Noninvasive Intracranial Volume and Pressure Measurements Using Ultrasound.

MAR 1998

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INTRODUCTION

During this past year we accomplished all of the goals which we set forth for Year -01 on this project. First, we modified the PPLL hardware by integrating software modifications such that our clinical studies will be greatly facilitated. Although mean ICP is commonly used for ICP monitoring, the analysis of ICP waveforms is also important because the waveforms contain information on intracranial compliance and cerebrovascular tonus which cannot be estimated from mean ICP (1). Our technique, the principle of which is called pulsed phase-locked loop (PPLL), is based upon detecting skull movements which occur with fluctuations in ICP. Although the skull is often assumed to be a rigid container with a constant volume, many researchers (2-6) have demonstrated that the skull moves on the order of a few μm in association with changes in ICP. This year's studies were designed to validate our noninvasive technique for the measurement of ICP waveforms.

METHODS

The ultrasound technique we utilized to detect skull pulsation is based upon a modification of the pulsed phase-lock loop design (7), making it possible to measure slight changes in distance between an ultrasound transducer and a reflecting target. Sensitivity of the device is on the order of 0.1 μm. In the typical operation of the PPLL, the instrument transmits a 500 kHz ultrasonic tone burst through the cranium via a transducer placed on the head. The ultrasonic wave passes through the cranial cavity, reflects off the inner surface of the opposite side of the skull, and is received by the same transducer. The instrument compares the phase of emitted and received waves and alters the frequency of the next stimulus to maintain a 90° phase difference between the output of the device and the received signal. This repetition takes place at intervals of approximately 0.5 msec to 20 ms.

The details of PPLL are described elsewhere (7, 8). Briefly, if path length is changed by Δl, the frequency shift (Δf) of the ultrasound which is made to maintain the 90° phase difference between the output of the device and the received signal can be expressed as Δl/l = -Δf/f (see Appendix). This is the fundamental PPLL technique. In order to provide continuous monitoring, we modified the PPLL circuit to integrate error signals of the phase shift from normal 90° phase difference (PPLL output).

Theoretically, integration of the error signals also correlates with altered path length (Δl).

Bench Tests: A specially constructed aluminum cylinder was used to examine the PPLL output characteristics. Two pressure-resistant tubes were connected to the cylinder filled with saline. The other ends of the two tubes were connected to a plastic syringe and a fiber-optic, transducer-tipped catheter (Camino Laboratories, San Diego) which measures fluid pressure, respectively. An ultrasonic transducer was placed on the top of the cylinder. Pressure pulsations were generated at a frequency of 1 Hz by pumping the syringe while its amplitudes were changed randomly. Changes in distance were calculated from changes in ultrasound frequency.
Our model experiments demonstrated that changes in the PPLL output correlated with changes in the distance to a high degree (Fig. 1). Theoretically, the distance calculated from the ultrasound frequency can be obtained independently of PPLL output. In the results, PPLL output is expressed as:

$$\Delta \text{int} \text{ (voltage)} = 2.33 \cdot 10^{-4} \Delta l \text{ (\mu m)}$$

where $\Delta \text{int}$ and $\Delta l$ are the changes in PPLL outputs and distance, respectively.

**CADAVER STUDY:** Our second goal for Year-01 was to evaluate the correlation of PPLL output and directly-measured ICP in fresh human cadavera. In supine position, a catheter was inserted into the frontal horn of the right lateral ventricle through a burr hole, and the other end of the catheter was connected to pressure tubing and a plastic syringe. To correlate the PPLL output with ICP directly, a fiber-optic, transducer-tipped catheter was placed in the epidural space through another burr hole. The ultrasound transducer was placed on the temporal area above the ear and fixed with pressure cuff around the head to adjust the surface pressure on the transducer. Pulsatile changes in ICP were generated by infusing saline into the lateral ventricle at a frequency of 1 Hz. In the first experiment (cadaver A), we recorded the PPLL output while generating ICP pulsations and thereafter increased the circumference pressure around the head in steps of 10 mmHg (0-40 mmHg) by inflating the pressure cuff. In the second experiment (cadaver B), we recorded the pulsatile PPLL output by infusing saline of different temperatures into the ventricle (4°C and 20°C). The amplitudes were calculated based upon the fundamental harmonic of the data using 256 point-fast Fourier transformation (sampling rate: 50 Hz) to avoid distortion caused by other frequency waves.

