

REVIEW ARTICLE

Chronic Nerve Root Entrapment: Compression and Degeneration.

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Abstract. Electrode mounts are being developed to improve electrical stimulation and recording. Some are tight-fitting, or even re-shape the nervous structure they interact with, for a more selective, fascicular, access. If these are to be successfully used chronically with human nerve roots, we need to know more about the possible damage caused by the long-term entrapment and possible compression of the roots following electrode implantation. As there are, to date, no such data published, this paper presents a review of the relevant literature on alternative causes of nerve root compression, and a discussion of the degeneration mechanisms observed.

A chronic compression below 40 mmHg would not compromise the functionality of the root as far as electrical stimulation and recording applications are concerned. Additionally, any temporary increase in pressure, due for example to post-operative swelling, should be limited to 20 mmHg below the patient's mean arterial pressure, with a maximum of 100 mmHg. Connective tissue growth may cause a slower, but sustained, pressure increase. Therefore, mounts large enough to accommodate the root initially without compressing it, or compliant, elastic, mounts, that may stretch to free a larger cross sectional area in the weeks after implantation, are recommended.

Keywords: Nerve root compression, electrical stimulation, long-term electrode implantation.

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1. Introduction

For over 30 years, various types of electrodes have been implanted in humans for the electrical stimulation of nervous structures. Applications such as phrenic nerve pacing and foot drop correction require the long term implantation of electrodes near or around peripheral nerves. Equally, nerve roots have long been targeted in electrical stimulation applications (Brindley 1994, Rushton et al. 1998, Donaldson et al. 1997). Compared with peripheral nerves, the roots offer the advantage of being available in a single surgical site in the spinal canal, especially at the level of the cauda equina (Rushton 1990). Their proximity to the spine is also exploited for indirect spinal cord stimulation (Minassian et al. 2004).

For any stimulating or recording implant to work successfully, it is, obviously, essential that the nerves and nerve roots at and below the implantation site remain intact. Great care must therefore be taken to design nerve-electrode interfaces that do not threaten the integrity of the structure they interact with. The implantation technique must minimise handling and the electrodes in their mount must be chronically safe, mechanically and biologically. Yet, advances in the fields of electrical stimulation and chronic nervous system monitoring move towards an ever closer contact between the nervous structure and the electrodes. There is indeed a push for a more fascicular approach that will put more strain on the nerves as they are physically split into their constitutive strands. While the effect of these tighter fitting mounts on peripheral nerves viability are being addressed (Navarro et al. 2005), no similar research is taking place for nerve roots. There is a lack of understanding of the consequences of long-term nerve root entrapment, especially with regards to the maximum compression level above which permanent damage may occur.

This paper presents a review of the literature on nerve root compression undertaken to study the consequences of disc herniation and acute compression during surgery. The findings are analysed, focusing on the degeneration mechanisms and consequences for the roots excitability. A final discussion attempts to establish the maximum pressure level a spinal nerve root can chronically sustain. This notion of a safe pressure level will have a direct impact on the design of electrode mounts for electrical stimulation and recordings from spinal nerve roots.

2. Safety of electrode mounts for nerve root stimulation

Intrathecal nerve root stimulation has so far always been achieved by means of hook electrodes (Brindley 1972). Other shapes of mounts have been proposed, but the hook remains the preferred option as: *(i)* it minimises the root handling as they are softly laid in a slot which intrinsically remains open hence limiting the risks of squeezing and stretching; *(ii)* it optimises the use of space in one direction by butting several slots next to one another and *(iii)* it was especially designed to lie harmlessly in the spinal canal amongst the roots of the cauda equina: it has no sharp edges and corners and the

cables originate below the roots for clearance.

All materials used have been shown to be suitable for chronic use in human (Black 1999, Helsen & Breme 1998, Yoda 1998). Implantation and biochemical risks are thus controlled. Movements of the mount after implantation may damage the structures by pulling and stretching them. With peripheral nerves, this is often blamed on unexpected limb movements or excessive cable tension. With the spinal placement of the book electrode, limb movements are not an issue. Nor is cable tension since the distance to the stimulator, most often implanted in the lower abdomen, just below the ribs, varies very little with the patient's position. If the cables are slightly loose at implantation, the risks due to cable tension can be disregarded (Brindley 1981). Note that this does not hold true for animal studies. Rats, for example, can bend and curve their backs in ways that may cause considerable movements of any electrode mount in the spinal canal.

Therefore, having excluded all other likely causes of damage, root compression must now be studied to establish the viability of human nerve roots trapped in a book electrode.

