UNIVERSITAT DE BARCELONA

Intraoperative neurophysiological monitoring through pedicle screw stimulation

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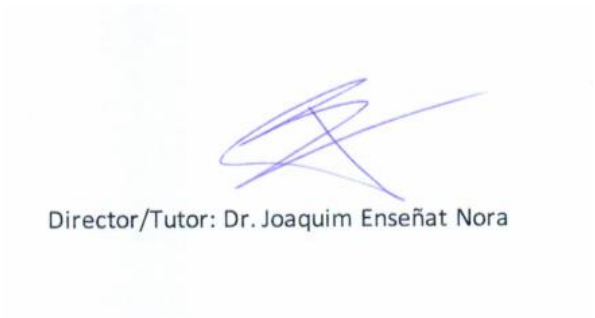

Dedication:

My deepest gratitude to those who stood by me, who showed support when I was low, raised me to where I am now and continue to watch me blossom. A special thank you to Jesus Christ, Mom, Dad, Theodora, Andrea, Rocco and Louie. I love you.

Εν οίδα, ότι ουδέν οίδα.

-Σωκράτης

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Abstract

Title: Intraoperative neurophysiological monitoring through pedicle screw stimulation.

Objectives: Study the interdependence between stimulus duration and stimulus strength, to observe if by changing the stimulus duration, the current threshold levels will also change during pedicle screw stimulation. Then comparing the pedicle screw threshold data to 3-Dimensional imaging to confirm the effectiveness of pedicle screw stimulation.

Background: This study examined the stimulus parameters of triggered electromyography in the operating room during posterior spinal fusions with pedicle screw fixation, and how changing stimulus duration would affect the threshold value of a pedicle screw. Triggered Electromyography (t-EMG) or pedicle screw stimulation has been used for years as Gold Standard to test whether pedicle screws are properly placed or well insulated by bone in the pedicle of the vertebrae. In a triggered EMG test, a stimulus is sent to the pedicle screw, when the electrical stimulus activates nervous tissue, a compound muscle action potential is elicited, at this point a current threshold value is recorded. This threshold is compared to normative values, which determine if the screw is located intrapedicular or has breached the pedicle wall. A breach in the pedicle wall by a pedicle screw would cause a post-operative neurological deficit, such as nerve irritation. To examine the effects duration has on threshold values, the same screw was stimulated three different times with three different durations. The

threshold values were statistically evaluated to see if there was a significance between each stimulus duration and its corresponding threshold value. Duration was examined because it is often overlooked as a parameter that may change the threshold value of a triggered EMG test. Having discrepancies due to duration can produce inaccurate results which could potentially harm the patient or change the surgical protocol. It may harm the patient by leaving a screw in place that has breached the pedicle wall of a vertebrae, which will most likely cause post-operative nerve irritation. Pedicle screw stimulation is an additional modality used to verify screw placement along with radiographic imaging in the operating theatre when posterior spinal fusions are taking place.

Methods: The current technique of pedicle screw stimulation using threshold numbers (in milliamperes) was evaluated against different stimulation parameters, and later the position of the screw was visually verified by a neurosurgeon with 3-dimensional imaging. Fundamentally, the imaging was used to validate the effectiveness that pedicle screw stimulation has on determining a well-positioned screw. Patients already scheduled to undergo spinal fusions with pedicle screw fixation were eligible for this study. A 3-Dimensional (3D) image of their spine was taken intraoperatively before insertion of spinal fixation instrumentation and one was taken after pedicle screws were inserted. These images were used to evaluate the position of the pedicle screw by a neurosurgeon. After screws were positioned, triggered EMG was utilized to check whether screws were properly placed. Screw measurements were taken from patients undergoing a posterior spinal fusion in either the thoracic, lumbar or sacral region. 213

screw measurements were taken in total from 40 patients. Factors like sex, age, height and weight were not considered for this study. The triggered EMG test threshold was then compared to the post screw insertion 3D image to verify the accuracy of the triggered EMG. In other words, the image was used to justify whether the triggered EMG test alone was an accurate indicator of a properly placed screw. In addition, the triggered EMG test itself was further evaluated, by stimulating the same screw three times, with three different stimulus durations, 300µsec, 200µsec, and 100µsec. The values produced by each stimulus duration were then compared to the corresponding stimulus threshold to see if there was a significant difference. Triggered EMG stimulus durations were assessed to see if stimulus parameter settings play a role in the threshold number. A change in stimulus duration, could change the triggered EMG threshold number, which when compared to normative data could possibly indicate a properly placed screw from a mal-positioned screw with a difference in threshold of as little as 1 milliampere. From all the stimulus parameters, a focus was put on the stimulus duration because this could directly affect the triggered EMG current threshold number, or the current value where a compound muscle action potential is elicited. Which depending on where the threshold value fell against pre-determined normative values, could directly affect whether a screw is interpreted as well-placed or not. To summarize, each pedicle screw was tested three times, at three different stimulus durations, then the corresponding threshold numbers were compared to currently established normative data thresholds and evaluated to see if duration could affect the results of a pedicle screw's position. Remember, thresholds have been established that

deem a properly placed screw, these have been used throughout the years, but no emphasis has been given to the stimulus parameters set for these thresholds. This study evaluated the importance of setting the proper stimulus parameters, mainly the stimulus duration, when using certain normative thresholds tested at specific durations to deem a properly positioned screw in the pedicle of a vertebrae. After stimulation, 3D imaging was taken intraoperatively to compare the triggered electromyography data to the actual placement of the screws. The threshold values were compared to the 3 D image of the same screws tested, to verify if indeed these established threshold values determined well-positioned screws.

Results: 213 screws were stimulated, out of the 213 screws, 2 screw measurements were excluded because stimulations were not obtained from all three durations. Thus 211 screws and 40 patients were included in this study. 211 screw measurements were taken in total from 40 patients with screws confirmed to be placed intrapedicular. The triggered EMG fell within normative data thresholds for 206 screws (98%), these screws were found to be intrapedicularly placed in the 3D imaging, which was confirmed by the neurosurgeon. Stimulation durations were found to be important in five of the screws, where there was a difference in the thresholds between the three stimulations, these were significant because the values were lying borderline on normative values, questioning if the screws were indeed well-placed or possibly causing a medial breach. These five screws were thoroughly examined by the neurosurgeon via 3-dimensional imaging and were found to be acceptable in placement, and not near nervous tissue.

Conclusion: Intraoperative 3D imaging has shown that triggered electromyography is a reliable indicator of properly placed pedicle screws. Statistical data has also shown that stimulus duration can affect the interpretation of a properly placed screw, and threshold values do vary with different durations. Threshold values were gathered from 211 screws at three different stimulus durations, the first at 300µsec, the second at 200µsec and the third at 100µsec. At 300µsec stimulus duration, the mean threshold value was at 27.25mA ($p=0.0078$). At 200µsec stimulus duration, the mean threshold value was at 35.46mA ($p=0.0028$). At 100µsec stimulus duration, the mean threshold value was at 50.90mA ($p=0.0676$). These mean values were found to be statistically significant when run by the Kruskal-Wallis test, a non-parametric statistical significance test. Since, three groups of data were being compared, and thus were not normally distributed, a non-parametric significance test was used. In conclusion, the stimulus duration should be considered when using certain thresholds to interpret data. Different durations change the stimulus strength and thus, affect the results of the screw stimulation thresholds.

Introduction

Intraoperative neurophysiologic monitoring (IONM/IOM) has been used for several years to detect insults to the central and peripheral nervous systems and the subsequent prevention of iatrogenic neurological injury.[1] Neurological deficits caused by inaccurate pedicle screw placement have been documented in clinical studies.[2] Its utilization quickly became Gold Standard for many procedures where neurological structures are at risk. Depending on the surgery, for example spine, brain, peripheral nerve, orthopedic, vascular or otorhinolaryngology, different modalities are used to monitor a variety of neurological structures. For this research project, the focus was on posterior spinal fusions involving pedicle screw fixation.

The purpose of a spinal fusion is to create stability in an unstable vertebral column. When a patient has spinal instability, scoliosis, spinal stenosis, degenerative disc disease, herniated nucleus pulposus, spondylosis, spondylolisthesis, spondylolysis, cauda equina syndrome, spinal cord tumor, tethered cord, and traumatic lumbo-sacral fractures,[3] this procedure is done to relieve pressure on the spinal cord as well as stabilize the vertebral bodies of the spine. Stabilization of the spine is done by inserting screws through the pedicle and into the vertebral body, then connecting the heads of the screws with a rod, in a similar fashion as braces are to teeth. Figure 1 provides a

visual of the vertebrae of the spinal column corrected with pedicle screw fixation, and then connected with rods.

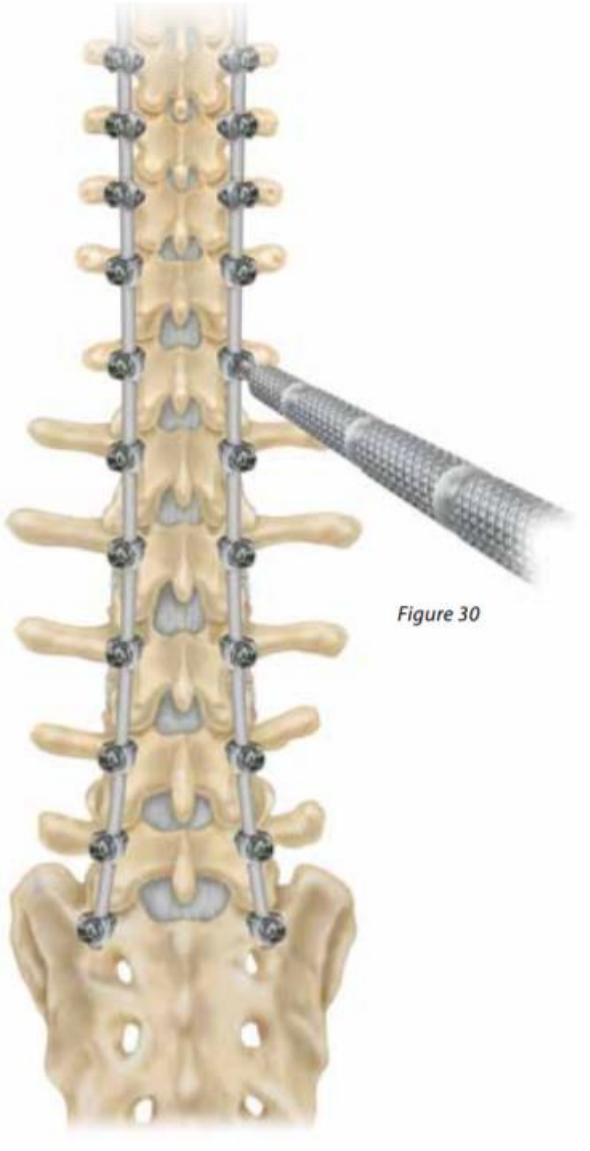


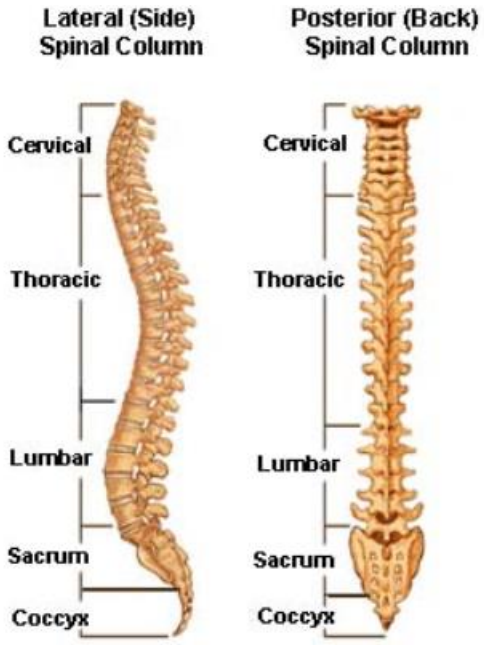
Figure 1: Medtronic CD Horizon Solera Spinal System[4]

This metal structure stabilizes or holds the spine in the correct position until the bone regenerates and fuses to stabilize the spine. This process usually takes a year, after a

year the rods and screws can be removed, but due to patient trauma of having another operation, the FDA/CE approved instrumentation is safe to stay permanently implanted.

The main neurological structure at risk for this type of procedure is the nerve root, especially if we are below the level of the spinal cord. The spinal cord starts from the cervical region and typically ends at the first lumbar vertebral body, also known as L1. Therefore, a fusion from lumbar vertebrae 2 down to the sacral bone (L2, L3, L4, L5, S1) would be at high risk for nerve root injury. For any fusions involving the cervical region to Lumbar 1, the spinal cord as well as the nerve roots would be at risk for injury. Please see Figure 2 for a visual on the spinal anatomy and nerve root involvement.

Figure 2: Spinal column anatomy. [5]

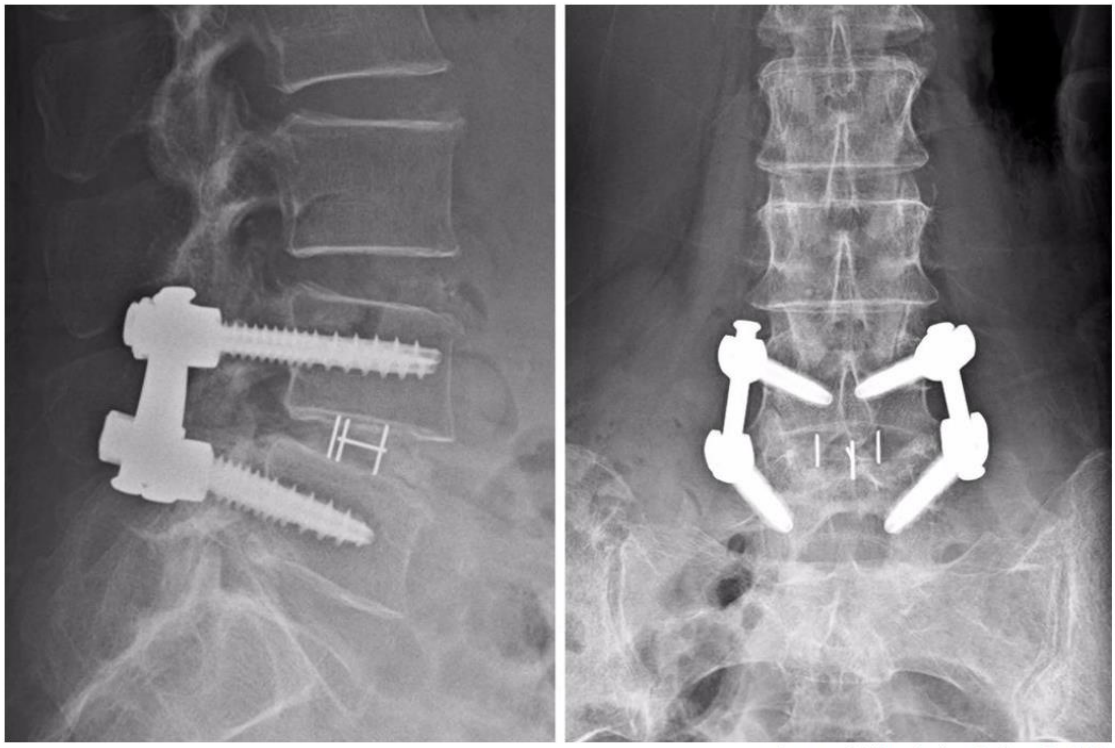


Term	# of Vertebrae	Body Area	Abbreviation
Cervical	7	Neck	C1 – C7
Thoracic	12	Chest	T1 – T12
Lumbar	5 or 6	Low Back	L1 – L5
Sacrum	5 (fused)	Pelvis	S1 – S5
Coccyx	3	Tailbone	None

For spinal fusions that involve the thoracic or cervical region, neurological damage to the spinal cord is also a concern and involves the use of evoked potentials to monitor the integrity of the spinal cord. For this study, whether the procedure involves the spinal cord (thoracic/cervical level), the focus will only be on the potential damage a

screw can do when it infiltrates the intervertebral foramen. The intervertebral foramen is the area where the nerve root passes from the spinal cord to its corresponding muscle. As the screw passes the pedicle, there is risk of the pedicle bone being fractured and thus the screw touching the nerve root and causing irritation. Neural structures are close to the pedicle and incorrect placement of the screws can lead to postoperative neurological deficits or radicular pain.[2] Neurological deficits caused by inaccurate pedicle screw placement have been documented in clinical studies.[6–8] Most often the fractures that occur are microfractures, they are not visible to the naked eye and are seldom picked up by radiograph. Post operatively, this type of breach can cause radiculopathy, which is also known as nerve root irritation. Insertion of screws into the pedicles is essentially a "blind" technique with radiographic assistance.[2] It has become Gold Standard to use intraoperative neurophysiologic monitoring (IONM) in combination with radiographic imaging in order to drastically reduce the possibility of an iatrogenic induced post-operative deficit. While 2-dimensional radiographs or X-Ray radiographs are valuable in verifying correct screw placement (please see figure 3), an unacceptable false-negative rate of 14.5% using radiography for incorrectly-placed screws was found.[9] The sensitivity of radiography is only 63%.[10] It was found that even experienced surgeons misdirect the screw medially in 5% and inferolaterally in 15% of the cases when using standard fluoroscopic imaging.[11 12] Evoked EMG is 93% sensitive in identifying misplaced hardware.[10] Therefore, using both methods in conjunction with one another deems a better post neurological outcome and decreases chances of false negatives or false positives.

Figure 3: Example of 2-Dimensional radiographs or X-rays showing a pedicle screw fixation system. [13] This figure shows 2-dimensional X-rays of post spinal fusion L4 and L5. The C-arm, which is the intraoperative X-ray machine, needs to be moved from a lateral position to show a sagittal view, and then an anterior/posterior position to show a coronal view.



Courtesy of Adjunct Assistant Professor Jacob Oh

X-rays, post-spinal fusion surgery, of titanium screws and a spacer to fuse bones in the spine.

Pedicular fixation of the lumbar spine has become an accepted technique in spinal fusion surgery.[2] A significant advantage to using the pedicle is the rigidity it provides for fixation of the vertebral motion segment.[2] However, there is considerable potential morbidity associated with incorrect placement of the screws into the vertebral pedicles.[2] Therefore, screws are stimulated by means of an electrically elicited electromyography test. Pedicle screw stimulation or triggered electromyography (t-EMG) or evoked EMG is the IONM modality used to evaluate the positioning of a screw within the vertebral body. In general, Electromyography (EMG) is a recording that directly relays information of the spontaneous activity of individual nerve roots from their corresponding muscle,[14] it does not involve the evaluation of the spinal cord. Free run EMG is a recording of muscle activity from the specific nerves that innervate that muscle. By sending electrical current through a stimulating probe, this transforms the free run EMG into a triggered EMG, as this stimulation can ignite a compound muscle action potential (cMAP). The stimulus is sent in the form of current measured in milliamperes (mA), through to the metal pedicle screw, and if this current reaches the nerve root, an action potential is elicited. An ampere is a measure of charge flow. One ampere is equivalent to one coulomb of charge moving past a given point in one second.[15] Metal is a good conductor of electricity and bone is a poor conductor of electricity. Therefore, if a lot of current is needed to be sent through the stimulating probe in order to elicit a cMAP, that in essence means that the pedicle screw is well encapsulated by bone, and that bone (which is a poor conductor) is not allowing or blocking the current from reaching the nerve root. On the other hand, it is possible to

send so much current that current spread[1,2] happens by bypassing the bone, infiltrating the adjacent muscle, causing the adjacent nerve root to ignite and elicit a cMAP. But even if this happens, it will still properly give a high threshold number, thus correctly implying a properly placed screw. Since, for the current to be diverted, it means the electricity had difficulty reaching nervous tissue, implying a screw fully insulated by bone. Current spread also known as current shunting, is not as significant of an issue with pedicle screw testing as it is when mapping individual nerve roots. Where it is imperative to measure the integrity of the nerve fibers and be able to individually identify nerve roots. To recap, the more current needed to be sent through the stimulating probe, the higher the threshold number will be when a compound muscle action potential is produced. When less current is needed to be sent through a stimulating probe, it will yield a lower threshold number in milliamperes because less current will be needed to elicit a compound muscle action potential. This low threshold value may imply a fracture in the pedicle, since the electricity easily reaches nervous tissue and causes a cMAP. Once again, bone is not a good conductor of electricity so if a screw is fully encapsulated by bone, it will yield a higher threshold number in milliamperes. A good conductor of electricity is tissue that allows electricity to flow freely, e.g. muscles, water content, where resistance is low and impedance is low.[16] A screw well encapsulated by bone will have a higher threshold because the current would find resistance in traveling through the bone, thus needing a higher electrical current to elicit a compound muscle action potential. A correctly placed screw should be fully surrounded by bone that has a high impedance to electrical current.[10] A screw

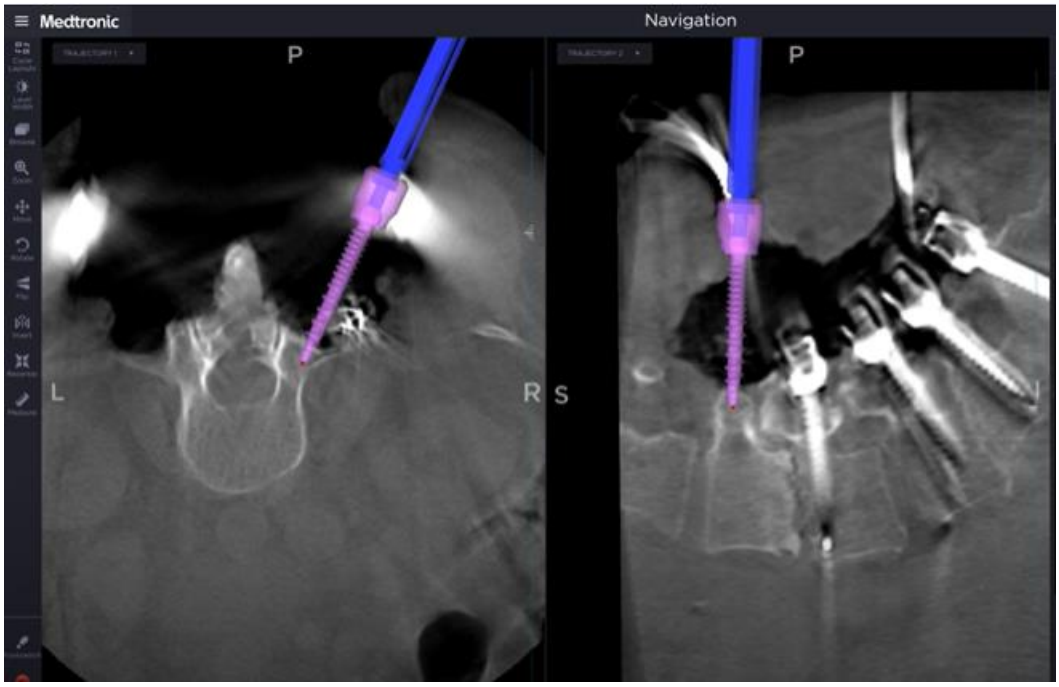
well positioned within the walls of the pedicle will have a high impedance to electrical stimulation of higher intensities.[17] The bone would act as an insulator, tissue that consists of cells that are not conducting electrical signals, where resistance is high and impedance is high.[16] If there is a microfracture in the bone, while stimulation is occurring, the current would leak through the microfracture to reach the nerve easily and ignite the nerve root to elicit an action potential at a lower threshold number. When a pedicle wall is violated, electrical stimulus introduced will readily reach nearby neural structures leading to excitation of the adjacent nerve root resulting in triggered EMG activity.[10] This evokes a compound muscle action potential at LOW current intensities. Depending on how low the number, it may indicate the screw would need to be removed and/or the trajectory changed for repositioning, so that the pedicle screw does not cause irritation to the nearby nerve root or push against the spinal cord. Triggered EMG or pedicle screw stimulation has been performed for the past several years proving a good indicator for assessing a well-positioned screw in the pedicle of a vertebral body, [18] and thus aiding in the prevention of post-operative neurological deficit. Once again, a well-positioned screw, is fully encapsulated by the bone of the pedicle and has no microfracture that would allow the screw to irritate a nerve root and possibly cause post-operative radiculopathy.

The second part of this study used three-dimensional imaging to evaluate the position of a screw and confirm the accuracy and specificity of the pedicle screw stimulation test. Plain radiographs, fluoroscopy, and computed tomography (CT scans) are used to

determine screw accuracy.[19] Although CT is considered the gold standard, radiographs and fluoroscopy are readily available and carry a lower radiation burden.[19] However, radiographs and fluoroscopy have been shown to be inferior to CT scan because of their biplanar nature of image acquisition.[19] Therefore it is ultimately preferred to view pedicle screw placement with at CT scan when available. A CT scan provides three-dimensional imaging versus the conventional two-dimensional imaging that X-rays provide. X-ray beams are non-parallel and originate from a very small source, leading to radiographs that are imperfect, with enlargements affected by the distance between the focus, the object and the film. [20] Please see figures three and five for comparison of the images and views, a 2-dimensional X-ray provides versus a 3-dimensional O-arm image for pedicle screws inserted at lumbar vertebral level five. For the spinal fusions done at the facility where data was collected, three-dimensional imaging was taken intraoperatively with the use of Medtronic's O-arm.[21] Imaging was taken after exposure to the incision site, but before instrumentation was inserted. Once this imaging was taken, the Medtronic stealth navigation wand was calibrated to those images, and the pedicle screws were inserted with the guidance of this navigation system. Screw hole placement, drilling, tapping, and screw sizing were performed under navigation using a surgical imaging system (O-arm Surgical Imaging System and Stealth Station S7 navigation system, Medtronic). Standard surgical techniques, tools, and practices were used throughout the surgical intervention. Basically, navigation was used to identify pedicles by touching anatomical landmarks. After a pedicle was identified with a probe, a pedicle feeler was used to confirm that there was no pedicle breach, and the hole was

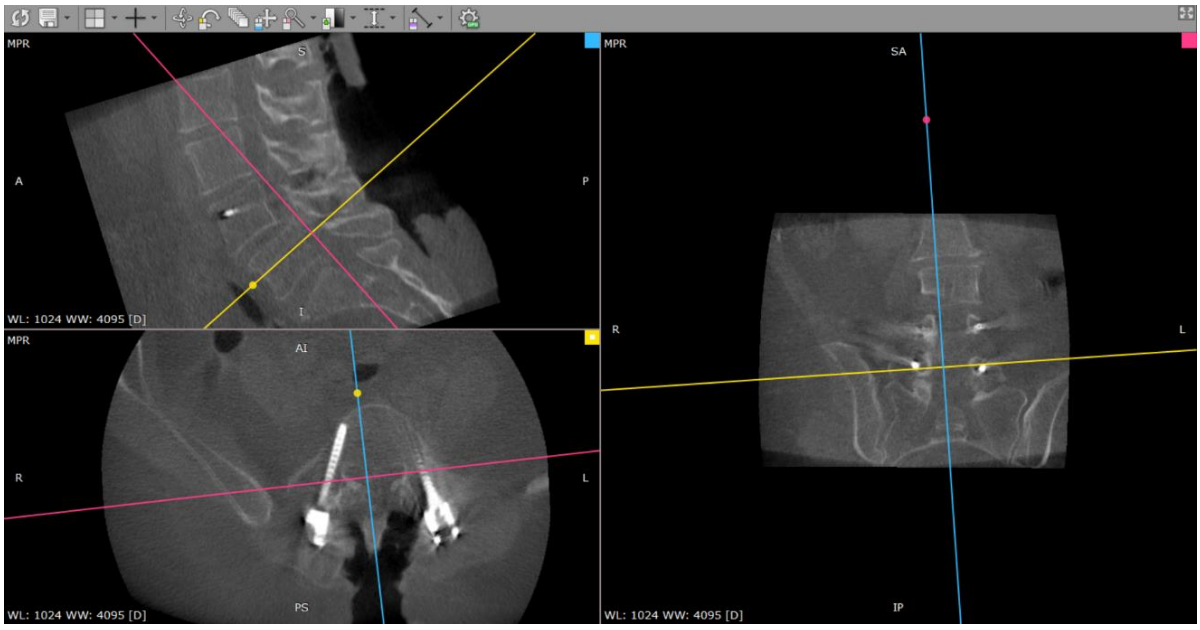
then tapped in the same trajectory.[22] After a pedicle feeler again confirmed no pedicle breach, the screw was placed.[22] Medtronic's O-arm navigation proved to be quite helpful in the placement of pedicle screws (please see figure 4).

Figure 4: O-Arm Surgical Navigation of Lumbar Pedicle Screw Trajectory.[23] This figure gives an idea on how navigation assists in the accurate placement of pedicle screws, by projecting how the pedicle screw would enter the pedicle.



