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PhD Thesis

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The mean flow index: the Emperor's new clothes?

– a critical investigation of reliability and validity of a measure for dynamic cerebral autoregulation

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Acknowledgement

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1 ACKNOWLEDGEMENT

"A balanced life is like a three-legged stool. Each leg – work, love, and friendship – is necessary and supports the other."

- Ellie Krieger (modified by Martin Kryspin)

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2 TABLE OF CONTENT

3 ORIGINAL PAPERS

The following articles and manuscripts form the present thesis:

I. **Reliability and validity of the mean flow index (Mx) for assessing cerebral autoregulation in humans: a systematic review of the methodology.**
Markus Harboe Olsen, Christian Gunge Riberholt, Jesper Mehlsen, Ronan M. G. Berg, and Kirsten Møller; J Cereb Blood Flow Metab. 2022; 42; 27–38.

II. **Reliability of the mean flow index (Mx) for assessing cerebral autoregulation in healthy volunteers.**
Markus Harboe Olsen, Christian Gunge Riberholt, Ronni R. Plovsing, Kirsten Møller, and Ronan M. G. Berg; Physiological Reports. 2021; 9; e14923

III. **Reliability of cerebral autoregulation using different measures of perfusion pressure in patients with subarachnoid haemorrhage.**
Markus Harboe Olsen, Tenna Capion, Christian Gunge Riberholt, Søren Bache, Ronan M. G. Berg, and Kirsten Møller; Manuscript submitted for publication

IV. **Diagnostic and prognostic performance of arterial pressure-derived mean flow index (Mxa): the influence of data pre-processing.**
Markus Harboe Olsen, Christian Gunge Riberholt, Ronni R. Plovsing, Ronan M. G. Berg, and Kirsten Møller; Manuscript submitted for publication

The following R-package is relevant to this thesis, but is not formally included

- **clintools: Tools for Clinical Research.**
Markus Harboe Olsen, Christian Gunge Riberholt, Ronan M. G. Berg, Kirsten Møller; CRAN. 2021; R package version 0.9.2 [1]

Funding and conflicts of interest

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4 ABBREVIATIONS

95%CI	95% confidence interval
ABP	Arterial blood pressure
AUC	Area under the curve
CBF	Cerebral blood flow
CPP	Cerebral perfusion pressure
ICC	Intraclass correlation coefficient
ICP	Intracranial pressure
IQR	Interquartile range
MCA	Middle cerebral artery
MCAv	Middle cerebral artery velocity
Mx	Mean flow index
Mxa	Mean flow index, *calculated using invasive ABP and MCAv*
Mxc	Mean flow index, *calculated using CPP and MCAv*
nMxa	Mean flow index, *calculated using non-invasive ABP and MCAv*
nTFA	Transfer function analysis, *calculated using non-invasive ABP and MCAv*
ROC	receiver operating characteristics
SAH	Subarachnoid haemorrhage
SD	Standard deviation
TBI	traumatic brain injury
TCD	Transcranial Doppler
TFA	Transfer function analysis
TFAa	Transfer function analysis, *calculated using invasive ABP and MCAv*
TFAc	Transfer function analysis, *calculated using CPP and MCAv*

5 SUMMARY

Cerebral autoregulation is a physiological mechanism that dampens changes in cerebral blood flow (CBF) during changes in cerebral perfusion pressure (CPP). Cerebral autoregulation can be investigated as a static or dynamic phenomenon. One popular approach to evaluating dynamic autoregulation based on spontaneous fluctuations or induced changes in perfusion pressure and CBF is the mean flow index (Mx). Mx is defined as the correlation coefficient between perfusion pressure (measured as CPP resulting in a measure termed Mxc, or arterial blood pressure (ABP) resulting in a measure termed Mxa) and flow velocity in the middle cerebral artery (measured by transcranial Doppler ultrasound) over time. Higher values of Mx generally indicate more impaired autoregulation. In the literature, Mx has been calculated using several different approaches, and they have been suggested to predict outcomes primarily in patients with acute brain injury. The primary aim of this thesis was to investigate the reliability and validity of Mx derived indices (Mxc or Mxa) and investigate different approaches for calculation. The thesis consists of four papers.