2.1. Nerve root damage associated with the presence of electrode mounts

Intrathecal book electrode have been chronically implanted in humans since the 1980s with the first Brindley sacral anterior root stimulators (Brindley et al. 1982). In these early years, occasional damage, as assessed by an alteration of the motor response to stimulation, was reported, and attributed to the surgical manipulation. Implant infection or movement of the book could then cause further root degradation. All causes were reduced or eliminated thanks to an improved book design, critically insuring that the slots were always much wider than the roots they trapped, and better implantation technique.

Depending on the nature, level and extend of their injuries, human nerve roots, especially anterior roots, may regenerate, like peripheral nerves (Gonzalez-Darder 1993, Ramon y Cajal 1991 translation, McCouch 1955). Although while they may regrow, they may fail to re-establish functional connections (Carlstedt et al. 1995). Effective regeneration in baboon was demonstrated in Brindley (1977). The anterior root (L7) of an implanted baboon was electrically destroyed, stimulation test after the destruction confirmed the absence of motor response. One year later the stimulation threshold had returned to its level prior to destruction, as assessed by the muscle response, confirming the possibility of functional anterior nerve root regeneration. As far as human nerve roots are concerned, two early patients implanted with a sacral anterior root stimulator exhibited both somatic and parasympathetic fibres recovery within 8 to 12 months post-implantation (Brindley et al. 1982). Likewise, in the first 50 patients reviewed in Brindley et al. (1986), 23 suffered some skeletal muscle weakness soon after implantation, but all showed recovery within a year, which was complete for most of them.

None of the reported damage was attributed to compression or long-term entrapment and there are no reports of such occurrences (Brindley 1990). Indeed Brindley &

Rushton (1990) have reported that human anterior nerve roots, trapped for 3.5 to 5 years as part of implants used regularly, appeared histologically normal.

3. Animal studies

3.1. Relevance for human nerve root compression

There are no data available on the pressure exerted on human roots when they are trapped in an electrode mount, whether implanted intra or extrathecally. There is however a large body of work on nerve root compression linked to back pain or muscle weakness following disc herniation with acute extrathecal compression of cauda equina and individual nerve roots. Inferring a safe pressure limit for the chronic implantation of any electrode mount from these animal studies, as done in this paper, is indeed limited by the primary focus of the investigations. Peripheral nerves, roots and spinal cord all react differently to constriction (Gelfan & Tarlov 1956, Fern & Harrison 1994, Rydevik et al. 1991, Garfin et al. 1995). What we may learn from any publication depends on answers to the following three questions: (i) How does the animal model compare with human nerve roots? (ii) How was the pressure applied? and (iii) What would be the influence of a spinal cord injury on the results?

(i) The most common animals in spinal cord and nerve root compression studies are the pig (Cornefjord et al. 1997, Olmarker et al. 1991) and the dog (Konno, Yabuki, Sato, Olmarker & Kikuchi 1995) due to the anatomical, morphological and vascular similarities of their spinal canal with the human sacrolumbar cord. In the dog, at the level of the 7th lumbar vertebrae, there are 8 to 12 pairs of roots in the cauda equina, and 2 to 3 pairs of individual, extrathecal, roots. The ratios of myelinated to non-myelinated axons are similar, as are the pia, arachnoid and dura. Rats, rabbits and cats are used less frequently (DeLeo & Winkelstein 2002, Winkelstein 2011).

(ii) There are different ways to apply pressure to the nervous structure. Most often the spinal cord and roots are exposed by a laminectomy of the lower lumbar, sacral or upper coccygeal vertebrae and the dura is left untouched. One or two inflatable balloons are then fixed to the spine and inflated to compress the underlying nerve roots and spinal cord to a known pressure. While this defines the pressure accurately (Konno, Yabuki, Sato, Olmarker & Kikuchi 1995, Olmarker et al. 1991), it also introduces some limitations (Pedowitz et al. 1992, Konno, Olmarker, Byrod, Rydevik & Kikuchi 1995, Olmarker 1991). Due to the nature of the operation, the measurements are usually acute, lasting up to 4 hours. A slightly different method has been used for week long experiments (Kikuchi et al. 1996, Takahashi et al. 2003). A simple nylon binder has also been used to constrict the spinal cord or individual nerve roots (Delamarter et al. 1990) while in their chronic work, Olmarker and co-workers use a special constrictor that shrinks slowly after implantation to increase the compression gradually. The balloon method only imposes a unidirectional pressure, but the level can be set and monitored accurately. The constrictors do not provide a mean of pressure

monitoring, but they allow for longer term experiments with shorter compression zones. The pressure is applied radially, evenly distributed around the nerve, root or cord.

(iii) Nerve roots do not change after spinal cord injury (Schalow et al. 1995) but there may be some alteration in the overall blood pressure which could affect the nutritional supply. The consequences of compression can therefore be studied on spinally intact animal models provided that blood pressure is known.

