Compressive Pressure versus Time in Cauda Equina Syndrome: A Systematic Review and Meta-Analysis of Experimental Studies.

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ABSTRACT

Study Design: Systematic review and meta-analysis

Objective: To examine the relationship between compressive pressure and its duration in cauda equina compression, and the effects subsequent decompression, on neurophysiological function and pathophysiology in animal studies. We further aim to investigate these relationships with systemic blood pressure to assess whether a vascular component in the underlying mechanism may contribute to the clinical heterogeneity of this disease.

Summary of Background Data: The complex relationship between pre-operative factors and outcomes in cauda equina syndrome (CES) suggests heterogeneity within CES which may inform better understanding of pathophysiological process, their effect on neurological function, and prognosis.

Methods: Systematic review identified 17 relevant studies including 422 animals and reporting electrophysiological measures (EP), histopathology, and blood flow. Modelling using meta-regression analysed the relationship between compressive pressure, duration of compression and electrophysiological function in both compression and decompression studies.

Results: Modelling suggested that electrophysiological dysfunction in acute cauda equina compression has a sigmoidal response, with particularly deterioration when mean arterial blood pressure is exceeded and, additionally, sustained for approximately one hour. Accounting for pressure and duration may help risk-stratify patients pre-decompression. Outcomes after decompression appeared to be related more to the degree of compression, where exceeding systolic blood pressure tended to result in an irreversible lesion, rather than duration of compression. Prognosis was most strongly associated with residual pre-decompression function.
Conclusions: Compressive pressure influences effects and outcomes of cauda equina compression. We suggest the presence of two broad phenotypic groups within CES defined by the degree of ischaemia as a potential explanatory pathophysiological mechanism.

Key Words: Animal models; Cauda equina syndrome; Lumbar disc hernia; outcomes; Pathophysiology; Predictive factor; Neurophysiology; Electrophysiology; prognosis; spinal surgery; Meta-Regression; biomechanics

Level of Evidence: 1
KEY POINTS

- Electrophysiological dysfunction in acute cauda equina compression has a sigmoidal response
- Electrophysiological function particularly deteriorates when mean arterial blood pressure is exceeded
- Compressive pressure has a larger effect than compression duration on electrophysiological outcomes after decompression
- Electrophysiological outcome is most strongly associated with residual pre-decompression function
- Neural ischaemia is suggested as an important mechanism in cauda equina syndrome pathophysiology
INTRODUCTION

The relationship between pre-operative factors and outcomes in patients with acute cauda equina syndrome (CES) is unclear and has been identified as a research priority\(^1\). Meta-analyses of human studies suggested that neurological outcomes are not improved when decompression is performed within 24-72 hours after onset or urinary incontinence\(^2,3\) but more recent studies have not supported this correlation\(^4,5\). It has been suggested that neurological deterioration, which appears to be a continuous rather than a step-wise phenomenon, may be a more important determinant of prognosis than the duration of compression\(^6\). Other examined predictive factors, such as rate of symptom onset\(^5,7-9\) and size of the herniating disc\(^10,11\) have yielded contradictory or non-significant results, respectively.

The variability in findings suggests that there is a large heterogeneity within CES and further knowledge about the pathophysiological process and its effect on neurological function and prognosis might help guide most effective management. One potential source of heterogeneity is the compressive pressure exerted by the herniating disc on the cauda equina.

A meta-analysis of animal studies testing spinal cord decompression suggested that higher compressive pressures and longer duration are associated with smaller treatment effects\(^12\). A power law relationship was found when the compressive pressure was plotted against duration that resulted in paraplegia, with higher pressures resulting in paraparesis faster compared to lower pressures, possibly due to variation in the degree of secondary ischaemia. Therefore, compressive pressure may have importance for both the management and the prognosis of CES. Animal models of cauda equina compression allow for controlled onset of compression in vivo and study of pathophysiological progression.

Aims

We aimed to examine any relationship of both compressive pressure and duration in cauda equina compression, and subsequent decompression, with neurophysiological function
and pathophysiology in animal studies using systematic review and meta-analysis. Further, we aimed to investigate any relationship with systemic blood pressure to assess whether a vascular contribution in the underlying mechanism might contribute to the clinical heterogeneity of this disease.

MATERIALS AND METHODS

Protocol

The *a priori* protocol was registered on the CAMARADES platform (http://www.dcn.ed.ac.uk/camarades).

Study Eligibility Criteria

Studies underwent two-stage screening to identify animal models that used constant, single-level, paracentral compression defined in mmHg of the cauda equina for a maximum 1 week duration with or without subsequent decompression (Supplementary Text 1, http://links.lww.com/BRS/B422).

Information Sources and Search

We searched MEDLINE, EMBASE, Web of Science and PubMed on 24 June 2017 using a broad, inclusive search strategy (Supplementary Text 2, http://links.lww.com/BRS/B422).

Data Extraction

We extracted study design and outcome measures for electrophysiology, compression-zone blood flow and histology (Supplementary Text 3, http://links.lww.com/BRS/B422).

Risk of Bias

Risk of bias assessment in individual studies was performed using an adapted version of the 10-point CAMARADES checklist ([13-15](Supplementary Text 4, http://links.lww.com/BRS/B422)).
Data Analysis

Effect Size

For compression studies, we defined effect size as the percentage loss of function after compression compared with pre-compression or sham operated control. For decompression studies, we calculated two measures of effect: an absolute measure, the percentage recovery with normal function set at 100% and no function at 0%; and a mean difference, the difference between pre- and post-decompression, both at 90min recovery.

