Supplementary File A. Data Collection and Tools

Arterial blood pressure (ABP) was obtained through radial or femoral arterial lines connected to pressure transducers (Baxter Healthcare Corp. CardioVascular Group, Irvine, CA, or similar devices). Intracranial pressure (ICP) was acquired via an intra-parenchymal strain gauge probe (Codman ICP MicroSensor; Codman & Shurtlef Inc., Raynham, MA), placed in the frontal lobe with transducers zeroed at the level of the tragus. Note no EVD were used to record ICP in this particular study cohort. These signals were captured simultaneously and digitized via an A/D converter (DT9804; Data Translation, Marlboro, MA), sampled at a frequency of 100 Hertz (Hz) or higher, using the Intensive Care Monitoring (ICM+) software (Cambridge Enterprise Ltd, Cambridge, UK, http://icmplus.neurosurg.cam.ac.uk).

BIS was recorded bilaterally using the Coviden Complete 4-Channel Monitor. Non-invasive adhesive pads are placed on the forehead, signals were recorded at 1 Hz with ICM+ software. BIS and BISopt values were obtained from the hemisphere that had no frontal lobe contusion, overlying hematoma or subgaleal/scalp hematoma, with visual inspection of the electromyography (EMG) signal of the frontalis indicating no large firing potentials, ensuring no muscle artifacts were present.

Supplementary File B. CPPopt Published Optimal Flex Methodology

CPPopt was determined in individual patients through the use of the published optimal Flex methodology (1–4). For this method, PRx values were divided and averaged into CPP bins spanning 5 mmHg. Then an automatic quadratic curve fitting method was applied to the binned CPP data to determine the CPP value with the lowest associated PRx value. CPPopt calculated in this way was recorded from a moving 4-hr to 20-hr time window, updated every minute. CPPopt requires at least 50% of the PRx data points, i.e., after a minimum of 2 hrs. of monitoring and was conducted over the course of the entire recording period for each patient.

References:

1. Liu X, Maurits NM, Aries MJH, Czosnyka M, Ercole A, Donnelly J, et al. Monitoring of Optimal Cerebral Perfusion Pressure in Traumatic Brain Injured Patients Using a Multi-Window Weighting Algorithm. J Neurotrauma. 2017 Nov 15;34(22):3081–8.

2. Depreitere B, Güiza F, Van den Berghe G, Schuhmann MU, Maier G, Piper I, et al. Pressure autoregulation monitoring and cerebral perfusion pressure target recommendation in patients with severe traumatic brain injury based on minute-by-minute monitoring data. J Neurosurg. 2014 Jun;120(6):1451–7.

3. Sorrentino E, Diedler J, Kasprowicz M, Budohoski KP, Haubrich C, Smielewski P, et al. Critical Thresholds for Cerebrovascular Reactivity After Traumatic Brain Injury. Neurocrit Care. 2012 Apr 1;16(2):258–66.

4. Donnelly J, Czosnyka M, Adams H, Robba C, Steiner LA, Cardim D, et al. Individualizing Thresholds of Cerebral Perfusion Pressure Using Estimated Limits of Autoregulation. Crit Care Med. 2017 Sep;45(9):1464–71.

Supplementary File C. Method to Determine the Optimal BIS Value

The method outlined here is similar to the work done by Aries et al. on the determination of CPPopt.(5) Initially PRx data were processed using Fisher Transform to achieve a normal distribution eliminating the ceiling effect of the maximum PRx value of ±1.(6) These PRx values were divided and averaged into BIS bins spanning 3 arbitrary units (au), chosen as 20 bins over a BIS range from 20 to 80 au. BIS values can range from 0 (isoelectric EEG) to 100 (awake) (7,8). BIS values from 0 to 20 are EEG burst suppression, and 80 to 100 are semi-conscious states, thus have been excluded from the assessment of BISopt (7,8). The mean value and standard deviation of each bin were then plotted against the bin mean BIS value in order to create the error bar chart representing the relationship between PRx and BIS. Theoretically, a U-shaped relationship should be demonstrated with cerebrovascular pressure reactivity getting worse (PRx increasing) for BIS values further away from the curve center. Thus, a quadratic algorithm was therefore used to fit a parabolic curve to the PRx-BIS error bar plot in order to estimate an optimal BIS value (BISopt), which is the BIS value for which PRx achieves the smallest value.

The following summarizes the process implemented:

1. Discard BIS bins that contain <2% of the data points.
2. Ensure that the BIS values span at least 4 bins (12 au.).
3. Ensure that PRx values span at least 0·2 au.
4. Fit a second-order polynomial to the boxplot, the fitted curve must fulfill the following criteria:
    a. In the first attempt, the curve fitted is expected to include a convex point (a sign change of the first derivative from negative to positive). If such a curve cannot be found or it does not fulfill all the remaining criteria, then the monotonically ascending or descending part of the curve can be used. However, the curve must follow a positive convex shape to some extent.
    b. The sequence of the mean PRx values of the last two bins at each edge of the curve must follow the correct, expected order depending on the part of the parabolic curve fitted (i.e., descending at the left edge and ascending on the right when fitting a parabolic curve including a clear minimum). The edge bins that do not fulfill this criterion are excluded, and the fitting process is repeated.
    c. Data corresponding to the bins used in successful curve fitting (i.e., after various exclusions mentioned above) must at least:
        i. represent 50% of all the data points in the analyzed window period
        ii. cover at least 50% of the range of PRx data available in that period
        iii. represent 12 au. of BIS fluctuation, so the number of bins used for data fit must be at least 4
        iv. fitted part of the curve must span the range of PRx values of at least 0·2; in other words, curves that are too "flat" are rejected

5. If all the criteria/restrictions are fulfilled, the fitting procedure is stopped and BISopt is determined. The BISopt value corresponds to the minimum point of the fitted curve that lies within the range of BIS values. It should be noted that when the fitted curve does not include a clear convex point, the estimated optimal value will be either underestimated (ascending curve) or overestimated (descending curve) depending on the shape of the fitted part.

6. If all attempts have been exhausted and no satisfactory curve was fitted, the procedure returns an invalid value (i.e., Not-A-Number value) for the selected period.

References:

5. Aries MJ, Czosnyka M, Budohoski K, Steiner L, Lavinio A, Kolias A, et al. Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury*. Crit Care Med. 2012 Aug;40(8):2456–63.

6. Czosnyka M, Miller C, Participants in the International Multidisciplinary Consensus Conference on Multimodality Monitoring. Monitoring of cerebral autoregulation. Neurocrit Care. 2014 Dec;21 Suppl 2:S95-102.

7. Mitchell-Hines T, Ellison K, Willis S. Using bispectral index monitoring to gauge depth of sedation/analgesia. Nursing2020 Crit Care. 2017 Jan;12(1):12–6.

8. Mathur S, Patel J, Goldstein S, Jain A. Bispectral Index. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 [cited 2020 Nov 7]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK539809/

Supplementary File D. Optimal BIS Value

To evaluate the general presence of BISopt in each patient, examples are shown in Supplementary File D1 Figure 1. It should be noted that when the fitted curve does not include the convex point, the estimated "optimal" value will be either overestimated (ascending curve) or underestimated (descending curve) depending on the shape of the fitted part (Fig. B-C). Error-bar plots of BIS vs. PRx were also manually inspected, to compare the BISopt values from visual inspection to those derived from the automated curve fitting methodology described in Supplementary File C.

Supplementary File D1 Figure 1. Different BISopt Methods

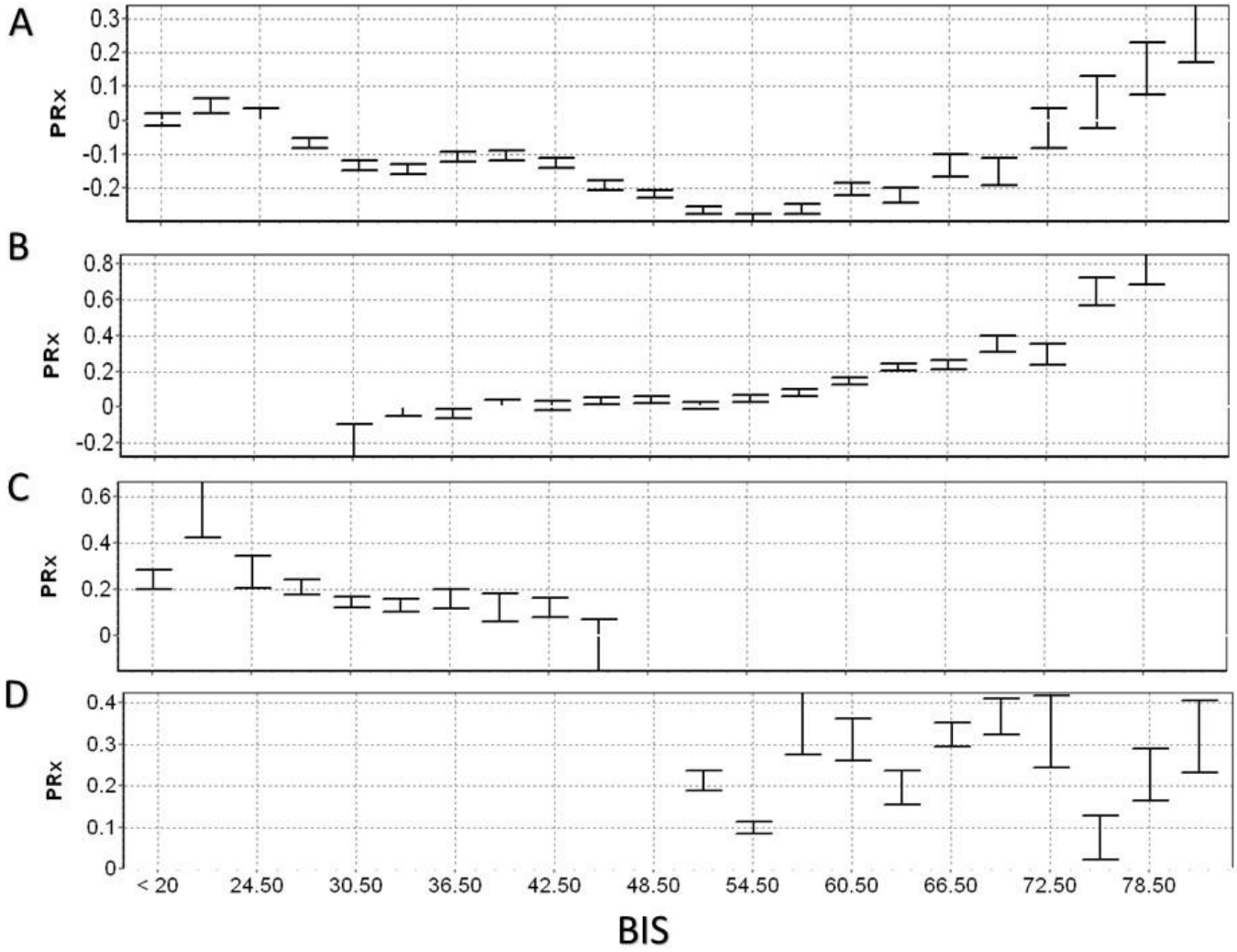

Figure demonstrates the relationship between BIS and PRx and shows the 4 main categories of responses. 'A' shows the U-shaped curve on which a full BISopt curve is found. 'B' shows an ascending BISopt curve, 'C' shows a descending BISopt curve. 'D' shows an unclear result where BISopt cannot be determined. BIS, bispectral index; BISopt, optimal BIS value; PRx, pressure reactivity index.

Supplementary File D2. Comments on BISopt values and Ranges

BIS values are bilaterally determined and can range from 0 to 100, with: BIS values from 0 to 20 being EEG burst suppression, 20 to 40 deep hypnotic state, 40 to 60 general anesthesia, 60 to 80 response to loud prompts and 80 to 100 are semi-conscious states (7,8). In our analysis we found that most patients had a BISopt 50±15au, this indicates that in many patients the optimal BIS value is in the state of what is considered to be general anesthesia. As previously indicated, these findings may suggest there is an optimal BIS value that occurs when sedation is given and an optimal amount. At very high levels of sedation (metabolic suppression levels) cerebral vessels may lose their innate ability to mediate vascular control and thus would demonstrated impaired PRx (9). Though less sedation post-TBI state is not significantly understood, we propose that less sedation either causes an increase in metabolic demand which could cause vasodilation or an increase in sympathetic tone and vasoconstriction, both may impaired homeostasis in patients and could have detrimental effects on cerebrovascular reactivity.(10–12)

However, this theory must be tempered by 2 facts; we currently do not know the full physiological impact and influence that is connected to BIS values and the particular influence that sedative agent have on cerebral physiology may vary. Thus, our understanding of sedation is highly limited and limits the conclusions of this study.

References:

7. Mitchell-Hines T, Ellison K, Willis S. Using bispectral index monitoring to gauge depth of sedation/analgesia. Nursing2020 Crit Care. 2017 Jan;12(1):12–6.

