Mechanical factors affecting intracochlear pressure variation during in vitro cochlear implantation

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This thesis is presented for the degree of Master of Surgery of
The University of Western Australia

School of Medicine
The University of Western Australia

Year of submission 2021

Abstract

In this in-vitro study, changes in intracochlear pressure were measured against: varying speeds, different depths; and level versus underwater insertions, of a dummy implant electrode array into an artificial cochlea model.

Two variables were used to measure intracochlear pressure variation, measuring both transient and aggregate changes in pressure. Additionally, a novel surgical assistance device was used to maintain consistent performance. A total of 240 insertions were performed to avoid type II error.

The study found that a deeper insertion was associated with a greater maximal transient intracochlear pressure variation (MTICPV) (0.059+/-0.007kPa versus 0.04+/-0.011kPa). The study also found that performing an insertion underwater was associated with increased MTICPV (0.069+/-0.022kPa versus 0.03+/-0.003kPa).

The study did not demonstrate a relationship between the speed of insertion and the MTICPV to a level of statistical significance. During the initial insertions, there were several large outliers. A portion of these experiments that were identified by analysis of a scattergram were subsequently repeated, demonstrating no statistically significant difference between the speeds over 30 seconds ((0.044+/-0.023kPa), 60 seconds

(0.055+/-0.018kPa) and 120 seconds (0.05 +/-0.021kPa). This may also suggest a relationship between surgeon experience and intraoperative ICPV.

The study of aggregate intracochlear pressure variation (AICPV) did not contrast significantly with the MTICPV, as deep insertions (35.08+/-5.4kPa versus 10.62+/-3.30kPa) and underwater insertions (39.818+/-6.94kPa versus 5.88+/-1.45kPa) were again associated with significantly greater pressure variation.

The present study contributes to the current understanding of the literature by producing what is currently the largest in vitro study looking at intracochlear pressure variation, and using it to further develop an understanding of key variables associated with soft surgical techniques. As well as redefining the role of speed in hearing preservation surgery, the present study gives reason for caution when undertaking underwater insertions in clinical settings. The study also correlates with current literature to support the growing significance of the upper basal turn of the cochlea as a point of vulnerability during cochlear implantation.

With ongoing surgical research, it is the hope of the author that consistent hearing preservation in cochlear implantation may be closer to reality.

Acknowledgements

Firstly, I would like to acknowledge and thank my supervisor, Professor Gunesh Rajan. This study would not have started without his encouragement and support.

I'd like to thank Mr Marty Firth of the University of Western Australia for his guidance regarding statistical analysis. He was an immense help.

I'd like to also thank Dr Aanand Acharya, whose logical thought process and meticulous nature ensured that my study adhered to a rigid scientific method.

I would like to deeply thank Professor David Fletcher, for his invaluable guidance and wisdom in helping me achieve completion of my thesis, and helping me to become a better surgeon.

Lastly, I am grateful to all of those with whom I have had the pleasure to work with during this and other related studies.

This research was supported by an Australian Government Research Training Program (RTP) Scholarship.

Declaration of candidate contribution

The content of this thesis is entirely of my creation, with the kind guidance and support of my supervisors.

It has been created entirely during the course of my degree and does not breach any ethical rules with regard to the conduct of the research.

[redacted]

Dr. William Crohan

30th August 2021

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Abbreviations

MTICPV	Maximal Transient Intracochlear Pressure Variation
AICPV	Aggregate Intracochlear Pressure Variation
UWA	The University of Western Australia
PC	Personal Computer
LED	Light Emitting Diode
CSF	Cerebrospinal Fluid

1. Introduction

1.1. Hearing loss and cochlear implantation

Hearing loss is a common and disabling impairment that is increasing in prevalence and significance worldwide. It was estimated in 2018 that 6.1% of the world's population (466 million people) were living with some form of a disabling hearing loss, which reflected an increase from an estimated 42 million people in 1985.(1) This significant increase is attributable to a number of factors including (but not limited to) increased life expectancy, global population growth and increased noise exposure.(1)

Sensorineural hearing loss, caused by damage to the inner ear, is most commonly an irreversible disability and is the most common cause of hearing loss worldwide.(1) It has been estimated that up to 50% of people over the age of 65 in Australia suffer from moderate or greater hearing loss.(2) Hearing aids are currently the most frequently used treatment for hearing loss, however, in the case of severe hearing loss, are often inadequate and insufficient.(3, 4)

Cochlear implantation is a surgical procedure whereby an electrode array is inserted directly into the inner ear. The array is then able to directly stimulate the cochlear nerve, bypassing the damaged inner ear and providing a sense of hearing to people with severe to profound hearing loss.

1.2. Electrode array trauma

It has long been appreciated that the act of inserting an electrode array into the cochlea has the potential to cause damage to the delicate inner ear structures.[5] Initially, it was held that the potential for loss of natural residual hearing caused by implantation was considered to be an acceptable casualty in those who were deemed to be severe to profoundly deaf, with the loss of vestibular function arguably disregarded.[6]

As the clinical observations of hearing preservation after cochlear implantation emerged in the late 1980's, surgeon heralded the advent of a new field of research, inquiring into the vulnerability of inner ear structures to trauma from cochlear implantation. This has subsequently resulted in a broader understanding of the nature of the trauma to the cochlea and highlighted the vulnerability of specific inner ear structures such as the basilar membrane and hair cells within the organ of corti, as well as the secondary involution of the organ of corti and the neural structures such as the spiral ganglion cells due to inflammation, fibrosis and a lack of auditory stimuli.[7-11]

The term “soft surgery” as a means of preserving inner ear structures was first used in 1993,[12] before the benefits of structure preservation became better appreciated. As the research has now progressed further, several theories have emerged extolling the importance of structure preservation in cochlear implantation, including functional hearing benefits, vestibular preservation and future proofing of the inner ear for new therapies such as hair cell regeneration or stem cell therapy.

1.3. Residual hearing preservation

The utility of electro-acoustic stimulation, where a person's residual hearing is supplemented by a cochlear implant, began to gain appreciation in the late 1990's.[13-16] The deficiencies of hearing aids and the understanding that there was a "gap" that could be addressed through cochlear implants became better understood from research demonstrating that hearing aids resulted in only partial improvements for individuals with hearing thresholds beyond 55-60dB hearing loss and was of limited benefit to individuals with ski-slope hearing loss.[3, 4, 17]

It was postulated by Adunka in his 2010 paper[18] that the preservation of residual hearing is necessitated by the inherent deficiencies in cochlear implants relative to natural hearing. Adunka surmised that acoustic input from a cochlear implant must undergo signal processing prior to presentation of a signal to the inner ear, which alters the volume and depth of information delivered to the auditory system. Furthermore, the signal received in the cochlear implant is split into tonotopic spectral segments, like pixels on a computer screen, rather than presenting the smooth frequency continuum of the inner ear, further compromising signal quality. Lastly, the direct electric stimulation of the spiral ganglion by the cochlear implant has a compressed dynamic range of only 10dB available for functionality, compared to over 100 dB in a healthy ear.[18]

Clinically, it has been established that preserving residual hearing during cochlear implantation leads to better speech recognition, speech perception in noisy environments, sound localisation,[3, 4, 13, 15, 19-24] and music perception.[25]

Further, with respect to electro-acoustic stimulation hearing, it has been established that following rehabilitation, the two methods of hearing (residual and inserted) are complementary rather than competitive. In his 2014 paper,[17] Skarzynski explored the impact of aiding preserved low frequency residual hearing with hearing bestowed by a cochlear implant. Skarzynski resolved that speech recognition scores improved significantly in both quiet (76% versus 36%) and in background noise of 10dB (68% versus 9%). Skarzynski also found that subjects with stronger preoperative low-frequency hearing experienced equal or greater improvements in speech perception, therein suggesting that cochlear implantation had an additive and synergistic effect with residual hearing. Consequently, research has focused on methods for preserving residual hearing in cochlear implantation.

The combination of the potential shortcomings of cochlear implants identified by Adunka, Skarzynski and others manifest in a clear argument for advocating hearing preservation to achieve better patient outcomes.

1.3.1. Anatomical factors affecting hearing preservation.

The cochlea is a spiral shaped structure divided into three compartments: the scala tympani; scala media; and scala vestibuli. The chemical composition of the scala tympani and scala vestibuli reflect that of an extracellular environment, with relatively high levels of sodium and low levels of potassium. In contrast, the scala media may be likened to an intracellular environment with comparatively high potassium and low sodium concentrations. Whilst the electrochemical gradient created by this disparity is essential to the perception of sound, a breach of these chemically distinct areas of the cochlea through a traumatic insertion is associated with a loss of hearing [(6, 26)].

The upper basal turn of the cochlea, between approximately 90 and 270 degrees of rotation, is an important region for the preservation of residual hearing. It contains a greater number of spiral ganglion cells than any other segment of the cochlea and of which the successful stimulation is essential for optimal implantation outcomes.[(27)] The upper basal turn has also frequently presented as a particularly vulnerable region during cochlear implantation, with disproportionately more histological trauma.[(28-32)] In a histological study, Biedron[(33)] demonstrated that the cochlear lumen diameter does not decrease in a linear fashion, but rather varies in the same rate at which the diameter decreases. The lumen of the cochlea is physically narrowed at the upper portion of the basal turn, which is an important finding considering the level of trauma that is found to occur at this location. It is theorised that the trauma may be attributable to a relatively narrow lumen, which is a consequence of the close proximity of the carotid artery during development.[33] Whilst the narrowing of this portion of the cochlea may leave the inner ear structures vulnerable to electrode array insertion trauma, it has also been demonstrated that a straight trajectory of insertion to the basal turn may produce higher insertion forces and consequently more focal trauma at the upper basal turn.

1.3.2. Intracochlear pressure variation

Many earlier in vitro studies investigating hearing preservation previously focused on insertional force as a marker for intracochlear trauma.[16, 34-36] As soft surgical techniques have developed, this has become problematic, as studies with relatively insignificant histological trauma have demonstrated poor hearing preservation.[32, 37-40] In his 2014 paper, Todt[41] points out that force and intracochlear trauma have occasionally operated in contradictory fashions,[34, 36] further suggesting that another factor is important for hearing preservation.

