Early detection of abnormal left ventricular relaxation in acute myocardial ischemia with a quadratic model.

Philippe Morimont [1], Antoine Pironet [2], Thomas Desaive [2], Geoffrey Chase [3], Bernard Lambermont [1]

GIGA - Cardiovascular Sciences, Hemodynamics, University of Liège, Belgium

[1] Medical Intensive Care Department, University Hospital of Liège, Belgium

[2] Faculty of Sciences, University Hospital of Liège, Belgium

[3] Mechanical Engineering Department, University of Canterbury, Christchurch, New Zealand

Corresponding author:

Docteur Philippe Morimont, Medical Intensive Care Unit, University Hospital of Liege, 4000 Liege

Fax: +3243667189, Tel: +3243667312, eMail: ph.morimont@chu.alg.ac.be

Abstract:

Aims: The time constant of left ventricular (LV) relaxation derived from a monoexponential model is widely used as an index of LV relaxation rate, although this model does not reflect the non-uniformity of ventricular relaxation. This study investigates whether the relaxation curve can be better fitted with a "quadratic" model than with the "conventional" monoexponential model and if changes in the LV relaxation waveform due to acute myocardial ischemia could be better detected with the quadratic model.

Methods and results: Isovolumic relaxation was assessed with quadratic and conventional models during acute myocardial ischemia performed in 6 anesthetized pigs. Mathematical development indicates that one parameter (Tq) of the quadratic model reflects the rate of LV relaxation, while the second parameter (K) modifies the shape of the relaxation curve. Analysis of experimental data obtained in anesthetized pigs showed that the shape of LV relaxation consistently deviates from the conventional monoexponential decay. During the early phase of acute myocardial ischemia, the rate and non-uniformity of LV relaxation, assessed with the quadratic function, were significantly enhanced. Tq increased by 16% ($p < 0.001$) and K increased by 12% ($p < 0.001$) within 30 and 60 minutes, respectively, after left anterior descending (LAD) coronary artery occlusion. However, no significant changes were observed with the conventional monoexponential decay within 60 minutes of ischemia.

Conclusions: The quadratic model better fits LV isovolumic relaxation than the monoexponential model and can detect early changes in relaxation due to acute myocardial ischemia that are not detectable with conventional methods.

Introduction

During acute myocardial ischemia (AMI), left ventricular (LV) relaxation remains incompletely understood, while it is a major determinant in diastolic dysfunction [1]. 'Relaxation' relates to the process where cardiac muscle returns, after contraction, to its initial length or tension [2]. The fall of LV pressure (P) is the in vivo manifestation of isometric relaxation and is the direct expression of cardiac muscle inactivation [3, 4]. The time constant of LV relaxation derived from a monoexponential model is usually used as an index for evaluating LV relaxation rate in both experimental and clinical studies [3, 5].

It is well established that LV relaxation is non-uniform and that there is a significant interaction between non-uniformity and loading conditions [6-8]. In acute LV ischemia, the loading conditions influence both the regional response to myocardial ischemia and the mechanical consequences of the interaction between the ischemic zone and non-ischemic areas [6, 9, 10]. Since LV diastolic dysfunction may precede systolic dysfunction during AMI, early detection of abnormal LV relaxation may be useful in clinical practice [11].

LV relaxation is usually assessed by a monoexponential model of LV P fall in time [5]. However, this model cannot capture the non-uniformity of ventricular relaxation and cannot discriminate early from late relaxation [5, 8]. Moreover, deviation of relaxation behaviour from this monoexponential decay model is well established in a number of clinically important disease states, such as regional ischemia associated with segmental coronary disease, hypertrophic cardiomyopathy and heart failure [8, 12-14]. Hence, a better model than the monoexponential model is required.

We investigated whether LV relaxation can be better assessed with a quadratic function, based on a logistic equation, during AMI [8, 15]. We used such a quadratic function to assess non-uniformity of LV relaxation in phase plane analysis. We examined the parameters of the quadratic function under control conditions and during experimental situations of AMI.

