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A NEW PREDICTIVE MODALITY

OF CRANIAL BONE THICKNESS

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ABSTRACT

Previous research has demonstrated regional variations in the thickness of the calvarium which can adversely affect surgery in this region. An accurate intraoperative method of skull thickness measurement is not available to enhance the safety and efficacy of these procedures. The aim of this research represents the first attempt to examine the reliability of A-mode ultrasound for this purpose.

Acoustic measures of bone thickness were analyzed followed by serial modifications of existing ultrasound probes. Standardized calvarial sites were identified and marked for experimentation with human cadaveric and live animal skull models. The individual points were insonified using an appropriately calibrated A-mode ultrasound transducer. As a gold standard, these values were then compared with digital caliper measurements and assessed for accuracy, validity and reliability.

Statistical analyses revealed strikingly convergent values in skull thickness using A-mode ultrasound. These results clearly show that A-mode ultrasonic measurements are accurate, valid and reliable in predicting the thickness of the calvarium. This preliminary study can allow for the development of a **new predictive modality of cranial bone thickness.**

ABRÉGÉ

Des recherches antérieures démontrent bien la grande variabilité de l'épaisseur de la boîte crânienne. Ceci a des implications cliniques importantes en chirurgie. Présentement, il n'existe pas de méthodologie précise pour mesurer l'épaisseur du crâne et assurer une plus grande sécurité de certaines procédures chirurgicales craniofaciales. Cette étude à notre connaissance représente la première du genre ayant pour but de valider l'utilisation des ultrasons à mode-A pour cette application.

A l'aide de mesures ultrasoniques et de plusieurs modifications des appareillages déjà disponibles, les valeurs d'épaisseur osseuse ont pu être analysées. Des sites spécifiques prédéterminés ont été utilisés pour l'expérience sur cadavres de même que pour l'expérience subséquente sur modèle animal vivant. Toutes les données ont été recueillies à l'aide d'un transducteur calibré ultrasonique de mode-A. Ces valeurs numériques ont été ensuite comparées aux valeurs obtenues avec un vernier à affichage numérique digital.

L'analyse statistique de nos résultats démontre que les mesures par ultrason (mode-A) fournissent une précision excellente. Ces résultats démontrent bien les multiples avantages de cette méthode fiable, précise et valide pour prédire l'épaisseur optimale du crâne.

Cette étude préliminaire est à la base du développement d'un nouvel outil de mesure et de son application pour déterminer l'épaisseur crânienne en chirurgie craniofaciale.

PREFACE

This thesis represents original work generated by the author during the fourth year of Residency Training in the Departments of Surgery (Division of Plastic and Reconstructive Surgery) and Otolaryngology at McGill University, Montréal, Québec, 1996-1997. The experimentation described in this thesis document was performed jointly at the Plastic Surgery and Ultrasound Research Imaging Laboratories at the Royal Victoria Hospital, under the direct supervision of Dr. M.L. Lessard and Dr. K.L. Watkin, respectively. These laboratories are devoted to the investigation of basic science problems and their clinical science correlates, and has provided an excellent collaborative atmosphere for the completion of this work. The clinical application of A-mode ultrasound in the assessment of cranial bone thickness has been the original idea of Dr. M.L. Lessard for several years now. I am indebted to her for seeing fit to allow me to pursue this area of investigative interest. The experimental protocols to validate this tool have been conceived by both myself and Dr. Lessard, along with Dr. Watkin and Dr. Hakim. Dr. John Sampalis, Assistant Professor, Department of Clinical Epidemiology, McGill University, has assisted in data analysis, while the cadaver specimens were obtained from the Department of Anatomy, McGill University, through the efforts of Dr. G.C. Bennett. Technical assistance in caliper and ultrasound measurements were partially performed by Dr. Pascale Dubé. Special thanks to Dr. Jean Tchervenkov and Dr. Jonathan

Fridell, Department of Surgery, McGill University, who facilitated the use of porcine skulls for experiment # 2. This project was funded by a 1997 Resident Research Grant from the American Academy of Facial Plastic and Reconstructive Surgery. The work contained herein has been recognized with the Best Poster/Mini-Platform Presentation by the *Plastic Surgery Research Council (PSRC)* in Galveston, Texas (February 26 - March 1, 1997), Basic Science First Prize in the Poliquin Xomed Resident Research Competition of the *Canadian Society of Otolaryngology - Head & Neck Surgery 51st Annual Meeting* held in Whistler, B.C. (June 22 - June 26, 1997), First Prize during the Oral Presentations for the Resident Research Competition of the *Congrès Conjoint Franco-Québécois de Chirurgie Plastique et Esthétique* held in Québec City, Québec (February 6 - February 9, 1997), First Prize - Clinical Science Research at the *Annual Fraser Gurd / McGill University Department of Surgery Resident Research Competition* (May 15, 1997), First Prize - Basic Science Research at the *Annual James D. Baxter / McGill University Department of Otolaryngology Resident Research Competition* (May 22, 1997) and Second Prize in the Student-Researcher Competition of the *Association Québécoise des Fabricants de l'Industrie Médicale (AQFIM)*, hosted at the Palais des Congrès, Montréal, Québec (November 4 - November 6, 1996). In addition, this project was awarded the 1997 Canadian Society of Clinical Investigation (CSCI) / Medical Research Council (MRC) Residents Research Prize for McGill University. Patent protection is pending for the concept and eventual

development of a portable ultrasonic bone thickness probe based upon the work contained in this thesis. The application has been filed with the Office of Technology Transfer (OTT), McGill University, Montréal, Québec, on January 13, 1997 (File # 97001).

ACKNOWLEDGEMENTS

As is usually the case with all innovative ideas, this undertaking was the product of Dr. Lucie Lessard's unique ability to foresee the potential clinical applications in everyday observations. It is this fresh and invigorating approach to specific problems, that I hope to emulate from my time spent with her. Dr. Lessard has been instrumental in guiding my attempts at research and in realizing my professional aspirations. I look forward to her continuing support and guidance in the future.

Dr. Watkin has been a constant source of support in seeing this project through to completion. His expertise in ultrasound imaging has been a powerful resource which I often relied upon. Likewise can be said of Souheil Hakim, who is not only a skilled co-worker, but someone that I can consider a dear friend. We have seemingly shared a lifetime of experience together in only one short year.

I could not have achieved any level of success without Dr. Pascale Dubé who has been an ongoing source of strength and encouragement throughout this trying year. Finally, I have been blessed to have parents and older brothers who have provided for and guided me to where I am today. I credit them with instilling in me a strong sense of societal obligation and appreciation for the pursuit of knowledge. Their exemplary model of combining devotion to both family and God, with a work ethic principled on

educational achievement and community service, has shaped, and will continue to shape, my personal ambitions and outlook on life.

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OVERVIEW

Cranial bone grafts have become the autogenous substrate of choice in the surgical reconstruction of the craniomaxillofacial skeleton. The superiority of the calvarium over other donor sites has been well established, both clinically and experimentally, by a number of investigators.[1-10]

The reported low morbidity and complication rate associated with this procedure has often been cited as a further testament to the utility of cranial bone grafts.[2,7,10-15] Nevertheless, significant donor site complications, with potentially devastating neurovascular sequealae have been reported.[14-18] As increasing numbers of surgeons with diverse surgical backgrounds harvest calvarial grafts, the number and degree of complications reported is likely to increase.[19]

To enhance the safety of cranial bone harvesting, knowledge of calvarial thickness at the donor site could provide useful information to the surgeon. Previous research has demonstrated regional variations in calvarial bone thickness, yet accurate methods for the intraoperative measurement of skull thickness are not available. Computerized tomography provides a good estimation of cranial thickness, however, the transfer of this information to a precise clinical-anatomical point, is less than optimal.

Ultrasound technology has been available for decades in the medical sector. The adoption of currently available ultrasonic probes, appropriately modified to assess the thickness of the calvarium, could provide the surgeon with an invaluable tool in mapping out optimal areas of bone for cranial bone harvesting. **This study represents the first such attempt, documented in the medical literature, to assess the capability of A-mode ultrasound in measuring skull thickness in a reliable, accurate and non-invasive fashion.**

It is expected that the validity of accurate A-mode acoustic measurements of true calvarial thickness will provide the crucial foundations to allow for the development of a non-invasive, hand-held, ultrasonic probe. In successive experimental models utilizing human cadaveric skulls and live porcine skulls, the validity of A-mode ultrasound as a new, perioperative, predictive modality of cranial bone thickness is explored. This type of tool has the potential to yield significant benefits for craniomaxillofacial patients, including intraoperative ultrasonic guidance for the optimal harvesting of cranial bone grafts, the precise placement of osseointegrated titanium implants and related craniofacial rehabilitation applications, its adjunctive use in aesthetic facial recontouring and potential anthropometric data generation.

BACKGROUND

CRANIAL BONE GRAFTS

HISTORICAL PERSPECTIVE

The earliest known report relating to osseous reconstruction with a bone graft dates back to 1632.[20] A Dutch physician, Meekren, reported on the performance of a bone xenograft from a dog, to rehabilitate a traumatic cranial defect in a Russian soldier. In 1821, Phillipe von Walther,[21] detailed the first human bone autograft, however, it was not until 1890 that the first case reports of autogenous cranial bone grafts were documented. Müller and König simultaneously described the performance of pedicled osseocutaneous calvarial flaps for use in the reconstruction of traumatic forehead defects.[22,23] These same authors later introduced the concept of using calvarial bone chips for similar applications (**Figure 1**).[22,23]

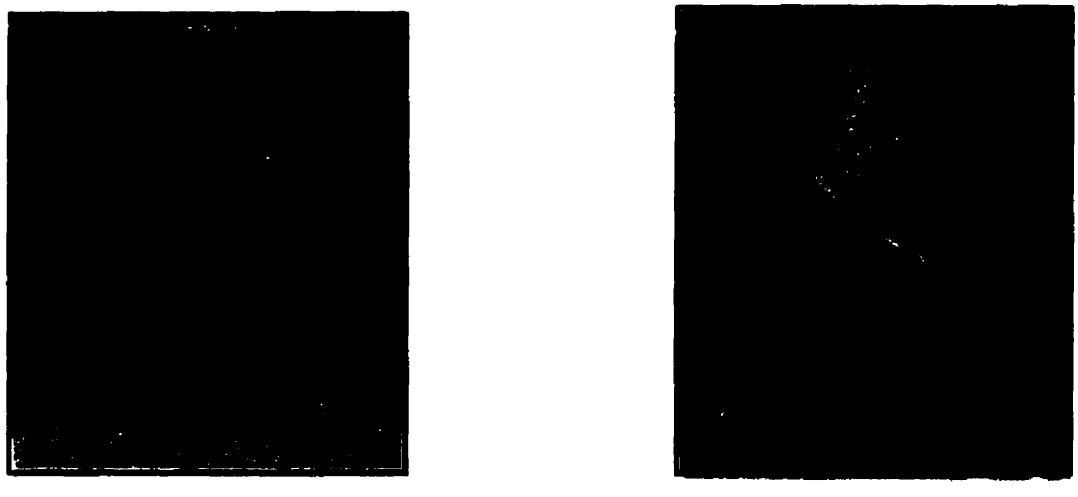

Figure 1. Fritz König and Wilhelm Müller, circa 1890 (photos reproduced, with permission, from Plastic Surgery of the Facial Skeleton, SA Wolfe & S Berkowitz, Lippincott-Raven Publishers, 1989, p.14).

Concurrent with these clinical achievements, was much laboratory investigation spearheaded by Marchand in Stuttgart, Germany.[24] In 1901, he first theorized that the surrounding host tissue was the source of neo-osteogenesis in bone grafts. It was he who coined the term ***"creeping substitution"***, (German translation of ***"schleichender Ersatz"***), which served to eloquently describe the invasion of a bone graft by active granulation tissue from the host, with subsequent resorption of the graft and production of new bone.[24] Further refinements in the advancement of this hypothesis were forwarded by Auxhausen, who succeeded in demonstrating the osteoinductive role of the surrounding host tissues with murine and porcine models.[25]

These basic science investigations culminated in 1929 when the pre-eminent neurosurgeon of the day, Dr. Walter Dandy, performed the first free autogenous cranial bone graft, ushering in a new era in reconstructive craniomaxillofacial surgery.[26] Since that time, intermittent case reports and patient reviews have been published in an attempt to both modify the original procedure and introduce its reconstructive potential to mainstream craniofacial surgery.[1,27-36] It was Tessier, however, in his landmark publication of 1982, who is generally credited with achieving these goals (**Figure 2**).[7]

Figure 2. Mr. Paul Tessier, former Chief of Plastic Surgery, Hôpital Foch, Paris, France (photo reproduced, with permission, from Plastic Surgery of the Facial Skeleton, SA Wolfe & S Berkowitz, Lippincott-Raven Publishers, 1989, p. xiv).