With respect to the identified association between intracochlear pressure variation during cochlear implantation and the potential resulting trauma, it is important to understand the transference of acoustic sound levels into intracochlear pressure variations; that is, the external sound level equivalent for a given intracochlear pressure change. Greene[42] makes an important contribution to explaining intracochlear pressure variations by demonstrating the two pressure levels (of the EAC and intracochlear pressure levels) to be roughly comparable during implantation. This is due to the frequency of transient intracochlear pressure variation. In vitro models frequently find these transients to last 0.1-0.2s,[42, 43] equivalent to 5-10hZ. At these low frequencies, the sound transfer function of the middle ear is 1, or unamplified, when travelling through the middle ear, and accordingly, the consequences of intracochlear pressure variation is clear.

A particularly good insertion may see a transient rise in pressure of approximately 0.1kPa inside the cochlea, and a poor insertion possibly 2.0kPa[41, 44] (this translates to approximately 133dB to 160dB). Of comparable sound frequencies, this threshold and frequency is comparable to blast trauma.[45]

Initial studies investigating the causes of residual hearing loss identified key histopathological events outlined above, such as basilar translocation or the electrode array tip fold-over, as critical events during structure preservation implantation. Even with major advances in soft surgery techniques however, a postoperative rate of 100% hearing preservation remains elusive.[46]

With speed[47], CSF fluid gusher,[48] and electrode array stabilisation[49] all demonstrating a significant effect on hearing preservation, it is highly likely that minimising intracochlear pressure variation has an important yet underappreciated role in structure preservation.

1.4. Factors affecting hearing preservation.

The “Two Hit" model is a helpful concept to describe the processes responsible for trauma to the inner ear during cochlear implantation.[49] The First Hit occurs during cochlear implantation surgery as a result of the various mechanical forces during the surgery. The Second Hit comprises of the different responses of the inner ear after the electrode array insertion.

1.4.1. The First Hit

The inner ear is a delicate, complex structure. Certain structures within the inner ear are more susceptible to trauma than others, the consequences of which can be seen in the immediate loss of residual hearing experienced by some patients. Certain complications during a cochlear implantation surgery logically may produce an immediate drop in all, or a portion of, a patients residual hearing. This may include a tear to the basilar membrane, such as in electrode array translocation, that allows the intermixing of the perilymph and endolymph and exposes the organ of corti and stria vascularis to toxic environments.[50] Further damage or violation of the endosteum (e.g during cochleostomy) may result in a Second Hit (which is discussed in greater detail below at paragraph 1.4.2) via an inflammatory response of the cochlear endosteum which in turn can lead to neoosteogenesis.[51] Similarly, penetration of the spiral ligament compromises blood flow through the stria vascularis, invoking an inflammatory response,[52] and disruption of the osseous spiral lamina would likely disrupt the dendrites from spiral ganglion cells present within, causing immediate hearing loss and eventual spiral ganglion cell degeneration.[39]

With respect to the vulnerable structures within the inner ear, it has been theorised that trauma to the stria vascularis, based laterally in the spiral ligament, risks blood vessels which are more susceptible to trauma, such as the posterior spiral vein and its tributaries. The lateral wall of the inner ear also contains microchannels through the spiral ligament connecting the scala tympani to the scala vestibuli, as evidenced by the presence of identical micropores on the surface of the round ligament, above and below the basilar membrane.[38, 39, 53]

Given the delicate structure of micropores, it can be theorised that these micropores when damaged may block off and prevent the balance of fluid between the scala vestibuli and scala tympani. This is supported experimentally by observations demonstrating the swelling of the scala tympani postoperatively, presumed to be a largely inflammatory reaction.[39]

Within the medial aspect of the cochlea, it has been shown that the osseous matrix (such as that covering the spiral ganglion and modiolar vasculature) is more fragile and fractures more easily relative to other elements of the cochlea.[39] Even without an osseous fracture, trauma due to pressure change may be enough to induce an inflammatory response.[38, 39, 53-55] Recent experimental studies have demonstrated this phenomenon histologically.[37] As such and as noted above, the medial aspect of the cochlea is more sensitive to electrode trauma, and especially meticulous care should be taken to reduce intracochlear pressure variation and protect the medial structures intraoperatively.[39]

1.4.2. The Second Hit

Following the direct tissue trauma of electrode insertion, a reaction occurs in the cochlea whereby residual hearing is reduced through an inflammatory response, which may result in apoptosis of the hair cells and neural structures followed by fibrosis and ossification of the affected parts of the inner ear.[40] These changes exhibit themselves in a manner commencing at the upper basal turn twelve hours post traumatic implant insertion, with a progressive increase in radicals and products associated with necrosis.[56] Reactive cytokines and inflammatory products including TNF-a, IL-1B, iNOS, COX-2, Caspase C,[57] and JNK[56, 58, 59] are critical to the inflammatory cascade and have been demonstrated as potential pharmacological targets.

Fibrosis and ossification are natural scar responses following inflammation, but have been demonstrated to be counterproductive to the preservation of residual hearing.[60] Products such as TGF-B1, TGF-B3 and CTGF are known to stimulate the scar response,[40, 57, 61] and yet have also been shown to be particularly responsive to topical corticosteroids.

As well as proliferation, inflammatory signals have also been demonstrated to be critical to the initial apoptotic signal via the classical pathway that disproportionately affect hair cells and neural tissue.[18, 40] The outer hair cells and spiral ganglion neuron fibres have shown to be particularly vulnerable to apoptosis.[62] This appears mediated by p-c-Jun, Caspase 3 amongst other factors, and is supported by the presence of reactive oxygen species and antihydroxynonenal, a highly reactive membrane peroxidation product, in apoptotic environments.[63]

As techniques for soft surgery have developed, more histological studies have emerged where the loss of residual hearing is seen despite the absence of any initial overt trauma to the cochlea. Loss of residual hearing in these cases is sometimes gradual and has been attributed to the invocation of inflammatory reactions during the initial cochlear implantation and the subsequent foreign body reaction to the inserted electrode array.[49] It is also possible that the magnitude of initial trauma, possibly through pressure variation, is correlated with loss of residual hearing, as demonstrated with CSF gusher,[48] and blast trauma.[37]

1.5. Structure Preservation Surgery

There has been extensive research into the modifiable factors of cochlear implantation surgery. The literature discussed below advocates for the use of a straight, flexible electrode, delivered through a round window approach, with adjunctive use of corticosteroids, to improve rates of hearing preservation. This study considers other factors such as the speed of insertion, depth of insertion, and use of an underwater surgical technique, all of which have been suggested as variables that may improve patient outcomes.

1.5.1. Corticosteroids

Even with a "textbook" perfect insertion, it has been suggested that the sheer presence of an electrode array as a foreign body produces an inflammatory response, evidenced by the histological obliteration of the scala tympani by fibrosis as a response to an inert foreign body.(64)

The perioperative administration of corticosteroids has been shown to be integral to the preservation of residual hearing, with a strong association between high dose dexamethasone applied topically, and a reduction in inflammatory products and apoptosis.(40, 57)

Furthermore, there is convincing evidence to support the administration of topical steroids, which have been shown to provide relief from an inflammatory response and act in a dose dependent fashion.(62, 65-67) The effect of the topical steroid is strongest at the basal turn with the opening of the round window, and comparatively weaker at the apex of the cochlea. In turn, there has been evidence to support the adjunctive and synergistic use of intravenous corticosteroids which likely have better distribution to the apex of the cochlea via a 'leaky' blood-labyrinth barrier in these apical regions of the cochlea.[65, 68]

Regarding future developments, there is likely promise for electrodes infused or coated with corticosteroid or other apoptosis inhibitors for slow delivery over time, and some studies have demonstrated significant hearing preservation using this method.[54]

1.5.2. Cochleostomy versus Round Window Access

The merits of accessing the cochlea through a cochleostomy or via the round window have been fiercely debated like few other areas within cochlear implant research. Compelling arguments have been historically made for both cases, with a consensus regarding the round window as the superior access point only emerging in recent years.

Briggs[69] in 2005 argued that soft surgery necessitates the use of a cochleostomy to guarantee insertion into the scala tympani because of the complexity of the hook region of the cochlea at the opening of the round window. Specifically, it was argued that cochleostomy should be placed inferior rather than anterior to the round window niche due to the risk of insertion into the scala vestibuli and of exposing the attachment of the basilar membrane and spiral ligament. Additionally, Briggs argued that a sup-optimal insertion trajectory associated with round window insertion could result in a loss of hearing preservation. Whilst an acute angle of trajectory in insertion has been correlated with increased insertion forces,[30] and histological trauma,[70, 71] no study has clinically demonstrated a link between poor trajectory in round window implantations and residual hearing loss thus far.

Studies that have found cochleostomy to be inferior to round window insertion have typically had small round window cohorts,[23, 72] though the feasibility of cochleostomy as an option for hearing preservation surgery has been previously demonstrated.[69, 73, 74]

Evidence from large institutions suggests that round window insertions are superior to cochleostomy for hearing preservation.[46, 75, 76] Although results vary between different academic institutions, it has been suggested that hearing preservation in over 90% of patients is routinely possible through round window insertion,[46, 77, 78] whereas even experienced cochlear implant surgeons will not be able to achieve hearing preservation in more than 80% of patients using a cochleostomy.[79, 80]

The reason for the abovementioned outcome has been attributed to the major histological trauma and subsequent inflammatory response potentially initiated by a cochleostomy.[10, 76, 81-83] Histological trauma is not always guaranteed, occurring in 40-50% of cochleostomies, and appears most pronounced in the first 90 degrees of insertion from the round window.[28, 76, 81]

An important criticism of round window insertions is the anatomic variation of the round window and the resulting electrode trajectory. A medial trajectory has the potential to cause histological trauma, as demonstrated in several cadaver studies.[30, 71] To prevent such trauma, it is critical to drill the bony overhang of the round window and increase exposure. Particularly in those patients with a posterior-facing round window, drilling of the bony overhang therein improving surgical access can prevent significant histological trauma in almost 90% of patients.[70]

If it is accepted that accessing the cochlea through the round window is the optimal method for hearing preservation, then there are numerous methods for opening the round window. The use of CO2 Laser has been previously advocated for but is associated with large negative pressure changes, the significance of which is uncertain.[84] . In most cases, a large, central round window opening that is accessed using a scalpel or microhook under moist conditions with good visualisation is suitable for hearing preservation.[44, 84-87]

1.5.3. Perimodiolar versus straight electrodes

The choice between a perimodiolar electrode or lateral wall electrode for hearing preservation surgery has only been settled in recent years and even so both electrodes may still be associated with intracochlear trauma. Whilst some degree of preserved residual hearing is technically possible for either technique,[46, 88] scientific advances in understanding over the last decade have made the case for a straight electrode more compelling.