Modelling

We fitted linear and non-linear mixed-effects models using the restricted maximum likelihood method (Supplementary Text 5). We explored the relations of pressure, duration, pressure x duration, pre-decompression function, electrophysiological measures and mean arterial/systolic blood pressure (MABP/SBP) with effects on neurophysiological function with our without decompression. Non-independence of points within a time series was accounted for by using continuous autoregression of order 1 (CAR1) structures.

Model Selection and Fit

We fitted models using the maximum likelihood approach, then used the Akaike and Bayesian Information Criteria (AIC and BIC, respectively) approaches to assess model fit during model selection. After model selection we calculated standard deviations of the population-level residuals to assess deviation from the model. I² and pseudo-R² values were also calculated (Supplementary Text 5, http://links.lww.com/BRS/B422). Analysis was conducted using the nlme and metafor packages and results presented as bubble plots ggplot2, scales, gridExtra packages, with the size of the points corresponding to the weight assigned to that point, in R (R Foundation for Statistical Computing, Vienna, Austria).
RESULTS

Study Selection

We identified 6393 unique English-language studies; 66 used animal models of acute cauda equina compression; 17 of these satisfied the inclusion criteria for this study\textsuperscript{17-33} (Supplementary Figure 1, http://links.lww.com/BRS/B422).
Study Characteristics

A total of 422 animals were included: 9 studies used canine models (218 animals) and 8 used porcine models (204 animals). Characteristics of the included studies are summarised in Table 1.

Risk of Bias

Median study quality was 3/10, interquartile range 3-4 (Supplementary Figure 2, http://links.lww.com/BRS/B422).

Analysis

Histology

Briefly, short compression (2-120min) at high pressure (50-200mmHg) resulted in oedema, which increased with both higher pressure and longer duration (Supplementary Table 1, http://links.lww.com/BRS/B422).

Blood flow

Low pressure compression (10-15mmHg) at either 24min or 7 days did not significantly reduce mean blood flow (Supplementary Table 2, http://links.lww.com/BRS/B422).

Electrophysiology (EP)

Global effect size

CE compression significantly reduced EP measures and decompression with 90mins recovery significantly improved EP measures (Table 2). There was substantial heterogeneity across studies (Supplementary Table 3, http://links.lww.com/BRS/B422).

Modelling of compression studies
The maximum predicted effect was a 94.3% (95% CI: 86.8%->100.0%) decline in electrophysiological function (Table 3). For duration of compression, the model suggests near maximal effects after 90mins, and a linear increase in deficit between 30 and 60mins (Figure 1A). For pressure, the model suggested that the near-maximum effect was reached at 140mmHg; there was little to no effect below 50mmHg; and the effect increased near-linearly from around 80mmHg to 115mmHg (Figure 1B). Incorporating MABP and SBP, as largely externally imposed constants onto the data, resulted in a mostly additive transformation but showed that with MABP the mid-point was near 0 suggesting that exceeding it largely increases effect size (Supplementary Figure 3, http://links.lww.com/BRS/B422).

Both the linear and univariate models performed poorly compared to the models above (p<0.0001) and had poor predictive validity (Supplementary Table 4 and Figure 4).

The Pressure x Duration model performed poorer by all measures compared to the main models (p<0.001, Table 3). Incorporating MABP and SBP resulted in an additive transformation revealing grouping of studies based on whether the aforementioned pressures were exceeded by compression (Figure 2; Supplementary Figure 5, http://links.lww.com/BRS/B422).

Modelling of decompression studies

The absolute measure model suggested that each minute delay to decompression reduced recovery of function by 0.21% (95% CI: 32.7-62.4, p=0.018; Table 3, Supplementary Figure 6A, http://links.lww.com/BRS/B422). Each additional mmHg of compression was predicted to reduce function by 0.53% of normal performance (95% CI: 0.42-0.65, p<0.0001, Figure 3A). For mean differences, the maximum improvement was at 128.9mmHg, and there were no effects below 51.0mmHg and above 206.7mmHg (Figure 3B). Duration of
compression was not a significant predictor of effect (p=0.44), and including it as moderator worsened AIC/BIC (Supplementary Figure 6B, http://links.lww.com/BRS/B422). The mean differences model incorporating MABP shifted the vertex of the curve closer towards 0 (Supplementary Figure 7, http://links.lww.com/BRS/B422).

The Pressure x Duration model for decompression also performed poorer than the main model (p<0.0001, Table 4, Supplementary Figure 8A-B) and including MABP and SBP again resulted in a mostly additive transformation (Figure 8C-F). The univariate models performed poorer compared to main model (p<0.0001, Supplementary Table 4, http://links.lww.com/BRS/B422).

Incorporating the precise electrophysiological measure used in compression and decompression studies led to a significant improvement in model fit (p<0.0001) but not in predictive utility (Supplementary Table 5, http://links.lww.com/BRS/B422).

Pre-decompression function was strongly related to recovery, more so than the pressure and duration models (Table 5, Figure 4AB, Supplementary Figure 9, http://links.lww.com/BRS/B422).

