Myocardial perfusion assessment with contrast echocardiography

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ABSTRACT

Assessment of intramyocardial perfusion by contrast echocardiography is a promising new technique that allows to obtain quantitative parameters for the assessment of ischemic disease. In this work, a new methodology and a software prototype developed for this task are presented. It has been validated with Coherent Contrast Imaging (CCI®) images acquired with an Acuson Sequoia scanner. Contrast (Optison® microbubbles) is injected continuously during the scan. 150 images are acquired using low mechanical index U/S pulses. A burst of high mechanical index pulses is used to destroy bubbles, thus allowing to detect the contrast wash-in. The study is performed in two conditions: rest and pharmacologically induced stress.

The software developed allows to visualize the study (cine) and to select several ROIs within the heart wall. The position of these ROIs along the cardiac cycle is automatically corrected on the basis of the gradient field, and they can also be manually corrected in case the automatic procedure fails. Time curves are analyzed according to a parametric model that incorporates both contrast inflow rate and cyclic variations.

Preliminary clinical results on 80 patients have allowed us to identify normal and pathological patterns and to establish the correlation of quantitative parameters with the real diagnosis.

Keywords: myocardium, perfusion, contrast agents, echocardiography, ultrasound, ischemic heart disease.

1. INTRODUCTION

The evaluation of myocardial perfusion is important in the prognosis of patients after myocardial infarction. The analysis of the movement of heart walls as provided different imaging modalities (MRI, ultrasound) is not accurate enough to determine the extension of necrotic tissue and to define myocardial viability [1]. For example, stunned myocardium is a post-ischemic dysfunction characterized by regions with absence of motion but normal flow, regions that in the following weeks may recover [2]. Myocardial hibernation is also a reversible dysfunction where there is reduced myocardial flow with possibility of recovery after coronary revascularization [3]. Necrotic tissues on the other hand, having lost microvasculature, have poor perfusion or not perfusion at all [4] and are not recoverable.

Myocardial viability has been traditionally analyzed by nuclear medicine imaging procedures, like ^{201}Tl-SPECT, which measure cell membrane integrity [5, 6], or more recently by PET-FDG, which shows metabolism and blood flow rates [7]. These techniques have the problem of their low spatial resolution and the use of ionizing radiation. In the last few years MRI with contrast agents like Gd-DPTA has also been proposed [8].

The availability, low cost and non-invasiveness of echocardiography have fostered an increasing interest in the possibilities of this modality to provide an accurate and quantitative diagnosis of the myocardial state. The intravenous injection of contrast agents (microbubbles) has allowed to visualize flow information and regional perfusion [1, 4, 9]. Microbubbles, or echo-enhancers (EE), increase the echo backscatter of perfused tissues and blood pool in cavities and are almost ideal tracers as they remain intravascular and have a particle size similar to red blood cells [1, 4]. However, interpretation of the results is very difficult without calculating quantitative parameters and discrepancies in preliminary results are frequent [10]. Mor-Avi et al. proposed methods for quantifying both regional blood flow distribution [11] and transit time along the myocardium [12], by frequency domain analysis of regional time curves.

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Quantitative parameters can also be obtained by using an interesting feature of microbubbles: they can be destroyed by an ultrasound pulse of sufficient energy (high mechanical index) [13]. It is then possible to obtain, not only the steady-state information, but also the wash-in curve, showing the refilling of microbubbles following their destruction by an ultrasound pulse (Figure 1). These wash-in curves have been fitted to mathematical models and quantitative parameters have been extracted [14]. Preliminary results on open-chest dogs have shown good correlation with coronary stenosis [15].

These results have also been enabled by the new advances in technology, such as Coherent Contrast Imaging (CCI®), that allow to better analyze the harmonic signal coming from the echo-enhancers. Through the use of single pulse cancellation, CCI shows in B-Mode the harmonic signal produced by EE, eliminating the fundamental component and improving the SNR and thus the visualization of EE in the myocardium.

