Pergamon

Ultrasound in Med. & Biol., Vol. 20, No. 8, pp. 751–758, 1994

0301-5629/94 $6.00 + .00

0301-5629(94)00063-8

Original Contribution

DETECTION OF INTRAOCULAR PRESSURE CHANGE IN THE EYE USING SONOELASTIC DOPPLER ULTRASOUND

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(*Received* 17 *August* 1993; *in final form* 7 *March* 1994)

Abstract—We report the first use of sonoelastic Doppler ultrasound for *in vivo* and *in vitro* clinical studies of intraocular pressure (IOP). The method involves low-amplitude and low-frequency sonic excitation of the eye, and detection of the resulting vibration using Doppler ultrasound. A dependence of the frequency of resonance of the eye on the IOP has been observed in both *in vitro* and *in vivo* experiments. Preliminary *in vitro* experiments have been performed using eviscerated and enucleated human and pig eyes. As little as 4 mm Hg change in IOP has been found detectable in these experiments. Preliminary *in vivo* experiments also showed promising results in this regard. We present a simple model for the resonances of the eye, a method to detect the amplitude of vibration using Doppler ultrasound and results from the *in vitro* and *in vivo* experiments.

Key Words: **Ophthalmology, Intraocular pressure, Glaucoma, Doppler ultrasound, Sonoelasticity.**

INTRODUCTION

Glaucoma is an insidious eye disease, which is typically manifested clinically by elevated intraocular pressure (IOP) (Quigley 1993). In general, the increase in IOP is due to abnormalities in drainage of aqueous humor from the eye to the venous circulation. The pathological changes resulting from the rise of IOP are characterized by atrophy of the optic nerve, which can cause irreversible blindness. The elevation in IOP should be detected in early stages if further nerve damage is to be prevented. Most current methods for the clinical determination of IOP require deformation of the cornea and measurement of the amount of deformation or the force required to obtain the deformation (Hoskins and Kass 1989). The only method of IOP measurement through a closed lid is digital palpation, which is inevitably subjective and physician-dependent. In the setting of uncooperative or pediatric patients, or in the presence of corneal disease, it would be clinically useful to have an objective method for IOP measurement that does not depend on gross deformation of a normal cornea, and which would operate despite the lid being closed. We have developed a technique called sonoelasticity imaging, for visualizing vibrations in tissue (Lerner and Parker 1987a, 1987b; Lerner et al. 1990), and have postulated that resonances in the eye can be assessed using sonoelasticity (Alam et al. 1992). Sonoelasticity utilizes a low frequency and low amplitude external source to vibrate tissue. The resulting vibration patterns depend on the frequency of vibration, tissue structure and tissue elastic constants. Pulsed Doppler ultrasound is used to determine the tissue vibration amplitude from the echoes reflected from the oscillating tissue. Sonoelasticity has recently been investigated as a tool for tumor detection and as a means of assessing the mechanical properties of tissues (Huang 1990; Lerner and Parker 1987a, 1987b; Lerner et al. 1990; Parker and Lerner 1992). The applied audio power is low, typically less than 10 W, and is expected to be safe if applied to the human head for IOP measurements. The reflection of ultrasound waves from oscillating bodies has been investigated by Holen et al. (1986) and Parker et al. (1990), and the spectrum was shown to have the characteristic FM-like Bessel function pattern (Carlson 1986). Various methods can be used for determining the vibration amplitude in the tissue. However, in the experiments, the vibration amplitude of the sclera was determined by counting the number of Bessel side bands in the power spectrum obtained in pulsed Doppler mode. (This is discussed in detail in the next section: theory).