8. Mathur S, Patel J, Goldstein S, Jain A. Bispectral Index. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 [cited 2020 Nov 7]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK539809/

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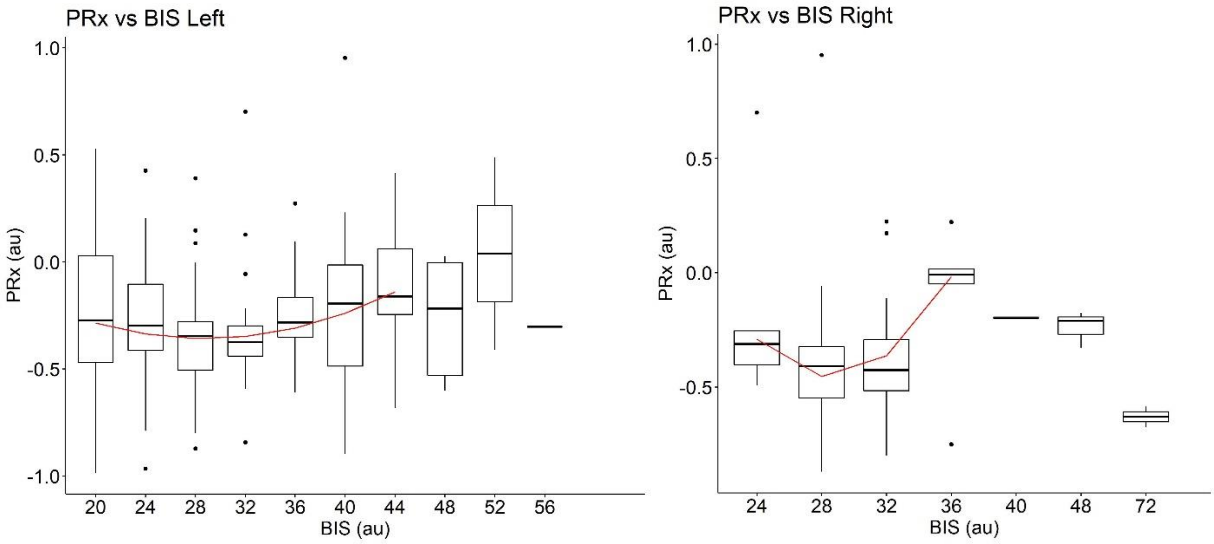
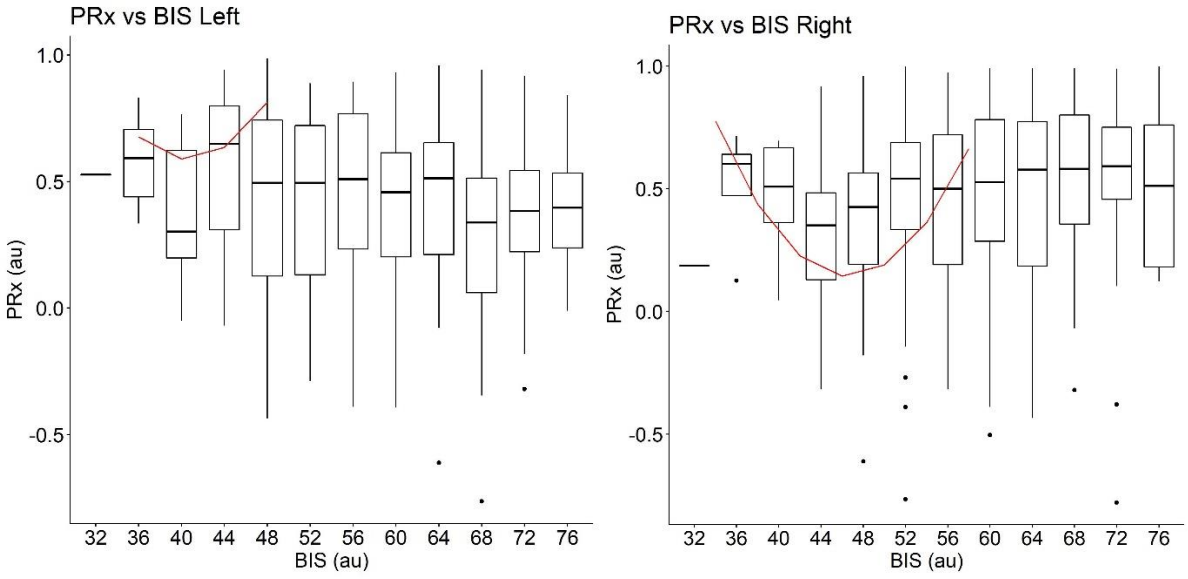
Supplementary Figures E. Examples of the 32 Patient's BISopt Derivation – Entire Recording

Boxplots represents the right or left side binned BIS values and the Fisher Z PRx values. Plots have been omitted for a patient's hemisphere having any factors that interfere with a BIS signal (hemisphere with hematoma and/or contusion). The line is a curve of our method on the data over the full recording patient data. For the bins where data is less than 2%, there will be no curve line, thus the curve will not extend to the full data span. A complete BISopt curve (a convex point with a clear U-shape) was on average present in 78.1% of the patients, with 12.5% ascending and 9.4% descending portions of the parabolic relationship. au, arbitrary units; BIS, bispectral index; PRx, pressure reactivity index

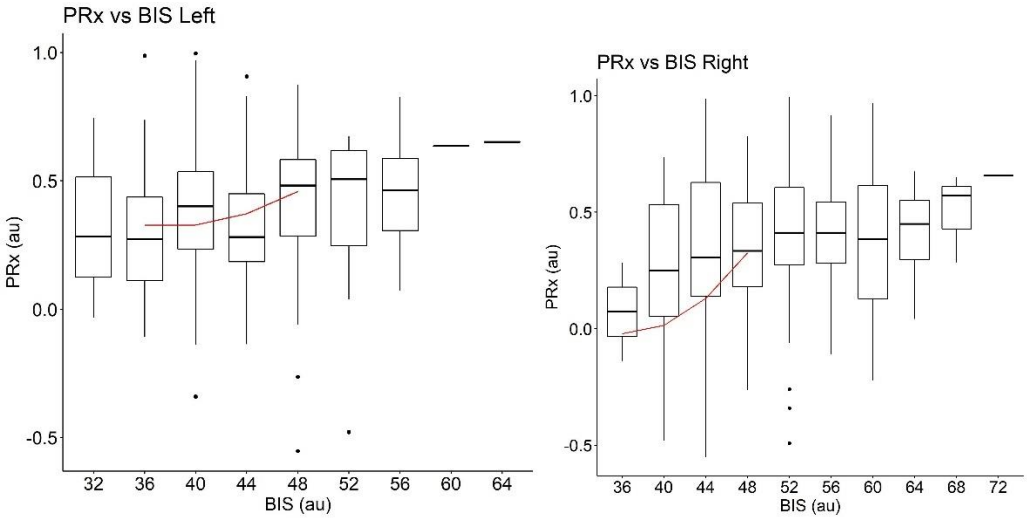
Patient 1 – U-shaped Curves



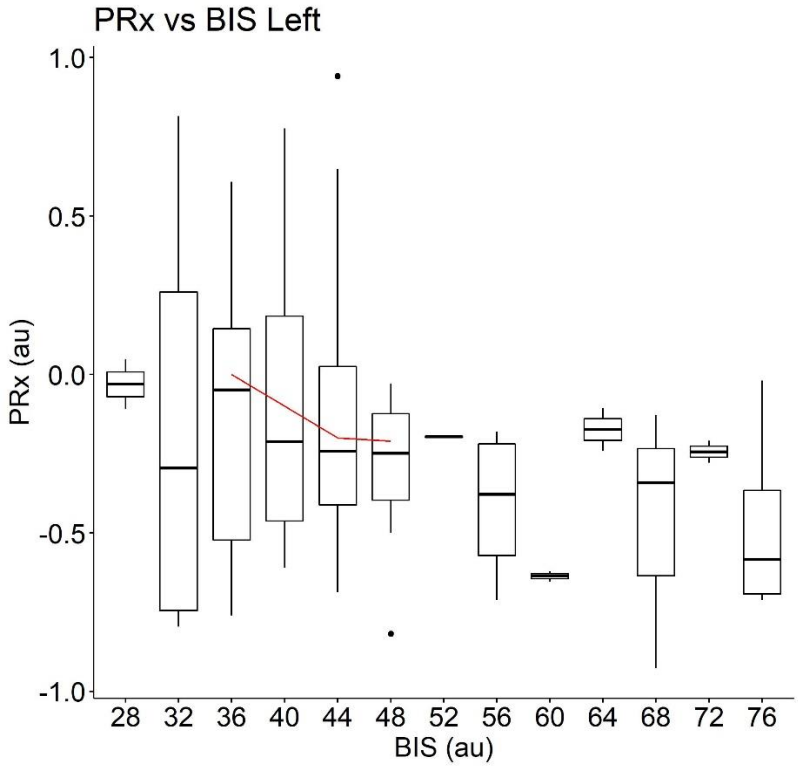
Patient 2 – U-shaped Curves



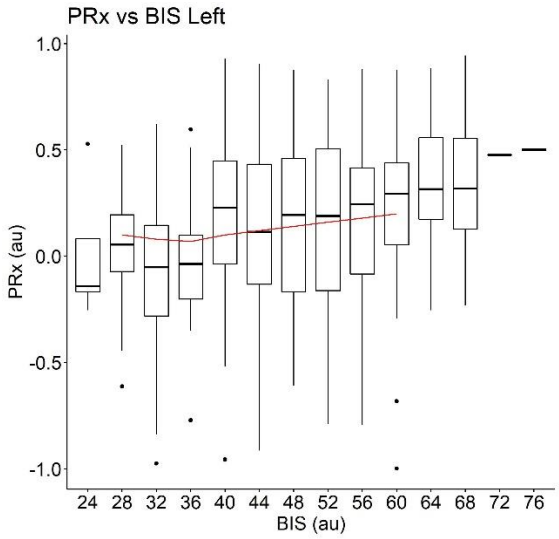
Patient 3 – Ascending Curves

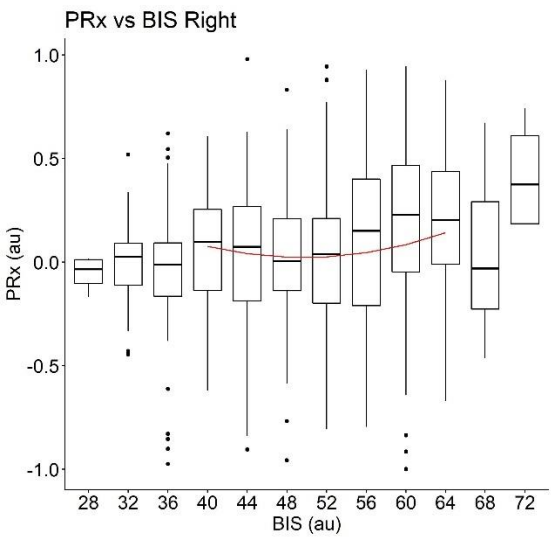


Patient 4 – Descending Curve

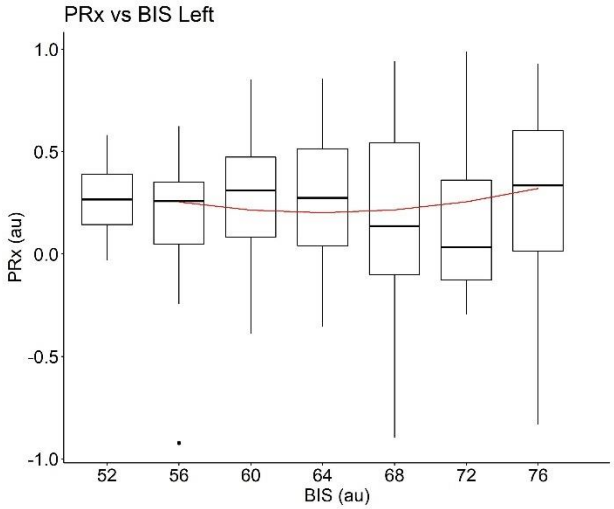


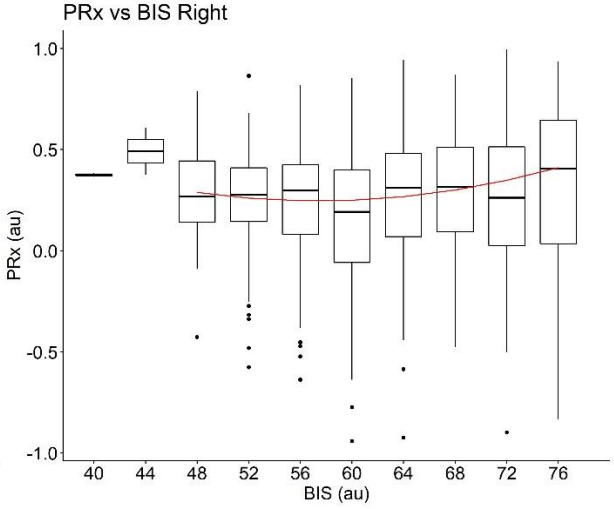
Patient 5 – U-shaped Curves



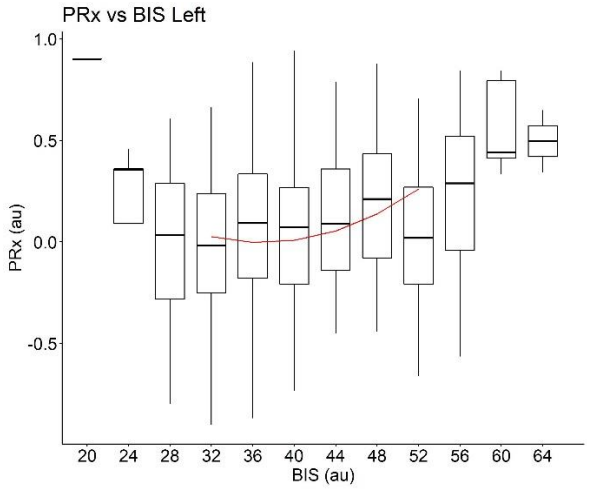


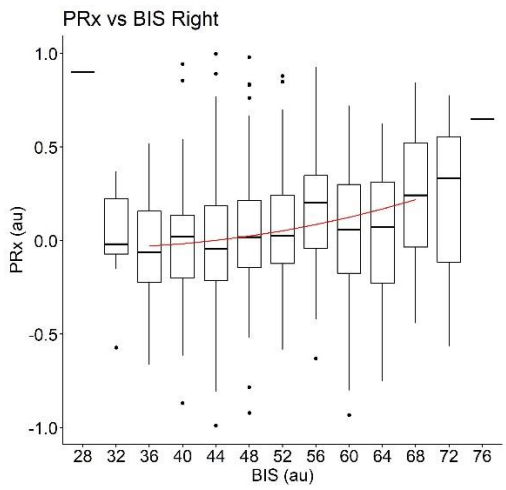
Patient 6 – U-shaped Curves



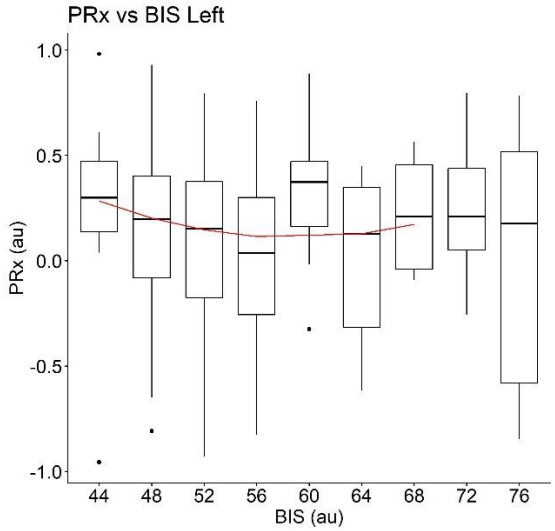


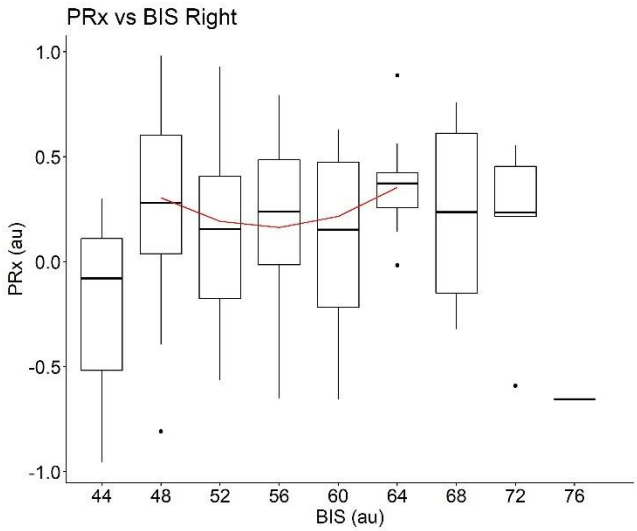
Patient 7 – U-shaped Curve and Ascending Curve



