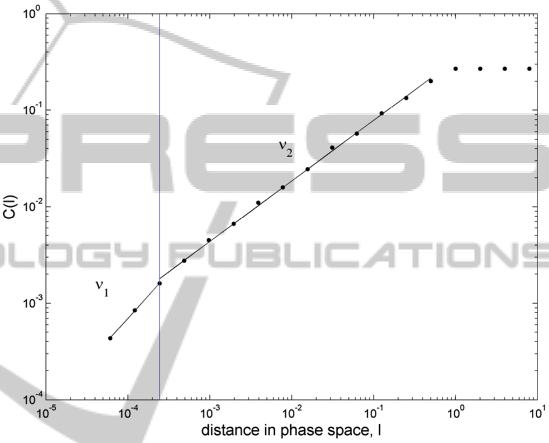

Figure 2: Calculation of the correlation dimensions ν_1, ν_2, for a synthetic signal consisting of the Cantor set with zero-mean added noise, in the range ±a, with a= $(1/2)2^{-11}$ (this value is overlaid as a vertical line). The higher-scale correlation dimension ν_2=0.627 agrees well with the theoretical fractal dimension of the Cantor set, notwithstanding the presence of the additive noise.

In order to investigate about the nonlinear features of the signals, we analysed also the surrogate time series derived by the originals signals with the iterative amplitude adjusting procedure, described in (Schreiber and Schmitz, 1996). With this technique, the amplitude distribution and the power spectrum of the original signal are simultaneously retained, for each generated surrogate. The algorithm consists of a simple iteration scheme: a sorted list is stored of the time-series values $\{x_n\} \equiv \{x(t_n)\}$, together with the squared amplitudes of the Fourier transform of $\{x_n\}$, denoted by $\{X_n^2\}$. A random shuffle (without replacements) $\{x_n^{(0)}\}$ of $\{x_n\}$ is calculated. Then, each iteration consists of two steps: 1) $\{x_n^{(i)}\}$ is brought to the desired power spectrum, using the

original squared amplitudes $\{X_n^2\}$ in the Fourier transform of $\{x_n^{(i)}\}$, retaining the phases of the transform itself and transforming back; 2) rank order the resulting series, in order to impart to it the original amplitude distribution given by $\{x_n\}$. The algorithm is iterated until a negligible change in the spectrum is attained between successive iterations.
Before extracting the correlation dimension of the surrogates, we checked for a possible nonstationarity, that would have biased the conclusions derived from the surrogate analysis. In particular, we adopted the weak stationarity criterion (Andrzejak et al., 2001), which compares the average deviation of the amplitudes and of the center frequency of the signal (F^x and F^ω, respectively) with the same quantities, calculated for each of the N surrogates (here, N=40). The criterion requires that F^x (F^ω) must fall within the range of $F^x_{surr,i}$ ($F^\omega_{surr,i}$), i=1,2,.. N.
An alternative measure of system complexity, Approximate Entropy (ApEn) (Pincus, 1991), was also adopted to analyze the data, in order to quantify the amount of regularity in left ventricular pressure recordings. Approximate Entropy represents a family of statistics, hence it is denoted as $\mathrm{ApEn}(m,r,N)$, where m is the dimension of the vectors built with the time series data (left ventricular pressure in the current study), r is a vector comparison distance and N is the length of the data array. In the present study, we set m=2 and $r = 0.2 \times \mathrm{std.\,dev.}(X)$; these values give reliable results for N>1000, as reported in (Pincus, 1991)

3 RESULTS

Fig. 3 reports the results of the correlation dimension analysis for the experiment A, at baseline condition, during the extracorporeal circulation, and during the post-ECC recovery phase (at 1, 30 and 90 minutes after ECC). Fig. 4 provides the same information for the experiment B.
The statistical analysis of the results for the correlation dimension relative to different phases of the experiments is reported in Table I and II, for case A and B, respectively.