**DISCUSSION**

**Compressive pressure, duration and electrophysiological function**

**Compression**

Our findings show that low compressive pressure had little effect on EP function but that once pressure is increased, EP function deteriorates near-linearly. Furthermore, once
compression exceeds MABP a large effect size is more likely, even at pressures less than SBP. Longer durations of compression also have a strong effect on deteriorating EP function and the product of duration and compressive pressure too shows a sigmoid relationship. There were still low effect sizes once MABP was exceeded but these data points had short durations of compression suggesting that duration may determine extent of the underlying pathological process that results in EP dysfunction. Our data suggests that once compression exceeds a certain limit deterioration occurs rapidly in under 1 hour. Conversely, at a low compressive pressure it appears that a lower level of dysfunction is reached that is unlikely to progress from longer duration. This is supported by the fit of the Pressure x Duration model which extrapolates the data points to achieve the asymptote around 50% and reveals an unmeasured group of low pressure/long duration not present in the included studies (Supplementary Figure 10, http://links.lww.com/BRS/B422). Accounting for pressure and duration may help risk-stratify patients for decompression: those who are unlikely to deteriorate further, those about to deteriorate rapidly and those for whom it is likely too late to recover sufficiently.

In patients undergoing discectomy for lumbar disc herniation compression pressures varied from 7mmHg to 256mmHg (53mmHg mean) and it was significantly higher in those who had neurologic deficits\(^{34}\). The pressure was especially high - mean 161mmHg, range 104-256mmHg - in patients with severe paralysis such as foot drop or bladder dysfunction. Similarly, CES symptoms occurred in patients with lumbar stenosis at epidural pressures of 116.5mmHg\(±38.4\)mmHg\(^{35}\). One study found that once the cauda equina is constricted to a certain size (60-80mm\(^2\)) then further constriction results in sharp increases of intrathecal pressure that normalise quickly until a size is reached where the pressure is sustained\(^{36}\). This potentially suggests a maximal limit of adaptation and fits with our findings above.
Decompression

Longer durations and higher pressure were both significant predictors of the degree of post-decompression EP function. The difference between pre- and post-decompression function was minimal at low (due to minor initial lesioning) and high pressures. Duration was not a significant predictor of the pre- and post-decompression difference.

Taken together, this indicates that decompression after a low pressure event has better outcomes as the decompression halts progression when little function has been lost, rather than by recovering the lost function. Decompression after a medium pressure event improves outcomes by both halting progression and also recovering the lost function. Decompression after a high pressure event has poor outcomes as much of the function has already been lost, and decompression is unable to recover the lost function. Earlier decompression improves outcomes by halting progression. Overall, it suggests that a reliably large lesion is produced above MABP, but that this can be reversible unless SBP is exceeded, which might be mostly independent of duration of compression.

This finding is similar to studies using other compression methodologies, for example Valone et al\textsuperscript{37} used forceps with 1N or 2N of force on a porcine lumbar root (approximately 75mmHg and 150mmHg assuming 1cm\textsuperscript{2} forceps area) and found that the higher pressure resulted in a drastically larger reduction of MEP amplitude which did not recover after 10 mins unlike with the lower pressure.

Our model, however, did not support the idea that earlier decompression leads to greater recovery of lost function, which may be attributed to a lack of data and power at durations above 120mins. Pre-decompression function appeared to be a stronger predictor of prognosis after recovery than either duration or pressure repeating the finding by Chau et al\textsuperscript{6}.

Relation with neurobehavioral function
It is difficult to correlate our models with neurobehavioral measures though they resemble those of motor function by Batchelor at al\textsuperscript{12}. Studies assessing neurobehavioral outcomes in CE compression use mostly murine models and/or circumferential compression and/or long duration simulating chronic spinal stenosis, e.g. Ma et al\textsuperscript{38}, rather than CES where neurologic deterioration occurs rapidly\textsuperscript{39}.

In decompression studies, two studies showed that motor function recovery after decompression occurred faster with shorter durations of CE compression\textsuperscript{40,41}, but both used imprecise compression methods and only recorded large deficits. Recovery may also be a longer process than that measured by our study, for example in one rat study motor function normalised at 4 weeks after decompression\textsuperscript{42}.

**Pathophysiology and proposed integrated model**

The cauda equina’s blood supply possibly results in an area of relative hypovascularity\textsuperscript{43,44} and the microscopic anatomy of nerve roots makes them especially sensitivity to compression\textsuperscript{45}. The anatomy of the CE in canine\textsuperscript{46} and porcine models\textsuperscript{47} closely resembles a human’s as does the pathology - intraradicular oedema has been found in both patients and animal models with lumbar disc herniation\textsuperscript{48,49}. Circulation disruption with consequential venous congestion has been proposed as a mechanism for neurogenic claudication in spinal stenosis\textsuperscript{50} and in post-spinal-surgery CES in patients with pre-existing spinal stenosis\textsuperscript{51}. Similarly, a cadaveric study of lumbar stenosis found pathological neural changes associated with venous obstruction even in the absence of direct compression\textsuperscript{52}. Animal studies suggest that vasodilators may be neuroprotective in CE compression\textsuperscript{21,24}.

Using graded compression, Olmarker et al found a significant correlation between MABP and the compressive pressure required to stop flow within arterioles, but not in capillaries or venules\textsuperscript{45}. Balloon pressures that stopped arteriolar blood flow tended to be lower than MABP and much lower in capillaries/venules. This agrees with our results and
may explain the variability between studies. Additionally, reduction in blood flow sufficient to initiate ischaemia, without cessation of flow, could result in a similar effect size at longer durations.