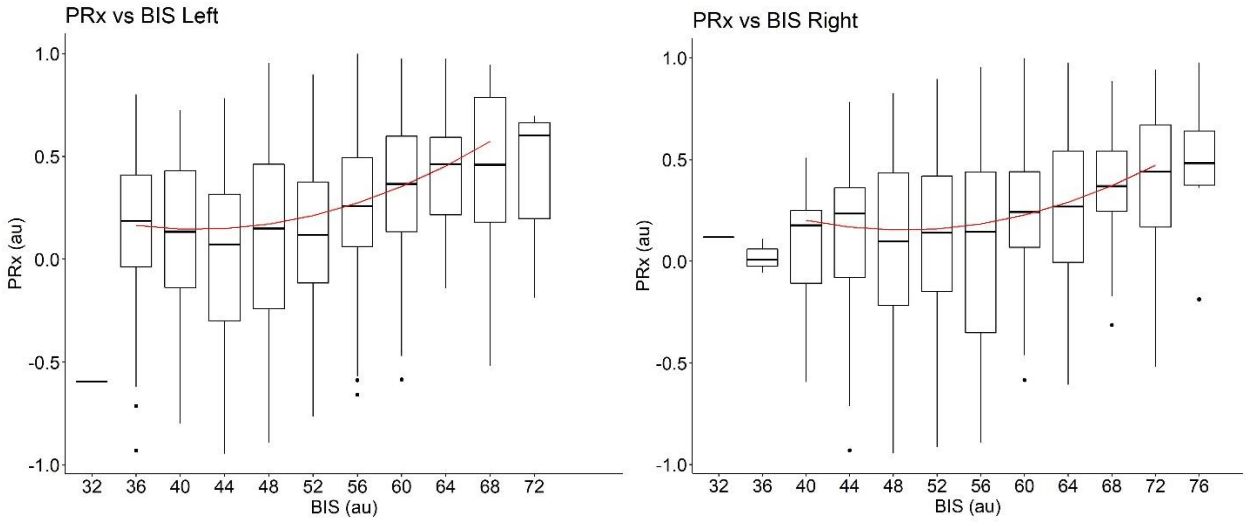


Patient 8 – U-shaped Curves

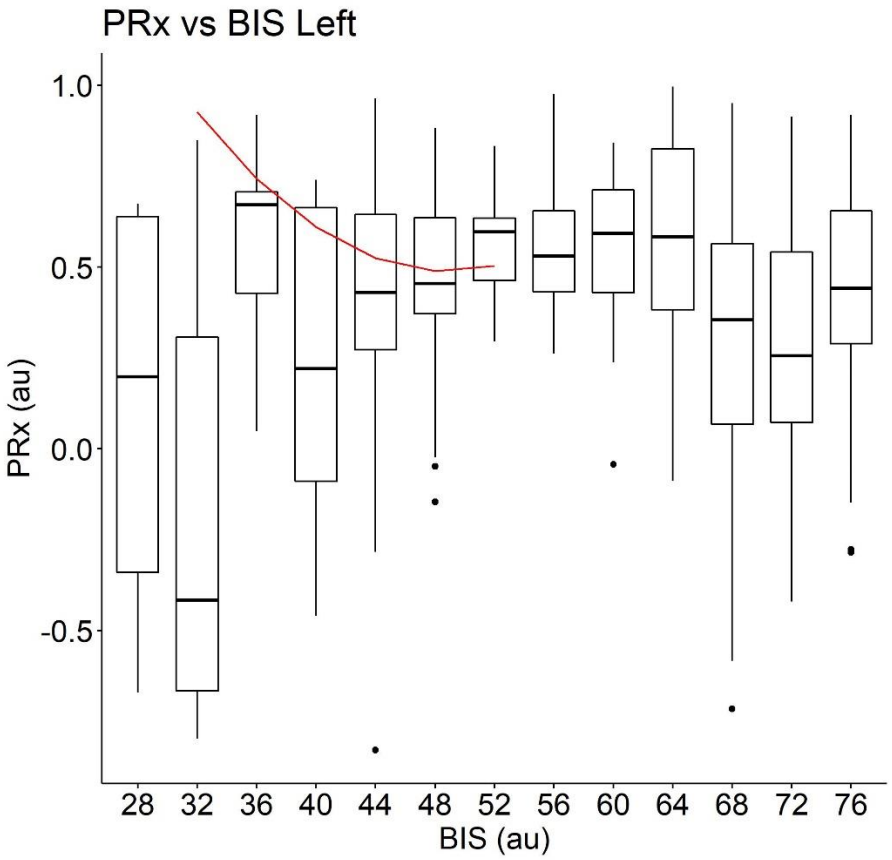




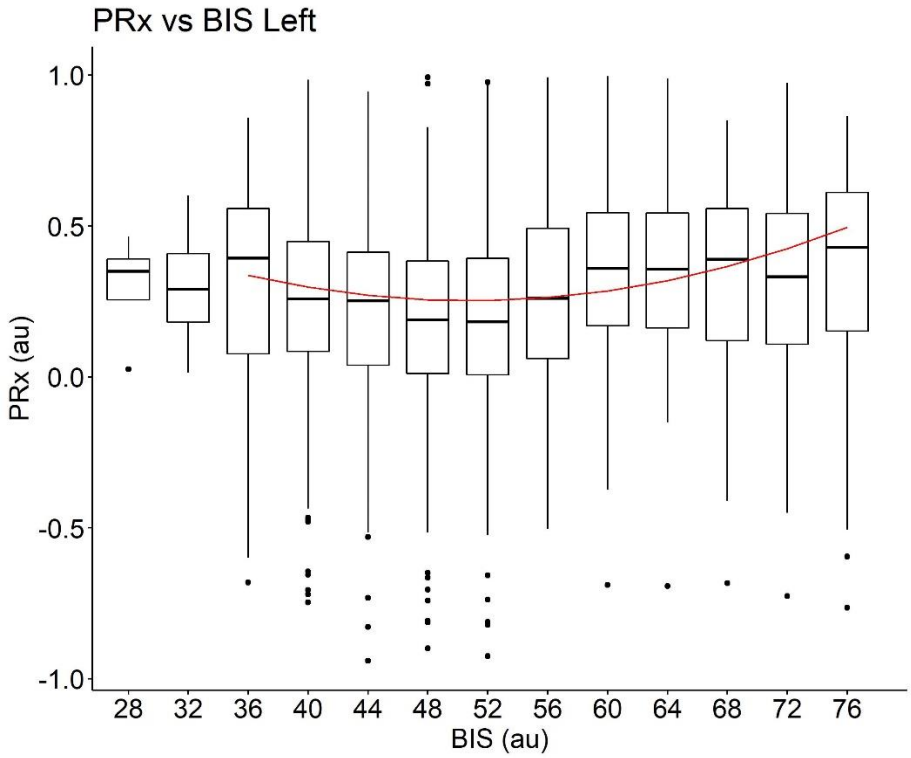
Patient 9 – U-shaped Curves



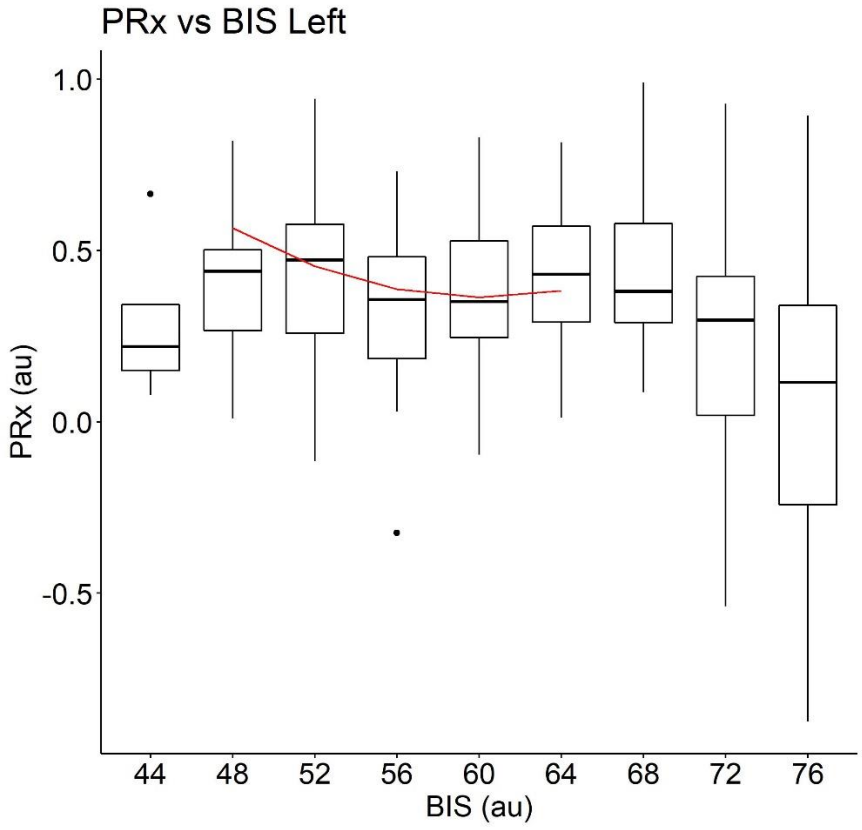
Patient 10 – U-shaped Curve



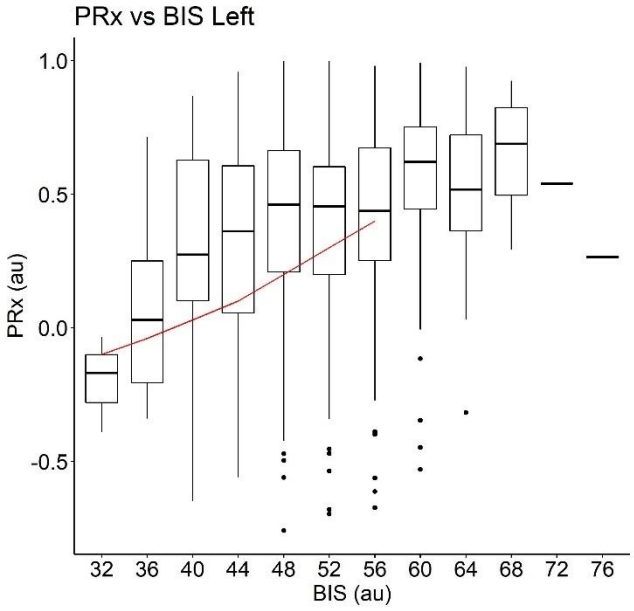
Patient 11 – U-shaped Curve

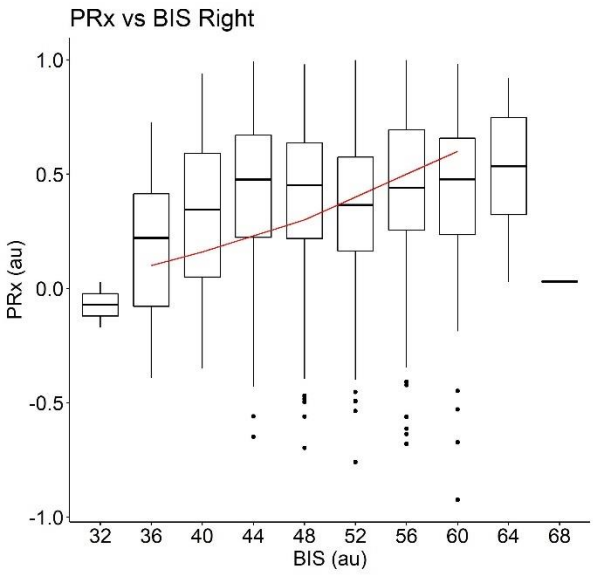


Patient 12 – U-shaped Curve

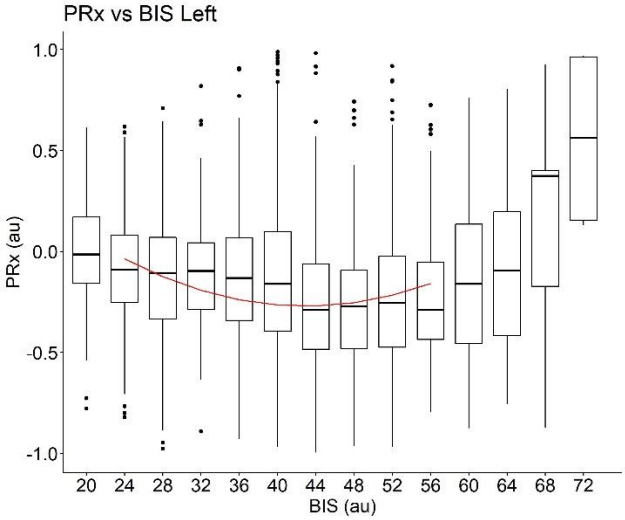


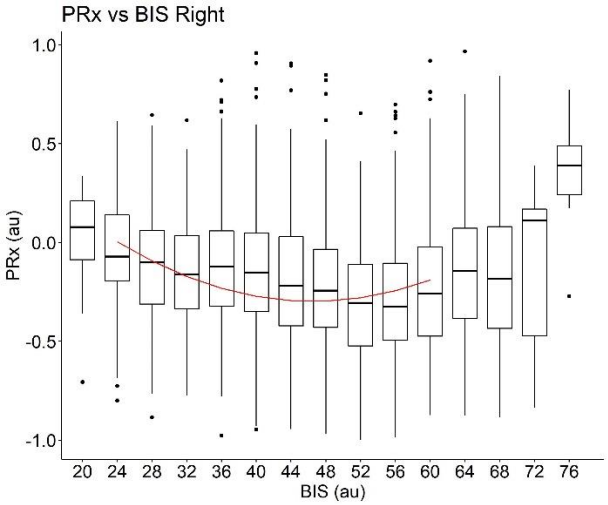
Patient 13 – Ascending Curves



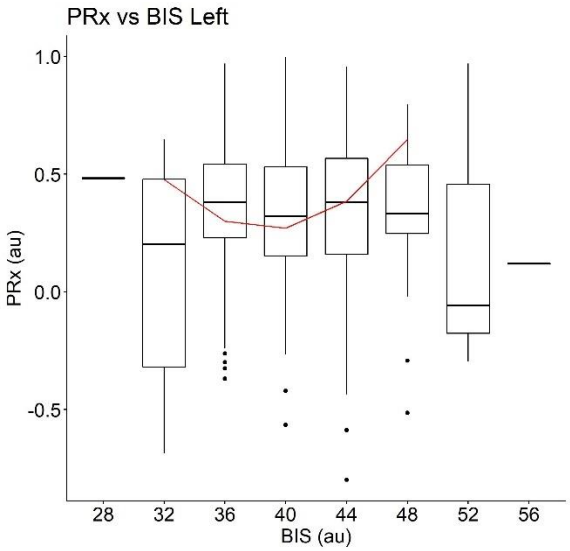


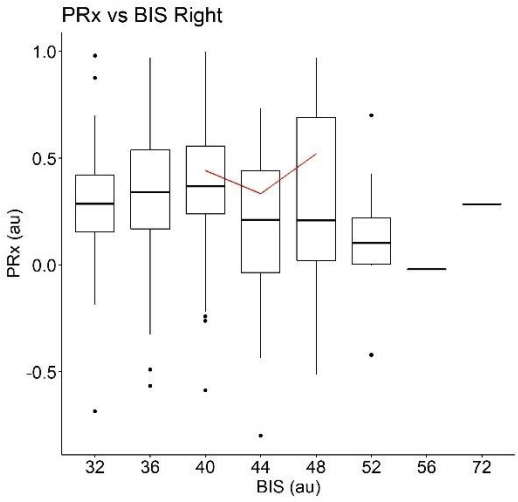
Patient 14 – U-shaped Curves



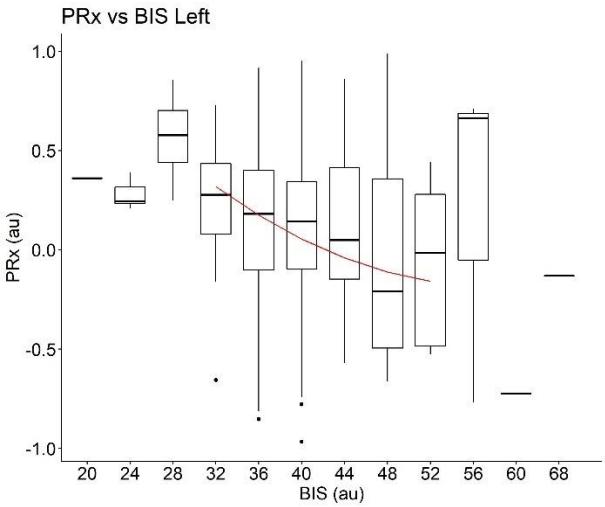


