Pulse Shaping for Improved Diagnosis of Portal Hypertension Using Subharmonic Aided Pressure Estimation

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Introduction

Subharmonic aided pressure estimation (SHAPE) is based on the inverse relationship between the subharmonic amplitude of contrast microbubbles (obtained by transmitting at the fundamental frequency f_o and receiving at $f_o/2$) and the ambient pressure (see fig.1).

A noninvasive ultrasound based pressure estimation procedure would be a major development in the diagnosis of portal hypertension and less invasive than the current catheter-based hepatic venous pressure gradient (HVPG) measurement.

The hypothesis of this study was that portal vein pressures can be monitored and quantified noninvasively in humans using SHAPE.

First selected waveforms were optimized *in vitro* and in canines, then SHAPE was correlated with measured HVPG in patients undergoing a transjugular liver biopsy (TJLB) .

Methods

- A Logiq 9 ultrasound scanner with a 4C curvi-linear probe (GE, Milwaukee, WI) was used to acquire radio frequency data.
- The SHAPE mode was set to transmit 4 cycle pulses at 2.5 MHz and receive subharmonic signals at 1.25 MHz.
- The contrast agent Sonazoid (GE Healthcare, Oslo, Norway) was infused at a rate of 0.024 µL/kg/min.
- 8 different pulse waveforms (3 narrowband and 5 broadband) were implemented (see fig.2) and tested *in vitro* and *in vivo* in 3 canines.
- Selection of the best waveform for SHAPE was based on the decrease in the subharmonic signal amplitude with increasing ambient pressure and correlation coefficients.
- TJLB subjects were enrolled in an ongoing IRB and FDA approved study (IND 124,465).
- Post TJLB, patients received an infusion of Sonazoid and were scanned by a sonographer blinded to HVPG results.
- An ROI within the portal vein was selected and an automated power control algorithm was initiated to determine the optimal acoustic output power for maximum SHAPE sensitivity.
- Cine loops were collected in triplicate, averaged and compared to the HVPG.

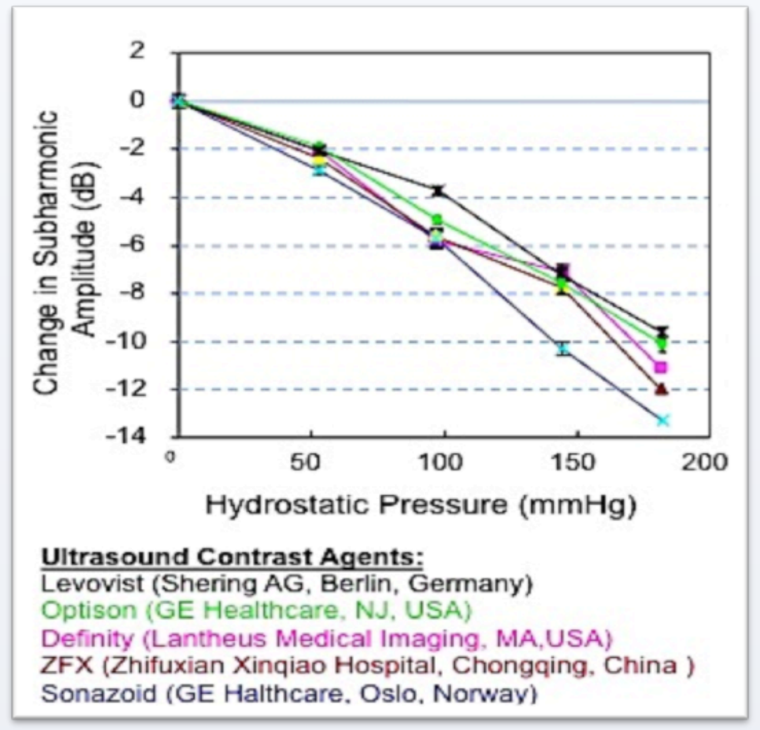

Figure 1. Inverse linear relationship between the subharmonic response and ambient pressure

