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To establish the feasibility of non-invasive ICP measurement in a field portable package, a variety of different non-invasive interrogation techniques were evaluated for potential to correlate with elevated ICP. ICP increase was simulated via head-down tilt, jugular occlusion and breath holding. Of the methods tested, spinal CSF pulse wave velocity and ultrasonic location of midline and pineal structures did not meet the requirements. Pulse wave velocity of blood through the head showed potential but further investigation is necessary to determine whether this measurement is truly separating out the superimposed carotid and jugular components of the cranial blood pulse profile. Skull distention measurement also correlated well with increased ICP but the measured displacement could not be distinguished unambiguously from venous engorgement in the fleshy tissue covering the temples. Low frequency acoustics showed excellent potential as a practical and easily implemented means of determining ICP level and showed good correspondence with all means of simulating the pressure elevation. The technique displayed consistent attenuation with ICP rise, in full agreement with the direction and magnitude predicted by our fundamental models. Cadaver studies with the low frequency technique confirmed the attenuation measurement during ICP elevation via simulated perfusion of blood through the head.

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Section I

Introduction

In modern warfare, head injury remains the second most common cause of death after exsanguination. In some cases, the injury will result in immediate death, but in many others, rapid diagnosis and treatment could save lives. The battlefield triage decision is relatively straightforward for the most severe head injuries which have readily identifiable and visible manifestations, but the decision is considerably more difficult for soldiers who are rendered immediately unconscious through blunt injury and concussion. Because the visible symptoms and immediate level of coma can be similar for both serious traumatic brain injury and simple concussion, a non-invasive ICP measurement device is needed to aid the battlefield medic. Thus the focus of this effort is to develop a small, lightweight, portable, highly sensitive ICP monitoring and diagnostic system which is compatible with existing data acquisition and/or telemetry systems.

While the development of ICP quantification techniques is the principal focus of this technical effort, the selected techniques will also be evaluated for detecting other collateral changes in cranial vault contents. The integrity and efficacy of the triage and early treatment decision is greatly enhanced when an indicator of elevated ICP is complimented by independent confirmation that there has been disruption or damage to the soft tissue of the brain. In fact, very early in the course of an expanding hematoma, at a time when there may be no significant ICP elevation (<15-20 mm Hg, the customary treatment threshold), there are probably significant detectable changes in the consistency, viscosity or elastic modulus of the cranial contents that could be detected, for example, as changes in tissue acoustical impedance. Similarly, it should be possible to detect loss of symmetry in cranial vault anatomy, as virtually all significant brain injuries are associated with lateral movement of midline brain structures. In most instances, it is only after fluid volume increases have been accommodated to the maximum extent possible, via the normal cranial vault compliance mechanisms, that ICP will rise. Prior to this point, significant movement or displacement of various brain structures can occur. Accordingly, the optimum approach for identifying severe traumatic brain injury requiring emergency treatment and evacuation, is to combine ICP information with determination of mechanical changes and physical property changes within the cranial vault.

The effect of ICP monitoring and treatment on outcome after traumatic brain injury (TBI) is clearly identified and is the basis for the current practice guidelines of the Brain Injury Association. Non-invasive ICP monitoring has several potential modes of use, each with a different clinical setting and value.

In the field, non-invasive ICP monitoring may help differentiate clinically serious unconsciousness due to traumatic brain injury with rising ICP from temporary loss of consciousness caused by intoxication or concussion. Early differentiation will lead to earlier appropriate treatment, which can have a beneficial effect on outcome.

The utility of non-invasive ICP monitoring in the hospital depends on the nature of the hospital and the location in the hospital. In small or rural hospitals and emergency departments (ED), non-invasive

ICP monitoring would have a similar utility to that in the field. Most small hospitals will transfer patients with traumatic brain injury to other hospitals or trauma centers; thus the non-invasive ICP device would help with more rapid triage and initiation of appropriate therapy. In those hospitals equipped to care for patients with traumatic brain injury, non-invasive ICP monitoring would serve as a bridging technique to guide early therapy until an invasive ICP device or ventricular catheter for CSF drainage could be inserted.

In the operating suite, non-invasive ICP monitoring may have application for extracranial procedures that are only now being associated with potential ICP deviation. For example, there is a growing body of evidence that ICP may be elevated during or after cardiac bypass. It is not yet clear whether this represents a causal mechanism for further brain injury as opposed to a marker of brain injury caused by another mechanism (i.e. a primary or a secondary rise in ICP). ICP monitoring by invasive techniques may be difficult to justify in the more than 500,000 per year in the United States who undergo cardiac bypass. On the other hand, non-invasive ICP monitoring may serve as an early warning technique that would become the indicator for more aggressive, invasive monitoring.

In the ambulatory setting, non-invasive ICP monitoring has the potential to guide treatment decisions regarding hydrocephalus, brain tumor or idiopathic intracranial hypertension (pseudotumor cerebri). Each of these diseases represents a chronic disorder of ICP, CSF circulation or cerebral edema in which ICP can be measured conventionally by invasive means intermittantly for only brief periods of time. Such intermittent ICP monitoring is known to have little relationship to the wide variation in ICP that occurs with posture, activity, wakefulness or sleep. Thus non-invasive ICP monitoring would present opportunities for better understanding of the pathophysiology of these diseases in addition to better ways to guide treatment decisions.

In summary, non-invasive ICP monitoring has tremendous potential to benefit patients with acute and chronic disorders of ICP. Existing methods of ICP monitoring are in limited use despite guidelines and expert opinions calling for more widespread use. The physician operator skills required to insert invasive devices is one of the limiting factors. Another is fear of brain injury in patients for whom ICP monitoring is not routinely considered. Non-invasive ICP monitoring would address many of these problems and would assist therapy and decision making for all such patients.

Section II

Approach

Because the non-invasive determination of ICP is a complex undertaking, the approach taken in this program was to seek out complimentary information from more than one method of interrogation, then combine and process the data to infer a pressure level.

The Phase I program objective was achieved by:

1) testing four types of sensing and interrogation methods and screening against specifically developed physical in-vitro models that replicate the mechanical and acoustical properties of the head and the contents of the cranial vault

2) ensuring sound theoretical basis by mathematically modeling the neurology and biophysics to guide technique development

3) developing biophysical models that predict the sensitivity and specificity of each of the techniques

4) downselecting to the most promising techniques

5) retest of the best methods in a cadaver head study to assess applicability with real human tissue

Numerous candidate methods were considered at the outset of the program for non-invasively gaging intracranial pressure. Following several internal team discussions and after weighing all the theoretical and practical considerations, the techniques selected for investigation were narrowed to:

- low frequency acoustic resonance -- frequency shift and peak width
- low frequency acoustic attenuation
- blood pulse wave velocity and associated phenomena through the head
- static skull expansion measurement
- ultrasonic location of brain midline structures

The following sections describe the experimental results obtained and conclusions drawn with each of these techniques:

Section III

Experimental Methods, Results and Discussion

DC Caliper Measurement of Skull Distention:

Rather than rely on a high resolution displacement measurement with all of its inherent drift and noise sensitivity issues, we had initially hoped to make an effective measurement of increasing skull stiffness as the internal pressure increased. In principle, it would be possible to slowly apply increasing amounts of pressure, say at the temple area of the skull, and measure the corresponding displacement to derive a mechanical modulus. However, this technique was eliminated before the first experiment because of the impracticality and safety concerns associated with imposing an external force against the head.

In order to measure simple static skull extension with increasing ICP, a fluid-filled pod was placed firmly against each temple of a volunteer subject and the fluid was then pressurized slightly against the head using a thumbscrew syringe. As the subject's position was changed from sitting upright to laying supine to head-down tilt at 45 degrees, the pressure in each pod was measured using an immersed pressure gage.

Measurements showed a reproducible pressure increase within the pods of approximately 20 mmHg as the subject was moved from upright to fully negatively inclined, a reading which looks very much in line with the change in ICP expected with this type of postural change. However, after more careful consideration of the data, it was concluded that the result could equally have been caused by increased blood pressure in the head or engorgement of the skin and flesh over the temples with blood in the head-down position. It was also concluded that there was no simple way of separating these effects from skull distention due to ICP shift. In addition, the theoretical basis for this method was called into question because the presence of strong arachnoid fiber strands within the dura suggests that mild pressure increases in the brain will be largely constrained by the dura and not transmitted through to the skull.

