Supplementary Text 1. Screening and inclusion criteria.

Two-stage screening:

1) Abstract screen: animal models of cauda equina compression for a maximum 1 week duration
2) Full-text screen: constant, single-level, paracentral pressure defined in mmHg.

Decompression: studies of compression followed by decompression that met the same criteria were also included.

Exclusion: studies using percentage or size of compression rather than pressure, and those using multi-level compression or circumferential compression.

Controls: we used either pre-compression values or those from concurrent sham operated animals, for decompression studies we used pre-decompression values.

Supplementary Text 2. Search terms.

Medline (In-Process & Other Non-Indexed Citations and Ovid MEDLINE, 1946 to Present [29/04/2017]) and **EMBASE** (1980 to 2017 Week 18) using OvidSP.

((cauda equina or lumbar or lumbosacral) adj2 (syndrome or compression or decompression or injury or stenosis)).ti,ab,kw.

AND

(cauda equina/ OR decompression, surgical/ OR polyradiculopathy/ OR radiculopathy/ OR spinal cord injuries/ OR spinal cord compression/ OR spinal diseases/ OR nerve compression syndromes/)

Pubmed* (Timespan: All years to Present [29/04/2017]):

(cauda equina[MeSH Terms] OR decompression, surgical[MeSH Terms] OR polyradiculopathy[MeSH Terms] OR radiculopathy[MeSH Terms] OR spinal cord injuries[MeSH Terms] OR spinal cord compression[MeSH Terms] OR spinal diseases[MeSH Terms] OR nerve compression syndromes[MeSH Terms])

AND

((cauda[Title/Abstract]) OR equina[Title/Abstract]) OR (lumbar[Title/Abstract]) OR (lumbosacral[Title/Abstract])) AND ((syndrome[Title/Abstract]) OR (compression[Title/Abstract]) OR (decompression[Title/Abstract]) OR (injury[Title/Abstract]) OR (stenosis[Title/Abstract]))

*Filter – Other Animals

Web of Science* (Timespan: All years [1900-2017]):

TS=((cauda OR equina OR lumbar OR lumbosacral) NEAR/2 (syndrome OR compression OR decompression OR injury OR stenosis))

*Medline® excluded as database, only English language, only Article document type

Supplementary Text 3. Data extraction.

We extracted data from within text or from graphs:

Study Design:

Animal species

Number of animals in each group

Spinal level of compression

Method of compression

Pressure and duration of compression

Duration of compression

Blood pressure

Time of assessment after decompression

Outcome Measures:

Electrophysiology

Neurobehaviour (motor and sensory)

Compression-zone blood flow

Compression-zone histology

- we extracted means and standard deviations, or qualitative summaries if numerical data were not available.

Supplementary Text 4. Adapted CAMARADES checklist for risk of bias.

We removed ‘blinded conduct of the experiment’ (because we expected reporting of this to be very low) and the addition of ‘stated exclusion with reasons’, given the recent importance attributed to this[14,15] and the expected rate of attrition.

Adapted checklist:

1. Peer review
2. Random group allocation
3. Comparable groups
4. Temperature control
5. Blinded assessment
6. Non-ketamine anaesthetic
7. Sample size calculation
8. Stated exclusion with reasons
9. Ethical compliance
10. Conflict of interest statement

Supplement 5. Statistical Analysis.

Modelling

Compression studies were fitted using the formula

$$Pred_{D,P} = \frac{Asym}{(1 + e^{\frac{Dmid - D}{Scal}}) \cdot (1 + e^{\frac{Pmid - P}{Scal}})}.$$

D is duration, P is pressure, Asym is the asymptote of the curve; Dmid and Pmid are the points at which the effect is 50% of asymptote, and also the points of the greatest rate of increase in effect for duration and pressure respectively; and Scal is the parameter that controls the steepness of the curve, where the slope at the midpoint (of duration, for example) is

$$Slope_{Dmid,P} = \frac{Pred_{Dmid,P}}{2 \times Scal}.$$

Where one variable is at midpoint and the other past the point of asymptote, this is further simplified to

$$Slope_{Dmid,Pmax} = \frac{Asym}{4 \times Scal}.$$

The general formula for the gradient can be determined by the formula

$$Slope_{D,P} = \frac{Pred_{D,P}}{Scal} \cdot (1 - \frac{Pred_{D,P}}{Asym}).$$

We also fitted a model using a Pressure x Duration product as a single variable

$$Pred_{D,P} = \frac{Asym}{(1 + e^{Mid - \frac{PxD}{Scal}})}.$$

The analytic method used averaged curves rather than data points so the fit is not a line-of-best-fit. We explored the influence of systolic blood pressure (SBP) and mean arterial blood pressure (MABP) using the previous equations by subtracting SBP or MABP from P. One study measured SBP (4 data points) and one MABP (132 data points) so 140mmHg and 100mmHg, respectively, were substituted as an approximation for the remaining studies resulting in a leftward shift of the plots. In the Pressure x Duration models we further added 140 and 100 as constants to P (to ensure all data points were positive), respectively. Linear and univariate models were also created

as comparators. We excluded the 4 data points with a duration of 10080mins (1 week) because they were well outside of the durations of other studies, risking falsely influencing the models.

Decompression studies were modelled after 90mins of recovery. A linear mixed-effects model was applied to decompression studies. For the absolute effect size measure:

$$Pred_{D,P} = a + b \cdot Duration + c \cdot Pressure.$$

For the mean differences measure:

$$Pred_{D,P} = a + b \cdot Duration + c \cdot Pressure + Pressure^2.$$

A normalised mean difference approach was not possible due to minimal effect on function of low pressure compression thereby inflating the effect size[16].

Pressure x Duration models were fitted to the quadratic model

$$Pred_{D,P} = a + b \cdot (Pressure\ x\ Duration) + c \cdot (Pressure\ x\ Duration)^2$$

and SBP/MABP were included as above.

