Experimental Studies

High Frame Rate Myocardial Integrated Backscatter. Does this Change our Understanding of this Acoustic Parameter?

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Aims: Integrated backscatter (IB) and its cyclic variation (CV) derived from radio-frequency (RF) data have been used as parameters to attempt myocardial tissue characterization. Prior imaging systems used to measure IB and its CV typically acquired data at frame rates of 20–30 Hz and at a resolution of 6–8 bits. If changes in IB levels are in part related to specific short-lived events, occurring within the cardiac cycle, this frame rate and resolution could have been too low to resolve adequately what might be a more complex data set.

Methods and Results: To investigate this possibility, we acquired real time two-dimensional (2D) myocardial IQ data (the ‘in-phase quadrature’ sampled RF data) at high frame rate (>100 Hz), high dynamic resolution (theoretical 19-bit) and a sector angle of 20°. Several consecutive heart cycles of myocardial data were acquired from individual cardiac walls in five closed chest dogs and 10 healthy, young volunteers at normal heart rates. On the reconstructed RF data regions of interest were indicated, and IB and its CV were calculated.

The extracted high frame rate curves showed that the CV of IB is not a smooth sinusoidal-like curve, but is made up of multiple reproducible peaks and troughs with local minima and maxima which are temporally related to active or passive mechanical events, i.e. systolic contraction, early ventricular relaxation and ventricular filling due to atrial contraction.

Conclusions: This study shows that increasing the rate of real-time RF data acquisition results in a more complex, reproducible IB curve. The resolved maxima and minima in IB levels are related to specific phases of the myocardial contraction. Furthermore, spectral analysis showed that IB curves acquired at normal heart rates contain information up to 40 Hz. Hence, cardiac imaging data sets used to analyse regional myocardial function obtained at frequencies lower than 80 frames per second can contain aliased information.

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Key Words: Cyclic variation; Integrated backscatter; Temporal resolution; Tissue characterization.

Introduction

Myocardial tissue characterization, based on the scattering of ultrasound, has been attempted by numerous investigators during the past 20 years. The original studies, performed in animal models, used single crystal M-mode data acquisition at a high acquisition rate (1 ms or less), while most subsequent studies (both in animals and patients) have obtained two-dimensional (2D) data using phased array technology at relatively low acquisition rates (typically 40 ms)[1,3]. The parameter usually extracted from such radio-frequency (RF) data sets for myocardial tissue characterization is
integrated backscatter (IB) (also referred to as frequency averaged backscatter)\cite{2}. This is calculated by integrating the power spectrum of the received signal over the meaningful bandwidth of the transducer. This implies that IB is a measure of the mean reflected ultrasonic energy from a particular region of tissue\cite{2}. The aspect of myocardial tissue characterization which has aroused most interest has been the potential predictive value of the cyclic variation (CV) of IB for determining myocardial viability, initially described in vivo in animal models\cite{5-8}. This work has also been reproduced in the clinical setting\cite{10-12}. Further correlative studies have linked changes in CV to changes in oxidative metabolism, and have suggested that this reflectivity parameter may measure something more fundamental than simply changes in wall thickness (i.e. contractility) during the cardiac cycle\cite{8,14,15}. Others disagree, and argue that CV represents more than wall thickness changes, pointing to the evidence for the return in CV in a myocardial segment following the release of severe prolonged ischaemia which precedes the return of any measurable changes in wall thickness during recovery\cite{16,17}. To date, this divergence in opinions is unresolved.

Extended clinical evaluation of the properties of myocardial IB has demonstrated that the magnitude, cycle-dependent variation and the timing of peak and trough IB levels are all influenced by a wide range of disease processes\cite{15,26}. In these studies, IB values were determined by either off-line processing of the acquired (RF) signal or by on-line processing using dedicated hardware incorporated in standard clinical equipment. All these systems acquired IB data at frame rates around 20–30 Hz at a resolution of 6–8 bits. However, re-examination of the findings of some of these studies suggests that IB changes during the cardiac cycle, with multiple peaks and troughs, might be more complex than the typical smooth sinusoidal curve\cite{8,18,25,26}.