Resonance/Attenuation of Cranial Vault Structures and Contents

In order to reliably and quantitatively measure the response of the cranium to low frequency acoustical input, the head brace illustrated below was designed and built to reproducibly position and hold appropriate transmitting actuators and receiving sensors. The transmitting actuators were broadly adjustable over a range of locations and angles in the vicinity of the temples and could be held against the head with a controlled amount of prestress. Similarly, the single receiving sensor on the forehead could be preloaded to any desired level, and located over a broad area to enable the user, for example, to avoid the upper sinus cavities which would complicate any acoustic response.

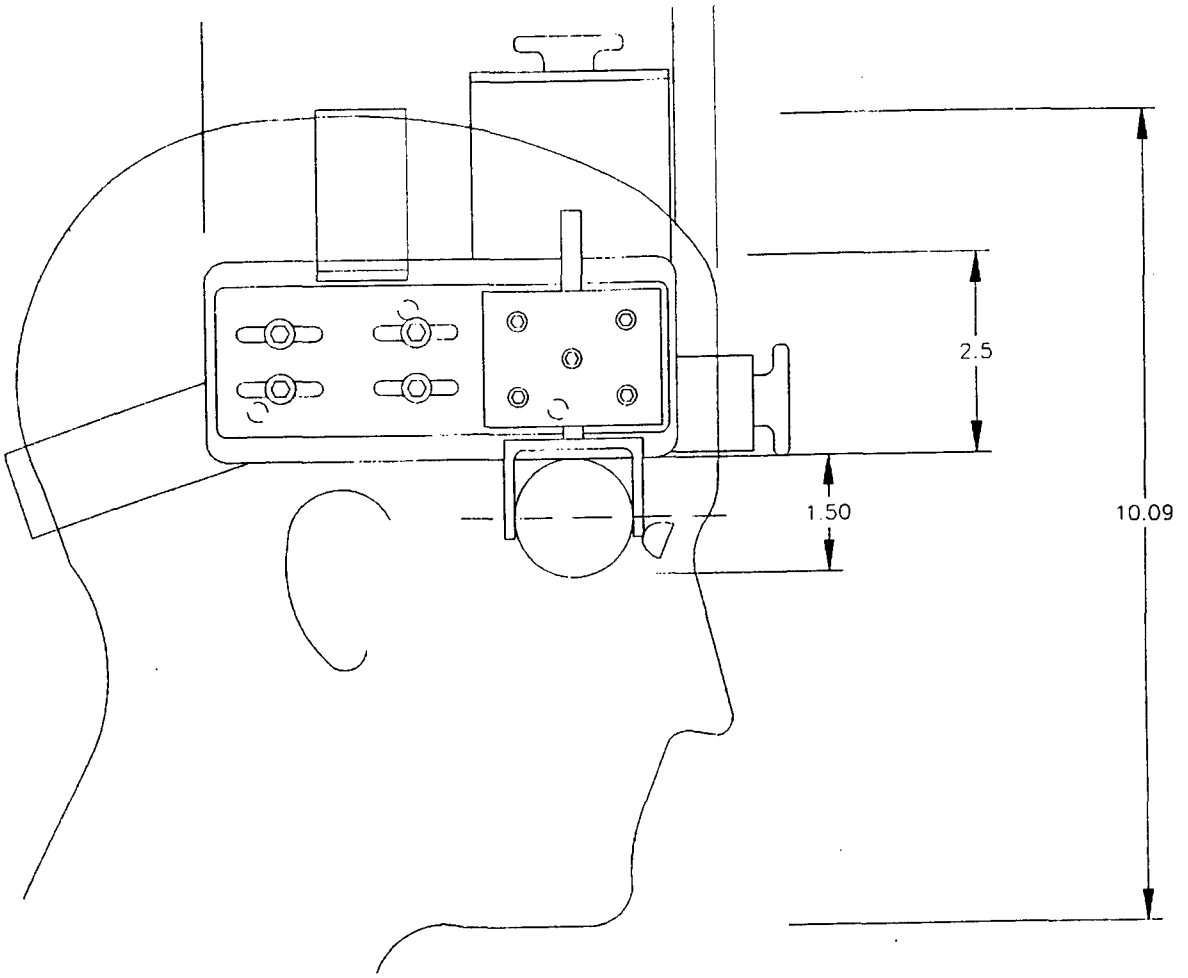


Figure 1. Concept drawing of cranial vault interrogation sensor suite.

The transmitting pods disposed against each temple consisted of impedence matched coupling elements with appropriate transducers for ultrasonic, low frequency acoustic and DC displacement measurements. Ultimately, as we accumulated evidence from our parallel internally funded volunteer study, it became apparent that higher ensonification source levels and better coupling would be required for the low frequency acoustic studies. Accordingly, while the sensor pods were ultimately used for the DC skull distention measurements, the acoustic experiments were run with small speaker cones or variable reluctance elements substituted for the sensor pods. These devices generated a higher level of sound in the head, still far below safety and toleration levels, and maintained signal strength well out of the noise at every frequency across the band of interest.

The head brace, ensonification elements and pick-up sensor were thoroughly evaluated in our parallel internal study on adult volunteers and then used to test the low frequency acoustic method on human cadavers at the University of Maryland.

Based on our experience to-date with the acoustic interrogation helmet, both in our own volunteer studies and in the cadaver experiments, a number of potential improvements have been identified. The original purpose of the prototype device was to incorporate several different interrogation techniques into one fixture. These included resonance, impedance, DC strain and modulus, dynamic resistance and time of flight measurements. Two days of experimentation on cadavers uncovered a couple of shortcomings in the head brace, and these are being used as the starting point for the redesign. The first, which was somewhat of a surprise was that our design did have adequate provision for the insertion of invasive catheters, which, at least in the early clinical trials will be critically important for providing the measured calibration data. The second difficulty was that the helmet was simply too massive and unwieldy. Since this was a prototype unit and was not intended to even come close to the final fielded configuration, this was more a question of anticipated use than a design problem. The unit was built as a multipurpose fixture for selecting the most promising techniques and subsequently incorporating them into a simplified design.

The guiding principles for the new design will be:

- *Swept sine and broadband noise measurement techniques incorporated in a 'sweatband' design*
- *Lightweight, ease of application and removal capability*
- *Minimum of connectors and wiring*
- *Simplified electronics, reducing the acquisition system to a laptop system at the most*
- *Adapters for measurement options where necessary, such as time of flight measurement.*

Parallel Internally-Funded Effort on Adult Volunteers

To complement the work being performed on the SBIR program, Active Signal initiated an internally funded effort to continue its investigation of the low frequency acoustic interrogation technique on healthy adult volunteer subjects. ICP elevation was inferred but not measured, and was induced by head-down tilt on a teeter-totter arrangement (tilt table) capable of +45 through -45 degrees elevation. Other experiments were run with transient bilateral jugular occlusion. Throughout these experiments, it was recognized that while the ICP was being elevated, other collateral effects were also occurring. For example, in a head-down tilt experiment, it is obvious that the blood pressure to the head will also increase and the head will become engorged with blood. During bilateral jugular occlusion, the ICP will rise but the venous blood pressure will also increase.

In most instances, ensonification was accomplished with a swept sine generator feeding a transducer coupled to the head, while a remotely positioned sensor on another part of the head was used to measure the resultant signal after interaction with the brain.

It was observed that while there were distinct resonance patterns for all subjects tested, there was a substantial difference in pattern between individuals, presumably based on anatomical and

physiological differences. In addition, while the resonant frequency shifted a little with increased ICP, the magnitude and direction of the shift was not consistent or predictable and did not appear to correlate with the ICP change. This result is quite consistent with the frequency shift predictions for ICP increase with hydrocephalus. For moderate pressure increases (of the type expected from postural change in normal subjects) the calculated amount of frequency change with pressure is negligible. Only when pressures rise into the hydrocephalus range (gamma > 0.25)is there a measurable drop in frequency. On the other hand, at the dominant resonance of the individual, no matter where the resonance appeared, there was significant attenuation of the signal when the ICP was elevated in the head-down tilt position.

The plot in Figure 1 is an example of swept sine excitation yielding low frequency resonance and attenuation data using head-down tilt to elevate ICP, and Figure 2 is an example of the same phenomenon using a broadband noise input on a supine volunteer in whom the ICP had been raised using transient bilateral jugular vein occlusion.