The relationship of pre-decompression function and post-decompression function was explored using a non-linear asymptotic regression of the form

$$Pred_{Fn} = Asym \cdot \left(1 - e^{-Fn \cdot e^{lrc}}\right).$$

lrc is the parameter for the steepness of the curve, and Fn is the pre-decompression function.

A quadratic curve was fitted for mean differences

$$Pred_{Fn} = a + b \cdot Fn + c \cdot Fn^2.$$

For the purposes of this paper, the threshold for *near-asymptote/near-maximum* was arbitrarily defined as gradient <= 0.1, where any further change in the parameter would result in minimal change to the predicted value. The *near-linear* portion of the graphs were defined as regions where the gradient is >= 0.5*steepest gradient.

Random Effects Structure

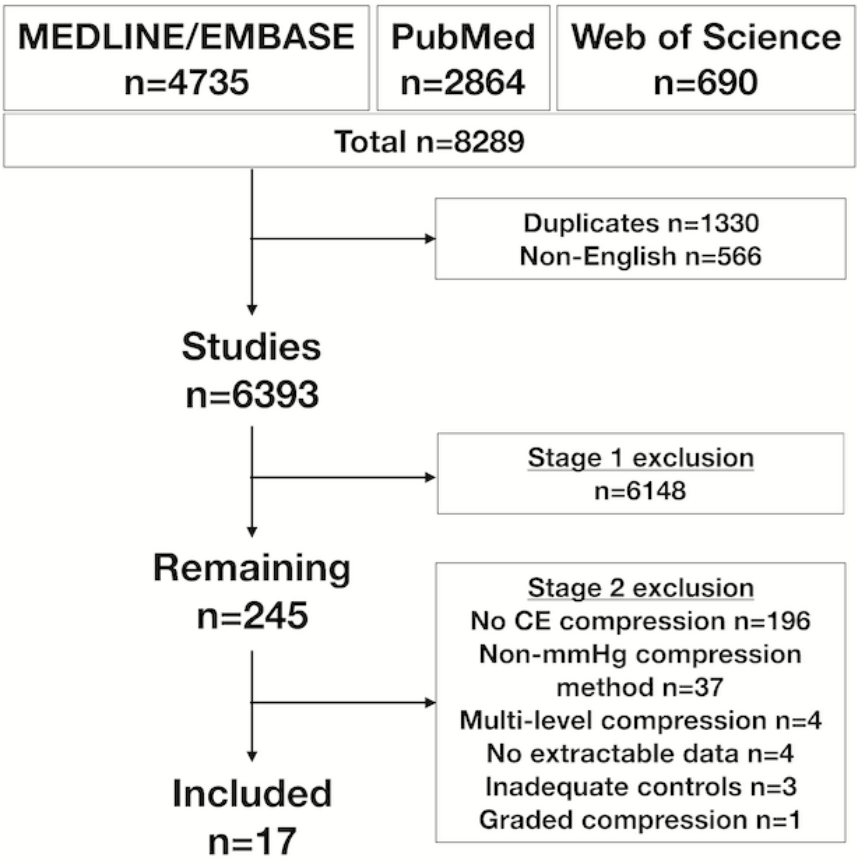
Models were fit for compression The influence of electrophysiological measures was investigated through random-effects structures. By the very nature of this being a meta-analysis, the independent experimental group (exp) was specified a priori as the grouping structure for random effects. Exploratory models nesting the electrophysiological measure within exp were also created to investigate the possible effect of the measure used. Asym, Dmid, Pmid were set as

random effects. Diagonal variance-covariance matrices were used with an assumption of independence of random effects.