Our postulate is that increasing IOP will stiffen

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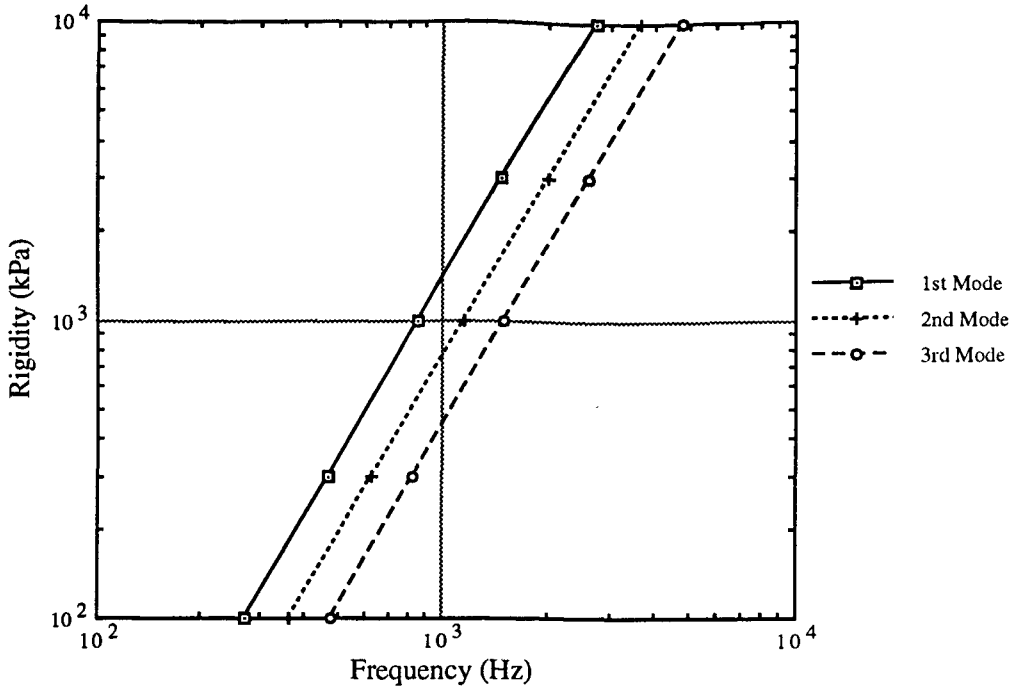


Fig. 1. Illustration of shift in modal frequency (horizontal axis) with shift in rigidity (vertical axis). Only the larger real positive solutions for the first three radial modes are shown.

the sclera, which is known to be a highly nonlinear elastic material (Taber 1984). The increased stiffness of the sclera shifts the resonance frequencies of the eye; thus, changes in IOP are linked to changes in the resonance frequency.

The use of resonance to detect change in IOP had been proposed independently by Hamelink and Cloud (1979) using laser velocimetry. The use of Doppler ultrasound, and more specifically, sonoelasticity, may offer a much simpler, widely available and less expensive technique for detecting the resonance of the eye, and may be of use for measuring IOP in the presence of significant corneal disease or through a closed lid. Further application of this alternative method might be in 24-hour monitoring of IOP.

In a recent *in vitro* study, sonoelasticity was applied to detect changes in IOP of eviscerated eyes (Alam et al. 1992). Instead of a single application of force (such as with air-puff, applanation or Schiotz tonometry), the eviscerated eyes immersed in ultrasonic gel were vibrated from below using low frequency (and low amplitude) sound waves. IOP was controlled using an infusion of normal saline solution under hydrostatic pressure. We postulated that changes in IOP would alter the effective elasticity of the scleral wall, and that in turn would change the resonance frequency of the eye. If the experimental results showed that resonance of the eye actually shifted due to change in the IOP, then this could be used for measurement and monitoring of IOP.