Bilateral screw holes were drilled and tapped in each vertebra.[24] Once all screws were inserted, another three-dimensional image was taken in order to assess the position of all the screws. Digital radiographs after screw insertion were obtained to document trajectory and proper placement.[24] Once that was complete, and the surgeons were satisfied with the screws' positioning on the images, the screws were individually tested with triggered EMG. In most cases IONM and O-arm findings corresponded well. There were one or two cases where the imaging was questionable, but a safe stimulation threshold, verified a good screw position, which allowed the surgeons to proceed with confidence. A study done by Nottmeier et al, found that only two nerve root injuries occurred in 1084 screws placed with three dimensional imaging in 220 patients, resulting in a 0.2% screw incidence and a 0.9% patient incidence of nerve root injury.[22] Strengthening the usefulness of three dimensional imaging when placing pedicle screws.

Figure 5: Pictures of 3D and 2D showing L5 screws and the superiority of 3D. The below 3D image was taken from a subject from the research study. It shows bilaterally screws in L5 in sagittal, coronal and axial views. The images below also offer tools that use navigation to decipher the desired trajectory for screw placement.

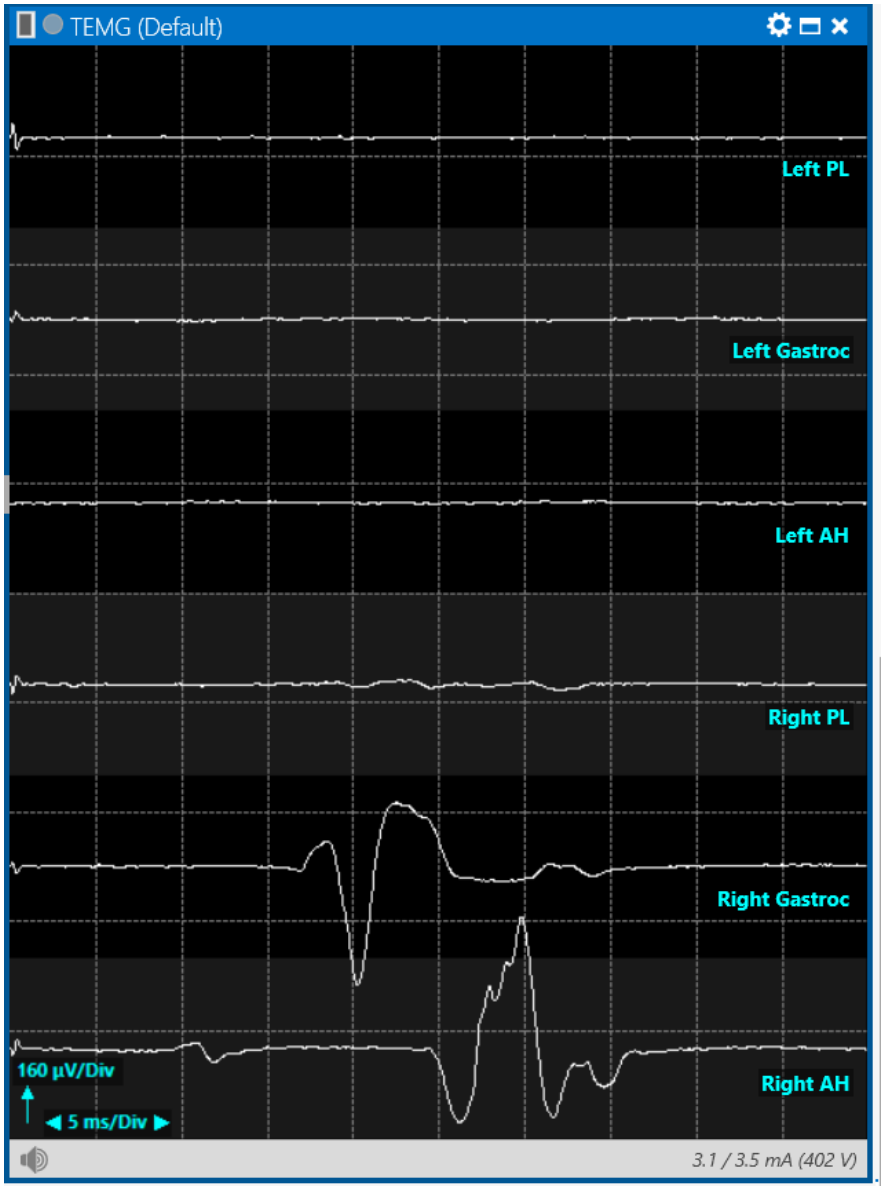


Background

Throughout the past several years, in spinal fusions, the position of pedicle screws has been evaluated using triggered electromyography (t-EMG) tests and radiographs. We will first discuss intraoperative neurophysiology, specifically the value of the electromyography (EMG), and then will discuss radiography. A triggered EMG or pedicle screw stimulation test has been used since the early 1990s,[25] and its use has since become gold standard in spinal fusions with pedicle screw fixations. Looking at the basic steps of pedicle screw stimulation… once all the pedicle screws have been inserted by the surgeon (neurosurgeon or orthopedic spine), a monopolar stimulating probe is handed to the surgeon by the neurophysiologist. The ball tip head of the stimulating probe is placed onto the groove of the screw's head (contacting the screw's inner shaft), and then electrical current is sent from the neuromonitoring equipment to the probe. Electricity passes through the uninsulated ball tip of the probe into the screw's shaft. The electrical current is in milliamperes. The electrical current is gradually increased until a compound muscle action potential is elicited and seen in a trace on the electromyography screen. Once the cMAP is elicited, the current value that elicits a cMAP is documented, and then compared to normative data. Please see Figure 6 to view the morphology of a compound muscle action potential. To interpret the triggered EMG test, well researched threshold values are in place that are used to determine a well encapsulated screw from one that has breached the pedicle bone. It should be noted that in this study, the threshold values that were used to compare a screw's

threshold, a current level (in milliamperes) that would deem a well-placed screw versus a mal-positioned screw, are from published work by Lawrence G. Lenke, MD, a leader in complex spine deformity surgery.[26] Basically, Lenke et al, deemed a screw that is well positioned in the pedicle bone (without any breach) would have a threshold number greater than eight milliamperes, >8 mA. To summarize, a high threshold value equates to a screw well inserted within the bone, and thus not causing any irritation to nearby neurological structures, i.e., nerves or spinal cord. A screw showing a low threshold value (<8mA), equates to one that has breached the bone and is therefore malpositioned. This breach allows the current to easily reach, and thus stimulate nervous tissue causing a compound muscle action potential at a low threshold. Please see figure 6, the compound muscle action potentials seen in this picture are elicited in muscles innervated by the right sacral root 1 (S1), peroneus longus, gastrocnemius and abductor hallucis, at a current as low as 3.5mA. This data would require the removal of the right S1 screw, and its repositioning. If the right S1 screw was not repositioned, at this position, the data from the stimulation would equate to a post-operative irritation, radiculopathy, or other neurological deficit. Since the point of spinal fusions is to correct deformities, reduce pain, and overall not induce unnecessary harm, the screw would be removed and actions would be decided if the screw would be inserted at a different trajectory which would not irritate nearby nervous tissue or if it would be better to forgo having a screw at the right S1 level.

Figure 6: Compound muscle action potentials elicited from stimulation of a right S1 screw. The action potential is seen at 3.5mA indicating a breach in the pedicle wall and signifying the removal and repositioning of the screw.



Although there are current triggered EMG threshold values in place, these values remain controversial. Many authors have studied the specificity of the universally used pedicle screw threshold values.[1,18 10 26 27 28 29 30] The most recognized studies on lumbosacral screw thresholds come from the works of Calancie, Lenke, Clements, Maguire, Raynor and Glassman. Please see figure 7 for citations and the determined safe threshold levels per study. The authors have varying threshold values for what they deem a properly placed screw, but with their varying thresholds, they each have specific stimulus durations. There is a need to emphasize that when authors are quoted or their threshold values used, the stimulus duration should also be used. From over fifteen years of hands on experience in triggered EMG, the stimulus duration is rarely emphasized or paid attention to with many intraoperative neurophysiologists or within the criteria from professional societies for performing the test. For that reason, this study focused on evaluating if the stimulus duration should be considered as an important parameter when setting up protocols. Perhaps this factor needs to be considered when evaluating a screw, not just the threshold level, for example, does changing the stimulus duration change the validity of the recommended normative threshold values. That is, if one used one author's normative threshold parameters, assessed a screw with those values but then did not set up the triggered EMG protocol with the author's corresponding stimulus duration. Referring to figure 7, would calling a screw safe at 8mA at a 200µsec duration be reasonable for Calancie, who states at 200µsec a screw is well placed at a minimum of 10mA. Many published papers evaluating mal-positioned screws use a threshold value of >8mA to label a screw as well

encapsulated, but the importance of stimulus parameters is rarely mentioned. This research assessed the importance of stimulus parameters, specifically stimulus duration, and if the duration should properly correspond with the ones used in each varying author's threshold values. Particularly when being used in conjunction with acquiring data, interpreting data, and making the decision to change a surgical protocol by repositioning a pedicle screw.

Figure 7: List of authors and acceptable or safe threshold values, where a screw is deemed correctly placed in the pedicle, fully encapsulated by bone and with no pedicle wall breach or defect. Along with the corresponding stimulus durations used.

Study	**Threshold (mA)**	**Duration (µsec)**
Calancie et al. 1994[30]	>10	200
Maguire et al. 1995[10]	>6	200
Lenke et al. 1995[26]	>8	300
Clements et al. 1996[29]	>11	200
Raynor et al. 2005[18]	>8	300
Glassman et al. 1995[31]	>10	50

Basically, this research evaluated the validity of intraoperative neurophysiological monitoring (IOM), specifically the triggered electromyography, in surgeries involving the stabilization of the spinal column. Once again, spinal fusions are a type of operation done to stabilize the spine. In stabilization, screws are inserted into the pedicle of the vertebrae, and then connected with a rod. In the same fashion as metal braces are used on teeth, except these screws are placed near spinal nerve roots or the spinal cord, therefore there is a risk of iatrogenic induced neurological deficit. The use of triggered EMG greatly reduces neurological deficits.

Objectives

The main objective was to study the interdependence between stimulus duration and stimulus strength, to observe if by changing the stimulus duration, the current threshold levels would also change during pedicle screw stimulation. Three different stimulus duration levels were applied to the commonly practiced method of pedicle screw stimulation, also known as triggered electromyography, to see what effect the different durations would have on the threshold values. Those threshold values were then compared to normative data. Then the triggered EMG's specificity in indicating a properly positioned screw was confirmed visually by the neurosurgeon with 3-Dimensional imaging. This not only validated the accuracy of the tEMG, but further examined the screw's placement within the pedicle. Lenke et al's normative threshold

numbers were used to determine adequate screw threshold. Lenke et al's study determined that triggered electromyographic stimulation was a valuable aid in determining appropriate placement of pedicle screws. Lenke et al recommends the use of the following threshold stimulus intensities for interpretation of a well-insulated pedicle screw: > 8 mA--screw entirely in the pedicle; 4.0-8.0 mA--potential for pedicle wall defect; < 4.0 mA--strong likelihood of pedicle wall defect with potential for nerve root and dura contact.[26] This study used these particular thresholds, but also evaluated the validity to paying emphasis on stimulus parameters, specifically duration. It examined the interdependence between stimulus strength and stimulus duration, and how it affected the compound muscle action potential's (cMAP) threshold values when determining a well encapsulated pedicle screw.

It is important to take time now to go into depth on the strength-duration curve of a compound action potential and what it means. The morphology, amplitude and duration of a compound muscle action potential changes as the stimulus duration increases. A bigger stimulus duration or progressively stronger stimulation activates more and more individual nerve fibers, whose individual action potentials summate to yield a cMAP.[32] When you have a stronger stimulus, a larger number of fibers reach threshold creating a higher amplitude cMAP. Please see the strength-duration curve below (Figure 8) taken from The McGill Physiology Virtual Lab.

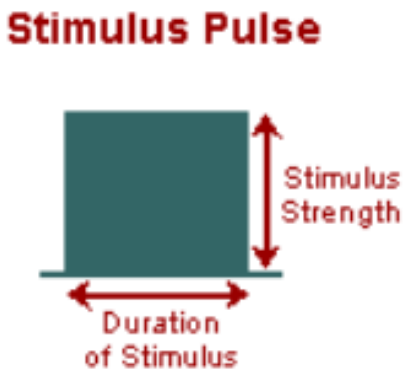


Figure 8: Strength-Duration Curve[32]

However, the threshold for activation of a fiber depends not only on stimulus strength, but also on the duration of the stimulus.[32] This study was set up to further investigate this theory, by testing the same screw with three different stimulus durations and documenting the number in milliamps or current level when a compound muscle action potential was elicited. In theory, a longer stimulus duration should result in a threshold being reached with a low current threshold, and a shorter stimulus duration should result in a threshold taking a longer time to elicit a cMAP and thus having a higher threshold number (in milliamps). Please see the mathematical equations below (figure 9).

Figure 9: Strength Duration Equations from the McGill Physiology Virtual Lab[32]

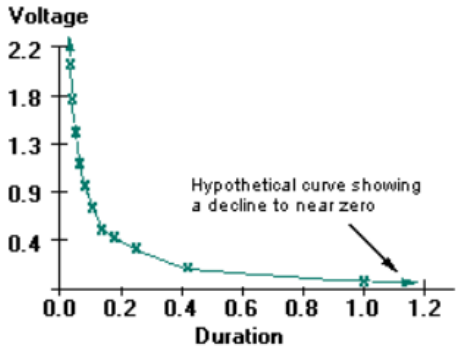
For a short duration stimulus generating a steady trans-membrane current, the charge (**Q**) transferred is proportional to the product of current **I** and time **T**:

$$Q = I \times T$$

Hence if the amount of charge required to activate the fiber is Q_t, and the stimulus duration is **D**, the current I_t required to achieve activation will be:

$$I_t = Q_t / D$$

This suggests that a graph of threshold stimulus strength versus stimulus duration should show a decline to near zero as stimulus duration is increased. In other words, the stimulus strength required to reach threshold should decrease during more prolonged stimulation. Note that we can use voltage (V) and current (I) interchangeably as the measure of stimulus strength.



This equation could be very critical in the operating room when it means positioning or repositioning a pedicle screw. But this theory has not been tested amongst all the current thresholds being used to determine a properly placed screw in the operating room. It should be noted that for this study, Lenke et al's normative values were used to compare the screw threshold data and make the determination if a screw is well-positioned in a pedicle or if it needs to be repositioned or removed. In other words, not setting the correct stimulus duration when using certain normative values could very well determine a successful surgery from an unsuccessful one. An unsuccessful surgery is one where a re-operation to correct a screw's position would be needed in order to

reverse nerve irritation from a poorly placed screw. An improperly placed screw could very likely lead to post-operative iatrogenic induced neurological deficit.[33] The most prevalent one being radiculopathy, which is nerve root compression, commonly referred to as a pinched nerve. Radiculopathy can manifest as pain, numbness or weakness, which can be a burden on the quality of life for a patient.

One way to reduce post-operative neurological deficit, is by evaluating the triggered EMG test and its specificity when determining pedicle screw placement. This was done by studying the interdependence between stimulus strength and stimulus duration and evaluating its effects on the cMAP's threshold values when determining a well encapsulated pedicle screw. It was also done by comparing the threshold value with a radiograph or by comparing the nerve root's threshold value with its corresponding screw threshold. For example, a healthy nerve root elicits an action potential at 2-3mA, a nerve with a pathology may elicit an action potential at 7mA. If a screw tests at 8mA for a patient with the above nerve pathology, this may be a red flag that there was a breach in the pedicle by the screw, since the nerve itself needs 7mA to elicit an action potential. The screw's threshold of 8mA minus the nerve root's threshold of 7mA, only leaves 1mA difference indicating the screw is not well encapsulated by bone, and thus may be irritating the nerve root since there is only 1mA difference. If a healthy nerve's action potential is at 2mA, and the screw tests at 11mA, you can safely say there is enough distance between the screw and the nervous tissue because there is a

difference of 9mA (screw threshold minus nerve threshold). Lenke et al states a well-positioned screw tests at >8mA.

During pedicle screw testing, the neurophysiologist communicates to the spine surgeon the pedicle screw threshold values, those values determine whether a screw is deemed mal-positioned or not. A threshold difference of 1mA could indicate a well-placed screw from a poorly placed screw. Evaluating the significance of using the correct stimulus duration when using standard threshold values to evaluate a screw, may show the importance of using duration in conjunction with specific threshold levels. This may save a surgeon from changing his surgical protocol. Which means it will save the patient from a second hole being bored into his/her pedicle body or a revision surgery.

Methodology

This was a multi-center study; therefore, approval was received from the University of Barcelona, Hospital Clinic to proceed with a multi-center study. This study was a collaboration between University of Barcelona and Vall d'Hebron University Hospital in Barcelona, Spain, as well as Aretaeio Private Hospital in Nicosia, Cyprus. Bioethics approval was given by Vall d'Hebron University Hospital's Bioethics Committee (CEIC), Barcelona, Spain and by Cyprus National Bioethics Committee, Nicosia, Cyprus for the

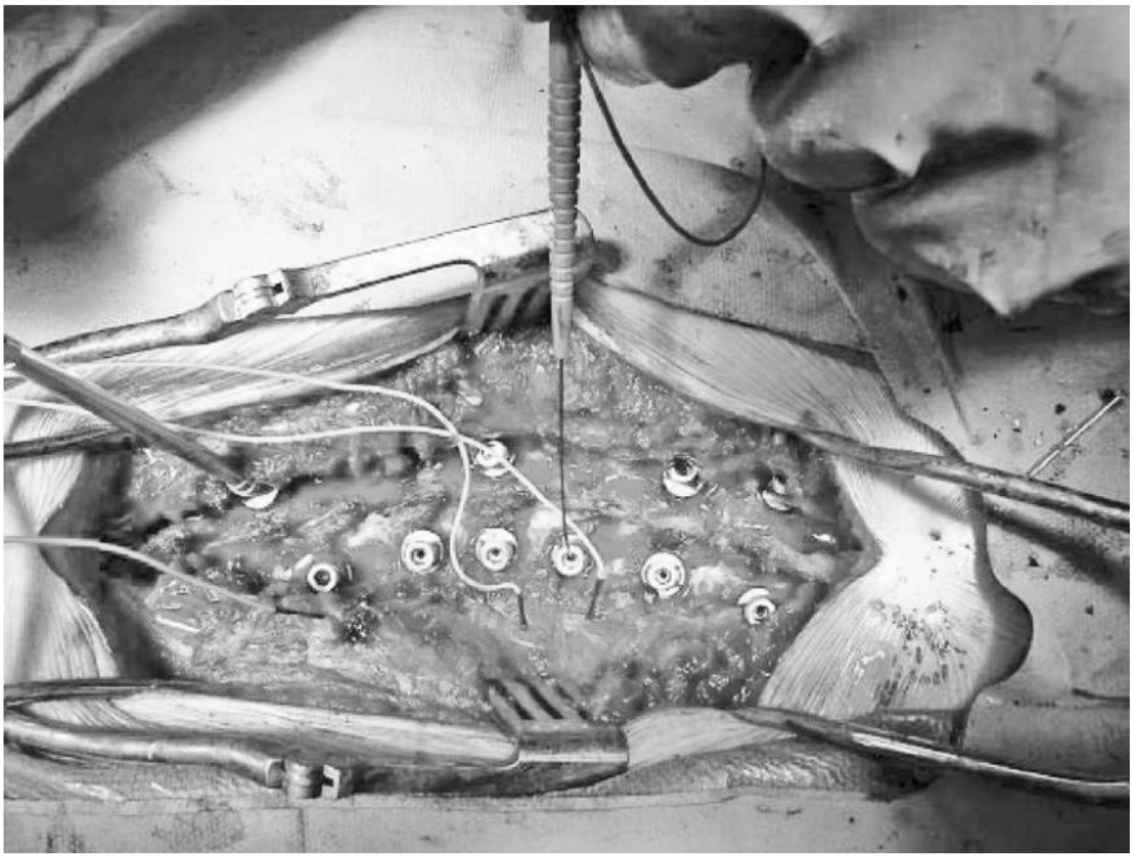
approval of safe data collection and patient protection. Per each committee's standards a specified informed consent was signed by each patient participating in the study within the bioethics country of origin. All patients were given an informed consent to read, understand and sign, so that they were aware that data collected from their surgery would be or may be used for research purposes. They were made aware that they would be assigned an identification number and their private information secured, remaining anonymous. This study used standard neuromonitoring techniques, with all EC and FDA preapproved stimulation and recording parameters. The patients were not subjected to experimental testing. The only additional protocol to the already established testing method was to check each pedicle screw three times at different stimulus durations (all deemed safe within the FDA and CE), instead of just once. This added 5 to 10 minutes to the surgery time, dependent on the number of screws inserted in each patient. The term patients and study subjects will be used interchangeably throughout the paper. The subjects qualifying for the study were patients of neurosurgeons or orthopedic-spine surgeons already undergoing posterior spinal fusions with pedicle screw fixation under general anesthesia and only if three-dimensional imaging was ordered pre and post screw insertion. No extra procedure or additional radiograph was ordered because of this study, this study did not contribute to additional radiation exposure. Only what was already prescribed in the pedicle fusion protocol. The patients became subjects of the study only if they met the above criteria, no one was asked to undergo a pedicle screw fixation for the purposes of this study. No study subject was asked to do anything more than what was already prescribed by their

attending physician. It is important to stress that subjects did not undergo extra radiation due to this study.

Screw fixation through open and minimally invasive procedures were evaluated for this study. Patients having osteopenia, osteoporosis were noted, with special consideration that data may be affected by their bone density, but after data evaluation their condition did not affect data collection. Pedicle screws implanted in the thoracic, lumbar and sacral area were evaluated. A mention must be made that screws inserted in the pedicles at lumbar 2, lumbar 3, lumbar 4, lumbar 5 and sacral 1 are well researched.[26] The thoracic screws are not as well researched but there is literature to support the use of paraspinal muscles in recording a compound muscle action potential (cMAP).[34] The ability to be able to measure an action potential from the paraspinals allows the measurement of thoracic screws especially in patients with extreme layers of adipose tissue around the abdominal area. Without the use of the paraspinals it would be difficult to monitor a cMAP if the abdominal muscles were only relied on, especially with a subject having excessive adipose tissue in the abdominals and intercostal region. Remember that the needle electrode is usually only 13 to 17mm and is not able to reach great depths when inserted into the patient's muscle. So, if a patient is obese, there would be less likelihood that the needle electrode would be inserted in muscle, it may only go as deep as the adipose tissue. Resulting in the inability to measure threshold responses from the abdominal muscles. In this study abdominal and intercostal muscles were set up for electromyography, along with paraspinals in order to obtain the best

possible results. Generally, the paraspinals were used to obtain cMAPs from the thoracic screws,[34] for the lumbar and sacral region, the iliopsoas, adductors, quadriceps, tibialis anterior, gastrocnemius and/or abductor hallucis muscles were used to record cMAPs.[1] This method proved to work very nicely with thoracic and lumbar screw stimulation, and it eliminated artifact from adipose tissue.

Figure 10 below gives a visual on what pedicle screw stimulation looks like in the surgical field, along with where needle electrodes are placed for paraspinal recording.



Intraoperative view of multiple thoracic pedicle screws in an idiopathic scoliosis surgery. Note the curvature of the spine. Picture provided, courtesy of Laurence E. Mermelstein, M.D.

Figure 10: Picture of pedicle screw stimulation with recording off paraspinal muscles.[34]

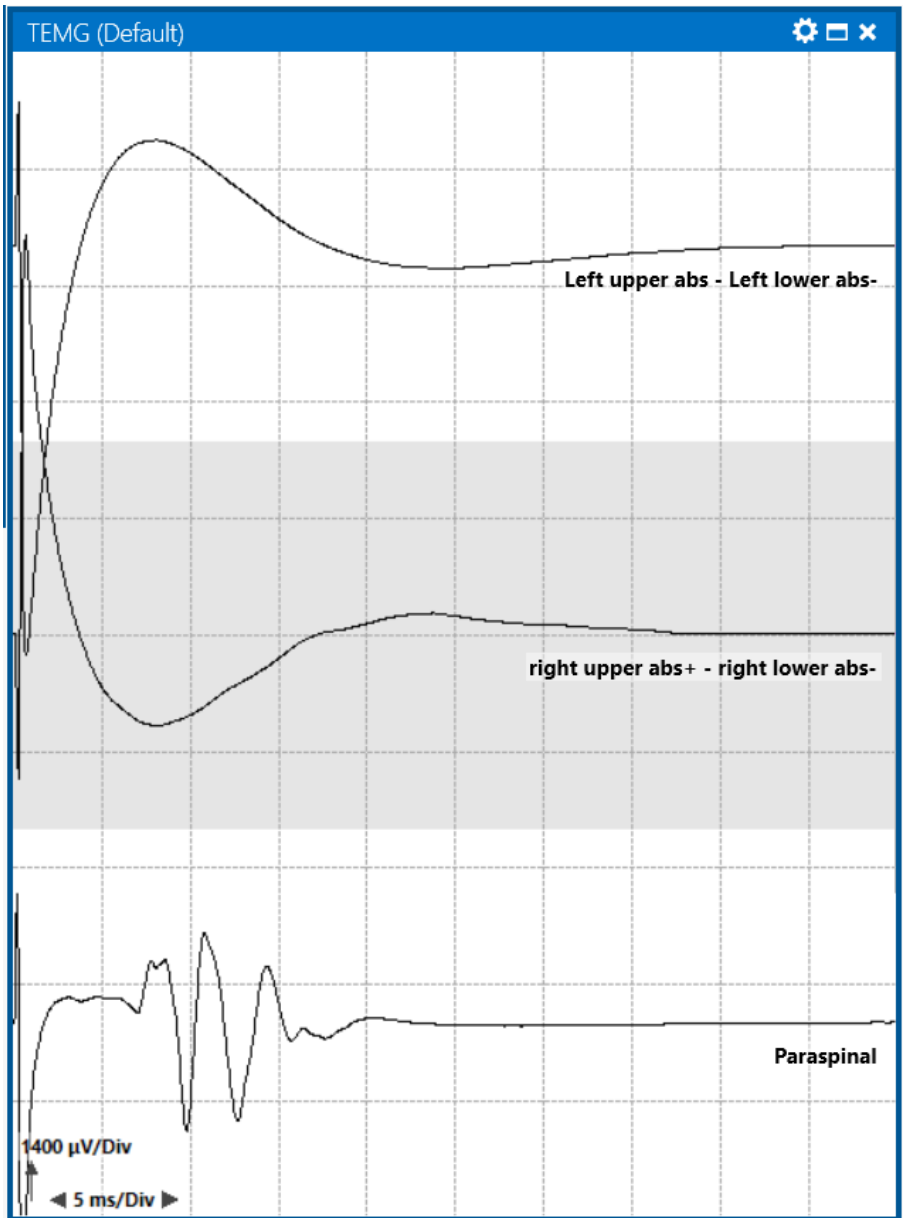


Figure 11: Image of a triggered EMG screen during pedicle screw testing with recording at the paraspinal muscles of a patient undergoing a posterior D5 to L3 spinal fusion with pedicle screw fixation for scoliosis correction. Please note how clear the cMAP is for the paraspinal trace, but the abdominal muscle traces did not pick up any activity and remained flat (probably because the needle electrodes were in adipose tissue as opposed to muscle).

Data collection for this study lasted about 18 months, it was contingent with the availability of patients that were cleared for the specific procedure of pedicle screw fixation and where the three-dimensional imaging would be used. Once the statistical analysis proved to have a strong power, and met a good sample size, data collection ceased, since the hypothesis was proven.

Data collection happened during the patient's scheduled posterior spinal fusion surgery. Data collection added up to ten minutes to the routine procedure and was collected by an intraoperative neurophysiologist. The patient's anesthetic regimen consisted of a total intravenous anesthetic, consisting of propofol and remifentanil, where gases were not used. Neuromuscular blockade was only administered for intubation. A train of four (TOF) test was used to monitor the level of neuromuscular blockade, where tEMG would only take place if there were at least two out of four twitches present.[35] The TOF was set up at the foot, electrodes placed medially at the ankle over the posterior tibial nerve, this nerve was stimulated and responses were recorded from electrodes placed in the abductor hallucis muscle. There were at least two out of four twitches throughout the pedicle screw fixation part of the procedure and throughout the triggered electromyography. This protocol was used to prevent the anesthetic medications from interfering with the quality of data, or the amplitude of the compound muscle action potential.

*****

After intubation .35 mm(28G) x 12mm stainless steel, 1.5-meter cable single use sterile subdermal needle electrodes were inserted bilaterally into the muscles corresponding with the spinal level being operated on.

The neuromonitoring equipment used was the Cadwell IOMAX 24 channel multi-modality system, the machine holds EC and FDA approval. Disposable ball tip monopolar direct nerve stimulator probe, 90mm, 2m cable was used for nerve root identification and pedicle screw testing.

