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Paper Session I-B - The Invention, Development and Commercialization of a Non-Invasive Intracranial Pressure Monitor

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The Invention, Development and Commercialization of a Non-Invasive Intracranial Pressure Monitor

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Introduction

Defining the Problem – Why is a non-invasive intracranial pressure monitor needed?

The monitoring of intracranial pressure and pressure volume index is of significant diagnostic and post-operative importance for many patients with cranial injuries and for patients who have undergone brain surgery. Cranial injuries often affect the pressure of the subarachnoidal fluid around the brain. Abnormally elevated intracranial pressure (ICP) occurs in about 60% of patients with head trauma. When ICP increases above 20mmHg, a 95% death rate occurs. High ICP reduces blood flow to the brain, preventing oxygen and nutrients from reaching brain tissue. This "starvation" results in the death of brain tissue.

ICP is now measured in several ways, all of which are invasive. The most common method uses a catheter-mounted pressure sensor inserted through a small hole drilled in the skull. To obtain a pressure volume index (PVI), the change in ICP is monitored after a known volume of saline solution is inserted into the cerebrospinal fluid. This simple procedure is not suitable for long term ICP monitoring because it creates and maintains an open wound that can easily become infected. Because antibiotics are only partially effective in treating intracranial infections, the implanted pressure sensor can only be left *in situ* for periods of two weeks or less.

Longer term monitoring of ICP is possible if a pressure sensor with a transmitter is implanted in the brain. The surgical opening is then closed and ICP can be monitored via a receiver located outside the patient's body. Such a solution is unattractive because of the risks involved in implanting anything in the cranial cavity and because of problems with providing power to the implanted transmitter.

There are several indirect methods for non-invasively monitoring ICP. These all measure quantities that depend on ICP, but do not have a fixed relationship with ICP. These indirect methods can be used as indicators of ICP, but absolute values of ICP cannot be obtained by these methods.

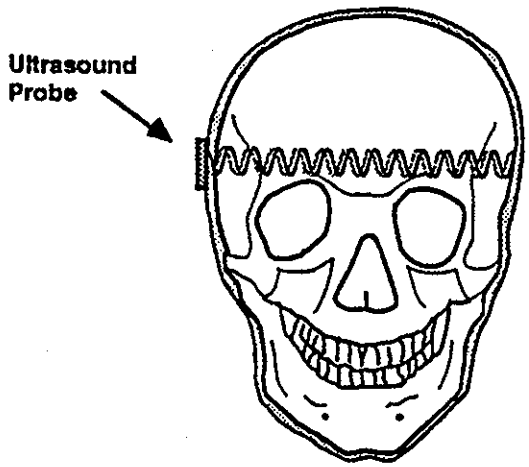
In summary, then, current ICP monitoring methods are either (1) invasive and measure absolute ICP, or (2) non-invasive, but cannot measure absolute ICP. Thus, a non-invasive ICP monitor that can measure absolute ICP would be a substantial improvement over currently available methods and monitors.

The Inventions

a. A "Non-Invasive Method and Apparatus for Monitoring Intracranial Pressure and Pressure Volume Index in Humans" is an invention made by NASA Langley Research Center (Langley) employees and protected by U.S. Patent No. 5,617,873. This invention provides a basis for subsequent NASA inventions by establishing a method for calculating ICP using an equation derived from an earlier equation describing the relationship between ICP and the cerebrospinal fluid volume. Several methods for non-invasively introducing known changes in cerebrospinal fluid volume are described in this Patent. Absolute values for PVI and a steady state ICP can be determined by this method.

b. A "Constant Frequency Pulsed Phased-Locked Loop Measuring Device" is another invention made by Langley employees. This invention is protected by U.S. Patent No. 5,214,955. This invention is very important because it can measure distances very accurately and can detect very small changes in those distances. This invention provides the "calibrated measuring device" required by Patent 5,617,873. A graphic representation of how this device uses ultrasound to measure intracranial distances is shown in the figure below.

A Pulse Phase-Locked Loop Concept for Measuring Changes in Intracranial Distances



Variable Frequency PPLL
(constant phase)

$$\Delta l = l\left(\frac{\Delta v}{v} - \frac{\Delta f}{f}\right)$$

Constant Frequency PPLL
(variable phase)

$$\Delta l = l\left(\frac{\Delta v}{v} - \frac{\Delta \phi}{\phi}\right)$$

l = ultrasonic path length
f = ultrasonic frequency
v = sound velocity in brain tissue
Φ = phase of received ultrasonic wave relative to reference wave

c. "Optimization of Ultrasonic Method for Assessment of Changes in Intracranial Pressure through Measurement of Skull Expansion" is an invention made by NASA employees (Langley and Ames Research Center) and employees of the University of California at San Diego. It is protected by a Patent Application. This invention provides additional capabilities used by the NASA ICP Monitoring System.

Commercialization

a. Selecting a Commercial Partner and Patent Licensee

After the NASA Technology Applications Engineering Program had matured this technology for three years, it was decided that it was time to select a commercial partner. The role of the commercial partner at this stage of commercialization is to work with us to further mature and test the technology, and to build a prototype product monitor. This prototype will be used to obtain clinical data required for Food and Drug Administration (FDA) review and approval. In most cases the commercial partner that works with NASA to mature the technology will also becomes the patent licensee.