Two different types of experiments were performed. In both cases, IOPs were chosen to correspond to typical clinical conditions, in that normal IOP ranges from 12–21 mm Hg, while abnormal IOP may reach a low of 0 mm Hg and highs of 80 mm Hg or greater. In one case, the frequency of vibration was fixed, and the IOP was varied in the range 6–100 mm Hg. Variation in the vibration amplitude was observed with change in IOP. In the other case, IOP was fixed somewhere between 6–65 mm Hg. Then the vibration frequency was swept through a predetermined range to determine the frequency response and resonances. The vibration amplitude was detected using an ultrasonic transducer placed above the eye. The resonance frequencies were found to depend on the IOP. We have seen a change in the frequency response with as little as 4 mm Hg change in the IOP (Alam et al. 1992). Currently, clinical IOP measurement is most accurately performed with the Goldman applanation tonometer (which requires contact with a normal cornea); accuracy of 2 mm Hg is typically quoted (Shields 1987).

For this *in vivo* study, the right eyes of the volunteers were vibrated by applying low frequency vibration source to the area over the cheek bone. The vibration amplitude was detected using an ultrasound transducer in contact with coupling gel applied to the closed

lid of the right eye. The vibration frequency was automatically varied using a calibrated vibration source. After the resonances for each eye were located by analyzing the Bessel side bands, they were compared against the convenient measurement of IOP, to assess possible correlations. The results from the study showed that a volunteer having higher IOP had a higher resonance frequency, which further supports our postulate. In our experiments so far, we have been able to detect changes in IOP from the shift in the resonance, but the method has not been calibrated as yet to permit absolute IOP measurement.

THEORY

Resonance of the eye

It is quite difficult to obtain an expression for the resonance of a spherical, fluid-filled, damped elastic sphere in terms of internal fluid pressure. Coquart et al. (1992) developed a very detailed model to find the resonance of the eye for both *in vivo* and *in vitro* situations. We will use a greatly simplified model for illustrative purposes, to arrive at the same conclusion, namely, that an increase in the IOP would drive the corresponding resonance frequencies higher. We approximate the spherical fluid-filled elastic shell as a hollow thin spherical shell. The pressure change is accounted for by changing the shell elastic constant. (This would not, however, account for effects such as viscous damping of the fluid media. But, we postulate that the damping would broaden and only slightly shift the resonances. The damping effect of the surrounding tissues in the *in vivo* situation is also not accounted for in this simple model.) The vibration of a hollow thin spherical shell has been investigated by Lamb (1882), and a more recent detailed analysis can be found in Love (1944). All the modes of vibration are extensional, and they fall into two classes that are characterized, respectively, by the absence of a radial component of displacement and the absence of a radial component of rotation. In any mode of either class, the displacement is expressible in terms of spherical surface harmonics of a single internal degree. In the case of vibrations of the first class, the frequency ω ($=2\pi f$) is related to the degree n of the harmonics by the equation

$$\frac{\omega^2 a^2 \rho}{\mu} = (n - 1)(n + 2), \qquad (1)$$

where a is the radius of the sphere, ρ is the density of the shell and μ is rigidity.

In case of vibrations of the second class, the frequency can be determined from the following equation, where σ is the Poisson's ratio,

$$\frac{\omega^4 a^4 \rho^2}{\mu^2} - \frac{\omega^2 a^2 \rho}{\mu}\left[(n^2 + n + 4)\frac{1 + \sigma}{1 - \sigma} + (n^2 + n - 2)\right] + 4(n^2 + n - 2)\frac{1 + \sigma}{1 - \sigma} = 0, \qquad (2)$$

and each resonance mode ($n = 1, 2, 3, \cdots$) corresponds to two positive real resonance frequencies that are solutions to eqn (2). We will limit our illustration to this type of vibration, namely the vibration having only the radial component of displacement and no rotation, because these modes will be detected in our setup by conventional Doppler methods.

We used the following values for the eye,

$a = 2.5$ cm, $\rho = 1$ g/mL,

$\sigma = 0.5$, $\mu \approx 1000$ kPa, for scleral tissues.