Figure 12: Cadwell neuromonitoring equipment.[36]

Surgical instrumentation systems used contained titanium, cobalt chrome, or other screws labeled as transition metals with similar electrical conductivity. Only screws of these materials were evaluated for this study, hydroxyapatite coated screws were excluded from this study. Most pedicle screws are composed of titanium or similar

metals with similar electrical resistance. Usually the differences in metals are not significant enough to be factors to be considered during pedicle screw testing. However, for osteoporotic patients a pedicle screw coated in hydroxyapatite is used because it improves the fixation to the pedicle bone.[37] The extra coating the hydroxyapatite provides may affect the threshold values of the pedicle screw test and must be taken into account. Figure 13 shows the difference from a non-coated and hydroxyapatite (HA) coated screw.

Pedicle screw instrumentation systems with pedicle screws of titanium or similar metals include, but are not limited to such manufacturers as Medtronic, Stryker, Nuvasive, DePuy, Biomet, Globus, Zimmer, etc. Please see figure 14. It should be noted that most screws came from Medtronic's pedicle screw system. This study did not have a collaboration with any of the above-mentioned biomedical manufacturers, it was completely independent.

Figure 13: Uncoated screw (top), partially HA-coated (middle) and fully HA-coated screws(bottom).[37]

Fig. 1

Photograph showing the 6 × 70 mm pedicle screws: (upper) uncoated; (middle) partly HA-coated; and (bottom) fully HA-coated.

Figure 14: Picture of pedicle screw and rod system.[38]

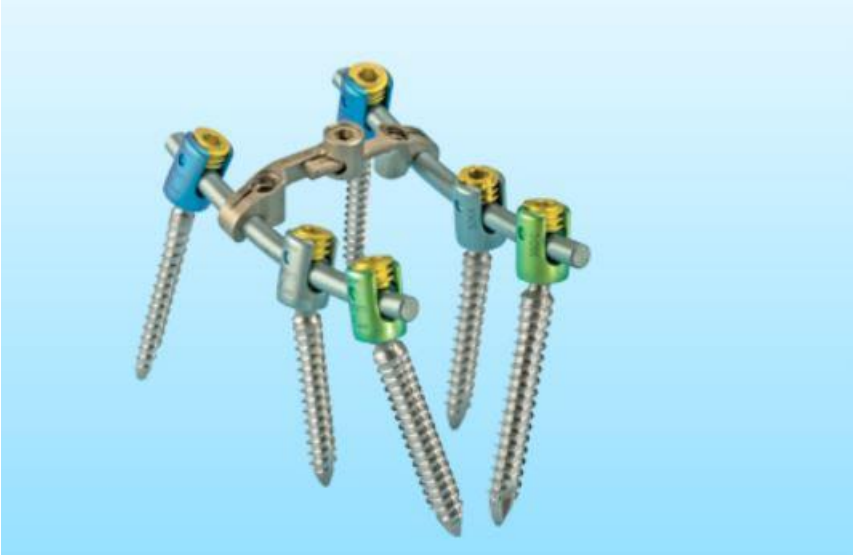
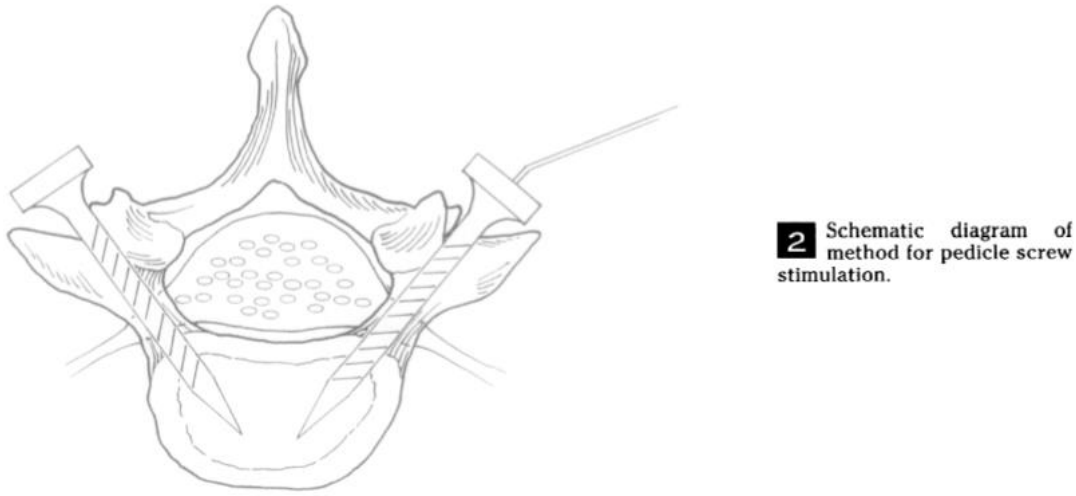


Figure 15: Picture taken from Morledge et al,[28] displaying a pedicle screw placed through the pedicle and into the body of a vertebra, and showing a stimulating probe touching the head of the screw.



2 Schematic diagram of method for pedicle screw stimulation.

Figure 16: Digital radiographs demonstrating different possible screw trajectories.[24]

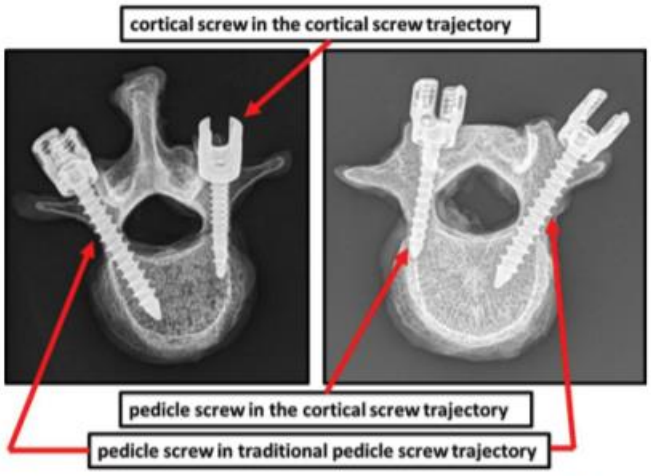


FIG. 1. Digital radiographs demonstrating the trajectories of the 3 treatment groups. The pedicle screw in the traditional pedicle trajectory variant was performed in all samples. Figure is available in color online only.

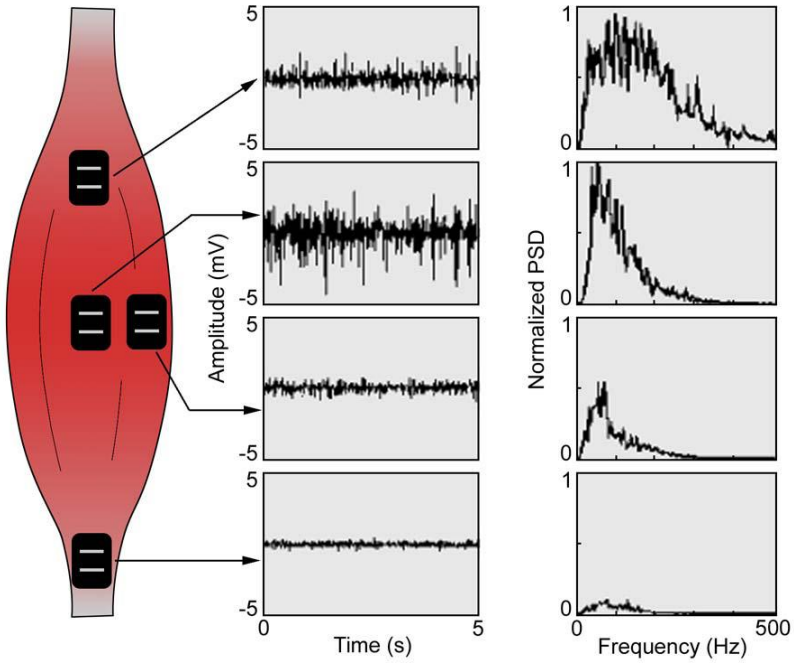
Intraoperative Neurophysiologic Testing Procedure:

In cases where the nerves were easily identifiable or in cases where the threshold obtained from a pedicle screw were in question, a direct nerve threshold was obtained. It is noted that an action potential is usually obtained at 2-3mA from a healthy nerve when one is directly stimulated. For direct nerve stimulation to happen, the surgeon visually identifies a possible nerve and then he or she places the tip of the monopolar probe perpendicular to the presumed nerve. When the surgeon places the tip of the monopolar probe in a perpendicular fashion on the nerve, the neurophysiologist sends cathodal stimulation to the nerve, thus eliciting an action potential. The stimulation starts at zero milliamperes (mA) and then gradually increases until a compound muscle action potential (cMAP) is elicited from either upper or lower extremity myotomes, depending on the nerve being tested. This same procedure was used to test the pedicle screws, where the tip of the monopolar probe was placed through the head of the screw and sat on the shaft of the screw. The cMAP identified from the test was documented in milliamps. For the purposes of keeping the study consistent, one person collected the data, and the same procedure was used to collect the data. Pedicle screws were tested three times each using triggered electromyography (EMG) with three different stimulus durations 300µsec, 200µsec, and 100µsec each time. The reason for the different durations was to see if there was a change in threshold between the three durations, and to see if this should be a factor considered when pedicle screws are tested and Lenke et al's thresholds used. Lenke et al used a threshold of 300µsec,

therefore this study used the threshold value taken at 300µsec to officially interpret a screw's position. This study compared the thresholds between the stimulus durations, and statistical analysis determined if duration was a factor to be considered when applied in the operating room during all surgical cases needing neurophysiologic monitoring.

Pedicle screw stimulation involves many steps to be done for an accurate result. After intubation, but before incision, it is important for the neurophysiologist to place the subdermal needles in the belly of each muscle being tested.[2 39] The belly of the muscle is dense in motor units, the origin and insertion include fascia, and are not optimal locations for needle placement. The amplitude and frequency spectrum of the EMG signal is affected by the location of the electrode with respect to the innervation zone (top electrode), the myotendonous junction (bottom electrode) and the lateral edge of the muscle (middle right electrode).[39] Please see figure 17, the preferred location is in the midline of the belly of the muscle between the nearest innervation zone and the myotendonous junction. In this location the EMG signal with the greatest amplitude is detected.[39] Figure 17 gives a visual showing the importance of the placement of the electrode within the various locations of the muscle and how those specific locations look on the EMG trace.

Figure 17: Below you can see that when electrodes are placed in the medial belly of the muscle, more motor units are picked up by the EMG trace, thus giving a more accurate EMG reading. This image is taken from CJ De Luca.[39]



It is important to insert the needles in an area dense in motor units because each needle only picks up 7-14 motor units.[14] Muscles have thousands of motor units, the needle only being able to represent just a handful limits the accuracy of the recording. Knowing this information, the needle is placed perpendicular into the belly of the muscle with the hopes of recording a clear cMAP response. After the recording needles are placed in the muscles, a ground electrode is placed in between the stimulus site and a recording side. This reduces electrical noise or artifact, for example, if we are stimulating the sacral pedicle screws and recording at the gastrocnemius, the biceps femoris would be an ideal

location for the ground. In setting up monopolar stimulation, a reference electrode (anode) would ideally be placed in the gluteus maximus, between the scapulae or sterilely in the incision site. For the purposes of remaining consistent, the reference was always placed in the gluteus maximus. The monopolar stimulating probe acted as the cathode, where electrical current would flow through to stimulate the pedicle screws. Triggered EMG is done through cathodal stimulation. Once all subdermal needle electrodes were inserted in the desired locations, an impedance check was done. Basically, checking to see if the electrodes had good contact with the patient's skin. The impedance of a well-placed or good electrode to skin contact, is an impedance of less than 5,000 Ohms. Once all electrodes were at the desired impedance, and it was approved by the neuromonitoring system, a train of four was run to check the twitch count. Before incision, it is expected that there would still be neuromuscular blockade present from the intubation dose, running a train of four gives the neurophysiologist an idea of how much the neuromuscular junction is blocked by neuromuscular blockade. At this point, running the train of four test is more to test that it is working properly, so that there are no issues when it is needed (prior to testing pedicle screws). After this, the EEG would be checked to verify that the patient was in a decent depth of anesthesia. In an anesthetic state, the EEG usually is in high alpha, low beta frequency. Once all is verified and functioning, and the rest of the team is ready, the patient is draped and prepped. Then incision is done. The major and basic steps of a spinal fusion procedure are, incision, exposure of muscles to get to the vertebral bodies, set up the

Medtronic Neuro-navigation system, take a 3-Dimentional image with the O-arm. Bore holes with the guidance of the navigation systems, and finally insert pedicle screws.

After screw insertion, the surgeon was sterilely given a monopolar ball tip stimulating probe. He or she placed the tip of a ball tip monopolar probe through the head of the screw, bypassing the head and placing the probe in a manner where it sat perpendicularly in the trough of the head of the screw without touching the exterior moveable head of the screw. Then the neurophysiologist sent current in milliamperes to stimulate the screw. An ascending method of cathodal stimulation was applied to each screw until a compound muscle action potential (CMAP) was elicited from lower extremity myotomes or until 100mA was reached with no response. Screws eliciting a cMAP, were retested with three different stimulus durations. Special notation was taken on any screws tested in patients with osteopenia and osteoporosis, but later was found not to be an issue with threshold values, and therefore was not an eliminating factor for the study. Values were documented and then compared to values determined by the literary works of Lenke et al, Calancie et al, Raynor et al, etc. The most popular or accepted universal guidelines are as follows: >8mA - no pedicle wall defect, 4 to 8mA - possible wall breach, 0 to 4 mA - high likelihood of pedicle screw breach.[26]

Protocol when a screw tested poorly:

A protocol was put in place for when a screw tested poorly. If a screw tested positive for a possible pedicle wall breach (<8mA), the following steps were completed by the surgeon to test the reliability of the triggered EMG pedicle screw test.

1. Manual Palpation: the surgeon palpated the area and decided if the screw would be removed or not. If the decision was to remove the screw, the surgeon used an instrumentation probe to check for any breaches in the circumference of the hole.
2. Triggered EMG: The surgeon used a monopolar ball tip stimulating probe to stimulate the hole and test for any microfractures. The surgeon slowly moved the probe in a circular fashion as to cover the full circumference of the hole. A threshold of >5mA[26] deduced that there was no microfracture in the hole.
    a. At this point, the surgeon decided whether to reinsert the screw at the same trajectory, slightly change the trajectory or abort placing a screw in the pedicle (depending on whether it was a strategic or non-strategic screw).
    b. Once the screw was re-positioned, it was tested again with a ball tip monopolar probe. If it tested >8mA it was left in place and a 3-dimensional image was taken to confirm its position within the pedicle bone.

3. 2D and 3D imaging: Medtronic's O-arm[21] was used to take images. It has the capability of taking 2-dimensional and 3-dimensional images and calibrating those images with a navigation system for surgical assistance in screw placement. Please see figures 18, 19, and 20 below. For this study, 3-dimensional images were always taken pre and post screw insertion. The surgeon used Kim et al's three criteria to examine the screw position on the radiograph.[40]
    a. Violation of the harmonious segmental change of the tips of the inserted screws with reference to vertebral rotation using the posterior upper spinolaminar junction.
    b. No crossing of the medial pedicle wall by the tip of the pedicle screw inserted
    c. If the above methods still yield an unproperly placed screw, the surgeon will decide if a laminectomy or flavectomy is necessary or if the screw will be left in place and a 3D scan will be done intraoperatively.

Figure 18: Figure showing the image (two dimensional and three dimensional) performance of the O-arm system. [21]

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You need 3D slice data. You need 2D fluoroscopy. You know your surgical needs. You know your procedure. We can help.

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Axial, coronal, sagittal, and oblique slice data give you an expanded view of your patient's anatomy.

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View your patient's image data while they are still on the surgical table. Be assured that your surgical goals are met.

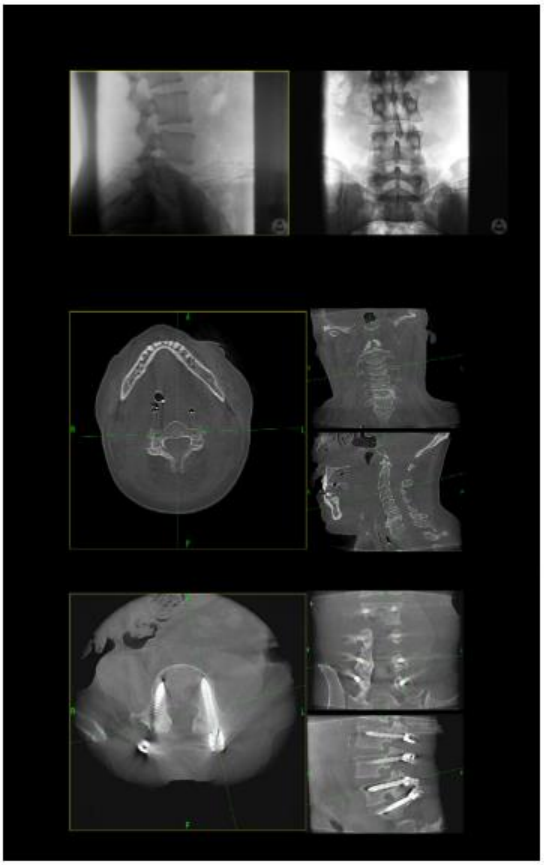


Figure 19: Figure showing where a correctly placed screw should be placed in the pedicle. As well as points that would be considered minor, moderate and severe violations.[41]

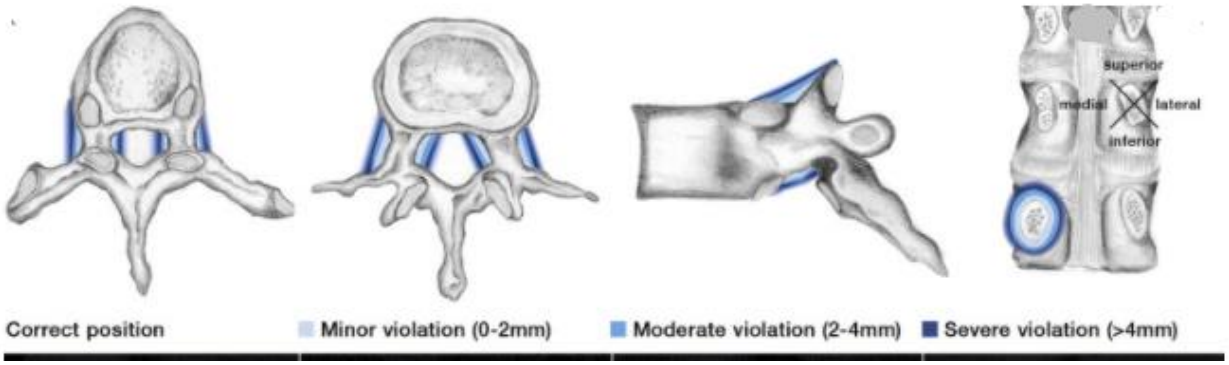


Figure 20: Screenshot of the navigation screen during pedicle screw insertion. [42]

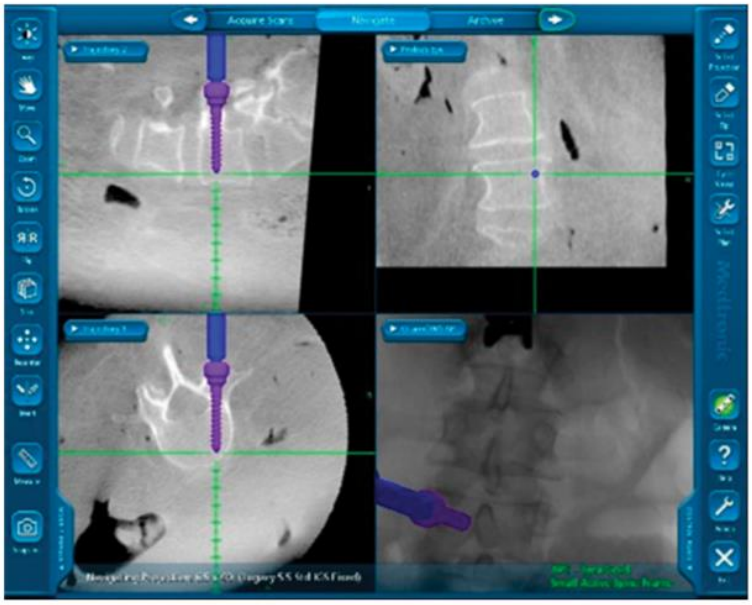


Fig. 2. Screen shot image of O-NAV monitor. The 3D imaging capabilities of O-NAV allow the surgeon increased visualization of the operative field. Up to 4 navigated images can be viewed at once when using O-NAV. The image configuration can be customized to the surgeon's preference.

For this study, the above stated protocol was used to examine every screw. Within this study, only 5 of the 211 screws tested at 8mA or below and were thus examined in greater detail as described above. It is important to note that the surgeries and methodology for nerve stimulation are routine, well-documented, and have been practiced in the operating room for several years. Well-researched triggered EMG parameters were used, and nothing was added to the routine technique of pedicle screw insertion because of this study. The insertion and evaluation of the pedicle screws were conducted with O-arm imaging and its navigation system, along with the triggered EMG test. All are already standard practice for pedicle screw insertion.

Information on Medtronic's O-arm and StealthStation Navigation System:

The O-arm advances modern medicine. Therefore, it is necessary to go into detail of its capabilities and what it offers in the operating theatre. The following information on the O-arm, was taken directly from Medtronic's website.

> *The O-arm™ system[21] is an intraoperative 2D/3D imaging system that is designed to meet the workflow demands of the surgical environment. The O-arm O2 Imaging System is a mobile x-ray system designed for 2D fluoroscopic and 3D imaging for adult and pediatric patients weighing 60 lbs. or greater and having an abdominal thickness greater than 16cm, and is intended to be used where a physician benefits from 2D and 3D information of anatomic structures and objects with high x-ray attenuation such as bony anatomy and metallic objects. The O-arm O2 Imaging System is compatible with certain image guided surgery systems.*

Along with StealthStation™ navigation, the O-arm system provides enhanced 3D visibility and surgical feedback. It also: The O-arm system's high quality, versatile imaging provides the information you need to guide your clinical decision making.

- *Provides current patient data in the OR*
- *Enables advanced surgical approaches like MIS*

- *Provides additional information in challenging procedures, like heavier patients or patients with unusual anatomy*
- *Automatic registration keeps the process simple*

The O-arm system also offers options for workflow efficiencies, such as:

- *In procedures where pre-op axial/coronal/sagittal slice data is necessary, it may be possible to use the O-arm system to provide the initial data set*
- *Eliminating the need to send patients to be scanned in radiology*
- *Violation of the imaginary midline of the vertebral body by the tip of the screw.*[21]

Figure 21: StealthStation Navigation Integration, picturing the O-arm and the navigation system. [21]

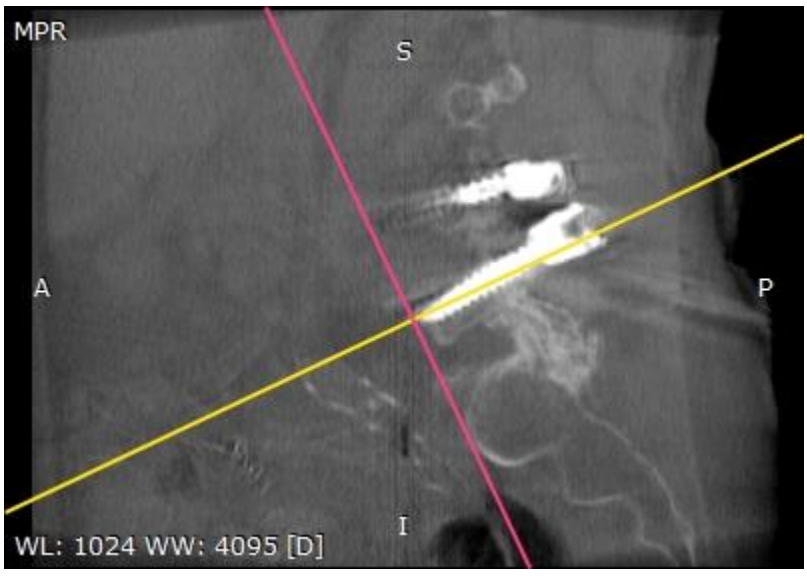
Spinal Fusion Surgery:

Now to take a closer look at a posterior spinal fusion with pedicle screw fixation. Starting at the point where the patient is anesthetized, prone, exposure complete, but prior to starting the process of boring holes and inserting screws in the pedicle. Before starting to insert pedicle screws, Medtronic's O-arm was used to take 3- Dimensional imaging. Once the pre-screw insertion imaging was taken, the navigation system was calibrated, and then the surgeons proceeded to start making a hole where a pedicle screw would be placed. Medtronic's Jamshidi was used to initialize the pedicle screw hole, then a K wire was inserted into the hole to keep the desired trajectory, and finally a self-tapping screw was placed. This process was repeated for each screw insertion. Once all screws were inserted, another 3-dimensional O-arm image was taken (post screw insertion image, please see figure 22 for examples). Pedicle screw stimulation commenced after all screws were inserted. Once the thresholds were taken at 300µsec, 200µsec and 100µsec durations, they were entered into an excel sheet for a future statistical analysis. At this point, data collection seized, but the actual operation continued as usual with either the addition of a decompression or by inserting rods and then closing.

Figure 22: The images below are from data subject 20190002. Images A and B give an idea how technology or navigation shows the trajectory of a placed screw or during screw placement, assists in finding the optimal angle to place the screw. Image A, L4 screw. Image B, L5 screw.

A)

B)



Results

Patient demographics

Screw measurements were taken from patients undergoing a posterior spinal fusion in either the thoracic, lumbar or sacral region. 213 screw measurements were taken in total from 40 patients. Factors like sex, age, height and weight were not considered for this study. One patient had osteoporosis. Osteoporosis was thought as a possible exclusion factor, but after taking the measurements of the patient's screws, the numbers were in par with the other patient screw threshold numbers and were thus kept in the study.

Screw stimulation

213 screws were stimulated, out of the 213 screws, 2 screw measurements were excluded because stimulations were not obtained from all three durations. Thus 211 screws and 40 patients were included in this study.

The screws were stimulated using three different stimulus durations, the first at 300µsec, the second at 200µsec and the third at 100µsec. The mean current threshold of the 300µsec stimulus duration was at 27.25mA (p=0.0078). The mean current threshold of the 200µsec stimulus duration was at 35.46mA (p=0.0028). The mean current threshold of the 100µsec stimulus duration was at 50.90mA (p=0.0676).

Table 1. Comparison of three different stimulus durations and their varying current thresholds for analysis of 211 screws (homogenous group of screws, all placed intrapedicularly). The mean values were found to be statistically significant, p value refering to current (mA) in relation to duration (µsec). The statistical analysis supported that different durations do change the stimulus strength and thus, affect the results of the screw stimulation thresholds.

	300 µsec	**200 µsec**	**100 µsec**
Mean	27.25mA	35.46mA	50.90mA
Median	24	32	48
Standard deviation	12.24	15.98	20.51
KS Test* **(p-sign: 0.05)**	p=0.0078	p=0.0028	p=0.0676

* Test for normality (Kolmogorov-Smirnov test).

A non-parametric statistical significance test was used because not all data was normally distributed and came from three different groups/durations. An appropriate test is the Kruskal-Wallis, which tests to see if the data comes from the same distribution (null hypothesis). The KW test is the non-parametric equivalent to an Analysis of Variance Test (ANOVA). This one was used to compare all three groups together. The test returns a p-value that is almost zero (and much less than the significance level that we can set, e.g. p=0.01, i.e. 99% significance level), so this means that the test rejects the null hypothesis. Then a follow-up test (a *post-hoc* test or analysis) was done, to identify which of the data exactly comes from a different distribution. From this analysis, the results indicate that there are significant differences between all the group pairings. Therefore, data from all 3 groups come from different distributions (this is also expected from the data histograms).