3.2. Blood pressure

To give some perspective, the compression data can be compared with normal blood pressure. In a healthy young adult, 20-30 years old, the mean arterial pressure (MAP) lies between 100 and 120 mmHg. It increases with age. It is similar in dogs (Mandel et al. 1954) and large pigs (Olmarker, Rydevik, Holm & Bagge 1989) but lower, down to 90 mmHg and 50 mmHg, in mini and micropigs commonly used in other scientific research areas (Smith et al. 1990). Venular pressure is also relevant as it affects nutritional support and oedema formation. While the arterial pressure changes in a cyclic manner as the heart beats, the venous pressure is not so predictable. It depends on the height, weight, muscular bulk and sex of the patient; it will vary with posture, level of activity, and the vein in which the pressure is measured. The closer the vein is to the heart, the lower the pressure. The average venous pressure, measured from veins on the top of the foot, of healthy human subjects was between 90 and 100 mmHg, with a variation of ± 65 mmHg during 1 minute of treadmill walking (Kugler et al. 2001). The pressure measured on the nerve roots of patients in prone position, suffering from lumbar disc herniation in Takahashi et al. (1999) ranged from 7 mmHg to 256 mmHg (mean \pm SD is 53 ± 49 mmHg).

The effect of the MAP on neurological deficit during root compression was assessed in Garfin et al. (1990) and Lind et al. (1993). Compression experiments performed on hypotensive and hypertensive pigs showed a correlation between the onset of electrophysiological changes and the arterial pressure. In pigs submitted to double-level compression by placing two extrathecal balloons over the cauda equina inflated to a known pressure, the blood flow dropped by 64 % for a 10 mmHg pressure, while total ischaemia occurred at 10 to 20 mm Hg below the MAP (Olmarker, Rydevik, Holm & Bagge 1989, Olmarker 1991, Takahashi et al. 1993). The extradural pressure required to interrupt arteriolar blood flow was close to the MAP in rabbit caudae equinae (Rydevik et al. 1981). Comparatively, the average pressure, for the presence of mild functional changes, measured in humans suffering from carpal tunnel syndrome is 31 mmHg (Gelberman et al. 1981).

4. The mechanisms of compression injury

While it is established that compression, chronic or acute, of a spinal root above a certain level is harmful, the mechanisms underlying nerve root damage are not

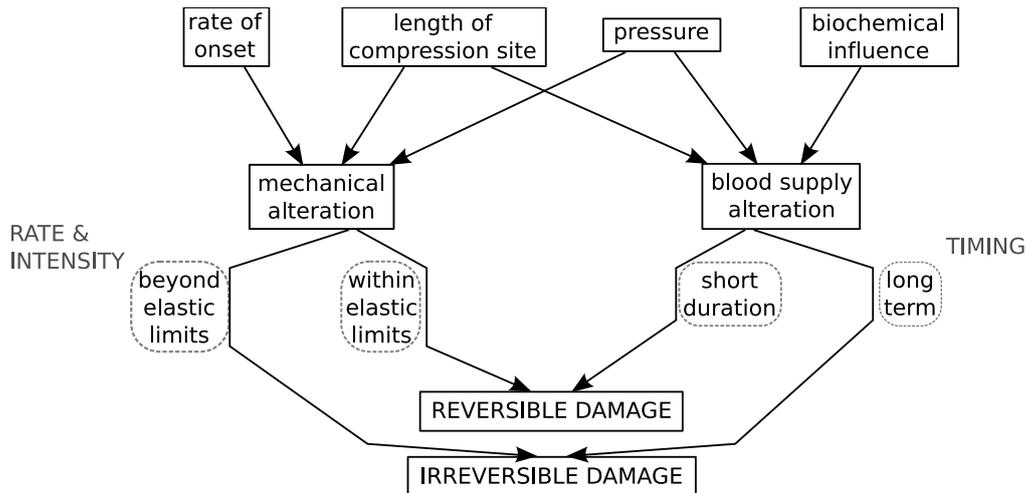


Figure 1. Summary of the various factors influencing nerve root function.

always clearly recognised (Garfin et al. 1991). As summarised in figure 1, the rate of onset of compression, the extent of the compressed area, the pressure amplitude and duration all influence the consequences of entrapment (Battista & Alban 1983, Olmarker, Rydevik & Holm 1989, Olmarker, Rydevik, Hansson & Holm 1990, Olmarker, Holm & Rydevik 1990). Compression introduces both a mechanical deformation and an alteration of the nutritional support of the root. The consequences are hypoxia or anoxia, endoneurial oedema, increased endoneurial fluid pressure, depolarisation and disruption of the physical integrity of the axons and supportive cells. These may lead to cell death, demyelination and degeneration (axotomy). In the following pages different factors leading to compression injury are analysed in an attempt to understand their individual contribution and interaction. A table overview of the papers reviewed, with animal model, pressure exerted and timing of compression and recovery is available as an appendix.

