Ann Ist Super Sanità 2004;40(4):401-409

Evolutive algorithms for beat-by-beat estimation of left ventricular mechanics

Mauro GRIGIONI, Carla DANIELE, Umberto MORBIDUCCI, Giacomo DI BENEDETTO, Giuseppe D'AVENIO, Costantino DEL GAUDIO, Mara ABBATE e Vincenzo BARBARO

Dipartimento di Tecnologie e Salute,
Istituto Superiore di Sanità, Rome, Italy

Summary. - Traditional methods to evaluate the ventricular mechanics need intraventricular pressure and volume recordings for multiple variably loaded beats. To do this, a complex and invasive procedure must be applied, that may decrease the clinical use. To overcome this limitation, a method to estimate the ventricular mechanics beat-by-beat is presented, modeling the ventricular pressure-volume relationship with a time-varying elastance function. The ability of the genetic algorithms (GAs) as identification technique is exploited. Applying GAs on surrogated data simulating variably loading conditions, the parameters of the time-varying elastance function, considered a measure of the contractility of the myocardial fibers are identified. These single-beat estimates are highly correlated with the end systolic pressure-volume relationship slope obtained by conventional multiple-beat analysis. The main advantage in using GAs for single beat analysis may lie, in the perspective of an use for *in vivo* investigations, both in their stochastic nature, and in the guaranteed better performance with respect to other search techniques on problems involving noisy signals. Future studies will approach the reduction in GAs computational costs, for a real time *in vivo* application.

Key words: myocardial contraction, ventricle, genetic algorithms.

Riassunto *(Algoritmi evolutivi per la stima battito-battito della meccanica ventricolare).* - La valutazione della meccanica ventricolare con i metodi tradizionali viene eseguita mediante l'acquisizione di segnali di pressione e volume ventricolari su più battiti, mentre viene fatto variare il carico sistemico. È evidente come una tale procedura possa risultare complessa ed invasiva, tanto da limitarne l'uso clinico. Al fine di superare una tale limitazione, viene proposto un metodo per la stima della meccanica ventricolare sul singolo battito, facendo uso di un modello matematico di elastanza tempo-variabile per rappresentare la relazione pressione-volume ventricolare, e valutando la abilità degli algoritmi genetici (AG) come tecnica di identificazione del modello stesso. Mediante la applicazione di AG, sono stati identificati i parametri del modello di elastanza tempo-variabile, considerati una misura della contrattilità delle fibre del miocardio. Le stime ottenute sul singolo battito risultano essere significativamente correlate con la pendenza della relazione pressione-volume di fine sistole, ottenuta tramite il metodo convenzionale che si basa su una analisi di più battiti. Il principale vantaggio nell'utilizzo degli AG potrebbe essere, nella prospettiva di un utilizzo in applicazioni cliniche, sia insito nella sua natura stocastica, sia nella superiorità rispetto ad altre tecniche di identificazione, in presenza di segnali rumorosi. In futuro, la ottimizzazione nella applicazione degli AG al problema affrontato, al fine di ridurre i costi computazionali, potrà permettere un uso *in vivo* del metodo proposto, in tempo reale.

Parole chiave: contrazione del miocardio, ventricolo, algoritmi genetici.

Introduction

The evaluation of the contractile state of the left ventricle is a fundamental topic both in the assessment of pathological heart behaviour and in physiological investigation. A functional characterization of the pumping properties of the heart, working under varying loading conditions, can be provided through the generation of ventricular pressure-volume relationships, that offers a very useful method to study cardiac diseases.

The end systolic pressure-volume relationship (ESPVR) was defined by Suga *et al*. [1] on the basis of the observation that the left upper corners of pressure-volume diagrams (named end systolic pressure-volume points), describing different loading conditions (in the

Indirizzo per la corrispondenza (Address for correspondence): Mauro Grigioni, Dipartimento Tecnologie e Salute, Istituto Superiore di Sanità, V.le Regina Elena 299, 00161 Roma. E-mail: grigioni@iss.it.

same inotropic state), can be considered as fitting a straight line throughout the physiological range: "the left upper corners of pressure-volume loops (the end systolic pressure-volume points) obtained at various loads at a constant inotropic state appeared to reach the same straight line" [2].

The approximate linearity of the ESPVR allows to describe it with two parameters, i.e. its slope, named E_{es}, and its intercept with the axis of volumes, named V_0. To date, the couple E_{es}, V_0 is considered as an index of contractility of the myocardial fibers. Suga *et al*. [1] assessed the extension of the linear relationship between pressure and volume to the entire cardiac cycle, giving rise to a time-varying elastance function model able to describe the contractile state of the heart. The traditional methods need intraventricular pressure and volume recordings for multiple variably loaded beats, to generate ESPVRs. To do this, a complex and invasive procedure must be applied: two features that may decrease their clinical applicability. In the last decade, particular attention was placed in the individuation of methods for the estimation of E_{es} from a single-beat analysis [3-10], with the aim to quantify contractile changes on a beat-by-beat basis.