Tessier described his extensive experience with 234 calvarial grafts in the successful rehabilitation of 103 patients, with both congenital and traumatic craniofacial abnormalities.[7] He meticulously documented the approach and technique for the harvest of these grafts over 15 years ago, which essentially remains as the standard surgical technique employed today. The pioneering efforts and large clinical series of Tessier over two decades, have firmly established the performance of cranial bone grafts in the armamentarium of reconstructive surgeons.[7]

ADVANTAGES OF CRANIAL BONE GRAFTS

The demonstrated superiority of calvarial bone and the parietal skull donor site over other bone grafts and donor areas, has lead to their

utilization as the standard reconstructive substrate in craniomaxillofacial reconstruction. Bone can be of membranous origin, in which there is no cartilage precursor, such as the flat bones of the skull, or of endochondral origin, in which there is cartilage precursor, such as in the long bones of the skeleton.[9] Experimental studies comparing the graft volume survival and bone resorption characteristics of the calvarium, a source of membranous bone, have consistently demonstrated enhanced survival over traditional, endochondral bone grafts (rib, ilium, tibia, etc.).[2,19,37-39] Authoritative clinical investigations by Smith and Abramson in 1974,[1] followed by Zins and Whitaker in 1983,[3] found large differences in graft volume survival when free endochondral and membranous bone grafts were transplanted into subperiosteal craniofacial regions of rabbits and monkeys. Remarkably, the rate of resorption of endochondral bone was upwards of 80% of its original volume, while the comparable rates for cranial bone approached only 20%.[1,3] The use of rigid fixation to stabilize the transplanted bone may minimize the resorption rates of these embryologically distinct bone types, nevertheless, the calvarium provides other advantages that further substantiate its role as the reconstructive craniofacial standard.[9,19]

These advantages have been primarily attributed to the location and characteristics of cranial bone. The accessibility and proximity of cranial bone to the surgical field obviates the need for a second operative site to contend with.[40,41] If a coronal incision is already in use for a craniofacial procedure, no additional exposure is required.[42,43] The donor site is inconspicuous, as the scar is usually hidden in hair-bearing skin.[19,39,48] This avoids any secondary deformity at the donor graft site, although an irregularity in bony contour may be perceived on the skull by palpation.[7,19,39,48] There is minimal pain and no limitation in ambulation and functioning, which results in a shorter period of hospitalization and an improved cost-benefit ratio in comparison to other autogenous grafts.[11,39,47] The inherent contour and abundance of harvestable bone, especially in the parietal region, allows for the reconstruction of defects with grafts of similar morphologic characteristics.[44-46] This is a particular concern in children, where traditional donor sites invariably fail in providing enough bone graft.[7]

TECHNIQUES OF HARVESTING CRANIAL BONE GRAFTS

Two distinct approaches are being used to harvest cranial bone grafts. The first involves the creation of a trough around the graft site on the parietal bone of the skull, followed by the development of a

separation plane between the outer and inner tables at the level of the porous cancellous bone layer.[7] The outer table is subsequently split away at this mechanically weaker space using an osteotome and mallet. In a variation of this first technique, the outer table cranial bone graft can be split away using a mechanized blade or saw of varying thickness and flexibility.[3,40,48] The second approach to cranial bone grafts involves the complete removal of the full thickness of the skull at the donor site.[7,42,43,49] The inner and outer tables are then divided outside of the patient, followed by the replacement of one of the split segments to cover the defect.

The choice of harvesting technique depends upon the clinical situation at hand, as advantages and disadvantages are associated with each. The use of a manual osteotome to elevate the outer-table of the skull risks fracturing the donor graft and/or the inner table of the skull, with resultant intracranial complications.[50] Likewise can be said of the harvest of full thickness segments of the calvaria, which is a considerably invasive procedure with its own inherent neurosurgical risks.[5,7,43,51] The relative ease and precision of electric saws in procuring grafts has been described, but requires a level of expertise and familiarity with this equipment and the procedure. Specialized training in craniofacial surgery is a necessary prerequisite for these techniques.

Furthermore, knowledge of potential complications, the attendant limitations in graft size that can be obtained with this technique, the loss of cancellous bone from the diploic space and the wider field of bone requiring thinning, must be appreciated.[19,43]

As the indications for the performance of cranial bone grafts have broadened in contemporary practice, the calvarium has been increasingly relied upon to satisfy the requirements for the effective functional and aesthetic rehabilitation of a wide variety of craniomaxillofacial osseous defects.[40,52-59] As a corollary to the widespread performance of this procedure by a rapidly diversifying surgical community, the importance of emphasizing the potential complications cannot be understated.[19,60-62]

COMPLICATIONS OF HARVESTING CRANIAL BONE GRAFTS

Despite the reported safety and low morbidity in harvesting calvarial grafts, the catalogue of untoward effects can indeed be impressive.[63-69] The most frequently encountered complications take the form of localized wound infections, hematomas, seromas and donor site contour irregularities.[48,65,69] These minor complications are self-limited in their natural history. However, other more severe complications can occur, with the potential for intracranial sequealae (**Figure 3**).

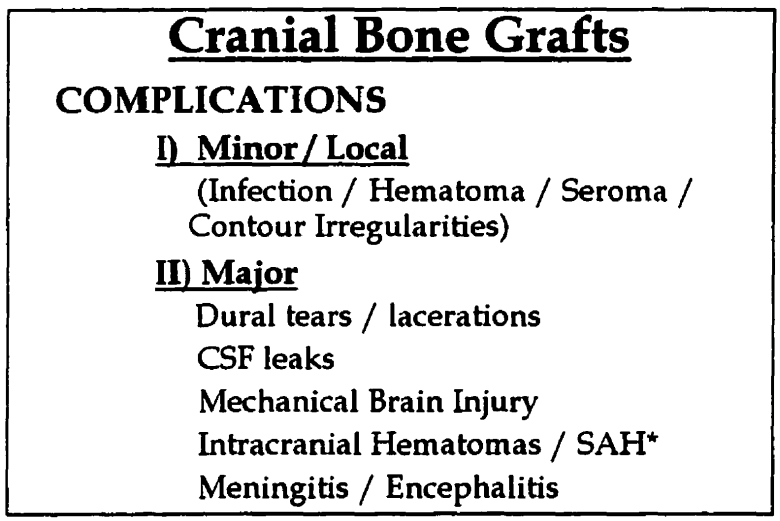

Figure 3. Potential complications encountered during the harvest of cranial bone grafts (SAH* = sub-arachnoid hemorrhage).

The major complications are secondary to fracture or penetration through the full thickness of the calvarium, otherwise referred to as "splintering" of the inner table of the skull (**Figure 4**).[2,19,69,70] The force, angulation and type of instrument responsible for breaching the inner table portends the extent of intracranial injury.[14,15] Dural tears and lacerations are an attendant risk in the harvest of full thickness calvarial bone grafts because of the intimate relationship between the inner cortex and the dura. This is of particular concern in older patients because the dura is often considerably thinner and more often tightly adherent to the overlying skull.[15,18]

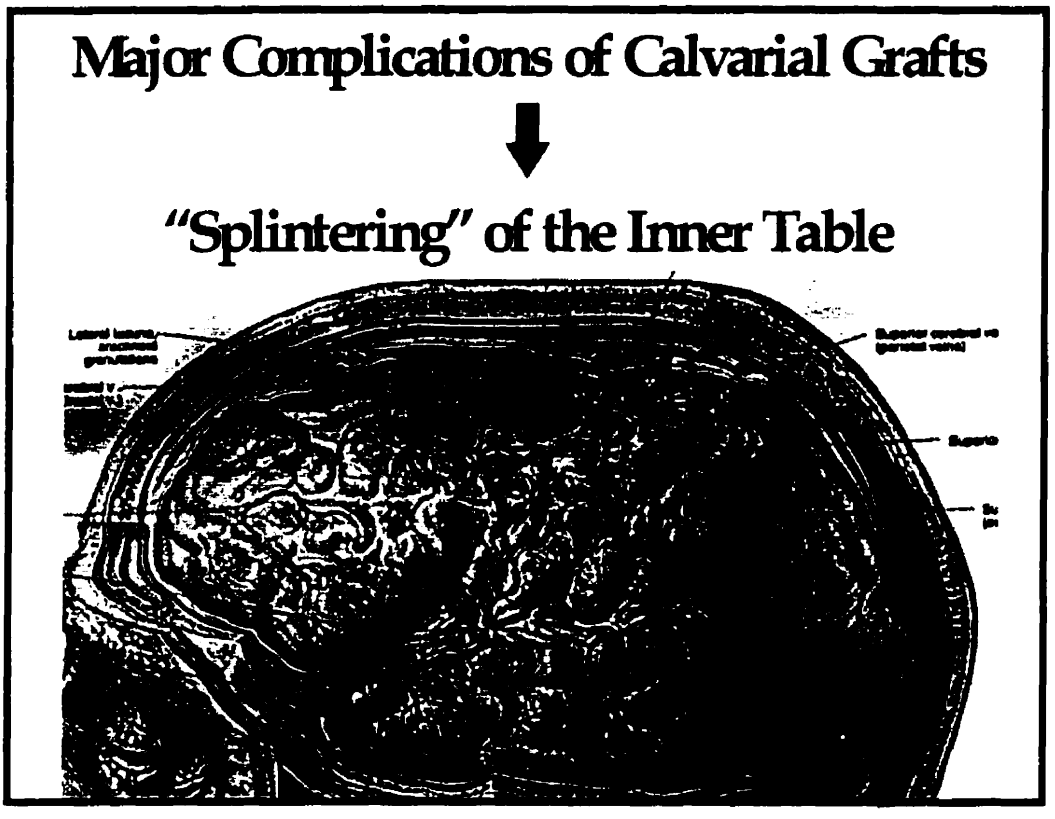

Figure 4. "Splintering" or fracture of the inner table of the calvarium can lead to devastating neurological complications (photo reproduced, with permission, from Plastic Surgery of the Facial Skeleton, SA Wolfe & S Berkowitz, Lippincott-Raven Publishers, 1989, p. 481).

Other complications include cerebrospinal fluid (CSF) leaks, mechanical brain injury, subarachnoid, subdural, epidural and intracerebral hematomas, which have all been reported in the literature.[16-19,68-70] Central nervous system infections, including meningitis and encephalitis, can occur through surgically created pathways predisposing to microbial spread.[15,65] All of these

complications share the possibility for even further damage via secondary neurological effects.[66-68]

Injury to the dural venous sinuses during calvarial harvest, particularly the superior sagittal sinus, has been associated with life-threatening hemorrhage, severe neurological deficit, air embolism and even death, precluding the importance of proper osteotome positioning.[5,15,63,67] For this reason, proper operative technique mandates leaving a minimum 2 cm margin from the midline, in addition to the avoidance of the cranial sutures, to safeguard the integrity of the dural venous channels.[63]

The inadvertent violation of the inner table of the skull, occurs more frequently than one may expect. This complication was documented to occur in 14.5 % of the split calvarial bone grafts in a publication by Kawamoto et al,[69] who is an experienced surgeon and recognized authority in craniofacial surgery. This point serves to underscore the relative prevalence of this occurrence and the inherent potential for neurovascular sequealae that accompanies it.[5,65,69] Moreover, recent reports have disturbingly implicated the transmitted energy from the harvesting procedure itself, without any associated fracture of the inner table of the skull, in leading to the development of intracerebral hematoma and contusion.[14,63] These injuries have been

termed "gutter wounds" by Harvey Cushing, and have long been recognized in neurosurgical circles as being associated with glancing, non-penetrating cranial injuries.[71] As a result, it has become accepted medico-legal practice to inform all patients of the potential for neurologic injury and to procure cranial bone grafts from the skull overlying the nondominant cerebral hemisphere, whenever possible.[14,15,63]

To effectively minimize the risk of complications, knowledge of calvarial thickness within the region of the potential harvest site could provide essential information to the craniofacial surgeon in enhancing the safety of this procedure.[44,47] It is known that there is significant variation in the thickness of cranial bone, ranging from 2.5 mm to upwards of 15 mm, in individuals as a function of age, race, sex and other parameters.[13,37,44,45] Intuitively, one can appreciate the difficulty that can be encountered in harvesting a cranial bone graft with such a high degree of unpredictability in thickness (**Figure 5**).

This problem is compounded by the lack of consensus amongst craniofacial surgeons regarding the thickness of skull required for safe and efficacious bone harvesting. It has been suggested that 6 mm of parietal bone thickness is the minimum threshold for safe in-situ calvarial harvesting.[45] Others have placed an emphasis on a 2 mm

thickness margin of the diploic space as the limiting factor in obtaining a safe separation plane in split cranial harvests.[6,43] Regardless of the apparent arbitrary nature of these guidelines, the **current knowledge on the topic of predictive studies in the assessment of potential calvarial bone harvest sites is limited.**