4.1. Morphology

Structurally, a peripheral nerve is surrounded by a thick sheath, the epineurium, and each fascicle is itself surrounded by its own protective perineurium, while the fibres are surrounded by the endoneurium. These sheaths provide valuable mechanical strength to the nerve ‡. The spine also is surrounded by several meninges: the dura, the arachnoid and the pia. The dura offers some degree of protection and may, in this role, be likened to the epineurium (Abbott et al. 1997). Inside the dura, the roots and rootlets are freely moving in cerebro-spinal fluid, simply surrounded by the thin pia, without any other protection (Olmarker 1991). In mice, the peripheral nerves and roots show a similar

‡ Rydevik inflated a fascicle to a pressure of about 1000 mmHg before bursting the perineurium. Although this is not a measure of rigidity, or resistance to external pressure, it gives some sense of the perineurium's mechanical strength (Rydevik et al. 1989).

elasticity §, but the nerves are 10 times stronger longitudinally || and 5 times stiffer ¶, hence less likely to deform under radial pressure (Beel et al. 1986).

4.2. Nutritional support

In a peripheral nerve, small blood vessels can be found in the endoneurium, with anastomoses to larger arterioles and venules running along the perineurium and epineurium. The nutritional support of the roots is more complex with contributions from both the cerebro-spinal fluid (CSF) and blood vessels (Garfin et al. 1991, Garfin et al. 1995, Parke et al. 1981, Parke & Watanabe 1985, Parke et al. 1999). According to Parke & Watanabe (1985), the nutrient contribution of CSF in human lumbar roots can be as high as 60 %. The arteries running in a root and feeding it receive blood from larger support arteries both proximally and distally; but have no connection with the extrinsic vessels running along the root (Olmarker 1991, Rydevik et al. 1990, Parke & Watanabe 1985, Parke et al. 1999). There is therefore a supply of blood to the nerve root from both ends, but no additional interconnections radially along it. This could make it more susceptible to an interruption of the vascular network (Mao et al. 1998, Matsui et al. 1997, Matsui et al. 1992). On the other hand, the occurrence of neo-vascularisation can help the root adapt to alterations of its vascular network (Cornefjord et al. 1997, Rydevik et al. 1989). CSF also contribute to a root's nutrition. In Sekiguchi et al. (2009), equal crush injuries applied either sides of the dorsal root ganglion showed a different rate of recovery and pain level, with better outcomes for the compression proximal to the DRG, in the cauda equina, in the presence of CSF. This supports the suggestion that the CSF nutritional support plays a major role in preventing or mitigating damage due to localised compression.

With intrathecal implantation, the portion of nerve root in the electrode mount might receive less nutrition from the CSF. This will make it more susceptible to compression at pressures sufficient to affect the blood vessels.

4.3. Damages of vascular origin

Compromised blood flow may cause oedema and anoxia. The pressure required to interrupt the arterial flow is directly related to the mean arterial blood pressure (Takahashi et al. 1993, Olmarker et al. 1991, Rydevik et al. 1981)⁺. A milder compression might result in increased endoneurial fluid pressure and oedema formation which decreases the excitability of the nervous tissue but may recede before the occurrence of anoxia and cell death (Matsui et al. 1992). Venular occlusion occurs

§ The elasticity was estimated as the ratio of the change in length over the un-stretched length of the structure (peripheral nerve or root) undergoing the longitudinal stretch test.

|| The strength was estimated by the ratio, just before the onset of non-linear behaviour, of the force exerted on the nervous structure to its cross-sectional area.

¶ The stiffness is estimated by the apparent Young's modulus.

⁺ Provided the onset of pressure is slow to avoid structural destruction

at lower pressures and may result in a localised interruption of the capillary flow. Yet as the venous network has more anastomoses with outward vessels, it is unlikely to be completely obstructed by local compression (Garfin et al. 1995, Matsui et al. 1992). Alteration of the venular system may lead to a slight decrease in CAP amplitude without signs of sensory or motor deficit (Delamarter et al. 1990). At the lowest pressure level this was followed by recovery within one to three months, with the compression maintained throughout, indicating that the micro-circulation was preserved despite the occlusion. The vascular network can also adapt to localised compression by neo-vascularisation, as seen by the improvements in blood flow speed recorded in dogs after two weeks or one month of low pressure when compared to one week (Otani et al. 2001). This is explained by the presence of both a distal and a proximal supply to the root. Neo-vascularisation has been shown to proceed from the non occluded end to compensate for the disturbance of the other vessels but no clear time-scale can be inferred from the literature, where the range is from 1 day to 2 months, as this process competes with others.

