Signal Heterogeneity in Contrast-enhanced Echocardiographic Imaging Despite Uniform Concentration of the Contrast Agent

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Abstract

To quantify the heterogeneity of contrast enhancement inside left ventricular (LV) cavity, 10 patients were studied by harmonic intermittent power Doppler following venous echo contrast administration. Regions of interest were drawn in the LV cavity along the main axis and transversally to derive time-intensity curves. Signal intensity at plateau (A) significantly decreased along LV longitudinal axis: from apex (48±6 dB), to center (41±7) and base (31±9 dB, $p < 0.05$), while intensity rise (b) was unaltered. A also was lower in proximity of the septum than in the center of LV cavity ($p<0.05$). Finally, beat-to-beat variability increased with increasing depth. Thus, LV contrast intensity varies despite a uniform concentration of the contrast agent at each time, due to ultrasound attenuation and heterogeneous beam intensity. Parameter b appears more consistent than A in deriving quantitative flow information.

1. Introduction

The venous administration of ultrasound contrast agents - commercially available today - consistently enhance the echocardiographic signal inside the heart. As the contrast effect in left ventricular (LV) cavity is higher than in the myocardium, contrast administration favors the detection of endocardial borders [1, 2]. This improved delineation of cavity boundaries facilitates the calculation of LV volumes and ejection fraction, as well as the detection of regional wall motion abnormalities [3-5]. Furthermore, the changes in ultrasound signal intensity recorded during the passage of the agent through the cardiac cavities could provide quantitative information on cardiac output and ejection fraction [6, 7].

To derive quantitative information from contrast-enhanced echocardiographic images, contrast agents should behave as flow tracers. If a tracer is injected as a bolus in a peripheral vein its input function in the left side heart is not instantaneous but dispersed over time [8, 9]. This is due to the mixing of the tracer with blood inside the vessels and the cardiac cavities and to its passage through the lung circulation, where the tracer crosses circuits of different length [9]. A uniform tracer concentration in blood is further favored by its venous infusion and by its recirculation, as occurring in this study. Contrast concentration reaches equilibrium when mixing is completed. Despite the above considerations, the intensity of contrast-enhanced ultrasound signal is not uniformly distributed inside LV cavity even at visual inspection of echocardiographic images (Figure 1). Thus, this study was undertaken to quantify the heterogeneity of echo contrast-enhancement inside LV cavity in a clinical model where the concentration of the agent at each time can be assumed to be uniform.

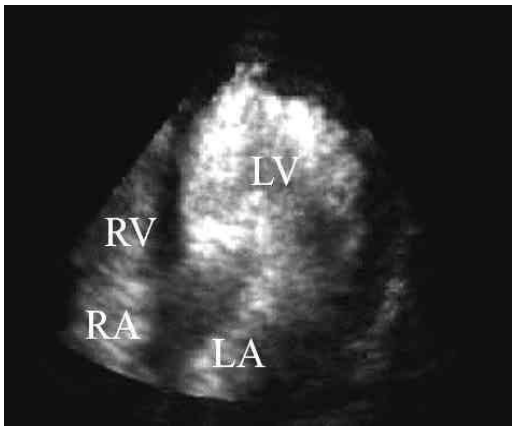

Figure 1. Representative image from the study. LV: left ventricle: RV: right ventricle; LA: left atrium; RA: right atrium.

2. Patients and image acquisition

Ten patients (8 males, mean age 62 years) underwent a contrast echocardiographic study for diagnostic purposes. Echocardiographic images were obtained by a commercial scanner (GE-Vingmed System 5) operating in harmonic power Doppler. Each image was sampled every two cardiac cycles, synchronously with EKG, at end-systole, in the apical horizontal view.

Echo contrast enhancement was obtained by the intravenous administration of a galactose-based contrast agent (Levovist, Schering AG, Germany). Eight ml of

this agent (4 g, 400 mg/ml) were injected in an antecubital vein initially as a bolus (2 ml over 4 s) and then as an infusion (4 ml/min, for 90 s), which was followed by a saline flush. The study was completed in every patient without side effects.

The echocardiographic images were recorded in a digital format on the scanner mass storage device. At every contrast administration a sequence of images was recorded from baseline conditions up to a visually apparent decline in contrast enhancement inside LV cavity.

2.1. Data analysis

Cine loops of the acquired sequences were reviewed to identify obvious misalignments due to ultrasound probe dislocation or deep respiration. Such images were excluded from the analysis. For all sequences of images, 7 square regions of interest (ROI), each of 11x11 pixels, were drawn in the LV cavity, as illustrated in Figure 2.