Decompression has been shown to completely restore circulation because blood flow proximal to CE compression is not affected. Our results may have underestimated the extent of recovery by measuring it at 90mins post-decompression and reperfusion oedema may explain some variation in our models.

It may be that primary injury is caused by the disc through direct pressure, haemorrhage, and myelin sheath damage (initiated molecular signalling pathways) whereas secondary injury to the cauda equina occurs through inflammatory and oedematous changes, including ischaemia if circulation is compromised. Our finding that low effect sizes still occur at high compressive pressures but low durations suggests that duration may determine the extent of ischaemia; a process similar to that in spinal cord injury. Our study suggests that a greater deterioration occurs when the compression pressure disrupts vascular supply and differences in this may explain the phenotypic heterogeneity of CES. Broadly, two separate groups may result from the presence/absence of ischaemia (Figure 5).
Clinical implications

Though measuring directly pressure is currently unfeasible in patients with CES, other techniques may be used as surrogate measures, such as diffusion tensor imaging (DTI), which in spinal stenosis and lumbar disc prolapse has identified parameters\textsuperscript{58,59} that correlate with neurophysiological measures, functional measures and outcomes\textsuperscript{60-62}. To our knowledge, DTI of the CE has only been evaluated in a goat model of CE transection\textsuperscript{63}.

Better understanding of the pathophysiology of CE compression may unveil a window period for adjuvant therapy, such as vasodilators like lipoprostaglandin E\textsubscript{1}\textsuperscript{64}, or anti-neuroinflammatory agents like S-nitrosoglutathione and methylprednisolone\textsuperscript{65,66}.

Limitations

The time points employed may not be applicable to human CES due to the short durations and 90mins recovery time but may be too early to determine maximum benefit. Furthermore, our study is not able to predict effects past 240mins. Though it is the first study to model the relationship with BP, few studies measured it and a constant was applied to simulate it. It also lacks neurobehavioral measurements therefore the implications for CES, which is identified through clinical features, are limited.

Conclusions

This systematic review and meta-analysis suggests that electrophysiological dysfunction in acute cauda equina compression occurs in a sigmoidal pattern with particularly deterioration when mean arterial blood pressure is exceeded and, additionally, sustained for approximately one hour. Accounting for pressure and duration may help risk-stratify patients prior to decompression. Outcomes after decompression appeared to be related more to the degree of compression, where exceeding systolic blood pressure tended to result in an irreversible lesion, rather than duration of compression. Prognosis was most strongly associated with residual pre-decompression function. We suggest the presence of two broad phenotypic groups within CES defined by the degree of ischaemia as a potential explanatory pathophysiological mechanism.
REFERENCES

1. van Middendorp JJ, Allison HC, Ahuja S, et al. Top ten research priorities for spinal cord injury: the methodology and results of a British priority setting partnership. Spinal Cord. 2016;54(5):341-6.

2. Ahn UM, Ahn NU, Buchowski JM, et al. Cauda equina syndrome secondary to lumbar disc herniation: a meta-analysis of surgical outcomes. Spine. 2000;25(12):1515-22.

3. DeLong WB, Polissar N, Neradilek B. Timing of surgery in cauda equina syndrome with urinary retention: meta-analysis of observational studies. J Neurosurg: Spine. 2008;8(4):302-20.

4. Bydon M, Lin JA, De la Garza-Ramos R, et al. Time to Surgery and Outcomes in Cauda Equina Syndrome: An Analysis of 45 Cases. World Neurosurgery. 2016;87:110-5.

5. Korse NS, Pijpers JA, van Zwet E, et al. Cauda Equina Syndrome: presentation, outcome, and predictors with focus on micturition, defecation, and sexual dysfunction. Eur Spine J. 2017;26(3):894-904.

6. Chau AM, Xu LL, Pelzer NR, et al. Timing of surgical intervention in cauda equina syndrome: a systematic critical review. World Neurosurgery. 2014;81(3-4):640-50.

7. Kennedy JG, Soffe KE, McGrath A, et al. Predictors of outcome in cauda equina syndrome. Eur Spine J 1999;8(4):317-22.

8. Kostuik JP, Harrington I, Alexander D, et al. Cauda equina syndrome and lumbar disc herniation. J Bone Joint Surg Am. 1986;68(3):386-91.

9. McCarthy MJ, Aylott CE, Grevitt MP, et al. Cauda equina syndrome: factors affecting long-term functional and sphincteric outcome. Spine. 2007;32(2):207-16.

10. Kaiser R, Nasto LA, Venkatesan M, et al. Time Factor and Disc Herniation Size: Are They Really Predictive for Outcome of Urinary Dysfunction in Patients With Cauda Equina Syndrome? Neurosurgery. 2018;83(6):1193-200.

11. Korse NS, Kruit MC, Peul WC, et al. Lumbar spinal canal MRI diameter is smaller in
12. Batchelor PE, Wills TE, Skeers P, et al. Meta-analysis of pre-clinical studies of early decompression in acute spinal cord injury: a battle of time and pressure. PLoS One. 2013;8(8):e72659.