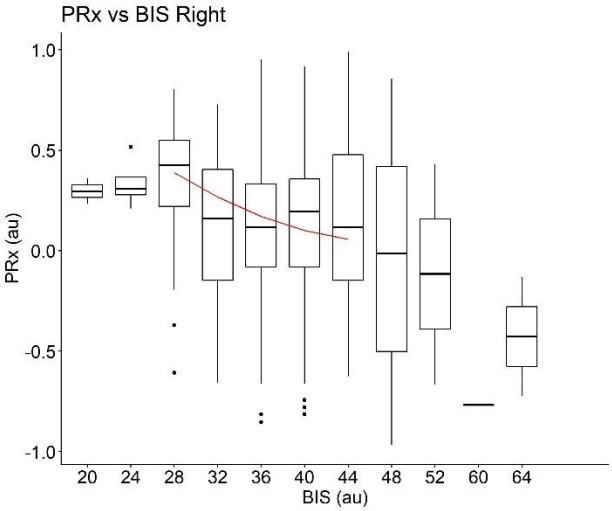
Patient 15 – U-shaped Curves



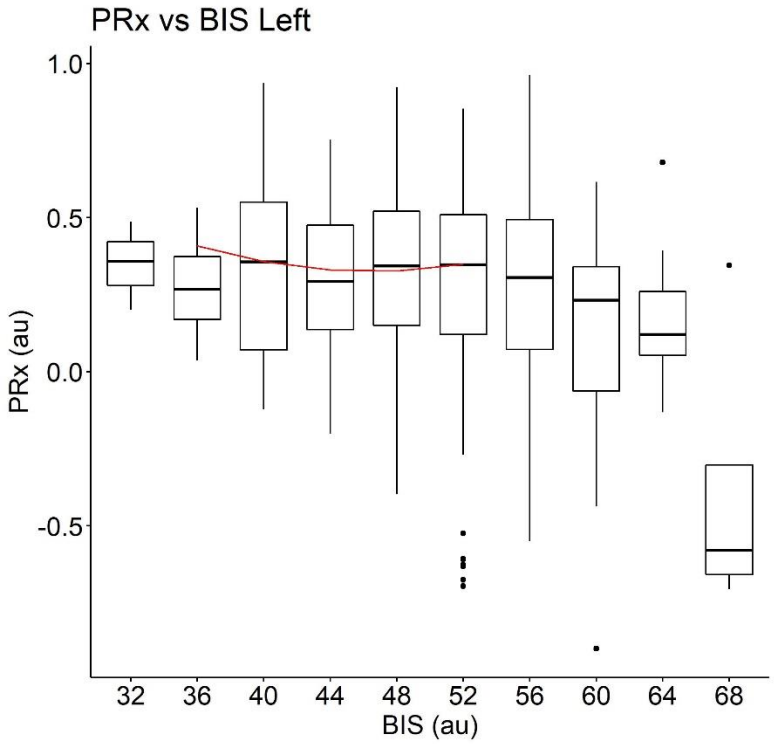


Patient 16 – Descending Curves

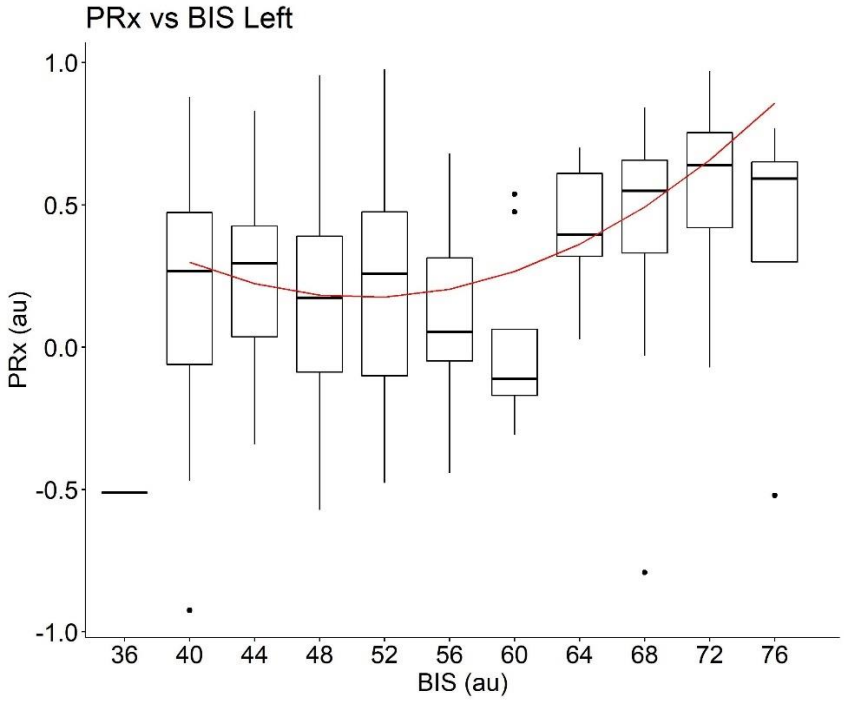




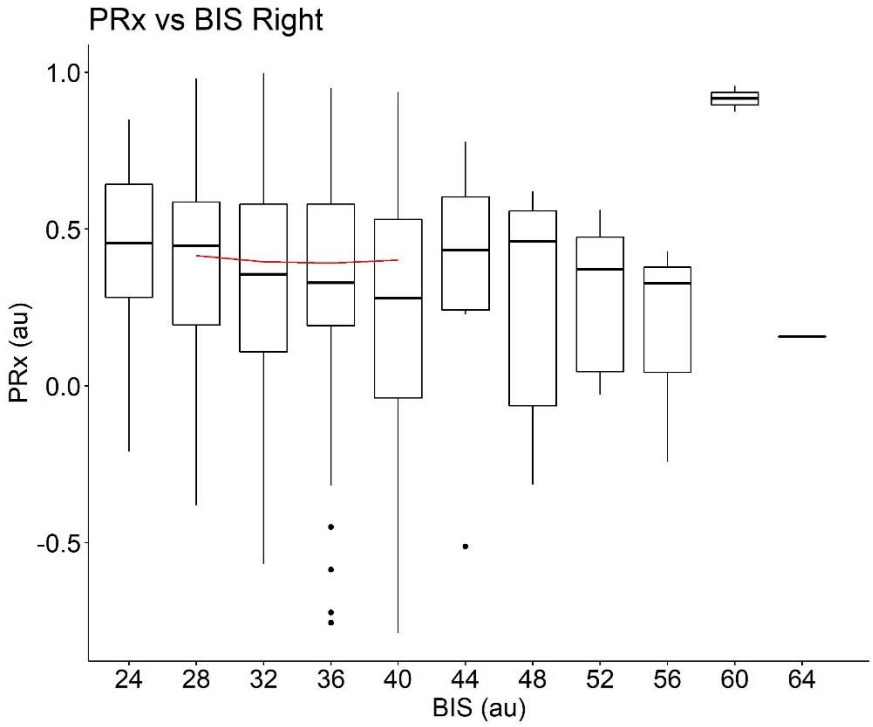
Patient 17 – U-shaped Curve



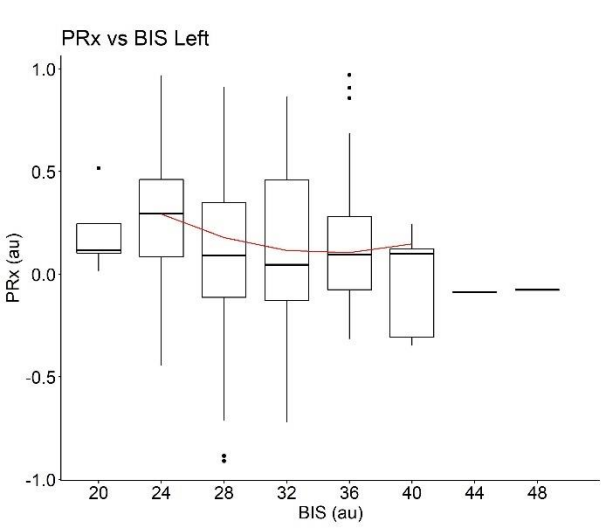
Patient 18 – U-shaped Curve

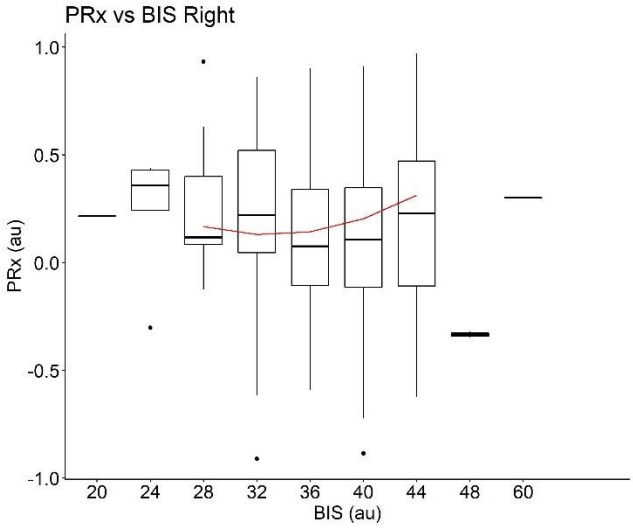


Patient 19 – U-shaped Curve

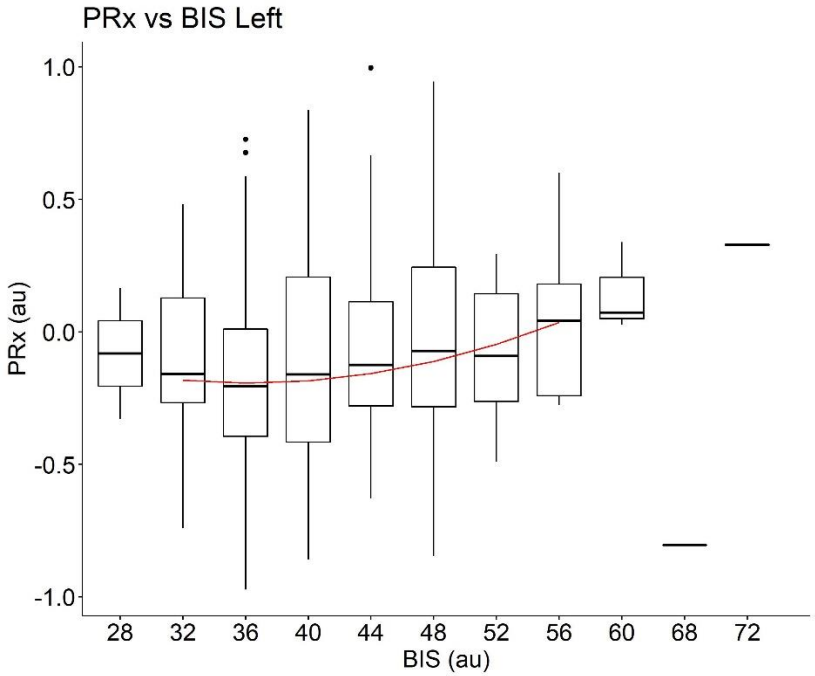


Patient 20 – U-shaped Curves

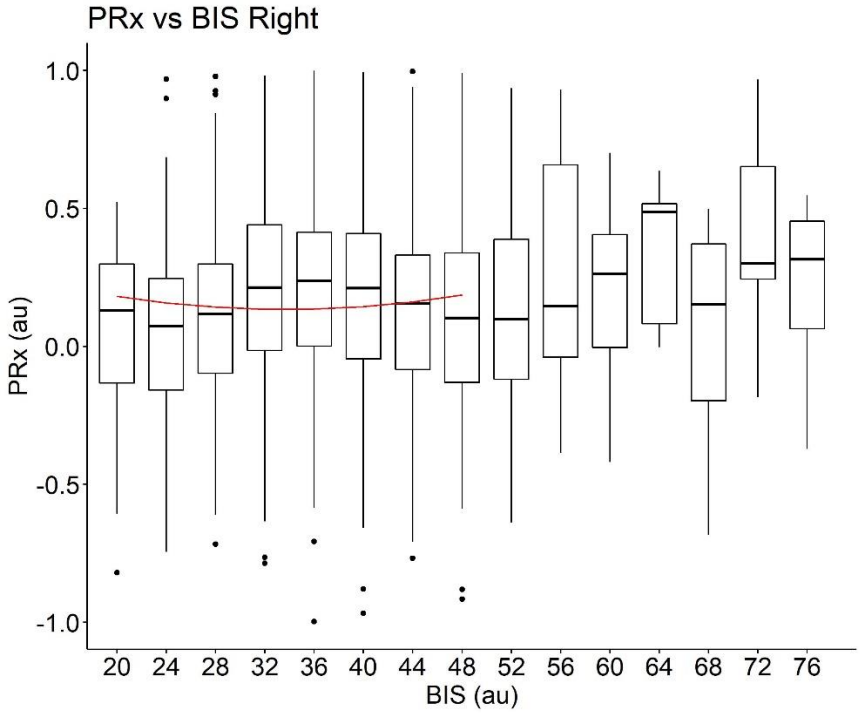




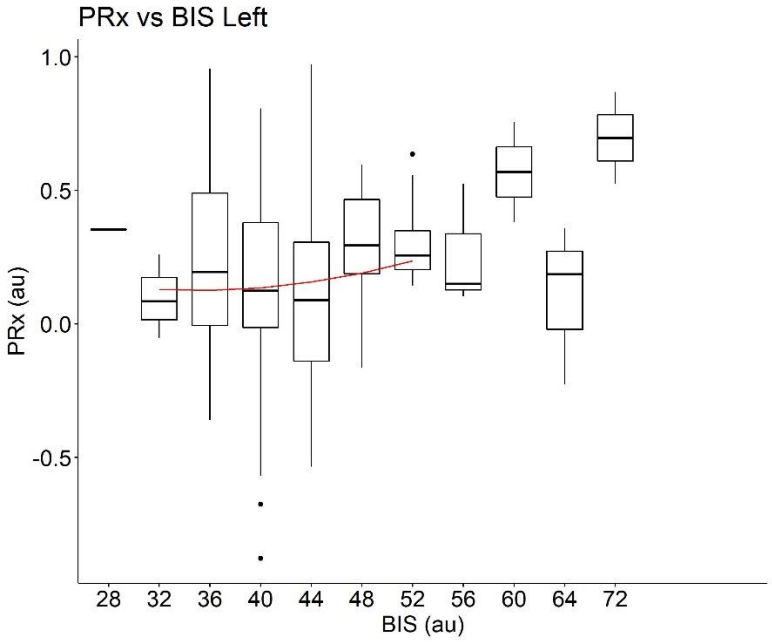
Patient 21 – U-shaped Curve



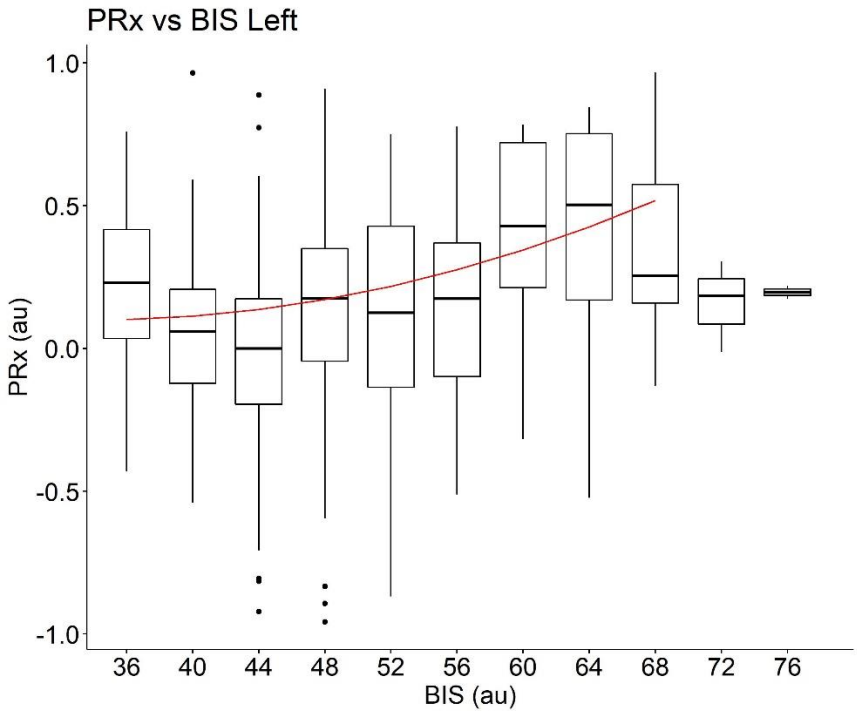
Patient 22 – U-shaped Curve



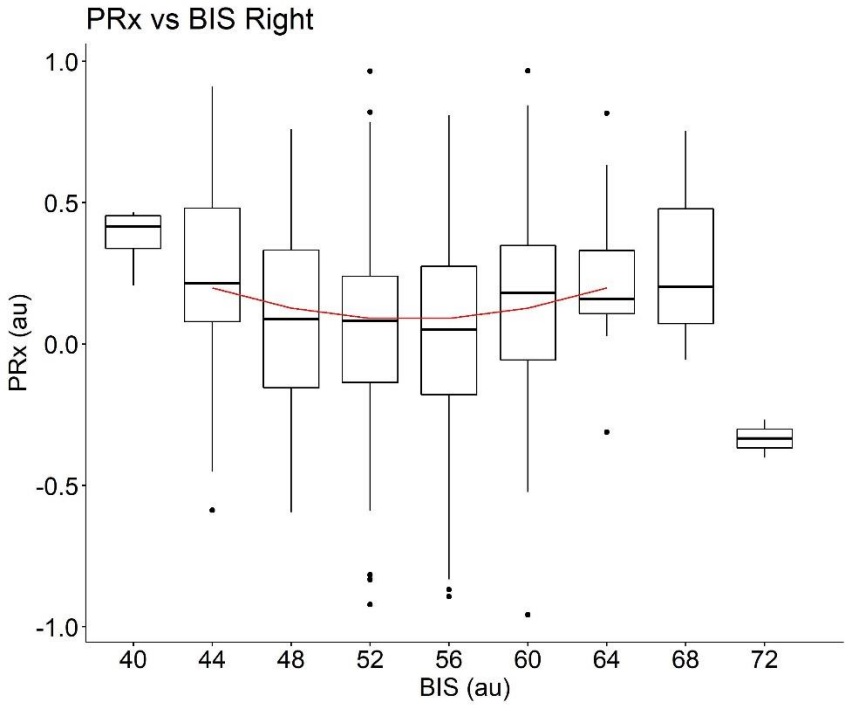