Senzaki *et al*. [3] proposed a very fast, real time method that may furnish an estimation of the ventricular contractility: this method requires just two points, the choice of one of them, being fixed *a priori*, may be a limitation in presence of noisy signals. Approximating the elastance of the ventricle with a bilinear function, Shishido *et al*. [10] estimated E_{es} over a wide range of contractility and loading conditions on a single beat basis without instantaneous ventricular volume values other than the end systolic one, but requiring the knowledge of the systolic time intervals, pressure values and stroke volume.

Object of the present study is a beat-by-beat estimation of the pumping properties of the left ventricle, modeling the left ventricular pressure-volume relationship with a time-varying elastance function, following the same law as proposed in [1]. The time-varying elastance function is characterized by three parameters, representing the maximum value of the elastance function, the time in the cardiac cycle when this function reach its maximum, and the value of ventricular volume in correspondence to which the ventricle is no more able to generate pressure, respectively.

The estimation was obtained by using genetic algorithms (GAs), recently applied in cardiovascular modeling [11]. GA is a random search algorithm for nonlinear problem based on the rules of natural selection. These algorithms shown to outperform alternative search techniques on difficult problems involving discontinuous, noisy, high dimensional, and multi-modal objective functions [12]. As test signals, surrogated foetal left ventricular pressure and volume waveforms were used. The surrogated data were synthetized by means of a mathematical model of the foetal cardiovascular system previously presented in Grigioni *et al*. [11].

To validate the proposed methodology, the conventional method of the ESPVR, based on multiple beats [1, 2], and another single-beat estimation method [3] were applied on the same data.

Methods

Model definition

In the present study, the relationship between left intraventricular pressure $P(t)$ and left ventricular volume $V(t)$ (as in. Suga *et al*., [1], and in Suga and Sagawa [4]) was assumed as model of the pumping properties of the heart:

$$P(t) = E(t) \cdot (V(t) - V_0) \tag{1}$$

where V_0 is a parameter representing the value of ventricular volume in correspondence to which the ventricle is no more able to generate pressure during the systolic phase [13], and $E(t)$ is the time varying ventricle elastance, defined by:

$$E(t) = E_{max} \cdot E_n(t) \tag{2}$$

E_n being the ventricular elastance function normalized in amplitude and E_{max} the maximum of $E(t)$ function. To model the systolic phase of the left ventricle we used the expression of $E_n(t)$ defined in [14], who interpolated the normalized elastance function in time and amplitude measured by Suga *et al*. [1] with the following function:

$$E_n\left(\frac{t}{T_{max}}\right) = 5.412 \cdot \left(\frac{t}{T_{max}}\right)^6 - 20.066 \cdot \left(\frac{t}{T_{max}}\right)^5 + 25.542 \cdot \left(\frac{t}{T_{max}}\right)^4 - 13.714 \cdot \left(\frac{t}{T_{max}}\right)^3 + 2.714 \cdot \left(\frac{t}{T_{max}}\right)^2 + 1.085 \cdot \left(\frac{t}{T_{max}}\right) + 0.029 \tag{3}$$

where T_{max} is the time elapsed between the beginning of the cardiac cycle and the instant corresponding to $E=E_{max}$. So, by using Eq. (3) it was possible to describe the pressure-volume relationship of the left ventricle during the systolic phase (isovolumic contraction, ejection, isovolumic relaxation) of the cardiac cycle after the identification of the values of the parameters E_{max}, T_{max} and V_0

characterizing the pumping properties of the left ventricle. The value of V_0 has been assumed to hold a constant value inside the single beat, its variability being considered interbeat only, but not intrabeat.

Test signals

The method presented in this paper was tested on foetal left ventricular pressure and volume signals, simulated by means of a mathematical model of the foetal cardiovascular system presented in [11].

The validation of the proposed methodology was based on the comparison of the obtained results with the ones from the conventional method of the ESPVR [1, 4], applied on the same surrogated data. To make a comparison between methods, ventricular pressure and volume data corresponding to eleven differently loaded beats were synthetized by means of the model presented in [11], and used as test cases. In fact, the conventional ESPVR analysis for the estimation of the left ventricular contractility is built up on multiple variably loaded beats: rapid ventricular preload variations are required to generate ESPVR, whose slope is a measure of the contractility of the myocardial fibers.

The varying ventricular loading conditions were obtained by simulating preload reduction by inferior vena cava (IVC) transient occlusion to the left ventricle To do this, a progressive augmentation, in the value of the resistance encountered by blood flowing towards the heart (i. e., the venous return) was imposed in the mathematical model of the foetal cardiovascular system [11]. Furthermore, in order to simulate a realistic ventricular behaviour, a light variation in afterload was also imposed. The other parameters in the foetal cardiovascular model were identified, for all the imposed variations in the cardiovascular system [11]. A similar variably loaded heart beat sequence was simulated by Menigault *et al*. [14].

