Cardiac Time-Area Curve Modelling Using Piecewise Linear Regression in Mice with Heart Failure

Magdalena Jabłońska[1,2], Urszula Tyrankiewicz[1], Anna Osiak[1], Henryk Figiel[2], Tomasz Skórka[1]

[1]Department of Magnetic Resonance Imaging, Institute of Nuclear Physics PAN, Krakow, Poland
[2]Department of Medical Physics and Biophysics, AGH University, Krakow, Poland

Abstract

Cardiac single-slice time-area curves (TAC) depict the left ventricle function at multiple time points throughout cardiac cycle. The character and number of observed TAC phases depends on several factors related to heart condition and experimental procedure. The aim of this work was to assess piecewise linear regression modelling (PLR) as a tool for the TAC shape analysis leading to the curve sectioning with estimation of the segments lengths and dynamics allowing the complex TAC parameterization.

Cardiac Magnetic Resonance images of the atherosclerotic and control mice obtained at rest and under pharmacologically induced stress condition were considered. TAC from each mouse was modelled by partitioning time into intervals and fitting using straight lines, where position of intervals boundaries were optimized numerically. The best fit model was selected from several candidate models (with different numbers of segments) according to Akaike Information Criterion.

PLR has been validated as the promising method for tracing qualitative and quantitative changes in TAC shapes showing different paths of stress response. The method is time saving, gives possibly objective results, extends analysis protocol and allows semi-automatic assessment of the TAC individual systolic and diastolic phases.

1. Introduction

Cardiovascular problems are great part of civilization-related diseases resulting in significant morbidity and mortality worldwide [1]. One of the important issues concerning cardiac research at the very early stage of pathology is the proper understanding of the observed functional changes in response to developing cardiovascular alterations.

Cardiac Magnetic Resonance Imaging (CMR) is a valuable tool in the assessment of heart function, especially in experimental models where early and subtle or atypical changes may be observed. Although there are many CMR techniques of heart condition analysis, the assessment of cardiac function based on the left ventricle (LV) volume changes over cardiac cycle is still the most common method. An important extension of the method is related to the use of β-adrenergic stimulation during CMR examination which can be described as the equivalent for the stress test. Allowing the assessment of cardiac reserve it may be used as a more precise parameter but also as an effective survival predictor [1].

CMR in small animals is more problematic than in humans. Small size of rodent heart and its rapid action result in restricted spatio-temporal resolution of the method [2-3]. Moreover, application of the bolus β-adrenergic stimulation in murine studies practically preclude from whole chamber imaging because of limited time for measurement after the bolus injection. In such conditions data is restricted to the area of the single LV cross sections measured over the cardiac cycle.

For the detailed description of LV performance, a time-volume curve or a single-slice time-area curve (TVC/TAC) should be analysed, however, the manual post-processing is subjective and time consuming. For the enhanced analysis of TAC/TVC computer aided techniques may be useful. Humans TVC shapes were previously reported to be analyzed by Fourier fitting [4-5] and spline smoothing [6-7], however these methods allow to calculate only peak ejection and peak filling values without any information about cardiac phases time-course neither filling/emptying profile, so still some information can be incomplete.

The goal of the presented work was to implement Piecewise Linear Regression to the CMR-based TAC for its shape modelling and calculating standard and supplementary cardiac parameters and Akaike Information Criterion to model selection. The algorithm has been tested on data from experiments with a stress protocol in healthy and diseased mice.

2. Methods and calculation

2.1. Subjects and CMR protocol

Images from seven ApoE/LDLR$^{-/-}$ mice with advanced arteriosclerosis (6 months old) and five control C57BL/6J mice (2 months old) were taken for the PLR analysis. Three data sets were analysed for each mouse: at rest and under stress condition after dobutamine i.p. injections with two increasing doses (low: 0.5 mg/kg and high: 5 mg/kg).