However, clinical application of these results is hindered by several problems. Heart motion complicates the regional analysis as it implies tracking particular regions within the heart wall during the cardiac cycle. Optimum model-fitting parameters, correlated with myocardial blood flow or its contractile capabilities, and eventually with the clinical prognosis of the patient, have not been defined yet [10, 15].

In this paper we present a method to quantify myocardial perfusion contrast studies that allows to perform a parametric analysis of time curves. The procedure also includes a semiautomatic position correction of wall ROIs that overcomes the problem of heart motion in an efficient way. With this method and the software prototype developed, clinical analysis of a number of patients and controls can provide robust and consistent data. Preliminary results on 80 patients have allowed us to identify normal and pathological patterns and to establish the correlation of quantitative parameters with the real diagnosis.

2. MATERIALS AND METHODS

2.1. Program features

A software prototype has been developed to visualize and analyze CCI images and to obtain global and local quantitative parameters. The program runs on a PC computer (PENTIUM III-500 MHz, 256MB RAM), Windows NT 4.0. It has been developed in Visual Basic® and Visual C® (Microsoft Corporation) using ImageGear® libraries (Accusoft Corporation). It accepts sequences of images (digital clips) in DICOM format.

A brief description of its main features follows:

- Visualization: The sequences of images can be visualized (cine) at user-selectable speed, or frame by frame. The usual zoom and panning tools are available. Time markers can be added to mark relevant moments (typically end-systole); these marks will be shown in all the time curves produced.

- ROI definition: for regional analysis, the user can define several regions-of-interest or ROIs on the image. Tools are provided to easily draw these ROIs. Although in principle ROIs can adopt any shape, based on the preliminary studies, it was decided that only elliptical shapes of different sizes would be used, since they produce more reliable results. ROIs are clearly visible on each image in the time sequence, and each one is identified by a different color (Figure 3).

- ROI repositioning: a critical step for the adequate regional time analysis is that ROIs should keep its position within the heart wall along the cardiac cycle, otherwise the time curves are distorted as the ROI does not represent the same region at any moment. Maximum error is obtained when the ROI invades the ventricle cavity, whose videointensity (VI) values are significantly higher than in the wall. To correct this problem the endocardial edge of the heart wall is found in the gradient image and the ROI is repositioned in such a way that it stays tangent to that endocardial edge, not invading the ventricular cavity. Gradient image is rather noisy and requires spatial and temporal averaging. Despite of this, in some images is not possible to find the position of the endocardial border in a reliable way and the automatic method does not move the ROI. For this cases, mechanisms for manual ROI repositioning are available.

- Quantification: the mean VI value of each ROI along the sequence can be depicted as a time-curve (Figure 4). Time curves can be exported as spreadsheet-compatible ASCII files, so that they can be further analyzed by standard software packages.

2.2. Quantification

The time-curve that represents the change in videointensity (VI) after applying the high mechanical-index pulse that destroy bubbles can be considered made of two components: A slow component that corresponds to the recovery of steady state VI values (wash-in) and a higher frequency component that conveys the cyclic variations due to the periodic contractions of the heart. These components can be easily separated with a low-pass filter, thanks to the marked difference in their spectral content. Most of the noise remains with the high frequency cyclic component. Figure 2 shows and example depicting both components.

According to the literature [1, 9, 14], the wash-in curves can be modeled by an exponential curve:

$$y = A(1 - e^{-\beta t})$$

From these curves, several parameters can be computed. The proposed program automatically obtains:

A: Maximal end-systolic videointensity previous to bubble destruction

β: Time constant of the exponential recovery after bubble destruction.

$A\beta$: slope during initial replenishment, as given by the equation:

$$\frac{dVI}{dt} = A\beta e^{-\beta t}$$

3. RESULTS AND DISCUSSION

3.1. Clinical validation

Clinical studies on different aspects of the technique are being carried out, enrolling 80 patients up to now. In this paper we include some results taken from these studies in order to support the validity of the technique.