Fig. 1a shows the surrogated ventricular pressure waveforms, while in Fig. 1b the corresponding computed ventricular volume waveforms are presented. In Fig. 1c the synthetic ventricular pressure-volume relationships are represented on the PV plane (PV loops). The surrogated ventricular waveforms were used to test GAs. The proposed beat-by-beat estimation method of the pumping ventricular function was not biased by the process of generation of the haemodynamic waveforms (i. e., once pressure and volume signals have been generated for each beat, both the basic model and GA estimation procedure are 'blind' with respect to the foetal cardiovascular model [11]). To make use of surrogated ventricular waveforms is, in the opinion of the authors, only a not crude and expensive way to obtain pressure and volume data without sacrificing, once the model is settled.

Method of identification

The estimation of the parameters characterizing the relationship between pressure and volume in the left ventricle, from Eq. (1) to Eq. (3), was obtained by using genetic algorithms [15]. GAs belong to the family of the evolutionary algorithms, optimization

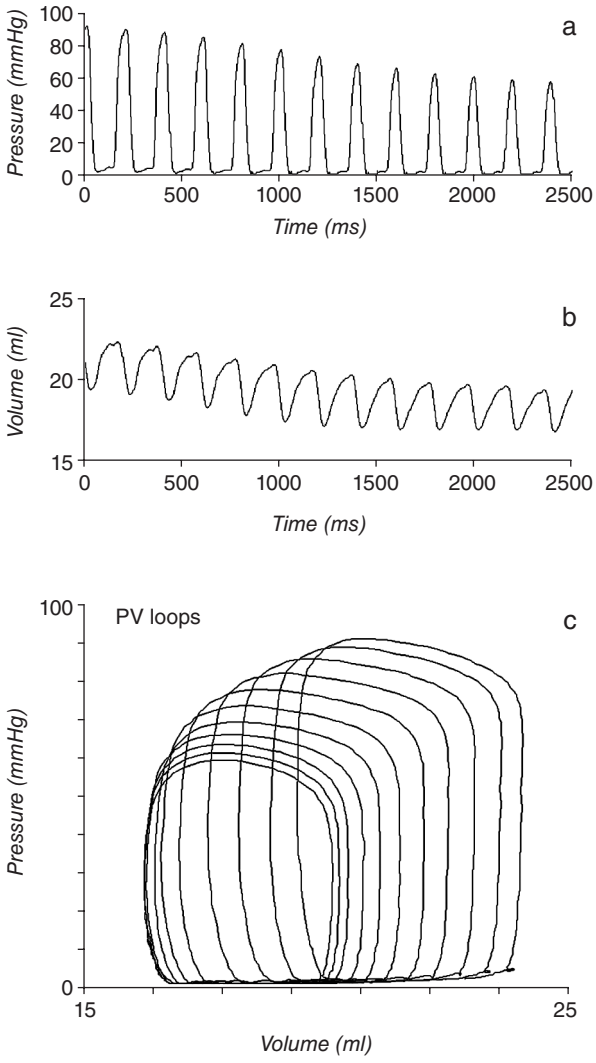

Fig. 1. - a) Simulated left ventricular pressure signals; b) simulated left ventricular volume signals; c) ventricular pressure-volume representation on the PV plane (PV loops). The computed waveforms are representative of the haemodynamics of ewe's foetus during a progressive caval occlusion manouver. It can be noticed the progressive reduction in the haemodynamic quantities.

and search procedures inspired by genetics and by the process of natural selection. The estimation of the contractile state has been executed, on each single beat, in two steps: in the first step, in order to estimate E_{max}, V_0, T_{max} simultaneously, a steady state GA was used with a population of 10 "individuals" ("chromosomes"). Each "chromosome" was composed of three "genes", i.e., E_{max}, V_0, T_{max}, each allowed to vary in a wide interval of values. This intervals of variation for the "genes" define the field of existence for the solution to be identified by GAs. The intervals were built starting from the data collected from literature, regarding the *ESPVR* slopes [14, 16].

The solution to the problem consists of three model parameters (three "genes"), which need to be encoded through a proper representation method, to be manipulated by genetic operators. The choice of representation is very flexible: several choices are acceptable, if suitable genetic operators can be developed to support the representation itself [17]. In the present study, floating-point representation [18] was chosen. As pointed out by Fleming and Purshouse [17], float-encoding is fast to be manipulated, and allows high precision.