Aside from the obvious advantage of not needing to perform a cochleostomy, it is worth acknowledging that a perimodiolar design necessitates a stiffer electrode.[39, 89] The cochlea is an asymmetric structure with an inconsistently narrowing lumen diameter[30] that varies between individuals.[30, 90] Given the inconsistent and nuanced anatomy of the cochlea, a stiff, uniformly shaped electrode is at risk of applying excessive traumatic force to surrounding inner ear structures.

It has also been argued that the loss of residual hearing seen in perimodiolar implantation can be attributed to surgical error,[88] and whilst this may sometimes be true, it does not allow for the inherent deficiencies of the stiff electrode design.

1.5.4. Other electrode characteristics

Certain electrode characteristics have been shown to have a significant impact on residual hearing preservation. Larger volume electrodes have been shown to correlate with larger intracochlear pressure variation in keeping with Poisson's equation of fluid dynamics,[89, 91-93] whilst stiffer electrodes have been experimentally shown to lead to greater insertion forces, intracochlear fluid changes and histological trauma.[81, 89, 94]

Shorter electrodes, whilst innervating a smaller proportion of the cochlea, have classically been associated with preservation of residual hearing, particularly at lower frequencies.[43, 89, 92, 95] This is likely explained by the drastic increase in insertion forces seen at greater angles of insertion. Beyond 180 degrees of insertion from the round window, the insertion force has been shown to drastically rise,[30] potentially causing greater histological trauma. Despite the challenge associated with longer electrodes and deeper insertions, residual hearing preservation can still be achieved with a soft surgery technique.[96]

1.6. Improving Surgical Techniques

It is essential to stabilise the electrode both during the insertion (such as through a two hand technique or insertion tool), and after when storing the electrode lead in the mastoid bowl.[41, 49, 97] Not fixing the electrode post insertion can cause large pressure changes in the cochlea, thereby compromising hearing preservation.[49]

Following a successful insertion, the cochleostomy or round window may be sealed. The optimal method for this is currently open to conjecture, however packing the opening has been shown to cause great intracochlear pressure variation and should be avoided.[97] Likewise, a drop in residual hearing has been associated with artificial grafts, possibly due to a foreign body or inflammatory response.[76]

1.6.1. Speed of Insertion

Clinically, a slow insertion has been associated with improved hearing preservation when an electrode is inserted over 2 minutes.[47] Small in vitro studies have attributed this to a reduction in intracochlear pressure variation during insertion.[36, 41] The relationship between intracochlear pressure variation and the speed of insertion has been shown to extend to "ultra-slow" insertions, with insertions of up to 30 minutes having a statistically discernible impact on intracochlear pressure variation. [98, 99]

Whilst speed is held to be an important factor to be considered for hearing preservation, there is little consensus regarding what the optimal speed of insertion should be. In vitro studies differentiating speed during insertion have not previously been performed to significance.[41] Evidently, more conclusive study is required to determine the optimal speed of insertion.

1.6.2. Depth of Insertion

Early histological studies have demonstrated a strong association between the depth of insertion and the damage to histological structures.[28, 81] This has been demonstrated most convincingly during round window insertions, possibly because the secondary fibrosis from a cochleostomy approach appears predominantly within the first 90 degrees of insertion, irrespective of depth.[28]

During in vitro studies, it has been demonstrated that the forces of insertion start to rise consistently after the first 180 degrees of insertion.[30] This is possibly because the direction of the implant is a changing vector, whereby as the insertion progresses, it begins to turn around the spiral of the cochlea, causing an increase in insertion forces associated with friction against the lateral wall.

Importantly, despite results from early studies, attaining hearing preservation during a deep electrode insertion is evidently possible,[46, 96] using a soft surgery technique. Skarzynski demonstrated the feasibility of maintaining residual hearing consistently (preservation rate of 90%) during deep implant insertions over a relatively large sample size of 40 patients,[46] whilst minimally traumatic insertions have been demonstrated histologically using deep perimodiolar insertions.[88, 100] Further investigation into the impact of depth on hearing preservation is required.

1.6.3. Underwater Insertion

Underwater insertions are not commonly practiced, but their use has been supported by several small studies. [101-103]

In clinical studies, it has been demonstrated that the use of an underwater insertion can double hearing preservation rates at 6-8 weeks postoperatively.[101] Subsequent studies of longer duration have demonstrated tempered outcomes. For example, a study by the same research group of two years duration produced no significant difference between underwater surgery and conventional surgery cohorts.[102] No explanation for this apparent disparity was given, but the results must be regarded seriously given the larger cohort number of the second study.

Alternatively, a small in vitro study looking at intracochlear pressure variation demonstrated a reduction using an underwater insertion.[103] Whilst the importance of results given the cohort size are of debatable merit, the results warrant consideration.

Some authors suggest that an underwater insertion operates by redistributing fluctuations in intracochlear pressure over a wider volume, in effect diluting the change in pressure. During cochlear implant surgery, there is a natural egress of fluid from the cochlea as the electrode array is inserted. If too much fluid is displaced too rapidly, a large rise and fall in intracochlear pressure will likely have a deleterious effect on hearing preservation. Similarly, if the fluid egress is restricted, such as through a tight round window opening, the leak of fluid will be inadequate and will result in a rise in intracochlear pressure variation. With a suitably large round window opening, it is considered that the use of an underwater insertion may blunt sudden changes in intracochlear pressure,[101] providing greater protection to the delicate inner ear structures.

1.7. Future directions

The expanding indications for cochlear implantation over the last decade now encompass patients with varying levels of residual hearing and/or single sided deafness. The realisation that future hearing restoration treatments rely on a viable tissue in the inner ear, and the reality that the paediatric patients implanted today are likely to need future re-implantation underpin the importance of preserving the inner ear structure and function.

Through the establishment and greater acceptance of principles of structural preservation during cochlear implantation, the future is likely to hold broader indications for surgery.

Within the literature, there is still an element of uncertainty regarding how to preserve residual hearing during implantation. Many factors have been suggested as having potential to reduce the mechanical trauma of implantation, but current studies are insufficient to attach certainty to many findings. This study will investigate key mechanical factors during cochlear implant surgery that may help preserve residual hearing, and improve patient outcomes. Specifically, the speed of insertion, the depth of insertion and the impact of an underwater insertion will be studied.

2. Study hypothesis and aims

This study will investigate factors which have been separately identified within the literature as having potential relevance for improving hearing preservation: the speed of insertion; the depth of insertion; and the impact of an underwater insertion.

2.1. Hypothesis

The author hypothesises that:

- a quick or rapid insertion will result in significantly greater intracochlear pressure variation;
- an insertion performed underwater will result in significantly less intracochlear pressure variation; and
- an insertion only partially performed, that is inserted to a smaller depth/angle, will result in significantly less intracochlear pressure variation.

2.2. Aims

The specific aim of this research therefore is to determine the relevant surgical factors affecting the intracochlear pressure variation during the cochlear implant insertion, as a surrogate marker for trauma to the cochlea, thereby promoting residual hearing preservation.

3. Materials and methods

3.1. Materials

3.1.1. FISO Mechano-optical pressure sensor

Intracochlear pressure variations were measured using a mechano-optical pressure sensor inserted into the apex of the cochlea model. The sensor was produced by FISO Technologies Inc. and has been used extensively by previous in vitro studies on intracochlear pressure variation.[43, 44, 84, 85, 104]

The tip of the sensor is a hollow glass tube, that is sealed over at one end by a thin plastic film diaphragm. The sealant is coated with a reflective surface of evaporated gold. The optical fibre is mounted on the glass tube at a distance of 50–100μm from the diaphragm tip and is attached to an LED light source and a photodiode sensor. Light from the LED source reaches the sensor tip of the optical fibre and the light then fans out as it exits the optical fibre and is reflected by the gold-covered flexible diaphragm.

Fluctuations in pressure are manifested and quantified in the sensor as displacement of the gold diaphragm, of which displacement consequently modulates the intensity of the reflected light. Fluctuations in intensity are transmitted via the optical fibre and are measured by a photodiode attached to the FISO module, which is linked to a PC.

Evolution Software, packaged with the module, was used to record intracochlear pressure. The sensor variables are as follows:

- resolution for the specific sensor/module combination is +/- 0.005 kPa.
- Time resolution is 5Hz.

Calibration was repeatedly performed against atmospheric pressure.