13. Macleod MR, O’Collins T, Howells DW, et al. Pooling of animal experimental data reveals influence of study design and publication bias. Stroke. 2004;35:1203-8.

14. Holman C, Piper SK, Grittner U, et al. Where Have All the Rodents Gone? The Effects of Attrition in Experimental Research on Cancer and Stroke. PLoS Biology. 2016;14(1):e1002331.

15. Landis SC, Amara SG, Asadullah K, et al. A call for transparent reporting to optimize the predictive value of preclinical research. Nature. 2012;490(7419):187-91.

16. Vesterinen HM, Sena ES, Egan KJ, et al. Meta-analysis of data from animal studies: a practical guide. J Neurosci Methods. 2014;221:92-102.

17. Sekiguchi M, Aoki Y, Konno S, et al. The effects of cilostazol on nerve conduction velocity and blood flow: acute and chronic cauda equina compression in a canine model. Spine. 2008;33(24):2605-11.

18. Sekiguchi M, Konno S, Kikuchi S. Effects of 5-HT2A receptor antagonist on blood flow in chronically compressed nerve roots. J Peripher Nerv Syst. 2004;9(4):263-9.

19. Takahashi N, Yabuki S, Aoki Y, et al. Pathomechanisms of nerve root injury caused by disc herniation: an experimental study of mechanical compression and chemical irritation. Spine. 2003;28(5):435-41.

20. Sekiguchi M, Konno S, Anzai H, et al. Nerve vasculature changes induced by serotonin under chronic cauda equina compression. Spine. 2002;27(15):1634-9.

21. Konno S, Arai I, Otani K, et al. Effects of beraprost sodium on canine cauda equina function and blood flow using a chronic spinal cord compression model. J Spinal Disord. 2001;14(4):336-8.
22. Otani K, Kikuchi S, Konno S, et al. Blood flow measurement in experimental chronic cauda equina compression in dogs: changes in blood flow at various conditions. J Spinal Disord. 2001;14(4):343-6.

23. Kikuchi S, Konno S, Kayama S, et al. Increased resistance to acute compression injury in chronically compressed spinal nerve roots. An experimental study. Spine. 1996;21(22):2544-50.

24. Konno S, Kayama S, Olmarker K, et al. Effects of OP-1206 (prostaglandin E1) on nerve-conduction velocity in the dog cauda equina subjected to acute experimental compression. J Spinal Disord. 1996;9(2):103-6.

25. Sato K, Konno S, Yabuki S, et al. A model for acute, chronic, and delayed graded compression of the dog cauda equina. Neurophysiologic and histologic changes induced by acute, graded compression. Spine. 1995;20(22):2386-91.

26. Baker AR, Collins TA, Porter RW, et al. Laser Doppler study of porcine cauda equina blood flow. The effect of electrical stimulation of the rootlets during single and double site, low pressure compression of the cauda equina. Spine. 1995;20(6):660-4.

27. Olmarker K, Rydevik B. Single- versus double-level nerve root compression. An experimental study on the porcine cauda equina with analyses of nerve impulse conduction properties. Clin Orthop Relat Res. 1992;(279):35-9.

28. Pedowitz RA, Garfin SR, Massie JB, et al. Effects of magnitude and duration of compression on spinal nerve root conduction. Spine. 1992;17(2):194-9.

29. Rydevik BL, Pedowitz RA, Hargens AR, et al. Effects of acute, graded compression on spinal nerve root function and structure. An experimental study of the pig cauda equina. Spine. 1991;16(5):487-93.

30. Garfin SR, Cohen MS, Massi JB, et al. Nerve-roots of the cauda equina. The effect of hypotension and acute graded compression on function. J Bone Joint Surg Am. 1990;72(8):1185-92.
31. Olmarker K, Holm S, Rydevik B. Importance of compression onset rate for the degree of impairment of impulse propagation in experimental compression injury of the porcine cauda equina. Spine. 1990;15(5):416-9.

32. Olmarker K, Rydevik B, Hansson T, et al. Compression-induced changes of the nutritional supply to the porcine cauda equina. J Spinal Disord. 1990;3(1):25-9.

33. Olmarker K, Rydevik B, Holm S. Edema formation in spinal nerve roots induced by experimental, graded compression. An experimental study on the pig cauda equina with special reference to differences in effects between rapid and slow onset of compression. Spine. 1989;14(6):569-73.

34. Takahashi K, Shima I, Porter RW. Nerve Root Pressure in Lumbar Disc Herniation. Spine. 1999;24(19):2003-6.

35. Takahashi K, Miyazaki T, Takino T, et al. Epidural pressure measurements. Relationship between epidural pressure and posture in patients with lumbar spinal stenosis. Spine. 1995;20(6):650-3.

36. Schönström N, Hansson T. Pressure changes following constriction of the cauda equina. An experimental study in situ. Spine. 1988;13(4):385-8.

37. Valone F 3rd, Lyon R, Lieberman J, et al. Efficacy of transcranial motor evoked potentials, mechanically elicited electromyography, and evoked electromyography to assess nerve root function during sustained compression in a porcine model. Spine. 2014;39(17):E989-93.

38. Ma B, Shi J, Jia L, et al. Over-Expression of PUMA Correlates with the Apoptosis of Spinal Cord Cells in Rat Neuropathic Intermittent Claudication Model. PLoS One. 2013;8(5):e56580.