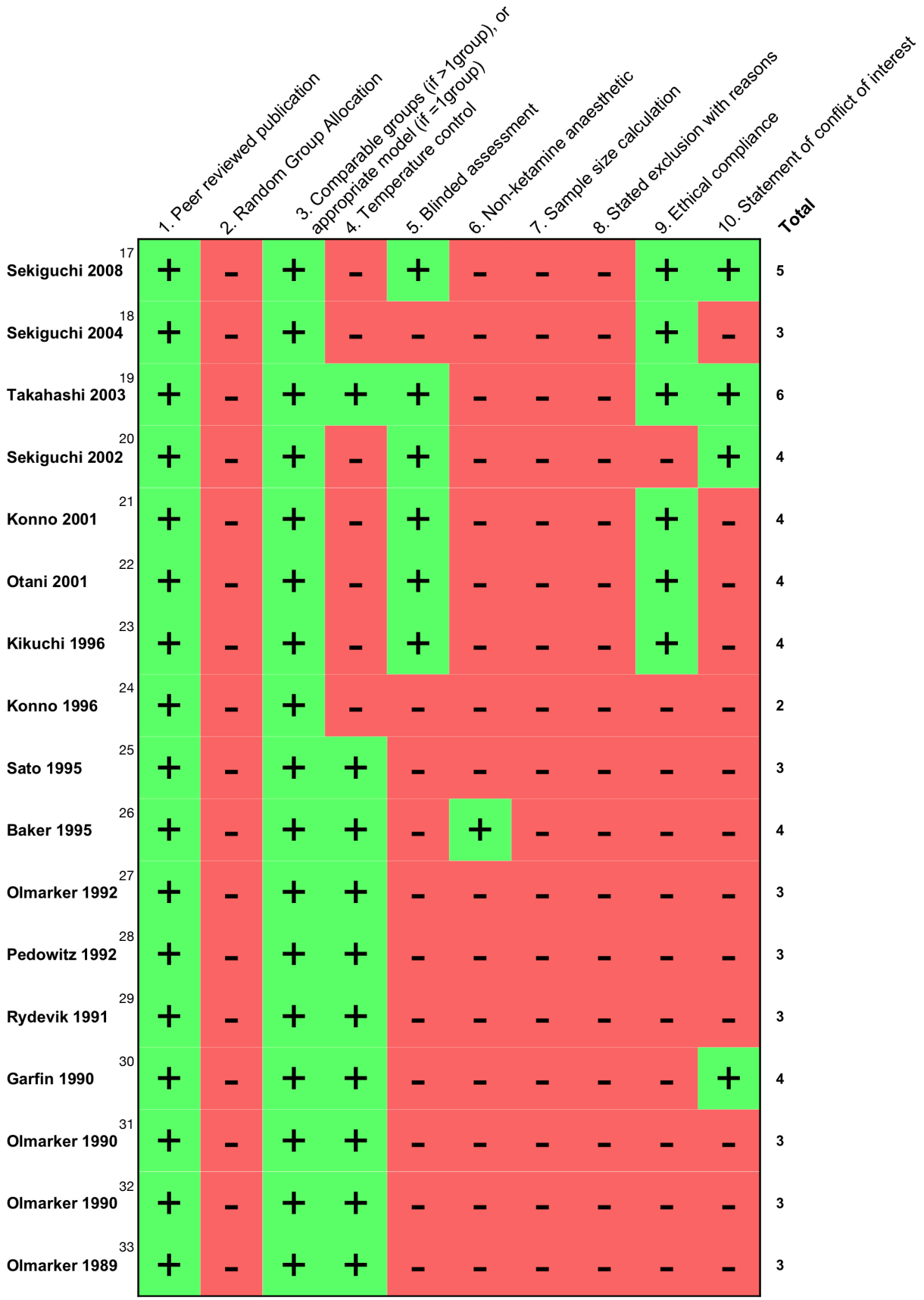
Model Selection and Fit

I^2-values were calculated using an approach outlined in Jackson et al[67]. Pseudo-R^2 values were calculated using the adjusted-McFadden's approach using log-likelihoods. However, there are well known limitations to R^2 for non-linear models, and I^2 has not been validated for non-linear models, as far as we are aware. These therefore should be interpreted as approximate figures for the percentage of heterogeneity accounted for by the regressors (R^2) and the percentage of residual variance that was due to residual heterogeneity (I^2).

Supplementary Figure 1. Flowchart of study screening and selection. CE - cauda equina.



Supplementary Figure 2. Risk of Bias.



+ = present. - = not present.
Note 1: 'comparable groups' in these studies was defined as same number of animals ±1 due to no study describing the characteristics of the animals once separated into groups.
Note 2: non-ketamine anaesthesia may not be appropriate due to no neurobehavioral assessment.

Supplementary Table 1. Summary of histological studies.

Study ID	Pressure (mmHg)	Duration (min)	Recovery end time (min)	BP (SD; mmHg)	Histology measure	Result Summary
Takahashi et al 2003[19]	10	10080	-	SBP - 145 (25)	Microscopy appearance	**10 mmHg:** Intraneural oedema ranged from 'no change' to 'oedema in a minor part of the nerve root'. Schwann cell oedema ranged from 'no change' to '10-25%' myelinated fibres. Nerve fibre injury ranged from 'no change' to '10-25%' myelinated fibres.' **Sham:** same as above but at most '<10% of myelinated fibre' for Schwann cell oedema and nerve fibre injury.
Sekiguchi et al 2002[20]	10	10080	-	-	Electron Microscopy appearance	"In the periphery of the compressed nerve, both the nucleus and the cytoplasm of endothelial cells became swollen. Thus, the vascular lumen became narrow. The chromatin granules in the nucleus condensed and showed high-electron density. A large number of irregular-shaped cytoprocesses projected from the inner surface of the endothelial cells to the vascular lumen. Interestingly, the tight junction between endothelial cells was destroyed, and the basement membrane of endothelial cells thickened"
Sato et al 1995[25]	50, 100, 200	120	90	-	Microscopy appearance	After recovery. No nerve fibre damage nor histologic changes related to the axon, myelin or Schwann cells in any compression pressure. Slight oedema of nerve roots at 200 mm Hg.
Rydevik et al 1991[29]	50, 75, 100, 200	120	90	-	Microscopy appearance	After recovery. **50 mmHg and 75 mmHg:** minimal changes in subperineurial oedema and occasional haemorrhage from microvessels inside nerve roots. **100 mmHg**: more widespread oedema. **200 mmHg:** more severe injury to myelin sheaths, haemorrhage of nerve fibres and more pronounced and diffuse endoneurial oedema.

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Table Cont.

Garfin et al 1990[30]	50, 100, 200	120	-	90	MABP - 92 (4), 60	Microscopy appearance	After recovery. **50 mmHg:** slight subperineurial oedema and rare microhaemorrhage, in both normotensive and hypotensive groups. **100 mmHg:** pronounced oedema with moderate haemorrhage from intramural microvessels, in both normotensive and hypotensive groups. **200 mmHg:** severe oedema and haemorrhage with injury to myelin nerve sheaths, in both normotensive and hypotensive groups. **Sham:** normal appearance.
Olmarker et al 1990[32]	10, 50, 200	30	Fast, Slow	-	-	Glucose transport - R/Rco ratio	**TABLE 1.** *Average* R/R_{CO} *ratio within the compression zones* Experimental series / Average R/R_{CO} ratio (%) ± SD / Reduction from control (%) Control: 79 ± 3 — Sham: 68 ± 5, 14 S: 10 mm Hg 65 ± 2, 18; 50 mm Hg 40 ± 2, 49; 200 mm Hg 27 ± 5, 66 R: 10 mm Hg 56 ± 4, 29; 50 mm Hg 27 ± 10, 66; 200 mm Hg 4 ± 2, 95 S, slow onset of compression; R, rapid onset of compression.
Olmarker et al 1989[33]	50, 200	120	Fast, Slow	-	-	Microscopy appearance	**Fast onset:** oedema was more pronounced and 2 hours and 10 minutes compression than at 2 minutes in both **50 mmHg** and **200 mmHg** groups. The magnitude and distribution of oedema was similar for the two pressures for corresponding durations. Oedema was more pronounced at the edges of the compression zone. **Slow onset:** no oedema at **50 mmHg** at 2 minutes and 10 minutes and no central oedema at 2 hours. At **200 mmHg** oedema was only at the edges of the compression zone at 2 minutes and 10 minutes; at 2 hours findings were similar to the fast onset group. **Sham:** no intraneural oedema.