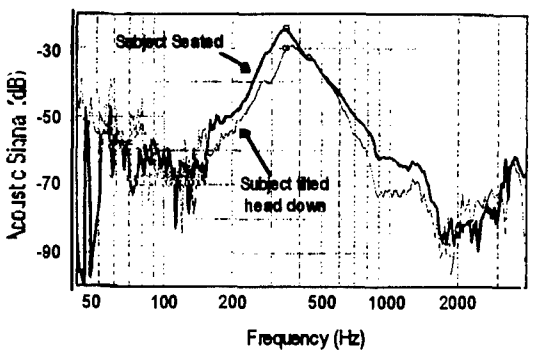


Figure 1: Acoustical attenuation of low frequency cranial resonance (swept sine excitation) in female adult volunteer with ICP elevation induced through postural change

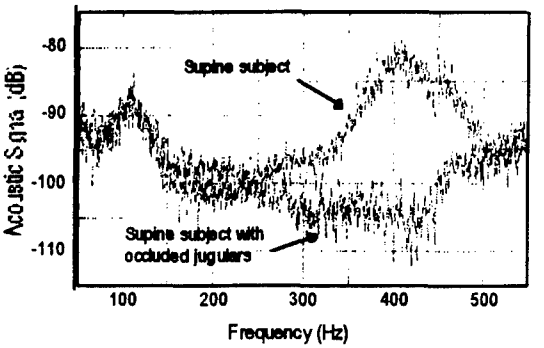
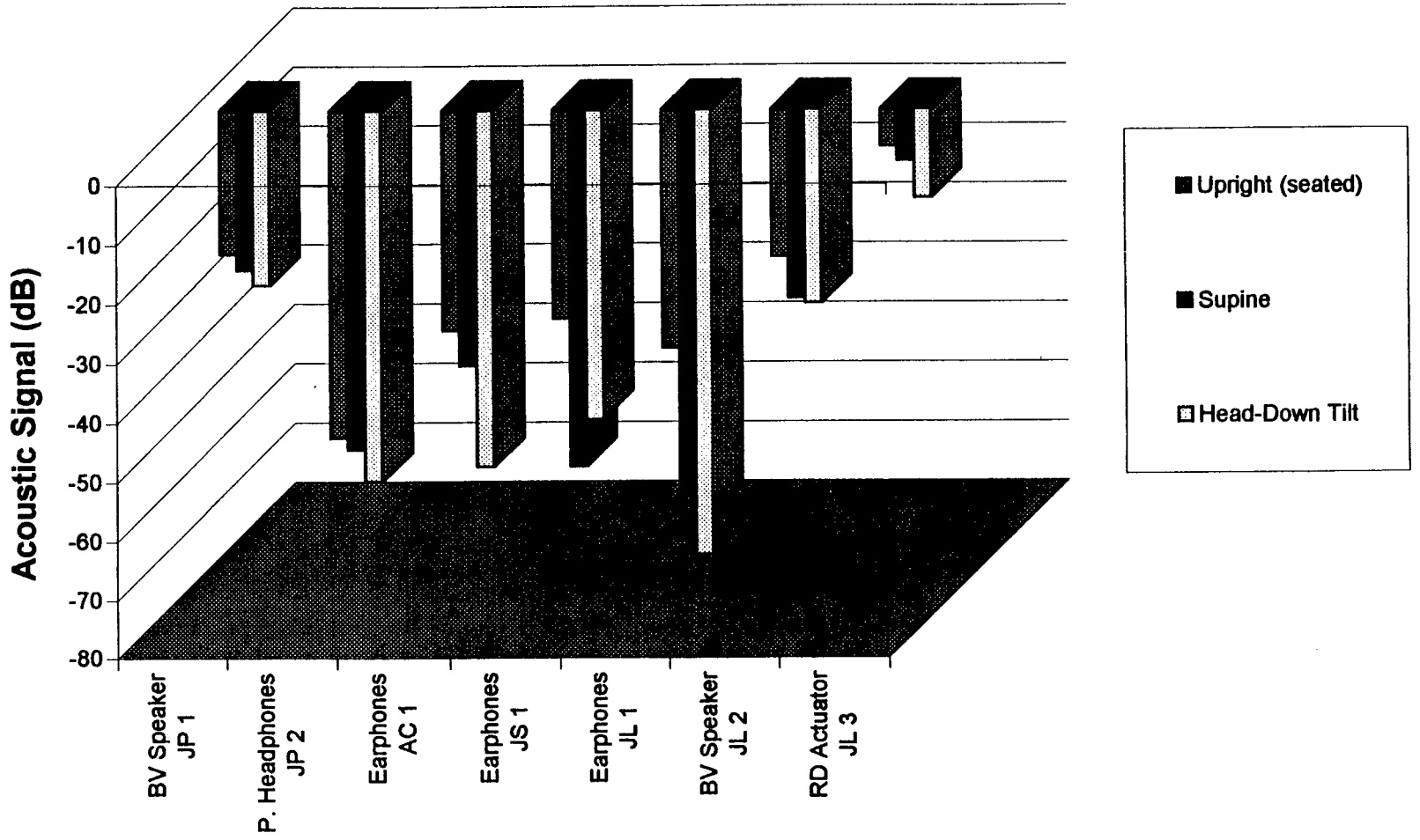


Figure 2: Increasing acoustical attenuation (broadband noise excitation) in an adult male volunteer with ICP elevation induced through jugular occlusion

The results clearly demonstrate that the same type of low frequency attenuation can be obtained with two types of acoustical excitation (swept sine and broadband), and two methods of inducing ICP increase (head-down tilt and jugular occlusion). It should be noted, particularly in Figure 1, that while the difference in signal strength appears small on a dB scale, the actual measured voltage difference is very large on the signal analyzer.

The data below compares attenuation measurements using a variety of different ensonifier / sensor combinations on a number of different subjects in the upright, supine and head-down-tilt positions. With one exception (data point JL1, where the settings on the analyzer were changed during the course of the experiment), the results show a consistent trend of greater attenuation with increase in posturally imposed ICP.

Acoustic Attenuation with ICP Increase in Head-Down Tilt Experiments



Cadaver Studies

The low frequency acoustic approach for measuring ICP non-invasively was assessed experimentally with a custom-designed active interrogation head brace in a study on three fresh cadavers with externally induced ICP elevation, with and without blood circulation through the parenchyma.

Experimental Set Up and Methods

The custom head brace above in Figure 1, was designed and built for the cadaver studies to accommodate the various equilibrium and dynamic modalities under investigation. The brace is capable of assessing resonant frequency, resonance shifts, attenuation, driving impedence changes, and velocity of sound, and can be operated in a swept frequency, broadband noise or impulse excitation mode. In addition, by virtue of its rigid metal frame, the unit can interrogate skull displacement and apparent skull modulus changes with ICP by substituting specially constructed and instrumented oil filled cavities to measure subtle amounts of oil displacement. To establish the optimum driving and sensing device types, a variety of different actuator (ensonifier) and sensor combinations, including piezoelectric bimorphs, motion amplified piezo disks, voice coils and variable reluctance drivers were tested in our parallel internally funded experiments on healthy volunteers. The ultimate configuration employed a low impedance bimorph forehead sensor and two variable reluctance drivers, one on each temple, for ensonification experiments, and a hydraulic syringe, pressure sensor arrangement with oil-filled urethane window pods for the displacement measurement.

While we had initially planned to use severed cadaver heads for our measurements, a decision was made later in the program to use whole cadavers in order to preserve as much normal anatomy and physiology as possible for the test. The use of whole cadavers also simplified the experimental issues associated with blood circulation and fluid / pressure sealing of the head. Three fresh cadavers (36-72 hours after death) were used without fixation at the Maryland State Anatomy Board employing two models of ICP elevation. The hydrocephalus model was accomplished by inserting a ventricular catheter for infusion of artificial CSF (Ringer's lactate solution) at controlled pressures. The epidural hematoma or expanding mass model was accomplished by inserting a Fogarty balloon catheter through a burr hole into the superficial brain parenchyma; the balloon was inflated to as much as 43cc volume with either whole blood or saline solution. Intracranial pressure was measured using a standard fiber optic ICP sensor (Camino Laboratories, San Diego, CA) within the ventricular catheter. To simulate cerebral circulation, the internal carotid arteries and the jugular veins were cannulated to permit circulation of whole blood (expired units from the Red Cross) or saline solution through the cerebrovascular bed using a pulsatile bypass perfusion pump.