For normal human eye, scleral Young's modulus, $E_s \approx 2700$ kPa (Woo et al. 1972). The rigidity μ is

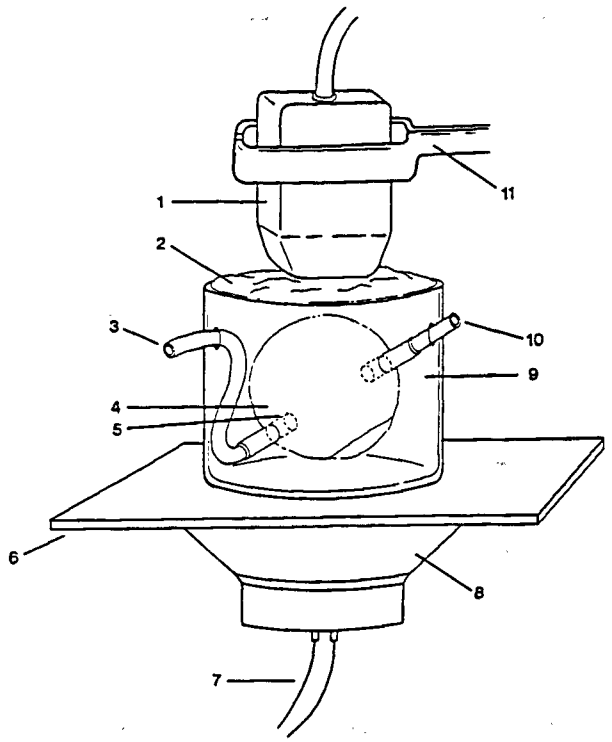


Fig. 2. Schematic diagram of *in vitro* experimental set up. 1) Doppler ultrasound transducer, 2) ultrasonic gel, 3) manometer, 4) eviscerated eye, 5) vitreous infusion port, 6) isolation plate, 7) audio signal input, 8) speaker, 9) specimen holder, 10) normal saline infusion, 11) adjustable clamp.

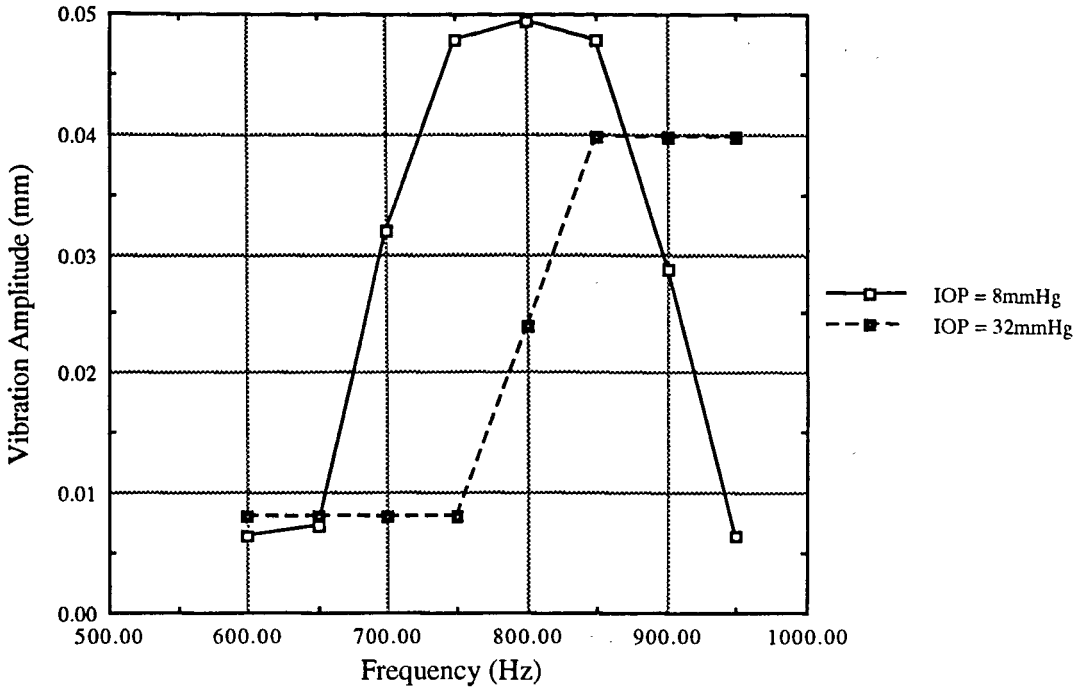


Fig. 3. *In vitro* response of a human eye-bank eye with shift in intraocular pressure (IOP). Vertical scale: estimated radial vibration amplitude. Horizontal scale: vibration frequency.