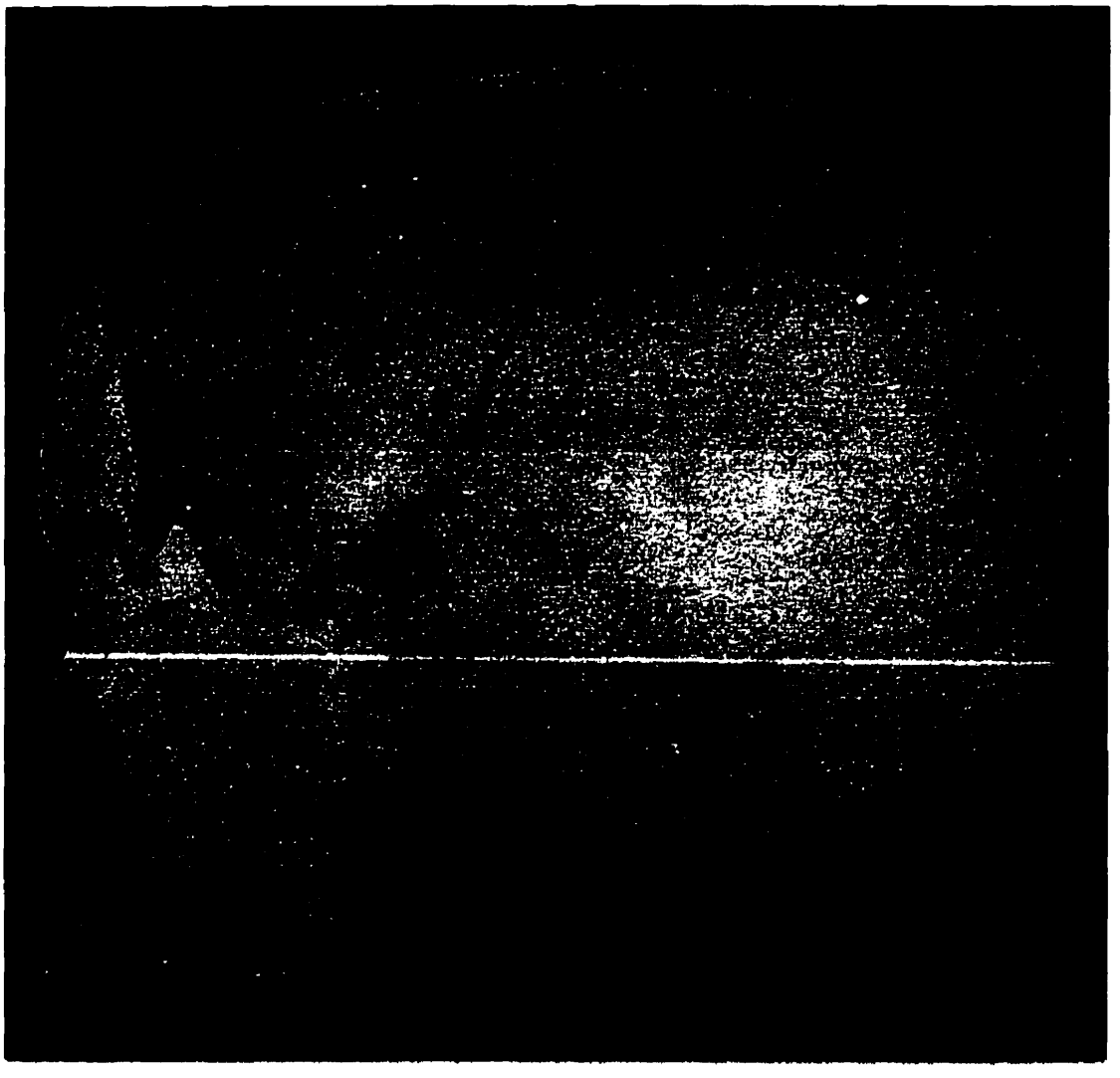

Figure 5. Variability in thickness of the human calvarium.

PREVIOUS WORK IN MEASURING CALVARIAL THICKNESS

Measurements of skull thickness have been reported as early as 1882 by an Irish anthropologist named Anderson.[72] Todd, however, is perhaps the first investigator to standardize bone thickness measurements across patient samples.[73] He performed direct calvarial thickness measurements with a hand-held gauge on 448 Caucasian male cadavers. Todd found that the average thickness at the glabella was 11.3 mm, 5.7 mm at the opisthion (occiput), 5.9 mm at the vertex and 3.6 mm at the euryon (the most lateral point of the skull in frontal view).[73] From these observations, Todd concluded that skull thickness increased rapidly during the first 2 decades of life, and then continued to increase slightly to the age of 60. More importantly, however, Todd noted that there was a **high degree of variability in skull thickness between each cadaver specimen and within each cadaver skull.**[73] He felt that this variability effectively precluded the ability to accurately predict the thickness of a particular individual's skull.

Similar anthropometric studies using direct bone thickness measurements followed Todd's work, however, some investigators opted to analyze bone thickness using indirect measures, with the goal of obtaining more objective data. Cephalometric radiography, first introduced by Broadbent in 1931,[74] was first employed by Roche for the

purpose of measuring cranial bone thickness.[75] He reported on a study of calvarial thickness as recorded on serial radiographs of 32 male and female children between the ages of 3 months and 17 years. He concluded that the average cranial thickness of males, exceeded that of females, and that the rate of increase in skull thickness decreased from 5 to 17 years old. Nevertheless, by Roche's own admission, the accuracy of his measurements were quite limited.[75]

In 1975, Adeloye et al performed a more detailed radiological study on a racially mixed population of 300 Black and 200 White patients.[76] These authors found differences in skull thickness, at 4 arbitrarily chosen skull points, as a function of age and sex in each of the 2 groups. Importantly, however, they pointed out that within each of the racial groups, the range of differences for the parameters cited was greater than the difference between the races.[76]

With the introduction of Mr. Paul Tessier's work in the late 1970's and early 1980's on cranial bone grafts, reconstructive surgeons began to focus on the dimensions and characteristics of the calvarial donor site.[7,41,77] In 1985, Pensler and McCarthy, examined cranial bone thickness in a clinically useful format, with the detailed performance of an anatomic cadaveric study.[37] Two hundred specimens were examined at 4 selected points on the skull and the results were analyzed as a

function of patient age, weight, sex and race. The mean values for skull thickness in their study population ranged from 6.80 mm to 7.72 mm **(Figure 6)**.[37]

Comparison of Right and Left Sides

Variable	Number	Mean	Std. Dev.	Median	Minimum	Maximum
Right side 1	200	6.80	1.04	6.80	3.50	10.00
Right side 2	200	7.03	1.06	7.01	3.50	10.25
Right side 3	200	7.45	1.03	7.38	4.25	11.25
Right side 4	200	7.72	1.07	7.60	4.00	12.00
Left side 1	200	6.86	0.99	6.89	3.75	10.25
Left side 2	200	7.03	1.05	7.00	3.75	10.25
Left side 3	200	7.46	1.09	7.49	3.00	11.50
Left side 4	200	7.72	1.11	7.55	4.00	12.00

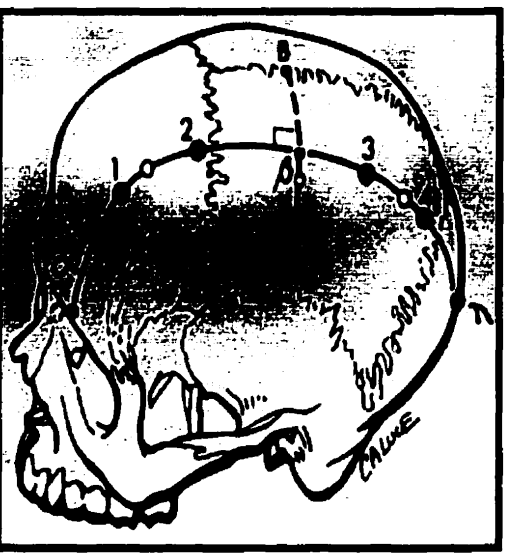

Figure 6. Reference table generated from cadaveric anatomic studies by Pensler and McCarthy at the points shown, revealing large differences between minimum and maximum bone thickness at specific points on left and right sides of the calvaria (reproduced with permission from Plastic and Reconstructive Surgery, "The Calvarial Donor Site: An Anatomic Study in Cadavers", vol 75, no 5, 648-651, May 1985).

Based on this collected data, the authors concluded that an estimation of adult skull thickness could be predicted by referring to a reference table for any of the points they had examined. However, the study emphasized that in their patient sample, the variation between minimum and maximum skull thickness, at a selected site from cadaver to cadaver, could be as high as 8 mm.[37] This variability is known to be

well beyond the margin of safety in the context of consistently harvesting cranial bone grafts without inner table compromise.

They concluded that based on their collected data, adult skull thickness could be predicted by referring to a reference table for any of the points examined. However, in contradiction to this conclusion, these authors also reported that the variation in the measurements at a selected point from cadaver to cadaver, could be well beyond several millimeters.[37]

More recently, Waitzman et al objectively documented the accuracy of computed tomography in assessing craniofacial dimensions, although thickness of the calvarium was not addressed in their study.[78,79] In 1995, Koenig et al examined the utility of this modality in the preoperative prediction of skull thickness in the parietal region, with a specific view towards cranial bone harvesting in the pediatric age group.[45] They found the predictive value of CT imaging to be accurate to ± 5% of the true thickness of the calvarium.[45] Measurements of skull thickness were performed with CT scans in 96 patients, ranging from newborns to young adults, aged 21 years. One CT scan image through the external auditory canal was used for the measurements, which were performed by a single observer.[45] The data obtained in this manner was used to formulate a graph of the mean and the range of

skull thickness as a function of age. Based on the data obtained from these 96 CT scans, the authors extrapolated the likelihood of the presence of a diploic space.[45] Only 5 of the 96 patients studied actually proceeded to surgery to verify the accuracy of the preoperative imaging. From these observations, the authors constructed guidelines on the harvesting of split calvarial bone grafts, suggesting a minimum of 6 mm of cranial bone in the parietal region be present.[45] Most importantly, however, this study fails to address the difficulties in correlating a 2-dimensional point on a CT image to the 3-dimensional clinical situation encountered intraoperatively.

The introduction of 3-dimensional CT reconstructions using elaborate software packages, such as the Allegro System™ , have attempted to overcome the limitation accompanying "static" CT scanning. Although initial experiences have been encouraging, the relative lack of availability, significant costs and cumbersome nature of the setup, have as yet, precluded a significant role for this technology.

Despite the limited number and nature of predictive studies published on the assessment of skull thickness, there is a consensus amongst these studies to stress the importance of recognizing the variation between minimum and maximum skull thickness at a particular site.[37,42,45,46] This variation could approach upwards of

8mm.[37] One's own observations on examining a model or cadaveric specimen of the calvaria confirms this thickness variation from one point to another on the skull. This observation is further compounded in patients with craniofacial abnormalities, such as Crouzon's or Apert's syndrome, a history of trauma, radiotherapy or previous surgery.[37,45] Patients at the extremes of age, with neoplastic disease or concurrent metabolic bone disorders, can all be assumed to have variability in skull thickness beyond that of the population at large.[44,46,48] Certainly, appropriate investigations are required to address the question of adequate calvarial thickness if the operating surgeon is contemplating a surgical procedure involving cranial bone. These factors effectively limit the usefulness of reference tables for skull thickness in individual patient cases.

With the increasing use of osseointegration systems that allow the direct structural and functional union between craniofacial bone and prosthetic appliances, the need for a portable diagnostic tool that can accurately predict the thickness of potential sites of bone implantation has been recognized as a priority. A recent publication articulated the difficulties with current diagnostic techniques of predicting cranial bone thickness.[80] These authors describe intraoperative bleeding during the placement of osseointegrated implants in preparation for a bone-

anchored hearing aid (BAHA). The procedure had to be abandoned in 2 of 15 patients due to insufficient cranial bone.[80] These experienced surgeons were of the opinion that an adequate measure of bone thickness, that would allow for preoperative planning of implant placement, would have avoided these complications. They point out that current attempts with fine-cut CT scanning appear to be unsatisfactory.[80] My co-workers and I wholeheartedly agree with their summation:

"Further attention [to a predictive modality of cranial bone thickness] is a necessary goal of future studies".[80]

ULTRASONOGRAPHY

INTRODUCTION

Ultrasound technology plays an important role in tissue characterization of numerous anatomical and physiological systems.[81-86] The popularity of this imaging modality is primarily derived from the ease and safety associated with its use. Ultrasonography can provide rapid topographic and depth observations of anatomic structures in a noninvasive, painless, relatively inexpensive and portable manner.[85-91]

Ultrasound, as applied to diagnostic instrumentation, is defined as acoustic waves with frequencies above those which can be detected by the ear.[81] The frequencies utilized range from 1 MHz to 10 MHz, due to the combined needs of good resolution, (short wavelength), and good penetrating ability, (limited frequency).[88] The waves are generated by small acoustic transducers containing specialized piezoelectric crystals, usually hand-held, that are placed on the surface of the tissue to be scanned.

BASIC PRINCIPLES

Ultrasound is based on the transmission and reflection of sound waves at anatomical interfaces of varying acoustic impedances. The energy that is reflected at these interfaces is picked up by the same emitting piezoelectric crystal housed within the ultrasound probe. The reflected acoustic sound waves or echoes mechanically deform the

crystal surface, which in turn, are converted to electrical voltages.[87] The product of this energy transforming process results in the amplification of electrical signals which can be displayed in various visual formats.

Under idealized conditions, all acoustic signals would be reflected back to the transducer at the boundary of a tissue interface.[85] However, some of the acoustic wave is transmitted through the breadth of the next structure, or **scattered**, at interface boundaries throughout the medium undergoing ultrasound scanning. The degree of change in the direction of sound waves as it crosses from one boundary to another, the property known as **refraction**, is proportional to the incident angle of the ultrasound beam and the varying acoustic impedances at tissue interfaces.[85-87] The distorting effect of scattering is further compounded if the tissue surface has contour irregularities that exceed the ultrasound's acoustic wavelength.[81,88]

The acoustic or sound waves displayed on an ultrasound system are the net result of complex interactions between the properties of the acoustic wave and the composition of the insonified medium. Varying degrees of **attenuation** of the ultrasound beam occur as a function of the density and compressibility of a tissue medium.[84-86] In a high density and low compressibility structure such as bone, for instance, the propagation of the waveform occurs at a high velocity in comparison to

structures of lesser density. However, these same characteristics, result in a higher level of resistance, or **impedance**, to the transmission of the acoustic signal.[87] The signal is also modified by **reflection** at the interface between substances of differing acoustic impedances. The echoes reach successive boundaries at various angles of incidence which determines the degree of reflection. The greater the angle of incidence, the greater the reflection, which compromises the amount of acoustic signal transmitted beyond the interface as a direct result of the increased attenuation.[87,91]

An **acoustic impedance mismatch** for an air-tissue interface results in all of the incident ultrasound signal being reflected. This complete level of attenuation of the beam is the basis for the use of a coupling gel medium in diagnostic ultrasound imaging. The gel provides a sound path from the transducer to the skin eliminating the thin layer of air, and hence the attenuation, that would have otherwise impeded sound energy transmission.[87] Transducer **frequency** selection also considers the effect of attenuation of the sound wave as it travels through the tissue.[81] The degree of attenuation is directly proportional to the frequency of the sound wave, where lower frequencies have longer wavelengths that are capable of traveling greater distances

through tissue media. This results in greater depth penetration at the expense of decreased signal intensity and poorer image **resolution.**[82]

A-MODE ULTRASONOGRAPHY

Ultrasound systems produce visual displays based on the electrical voltages created by the displacement of the transducer's piezoelectric elements from returning echo signals.[84,88] The acoustic information received by the transducer is subsequently converted and displayed in the format desired. The most commonly used visual format is the B-mode display, which is a product of a series of aligned crystals.[81] This process generates the familiar 2-dimensional, cross-sectional images of soft-tissue structures that are commonly used in everyday medical and obstetrical practice.