Materials and Methods

All experimental procedures and protocols in this investigation were reviewed and approved by the Ethics Committee of the Medical Faculty of the University of Liege. All procedures conformed to the Guiding Principles in the Care and Use of Animals of the American Physiological Society and were performed according to the Guide for the Care and Use of Laboratory Animals (NIH publication no. 85-23, revised 1996).

Experiments were performed on 6 healthy pure pietran pigs of either sex (20–28 kg). The animals were premedicated with intramuscular administration of ketamine (20 mg/kg) and diazepam (1 mg/kg). Anesthesia

was then induced and maintained by a continuous infusion of sufentanil (0.5 μg/kg/h) and sodium pentobarbital (3 mg/kg). Spontaneous movements were prevented by pancuronium bromide (0.1 mg/kg). After endotracheal intubation through a cervical tracheostomy, the pigs were connected to a volume cycled ventilator (Evita 2, Dräger, Lübeck, Germany) set to deliver a tidal volume of 10 mL/kg at a respiratory rate of 20/min. End-tidal PCO2 measurements (Capnomac, Datex, Helsinki, Finland) were used to monitor the adequacy of ventilation. Respiratory settings were adjusted to maintain end tidal CO2 in the range of 35 to 40 torr (4.67 to 5.33 kPa). Arterial oxygen saturation was closely monitored and maintained above 95% by adjusting the FiO2 as necessary. Central temperature was measured with a rectal probe and maintained at 37°C by means of a heating blanket. A standard lead electrocardiogram was used for the monitoring of heart rate (HR).

The chest was entered through median sternotomy, the pericardium was incised and sutured to the chest wall to form a cradle for the heart, and the root of the aorta was dissected clear of adherent fat and connective tissue. A combined conductance-micromanometer catheter (CD Leycom, Zoetermeer, The Netherlands) was inserted through the right carotid artery and advanced into the left ventricle. Right atrial P was measured with a micromanometer-tipped catheter inserted into the cavity through the superior vena cava.

Thrombus formation along the catheters was prevented by administration of 100 U/kg of heparin sodium intravenously just before the insertion.

Experimental Protocol

To provide similar states of vascular filling, the animals were continuously infused with Ringer lactate (5 mL/kg/h) and, when necessary, with hydroxyethylstarch 6% to increase central venous pressure up to 6–7 mm Hg over 30 minutes.

LV volume and P baseline measurements were recorded. All measurements were taken immediately after the animal was briefly disconnected from the ventilator to sustain end-expiration. Thereafter, the left anterior descending (LAD) coronary artery was ligated after the origin of the first diagonal artery. In all animals, measurements were obtained at baseline (T0) and each 30 minutes during 120 minutes (T30, T60, T90, T120) after LAD occlusion.

Data analysis

All measurements were performed at end-expiration. The conductance catheter was connected to a Sigma-5 signal conditioner processor (CD Leycom, Zoetermeer, The Netherlands). All analog signals and the ventricular P–volume loops were displayed on screen for continuous monitoring. The analog signals were continuously

converted to digital form with appropriate software (Codas, DataQ Instruments Inc, Akron, OH) at a sampling frequency of 200 Hz.

Mathematical analysis

First derivative of LV P (dP/dt) was plotted against LV P to generate phase plane loops [16]. Indeed, information about diastolic function that cannot be discerned from the usual P vs. time display format is easily visualized and quantitated using the phase plane plot. Phase plane analysis is carried out on graphs of precisely periodic or nearly periodic functions plotted such that the function is the abscissa and its time derivative is the ordinate [5, 16].The isovolumic relaxation period was defined as the period between the time point of peak negative dP/dt (dP/dt_{min}) and the time at which dP/dt reached 10% of the dP/dt_{min} value (Fig. 1).

The quadratic model for LV P(t) during isovolumic relaxation was based on the logistic function and defined[15]:

$$\frac{P}{P^\circ} = \frac{e^{-t/Tq}}{1+K.P^\circ.(1-e^{-t/Tq})} \qquad \text{Equation 1}$$

where P° is the initial P at the start of the relaxation, K is a constant and Tq is the time constant of the exponent. It was assumed here that there was no non-zero asymptote. This assumption seems to hold from previously published results on the logistic model [7,16].