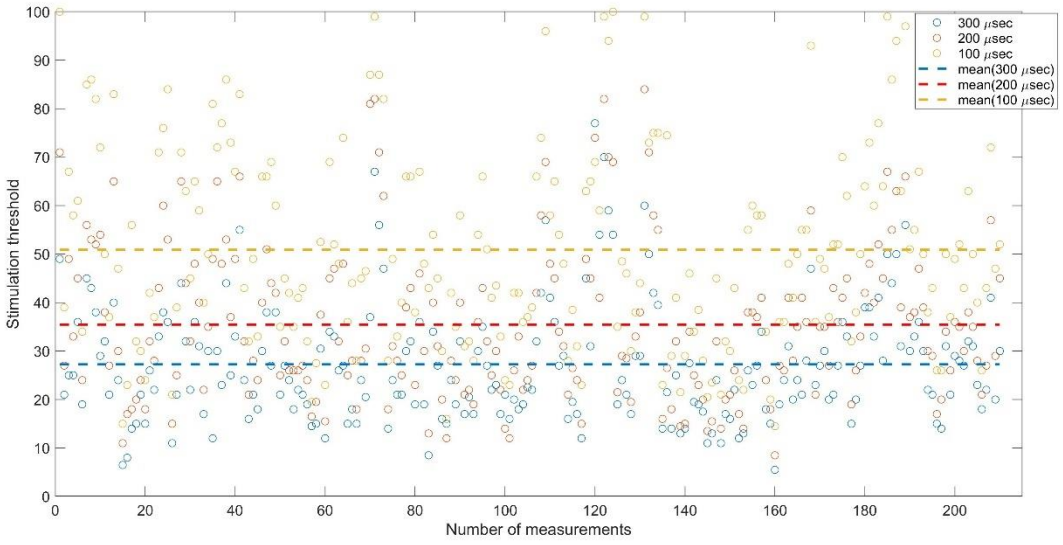
When the data was grouped by location (see Table 2), the following results were obtained (same statistical tests; NS: not significant). Categories that have more samples are more accurate. In general, the difference between 300 and 100 μsec seems to be significant for all locations. The difference between 200 and 100 μsec is significant for specific locations, while the difference between 300 and 200 μsec is never significant (i.e. not location-dependent). So, from these results, the conclusion would be that if somebody is using stimulations that are either 300 or 200 μsec, the location of the screw doesn't play a part in the choice of the stimulation threshold. But, if somebody

was to place a screw at, e.g. Right L3, the stimulation threshold would need to be adjusted differently for 300 or 100 μsec.

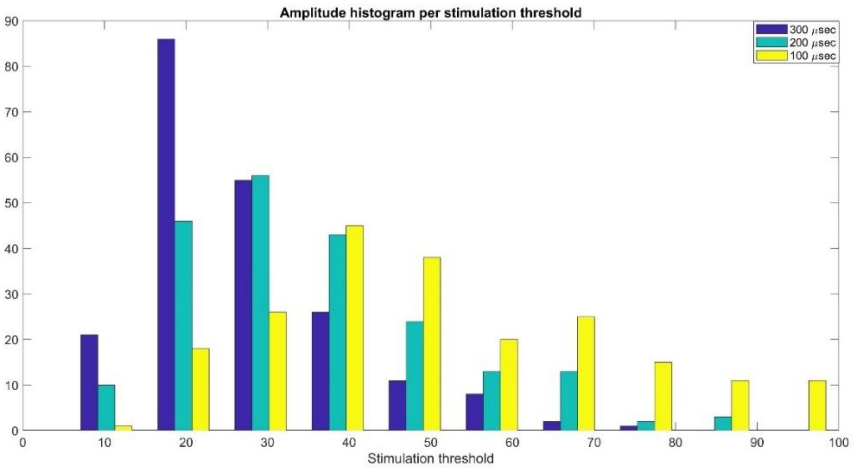
Table 2. Data grouped by location, vertebral level, and durations compared for significance per screw location.

Location (group significant, number of samples)	**{300μ,200μ}**	**{300μ,100μ}**	**{200μ,100μ}**
Left L3 (p<0.01, 13)	NS	p<0.01	p<0.05
Right L3 (p<0.01, 12)	NS	p<0.01	NS
Left L4 (p<0.01, 21)	NS	p<0.01	p<0.05
Right L4 (p<0.01, 21)	NS	p<0.01	p<0.01
Left L5 (p<0.01, 22)	NS	p<0.01	p<0.05
Right L5 (p<0.01, 21)	NS	p<0.01	p<0.05
Right L1 (p<0.01, 7)	NS	p<0.01	NS
Right L2 (p<0.05, 9)	NS	p<0.05	NS
Left S1 (p<0.05, 11)	NS	p<0.05	NS
Right S1 (p<0.05, 11); p=0.0110	NS	p<0.01	NS

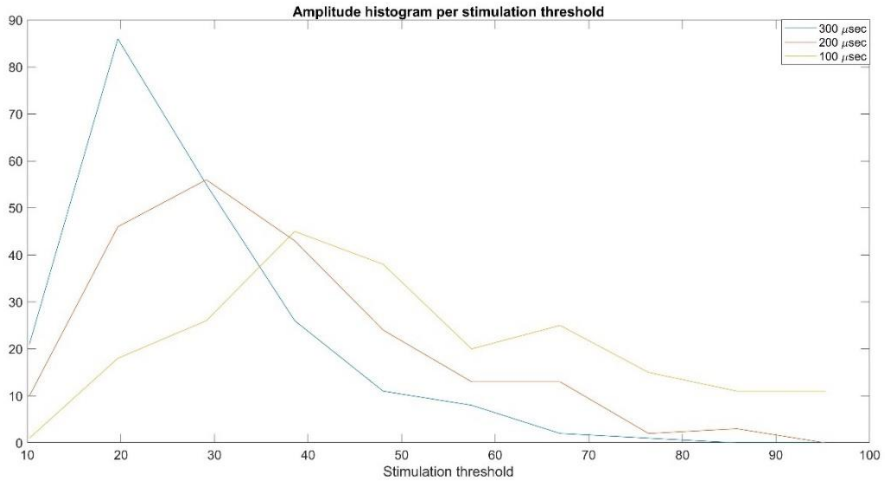
Data Plot: The lines signify the mean threshold in mA. Each color represents different stimulus durations. Basically, the shorter the stimulus duration the higher the stimulus threshold obtained. The longer the stimulus duration, the lower the stimulus threshold obtained. Stimulation threshold in milliamperes (mA). Measurements for 211 screws, all located intrapedicularly and checked by intraoperative 3-dimensional imaging.



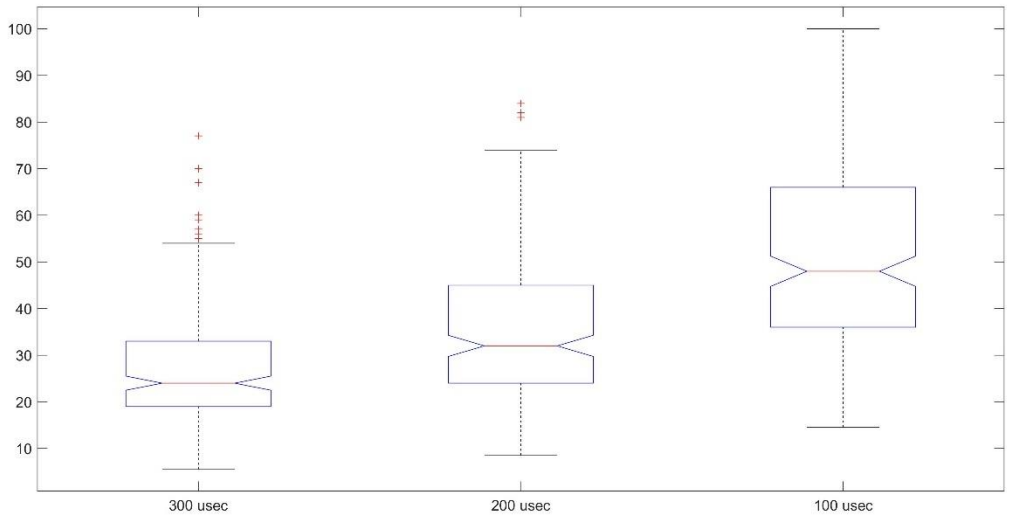
Histogram 1: Bars are durations at different stimulation thresholds for screws located intrapedicularly and checked by intraoperative 3D imaging. X-axis: Stimulation threshold in mA. Y-axis: number of screws.



Histogram 2: Lines for different durations in mA for screws located intrapedicularly and checked by intraoperative 3D imaging. X-axis: Stimulation threshold in mA. Y-axis: number of screws.



Box Plot: The box plots show where the mean threshold values (mA) fall in average for the 211 screws stimulated at each duration. X-axis shows duration(µsec), Y-axis shows stimulation threshold (mA). Mean for 300µsec is 27.25mA (p= 0.0078), mean for 200µsec is 35.46mA (p=0.0028), and mean for 100µsec is 50.90mA (p=0.0676).



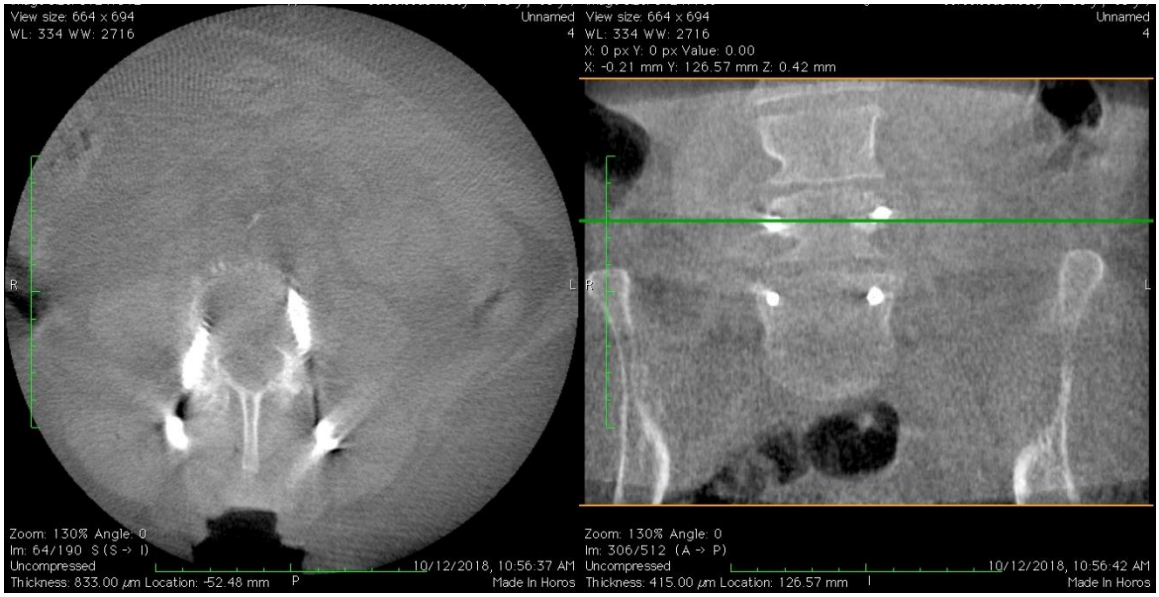
All these graphs show that stimulus duration plays a significant role in the current threshold number. The higher the stimulus duration, the lower the current threshold. The lower the stimulus duration, the higher the current threshold.

Screw imaging

A total of 211 screws were evaluated. Specifically, 13 screws were places at Left L3, 12 screws were placed at right L3, 21 screws were placed at left L4, 21 screws were placed at right L4, 22 screws were placed at left L5, 21 screws were placed at right L5, 7 screws were placed at right L1, 9 screws were placed at right L2, 11 screws were placed at left S1, and 11 screws were placed at right S1, and 63 screws were placed in the thoracic vertebrae.

After the statistical analysis was completed with the triggered EMG thresholds, O-arm images were evaluated. Just a reminder that the threshold is the current level in milliamperes at which a compound muscle action potential is produced. Below there are a few examples of O-arm images and a table of their corresponding triggered EMG threshold values. Emphasis was given to the threshold current value obtained at a 300µsec stimulation duration because that is the one most commonly referred to and used.[1 26] Therefore, interpretation of data was only done at 300µsec. The following figures will show well placed pedicle screws, and to follow mal-positioned or questionably placed screws, along with their triggered EMG threshold values.

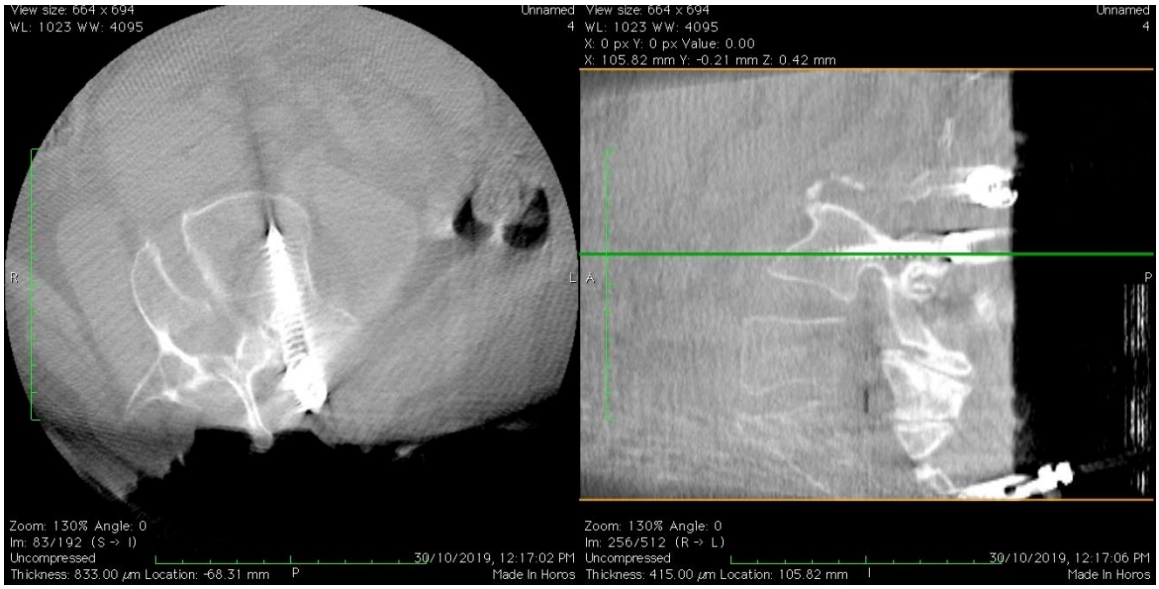
Figure 23: 3D radiographic imagining of well positioned screws. Data subject 20190028 showing pedicle screws placed at left L4 and right L4. The imaging shows that the pedicle screw is free of the medial wall (axial view), and well placed in the vertebral body (coronal view). The threshold numbers in the triggered EMG, also fall within safe values. Therefore, the imaging and threshold numbers correspond to indicate well positioned screws.



Triggered EMG threshold results for data subject 20190028.

Pedicle Screw	**300µsec duration**	**200µsec duration**	**100µsec duration**
Left L4	13.0mA	14.5mA	21.5mA
Right L4	14.0mA	15.0mA	29.0mA

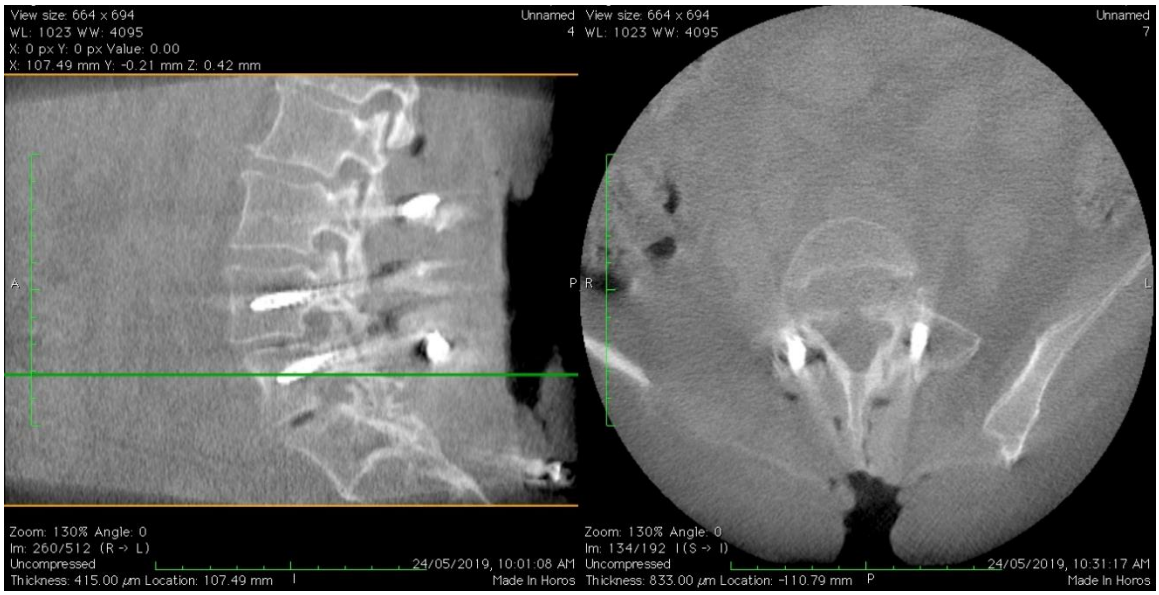
Figure 24: Another example of a well-placed left L4 screw from data subject 20190007. As you can see from the imaging, especially in the sagittal view, there is no fear of low trajectory screw position infiltrating the intervertebral foramen, and the triggered EMG threshold values fall within safe values. Both corresponding for a well-positioned screw.

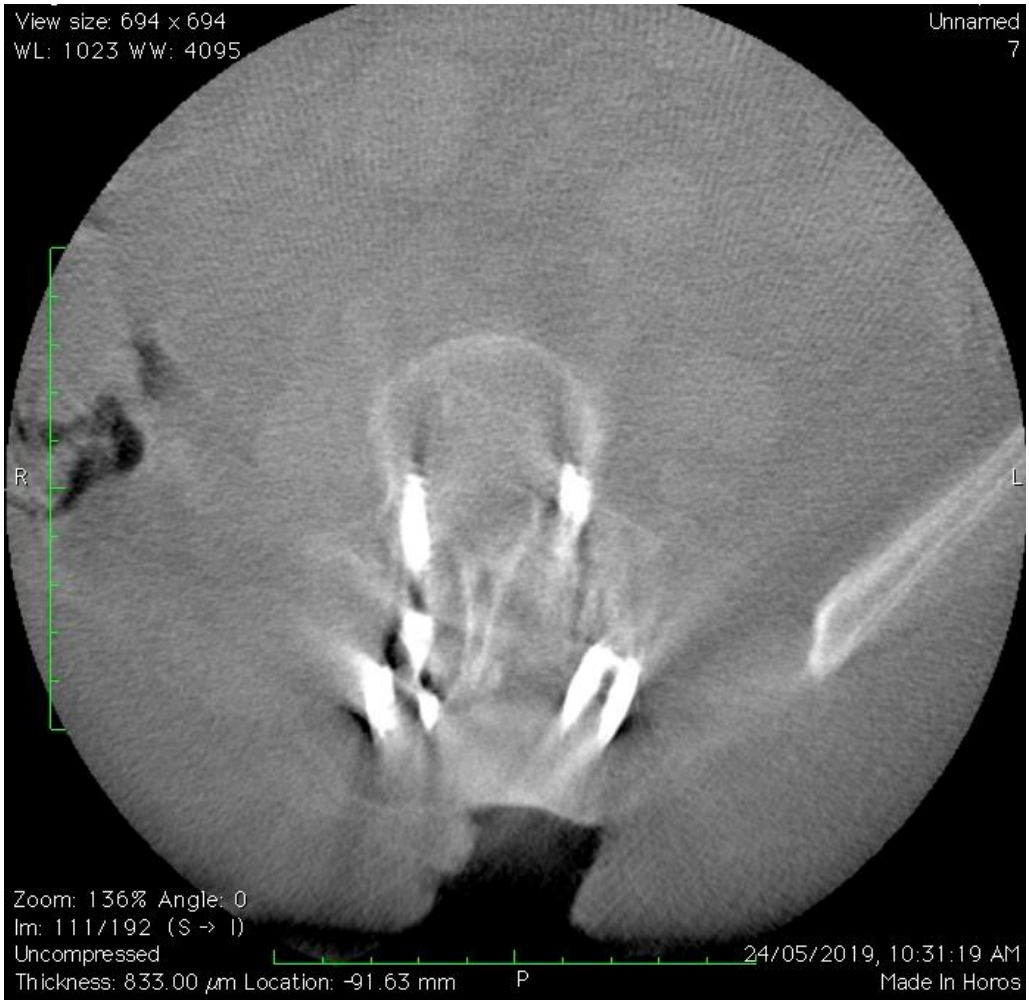


Triggered EMG threshold results for data subject 20190007.

Pedicle Screw	**300µsec duration**	**200µsec duration**	**100µsec duration**
Left L4	16.0mA	21.0mA	32.0mA

Figure 25: The below 3D scans and triggered EMG data is from data subject 20190021. As you can see in the sagittal view, L3, L4, and L5 screws are well within the pedicle bone, and so do not penetrate the intervertebral foramen. The two axial views of the left and right L5 screws show well placed screws with no fear of a breach in the median wall. The triggered EMG threshold values also fall within safe limits.



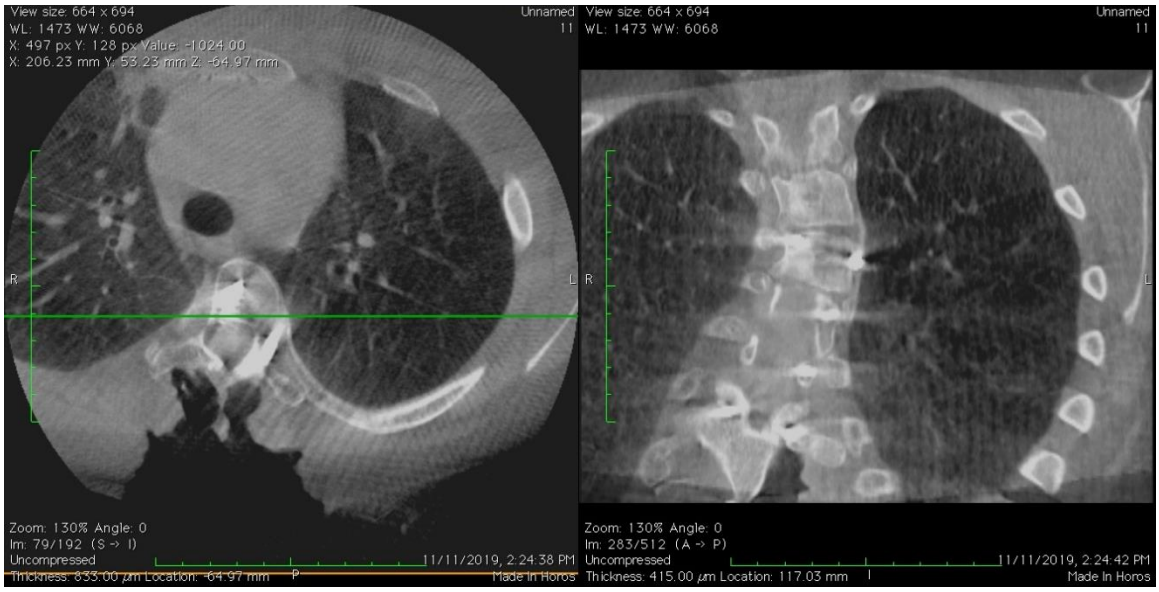


Triggered EMG threshold results for data subject 20190021.

Pedicle Screw	**300µsec duration**	**200µsec duration**	**100µsec duration**
Left L3	27.0mA	34.0mA	54.0mA
Right L3	29.0mA	31.0mA	48.0mA
Left L4	16.0mA	21.0mA	28.0mA
Right L4	19.5mA	26.5mA	38.5mA
Left L5	17.0mA	24.0mA	31.0mA
Right L5	12.0mA	15.0mA	23.0mA

Figure 26: 3D of borderline positioned screw.

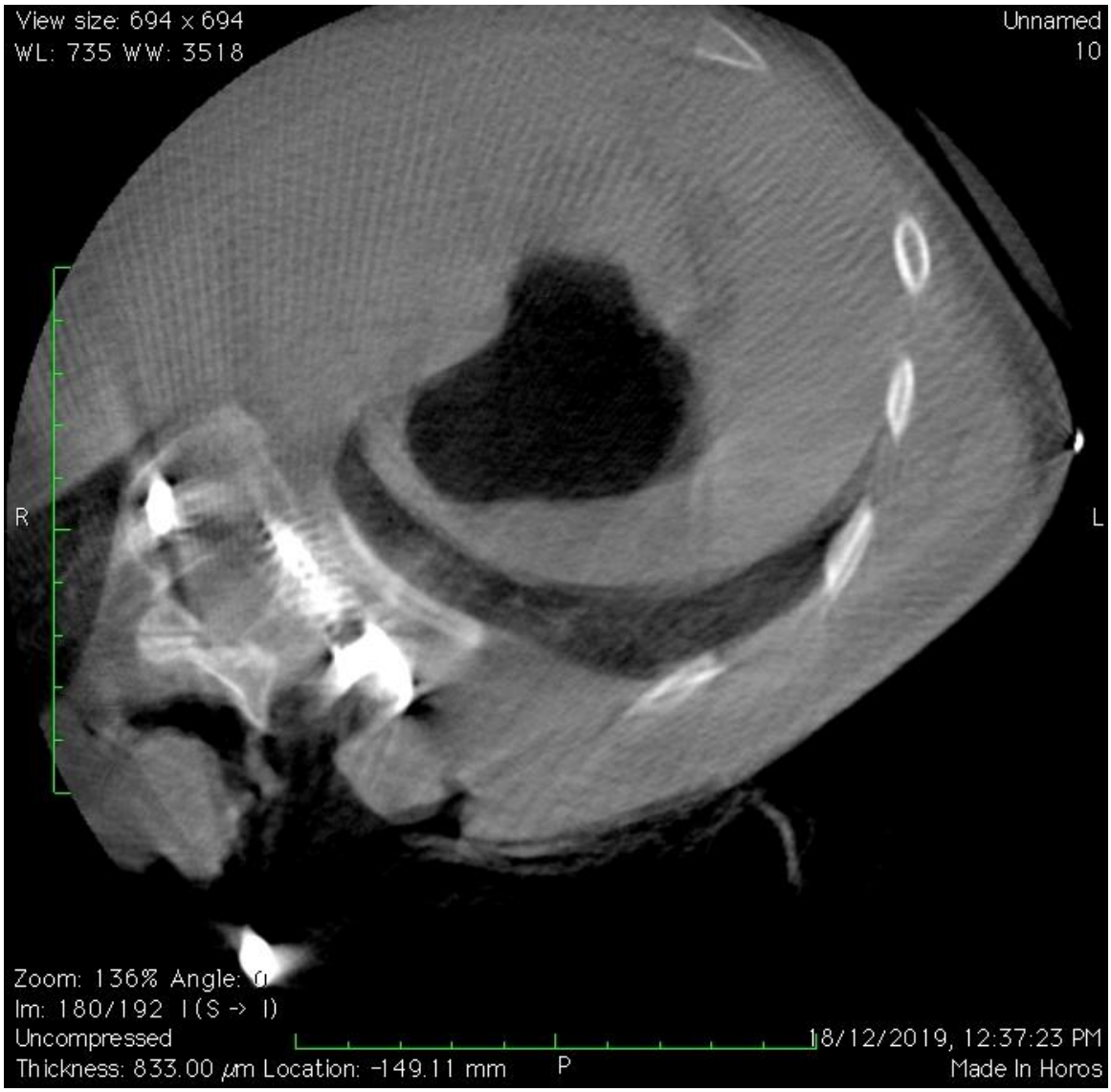
Below is the O-arm image for data subject 20190005. It displays the right and left D4 pedicle screw. Below the image is the table with the triggered EMG threshold levels. As you can see in the 3D image that the position of the pedicle screws is questionable, and the image corresponds with the low threshold triggered EMG values. The current thresholds at 300µsec are the ones most used in IONM for interpretation.



Triggered EMG threshold results for data subject 2019005

Pedicle Screw	**300µsec duration**	**200µsec duration**	**100µsec duration**
Left D4	6.5mA	11.0mA	15.0mA
Right D4	8.0mA	17.0mA	23.0mA

Figure 27: Below is the O arm image for data subject 20190034, showing the pedicle screw at left D8. Along with the triggered EMG threshold values. The O-arm image with the triggered EMG threshold values correlate with the questionable medial screw position, possibly indicating a medial wall breach.