Paper I, a systematic review of studies calculating and reporting Mx and included 128 studies. The reliability and validity of Mx were highly variable, and neither an optimal nor a consensus on the approach for calculating Mx was identified.

Paper II investigated Mxa in relation to healthy volunteers and analyzed the stability over time as well as the influence of recording length and artefacts. By comparing the first and last half of a recording, we found that Mxa had poor to moderate stability. Further, Mxa was heavily influenced by approach for calculation, recording length, and artefacts.

Paper III compared the time-based indices of autoregulation, Mx, as well as the measures of a different, frequency-based approach, so-called transfer-function analysis (TFA), when calculated using three different measures of perfusion pressure, i.e. CPP, invasive ABP, and non-invasive ABP. In 39 participants with aneurysmal subarachnoid haemorrhage (SAH), demonstrated pressure variable used for calculating Mx had moderate reliability and varied depending on which measure of perfusion pressure was used; invasive measurement of ABP yielded the highest values. TFA measures had moderate to excellent reliability and depended on the pressure measurement.

Summary

Paper IV assessed the diagnostic and prognostic performance of Mxa. The diagnostic performance was ‘no better than chance’ at distinguishing between healthy volunteers and patients with sepsis, patients with traumatic brain injury (TBI), and patients who were admitted to a neurorehabilitation unit. Similarly, the prognostic performance was ‘no better than chance’ at predicting functional outcome in patients with TBI and mortality in patients with sepsis and TBI. Furthermore, different approaches to calculating Mxa yielded significantly different values.

Overall, Mx and Mxa, though widely used, appear to be unreliable measures of dynamic cerebral autoregulation. The studies reported here showed a lack of consensus in the literature on the specific approach to calculating Mx and Mxa, which renders previously collected data largely incomparable. The evidence for Mx or Mxa being valid measures of dynamic cerebral autoregulation is questionable at best and alternative methods should be pursued.

6 DANISH SUMMARY (DANSK RESUMÉ)

Hjernens autoregulation er en fysiologisk mekanisme, som dæmper ændringer i cerebral blodgennemstrømning (cerebral blood flow, CBF) under ændringer i cerebralt perfusionstrykket (cerebral perfusion pressure, CPP). Hjernens autoregulering kan undersøges som et statisk eller dynamisk fænomen. Sidstnævnte måles under spontane eller inducerede ændringer over tid og kan vurderes ved hjælp af det såkaldte mean flow index (Mx). Mx er defineret som korrelationskoefficienten mellem perfusionstryk (målt som CPP) eller det arterielle blodtryk (arterial blood pressure, ABP) og lineær strømningshastighed i arteria cerebri media (målt ved transkraniel Doppler-ultralyd) over tid. Korrelationskoefficienten mellem ABP og lineær strømningshastighed kaldes Mxa. Højere værdier af Mx indikerer generelt en mere svækket autoregulation. I litteraturen er Mx blevet beregnet ved hjælp af flere forskellige tilgange, og de er blevet foreslået til at forudsige kliniske effektmål primært hos patienter med akut hjerneskade. Det primære formål med denne afhandling var at undersøge pålideligheden og gyldigheden af Mx-afledte indekser (Mxc og Mxa) og undersøge forskellige tilgange til beregning. Afhandlingen består af fire studier.

Studie I er et *systematisk review* af publikationer der beregner og rapporterer Mx og inkluderede 128 studier. Pålideligheden og validiteten af Mx var meget varierende, og der kunne hverken identificeres en optimal tilgang til beregning af Mx eller konsensus om dette.

Studie II blev udført på raske frivillige og undersøgte stabiliteten af Mxa over tid, samt indflydelsen af optagelseslængde og artefakter. Mxa havde dårlig til moderat stabilitet vurderet ud fra en sammenligning af første og sidste halvdel af en optagelse, ligesom Mxa påvirkedes af beregningsmetode, optagelseslængde og støj.