The monoexponential model was defined [5, 13]:

$$P(t) = (P^\circ - Pend).e^{\frac{-t}{Te}} + Pend \qquad \text{Equation 2}$$

where P_{end} is a non-zero asymptote, P° is the initial P at the start of the relaxation, t is time, and Te is the time constant of the exponent that has conventionally been used as the time constant of the monoexponential function. Unlike the logistic model, the asymptote of the monoexponentiel model has been shown to be non-zero [5].

Differentiating Equation 1 yields dP/dt for the quadratic model (see Appendix A):

$$\frac{dP(t)}{dt} = \frac{-1}{Tq}.P(t) + \frac{-1}{Tq}.K.P(t)^2 \qquad \text{Equation 3}$$

Differentiating Equation 2 yields dP/dt for the monoexponential model:

$$\frac{dP(t)}{dt} = \frac{-1}{Te}.(P(t) - Pend) \qquad \text{Equation 4}$$

Equations 1 and 3 consider that dP/dt = 0 when P = 0. Equations 2 and 4 assume that dP/dt = 0 when $P = P_{end}$. These two models lead to different LV relaxation curves in the phase plane diagram. When plotting first

derivative of LV P (dP/dt) against LV P, the trajectory of Equation 3 shows downward convexity, whereas that of Equation 4 shows linearity, as shown in Fig.2.

Equation 1 clearly shows that Tq reflects the rate of LV relaxation (time constant of isovolumic relaxation) and K modifies the shape of the relaxation curve in the time space. Effectively, when K < -1/2P°, the relationship becomes biphasic and deviates from the exponential decay. At start of LV relaxation, t/Tq << 1 and relaxation rate is $\frac{dP}{dt} = -\frac{1}{Tq}.P°.(1 + K.P°)$ and the relaxation phenomenon can be described as $\frac{P}{P°} = 1 - (1 + K.P°).\frac{t}{Tq}$. This formula suggests that early relaxation depends directly on P°. During late relaxation, t/Tq >> 1 and P/P° = $e^{(-t/Tq)}/(1+K.P°)$, which corresponds to the classical monoexponential decay.

We calculated the best-fit set of the two parameters (K and Tq) for the quadratic model (Equation 3) and the time constant of the monoexponential model, Te (Equation 4) for each experimentally observed P(t) curve by nonlinear curve fitting on a computer. To evaluate the goodness of fit of each model, we compared the regression coefficient for each of the best fit model curves. We then compared parameters of both models before and during AMI. All time constants were normalized to cycle length.

Statistical analysis

Changes in LV relaxation and hemodynamic parameters were evaluated by a repeated-measures analysis of variance. Data were expressed as mean ± standard deviation (SD).

Results

When dP/dt was plotted versus P(t), the relaxation curve appeared curvilinear before and after AMI. The coefficient of determination (R^2) was 0.97 ± 0.02 using the quadratic model versus 0.73 ± 0.14 using the monoexponential model, p < 0.001 (Fig. 2). The time constant of the quadratic model, Tq, progressively increased after AMI and significantly changed at T30, compared to baseline data (28.45 ± 0.96 vs. 25.40 ± 0.96 msec, p < 0.001) (Fig. 3). Similarly, the time constant of the monoexponential model, Te, progressively increased after AMI and significantly changed at T90, compared to baseline data (45.03 ± 1.59 vs. 39.36 ± 1.67 msec, p < 0.001) (Fig. 4). The curvilinearity coefficient, K, progressively increased after AMI, as shown on Fig. 5, and significantly changed at T60, compared to baseline data (27.60 ± 2.21 vs. 25.13 ± 2.48 mm Hg^{-1}, p < 0.001). Isovolumic relaxation time (IVRT) regularly increased from T0 to T120 but without significant change, as shown on Fig. 6. Hemodynamic data before and during myocardial ischemia are depicted on Table 1.