All studies were acquired with an ACUSON Sequoia® System with CCI. The echo-enhancer administered consisted of microbubbles of octafluoropropane (Optison®). For each patient, sequences of 150 consecutive frames (temporal resolution of 50-75 ms) in both four-chamber and two-chamber apical views were acquired and stored for posterior review and analysis.

Studies were acquired in rest (R) and, when necessary, under pharmacological stress (S) conditions. In this latter case images were obtained 8 minutes after the infusion of 0.56 mg/Kg of Dipiridamole.

Videointensity (VI) and curve values are expressed in dB. Statistical results are provided as mean±SEM. For all the comparisons, non-parametric statistical tests were used (Mann-Whitney and Wilcoxon tests for non-paired and paired data respectively).

3.2. Feasibility

Feasibility of this technique was assessed on 547 different segments obtained from 54 patients. Segments were evaluated by scoring its image quality according to the following scale: 0=Not visualized, 1=suboptimal (myocardial boundaries undefined), 2=acceptable (endocardial boundaries well defined) and 3=optimal (both endo and epicardial boundaries well defined). Figure 5 and 6 shows the results; the average score was 2.26±0.04, 79.2% of the segments showed optimal or acceptable visualization (60.9% optimal, 18.3% acceptable). Considering the results by region, only basal anterior

(optimal/acceptable= 14.9%), basal lateral (optimal/acceptable= 36.2%) and basal medial (optimal/acceptable= 43.4%) segments showed bad visualization that could compromise its clinical validity.

3.3. Cyclic variations

This analysis included 75 normokinetic segments corresponding to nine consecutive patients without any cardiomiophaty both in rest (R) and stress (S) conditions, as described above. In (R) videointensity was higher in diastole than in systole (10.9±0.4 vs. 9.1±0.3 $p<0.001$). In (S) videointensity values increased (12.2±0.4 vs. 10.3±0.3) but the difference between systole and diastole did not change significantly in global values. The distribution was homogeneous in all the segments in (R), but in (S) showed a higher increase in septal regions compared to basal segments (Figure 7).

Classic studies in physiology showed the cyclic behavior of the coronary flow, reaching a maximum during the diastolic period and a minimum during the systolic phase. We hypothesized that this flow pattern at myocardial level can be assessed through the quantification of contrast images. According to our results, it seems that quantitative CCI is able to detect cyclic variations of coronary flow and its modification after pharmacological interventions. However, it is not clear yet whether this information can be used to assess the existence of ischemic heart disease with more reliability than other methods (for instance, quantification of the wash-in curve as shown below).

3.4. Myocardial perfusion

This analysis included 50 patients, 12 without any cardiomiopathy and 38 with ischemic heart disease (IHD), from whom 73% had previous well documented myocardial infarction. 395 segments were evaluated: 97 normokinetic from normal patients, 167 normokinetic from IHD and 131 disynergic from IHD. Results show that end-diastolic (R-wave synchronous) intensity was maximal in normokinetic segments of normal patients (10.68±0.35); in IHD, normokinetic segments showed smaller intensity (9.39±0.26, $p<0.01$) but even smaller in disynergic segments (8.08±0.31, $p<0.01$).

4. CONCLUSIONS

From the results shown in this paper, it seems that CCI can contribute to the identification of viable myocardium. Quantitative assessment of time curves produces reliable figures that according to our results are easy to obtain for most cardiac segments, reflect the cyclic variations of wall perfusion and seem to be related to the clinical situation (ischemia).The experience in the assessment of myocardial perfusion with this new tool is still very limited, and it is not clear yet whether the slow or high frequency component of the wash-in curves may yield more significant results.