Patient 23 – Ascending Curve



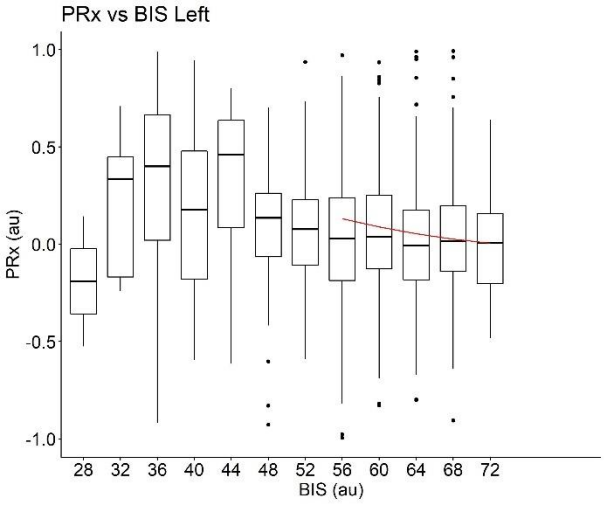
Patient 24 – Ascending Curve

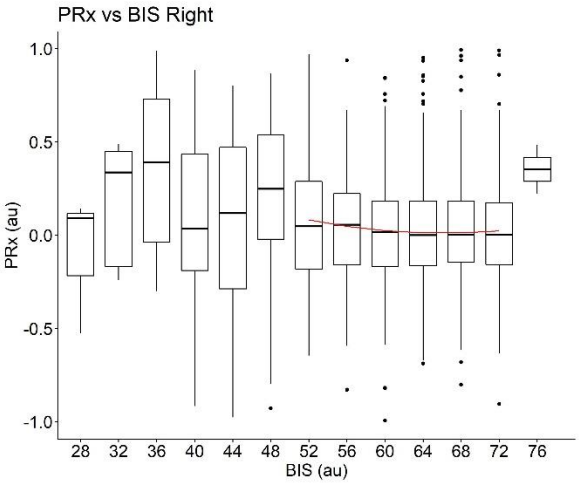


Patient 25 – U-shaped Curve

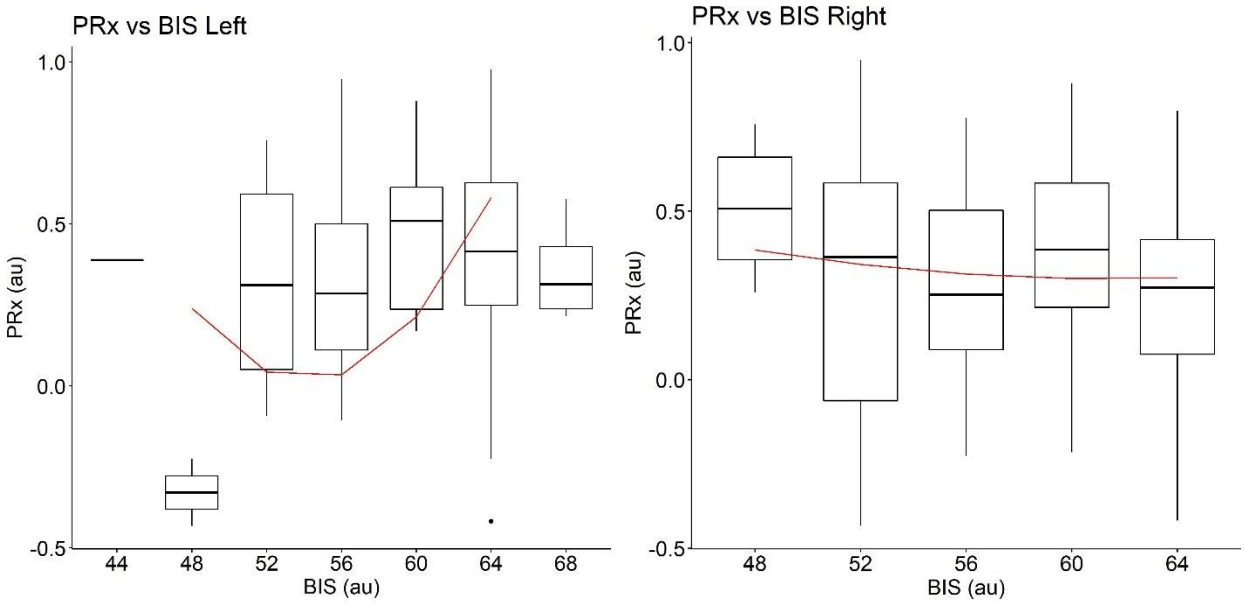


Patient 26 – Descending Curves

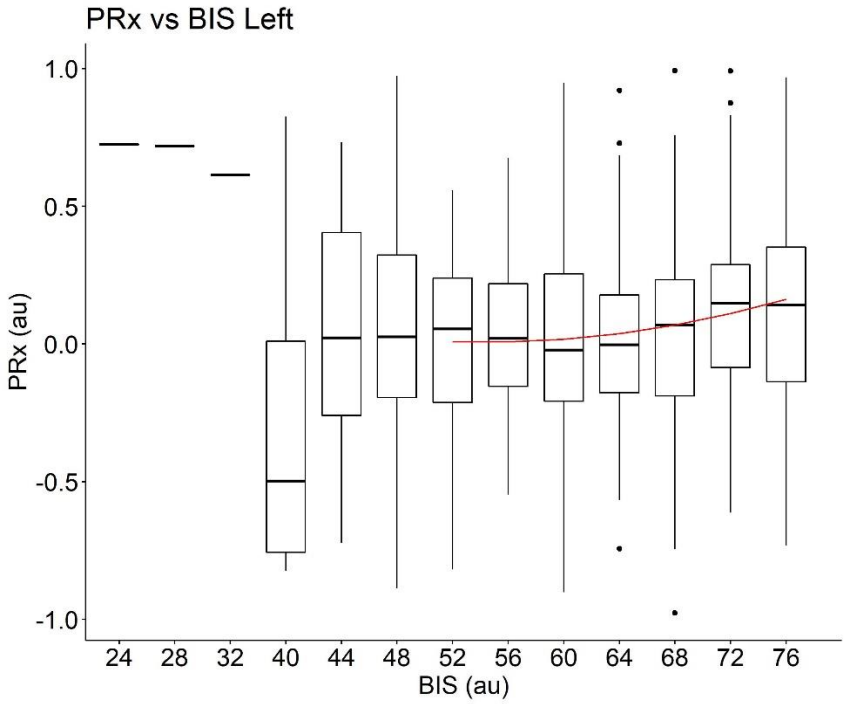




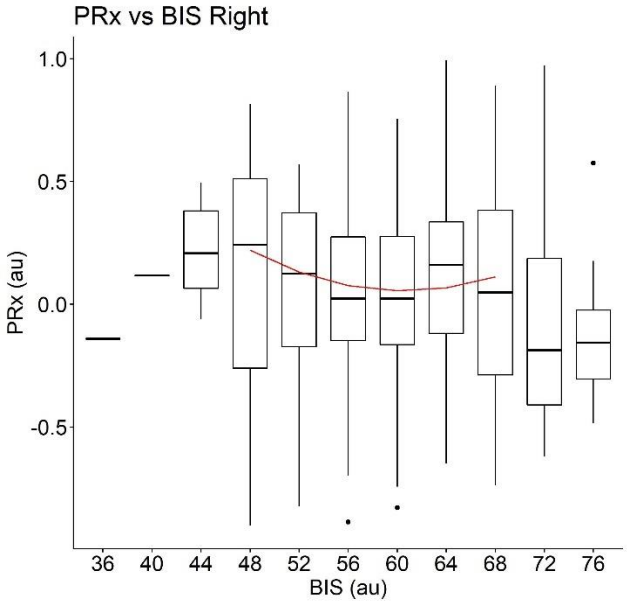
Patient 27 – U-shaped Curves



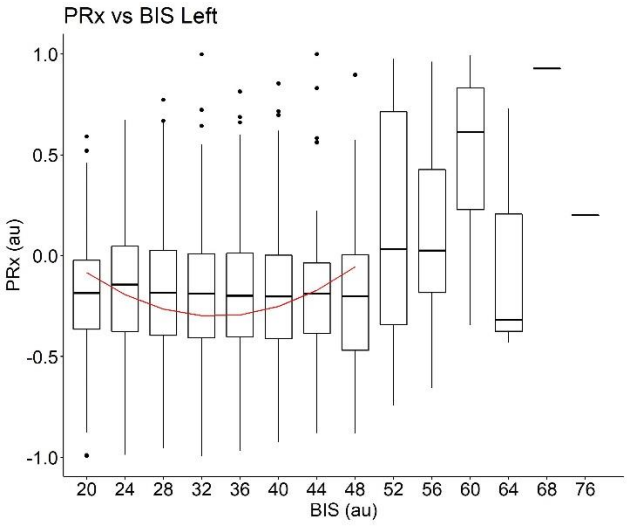
Patient 28 – U-shaped Curve

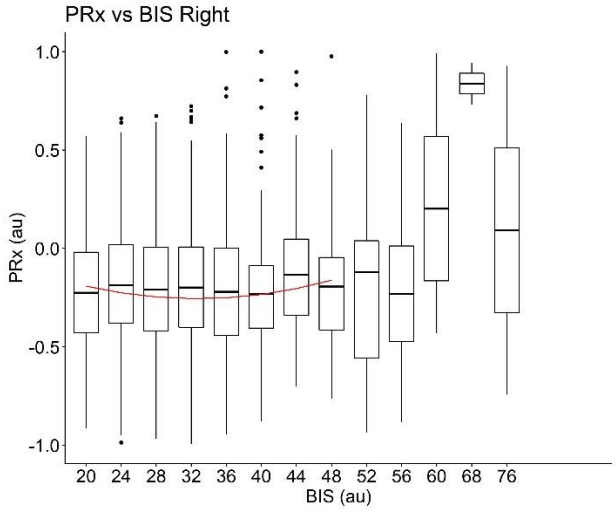


Patient 29 – U-shaped Curve

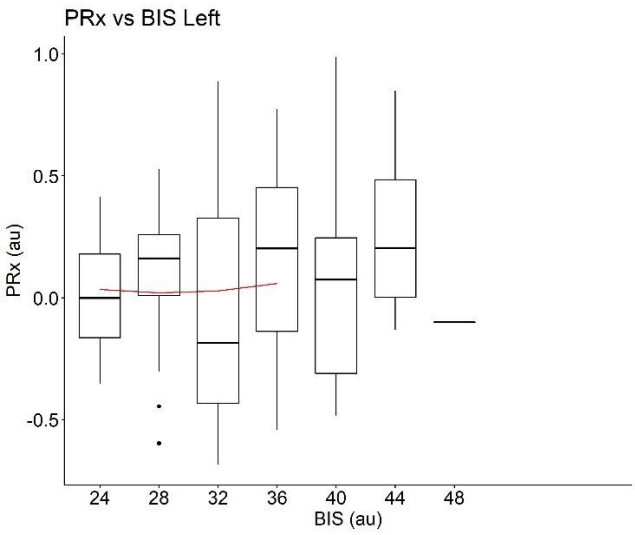


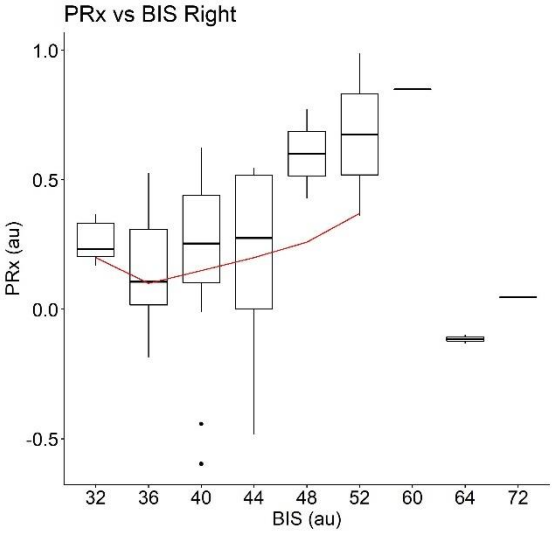
Patient 30 – U-shaped Curves



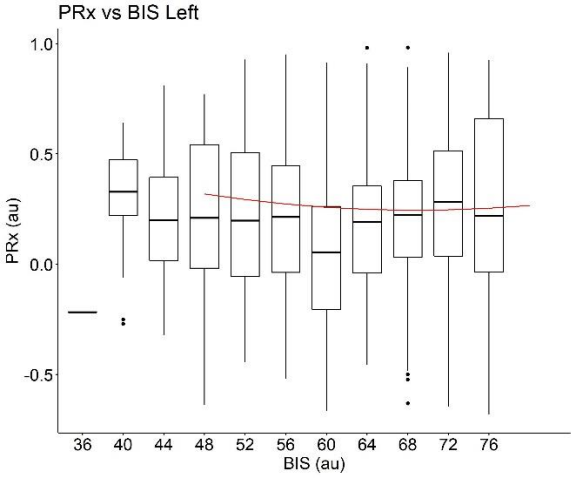


