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(54) **IMAGING REDUCTIONS IN CEREBROVASCULAR REACTIVITY**

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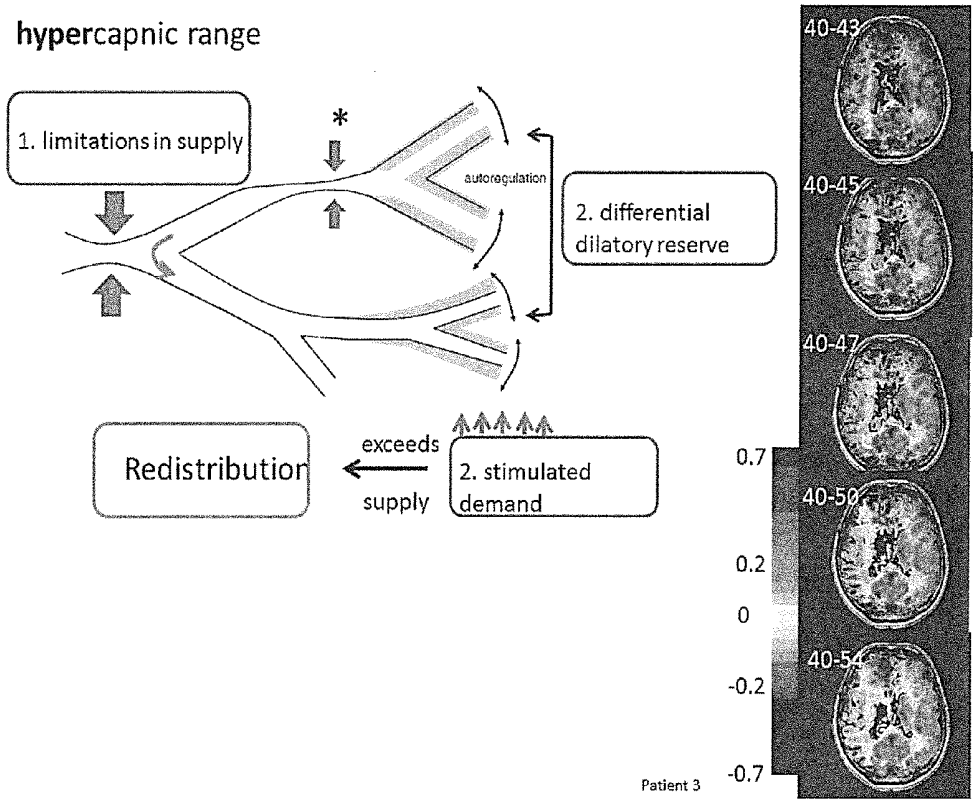
(57) **ABSTRACT**

An algorithm including program code for analyzing a specific portion of the vasoactive response to the vasoactive stimulus corresponding to a to sub-range of increments and/or decrements of stimuli within the full range of the vasoactive stimulus, the sub-range characterized in that is more sensitive to identifying reductions in vascular reactivity in the ROI.



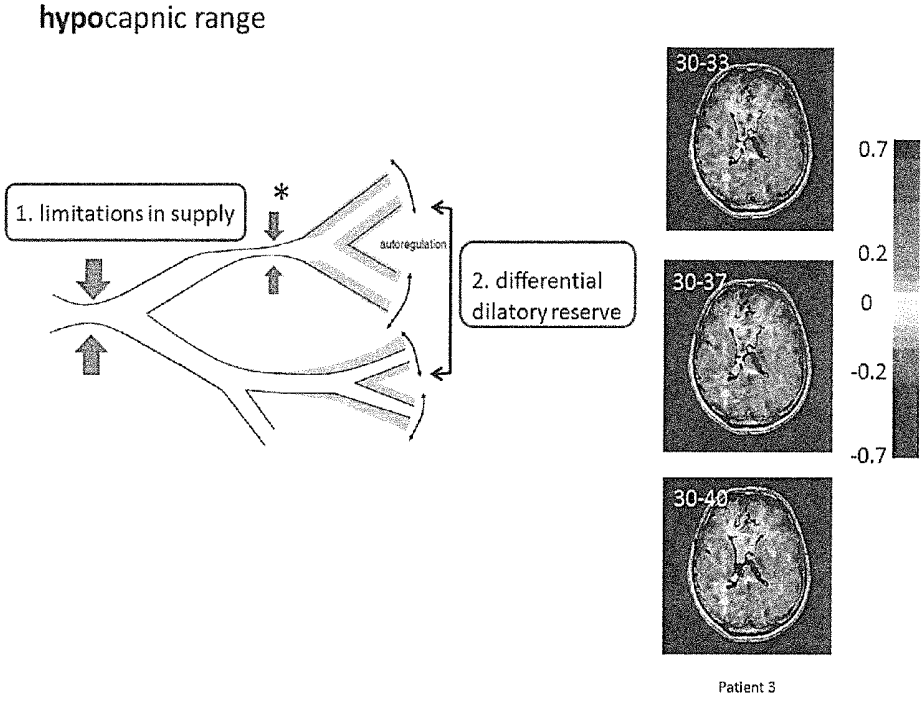

hypocapnic range
1. limitations in supply
*
autoregulation
2. differential dilatory reserve
30-33
30-37
30-40
0.7
0.2
0
-0.2
-0.7
Patient 3

Figure 1

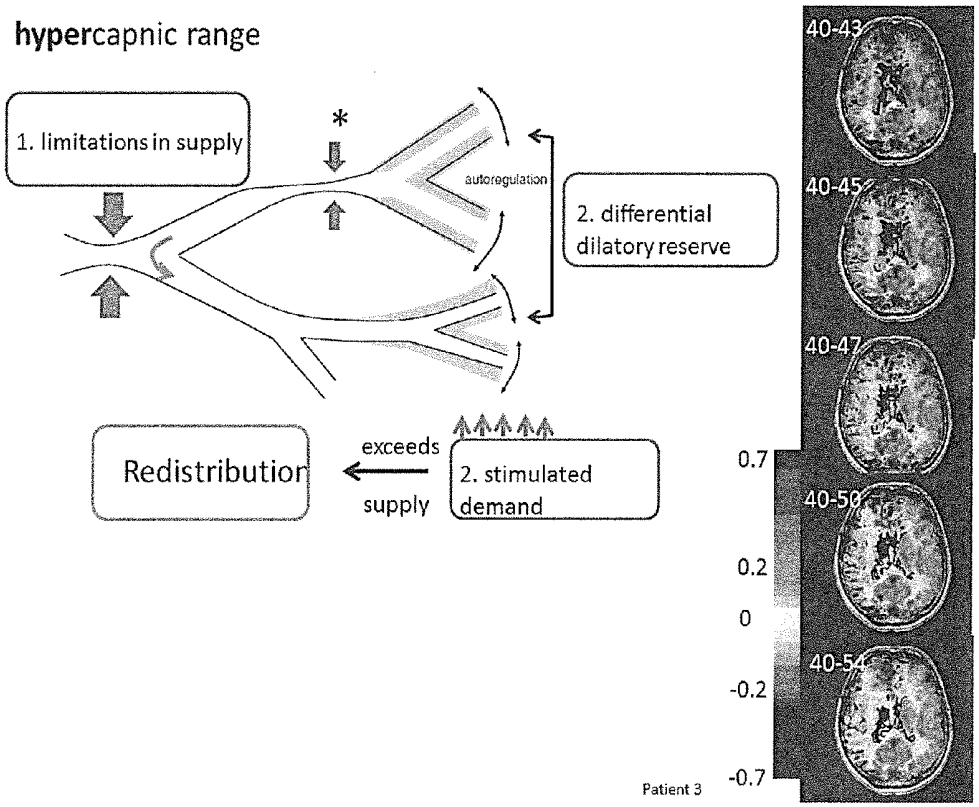
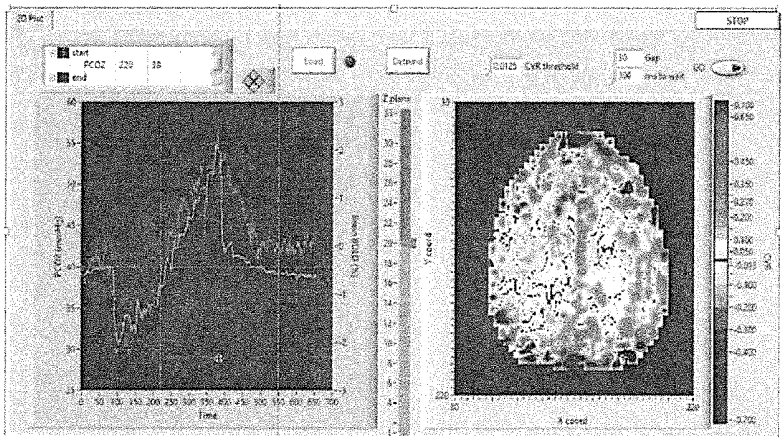

hypercapnic range
1. limitations in supply
*
autoregulation
2. differential dilatory reserve
Redistribution
exceeds supply
2. stimulated demand
40-43
40-45
40-47
40-50
40-54
0.7
0.2
0
-0.2
-0.7
Patient 3