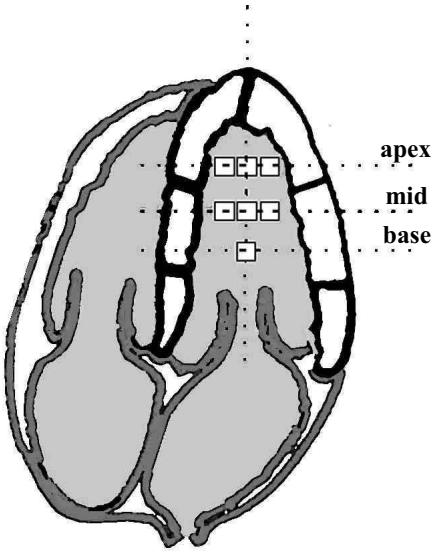

Figure 2. Location of the regions of interest (ROIs) inside left ventricular cavity.

Mean signal intensity (in dB) inside each ROI was measured by means of a scanner built-in program; numerical data were transferred to an external personal computer. For each ROI, intensity values were plotted versus time to obtain time-intensity curves, as shown in Figure 3. Each curve was fitted according to the equation:

$$I(t) = A(1 - e^{-bt}) \qquad [1]$$

where I(t) is signal intensity at time t, A is plateau signal intensity, b is the coefficient of intensity rise and t is the time after initial contrast appearance in the LV cavity [10].

2.2. Statistical analysis

The extracted A and b values were analyzed by means of statistical comparisons. Student's paired t-test analysis was applied to detect differences along the ultrasonic propagation line from apex to mid mitral valve. ANOVA (Scheffé's post-hoc test) was employed to get evidence of transversal differences. A p value <0.05 was considered statistically significant.

3. Results

3.1. Curve fitting

In every patient the fitting of the curves according to the equation [1] was good, although it slightly declined as the depth from the transducer increased. As a matter of fact, the average correlation coefficient r was 0.96 (range 0.73 - 0.99) at the apex, 0.95 (range 0.85 - 0.99) in the mid LV cavity and 0.91 (range 0.84 - 0.98) at LV base.

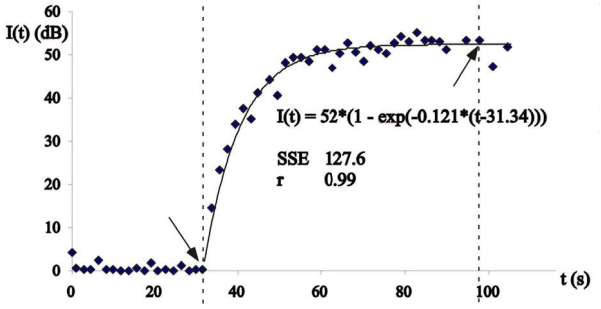

Figure 3. Time-intensity curve corresponding to contrast appearance in LV cavity up to the plateau phase. The arrows mark the starting and ending points of curve fitting.

3.2. Heterogeneity in signal intensity

Data analysis showed heterogeneity in plateau signal intensity along the longitudinal axes, as shown in Figure 4, although differences were significant between apex and base, and between center and base.

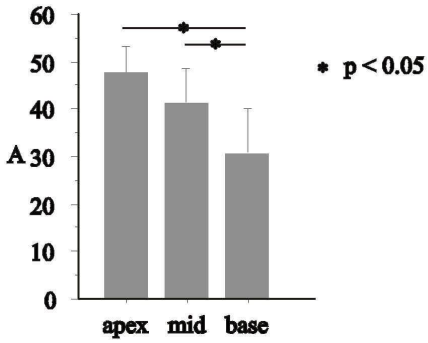

Figure 4. Changes in plateau signal intensity (A) along the longitudinal axis marked in Figure 1.

A minor heterogeneity was present in the transverse axes, being the plateau intensity A higher in the center of the LV cavity than in proximity to the interventricular septum (Figure 5).

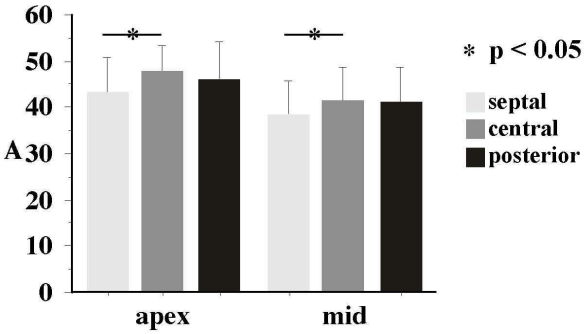

Figure 5. Changes in plateau intensity along the transversal axis in proximity of the apex and in the center of LV cavity.

3.3. Heterogeneity in intensity rise

At variance with the parameter A, b showed any significant difference nor in the longitudinal neither in the transverse axes. Behavior of this parameter is exemplified in Figure 6.