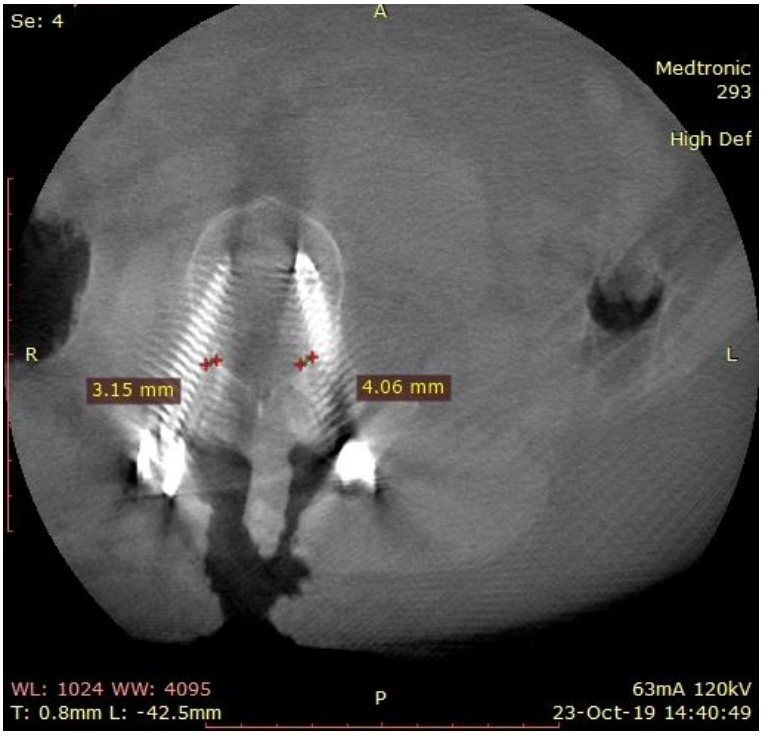
Pedicle Screw	300µsec duration	200µsec duration	100µsec duration
Left D4	5.5mA	8.5mA	14.5mA

*****

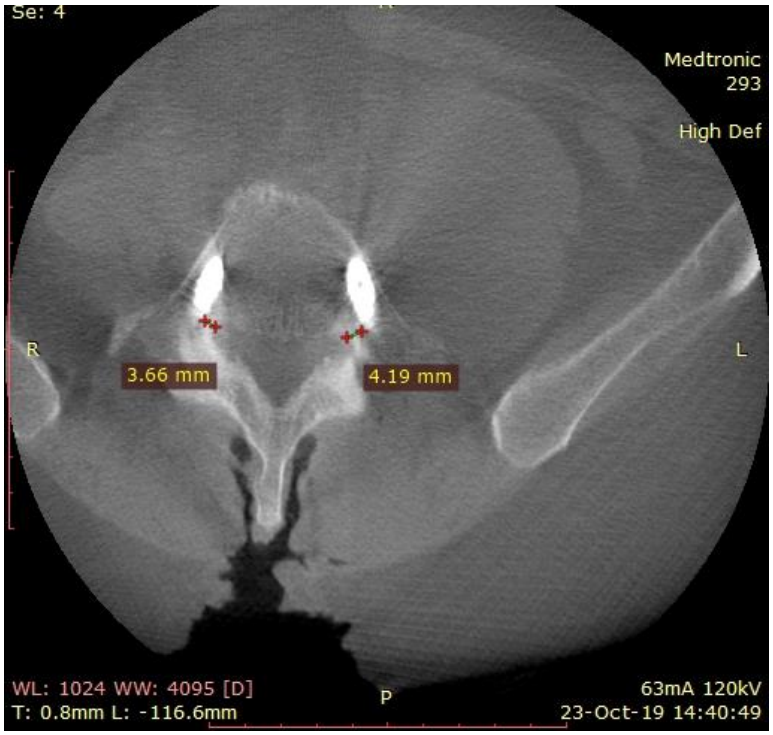
To further investigate the validity of pedicle screw stimulation as a good indicator of pedicle screw placement, a closer look was taken at the 3-dimensional O-arm images. An analysis of the O-arm scans was done by taking measurements from the pedicle screw to the lateral recess in the axial view, and/or taking a measurement in the sagittal view from the pedicle screw to the intervertebral foramen. Basically, taking measurements from the pedicle screw to the point where it was thought that a nerve root would be.

Figure 28: Below O-arm images are taken from data subject 20190001. A) Illustrates an axial view of the left and right pedicle screw at the L3 vertebral level. In this view a measurement is done from the pedicle screw to the lateral recess where nervous tissue is expected to be. B) Pictures an axial view of the pedicle screws placed bilaterally at the L5 level. Again, in this view, a measurement is taken from the pedicle screw to the lateral recess of the vertebrae. C) Illustrates a sagittal view of the screws placed in spinal levels L3, L4, and L5. In the sagittal view a measurement is taken from the L3 screw to the intervertebral foramen where the nerve root is thought to be. D) Pedicle screw thresholds from the screws, which were only viable at the left and right L3 vertebral level.

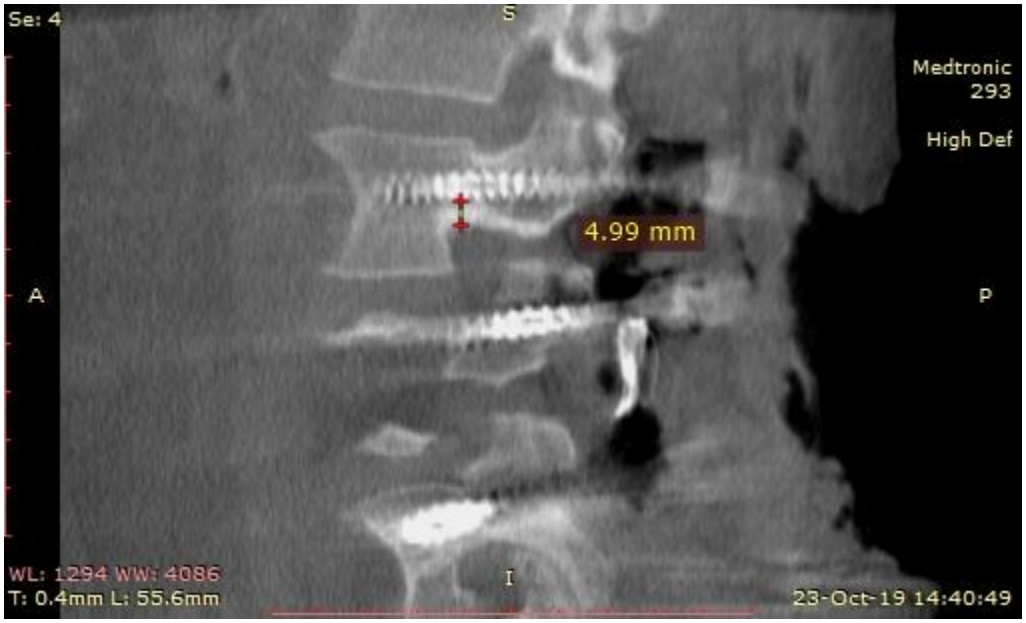
A)


Se: 4
A
Medtronic
293
High Def
R
L
3.15 mm
4.06 mm
WL: 1024 WW: 4095
T: 0.8mm L: -42.5mm
P
63mA 120kV
23-Oct-19 14:40:49

B)


Se: 4
Medtronic
293
High Def
R
L
3.66 mm
4.19 mm
WL: 1024 WW: 4095 [D]
T: 0.8mm L: -116.6mm
P
63mA 120kV
23-Oct-19 14:40:49

C)



D)

Pedicle Screw	**300µsec duration**	**200µsec duration**	**100µsec duration**
Left L3	49.0mA	71.0mA	100.0mA
Right L3	21.0mA	27.0mA	39.0mA

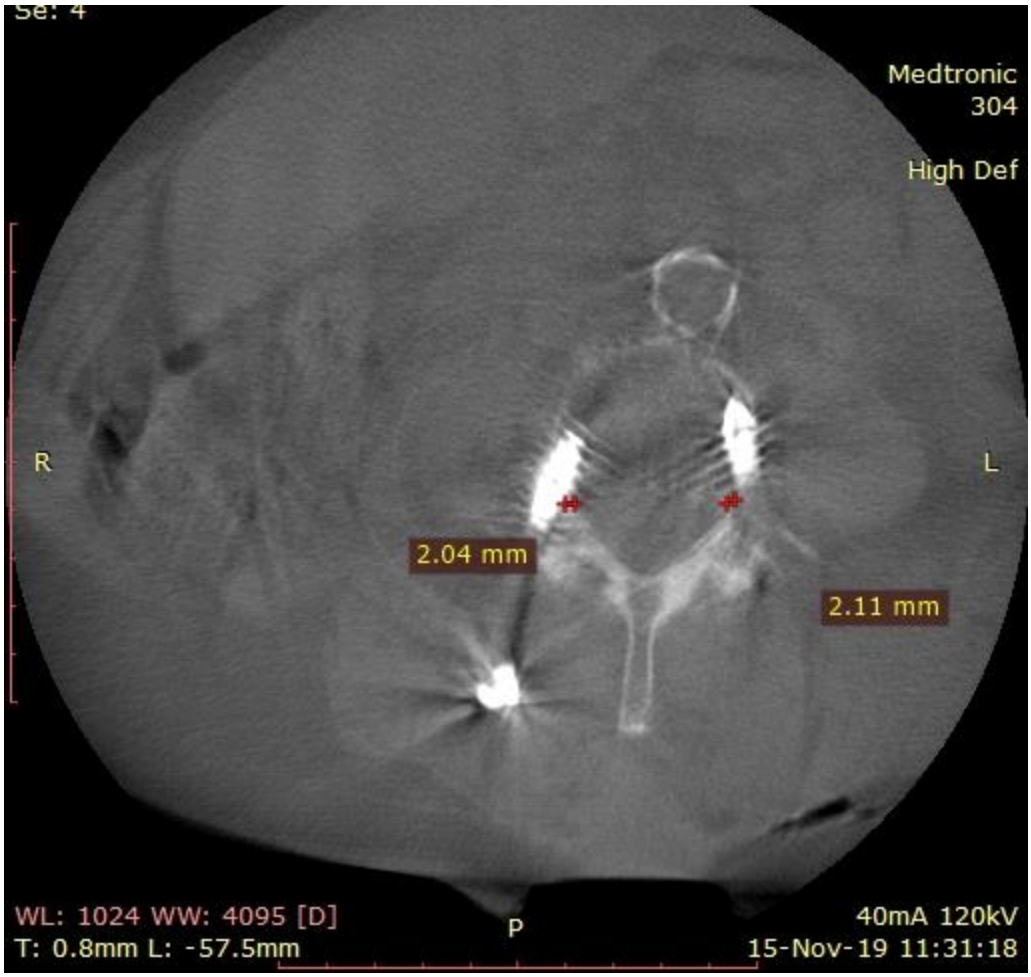
Comparing the triggered EMG results with the 3D radiographs and looking at the measurements, it can be assumed that at >3.0 millimeters (mm) from the pedicle screw to the lateral recess or intervertebral foramen, one could conclude that there is no breach in the medial or lower pedicle wall for this particular case. The safe threshold numbers correspond to the distance of the screw to the lateral recess or intervertebral foramen. To clarify, the right L3 screw had a 3.15mm distance from the screw to the

lateral recess, and a threshold value was elicited at 21.0mA at 300µsec, remembering, any value over 8mA is deemed a well-placed screw or fully encapsulated by bone with no breach. The left L3 screw had a 4.06mm distance from the lateral recess, a greater distance than the right side, and has a corresponding greater threshold value at 49.0mA at 300µsec. From this data subject, it is safe to say, the greater the distance from the pedicle bone to the nervous tissue, the higher the threshold value due to electrical resistance in the bone tissue. To strengthen this argument, an additional random selection of pedicle screw O-arm images was investigated. Please see them to follow.

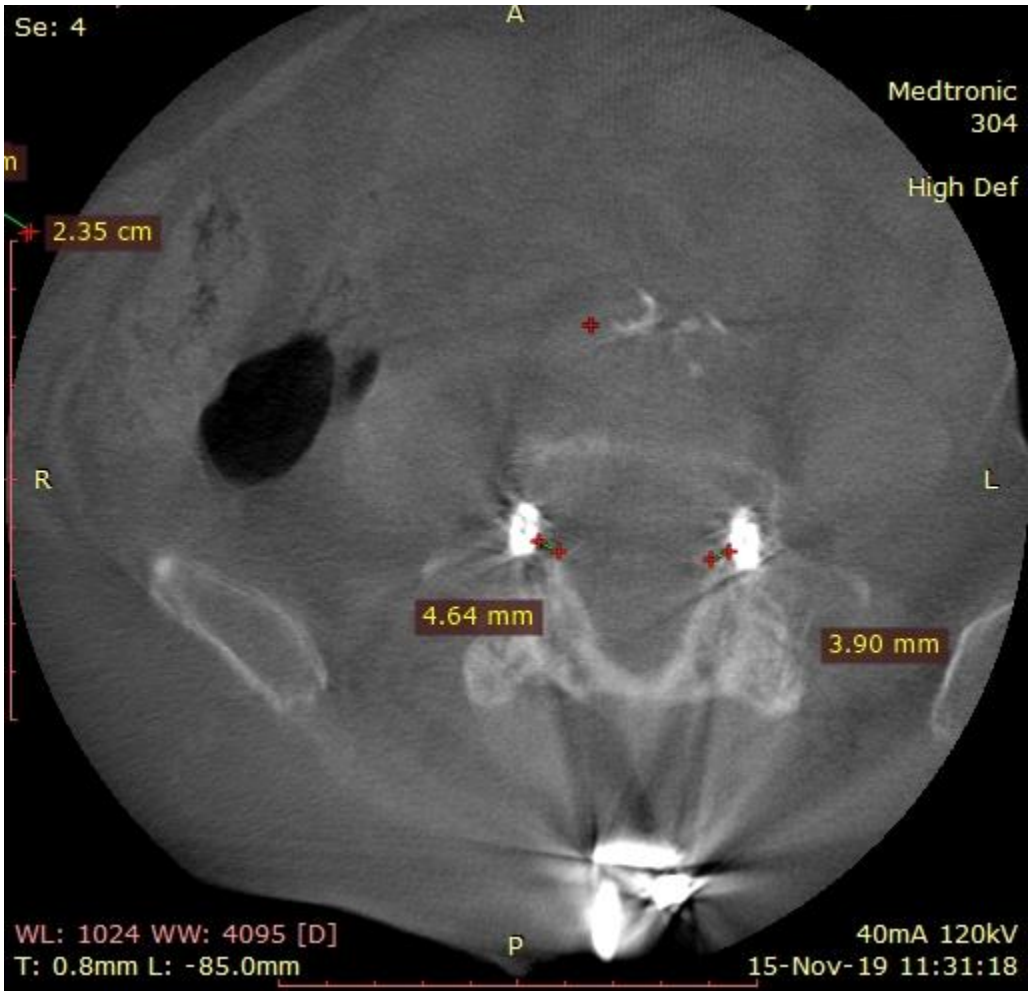
Figure 29: The images below are taken from data subject 20190002. A) Illustrates an axial view of the left and right pedicle screw at the L4 vertebral level. In this view a measurement is done from the pedicle screw to the lateral recess where nervous tissue is expected to be. B) Pictures an axial view of the pedicle screws placed bilaterally at the L5 level. Again, in this view, a measurement is taken from the pedicle screw to the lateral recess of the vertebrae. C) Threshold values of the pedicle screws, where all tested above 8mA, indicating the screws did not breach the pedicle wall. It is interesting to note that bilaterally at L4 the screws were both at a distance of 2.0mm from the screw to the lateral recess, and both screws elicited a compound muscle action potential at the same threshold value, 25.0mA. Now looking at the left L5 screw, it measured at 3.90mm and tested at 36.0mA, and the right L5 screw measured at 4.64mm and tested at 19.0mA. Both the L5 screws did not breach the lateral recess and tested within safe limits. Perhaps though, since the numbers don't match up, i.e.,

greater distance equating to higher threshold intensities, other factors must be taken into account, such as bone density from vertebrae to vertebrae or patient to patient, or even human error while measuring distances in the images or measuring the current thresholds as the screws were being stimulated. All in all, though, as we dissect the O-arm and tEMG data, the argument of triggered EMG's efficacy is strengthened as an indicator of a properly placed screw.

A)



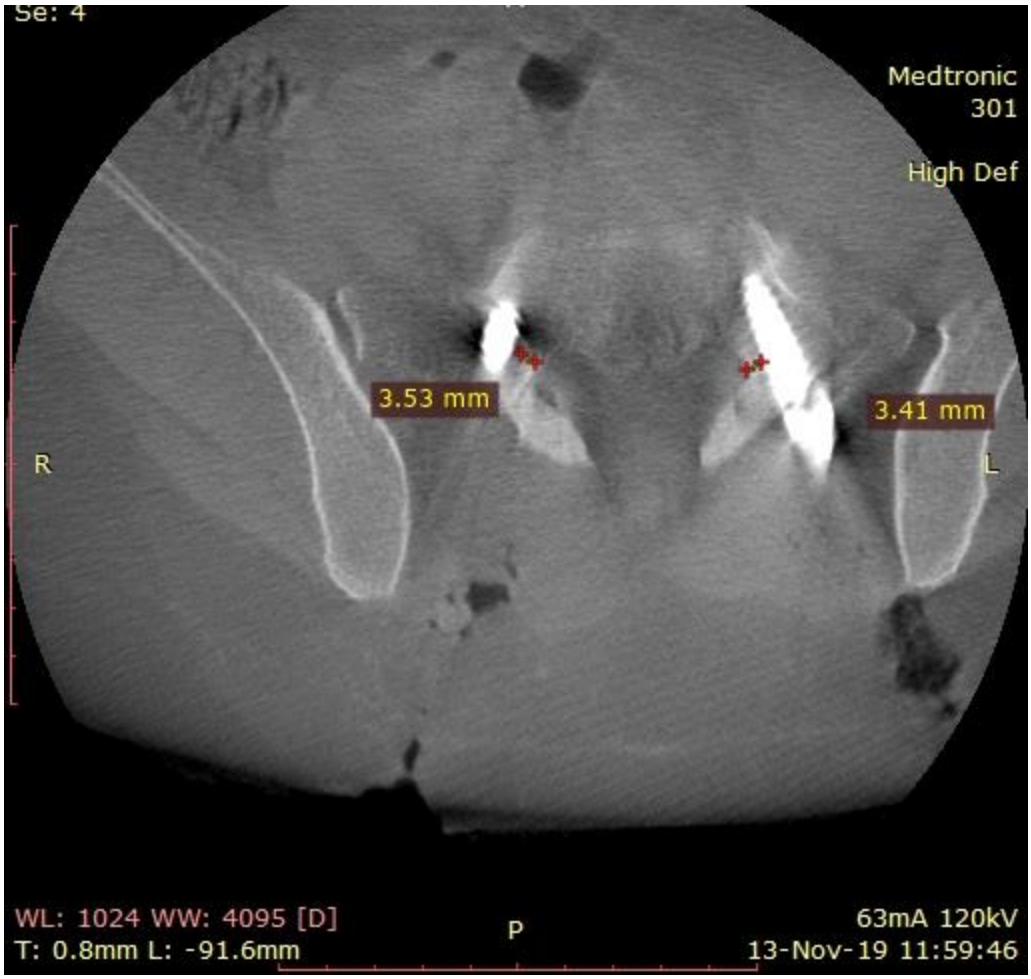
B)



C)

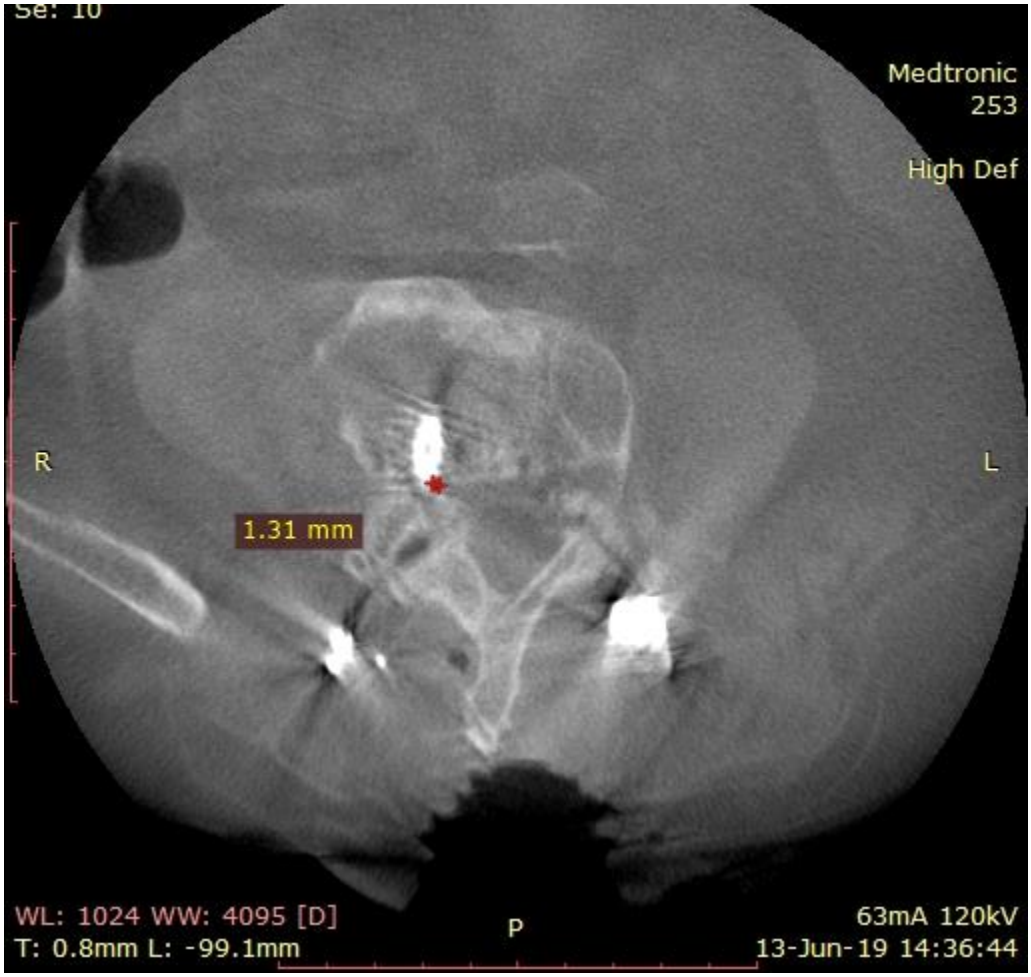
Pedicle Screw	300µsec duration	200µsec duration	100µsec duration
Left L4	25.0mA	49.0mA	67.0mA
Right L4	25.0mA	33.0mA	58.0mA
Left L5	36.0mA	45.0mA	61.0mA
Right L5	19.0mA	24.0mA	34.0mA

Figure 30: The below axial view is taken from data subject 2019004. Bilaterally S1 screws are over 3.0mm from the lateral recess and their triggered EMG threshold values are over 8mA. Indicating properly placed screws both in the 3-dimensional image and the pedicle screw stimulation test.



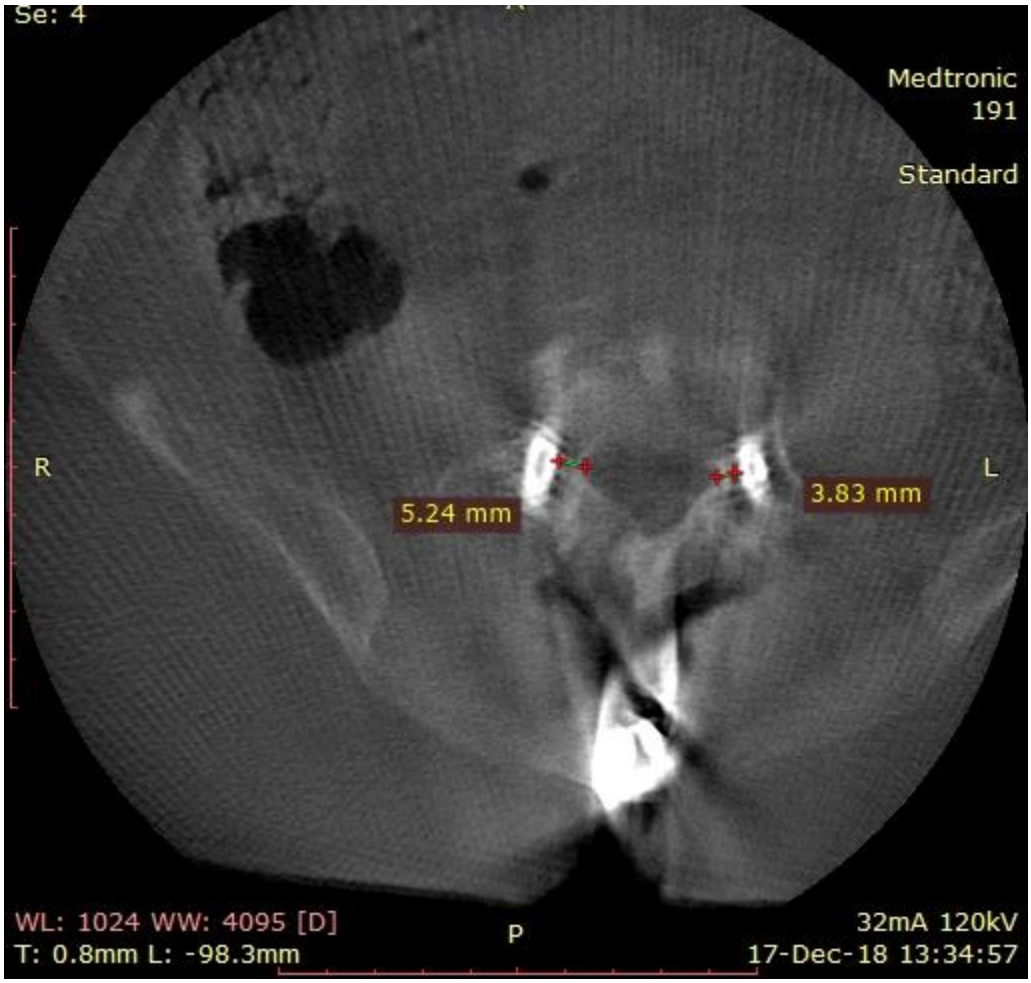
Pedicle Screw	300µsec duration	200µsec duration	100µsec duration
Left S1	40.0mA	65.0mA	83.0mA
Right S1	24.0mA	30.0mA	47.0mA

Figure 31: The below axial view is taken from data subject 20190015. In this image the right L5 screw is 1.31mm from the lateral recess, and the triggered EMG threshold value is at 8.5mA. Going back to Figure 7 and noting that Lenke et al would have interpreted this screw as a borderline acceptable screw, again supports the accuracy of the triggered EMG test. Please note that this is an interesting example, in the fact that at a stimulus duration of 300µsec the screw's threshold value is borderline safe and may be questionable for a medial breach. But at stimulus durations of 200µsec and 100µsec, the screw's thresholds fall within safe values, respectfully, 13.0mA and 43.0mA. Calancie et al states a screw >10mA with a 200µsec duration to be safely placed, so with this criterion, the screw would have been interpreted well placed and not seen as borderline. But if Calancie et al's threshold criteria was used to interpret a screw without paying attention to the stimulation duration, this screw would have been deemed a definite breach in the pedicle at 8.5mA, and possibly called for a removal of the screw and a change in the surgical protocol. Which would have all been unnecessary, since with the proper stimulus duration, the screw was satisfactory in placement. Supporting, that stimulus duration should be noted when using certain threshold values as indicators for calling a screw safely placed within bone or malpositioned.



Pedicle Screw	300µsec duration	200µsec duration	100µsec duration
Right L5	8.5mA	13.0mA	43.0mA

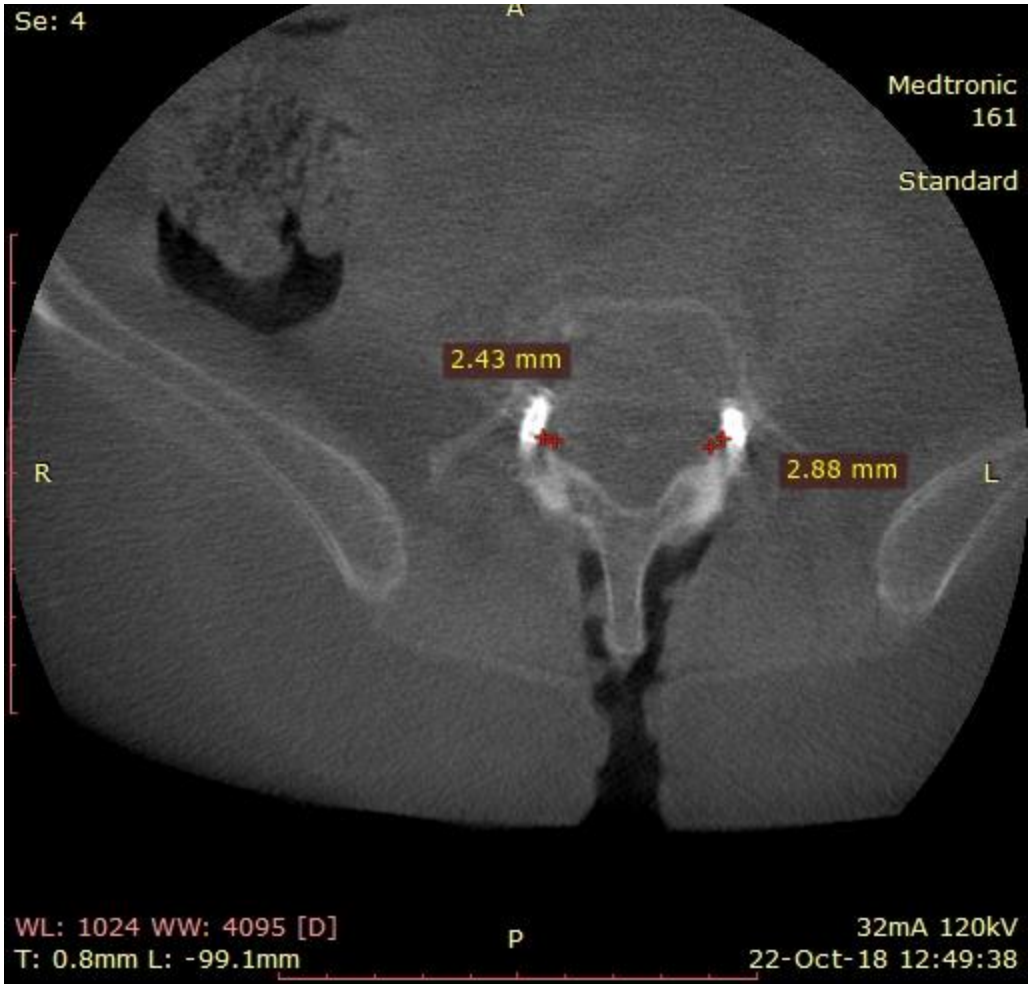
Figure 32: The below axial view is taken from data subject 20190027. Bilaterally L5 screws are over 3.0mm from the lateral recess and their triggered EMG threshold values are over 8mA. Indicating properly placed screws both in the 3-dimensional image and the triggered EMG test.