If anoxia does occur, the large myelinated axons will degenerate first (Gelfan & Tarlov 1956, Fern & Harrison 1991, Dahlin et al. 1989). This early degeneration of larger fibres is also observed in peripheral nerves (Struijk et al. 1999, Jellema & Teepen 1995). Small, non-myelinated fibres in the frog sciatic nerve have been described in Fern & Harrison (1991) as having a “disproportionately high resistance to ischaemia”. The situation, when anoxia results from compression, is however more complex as the blood supply to fascicles made principally of smaller fibres may be interrupted at lower compression levels. Fern & Harrison (1994) showed, on cat sciatic nerves, that at a low pressure level (70 mmHg), conduction was first interrupted in slower fibres, after 56 minutes, while at 250 mmHg, faster fibres failed first, after only 35 minutes. They compared their results to conduction failure following ischaemia to conclude that conduction failure in the 70 mmHg situation is most likely due to the blood supply being first interrupted in smaller fascicles, containing mainly non-myelinated fibres. Conduction failure at 250 mmHg was mainly attributed to mechanical deformation.

4.4. Damage of structural origin

Nerve roots (in human and animal models) are somewhat viscoelastic (Ommaya 1968, Singh et al. 2005) and may adapt to mechanical deformation provided the compression is applied slowly with respect to the remodelling rate, 15-20 s in Pedowitz et al. (1992), and remains below a deformation limit above which direct mechanical destruction takes place (Hubbard et al. 2008). When applying rather large pressures, 1500 to 9000 mmHg, to exposed rat’s cervical dorsal roots, Nicholson et al. (2012) established that at these levels, there exist a critical time, estimated to be around 6 minutes, above which the compression will lead to the development of persistent pain as assessed after 7 days of recovery. This critical period is independent of the applied pressure provided it exceeds a “structural integrity limit”. Until this limit is reached there are few alterations to

the nerve root integrity and those are mainly transient, in analogy with elastic and plastic deformation. The structural pressure limit for extrathecal roots and cauda equina appears to be above 200 mmHg in pig and dog models and is likely to be rather high in humans too. Rydevik states that the cauda equina and extrathecal nerve roots can sustain a pressure of 75 mmHg without significant reduction of the amplitude of the nervous signal, and no alteration of the root structure (Rydevik et al. 1991). Comparatively, the same author considers the long term viability of a peripheral nerve to be at risk from 60 mmHg (Rydevik et al. 1989).

Faster onset rate or higher pressures will damage the nervous cells, causing demyelination and degeneration before anoxia becomes critical. This explains why damage may be observed for short compression sites ($\approx 5mm$), where neo-vascularisation can compensate for occluded blood vessels with slow compression (Gelfan & Tarlov 1956). If the compression is applied radially along a preferential axis, the nerve or root will flatten and the cross-section becomes more ellipsoidal. As the perimeter increases, the outer layers will stretch and suffer most damage. If, on the other hand, the nerve is wrapped within a constricting cuff, the compressed tissue stretches lengthwise as it is squeezed out of the cuff to adapt to the confinement; and the displacement, as well as the pressure gradient, is maximum at the edges of the constrictor (Macgregor et al. 1975). The shear stress may then cause acute structural damage to the nerve fibres and blood vessels (Rydevik et al. 1989), although the effect depends on the onset rate. In Olmarker, Rydevik, Holm & Bagge (1989), the pressure was slowly increased up to 200 mmHg on extradural roots and cauda equina, without any permanent damage to the vascular system, as seen by the instantaneous return of blood flow without oedema formation upon pressure release. Preserving the integrity of the micro-vascularisation has long been seen as a key to prevent functional deficit (Fairholm & Turnbull 1971). Because of their radius of curvature, the larger fibres are compressed to a higher level, hence failing at a lower overall applied pressure than the smaller ones. At extradural pressures of 100 to 150 mmHg, the motor fibres of the spinal cord and roots in dogs were shown to be less resistant than the sensory fibres (Gelfan & Tarlov 1956). For nerve roots, $\geq \frac{2}{3}$ of all fibres in the anterior root are myelinated while the ratio is reversed in the posterior root (Carpenter 1996, Mathers 1985). This suggests that the earlier compression failure of motor fibres may be due to the presence of myelin.