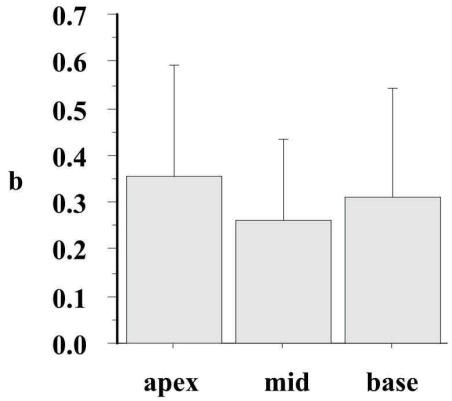

Figure 6. Changes in intensity rise (b) along one of the transversal axes marked in Figure 1.

3.4. Beat to beat variability

To evaluate the difference in signal intensity among consecutive beats once the plateau signal intensity was reached, a subset of subsequent values (x_n) has been considered for comparison with the fitted A plateau value and the following formula was adopted:

$$\text{Variability} = \frac{1}{A}\sqrt{\frac{1}{N}\sum\nolimits_n (x_n - A)^2}$$

where N is the total number of considered frames.

Along the longitudinal axis the beat-to-beat variability increased with increasing depth, corresponding to 4±2% at the apex, 11±6% in the centrum of LV cavity and 14±8% at the base. Along the transversal axes beat-to-beat variability was higher in the lateral ROIs than in the center of LV cavity (9±5%, 4±2%, 5±4% at apex; 12±4%, 12±6%, 15±14% at center; 14±8%, at base).

4. Discussion

This study demonstrates that the echo contrast effect inside LV cavity is very heterogeneous, both in the space and the time domain, despite LV concentration of microbubbles can be assumed to be uniform at each time.

The intensity of the Power Doppler signal, after contrast microbubbles implosion, declines with increasing depth from the transducer [11]. This phenomenon is very similar to that observed in B-mode imaging, where the signal intensity decreases away from the transducer due to ultrasound attenuation. In this study signal attenuation is mainly caused by microbubble gaseous content.

A minor heterogeneity in contrast effect occurs in space transversally to the ultrasound beam, being signal intensity higher in the central area of the sector than in the lateral regions. Contrast effect in power Doppler is caused by the implosion of microbubbles induced by high intensity ultrasound (high mechanical index) [11]. As ultrasound intensity is higher in the central area of the sector than laterally, microbubble implosion – and thus signal intensity - is also higher in this area, which corresponds to the centrum of LV cavity in the apical horizontal view.

A minor heterogeneity in contrast effect occurs in time domain. At variance with signal intensity, intensity rise appears to be independent of the location of the ROI. Combining spatial and temporal information, as in curve fitting and in the analysis of beat-to-beat variability, again, the validity of the information declines with increasing depth. Specifically, beat-to-beat variability in the apex of LV cavity is very limited (4%) and similar to the beat-to-beat variability measured in nuclear cardiology (5%) and caused by physiologic variables, such as respiration. However, the variability between consecutive beats observed far from the transducer (reaching 15%) should be considered mainly artifactual, supporting the observation of a decline in the accuracy of contrast echocardiographic measurements with depth.

4.1. Implications of signal heterogeneity

The heterogeneity of contrast effect inside LV cavity can affect the extraction of quantitative parameters from echocardiographic images. This heterogeneity has a minor effect on the ability to identify the endocardial boundaries, as the difference between cavity and myocardial intensity is sufficiently high despite depth dependent attenuation.

The heterogeneity in signal intensity in the LV cavity

can dramatically affect the quantification of coronary blood flow by contrast echocardiography when based on contrast intensity and intensity rise in the myocardium. Myocardial perfusion can be assessed by visual grading of the contrast effect [12]. According to this method, tissue perfusion is scored as normal, totally absent or reduced based on subjective evaluation of the signal intensity. Considering the variability of signal intensity inside LV cavity, where the concentration of microbubbles can be assumed to be uniform, one can realize how regional differences in myocardial contrast effect can be affected by the above limitations. To extract a quantitative information on coronary blood flow, the same wall (in the same geometric conditions) should be compared under different circumstances, as at baseline and during stress, or before and after treatment. Finally, a more sound approach is to compare signal intensity rise in different areas of the myocardium. In flash echocardiography, myocardial intensity rise represents myocardial refilling by new microbubbles following old microbubble implosion. The observation that signal intensity rise in the LV cavity is not significantly affected by regional variability indirectly supports this approach.

4.2. Overcome of the limitations

Power Doppler signal after contrast administration is generated by microbubble implosion. To favor this phenomenon power Doppler operates at high ultrasound energy, commonly referred to as high mechanical index. Recently, alternative approaches - which are characterized by low ultrasound energy and an increased sensitivity to microbubbles - have been proposed. The spatial heterogeneity of contrast effect with these new equipments seems lower, favoring the extraction of quantitative flow information. Further alternative approaches are represented by probes of uniform ultrasound intensity.

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