With the recent introduction of a new generation of ultrasound machines in which parallel processing of data allows the acquisition of myocardial reflectivity data at high temporal resolution (>100 Hz), and at high dynamic range (theoretical 19-bit), it seemed appropriate to examine what influence high resolution RF data acquisition might have on our understanding of IB and its CV.

**Methods**

A prospective study was carried out to attempt to determine what effect high frame rate, high-resolution RF data acquisition might have on our understanding of normal IB levels during the cardiac cycle. The study was constructed in three parts: an initial theoretical study based on computer modelling in which the effect of parallel processing on reflected RF data was determined; secondly, an in vivo animal study was carried out in which IB data was obtained from normal canine myocardium, and finally a study was performed on healthy volunteers in which the nature and timing of IB changes were determined and related to cardiac events defined from regional Doppler myocardial imaging velocity curves, obtained from the same myocardial segment.

**Mathematical Simulations**

**Rationale**

Since sound velocity in soft tissue is typically 1540 m s\(^{-1}\), and since a pulse typically has to travel over a distance of 20 cm before its reflections (which travel twice the distance) become negligible in amplitude, the acquisition of a single image line takes approximately 260 \(\mu\)s. Thus, using conventional cardiac ultrasound imaging, an image of 120 lines can be constructed in 32 ms. This will result in a maximum achievable frame rate of approximately 30 Hz. To increase frame rate, the number of scan lines could be reduced. However, as this will compromise image quality, modern scanners make use of an alternative approach: parallel beam-forming\cite{27}. In this technique either two or four image lines (depending on the manufacturer) are constructed from the received RF signals for each emitted pulse. This implies that the image can be constructed either twice or four times as fast, since only half (a quarter of) the number of pulses are required to construct the same image.

However, parallel beam-forming requires different processing of the received RF signals, which could in itself influence the measured IB values or its CV, since adjacent image lines become more correlated (they are constructed from the reflections from the same transmitted pulse). In order to investigate the possible influence of parallel beam-forming on IB and CV measurements, a series of computer simulations were performed.

**Methods**

RF images, consisting of 40 lines within an angle of 30 degrees, from different software phantoms were generated using a computer simulation environment developed in our laboratory\cite{28,29}. The phantoms were defined as 2D regions of 3 cm \(\times\) 3 cm, containing a random distribution of point scatterers, with a concentration of 20, 40 or 80 scatterers \(\cdot\) mm\(^{-2}\) and were positioned at a distance of 7 cm from a phased array transducer. Since IB measurements are stochastic in nature (due to the random distribution of the scatterers)\cite{30}, 10 phantoms were constructed to represent each scatterer concentration in order to minimize the influence of any statistical variations. The simulated transducer used to image these phantoms was a dynamically focused phased array
Parallel beam-forming was simulated by focusing the transmitted pulse at a depth of 7 cm (at the centre of the phantom) in the centre between the receive lines, as illustrated in Figure 1. Each phantom was simulated using one, two and four parallel lines in receive. This resulted in a total of 90 simulated images. Figure 2 illustrates the resulting (non-scan-converted) images. At the top left is the image resulting from the traditional imaging (one beam), and at the top right the result when using two parallel receive lines is shown. In order to illustrate the difference, the result after subtraction of both images is shown at the bottom of Figure 2. As can be observed, both the grey values, as well as the texture of the two images, differ. Note that a different dB scale was used for the subtraction image in order to make better use of the available colour map.

Data Analysis

The resulting RF data were processed using a dedicated software package (SPEQLE) developed in our laboratory\(^{[32,33]}\). On all images, an identical region of interest of 1 cm $\times$ 1 cm was placed in the middle of the scattering region. The IB values from these regions were calculated as the sum of the squared RF data divided by the number of pixels in the region of interest\(^{[32,33]}\).

In order to evaluate the effect of the number of parallel lines on the IB values, a one-way analysis of variance (ANOVA) test was done on the IB values obtained from identical phantoms with different numbers of parallel receive lines. Then a mean IB value and its standard deviation were calculated for each concentration of scatterers for each number of parallel receive lines. Finally, in order to check the potential influence of parallel beam-forming on CV measurements (cf. Discussion), another ANOVA test was done to verify whether changes in IB level with scatterer concentration were significantly different for different numbers of parallel receive lines.