approximately one third of the Young's modulus, and thus, for the sclera, we took $\mu_s \approx 1000$ kPa. To see how the resonance shifts with changing rigidity, we evaluated the resonance frequencies for $\mu = 100$, 300, 1000, 3000 and 10,000 kPa. The resonance is seen to shift significantly for these changes, as shown in Fig. 1, which gives the larger real positive frequency solutions to the first three resonance modes ($n = 1, 2, 3$). We see that all resonances increase with the increase in rigidity. Thus, we expect the resonance frequencies to shift upward as IOP increases. This hypothesis is supported in the detailed analysis in Coquart et al. (1992) for both the *in vitro* (eye being out of the socket) and *in vivo* (eye being inside the socket) cases.

Estimating the vibration amplitude

When a scattering object vibrates in a manner to produce a wavelength much larger than the geometric dimensions of the scatterer itself, the Doppler spectrum of the signals returning from sinusoidally oscillating structures is similar to that of a pure tone frequency modulation process (Holen et al. 1986).

The received or scattered wave can be written as (Carlson 1986; Huang 1990):

$$s_r(t) = A \cos\left\{2\pi f_0 t + \frac{2\pi \Delta f_m}{2\pi f_L} \sin(2\pi f_L t + \varphi)\right\}, \quad (3)$$

where A is the amplitude of $s_r(t)$, f_0 is the center frequency, f_L is the vibration frequency, φ is the vibration phase and

$$\Delta f_m = \frac{2 v_m f_0 \cos\theta}{c_0}, \quad (4)$$

where $v_m = 2\pi f_L \xi_m$ is the vibration amplitude of the velocity field, ξ_m is the vibration amplitude, f_0 is the propagation speed of the wave and θ is the angle between the wave propagation and the vibration vectors.

Using trigonometric identities:

$$s_r(t) = A \sum_{n=-\infty}^{n=\infty} J_n(\beta)\cos[2\pi f_0 t + n(2\pi f_L t + \varphi)], \quad (5)$$

where the modulation index β is directly related to the vibration amplitude as follows:

$$\beta \equiv \frac{\Delta f_m}{f_L} = 4\pi \frac{\xi_m}{\lambda_0} \cos\theta, \quad (6)$$

where λ_0 = ultrasound wavelength.

For the experiments, it was necessary to estimate the vibration amplitude (or β) from the available Doppler data. Several techniques have been proposed in the past (Holen et al. 1986; Huang 1990; Huang et al.