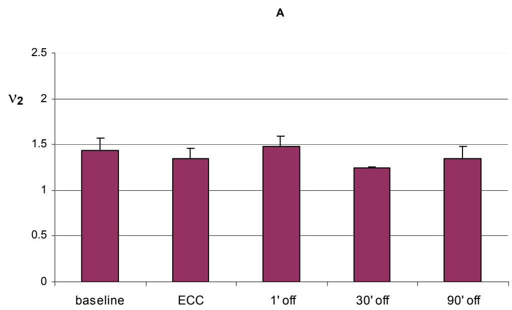

Figure 3: Correlation dimension ν_2 during the course of the experiment A (mean value + s.d.).

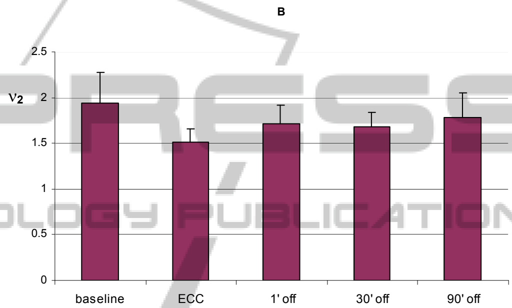

Figure 4: Correlation dimension ν_2 during the course of the experiment B (mean value + s.d.).

As shown in the error bars in Figs. 3-4, the standard deviation of the measurements for the fractal dimension was small, assuring a satisfying repeatability of the measurements (typically three consecutive recordings were used in each phase).
The effect of the ECC phase on the dimension of the relative attractor is evident in case B, where lower values of the correlation dimension ν_2 were found with respect to the baseline. On the other hand, a less evident effect, if any, was found in case A. The t-test for the difference in ν_2 between baseline and ECC supports this view (Table 1 and 2).
As for the surrogate analysis, the weak stationarity criterion was always met by the signals and the respective surrogates, then we proceeded to compare the correlation dimension for the two types of data. Fig. 5 reports the results of the surrogate analysis for one recording relative to each of three phases of the experiment (case A, baseline and 30 and 90' off-ECC). A slight variation of the calculated value from the one reported in Fig. 3, for the relative phase, is due to the fact that, in the same graph, values were averaged over three runs, whereas in Fig. 5 only one run and the relative surrogates were depicted, for the

sake of clarity. It is evident how the calculated correlation dimension ν_2 of the original was found to lie outside of the range of the respective surrogate ensemble (with only one exception for the 30' off case), so that there is a strong indication for nonlinearity.

Table 1: Results of t-tests between the correlation dimension values ν_2 relative to different phases of experiment A.

exp. A	basal	ECC	1' off	30' off	90' off
basal		0.139	0.403	**0.037**	0.443
ECC			**0.038**	0.155	0.273
1' off				0.152	0.344
30' off					**0.025**

Table 2: Results of t-tests between the correlation dimension values ν_2 relative to different phases of experiment B.

exp. B	basal	ECC	1' off	30' off	90' off
basal		**0.003**	**0.024**	**0.007**	0.057
ECC			0.135	0.378	0.083
1' off				0.670	0.783
30' off					0.298

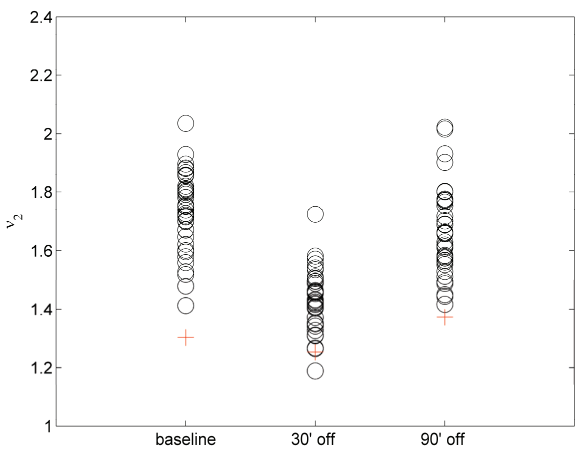

Figure 5: Surrogate analysis, case A, baseline and 30 and 90' off-ECC. Crosses (circles): correlation dimension ν_2 relative to the original (surrogate) data.