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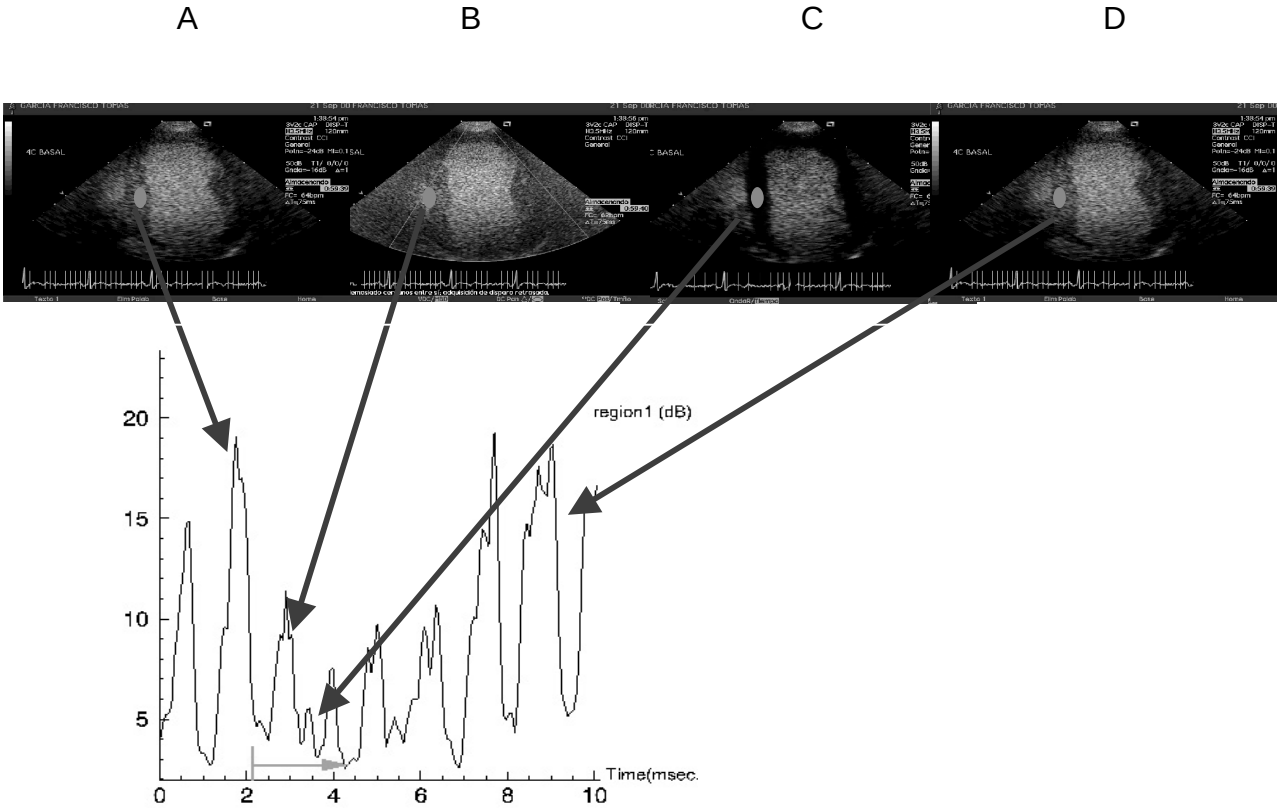

Figure 1: *(Top)* Images acquired in four different moments: A, B during the steady state; C immediately after bubble destruction; D during the replenishment phase. A ROI drawn within the heart wall is also shown. *(Bottom)* Time-curve obtained from the ROI.