Summary

Compression at low pressures and long durations (10mmHg for 1 week) resulted in a small increase in nerve fibre oedema injury with vascular endothelial changes on electron microscopy[19,20]

All pressures (10-200mmHg) resulted in reduced glucose transport to nerve roots within 30min of compression[32]. Short compression at high pressure (e.g. 2-120min at 50-200mmHg) resulted in oedema, which increased with both higher pressure and longer duration, but myelin sheath damage was present only at 200mmHg; no differences were found between normotensive or hypotensive animals at any pressure[25,29,30,33].

Recovery results at 90min varied from normal appearance to oedema, haemorrhage and myelin damage but at 200mmHg all studies reported oedema[25,29,30].

Supplementary Table 2. Blood flow study results.

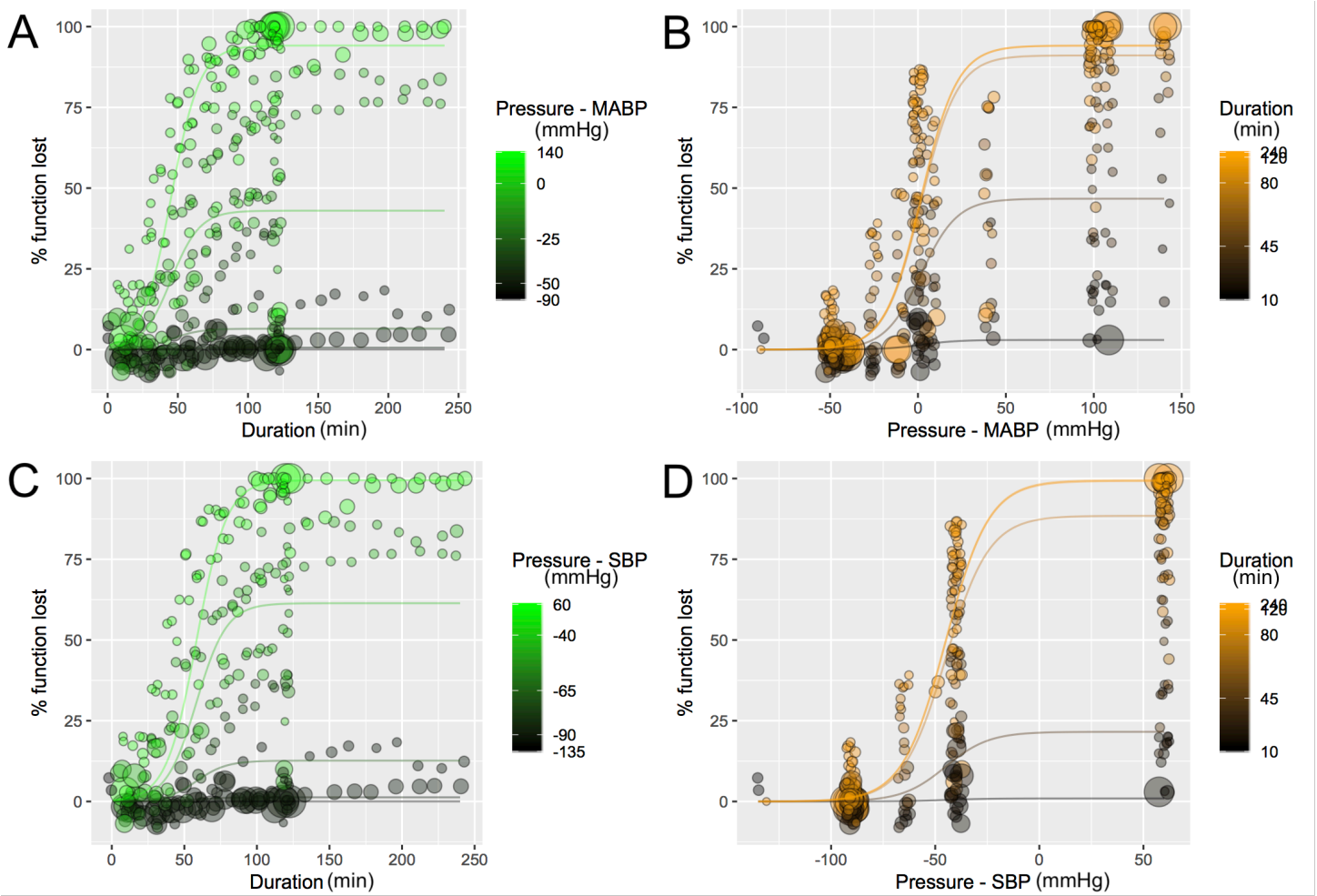
Study ID	Pressure (mmHg)	Duration (mins)	Number of compressed animals	Mean blood flow compressed (SD), %	Number of control animals	Mean blood flow control (SD), %
Sekiguchi et al 2004[18]	10	10080	20	**91 (73.5)**	15	**100 (71.2)**
Sekiguchi et al 2002[20]	10	10080	10	**107.8 (45.8)**	10	**100 (43.9)**
Otani et al 2001[22]	10	10080	5	**60 (66.7)**	5	**100 (30)**
Baker et al 1995[26]	15	24	5	**91.6 (3.4)**	5	**87.1 (11.1)**

Supplementary Table 3. Heterogeneity analysis of compression and decompression studies.

	df	Q	Tau	I^2	*p*
Compression	352	32633.2	36.89	99.89%	<0.0001
Decompression – Absolute Measure	46	12706.52	36.14	99.74%	<0.0001
Decompression – Mean Differences	46	1757.53	18.79	99.09%	<0.0001

Note: df - degrees of freedom using number of animals

Supplementary Figure 3. Models of compression studies. A) by duration and accounting for MABP; B) by pressure and accounting for MABP; C) by duration and accounting for SBP; D) by duration and accounting for SBP. MABP - mean arterial blood pressure; SBP - systolic blood pressure