4.5. Length of compression site

The length of the compression site has various influences. A short constriction will lower the pressure limit for structural damage. Surrounding the root with a silicone rubber mount, even without compressing it, limits the interaction with the CSF locally, around the entrapped area. This effect will be worse for longer mounts. Further, neo-vascularisation does not return blood flow through the compressed area, it merely reaches its periphery and is therefore more likely to prevent damage for shorter compression zones. During double-level compression, the section of root between the

two compression sites is affected by similar, albeit less severe, symptoms than the area directly under pressure. Even at a level (200 mmHg) well above that sufficient to interrupt the blood flow in the free area between the two compression sites, recovery is complete if the compression only lasts 10 minutes. If it lasts 2 hours, the blood flow returns to 80 % of its initial value within 10 minutes (Takahashi et al. 1993). This highlights the importance of CSF in providing some nutritional supply to the root and preventing permanent damage. While the roots under pressure no longer receive nutrition from their blood vessels, the CSF is probably still able to percolate through the compressed area to reach the intermediate zone.

4.6. Biochemical influence

Cornefjord et al. (1996) also studied the biochemical effect of nucleus pulposus, applied for seven days around the sacral root (S1) of a pig. The reduction in conduction velocity is comparable to that caused by mechanical compression as seen when constricting the root distal to the dorsal root ganglion (DRG). This reduction, when caused by nucleus pulposus exposure was attributed to a chemical disruption of the blood supply* as there was little axonal damage. The biochemical and mechanical effects did not add, when the causes were combined by trapping some nucleus pulposus on the root under a constrictor: the conduction velocity did not decrease as much as could have been expected by adding the absolute reductions observed when applying the causes separately. In Abbed & Coumans (2007), pain was related to both pressure and an inflammatory response. Takahashi et al. (2003) showed that both irritation by nucleus pulposus and compression could lead to neurological deficit and pain. This highlights the fact that different mechanisms contribute to the integrity of a nerve root, and that alteration of any one of them is enough to cause noticeable disruption. However, in the context of electrical stimulation and mount placement, only the compression should be considered.

4.7. Regeneration and the influence of time

At 10 mmHg with double site compression, Mao et al. (1998) showed a slowing of the nerve root conduction velocity after one week of compression, followed by some recovery as the pressure was maintained for a month. Complete recovery might have occurred had the experiment lasted longer. Delamarter et al. (1990) studied, in dogs, the long term effects (3 months) of cauda equina compression using a nylon cable-binder to constrict the spinal canal to 25, 50 or 75 % of its original cross-sectional area. In the latter case, recovery of motor and sensory functions took place during up to 2 months after the constriction had been removed. Mackinnon et al. (1984), working on rat sciatic nerves, showed that alterations could take up to four months to become noticeable while regeneration was already observed after three months.

* The proposed mechanism of action of the nucleus pulposus is a disturbance of the nutritional blood supply causing ischaemia.

In cases when the root is only compressed for a limited time, recovery after pressure release is important. Four hours of compression do not affect the CAP amplitude significantly more than two, indicating that the reduction of the nervous signal amplitude may be exponential. However, the longer compression period alters the recovery, which is slower and starts later (Garfin et al. 1995, Pedowitz et al. 1992). This might be due to the presence of an intraneural oedema whose importance was correlated to the duration of compression in Olmarker (1991).

4.8. Post operative swelling and connective tissue growth

Cornefjord et al. (1997) placed an aneroid constrictor around pigs spinal nerve roots caudal to the dorsal root ganglion for up to 4 weeks. Its inner diameter was 3.5 mm and it gradually narrowed to 3 mm after 3 weeks. The nerve root diameter was less than 3 mm and the compression was due to post operative swelling and scar tissue growth. The conduction velocity of motor fibres decreased during the first week, then remained constant. Upon histological examination, nerve fibre damage was seen under the constrictor, distal and proximal to it. Endoneural damage was reported mainly on the compressed side while epineural damage was present on both the compressed and the contralateral control root that had been exposed in a similar procedure, but had no constrictor. This may indicate mechanical irritation due to the implantation operation. Post-operative swelling increases the pressure on the trapped root. It may not cause ischaemia as long as the maximum pressure does not exceeds 200 mmHg. Complete recovery is still possible with 2 hours compression followed by 90 minutes or less for recovery (Garfin et al. 1995). A post-operative oedema may also form as a reaction to the implantation procedure. This might cause a root, whose cross-sectional area was originally smaller than that of its electrode mount, to swell and become compressed. However, the oedema will eventually disappear, provided the vascular flow has not been interrupted, and the pressure will decrease consequently. There may therefore only be a transient decrease in conduction velocity. If resorption of the swelling happens at a rate comparable to that of connective tissue growth, the volume freed by one process is taken up by the other and the pressure decreases only slowly if at all. The growth of connective tissue has been shown to cause an added pressure increase responsible for nerve fibre damage and a slowing down of the conduction velocity after a month of entrapment (Cornefjord et al. 1997). Although these results relate to extradural compression, a similar process probably takes place within the slots of a book electrode. The excitability of anterior nerve roots has been seen to decrease in the days after the implantation of a Finetech-Brindley stimulator ‡. After this initial increase, the excitation threshold stabilises and sometimes increases slightly for a few month to a year post operation. This recovery is attributed to swelling resorption. It is slow and incomplete since connective tissue growth maintains a raised pressure. Partial