Figure 2

Effect of Δ $PaCO_2$ on CVR In hypercapnic range



Noise in BOLD signal:

- the smaller the Δ $PETCO_2$ the greater the **noise**
- can resolve CVR over range of only **2 mmHg**

Patient 3

Figure 3a

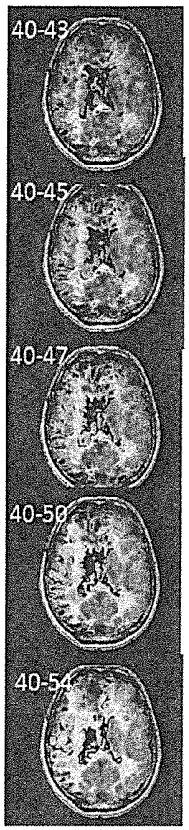


Figure 3b

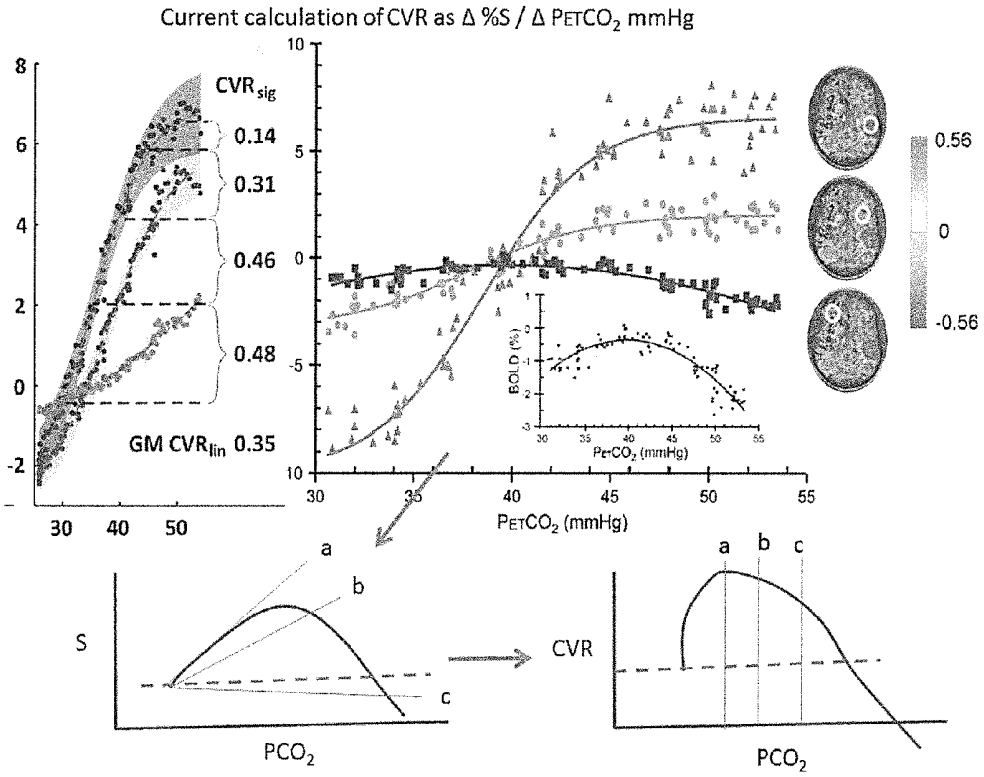

Current calculation of CVR as Δ %S / Δ PETCO2 mmHg
CVRsig
0.14
0.31
0.46
0.48
GM CVRlin 0.35
PETCO2 (mmHg)
BOLD (%)
0.56
0
-0.56
S
PCO2
CVR
PCO2
a
b
c

Figure 4

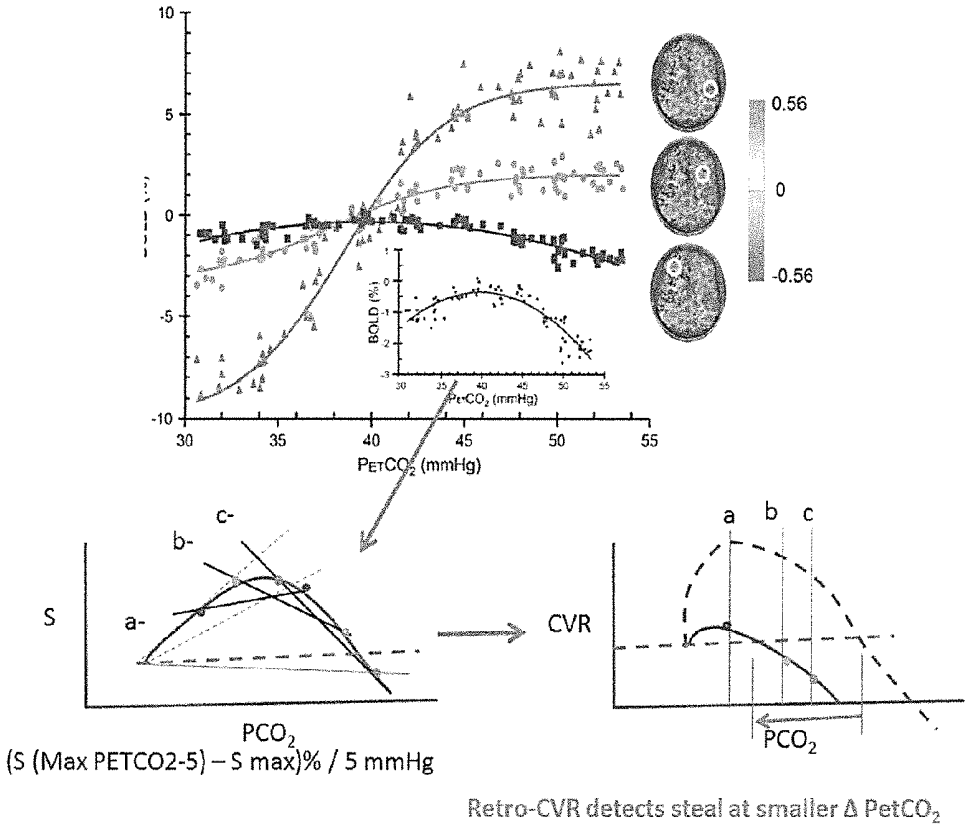

10
5
0
-5
-10
30
35
40
45
50
55
PETCO2 (mmHg)
0.56
0
-0.56
BOLD (%)
PETCO2 (mmHg)
S
a-
b-
c-
PCO2
(S (Max PETCO2-5) – S max)% / 5 mmHg
CVR
a
b
c
PCO2
Retro-CVR detects steal at smaller Δ PetCO2