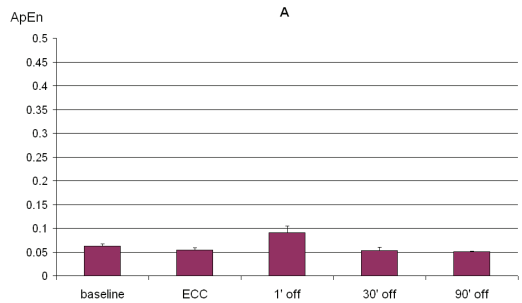

Figure 6: Approximate Entropy (ApEn) during the course of the experiment A (mean value + s.d.).

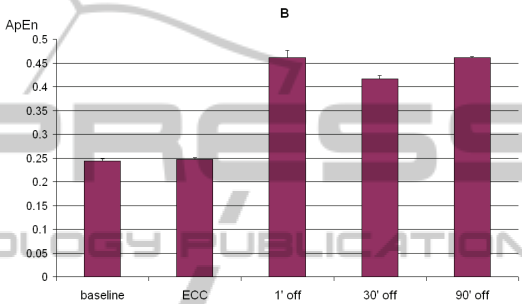

Figure 7: Approximate Entropy (ApEn) during the course of the experiment B (mean value + s.d.).

With regard to the Approximate Entropy values (Fig. 6 and 7), in case A we did not find a very large difference between the start and the end of the experiment (Fig. 6). A slight decrease of ApEn was observed during ECC with respect to baseline, as also in Fig. 3 for correlation dimension.

Instead, for case B (Fig. 7) a marked increase of ApEn can be seen for the off-ECC phases with respect to both basal and ECC. In this case, the transition from the basal state to any of the post-ECC phases was always significant; the same applies also for the transition from the ECC phase to any of the post-ECC phases.

A clear increase of ApEn was found for the post-ECC pahse with respect to baseline, for both cases. This confirms that a higher degree of irregularity characterize the phase immediately after return to unassisted circulation.

Later on, during the experiments, in case A ApEn returned to the lower values observed during baseline (Fig. 6), whereas for case B the values remained high at 30' and 90' post-ECC phases (Fig. 7).

The transition between 1' off and 90' off is related to significant difference for both correlation dimension and ApEn, for case A. In this case, we recall that the experiment could be carried out with no apparent problem until the end of the protocol. Thus, it can be assumed that from 1' to 90' a normalisation of the foetus conditions took place. As opposed to this, in case B the same transition is not statistically significant, for both analysis techniques. Probably, the lack of a satisfying return of the cardiac function to normal values, in this case, is reflected by a not statistically significant difference between the start and the end of the post-ECC phase.

4 DISCUSSION

The estimation of the fractal dimension according to the method of Grassberger and Procaccia (1983) is especially useful for the analysis of single-variable temporal series.

As already reported in the Methods section, we considered more than a single fractal dimension in order to have a more general estimation scheme. Thus, a pair (ν_1,ν_2) of fractal dimensions was calculated, ν_1 (ν_2) being the slope of the regression line relative to lower (higher) distances *l* in the phase space.

The presented results refer only to the fractal dimension ν_2, because at the lower distances the effect of noise can be important, possibly masking useful information connected to the physiological conditions. For instance, noise is produced by the A/D conversion of the LV pressure (quantization noise), acting at the scale corresponding to the minimum difference between levels at the output of the converter. Moreover, the effect must be also considered of the noise related to the electronics of the acquisition apparatus before sampling. A well-known property of noise is that its correlation dimension is ideally equal to the embedding dimension, because the phase space tends to be filled uniformly by the vectors (Grassberger and Procaccia, 1983). Even though this is rigorously true only for an infinite time series, it has been observed (e.g., Osorio et al., 2001) that also for finite-size data there is an increase of the correlation dimension with the embedding dimension. Therefore, we chose to retain only the correlation dimension ν_2 relative to higher spatial scales, which is less affected by the presence of noise. This procedure may be viewed as a nonlinear filtering of the pressure signals, which allows to discard their noisiness' effect on the fractal dimension estimation. It is evident that, in the ideal case of a signal for which at all scales, we would find $\nu_1 = \nu_2$, hence the proposed scheme is a generalization of the more usual single dimension analysis. The correlation dimension technique has already been used in (Yambe et al., 1996) to estimate the complexity in physiological signals; specifically, the arterial blood pressure waveform was analysed to derive the fractal dimension during natural and assisted blood flow. A lower dimension was found for the assisted circulation phase, which is in agreement with the results of the present paper (see Figs. 3 and 4). However, it must be taken into consideration that the results in (Yambe et al. 1996) refer to a single fractal dimension, not allowing for an eventual multifractal nature of the signal, as opposed to the present study.