Studie III sammenlignede de tidsbaserede indekser for autoregulering, Mx, samt målene for en anden frekvensbaseret tilgang, såkaldt transfer-function analysis (TFA), når de blev beregnet ved hjælp af tre forskellige mål for perfusionstryk, dvs. invasiv ABP og ikke-invasiv ABP. Hos 39 deltagere med aneurismal subaraknoid blødning (subarachnoid haemorrhage, SAH) havde den påviste trykvariabel, der blev brugt til at beregne Mx, moderat pålidelighed og varierede afhængigt

af hvilket mål for perfusionstryk, der blev anvendt; invasiv måling af ABP gav de højeste værdier. TFA-mål havde moderat til fremragende pålidelighed og afhang også af trykmålet.

Studie IV vurderede den diagnostiske og prognostiske styrke af Mxa. Mxa var ikke i stand til at differentiere mellem raske og patienter med sepsis, patienter med traumatisk hjerneskade (TBI) og patienter der var indlagt til højt specialiseret neurorehabilitering. Mxa var heller ikke i stand til at forudsige et senere funktionsniveau hos patienter med TBI og dødelighed hos patienter med sepsis og TBI. Desuden gav forskellige tilgange til beregning af Mxa væsentligt forskellige værdier.

Samlet set synes Mx og de afledte indekser (som fx Mxa) trods deres udbredelse at være upålidelige mål for dynamisk cerebral autoregulering. Studierne inkluderet i denne afhandling, viste en mangel på konsensus i litteraturen om den specifikke tilgang til beregning af Mx, hvilket gør tidligere indsamlede data stort set usammenlignelige. Beviset for, at Mx eller de Mx-afledte indekser er gyldige mål for dynamisk cerebral autoregulering, er i bedste fald tvivlsom, og alternative metoder bør forfølges.

7 BACKGROUND

The brain has a limited energy reserve and even a small drop in cerebral blood flow (CBF), without a corresponding increase in oxygen extraction, can lead to dizziness or altered mental state [5,6]. Thus, CBF must be kept relatively constant. The physiological mechanism responsible for this is cerebral autoregulation which helps dampen changes in CBF during changes in cerebral perfusion pressure (CPP), i.e. the difference between arterial blood pressure (ABP) and intracranial pressure (ICP) [7]. The notion of cerebral autoregulation was initially described in 1890, and it took nearly 70 years before Niels A. Lassen again described this mechanism in humans and kickstarted modern research in the field [7,8]. Lassen's work outlined – what would later be known as the *autoregulation curve* – that an ABP from 50 to 150 mmHg resulted in a constant CBF [8]. The curve was since expanded showing a drop in CBF at CPP values below 50 mmHg and a rise in CBF above the upper threshold of CPP [9]. The horizontal line, depicting the zone of autoregulation, has since been modified into a line with a small increase – the *gradient phase* – in CBF with an increase in CPP [7,10] (**Figure 1**).

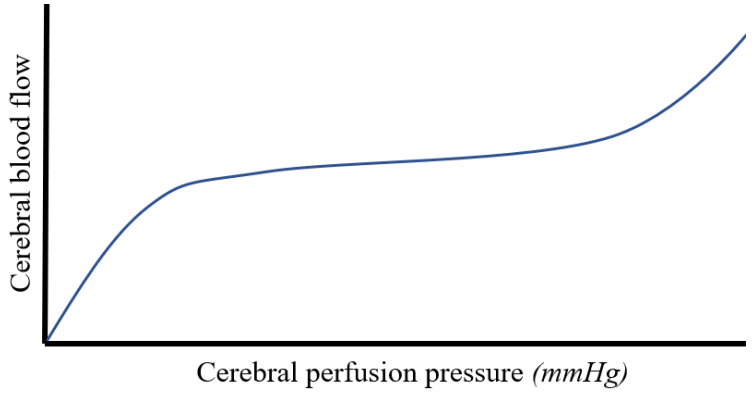

Figure 1 – Depiction of cerebral autoregulation according to the current understanding with a lower and upper threshold of cerebral autoregulation and a small increase in the originally horizontal line. (*Modified from* [7–10]).