Figure 5

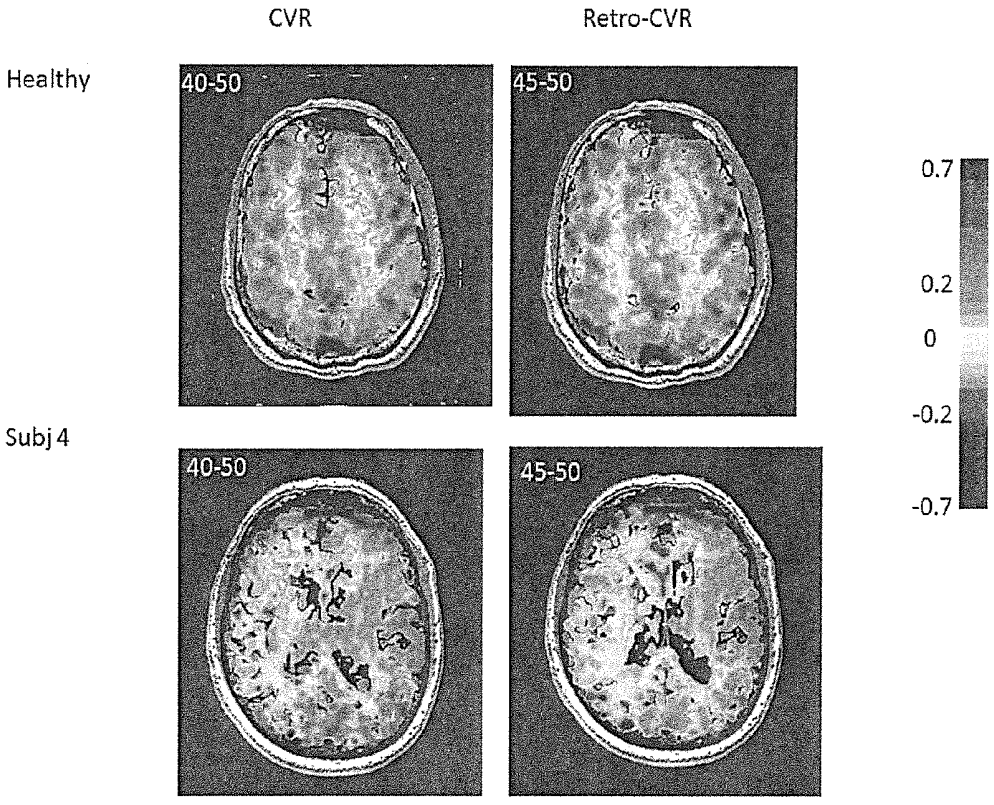


Figure 6

IMAGING REDUCTIONS IN CEREBROVASCULAR REACTIVITY

CROSS-REFERENCE TO RELATED APPLICATION

[0001] The present application is a continuation of U.S. patent application, Ser. No. 14/614,310, filed Feb. 4, 2015, the disclosure of which is hereby incorporated by reference as if set forth in full herein.

FIELD OF THE INVENTION

[0002] The present invention relates a system and method for locating and assessing pathophysiological changes in cerebrovascular reactivity.

BACKGROUND OF THE INVENTION

[0003] Cerebrovascular reactivity (CVR) is the change in cerebral blood flow (CBF) in response to a change in a vasoactive stimulus. Paradoxical reductions in the amplitude of CBF response to vasodilatory stimulation ('steal') are associated with vascular pathology. However, vascular pathology may exist without overt steal. A sensitive measure of abnormal CVR and vascular physiology requires a comprehensive conceptual model linking vascular pathology and changes in blood flow and a system of data analysis capable of detecting changes in regional CBF.

SUMMARY OF THE INVENTION

[0004] The inventors have discovered a system for detecting an abnormality in a subject's cerebrovascular response to a vasoactive stimulus. The system includes a system for generating a step change (step), or a series of increments, or decrements (Ramp) in the vasoactive stimulus (an SVS) and an imaging system (an IS) that provides sufficient spatial and time resolution for analyzing a response to a step and/or Ramp stimulus. The vasoactive response preferably constitutes a surrogate measure of blood flow in a region of interest (ROI) of the subject's brain. The system includes a computer for implementing an algorithm for analyzing the signal responses, as a function of the Ramp (increment or decrement) change for (or optionally as a function of time following a step change in the vasoactive stimulus). The algorithm including program code for analyzing a specific portion of the vasoactive response to the vasoactive stimulus corresponding to a to sub-range of increments and/or decrements of stimuli within the full range of the vasoactive stimulus, the sub-range characterized in that is more sensitive to identifying reductions in vascular reactivity in the ROI. The inventors have discovered that using the response signals corresponding to this sub-range of increments and/or decrements in the vasoactive stimulus, for example, to compute a value representing a quantitative measure of cerebrovascular reactivity for the ROI, is more sensitive to discriminating a reduction in cerebrovascular reactivity for the ROI than making the determination from the collection of responses over the full range of the stimulus. In general, the value is used to quantify the amount of change in a surrogate measure of blood flow that is associated with a change in the vasoactive stimulus.

[0005] The value can be used to construct a CVR map by visually depicting the value or an interpretive score corresponding to the value, in a precise anatomical location on an image of the ROI. For example, the value or score may be color coded and/or illustrated topographically. Optionally, the value or score may be statistically interpreted on an image of the ROI to provide a degree of statistical confidence that the value reflects a pathophysiological change in CVR/blood flow. For example, by computing, on a ROI by ROI basis, for at least one ROI, at least one score per ROI, that evaluates the extent to which the value deviates from the range of values representing the CVR for the ROI in a healthy cohort (e.g. individuals without neurological disease for whom a CVR per ROI is computed using the response signals corresponding to the same sub-range of increments and/or decrements in the vasoactive stimulus), one can obtain a degree of statistical confidence that this computed value represents a pathophysiological reduction in CVR for the ROI, that is, being outside of the normal range of CVR. This score can be color coded and represented on a ROI by ROI basis, on a CVR map of the subject's brain. Optionally, the ROI is a voxel within a large ROI that is composed of a set of voxels. The inventors have applied this analysis to one or more ROIs, on a voxel by voxel basis, to obtain a set of respective computed values, and respective scores for each voxel in ROI, and when the voxels are colored by a color corresponding to the magnitude of the score, resulting in a CVR map.

[0006] Thus, according to one aspect the invention is directed to a system for detecting an abnormality in a subject's cerebrovascular response to a vasoactive stimulus in at least one region of interest (ROI) of the subject's brain:

[0007] (A) a system for generating the vasoactive stimulus (SVS);

[0008] (B) an imaging system (IS) characterized in that it provides sufficient spatial and time resolution for analyzing a vasoactive response to a step change or series of increments and/or decrements in the vasoactive stimulus, the vasoactive response preferably constituting a surrogate measure of blood flow in the at least one ROI;

[0009] (C) a computer for implementing an algorithm for analyzing the vasoactive response to a series of increments and/or decrements in a vasoactive stimulus, the algorithm including program code:

[0010] (a) for computing at least one value representing a quantitative measure of cerebrovascular reactivity for the ROI, wherein the at least one value is obtained for a specific portion of the vasoactive response in the ROI, the specific portion of the response corresponding to a to sub-range of increments and/or decrements in the vasoactive stimulus within the full range of the vasoactive stimulus, the sub-range characterized in that it is sensitive to quantifying a reduction in cerebrovascular reactivity; and optionally

[0011] (b) computing on a ROI by ROI basis (for at least one ROI), at least one score (per ROI) adapted for interpreting the at least one value.

[0012] The score is optionally adapted to visually represent the value and its location in a depiction of the brain or the ROI. The value is optionally the CVR for the selected sub-range of increments and/or decrements in the vasoactive stimulus within the full range of the vasoactive stimulus. Optionally, the score is adapted to grade the amplitude of the CVR and its course as a function of the changes in the vasoactive stimulus such as the ramp changes in PCO_2. Optionally, a visual representation such as a color, of the value of the interpretive score is mapped onto a depiction of the brain to provide a visual depiction where each voxel or ROI is associated with its score. Optionally, the score is computed on a voxel by voxel basis and is, for example, geared to visually depicting

the amplitude of the CVR on an anatomical image of a slice of the brain composed of a set of voxels constituting the ROI.

[0013] Optionally, the score quantifies the extent to which that the at least one value deviates from a range of that value computed for corresponding ROI in a control cohort, wherein the score reflects the statistical confidence that the at least one value computed as in (a) represents a reduction in CVR.

[0014] The sub-range of the vasoactive stimulus is characterized in that it is more sensitive to quantifying a reduction in cerebrovascular reactivity relative to a quantitative measure of CVR computed using an alternative set of response signals, the alternative set of response signals corresponding to at least one of a full range of the vasoactive stimulus or a range of the vasoactive stimulus for which the corresponding set of response signals better identifies a reduced CVR for the ROI than the set of response signals corresponding to a full range of the vasoactive stimulus. Optionally, the algorithm includes program code for identifying a sub-range of the vasoactive stimulus that is sensitive to quantifying a reduction in cerebrovascular reactivity. Alternatively or additionally, the sub-range of the vasoactive stimulus for which the at least one value is computed includes a portion of the vasoactive stimulus for which the signal to noise ratio is best adapted to discriminate a reduction in CVR. For example if, the series of increments and/or decrements in a vasoactive stimulus is a series of target end tidal concentrations of carbon dioxide, the portion of vasoactive stimulus in question may be the increments and/or decrements corresponding to the highest 4 to 6 mm of Hg in the partial pressure of carbon dioxide (provided the upper range of the stimulus is one in which stimulated blood flow demand for the ROI sufficiently exceeds the blood flow supply to result in a relative distribution of blood flow in favor of healthy vessels at the expense of vessels that have a reduced CVR).

[0015] Optionally, the ROI is a voxel within a larger ROI. Accordingly, the at least one value and the at least one score is a set of respective values and corresponding scores computed on a voxel by voxel basis for a series of voxels within the larger ROI.

[0016] Optionally, these scores are color coded and represent the ROI on a CVR map.

[0017] Optionally, the series of increments and/or decrements in a vasoactive stimulus is a series of target end tidal concentration of carbon dioxide (end tidal concentrations of carbon dioxide are deemed reliable surrogate measures of the arterial partial pressure of carbon dioxide).