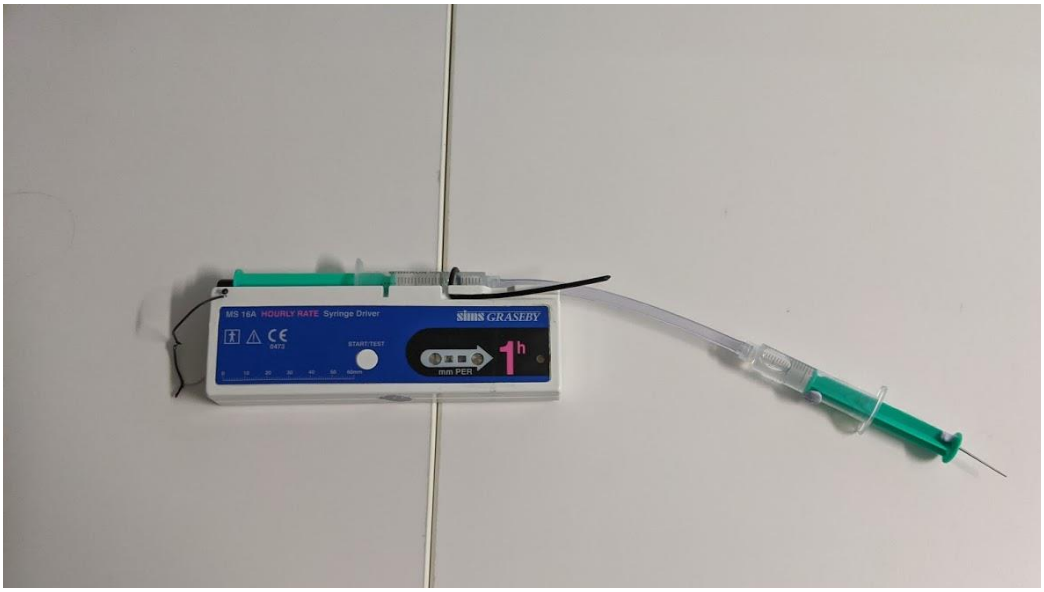
3.1.2. Insertion assistance device

To facilitate a consistent, repeatable insertion of a specific speed, a syringe driver was repurposed to deliver the electrode, which is shown below at Figure 1.1.

Non-elastic polymer tubing was connected between two different syringes, which were filled with deionised water. Water, rather than air, was used to ensure that compression of the medium inside the tubing did not occur. At one end of the tubing, a syringe of a certain determined size was attached to the syringe driver. At the other end of the tubing, an implant electrode was fastened to the end of a syringe with a waterproof adhesive. The syringe holding the electrode was then mounted on a specifically built stand, holding the syringe and electrode steady, whilst also allowing for the electrode to be guided into the cochlea model.

The use of a syringe driver ensured that a steady, reproducible insertion was achieved.

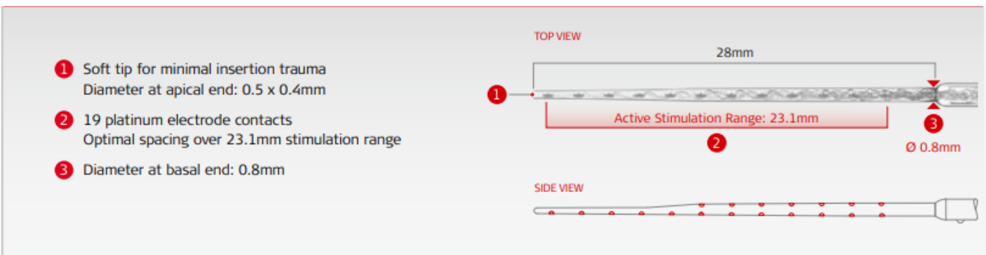
Figure 1.1. Insertion device consisting of programmable syringe driver, two syringes, hydraulic tubing and an electrode holder



3.1.3. Electrodes

A model of the Flex28 Electrodes, a slim, straight electrode produced by MedEl, was used for all insertions. The Flex28 is a common, atraumatic electrode array that has been used previously used for in vitro studies investigating intracochlear pressure variation.(41, 91, 97, 103, 105)

Figure 1.2. Dimensions of Flex28 Electrode(106)



The electrodes were dummy models, having been constructed without internal wiring, which meant that the electrodes could be used and reused for experimentation multiple times without becoming kinked or their form becoming compromised.

The volume of the electrode was 0.325mm^3, as demonstrated in the figure above (see Figure 1.2), the electrode is tapered. The diameter of the apex of the electrode is 0.5mm, whereas the diameter at the base is 0.8mm. Consequently, the volume of the electrode inserted during a deep insertion is 0.0896mm3, and for a shallow insertion it is 0.0509mm3.

3.1.4. Underwater insertion

Underwater insertions were performed in a one litre container of deionised water. The stand holding the electrode-driving syringe was placed inside the container, whilst the syringe driver was outside the container and attached by tubing. The cochlea model was then placed underwater, and all insertions were performed at a depth of 1cm of H20, which is equal to 0.01kPa. Because the pressure reading on the module was recalibrated to zero before each insertion, the additional pressure did not affect the reading.

The procedure and the insertion device used, was underwater during insertion. Visual guidance was utilised in the procedure to ensure the electrode was inserted smoothly into the round window. Similarly to clinical scenarios, gentle adjustments of trajectory were performed to ensure the electrode did not buckle or kink.

3.1.5. Perspex model of the cochlea

A Perspex, 3D printed model of the cochlea was used for all insertions. Produced with a 3D printer by MedEl, the model has been used extensively in previous in vitro studies investigating intracochlear pressure variation.[41, 44, 84, 85]

The model contains a 5mm opening in diameter at the round window, and a smaller 2mm opening at the apex of the cochlea where the pressure sensor was inserted. The opening of the round window would be considered a large opening.[84] The model completes 540 degrees of rotation, before reaching the pressure sensor.

With respect to maintaining the model, deionised water was used inside the cochlea. Whilst previous clinical studies have used Ringers lactate to better represent the chemical composition of perilymph, it was felt that the salt solution would affect the durability of the Perspex model, with evaporation and crystallization of salt potentially compromising the delicate pressure sensor and model.

3.1.6. Cochlea sealant

Tiseel glue[107] was used to seal the pressure sensor in the apex of the cochlea. During application, great care was taken to ensure that no glue fell into the cochlea model itself. After a series of insertions, ethanol was used to dissolve the tiseel glue entirely, to avoid any falling into model.

3.2. Methods

3.2.1. Insertion method

With respect to the insertion method, with reference to the controlled variables, the sealed cochlea model was microscopically inspected before each insertion for the presence of any bubbles. The hydraulic insertion device was also inspected for the presence of bubbles, and for the presence of a leak if not performed underwater.

For the insertions that were not performed underwater, the cochlea was filled to a level marginally below the rim of the round window opening. The insertion device was set up in such a way that the tip of the electrode was at the entrance of the round window, without being inside the cochlea nor breaching the air-fluid interface. Electrodes were not dried between insertions, and so may be considered moistened.

If an electrode became kinked, stuck, or demonstrated any foldback, the particular experiment was terminated. This was done with the intention of creating the most consistent data possible, at the expense of clinical translatability. It has been demonstrated however that the forces of friction are lower in vivo,[94] so it was deemed self-defeating to let friction forces dictate outcomes in an in vitro setting.

After the statistical analysis, several large outliers were noted to come from a very early subset of insertions performed. It was inferred that there must be a learning curve associated with the use of the insertion device, and further experiments to compensate for the perceived learning curve of the initial insertions were performed. These insertions replaced the small number of extreme outliers.

3.2.2. Independent Variables

There are three variables that were studied that are outlined below.

3.2.2.1. Speed

Three different speeds were used to conduct an insertion of the Flex28 electrode. These three speeds were: 30 seconds for a full insertion (0.9mm/sec), 60 seconds (0.45mm/sec), 120 seconds (0.225mm/sec). It should be noted that for a shallow insertion, the speed was not changed. Thus, the insertions took 2/3rds the time.

3.2.2.2. Depth of Insertion

Deep insertions were inserted a full 27mm, which equates to approximately a 360 degree insertion.

Shallow insertions inserted to a depth of 18mm, which corresponded approximately with 200 degrees of insertion, or just past the basal turn.

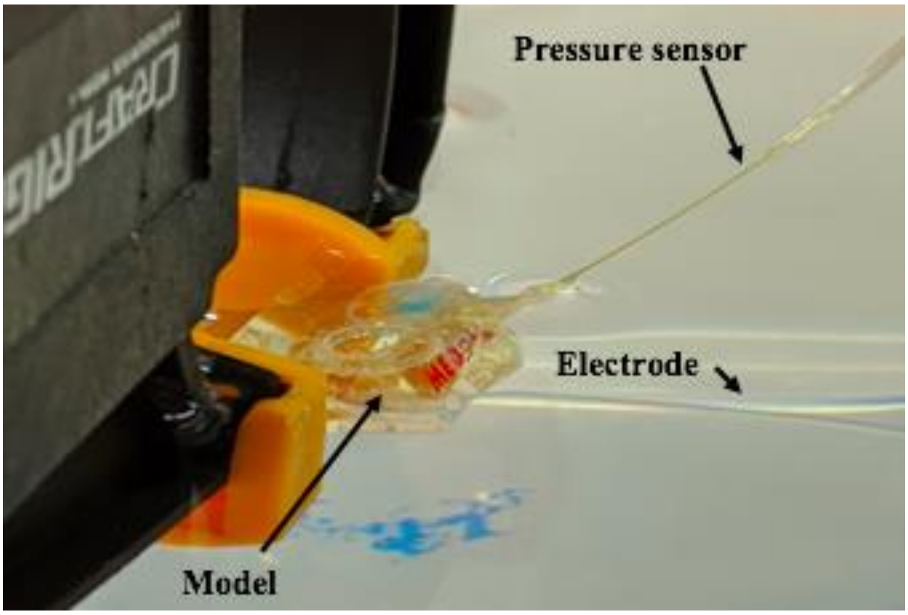
Whilst simple mathematics may suggest a 240 degree insertion should be achieved instead, it should be noticed that the cochlea forms a tapering spiral pattern, with the first turn being longer than the second.

3.2.2.3. Underwater insertion

Half of the insertions were performed underwater.

The electric syringe driver was set up outside of the water. Connected to the syringe driver via polymer tubing was the electrode holder. The electrode holder and associated syringe were fixed in the one litre container using waterproof adhesive.

Figure 2.1. Surgical set up for underwater insertion



4. Statistical Analysis

Inbuilt imprecision of the FISO module and pressure sensor was known and was also demonstrable during the preliminary testing. The pressure sensor had an inbuilt error of +/- 0.005 kPa.