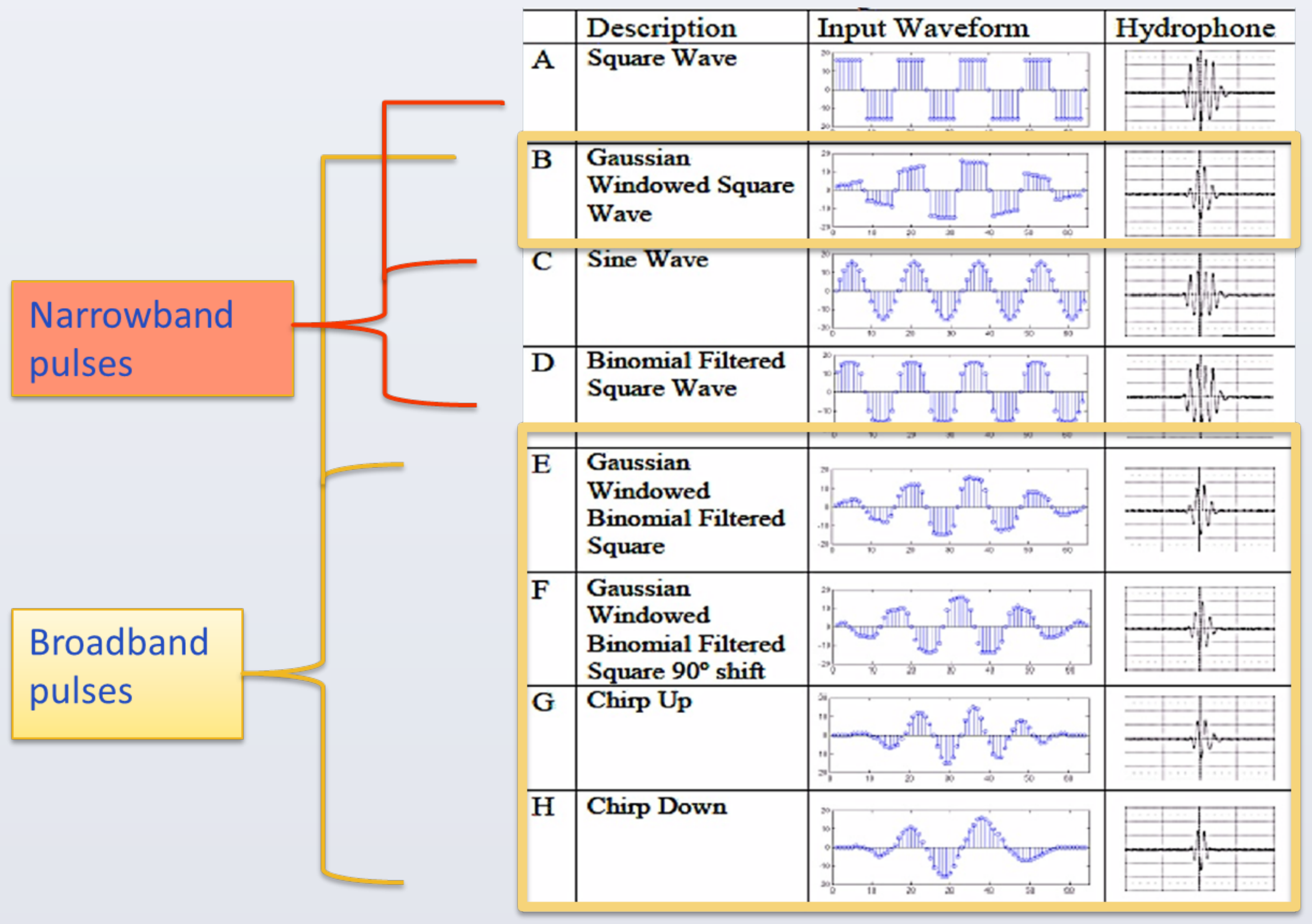

Figure 2. Pulse Shapes

Results

- A linear decrease in subharmonic amplitude with increased pressure was observed for all waveforms (r from -0.77 to -0.93; p<0.001) *in vitro* (see Fig.3).
- Data from 1 of the 3 canines was eliminated for technical reasons, while the other 2 produced similar results to those obtained *in vitro* (r from -0.72 to -0.98; p<0.01).
- Overall, the broadband pulses performed better (p<0.05). Within the broadband group, the Gaussian windowed binomial filtered square wave was the most sensitive.
- 72 TJLB subjects have been studied to date (median age 59 ± 11.8, 61.1% male). The linear relationship between the SHAPE gradient and HVPG showed good correlation (r = 0.80) (see Fig.4).