[0018] Optionally, the algorithm includes program code for computing at least one CVR for the specific portion of the response identified in step (a) and program code for determining whether the CVR that is computed for this specific portion of the response represents a reduction in CVR. For example, the algorithm may include program code for identifying a stimulus range or time range of the at least one portion of the vasoactive response for which the signal to noise ratio is sufficient to discriminate a reduced CVR within a relatively broader range of the vasoactive response, the analysis of which would result in a greater CVR value. For example, the algorithm may include program code for identifying at least one portion of response that satisfies at least one of the following conditions:

[0019] i) the stimulus range is sufficiently large to identify a reduced CVR (at least to compute a slope or a tangent to the response curve);

[0020] ii) the upper range of the stimulus is one in which stimulated blood flow demand sufficiently exceeds the blood flow supply to result in a relative distribution of blood flow in favor of healthy vessels at the expense of vessels that have a reduced CVR.

[0021] Step (a) may be executed on a voxel by voxel basis and/or for the ROI as a whole.

[0022] Optionally, the system of generating the vasoactive stimulus is an end tidal forcing system or a CO_2/O_2 rebreathing circuit, virtual (see WO/2013/138910) or physical (see WO/2004/073779). Optionally, the system of targeting a step increase or decrease in the arterial partial pressure of carbon dioxide (e.g. a jump of 5 to 10 mm of Hg in one breath) or a series increments/decrements in the end tidal partial pressure of carbon dioxide may be done with a controller for controlling a gas blender which employs a prospective model, a feedback model or a combination of both (see our published application WO/2014/194401) to determine how much gas to deliver to the subject at each interval e.g. in each breath to attain a target end tidal partial pressure of carbon dioxide for the interval. These control systems can be used to simultaneously maintain desired partial pressure of oxygen.

[0023] Optionally, the system for generating the vasoactive stimulus comprises an apparatus for controlling an amount of carbon dioxide (CO_2) in a subject's lung to attain a series of targeted end tidal partial pressures of CO_2 ($PetCO_2^T$), the apparatus comprising:

[0024] (a) a gas delivery device;

[0025] (b) a control system for controlling the gas delivery device, wherein the control system is programmed to target a series of $PetCO_2^T$ values for a series of respective intervals, the series of $PetCO_2^T$ values comprising at least one of a set of $PetCO_2^T$ increments and a set of $PetCO_2^T$ decrements, the control system including means for:

[0026] a. Obtaining (e.g. by pre-programming, by electronic communication or by providing input via an input device) input of a series of logistically attainable $PetCO_2^T$ values for the series of respective intervals; and

[0027] b. Determining an amount of CO_2 required to be inspired by the subject in an inspired gas to target the $PetCO_2^T$ for a respective interval;

[0028] c. Controlling the amount of gas CO_2 in a volume of gas delivered to the subject in a respective interval to target the respective $PetCO_2^T$ for the interval.

[0029] Optionally, at least one of:

[0030] (a) the respective sizes of the at least one of the set of $PetCO_2^T$ increments and the set of $PetCO_2^T$ decrements and the size of the respective intervals; and

[0031] (b) the time over which the response is measured and the range of the vascular response; is predetermined to reveal a dose response to at least one of the set of $PetCO_2^T$ increments and the set of $PetCO_2^T$ decrements.

[0032] Optionally, each interval is a respective breath [i].

[0033] Optionally, the vasoactive response is a vasodilatory response to a set of $PetCO_2^T$ increments. The set of logistically attainable $PetCO_2^T$ values produces a range of a vasodilatory stimulus sufficient to reveal a reduced CVR for each respective ROI of interest, the series of intervals is selected to satisfy a condition, the condition defined by attainment of at least a minimum increment in the vasodilatory response to an increment in the subject's end tidal partial pressure CO_2 (optionally the series of $PetCO_2^T$ values for the series of respective intervals also revealing the time course of

at least one of a partial range of a vasodilatory response and a full range of a vasodilatory response).

[0034] Optionally, the set of increments in $PetCO_2^T$ for the series of respective intervals is predetermined to produce one to two time constants in the progress of the vasoactive response in a respective interval.

[0035] Optionally, the at least one set of increments in $PetCO_2^T$ for the series of respective intervals is predetermined to produce two to three time constants in the progress of the vasoactive response in a respective interval.

[0036] Optionally, the imaging system is an MRI scanner. A standardized set of MR imaging protocols is used to generate a set of hemodynamic response signals corresponding to each of the increments and/or decrements in vasoactive stimulus (for example, each increment and/or decrement in a set of target end tidal partial pressures of carbon dioxide ($PetCO_2^T$). The response signals are a surrogate measure of blood flow. For example, the images optionally represent a change in a blood oxygen level dependent (BOLD) magnetic resonance imaging (MRI) response to a set of targeted incremental increases in a subject's end tidal PCO_2 ($P_{ET}CO_2$), the vascular response values representing a change in BOLD MRI signal (ΔS), in response to a standardized increase in the $P_{ET}CO_2$ ($CVR=\Delta S/\Delta P_{ET}CO_2$). The stimulated rise and/or decline is preferably implemented at a controlled rate (which may include a sinusoidal pattern), and optionally at a constant rate (i.e. the size of the increments/decrements are equal and intervals between them are the same). Optionally, the constant rate of increase is sufficiently slow to reveal at least one to two time constant in progress of the response, optionally two to three time constants in the progress of the response. It is generally understood that the time constants of the response vary throughout the brain and may vary even more in areas with vascular pathology. By changing the vasoactive stimulus a constant rate, a steady state relationship between PCO_2 and cerebral blood flow (CBF) is approached. There is a trade off between the time to reach CBF equilibrium and the time taken for the scan which is limited due to subject comfort, drift of the MRI signal over time, and cost for MRI time. At any rate of rise, the slope $\Delta S/\Delta PCO_2$ (or, CVR) will be the same so coming to equilibrium is not crucial.

[0037] Optionally, a CVR is computed for each of a series of specific portions of the vasoactive response, which portions are collectively sufficient to identify at least one of the following: (A) a reduced CVR per voxel in the ROI; (B) a CVR which is or approximates a lowest CVR for the voxel, the CVR preferably computed for a portion of the response in which stimulated blood flow demand sufficiently exceeds the blood flow supply to identify a reduced CVR in the ROI. In practical terms, selecting a range of the vasoactive stimulus at which the blood flow sufficiently exceeds the demand occurs at the upper end of the stimulus range (the higher the CO_2 the greater the tendency to cause steal between vascular territories of unequal vasodilatory reserve; therefore the responses at the highest PCO_2 range will be the most sensitive in picking up steal. Also, whereas vascular territories with reduced reserve may be able to increase their flow at small increments of PCO_2 from resting values, at higher PCO_2 levels, they change direction and begin to reduce their flow with each increment in pCO2). For example, a range of the stimulus which is either 7 to 12, 7 to 13, 8 to 12, 8 to 13, 8 to 14, 9 to 13, 9 to 14, 9 to 15, 10 to 15 or 10 to 16 mm of Hg above a baseline for the subject are each likely, and in the order presented, each increasingly more likely, to identify a portion of the response in which stimulated blood flow demand sufficiently exceeds the blood flow supply to identify a reduced CVR in the ROI.

[0038] Optionally, a CVR is computed for at least one portion of the vasoactive response (optionally each of a series of specific portions of the vasoactive response), which portion (s) is/are individually/collectively sufficient to yield at least one of the following: (A) a score representing a negative CVR per ROI (B) a score corresponding to the lowest CVR for the ROI; and (C) a score identifying whether or not (and/or the extent to which) a CVR can be computed for the ROI which is less than a second CVR which is the lowest positive CVR for the ROI. The CVR(s) is preferably computed for a portion of the response in which stimulated blood flow demand sufficiently exceeds the blood flow supply to identify a reduced CVR.

[0039] Optionally, the algorithm includes program code for: a) fitting a polynomial to the entire vasoactive response (which corresponds to a full range of the vasoactive stimulus selected for analysis); b) computing a first derivative of the polynomial; and c) identifying negative slopes corresponding to a specific portion of the vasoactive response for which the signal to noise ratio is sufficiently high to discriminate a reduced (e.g. a negative) CVR within a relatively broader range of the vasoactive response for which the CVR may be positive.