Animal Study

Animal Preparation

Five closed chest mongrel dogs (17–25 kg) were studied. All the procedures carried out were in accordance with the Standard Institutional Guidelines laid down by the University of Leuven. All animals were sedated using xylazine (Rompun\(^{[31]}\), Bayer) 50 mg IM. After anaesthesia with Na-pentobarbital (15 mg $\cdot$ kg$^{-1}$ IV for induction and 0–1 mg $\cdot$ kg$^{-1}$ min for maintenance–Nembutal\(^{[32]}\), Synthelabo). Ventilation was adjusted during the study to maintain pH and arterial blood gasses within the physiological range. Body temperature was maintained with a heating pad.

RF Data Acquisition

Cardiac ultrasound data were acquired in fundamental imaging mode using a scanner (Vingmed, System V, Horten, Norway) which enabled the continuous acquisition of the digital IQ data within a sector angle of 20–30° at 195 Hz and at a theoretical 19-bit resolution (each of the 96 crystals in the array is digitized with 12-bit resolution; summing these values in the beamformer results in a 19-bit value). Three consecutive heart cycles were acquired during apnoea from a standard posterior left ventricular mid-wall segment using the parasternal long axis view. A transducer with a centre frequency of 3.5 MHz was used for imaging.

In order to relate changes in IB levels to events on the ECG, the ECG signal was digitized simultaneously by the scanner. To make sure that both ECG and image data were perfectly time aligned during analysis, any difference in delay of the ECG digitizing versus image reconstruction circuits would have to be compensated for. To measure if any such delay existed, the three standard ECG leads were fixed to the ultrasonic probe so that the surface of the probe and the most distal part of the electrodes were aligned. Then the probe was immersed suddenly in a water tank. The exact timing...
where the probe touched the water surface could be determined with high temporal resolution on both the ultrasonic images (going from black with the probe in air to white with the probe in water) and the ECG trace (showing a distinct spike).

**Data Processing**

The RF signals were reconstructed off-line from the acquired IQ data and were processed using the software package SPEQLE (see simulation Analysis). A standard oval region of interest of approximately 1 cm² was manually positioned in the posterior wall on all images, so that the region avoided the inclusion of endo- and epicardial reflections. An attempt was made to track the same region of myocardium during the cardiac cycle, based on the visual appreciation of standard anatomical landmarks within the image. From these regions, IB values were calculated as the sum of the squared RF data divided by the number of pixels in the region of interest and were expressed on a dB scale (without using a specific reference value, thus calculating the dB values by taking 10 times the logarithm of the IB values). CV was calculated as the difference between the maximal and minimal IB value occurring during the cycle.

Spectral information from each curve was extracted using standard FFT. The frequency up to which the signal contained 98% of its energy was defined as the highest frequency component of the IB curve containing information. The higher frequencies (almost not contributing to the signal) were defined as noise. Thus, in order to sample all information in the IB curves correctly, the Nyquist frequency was defined as twice this frequency.

End-diastole was indicated as the frame corresponding to the top of the R-wave on the ECG. All IB traces were resampled by linear interpolation to give all R–R intervals (intra- and inter-animal) the same number of sample points. A mean IB curve for each animal, representing one R–R interval, was constructed by averaging the IB waveform obtained from three consecutive cardiac cycles. These means were then averaged to obtain an overall mean IB curve for the whole population.

**Figure 2.** An example of simulated (non-scan-converted) images. At the top left is the result from the traditional imaging (one beam), and at the top right the result when using two parallel receive lines is shown. In order to illustrate the difference, the result after subtraction of both images is shown at the bottom of the figure. As can be observed, both the grey values, as well as the texture of the two images, differ.
Study on Volunteers

In order to assess high frame rate and high-resolution IB cyclic variations in humans, and in order to elucidate the precise timing of the changes in IB relative to the different phases of the cardiac cycle, 10 healthy male volunteers (age 28 ± 4 years) were studied.