Starting with an initial population of 10 "individuals" (i.e., 10 triplets of "genes") randomly generated, all of them were evaluated. To do that, a cost function appropriate to make the GA search progress in an acceptable direction was built up:

$$ff = \frac{1}{T}\sqrt{\sum_{i=1}^{N}\left(\frac{P(t_i)}{(V(t_i)-V_0)} - E(t_i)\right)^2} \qquad (4)$$

where $P(t_i)$ and $V(t_i)$ are the pressure and volume data at time i-th from the beginning of the isovolumic contraction, T is the temporal interval of the cardiac cycle between the beginning of the isovolumic contraction and the end of the isovolumic relaxation, N is the number of computational time steps ($t_1=0$, $t_N=T$). The minimization of *ff* was considered the objective of the fitting, being Eq. (4) the mean square error calculated over the systolic phase of the cycle. However, as GA seeks to maximize the fitness, to accomplish the transformation of the minimization problem into a maximization problem, the opposite in sign of the mean square error can be simply considered (i.e., the minimization of *ff* is equivalent to the maximization of *-ff*).

After the evaluation step a new population was selected through a selection function that reintroduces past high performance individuals [17, 19, 20]. This step guarantees the convergence and protects from stagnation (Rank Elitist selection procedure [19, 20]: when all the individuals have about the same quality around the average value, the best solutions are favoured only slightly with respect to the worst ones).

On the individuals of the newly selected population two genetic operators were applied to create new solutions:

1) "cross-over" operator takes two parents P_1, P_2 and performs a sort of interpolation between them, picking a random number Ω ($\Omega \in (0, 1)$) and creating two children C_1 and C_2 as follows:

$$C_1 = P_1 \times \Omega + P_2 \times (1-\Omega)$$
$$C_2 = P_1 \times (1-\Omega) + P_2 \times \Omega;$$

2) "non-uniform mutation" operator changes one of the parameters of the parent on the basis of a non-uniform probability distribution. This distribution starts wide, and narrows to a point distribution as the current generation approaches the maximum fixed number of generations.

On the newly created population the previous steps were repeated.

In order to reach convergence, (i.e., the number of generations necessary to the desired evolution), 500 iterations were required both for the first and the second step, for each single beat. It must be stated that no sensitivity study other than a comparison between a 1000 + 1000 generations and the 500 + 500 generations was made by the authors, obtaining the same results (data not shown).

These passages have been repeated, for each single beat, 10 times, obtaining ten solutions (i.e., ten triplets E_{max}, V_0, T_{max} minimizing the Eq. (4)). It must be bornt in mind that GAs are commonly tested many times, due to the algorithms' stochastic nature (that is, more than one cycle of parameter estimation is performed).

In the second step, the limits of variation for the three genes were reduced on the basis of the results obtained in the first step, with the aim to identify the fittest solution (i.e., the one minimizing the fitness function). The step one was repeated with these refined intervals of variation for the genes.

The refinement of the interval of variation for each parameter was carried out considering as new upper and lower bounds the mean value plus or minus 1.5 times the standard deviation as calculated at the end of the first step, respectively.

The parameter estimations for each single beat were obtained from the mean over the ten solutions mentioned above. The two-steps procedure was needed to better identify the range of existence of T_{max}, being this last the most critical parameter (due to the discrete nature of the hemodynamic signals, and to the sharp transition of the ventricular pressure around the end systolic pressure-volume point).

The numerical implementation for the GAs was performed with a proper own code, using the MATLAB programming language.

Results

Table 1 summarizes, for each beat (where each beat corresponds to a different occlusion level of the caval vein), mean values and standard deviations obtained the three parameters describing the pumping properties of the ventricle. The results of the maximization of the fitness function *-ff* (i.e., the opposite in sign of the mean square error represented by Eq.(4), for the reasons mentioned in the Methods section) are also shown. The parameters estimation, on the single beat, comes from the average over the ten obtained solutions. Fig. 2 shows, for each level of IVC occlusion, the PV loop under test and the corresponin-gly estimated one: only the fraction corresponding to the systole was reported in the pressure-volume plain, being the proposed method related to the systolic phase of the cardiac cycle.