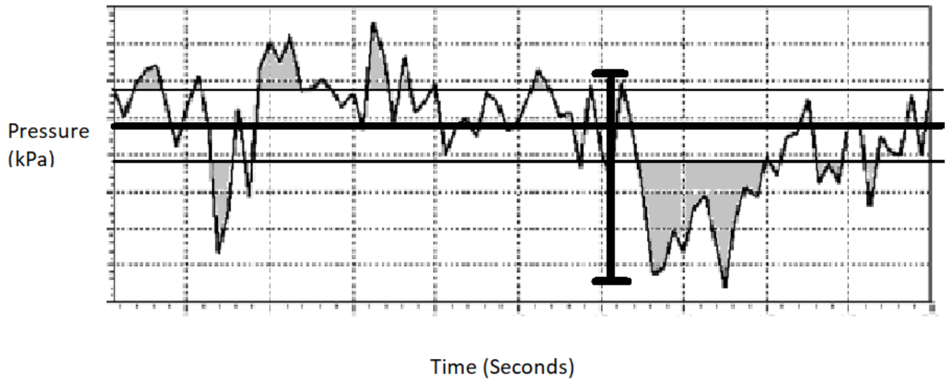
It was calculated, based on the inbuilt error of the FISO module and pressure sensor, that eighteen insertions were needed for a given permutation to produce significant measurements to a power of 80%. A freely available online statistical software was used to calculate this specifically.[108] This was rounded up to twenty insertions. Given that there were twelve permutations, there were 240 experiments planned.

A regression analysis was performed using SPSS. ANOVA Regression analysis was performed to test the significance of speed, and a Mann Whitney regression analysis was performed for depth and underwater versus level experiments as a variable. The reasoning for choosing these tests was based on the number of variables involved, and the possibility that the existence of a learning curve using the insertion device could cause the data to be not normally distributed. This was additionally supported by a scattergram initially produced from the data.

4.1. Variables studied

There were two dependant variables studied: the MTICPV and the AICPV. They are demonstrated graphically in Figure 4.1.

Figure 4.1. Demonstration of statistical variables using example insertion of intracochlear pressure variation versus time. See MITCPV (vertical black line) and AICPV (grey shading)



4.1.1. MTICPV

For each insertion, the maximal transient pressure change was identified visually and measured, from the peak to the trough of the transient variation (see vertical black line in Figure 4.1).

4.1.2. AICPV

The natural pressure variation of intracochlear pressure inside the Perspex model in a quiet room was measured as a baseline for statistical analysis. This was measured as 101.325 +/- 0.01 kPa.

All values outside of these parameters were measured and an integral function was performed. This resulted in a differential of pressure values outside normal intracochlear pressure variation (see grey shadowing in Figure 4.1).

5. Results

5.1. Outline

Permutations of the different variables split the cohort into twelve cohorts. Insertions were underwater or conducted level, conducted at 30 seconds, 60 seconds, or 120 seconds, and conducted to a full insertion or a shallow insertion. In total 240 insertions were performed.

Table 5.1. Summary of maximal transient and aggregate intracochlear pressure variation (kPa) against insertion speed, depth and underwater versus level

	n	MTICPV (sd)	AICPV (sd)
120	80	0.05 (0.021)	34.312(6.72)
60	80	0.055 (0.018)	24.41 (5.88)
30	80	0.044 (0.023)	9.825 (2.09)
Deep	120	0.059 (0.007)	35.081 (5.41)
Shallow	120	0.04 (0.011)	10.617 (3.30)
Level	120	0.03 (0.003)	5.88 (1.45)
Underwater	120	0.069 (0.022)	39.818 (6.94)

Table 5.2. ANOVA regression analysis of insertion speed versus Intracochlear pressure variation, including further subset analysis (Heteroscedasity)

MTICPV		**AICPV**	
ANOVA	**Hetero**	**ANOVA**	**Hetero**
0.283	0.231	0.005	<0.001
30v60	0.223		0.012
60v120	0.082		0.034
30v120	0.308		0.022

Table 5.3. Mann Whitney regression analysis of depth of insertion and level versus underwater insertion

	MTICPV	AICPV
Deep vs Shallow	<0.001	<0.001
Level vs Underwater	<0.001	<0.001

Figure 5.1. MTICPV (kPa) versus speed, depth and level versus underwater

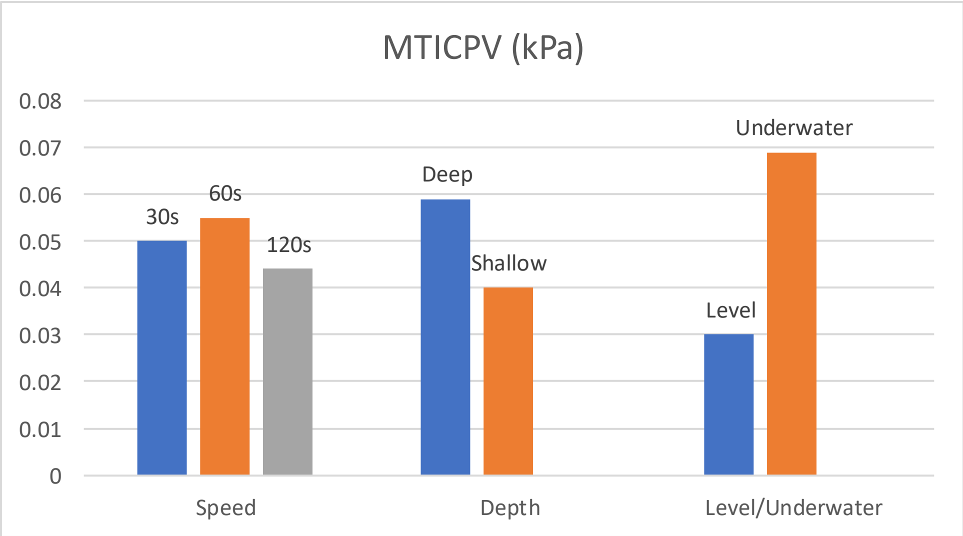
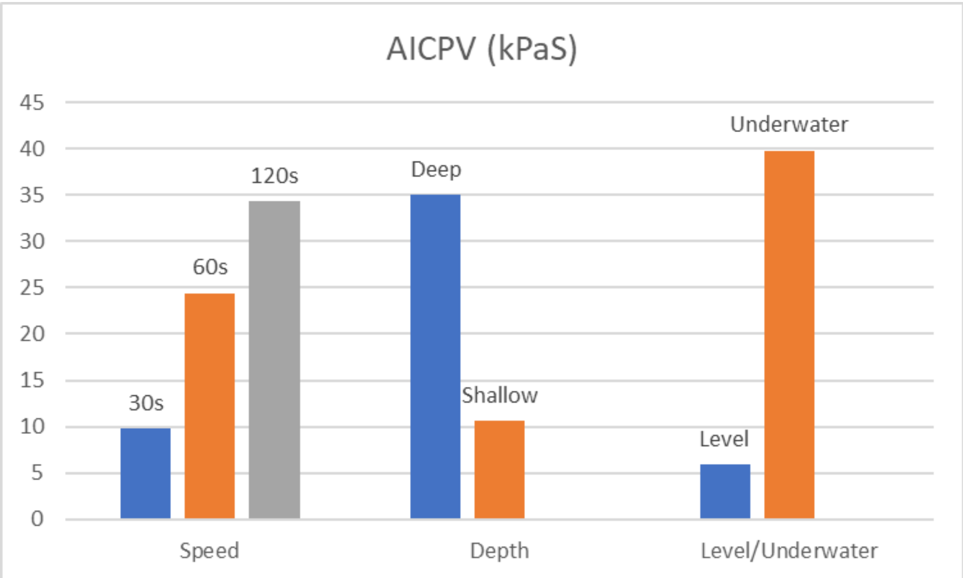


Figure 5.2. AICPV (kPa) versus speed, depth and level versus underwater



5.2. Depth of Insertion

The mean maximal variation was 0.059kPa for a deep insertion and 0.04kPa for a shallow insertion. This was found to be significant on Mann Whitney test (<0.001, p<0.05).

The AICPV was 35.1kPas for a deep insertion and 10.62kPas for a shallow insertion. This was found to be significant on a Mann Whitney test (<0.001, p<0.05).

5.2.1. Depth - results discussion

The study demonstrated that a greater depth of insertion was associated with both an increase in maximal transient intracochlear pressure variation and AICPV.

Depth was constructed as a binomial variable. Owing to strict study design, each shallow insertion was inserted to 18mm of depth, corresponding to an angle of insertion of 200 degrees, whilst each deep insertion was performed to 27mm, corresponding to an angle of 360 degrees.

The results demonstrated an increase in intracochlear pressure variation that did not correspond with a linear increase during insertion, but rather a dramatic increase during 200 and 360 degrees of insertion, compared with an initial increase in intracochlear pressure variation across the first 200 degrees.

Speaking in terms of differing proportions, the angle of insertion was 50% greater for a deep insertion, and had a 50% increase in MTICPV, and 350% increase in AICPV.

Regarding the reasoning for the above results, there are two possible explanations. Firstly, the results could be attributable to design of the MedEl Flex28 electrode. The electrode is tapered, meaning that its diameter progressively increases. Consequently, an exponentially larger volume is inserted as the electrode progresses.

Applying laws of simple fluid dynamics, the Archimedes principle states that the force exerted by an object on a fluid is proportional to its mass. It would be expected with an increasingly larger electrode that increases in pressure inside the cochlea would be experienced in a proportionate manner.

Turning to the literature, it has been previously suggested in critical reviews and small in vitro studies(89, 91) that large volume electrodes are associated with greater intracochlear pressure variation. The application of Archimedes principle would explain the association between pressure variation and volume, as well as some of the results seen in this study.

Complicating this however, is that the cochlea and the middle ear are not a fixed space during cochlear implantation following a tympanotomy and opening of the round window. As the electrode is inserted into the cochlea, it would likely cause displacement of fluid, rather than a gradual increase in pressure. Fluctuations in pressure would be a consequence of the interplay between surface tension and volume of electrode inserted. When a sufficient volume of electrode is inserted into the cochlea, the force exerted by the liquid is sufficient to overcome surface tension at the air fluid interface, causing a shift in the air fluid interface and a drop in intracochlear pressure. Larger volume shifts would likely cause larger fluctuations in pressure, however it is uncertain whether this would sufficiently explain the findings in this study.