[0040] Optionally, in order to score a CVR relative to a control cohort, an imaging system and a standardized set of imaging protocols are used to generate for members of a group of control subjects, a set of vascular response signals depicting a non-pathological vascular response, in at least one common ROI of each control subject's brain, wherein the vascular response is a reaction to a controlled vasoactive stimulus, and wherein the vascular response is quantifiable from images corresponding to the vascular response signals, on an ROI-by-ROI basis (optionally on a voxel-by-voxel basis), in the form of response value per voxel for the particular sub-range of the stimulus employed. A standardized algorithm is used to co-register the respective control subject images to a standardized space based on a set of anatomic landmarks. A computer computes, for the co-registered set of control subject images, on a ROI by ROI basis (e.g. a voxel by voxel basis), a mean and standard deviation of the vascular response values for voxels corresponding to the at least one ROI to define, for the control group as a whole, a set of statistical values respectively associated an ROI (optionally, for each voxel constituting the ROI). The imaging system and standardized set of imaging protocols is used to compute a value representing a quantitative measure of cerebrovascular reactivity for the ROI for a subject in need of an assessment of a vascular response, employing the standardized vasoactive stimulus by scoring the respective responses for the ROI e.g. individual voxels in the ROI (or for the ROI as a whole), relative to the respective corresponding computed means and standard deviations, using z values. Optionally, this method further comprises the step of color-coding the z values and mapping the color-coded values back onto an anatomical representation of the standardized space to produce a z map. Optionally, the images represent the changes in blood oxygen level dependent (BOLD) magnetic resonance imaging (MRI) response to a targeted increase in a subject's end tidal PCO_2 ($P_{ET}CO_2$), the vascular response values representing, for example, a change in BOLD MRI signal (ΔS), in response to a standardized increase in the $P_{ET}CO_2$ ($CVR=\Delta S/\Delta P_{ET}CO_2$)

scored in terms of the standard deviation of the CVR for the corresponding voxel in the healthy cohort, that is, its z score. CVR which is a measure of the slope of the line can be computed only from the respective response values corresponding to lowest and higher increments in $PETCO_2$ or using a linear regression analysis based on all of the response values obtained for a selected sub-range of the vasoactive stimulus, for example, by fitting a least squares regression line to the data.

[0041] Optionally, the set of control subjects are selected on the basis that they report being free of neurological disease.

[0042] Optionally, the control subjects are matched for a parameter that is appropriate for the condition being examined in a patient. The term patient is used broadly to define a subject being tested with reference a selected control population.

[0043] Optionally, the set of control subjects are matched for at least one of age and gender.

[0044] In another aspect, the invention is directed to a computer program product for implementing an algorithm for analyzing the vasoactive response to a series of increments and/or decrements in a vasoactive stimulus, the algorithm including program code:

[0045] (a) for computing at least one value representing a quantitative measure of cerebrovascular reactivity for the ROI, wherein the at least one value is obtained for a specific portion of the vasoactive response in the ROI, the specific portion of the response corresponding to a to sub-range of increments and/or decrements in the vasoactive stimulus within the full range of the vasoactive stimulus, the sub-range characterized in that it is sensitive to quantifying a pathological reduction in cerebrovascular reactivity; and optionally

[0046] (b) computing on a ROI by ROI basis (for at least one ROI), at least one score (per ROI) adapted for interpreting the at least one value.

[0047] The score is optionally adapted to visually depict the value. The value is optionally the CVR for the selected sub-range of increments and/or decrements in the vasoactive stimulus within the full range of the vasoactive stimulus. Optionally, the score is adapted to grade the amplitude of the CVR. Optionally, the value or interpretive score is visually depicted on an image of the ROI. Optionally, the score is computed on a voxel by voxel basis and is, for example, geared to visually depicting the amplitude of the CVR on an anatomical image of a slice of the brain composed of a set of voxels constituting the ROI.

[0048] Optionally, the score quantifies the extent to which that the at least one value deviates from a range of that value computed for corresponding ROI in a control cohort, wherein the score reflects the statistical confidence that the at least one value computed as in (a) represents a reduction in CVR.

[0049] The aforementioned computer program product optionally includes program code for controlling a gas delivery device, the gas delivery device adapted for controlling an amount of carbon dioxide (CO_2) in a subject's lung to attain a series of targeted end tidal partial pressures of CO_2 ($PetCO_2{}^T$) for a series of respective intervals, including program code for:

[0050] a. Obtaining input of a series of logistically attainable $PetCO_2{}^T$ values for the series of respective intervals; and

[0051] b. Determining an amount of CO_2 required to be inspired by the subject in an inspired gas to target the $PetCO_2{}^T$ for a respective interval; and

[0052] c. Controlling the amount of gas CO_2 in a volume of gas delivered to the subject in a respective interval to target the respective $PetCO_2{}^T$ for the interval; and optionally

[0053] d. maintaining the subject's end tidal PO_2 at a constant level (i.e. within 20 mmHg of a baseline level for the subject)

[0054] The invention is also directed to an IC chip for implementing an algorithm as described herein (optionally a programmable IC chip) and optionally for also controlling a gas delivery device as aforesaid.

[0055] According to another aspect, the invention is directed to a neuro-imaging assessment method in aid of diagnosing at least one of the existence, location, deterioration and amelioration of a brain disorder associated with abnormal vascular reactivity, for example a cerebrovascular disorder.

[0056] The neuro-imaging assessment protocol of the present invention, including any permutations of the steps defined above or below, enables images to be produced from which such diagnostic assessments may be carried out and/or confirmed. According to one embodiment the invention, we describe a novel cerebrovascular reactivity assessment protocol for producing a reference atlas, for example an atlas of non-pathological cerebrovascular reactivity, wherein the CVR values computed for the reference atlas are specific to a sub-range of the response stimulus that is selected for discriminating a reduction in cerebrovascular reactivity, a sub-range particularly suitable to identify steal.

[0057] Accordingly in a further embodiment, the invention provides for a method and for the use such an atlas of non-pathological cerebrovascular reactivity to produce neuro-imaging results from which a subject in need of assessment of abnormal cerebrovascular reactivity can be assessed for the abnormality. The method optionally comprises producing a reference atlas and comparing voxel by voxel (adjacent voxels may be taken in account in assigning voxel values in give a region of interest according to standardized algorithms well known to persons in the field) test vascular response values of a patient to the corresponding reference atlas value by scoring those values, preferably in a manner that accounts for relative departure of the test value from a quantity describing a characteristic value (e.g. mean/SD for normal distributions of value or normal distributions of log values) such as to account for the variability or distribution of the control values.

[0058] According to another aspect the invention is directed to a diagnostic tools in the form of a neuro-image and other visual depictions such as graphs derived from such images that incorporate statistical transformations of MR signals generated in response to a sub-range (as described above) of the response stimulus that is selected for discriminating a reduction in cerebrovascular reactivity, optionally one or more step changes or a set of increments/decrements in end-tidal PCO_2. According to one embodiment the invention is directed to a cerebrovascular reactivity response map in the form a z map.

[0059] For example, according to one embodiment the invention is directed to a diagnostic tool comprising color-coded z values mapped onto an anatomical representation of a standardized 3D map of at least one region of interest (ROI) of the brain, the z values and 3D map characterized in that a

standardized set of MR imaging protocols are employed to generate for members of a group of control subjects, a set of CVR response signals corresponding to a sub-range of the response stimulus that is selected for discriminating a reduction in cerebrovascular reactivity, wherein the response signals depict a non-pathological CVR response, in at least one common ROI of each control subject's brain, wherein the CVR response is a reaction to a standardized vasoactive stimulus, and wherein the CVR response is quantifiable from images corresponding to the response signals, on a voxel-by-voxel basis, in the form of CVR response value per voxel; and wherein

[0060] a) a standardized algorithm is used to co-register the respective control subject images to a standardized space based on a set of anatomic landmarks;

[0061] b) a computation, for the set of control subjects, on a voxel by voxel basis, of a mean and standard deviation of the CVR response values for voxels corresponding to the at least one ROI is used;

[0062] c) the MR scanner and the standardized set of MR imaging protocols is used to measure a CVR response for a subject in need of an assessment of an abnormality in CVR, employing the standardized vasoactive stimulus (a sub-range of the response stimulus that is selected for discriminating a reduction in cerebrovascular reactivity, optionally one or more step changes or a set of increments/decrements in end-tidal PCO_2) by scoring the respective responses for individual voxels in the at least one ROI, relative to the computed mean and standard deviation, using z values.

[0063] Optionally, z values can be generated for test subjects that are based on a measurement of a plurality of CVR test values, on a voxel by voxel basis, for each respective control subject. Multiple CVR values per control subject are obtained from a plurality of imaging tests generated using a standardized stimulus and therefore reflect expected test/re-test variability in CVR measurements. The successive tests are preferably conducted on different days and optionally at different times of day, such that the plurality of variant values reflect primarily the inevitable variations corresponding to normal variations in physiology and in the technology (even despite using a single scanner), over time. The different values may also reflect in minor part differences due to other categories influences (e.g. unidentified sources of small variation or, identifiable sources of small variation of the type not generally subject to practical control).