Acoustic and ICP measurements were obtained under six conditions:

1) Baseline with no ICP elevation or simulated cerebral circulation

2) ICP elevation from CSF infusion (hydrocephalus model) **without** simulated cerebral circulation

3) ICP elevation from Fogarty balloon inflation (epidural hematoma model) **without** simulated cerebral circulation

4) ICP elevation from CSF infusion (hydrocephalus model) **with** simulated cerebral circulation

5) ICP elevation from Fogarty balloon inflation (epidural hematoma model) **with** simulated cerebral circulation

6) ICP elevation resulting from simulated cerebral circulation alone (i.e. without supplemental ICP elevation from CSF infusion or Fogarty balloon inflation).

Results and Observations:

Compared to baseline measurements, there was no appreciable acoustic change with ICP elevation as much as 100 mm Hg (and higher) in the hydrocephalus model or the epidural hematoma model, ***without*** simulated cerebral circulation. On the other hand, there was a marked acoustic attenuation with ICP elevation in both the hydrocephalus model and the epidural hematoma model ***with*** simulated cerebral circulation. We also observed that ICP became elevated to 100 mm Hg or higher, and there was significant acoustic attenuation compared to baseline during simulated cerebral circulation at very low flow rates (0.1 - 0.2 liters/min) without CSF infusion or Fogarty balloon inflation (Figure 4). As the flow rate was increased, the ICP rose and the acoustic attenuation became more marked.

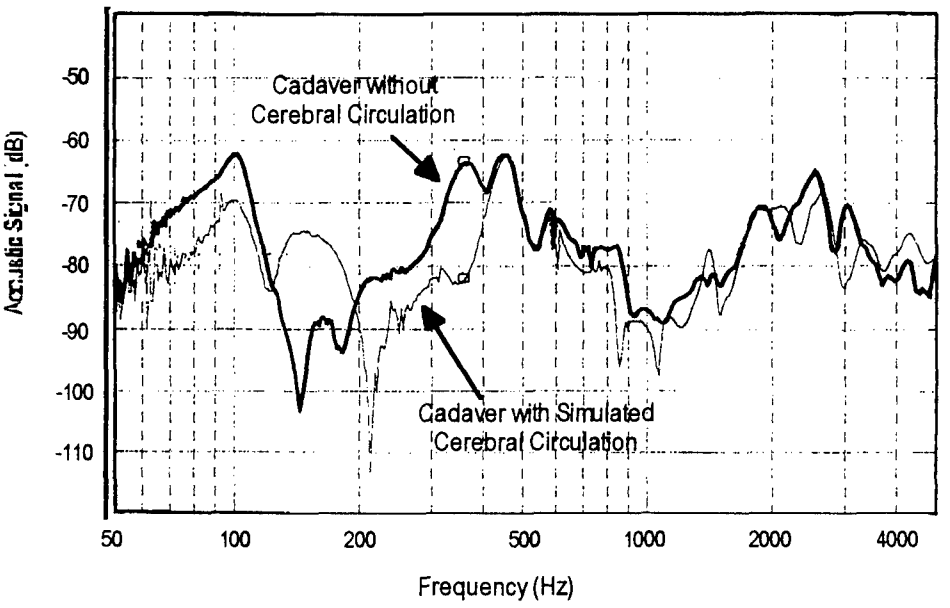


Figure 4: **Effect of Increase in Imposed Flow Rate of Ringers Lactate through the brain on Measured Acoustical Attenuation**

Additional observations were made during the use of the bypass pump to perfuse the head. There was little, if any venous return, but there clearly was development of facial edema in addition to the rise of ICP with ongoing simulated cerebral circulation. From this, we believe that the brain was also becoming edematous from increase in interstitial water as the perfusion continued.

Discussion and Proposed Mechanisms

Two alternative mechanisms can be proposed to account for the acoustic activity associated with imposed cerebral circulation.

1) Brain Water Content Hypothesis:

The observation of extensive edema suggests that the changes detected acoustically are primarily related to change in brain water content. The absence of brain water content change in the hydrocephalus and Fogarty balloon inflation models is consistent with the lack of acoustical change. The hydrocephalus model infused CSF only into the ventricular cavities, but there probably was no significant change of the water content of the brain because the CSF was contained within the ventricles. Likewise, Fogarty balloon inflation only added mass to the intracranial vault and displaced brain, but did not change brain water content. Thus the absence of acoustic change with these models also supports the hypothesis that change in brain water content is the variable most closely linked to change in acoustic attenuation as ICP is elevated.

2) Cerebral Blood Volume Change:

An alternative, or supplemental hypothesis is that simulated cerebral circulation resulted in change in cerebral blood volume in the cadaver. However, the relationship between intravascular volume (i.e. cerebral blood volume), edema and ICP after the start of brain perfusion is unclear. Several different hypotheses (see a), b) and c), below) can be advanced that are consistent with the data. The theories each make the following assumptions about the initial state of the cerebrovascular bed in the cadaver:

> *1) It is flaccid and essentially collapsed at baseline, and*
>
> *2) The blood brain barrier is partially or completely disrupted throughout, which means that interstitial edema formation from transluminal pressure occurs very easily (The Director of the State Anatomy Board advised us prior to the experiments that brain edema would develop during brain perfusion.).*

a) One hypothesis is that initially the arterioles and possibly capillaries would distend, followed by the venules and veins. If this is true, then the experimental data would be consistent with the theoretical model we developed which associates the acoustic activity of the brain with the blood volume and the amount of distension of the vascular bed. The flaccid, collapsed vascular bed in the cadaver prior to perfusion does not display much interaction with the incident acoustic pressure waves. In addition, simple compression of the parenchyma by ventricular distension from the hydrocephalus model or Fogarty balloon inflation in the epidural hematoma model would be predicted to have little effect on attenuation or resonance phenomena. But as soon as simulated cerebral circulation is begun, acoustic attenuation is detected at the same time that ICP rises.

b) The other proposition would be that the longer the perfusion, and thus the more the interstitial edema, the smaller the cerebral blood volume would become because perivascular interstitial edema would presumably lead to some collapse of the vessels. According to the Starling resistor model, the

vessels should collapse after ICP exceeds ~50 mm Hg-- provided they behave like living vessels.

c) Since there is no way of confirming either of the above hypotheses about the state of cerebral vessel distension as perfusion persists, a reasonable alternative hypothesis is that the intraluminal and extraluminal pressures reached a point of equilibrium so that a certain amount of vessel distension (and thus cerebral blood volume) was maintained during perfusion. Further studies on animals or human subjects will be necessary to elucidate the mechanisms.

Summary and Conclusions

The significant findings of the cadaver experiments are that acoustic attenuation occurred as ICP rose during simulated cerebral circulation. We postulate that this is due either to an increase in cerebral insterstitial edema or to distention of the cerebral vascular. No acoustic attenutation was seen with the hydrocephalus or epidural hematoma models of ICP elevation in the absence of simulated cerebral circulation. Although the exact cause of acoustic attenuation associated with cerebral perfusion in the cadaver is not yet known, either of the mechanisms hypothesized to explain the acoustic change would occur in live humans during acute traumatic brain injury. Thus we conclude that we have proven feasibility of a method for non-invasively detecting ICP elevation or significant changes in brain parenchyma that would occur in traumatic brain injury.

Pulse Wave Velocity and Associated Methods

A variety of measurements were made during the course of the program using a special configuration of fiber optic coupler which behaves as an extremely sensitive displacement gage. The all-optical device has a sensing area of about 1 cm in diameter where impinging pressure waves modulate the light coupling ratio of the fiber optic coupler. Photodiodes and transimpedance amplifiers convert the optical signal into a voltage signal which is measured and recorded using a computer-mounted 16 bit D/A card. All data were collected at a rate of 256 Hz.

Based on early discussions within the team, a potentially promising avenue with regard to the measurement of an accessible parameter proportional to the ICP, or change thereof, was explored. Heart beat signals collected on the neck are a superposition of two pulses, one traveling up the carotid artery while the return pulse travels down the jugular vein. One observes a typical heartbeat signal in the upright position, indicating either an essentially complete overlap of the two pulses or the absence of the return pulse as it is too weak to be observed. Since the delay time between up and down pulse depends among other things on the ICP, changes in the ICP should produce changes in the line shape of the composite heart beat signal if two pulses are present. To investigate these considerations, heart beat spectra collected at the neck and, for reference, at the wrist were obtained for different body positions (upright, laying flat, and inclined down).