Discussion

This study provides a complete evaluation of LV relaxation before and during AMI. The major findings are: (a) LV relaxation is better fitted with the quadratic model than with the monoxeponential model; (b) curvilinearity of LV relaxation in phase plane is enhanced during myocardial ischemia; and (c) the quadratic model allows detection of changes earlier than the classical monoexponential model.

Our results showed LV relaxation was better fit with the quadratic model than with the monoexponential model. Curvilinearity of LV relaxation in the phase plane has already been noted in several studies [12, 17, 18]. The monoexponential model and its modifications are merely empirical [15, 18, 19]. Many investigators have attempted to derive reliable indexes for assessing LV relaxation from observed cardiac hemodynamics and mathematical models expressing LV P decrease during isovolumic relaxation [15, 20]. In 1976, Weiss et al. originally determined the time constant by fitting the monoexponential model with a zero asymptote to LV P decrease during isovolumic relaxation after the peak negative value of the first derivative of LV P (dP/dt) [3]. Some investigators added a non-zero asymptote to the monoexponential model [17, 18, 21]. Some of these investigators demonstrated that the LV relaxation P fall is non-uniform and cannot be precisely determined by a monoexponential model [7, 12, 17]. Indeed, a monoexponential relationship between LV P and time corresponds to a linear relation between LV dP/dt and P while the LV relaxation curve appeared to be curvilinear in the phase plane (Fig.1, 2).

Several methods have been proposed to consider deviation from monoexponential model. A two–sequential monoexponential model was proposed to improve the goodness of fit of the curve. Rousseau et al.[22] fitted the early and late phases of LV relaxation to two different monoexponential functions. This model provided a discontinuous LV P curve and, consequently, phase-plane curves derived from this model are also discontinuous and cannot precisely fit the observed curves. Mirsky et al.[19] suggested a polynomial fitting to the LV P during isovolumic relaxation but without direct theoretical meaning on the coefficients of the polynomial terms. Matsubara et al.[15] proposed a logistic model and demonstrated that their logistic model better fitted LV relaxation. They defined a logistic time constant of LV relaxation, but one parameter was always close to zero, this is why it was neglected here.

The advantage of our quadratic model is that one parameter gives the rate of LV relaxation, while the second reflects its non-uniformity. It accomplishes this outcome while also providing a continuous curve. Finally, changes in its parameters can thus be correlated to changes in conditions. In particular, curvilinearity of the LV relaxation curve in phase plane was significantly enhanced after AMI. At the cellular and molecular levels, the

calcium ion released from the troponin is sequestered in the sarcoplasmic reticulum against the ionic gradient [17]. A disturbance of this process, calcium binding and uptake of the sarcoplasmic reticulum, has been reported in various experimental animal models of congestive heart failure and in the failing human ventricle [18]. These observations suggest that LV relaxation is disturbed in congestive heart failure or myocardial ischemia [4]. Moreover, the fact that a more uniform rate is restored by beta-adrenergic stimulation suggests an important role of calcium handling [6, 17].

To our best knowledge, no previous studies quantified the degree of curvilinearity of LV relaxation curve in phase plane, reflecting deviation from monoexponential waveform. Prahbu et al.[12] showed that load sensitivity of LV relaxation was enhanced in heart failure, highlighting the importance of load profile as an underlying mechanism. However, LV relaxation was assessed with monoexponential decay at different loading conditions. Non-uniformity of LV relaxation curve for constant given loading conditions was not considered. Senzaki et al.[8] showed that isovolumic relaxation deviates from monoexponential waveform in failing heart leading to overestimation of load sensitivity of monoexponential time constant. However, while Senzaki et al.[8] suggested that deviation from monoexponential decay could be related to disturbance in calcium release, their logistic model did not quantify the shape of the waveform and the non-uniformity of the LV P fall. Hence, the model and results presented here capture unique behaviours that prior approaches could not.