[0064] The standard CVR atlas may reflect this retest value in the means and standard deviation per voxel. Alternative the probative value of such re-test values can be accentuated by generating a specialized reference atlas (an Interval Difference atlas) in which the control group ROI or voxel means and standard deviations are calculated with respect to intra-subject differences e.g. say between the two test values for a subject which are subtracted from one another. The intra-subject test/re-test variability, however quantified or accounted for, both from an intra-control subject perspective and across a group of control subjects, is important for assessing a patients change in CVR per voxel against a backdrop of normal re-test variability.

[0065] These so-called Interval Difference (ID) variations may be used to compute ID Z values for a given control or diseased subject, and for creating for the group of subjects, an atlas of test-retest value differences, on a voxel by voxel basis. This enables an attribution of the statistical probability that changes in CVR to true interval change in pathophysiology. Optionally resulting ID-Z values may be as reference maps to monitor progression of the disease over time or responses to treatment.

BRIEF DESCRIPTION OF THE DRAWINGS

[0066] FIG. **1** is diagrammatic representation of how CVR is affected in a hypocapnic range of a PCO_2 stimulus in a patient with R carotid artery stenosis. FIG. **1** includes color coded CVR maps. Demand does not exceed supply so there is no steal.

[0067] FIG. **2** is a diagrammatic representation of how CVR is affected in a hypercapnic range of a PCO_2 stimulus in the same patient with R carotid artery stenosis. FIG. **2** also includes color coded CVR maps. FIG. **2** shows that in a patient with severe inflow limitation such as this patient with complete carotid artery occlusion, (a) the degree of steal increases with increasing $PETCO_2$; (b) at low increases in PCO_2 many voxels that show steal at high PCO_2 have positive flow at initial increments in PCO_2 in other words, in voxels with steal, the signal vs. $PETCO_2$ curve is concave downwards (c) mall increments of $PETCO_2$ make obvious differences in distribution and intensity of steal.

[0068] FIG. **3***a* shows a graph of PCO_2 and BOLD signal over time and a corresponding CVR map. FIG. **3***b* illustrates a series of CVR maps.

[0069] FIG. **4** is a set of graphs depicting response signals corresponding to a set of increments in PCO_2 from which CVR can be seen to be calculated as a change in BOLD signal as a function of increment changes in $PETCO_2$, and related CVR maps and conceptual graphs.

[0070] FIG. **5** is a set of graphs depicting response signals corresponding to a set of increments in PCO_2 from which CVR can be seen to be calculated as a change in BOLD signal as a function of increment changes in $PETCO_2$, and related CVR maps and conceptual graphs.

[0071] FIG. **6** is a series of CVR maps.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENT

[0072] The description herein contemplates a variety of suitable criteria for revealing a reduced CVR. Each has useful discriminatory ability for initial test purposes. For example, a negative CVR may constitute, a priori, a useful indicator of impaired CVR for a voxel. However, for some ROIs (e.g. voxels) this measure alone might prove to be a false indicator of impaired reactivity as revealed by comparing the value with a corresponding value computed for the same sub-range of increments in stimulus in a normal cohort. Scoring the value, and quantifying the extent to which that the value deviates from a range of that value computed for corresponding ROI in a control cohort provides a enhanced level of discriminatory ability, the score thus reflecting the statistical confidence that the value represents a pathological reduction in CVR.

[0073] In the disclosure herein, the term Ramp sequences are used to refer to increments or decrements in $PaCO_2$. One method for producing Ramp sequences is described in our co-pending U.S. patent application Ser. No. 14/398,034 (the '034 application) for an invention entitled A NEW METHOD AND APPARATUS TO ATTAIN AND MAINTAIN TARGET ARTERIAL BLOOD GAS CONCENTRATIONS USING RAMP SEQUENCES (see also our publication Sobczyk O, et al. A conceptual model for CO_2-induced redistri-

bution of cerebral blood flow with experimental confirmation using BOLD MRI. Neuroimage. 2014 May 15; 92:56-68).

[0074] The disclosure of '034 application also describes how to independently target and maintain a particular partial pressure of oxygen. This can also be done by well know methods of end tidal forcing.

[0075] A method of stastically scoring CVR values and a method producing a CVR atlas to facilitate such scoring is described in our co-pending U.S. Provisional Patent Application No. 61/984,617 filed Date: Apr. 25, 2014 for an invention entitled "IMAGING ABNORMALITIES IN VASCULAR RESPONSE" (see also our publication: Sobczyk O, et al. Assessing cerebrovascular reactivity abnormality by comparison to a reference atlas. J Cereb Blood Flow Metab. 2015 February; 35(2):213-20)

[0076] The disclosures of all aforementioned patent applications and scientific publications are hereby incorporated in their entirety by reference.

[0077] In the hypercapnic range, the increase in demand resulting from the ramping up of $P_{ET}CO_2$ and thus $PaCO_2$ results in progressive steal. The higher the $\Delta PaCO_2$, the greater the steal. FIG. **2** shows that

[0078] 1. The hypercapnic region is different from the hypocapnic in that vasodilatation begins the competition between inflow and steal.

[0079] 2. Small changes in $PaCO_2$ result in obvious different degrees and distribution of steal. No method that uses breath-hold or fixed inspired PCO_2 (carbogen) can target $PaCO_2$ within even 3-5 mmHg. Total rebreathing with oxygen supplementation to maintain normoxia, or computerized targeting such as prospective targeting using sequential gas delivery, or end-tidal forcing, may target within 2 mmHg with variable consistency. However, due to continuous ramping change, all $PaCO_2$ values in the range are obtained and precise A $PaCO_2$ can be accessed for analysis.

[0080] 3. Methods that target a single $P_{ET}CO_2$ (breath holding, fixed inspired PCO_2, DEF, prospective targeting) take variable durations of time to attain a target level and further variable durations to reach a steady state such that any S can be related to $PaCO_2$. This time to equilibration is considerable and variable, but only follows on the attainment of a steady $PaCO_2$. No method other than DEF and RA can sustain a specific target level. With the Ramp, all values are at the same near equilibrium state; in any case the $\Delta S/\Delta P_{ET}CO_2$ will be the same as the steady state.

[0081] FIGS. **3***a* and **3***b* (FIG. **3**) illustrate that small $\Delta PaCO_2$ as occur in step changes with fixed inspired CO_2 and breath-holding result in noisy data and unreliable and poorly repeatable CVR. However, the $PaCO_2$ effect is stronger than the signal noise. Ramp sequences enable the generation of a large amount of signal data to regress against the $PaCO_2$. This is not available with square wave data due to the unknown dynamic effect resulting in "intermediate" S values while coming to equilibrium but attributed to the equilibrium $P_{ET}CO_2$. FIG. **3** also illustrates the noise in BOLD signal.

[0082] FIG. **4** includes a set of graphs from which CVR can be seen to be calculated as a function of $P_{ET}CO_2$, and related conceptual graphs. In the top left panel, the results of BOLD vs. $P_{ET}CO_2$ is illustrated in healthy gray matter and white matter with a Ramp sequence. The top right panel graph shows relationships between BOLD and PCO_2 in a pathological voxel in a scan in a patient with carotid stenosis. The bottom right panel show the analysis of CVR (slope) for a pathological voxel in the course of progressively greater $P_{ET}CO_2$. The bottom right panel shows the same data in which CVR is a function of $P_{ET}CO_2$. Even after the BOLD signal begins to decline with increasing $PaCO_2$, the CVR stays positive, reducing the sensitivity of the CVR measure.

[0083] As seen in FIG. **5**, in one embodiment, an analysis can be performed to increase the sensitivity of identifying a pathological vascular response: the "reduced CVR". The upper graph is taken from Sobczyk et al 2014. In the lower left we present a schematic representation of the BOLD signal over the full range of increments in PCO_2. The lower left schematic also shows CVRs (slopes) computed for specific portions of the vasoactive response in the ROI, the specific portions of the response corresponding to a sub-range of increments and/or decrements in the vasoactive stimulus within the full range of the vasoactive stimulus. The highest sub-range of the vasoactive stimulus (the upper 5 mm of Hg) can be seen to most sensitive to quantifying a reduction in cerebrovascular reactivity. CVRs calculated for these sub-ranges, from the signals corresponding to the top of the investigated range (Smax):(S(max)-S(Smax minus 5 mm))/($P_{ET}CO_2$(max)-$P_{ET}CO_2$ (Smax-minus 5 mm of Hg) as well as from less discriminatory sub-ranges, from which the reduced slope is less apparent. Bottom right is a resulting graph of CVR vs. $P_{ET}CO_2$ (max)). It can be seen that this markedly increases the sensitivity of identifying abnormal vasculature and reduces the extent of $P_{ET}CO_2$ that must be attained to identify the dysfunction.