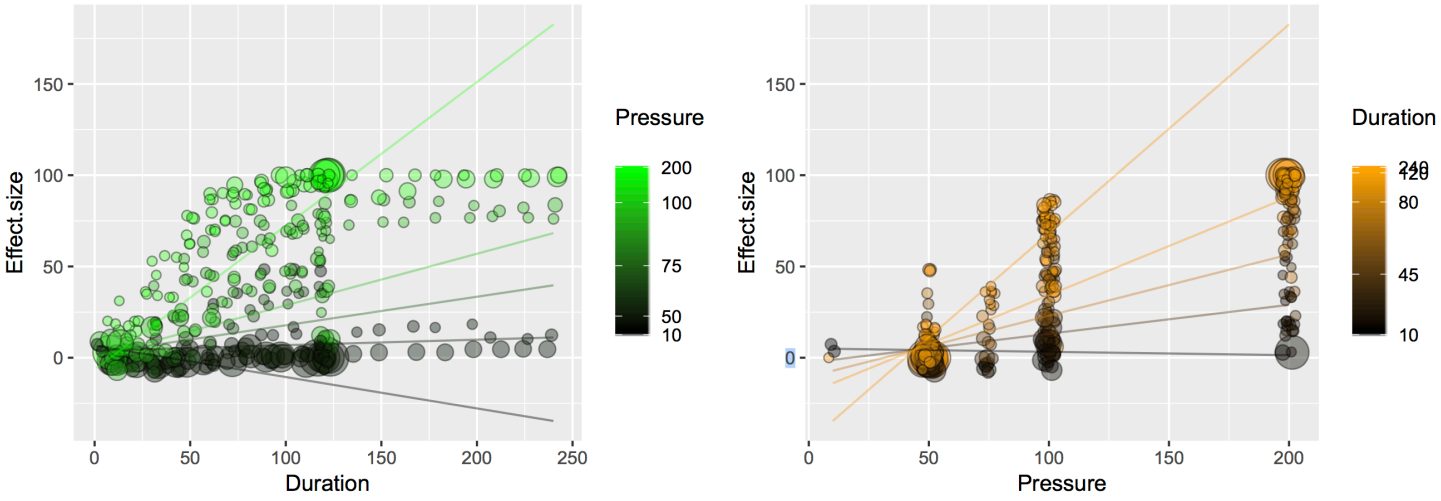


Supplementary Table 4. Linear and univariate models of compression and decompression studies.

	AIC	BIC	SD residuals	I^2	Pseudo-R^2
Compression					
Linear	3320	3343	21.6	97.9	59.2
Univariate	8188	8199	36.6	99.9	-0.77
Decompression					
Absolute measure univariate	491	496	34.6	99.7	-0.13
Mean differences univariate	549	554	17.0	99.1	-0.90

Note: AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; SD - standard deviation.

Supplementary Figure 4. Plots of linear models for compression studies.

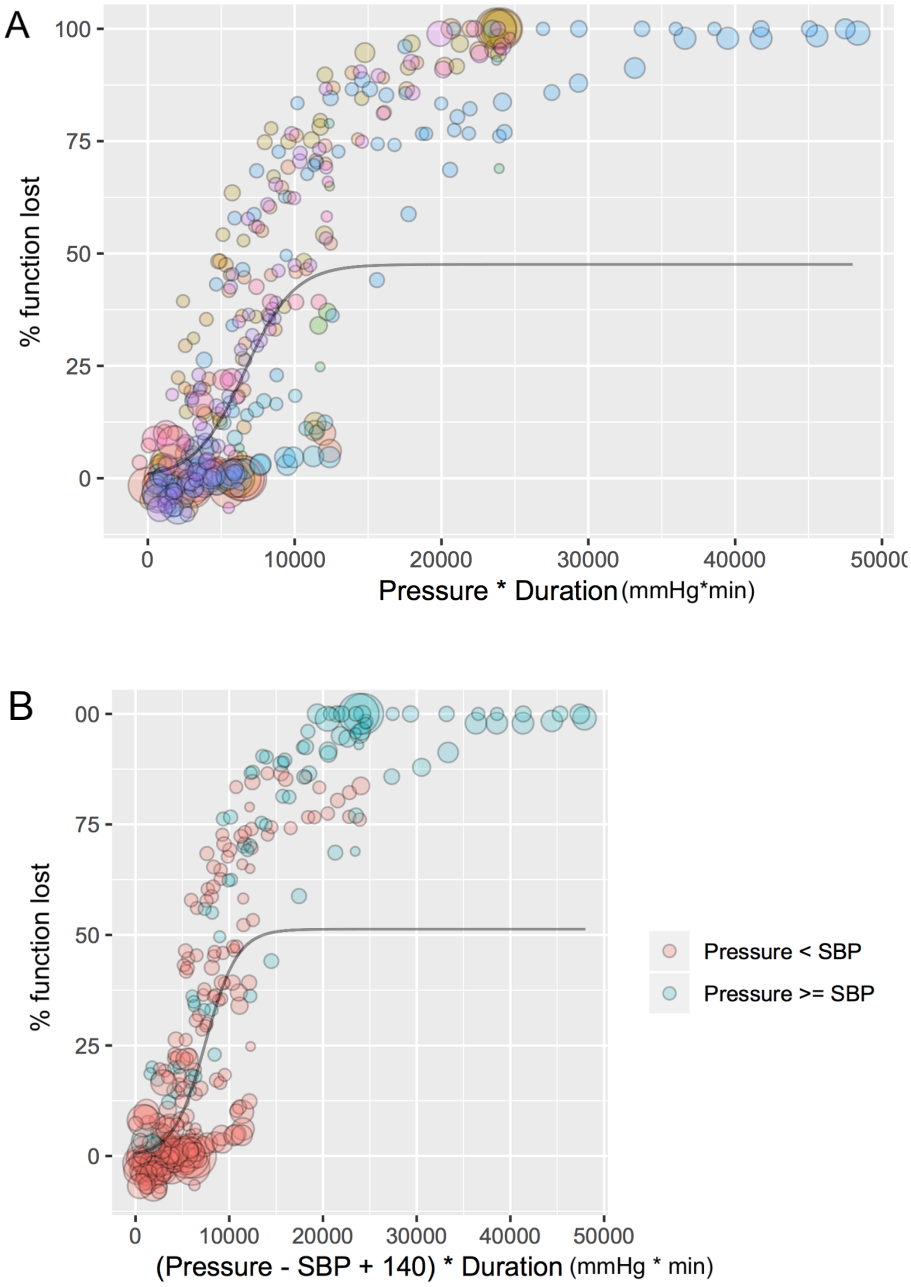


Supplementary Table 5. Parameters for model incorporating electrophysiological measure as random effect in compression and decompression studies.