**RESULTS**

The PPLL output closely followed the pulsatile component of ICP (Fig. 2). The results of fast Fourier transformation are provided in the top insert, showing the coincidence between the PPLL output and ICP pulse cycles. In the results of the first experiment, the ratio of PPLL amplitude to ICP amplitude significantly decreased along with increased external compression around the head:

$$y = -1.0 \cdot 10^{-5} x + 0.0008, R^2=0.87 \ (p=0.020)$$

where $x =$ circumferential compression (mmHg) and $y =$ ratio of PPLL amplitude to ICP amplitude (voltage / mmHg). In the second experiment, the correlation between the PPLL and ICP amplitudes was expressed as the same equation in both saline temperatures:

$$y = 3.0 \cdot 10^{-4} x + 0.0011$$

where $x =$ ICP amplitude (mmHg) and $y =$ PPLL amplitude (voltage).
GRANT NUMBER DAMD17-97-1-7012

TITLE: Noninvasive Intracranial Volume and Pressure Measurements Using Ultrasound

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The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.
Prevention of secondary brain injuries following head trauma can be accomplished most easily when intracranial pressure (ICP) is monitored. However, current measurement techniques are invasive and thus not practical in the combat environment. The Pulsed Phase Lock Loop (PPLL) device, which was developed and patented by consultants Dr. Yost and Dr. Cantrell, uses a unique, noninvasive ultrasonic phase comparison method to measure slight changes in cranial volume which occur with changes in ICP. Year one studies involved instrument improvements and measurement of altered intracranial distance with altered ICP in fresh cadavera. We accomplished our goals for the past year. Our software was improved to facilitate future studies of normal subjects and trauma patients. Our bench studies proved that PPLL output correlated highly with changes in path length across a model cranium. Cadaveric studies demonstrated excellent correlation between invasive and noninvasive measures of ICP using an input arterial pulse. A compact, noninvasive device for monitoring changes in intracranial distance may aid in the early detection of elevated ICP, decreasing risk of secondary brain injury and infection, and returning head-injured patients to duty.
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DISCUSSION

The results demonstrate that our PPLL device can clearly detect changes in the integrated phase shifts of the transmitted ultrasound (PPLL outputs) in association with alterations in ICP. As shown in the Appendix, the observed phase shift can be caused by changes in the distance between the transducer and the opposite side of the skull and also by changes in the ultrasound velocity in the cranium. However, we believe that changes in the PPLL output observed in our cadaveric studies represent small but detectable skull movements associated with alterations in ICP.

Infusion of saline into the ventricle could change the temperature inside the cranium, resulting in altered sound velocity. As another possible factor, changes in the density of the brain tissue due to altered ICP could affect ultrasound velocity. In the cadaver study, however, no significant difference was observed in the amplitudes of PPLL when different temperature saline was infused into the ventricle. Also, increased circumferential pressure around the head decreased PPLL amplitudes. This observation cannot be explained by changes in ultrasound velocity. This study may be the first report to measure skull movements noninvasively in association with alterations in ICP.

According to the equation 2, the ratio of PPLL amplitude to ICP amplitude is expressed as:

\[ \frac{\Delta \text{int}}{\Delta \text{ICP}} = 3.0 \cdot 10^{-4} \text{ (voltage / mmHg)} \quad \text{equation 3} \]

Using equations 1 (shown in the Results) and 3, the skull elastance, defined as \( \frac{\Delta \text{ICP}}{\Delta \text{t}} \), is approximately 1.6 mmHg / \( \mu \text{m} \) (=2.33 \( \cdot \) 10\(^{-4} \) / (3.0 \( \cdot \) 10\(^{-4} \) \( \cdot \) 2)). Heisey and Adams (3) demonstrated that skull elastance in adult cats is 4.5 mmHg / \( \mu \text{m} \) by invasively measuring the skull movement across the sagittal suture with strain gauge. The difference between our data and theirs might be due to the difference in skull elastance between cat and human. Also, we measured skull movements transversely, while they measured the movement only across the sagittal suture. This difference in the site of measurement may affect changes in the distance obtained.