Pedicle Screw	**300µsec duration**	**200µsec duration**	**100µsec duration**
Left L5	14.0mA	18.0mA	29.0mA
Right L5	25.0mA	32.0mA	41.0mA

Figure 33: The below axial view is taken from data subject 20190030. A) Bilaterally L5 screws are over 2.0mm from the lateral recess and their triggered EMG threshold values are over 8mA. Indicating properly placed screws both in the 3-dimensional image and the triggered EMG test. B) For this subject, the multiplanar reconstruction view was also included to show the benefits of a 3-dimensional image, and the different planes in which you can view the same screw.

A)



Pedicle Screw	300µsec duration	200µsec duration	100µsec duration
Left L5	11.0mA	13.5mA	20.5mA
Right L5	13.0mA	15.5mA	23.5mA

B)

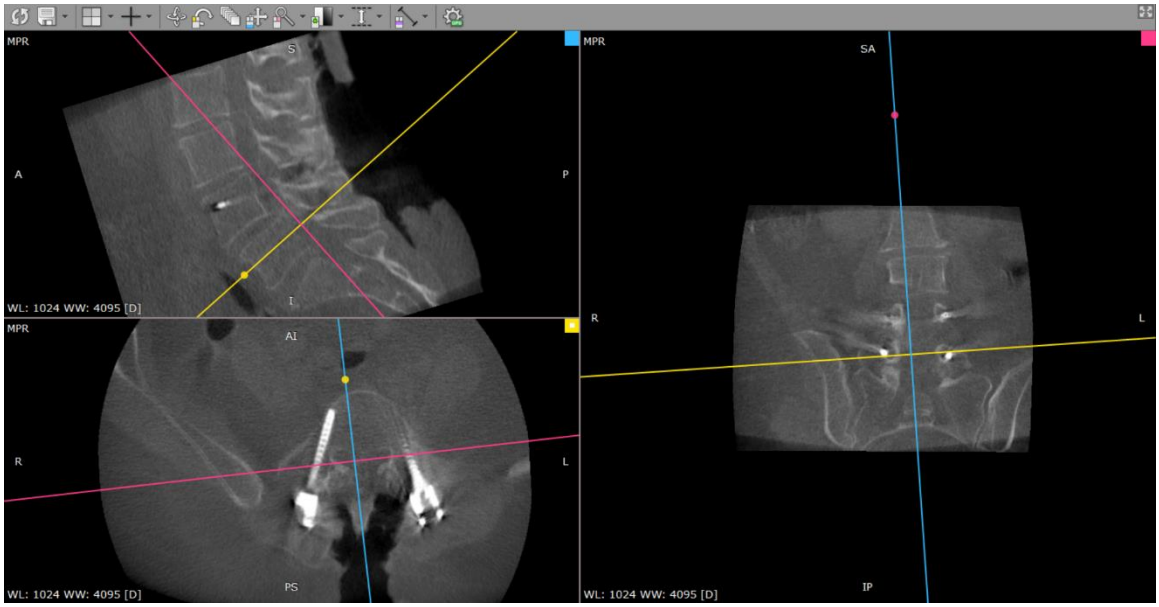
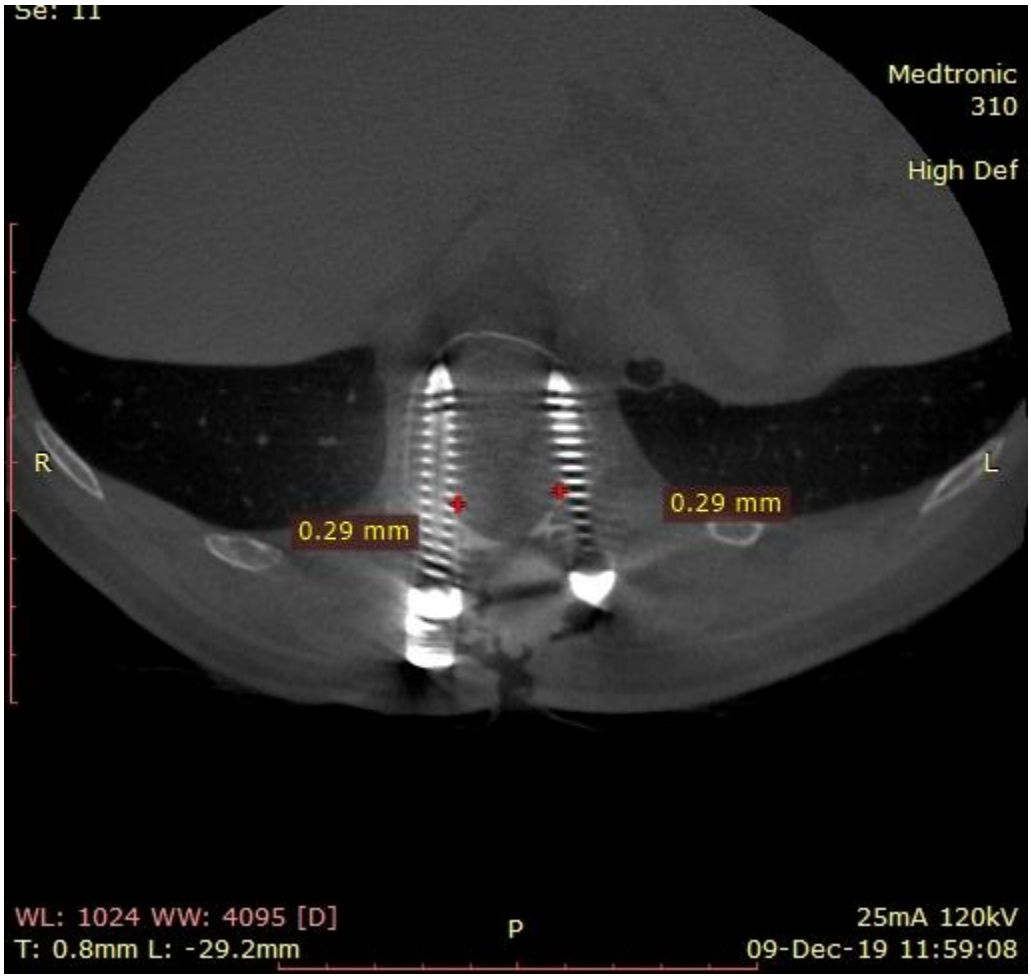


Figure 34: The below axial view is taken from data subject 20190033. This patient has osteoporosis. Bilaterally D12 and L2 screws have significantly less distance from the screw to the lateral recess (≥ 0.29mm), but the triggered EMG values are above 8mA. Indicating the electrical current is not reaching nervous tissue easily, and thus the screws are well encapsulated by bone. Even though with the osteoporotic bone, the

screws appear closer to the lateral recess on the 3D image than the previous examples, they still fall within the safe values in the tEMG test.

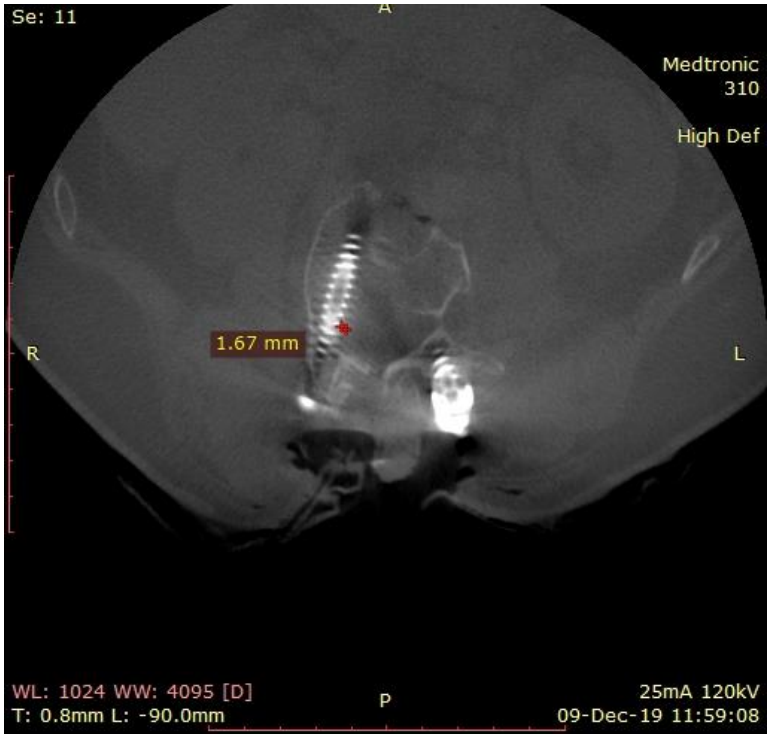
A) Bilateral D12 screws



Triggered EMG threshold values

Pedicle Screw	**300µsec duration**	**200µsec duration**	**100µsec duration**
Left D12	26.0mA	38.0mA	55.0mA
Right D12	23.0mA	38.0mA	60.0mA
Left L2	27.0mA	37.0mA	58.0mA
Right L2	34.0mA	41.0mA	58.0mA

B) Right L2 screw



C) Left L2 screw

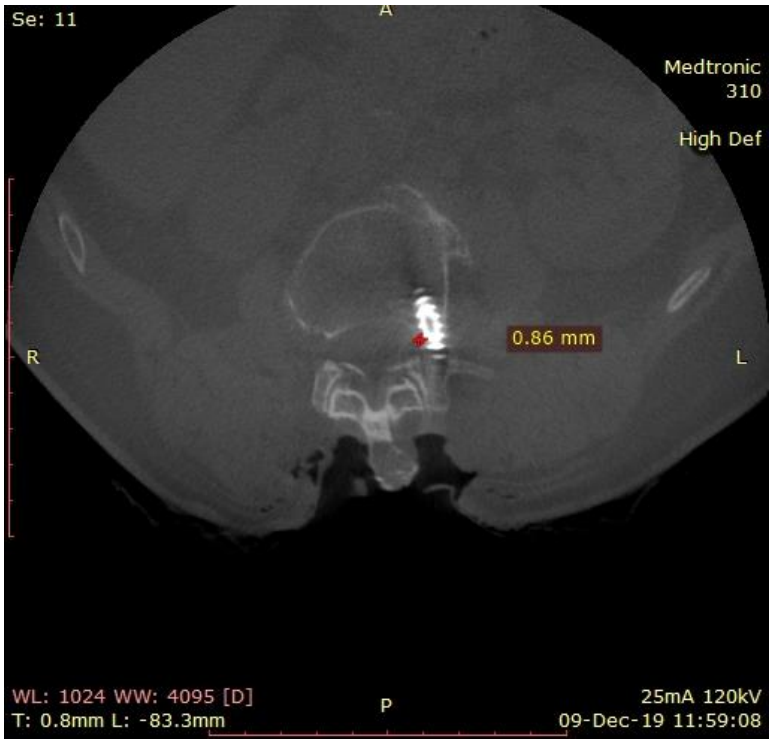
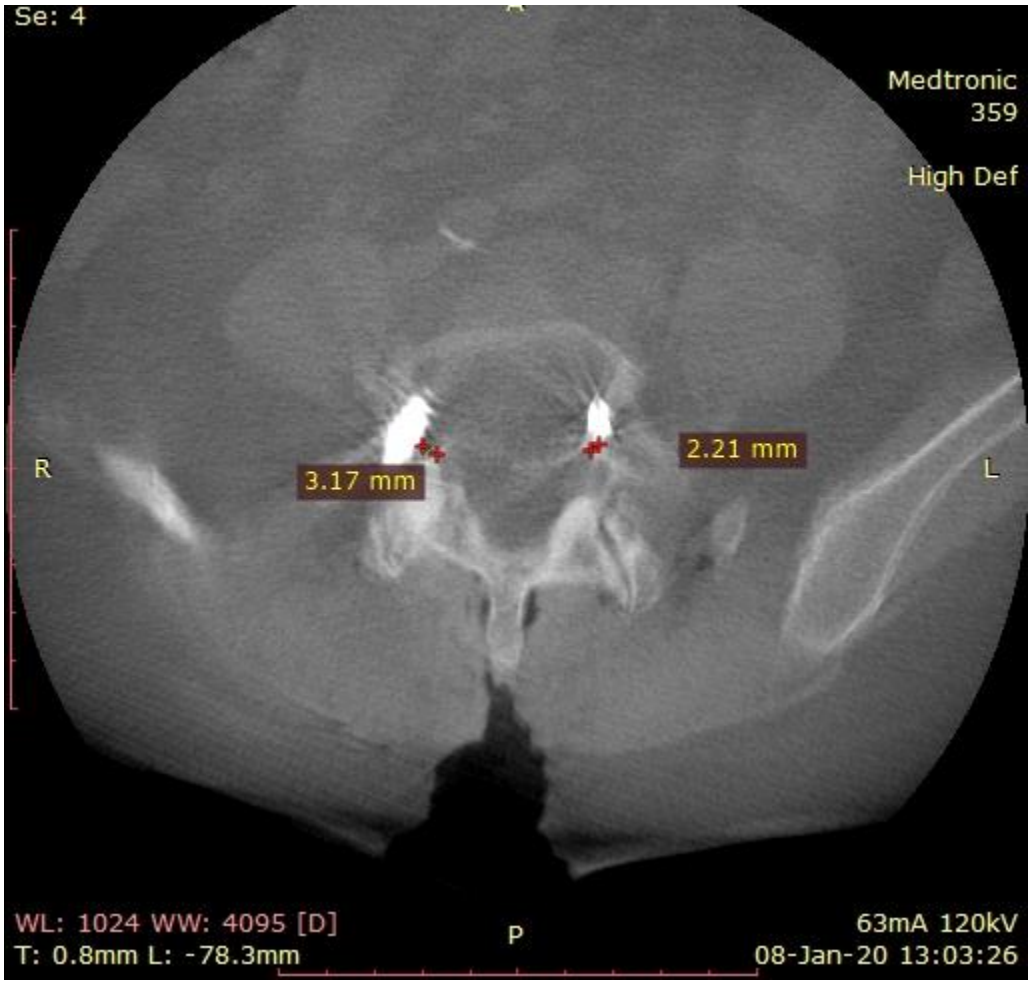


Figure 35: The below sagittal view is taken from data subject 20190032. L3, L4 and L5 screws are respectfully at a 2.57mm, 2.17mm, and 1.62mm distance from the intervertebral foramen. Their triggered EMG threshold values are over 8mA. Indicating properly placed screws both in the 3-dimensional image and the triggered EMG test.

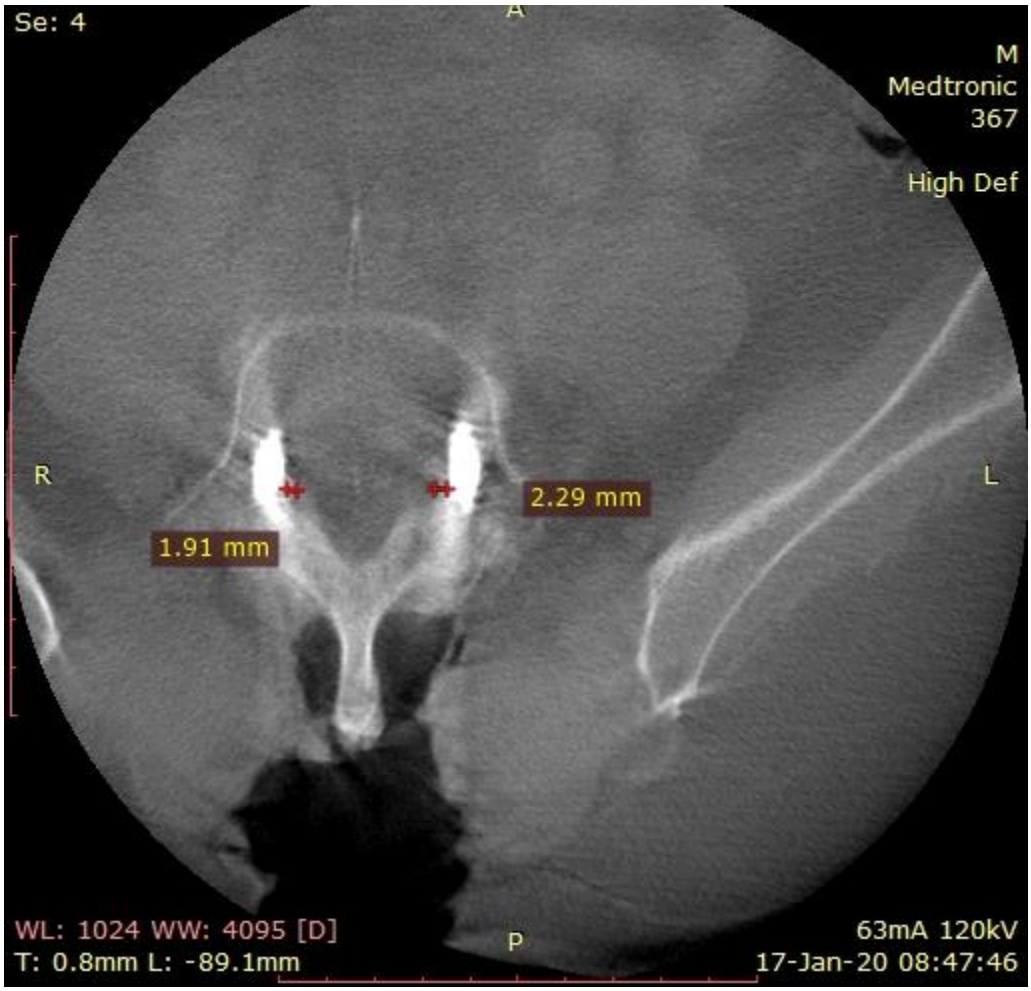
Pedicle Screw	**300µsec duration**	**200µsec duration**	**100µsec duration**
Left L3	24.0mA	32.0mA	45.0mA
Right L3	17.0mA	20.0mA	32.0mA
Left L4	16.0mA	21.0mA	30.0mA
Right L4	22.0mA	26.0mA	43.0mA
Left L5	12.0mA	17.0mA	24.0mA
Right L5	13.0mA	14.0mA	22.0mA

Figure 36: The below axial view is taken from data subject 20190035. Bilaterally L5 screws are over 2.0mm from the lateral recess and their triggered EMG threshold values are over 8mA. Indicating properly placed screws both in the 3-dimensional image and the triggered EMG test.



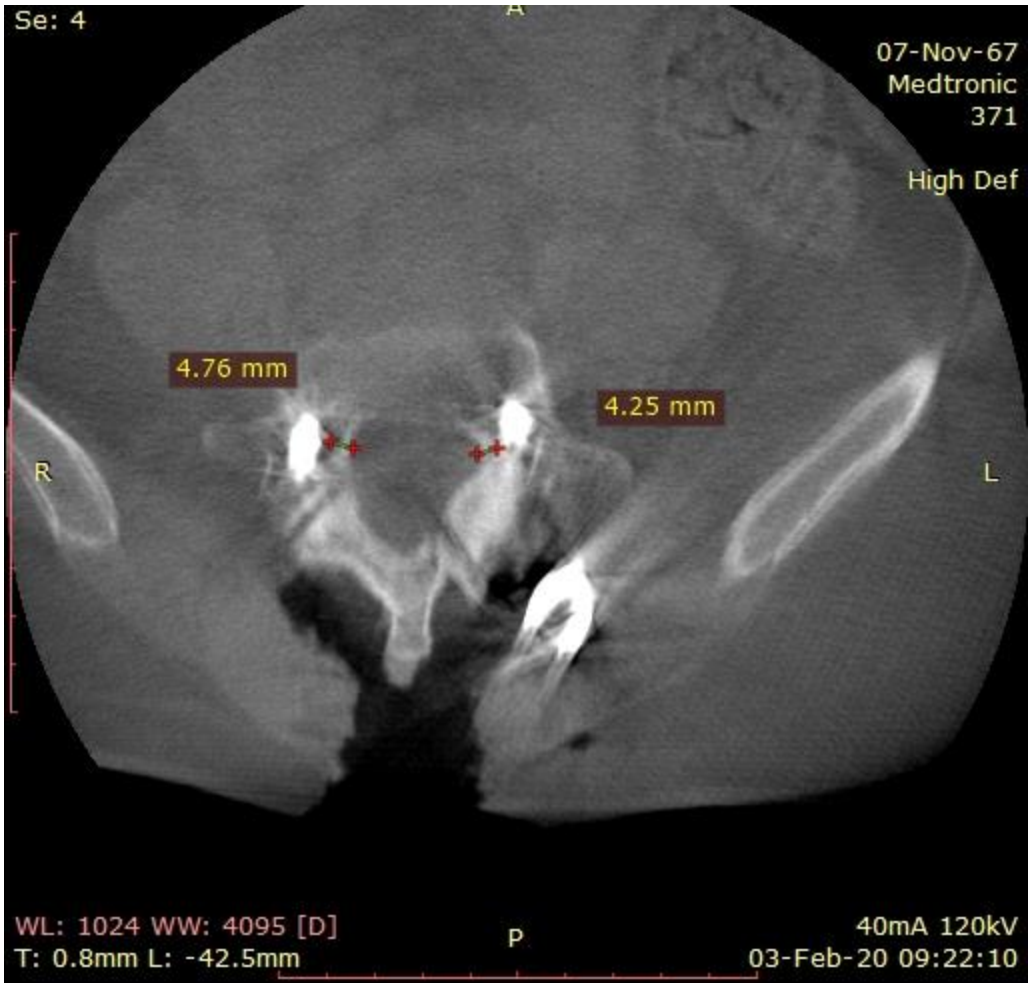
Pedicle Screw	300µsec duration	200µsec duration	100µsec duration
Left L5	33.0mA	45.0mA	62.0mA
Right L5	20.0mA	26.0mA	38.0mA

Figure 37: The below axial view is taken from data subject 20190036. Bilaterally L5 screws are over 1.9mm from the lateral recess and their triggered EMG threshold values are over 8mA. Indicating properly placed screws both in the 3-dimensional image and the triggered EMG test.



Pedicle Screw	300µsec duration	200µsec duration	100µsec duration
Left L5	33.0mA	40.0mA	60.0mA
Right L5	28.0mA	45.0mA	64.0mA

Figure 38: The below axial view is taken from data subject 20190038. Bilaterally L5 screws are over 4.0mm from the lateral recess and their triggered EMG threshold values are over 8mA. Indicating properly placed screws both in the 3-dimensional image and the triggered EMG test.



Pedicle Screw	300µsec duration	200µsec duration	100µsec duration
Left L5	22.0mA	30.0mA	38.0mA
Right L5	21.0mA	29.0mA	43.0mA

Overall, O-arm images indicated that pedicle screw stimulation was indeed accurate. If a screw was poorly positioned, it had a low threshold and was questionable on the imaging as well. Only two screws were repositioned in this study, and there were no nerve or spinal cord injuries.

In this study, a pattern was noticed with pedicle screw fixation cases using the O-arm. That with the use of the O-arm in open surgeries, the O-arm was 99% accurate in the placement of screws. Medtronic reports the O-arm and StealthStation Navigation unit to be 97% accurate on their website.[21] But with percutaneous screw fixations the O-arm was not as effective in determining a safe trajectory for placing the dilators, nor the screws. In other words, the navigation was not able to project a safe trajectory where the dilators or percutaneous tools would avoid hitting or injuring nerve roots. In the few cases done percutaneously, the navigation was thought to have projected a safe trajectory, but the free run electromyography showed spontaneous activity indicating nerve irritation during either Jamshidi, K wire, dilator placement and or screw insertion. This was discussed with the surgeons and will be investigated in the future as a separate study. In conclusion, with O-arm imaging and navigation assistance for open procedures, the accuracy rate was very high. Larson et al also found their screw accuracy rate was quite high at 99% with the use of intraoperative CT and 3D image-guidance.[43] The accuracy of pedicle screw placement without navigation for all types of spinal deformity has been reported from 77% to 99%.[44 45 46 47] Modi et al reports a 73% accuracy for free-hand screw placement in patients with neuromuscular scoliosis.[48] Wu

et al describes 86.1% accuracy of pedicle screw placement for hemivertebra excision using only a fluoroscopic technique (X-Ray).[49] Therefore, there is a pattern amongst several studies that the O-arm with StealthStation Navigation greatly increases the accuracy of pedicle screw placement, and the adjunct of triggered EMG, strengthens the deduction of a well-placed screw.

The three-dimensional O-arm images were compared to the pedicle screw thresholds to verify the accuracy and specificity of the triggered EMG. All O-arm images showed the pedicle screw at a distance from an anatomical exit point of a nerve root/tissue (the lateral recess or intervertebral foramen). The triggered-EMG thresholds also coincided with the distance of the screw to the nerve root with the t-EMG threshold value >8mA. There were five screws that were questionable on the O-arm imaging that were also borderline with the tEMG threshold value of a safely placed screw. In this instance the pedicle screw was further examined with the 3D imaging, and after careful consideration of the imaging and the triggered EMG threshold values, only two of the five screws were repositioned. Based on this, both the O-arm and triggered EMG are highly valuable when used together in a spinal fusion with pedicle screw fixation, but when 3D imaging or the O-arm is not available, pedicle screw testing has proven to be an accurate indicator of proper screw position and should be used as Gold Standard with fluoroscopy (X-ray).