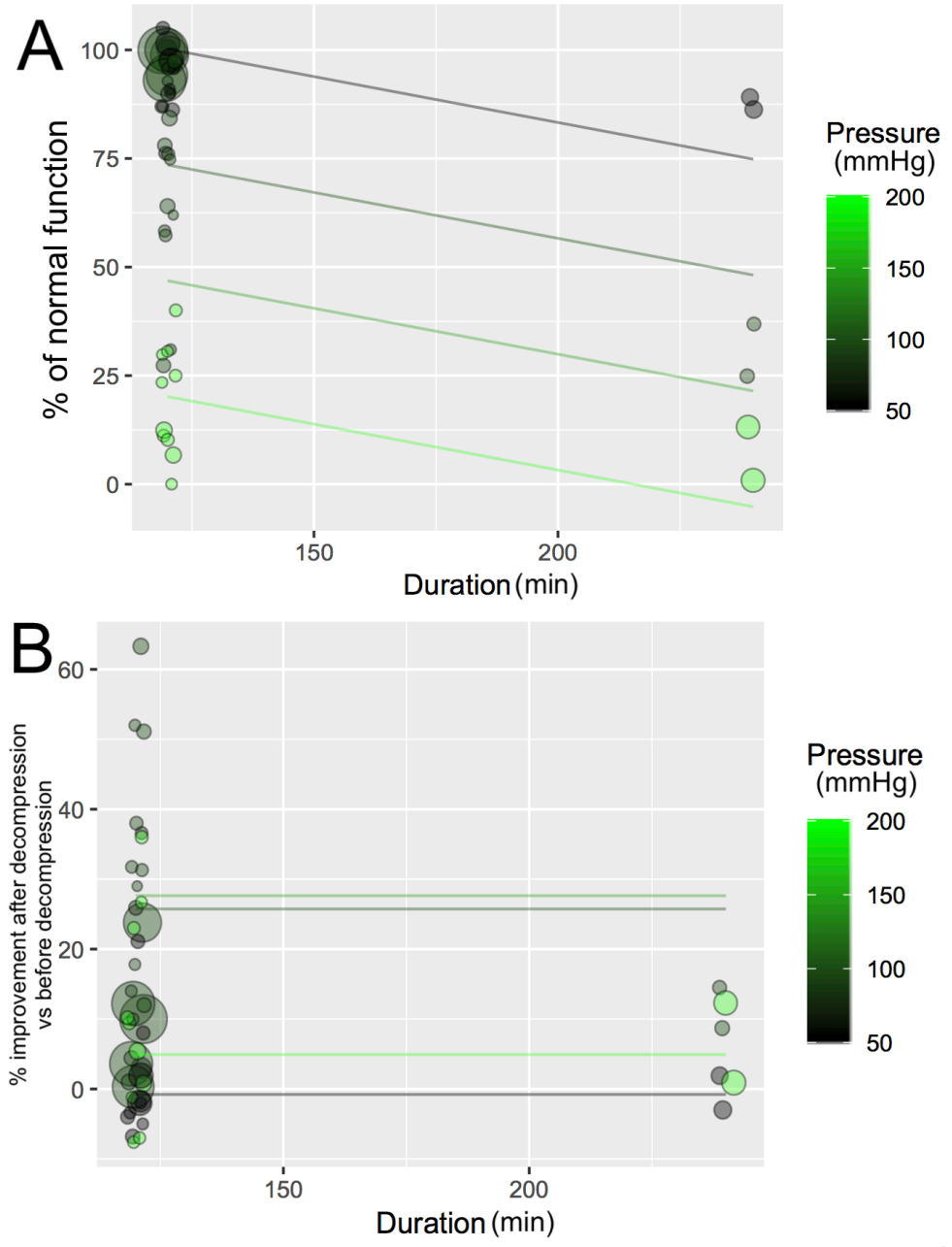
	AIC	BIC	Asym	Dmid	Pmid	Dscal	SD residuals	I^2	Pseudo-R^2
Compression	2283.3	2314.2	94.8	47.6*	95.9*	10.5*	14.0	94.8	72.0
Decompression									
Absolute measure	228	457	-	-	-	-	16.7	97.1	6.8
Mean differences	544	533	-	-	-	-	14.8	98.3	-0.09

*p<0.001
Note: AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; SD - standard deviation