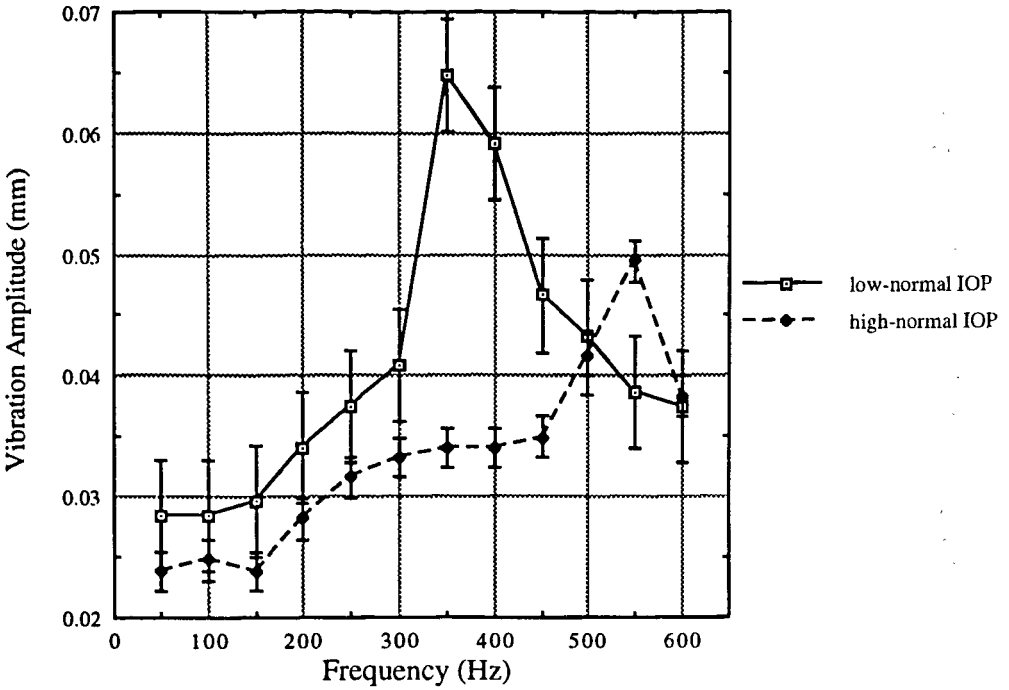


Fig. 4. *In vivo* results. The average and average variation of three individual measurements are shown for the low-normal curve. For the only volunteer with high-normal intraocular pressure (IOP), the average and average variation of two measurements from the same eye are shown.

1990; Yamakoshi et al. 1990) to estimate the vibrational parameters. We used a simple approach proposed by Holen et al. (1986), who measured the vibration amplitude of oscillating heart valves by counting the number of significant harmonics over a certain threshold. This procedure, albeit relatively coarse, is sufficient for resolving submillimeter vibration amplitudes, and is related to the fact that the Doppler bandwidth is proportional to the modulation parameter, or amplitude of oscillation. Future studies may, however, use a more accurate estimator, such as the standard deviation or spectral spread of the power spectrum (Huang et al. 1990).

LABORATORY STUDIES

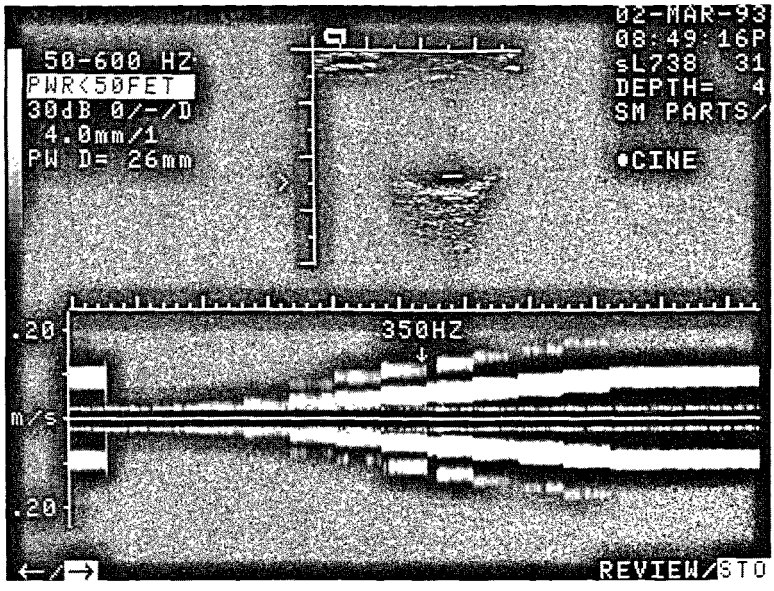
In vitro studies

Eviscerated human and pig eyes were used for the experiment. Human eye bank eyes were obtained through the cooperation of Central Florida Lions Eye and Tissue Bank. The eyes were free of known ophthalmic disease or effects of systemic disease. Two infusion ports, 90° apart at the equator, were created. One port was connected to a collapsible bottle of normal saline; the other port to an open-ended, elevated tube to be used as a manometer. Bottle height was varied to change the IOP, as measured by the fluid level in the manometer. Leakage from incision sites was minimal.