A-mode ultrasonic signals represent the pure acoustic signal that is generated by a single piezoelectric crystal, contrary to the B-mode display. A-mode ultrasound is primarily based upon the pulse-echo technique, wherein a short pulse of acoustic signal is transmitted by a low energy transducer into the tissue regions being investigated.[88] Reflections from each of the various tissue boundaries, due to changes in acoustical impedance, are received back at the transducer. The total transit time from initial pulse transmission to reception of the echo, is

proportional to the tissue depth.[81,82,88,90] This makes possible the one-dimensional mapping of the tissue interfaces along the line of propagation of the beam.

A short-coming in the interpretation of A-mode ultrasound results, is the high degree of overlap in the returning acoustic signals. These waves are generated from successive tissue media at tissue interfaces, resulting in the appearance of multiple reflections perceived at the visual display, usually an oscilloscope. Because the acoustic intensity of the reflected signals is not uniform across the range of insonifying frequencies, the ability to discriminate different interfaces of varying tissue depths can be restricted.[82] Identifying which interface the A-mode signal represents is a crucial requirement in the analysis of these waveforms. The use of established criterion of propagation speeds of sound through tissues such as bone and water, aids in the determination of anatomical characterization.

It is the central postulate of this work that A-mode ultrasound can determine the thickness of bone by characterizing the respective interfaces associated with the outer and inner cortex of the calvaria (**Figure 7**). The time of flight of the ultrasound wave between these interfaces is presumed to be equivalent to the thickness of the bone being scanned.

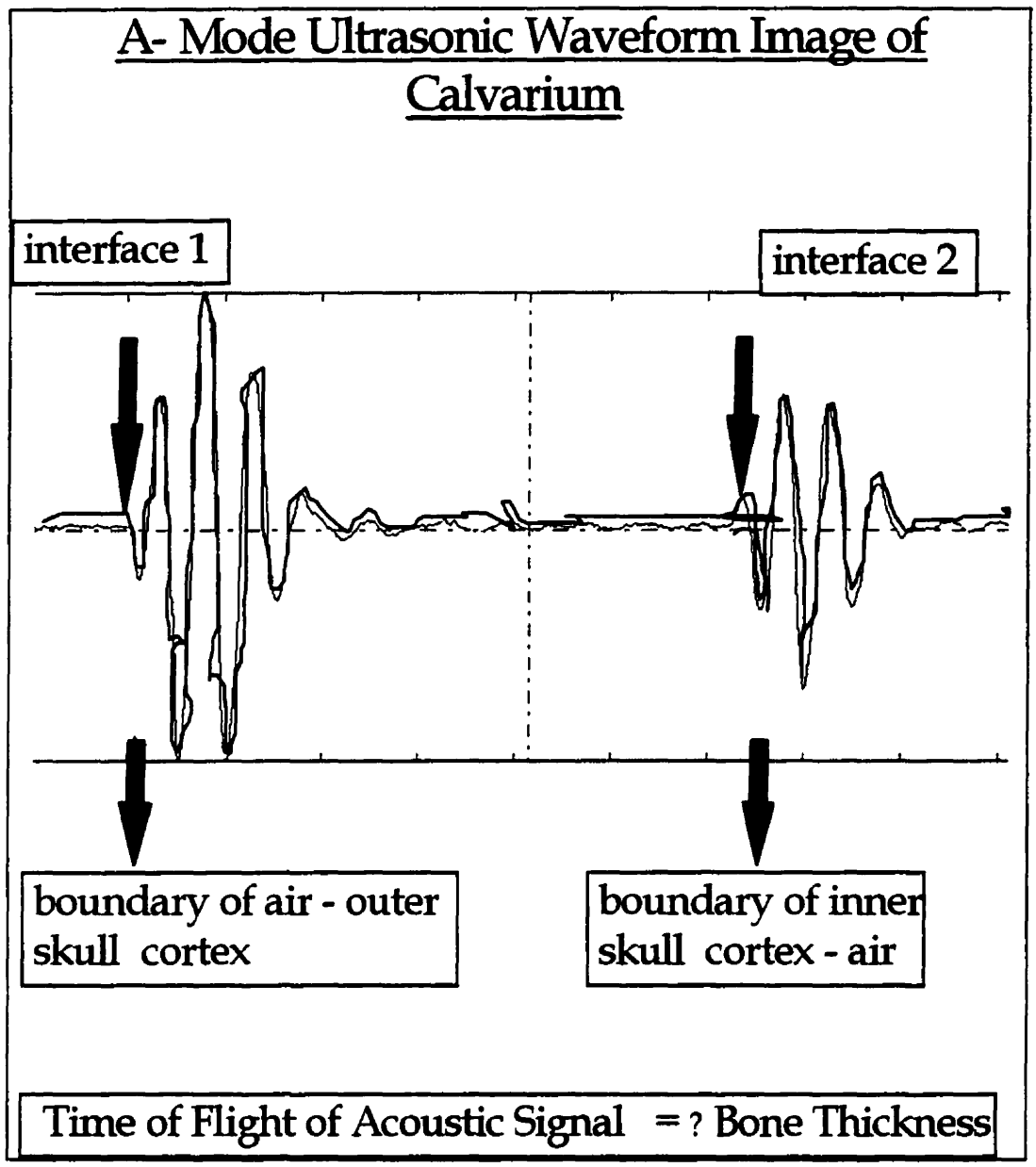

Figure 7. Idealized oscilloscopic display of A-mode acoustical signals through a segment of calvarial bone.

PURPOSE

Autogenous sources of bone are superior to allografts and xenograft donor sites.[92-99] Both of these reconstructive substrates are associated with significant levels of attendant morbidity related to immunologic rejection, poor healing, extrusion and graft resorption.[93-95] Since their re-introduction to plastic and reconstructive surgery, cranial bone grafts have received widespread acclaim in providing a viable autogenous reconstructive option. Today, the calvarium represents the graft of choice in contemporary craniomaxillofacial reconstruction.[100]

Preoperative knowledge of calvarial thickness at the donor site could clearly enhance the dual objectives of safety and efficacy in the procurement of these grafts. The relative lack of studies and diagnostic tools for the prediction of calvarial bone thickness provided the impetus for this investigation. **The purpose of this series of experiments is to objectively test, evaluate and validate the accuracy of A-mode ultrasonic measurements in both human cadaveric and animal skull models for the assessment of cranial bone thickness.** Invariably, a diagnostic tool that has the ability to perform this task could provide the reconstructive surgeon with an invaluable instrument in choosing the optimal location for cranial bone grafts and related craniomaxillofacial applications.

HYPOTHESIS

The harvest of cranial bone grafts has been associated with significant, albeit uncommon, donor site complications. Penetration of the inner table of the skull, with the inherent devastating neurovascular sequelae of such an event, could be avoided if a diagnostic tool were available to map out areas of variable cranial bone thickness. Based on the literature reviewed, there is currently no such tool available for this task. The feasibility of ultrasound technology, appropriately modified for this clinical application is the basis of this work. The following hypothesis was formulated accordingly:

"It is possible to estimate cranial bone thickness, with a high degree of precision, using an A-mode ultrasonic probe."

To realize this hypothesis, a pair of experiments were devised in order to set the framework for the end-stage development of a portable, ultrasound probe, capable of performing these measurements. The first experiment focuses on the preliminary validation of A-mode ultrasound in assessing cranial bone thickness in human cadaveric skulls. The principles learned in acoustic insonification were then subsequently applied to a live animal model to verify the effectiveness of this technique in a simulated, in-vivo, clinical scenario.

EXPERIMENT # 1

CADAVERIC SKULL MODEL

INTRODUCTION

In the past, the use of imaging technologies to examine calvarial thickness have focused on the use of plain radiographs, which have now been supplanted with thin-section computerized tomography. A major drawback of these modalities is their inability to extrapolate to the real-time requirements of the intraoperative situation. This limiting factor severely restricts clinical freedom in acute decision-making processes. Recent technological advancements in the utilization of ultrasound, have re-awakened interest in this modality. Refinements in the acquisition and processing of acoustic signals have encouraged the pursuit of this work to allow for the development of a versatile instrument, capable of overcoming weaknesses associated with present day, static techniques.

On reviewing the medical literature, this experiment is unique in its goal of studying the relationship of A-mode ultrasound in the prediction of calvarial bone thickness. There are many factors that contribute to variability in cranial bone thickness, previously alluded to in the background discussion. The choice of a model that controlled for as many variables as possible was important for the initial validation of this modality. For this reason, a uniform population of cadaveric skulls

was chosen for the preliminary assessment of A-mode ultrasound in calvarial thickness measurements.

MATERIALS AND METHODS

The first study group consisted of 10 Caucasian cadaver skulls, with patient age greater than 50 years old. All cadaver skulls were free of skin disease and underlying brain pathology, with no evidence of skull trauma or injury. Based on the patient information annoted to the respective specimen, history of craniofacial abnormality, surgery, malignancy, radiotherapy or metabolic bone disease were criteria for exclusion.

The scalp was retracted and 4 sampling points were marked with India ink dye. The points of study on the calvaria were chosen as previously described by Pensler and McCarthy[37](**Figure 8**). The most superior aspect of the squamosal suture line was designated as *Point A*. *Point B* represented the corresponding perpendicular point on the sagittal suture. *Point* β was selected to identify the point 60 percent of the distance of line AB. *Point* β served as a reference point for a line drawn parallel to the sagittal suture. The most anterior point of the line at the supraorbital rim and the most posterior point of this line at the occiput were designated as *points* α and π, respectively. The sampling

points identified in this study were located as follows: **Point 1** = 60% of line αβ; **Point 2** = 30% of line αβ; **Point 3** = 30% of line βπ and **Point 4** = 60% of line βπ (**Figure 8**).

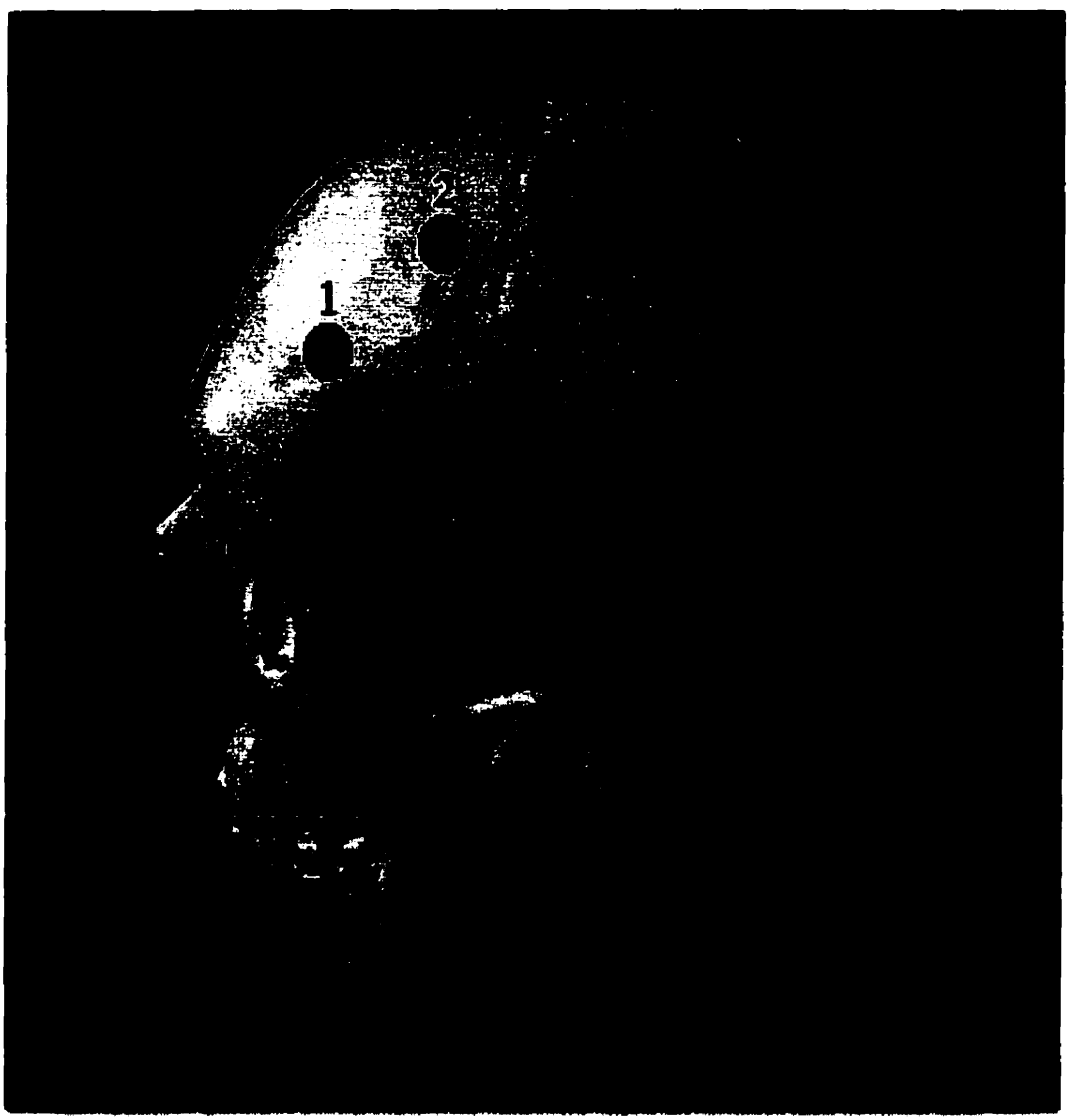

Figure 8. Calvarial points of study.