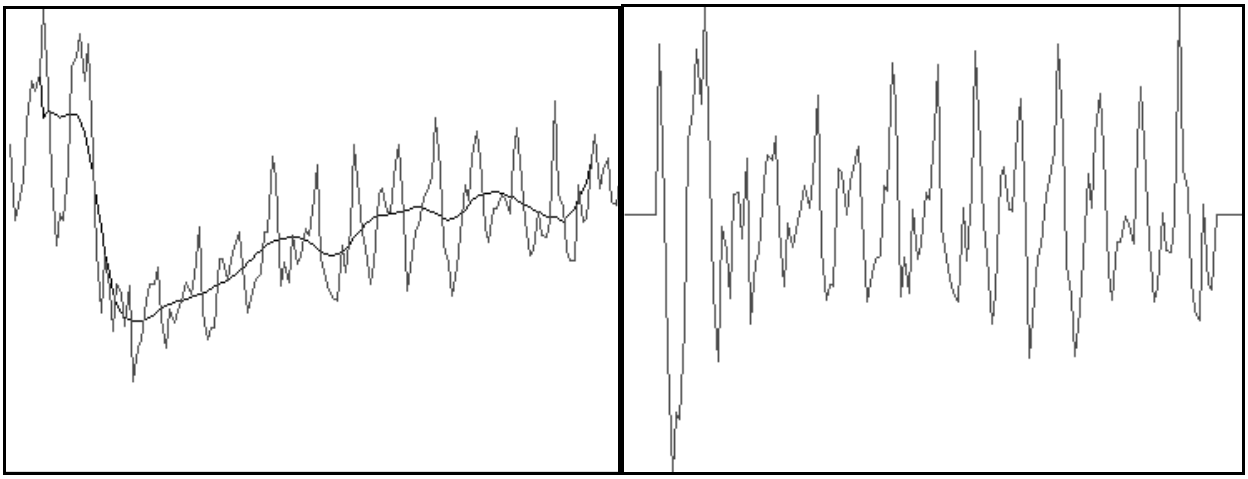

Figure 2: *(Left)* This figure shows the time-curve together with the slow component. *(Right)* High frequency component of the curve from the left side. Horizontal axis represents time and vertical axis represents Videointensity.

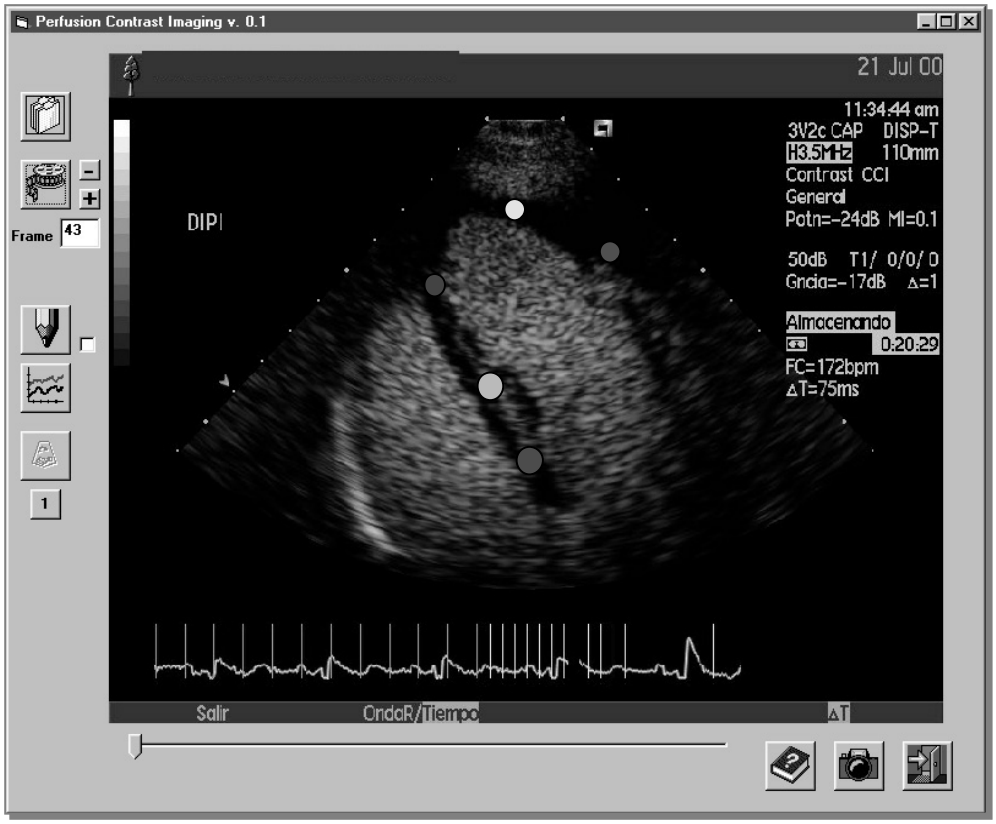

Figure 3. Program screen layout showing several ROIs defined on the image.