Figure 1 presents three traces of the neck heart beat signal for three body positions. The line shapes of the pulses change noticeably as the body changes from upright to flat to downward inclined and the pressure increases. While each heart beat pulse in the upright position rises sharply and smoothly, for the flat position and the downward inclined position a noticeable bulge develops in the front section of each heart beat, significantly broadening the line shape. Figure 2 presents two traces, taken at the wrist, in the upright position and the laying flat position. The traces are qualitatively the same as would be expected, since no superposition of pulses is possible here.

The change in pressure between the upright position and the laying flat position should be on the order of the distance between the brain and some body centroid, probably in the vicinity of the heart. That distance is in the case of the subject of these measurements, Dr. Baruch, on the order of 450 mm. According to Dr. Pearce of Walter Reed Hospital, a pressure change of 1 mm corresponds to a pulse time delay change of about 1 millisecond. A very rough estimate of the pressure change would therefore predict time delay changes on the order of hundreds of milliseconds.

To facilitate measuring the changes in the line shape widths, the second derivative of the line shapes taken in the upright and the downward inclined position was taken, resulting in sharp peaks at the maximum slope sections of the primary heartbeat section. The results are presented in Figure 3. The line shape's width increased from about 210 milliseconds to about 310 milliseconds by changing the body position from sitting upright to downward inclined, in line with the order of magnitude estimate given above.

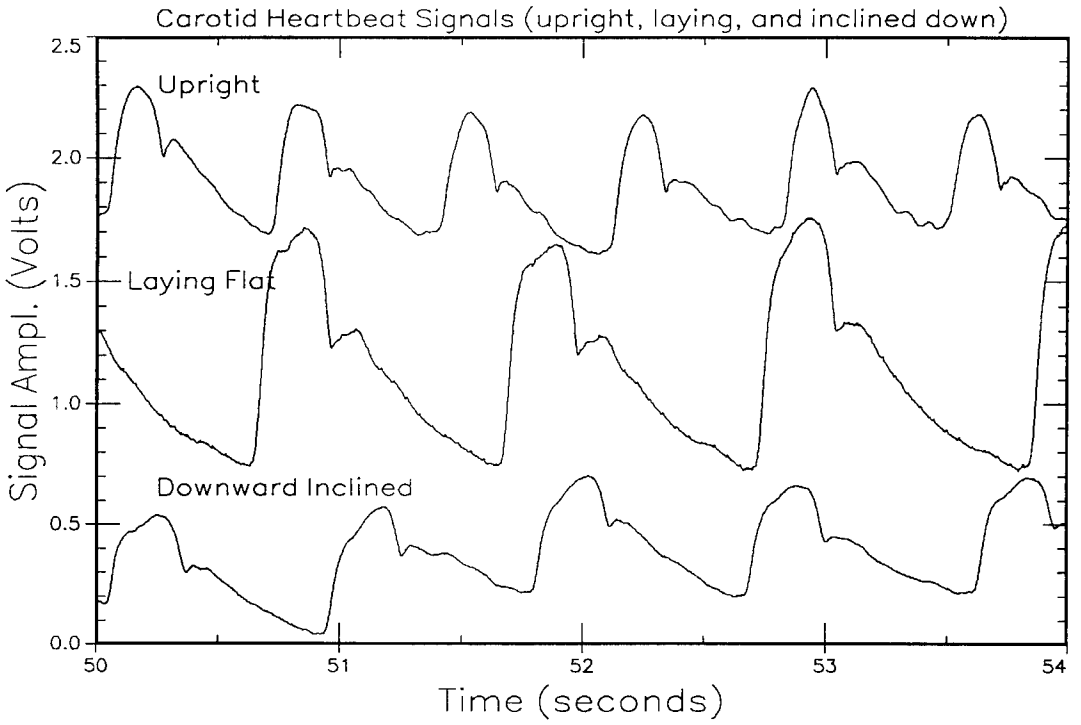


Figure 1: Carotid heartbeats for three positions: sitting upright, laying flat, and inclined downward.