Besides correlation dimension, as an alternative measure of system complexity, Approximate Entropy was also used to characterize the evolution of the experiments. As demonstrated in (Pincus, 1991), ApEn is capable of capturing the increasing complexity of low-dimensional nonlinear deterministic systems and of stochastic models, being positively correlated with the degree of such complexity.

The results for ApEn were in agreement with those relative to the correlation dimension ν_2. In particular, comparing the two quantities, the variation between consecutive phases was almost always of the same sign, for case A as well as for case B. It must be also underlined the fact that ApEn increased for both experiments after the return to the unassisted circulation, with respect to the ECC phase; the same effect was observed for ν_2.

The starting condition of the two experiments was quite different, as shown by the higher blood concentration of endogenous catecholamine in experiment B compared to experiment A. This difference could be related to a different response to general anesthesia, as previously reported (Reddy et al., 1996b).

Since the "baseline" condition is actually the state after the delivery of anaesthesia, the comparison of this phase in Fig. 3 and 4 shows that there is a possible positive correlation between the fetal stress (and the consequent release of agents capable of increasing the ventricular contractility) and the values of ν_2. Another evidence of the correlation between fetal stress and fractal dimension may be recognized in Figs. 3 and 4, observing that the transition ECC – 1' off, which is an obviously stressful event, is in both cases related to an increse in ν_2. This result was statistically significant only for experiment A, though (see Tables I and II).

A difference in fractal dimension between the beginning and the end of the procedure was found to be much more statistically significant in experiment B than in case A (see basal – 90' off ECC transitions in Tables I and II). This may confirm that in case A the mechanical assistance to the circulation was followed by a favourable outcome of the experiment, since the ventricular function 90 minutes after the return to the normal circulation was found to be associated to a not statistically significant difference with respect to the pre-bypass phase, (p=0.443), whereas the p value associated to the same transition for case B was just above p=0.05. The values of ν_2 were already high in the basal condition for case B (Fig. 4), probably as a consequence of a poor response to general anesthesia, and the highly statistically significant lessening of ν_2 in the post-bypass phase with respect to the baseline is probably closely related to such conditions. The general trend is the same for the two experiments, with a decrease of ν_2 at 30' off after a high value of ν_2 at 1' off, and a slight increase found at the end of the experiment (90' off). The results of 1' off ECC phase confirm that the phase immediately following the stop of the extracorporeal circulation is particularly critical. In Table I the transitions ECC-1' off and 30' off – 90' off for case A are statistically significant. Instead, in case B such transitions are not significant. This could be related to a less successful clinical outcome of the procedure, with lower blood pH values than in case A (Grigioni et al, 2000). In particular, the comparison of the values related to ECC - 1' off, p=0.038 vs. 0.135, could indicate the loss of a clear recovery from the withdrawal of the assistance, due to the already compromised metabolic conditions, for case B.

Estimation of fractal dimension can be very useful to characterize the complexity of physiological signals, which can be related to the state of the cardiovascular system. Moreover, this analysis could be used in conjunction with other, more traditional types of analysis, such as the end-systolic pressure-volume relationship (ESPVR), already employed in (Grigioni et al, 2000) to evaluate the recovery of the ventricular contractile state after steady-flow support.

Since the methods hereby presented require the calculation of the distances between N points in the phase space, its complexity is O(N^2). A possible real-time implementation is related to the improvement in computing power and to the significance of the use of data segments of reasonable length.

5 CONCLUSIONS

The proposed generalization of the usual single-dimension analysis, allowing for the possible multifractal nature of the ventricular pressure signal, proved to be effective in tracking the evolution of the ventricular contractility in the considered experiments.

In particular, a decrease of the fractal dimension associated with the physiological signal of interest was observed during the assisted circulation phase, consistently with earlier findings (Yambe et al., 1996). The considered method does not require very long data segment, thus it could also be used to monitor in real time the heart's conditions, in assisted conditions as well as in the normal functionment.

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