Each data set consisted of the series of midventricular short axis images evenly distributed over cardiac cycle. They were collected using the 4.7 MRI system consisting of MARAN DXR console (Resonance Instruments Ltd, United Kingdom) and 4.7 T magnet (Bruker, Germany) using prospectively ECG triggered cine gradient echo sequence (FLASH) with the field of view (FOV) equal to 30x30mm^2 and spatial resolution 0.24 mm per pixel [8]. Number of images per cardiac cycle was dependent on the cardiac cycle length (from 18 to 29) and was set to maintain temporal resolution not worse than 5.3 ms. Heart rates used for cardiac cycle length normalization were recorded independently during the imaging protocol (SA Instruments Inc, USA).

CMR-based images were semi-automatically segmented in order to LV endocardium detection, delineation and its area evaluation using Aphelion software (ADCIS, France) [9]. TACs were generated by plotting segmented LV area normalized to end-diastolic area against the time after the R-wave normalized to the length of the cardiac cycle, so both coordinates were in the range between 0 and 1.

2.2. TAC Modeling using PLR

TAC shapes were modeled by applying piecewise linear regression (PLR) method (Figure 1).

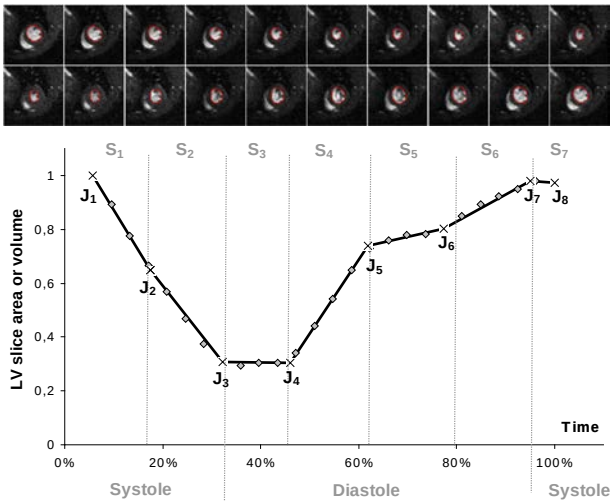

Figure 1. An example of Piecewise Linear Regression method applied to the TAC based on segmented LV MR images. J_1 to J_8 are breakpoints, S_1 to S_7 are linear segments interpreted as: S_1 – rapid ejection (ER), S_2 – reduced ejection, S_3 – IVRT, S_4 – rapid inflow (FR), S_5 – diastasis, S_6 – atrial systole, S_7 – IVCT. Systole time (Ts) is a duration of rapid and reduced ejection [12].

The PLR model [10,11,13] was obtained by piecing together separate segments given by the linear regression function $Y=a_iX+b_i$ defined over the time intervals breakpoints (J_i):

$$Y = a_1 X + b_1, \quad X \le J_1$$
$$Y = a_2 X + b_2, \quad J_1 \ge X \ge J_2$$
$$\vdots$$
$$Y = a_n X + b_n, \quad X \ge J_n$$

where Y – normalized LV single-slice area, X – time.

The unknown positions of segment boundaries (J_i) was optimized numerically using Levenberg-Marquard algorithm (MATLAB, MathWorks Inc, USA), the most frequently used to solve nonlinear data fitting problems in least-squares sense (by minimize mean sum of squares) [10]. According to breakpoints position linear intercepts b_i and slopes a_i were calculated.

2.3. Model selection according to AIC

For each dataset PLR algorithm was applied six times with variant number of segments. The simplest one consisted of three segments, whereas the consecutive, more complicated models were produced by increasing number of segments by one, up to eight segments which was one more than the maximum number identifiable and interpretable in cardiac cycle [12].

The proper number of TAC segments was chosen using Akaike Information Criterion (AIC), a method for model selection, based on information theory, which estimates the relative discrepancy between the unknown true model and the approximating model as a measure of the Kulblack-Leibler information loss [10, 13]. AIC value is defined by the equation:

$$AIC = N \ln\left(\frac{SSE}{N}\right) + 2K$$

where N is the number of raw data points from CMR-based images (at least two times greater than number of estimated parameters), K is the number of parameters plus one, and SSE is the sum of the squares of the vertical distances between the data points and the model.