Additionally, the shift in pressure was not proportionate to the shift in electrode volume. The shift in pressure as depth increased resulted in a 50% increase in MTICPV, and 350% increase in AICPV. In contrast, volume of the electrode increased to $0.0896mm^3$ from $0.0509mm^3$, an increase of 76.0%. As such, it is unlikely that the change in electrode volume sufficiently explains the large change in pressure, though it may help explain the change in MTICPV.

A second possible explanation for the increasing pressure change during increasing depth of insertion is that the turn of the cochlea at 180 degrees is particularly important. At this point, the vector of insertion changes dramatically from corresponding with the vector of force applied to the cochlea, to perpendicular with the vector of force as the electrode curves around the upper basal turn and then, to inversely so as the direction the tip the electrode travels in the opposite direction to the vector force of the insertion. Whilst this aspect of insertion may explain higher insertion forces required as the insertion progresses, it does not immediately explain the intracochlear pressure variation.

It was noted coincidentally during experimentation using a microscope that the electrode does not travel through the cochlea in a particularly smooth manner. Rather, the electrode tends to “jump” and “stutter” as it is forced across the lateral wall of the cochlea. This was noted to correspond with changes in pressure. The greater the magnitude of the “stutter”, the greater the rise in intracochlear pressure. These “stutters” have been noted previously within the literature,(39, 109) but are still yet to have their impact quantified.

Unfortunately, it is not possible to measure the specific relationship between the magnitude of these “stutters” and the change in intracochlear pressure variation in this experiment. A new study design incorporating measurement of these "stutters" would be required in order to do so.

Assuming that there is a true relationship between the magnitude of the "stutters" along the lateral wall and changes in pressure, it then holds that an increase in the force of insertion may result in larger "stutters" along the lateral wall as more work is put into the system. This would result in greater variation in intracochlear pressure.

Regarding the literature on the depth of insertion during in vitro trials, this study appears to contradict two previous papers published on the subject, suggesting that intracochlear pressure rose in a linear fashion corresponding to the depth of insertion.[43, 104] However, the quantity of these studies were only ten and six insertions respectively, in contrast to the 240 performed in this study. In consideration of the power calculation discussed above, and with the utmost respect to the group that published the two papers, the prospect of a linear relationship is doubtful.

Pertinently, other studies within the literature appear to concur with the study's findings, even if not directly so. Avci[30] has demonstrated a significance of the turn at 180 degrees of insertion, with substantially higher forces of insertion noted thereafter using a lateral wall electrode. This finding is very similar to the present study, despite the use of a different dependant variable in force, rather than pressure.

The link between intracochlear pressure variation and insertion forces has not been noted previously to the knowledge of the author, and both are independently held to affect hearing preservation. Crucially, it could be theorised from this study that higher insertion forces may contribute to greater pressure variation, as the electrode may "jump" along the lateral wall periodically when friction is overcome by the force of insertion and the potential energy within the electrode. The possibility of this has been noted previously[39] and the importance of the tip of an electrode has been long-established in literature.[9]

The results regarding depth of insertion are unique and important by disputing the linear relationship between insertion depth and intracochlear pressure variation. Furthermore, an important correlation between intracochlear pressure variation and insertion forces can be drawn from the data of this study.

5.3. Speed

This study did not demonstrate a relationship between the speed of insertion and the MTICPV to a level of statistical significance. The MTICPV was 0.05 for 120 seconds, 0.055 for 60 seconds and 0.044 for a 30 second insertion. ANOVA regression analysis did not find this to be a statistically significant difference.

Unlike MTICPV, AICPV demonstrated an association with speed of insertion. Extra-physiological pressure variation was 34.312kPas for 120 seconds, 24.4kPas for 60 seconds, and 9.825 kPas for a 30 second insertion.

5.3.1. Speed - results discussion

The speed of insertion had a complex effect on intracochlear pressure variation. Whilst the study ultimately demonstrated no impact of speed upon intracochlear pressure variation at the speeds measured, the initial findings did demonstrate that 60 second insertions were associated with the greatest intracochlear pressure variation, rather than falling between 30 and 120 seconds as anticipated. The probable explanation for this is detailed in the following paragraphs.

The experimental design of this study split the experiment into 12 different cohorts, three of which were 60 second insertions. Whilst a randomised order of insertions during experimentation would have been ideal, pragmatically the prolonged setup time changing the speed, timing and underwater setup rendered this non-feasible. It is important to note that the 60 second insertion was the default setting on the insertion device, hence this setting was the first tested. Additionally, switching between deep and shallow insertions could be an efficient process in comparison to other variables of this study.

Consequently, the 60 second insertions, both shallow and deep, were the first performed during the study. Likewise, during the study of underwater insertions, the 60 second insertions were the first performed underwater. Initial analysis on scattergram found that the first several insertions performed at 60 seconds duration resulted in greater intracochlear pressure variation by several orders of magnitude.

It was hypothesised that the findings were likely a reflection of the learning curve associated with the use of the insertion device. As 60 second insertions were the first tested for the study, it may be that the pressure variation was greater in the 60 second insertion cohort due to inexperience conducting the experiment. After the outliers were identified on a scattergram, 6 new experiments were performed to demonstrate whether the outliers were an anomaly produced from first using the insertion device, or a true representation of 60 second insertions. Results demonstrated the latter to be likely true, and the results of the repeated insertions are contained within the present study.

Importantly, the effects were not immediately noticeable whilst carrying out the experiment, otherwise the experiment would have been ceased. Whilst outliers were statistically obvious, they were not discernible when conducting the experiment.

Regarding other insertion speeds, comparisons between 30 second insertions and 120 second insertions yielded no observable difference regarding MTICPV.

The associated effects of maximal amplitude give credence to this as an important aspect of hearing preservation, compared to the sum of total energy transferred.

The AICPV should be interpreted with caution, as the aggregate total is clearly affected by the time of insertion. A 30 second insertion was found to have less AICPV, as there was less time during insertion. When it is considered that the 30 second insertion was four times shorter than the 120 second insertion, the total pressure variation is likely comparable, as the AICPV of the 30 second insertion was also approximately four times smaller than the AICPV of the 120 second insertion.

The association of slow speed and hearing preservation has been well established in the literature. The ideal duration of insertion is yet to be fully determined within the literature, but certain in vitro studies have demonstrated efficacy for longer insertions than two minutes.[(99)]

The speed of insertion in the current study consisted of 13.5mm/min for a 120 second insertion, 27mm/min for a 60 second insertion, and 54mm/min for a 30 second insertion. Within the literature, these insertions are quite slow.

There is little literature regarding the average time of electrode insertion amongst the surgical community, but a large cohort study has previously found 96mm/min to be the average speed of insertion intraoperatively at a centre practising a soft surgical technique.[(36)] A similar study comparing speed and intracochlear pressure variation found general differences comparing insertions ranging from 6mm/min to 120mm/min.[(41)] Unfortunately the similar study only contained 15 insertions in total, spread amongst 5 random speeds and did not include a calculated confidence interval, rendering further comparison problematic. That study, by Todt, notably found a 300% increase in MTICPV between a 15mm/min insertion and a 60mm/min insertion. However, the MTICPV during the 60mm/min insertion was 300% higher than the MTICPV of the current study at 54mm/min. Given that the similar study had only 3 insertions at 60mm/min, compared to 80 insertions at 54mm/min in the present study, the finding of the smaller study may not have been statistically significant.

The other relevant in vitro study within the literature is a study investigating insertional forces as a marker of insertional trauma against the speed of insertion. In that 2012 paper, the maximal insertional forces were measured at 9mm/min, 30mm/min and 90mm/min. Again only 18 insertions were performed in total, but that 2012 study at least had a confidence interval and found no observable difference in force between the different speeds.

Lastly, it is important to note that this study used an insertion device to ensure precision and consistency during experimentation. It is possible that this same precision may have manifested in reduced intracochlear pressure variation at the speeds measured, relative to the current body of literature.

It may be that speed as a variable is more nuanced than previously thought. It has been demonstrated that a slow speed of insertion is critical to preserving residual hearing, and there is broad consensus on this matter. There exists scope for debate regarding the optimal speed for preservation of residual hearing, in which lay the basis of this study. The speeds studied were broadly slower than what is commonly practiced. As such, the nonsignificant result may indicate that there is little difference between a 30 second insertion and a two minute insertion whilst using an insertion device for the purposes of hearing preservation.

5.4. Underwater versus level insertion

The MTICPV was 0.117kPa for an underwater insertion and 0.043kPa for a level insertion.

This was found to be significant on both a t-test (0.006, $p<0.05$) and Mann Whitney test (<0.001, $p<0.05$). The AICPV pressure variation was 45.86kPas for an underwater insertion and 8.38kPas for a shallow insertion.

This was found to be significant on both a t-test (0.001, $p<0.05$) and Mann Whitney test (<0.001). It was found that an underwater insertion was significantly associated with both greater maximal pressure variation and sum total energy transferred.

5.4.1. Underwater - results discussion

The experiment demonstrated the inferiority of an underwater insertion with respect to intracochlear pressure variation, measuring both maximal transient and aggregate pressure variation.

A likely explanation for this finding was noted during testing, as intracochlear pressure variation was noticeably greater during certain surgical actions, such as the accidental displacement of large volumes of water, typically outside of the experiment but possibly also during adjustments to the electrode during an insertion.

The procedure, and the insertion device used, were underwater during insertion. Visual guidance was required to ensure the electrode was inserted smoothly into the round window. Similarly to clinical scenarios, gentle adjustments of trajectory were performed to ensure the electrode did not buckle or kink. This was carried out with surgical forceps, which consequently introduced an opportunity for surgical error to influence results.

It was determined observationally that any movement or shift in the position of the electrode outside the cochlea produced subtle pressure variations in the water which were clearly measured inside the cochlea. Similarly, any movement of the insertion device or cochlea produced a large shift in fluid volume and subsequently larger variation in pressure inside the cochlea.