More specifically, our results showed that the quadratic model was more sensitive to LV relaxation changes due to AMI than the monoexponential model. Indeed, no significant changes in LV relaxation rate were observed within the first hour following LAD coronary artery occlusion with the conventional method, while significant changes were detected in the rate and shape of LV relaxation with the quadratic model at 30 and 60 minutes. Enhanced non-uniformity of LV relaxation could be a manifestation of disturbed LV relaxation due to LV ischemia. In this way, the monoexponential model and its modifications could be less sensitive to early changes in LV relaxation due to myocardial ischemia than the quadratic model. These findings may be of particular clinical importance in the early detection and treatment of myocardial ischemia.

We concluded that the quadratic model provided a better fit to the LV P decrease during isovolumic relaxation than the classical monoexponential model. The two parameters of the quadratic function completely characterized LV relaxation as well as its changes with changes in conditions, thus yielding valuable diagnostic information. One parameter corresponds to the rate of LV relaxation, while the second parameter gives the shape of the curve. Finally, the quadratic model was more sensitive to changes in LV relaxation in the early

phase of acute myocardial ischemia than the classical monoexponential model, thus providing a more sensitive monitoring diagnostic.

Acknowledgments

This study was supported by a grant from the Leon Fredericq Foundation of the University of Liege.

Conflict of Interest

None declared.

Ethical Approval

All experimental procedures and protocols in this investigation were reviewed and approved by the Ethics Committee of the Medical Faculty of the University of Liege. All procedures conformed to the Guiding Principles in the Care and Use of Animals of the American Physiological Society and were performed according to the Guide for the Care and Use of Laboratory Animals (NIH publication no. 85-23, revised 1996).

References

[1] Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part II: causal mechanisms and treatment. Circulation. 2002;105:1503-8.

[2] Gillebert TC, Brutsaert DL. Regulation of left ventricular pressure fall. Eur Heart J. 1990;11 Suppl I:124-32.

[3] Weiss JL, Frederiksen JW, Weisfeldt ML. Hemodynamic determinants of the time-course of fall in canine left ventricular pressure. J Clin Invest. 1976;58:751-60.

[4] Pasipoularides A. Right and left ventricular diastolic pressure-volume relations: a comprehensive review. J Cardiovasc Transl Res. 2013;6:239-52.

[5] Craig WE, Murgo, J. P., Pasipoularides, A. Calculation of the time constant of relaxation. In: Lorell WGB, editor. Diastolic relaxation of the heart. The Hague: Martinus Nijhoff; 1987. p. 125-32.

[6] Gillebert TC, Lew WY. Nonuniformity and volume loading independently influence isovolumic relaxation rates. Am J Physiol. 1989;257:H1927-35.

[7] Leite-Moreira AF, Gillebert TC. Nonuniform course of left ventricular pressure fall and its regulation by load and contractile state. Circulation. 1994;90:2481-91.

[8] Senzaki H, Kass DA. Analysis of isovolumic relaxation in failing hearts by monoexponential time constants overestimates lusitropic change and load dependence: mechanisms and advantages of alternative logistic fit. Circ Heart Fail. 2010;3:268-76.

[9] Gillebert TC, Sys SU, Brutsaert DL. Influence of loading patterns on peak length-tension relation and on relaxation in cardiac muscle. J Am Coll Cardiol. 1989;13:483-90.

[10] Pasipoularides A, Palacios I, Frist W, Rosenthal S, Newell JB, Powell WJ, Jr. Contribution of activation-inactivation dynamics to the impairment of relaxation in hypoxic cat papillary muscle. Am J Physiol. 1985;248:R54-62.

[11] Hirota Y. A clinical study of left ventricular relaxation. Circulation. 1980;62:756-63.

[12] Prabhu SD. Load sensitivity of left ventricular relaxation in normal and failing hearts: evidence of a nonlinear biphasic response. Cardiovasc Res. 1999;43:354-63.

[13] Pasipoularides A, Mirsky I. Models and concepts of diastolic mechanics: pitfalls in their misapplication. Mathematical and Computer Modelling. 1988;11:232-4.

[14] Mirsky I, Pasipoularides A. Clinical assessment of diastolic function. Prog Cardiovasc Dis. 1990;32:291-318.

[15] Matsubara H, Araki J, Takaki M, Nakagawa ST, Suga H. Logistic characterization of left ventricular isovolumic pressure-time curve. Jpn J Physiol. 1995;45:535-52.