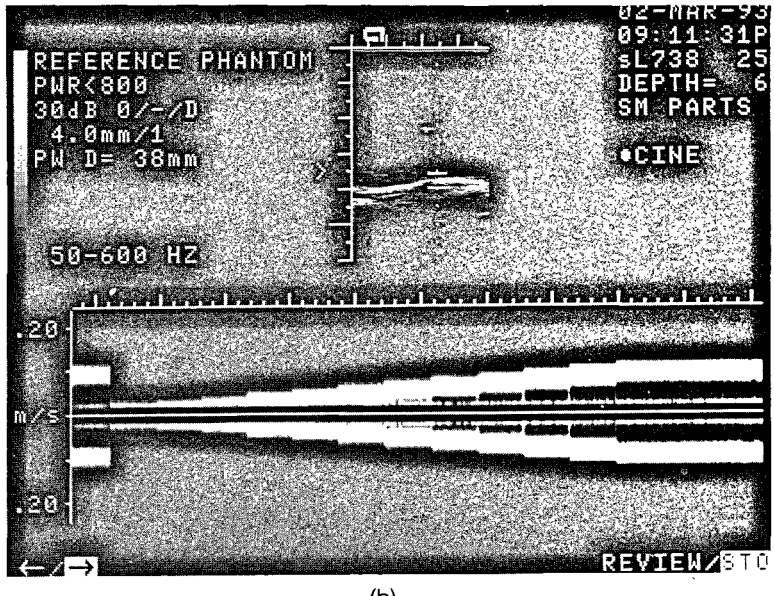
Eyes thus prepared were immersed in ultrasound gel and held in place by stand-off rings to prevent contact between the Doppler ultrasound transducers (5 MHz and 7.5 MHz) and the eye. The eye was vibrated from below using a standard 4-inch speaker. The speaker was coupled to the experimental apparatus and excited so as to produce a uniform vibration amplitude between 200 Hz and 900 Hz. A Tektronix TM 5003 (Tektronix Instruments, Beaverton, OR) function generator was used. The sample volumes used for Doppler measurement were typically 2–3 mm in each dimension. The ultrasound machines used in the experiment were the Toshiba SSH 40-A Sonolayer (Toshiba Instruments, Tokyo, Japan), the Acoustic Imaging AI 5200 (Acoustic Imaging, Tempe, AZ) and the Quantum Instruments QAD 1 (Quantum, Ipsequah, WA). The experimental set up is shown in Fig. 2.

In vivo studies

Preliminary *in vivo* studies were done on the eyes of four volunteers from whom informed consent had been obtained. Vibration was applied by a mini shaker type 4810 (Brüel & Kjær, Denmark) pressed gently over the right cheek bone. After some trial and error, the cheek bone seemed to be the best location for propagation of vibration. The mini shaker was driven by a power amplifier type 2706 (Brüel & Kjær, Denmark). The function generator was a Kron Hite IEEE-



(a)



(b)

Fig. 5. (a) Vibration response of a volunteer's eye. The Doppler gate is positioned at the posterior, inferior sclera. The response peaks around 350 Hz, as evidenced by the presence of strong second side bands. (b) Vibration response of the reference phantom to the excitation in the range 50–600 Hz; the response is essentially flat over the entire range.