Data Acquisition

RF data was analyzed using a parasagittal long axis view with the same equipment and methodology as used in the animal study. However, in order to use a clinically relevant transducer frequency, a more narrow band pulse with a center frequency of 2.2 MHz was used. Moreover, in order to obtain information on the precise timing of the different phases of the cardiac cycle, corresponding color Doppler myocardial imaging (CDMI) velocity data sets were acquired at very high temporal resolution (>170 Hz) from the same myocardial segments immediately after acquisition of the RF data.

As in the animal study, the ECG was digitized simultaneously and potential delays between the ECG and the RF images were measured and corrected for.

Data Processing

RF data was analyzed over a broad bandwidth (1.3–5.3 MHz). As in the animal study, a region of interest of approximately 1 cm² was positioned within the posterior mid-wall myocardial segment avoiding epicardial and endocardial reflections and a mean IB curve (obtained by averaging over three R–R intervals) was extracted for each volunteer.

By post-processing the CDMI data sets, a mean velocity profile over one R–R interval was extracted for each individual. The velocity data were extracted from the same location in the posterior wall as the position of the region of interest used to define the IB curve. The timing of the onset and duration of ejection, fast filling, and late diastolic filling due to atrial contraction were determined based on the CDMI data sets similar to the technique described by Zamorano et al. Since isovolumetric contraction and relaxation phases are not clearly identifiable on all CDMI velocity curves (although identifiable on some) acquired from a parasternal view, these phases were not indicated. The timings were used to average the inter-individual IB curves, since the changes in duration of the different phases of cardiac contraction are not linearly related to changes in duration of the whole cardiac cycle (i.e. the relative duration of systole is longer at higher heart rates). As a consequence, merely averaging the mean R–R traces could result in erroneous results. Therefore, each part of the IB curve corresponding to a specific phase of the cardiac cycle was interpolated to have the same number of samples for all volunteers and was then averaged over the number of volunteers. Since mean IB and CV can differ between individuals, standard averaging could not be used, as the behaviour of the curve of an individual with high IB or CV would have more influence on the overall averaged behaviour. Therefore, all parts were normalized to have the same mean IB and variation between minimal and maximal value within that part before the mean of the curves was actually defined. The mean IB level and mean variation was calculated from all volunteers and used to rescale the average (normalized) IB curve. In this way, the mean behaviour of the IB curve during each phase of the cardiac cycle was obtained. Finally, these IB curves were merged in order to obtain one representative average heart cycle.

The Nyquist frequency of the individual IB curves was defined as in the animal study.

Results

Mathematical Simulations

Table 1 summarizes the mean IB values and their standard deviations obtained as a function of scatterer concentration and number of parallel receive lines. The ANOVA test showed that the predicted IB values decreased significantly (P<0.05) with decreasing scatterer concentration (80–40, 40–20 and 80–20 scatterers . mm⁻²) and with increasing number of parallel receive lines (one to two, two to four, and one to four). However, the second ANOVA test showed that the change in IB value with scatterer concentration was not significantly different for different numbers of parallel receive lines (P=NS).

### Table 1.

<table>
<thead>
<tr>
<th>Scatterer Concentration</th>
<th>One parallel line</th>
<th>Two parallel lines</th>
<th>Four parallel lines</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 scatterers . mm⁻²</td>
<td>−6.9 ± 0.8 dB</td>
<td>−7.4 ± 0.8 dB</td>
<td>−8.7 ± 0.8 dB</td>
</tr>
<tr>
<td>40 scatterers . mm⁻²</td>
<td>−4.3 ± 0.7 dB</td>
<td>−4.7 ± 0.7 dB</td>
<td>−5.9 ± 0.8 dB</td>
</tr>
<tr>
<td>80 scatterers . mm⁻²</td>
<td>−0.9 ± 0.4 dB</td>
<td>−1.2 ± 0.4 dB</td>
<td>−2.6 ± 0.5 dB</td>
</tr>
</tbody>
</table>

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Animal Study

Figure 3 shows a representative example of a high frame rate IB curve (left) and its spectral components (right) obtained from a left ventricular posterior mid-wall segment. The curve shows that IB is not a smooth sinusoidal-like curve with only a maximum near end-diastole and a minimum near end-systole, but is comprised of multiple reproducible peaks and troughs during the heart cycle, with local minima and maxima. For the heart rates encountered in this study (90±15 bpm), spectral analysis of the individual IB curves showed that the IB signal typically contains information up to 37 Hz on the average. Thus, at these heart rates the Nyquist frequency for resolving all IB changes for normal myocardium lies around 74 Hz.