39. Germon T, Ahuja S, Casey AT, et al. British Association of Spine Surgeons standards of care for cauda equina syndrome. Spine J 2015;15(3 Suppl):S2-4.

40. Tarlov IM, Klinger H. Spinal cord compression studies. II. Time limits for recovery after acute compression in dogs. AMA Arch Neurol Psychiatry. 1954;71(3):271-90.
41. Delamarter RB, Sherman JE, Carr JB. 1991 Volvo Award in experimental studies. Cauda equina syndrome: neurologic recovery following immediate, early, or late decompression. Spine. 1991;16(9):1022-9.

42. Glennie RA, Urquhart JC, Staudt MD, et al. The relationship between the duration of acute cauda equina compression and functional outcomes in a rat model. Spine. 2014;39(19):E1123-31.

43. Parke WW, Gammell K, Rothman RH. Arterial vascularization of the cauda equina. J Bone Joint Surg Am. 1981;63(1):53-62.

44. Kobayashi S, Yoshizawa H, Nakai S. Experimental Study on the Dynamics of Lumbosacral Nerve Root Circulation. Spine. 2000;25(3):298-305.

45. Olmarker K, Rydevik B, Holm S, et al. Effects of experimental graded compression on blood flow in spinal nerve roots. A vital microscopic study on the porcine cauda equina. J Orthop Res. 1989;7(6):817-23.

46. Konno S, Yabuki S, Sato K, et al. A model for acute, chronic, and delayed graded compression of the dog cauda equina. Presentation of the gross, microscopic, and vascular anatomy of the dog cauda equina and accuracy in pressure transmission of the compression model. Spine. 1995b;20(24):2758-64.

47. Olmarker K, Holm S, Rosenqvist AL, et al. Experimental nerve root compression. A model of acute, graded compression of the porcine cauda equina and an analysis of neural and vascular anatomy. Spine. 1991;16(1):61-9.

48. Kobayashi S, Uchida K, Takeno K, et al. Imaging of cauda equina edema in lumbar canal stenosis by using gadolinium-enhanced MR imaging: experimental constriction injury. AJNR Am J Neuroradiol. 2006;27(2):346-53.

49. Kobayashi S, Yoshizawa H, Hachiya Y, et al. Vasogenic edema induced by compression injury to the spinal nerve root. Distribution of intravenously injected protein tracers and gadolinium-enhanced magnetic resonance imaging. Spine. 1993;18(11):1410-24.
50. Porter RW, Ward D. Cauda equina dysfunction. The significance of two-level pathology. Spine. 1992;17(1):9-15.

51. Podnar S. Cauda equina lesions as a complication of spinal surgery. Eur Spine J. 2001;19(3):451-7

52. Hoyland JA, Freemont AJ, Jayson MI. Intervertebral foramen venous obstruction. A cause of periradicular fibrosis? Spine. 1989;14(6):558-68.

53. Kobayashi S, Kokubo Y, Uchida K, et al. Effect of lumbar nerve root compression on primary sensory neurons and their central branches: changes in the nociceptive neuropeptides substance P and somatostatin. Spine. 2005;30(3):276-82.

54. Konno S, Olmarker K, Byröd G, et al. Intermittent cauda equina compression. An experimental study of the porcine cauda equina with analyses of nerve impulse conduction properties. Spine. 1995;20(11):1223-6.

55. Olmarker K, Rydevik B, Nordborg C. Autologous nucleus pulposus induces neurophysiologic and histologic changes in porcine cauda equina nerve roots. Spine. 1993;18(11):1425-32.

56. Jonsson D, Finskas O, Fujioka Y, et al. Experimental Disc Herniation in the Rat Causes Downregulation of Serotonin Receptor 2c in a TNF-dependent Manner. Clin Orthop Relat Res. 2015;473(6):1913-9.

57. Kwon BK, Tetzlaff W, Grauer JN, et al. Pathophysiology and pharmacologic treatment of acute spinal cord injury. Spine J. 2004;4(4):451-64.

58. Hou ZJ, Huang Y, Fan ZW, et al. Changes in lumbosacral spinal nerve roots on diffusion tensor imaging in spinal stenosis. Neural Regen Res. 2015;10(11):1860-4.

59. Wu W, Liang J, Ru N, et al. Microstructural Changes in Compressed Nerve Roots Are Consistent With Clinical Symptoms and Symptom Duration in Patients With Lumbar Disc Herniation. Spine. 2016;41(11):E661-6.

60. Chiou SY, Hellyer PJ, Sharp DJ, et al. Relationships between the integrity and function of lumbar nerve roots as assessed by diffusion tensor imaging and neurophysiology.
61. Ellingson BM, Salamon N, Grinstead JW, et al. Diffusion tensor imaging predicts functional impairment in mild-to-moderate cervical spondylotic myelopathy. Spine J. 2014;14(11):2589-97.

62. Zhang J, Zhang F, Xiao F, et al. Quantitative Evaluation of the Compressed L5 and S1 Nerve Roots in Unilateral Lumbar Disc Herniation by Using Diffusion Tensor Imaging. Clin Neuroradiol. 2018;28(4):529-37.

63. Chen WT, Zhang PX, Xue F, et al. Large animal models of human cauda equina injury and repair: evaluation of a novel goat model. Neural Regen Res. 2015;10(1):60-4.