Initially, we took a direct approach to marketing this technology, i.e. we identified the principal U.S. manufacturers of intracranial pressure (ICP) monitors and discussed the technology and its potential markets with key manager(s) at those companies. Our technology assessment and commercialization contractor, the Technology Applications Center at Research Triangle Institute (RTI), was very helpful in identifying the companies and establishing the right contacts at those companies. However, we had little success in interesting those companies in partnering with Langley to further develop and commercialize this technology. There seemed to be two primary reasons why this approach was not successful. First, this is a revolutionary approach to intracranial pressure measurement, and thus its commercialization could be fraught with obstacles such as the FDA Pre-Market Approval process instead of the 510(k) process. Second, the manufacturers of invasive ICP monitors have a large financial stake in their current products and are thus reluctant to embrace a technology capable of replacing those products in the ICP monitor marketplace.

Our second approach was to use a locally developed marketing tool called the Commercial Opportunities Program (COOPPR) process. This process casts a much wider net in its effort to attract companies interested in working with Langley to mature a technology with the goal of producing one or more commercial products. In addition to those companies currently in the target market, other capable manufacturers having an interest in expanding their product line to compete in the target market are also contacted. In this case, a group of technologies developed at Langley and targeted toward the medical market were marketed by the COOPPR process. About 50 medical manufacturing companies were identified and contacted to determine if they might be interested in commercializing one or more of the technologies. The RTI Technology Applications Center also supported this process. Those companies that expressed an interest in commercializing one or more of the Langley medical technologies were invited to a technical briefing at Langley where they were able to learn more details about the technologies, see prototypes in operation, and ask the inventors questions. In addition, the company representatives were also provided information about the COOPPR process, including the requirement to submit a commercialization plan or patent license application, and the selection criteria to be used when more that one company was interested in the same technology.

As a result of the COOPPR process approach, several companies expressed interest in commercializing the ICP technology. They were invited to submit either a commercialization plan or a patent license application within 60 days of the technical briefing. At the end of that period only one company, Kinetic Concepts, Inc. (KCI), of San Antonio, Texas, had submitted an application or a plan. KCI is one of the largest medical equipment manufacturers in the U.S., having 1997 sales of almost $307M, up 13.7% over 1996. KCI specializes in therapeutic surfaces that treat and prevent complications associated with patient immobility, for example pressure sores and the harmful buildup of fluid in the lungs. The ICP monitor would give them entry into an entirely new medical market. A review panel read KCI's proposal and found that it met our advertised criteria. The panel selected KCI as a qualified commercial partner and recommended them as a patent licensee, and they were so notified.

b. Patent Licensing

Since NASA Field Centers (Langley, Lewis, Ames, Johnson, etc.) do not have authority to grant patent licenses, the first step in licensing a patent is usually for the Field Center to recommend to the Associate General Counsel (Intellectual Property) at NASA Headquarters that NASA grant a patent license to the selected company. When the proposed license is an exclusive license, the recommending Center also must include a Notice of Intent to License for publication in the Federal Register. This procedure was followed for KCI. Federal law (37 CFR 404.1 et seq.) requires a 60-day waiting period after the publication of the Federal Register notice, to allow for the filing of objections. During this period, the terms and wording of the license can be negotiated between the potential licensee and the Center. One of the key points to be negotiated is the time allowed for the licensee to reach "Practical Application", i.e. the time needed before the licensee is ready to begin manufacture of the technology-based product. This period is usually based on the company's estimate provided in their patent license application, and can range from 6 months for very mature, non-medical technologies to 4 years for medical technologies at the proof of concept stage. For this commercialization effort the Practical Application period was originally two years, but was later extended to three years. Another key point to be negotiated is the "field of use" for the license. This term defines the restrictions in geography, market or applications within which the licensee may exercise its rights. The KCI license to U.S. Patent No. 5,617,873 is exclusive with no field of use restrictions.

c. Development of a Memorandum of Agreement (Space Act Agreement) with the Licensee for Joint Technology Development and Commercialization

Since NASA patent licenses do not traditionally provide a capability for establishing commercialization milestones other than Practical Application, a Memorandum of Agreement (MOA) between the licensee and the Center is often used to establish those interim milestones in a contractual framework. These milestones are designed to ensure prompt commercialization of the technology. The MOA usually exists for one or two

years, during which the licensee and NASA each may have as many as 10 milestones to achieve. Someone in the Commercial Technology Office at the Center or one of the Civil Service inventors drafts the MOA. In the Responsibilities Section of the MOA each milestone action is defined and a time is established for its completion. The MOA between Langley and KCI contains twelve commercialization milestones, five for Langley and seven for KCI. The period of the KCI-Langley MOA is two years.

These MOAs also establish mutually agreed upon goals for the joint development and commercialization effort, and guidelines for Property Rights in Data, Approval of Publications (by either party), Reporting Inventions, Property Rights in Inventions, and Liability claims. These MOAs are usually executed by the Field Center Director or his designee and the CEO or a Senior Vice President of the company. It is critical to the success of the commercialization effort that visibility be established and maintained at the highest possible level in the company.

d. Status of the Joint Development/Commercialization Effort with KCI.

This commercialization effort is being monitored and managed primarily through weekly telephone conferences between key individuals at Langley and KCI. As the Technology Lead for this commercialization, I have participated in most of these meetings. These meetings have been supplemented by occasional visits to Langley by KCI's key engineering and medical personnel. Decisions are usually made by consensus whenever possible. To date it has not been necessary to involve high-level managers in these meetings.

This joint development/commercialization work is proceeding satisfactorily. Technical problems are being solved and critical issues are being resolved. We are couple of months behind schedule, but there is potential for catching up on these postponed objectives later in the effort. The major challenge for KCI has been the evolution of the monitor from a rack mounted, proof of concept prototype system (requiring an experienced engineering technician to operate and obtain data, and a Ph.D. physicist to analyze the data) to a more compact, user friendly (operated by a nurse or a medical technician) system with internal data analysis and digital data output. Also, there a still a few data interpretation and algorithm development hurdles that need to be surmounted.