‡ The stimulator produced by Finetech Medical Ltd is the only commercial device using book electrodes for chronic intra-dural nerve root stimulation

degeneration may therefore occur, followed by regeneration. If the oedema recedes soon after the implantation, the excess pressure due to post-operative swelling and connective tissue growth may not lead to cell death, as seen in the histological sections presented in Brindley & Rushton (1990) which appear normal, with neither signs of degeneration nor any newly-grown axons.

5. Discussion

It is regularly observed that the roots can tolerate a certain level of disturbance. For example, for a pressure applied on extrathecal nerve roots of up to 50 mmHg, the short term histological changes have no apparent consequences on the amplitude of the nervous signal (Baker et al. 1995, Garfin et al. 1995, Kikuchi et al. 1996, Mao et al. 1998, Matsui et al. 1992, Olmarker, Rydevik & Holm 1989, Olmarker, Rydevik, Holm & Bagge 1989, Pedowitz et al. 1992, Rydevik et al. 1991).

Which are, therefore, the consequences of nerve root compression that are considered harmful for potential root stimulator patients? Without an answer to that question, no safe pressure limit can be inferred from the literature.

Some reduction in conduction velocity can be tolerated for motor roots. If recording from sensory fibres is envisaged, a decrease in afferent CAP amplitude should be avoided, although afferent fibres are more resistant to pressure.

Anterior nerve roots may regenerate, provided they have the room for it, which may not be the case if the compression is maintained. Degeneration should therefore be avoided. To avoid anoxia, the pressure exerted on the root should be lower than the mean arterial blood pressure of the patient. Oedema formation should be limited as it disturbs the blood flow and may induce ischaemia. Consequently, the pressure exerted on intradural nerve roots just after the implantation should be below 40 mmHg to avoid venular stasis. This will help limit oedema formation during the first days after the operation.

In the longer-term, swelling and connective tissue growth may cause a slow rise of pressure, which, based on table A1, should at all time remain below 100 mmHg to guarantee a sufficient arterial blood flow and be lower for patients with low MAP.

With the current state of the knowledge, it is difficult to quantify how much a root will swell, and how thick a layer of connective tissue will form around it. Predicting, during surgery, how much the root will become compressed chronically is therefore unlikely. Hence, very large mounts are used, leaving ample volume for swelling and connective tissue growth. As the root is free to move inside the mount, its contact with the electrodes is therefore inconsistent, which may severely affect the performances of the device. This discussion does however open an alternative option: to use mounts that actively adapt to the root's swelling. These offer a compromise between the need for a closer and more consistent contact between the electrodes and the root, and the latter's preservation by ensuring a limited compression level, through the inherent reshaping of the mount in situ at low applied pressure.

6. Conclusion

Considering the success of Finetech-Brindley implantations (Vignes et al. 2007), especially the absence of signs of degeneration, the large dimensions of the slot used with this device must be sufficient to accommodate both swelling and connective tissue growth. Any mount offering a similar cross-section would therefore be unlikely to cause entrapment damage of the root, hence be safe for chronic intradural implantation. However, what of the safety of tighter fitting mounts? The following answer is only tentative as it is based on a review of the literature, where data were essentially obtained from short to medium term extrathecal compression of dog and pigs nerve roots. However, the following values should be good candidates for further research. Therefore, the chronic compression level should be lower than 40 mmHg even for the largest roots. Additionally, post-operative swelling and connective tissue growth may cause temporary rises in the compression level. This should be limited to 20 mmHg below the patient MAP, with a maximum of 100 mmHg. This may require a compliant, elastic mount, or one that may stretch to free a larger cross sectional area in the first weeks after implantation.

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Appendix A. Literature review

Table A1 summarizes the different pressure levels applied to the cauda equina by various researchers, along with the consequences on the nerve root conduction and its nutritional support. This review is limited to mild to moderate compression, with 200 mmHg as the largest pressure considered. Except for data from Sharpless (1975), the roots were not exposed and the compression was applied to the spine or cauda equina as a whole. Several studies, looking into the causes of persistent pain after traumatic nerve root damage (whiplash injury), have applied considerably higher pressures (500 to 9000 mmHg) to individual roots for short periods (3 to 15 minutes) (Nicholson et al. 2012, Hubbard et al. 2008). These are not included in table A1 as electrode mounts are unlikely to cause such elevated pressures.