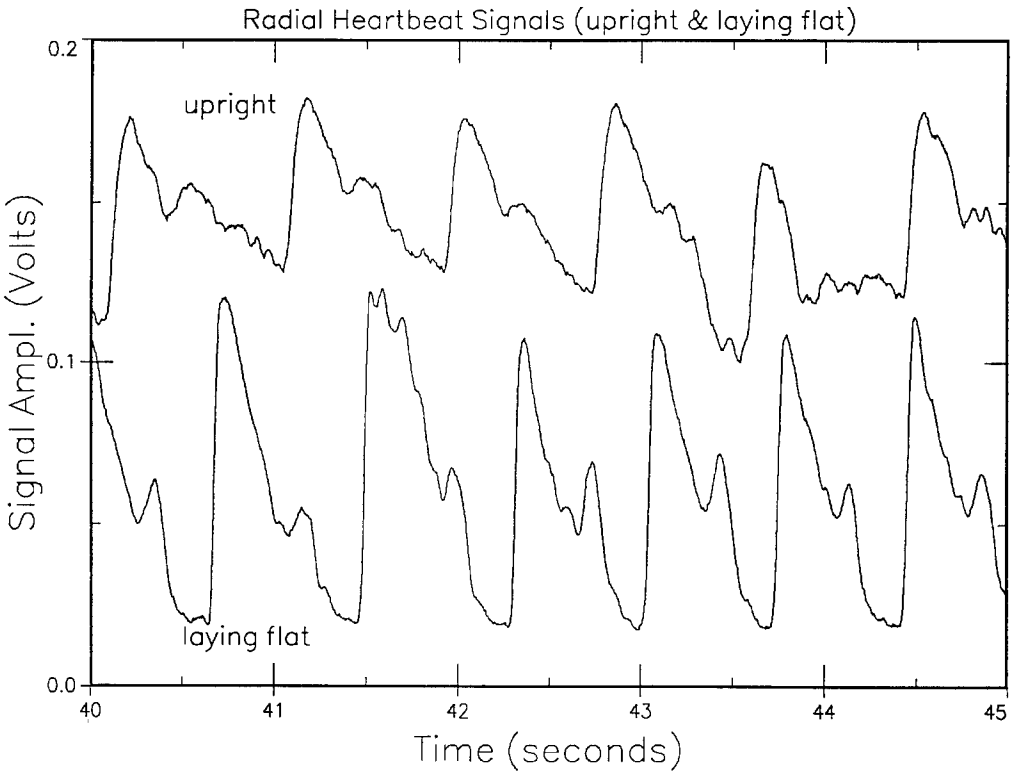


Figure 2 :Radial Heartbeats for two positions: upright and laying flat

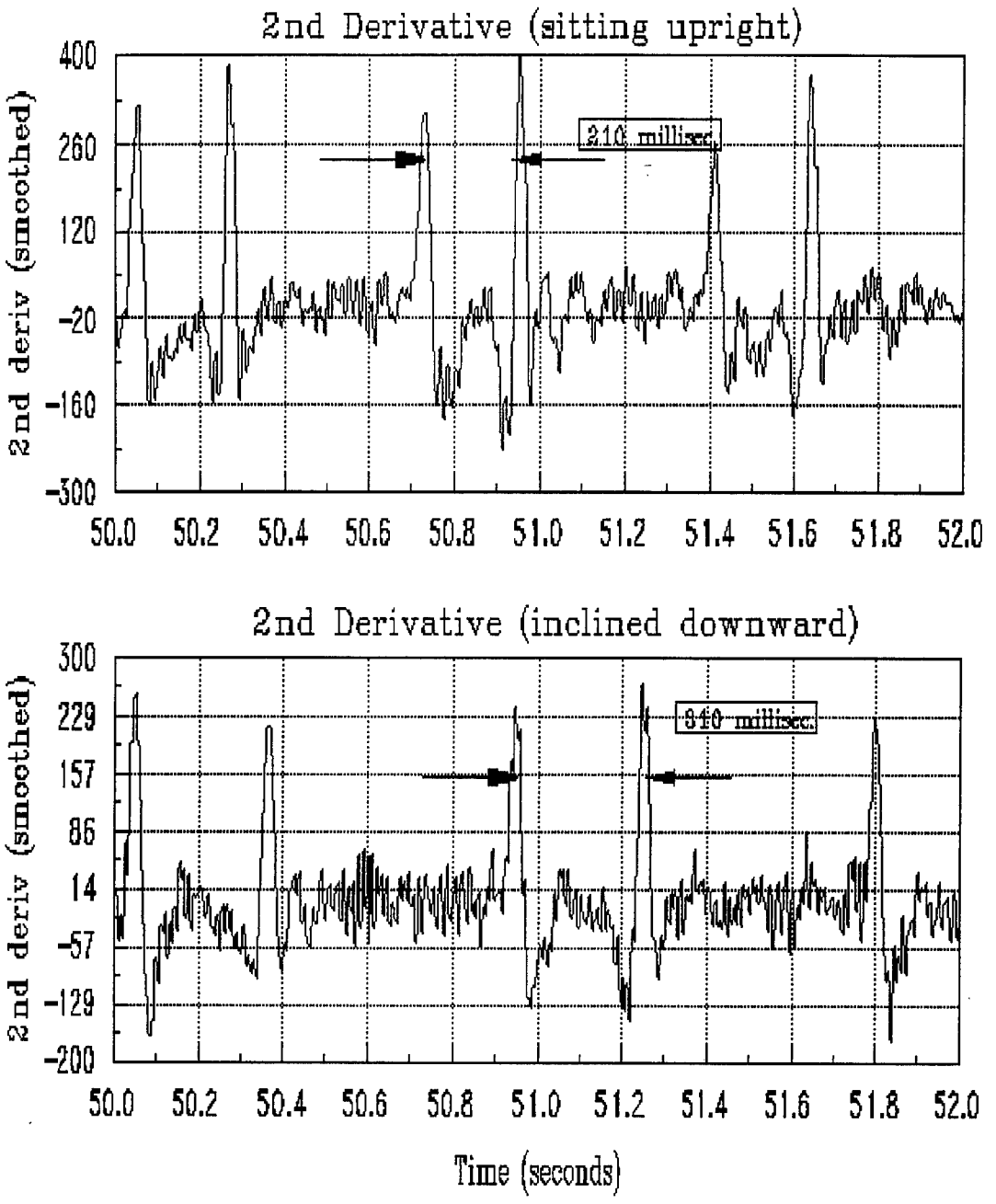


Figure 3: Second derivatives of heart beat traces in Figs. 1 & 2; top: upright position; bottom: inclined downward

Further data were collected while holding breath and while pushing on the jugular, two methods to raise the ICP. In contrast to position changes, which change ICP, venous pressure, and arterial pressure, these methods change only the ICP and the venous pressure. While dramatic changes in the heart beat spectra were recorded, as presented Figures 1 & 2, there are no simple methods, position changes or similar, to independently raise the ICP. Final proof of feasibility can only be established if the ICP of a subject can be modified independently of other pressures , such as through chemicals, and measured with traditional methods while the presumed phase delay between the pulses is monitored.

Figure 1 shows the data collected at the neck while laying flat and breathing normally. Figure 2 presents the data collected after the subject held his breath for 10 seconds. The two spectra are qualitatively drastically different, Figure 2 showing what appears to be a new peak separated by about 300 milliseconds from the main pulse. However, none of the features in the spectra can be identified with certainty.

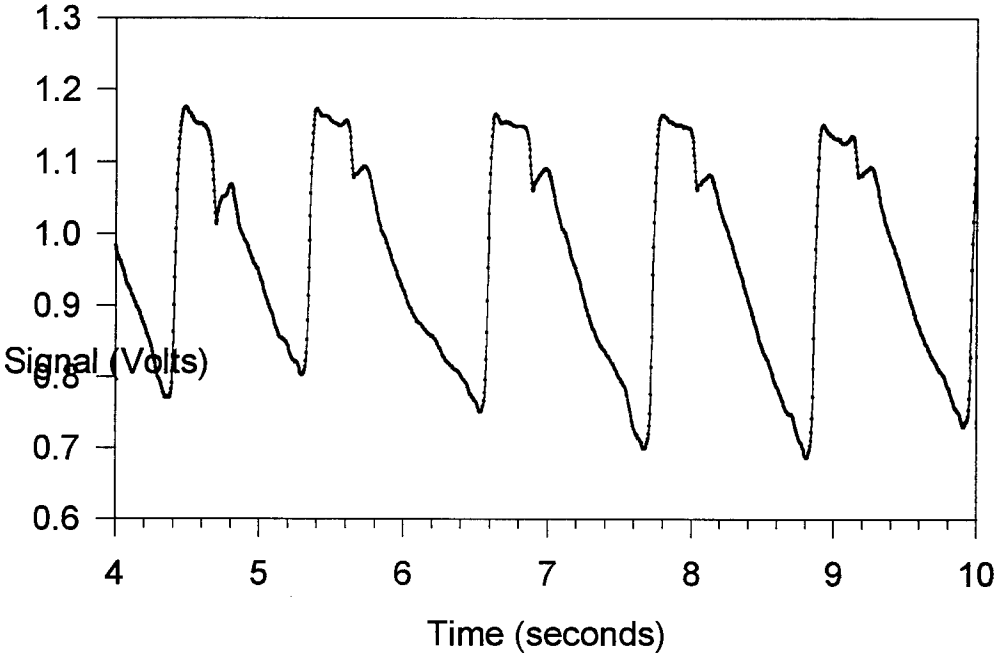


Figure 4: Carotid pulse - laying flat, normal breathing

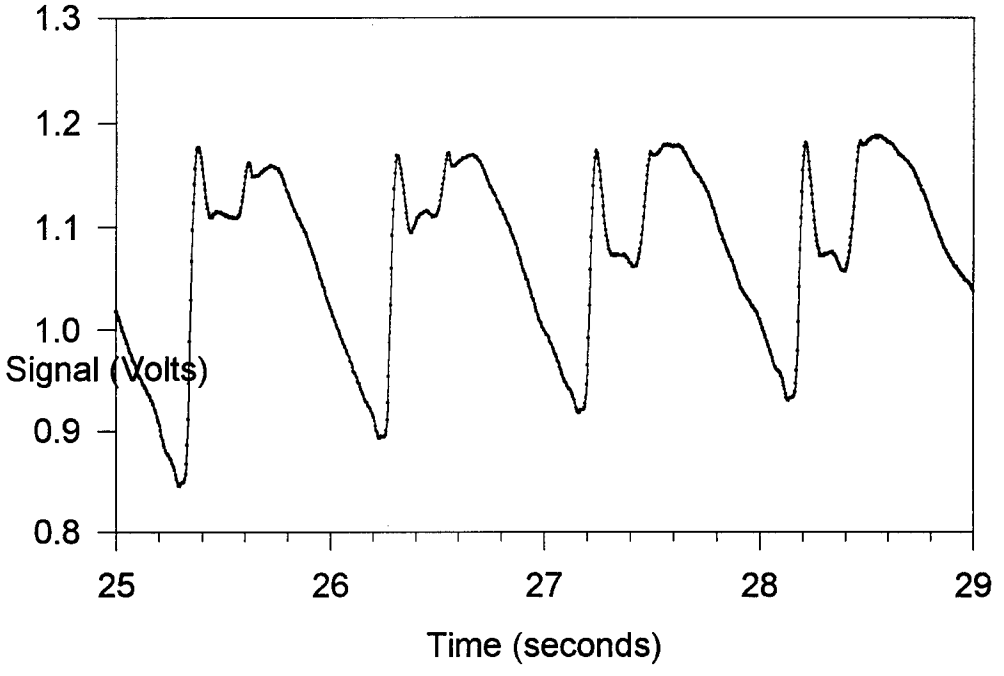


Figure 5: Carotid pulse - laying flat, after 10 seconds of not breathing

In order to make a more practical embodiment of the fiber optic coupler, applicable to live animal or human measurements, a different type of probe was designed in the form factor of a fountain pen with a hemispherical tip enclosing a coupler sensor. The pen body would eventually house the laser source, detector electronics, a liquid crystal display, and a signal processor. The pen would be held against the carotid-jugular pulse for a few seconds while a signal is acquired and analyzed. A measured time delay would be converted to an ICP level and displayed.