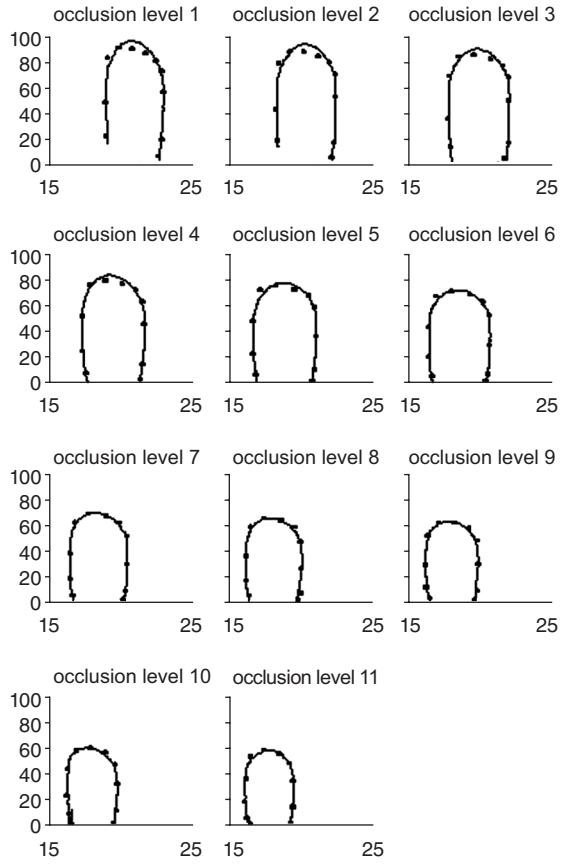

Fig. 2. - Pressure - Volume diagrams for each single beat (each beat corresponding to an imposed caval occlusion level): (*) PV loops built from the test signals shown in figure 1; (continuous line) PV loops built by means of GAs estimation, together with Eq. (1).

In Fig. 3, in the plane E_{max}-V_0, the trend followed by the pairs (E_{max}, V_0) is shown as a consequence of the progressive occlusion of the IVC. Fig. 3 highlights two distinct behaviours for the pairs (E_{max}, V_0): starting from the onset of the caval occlusion, there is, at first, a reduction of the values either of E_{max} and V_0 (while increasing the occlusion of the IVC); then, reached a certain level of caval occlusion, there is an inversion of the trend previously observed, with an increase either for E_{max} and V_0 following the progressively increasing IVC occlusion. As for the trends of the three identified model parameters E_{max}, V_0, and T_{max} during the progressive caval occlusion, while both E_{max} and V_0 show a reduction of their values as answer to the start of caval occlusion manouvre, followed by a progessive increase going on with the caval narrowing, T_{max}, decreases monotonically with the increase of the occlusion, with the same trend followed by the EDV (they exhibit a coefficient of determination R^2=*0.97*).

In order to evaluate if the estimated parameters are representative of the contractile state of the left ventricle, a linear regression has been computed in the P-V plane (where P is expressed in mmHg and V in ml) on the single beat points ($P(T_{max})$, $V(T_{max})$) identified by GAs, described by the equation:

$$P = 14.0\ V - 42.1 \qquad (5)$$

where the confidence limits (95% prediction interval) are ± 2.7 mmHg ml^{-1} for the slope and ± 12.1 mmHg for the intercept.

On the same waveforms, the conventional measurement (the "gold standard", as defined in [1, 2, 10, 21]) of the ESPVR was carried out. On the serial left ventricular pressure-volume loops obtained during

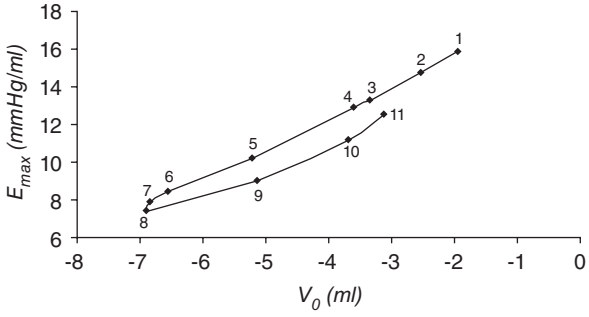

Fig. 3. - Graphic representation, in the plane (Emax, V0), of the beat-to-beat relationship between the couple of parameters representative of the myocardial contraction, as estimated by GAs, during the progressive caval occlusion manouver. Numbers in the graph indicate the progressive beat number.

Table 1. - Mean values, standard deviation, and the opposite in sign *(-ff)* of the maximum value of the mean square error represented by Eq. (4) of the three estimated parameters, for each occlusion level

Occlusion level		1	2	3	4	5	6	7	8	9	10	11
T_{max} [s]	mean	0.132	0.130	0.126	0.123	0.122	0.121	0.118	0.118	0.115	0.112	0.109
	SD	0.006	0.007	0.004	0.004	0.006	0.006	0.006	0.003	0.004	0.004	0.005
E_{max} [mmHg/ml]	mean	15.84	14.72	13.26	12.87	10.24	8.45	7.90	7.44	9.06	11.19	12.52
	SD	0.10	0.11	0.07	0.07	0.12	0.11	0.13	0.06	0.08	0.09	0.14
V_0 [ml]	mean	-1.97	-2.55	-3.35	-3.61	-5.23	-6.56	-6.85	-6.91	-5.14	-3.70	-3.14
	SD	0.06	0.06	0.04	0.042	0.08	0.12	0.15	0.07	0.05	0.05	0.08
$(-ff)_{max}$	mean	-0.55	-0.53	-0.50	-0.45	-0.47	-0.48	-0.45	-0.46	-0.38	-0.33	-0.26
	SD	0.04	0.03	0.02	0.01	0.02	0.01	0.01	0.00	0.01	0.03	0.16

transient caval occlusion, by means of an iterative linear regression method [1, 2, 21], the slope and the intercept with volume axis (in the pressure-volume plane, as mentioned in section 1) of the ESPVR line was computed. The following equation was obtained for the ESPVR:

$$P = 13.9\ V - 43.9 \qquad (6)$$

where the confidence limits (95% prediction interval) are ± 2.1 mmHg ml^{-1} for the slope and ± 8.8 mmHg for the intercept.