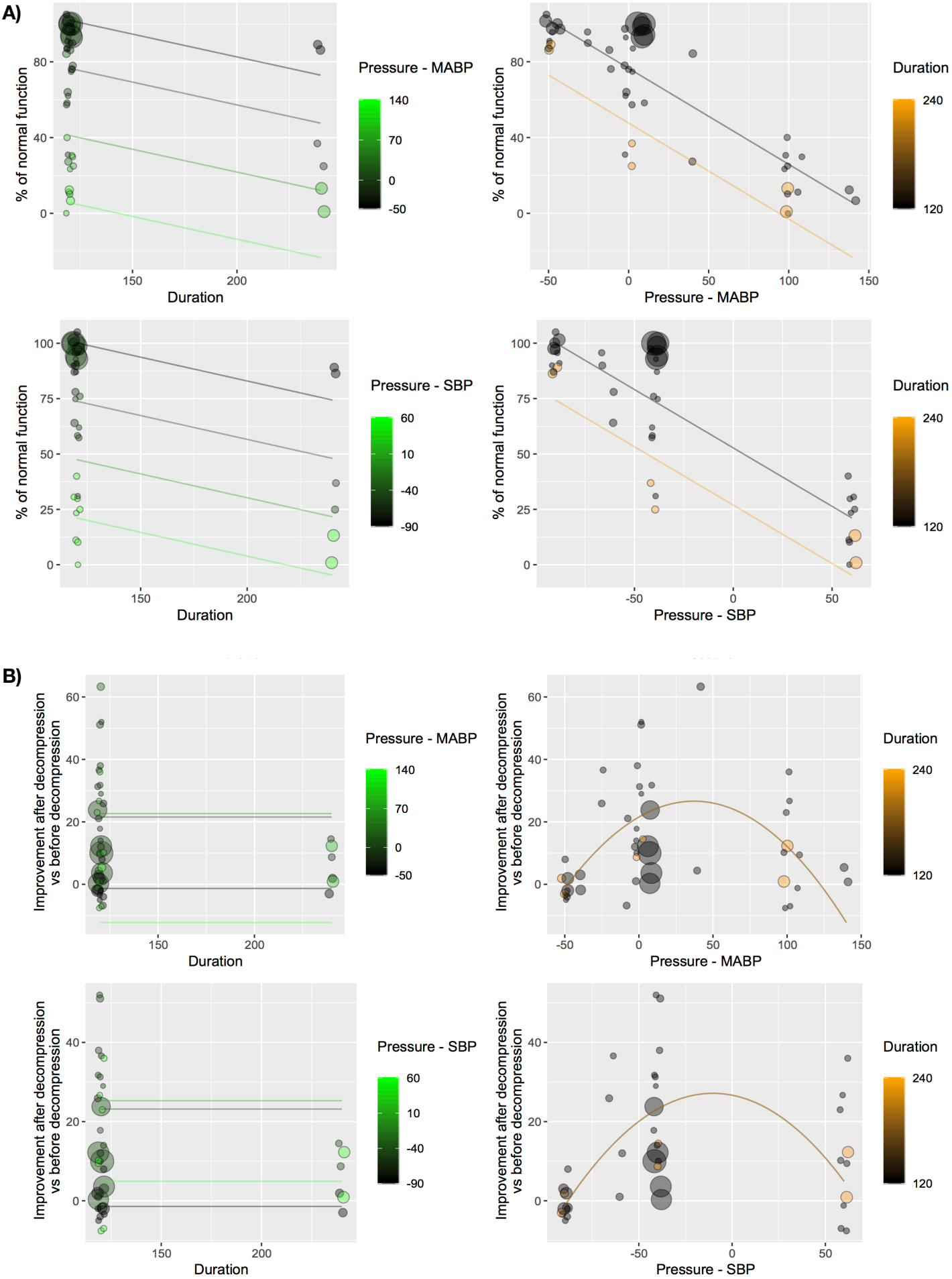
Supplementary Figure 5. Pressure x duration models of compression studies, A) main model; B) accounting for SBP. SBP - systolic blood pressure



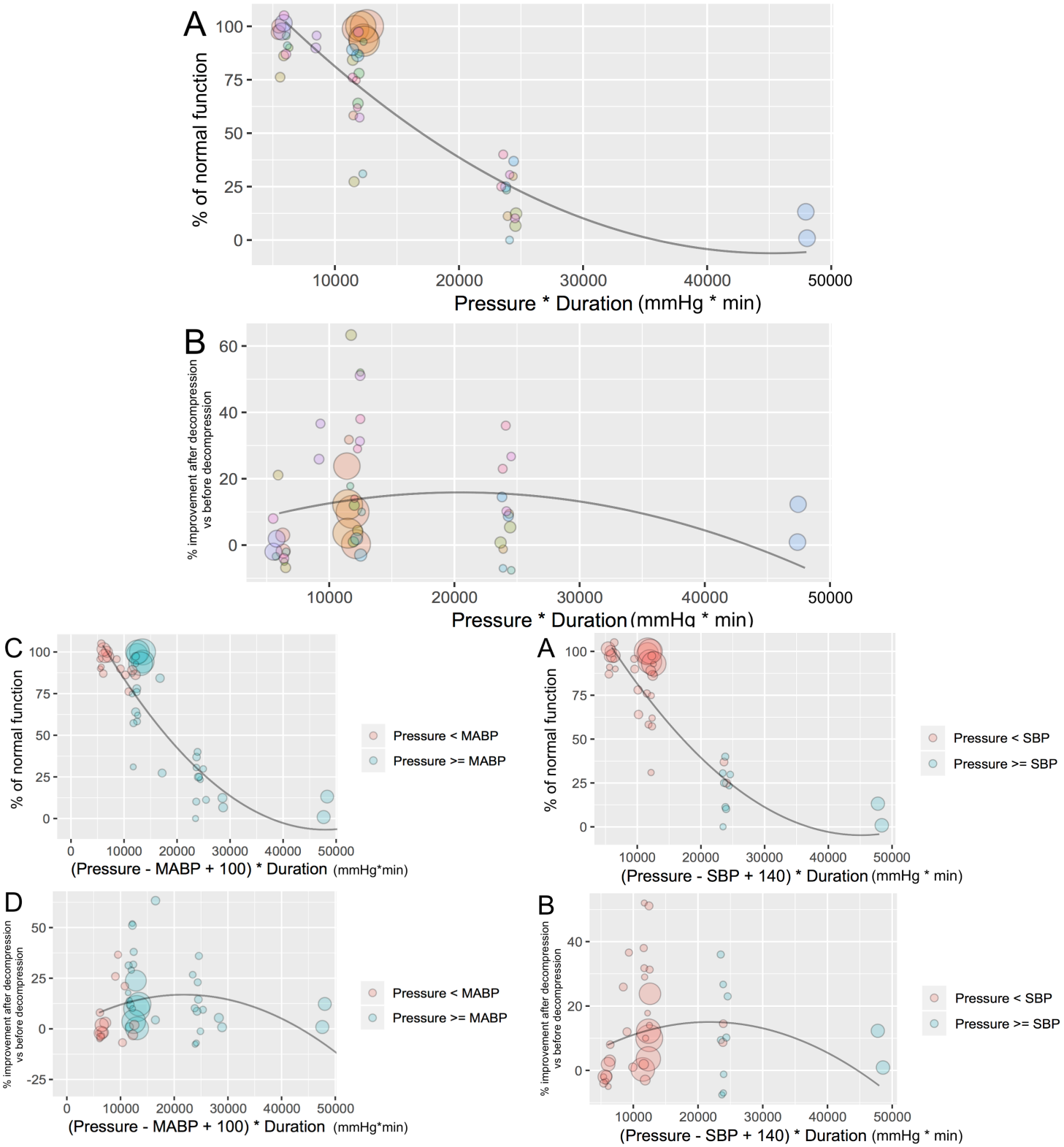
Supplementary Figure 6. Models of decompression studies after 90min recovery. A) using absolute measure by duration; B) using mean difference by duration.