The autoregulation curve is now widely considered to over-simplify the complex system that regulates CBF [7]. Physiological changes such as a change in body temperature, arterial carbon dioxide tension ($PaCO_2$), and age are merely some of the factors that influence cerebral flow-pressure relationships [7,11,12]. Moreover, cerebral autoregulation is impaired in a wide array of both acute and chronic conditions, such as stroke and obstructive sleep apnoea [13,14], and in patients with acute brain injury, impaired cerebral autoregulation has been reported to be associated

with poor functional outcome [15]. This highlights that clinical assessments of cerebral autoregulation have the potential to diagnose patients with complex symptomatology, forewarn clinical worsening, and potentially personalise neuroprotective treatments [7,16]. As an example, a recent randomised feasibility trial compared fixed CPP targets with implementation of CPP optimisation (CPPopt) targeted treatment guided by changes in cerebral autoregulation in patients with severe traumatic brain injury (TBI) was found to be both feasible and safe [17].

The concept of cerebral autoregulatory function may be divided into two main mechanisms, static and dynamic cerebral autoregulation. Static cerebral autoregulation assumes that the variable for pressure (e.g. ABP) and the variable for CBF are in a steady state [18]. It generally requires at least 10 minutes to achieve a measure of static cerebral autoregulation [18,19]. This is typically done in the experimental setting, but derivation of the entire autoregulation curve from severe hypotension to severe hypertension in humans is nearly impossible [20]. Thus, the autoregulation curve in humans is based on different measurements from different studies [7]. Together with the advances in technology, this issue has paved the way for the introduction of the concept of dynamic cerebral autoregulation [18,19].

7.1 Dynamic cerebral autoregulation

The principle of the autoregulation curve, where CBF is kept relatively stable during changes in cerebral perfusion, mainly applies to low-resolution measures (several minutes), but CBF clearly fluctuates when measured at higher resolution (seconds) [7]. Dynamic cerebral autoregulation refers to the immediate cerebrovascular responses that occur with rapid changes in ABP (or CPP), and was initially described in 1989 [18,19,21]. Dynamic cerebral autoregulation can be measured in a time or a frequency domain [19]. The time domain primarily focuses on the response time after changes in ABP, while the frequency domain interprets cerebral autoregulation as a filter that lessens the impact of spontaneous fluctuations in ABP that occur at distinct frequencies on CBF.

The most accurate methods for measuring CBF in humans are time-consuming, costly, and requires continuous access to a scanner; their temporal resolution is also very low, rendering them unhelpful for frequent measurements, such as is necessary for assessing dynamic autoregulation [15,22]. In contrast, transcranial Doppler (TCD) insonation of the middle cerebral artery (MCA), usually for

measuring the mean MCA flow velocities (MCAv), is scanner-independent, can be carried out bedside using a simple device, and provides values at a very high temporal resolution. MCAv is often used as a surrogate of CBF for assessing dynamic autoregulation [23,24]. The advantages of TCD is that it can be used bedside and pose minimal risk for the patient, even in those that are severely ill and admitted to an intensive care unit (ICU) [19], but is, among other things, limited by only investigating focal disturbances [15].

Two common measures of dynamic cerebral autoregulation are the mean flow index (Mx) in the time domain and transfer function analysis-based indices (TFA) in the frequency domain.

7.2 Mean flow index (Mx)

Mx is was originally introduced in 1996 [25]. Mx is developed to evaluate to what extent spontaneous fluctuations of CPP affects CBF, measured using TCD-based MCAv [25,26]. Since then, indices have been developed, in which the CPP input is replaced by either invasive or non-invasive ABP [27–29].

Mx is generally calculated using raw waveform recordings, which is averaged over a period of 3 to 10 seconds (called ‘blocks’). These blocks are split into groups of 20 to 40 (called ‘epochs’). The blocks of pressure and MCAv measurements are then correlated using Pearson’s correlation coefficient for every epoch. Recordings with more than one epoch, and thereby more than one correlation coefficient, are then averaged into one Mx (**Figure 2**) [25]. Mx ranges from -1 to +1. Simultaneous passive fluctuations of result in high values and are interpreted as impaired cerebral autoregulation [25,30,31]. Conversely, lower values positive and negative values are suggested to indicate a more intact autoregulation.