Four full thickness bone samples measuring 3 cm x 3 cm x 1 cm, centered around the previously identified points, were cut and

prepared for each of the 10 skulls. The individual bone samples were then immersed in a water tank at room temperature and insonified at the predetermined points. The ultrasound measurement was carried out with a single crystal 1.0 Megahertz, 12.7mm diameter, broadband, non-focused (50.8mm) ultrasonic pulse-echo device (model SR 9000, Matec Corporation, Nautick, MA). The time of flight of the ultrasound waves propagating in the bone samples was recorded from the reflected signals (**Figure 9**). Known mean velocity of sound in water and bone at room temperature were used to calculate bone thickness. As a gold standard, bone thickness of the same samples were measured using standardized digital calipers (resolution: 0.01mm, instrumental error: 0.02mm, model 500, Mitutoyo Limited, London, UK).

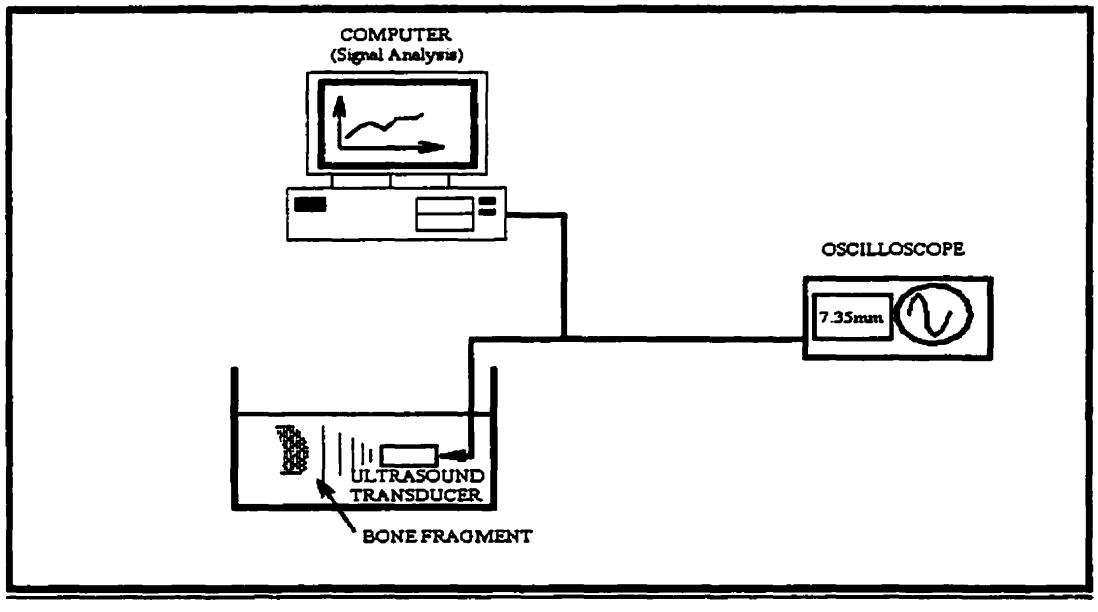

Figure 9. Schematic representation of ultrasound set-up.

STATISTICAL ANALYSIS

The accuracy of the measurements obtained using A-mode ultrasound were evaluated on two axes; reliability and validity.

Reliability is an indicator of reproducibility and is essential in clinical measurement in order to estimate the margin of error. In this study, inter-rater reliability, as well as intra-rater reliability, was assessed. Inter-rater reliability was assessed by having the same measurement obtained by three different individuals at the same point in time for the digital caliper, and ten times by the computer program for the ultrasound probe (the unit is already programmed for this number of measurements). Intra-rater reliability was evaluated by having the same individual obtain the same measurement at different points in time. The reliability coefficient was then calculated as the ratio of the true to total variance in these observations. The definition of true variance for this experiment included the subject related variance. In this analysis, other factors that my be related to the variance of skull thickness, including anthropometric measures and age, were considered as sources of the true variance. As mentionned previously, race has been controlled for by choosing only Caucasian skulls for study in this first experiment. The reliability coefficient normally ranges from 0 to 1, with higher values indicating better reproducibility. The

standard error of the measurement from the same observation was subsequently used to estimate the margin of error for the estimates of skull thickness, as obtained using the ultrasound.

The **validity** assessed in the present study was criterion related concurrent validity, because the exact measurements of the skull thickness could be considered the "gold standard". The validity was evaluated by the association between the estimates obtained using the ultrasound and the exact thickness measurements. This association was assessed by the difference between the 2 measurements, the student's t-test, the Pearson moment correlation coefficient, and multiple linear regression models.

The difference between ultrasound measured thickness and that measured by the calipers was calculated for all observations. The mean differences, with associated standard deviations and standard errors, allowed for a simple gross comparison of the two modalities. The paired student's t-test for dependent samples was then applied to this data. This statistical test allowed for the determination of the degree of significance in the difference of the mean values for the two modalities of testing bone thickness. Our hypothesis will be supported if by testing the null hypothesis, (that there is no difference between the

means of the two bone thickness measurement modalities), we **fail to reject** it.

In considering correlation coefficients, a low difference and high correlation coefficient are indicators of validity. Moreover, the intra-class correlation coefficient was used to measure the agreement between the two measures. The intra-class correlation coefficient is equivalent to a kappa statistic with quadratic weights when applied for continuous variables. This test will take into account the variance in calvarial thickness due to cadavers and bone fragment location, which we anticipated would yield a high degree of agreement.

To this end, multiple linear regression models aimed at specifically evaluating the association between the measurements obtained by the ultrasound and those obtained by the digital calipers. The first model included only the ultrasound measure as a predictor of the caliper measurement. This model assessed whether the variance within the caliper measurements can be explained by the ultrasound measurements. Subsequent models assessed the agreement between the **test measurement, (ultrasound)**, and the **"gold standard" (digital calipers)**. The assessment of agreement should be adjusted for and should take into account other factors that may cause variation in the "gold standard". Not adjusting for these factors may cause spurious

estimates of agreement. In this experiment the factors that could cause variation in the thickness of the calvarium is the choice of cadaver skull, (or choice of porcine skull in experiment # 2), and the respective location of the points tested. The inclusion of these variables in a multiple linear regression model allowed for the removal of these potentially confounding factors.

RESULTS

The mean age of the cadavers under study was 60.5 years with a standard deviation of 5.7 years. The age range of the 10 cadaver skulls was 53 to 68 years of age. **Table 1** displays the average of 6 measured values, 3 inter-observer and 3 intra-observer values, of skull thickness. These values were derived from both the digital calipers and the ultrasound probe, for each of the 4 sampled points, across all cadaver skulls. Inter-observer differences for the caliper and ultrasound measures did not exceed 0.23mm and 0.47mm, respectively. Similarly, intra-observer differences ranged from a maximum of 0.18mm for the calipers and 0.43mm for ultrasound, confirming the reliability and reproducibility of the measurements obtained. Intra-observer agreement was greater than inter-observer agreement for each of the measurement modalities.

	Point 1		Point 2		Point 3		Point 4	
	caliper (mm)	u/s (mm)	caliper (mm)	u/s (mm)	caliper (mm)	u/s (mm)	caliper (mm)	u/s (mm)
cadaver 1	5.43	5.14	5.73	5.67	5.69	5.45	7.68	7.44
cadaver 2	4.72	4.42	4.23	4.50	5.90	5.79	5.43	5.25
cadaver 3	4.87	4.71	5.84	5.65	7.72	7.81	7.29	7.11
cadaver 4	5.19	5.01	4.81	4.69	5.34	5.22	6.74	6.34
cadaver 5	6.89	6.65	6.43	6.24	7.14	6.82	7.35	7.13
cadaver 6	4.77	4.45	4.65	4.56	4.73	4.65	5.53	5.45
cadaver 7	6.57	6.50	7.15	7.07	5.78	5.54	8.10	8.00
cadaver 8	6.74	6.69	6.50	6.41	7.07	6.86	7.41	7.35
cadaver 9	4.58	4.49	5.13	5.06	7.66	7.55	6.22	6.14
cadaver 10	4.87	4.78	7.61	7.55	6.44	6.23	6.55	6.54

Table 1. Comparison of caliper (direct) and ultrasonic (indirect) skull thickness measurements.

The difference between the ultrasound measured thickness and that measured by the caliper was calculated for all 40 observations (10 cadavers and 4 sampling points for each cadaver skull). The mean (S.D.) for the caliper measurements was 6.11mm (1.09mm), and that of the ultrasound was 5.97mm (1.09mm). The mean difference was 0.16mm with a standard deviation of 0.09mm and a standard error of 0.04mm. Paired student's t-test for dependent samples showed that this difference was not statistically significant (P=0.569). **Table 2** shows the difference between the direct and indirect methods of skull thickness measurement.

	Point 1		Point 2		Point 3		Point 4	
	Diff 1 (mm)	Diff 2 (%)	Diff 1 (mm)	Diff 2 (%)	Diff 1 (mm)	Diff 2 (%)	Diff 1 (mm)	Diff 2 (%)
cadaver 1	**0.29**	**5.3**	**0.06**	**1.1**	**0.23**	**4.0**	**0.24**	**3.1**
cadaver 2	**0.30**	**6.3**	**-0.27**	**-6.4**	**0.11**	**1.9**	**0.19**	**3.5**
cadaver 3	**0.16**	**3.3**	**0.19**	**3.3**	**-0.09**	**-1.2**	**0.18**	**2.5**
cadaver 4	**0.18**	**3.5**	**0.12**	**2.5**	**0.12**	**2.2**	**0.40**	**5.9**
cadaver 5	**0.24**	**3.5**	**0.19**	**2.9**	**0.32**	**4.5**	**0.22**	**2.9**
cadaver 6	**0.32**	**6.7**	**0.09**	**1.9**	**0.08**	**1.6**	**0.08**	**1.4**
cadaver 7	**0.07**	**1.1**	**0.08**	**1.1**	**0.23**	**3.9**	**0.10**	**1.2**
cadaver 8	**0.05**	**0.7**	**0.09**	**1.3**	**0.21**	**2.9**	**0.06**	**0.8**
cadaver 9	**0.09**	**1.9**	**0.07**	**1.3**	**0.11**	**1.4**	**0.07**	**1.1**
cadaver 10	**0.09**	**1.8**	**0.07**	**0.9**	**0.20**	**3.1**	**0.01**	**0.1**

Diff 1 = Difference of caliper and ultrasonic measurement (mm)
Diff 2 = % Difference of caliper and ultrasonic measurements (%)

Table 2. Difference between caliper (direct) and ultrasonic (indirect) calvarial thickness.

The percent differences in calvarial thickness ranged from 0.1% to 6.7% of the actual (direct) values. However, almost half of the 40 observations had only a 2% discordancy rate between measurements, with the thinner sections of calvaria having higher percent differences. For 38 of the 40 total observations, the ultrasound measurement underestimated the caliper measure (**Tables 1** and **2**). This would suggest that the ultrasound systematically produced estimates which were less than those obtained by the digitized calipers.

Comparison of the 4 sampling points in each of the 10 calvaria, measured by the digital calipers and the ultrasonic probe, failed to

reveal any significant differences in mean calvarial thickness, according to the student's t-test (**Table 3**).

All Cadaver Skulls		Point 1 (most anterior)	Point 2	Point 3	Point 4 (most posterior)
MEAN DATA	caliper	5.457	5.808	6.355	6.830
	u/s	5.288	5.741	6.183	6.670
STANDARD DEVIATION	caliper	0.903	1.118	1.032	0.898
	u/s	0.954	1.070	1.023	0.891
MEDIAN	caliper	5.031	5.783	6.168	7.013
	u/s	4.895	5.658	6.012	6.825
MINIMUM	caliper	4.578	4.225	4.733	5.433
	u/s	4.420	4.498	4.654	5.245
MAXIMUM	caliper	6.890	7.613	7.806	8.098
	u/s	6.735	7.562	7.715	7.996
RANGE	caliper	2.312	3.388	3.073	2.665
	u/s	2.315	3.064	3.061	2.751
t-TEST *		t=.406 P=.689	t=.137 P=.893	t=.374 P=.713	t=.389 P=.702
PEARSON CORRELATION **		r=.993 p<<.05	r=.994 p<<.05	r=.997 p<<.05	r=.992 p<<.05

* the difference between the caliper and the ultrasound measurements are not statistically significant

** extremely strong correlation (i.e. complete correlation between 2 variables: r=1)

Table 3. Comparison of caliper (direct) measurements vs ultrasonic (indirect) measurements.