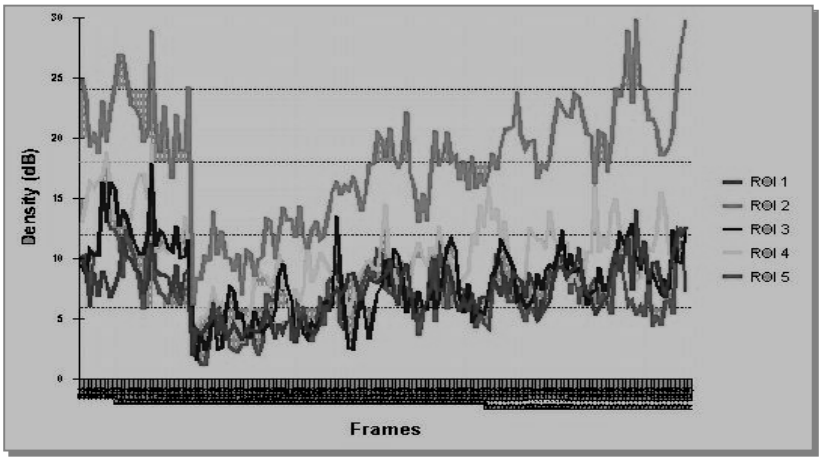

Figure 4. Time curves obtained from ROIs in Figure 2.

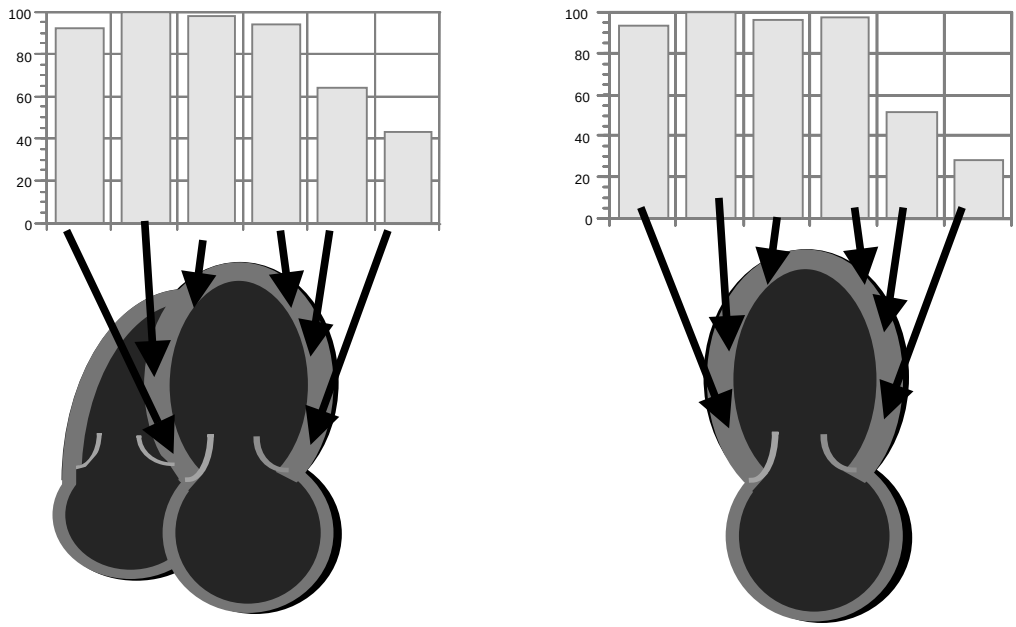

Figure 5. Percentage of segments with optimal/acceptable visibility. Results from 547 segments scored by an expert.