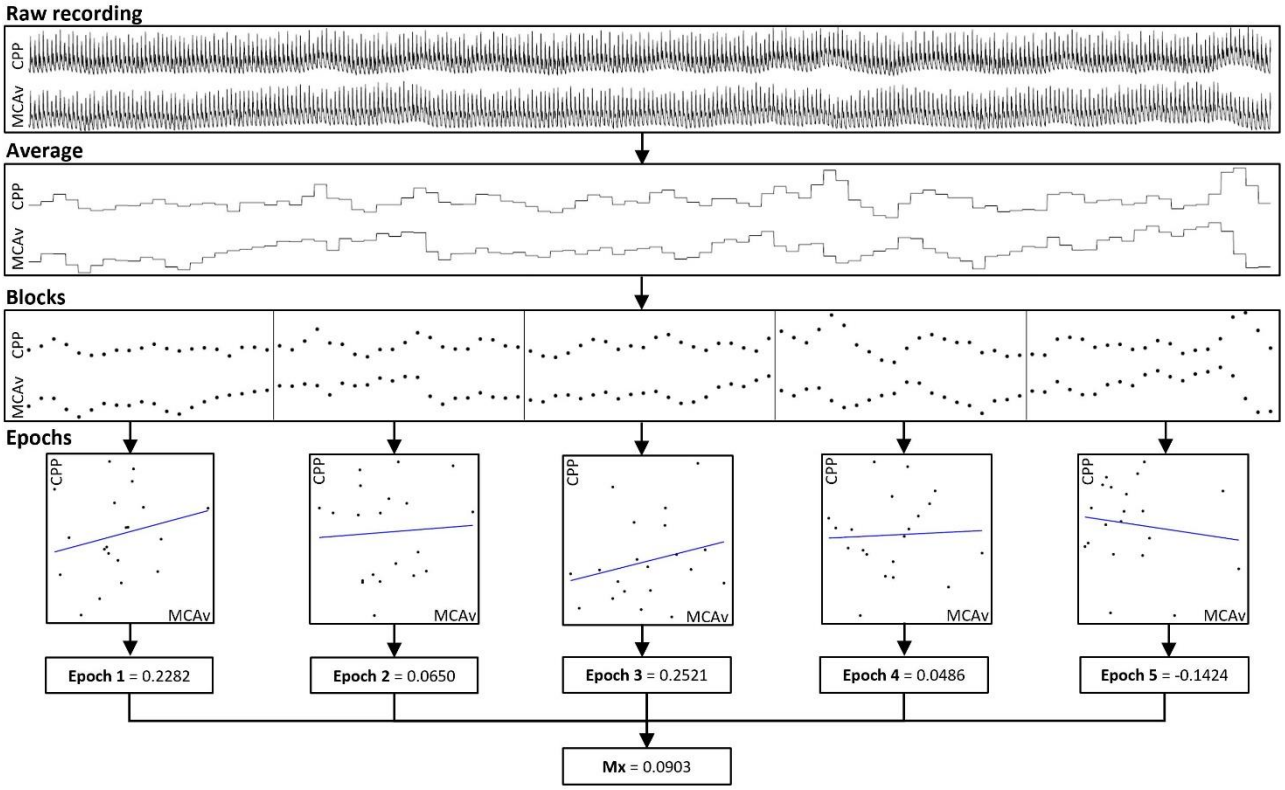

Figure 2 – The process of calculating Mx from a raw recording *(Figure from **Paper I**)*.
CPP: cerebral perfusion pressure; MCAv: middle cerebral artery velocity; Mx: mean flow index.

7.3 Transfer function analysis (TFA)

TFA of spontaneous fluctuations is an alternative method for estimating dynamic cerebral autoregulation and operates in the frequency domain. The oscillations in CBF and ABP are subjected to spectral analysis and commonly investigated in three frequency domains [32]. Gain, phase, and coherence in the low-frequency domain between 0.07 and 0.20 Hz are generally accepted as measures of dynamic cerebral autoregulation, as they are interpreted as a result of the vasomotor tonicity [32].