A sensor with a hemispherical cap of silicone rubber was constructed and used to test, subjectively, the ergonomic aspects of the system. The hemispherical cap does seem to make the pulse sensor much easier to use than the flat sensor. The flat sensors are definitely more prone to DC changes due to rocking the sensor back and forth as the sensor is being held by the hand. However, the flat sensors appear adequate for observation of the time shift between carotid and jugular pulses. Further improvements in the ergonomic properties of coupler sensor are expected with the advent of the fountain pen configuration.

The carotid pulse sensors shown below in figures 1. and 2. were built.

The sensor illustrated below shows a somewhat larger membrane area, ¾ inch, allowing a spherical cap to be secured to the membrane. Provisions were also added to allow for securing the sensor to the neck using tape (see figure 3). In the final package, the rear side of the sensor is protected by a plastic plate which protects but, otherwise, does not interfere with

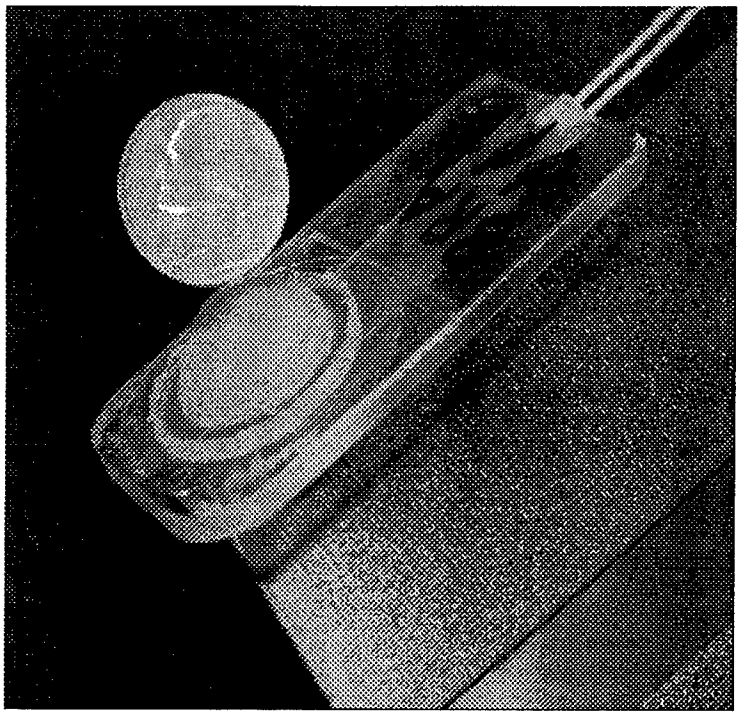


Figure 6: Carotid heart beat sensor with hemispherical coupling interface.

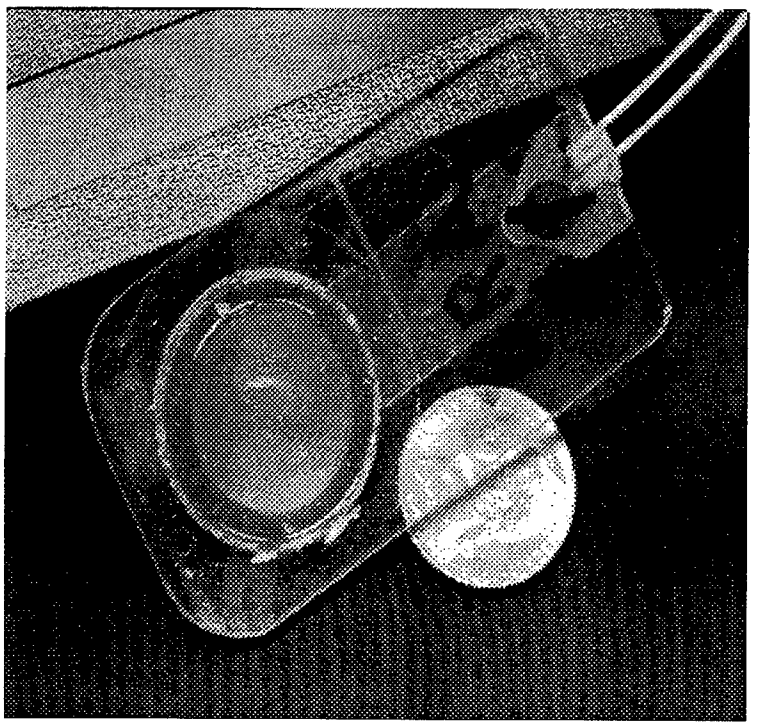


Figure 7: Different view of Figure 1 sensor.

movements of the membrane caused by the mechanical disturbance of the pulse. It should also be noticed that there are only two fiber optic leads. One lead feeds light to the sensor from the laser, the other goes to the detector. Reducing the leads to the sensor from three to two causes a marginal decrease in sensitivity but, results in a simpler package.

Figure 3 shows the complete package with the addition of a protective sheath surrounding the fiber optic leads. Figure 3 also shows the addition of fiber optic connectors used to interface the sensor with various measurement devices using standard ST type fiber optic connectors. This new sensor configuration has been shipped to WRAIR for their analysis.

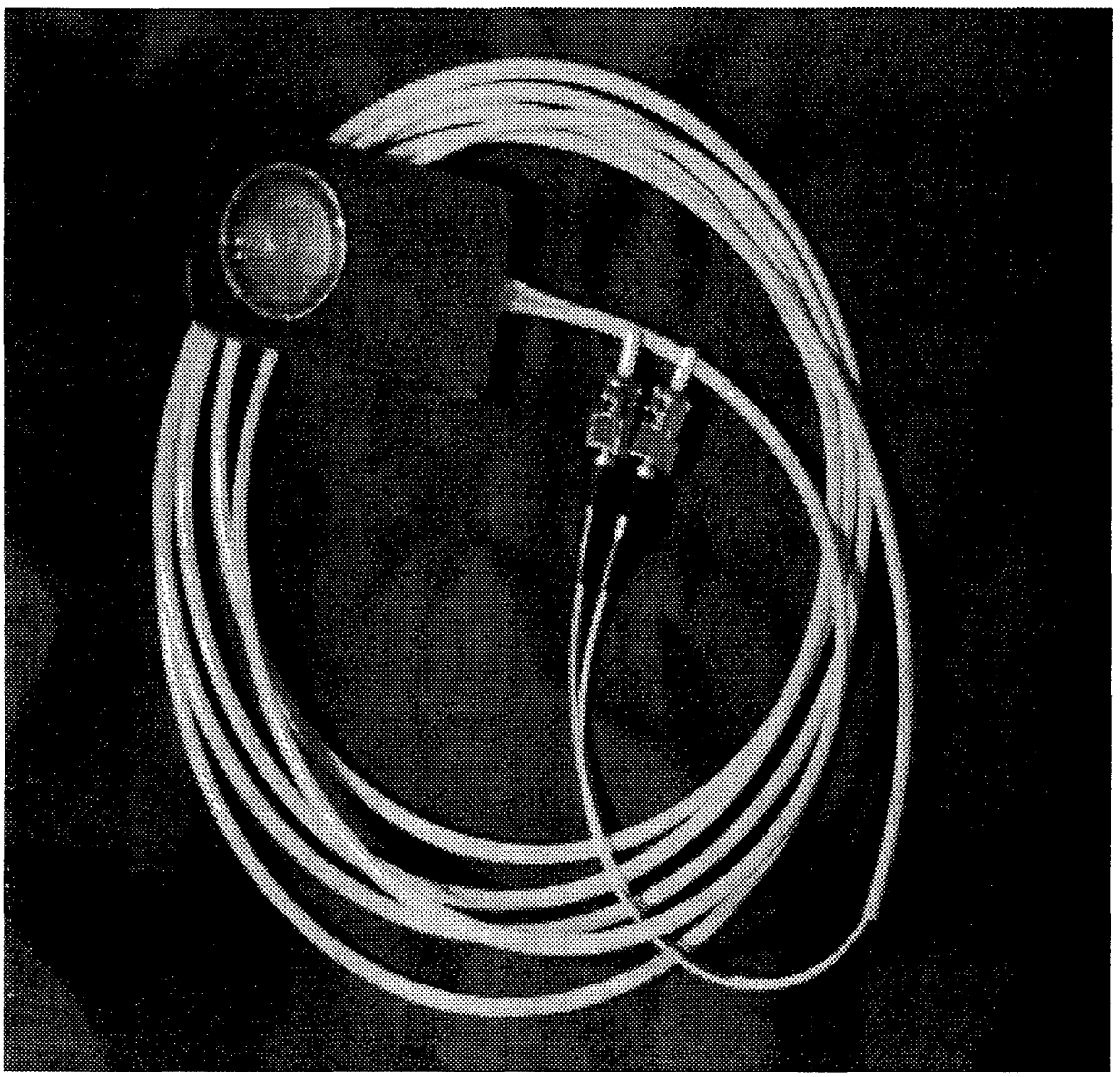


Figure 8 : Completed pulse sensor for ICP

Spinal Pulse Wave Velocity

Another approach that was attempted for measuring ICP was monitoring pressure signals in the spine area on the basis that within the heartbeat cycle a double pulse is present in the spinal column since the heartbeat-induced pulse in the CBF travels down the spinal column and is reflected at its end due a significant impedance mismatch. In principal it should be possible to observe both pulses and, since the pulse velocity is highly dependent on the ICP, the separation of the two pulses in time should be highly correlatible with the variations in the ICP.