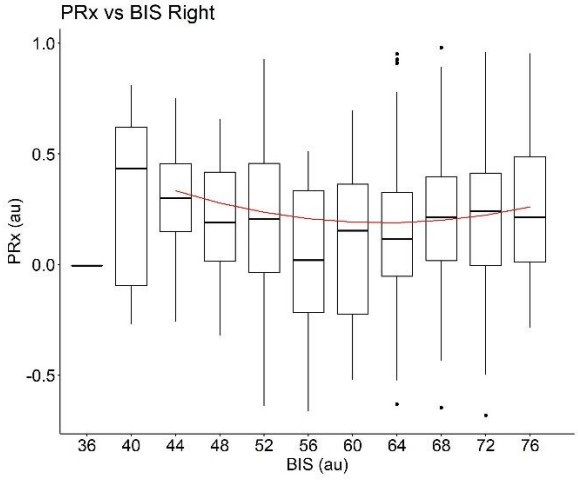
Patient 31 – U-shaped Curves





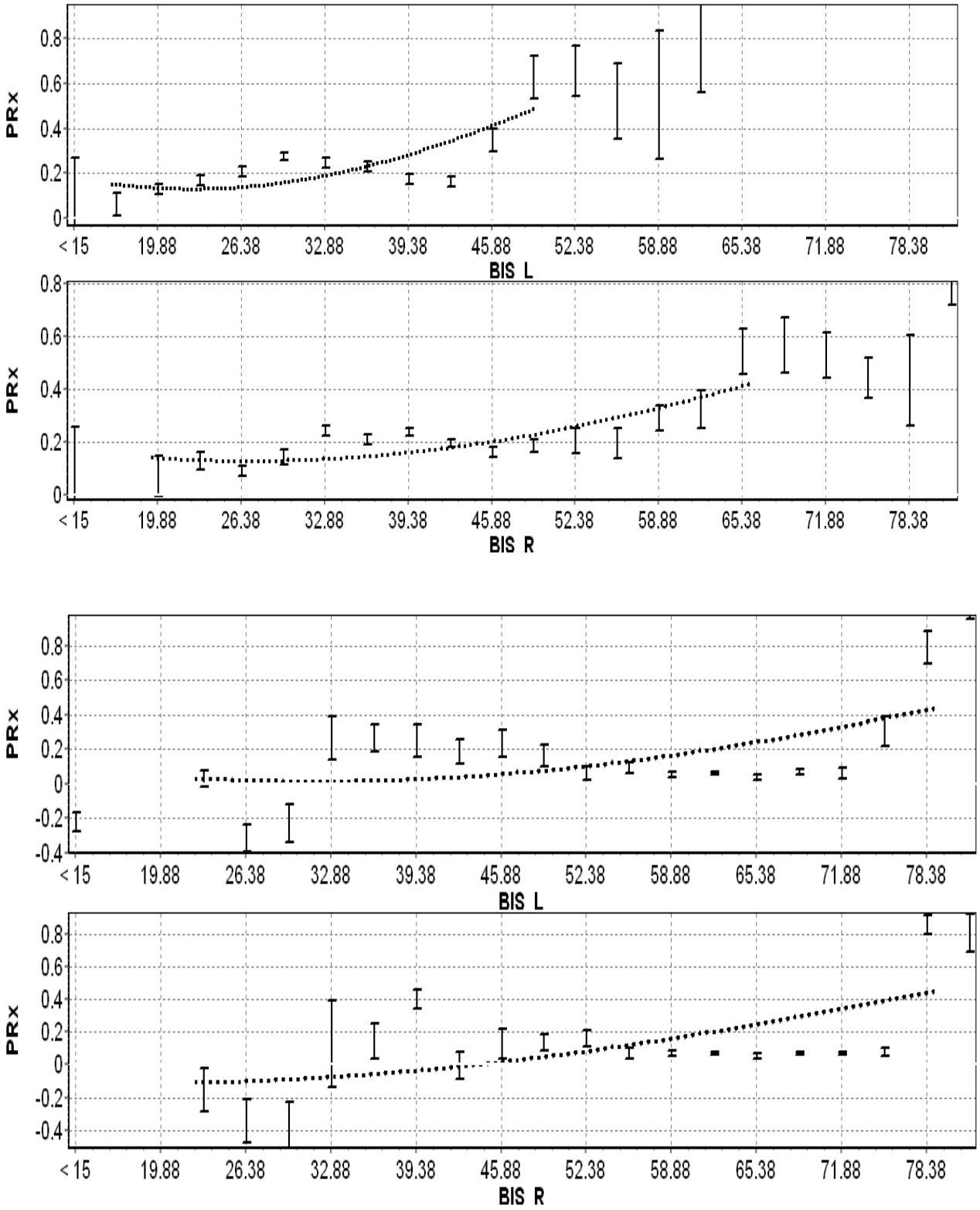
Patient 32 – U-shaped Curves





Supplementary Figure F. Incorrect BISopt Values using Optimal Flex

For BISopt determined over the entire recording period for each patient, both our algorithmic method and the optimal Flex method consistently determined a similar BIS value when there was a clear U-shaped curve or sufficient data to achieve a clear convex point. However, the optimal Flex method produced slightly inaccurate results in comparison to our method, especially when BIS data spans were wide, where the Flex method appeared to be influenced by the tails of data found at extremes.



