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Comparison of Spectral and Temporal Criteria for Inertial Cavitation Collapse

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Dilute solutions of *Optison* and *Definity* were studied using a passive cavitation detector (PCD) with a 2.8-MHz transmitter and 13-MHz receiver. The dilution was such that each received signal should, on average, arise from a single microbubble. Several hundred microbubble responses were acquired at each of three rarefactional pressure ranges (1.6+/-0.2, 2.0+/-0.2 and 2.4+/-0.2 MPa). Each microbubble response was grouped with signals presenting post-excitation emissions (transient Inertial Cavitation) or those with no evidence of post-excitation emission (non-transient Inertial Cavitation). For each incident pressure, we compared discrimination of signals from the two groups according to peak-voltage, broadband noise (12-17.6 MHz) and power at the fundamental, 2nd, 3rd, and 4th harmonic peaks. In addition to increased peak-voltage and broadband noise, spectra from transient IC groups consistently presented increased 2nd, 3rd and 4th harmonics compared to the Non-Transient IC group. Throughout the studied pressure range, best separation between the two groups was obtained with peak-voltage (4.7+/-1.8dB), broadband noise (4.4+/-1.8) and 4th harmonic (5.6+/-2.2) for *Optison*. For *Definity*, all harmonics (2nd to 4th) increased strongly for the transient IC group (approximately 6 dB) as well as peak-voltage (5.3+/-1.2dB) and broadband noise (5.8+/-2dB). Results should contribute to relating PCD criteria to IC activity.

1 Introduction

During inertial cavitation, a violent collapse dominated by the surrounding medium's inertia, energy is radiated in the form of broadband acoustic emissions. Expansion of the bubble radius exceeding approximately twice the equilibrium radius generally leads to subsequent, inertially dominated collapse [1]. Under these conditions, bubbles often break up, but it has been shown, based on sonoluminescence from single bubbles in a standing wave field, that inertial collapse can be repeated many times for the same bubble [2]. It has thus been suggested that two incident pressure thresholds need to be considered [3] when characterizing bubble oscillations. The lower threshold represents the transition between *noninertial cavitation* and *stable inertial cavitation*. The stable inertial cavitation threshold can, in principle, be identified as the acoustic pressure at which broadband acoustic emissions are first detected. The higher threshold represents the transition between *stable inertial cavitation* and *transient inertial cavitation*. Transient inertial cavitation should present evidence of bubble break-up as well as strong broadband acoustic emissions.

The nature of the bubble response is related to the effect the bubble can induce on a surrounding biological medium. Mechanisms of acoustic streaming, radiation force and bubble oscillation can act on a medium even without reaching the strong bubble-expansions and violent collapses necessary for inertial cavitation [4]. Working in this range could be favourable for imaging or therapeutic stimulation. Inertial cavitation can also produce acoustic streaming and stronger effects such as shock waves, high-velocity jets, free radicals and high local temperatures. It has been shown, for example, that absorption of the broadband emissions associated with inertial cavitation is the dominant source of bubble-enhanced heating in biological media when relatively low-level HIFU exposures are used [4]. Considering that inertial cavitation can be either non-transient or transient, it is interesting to note that many cavitation-related bioeffects may potentially be produced without requiring the bubble to break apart. This could enable the harnessing of non-transient inertial cavitation for therapeutic applications that require sustained stimulation or heating. Other effects, however, that do not require sustained stimulation may require transient inertial cavitation.

Beyond the detection of broadband emissions, the specific harmonic content of PCD data and its modification when inertial cavitation occurs has remained largely unexplored. A few exceptions can be cited. MacDannold et al [5] approached the problem of detecting inertial cavitation *in vivo*. They found that blood brain barrier disruption (BBBD) – as detected with contrast-enhanced MRI - was associated with increases in the second and third harmonic peaks in the spectra from signals acquired with a passive cavitation detector *in vivo*. Broadband emissions in the PCD data were associated with extravasation of red blood cells, but neither broadband emissions nor extravasation was necessary for BBBD to occur. This may imply that BBBD is occurring without inertial cavitation. Further data were called for to explore if the increased second and third harmonics were due to nonlinear bubble oscillation alone. Biagi et al [6] examined subharmonic emissions and the stability of these emissions with insonation time in Sonovue microbubbles isolated by strong dilution in a PCD configuration. Using approximately 30-cycle pulses either centered at 3.3. or 5 MHz, they identified pressure regimes associates with no subharmonic emissions, subharmonic emissions that were stable in time and (at highest pressures tested) a regime lacking subharmonic response until shortly before bubble disappearance. Thus, it appears that spectral content other than broadband emission production may also be modified as the nature of the bubble response changes.