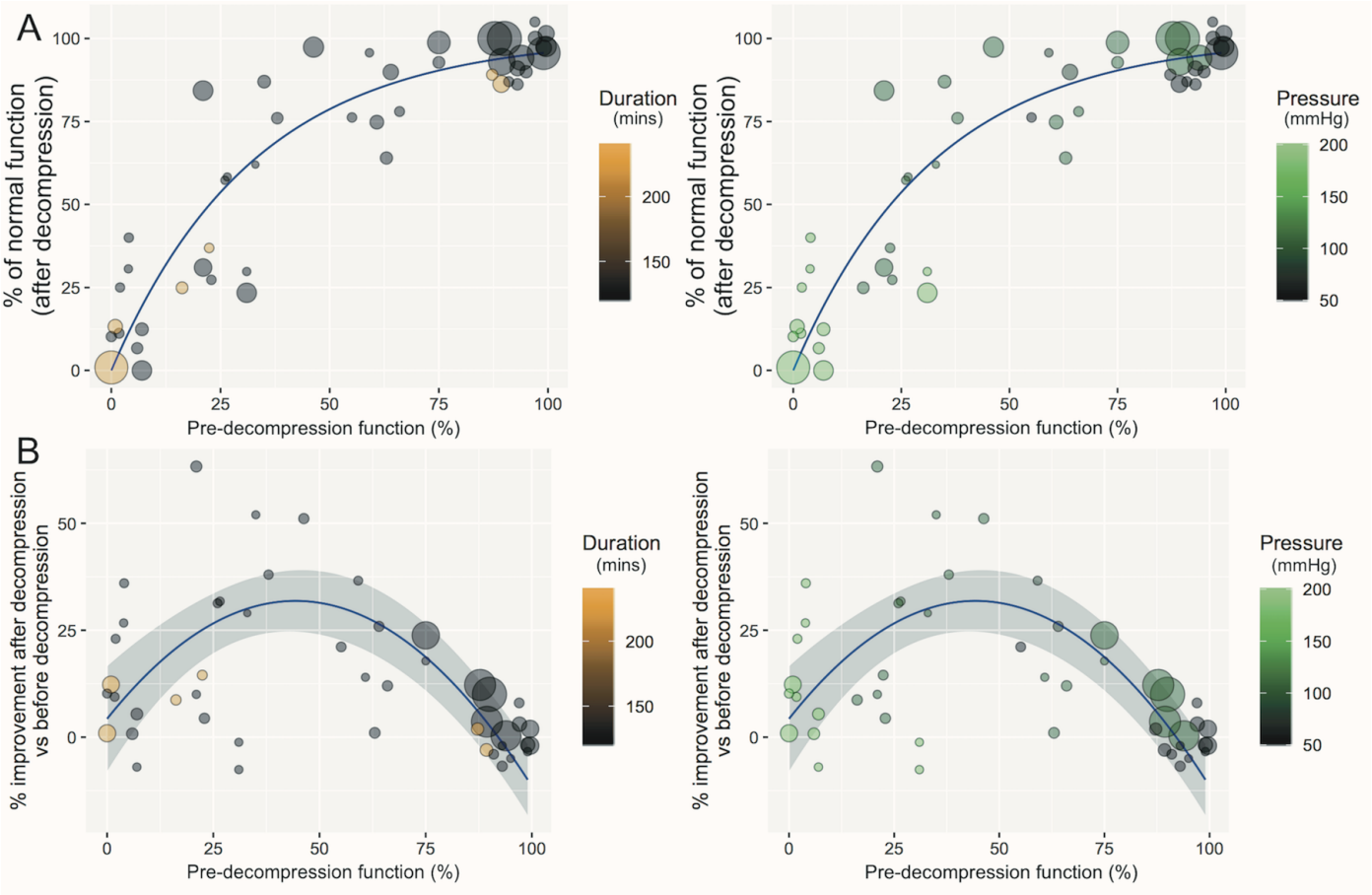
Supplementary Figure 7. Models of decompression after 90min recovery accounting for the difference between compressive pressure and MABP/SBP; by A) absolute measure, B) mean differences. MABP - mean arterial blood pressure; SBP - systolic blood pressure



Supplementary Figure 8. Pressure x duration models of decompression studies after 90min recovery. A) using absolute measure by pressure; B) using mean difference; C) accounting for MABP in absolute measure model; D) accounting for MABP in mean different model; E) accounting for SBP in absolute measure model; F) accounting for SBP in mean difference model. MABP - mean arterial blood pressure; SBP - systolic blood pressure



Supplementary Figure 9. 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.



Supplementary Figure 10. Pressure x Duration model of compression accounting for MABP with approximate extrapolated data points visualised. MABP - mean arterial blood pressure.