Figures show the curves determined through the ICM+ optimal Flex method between BIS and PRx are incorrect in this scenario, the values are shifted to the lower end. BIS, bispectral index; BIS_L, left side; BIS_R, right side; ICM+, intensive care monitoring plus; PRx, pressure reactivity index;

Supplementary Figure G. BISopt Values and Agent Infusions

Table G1. Agent Dose and BISopt % Yield

Dose	Median %Yield (IQR)	Number of Patients	Median Recording Time (IQR) hrs.
High Dose Fentanyl (> 200 ug/kg/min)	0.834 (0.79-0.878)	2	5.892 (4.954-6.829)
Moderate Dose Fentanyl (51-200 ug/kg/min)	0.604 (0.402-0.634)	6	50.633 (16.417-61.962)
Low Dose Fentanyl (0-50 ug/kg/min)	0.608 (0.148-0.742)	16	11.358 (3.608-24.746)
High Dose Propofol (> 3 ug/kg/min)	0.373 (0.187-0.56)	2	3.933 (2.017-5.85)
Moderate Dose Propofol (1-3 ug/kg/min)	0.593 (0.221-0.829)	22	5.267 (3.692-24.204)
Low Dose Propofol (0-1 ug/kg/min)	0.735 (0.416-0.931)	19	5.3 (2.4-16.642)

Table G2. Agent Type and BISopt % Yield

Agent	Median %Yield (IQR)	Number of Patients	Median Recording Time (IQR) hrs.
Fentanyl	0.482 (0.15-0.702)	9	10.267 (3.217-13.683)
Propofol	0.527 (0.342-0.814)	15	15.9 (5.217-32.2)
Fentanyl and Propofol	0.655 (0.273-0.742)	14	5.383 (3.642-22.054)
Fentanyl and Ketamine	0.72 (0.67-0.753)	3	62.333 (41.508-84.558)
Fentanyl, Propofol and Ketamine	0.004 (0.002-0.006)	2	32.517 (17.258-47.775)
Milrinone	0.747 (0.747-0.747)	1	7.767 (7.767-7.767)
Norepinephrine	0.713 (0.317-0.931)	22	7.608 (3.05-11.517)
Phenylephrine and Vasopressin	0.755 (0.396-0.777)	3	7 (4.183-10.742)

Tables for the median recording time and median % yield for a respective combination of agent or dose amount. All other combinations of sedative agents or vasopressor agents did not occur, with other prn medications not captured. Note that we did not separate the vasopressor agent and sedative agent group. BISopt, optimal bispectral index value; Hrs. hours; IQR, interquartile range; kg, kilogram; min, minute; ug, microgram;

Supplementary Table H. Kendall's Correlation between BIS/BISopt values and CPPopt/MAP

Supplementary Table H1. BISopt Values and MAP with Impaired Autoregulation (PRx >0·2)

	Right Side		Left Side	
Patient	**Correlation**	**P Value**	**Correlation**	**P Value**
Patient 1	-0·29458322	1·39E-03	0·39587531	5·53E-13
Patient 2	-0·044561705	1·15E-02	0·02098318	4·26E-01
Patient 3	-0·353153969	1·05E-27	0·31945676	3·24E-12
Patient 4			-0·24376325	4·57E-04
Patient 5	-0·20348473	1·29E-14	-0·700562	8·06E-13
Patient 6	0·150532926	3·24E-02	0·12622516	8·32E-02
Patient 7	0·214965249	5·78E-22	-0·02738321	4·59E-01
Patient 8	-0·02035336	5·39E-01	-0·13809365	4·50E-03
Patient 9	-0·299738847	1·73E-07	0·09081096	7·83E-02
Patient 10			-0·05793243	5·46E-02
Patient 11			0·46064713	9·12E-59
Patient 12			-0·16028561	4·40E-25
Patient 13	0·301586879	4·26E-06	0·23889861	1·46E-06
Patient 14	0·168375602	3·18E-21	-0·20446272	2·83E-31
Patient 15	0·029352431	2·70E-01	0·09018465	1·81E-04
Patient 16	0·08992315	1·82E-11	0·12094397	8·22E-18
Patient 17			-0·18370724	3·82E-08
Patient 18			0·04054011	8·00E-02
Patient 19	0·03166003	2·68E-01		
Patient 20	-0·064940582	1·08E-01	0·19058628	5·93E-05
Patient 21			-0·19253858	6·35E-06
Patient 22	-0·246573491	1·46E-04		
Patient 23			-0·26982802	2·66E-45
Patient 24			-0·19642426	6·75E-09
Patient 25	-0·022670401	2·11E-01		
Patient 26	0·121459615	6·35E-10	0·09025284	4·12E-05
Patient 27	0·48386734	1·93E-15	0·35703735	4·30E-11
Patient 28			0·04344071	1·14E-01
Patient 29	-0·239944256	3·77E-09		
Patient 30	0·163004374	1·95E-14	0·17911657	2·87E-17
Patient 31	-0·471156609	7·63E-08	-0·03780835	6·32E-01
Patient 32	-0·095882053	7·94E-04	0·01983533	4·87E-01

Supplementary Table H2. BISopt Values and MAP with Intact Autoregulation (PRx <0·2)

	Right Side		Left Side	
Patient	**Correlation**	**P Value**	**Correlation**	**P Value**
Patient 1	-0·31942835	3·72E-21	0·115474005	3·52E-11
Patient 2	-0·044391075	2·83E-01	-0·010168958	8·58E-01
Patient 3	-0·301221771	2·05E-06	0·467935831	2·63E-10
Patient 4			-0·025237262	5·69E-01
Patient 5	-0·270245413	1·94E-44	-0·512974044	3·93E-96
Patient 6	0·129099445	5·16E-01	-0·11140133	5·87E-01
Patient 7	0·136548712	4·38E-06	-0·053406593	2·97E-01
Patient 8	0·070532553	4·90E-03	-0·098492732	6·92E-03
Patient 9	-0·1523818	3·97E-03	0·065917946	1·33E-01
Patient 10			-0·081554649	5·03E-03
Patient 11			0·064817806	3·00E-01
Patient 12			-0·224412251	8·52E-30
Patient 13	0·27119115	3·29E-04	0·302309038	6·64E-06
Patient 14	0·066319974	2·25E-02	-0·271371426	1·00E-19
Patient 15	-0·069180732	4·06E-14	0·007729397	3·99E-01
Patient 16	-0·196740724	5·40E-16	-0·064754981	1·16E-02
Patient 17			-0·097385396	7·02E-04
Patient 18			0·18989929	2·44E-06
Patient 19	-0·136706392	8·59E-05		
Patient 20	0·203497167	7·71E-08	0·329654586	1·34E-17
Patient 21			-0·090403654	1·65E-01
Patient 22	0·073663416	9·53E-03		
Patient 23			-0·262931899	4·23E-51
Patient 24			-0·039737457	2·51E-01
Patient 25	0·1072165	2·66E-12		
Patient 26	0·140530904	1·14E-32	0·053759517	5·16E-05
Patient 27	0·577999342	9·90E-04	0·594008021	3·76E-05
Patient 28		1·12E-01	0·083330047	9·07E-05
Patient 29	-0·278497976	3·08E-15		
Patient 30	0·233971728	2·24E-09	0·35090964	1·61E-19
Patient 31	-0·704096646	7·75E-32	-0·254888806	9·67E-09
Patient 32	-0·101512434	6·58E-04	-0·117627811	9·11E-05

Supplementary Table H3. BISopt Values and CPPopt with Impaired Autoregulation (PRx >0·2)

	Right Side		Left Side	
Patient	**Correlation**	**P Value**	**Correlation**	**P Value**
Patient 1	-0·213188628	1·89E-02	0·356121028	8·44E-11
Patient 2	-0·143373694	6·43E-15	0·594300229	4·00E-97
Patient 3	-0·043205558	3·51E-01	0·190041719	8·99E-03
Patient 4			-0·676110784	2·84E-21
Patient 5	-0·028206426	3·86E-01	-0·142634156	1·83E-03
Patient 6	-0·602414497	7·82E-04	-0·662713505	1·31E-03
Patient 7	0·25496953	2·15E-26	-0·295921008	1·93E-12
Patient 8	0·232998339	3·83E-11	-0·006342508	8·97E-01
Patient 9	-0·110015076	1·31E-01	-0·529963877	3·45E-18
Patient 10			0·274255263	4·22E-13
Patient 11			-0·470636872	2·23E-42
Patient 12			-0·12790764	4·04E-15
Patient 13	0·737660427	9·82E-15	0·30552029	3·06E-06
Patient 14	0·200368673	2·08E-21	-0·363441219	1·08E-72
Patient 15	0·375032994	2·13E-39	0·419553932	2·92E-61
Patient 16	0·082200691	5·40E-06	0·004545573	8·13E-01
Patient 17			0·045689073	3·83E-01
Patient 18			0·271524462	5·08E-28
Patient 19	-0·589326751	4·01E-38		
Patient 20	-0·230307181	1·33E-06	0·667178967	7·30E-45
Patient 21			0·716824005	1·27E-43
Patient 22	-0·165505348	2·09E-02		
Patient 23			-0·050910182	2·93E-02
Patient 24			0·481074627	2·34E-40
Patient 25	0·060073759	1·50E-03		
Patient 26	0·211756909	1·36E-21	0·243389841	1·74E-22
Patient 27	0·161479327	1·21E-05	-0·087259413	2·84E-01
Patient 28			0·234615984	1·18E-12
Patient 29	-0·146969755	7·71E-04		
Patient 30	0·229365271	1·43E-23	0·103567212	6·25E-06
Patient 31	0·229611644	1·25E-02	-0·563715162	4·63E-12
Patient 32	0·389202206	2·66E-19	0·167944216	9·74E-05

Supplementary Table H4. BISopt Values and CPPopt with Intact Autoregulation (PRx <0·2)

	Right Side		Left Side	
Patient	**Correlation**	**P Value**	**Correlation**	**P Value**
Patient 1	0·223600588	3·34E-11	0·0969854	7·43E-08
Patient 2	-0·028209642	5·03E-01	0·46492704	8·27E-16
Patient 3	0·199913086	1·31E-02	0·14317313	1·11E-01
Patient 4			-0·50877157	2·96E-30
Patient 5	-0·279144305	4·52E-39	-0·38587226	1·53E-42
Patient 6				
Patient 7	0·063661016	4·96E-02	-0·34641846	6·84E-08
Patient 8	0·21251521	8·80E-15	0·07001983	5·58E-02
Patient 9	-0·127043887	5·61E-02	-0·42562966	5·22E-17
Patient 10			0·20281069	3·26E-09
Patient 11			-0·46310183	3·63E-11
Patient 12			-0·031842239	1·25E-01
Patient 13	0·560393851	7·85E-08	0·50888156	1·40E-08
Patient 14	0·06287434	7·06E-02	-0·38993716	4·56E-31
Patient 15	0·31353281	1·59E-206	0·34917278	1·22E-265
Patient 16	0·043959141	1·20E-01	0·12312139	5·20E-05
Patient 17			0·18241814	7·45E-07
Patient 18			0·25283194	8·23E-10
Patient 19	-0·617084257	8·84E-28		
Patient 20	-0·272510913	3·83E-12	0·35812823	1·93E-20
Patient 21			0·38663505	3·09E-07
Patient 22	-0·005207294	8·64E-01		
Patient 23			-0·24245889	2·44E-33
Patient 24			0·44696754	4·15E-33
Patient 25	0·062764156	7·68E-05		
Patient 26	0·198468736	7·15E-48	0·20463079	1·39E-39
Patient 27	-0·047488475	1·62E-02	-0·03311331	9·04E-01
Patient 28			0·10917061	1·73E-05
Patient 29	-0·242702947	4·39E-11		
Patient 30	0·288048586	1·08E-11	0·3422781	6·66E-16
Patient 31	-0·045044591	4·84E-01	-0·4347307	1·06E-21
Patient 32	0·375686381	5·64E-20	0·21779514	9·17E-08

Supplementary Table H5. BIS Values and MAP with Impaired Autoregulation (PRx >0·2)

	Right Side		Left Side	
Patient	**Correlation**	**P Value**	**Correlation**	**P Value**
Patient 1	-0·032340437	7·43E-01	0·218184991	9·83E-06
Patient 2	0·192776622	2·93E-31	-0·027961793	2·29E-01
Patient 3	-0·380993826	2·29E-42	0·14108196	4·01E-05
Patient 4			0·367330231	1·11E-08
Patient 5	-0·293479371	7·70E-39	-0·042830841	1·23E-01
Patient 6	-0·128867106	6·00E-03	-0·078340338	5·43E-02
Patient 7	0·445903584	1·49E-106	0·418247455	1·27E-38
Patient 8	0·390457671	4·70E-36	0·258122197	1·01E-13
Patient 9	0·317839291	1·33E-11	0·309158302	1·94E-13
Patient 10			0·583227431	8·59E-122
Patient 11			0·472534403	1·83E-78
Patient 12			0·306991281	5·30E-103
Patient 13	0·05948119	6·64E-02	0·137032192	2·30E-05
Patient 14	-0·088020337	8·51E-09	0·003414409	8·22E-01
Patient 15	0·129244952	2·15E-08	0·067410246	1·50E-03
Patient 16	-0·019661576	1·09E-01	0·018117775	1·51E-01
Patient 17			0·005461478	8·48E-01
Patient 18			0·337757948	4·10E-55
Patient 19	-0·043593336	7·20E-02		
Patient 20	-0·084805117	1·16E-02	0·032161812	3·34E-01
Patient 21			0·311372319	8·07E-24
Patient 22	-0·059675066	2·04E-01		
Patient 23			0·000281754	9·87E-01
Patient 24			0·047949359	1·10E-01
Patient 25	0·166435805	2·06E-24		
Patient 26	0·242716893	5·62E-42	0·266177505	9·68E-41
Patient 27	0·559763632	4·36E-26	0·581299652	3·72E-35
Patient 28			0·037319677	5·22E-02
Patient 29	0·041149288	2·15E-01		
Patient 30	0·167489723	6·13E-19	0·167275148	4·21E-19
Patient 31	0·089189878	1·19E-01	0·050886429	3·11E-01
Patient 32	0·109740351	1·35E-05	0·070320333	5·33E-03

Supplementary Table H6. BIS Values and MAP with Intact Autoregulation (PRx <0·2)