In this manner, rather than the water dampening intracochlear pressure variation throughout the extracochlear water volume, it served to effectively transmit extracochlear pressure variation to inside the cochlea, where it was measured at the cochlea apex. Critically, the underwater insertions were performed inside a one litre container, which ensured that even modest extracochlear movement produced a relatively large pressure change by the large volume displaced, with respect to the Perspex cochlea model. The volume of the Perspex model is approximately 1mL.

The author considers it would be much less likely that similar movements in vivo on a cochlea and middle ear, both 1-2mL in volume,[110] would produce the same magnitude in pressure variation.

The inferiority of an underwater insertion appears to conflict with findings in the literature. It is important to examine this further. Anagiotos and Stuermer[101, 102] have both clinically found an association between underwater insertions and improved hearing preservation. In 2016 Anagiotos found an improvement in residual hearing preservation of any observable amount, from 47% to 87% at six to eight weeks within his own centre, using an underwater insertion technique. Subsequent testing at 15 months, and later by Stuermer demonstrated further residual hearing loss in the underwater cohort, with 57% of patients maintaining some degree of residual hearing.

The results of the current study demonstrate a possibility for consideration: whilst previous studies within the literature have suggested that opening a cochlea and performing an insertion underwater may help preserve residual hearing by dampening intracochlear pressure variation, the opposite outcome may also eventuate if the extracochlear water volume is disturbed, producing pressure variation which may be transmitted through the lumen of the cochlea. The magnitude of this pressure variation, with respect to the volume of the middle ear, may be much smaller.

It could be concluded that whilst there may be a role for an underwater insertion, the volume of water used should be modest. A relatively large volume of water such as that used in the present study (one litre) may produce greater variation in intracochlear pressure variation.

6. General discussion

6.1. Summary of results

In this in vitro study, the effect of insertion speed, insertion depth and underwater medium on intracochlear pressure variation was investigated. Speed did not have a relationship with intracochlear pressure variation at the speeds studied using an insertion device, whilst underwater insertions and deeper insertions were associated with increased intracochlear pressure variation. To apply results clinically, it is important to explore the variables used.

Two variables were used to measure intracochlear pressure variation. MTICPV is a variable used previously in in vitro studies.[42, 111] The relevance of measuring intracochlear pressure variation can be derived from studies demonstrating equivalence with blast trauma in certain circumstances.[42]

Transient intracochlear pressure changes are commonly held to have an important impact on inner ear structures, but aside from theoretical comparisons there is no direct experimental evidence to support this conclusion. This is largely because it is difficult to accurately measure intracochlear pressure changes in a human in vivo environment. The present study is able to measure pressure at the apex of the cochlea in a custom-designed Perspex model, however replicating this in a human cochlea would likely inflict substantial trauma to the inner ear structures, rendering the exercise futile.

Consequently, clinical studies supporting the importance of intracochlear pressure variation typically take a variable such as speed of insertion[47] or insertion underwater,[101] and reasonably take this finding to support the minimisation of intracochlear pressure variation.

Intracochlear pressure variation is not the only variable which has importance within the literature. The force associated with insertion has been held to have an important impact on structure preservation,[16, 34-36, 112-114] through association between the force of insertion and histological trauma to the cochlea.[39] Although still rightfully regarded as an important variable, approximately 10 years ago studies started demonstrating residual hearing loss in spite of soft surgical techniques and minimal demonstrable histological trauma.[46, 49] Consequently, it was suggested that intracochlear pressure variation was an important variable. This has been predominantly defined as MTICPV, but also by the number of transient pressure spikes during an insertion.[42]

This study produced an additional variable for investigation, in an effort to recognise the aggregate of additional pressure changes within the cochlea during insertion.

This was achieved by measuring all pressure values outside of the normal pressure variation inside the model in a quiet room at sea level and performing an integral function on these values to give the area under the curve. Several obvious criticisms emerge.

Firstly, not all values outside of the parameters chosen would be inherently damaging to the cochlea. The cochlea is capable of interpreting a wide range of sound pressure levels without becoming traumatised by loud sounds. The decibel level of a normal conversation would be outside of the set parameters, yet unlikely to cause trauma. Furthermore, there is no established threshold for when a sound pressure level becomes damaging. Rather, there is an accumulative effect, where there is balance between the sound pressure level and the time of exposure to determine the trauma inflicted on the cochlea.[115] Accordingly, it may be that a day at a loud rock concert may produce more trauma than standing in close proximity to a single gunshot.

Whilst the use of sound pressure as a variable in theory may be appealing and logical, the pragmatic limitations of establishing a threshold for when a sound pressure level becomes damaging compromises the utility of the results. The decision to designate pressure variation in a quiet room is a pragmatic compromise, rather than an ideal solution.

The study found AICPV to be statistically significant. Regardless of limitations, the results of the study cast doubt on the utility of AICPV. In calculations regarding speed of insertion, the insertion of the greatest duration predictably also had the greatest AICPV.

6.1.1. Speed

The statistical non-significance of speed was an important finding within this study that clearly contradicts previous studies within the literature by Todt.[41]

It is accepted within the literature that a slow insertion speed is associated with improved hearing preservation. In 2013, Rajan found that speed had an important effect on facilitating and promoting hearing preservation.[47] The reason for this was not determinable from the study, but other researchers have subsequently found improved hearing preservation associated with a slower insertion.[49, 96]

In a 2014 in vitro study, Todt found that a slower insertion was associated with a lower MTICPV. This was measured by three attempts of five different insertions speeds.[41] A later paper published by Todt demonstrated non-significance of speed,[91] but this study was predominantly investigating different electrode models.

The findings of the present study are important as they suggest that speed may have a limited effect on hearing preservation at the speeds studied, at least with the use of an insertion device. The evidence for this is further supported by the number of insertions performed during this experiment

(240 experiments measured) compared to the number of insertions during Todt's 2014 paper (15 experiments). To the knowledge of the author, the number of insertions performed in this present study is the most of any in vitro study thus far.

6.1.2. Underwater

The study found underwater insertions to be associated with greater intracochlear pressure variation. The reasoning for this is important, as it is likely that the study design, through the use of a 1 litre bucket, was inappropriate in retrospect for studying an underwater insertion in the middle ear. In the opinion of the author, the result does not rule against the use of an underwater insertion for hearing preservation. Rather it gives reason for caution, demonstrating the potential consequences of an underwater insertion if the technique is used incorrectly.

6.1.3. Depth

Lastly, the study found depth of insertion to be associated with intracochlear pressure variation, as anticipated. What is perhaps more surprising is the magnitude of the relationship suggested by the present study. It is well appreciated that depth of insertion is associated with a reduction in hearing preservation. Studies demonstrating hearing preservation with a deep insertion are regarded with special interest.[46, 96] The importance of the present findings is not that they demonstrate a relationship already well established, but rather that the findings help develop an understanding of the interplay between different variables regarded as important for hearing preservation, namely intracochlear pressure variation and the force of insertion. The rise in both variables seen at the upper basal turn is given added importance considering the dense proportion of spiral ganglion cells at this location. Additionally, it is notable that depth was more impactful than speed or an underwater insertion with regards to intracochlear pressure variation.

6.2. Novelty of the findings

A novel aspect of this study was the integration of an automated insertion device for consistent experimentation.

A new developing field within cochlear implantation is the use of robots to carry out implant insertions. More clinical trials are needed to test and validate findings seen in in vitro models, animal studies, and smaller pre-existing studies. The use of an automated insertion device was a practical decision to achieve consistent results within the experiment, but will also expectantly contribute to the growing body of literature regarding surgical assistance devices for implantation.

Another important and novel aspect of the study was the use of a power calculation to establish significance. To the knowledge of the author, this has not been done previously in the literature whilst studying in vitro insertions. The decision was made to include a power calculation due to inherent variation within the pressure sensor at atmospheric pressure. In a static environment, a variation of +/- 0.005kPa was noted, due to either Brownian motion or inaccuracy within the sensor.

As a consequence of incorporating a power calculation, the study was much larger than previous in vitro studies and can also be regarded with a higher degree of confidence.

6.2.1. Current Literature

This research demonstrated the importance of the change in pressure at the upper basal turn between 180 and 270 degrees from the round window opening. Several studies have attributed importance to this region of the cochlea during insertion. The current study provides a theory on the importance of the upper basal turn, specifically the magnitude of intracochlear pressure variation at this point. There are several important studies tying in with this.

In 2020, Snels published a cadaver study investigating the relationship between speed, round window opening size, intracochlear pressure variation and insertional forces across 80 different insertions.[116] Aside from the strength of a cadaver-based study with a large number of insertions, the study found that a slower speed was associated with a greater pressure change. This finding is likely explained by the variable for pressure. Rather than use MTICPV for investigation of pressure, Snels study investigated overall pressure change. A lack of distinction between MTICPV, and the overall change in intracochlear pressure may have falsely attributed an association between slow speed of insertion and high intracochlear pressure changes. Nevertheless, it is an important study for inviting important scrutiny to speed of insertion.

Regarding the forces of insertion, Snels found a slower insertion speed to be associated with lower insertional forces. This was particularly pronounced over the lateral wall of the upper basal turn. This finding is more meaningful when interpreted with the findings of the current study, as it again bestows new importance to this region of the cochlea during cochlear implantation.

Another study released in 2020 also attributed importance to the upper basal turn of the cochlea: a cadaver study by Gonzalez which developed a new method for intracochlear pressure variation.(117) The results demonstrated a likely association between the upper basal turn of the cochlea and increased intracochlear pressure variation, corresponding very closely with the current study. Although the study by Gonzalez only contained twelve different insertions by multiple operators using a lateral wall electrode, the correlation with the present study gives greater credence to both experiments.