When N is small compared to K (as in this case) the corrected AIC value (AIC_C) is more accurate [14]:

$$AIC_C = AIC + \frac{2K(K+1)}{N-K-1}.$$

Each model was compared with the next one according to increasing number of segments and the one with the smaller AIC_C value was selected. When addition of the next segment did not improve fitting quality the algorithm was stopped. Even when addition of next segment improve model fitting (smaller AIC_C value, but less than 2) the model with smaller number of parameters was selected,.

The compliance between the segments and corresponding cardiac phases was evaluated by an expert knowledge.

P-values smaller than 0.05 were considered statistically significant.

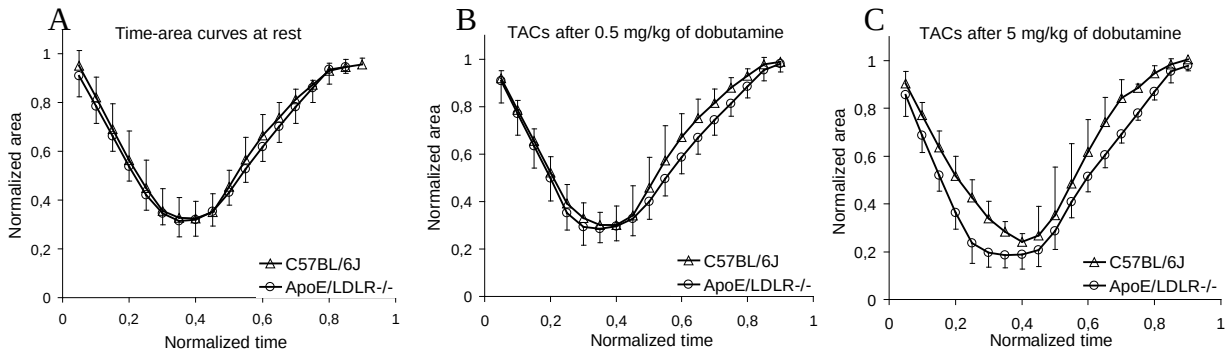

Figure 2. TAC shapes for ApoE/LDLR$^{-/-}$ and C57BL/6J mice averaged over the whole group at rest (A) and after two consecutive dobutamine doses (B and C). The averaged curves were built by adding individual single slice area values in proper cardiac phase. Whiskers indicate SD.

Table 1 Cardiac parameters and number of linear segments calculated at rest and after low (0.5 mg/kg) and high (5 mg/kg) dose of dobutamine for ApoE/LDLR$^{-/-}$ and control (C57BL/6J) mice.

Cardiac parameter	C57BL/6J mice (N=5)			ApoE/LDLR$^{-/-}$ mice (N=7)		
	Basal	Low dose	High dose	Basal	Low dose	High dose
Segment no	4.2(1.1)	4.4(0.6)	4.8(0.5)	3.7(0.5)	3.9(0.7)	4.5(1.1)
FAC [%]	68 (7)	71 (7)	77(4)*	70(7)	72(6)	82(5)**
Ts [% RR]	33(6)	31(8)	37(6)	32(7)	28(3)	28(4)
IVRT [% RR]	13(8)	14(8)	10(4)	12(9)	17(3)	18(4)
ER [EDA/RR]	2.6(0.5)	2.6(0.3)	2.7(0.5)	2.5(0.5)	2.7(0.2)	3.4(0.6)**
FR [EDA/RR]	2.6(0.6)	3.0(0.5)	3.4(0.9)	2.0(0.5)	1.9(0.5)	2.4(0.7)

* – $p<0.05$ for comparison between high dose and basal, ** – $p<0.05$ between high dose and basal and high and low dose.