In TFA, ABP, or CPP are considered the input, while the CBF surrogate measure (assessed as MCAv) is considered the output. *Gain* is a quantification of the dampening of fluctuations when comparing the input and output; *phase* refers to the delay between input and output; and *coherence* refers to the relationship between the input and output (**Figure 3**) [19,32–34]. Higher values of gain and phase are interpreted as more intact dynamic cerebral autoregulation, while coherence is a quality measure that principally assesses the linearity between input and output [34]. Phase and gain can only be interpreted as a measure of dynamic cerebral autoregulation if the corresponding coherence is high [19,33].

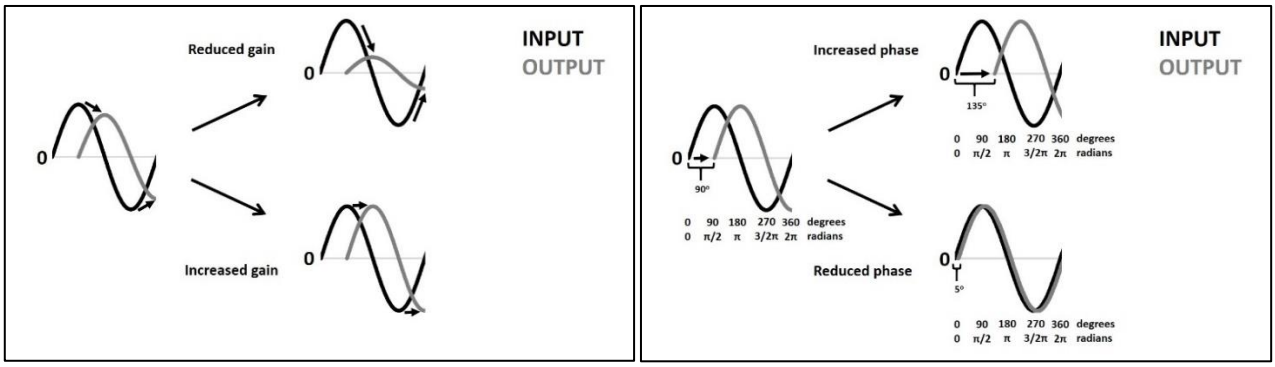

Figure 3 – TFA measure of gain (left) and phase (right). Gain refers to the dampening of the input, while phase refers to the delay of the signal *(Courtesy of Ronan M. G. Berg)*.

7.4 Biomarkers as outcomes

The optimal outcomes of randomised clinical trials are mortality and valid measures of functional outcome or quality of life [35,36], outcomes that are clinically meaningful for the patients. Randomised clinical trials should always strive to use one of these as their primary outcome, but this usually requires a lot of participants and are therefore costly and time-consuming. To achieve a statistically significant interventional effect, trials often use surrogate markers such as biomarkers to reduce sample size, and thereby also the duration of the trial [37]. Biomarkers are *"physiological measurements, blood tests and other chemical analyses of tissue or bodily fluids, genetic or metabolic data, and measurements from images*" [38]. Biomarkers chosen as outcomes should be a valid surrogate of one or more clinically meaningful outcomes [39]; e.g. a treatment that changes mortality should also change the biomarker. Simple correlation analyses between clinical outcomes and biomarkers might not reflect its ability to perform as a surrogate marker, as the biomarker may reflect disease severity and pathophysiological epiphenomena rather than being causally related to outcome [40,41].

Both Mx and TFA-based indices of dynamic cerebral autoregulation, as described above, are physiological measurements that can be classified as biomarkers. It is important that biomarkers used as surrogate markers are both reliable and valid [37,42,43]. Simple correlation analyses between clinical outcomes and biomarkers are insufficient, as a potential correlation between the biomarker and a clinical outcome may reflect disease severity and pathophysiological

epiphenomena rather than being causally related to that outcome [40,41]. Accordingly, other methods are necessary to appraise these characteristics critically.

7.5 Reliability

Reliability reflects the consistency of a measurement and can be divided into repeatability and reproducibility. The reliability also includes the stability, i.e. the ability of repeated measurements under the same condition to obtain the same results, also coined *'test-retest'*, and the internal consistency, which evaluates the measurements on a group level and ignores the individual measurement [44]. Repeatability reflects the ability of a measurement's ability to achieve the same results in identical settings, while reproducibility reflects the ability to achieve the same results when measuring the same subject under changing conditions [43].