	Right Side		Left Side	
Patient	**Correlation**	**P Value**	**Correlation**	**P Value**
Patient 1	-0·06964954	1·33E-02	0·06103383	5·97E-05
Patient 2	0·09398916	1·32E-02	-0·01941013	7·06E-01
Patient 3	-0·47051597	5·53E-21	-0·08883932	1·44E-01
Patient 4			-0·13956543	7·59E-07
Patient 5	-0·22252693	6·76E-38	-0·41012316	8·93E-63
Patient 6	-0·2101639	1·04E-01	-0·1592139	1·87E-01
Patient 7	0·26408835	3·73E-24	0·37280757	1·16E-21
Patient 8	0·02807294	1·87E-01	-0·10171293	5·09E-04
Patient 9	0·34917744	1·15E-12	0·28834034	7·08E-12
Patient 10			0·55162083	2·02E-107
Patient 11			0·30761748	1·42E-11
Patient 12			0·17357509	4·04E-22
Patient 13	-0·03932993	3·12E-01	0·04962891	2·01E-01
Patient 14	-0·10993998	1·04E-05	-0·13838546	6·07E-08
Patient 15	0·02000746	1·89E-02	0·04428461	2·69E-07
Patient 16	-0·17241538	4·63E-15	-0·04433806	4·99E-02
Patient 17			-0·11418512	1·09E-05
Patient 18			0·37378775	3·62E-22
Patient 19	-0·22226495	1·79E-12		
Patient 20	-0·06305013	5·29E-02	0·20518956	1·24E-10
Patient 21			0·26617884	5·05E-09
Patient 22	-0·12936713	1·61E-08		
Patient 23			-0·06776861	3·70E-05
Patient 24			0·03152268	2·85E-01
Patient 25	0·08175226	4·04E-09		
Patient 26	0·20143789	1·19E-74	0·21424048	9·83E-65
Patient 27	0·59334643	1·71E-13	0·60794677	4·36E-14
Patient 28			-0·07866217	1·09E-14
Patient 29	-0·14816493	8·61E-09		
Patient 30	0·13258037	4·88E-05	0·12352456	1·38E-04
Patient 31	0·48773624	8·18E-43	0·30249935	8·27E-30
Patient 32	0·22702981	6·92E-17	0·11726635	1·65E-05

The tables show the relationship between different patients BIS/BISopt values and CPPopt/MAP using a Kendall Tau's correlation. Though some individual values that had significant correlations over 0·5 (as highlighted in gray), no one variable was significant for all patients, thus demonstrating that BIS and MAP as well as BISopt and CPPopt/MAP are unrelated over large datasets for both intact and impaired autoregulation. Note sides have been removed if they had any factors that interfere with BIS signal (hemisphere must be free of hematoma and contusion). BIS, bispectral index; BISopt, optimal BIS value; CPPopt, optimal cerebral prefusion pressure; MAP, mean arterial pressure; PRx, pressure reactivity;

Supplementary File I. BISopt Values and CPPopt for each Patient over the Full Data

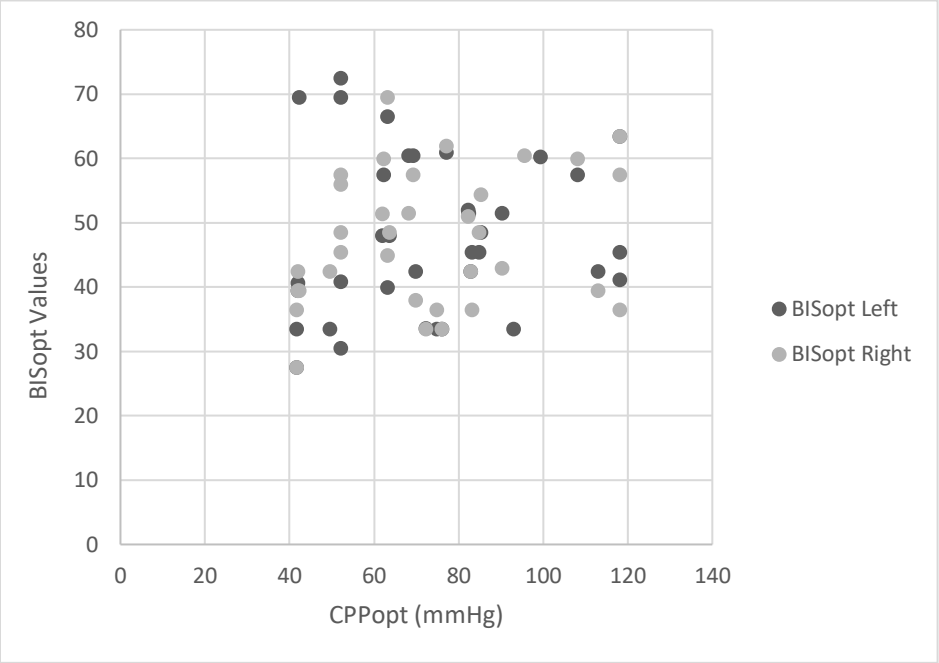


Figure demonstrates the relationship between different BISopt values and CPPopt values for each patient. BISopt, optimal BIS value; CPPopt, optimal cerebral perfusion pressure; mmHg, millimeters of mercury.

Supplementary File J. BISopt Values and ICP for each Patient over the Full Data

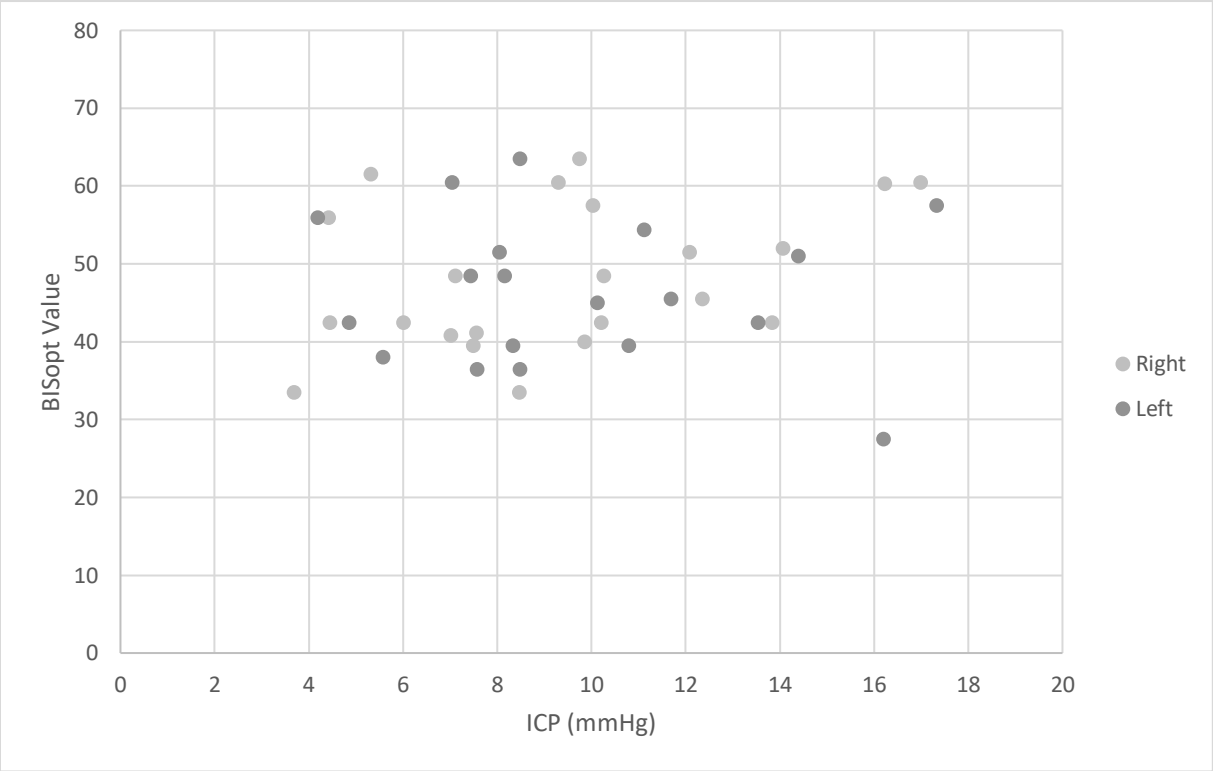


Figure demonstrates the relationship between different BISopt values and ICP values for each patient. BISopt, optimal BIS value; ICP, intracranial pressure; mmHg, millimeters of mercury.

Supplementary Table K1. BIS Values and ICP

	Right Side		Left Side	
Patient	**Correlation**	**P Value**	**Correlation**	**P Value**
Patient 1	-0.034269456	0.189792951	0.103317933	8.40E-12
Patient 2	0.069067691	6.08E-06	-0.077064409	0.000450977
Patient 3	0.253511672	1.74E-25	-0.098541991	0.00090325
Patient 4			0.163925537	4.22E-10
Patient 5	-0.357118743	2.32E-150	-0.347877419	1.77E-80
Patient 6	0.027356245	0.594484941	-0.382181279	2.63E-21
Patient 7	-0.202485398	2.21E-32	-0.046037858	0.088022591
Patient 8	-0.091322813	1.65E-07	-0.262984854	2.05E-32
Patient 9	0.202213031	1.42E-09	0.214512531	3.65E-13
Patient 10			0.265809432	7.52E-52
Patient 11			0.43642988	1.10E-85
Patient 12			0.190774812	3.48E-63
Patient 13	0.382804968	1.16E-36	0.275942324	1.04E-23
Patient 14	0.106680018	1.30E-17	0.187606921	1.03E-50
Patient 15	-0.279963026	3.33E-264	-0.275297889	1.01E-256
Patient 16	-0.105459341	5.09E-23	0.100632667	4.33E-20
Patient 17			0.002384958	0.902757499
Patient 18			0.124085978	3.80E-11
Patient 19	-0.039011203	0.049207337		
Patient 20	0.024622555	0.287375651	0.271695296	1.74E-28
Patient 21			-0.186527169	9.68E-09
Patient 22	0.056430255	0.005773685		
Patient 23			0.205985081	5.39E-64
Patient 24			0.126284648	1.54E-09
Patient 25	0.103410154	1.54E-22		
Patient 26	-0.247961314	7.62E-156	-0.209991669	1.93E-87
Patient 27	0.509050604	1.95E-31	0.461980499	8.19E-31
Patient 28			-0.184554241	1.99E-57
Patient 29	-0.136392691	1.38E-10		
Patient 30	0.21071361	3.44E-154	0.309505694	0
Patient 31	0.282675416	4.54E-16	0.278149941	9.75E-25
Patient 32	0.271898374	8.11E-48	0.195101582	1.00E-25

Supplementary Table K2. BISopt Values and ICP

	Right Side		Left Side	
Patient	**Correlation**	**P Value**	**Correlation**	**P Value**
Patient 1	-0.348156787	7.91E-31	0.285229448	1.37E-44
Patient 2	0.071834427	4.89E-05	0.123925342	3.32E-08
Patient 3	-0.093327645	0.039760552		
Patient 4			-0.323335116	2.03E-09
Patient 5	0.11803456	3.23E-05	0.199438972	5.55E-24
Patient 6				
Patient 7	0.237268927	2.73E-29	0.151027495	2.68E-05
Patient 8	-0.073854025	0.003068084	-0.071092137	0.001784988
Patient 9	-0.009655241	0.838005557	-0.247259826	0.000264372
Patient 10			-0.04768043	0.026838215
Patient 11			0.589562735	7.98E-150
Patient 12			0.183338387	1.30E-58
Patient 13	0.220320291	1.34E-78	0.131974392	0.003657341
Patient 14	-0.00738759	0.633766045	0.083070058	3.18E-07
Patient 15	0.024397212	0.075192297	-0.23011184	3.27E-48
Patient 16	0.226789296	1.92E-05	0.43449732	5.90E-15
Patient 17			0.302388463	4.52E-06
Patient 18			0.005314128	0.78359046
Patient 19	0.490923298	5.15E-11		
Patient 20	-0.028068495	0.361226568	-0.329403887	1.43E-26
Patient 21			0.257249645	1.42E-07
Patient 22	-0.11405214	6.09E-05		
Patient 23			0.208382987	9.72E-49
Patient 24			-0.258611834	1.00E-13
Patient 25	0.051451277	0.000506228		
Patient 26	-0.318614488	5.27E-90	-0.125721519	1.07E-17
Patient 27	-0.318614488	5.27E-90	-0.125721519	1.07E-17
Patient 28			-0.351418834	2.89E-101
Patient 29	0.097122793	0.000218335		
Patient 30	0.027665441	0.00381275	0.03658628	0.001997405
Patient 31	0.041447388	0.250343858	-0.098462816	0.001700071
Patient 32	-0.176354087	9.92E-17	-0.252111691	1.95E-33

The tables show the relationship between different patients BIS/BISopt values and ICP using a Kendall Tau's correlation. Though som e individual values that had significant correlations over 0·5 (as highlighted in gray), no one variable was significant for all patients, th us demonstrating that BIS and ICP are unrelated. Note sides have been removed if they had any factors that interfere with BIS signal (hemisphere must be free of hematoma and contusion). Also note that 20 patients had intracranial hypertension episodes occurring with a median of 0.12hrs. (0.00 to 1.74hrs.). BIS, bispectral index; BISopt, optimal BIS value; ICP, intracranial pressure;

Supplementary File L. Abbreviation and Terminology

Cerebral autoregulation- inherent ability of blood vessels to keep cerebral blood flow relatively constant over a wide range of systemic blood pressure levels by means of complex myogenic, neurogenic, and metabolic mechanisms

CO_2 reactivity- physiological mechanism that regulates blood flow in the brain according to metabolic requirements

Neurovascular coupling- mechanism that links the transient neural activity to the subsequent change in cerebral blood flow, which is regulated by both chemical signals and mechanical effects

Cerebrovascular reactivity- reflects the ability of the blood vessels to dilate in order to match tissue blood supply to increased demand

Bispectral index (BIS)- one of several technologies used to monitor depth of anesthesia