Discussion

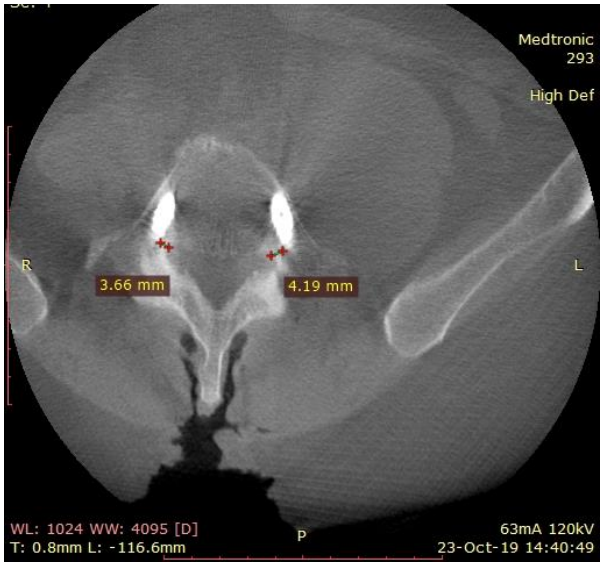
Throughout the years, in spinal fusions with pedicle screw fixations, intraoperative neurophysiologic monitoring (IONM/IOM) has been used as a tool to test whether a pedicle screw was well encapsulated by pedicle bone or not after its placement in the vertebrae. The IONM modality called pedicle screw stimulation or triggered EMG, is a technique of sending an electrical stimulus through a medal conducting screw and recording its current threshold in milliamperes. This technique has been reported to be 93-98% accurate.[1 29 31 50] Previous research states that 2-Dimensional X-ray can show false negatives where a pedicle screw may look well placed, but in fact has breached the pedicle wall. With the use of pedicle screw stimulation in conjunction with imaging, when this same screw is tested with triggered-EMG, it should yield a low threshold, and thus indicate for a screw reposition. Concluding that the two techniques together will increase the likelihood of ruling out a poorly placed screw. Placement of pedicle screws is essentially a blind technique. The surgeon cannot visually see where the screw is going in the vertebrae, but with the use of intraoperative imaging he or she is guided in the placement of the screw. Another issue that cannot be seen by the surgeon or imaging, is if the insertion of the screw causes a microfracture. A microfracture is a small fracture in the bone, that an X-ray may not pick up. A triggered-EMG test would pick up a possible microfracture. The electrical current would easily travel from the screw to the nervous tissue through the fracture and cause a compound muscle action potential with little electrical stimulus. A screw well encapsulated in bone (bone not

being a good conductor of electricity) would yield a high current threshold value because there is no fracture for the electricity to easily travel through to nervous tissue. In other words, a low threshold could indicate a microfracture, a tunnel that allows the current to travel to the nerve root with ease. In these scenarios, if only an X-ray (2-Dimesional) was used, the patient would have likely woken with a post-operative neurological deficit. X-ray, which is done by a C-arm and is two dimensional has a 14.5% error rate.[7] A recent option for 3-D imaging in the operating room is Medtronic's O-arm. Being able to view the screw in an additional dimension allows for further examination of its position within the pedicle, and likely reduces the 14.5% inaccuracies of viewing it with only 2 dimensions. Sarwahi, et al also exhibited that a CT scan or 3-dimensional imaging was far superior in evaluating screw placement than an X-ray.[19] Throughout this study, if a screw threshold was questionable, it correlated with the 3-dimensional O-arm imaging. Medtronic has claimed that the O-arm has a 97% accuracy.[21] The negative aspect with the O-arm is that it is a very expensive machine and many facilities do not have the budget to purchase one. Until the O-arm is readily available, it is essential to use triggered EMG along with 2-dimensional X-ray to assess the placement of a properly placed screw and thus reduce post-operative iatrogenic injury. It is also necessary to use the correct stimulus parameters when using certain recommended thresholds when interpreting pedicle screw threshold values. The statistical data of this study has shown differences in thresholds between different stimulus durations, more significant ones between 100µsec and 300 µsec, therefore care must also be taken to use correlating stimulus durations with specific author

threshold values, i.e. 300µsec for Lenke et al. In this study, although only 5 out of the 211 pedicle screws placed would have drastically changed the protocol of the operation, by reinsertion or repositioning of a screw, it is important to take stimulus duration into account during pedicle screw stimulation. Perhaps, in the past, stimulus duration was not given too much emphasis because the overall results of the differences in milliamperes of a good threshold versus a bad threshold were not significant, i.e. maybe a difference of 1 to 2mAs. But to an individual patient, who happens to fall into the small percentage, where that 1-2mA difference could detect a pedicle wall breach and prevent a postoperative deficit, such as radiculopathy (nerve root injury), it is important to acknowledge the importance of stimulus duration and the effects it has on the threshold number. The addition of triggered EMG to the surgical protocol would later save on patient distress if a revision surgery could be avoided to correct a mal-positioned screw. Avoiding a revision surgery, patient burden, or keeping one more bed open and saving the time of the hospital staff is priceless in any hospital setting.

To recap how the imaging was examined, after threshold data collection, the O-arm images were gathered and examined by the neurosurgeon. Several patients' 3-dimesional images were randomly selected. Axial and saggital views were studied. For the axial view, the screw distance was measured from the lateral recess of the vertebra (or where the nerve root was expected to be). This would be where if a screw was too medial, a medial breach would be detected. Please see figure 39 below.

Figure 39: Axial view of bilateral screws displaying measurements of screw to lateral recess where a nerve root is expected to be.



Then, sagittal views were investigated. Measurements were taken from the distance of the screw to the anterior part of the intervertebral foramen (the projected location of the nerve root). In the sagittal view one would be able to identify a low pedicle breach, where if the screw trajectory deviated downwards it would pinch a nerve root. Please see figure 40 below.

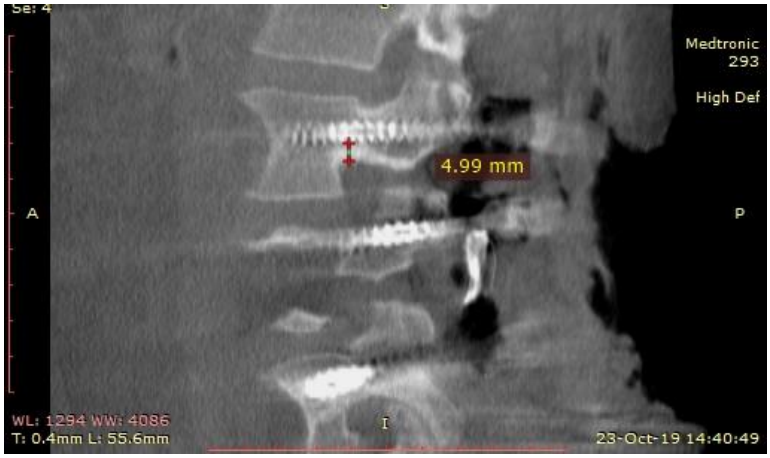


Figure 40: Sagittal view

Other measurements could have been taken, but the medial and low breach are the most common. After analysis, it was found, that the measurements in the images correlated with the threshold values as discussed earlier in the results section. To give a visual of the different possibilities of malpositioned screws, please see figure 41.

Figure 41: The image below displays different types of pedicle screw misplacements. Drawing done by Abul-Kasim, K (2009).[51,52]

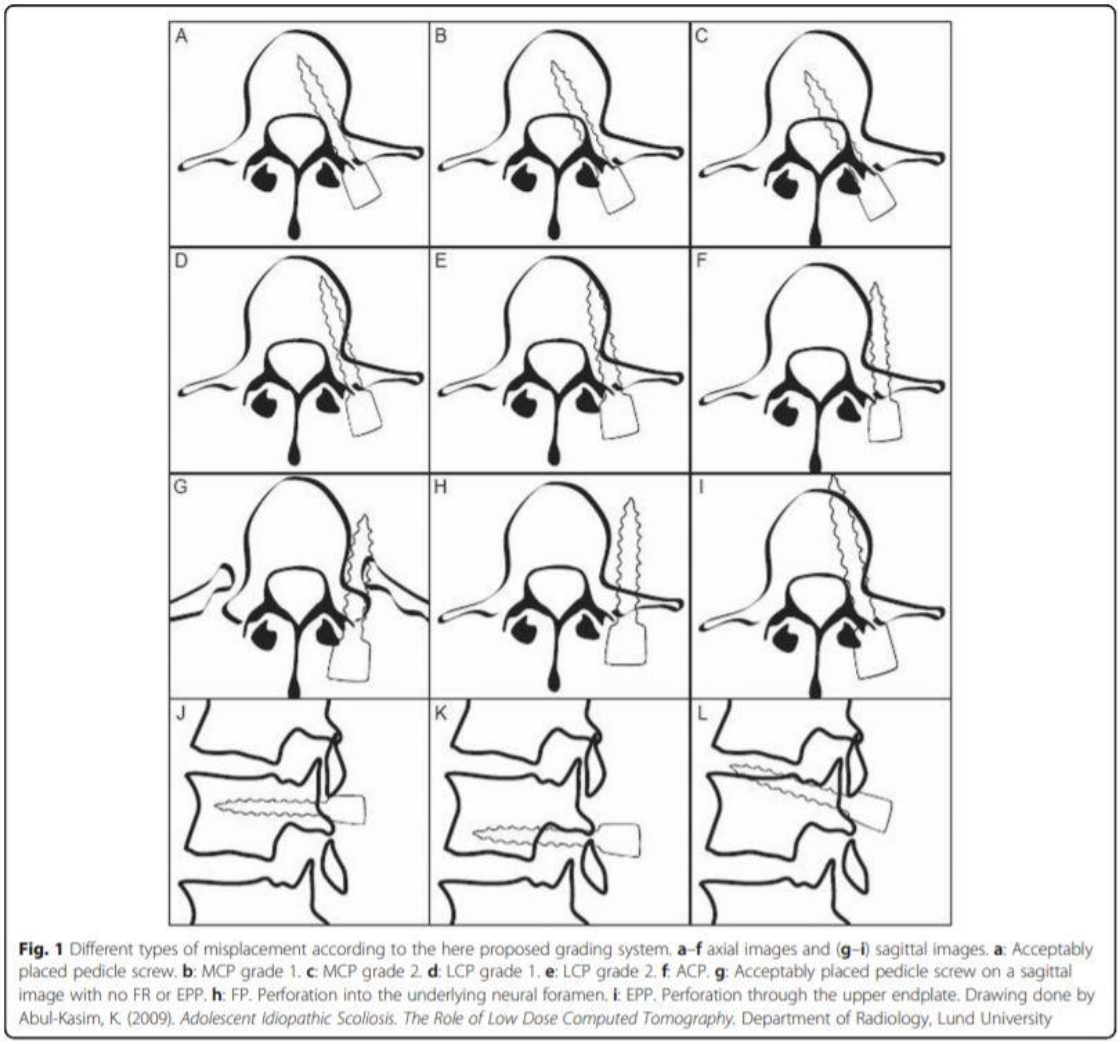


Fig. 1 Different types of misplacement according to the here proposed grading system. **a**–**f** axial images and (**g**–**i**) sagittal images. **a**: Acceptably placed pedicle screw. **b**: MCP grade 1. **c**: MCP grade 2. **d**: LCP grade 1. **e**: LCP grade 2. **f**: ACP. **g**: Acceptably placed pedicle screw on a sagittal image with no FR or EPP. **h**: FP. Perforation into the underlying neural foramen. **i**: EPP. Perforation through the upper endplate. Drawing done by Abul-Kasim, K. (2009). *Adolescent Idiopathic Scoliosis. The Role of Low Dose Computed Tomography.* Department of Radiology, Lund University

It was found that the O-arm was quite precise in indicating a properly placed screw, and the navigation was very helpful in accurate screw placement, especially with open procedures. An open procedure meaning not minimally invasive where dilators are used. Please note that when minimally invasive fusions were done, the O-arm did not effectively show where the nerve root was, and only the electromyography presented with spontaneous activity indicating nerve root irritation when the Jamshidi, K wire or dilator were close to a nerve. The O-arm was not helpful for percutaneous guidance through tissue, but the O-arm with navigation did prove helpful when an open fusion was being done.

3-Dimensional versus 2-Dimensional images:

3-dimensional images have been reported to be gold standard when assessing the placement of a pedicle screw. Unfortunately, because of extra cost and radiation exposure, they are not often utilized. The extra cost of a CT scan or the cost of having an O-arm is one that many facilities cannot take on. To have a patient go through 3-dimensional imaging before and after a procedure exposes him or her to extra radiation. There is minimal research on the effects of radiation exposure and its absorption into human tissue. Vila-Casademunt et al stated an increase incidence of cancer in adolescents who were exposed to X-ray during their spinal fusions and found in some cases the post-operative follow-up radiation to be unjustified and should be avoided.[53]

Apparently, once exposed to radiation, it never dissipates, but remains in human tissue and collects throughout the life span of the individual. Knowing this, many facilities prefer to be cautious and limit the patient's exposure to radiation. Some experienced spinal surgeons are confident in relying on their skill and knowledge of anatomy for inserting screws and are not so insistent on using 3-dimensional imaging. But they do verify the placement of pedicle screws with triggered electromyography and 2-dimensional X-ray. Pedicle screw testing through triggered electromyography has proven to be greater than 93% accurate in healthy patients getting a spinal fusion with pedicle screw fixation. While other surgeons trained with the O-arm feel more comfortable with its use during spinal fusions. Sarwahi et al stated 3-dimensional imaging is gold standard for identifying pedicle screw position.[19] The use of imaging, 3D or 2D, is dependent on the surgeon, the technique he or she feels more comfortable with, the best interests of the patient, and/or what is available at the hospital.

Neurophysiologic Tests and The Importance of Duration:

Stimulus duration is a very important factor in neurophysiological tests, and more emphasis needs to be put on having the correct duration with each modality or test. Expanding into other modalities, other than the triggered electromyography, if we look at the motor evoked potentials, duration is extremely important. The FDA and CE have put limitations on the duration allowed because of the harm it could cause to the

patient. The stimulus electrodes are inserted in the scalp, normally at either the C1, C2, C3, and or C4 locations of the International 10-20 EEG system on the head. Since these electrodes let out stimulus trans-cranially, they can be very dangerous to the patient, especially in terms of possibly causing seizures, stimulating the masseter muscles so intensely that the patient bites or lacerates his or her tongue or perhaps even go as far as short circuiting a pacemaker. The FDA and CE have allowed up to 1000 volts of electricity to be sent through the body to elicit motor evoked potentials, but the duration must remain at 50µsec. The FDA and CE have recently allowed 75µsec stimulus duration, but the voltage must remain below 816 volts. Remembering the stimulus duration settings can go as high as 300µsec for a triggered EMG and will not harm a nerve root but going over 75µsec in a motor evoked potential could cause harm to the patient. Therefore, stimulus duration or the amount of time a stimulus is applied to nervous tissue is an important parameter to keep in mind, especially when stimulating central versus peripheral nervous system.

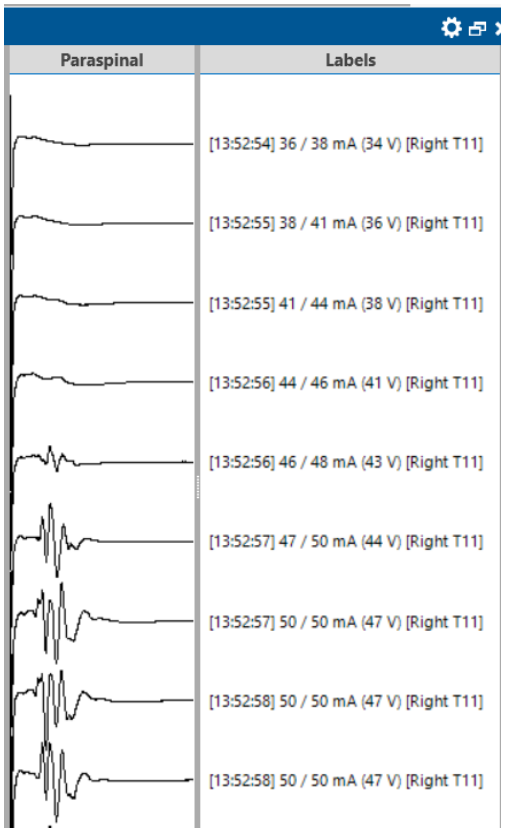
Looking at the insertion of an electrode for deep brain stimulation (DBS), commonly done for Parkinson's Disease, the stimulus duration should be considered since the electrode will be implanted directly on nuclei. The electrode stimulation parameters are pre-set but some clinicians placing the electrode overlook the stimulus parameters because they assume factory settings are compatible and safe for most patients. Unfortunately, there are not enough DBS cases to investigate this further to see the relevance of stimulus duration and the effect it may or may not have on patient

recovery or reduction of symptoms. But perhaps in the future it can be investigated if for example, having a 75µsec stimulus duration with a lower stimulus current would be more beneficial to a patient than having a 50µsec duration with a higher current or vice versa. Intraoperative neurophysiological monitoring is a field that is constantly growing and expanding, many possibilities and factors need to be investigated to make sure that they are fully benefiting the patient.

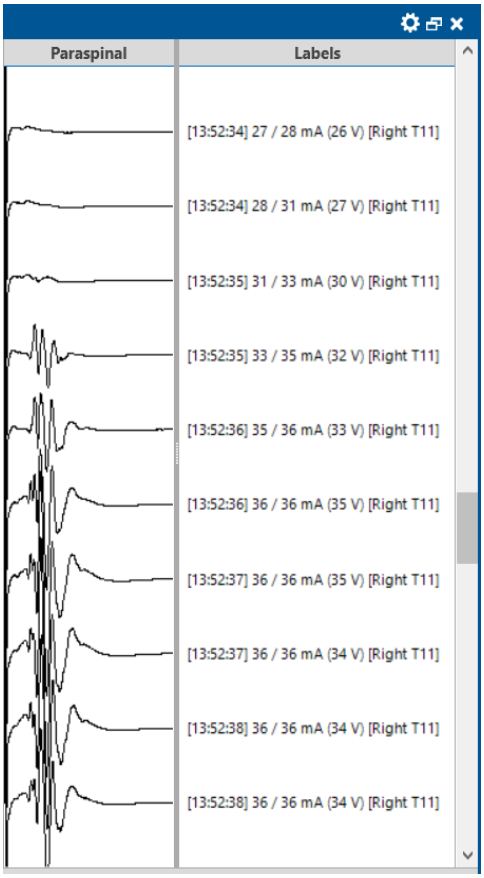
Through this study it was made clear that the duration of the stimulus parameters for pedicle screw stimulation must be considered when data is collected and interpreted. For a clearer picture of the triggered EMG screen, to follow (figure 42) are three snapshots of triggered EMG stimulation thresholds for one screw, at 300µsec, 200µsec and 100µsec. Differences in their thresholds are very apparent in the screenshots between the three different durations.

Figure 42: Pedicle screw stimulation images below showing the right D11 screw stimulated three times. Stimulation at 100µsec with cMAP at 48mA, at 200µsec with cMAP at 35mA and at 300µsec with cMAP at 24mA.

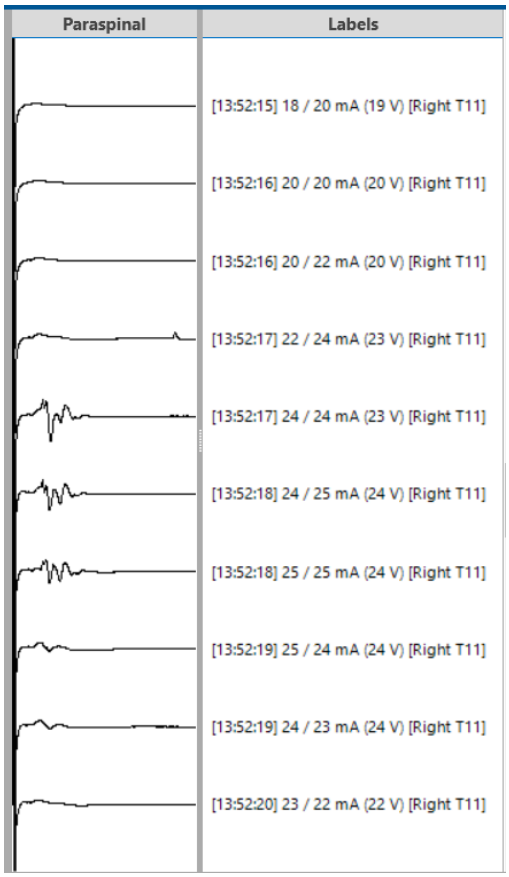
Right D11 screw stimulation at 100µsec.



Right D11 screw stimulation at 200µsec.



Right D11 screw stimulation at 300µsec.



The above screenshots display the drastic difference stimulus duration can play on how quickly or slowly a compound muscle action potential is elicited in pedicle screw stimulation for each screw in spinal fusion surgeries.

Moving over to the realm of brain mapping, techniques of mapping the central sulcus or primary motor area of the cortex and subcortical mapping to identify the white matter

or internal capsule with a stimulator have been implemented for the past several years. For the craniotomy, when cortical mapping is done, setting the correct duration and stimulus parameters could affect patient safety by reducing the amount of time stimulation is applied to the cortical tissue, thus avoiding a stimulus induced seizure. But not only that, duration along with its corresponding stimulus parameters could easily affect whether gray matter/cell bodies are elicited or whether white matter/axons are being correctly stimulated.[54] Cortical and subcortical mapping has been quite successful in preserving eloquent areas of the primary motor cortex as well as preserving the internal capsule. But it is not safe to assume that the same stimulus parameters will elicit responses in both gray and white matter equally. Therefore, data misinterpretation can result with a neurophysiologist not properly trained in the technicalities of this field. To the novice neurophysiologist, the neuromonitoring system can be set up with any stimulus parameters and responses will be seen on the screen, but if the correct stimulus parameters are not used, it will not be clear from where (cortical or subcortical region) those responses are being elicited. For example, cathodal stimulation is used with multi train technique on the cortex, a response is seen, but cortical neurons are not the ones that are ignited, it is the subcortical matter. If the neurophysiologist does not recognize the difference and misinterprets the data by calling either false positives or false negatives, the direction of the tumor resection will change thus affecting the post neurological outcome of the patient. Therefore, it is very important to consider all stimulus parameters when mapping occurs. Going back to triggered EMG in a posterior spinal fusion. A surgeon may ask to use triggered EMG to

find a nerve. He or she places the stimulator on muscle, but the neurophysiologist is not aware of this. The neurophysiologist does not initially see an action potential at 2mA and so increases the stimulus to 20mA until finally a cMAP is seen. A response is seen at 20mA, the novice neurophysiologist calls it as nerve, but it is not true. The stimulator was on muscle, not nerve. If the stimulus was kept under 5mA and the duration at 200µsec (which is commonly used to map individual nerves), the current would not have shunted into the surrounding tissue and caused a false action potential to occur. The American Society of Neurophysiological Monitoring has released guidelines stating that 200µsec with constant current and repetition rate between 1-3Hz is a common and safe duration to use for peripheral and spinal nerve triggered electromyography.[2] Knowing the correct stimulus parameters to set would make for an ideal and more specific nerve mapping protocol, because a nerve elicits an action potential at 2-3mA. A cMAP at 20mA already concludes current shunting and a false positive response, meaning the response did not come from the nerve a response was sought from, but from surrounding tissue or neighboring nerves. Supporting the importance of knowing the correct stimulus parameters to use when implementing neurophysiological tests and interpreting the data.

EMG and Minimally Invasive Procedures:

This study discussed open pedicle screw procedures, but only slightly touched upon minimally invasive pedicle screw procedures. The main difference between these procedures is that with a minimally invasive surgery (MIS), dilators are blindly inserted percutaneously down to the intervertebral foramen. 2-dimensional X-ray is usually used and in some cases 3-dimensional (where available) but imaging itself has not shown to effectively protect the nerve roots as the dilators approach the spine. For instance, in one MIS procedure in this study, the O-arm alone did not aid the surgeon in avoiding the nerve root, but the EMG instantaneously caught the irritation the dilator was causing the nerve root. With this information, the surgeon immediately changed the trajectory of the dilator and preserved neuronal function. Again, justifying the use of intraoperative neurophysiologic monitoring within pedicle screw fixation procedures, open and minimally invasive.

EMG and Cranial Nerves:

The use of EMG has been underestimated in many types of surgeries, especially in hospitals where a certified neurophysiologist is not available. One common surgery that comes to mind is the thyroidectomy where the preservation of the recurrent laryngeal

nerve is important. The recurrent laryngeal nerve controls the vocal cords which regulates the ability to speak. Another nerve that may be affected during thyroid resection is the superior laryngeal nerve, which is found on the cricothyroid muscle, a tensor muscle of the larynx helping in phonation. During a radical neck dissection, more nerves can be involved, i.e. the phrenic nerve that controls the diaphragm, the spinal accessory nerves involving the trapezius and C4 nerve root, the hypoglossal involving the tongue and the glossopharyngeal involving the soft palate, possibly even the facial nerve. All these nerves are at risk during a radical neck dissection. For a patient to have a surgery to remove lymph nodes, tumor, etc., it would be prudent to try and preserve the surrounding nerves so that the patient does not lose neurologic function on top of everything else he or she is going through. Imagine losing your ability to speak after a thyroidectomy when that could have completely been avoided with the use of EMG monitoring. Furthermore, imagine after a radical neck dissection the phrenic nerve is injured causing paralysis or partial dysfunction of the diaphragm affecting someone's ability to breath properly, something that again could have been avoided with monitoring. Emphasizing, intraoperative monitoring preserves neurologic function and is highly valuable.

Craniotomies or brain surgeries involving the posterior fossa and thus the cranial nerves are another area that should be discussed. The most monitored cranial nerves via electromyography are the trigeminal, facial, glossopharyngeal, vagus, spinal accessory, hypoglossal, and sometimes the abducens. Visualizing the enormity of the functions

these cranial nerves provide; it is essential to use triggered electromyography to map/locate these nerves and prevent iatrogenic injury during tumor resection. All these nerves are important, and so are the functions they carry out. Intraoperative electromyography with nerve mapping could prevent or drastically reduce the rate of iatrogenic injury. The increasing incorporation in recent years of intraoperative neurophysiological monitoring, its application to the [nerves] is possible in procedures with a risk of injury and, thus, the reduction of iatrogenic injury rates.[55]

EMG and Peripheral Nerves:

Brachial plexus repair is another type of surgery involving the brachial plexus. The brachial plexus is a network of nerves that begins at the spine, passes through the axilla and extends through the upper extremity. Injury to this area is commonly caused after motorcycle accidents. During a brachial plexus repair, electromyography is used to locate the injured nerve. Then another technique called a nerve action potential is done to assess where exactly the nerve is injured. At the point of injury, where there is absolutely no response from the nerve, the surgeon severs the nerve and sews a nerve graft in its place to promote the regeneration of nerve growth. It is critical that healthy nerve is not cut during this procedure because that would hinder the patient's recovery and possibly cause further neurological deficit. With correct stimulus parameters, neurophysiological tests accurately decipher the integrity of a nerve root and preserve

as much healthy nervous tissue as possible, reducing further iatrogenic injury and reducing a patient's recovery time.

Conclusion

Intraoperative 3D imaging has shown that triggered electromyography is a reliable indicator of properly placed pedicle screws. Statistical data has also shown that stimulus duration can affect the interpretation of a properly placed screw, and threshold values do vary with different durations. Threshold values were gathered from 211 screws at three different stimulus durations, the first at 300µsec, the second at 200µsec and the third at 100µsec. At 300µsec stimulus duration, the mean threshold value was at 27.25mA ($p=0.0078$). At 200µsec stimulus duration, the mean threshold value was at 35.46mA ($p=0.0028$). At 100µsec stimulus duration, the mean threshold value was at 50.90mA ($p=0.0676$). These mean values were found to be statistically significant when run by the Kruskal-Wallis test, a non-parametric statistical significance test. Since, three groups of data were being compared, and thus were not normally distributed, a non-parametric significance test was used. In conclusion, the stimulus duration should be considered when using certain thresholds to interpret data. Different durations change the stimulus strength and thus, affect the results of the screw stimulation thresholds.

This research evaluated the validity of intraoperative neurophysiological monitoring, specifically triggered electromyography, in surgeries involving the stabilization of the spinal column. In stabilization, screws are inserted into the pedicle of the vertebrae, and then connected with a rod. These screws are placed near spinal nerve roots or the spinal cord, therefore there is a high risk of iatrogenic induced neurological deficit. Meaning, the surgeon's placement of the pedicle screws in proximity to nervous tissue increases the likelihood of post-operative neurologic deficit. To reduce the risk of injury, triggered EMG and radiographs are used to properly assess the position of a screw within the pedicle. To test the position of the pedicle screw with triggered EMG, electricity is used to stimulate the screw, which stimulates nerve roots, which then produces compound muscle action potentials that are recorded as thresholds on the EMG screen from the nerve roots' corresponding muscles. For the past several years, certain EMG values have been used to determine a well-placed screw from a mal-positioned screw. A low threshold would indicate a breach since the electricity would easily flow to the nerve root and almost immediately cause an action potential. A higher threshold number would indicate that the electrical current had difficulty reaching the nerve root and thus would predict a screw well insulated by bone. Triggered electromyography (tEMG) is used to evaluate the position of a screw within the vertebral pedicle. Universally, surgical neurophysiologists, orthopedic spine specialists and neurosurgeons use Lenke et al's pedicle screw threshold values[26] when interpreting triggered EMG values to determine whether a pedicle screw is fully encapsulated by the pedicle bone or whether there is a breach. Although the use of

these predetermined values has become standard, it is not always emphasized that when these numbers are used for interpretation, corresponding stimulation parameters must also be utilized, specifically stimulus duration. A pulse duration is the time from the start of the first phase of the stimulus to the end of the last phase. A duration is the pulse's width. In principle, the longer a stimulus duration is, the quicker a compound muscle action potential will appear because the strength of the stimulus will activate more nerve fibers and reach threshold sooner. If a high stimulus duration is used, cMAPs should appear at a lower current threshold, and vice versa if a low stimulus duration is used, cMAPs should appear at a higher current threshold. Therefore, this study investigated the interdependence between stimulus strength and stimulus duration, and the effect it had on the threshold values for a well-placed screw. After the pedicle screw stimulation test, 3-dimensional imaging was used to evaluate the position of the screw and examine the efficacy of the triggered EMG. The statistical analysis did indeed find significance in using the correct stimulus duration when using standard predetermined thresholds to evaluate a screw. In addition, the 3-dimensional O-arm images supported that pedicle screw stimulation is highly predictive in foretelling a safe and well insulated pedicle screw. Therefore, triggered electromyography is highly recommended for use in posterior spinal fusions with pedicle screw fixations.

The purpose of intraoperative neurophysiologic testing is to provide guidance and reduce iatrogenic post-operative neurological deficit. Nevertheless, with these tests, the correct stimulation parameters should be used so that the interpretation of the test

is precise. IONM's utilization also saves the patient prolonged recovery time and/or reduces chances of needing for example, a revision surgery to correct a mal-positioned screw or possibly to reverse an iatrogenic injury. All in all, it saves recovery time, thus reduces unnecessary distress on the patient, as well as overall cost to the patient and hospital. This indirectly keeps hospital beds open for other patients in need. Intraoperative neurophysiology also offers peace of mind to the surgeon and to the patient that there is an extra layer of protection for the preservation of the patient's nervous system. It is without question that intraoperative neurophysiologic monitoring should be used in surgeries where there is a possibility of neurological deficit, especially triggered electromyography in spinal fusions.