The majority of reliability assessments can be carried out by the intraclass correlation coefficient (ICC) and a Bland-Altman plot [45,46]. At the same time, internal consistency can be assessed using the Student's t-test [46]. There are two main types of ICC, 'ICC agreement' and 'ICC consistency' [46]. ICC agreement refers to the ability of different raters being able to give the same score, while ICC consistency refers to the stability of the difference between raters. In the following, ICC agreement is described unless otherwise stated, and more specifically, the two-way mixed effect, absolute agreement, single measurement ICC [46]. The full 95% confidence interval of ICC is used in the interpretation of the true reliability, where an ICC below 0.5 indicates poor reliability; an ICC between 0.5 and 0.75 indicates moderate reliability; an ICC between 0.75 and 0.9 indicates good reliability; and an ICC above 0.9 indicates excellent reliability [46].

The Bland-Altman plot addresses the difference between two measurements [45]. The plot shows the mean difference, the bias, and 95% limits of agreement [47]. The 95% limits of agreement reflect the size of measurement error to expect, and thereby the precision between the measurements. Combining the Bland-Altman plot and ICC yields superior reliability compared to Pearson's correlation coefficient alone [47,48].

Student's t-test can be used to address the internal validity of the measurements on a group level. In this context, the t-test is used to compare the means of two groups, with the underlying assumption

that the measured variable is continuous and normally distributed [49]. A subtype is the paired t-test which assumes dependence between the two samples and that the difference between the pairs is normally distributed and will inform us if there is a statistically significant difference in the mean between the two paired measurements [50].

7.6 Validity

In the present context, validity refers to the ability of the surrogate measure to represent the outcome that should ideally be measured [44]. If the biomarker is assumed to represent one of the above-described clinical outcomes, validity can be assessed by estimating its prognostic performance, e.g. by comparing the value of the biomarker with the 'ideal' outcome in a cohort of patients [51]. Conversely, if the biomarker is assumed to reflect the presence or severity of a disease, its validity can be investigated by comparing persons with and without, or with different severities of, that disease. The ability to detect a disease, i.e. the diagnostic performance, is sometimes tested by comparing the value of the biomarker in healthy volunteers and patients (or in patients with and without the disease) [52].

The validity of a diagnostic biomarker should usually be assessed using sensitivity and specificity. Sensitivity is defined as the proportion of the true positives among all that is measured as positive, while specificity is defined as the proportion of the true negatives among all that is measured as negative [53]. Sensitivity and specificity thus require a dichotomous outcome (e.g. positive / negative, present / absent, dead / alive) of the test and thereby requires that the outcome of a continuous biomarker is dichotomised by setting a threshold. This threshold is not always fixed; thus, continuous scales can be investigated using receiver operating characteristic (ROC) analysis, which compares the fraction of true and false positive test while changing the threshold [54]. The outcome of the ROC analysis is usually reported as the area under the curve (AUC). AUC, which reflects the accuracy of the measurement, varies between 0 and 1. In the present context, AUC of around 0.5 was interpreted to reflect an accuracy 'no better than chance', 0.5-0.7 to reflect low accuracy, 0.7-0.9 to reflect moderate accuracy, and >0.9 to reflect high accuracy [55].

7.7 Change of plans

In 2018, my supervisors and I discussed the local clinical guidelines for ABP and CPP targets in patients with aneurysmal subarachnoid haemorrhage. Our local guidelines, and the underlying international guidelines, were based on flimsy evidence [56,57], that is, underpowered randomised clinical trials and observational studies with varying associations [58–60]. Therefore, we decided to design a physiological study, the primary aim of which using Mx to evaluate whether a short period of induced hypertension would improve dynamic cerebral autoregulation (clinicaltrials.gov identifier: NCT03987139; 14 June 2019). During the data collection for this physiological study, one of our collaborators, Christian Gunge Riberholt, needed assistance to calculate Mxa for a paper not directly related to this thesis [61]. We could not find any consensus in the literature for how to calculate Mx or Mxa, and for every reference we used, small differences in the source code needed to be implemented to follow their methodology. To our surprise, the reference chosen to create the script could decide whether a given individual had impaired or intact cerebral autoregulation. After long and heated discussions, we decided to investigate the methodology of Mx and Mxa, including their reliability and validity.