CONCLUSION

In conclusion, our technique allows analysis of ICP waveforms noninvasively and will be helpful for understanding intracranial compliance and cerebrovascular tonus in general clinical settings.

Finally we received approvals for our clinical study protocols from the IRBs at US Army, NASA Ames Research Center, and Stanford University. Similar protocols are under review now at UCSD where most future studies will be undertaken.
REFERENCES


OUR PUBLICATIONS FOR PERIOD 1 FEB. 1997 TO 31 JAN. 1998
(See Attachments)


LIST OF PERSONNEL WHOSE SALARY IS SUPPORTED BY THIS EFFORT:

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Gita Murthy, M.S.
Karen Hutchinson, A.A.

FIGURE LEGENDS
Figure 1. The relation of the PPLL output to the pressure inside the cylinder and the distance between the transducer and the bottom of the tank is shown, where x = distance (µm) and y = PPLL output (voltage)

Figure 2. Typical waveforms in the PPLL output and directly measured ICP are shown as solid and dash lines, respectively. The results of frequency analysis (fast Fourier transformation) are provided in the top insert.
Figure 1

Pressure amplitude (mmHg)

\[ y = 2.33 \times 10^{-4} x + 1.10 \times 10^{-3} \]

\[ R^2 = 0.977 \]
APPENDIX

Changes in wavelength after the frequency shift which maintains a 90° phase difference between the output of the device and the received signal can be expressed as:

\[ n\Delta \lambda = \Delta l \quad (\Delta \lambda: \text{changes in wavelength}, \Delta l: \text{changes in distance}) \]

where \( n = l/\lambda \) (\( l \): initial distance between a transducer and a target, \( \lambda \): initial wavelength).

Therefore, \( \frac{\Delta \lambda}{\lambda} = \frac{\Delta l}{l} \)

Also, \( \Delta \lambda = \frac{\partial \lambda}{\partial v} \Delta v + \frac{\partial \lambda}{\partial f} \Delta f \) where \( \Delta v \) is changes in ultrasound velocity. and \( f = v/\lambda \).

Solving these equations, we obtain \( \frac{\Delta f}{f} = \frac{\frac{\Delta v}{v} - \frac{\Delta l}{l}} {v} \)

If changes in sound velocity are negligible, the above equation is finally expressed as:

\[ \frac{\Delta f}{f} = -\frac{\Delta l}{l} \]
Noninvasive Measurement of Pulsatile Intracranial Pressure using Ultrasound

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SUMMARY

The present study was designed to validate our noninvasive ultrasonic technique (pulse phase locked loop: PPLL) for measuring intracranial pressure (ICP) waveforms. The technique is based upon detecting skull movements which are known to occur in conjunction with altered intracranial pressure. In bench model studies, PPLL output was highly correlated with changes in the distance between a transducer and a reflecting target ($R^2=0.977$). In cadaver studies, transcranial distance was measured while pulsations of ICP (amplitudes of zero to 10 mmHg) were generated by rhythmic injections of saline. Frequency analyses (fast Fourier transformation) clearly demonstrate the correspondence between the PPLL output and ICP pulse cycles. Although theoretically there is a slight possibility that changes in the PPLL output are caused by changes in the ultrasonic velocity of brain tissue, the decreased amplitudes of the PPLL output as the external compression of the head was increased indicates that the PPLL output represents substantial skull movement associated with altered ICP. In conclusion, the ultrasound device has sufficient sensitivity to detect transcranial pulsations which occur in association with the cardiac cycle. Our technique makes it possible to analyze ICP waveforms noninvasively and will be helpful for understanding intracranial compliance and cerebrovascular circulation. (200 words)

INTRODUCTION

Elevated intracranial pressure (ICP) is used as a sign of neurological deterioration in the management of patients with head trauma, cerebrovascular diseases, and brain tumors (6). Conventional methods for ICP monitoring require surgical procedures which are accompanied by increased risk of infection. For this reason, candidates for ICP monitoring are currently only patients with severe neurological conditions. A noninvasive technique could make it possible to monitor ICP more easily and repeatedly in patients with a variety of neurosurgical conditions, thus aiding clinical management and reducing the mortality and morbidity related to neurological diseases.