To compare the capability of the herein proposed framework, with other single-beat estimation methods, the most popular of them [3] was applied on the same simulated data, and comparable estimated values for the parameters (E_{max}, V_0) were obtained: the two populations, i.e., the GA estimes and the ones from Senzaki *et al*. method [3], did not show statistically significant difference (both for E_{max} and V_0, the differences in the two corresponding variably estimated populations were assessed with the two tailed Student's test, p value = 0.6).

Discussion

In recent years interest has grown in the reliability of methodologies to estimate the pumping function of the heart beat-by-beat. The aim is the individuation of useful, clinically applicable, reliably instruments for assessing systolic function, therapeutic response and ventricular-arterial interaction [3, 5-10]. Moved from these motivations, the goal of the present study is to develop and validate a method to estimate single-beat parameters representative of the left ventricular mechanics. The estimated parameters (E_{max}, T_{max} and V_0), obtained for each variably loaded beat, represent the maximum of time-varying elastance function, the time elapsed between the beginning of the cardiac cycle and the instant corresponding to E_{max}, and the value of the unbiased volume V_0 (i.e., the volumetric dimension in correspondence to which the ventricle is no more able to generate pressure during the systolic phase [13]).

The traditional methods, based on multiple beats, furnish a synthetic information on the contractile state of the heart and they cannot investigate on the beat-by-beat evolution. On the contrary, estimating the three parameters on the single beat, it is possible to obtain information on the contractility of the myocardial fibers without more invasive measures on multiple variably loaded beats. By using this analytical single beat method, it is possible to follow the beat-by-beat physiological modifications and to highlight the control mechanisms due to the caval occlusion manouvre: the high variability of E_{max} and V_0 could be correlated to a similar variability occurred to SV and E_a (with a coefficient of determination R^2 of 0.85) and so it can witness the contemporary presence of afterload variations.

The good agreement between a linear regression computed in the pressure-volume plane on the GAs identified ($P(T_{max})$, $V(T_{max})$) points (one for each occlusion level), and the ESPVR (computed on the multiple beats with the standard method [1, 2]), allows to conclude that the results obtained with an analytic method are congruent with those individuated by a synthetic one. The slope of linear regression on the points corresponding to the estimated parameters is 14.0 mmHg/ml, while the ESPVR one (e.g., E_{es}) is 13.9 mmHg/ml: it is evident as the linear regression computed on the GAs identified points, where the time-varying elastance function is maximal for each beat, reproduces the Ees, that is considered as a measure of myocardial fibers contractility capability. Also the intercept with the volume axis of the linear regression (-3.0 ml) is quite equal to that one of the ESPRV (-3.2 ml), so it could furnish the same information.

In order to validate the capability of the herein proposed framework, another single-beat estimation method [3] was applied on the same surrogated data, and comparable values for the estimated parameters (E_{max}, V_0 and T_{max}) were obtained. The major difference between the two approaches is that the GA method is based on the entire systolic PV loop, while the Senzaki one [3] needs to have just two points: so the information obtained by GA could be more complete than the other one. On the contrary Senzaki method, being very fast, may furnish the E_{max} and V_0 values in real time, during the ventricular signals recordings, while the GA-based proposed method has to be intended to date, as off line, and the present study as a feasibility analysis.