Figure 4 shows the mean IB curve for the posterior wall data acquired from all animal experiments. This mean IB curve shows a decrease in IB during systole and two local maxima during diastole. The mean IB level was 91.5 dB and the mean CV 8.5 dB.

Volunteer Study

Figure 5 (left) shows a typical example of a single R–R interval, high frame rate IB curve taken from a left ventricular posterior mid-wall segment obtained from one of the normal volunteers, together with the corresponding CDMI velocity data set (right). The different phases of the cardiac cycle (isovolumetric contraction (IVC), ejection (E), isovolumetric relaxation (IVR), fast filling (FF), diastasis (D) and atrial contraction (AC)) can clearly be identified on the velocity curve. However, because the onset and duration of the isovolumetric phases is not always clearly identifiable on the velocity curves, only the beginning of E, FF and AC and the end of FF and AC were indicated and used for the analysis of the corresponding IB curves (indicated as vertical lines).

Discussion

Although increasing frame rate by means of parallel beam-forming clearly influences the absolute measurement of IB, the simulations show that changes in relative IB levels related to scatterer concentration are not significantly influenced by differing implementations of parallel beam-forming. As a consequence, if CV is
predomminately determined by changes in scatterer concentration, then CV values are also not influenced by parallel beam-forming.

As absolute IB measurements in clinical practice are made relative to a reference reflector which will change accordingly, and since CV is not influenced by parallel beam-forming, we can conclude that IB traces acquired with parallel processing can be directly compared with those obtained using conventional technology (i.e. acquired without parallel beam-forming). Thus, parallel beam-forming by itself does not explain the significant differences between the low and high frame rate IB curves found in this study.

The IB curves obtained using high frame rate acquisition in the animal study showed the maximum level to be at end-diastole, with a pronounced decrease during systole and with a minimum near end-systole. This is in keeping with the prior findings of other investigators, who acquired data at a relatively low temporal resolution. However, the increase in the rate of acquisition of the IB samples to 195 Hz resulted in the delineation of a more complex IB curve, with multiple, reproducible peaks and troughs occurring during the cardiac cycle. Since these peaks and troughs were highly reproducible over a range of different heart cycles in all animals, these high frequency changes could not be explained by

Figure 5. Example of an IB curve of one volunteer acquired at high frame rate and averaged over the several R–R intervals (left) and its corresponding velocity profile (right). Specific phases of the cardiac cycle are defined on the velocity curves (isovolumetric contraction (IVC), ejection (E), isovolumetric relaxation (IVR), fast filling (FF), diastasis (D), atrial contraction (AC)) and are indicated on the IB curves by vertical lines.

Figure 6. Overall mean IB curve ± standard deviation acquired at high frame rate (left) and the overall average velocity profile ± standard deviation (right) for a posterior mid-wall segment of the human posterior wall in a parasternal long axis view. Clearly, there is a relationship between IB behaviour and the different phases of the cardiac cycle.
This behaviour could potentially be related to inherent differences in timing and sequence of myocardial depolarization and onset of regional contraction between the two species.

Relating the regional IB changes to the concomitant regional myocardial Doppler velocity profiles in the volunteers enabled the temporal relationship between local changes in IB levels and the different phases of the cardiac cycle to be defined. The rapid onset of motion induced by myocardial contraction was associated with an initial increase in reflectivity. This was immediately followed by a progressive decrease in reflectivity during mid- to late systole, which reached a minimum around end-systole. (Although the mean IB curve reached a minimum just before FF commenced (and hence after end-systole), it has to be remembered that the timing of end-systole, defined on the velocity curves, was not very accurate.) The onset of fast filling was associated with a rapid progressive increase in reflectivity which returned to basal (end-diastolic) value at mid-diastasis after a small over- and undershoot. Then there was a further clear increase occurring during passive ventricular filling due to atrial contraction. Although this increase was less pronounced in the overall average of the volunteers’ traces, it can clearly be observed in some of the individual traces (Fig. 5) and in all of the animal studies. This variability in young normals is likely to be explained by the fact that this increase is relatively small and thus will only be observed in very echogenic individuals, being lost in noise in less echogenic subjects.