In previous work, we applied PCD to evaluate very dilute solutions of *Optison*. Post-excitation signals were observed and linked to shell rupture (transient inertial cavitation). Spectral content and the presence of broadband emissions were not systematically considered in the previous work although broadband emissions were observed in spectrograms of the power spectra as a function of time both during the principal response of the bubble under excitation and during the post-excitation collapses. This work characterizes harmonic and broadband acoustic emissions as well as peak-to-peak voltage values, in PCD signals measured from similar PCD measurements in dilute solutions of *Optison* and *Definity* contrast microbubbles.

Our goal is to compare the variation of several criteria at the onset of transient inertial cavitation. Strong incident pressures have been used in this study (1.6 to 2.4 MPa, peak rarefactional pressure). Data were acquired with a passive cavitation detector. The peak-to-peak voltage, spectral components and broadband emission levels in detected signals are then compared between groups of bubbles classified based on absence or presence of post-excitation signal as undergoing non-transient or transient inertial cavitation, respectively.

2 Materials and Methods

2.1 Passive cavitation detector and contrast agents

Dilute solutions of ultrasound contrast agents were studied using a passive cavitation detector (PCD) with a 2.8-MHz transmitter and 13-MHz receiver. A diagram of the experimental set-up is presented in Figure 1. The dilution of the contrast agent was such that each received signal should, on average, arise from a single microbubble insonified within the confocal volume determined by the intersecting volume of the two –6dB beam volumes. Several hundred microbubble responses were acquired within each of three ranges of incident rarefactional pressure ranges (1.6 ± 0.2, 2.0 ± 0.2 and 2.4 ± 0.2 MPa). Further details describing this system have been provided previously [7].

Incident maximum rarefactional pressure was characterized for each emitter setting in a separate experiment using a PVDF bilaminar shielded membrane hydrophone (0.5 mm-diameter, 699/1/00001/100, GEC Marconi Ltd., Great Baddow UK) placed at the focal point. The contrast agents used were *Optison* and *Definity*. Both contain a perflutren C_3F_8 gas core encapsuled by a shell . *Optison*'s shell is made of Albumin whereas *Definity*'s shell is based on a phospholipid. According to the manufacturers, both have a mean initial radius R_0 between 1.0 and 2.3 μm.

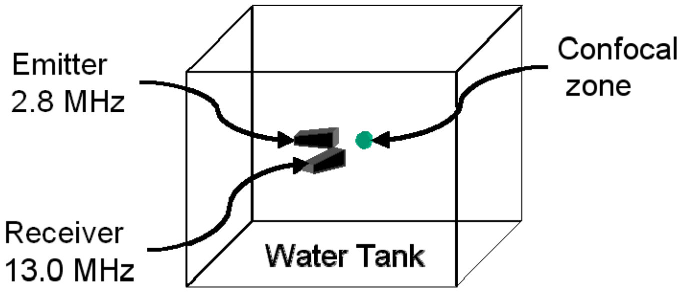


Fig.1 Diagram of the PCD system.
The water tank contains a very weakly concentrated solution of contrast agent, gently agitated with a magnetic stirrer to maintain uniform distribution with, on average, only one contrast microbubble within the confocal zone at a time.

2.2 Data analysis

Within each of the selected incident pressure ranges, the microbubble responses that presented a clear principle response with no post-excitation signal (oscillation during acoustic excitation only) were classified as non-trasient inertial cavitation response. Those that presented a clear principle response followed by a post-excitation emission after the principle response were classified as a transient inertial cavitation response. . The average spectral density and the average peak-to-peak voltage values were calculated for the group of N_t signals in a selected incident pressure range with post-excitation emissions (transient IC-Collapse group). The same average parameters were calculated for the group of N signals with no evidence of post-excitation emission (non-transient IC-Collapse group). The group selection criteria and steps towards calculation of average parameters are illustrated schematically in Figure 2. For each incident pressure range, we compared discrimination between these two groups based on peak-to-peak voltage, broadband noise, power at the fundamental, 2nd, 3rd and 4th harmonic peaks. For spectral power comparisons, the average value of the power was measured in the following bandwidths: broadband noise, 12-17.6 MHz; fundamental, 2.6 to 3 MHz; 2nd harmonic, 5.3 to 5.9 MHz; 3rd harmonic, 8 to 8.8 MHz and 4th harmonic 10.7 to 11.7 MHz. These bandwidth limits are approximately –6 dB down from the peak values. Noise levels were estimated from the peak-to-peak voltage and power levels in the spectral density calculated for segments of signals acquired at the same insonification settings in the absence of contrast microbubbles (water only).