Robotic insertions are also rapidly developing and gaining greater appreciation within the literature. A recent study published by Kaufman(118) in 2020 introduces a similar device to the one presented in the present study, and demonstrates its superiority in comparison to a human insertion, at least in an in vitro setting. The study graded histological trauma and forces of insertion as surrogate markers of hearing preservation to produce an overall “trauma score”. Whilst the study is difficult to translate to the present one, they both contribute to the growing literature regarding surgical assistance devices.

Another study released within the last year is a small in vitro study investigating the role of an underwater insertion by Riemann.(103) This study suffers the same flaw as other in vitro models by a lack of significance owing to its small sample size. The results do suggest that an underwater insertion through a filled middle ear is inferior to a small pool of fluid with regards to intracochlear pressure variation, keeping with the findings of the present study, but more trials were needed to achieve statistical significance.(103)

6.2.2. Limitations of the study

An in vitro study will naturally have limitations, particularly when being translated to in vivo and real world applications.

Possibly the most serious limitation with the current study was the obvious bias produced by not performing studies in a random manner, but rather performing all insertions of 60 seconds first. The reason for this decision was due to the practical benefits in carrying out the experiment, as it took approximately 2-3 minutes to set up for each insertion, whilst it took approximately 15-30 minutes to change between different variables, due to having to configure measurement settings and change the experimental setup. This was particularly pronounced for an underwater insertion, which required glue to be set prior to exposure to water. Great care was taken to ensure the glue was consistently set and would not influence the pressure variation by the glue being too soft or inadvertently dissolving.

A consequence of performing the 60 second insertions first was the impact of the learning process, which initially resulted in several outliers. The author of this study notes that the requirement to repeat insertions to investigate and scrutinise the outliers recognised the impact of the learning curve. Subsequent repeated insertions demonstrated no statistical significance associated with 60 second insertions.

Evidently, there is a learning curve associated with cochlear implantation, at least with a Perspex model and insertion device as used in this study. This conclusion concurs with the literature, with previous studies also having demonstrated the significance of experience regarding cochlear implantation.(46)

Another limitation to the study was regarding the use of dummy electrodes, rather than real ones. Dummy electrodes were determined to be a necessity early in preliminary experiments, as multiple insertions using an electrode with a wire inlay caused damage to the electrode. Specifically, the wire inlay soon became kinked and misshapen. Anecdotally, it became obvious that any insertions with the misshapen electrodes were a very poor representation of a clinical insertion.

There were two options to address the limitations of the electrode: firstly, the study could be conducted with a new electrode for each insertion. This was determined to be unsuitable given it was prohibitively expensive, as at least 240 electrodes would have been needed. In reality, this number would have been even greater, as many failed insertions had to be discounted. The second option, far more feasibly, was the use of dummy electrodes, which are silicone electrodes of exact dimension but without the wire inlay.

Any impact associated with the absence of wire inlay was not demonstrably obvious during testing but is a clear point of difference between an in vivo insertion and the present study. An important step for the validation of dummy electrode use should be an in vitro study comparing them to natural electrodes.

If this was to have an effect on intracochlear pressure variation, it might be supposed that the stiffness of an electrode would be increased by the presence of a wire inlay. Stiff electrodes are known to have a negative impact on structure preservation,[89] possibly due to increased insertion forces associated with them. As discussed, this present study has highlighted a possible association between insertion forces and intracochlear pressure variation, and it is not unreasonable to assume that a stiffer electrode may produce greater pressure variation as an insertion progresses. Consequently, effects seen within the present study may be magnified in vivo. It may even be that speed is a significant variable in a study utilising a standard electrode, as the stiffer inlay could produce greater frictional forces.

An important limitation of the study is the reduced depth of insertion. It should be said that the insertion of a Flex28 reaches 450 degrees, rather than 360 degrees, based on pre-existing literature. This key limitation became apparent after the study had begun. On further clarification, this shortcoming was attributed to the lack of internal architecture within the cochlea model (for example there was no scala tympani, scala media or scala vestibuli), a design choice that reflected how the different compartments correspond very closely with regards to intracochlear pressure variation.[(42)]

This model has been used extensively within the literature, yet to the knowledge of the author the shortcomings of the model has not been addressed previously. It is uncertain whether this is a reflection of the quality of the literature, or a design flaw within the present study. It should be acknowledged that this study is the largest of its nature so far. Regarding the consequence of this disparity, the obvious point is that any clinical translation is compromised.

With respect to the potential issues when translating the study findings clinically, one final important of consideration is the applicability of trials conducted using a model of a cochlea, rather than a cochlea itself, even if only a cadaver model. Thankfully there are trials demonstrating the similarities and differences between cochlea models. An important trial compared the insertion forces of both models and found higher insertion forces with a Perspex model. This was attributed to the higher friction associated with plastic, in comparison to the soft tissues of an animal model. The consequence of this would likely be an amplification or accentuation of factors found to influence intracochlear pressure. Within Lo's study, a deep insertion was associated with twice as much force in a Perspex model compared to cadaver model.

Another limitation of the Perspex model was the impact of having the sensor located at the apex of the cochlea, rather than at a region of more importance (such as the upper basal turn). Studies have performed measurements at multiple regions within the cochlea however and have previously found no association between sensor location and outcome.(42, 49)

6.3. Clinical implications

Through the establishment and greater acceptance of principles of hearing preservation during cochlear implantation, the future is likely to hold broader indications for surgery.

An important aspect of the present study is the non-significant finding of speed, and the potential for increased intracochlear pressure variation during an underwater insertion. Both variables have the potential to influence the surgical method for hearing preservation during cochlear implantation.

It has been previously held that the effect of both speed(41) and an underwater insertion(101-103) on hearing preservation is evidence to support the minimisation of intracochlear pressure variation in the pursuit of hearing preservation. With the findings of the present study however, it is perhaps important to reconsider this assertion, as the evidence to support the importance of minimising intracochlear pressure variation has been compromised. The results of the present study are likely not sufficient to disregard the impact of intracochlear pressure variation on hearing preservation however, particularly considering how a possible relationship between insertion forces and intracochlear pressure can be seen in the form of similar results at the upper basal turn.

With regards to speed, the results likely demonstrate that speed is only applicable within reason. At a certain speed, the impact on hearing preservation is negligible, as demonstrated by a lack of statistical significance between 30 second and 120 second insertions for MTICPV. If nothing else, the advent of shorter surgery would overall result in increased efficiency and reduced operating times. Further in vivo experimentation would likely be required to determine this threshold. The effect of using an insertion device and the impact of experience levels are two factors of intracochlear pressure variation highlighted within the present study that require further study and differentiation before an appropriate threshold for speed of insertion is determined in an in vivo setting.

With regards to an underwater insertion, the results likely demonstrate that underwater insertions have the potential to damage residual hearing if used incorrectly. Shifts in fluid volume in the study produced great intracochlear pressure variation, however this was conducted using a 1 litre bucket. In vivo, the volume of the middle ear is ~3-4mL, and unlikely to produce the same fluid shifts. Nevertheless, it is important to remember this potential pitfall when introducing underwater insertions.

Lastly, the study demonstrates an important correlation with insertion force regarding the importance of the insertion at the upper basal turn. At this point, both a spike in intracochlear pressure variation seen in the current study, and a spike in insertion forces seen in high quality studies in the literature support this region as a point of importance, especially given it has the highest proportion of spiral ganglion nerve cells within the cochlea. Both variables have been investigated independently within the literature, but their correlation would improve the current understanding of hearing preservation in cochlear implantation, and provide an important target for further research.

6.4. Future directions

In future studies, there are many other factors which could be investigated in an in vitro setting, such as the size of the electrode, different insertion devices and the implementation of intracochlear infusion devices.

It would also be pertinent to venture into in vivo studies and clinical trials measuring intracochlear pressure variation. By further clarification of which variables are deemed critical for hearing preservation, in vitro studies measuring intracochlear pressure variation become more easily translatable. One possible development would be to use an intracochlear pressure sensor intraoperatively.

In future calculations, there may be utility in redefining the parameters for AICPV. Within the current study, parameters were set to include all sound pressure levels above what would be expected within a quiet room. In future, different thresholds of wider range may be chosen to differentiate between safe and unsafe sound pressure levels. This would require a better understanding of what sound pressure levels are traumatic during implantation, which is information not currently well understood in the literature.

It is the hope of the author that this thesis leads to more consistent preservation of residual hearing with an evolved understanding of the factors affecting hearing preservation.

There is enormous potential for expanding the indications of cochlear implantation. In Australia, approximately 115,000 people have live with severe to profound hearing loss, of which 102,000 are over the age of 60. There are a number of studies that have shown that for thresholds beyond 55 to 60 dB HL, provision of high-frequency speech information via acoustic amplification with HAs often provides little or no benefit for speech understanding,(3, 4, 17) meaning that these individuals often are disabled by their hearing loss.

Worse still, it has been demonstrated that hearing loss is the leading preventable risk factor for the development of dementia, according to the World Health Organisation, with almost 10% of dementia caused directly by hearing loss, either through the loss of neural stimulation or by the social isolation that follows its onset.(119)

If cochlear implantation could be improved to a point where the indications are suitably expanded to encompass the growing deaf population of the developed world, the benefits would be enormous.

6.5. Conclusions

In the present study, changes in intracochlear pressure were measured against changes to speed, depth and whether the insertion of a cochlear implant was conducted underwater.

Two variables were used to measure intracochlear pressure variation, measuring both transient and aggregate changes in pressure, and a novel surgical assistance device was used to maintain consistent performance.

The study found that a deeper insertion was associated with greater intracochlear pressure variation, as was performing the insertion underwater. Notably, the study identified the upper basal turn of the cochlea as a region of importance for hearing preservation.

The present study found no statistically significant effect of speed upon intracochlear pressure variation. Importantly, insertions were performed using a robotic insertion device to reduce variability and improve precision, and the presence of early outliers warranted the repetition of a portion of the experiment, once the learning curve of guiding an insertion was mastered.

The present study contributes to the current understanding of the literature by producing what is currently the largest in vitro study looking at intracochlear pressure variation and using it to further develop an understanding of key variables associated with soft surgical techniques. It is the hope of the author that with ongoing surgical research, consistent hearing preservation in cochlear implantation may be achieved.

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