Since the exact definition of the timing of the onset and duration of the isovolumetric periods was impossible in this study, and since these time periods last only for a relatively small fraction of the cardiac cycle, they could not be analysed in detail. As a consequence, the apparent decrease of IB during the isovolumetric relaxation phase is probably explained by the relatively inaccurate definition of both the end of systole and the precise onset of fast filling.

Finally, it should be noted that the average IB curve obtained from normal volunteers shows relatively large standard deviations (Fig. 6). This property is inherent to IB measurements[20], and it should be emphasized that although increasing the rate of data acquisition results in more accurate temporal information of the IB curve, it will not change the stochastic nature of this measurement.

**Clinical Implications**

The acquisition of IB curves at high temporal resolution should give a new impetus to the research on ultrasonic tissue characterization, as it extracts more accurate information on myocardial reflectivity. As a consequence, subtle alterations of the IB curve due to pathologies, which could not be detected previously because of the relatively low temporal resolution of data acquisition, can now be detected.
Implications of this Study for all Imaging Techniques Attempting to Quantify Regional Myocardial Function

Since the Nyquist frequency of the IB curves in the animal study lay around 70 Hz and around 80 Hz in the volunteer study, a frame rate of 80 Hz would appear to be adequate to resolve the complexities of the IB curve at normal heart rates. However, this value was derived as a mean value by averaging all data from the five animals and 10 volunteers. This implies that some of the curves contained information above 40 Hz (the highest being 65 Hz). As a consequence, in order to avoid undersampling of the IB curve, a frame rate around 130 Hz should be used to acquire RF data. However, no exact method exists in order to separate information from noise in these curves or, in other words, to define the true Nyquist frequency. Therefore, an acquisition frame rate of 80 Hz should not be used as an exact rule but as a guideline.

However, this result implies that whatever cardiac imaging modality or imaging technique is used to attempt to quantify regional myocardial function, it must acquire data at a high temporal resolution, since changes in extracted parameters might be related to short-lived cardiac events. Low temporal resolution might result in aliasing of the extracted curves, making a correct interpretation much more difficult, if not impossible.

Study Limitations

It has been shown by other investigators that changes in IB levels depend on both the imaging view and the myocardial segment studied. Neither of these factors was taken into account in this study, where only a mid-wall segment from the posterior wall in a parasternal long axis view was investigated. Moreover, transmural differences in reflectivity, which have been described by other investigators, were not attempted in this study.

A more methodological limitation of the study is the fact that a comparative dataset was used to extract information on the timing of the mechanical, myocardial events (colour myocardial Doppler data) and timings superimposed on the extracted reflectivity data (RF data). In principle this could induce errors, since both the heart rate of the volunteer and the imaging plane could have changed between data acquisitions. (Unfortunately, it was impossible to extract the velocity and reflectivity information at high temporal resolution from the same dataset.) However, in order to avoid these methodological problems as much as possible both datasets were recorded immediately after one another, and both heart rate and imaging plane were verified not to have changed significantly.

Finally, the methodology used made it impossible to study accurately the behaviour of IB levels during the isovolumetric phases of the cardiac cycle. However, since these phases are associated with a fast shape-change of the myocardium and induces significant out-of-plane motion, it should be studied by three-dimensional imaging techniques at high temporal resolution. This, again, is left for future work.

Conclusion

This study shows that increasing the rate of real-time RF data acquisition results in a more complex, reproducible IB curve. The resolved maxima and minima in IB levels are related to specific phases of the myocardial contraction.

Furthermore, spectral analysis of the high frame rate IB data set showed the Nyquist limit to be around 80 Hz. This implies that any IB dataset, or whatever parameter used for detailed (regional) temporal myocardial evaluation, obtained at lower frequency will contain aliased and thus corrupted information.

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References