[16] Eucker SA, Lisauskas JB, Singh J, Kovacs SJ. Phase plane analysis of left ventricular hemodynamics. J Appl Physiol (1985). 2001;90:2238-44.

[17] Raff GL, Glantz SA. Volume loading slows left ventricular isovolumic relaxation rate. Evidence of load-dependent relaxation in the intact dog heart. Circ Res. 1981;48:813-24.

[18] Yellin EL, Hori M, Yoran C, Sonnenblick EH, Gabbay S, Frater RW. Left ventricular relaxation in the filling and nonfilling intact canine heart. Am J Physiol. 1986;250:H620-9.

[19] Mirsky I. Assessment of diastolic function: suggested methods and future considerations. Circulation. 1984;69:836-41.

[20] Frederiksen JW, Weiss JL, Weisfeldt ML. Time constant of isovolumic pressure fall: determinants in the working left ventricle. Am J Physiol. 1978;235:H701-6.

[21] Martin G, Gimeno JV, Cosin J, Guillem MI. Time constant of isovolumic pressure fall: new numerical approaches and significance. Am J Physiol. 1984;247:H283-94.

[22] Rousseau MF, Veriter C, Detry JM, Brasseur L, Pouleur H. Impaired early left ventricular relaxation in coronary artery disease: effects of intracornary nifedipine. Circulation. 1980;62:764-72.

Figures Captions

Fig. 1

Time course of LV pressure and corresponding phase plane plot (at baseline). The isovolumic relaxation period corresponds to the period between the time point of peak negative dP/dt (dP/dt_{min}) (solid arrow) and the time at which dP/dt reached 10% of the dP/dt_{min} value (dashed arrow).

Fig. 2

Phase plane plot of LV isovolumic relaxation and corresponding time course of LV pressure fall (at baseline). Curve fitting with the monoexponential model ($R^2 = 0.72$) and the quadratic model ($R^2 = 0.98$).

Fig. 3

Evolution of the LV relaxation time constant (Tq) derived from the quadratic model. * $p < 0.001$ compared to baseline.

Fig. 4

Evolution of the LV relaxation time constant (Te) derived from the conventional monoexponential model. * $p < 0.001$ compared to baseline.

Fig. 5

Evolution of the LV relaxation curvilinearity coefficient (K) derived from the quadratic model. * $p < 0.001$ compared to baseline.

Fig. 6

Evolution of the LV isovolumic relaxation time (IVRT) during acute myocardial ischemia.

Table 1

	T0	T30	T60	T90	T120
CO (mL/sec)	56,7 ± 2,8	52,1 ± 2,8 *	51,7 ± 2,5 *	52,9 ± 2,7 *	49,9 ± 2,0 *
EF	0,52 ± 0,02	0,46 ± 0,02 *	0,45 ± 0,01 *	0,44 ± 0,01 *	0,41 ± 0,01 *
SAP (mm Hg)	109 ± 12	98 ± 11	99 ± 10	100 ± 16	99 ± 17
HR (BPM)	100 ± 4	116 ± 4 *	120 ± 3 *	131 ± 4 *	136 ± 3 *

Hemodynamic data. * $p < 0.001$ compared to baseline. CO = cardiac output; FE = LV ejection fraction; SAP = systemic arterial blood pressure; HR = heart rate.

Appendix A

The time derivative of Equation 2 is:

$$\frac{dP(t)}{dt} = \frac{1}{K} \cdot \frac{1}{(1 + e^{t/Tq})^2} \cdot \frac{1}{Tq} \cdot e^{t/Tq}.$$

282 Using Equation 2 to substitute for $e^{t/Tq}$ gives:

$$\frac{dP(t)}{dt} = K \cdot P(t)^2 \cdot \frac{1}{Tq} \cdot \left(-\frac{1}{K \cdot P(t)} - 1\right).$$

283 Rearranging this Equation finally gives Equation 3:

$$\frac{dP(t)}{dt} = -\frac{1}{Tq} P(t) - K.\frac{1}{Tq}.P(t)^2.$$