3 Results

The average spectral content of the post-excitation signals is compared to the spectral content of the entire voltage-time response in Figure 3. Post-excitation signals were selected with a temporal gate. The power spectrum from each post-excitation signal was calculated and averaged for signals from 10 events acquired at 2.0 MPa. The average power spectra from the same 10 events was then calculated using a time-gate that included both the post-excitation and the principle response. The post-excitation signal is very broadband but also very weak (12 dB lower) compared to broadband noise of the whole bubble response. The spectral response from the entire voltage-time response presents strong harmonics.

Throughout the studied pressure range, best separation between transient and non-transient IC groups was obtained with peak-voltage (4.7 ± 1.8 dB) and broadband noise (4.3 ± 1.9 dB) for *Optison*. For *Definity*, peak-to-peak voltage (5.3 ± 1.2 dB) and broadband noise (5.8 ± 2 dB) also provide separation between the two groups. Harmonics (2nd to 4th) increased more strongly between the transient and non-transient IC groups (on the order of 6 dB) for *Definity* than for *Optison*. As could be expected, response at the fundamental frequency is overlapped for the transient and non-transient IC groups.

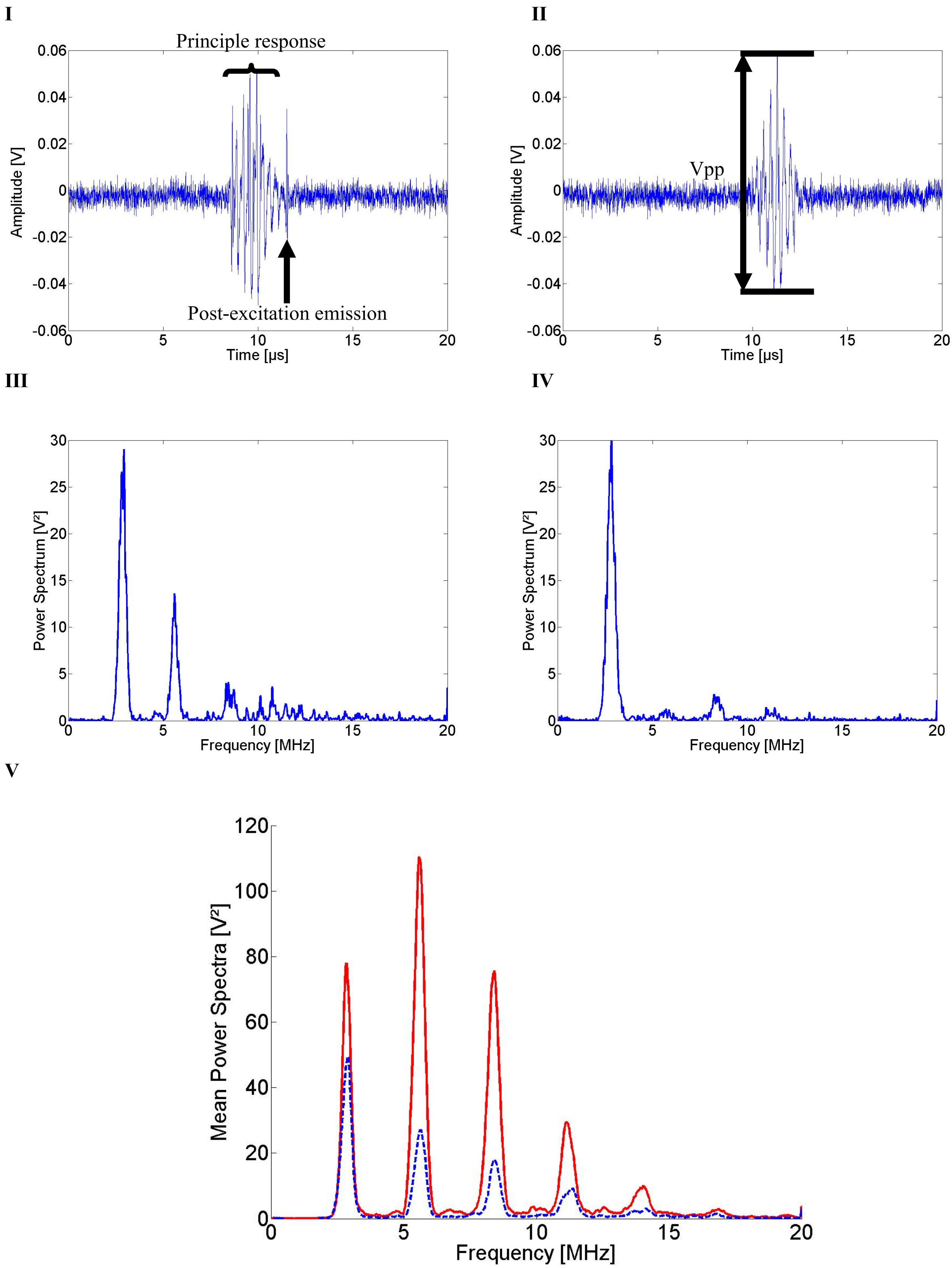
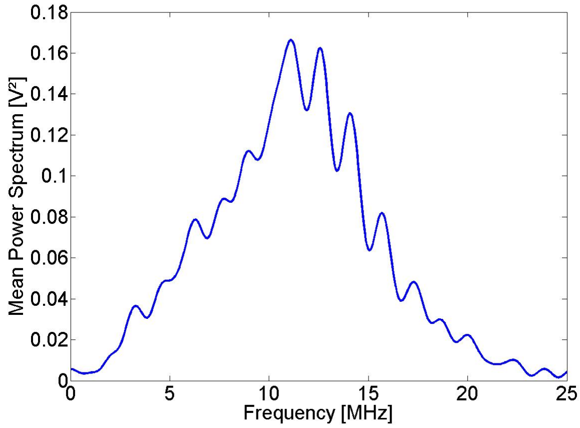