At this stage of our ongoing investigation we focused to test the ability of GAs as identification technique of ventricular biomechanical parameters. Notwithstanding no particular attention was paid to the optimization of the method at this step on the study, the obtained results make the authors optimist for an on line optimised implementation. The immediate future step will be oriented towards the reduction in computational times: a sensitivity study will be carried out to find the minimum number of iterations required for convergence, i.e., the number of generations necessary to the desired evolution. In fact, the future aim is in the approach of an algorithm able to furnish continuous, real time evaluation of the pumping function of the heart. The main advantage in using GAs for single beat analysis may lie, in the perspective of an application both for in vivo research and clinical investigations, in the guaranteed better performance with respect to other search techniques on difficult problems involving noisy signals [12], like in vivo ventricular pressure and volume recordings frequently are [22, 23], and high dimensional functions. From this viewpoint the proposed identification method, based on the entire ejection phase, could be useful for a more complete and less invasive (i.e., no ventricular catheterisation) beat-to-beat information on the contractile state of the heart. This could be done by means of *in vivo* recorded peripheral hemodynamic waveforms plus the modeling of the cardiovascular system from the left ventricle to the vascular site of measure: thanks to the model approach, from simple measurements in the peripheral circulation, estimation of cardiac function could be obtained. In this direction, a preliminary *in vivo* study was recently carried out [24]. GAs, in virtue of their conceptual semplicity, the ease of programming entailed, and the small number of parameters to be defined, not requiring to set an initial value for model parameters to be estimated, may be possible canditates in the identification of models with an high number of parameters (i.e., vascular resistances, compliances and inertances) whose real values are widely variable on individual basis. It must be pointed out that the proposed method, with respect to the one of Shishido *et al*. [10], suffers from the only apparent disadvantage to need of instantaneous ventricular volume measurements, because the method of Shishido needs, however, to know both the stroke volume and the end systolic volume (that is like to say that the P-V loop has to be positioned in the pressure - volume plain), together with the systolic times; on the contrary, GAs need only of the approximate instant of the beginning of the systole. A limitation in the analytical formulation (from Eq. (1) to Eq. (3)) for the ventricular pressure-volume relationship, with respect to the one proposed in [10], may be in the fact that the elastance waveform could not be held when loading conditions or contractility significantly change (assuming values outside of the physiological range).

Moreover, applying a non linear regression to the same points of maximal time-varying elastance, we obtain a better coefficients of determination (R^2 of 0.99 instead of 0.92 obtained by means of a linear regression), this being in agreement with literature works considering the ESPRV curvilinear [25, 26].

The present study suffers from the limitation that only normal loading conditions for the ventricle were investigated (i.e., in a physiological range, inside of which linearity and load independence can be considered for ventricular contractility [3, 27]: although recent studies challenged the initial concept of linear and load-insensitive ESPVR by demonstrating contractility-dependent curvilinearity [25, 26] and load dependence [28], as also assessed in [10]: “the slope of the ESPVR still remains a powerful index to assess the inotropic state in experimental as well as clinical settings”.

The evolutionary techniques, combining elements of directed and stochastic search, exhibit a number of advantages over other search methods: in particular, the need of a smaller amount of knowledge and fewer assumptions about the characteristics of the search space. Furthermore, they can avoid the 'entrapping' in local optima more easily than other search methods [29]. Genetic algorithms, proposed by Holland [30, 31], are the best-known class of evolutionary algorithms. The GA approach does not require that a curve fit passes exactly through any of the data points; this allows the GA to locate improved solutions in some instances. Moreover, GAs do not require good initials guesses for the parameters, being the initial population completely randomly generated. Another strenght of GA methodology is that no manipulation of the equations of the model is needed: only access to the model is required in order to compute a fitness function. Conversely, in traditional least squares techniques derivatives of the model equations with respect to unknown parameters must often be computed.

However, it is mandatory to mention that for well-understood problems for which trusted solutions exist, GAs are unlikely to produce competitive results (if a problem can be solved analytically with an acceptable level of assumptions, then that approach is probably the best). If such a solution cannot be found, the use of a GA could be highly profitable and worthwhile.

Acknowledgements

This research was supported by a grant from the Istituto Superiore di Sanità within the research project "Messa a punto di un banco di prova per la valutazione biomeccanica dell'assistenza e del recupero cardiaco".

Received on 28 July 2004.
Accepted on 12 October 2004.

REFERENCES

1. Suga H, Sagawa K, Shoukas AA. Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. *Circ Res* 1973;32(3):314-22.

2. Kass DA, Maughan WL. From Emax to pressure-volume relations: a broader view. *Circulation* 1988;77(6):1203-12.

3. Senzaki H, Chen CH, Kass DA. Single-beat estimation of end-systolic pressure-volume relation in humans. *Circulation* 1996;94(10):2497-506.

4. Suga H, Sagawa K. Instantaneous pressure-volume relationships and their ratio in the exercised, supported canine left ventricle. *Circ Res* 1974;35(1):117-26.

5. Takeuchi M, Igarashi Y, Tomimoto S, Odake S, Hayashi T, Tsukamoto T, Hata K, Takaoka H, Fuzuzaki H. Single beat estimation of the slope of end systolic pressure-volume relation in the human left ventricle. *Circulation* 1991;83(1):202-12.

6. Segers P, Steendijk P, Stergiopulos N, Westerhof N. Predicting systolic and diastolic aortic blood pressure and stroke volume in the intact sheep. *J Biomech* 2001;34(1):41-50.

7. Shih H, Hillel Z, Declerck C, Anagnostopoulos C, Kuroda M, Thys D. An algorithm for real-time, continuous evaluation of left ventricular mechanics by single-beat estimation of arterial and ventricular elastance. *J Clin Monit* 1997;13(3):157-70.