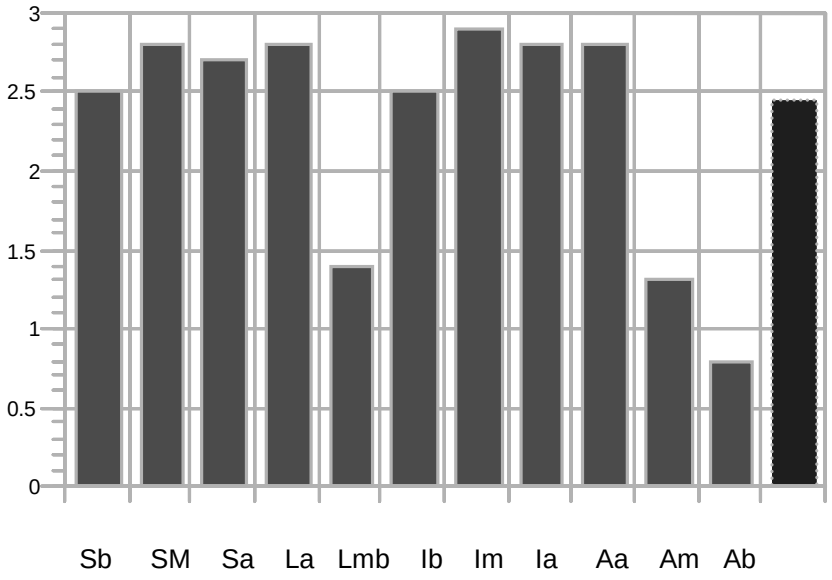

Figure 6. Scoring by an expert of 547 segments in the cardiac wall, according to the criteria: *0-Not visualized; 1-Suboptimal; 2-Acceptable; 3-Optimal*. Results show the mean value for each type of segment as in Figure 4. The right column is the global result for all segments..

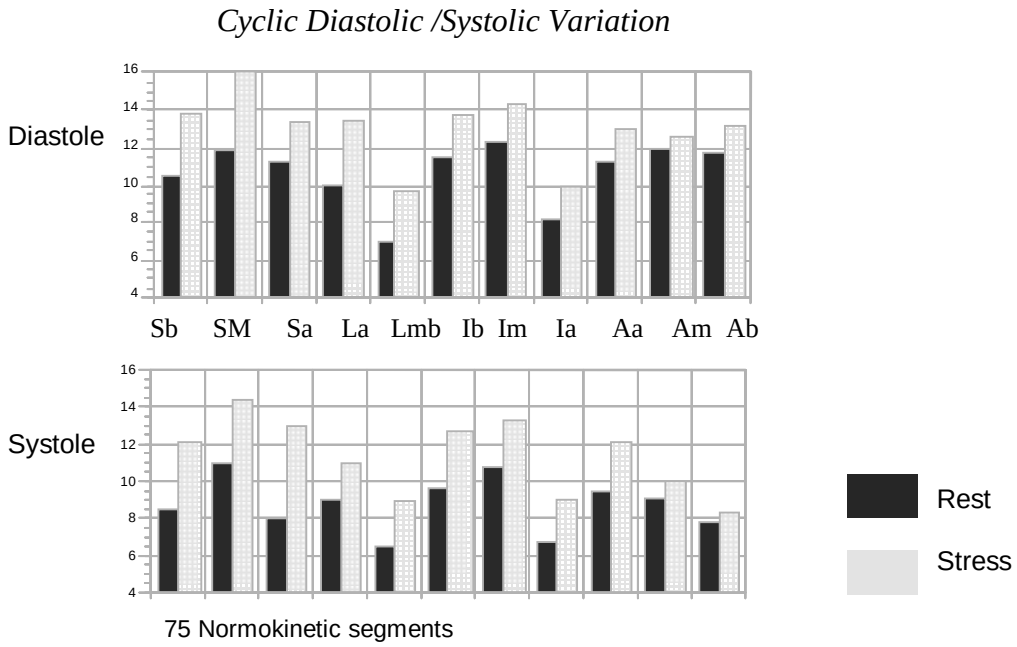

Figure 7. Cyclic variations of videointensity under rest or stress conditions.