64. Yone K, Sakou T, Kawauchi Y. The effect of Lipo prostaglandin E1 on cauda equina blood flow in patients with lumbar spinal canal stenosis: myeloscopic observation. Spinal Cord. 1999;37(4):269-74.

65. Gök A, Uk C, Yilmaz M, et al. Efficacy of methylprednisolone in acute experimental cauda equina injury. Acta Neurochir. 2002;144(8):817-21.

66. Shunmugavel A, Khan M, Martin MM, et al. S-Nitrosoglutathione administration ameliorates cauda equina compression injury in rats. Neurosci Med. 2012;3(3):294-305.

67. Jackson D, White IR, Riley RD. Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. Stat Med. 2012;31(29):3805-20.
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Figures

Figure 1. Models of compression studies. A) by duration; B) by pressure.
Figure 2. Pressure x duration models of compression studies accounting for MABP. MABP - mean arterial blood pressure.
Figure 3. Models of decompression studies after 90min recovery. A) using absolute measure by pressure; B) using mean difference by pressure.
Figure 4. Models of pre-decompression function vs recovery, with relationship to MABP displayed. A) using absolute measure; B) using mean difference, with 95% confidence intervals. MABP - mean arterial blood pressure.
Figure 5. Schematic of proposed pathophysiology of acute cauda equina compression. EP - electrophysiological function; MABP - mean arterial blood pressure.
| Study ID      | Animal     | Level | Pressure (mmHg) | Duration (min) | Recovery end time (min) | BP (SD; mmHg) | Histology | Electrophysiology | Blood Flow |
|--------------|------------|-------|----------------|----------------|------------------------|---------------|-----------|-------------------|------------|
| Sekiguchi    | Canine     | L7    | 10             | 120            | 90                     | -             | -         | MNCV              | -          |
| Sekiguchi    | Canine     | L7    | 10             | 10080          | -                      | SBP - 104 (16) | -         | -                 | Yes        |
| Takahashi    | Canine     | L7    | 10             | 10080          | -                      | SBP - 145 (25) | Morphology | SNCV, SEP (amplitude) | -          |
| Sekiguchi    | Canine     | L7    | 10             | 10080          | -                      | Morphology   | -         | MNCV              | -          |
| Konno        | Canine     | L7    | 10             | 10080          | -                      | -             | -         | MNCV              | -          |
| Otani        | Canine     | L7    | 10             | 10080          | -                      | -             | -         | -                 | Yes        |
| Kikuchi      | Canine     | L7    | 10, 50, 100    | 120            | 10080                  | -             | -         | MNCV              | -          |
| Konno        | Canine     | L7    | 100            | 90             | -                      | MNCV, MEP (area) | -         | -                 | -          |
| Sato         | Canine     | L7    | 50, 100, 200   | 120            | 120                    | Morphology   | MNCV, MEP (area) | -          |
| Baker        | Porcine    | Co1/2 | 15             | 24             | -                      | -             | -         | MEP (amplitude)    | -          |
| Olmarker      | Porcine    | Co1/2 | 10, 50         | 120            | 90                     | -             | -         | MEP (amplitude)    | -          |
| Pedowitz     | Porcine    | Co1/2 | 50, 100, 200   | 240            | 90                     | -             | -         | MEP (amplitude), SEP (amplitude) | -          |
| Rydevik      | Porcine    | Co1/2 | 50, 75, 100, 200 | 120   | 90                     | Morphology   | MNCV, SNCV | MEP (amplitude)    | -          |
| Garfin       | Porcine    | Co1/2 | 50, 100, 200   | 120            | 90                     | MABP - 92 (4), 60 | Morphology | MNCV, MEP (amplitude), SNCV | -          |
| Olmarker      | Porcine    | Co1/2 | 50, 100, 200   | 120            | 90                     | -             | -         | MEP (amplitude)    | -          |
| Olmarker      | Porcine    | Co1/2 | 10, 50, 200    | 30             | -                      | Glucose transport | -         | -                 | -          |
| Olmarker      | Porcine    | Co1/2 | 50, 200        | 120            | -                      | Morphology   | -         | -                 | -          |
Table 2. Global effect size of compression and decompression studies.

|                       | Effect Size | 95% CI        | k  | p           |
|-----------------------|-------------|---------------|----|-------------|
| Compression           | 34.77       | 20.91 – 48.63 | 28 | <0.0001     |
| Decompression – Absolute Measure | 50.91       | 65.28 – 79.65 | 27 | <0.0001     |
| Decompression – Mean Differences | 12.23       | 4.623 - 19.83 | 27 | 0.0027      |

Note: CI - Confidence Interval.