2.4. Data and statistical analysis

For the LV condition description the following functional parameters based on the TAC were calculated: fractional area change (FAC=(EDA-ESA)/EDA in percents, where ESA and EDA indicate an end-systolic area and an end-diastolic area respectively), isovolumic relaxation time (IVRT) assigned to the length of the segment with relatively small changes and located after systolic phase, systole duration (Ts), ejection and filling ratios (ER, FR respectively) as regional slopes of linear fit at the beginning of the systole and diastole (rapid ejection and rapid inflow).

ANOVA for repeated measurements were used to compare LV parameters before and after dobutamine injection (cardiac reserve assessment). For detailed comparison Tukey post-hoc test was applied. Comparison between two methods (manual and semi-automatically PLR) was performed using Spearman correlation analysis and Bland-Altman analysis. Statistical analysis was conducted in STATISTICA package (Stat Soft Inc., USA).

3. Results

Shapes of basal curves for ApoE/LDLR$^{-/-}$ and C57BL/6J are roughly similar (Figure 2A). The first noticeable difference between groups is visible on the diastolic limb for the low dobutamine dose stimulation (Figure 2B): control group have steeper slope on the diastolic limb (FR) and shorter IVRT. After second injection with high dobutamine dose the differences in TAC shapes between groups are pronounced: IVRT shortened and FR became steeper due to more rapid inflow in control group (Figure 2C). Quantitative analysis were performed and results are presented in Table1.

For the pairs of cardiac parameters estimated by the algorithm and manually the Spearman`s correlation analysis was conducted. FAC_{alg} vs FAC_{man}: rs = 0.98 ($p<0.0001$; N = 35), ER_{alg} vs ER_{man}: rs = 0.84 ($p<0.0001$), FR_{alg} vs FR_{man}: rs = 0.91 ($p<0.0001$), Ts_{alg} vs. Ts_{man}: rs = 0.80 ($p<0.0001$), $IVRT_{alg}$ vs $IVRT_{man}$: rs = 0.68 ($p<0.0001$). A Bland-Altman plot of residual values of parameters showed no clear evidence of a systematic

difference between the methods.

4. Discussion and conclusion

Presented work depicts the application of PLR modeling for the assessment of cardiac function in course of the experimental heart failure analysis. Detailed TAC analysis can give various markers of systolic and diastolic function, what is of great importance especially in models of diastolic or suspected diastolic dysfunction.

The PLR method adopted for TAC modeling provides the TAC analysis and parameterization. In contrast to the attempts being used previously and based mostly on the curve smoothing the proposed method gives the opportunity of the TAC segmentation into intervals related to the cardiac phases. Moreover, the number of visible phases is assigned using AIC, a tool for the automated model search and comparison, what gives additional information, prevents the use of overly complex description and, additionally, leaves less decision for the operator making the process of the TAC analysis more objective. However, in case of difficulties in segments assessment due to ambiguous curve shape, operator supported decision still has to be made as well as the compliance between the segments in PLR and corresponding phases in cardiac cycle should be verified.

PLR method applied to the results of the CMR measurements of the cardiac function in the murine model of atherosclerosis demonstrates changes in cardiac function in diseased mice and uncovers stress induced difference between healthy mice: decreased FR at low stimulation and prolonged IVRT at high stimulation. This can indicate a progressing diastolic dysfunction and, consequently, the early stage of cardiovascular problems which is one of the manifestations of atherosclerosis.

To conclude the PLR method is more time efficient, provides a step towards a more objective characterization of heart function in cardiac MRI in animals and could be potentially promising tool for automatic or at least semi-automatic tracing of qualitative and quantitative changes in TAC shapes. Additionally, combined with the extended protocol with application of the stress test, it could give more complex information of developing heart dysfunction not noticeable at rest condition.

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Address for correspondence:
Magdalena Jabłońska
Institute of Nuclear Physics
Polish Academy of Sciences
ul. Radzikowskiego 152
31-342 Kraków
Magdalena.Jablonska@ifj.edu.pl