488 Programmable Arbitrary/Function Generator Model 5926 (Kron Hite Corp., Avon, MA). The frequency was swept from 50 Hz to 600 Hz in 50 Hz increments in ~0.1 s constant intervals; thus, the frequency sweep took about 1.5 s. The amplitude was programmed to drive the loaded mini shaker at constant displacement over the frequency range. The vibration was sensed by a 7.5 MHz ultrasound transducer (L7384) in contact with coupling gel applied over the closed lid of the eye. The vibration amplitude was picked up at the posterior sclera, with the Doppler sample volume set to 4.0 mm range. The ultrasound scanner used in the *in vivo* experiment was an Acuson Computed Sonography 128XP (Acuson Corp., Mountain View, CA).

RESULTS

From the *in vitro* experimental data, one representative graph (Fig. 3) is presented. It shows the response

of one human eye at IOPs of 8 mm Hg and 32 mm Hg. As expected, the upward shift in the resonance as the IOP increases is seen.

In the *in vivo* studies on the right eye of the volunteers, the IOPs measured by conventional tonometry ranged from 16–23 mm Hg. Three had resonances at 350 Hz. Their IOPs were found to be in the low normal range, around 16 mm Hg. Only one volunteer had the resonance at a higher frequency of 550 Hz. His IOP was 23 mm Hg, on the high end of the normal range. The higher IOP was very clearly demonstrated in the resonance of the eye. In Fig. 4, the average and average variation of three individual measurements are shown for the low-normal curve. For the only volunteer with high-normal IOP, the average and average variation of two measurements from the same eye is shown. For the low normal IOP cases, the error bars show the average intersubject variation (n = 3 subjects × 12 sample frequencies), and for the high normal IOP case, the error bars show the average intrasubject variation (n = 2 measurements × 12 sample frequencies).

Figure 5a depicts the B-scan image of a volunteer's eye and the pulsed Doppler data from the range gate, which was positioned on the posterior scleral wall. It should be noted that the scan takes place through the closed eyelid and therefore causes no discomfort. The frequency sweep in lower half of Fig. 5a is sufficiently rapid (0.1 s/freq. step) so as to minimize artifacts introduced by movements of the eye during data collection.

Figure 5b demonstrates the pulsed Doppler data from a nonresonating phantom. This was used to verify the flat response of the vibration source as programmed from 50 to 600 Hz.

DISCUSSION AND CONCLUSION

The evidence collected from four *in vitro* and four *in vivo* Doppler studies of eyes supports the postulate that resonances are a function of intraocular pressure. Also, the resonance *in vivo* appears rather damped compared to the *in vitro* case due to the eye being enclosed by bones and muscles. An estimation of quality factor Q (for the low IOP cases) from the response shows the *in vivo* Q (~1.0) to be much smaller than the *in vitro* Q (~3.4).

The quality factor Q at the resonance frequency is a measure of how damped the resonance is. It is defined as $Q = \frac{f_0}{f_{3\,\mathrm{dB}}}$, where f_0 is the frequency of resonance and $f_{3\,\mathrm{dB}}$ is the 3-dB bandwidth.

For the *in vitro* case, with IOP = 8 mm Hg, $f_0 \approx$ 800 Hz, and $f_{3\,\mathrm{dB}} \approx (910 - 675)$ Hz = 235 Hz. Then $Q \approx 3.4$. Similarly, the *in vivo* $Q \approx \frac{350}{600 - 250} = 1.0$.

If a standardized normal range of the known resonances for the human eye can be established, any abnormality in the detectable resonances can then be used to detect abnormalities in the IOP. Further simulations and experiments (both *in vivo* and *in vitro*) will be required to determine whether these effects have a useful clinical application, especially *in vivo* where natural variations in the eye are to be expected. However, the results from both *in vitro* and *in vivo* experiments support the postulate that sonoelastic resonances can be used to detect alterations in IOP. It remains to be determined whether or not absolute IOP levels can be reliably measured in this way in a clinical setting.

Acknowledgements—This work was supported by the University of Rochester, Department of Electrical Engineering, the NSF and the NYS Science and Technology Foundation. The help of Ken Henderson of Xerox Corporation is appreciated.

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