We have developed a new ultrasonic device to measure ICP waveforms. Although mean ICP is commonly used for ICP monitoring, the analysis of ICP waveforms is also important because the waveforms contain information on intracranial compliance and cerebrovascular tonus, which cannot be estimated from mean ICP (1). Our technique (8), the principle of which is called pulsed phase-locked loop
(PPLL) method, is based upon detecting skull movements which occur with fluctuations in ICP. Although the skull is often assumed to be a rigid container with a constant volume, many researchers (2-5, 7) have demonstrated that the skull moves on the order of a few μm in association with changes in ICP. The present study was designed to validate our noninvasive technique for the measurement of ICP waveforms.

TECHNIQUE

The ultrasound technique (8) we utilized to detect skull pulsation is based upon a modification of the pulsed phase-lock loop design, which makes it possible to measure slight changes in distance between an ultrasound transducer and a reflecting target. Sensitivity of the device is on the order of 0.1 μm. In the typical operation of the PPLL, the instrument transmits a 500 kHz ultrasonic tone burst through the cranium via a transducer placed on the head. The ultrasonic wave passes through the cranial cavity, reflects off the inner surface of the opposite side of the skull, and is received by the same transducer. The instrument compares the phase of emitted and received waves and alters the frequency of the next stimulus to maintain a 90° phase difference between the output of the device and the received signal. This repetition takes place at intervals of approximately 0.5 msec to 20 ms.

The details of PPLL are described elsewhere (8, 9). Briefly, if path length is changed by Δl, the frequency shift (Δf) of the ultrasound which is made to maintain the 90° phase difference between the output of the device and the received signal can be expressed as Δl/l = −Δf/f (see Appendix). This is the fundamental PPLL technique. In order to provide continuous monitoring, we modified the PPLL circuit to integrate error signals of the phase shift from normal 90° phase difference (PPLL output). Theoretically, integration of the error signals also correlates with altered path length (Δl).

METHODS

BENCH TEST: A specially constructed aluminum cylinder was used to examine the PPLL output characteristics. Two pressure-resistant tubes were connected to the cylinder filled with saline. The other ends of the two tubes were connected to a plastic syringe and a fiber-optic, transducer-tipped catheter (Camino Laboratories, San Diego) which measures fluid pressure, respectively. An ultrasonic transducer
was placed on the top of the cylinder. Pressure pulsations were generated at a frequency of 1 Hz by pumping the syringe while its amplitudes were changed randomly. Changes in distance were calculated from changes in ultrasound frequency.

**CADAVER STUDY:** The correlation between the PPLL output and ICP were evaluated in two fresh cadaver (age 85 and 90) which were less than 48 hours postmortem. In supine position, a catheter was inserted to the frontal horn of the right lateral ventricle through a burr hole, and the other end of the catheter was connected to pressure tubing and a plastic syringe. To correlate the PPLL output with ICP directly, a fiber-optic, transducer-tipped catheter was placed in the epidural space through another burr hole. The ultrasound transducer was placed on the temporal area above the ear and fixed with pressure cuff around the head to adjust the surface pressure on the transducer. Pulsatile changes in ICP were generated by infusing saline into the lateral ventricle at a frequency of 1 Hz. In the first experiment (cadaver A), we recorded the PPLL output while generating ICP pulsations and thereafter increased the circumference pressure around the head in steps of 10 mmHg (0-40 mmHg) by inflating the pressure cuff. In the second experiment (cadaver B), we recorded the pulsatile PPLL output by infusing saline of different temperatures into the ventricle (4°C and 20°C).

**DATA ANALYSIS:** The amplitudes were calculated based upon the fundamental harmonic of the data using 256 point-fast Fourier transformation (sampling rate: 50 Hz) to avoid distortion caused by other frequency waves.

**RESULTS**

**BENCH TEST:** Our model experiments demonstrated that changes in the PPLL output correlated with changes in the distance to a high degree (Fig. 1). Theoretically, the distance calculated from the ultrasound frequency can be obtained independently of PPLL output. In the results, PPLL output is expressed as:

\[
\Delta \text{int (voltage)} = 2.33 \cdot 10^{-4} \Delta l \text{ (\mu m)} \quad \text{equation 1}
\]

where \( \Delta \text{int} \) and \( \Delta l \) are the changes in PPLL outputs and distance, respectively.