Furthermore, the Pearson moment correlation test supported an extremely strong and positive relationship between the 2 measurement modalities ($r > .992$). The comparison of ultrasonic versus caliper measurements, rearranged in ascending order of bone thickness, clearly shows this relationship (**Figure 10**).

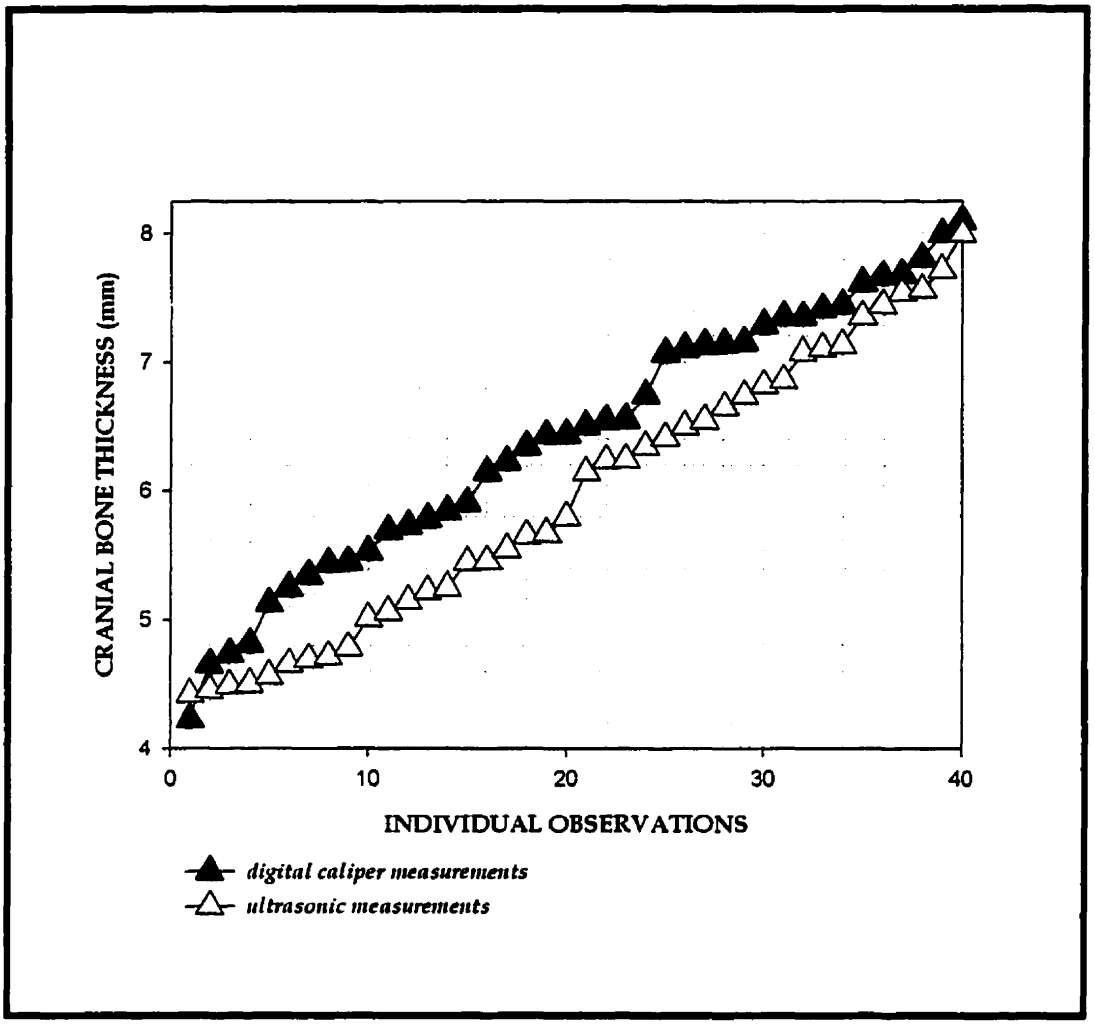

Figure 10. Comparison of digital caliper (direct) vs ultrasonic (indirect) calvarial thickness measurements (arranged in ascending order of bone thickness).

There was a tendency towards an increasing degree of thickness of the calvaria proceeding posteriorly (**Table 3**). However, a great degree of variability from point to point within each bone fragment was observed with both diagnostic modalities (**Figure 11**).

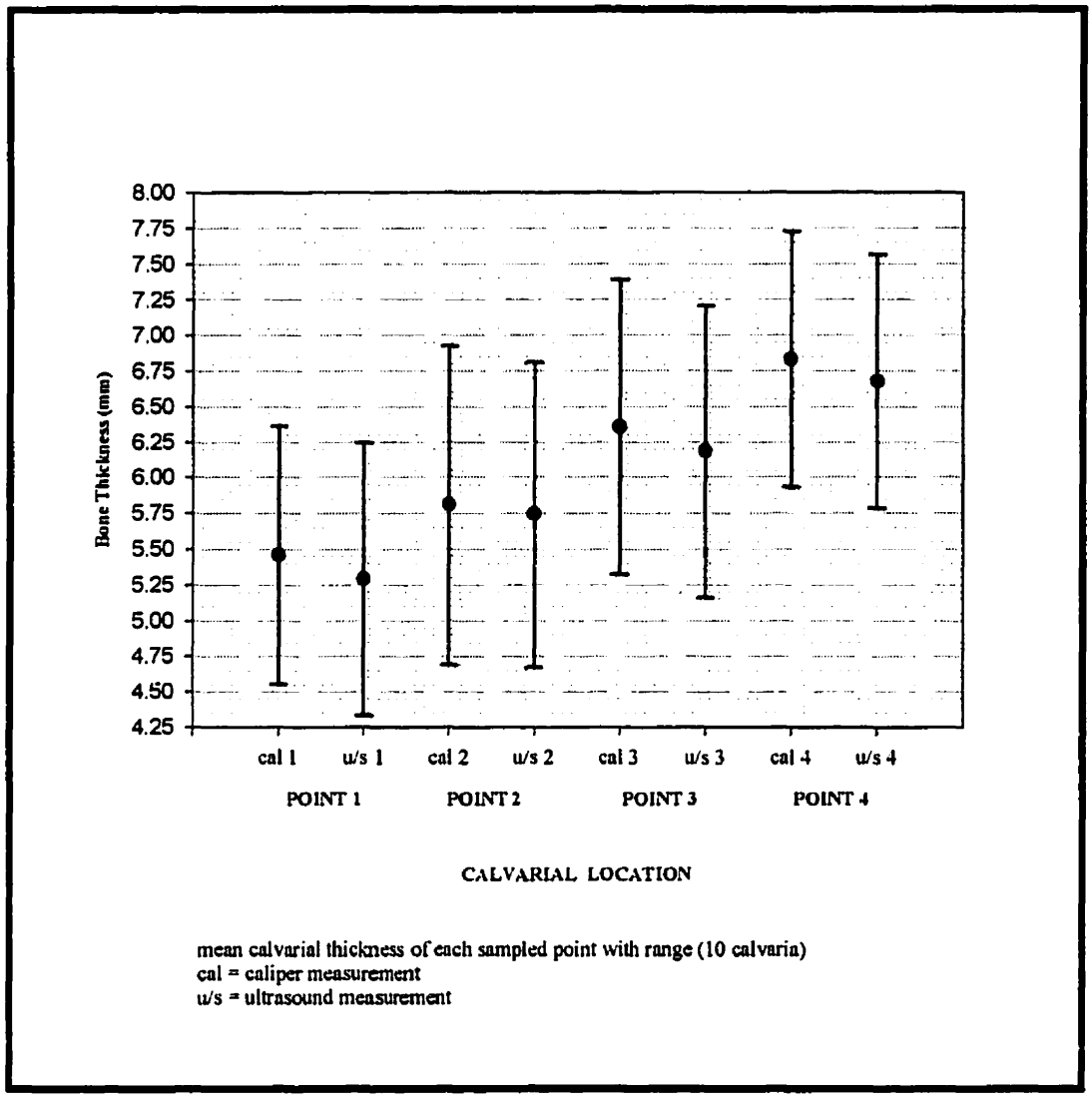

Figure 11. Variability in calvarial bone thickness of 10 cadaveric skulls.

Linear regression models were utilized to critically evaluate the association between the measurements obtained by the ultrasound and those obtained by the calipers. The first model included only the ultrasound measure as an indicator of the caliper measurement. This model showed that the adjusted R^2=0.988, which indicates an excellent

fit. It was further revealed that the majority of the variance within caliper measurements could be explained by the ultrasound. The parameter estimation for the ultrasound measurement was 0.997 with 95% confidence intervals between 0.962 and 1.032. What is important with this estimate is not only that it was significantly different than zero ($p < 0.001$), but that it was extremely close to 1, indicating near perfect agreement between the ultrasound and caliper measurements. This is indicated by the 95% confidence level which includes 1.

In any evaluation of measurement accuracy, it is important to assess the agreement between the test measurement and a gold standard. In this study, the experimental measurement is the ultrasound and the gold standard is the caliper measure. The assessment of agreement should be adjusted to take into account other factors that may cause variation in the gold standard. Not adjusting for these factors may cause spurious estimates of agreement. In this experiment, the factor that could cause a variation in the thickness of the skull were the cadavers and the location of the sampled points. Inclusion of these variables in a multiple linear regression model produced an adjusted R^2 of 0.988, which mirrored the result for the model with only the ultrasound measure. This finding indicates that the caliper measure could be accurately predicted by the ultrasound

without consideration to cadaver specimen or sampling point location. This is further supported by the fact that the parameter estimates for these 2 variables were not statistically significant. The parameter estimate for the ultrasound was 1.002 with a standard error of 0.02 which is not different than the one produced for the more simpler model. This parameter estimate was significantly different than zero ($p<0.001$), and not different than 1, again indicating almost perfect agreement between the two measures.

EXPERIMENT # 2

LIVE PORCINE SKULL MODEL

INTRODUCTION

In validating A-mode ultrasound as outlined in experiment # 1, a concerted attempt was made to control for potential confounding factors. Indeed, the contents of the cranial cavity, skin, periosteum and blood were conspicuously absent. This created an artificial situation, which nevertheless, served the purpose of examining the feasibility of acoustic signal measurements.

A condition that more aptly parallels the state encountered in the in-vivo, intraoperative setting, is necessary for further studies of validation, prior to extrapolating to the clinical situation. Moreover, the accuracy and precision of ultrasonic measurements under idealized conditions, documented in the first experiment, require a more critical examination.

This second experiment, evaluates A-mode ultrasound in a living, porcine model. The model was chosen because of the comparable degree of variability in calvarial thickness known to exist in this species, in addition to the relative ease and availability of obtaining enough specimens. The effects of underlying calvarial structures, including the hemodynamic contributions of blood flow within the diploic space and emissary vessels, will be examined for their respective impact on the acoustic measures. Diagnostic attempts at predicting calvarial thickness

in the more unpredictable environment of life, is a necessary stepping stone to future, human, clinical applications.

MATERIALS AND METHODS

The second study group consisted of 10 female Landrace pigs (25 ± 2 kg), obtained from the Animal Care Facilities and the Department of Surgery, Royal Victoria Hospital, Montréal, Canada. These animals were made available to us prior to the initiation of euthanasia for their primary experimental purpose of studying the effects of hepatic xenografts. They had been previously sedated with an intramuscular injection of diazepam (2 mg/kg), and anesthetized with inhalation of isofluorane 1-2%, mixed with 95% oxygen and 5% carbon dioxide. Following intubation, repeated doses of intravenous sodium pentobarbitol were titrated to achieve and maintain complete anesthesia. Intravenous buprenorphine 0.1 mg/kg was administered prophylactically, every 8 hours, to ensure appropriate analgesia.

The scalp of the pigs was incised and retracted to the level of the supraorbital rims bilaterally. A periosteal elevator ensured removal of any remaining soft tissues overlying the calvarium. The points chosen for sampling reflected the desire to include the spectrum of variability in the thickness of the porcine skull (**Figures 12a** and **12b**). The junction

of the median sagittal suture with the caudal coronal suture was designated as *point λ*. **Point 1** was identified for both left and right segments of the calvaria 2 cm anterior and lateral to the *point λ*. Similarly, **Point 2** was marked 2 cm posterior and lateral, bilaterally, to the suture line confluence.

Figures 12a and 12b. Calvarial points chosen for study from the porcine skull. Point 2 is situated over the temporal bone which is approximately triple the thickness of the calvarium underlying Point 1 (located over the frontal sinus).