A	B	C	D	E	F	G	H
Square Wave	Gaussian Windowed Square	Sine Wave	Binomial Filtered Square	Gaussian Windowed Binomial Filtered Square	'E' with 90° Shift Wave	Chirp Up	Chirp Down

In Vitro (p < 0.001)

	A	B	C	D	E	F	G	H
SLOPE(dB/mmHg)	-0.10	-0.17	-0.06	-0.09	-0.17	-0.14	-0.13	-0.14
r	-0.88	-0.90	-0.79	-0.77	-0.95	-0.93	-0.91	-0.81

Canine 1 (p < 0.01)

	A	B	C	D	E	F	G	H
SLOPE(dB/mmHg)	-0.25	-0.37	-0.32	-0.33	-0.44	-0.2	-0.28	-0.33
r	-0.91	-0.84	-0.91	-0.92	-0.95	-0.98	-0.72	-0.96

Canine 2 (p < 0.01)

	A	B	C	D	E	F	G	H
SLOPE(dB/mmHg)	-0.01	-0.26	-0.16	-0.2	-0.46	-0.28	-0.49	-0.51
r	0	-0.92	-0.85	-0.98	-0.96	-0.85	-0.94	-0.92

Figure 3. *In Vitro and In Vivo* results

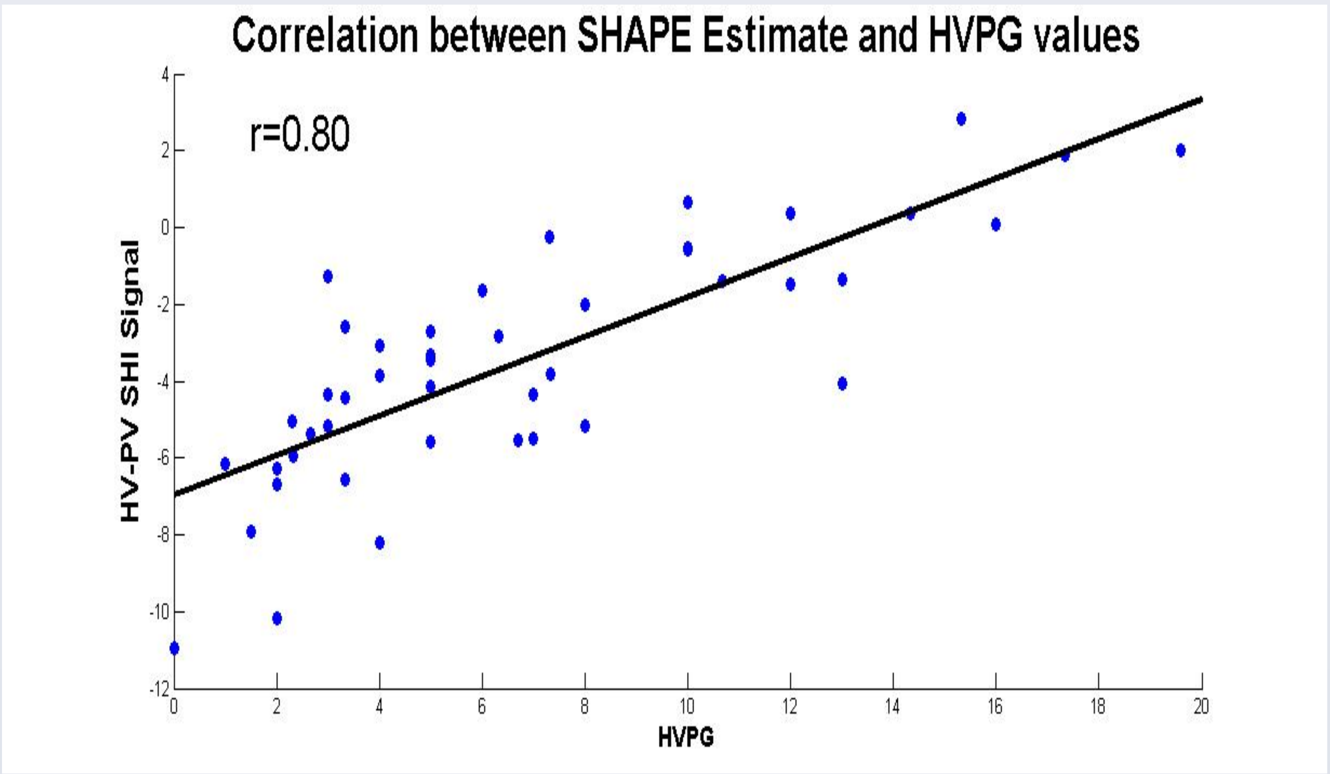

Figure 4. Measurement of SHAPE estimate vs HVPG

Conclusions

- **The Gaussian windowed binomial filtered square wave makes the SHAPE technique more sensitive to pressure estimation.**
- **Good correlation is exhibited between SHAPE estimate and measured HVPG**
- **Results from this ongoing clinical trial indicate that SHAPE may be useful for non-invasive estimation of portal pressures.**

Disclosures

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