Appendix 1:

Screw Threshold Data

#	screw	300µsec	200µsec	100µsec
1	Left L3	49	71	100
2	Right L3	21	27	39
3	Left L4	25	49	67
4	Right L4	25	33	58
5	Left L5	36	45	61
6	Right L5	19	24	34
7	Left L1	45	56	85
8	Right L1	43	53	86
9	Left L2	38	52	82
10	Right L2	29	54	72
11	Left L5	32	38	50
12	Right L5	21	27	37
13	Left S1	40	65	83
14	Right S1	24	30	47
15	Left T4	6.5	11	15
16	Right T4	8	17	23
17	Left T5	14	18	56
18	Left T6	15	20	32
19	Left T7	21	24	30
20	Right T7	15	18	24
21	Left T9	26	32	42
22	Right T9	22	28	37
23	Left T10	33	43	71
24	Left T11	38	60	76
25	Right T11	36	53	84
26	Left T12	11	15	21
27	Left L1	21	25	39
28	Right L1	44	65	71
29	Left L4	32	44	63
30	Right L4	22	32	45
31	Left L5	36	48	65
32	Right L5	31	40	59
33	Left S1	17	22	40
34	Right S1	30	35	50
35	Left T11	12	49	81
36	Right T11	30	65	72

37	Left T12	23	48	77
38	Right T12	44	53	86
39	Left L1	25	37	73
40	Right L1	33	49	67
41	Right L2	55	66	83
42	Left L3	24	32	43
43	Left L4	16	21	32
44	Right L4	21	28	49
45	Left L5	18	24	33
46	Right L5	30	40	66
47	Left S1	38	51	66
48	Right S1	27	44	69
49	Left L3	38	42	60
50	Right L3	21	25	35
51	Left L4	27	32	45
52	Right L4	24	26	42
53	Left L5	18	26	35
54	Right L5	22	26	41
55	Left L3	21	27	43
56	Right L3	19	24	32
57	Left L4	14.5	16.5	19.5
58	Right L4	15	19.5	27.5
59	Left L5	30.5	37.5	52.5
60	Right L5	12	15.5	23
61	Left L2	34	45	69
62	Right L2	33	47	52
63	Left L3	26	32	48
64	Right L3	27	48	74
65	Left L4	15	25	36
66	Right L4	18	28	44
67	Left L5	15	18	28
68	Right L5	24	28	45
X	no screw stim			
69	Right L2	20.5	30.5	46.5
70	Left T11	37	81	87
71	Right T11	67	82	99
72	Left L1	56	71	87
73	Right L1	47	62	82
74	Left L5	14	18	28
75	Right L5	24	31	49
76	Left S1	21	28	33
77	Right S1	21	25	40
78	Left L3	30	39	66
79	Right L3	32	43	66
80	Left L4	19	23	38

81	Right L4	36	46	67
82	Left L5	19	30	48
83	Right L5	8.5	13	43
84	Left S1	34	40	54
85	Right S1	27	31	45
86	Left L2	16	20	30
87	Right L2	15	12	16
88	Left L4	24	28	42
89	Right L4	19	24	35
90	Left L4	32	40	58
91	Right L4	17	21	31
92	Left L5	20.5	22	32
93	Right L5	17	19	28
94	Left L3	30	36	54
95	Right L3	35	43	66
96	Left L4	27	32	51
97	Right L4	22	25	41
98	Left L5	23	30	43.5
99	Right L5	17	22	33
100	Left S1	21	14	24
101	Right S1	16	12	23
102	Left L3	20	26	42
103	Right L3	18	33	42
104	Left L4	19	22	36
105	Right L4	22.5	24	37
106	Left L4	22	27	39
107	Right L4	32	42	66
108	Left L5	42	58	74
109	Right L5	57	69	96
110	Left L2	41	48	58
111	Right L2	36	45	65
112	Left L3	27	34	54
113	Right L3	29	31	48
114	Left L4	16	21	28
115	Right L4	19.5	26.5	38.5
116	Left L5	17	24	31
117	Right L5	12	15	23
X	no screw stim			
118	Left T11	45	49	63
119	Right T11	31	45	65
120	Left T12	77	74	69
121	Right T12	54	41	59
122	Left L1	87	100	>100
123	Right L1	70	82	99
124	Left L2	59	70	94

125	Right L2	54	69	100
126	Left L5	19	21.5	35
127	Right L5	24	29	48.5
128	Left S1	21	28.5	46
129	Right S1	17	19.5	30
130	Left L4	29	33	38
131	Right L4	29	38	44
132	Left S1	60	84	99
133	Right S1	50	71	73
134	Left L1	42	58	75
135	Right L1	39.5	55	75
136	Left L4	14	16	23
137	Right L4	21.5	26.5	74.5
138	Left L5	14	18	29
139	Right L5	25	32	41
140	Left L4	13	14.5	21.5
141	Right L4	14	15	29
142	Left L5	27.5	34	46
143	Right L5	19.5	25	34
X	excluded			
144	Left L4	19	23	38.5
145	Right L4	17.5	20	28
146	Left L5	11	13.5	20.5
147	Right L5	13	15.5	23.5
X	excluded			
148	Left L3	24	32	45
149	Right L3	11	14	21
150	Right L3	17	20	32
151	Left L4	16	21	30
152	Right L4	22	26	43
152	Left L5	12	17	24
153	Right L5	13	14	22
154	Left T12	26	38	55
155	Right T12	23	38	60
156	Left L2	27	37	58
157	Right L2	34	41	58
158	Left T6	8.5	15	NR
159	Right T6	18	24	34
160	Left T7	15	18	20
161	Left T8	5.5	8.5	14.5
162	Left T9	19	27	36
163	Right T9	24	26	36
164	Left T10	31	41	48
165	Left T11	20	28	41
166	Right T11	24	35	50

167	Left T12	21	41	55
168	Left L1	28	36	55
169	Right L1-Quad	47	59	93
170	Right L1-Pspinal	23	21	36
171	Left L3	27	35	49
172	Right L3-Quad	30	35	47
173	Right L3-Pspinal	20	27	37
174	Left L4	21	43	52
175	Right L4-Quad	27	36	52
176	Right L4-TA	36	41	70
177	Left L5	33	45	62
178	Right L5-Quad	15	19	32
179	Right L5-TA	20	26	38
180	Left L4-Quad	27	33	50
181	Left L4-TA	39	42	64
182	Right L4	39	48	73
183	Left L5-Quad	33	40	60
184	Left L5- TA	41	52	77
185	Right L5-Quad	28	45	64
186	Right L5-TA	50	67	99
187	Left L3	44	55	86
188	Right L3	50	63	94
189	Left L4	31	39	63
190	Right L4	56	66	97
191	Left L5	30	37	51
192	Right L5	33	38	55
193	Left S1	36	47	67
194	Right S1	30	39	50
195	Left L5	22	30	38
196	Right L5	21	29	43
197	Left S1	15	17	26
198	Right S1	14	20	26
199	Left L3	31	34	50
200	Right L3	21	26	37
201	Left L4	29	36	49
202	Right L4	28	35	52
203	Left L5	27	30	43
204	Right L5	32	38	63
205	Left S1	31	35	50
206	Right S1	23	28	40
207	Left T7	18	21	26
208	Left T12	22	27	43
209	Right T11	41	57	72

210	Right L1	20	29	47
211	Right L2	30	45	52

Appendix 2: Bioethics approval Barcelona

Vall d'Hebron
Hospital

Pg. Vall d'Hebron, 119-129
08035 Barcelona
Tel. 93 489 38 91
Fax 93 489 41 80
ceic@vhir.org

VALL D'HEBRON UNIVERSITY HOSPITAL RESEARCH ETHICS COMMITTEE WITH MEDICINES AND RESEARCH PROJECT COMMISSION REPORT

Mrs. Mireia Navarro Sebastián, Secretary of the Research Ethics Committee with Medicines at the Hospital Universitari Vall d'Hebron from Barcelona,

CERTIFIES

The Hospital Universitari Vall d'Hebron Research Ethics Committee with Medicines, in which the research project commission is integrated, met in regular session No 336 last 27/04/2018 and evaluated the research project PR(ATR)143/2018 , entitled "*Evaluate the current acceptable triggered electromyography (tEMG) threshold values used in pedicle screw stimulation by manipulating stimulation durations, followed by testing the specificity of the triggered EMG test by assessing the position of the pedicle screw with radiography*" whose principal investigator Dr. Ferran Pellisé Urquiza of Spine Surgery Unit our center.

Version of documents:

- Memoria V2_18.04.2018
- Informació al pacient per a un estudi sense cap procediment invasiu V2_18.04.2018
- Model de consentiment informat per a un estudi V2_18.04.2018
- Solicitud informe CEIC Versión 23.03.2018

And after issuing a report approved at this meeting conditioned and assess documentation subsequently received in response to this report.

APPROVED

The Committee in its composition as in the SOP (Standard Operating Procedure) meets GCP (CPMP/ICH/135/95) and Royal Decree 1090/2015, and its current composition is:

Chain person: Gallego Melcón, Soledad. Doctor
Vice President Segarra Sarries, Joan. Lawyer
Secretary: Navarro Sebastián, Mireia. Chemist
Vocals: Armadans Gil, Lluís. Doctor
Azpiroz Vidaur, Fernando. Doctor
Balasso, Valentina. Doctor
Cucurull Folgera, Esther. Physician Pharmacologist
De Torres Ramírez, Inés M. Doctor
Fernández Liz, Eladio. Primary care Pharmaceutics
Fuentes Camps, Inmaculada. Physician Pharmacologist
Gálvez Hernando, Gloria María.Nurse
Guardia Massó, Jaume. Doctor
Hortal Ibarra, Juan Carlos. Law University Profesor
Iavecchia, María Luján. Physician Pharmacologist
Joshi Jubert, Nayana. Doctor
Martínez Muñoz, Montserrat. Nurse
Rodríguez Gallego, Alexis. Physician Pharmacologist
Sánchez Raya, Judith. Doctor
Solé Orsola, Marta. Nurse
Suñé Martín, Pilar. Hospital Pharmacologist
Vargas Blasco, Víctor. Doctor

At the meeting of the Research Ethics Committee with Medicines fulfilled the quorum provisions of law.

In the case of a project to evaluate where a member is a researcher / collaborator, he will be absent from the meeting during discussion of the project.

MIREIA NAVARRO SEBASTIAN

Firmado digitalmente por MIREIA NAVARRO SEBASTIAN
Nombre de reconocimiento (DN): c=ES, ou=Vegeu https://www.aoc.cat/CATCert/Regulacio, sn=NAVARRO SEBASTIAN, givenName=MIREIA, serialNumber=38121226Z, cn=MIREIA NAVARRO SEBASTIAN
Fecha: 2018.08.23 12:38:45 +02'00'

Sra. Mireia Navarro
Secretary of the Research Ethics Committee with Medicines
Hospital Universitario Vall d'Hebron

Barcelona, June 15th, 2018

Appendix 3: Bioethics Approval Cyprus

ΚΥΠΡΙΑΚΗ ΔΗΜΟΚΡΑΤΙΑ

ΕΘΝΙΚΗ ΕΠΙΤΡΟΠΗ ΒΙΟΗΘΙΚΗΣ ΚΥΠΡΟΥ

Αρ. Φακ.: ΕΕΒΚ/ΕΠ /2019/21
Αρ. Τηλ.: 22809038 / 22809039
Αρ. Φαξ: 22353878

03 Ιουνίου, 2019

Κυρία Μέλανη Πογιατζή
Ευαγόρα Παπαχριστοφόρου 27
2019 Στρόβολος
Λευκωσία

Ερευνητική πρόταση με τίτλο:
«Τα οφέλη της νευροφυσιολογίας στο χειρουργείο και το κλινικό περιβάλλον»

Σε σχέση με την πιο πάνω ερευνητική πρόταση, επιθυμώ να σας πληροφορήσω ότι η Επιτροπή Βιοηθικής Αξιολόγησης Βιοϊατρικής και Κλινικής Έρευνας Α΄, ενεργώντας με βάση την εκχωρηθείσα σ΄ αυτήν αρμοδιότητα από την Εθνική Επιτροπή Βιοηθικής Κύπρου να αξιολογεί βιοηθικά ερευνητικές προτάσεις που αφορούν την βιοϊατρική και κλινική έρευνα στον άνθρωπο, έχει πραγματοποιήσει την βιοηθική αξιολόγηση της πιο πάνω ερευνητικής σας πρότασης, η οποία σας αποστέλλεται συνημμένα.

Με εκτίμηση,

Δρ Χρίστος Πέτρου
Πρόεδρος
Επιτροπής Βιοηθικής Αξιολόγησης
Βιοϊατρικής και Κλινικής Έρευνας Α΄

Κέντρο Υγείας Έγκωμης, Γωνία Μακεδονίας και Νίκου Κρανιδιώτη, 1ος όροφος, 2411 Λευκωσία
Ηλεκτρονικό Ταχυδρομείο: cnbc@bioethics.gov.cy, *Ιστοσελίδα*: www.bioethics.gov.cy

ΕΕΒΚ/ΕΠ/2019/21

ΕΜΠΙΣΤΕΥΤΙΚΟ

ΑΠΟΦΑΣΗ
ΕΠΙΤΡΟΠΗΣ ΒΙΟΗΘΙΚΗΣ ΑΞΙΟΛΟΓΗΣΗΣ
ΓΙΑ
ΕΓΚΡΙΣΗ Ή ΑΠΟΡΡΙΨΗ
ΠΡΟΓΡΑΜΜΑΤΟΣ

Η απόφαση της Επιτροπής Βιοηθικής Αξιολόγησης (ΕΒΑ) θα πρέπει να κοινοποιηθεί προς την Εθνική Επιτροπή Βιοηθικής Κύπρου μαζί με όλα τα υπόλοιπα έντυπα που αφορούν το πρόγραμμα για το οποίο λήφθηκε σχετική απόφαση.

Συμπληρώνεται από την Επιτροπή Βιοηθικής Αξιολόγησης

Τίτλος Προγράμματος για το οποίο γίνεται η αίτηση
«Τα οφέλη της νευροφυσιολογίας στο χειρουργείο και το κλινικό περιβάλλον»
Επιστημονικός Υπεύθυνος του Προγράμματος
Κυρία Μέλανη Πογιατζή

Όνομα Επιτροπής Βιοηθικής Αξιολόγησης	
Επιτροπή Βιοηθικής Αξιολόγησης Βιοϊατρικής και Κλινικής Έρευνας Α΄	
Μέλη της Επιτροπής Βιοηθικής Αξιολόγησης	
Όνομα	Επίθετο
Αθηνά	Σοφοκλέους
Αναστασία	Κωνσταντινίδου
Βίκυ	Νικολαΐδου
Μαρία	Παντελίδου
Μάριος	Φυλακτίδης
Πολυξένη	Γεωργιάδου
Στέλιος	Στυλιανού
Χρίστος	Ανδρέου
Χρίστος	Πέτρου

Σχόλια από την Επιτροπή Βιοηθικής Αξιολόγησης με βάση τα οποία λήφθηκε η απόφαση για την αίτηση που υποβλήθηκε

Η Επιτροπή κατά τη σημερινή συνεδρίασή της ημερομηνίας 03/06/2019, πραγματοποίησε τη βιοηθική αξιολόγηση των πρόσθετων ή/και αναθεωρημένων εγγράφων που κατατέθηκαν στις 27/05/2019, σε συνέχεια απόφασης της Επιτροπής ημερομηνίας 06/05/2019.

Τα σχόλια της Επιτροπής κατά τη σημερινή συνεδρίαση παρουσιάζονται με έντονα μαύρα γράμματα.

Σχόλια για το έντυπο ΕΕΒΚ02:

1. Σελ. 6/21 Στο έντυπο ΕΕΒΚ02 αναφέρεται ότι στην μελέτη δεν θα συμμετέχουν ανήλικοι ενώ με την αίτηση επισυνάπτεται έντυπο ΕΕΒΚ03 για ανήλικους. Παρακαλούμε όπως διευκρινιστεί εάν στη μελέτη θα συμμετέχουν ανήλικοι και να γίνουν οι αναγκαίες διορθώσεις σε όλα τα έντυπα. *Σχόλιο 06/05/2019: Δεν απαντήθηκε. Εφόσον ενδέχεται να συμμετέχουν ανήλικοι, ακόμη και εάν η συμμετοχή τους είναι απίθανη, τα σχετικά πεδία στο έντυπο ΕΕΒΚ02 (πώς θα ληφθεί η συγκατάθεση και ποια είναι η ανάγκη συμμετοχής αυτών των ατόμων) πρέπει να συμπληρωθούν σωστά. Επίσης, οποιεσδήποτε*

αλλαγές γίνουν στο έντυπο ΕΕΒΚ03 για ενήλικες πρέπει να γίνουν και στο αντίστοιχο έντυπο για ανήλικους/ανήλικες. **Απαντήθηκε**

Σχόλια για το έντυπο ΕΕΒΚ03:

2. Σελ. 3/6 Οι πληροφορίες προς τους ασθενείς δεν είναι σαφείς και αναλυτικές. Δεν είναι κατανοητό τι θα κάνουν οι ερευνητές. Δεν είναι σαφές τι στοιχεία των ασθενών θα συλλέγονται. *Σχόλιο 06/05/2019: Δεν απαντήθηκε. Οι πληροφορίες προς τους ασθενείς να δοθούν σε πιο κατανοητή γλώσσα.* **Απαντήθηκε**

3. Σελ. 5/6 Στις συνθήκες τερματισμού αναφέρεται *'Μόλις χρειαστούν αρκετά δεδομένα για μια σωστή στατιστική ανάλυση, η έρευνα θα τερματιστεί.* Δεν είναι σαφές τι σημαίνει αρκετά δεδομένα. *Σχόλιο 06/05/2019: Δεν απαντήθηκε. Πρέπει να διασαφηνιστεί το μέγεθος του δείγματος ούτως ώστε να μην συμπεριληφθεί μεγαλύτερος αριθμός ασθενών από ό,τι χρειάζεται για σκοπούς εκπλήρωσης των στόχων της έρευνας.* **Απαντήθηκε**

Γενικά Σχόλια:

4. Η επιστημονική υπεύθυνος είναι υποψήφια διδάκτορας στο Πανεπιστήμιο της Βαρκελώνης. Παράκληση όπως κατατεθεί βεβαίωση φοίτησης από το Πανεπιστήμιο της Βαρκελώνης με στοιχεία και βιογραφικό του επιβλέποντα. Ο επιβλέπων θα πρέπει επίσης να συμπεριληφθεί και στο έντυπο ΕΕΒΚ 02, να επεξηγηθεί ο ρόλος του και να υπογράψει στα σχετικά πεδία. *Σχόλιο 06/05/2019: Απαντήθηκε μερικώς. Η υπογραφή του επιβλέποντα μπορεί να δοθεί σε ηλεκτρονική μορφή.* **Απαντήθηκε**

5. Χρειάζεται συγκατάθεση των συνεργαζόμενων Φορέων πχ Αρεταίειο Νοσοκομείο και Πανεπιστήμιο Βαρκελώνης. Ο Δρ Στυλιανού εργάζεται στο Mediterranean Hospital στη Λεμεσό. Στο Πρωτόκολλο αναφέρεται και το Πανεπιστήμιο Λευκωσίας. Ποιο μέλος της ομάδας ανήκει στο Πανεπιστήμιο Λευκωσίας; *Σχόλιο 06/05/2019: Απαντήθηκε μερικώς. Η Επιτροπή παρακαλεί όπως προσκομιστεί έγκριση από το Διοικητικό Συμβούλιο των νοσοκομείων που συμμετέχουν για τη διεξαγωγή της έρευνας από τα νοσοκομεία.* **Απαντήθηκε**

6. Δεν είναι σαφής ο αριθμός του δείγματος. Στο έντυπο ΕΕΒΚ02 απλώς αναφέρεται <200. *Σχόλιο 06/05/2019: Δεν απαντήθηκε. Πρέπει να διασαφηνιστεί το μέγεθος του δείγματος ούτως ώστε να μην συμπεριληφθεί μεγαλύτερος αριθμός ασθενών από ό,τι χρειάζεται για σκοπούς εκπλήρωσης των στόχων της έρευνας.* **Απαντήθηκε. Η Επιτροπή παρακαλεί όπως γίνει σαφής αναφορά στον αριθμό του δείγματος, το οποίο θα έχει στρατολογηθεί μέχρι τη συγκεκριμένη χρονολογική στιγμή.**

Συμπληρώνεται από την Επιτροπή Βιοηθικής Αξιολόγησης

Στοιχεία	ΝΑΙ	ΟΧΙ
Βιογραφικά Στοιχεία ΟΛΩΝ των ερευνητών και των συνεργατών τους	√	
Δήλωση μη συγκρουόμενων συμφερόντων	√	
Περιγραφή του είδους του Προγράμματος	√	
Περιγραφή του πληθυσμού που θα μελετηθεί	Σχόλια	
Ο τρόπος με τον οποίο θα στρατολογηθούν άτομα για το Πρόγραμμα	√	
Μελετήθηκαν προσεκτικά τα έντυπα συγκατάθεσης (ΕΕΒΚ03);	√	
Τα έντυπα που θα χρησιμοποιηθούν για την στρατολόγηση ατόμων		√
Ολόκληρο το πρωτόκολλο του Προγράμματος	√	
Δικαιολόγηση για την χρήση εικονικής φαρμακευτικής αγωγής	ΔΙ	
Υπεύθυνη δήλωση από όλους τους ερευνητές και συνεργάτες τους ότι τα έντυπα πληροφόρησης και συναίνεσης τους δεσμεύουν	√	
Διασφάλιση της προστασίας των δεδομένων που αφορούν τα άτομα που θα λάβουν μέρος στο Πρόγραμμα	√	
Λεπτομέρειες για την χρηματοδότηση του Προγράμματος	√	
Έχουν εκδοθεί ειδικά συμβόλαια σε σχέση με αμοιβές ;		√
Θα δίδονται αμοιβές στα άτομα που θα συμμετάσχουν στο Πρόγραμμα ;		√
Θα υπάρξουν οποιεσδήποτε οικονομικές επιβαρύνσεις για τα άτομα που θα συμμετάσχουν στο Πρόγραμμα ;		√
Οι ερευνητές ή/και συνεργάτες τους θα παίρνουν αμοιβές ;		√
Έχουν περιγραφεί τα αναμενόμενα οφέλη του Προγράμματος ;	√	
Έχει διαφανεί ότι προκύπτουν οποιαδήποτε οφέλη προς τον χρηματοδότη, τους ερευνητές και τους συνεργάτες τους από το Πρόγραμμα;		
Εάν πιο πάνω είναι ΝΑΙ, να εξηγηθεί: Δημοσιεύσεις	√	
Έχουν τεκμηριωθεί όλες οι διευθετήσεις που έγιναν σε σχέση με τις υπηρεσίες που τυχόν θα παρασχεθούν για το Πρόγραμμα ;	√	
Θα υπάρχει συνεχής ενημέρωση για την ασφάλεια των ατόμων που θα λαμβάνουν μέρος στο Πρόγραμμα ;	√	
Υπάρχουν διαδικασίες για την υποβολή παραπόνων/καταγγελιών;	√	
Διασφαλίζονται επαρκώς τα δικαιώματα των ερευνητών για τις δημοσιεύσεις των αποτελεσμάτων;	√	
Έχει δεσμευθεί ο/η Επιστημονικός Υπεύθυνος ότι δεν θα γίνουν οποιεσδήποτε αλλαγές στο Πρόγραμμα από την ημέρα που θα εγκριθεί από την Επιτροπή Βιοηθικής;	√	

***Αποτελεί ευθύνη της Επιτροπής Βιοηθικής Αξιολόγησης να σταθμίσει όλα τα στοιχεία που έχουν δοθεί, να δώσει την απαραίτητη βαρύτητα εκεί που χρειάζεται και να λάβει απόφαση ως προς το κατά πόσον έχουν δοθεί ικανοποιητικές επεξηγήσεις σε σχέση με το προτεινόμενο Πρόγραμμα.**

Δήλωση για «μη συγκρουόμενα συμφέροντα» από την Επιτροπή Βιοηθικής Αξιολόγησης		
Εμείς τα μέλη της Επιτροπής Βιοηθικής Αξιολόγησης που λάβαμε μέρος στις συνεδρίες σε σχέση με την παρούσα αίτηση, υπογράφοντας πιο κάτω δηλώνουμε υπεύθυνα ότι δεν έχουμε οποιαδήποτε άμεσα ή έμμεσα συγκρουόμενα συμφέροντα σε σχέση με το Πρόγραμμα που μελετήσαμε και εκδώσαμε σχετική απόφαση.		
Ονοματεπώνυμο	Υπογραφή	Ημερομηνία
κα Αθηνά Σοφοκλέους		03/06/2019
Δρ Αναστασία Κωνσταντινίδου	**ΑΠΟΥΣΑ**	03/06/2019
Δρ Βίκυ Νικολαΐδου		03/06/2019
Δρ Μαρία Παντελίδου		03/06/2019
Δρ Μάριος Φυλακτίδης		03/06/2019
Δρ Πολυξένη Γεωργιάδου		03/06/2019
Δρ Στέλιος Στυλιανού		03/06/2019
Δρ Χρίστος Ανδρέου		03/06/2019
Δρ Χρίστος Πέτρου		03/06/2019

Τίτλος Προγράμματος
«Τα οφέλη της νευροφυσιολογίας στο χειρουργείο και το κλινικό περιβάλλον»
Αριθμός Πρωτοκόλλου Εθνικής Επιτροπής Βιοηθικής Κύπρου
ΕΕΒΚ/ΕΠ 2019/21
Απόφαση της Επιτροπής Βιοηθικής Αξιολόγησης (Εγκρίνεται ή Ζητούνται επιπρόσθετα στοιχεία ή Απορρίπτεται)
Εγκρίνεται 1. Νοείται ότι την νομική ευθύνη της επιστημονικής εγκυρότητας, αναγκαιότητας, πληρότητας και της συνολικής επιστημονικής αξίας της προτεινομένης έρευνας έχουν οι επιστημονικοί υπεύθυνοι της έρευνας και ο Φορέας του επιστημονικού υπεύθυνου. Όλοι οι πιο πάνω έχουν επίσης την νομική ευθύνη της διεξαγωγής της έρευνας με τη δέουσα επιστημονική επιμέλεια και φροντίδα. 2.Από 01/08/2012 η Εθνική Επιτροπή Βιοηθικής Κύπρου διενεργεί δειγματοληπτικό έλεγχο σε ερευνητικές προτάσεις που λαμβάνουν έγκριση. Περισσότερες λεπτομέρειες είναι διαθέσιμες στην ιστοσελίδα της Επιτροπής σε σχετική ανακοίνωση. 3.Το παρόν έντυπο απόφασης κοινοποιείται και στον χρηματοδότη της ερευνητικής πρότασης. 4. Οι ερευνητές υποχρεούνται να υποβάλλουν προς την Επιτροπή ανά εξάμηνο από σήμερα έκθεση για την εξέλιξη της έρευνας μέσα του εντύπου ΕΕΒΚ05. 5. Με το πέρας της έρευνας, οι ερευνητές υποχρεούνται όπως υποβάλουν στην Επιτροπή αναφορά μέσω του Εντύπου ΕΕΒΚ06. 6. Τονίζεται στους ερευνητές η υποχρέωσή τους να τηρούν τις εκάστοτε υποχρεώσεις τους με βάση την κείμενη νομοθεσία και κανονισμούς και ιδιαιτέρως η υποχρέωσή τους να ενημερώνουν άμεσα την Επιτροπή για οποιοδήποτε έκτακτο συμβάν ή οποιαδήποτε τροποποίηση στην πρόταση ως εγκρίθηκε, με την υποβολή των προνοουμένων εντύπων.
Μέλη που ήταν παρόντα στη λήψη απόφασης/Αποτέλεσμα Ψηφοφορίας
Ως αναφέρεται στη σελίδα 5 ανωτέρω και η απόφαση ήταν ομόφωνη.
Ημερομηνία έκδοσης απόφασης ΕΒΑ: Ημέρα: .....03..... Μήνας: .....Ιουνίου..... Έτος: .....2019.....

Υπογράφει ο Πρόεδρος και ο Αντιπρόεδρος της Επιτροπής Βιοηθικής Αξιολόγησης

Αξίωμα	Όνομα	Επίθετο	Υπογραφή
Πρόεδρος	Χρίστος	Πέτρου	
Αντιπρόεδρος	Μαρία	Παντελίδου	

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