Fig.2 Illustration of group selection criteria and the steps for parameter calculation.
The signals shown were acquired with the PCD system from *Definity* insonified at an incident peak rarefactional pressure within the range of 2.0+/-0.2 MPa.
I. Signal presenting a post-excitation signal after the principle response during acoustic excitation. This type of signal was classified in the group for transient inertial cavitation. The principle response and the post-excitation signal are indicated.
II. Example presenting no post-excitation signal. This type of signal was classified in the group non-transient inertial cavitation. The peak-to-peak voltage measurement is demonstrated graphically.
III. The power spectral density of the signal in **I**.
IV. The power spectral density of the signal in **II**.
V. The average power spectra for the transient IC (solid line)and the non-transient IC groups (dotted line).

I



II

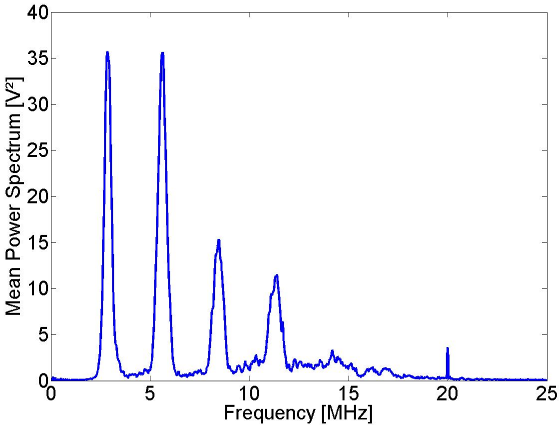


Fig.3 **I**. Mean power spectrum from 10 time-gated post-excitation signals obtained with an peak rarefactional pressure of 2.0 MPa.
II. Mean power spectrum obtained with the entire voltage-time response for the same signals.

4 Discussion and Conclusions

The level of the broadband noise with respect to the background was elevated both for transient and non-transient IC groups of *Optison* (SNR levels from approximately 20 to 30 dB) and *Definity* (SNR levels from approximately 14 to 35 dB). These levels appear to be consistent with increases reported by others [8-10] searching to detect inertial cavitation. Sassaroli and Hynynen used an increase of at least 20 dB above background in the wideband noise to characterize *Optison* inertial cavitation. Tu et al found relative increases in normalized inertial cavitation doses from 10 to 20 dB between solution with or without Optison.

The transition from non-transient to transient (or ruptured) IC activity appears to lead to an additional increase of approximately 5 dB in peak-to-peak voltage and 4 to 6 dB for broadband noise with respect to the background value.

These data characterize the increase in peak-to-peak voltage and spectral criteria observed at the transition from non-transient to transient IC of *Optison* and *Definity*. Peak-to-peak voltage provided good separation between the two groups but with relatively lower SNR than for spectral criteria. Broadband noise (as well as 2nd and 3rd harmonic levels, for *Definity*) were increased for transient IC as compared to the non-transient IC group although this increase remains within a modest, 4 to 6 dB range.

If considering the use of these modifications for *in vivo* detection of transient cavitation, the effect of frequency-dependent attenuation in the propagation path must also be considered. For example, attenuation effects may favor the monitoring of increases in 2nd and 3rd harmonic amplitudes as opposed to increases in broadband noise when searching for transient IC from *Definity* in deeper organs. Although it is beyond the scope of this work, it should be possible to extrapolate from these results to estimate the collective response for a population of microbubbles with a specific percentage undergoing non-transient and transient events. Thus, the results presented here may contribute towards the goal of non invasive characterization of bubble destruction *in vivo*.

Acknowledgments

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