[0084] FIG. **6** provides an example of an increased sensitivity of CVRs computed for upper sub-ranges in the vasoactive for quantifying a reduction in cerebrovascular reactivity in a healthy brain and diseased brain. On left are CVR maps computed for the entire range of the vasoactive stimulus. On right are the corresponding CVR maps computed a sub-range of the vasoactive stimulus. Both show greater sensitivity. The patient scan is more dramatic because there are more areas with abnormal vasculature and various degrees of abnormality, resulting in greater redistributions of blood flow.

[0085] Without being bound to a theory, the empirical observations of the inventors, are consistent with the following explanation. Because the vasodilatory response to increments in $PaCO_2$ is greatest at lower increments from baseline and begins to flatten out as $PaCO_2$ climbs, the lowest CVR will be at the high end of the $PaCO_2$ range. Since the measure of the cerebrovascular flow (e.g. BOLD signal) exhibits substantial measure-to-measure variability, larger ranges over which CVR is averaged result in principle, in better signal to noise ratios—but at the expense of averaging in CVR from parts of the stimulus profile that include higher CVR values; values that when included in the calculation, lead to the overestimation of the CVR.

[0086] In practice, the greater the range of $PaCO_2$ over which the CVR value is computed, the greater the number of measures and the less the influence of noise on the CVR. But, by including measures taken at lower $PaCO_2$s, the higher BOLD signals overestimate the CVR. Thus, by computing at least one CVR over a sub-range, the sub-range including approximately a 4 to 6 mm range (e.g. a 5 mmHg range) at approximately the top of the investigated range (the investigated range including, for example, approximately an 8 to 12 mm of Hg over baseline for the subject), enough data points are available with reduced weighting from the lower increments in stimulus and advantageously with a greater chance

of revealing a pathology reflected in "steal", which might also be greatest at the highest range of $PaCO_2$s investigated.

[0087] The IS is optionally a "high resolution" imaging system. The term "high resolution" used with reference to imaging modality or device refers to an imaging modality enjoying a spatial resolution of 1 cubic centimeter or smaller. The term includes MRI imaging modalities (for example BOLD, T2*, ASL) and other imaging modalities well known as being useful to quantify surrogate measures of blood flow (CT, SPECT, PET). Proprietary and non-proprietary software for analyzing images in available to persons skilled in the art.

[0088] The present invention extends the analytic methods of CVR measurement to determine the region by region normal range of CVR and thereby enable quantification of abnormality by the assessment of CVR in terms of its deviation from a statistical mean. The inventors took an approach similar to that of Guimond et al. [Guimond A, 2000] and Seitz et al. [Seitz, 1990] who co-registered scans of healthy subjects into a standard space and determined the normal mean and variance of CVR, voxel-by-voxel. In one aspect, the present invention is directed to generating an atlas of images for non-pathological CVR response by co-registering CO_2 stimulated BOLD MRI CVR maps from a healthy cohort into a standard space, and calculating the mean and SD of the CVR for each voxel.

[0089] Example of MRI Protocol and CVR Map Generation

[0090] Magnetic resonance imaging may be performed with a 3.0-Tesla HDx scanner using an 8-channel phased-array receiver coil (Signa; GE Healthcare, Milwaukee, Wis.), and consisted of BOLD acquisitions with echo planar imaging (EPI) gradient echo (TR/TE=2000/30 ms, 3.75×3.75×5 mm voxels, field of view 24×24 cm, 39 slices, slice thickness 5 mm, matrix size 64×64, number of frames=254, flip angle (FA)=85°).

[0091] The acquired MRI and $P_{ET}CO_2$ data may be analyzed using AFNI software (National Institutes of Health, Bethesda, Md.; http://afni.nimh.nih.gov/afni; Cox, 1996 #16172]). $P_{ET}CO_2$ data may be time-shifted to the point of maximum correlation with the whole brain average BOLD signal. A linear, least-squares fit of the BOLD signal data series to the $P_{ET}CO_2$ data series (i.e., CVR) may then be performed on a voxel-by-voxel basis. For displaying CVR maps, voxels with a correlation coefficient between −0.25 and +30 0.25 may be eliminated before color-coding the remaining CVR values.

[0092] BOLD images may then be volume registered and slice-time corrected and co-registered to an axial 3-D T1-weighted Inversion-Recovery prepared Fast Spoiled Gradient-Echo (IR-FSPGR) volume (TI/TR/TE=450/8/3 ms, voxel size 0.86×0.86×1.0 mm, matrix size 256×256, field of view 22×22 cm, slice thickness=1 mm, FA=15°) that was acquired at the same time [Saad, 2009]. This method has been described in greater detail elsewhere [Fierstra, 2010].

[0093] Example of Analysis of CVR Maps

[0094] Constructing the Atlas (see also Guimond, A 2000, and Seitz, 1990).

[0095] Analytical processing software (SPM5; Wellcome Department of Imaging Neuroscience, University College, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm5), may be used to co-register each of the individual brain volumes from the healthy cohort into MNI (Montreal Neurologic Institute) standard space using a 12-parameter [Ashburner, 1997] affine transformation followed by nonlinear deformations to warp the brain volume of interest into an MNI template of identical weighting contrast. The T1-weighted FSPGR volume may be used to estimate the transformation normalization into standard space, as defined by a T1-weighted MNI152 standard template [Ashburner, 1999].

[0096] A spatial smoothing of Full-Width Half-Maximum (FWHM) 5 mm may be applied to each voxel. Assumption for normality was tested using the Anderson-Darling test (the statistical test for normality provided in AFNI) with p values greater than 0.05 assumed to pass the test. As most voxels (60%) did pass this threshold, and these were diffusely distributed throughout the brain, the simplifying assumption was made that the CVR for each voxel was normally distributed. The mean (μ) and associated standard deviation (σ) of CVR may be calculated (AFNI software [Cox, 1996]). Maps may then constructed for μ and coefficient of variation (σ/μ) to characterize the atlas.

[0097] Example of CVR Z-map Generation

[0098] The generation of an individual's CVR z-map may consist of three steps. First, a spatial normalization of the individual's anatomical scan and CVR map [Ashburner, 1999] using a MNI152 SPM distributed template may be produced. Second, the CVR of each voxel (x) may be scored in terms of a z value (i.e., $z=(x-\mu)/\sigma$). Finally, a color may be assigned to each z score to indicate the direction and magnitude (in z values) of the differences from the mean of the corresponding atlas voxel. CVR and CVR z scores may be superimposed on the corresponding anatomical scans to allow comparison of the CVR and its z score. Note that CVR voxels that are positive but lower than the atlas mean for that voxel will have negative z scores. Greater specificity for identifying underlying vascular pathophysiology is optionally assumed to be connoted by greater absolute value of z scores and the confluence of similarly scored voxels in both CVR and CVR z-maps.

[0099] To clarify the colour coding used, it is pointed out that in the resulting z-map: (1) Patient CVR map voxels that are negative (blue) where the corresponding atlas CVR map voxels are positive, will have negative z-scores coded light blue to purple. (2) Patient CVR voxels that are positive but lower than the atlas CVR voxels will also have negative z-scores. (3) However, negative CVR voxels that are greater (towards the positive direction) than the corresponding atlas CVR voxel will nevertheless have a positive z-score. Greater specificity is connoted by greater z scores (for z-maps) and the confluence of similarly scored voxels (both CVR and z-maps).

[0100] All references identified herein are hereby incorporated by reference.

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1. A system for detecting an abnormality in a subject's cerebrovascular response to a vasoactive stimulus in at least one region of interest (ROI) of the subject's brain, comprising:

(A) a system for generating the vasoactive stimulus (SVS);

(B) an imaging system (IS) characterized in that it provides sufficient spatial resolution for analyzing a vasoactive response to a series of increments and/or decrements in the vasoactive stimulus, the vasoactive response preferably constituting a surrogate measure of blood flow in the at least one ROI;

(C) a computer for implementing an algorithm for analyzing the vasoactive response to a series of increments and/or decrements in a vasoactive stimulus, the algorithm including program code for computing at least one value representing a quantitative measure of cerebrovascular reactivity for the ROI, wherein the at least one value is obtained for a specific portion of the vasoactive response in the ROI, the specific portion of the response corresponding to a to sub-range of increments and/or decrements in the vasoactive stimulus within the full range of the vasoactive stimulus, the sub-range characterized in that it is sensitive to quantifying a reduction in cerebrovascular reactivity.