The data were obtained using a fiber-optic coupler based heart beat sensor placed on the spine in kidney height since the best contact could be achieved there. The all-optical device has a sensing area of about 1 cm in diameter where impinging pressure waves modulate the light coupling ratio of the fiber optic coupler. Photodiodes and transimpedance amplifiers convert the optical signal into a voltage signal which is measured and recorded using a computer-mounted 16 bit D/A card. All data were collected at a rate of 256 Hz.

While a very rich spectrum of data was recorded (see Figure 1), no conclusions could be drawn from it and the experiments will be repeated, keeping the following considerations in mind. Since the pressure signatures of a number of other bodily functions appear in the spectrum, it will be necessary to employ two sensors during the next run. One sensor will record a heartbeart signal with high S/N (such as at the wrist), while the other will be placed on the spine just below the neck. By correlating the "good" heart beat spectrum with the spine data, it may be possible to extract the heartbeat related components, rejecting other spectral components. Placing the spine sensor below the neck should remove the major shortcoming of the first run, namely, that, assuming a pulse velocity of ~275 inches/sec. , and a "duty cycle" of ~30% for a heartbeat pulse with a repetition rate of 1 Hz, a sensor placed at kidney height would observe two broad pulses separated by only about 43 milliseconds, making them essentially indistinguishable (see Figure 2). By placing the sensor in neck height, a delay of ~142 milliseconds can be achieved, which should be sufficient to resolve the two pulses. Figure 2 is an artificial spectrum showing the overlaps of two Gaussian pulses with a duty cycle comparable to a 1 Hz heartbeat.

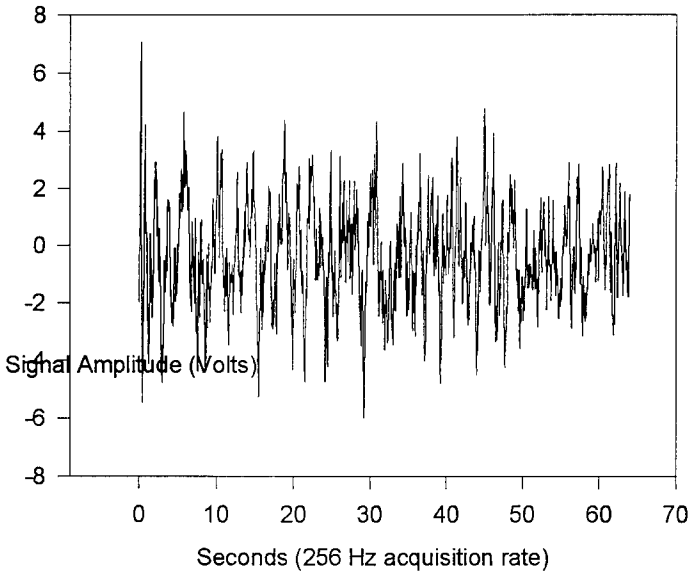


Figure 9: Spine data collected with fiber optic sensor

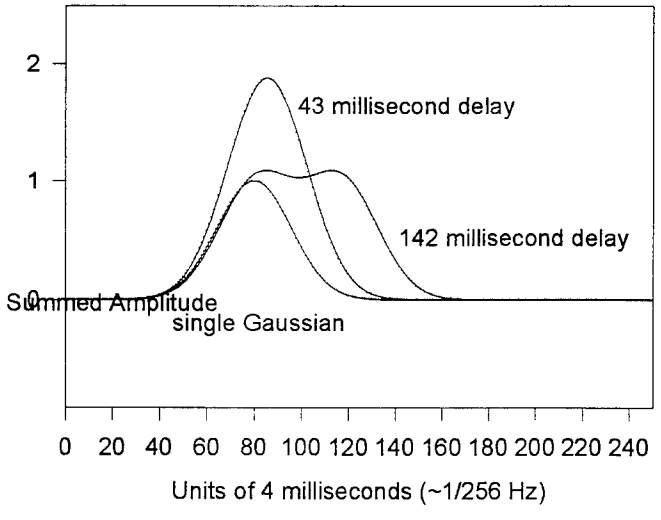


Figure 10: Overlap of representative Gaussian pulses

Section IV

Conclusions

While the conclusions drawn from our evaluation of the candidate non-invasive interrogation techniques have already been discussed in detail in the section covering each of the techniques individually, it is still valuable to pull together an overall summary of our findings under the Phase I project.

- Measurement of blood pulse wave velocity through the brain by precision timing of the relative delay between carotid and jugular pulses continues to show potential as a measurement corresponding to elevated intracranial pressure. Since the technique is based on fine separation of overlapping pulse traces, more work is needed to identify precisely what the two traces represent and hence how the measure relates to ICP.
- Spinal pulse wave velocity as gaged by the travel time of a CSF wave in the lumbar space proved to be technically too demanding to pick up with the fiber optic coupler heart beat sensor. Numerous other competing biological signals of comparable or greater amplitude were mixed in with the lumber pulse and could not be readily deconvolved.
- Ultrasonic location of midline structures in the brain was dismissed prior to experimental evaluation because of the difficulty of accurately calibrating displacement versus ICP and the ambiguity in such a measurement with a medial contusion. Pineal displacement was also considered since the pineal gland has greater latitude of movement in 3 dimensions. However, the type of imaging system necessary to locate the pineal could not be readily made field portable.
- Skull distention as measured by pressure increase in calibrated pods pushed up against the temples showed definite potential to measure ICP increase. However, without benefit of an animal model or instrumented head-injury patient, it was not possible to determine how much of the observed pressure increase derived from engorgement in the fleshy tissue covering the temples and how much was truly ICP related.
- Low frequency acoustic interrogation continues to show tremendous potential versus every metric we have been able to apply in the Phase I program and should urgently be tested on head-injury patients with installed pressure measurement catheters. From a theoretical standpoint, our physiological and physical models predict the low frequency resonances actually observed in practice. The models also predict the direction and magnitude of attenuation and frequency shift with increasing ICP – trends that are fully consistent with every measurement we have been able to make to date. Consistent attenuation has been observed with head-down tilt and bilateral jugular occlusion. The same acoustic effects have also been obtained with swept sine excitation and broadband noise, and with a variety of different excitation sources.

Individuals receiving pay under this project:

Arthur Cooke
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August 14, 1997

VIA FEDERAL EXPRESS

Commander, US Army Medical Research and Materiel Command
Attn: MCMR – RMI – S
504 Scott St.
Fort Detrick
MD 21702-5012

RE: Final Report
Contract # DAMD17-97-C-7023
MRMC SBIR Solicitation No. A96 - 132

"MULTI-SENSOR FUSED INTERROGATION OF BRAIN TO DETERMINE ICP LEVEL"

Dear Sir / Madam:

Enclosed please find the final report on the above referenced program submitted in accordance with the format and instructions of your letter dated July 11, 1997.

Sincerely

Arthur V. Cooke
President

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y) 4 Dec 02

MEMORANDUM FOR Administrator, Defense Technical Information Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir, VA 22060-6218

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1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for this Command. Request the limited distribution statement for the enclosed accession numbers be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

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FOR THE COMMANDER:

Encl

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Deputy Chief of Staff for
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