8. Karunanithi MK, Feneley MP. Single-beat determination of preload recruitable stroke work relationship: derivation and evaluation in conscious dogs. *J Am Coll Cardiol* 2000;35(2):502-13.

9. Hayashi K, Shigemi K, Shishido T, Sugimachi M, Sunagawa K. Single-beat estimation of ventricular end-systolic elastance-effective arterial elastance as an index of ventricular mechanoenergetic performance. *Anesthesiology* 2000;92(6):1769-76.

10. Shishido T, Hayashi K, Shigemi K, Sato T, Sugimachi M, Sunagawa K. Single-beat estimation of end-systolic elastance using bilinearly approximated time-varying elastance curve. *Circulation* 2000;102(16):1983-89.

11. Grigioni M, Carotti A, Daniele C, D'Avenio G, Morbiducci U, Di Benedetto G, Albanese S, Di Donato R, Barbaro V. A mathematical model of the fetal cardiovascular system based on genetic algorithms as identification technique. *Int J Artif Organs* 2001;24(5):286-96.

12. Lin H, Yamashita K. Hybrid simplex genetic algorithm for blind equalization using RBF networks. *Math Comput Simul* 2002;59(4):293-304.

13. Sagawa K. The end-systolic pressure-volume relation of the ventricle: Definition, modifications and clinical use. *Circulation* 1981;63:1223-7.

14. Ménigault E, Vieyres P, Lepoivre B, Durand A, Pourcelot L, Berson M. Fetal heart modelling based on a pressure-volume relationship. *Med Biol Eng Comput* 1997;35(6):715-21.

15. Goldberg DE. Genetic *Algorithms in search, optimization and machine learning*. New York: Addison Wesley; 1989.

16. Grigioni M, Carotti A, Daniele C, D'Avenio G, Morbiducci U, Iannace E, Albanese S, Costa D, Formigari R, Ferretti E, Di Donato R. Extracorporeal circulation in ewe's foetus: towards a reliable foetal cardiac surgery protocol. *Int J Artif Organs* 2000; 23(3):189-98.

17. Fleming PJ, Purshouse RC. Evolutionary algorithms in control systems engineering: a survey. *Control Engineering Practice* 2002;10(11):1223-41.

18. Michalewicz Z. Genetic algorithms+data structures=evolution programs. Berlin: Springer; 1996.

19. Brooks RR, Iyengar SS, Chen J. Automatic correlation and calibration of noisy sensor readings using elite genetic algorithms. *Artif Intelligence* 1996;84(1-2):339-54.

20. Douglas TS, Solomonidis SE, Sandham WA, Spence WD. Ultrasound image matching using genetic algorithms. *Med Biol Eng Comput* 2002;40(2):168-72.

21. Kass DA, Yamazaki T, Burkhoff D. Determination of left ventricular pressure-volume relationships by the conductance (volume) catheter technique. *Circulation* 1986;73:586-95.

22. Soderqvist E, Carlsson C, Brodin LA. Conductance measurements in the left ventricle: a pressure-flow approach. *Proceedings on 2nd European Medical and Biological Engineering Conference*. Wien, 4-8 December 2002. p. 1012-3.

23. Baan J, van der Velde ET, de Bruin HG, Smeenk GJ, Koops J, van Dijk AD, Temmerman D, Senden J, Buis B. Continuous measurement of left ventricular volume in animals and humans by conductance catheter. *Circulation* 1984;70(5):812-23.

24. Grigioni M, Daniele C, Morbiducci U, Del Gaudio C, D'Avenio G, Di Benedetto G, Barbaro V. Beat-by-beat estimation of the pumping function of the heart from arterial hemodynamic waveforms. *Int J Artif Organs* 2002;25(7):695.

25. Krosl P, Abel FL Problems with use of the end systolic pressure-volume slope as an indicator of left ventricular contractility: an alternate method. *Shock* 1998;10:285-291.

26. Kass D.A, Beyar R, Lankford E, Heard M, Maughan WL, Sagawa K. Influence of contractile state on curvilinearity of in situ end-systolic pressure-volume relations. *Circulation* 1989; 79:167-78.

27. Kass DA. Clinical evaluation of left heart function by conductance catheter tecnique'. *European Heart Journal* 1992;13(Suppl E):57-64.

28. Baan J, van der Velde ET. Sensitivity of left ventricular end-systolic pressure-volume relation to type of loading intervention. *Circ Res* 1988;62(6):1247-58.

29. Pena-Reyes CA, Sipper M. Evolutionary computation in medicine: an overview. *Artificial Intelligence in Medicine* 2000;19:1-23.

30. Holland JH. Outline for a logical theory of adaptive systems. *J ACM* 1962;9:297-314.

31. Holland JH. *Adaptation in natural and artificial systems*. Ann Arbour: University of Michigan Press; 1975.