Acoustic signal measurements were performed at the predetermined points, using a single crystal 1 MHz, 12.7 mm diameter, broadband, non-focused pulse-echo device (model SR 9000, Matec Corporation, Nautick, MA). The transducer was placed on an acoustic stand-off device, commensurate with the transition zone of the near and far acoustic field, with the application of coupling gel. This acoustic window is a cylindrical tube which couples the transducer to the skull in order to maintain and facilitate acoustic signal propagation when performing ultrasound outside of a fluid medium (**Figure 13**).[86,101]

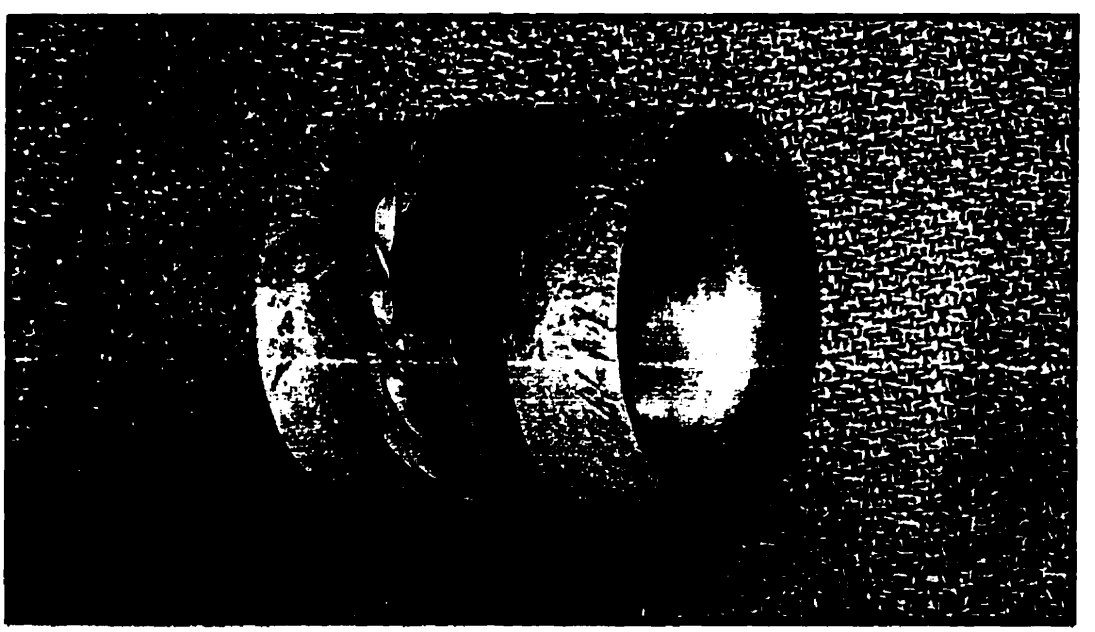

Figure 13. Acoustic window used as a stand-off device to facilitate ultrasound wave propagation through the calvarium.

After completion of the ultrasonic measurements, full thickness bone wedges were created using a sagittal saw. As a gold standard, these

bone segments subsequently underwent calvarial thickness measurements at the same marked points using standardized digital calipers (resolution: 0.01 mm, instrumental error: 0.02 mm, model 500, Mitutoyo Limited, London, UK.

STATISTICAL METHODS

A similar statistical method was employed to that used in Experiment #1. In summary, the accuracy of the measurements obtained using the digital calipers and the ultrasound were evaluated for both reliability and accuracy. Inter-rater (inter-observer) reliability was assessed by having the same measurement obtained by 3 different individuals at the same point in time. Intra-rater (intra-observer) reliability was evaluated by having the same individual obtain the same measurement at 3 different points in time. The validity assessed in the present study was evaluated by the association between the estimates obtained using the ultrasound and the calipers. This association was assessed by the difference between the 2 measurements, the student's *t*-test, multiple linear regression models and the Pearson correlation test.

RESULTS

The mean weight of the study population was 26.7 kg (range 24.1 - 29.3 kg). **Table 4** displays the average of 6 measured values, 3 inter-observer and 3 intra-observer values, for porcine calvarial thickness at each of the points sampled in millimeters.

	LEFT SIDE				RIGHT SIDE			
	Point 1		Point 2		Point 1		Point 2	
	caliper (mm)	u/s (mm)	caliper (mm)	u/s (mm)	caliper (mm)	u/s (mm)	caliper (mm)	u/s (mm)
pig 1	3.07	2.62	9.69	9.31	3.15	2.87	9.53	9.08
pig 2	3.43	3.12	8.94	8.62	3.31	3.03	9.04	8.88
pig 3	2.94	3.07	9.40	8.92	2.90	2.78	9.33	8.94
pig 4	3.02	2.88	9.57	9.76	3.11	3.00	9.43	9.20
pig 5	3.21	2.95	9.99	9.43	3.14	2.89	10.02	9.84
pig 6	3.33	2.81	8.91	8.21	3.41	3.06	9.32	9.10
pig 7	3.09	3.17	9.14	8.62	3.16	2.94	9.54	8.89
pig 8	2.81	2.35	9.21	8.68	3.01	2.70	9.08	9.19
pig 9	3.11	2.85	8.85	8.61	3.33	2.78	8.94	8.21
pig 10	3.17	2.94	9.07	8.74	3.11	3.20	9.21	8.59

Table 4. Comparison of caliper and ultrasonic porcine skull thickness measurements.

Inter-observer differences for the caliper and ultrasound measures did not exceed 0.29 mm and 0.65 mm, respectively. Intra-observer differences ranged from a maximum of 0.20 mm with the calipers and 0.59 mm for the ultrasound. This data confirms the relative reliability and reproducibility of the data set generated for this experiment.

The difference between the ultrasound and the caliper measurements of calvarial thickness were tabulated for all observations. As in experiment # 1, 10 calvaria and 4 sampled points on each skull were tested, for a total of 40 observations to compare the 2 diagnostic modalities. The mean (S.D.) for all caliper measurements was 6.23 mm (2.36 mm), and that of the ultrasound was 5.92 mm (3.07 mm). The mean difference between the 2 modalities was 0.31 mm, with a standard deviation of 0.22 mm and a standard error of 0.06 mm. The paired student's t-test for dependent samples revealed that the 95% confidence interval for the difference in means to reach statistical significance, the value would have to be outside the range of values between 0.23 mm and 0.38 mm. Therefore, the difference between the ultrasound and caliper measurements is not statistically different.

Table 5 displays the gross difference between the acoustic and direct, caliper bone thickness measurements.

	LEFT SIDE		RIGHT SIDE	
	Point 1 Difference (mm)	Point 2 Difference (mm)	Point 1 Difference (mm)	Point 1 Difference (mm)
pig 1	0.45	0.38	0.28	0.45
pig 2	0.31	0.32	0.28	0.16
pig 3	-0.13	0.48	0.12	0.39
pig 4	0.14	-0.19	0.11	0.23
pig 5	0.26	0.57	0.25	0.18
pig 6	0.52	0.70	0.35	0.22
pig 7	-0.08	0.52	0.22	0.65
pig 8	0.46	0.53	0.31	-0.11
pig 9	0.26	0.24	0.55	0.73
pig 10	0.23	0.33	-0.09	0.62

Table 5. Difference between caliper and ultrasonic porcine calvarial thickness.

As noted previously in experiment # 1, the acoustic measurements consistently underestimated the caliper measure in the vast majority of sampled points (**Tables 4** and **5**). The mean ultrasound value was lower in 35 of 40 observations. Nevertheless, the Pearson moment test, supported both a strong and positive correlation between the 2 measurement modalities ($r > .888$).

A visual representation comparing the bone thickness measurements using ultrasound with the true calvarial thickness, rearranged in ascending order of bone thickness, depicts the convergent accuracy of this modality (**Figure 14**).

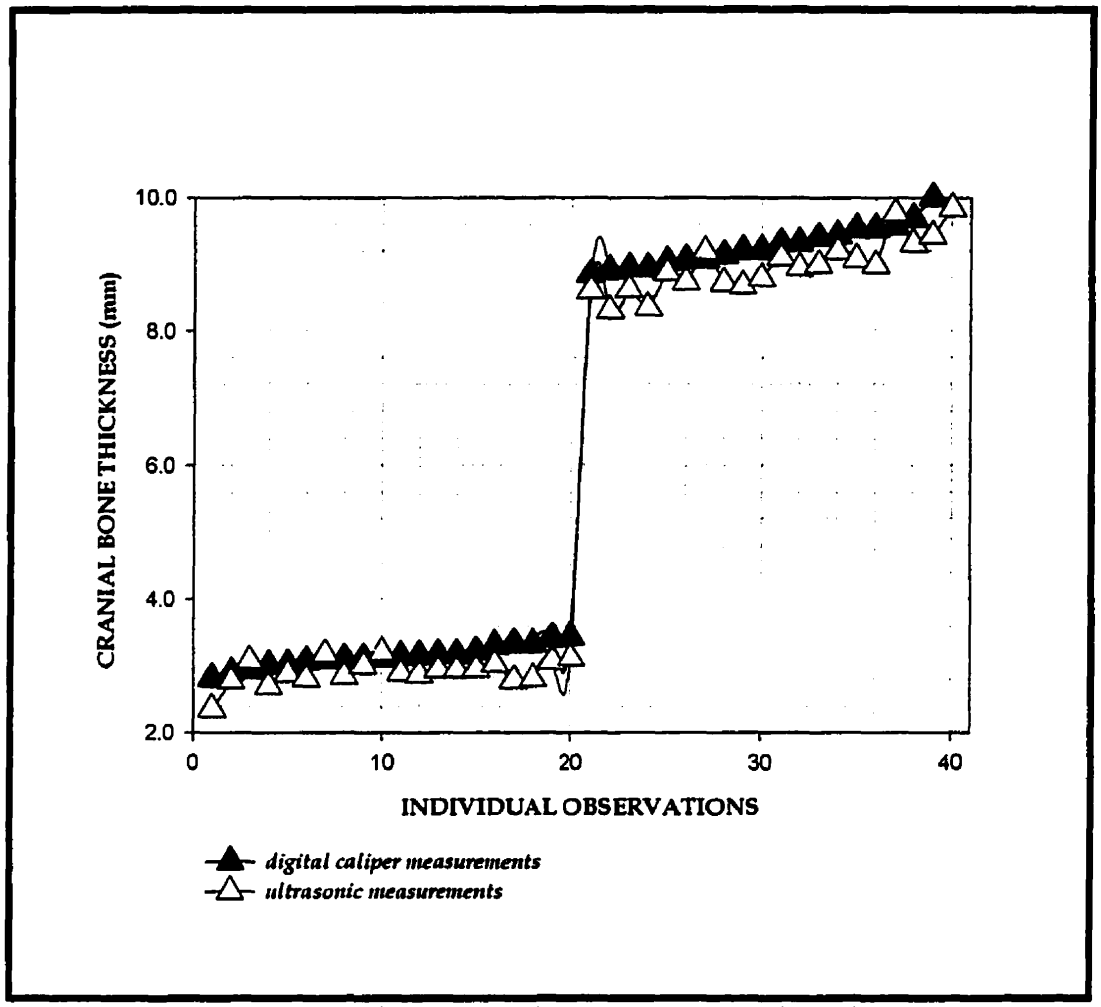

Figure 14. Comparison of caliper vs ultrasonic porcine calvarial thickness measurements (in ascending order of bone thickness).

The degree of variability in the measurements for each of the points sampled is shown in **Figure 15.**

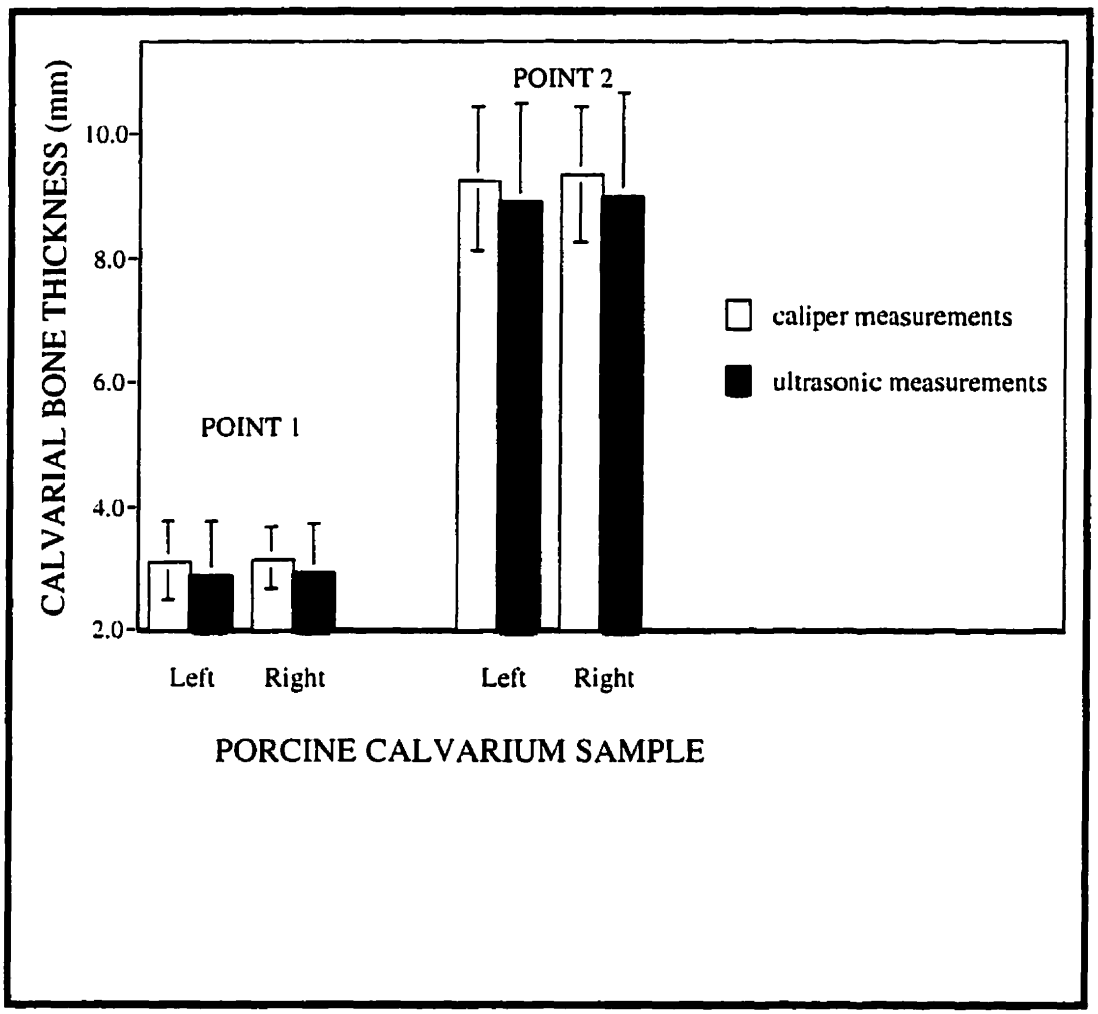

Figure 15. Variability in calvarial bone thickness in 10 porcine skulls using ultrasound and caliper measurements.