2. A system as claimed in claim **1**, further comprising the step of computing, on a ROI by ROI basis (for at least one ROI), at least one score (per ROI) adapted for interpreting the at least one value.

3. A system as claimed in claim **1**, wherein the value is a CVR for sub-range of increments and/or decrements in the vasoactive stimulus within the full range of the vasoactive stimulus.

4. A system as claimed in claim **2**, wherein the score is adapted to visually depict the value.

5. A system as claimed in claim **2**, wherein the score is computed to grade the amplitude of the CVR.

6. A system as claimed in claim **1**, wherein the at least one of value per ROI and a score computed for interpreting the at least one value is visually depicted on an image of the ROI.

7. A system as claimed in claim **1**, wherein the at least one of value and a score computed for interpreting the at least one value is computed on a voxel by voxel basis.

8. A system as claimed in claim **1**, wherein the at least one of value and a score computed for interpreting the at least one value is adapted to visually depict the amplitude of the CVR on an anatomical image of a slice of the brain composed of a set of voxels constituting at least one ROI.

9. A system as claimed in claim **2**, wherein the score quantifies the extent to which that the at least one value deviates from a range of that value computed for the corresponding ROI in a control cohort, the value computed for the control cohort per ROI for the specific portion of the response corresponding to the same sub-range of increments and/or decrements in the vasoactive stimulus, wherein the score reflects the statistical confidence that the at least one value represents a pathophysiological reduction in CVR.

10. A system as claimed in claim **1**, wherein the sub-range of the vasoactive stimulus is characterized in that it is more sensitive to quantifying a reduction in cerebrovascular reactivity than a quantitative measure of CVR computed using an alternative set of response signals, the alternative set of response signals corresponding to at least one of a full range of the vasoactive stimulus or a range of the vasoactive stimulus for which the corresponding set of response signals better discriminates a reduced CVR for the ROI than the set of response signals corresponding to a full range of the vasoactive stimulus.

11. A system as claimed in claim **1**, wherein the algorithm includes program code for identifying a sub-range of the vasoactive stimulus that is sensitive to quantifying a reduction in cerebrovascular reactivity.

12. A system as claimed in claim **1**, wherein the sub-range of the vasoactive stimulus for which the at least one value is computed includes a portion of the vasoactive stimulus for which the signal to noise ratio is adapted to discriminate a reduction in CVR e.g. a negative CVR.

13. A system as claimed in claim **1**, wherein the series of increments and/or decrements in a vasoactive stimulus is a

series of target end tidal concentrations of carbon dioxide, and wherein the vasoactive response signals correspond approximately to the sub-range of the vasoactive constituting the highest 4 to 6 mm of Hg in the target end tidal partial pressure of carbon dioxide, the upper range of the stimulus selected such that the stimulated blood flow demand, for the ROI, sufficiently exceeds the blood flow supply to result in a relative distribution of blood flow in favor of healthy vessels at the expense of vessels that have a reduced CVR.

14. A system as claimed in claim **13**, wherein the upper range of stimulus is at least 8 to 12 mm of Hg above the subject's baseline $PaCO_2$.

15. A system as claimed in claim **1**, wherein each ROI is a voxel within a larger ROI and wherein at least of the value and the score is computed on a voxel by basis for a series of voxels within the larger ROI.

16. A system as claimed in claim **2**, wherein the scores are color coded and represented on a CVR map of the ROI.

17. A system as claimed in claim **1**, wherein the algorithm includes program code for computing at least one CVR for the specific portion of the response corresponding to the sub-range of increments and/or decrements in the vasoactive stimulus (within the full range of the vasoactive stimulus) and program code for determining whether the CVR that is computed for this specific portion of the response represents a reduction in CVR, the algorithm optionally including program code for identifying a stimulus range or time range of the at least one portion of the vasoactive response for which the signal to noise ratio is sufficient to discriminate a reduced CVR within a relatively broader range of the vasoactive response, the analysis of which would result in a greater CVR value.

18. A system as claimed in claim **17**, wherein the algorithm may include program code for identifying at least one portion of response that satisfies at least one of the following conditions:

i) the stimulus range is sufficiently large to identify a reduced CVR (at least to compute a slope of a tangent the response curve);

ii) the upper range of the stimulus is one in which stimulated blood flow demand sufficiently exceeds the blood flow supply to result in a relative distribution of blood flow in favor of healthy vessels at the expense of vessels that have a reduced CVR.

19. A system as claimed in claim **1**, wherein the imaging system employs an MRI scanner, and wherein a standardized set of MR imaging protocols is used to generate a set of hemodynamic response signals corresponding to each of the increments and/or decrements in vasoactive stimulus (optionally, increments and/or decrements in a set of target end tidal partial pressures of carbon dioxide ($PetCO_2^T$).

20. A system as claimed in claim **19**, wherein the response signals represent a change in a blood oxygen level dependent (BOLD) magnetic resonance imaging (MRI) response to a set of targeted incremental increases in a subject's end tidal PCO_2 ($P_{ET}CO_2$), the vascular response values representing a change in BOLD MRI signal (ΔS), in response to a standardized increase in the $P_{ET}CO_2$ ($CVR=\Delta S/\Delta P_{ET}CO_2$).

21. A system as claim in claim **19**, wherein the increments and/or decrements in vasoactive stimulus are administered at a controlled rate, optionally at a constant rate (i.e. the size of the increments/decrements are equal and intervals between them are the same), optionally, the constant rate of increase is sufficiently slow to reveal at least one to two time constant in progress of the response, optionally two to three time constants in the progress of the response.

22. A system as claimed in claim **1**, wherein the algorithm includes program code for: a) fitting a polynomial to the entire vasoactive response (which corresponds to a full range of the vasoactive stimulus selected for analysis); b) computing a first derivative of the polynomial; and c) identifying negative slopes corresponding to a specific portion of the vasoactive response for which the signal to noise ratio is sufficiently high to discriminate a negative CVR within a relatively broader range of the vasoactive response for which the CVR is positive.

23. A system as claimed in claim **1**, wherein the system for generating the vasoactive stimulus comprises an apparatus for controlling an amount of carbon dioxide (CO_2) in a subject's lung to attain a series of targeted end tidal partial pressures of CO_2 ($PetCO_2^T$), the apparatus comprising:

(a) a gas delivery device;

(b) a control system for controlling the gas delivery device, wherein the control system is programmed to target a series of $PetCO_2^T$ values for a series of respective intervals, the series of $PetCO_2^T$ values comprising at least one of a set of $PetCO_2^T$ increments and a set of $PetCO_2^T$ decrements, the control system including means for:

a. Obtaining (e.g. providing via an input device) input of a series of logistically attainable $PetCO_2^T$ values for the series of respective intervals; and

b. Determining an amount of CO_2 required to be inspired by the subject in an inspired gas to target the $PetCO_2^T$ for a respective interval;

c. Controlling the amount of gas CO_2 in a volume of gas delivered to the subject in a respective interval to target the respective $PetCO_2^T$ for the interval.

24. A computer program product for implementing an algorithm for analyzing a vasoactive response to a series of increments and/or decrements in a vasoactive stimulus, the algorithm including program code:

(a) for computing at least one value representing a quantitative measure of cerebrovascular reactivity for the ROI, wherein the at least one value is obtained for a specific portion of the vasoactive response in the ROI, the specific portion of the response corresponding to a to sub-range of increments and/or decrements in the vasoactive stimulus within the full range of the vasoactive stimulus, the sub-range characterized in that it is sensitive to quantifying a reduction in cerebrovascular reactivity; and optionally

(b) computing on a ROI by ROI basis (for at least one ROI), at least one score (per ROI) adapted for interpreting the at least one value.

25. A programmable IC chip including program code for implementing an algorithm for analyzing a vasoactive response to a series of increments and/or decrements in a vasoactive stimulus, the algorithm including program code:

(a) for computing at least one value representing a quantitative measure of cerebrovascular reactivity for the ROI, wherein the at least one value is obtained for a specific portion of the vasoactive response in the ROI, the specific portion of the response corresponding to a to sub-range of increments and/or decrements in the vasoactive stimulus within the full range of the vasoactive stimulus, the sub-range characterized in that it is sensitive to quantifying a reduction in cerebrovascular reactivity; and optionally

(b) computing on a ROI by ROI basis (for at least one ROI), at least one score (per ROI) adapted for interpreting the at least one value.

* * * * *

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摘要(译)

一种算法，包括用于分析对血管活性刺激的血管活性反应的特定部分的程序代码，所述血管活性刺激对应于血管活性刺激的整个范围内的刺激的增量和/或减量的子范围，该子范围的特征在于，对识别ROI中血管反应性降低更敏感。