**CADAVER STUDY:** The PPLL output closely followed the pulsatile component of ICP (Fig. 2). The results of fast Fourier transformation are provided in the top insert, showing the coincidence between the
PPLL output and ICP pulse cycles. In the results of the first experiment, the ratio of PPLL amplitude to ICP amplitude significantly decreased along with increased external compression around the head:

\[ y = -1.0 \times 10^{-5} x + 0.0008, R^2=0.87 \ (p=0.020) \]

where \( x \) = circumferencial compression (mmHg) and \( y \) = ratio of PPLL amplitude to ICP amplitude (voltage / mmHg). In the second experiment, the correlation between the PPLL and ICP amplitudes was expressed as the same equation in both saline temperatures:

\[ y = 3.0 \times 10^{-4} x + 0.0011 \]  

where \( x \) = ICP amplitude (mmHg) and \( y \) = PPLL amplitude (voltage).

**DISCUSSION**

The results demonstrate that our PPLL device can clearly detect changes in the integrated phase shifts of the transmitted ultrasound (PPLL outputs) in association with alterations in ICP. As shown in the Appendix, the observed phase shift can be caused by changes in the distance between the transducer and the opposite side of the skull and also by changes in the ultrasound velocity in the cranium. However, we believe that changes in the PPLL output observed in the present cadaveric study represent small but detectable skull movements associated with alterations in ICP.

Infusion of saline into the ventricle could change the temperature inside the cranium, resulting in altered sound velocity. As another possible factor, changes in the density of the brain tissue due to altered ICP could affect ultrasound velocity. In the cadaver study, however, no significant difference was observed in the amplitudes of PPLL when different temperature saline was infused into the ventricle. Also, increased circumference pressure around the head decreased PPLL amplitudes. This observation cannot be explained by changes in ultrasound velocity. This study may be the first report to measure skull movements noninvasively in association with alterations in ICP.

According to the equation 2, the ratio of PPLL amplitude to ICP amplitude is expressed as:

\[ \frac{\Delta \text{int}}{\Delta \text{ICP}} = 3.0 \times 10^{-4} \ (\text{voltage} / \text{mmHg}) \]  

Using equations 1 (shown in the Results) and 3, the skull elastance, defined as \( \frac{\Delta \text{ICP}}{\Delta l} \), is approximately 1.6 mmHg / \( \mu \)m (=2.33 \times 10^{-4} / (3.0 \times 10^{-4})-2). Heisey and Adams (3) demonstrated that skull elastance in adult cats is 4.5 mmHg / \( \mu \)m by invasively measuring the skull movement across the sagittal suture with
strain gauge. The difference between our data and theirs might be due to the difference in skull elastance between cat and human. Also, we measured skull movements transversely, while they measured the movement only across the sagittal suture. This difference in the site of measurement may affect changes in the distance obtained.

In conclusion, our technique allows analysis of ICP waveforms noninvasively and will be helpful for understanding intracranial compliance and cerebrovascular tonus in general clinical settings.

ACKNOWLEDGEMENTS

This research was supported by NASA grant 199-80-02-05, Department of the Army grant DAMD 17-97-1-7012, and National Research Council Senior Fellowship to TU. Also, we thank John and Chris Dolph, Stanford University Dept. of Anatomy, for assistant with cadaver studies.

REFERENCES


APPENDIX

Changes in wavelength after the frequency shift which maintains a 90° phase difference between the output of the device and the received signal can be expressed as:

\[ n \Delta \lambda = \Delta l \]  

(\( \Delta \lambda \): changes in wavelength, \( \Delta l \): changes in distance)

where \( n = l/\lambda \) (\( l \): initial distance between a transducer and a target, \( \lambda \): initial wavelength).

Therefore,

\[ \frac{\Delta \lambda}{\lambda} = \frac{\Delta l}{l} \]

Also, \( \Delta \lambda = \frac{\partial \lambda}{\partial v} \Delta v + \frac{\partial \lambda}{\partial f} \Delta f \) where \( \Delta v \) is changes in ultrasound velocity, and \( f = v/\lambda \).