5 to 10	dog dog dog dog dog pig	1 week - none 1 week - none 1 month - none 1 week - none 1 month - none 120 min - 90 min	lumbar lumbar lumbar lumbosacral ^b lumbosacral ^b sacral ^b	Reduction in nerve conduction velocity Reduction in blood flow speed No difference in conduction velocity Reduction in root conduction velocity Lesser reduction in root conduction velocity Significant changes in the venous blood flow of the lumbosacral nerve root	Kikuchi et al. (1996) Otani et al. (2001) Otani et al. (1997) Mao et al. (1998) Mao et al. (1998) Matsui et al. (1992)
	pig	45 min - 30 min	sacral ^b	7.5 mmHg: no effect on blood flow 11.5 mmHg: 70% decrease within 15 minutes, recovery to 10% below normal	Baker et al. (1995)
30-40	pig	120 min - none	L4 to L7 exposed ^c	Blood flow interrupted in venules (30 mmHg) and capillaries (40 mmHg) Decrease in CAP amplitude	Olmarker (1991) Sharpless (1975)

^a whole cauda equina compression unless otherwise specified.

^b Double site compression.

^c Dura dissected for intrathecal compression, possible damage to blood supply.

? Paper not read, reference from abstract.

	pig	120 min - 90 min	sacrococcygeal	velocity, no histological changes No significant changes in efferent EMG or afferent CAP amplitude nor conduction velocity, no histological changes	Pedowitz et al. (1992)
	dog	120 min - 90 min	lumbosacral	No reduction in conduction velocity ^d	Otani et al. (1997)
	dog	120 min - 90 min	lumbosacral	No reduction of conduction velocity ^e	Kikuchi et al. (1996)
60	rabbit			Blood flow interrupted in capillaries (50-70 mmHg)	Rydevik et al. (1981)
		360 min - none		Functional changes, viability of nerve root jeopardized ^f	Rydevik et al. (1989)
70 - 75	rabbit			Interrupted blood flow (MAP 78 mmHg)	Rydevik et al. (1981)
		120 min -40 min		No histologic damage Threshold to cause afferent and efferent neurophysiologic changes Decrease in nerve signal amplitude, full recovery	Rydevik et al. (1991)

^a Whole cauda equina compression unless otherwise specified.

^d Mean arterial pressure 90-150 mmHg.

^e Acute compression applied after 1 month of 10 mmHg compression.

^f Interpretation based on a study of peripheral nerve compression (Rydevik et al. 1981).

^g Mean arterial pressure 70-100 mmHg.

			oedema, decrease in roots conduction velocity more noticeable for efferent, incomplete recovery, better for efferent than afferent Reduction of muscle action potential amplitude Complete motor block	(1992) Olmarker (1991) Gelfan & Tarlov (1956) Otani et al. (1997) Kikuchi et al. (1996) Kobayashi et al. (2004) Gelfan & Tarlov (1956)
	120 min - none 45 min - none			
dog	120 min - 90 min	lumbosacral	No reduction in root conduction velocity ^e	
dog	120 min - 90 min	lumbosacral	Slight reduction in root conduction velocity followed by rapid recovery ^h	
	1 week - none		Disturbance of axonal flow of essential elements (proteins, lipids) Incomplete ischaemia, mechanical deformation more damaging to the nerve	

^a Whole cauda equina compression unless otherwise specified.

^d Mean arterial pressure 90-150 mmHg.

^e Acute compression applied after 1 month of 10 mmHg compression.

^g Mean arterial pressure 70-100 mmHg.

^h Acute compression applied after 1 week of 10 mmHg compression.

pig ^g	240 min - 90 min 120 min - none 120 min - 90 min 60 min - none 10 min- 20 min 120 min - 20 min	incomplete ischaemia ⁱ , complete block for both afferent (120 min) and efferent (180 min), better recovery of efferent than afferent Reduction of muscle action potential amplitude Decrease of CAP amplitude with full recovery Incomplete ischaemia, mechanical deformation more damaging to the nerve Complete motor block Complete interruption of blood flow in intrinsic vessels, full recovery ^j no oedema formation Idem with oedema formation	Pedowitz et al. (1992) Olmarker (1991) Garfin et al. (1995) Gelfan & Tarlov (1956) Gelfan & Tarlov (1956) Olmarker, Rydevik, Holm & Bagge (1989) Olmarker, Rydevik, Holm & Bagge (1989)
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^a whole cauda equina compression unless otherwise specified.

^g Mean arterial pressure 70-100 mmHg.

ⁱ Oxygen reached compression site either by diffusion from adjacent tissue or through the air (Pedowitz et al. 1992, Rydevik et al. 1991).

^j Only blood flow data, no CAP monitoring.

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