Note: Co - coccygeal; Fast - 0.05-0.1 seconds; L - lumbar; MABP - mean arterial blood pressure; MEP - motor evoked potential; MNCV - motor nerve conduction velocity; S - sacral; SBP - systolic blood pressure; SD - standard deviation; SEP - sensory evoked potential; Slow - 10-20 seconds; SNCV - sensory nerve conduction velocity
Table 3. Parameters of main models for compression and decompression studies.

| Compression | Parameter | Estimate | 95% CI       | p   | σ  | I² param | I² overall | R² | AIC | BIC | SD residuals |
|-------------|-----------|----------|--------------|-----|----|----------|------------|----|-----|-----|-------------|
|             | Asym:     | 94.3     | 86.8-100     | <0.00 | 1  | 9.9      | 98.3%      | 95.7% | 96.7% | 70.0% | 244.20      | 2473.0 | 14.1 |
|             | Dmid:     | 44.9     | 37.5-52.3    | <0.00 | 1  | 10.7     | 92.2%      |       |       |       |             |         |      |
|             | Pmid:     | 96.2     | 89.0-103.3   | <0.00 | 1  | 12.8     | 98.4%      |       |       |       |             |         |      |
|             | Scal:     | 10.1     | 9.0-11.2     | <0.00 | 1  | -        | 18.5%      |       |       |       |             |         |      |

Decompression – Absolute measure

| Intercept : | Estimate | 95% CI        | p   | σ  | I² param | I² overall | R² | AIC | BIC | SD residuals |
|-------------|----------|---------------|-----|----|----------|------------|----|-----|-----|-------------|
| D:          | -0.21    | -0.38-0.04    | 0.018 | -  | 98.3%    | 99.1%      | 99.1% | 5.83% | 448.5 | 457.4 | 16.7 |
| P:          | -0.53    | -0.65-0.42    | <0.00 | 1  | -        | 97.2%      |       |       |       |             |         |      |

Decompression – Mean Difference

| Intercept : | Estimate | 95% CI        | p   | σ  | I² param | I² overall | R² | AIC | BIC | SD residuals |
|-------------|----------|---------------|-----|----|----------|------------|----|-----|-----|-------------|
| P:          | 1.27     | 0.60-1.93     | 0.001 | -  | 98.5     | 98.3%      | 98.3% | 0%    | 544.4 | 553.3 | 14.8 |
| P²:         | -0.00    | -0.01-0.00    | 0.001 | -  | -        | 98.5       |       |       |       |             |         |      |

Note: AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; CI - confidence interval; D - duration; P - pressure; SD - standard deviation
Table 4. Parameter of Pressure x Duration models for compression and decompression studies.

| Parameter          | Estimate (95% CI) | p     | σ    | $I^2$ Parameter | $I^2$ overall | $R^2$ | AIC  | BIC   | SD residuals |
|--------------------|-------------------|-------|------|-----------------|---------------|-------|------|-------|--------------|
| **Compression**    |                   |       |      |                 |               |       |      |       |              |
| Asym:              | 47.57 (32.72-62.43) | <0.00 | 1    | 37.3            | 99.5%         | 68.9% | 2530.0 | 2553.2 | 23.6         |
| Mid:               | 6598.5 (5295.8-7901.3) | <0.00 | 1    | 1948.6         | 97.6%         | 99.5% | 68.9% | 2530.0 | 2553.2 | 23.6         |
| Seal:              | 1471.3 (1683.6-1896.0) | <0.00 | 1    | -              | 55.2%         | -     | 68.9% | 2530.0 | 2553.2 | 23.6         |
| **Decompression – Abs Measure** |                   |       |      |                 |               |       |      |       |              |
| Intercept:         | 137.9 (115.9-159.9) | <0.00 | 1    | 16.7            | 98.0%         | 98.0% | 491.3 | 500.3 | 17.2         |
| PxD:               | -0.006 (-0.009-0.004) | <0.00 | 1    | -              | 97.8%         | 98.0% | <0%  | 491.3 | 500.3 | 17.2         |
| (PxD)^2:           | 7.0 e-8 (2.2e-8-1.2e-7) | 0.006 | 5    | -              | 98.4%         | -     | 98.4% | <0%  | 587.5 | 596.4 | 16.8         |
| **Decompression – Mean Diff** |                   |       |      |                 |               |       |      |       |              |
| Intcp:             | 3.3 (21.4-28.0) | 0.79  | 18.9 | 98.4%          |                |       |      |       |              |
| P:                 | 0.001 (0.001-0.004) | 0.35  | -    | 98.3%          | 98.4% <0%     |       |      |       |              |
| P^2:               | -3.0 e-8 (-8.5e-8-2.5e-8) | 0.27  | -    | -              | 98.8%         |       |      |       |              |

Note: AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; CI - confidence interval; D - duration; P - pressure; SD - standard deviation
Table 5. Parameters of pre-decompression function models.

| Parameter   | Estimate | 95% CI   | p     | $I^2$ param | $I^2$ overall | $R^2$ | AIC | BIC | SD residuals |
|-------------|----------|----------|-------|-------------|--------------|-------|-----|-----|--------------|
| **Absolute Measure** |          |          |       |             |              |       |     |     |              |
| Asym:       | 100.5    | 96.3-104.8 | <0.001 | 72.0%       |              | 72.1% | 13.9% | 424.5 | 433.7 | 14.5 |
| lrc:        | -3.49    | -3.8-03.1 | <0.001 | 93.9%       |              |        |     |     |              |
| **Mean Differences** |          |          |       |             |              |       |     |     |              |
| Intercept:  | 4.3      | -8.6-17.2 | 0.50  | 98.3%       |              | 98.3% | 20.4% | 433.7 | 442.6 | 14.5 |
| ES:         | 1.2      | 0.8-1.7   | <0.001 | 95.0%       |              |        |     |     |              |
| Intercept*(ES^2): | -0.014 | -0.02 - 0.01 | <0.001 | 92.0%       |              |        |     |     |              |

Note: AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; CI - confidence interval; D - duration; ES - effect size/\% function pre-decompression; P - pressure; SD - standard deviation