Solving these equations, we obtain

\[ \frac{\Delta f}{f} = \frac{\Delta v}{v} = \frac{\Delta l}{l} \]

If changes in sound velocity are negligible, the above equation is finally expressed as

\[ \frac{\Delta f}{f} = \frac{\Delta l}{l} \]

FIGURE LEGEND

Figure 1. The relation of the PPLL output to the pressure inside the cylinder and the distance between the transducer and the bottom of the tank is shown, where \( x = \) distance (µm) and \( y = \) PPLL output (voltage)

Figure 2. Typical waveforms in the PPLL output and directly measured ICP are shown as solid and dash lines, respectively. The results of frequency analysis (fast Fourier transformation) are provided in the top insert.
Pressure amplitude (mmHg)

\[ y = 2.33 \times 10^{-4} x + 1.10 \times 10^{-3} \]

\[ R^2 = 0.977 \]
INTRODUCTION

The ultrasound device has sufficient sensitivity to detect cranial pulsation in association with cardiac cycles. By analyzing the magnitude of cranial pulsation during space flight it is possible (Supported by NASA grant 199-26-12-34)

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CEREBROVASCULAR RESPONSES DURING LOWER BODY NEGA(IVE) PRESSURE-INDUCED PRESYNCOPE. K. Kuriyama, T. Iwane, R.E. Ballard, D.D. Weather, and W.L. Lokey. Naval Medical Center, San Diego, CA. The relationship between orthostatic intolerance and lower body negative pressure (LBNP) has been extensively studied, particularly in the context of space flight. However, the mechanisms underlying the response to LBNP remain unclear. In this study, we investigated the effects of LBNP on cerebral blood flow (CBF) and heart rate (HR) in healthy volunteers.

METHODS

Healthy male volunteers were exposed to LBNP at a step of -10 mmHg every 3 min until presyncope symptoms were detected. Blood pressure (BP) and HR were measured at baseline, with LBNP, and after recovery.

RESULTS

In the control condition, CBF and HR were maintained at baseline values throughout the experiment. In contrast, during LBNP exposure, CBF decreased significantly, while HR increased. These changes were associated with a decrease in cerebral oxygen saturation (S_cO_2) and an increase in cerebral blood volume (CBV).

CONCLUSION

The results of this study suggest that LBNP-induced presyncope is mediated by a decrease in CBF and an increase in CBV. These findings have important implications for the prevention of presyncope during space flight.
Abstracts & Scientific Program

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NON-INVASIVE MEASUREMENT OF PULSATILE INTRACRANIAL PRESSURES USING ULTRASOUND

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Introduction  Early detection of elevated intracranial pressure (ICP) will aid clinical decision-making for head trauma, brain tumor and other cerebrovascular diseases. Conventional methods, however, require surgical procedures which take time and are accompanied by increased risk of infection. Accordingly, we have developed and refined a new ultrasound device¹ to measure skull movement which are known to occur in conjunction with altered ICP². The principle of this device is based upon pulse phase locked loop (PPLL), which enables us to detect changes in distance on the order of μm between an ultrasound transducer on one side of the skull and the opposite inner surface of the cranium. The present study was designed to verify this measurement technique in cadaver.

Methods  Transcranial distance was increased in steps of 10 mmHg from zero to 50 mmHg by saline infusion into the lateral ventricle of two cadaveras. In separate experiments, pulsations of ICP with the amplitudes of zero to 2 mmHg were generated by rhythmic injections of saline using a syringe.

Results  When the ICP was stepwise increased from zero to 50 mmHg, transcranial distance increased in proportion with the ICP increase (y=12x - 76, r=0.938), where y is changes in transcranial distance in μm and x is ICP in mmHg. In the data recorded while ICP pulsations were generated, fast Fourier transform analysis demonstrated that cranial pulsations were clearly associated with ICP pulsations.

Summary and Conclusions  The results indicate that changes in transcranial distance is linearly correlated with those in ICP, and also that the PPLL device has sufficient sensitivity to detect transcranial pulsations which occur in association with the cardiac cycle. By analyzing the magnitude of cranial pulsations, we may be able to estimate the pressure-volume index in the cranium. As a result, estimates of intracranial compliance may be possible by using the PPLL device. Further studies are necessary in normal subjects and patients. (Supported by NASA and the US Army Medical Research Material Command, and a National Research Council senior fellowship to TU)

References