Linear regression models were utilized to evaluate the association between the measurements obtained by the ultrasound and those obtained by the calipers. The first model included only the ultrasound measure as an indicator of the caliper measurement. This model showed that the adjusted $R^2 = 0.901$, supporting a strong fit. It was

further revealed that the majority of variance within caliper measurements could be explained by the ultrasound. The parameter estimation for the ultrasound measurement was 0.898 with 95% confidence intervals between 0.854 and 1.109. This clearly indicated convergence in agreement between the ultrasound and caliper measurements.

DISCUSSION

The acoustical impedance mismatch at the ultrasound wave - cranial bone interface provided the impetus for this investigation. The acoustic wave generated at the initial contact point with the outer cortex, and the corresponding reflection of the wave leaving the inner table, has been shown by this study to be an extremely reliable measure of actual skull thickness. The maximum discordance between the caliper (direct) measurements and the ultrasound (indirect) measurements was less than a third of a millimeter (0.32 mm) in experiment #1 (**Table 2**), and did not exceed three quarters of a millimeter (0.73 mm) in the live animal model (**Table 5**).

Experiment # 1 examined an in-vitro condition, where a great number of variables were controlled for. Specifically, the periosteum, scalp and all underlying structures were removed. Moreover, the ultrasound measurements were performed with the points of study chosen in a standardized format, with the segment of bone isolated and fixed in space relative to the ultrasound probe. These idealized conditions clearly served the purpose of validating A-mode ultrasound in the assessment of calvarial bone thickness. Acoustic measurements were revealed to be extremely accurate, valid and reproducible. Inter-observer and intra-observer differences were less than 0.47 mm across 3 different investigators at 3 different times, for both ultrasound and

caliper values. The precision of ultrasound, as evidenced by the consistently, near-accurate measurements, clearly warranted further investigation.

Cadaveric skull dissections, correlated with appropriate patient-based studies, have demonstrated significant regional variations in the thickness of the human skull. The experimental model chosen for the first experiment attempted to parallel the state encountered in-vivo, however, many ambient factors were not at play. The effects of these variables needed to be better defined, which was the stated outcome of the second experiment.

The variability in calvarial thickness is less pronounced in the pig, but nevertheless, provided for a simple model to test ultrasonic thickness measurements in the living condition. The first point chosen for study was situated over the frontal sinus, a region of bone known to be relatively thin in the pig, while the second point was chosen from a region of significantly thicker bone, the temporal skull. These 4 points of study, (both right and left sides), allowed for the evaluation of the applicability of ultrasound across disparate segments of calvarial bone.

In examining the reproducibility and reliability of the caliper measurements, the results mirrored those seen in the first experiment. However, similar parameters for the ultrasound were approximately

double than encountered in experiment # 1. The reason for this was not quite clear, but could be related to the underlying cranial bone structures that compromised the definition of the interface between the inner cortex of the skull and the intracranial cavity. While harvesting cranial bone at the studied points of reference after the ultrasound measurements, it was noted that the dura appeared quite adherent to the inside of the cranium. The proximity of the dura to the inner cortex of the skull could be a reasonable explanation for this observation, however, further attention to this detail is needed to arrive at a definitive conclusion. Regardless of the contributions of the dura, the underlying brain and blood within the diploic space, this segment of the study yielded reasonably precise ultrasonic measurements. The mean difference from the true calvarial thickness approached 0.31 mm, which although accurate in its own right, was still double that obtained in the cadaver skull model.

The ultrasound thickness measure consistently underestimated the actual cranial bone thickness. In experiments #1 and # 2, the caliper estimate was greater for 95% (38 of 40) and 88% (35 of 40) observations, respectively. This would suggest that the ultrasound systematically produced estimates which were less than those obtained by the digital calipers. The reasons for this minimizing systemic bias are unclear,

however, it is felt that the attenuation of the ultrasound beam through inhomogenous calvarial bone is responsible. This characteristic of calvarial bone could not be appropriately factored into the acoustic signal measurements. The different regions of bone architecture and relative density most likely results in a diminished, or at least variable, time of flight of the ultrasound wave. This translated into a decreased ultrasonic thickness measurement as our methodology does not, and frankly, cannot, adapt for the variation in the proportion of cancellous to cortical bone existent in a segment of scanned calvarium. In a final A-mode ultrasound prototype, this error could be simply offset with proportional calibration. In any event, the ultrasound values did not underestimate the direct (caliper) measurements by more than an average of 0.16mm (S.D. = 0.09mm) in experiment # 1, and 0.31 mm (S.D. = 0.22 mm) in experiment # 2. More importantly, as applied to the clinical situation, in the instances where the ultrasound measurement exceeded the true calvarial thickness, the maximum error amounted to only a 0.19 mm overestimate; a value of limited, if not negligible, importance. Furthermore, there did not appear to be any specific pattern to the ultrasound's estimate of this particular error (**Tables 2** and **5**).

The underestimation of cranial bone thickness by the ultrasound probe, on the other hand, was predictable across the vast majority of points sampled. These points covered the entire spectrum of calvarial thickness measurements from a minimum of 2.35 mm to a maximum of 10.02 mm (**Tables 1** and **4**). Proportional calibration with the appropriate coefficient can be introduced to offset this incongruity. Nevertheless, the minimal discrepancies in bone thickness do not pose any clinical consequences, and actually can serve as a benchmark for the least possible thickness measure for a scanned segment of calvarium.

The importance of the diploic space in the successful harvest of split calvarial bone grafts has been alluded to by a number of authors.[4,44,47] Attempts to delineate the thickness of the diploic space in this study were limited by artifact and interference, which made it difficult to distinguish its boundaries. A change in ultrasonic waveform amplitude in the reflected signal as it traveled through the substance of the calvaria was indeed recognized. However, due to the lack of a clear interface from cortical to cancellous bone, this potential space could not be accurately identified at the present time. Furthermore, as previously described, the overlying soft tissues and periosteum were removed prior to the direct and indirect thickness measurements in both experiments. Trials of acoustic signals with these tissues in place

created significant interference and unreliability of the probe's measurements. It appears that the ultrasound technique that we have described in the materials and methods, requires an uninhibited ultrasound probe - outer calvarial cortex interface in order to achieve the precise and accurate measurements that we have obtained. Newer, "contact" transducers, which are more powerful and less affected by tissue interface artefacts, could overcome this limitation. Clearly, these issues represent further avenues of investigative study, perhaps requiring experimentation with the use of different frequencies of insonification and refinements in waveform analysis. Indeed, the ideal ultrasonic probe should be capable of measuring the overall thickness of various aspects of the cranial skeleton, as well as demarcating the boundaries of the diploic space. It is of important clinical significance that this be performed in the presence of both over and underlying soft tissues, in-situ, over the scalp, facial skin or mucosa.

In addition to minimizing the intracranial complications and overall surgical morbidity from overestimation of calvarial thickness during cranial bone harvesting, the potential for this predictive modality has significant implications for the craniomaxillofacial and neurosurgical patient. Other applications can be anticipated as progress is made in the refinement of this ultrasound probe. Specifically, this

tool can be used in the assessment for the optimal placement site of intra-oral (dental) and extra-oral osseointegrated implants for maxillofacial, external ear and/or hearing rehabilitation.[102-105] Further uses could allow for the development of detailed data on skull thickness anthropometrics as a function of age.

Ultrasound technology has been used in the tissue characterization of a variety of anatomic structures, but never, to our knowledge, to assess the thickness of the calvarium. This series of experiments represents the first such attempt to document the validity of ultrasonic measurements for this purpose. The results have shown that ultrasound can provide immediate real-time measurements in a reliable, repeatable and accurate fashion, in both in-vitro and in-vivo conditions. This study has revealed minimal discrepancies between the direct (caliper) and indirect (ultrasonic) measurements, reflecting the validity of A-mode ultrasound in assessing calvarial thickness. This degree of reliability and accuracy can offer the reconstructive surgeon an invaluable tool in mapping out areas ideal for cranial bone harvesting. Ultrasound should allow for the immediate preoperative and intraoperative measure of skull thickness that can identify those areas of the calvarium that have the potential to cause complications. It is presumed that a portable ultrasound probe will result in enhancing

the efficacy and ultimate safety of calvarial bone harvesting and related procedures in a non-invasive, inexpensive and technically simple fashion.

Many issues in refining this type of device remain to be elucidated. Nevertheless, it is hoped that this work offers further insight, through objective data documentation, of the ever-increasing value of ultrasonic evaluation. A particular strength of this work is that the ultrasonic measurements have been correlated with clinical data in both experiments. A-mode ultrasound has proven accurate and valid in both of these clinical situations. This preliminary investigation allows for a reasonable conjecture of the application of this technology to the real, clinical scenario.

CONCLUSION

The current knowledge on the topic of predictive studies of calvarial thickness is limited. With the increasing performance of cranial bone grafts and related craniomaxillofacial procedures, a new modality to determine the thickness of bone has been recognized as a priority.[80] These initial set of experiments have clearly shown that measurements of skull thickness obtained through the use of A-mode ultrasound, in both human cadaveric and living animal skull models, are valid, reliable and accurate. In addition to minimizing the intracranial complications and overall surgical morbidity from overestimation of calvarial thickness during cranial bone harvesting, the possible implications of this imaging modality are many. These potential applications range from its adjunctive use in the optimal placement of osseointegrated implants, to adequate timing for craniofacial surgery in the pediatric population and the development of detailed data pertaining to skull anthropometrics.

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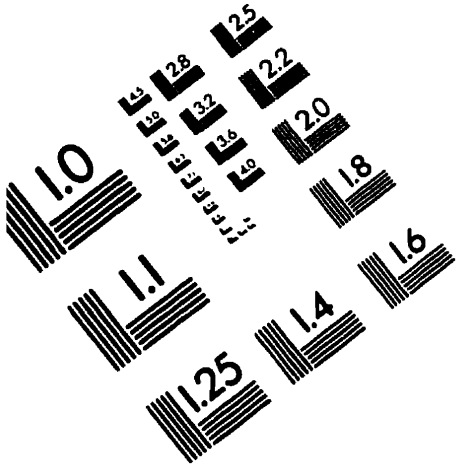
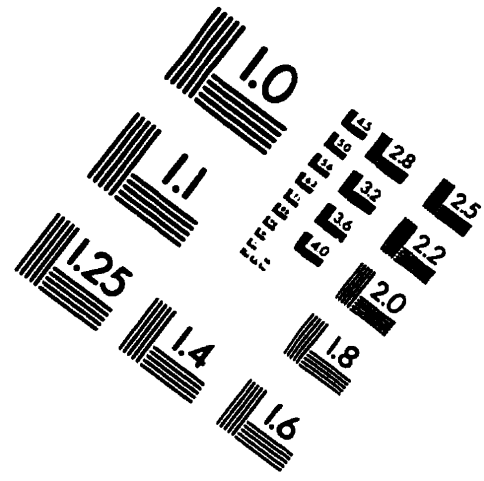
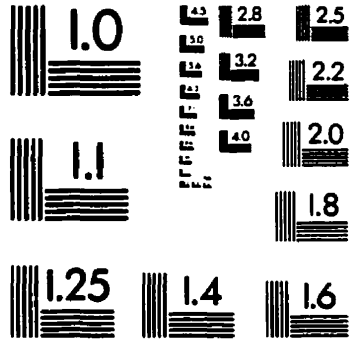
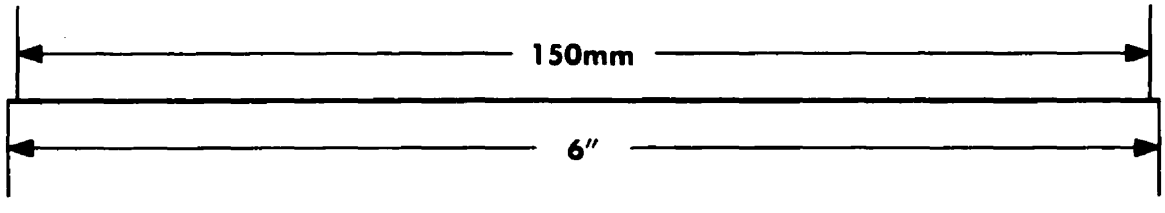
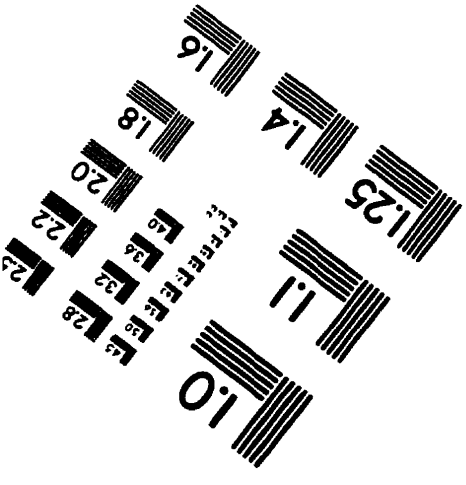
IMAGE EVALUATION
TEST TARGET (QA-3)











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