8 OBJECTIVES

This thesis aimed to investigate the reliability and validity of Mx as a primary aim, and reliability of TFA as a secondary aim. Mx and TFA were chosen because they are by far the most popular measures of dynamic cerebral autoregulation to spontaneous changes in ABP (or CPP) in clinical studies. The reliability and validity of these measures of dynamic cerebral autoregulation were investigated in four papers.

The aim of **Paper I** was to systematically evaluate current knowledge of the reliability and validity of Mx. This was carried out as a systematic review including all articles that calculated Mx.

The aim of **Papers II and III** was to assess the reliability of Mx. **Paper II** evaluated the reliability of Mxa (Mx calculated using ABP) in healthy volunteers. We calculated Mxa using different lengths of blocks and epochs, its stability over time, the influence of artefacts, and the internal consistency of Mxa on a group level. **Paper III** aimed to assess the reliability of Mx and TFA. We calculated these using different measures of the pressure input in patients with SAH, comprised of CPP, invasive ABP, and non-invasive ABP.

The aim of **Paper IV** was to assess the validity by evaluation of the diagnostic and prognostic performance of Mxa. The diagnostic performance was assessed by comparing Mxa between healthy volunteers to patients with sepsis, to patients with TBI, and to patients admitted to a neurorehabilitation unit. The prognostic performance of Mxa was assessed by comparing it to mortality and functional outcome in patients with sepsis and TBI.

9 METHODS AND MATERIAL

The following is an overview of the methods and material used in the papers related to this thesis. The methodologies are described in full in **Papers I-IV**.

9.1 Systematic review

Paper I is a systematic review carried out using the methodology outlined in the Cochrane Handbook for Systematic Reviews [62] and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [63]. The review was preregistered on PROSPERO (protocol id: CRD42020164028, 28 April 2020). All articles calculating any form of Mx in humans using original data were included.

The articles were acquired from two databases (MEDLINE and EMBASE) using a broad search string: "(Mxa OR Mx OR (Flow index)) AND (cerebral OR brain OR MCA OR (Middle cerebral artery)) AND (autoregulation OR (blood flow))" yielding 6,580 publications. After removal of duplicate publications, two authors independently screened abstracts and titles. Full-text screening and data extraction were also carried out by two independent authors. Included abstracts without full-text available were only excluded after three contacts to the corresponding author. The online tool Rayyan was used for screening [64].

9.2 Study populations

Raw data for **Papers II, III, and IV** were assembled from participants from six different studies, here designated Study A to F [61,65–69]. In brief, *Study A* investigated static and dynamic cerebral autoregulation in healthy volunteers before and after infusion of lipopolysaccharide and in patients with sepsis [65]. *Study B* investigated dynamic cerebral autoregulation in healthy volunteers during infusion of lipopolysaccharide and the influence of isocapnic hypoxia and hyperoxia [66,67]. *Study C* investigated dynamic cerebral autoregulation in patients admitted to a neurorehabilitation unit before and after head-up tilt compared to healthy volunteers [69]. *Study D* investigated the reproducibility of Mx in healthy volunteers depending on the approach [61]. *Study E* investigated changes in Mx in patients with severe TBI randomised to either daily head-up tilt or treatment as usual [68]. In *Study F,* we investigated the impact of noradrenaline-induced hypertension in patients with SAH (see below) (**Figure 4**). The full descriptions of the study populations from *Study A-E* are available in the original articles [61,65–69].

For *Study F* we sought consent from next-of-kin to all adult patients admitted with SAH with an external ventricular drain (EVD) to the neuro-ICU at Rigshospitalet, Copenhagen, Denmark. The exclusion criteria were (1) conservative or failed aneurysm treatment; (2) pupils fully dilated and unresponsive to light on admission; (3) brain herniation before inclusion or expected death within 48 hours; (4) other diseases or conditions associated with impaired autoregulation (e.g. ischaemic stroke, TBI, bacterial meningitis, or sepsis within a year; or diabetes mellitus with organ manifestations); and (5) no consent. In the early phase after ictus (within five days), a recording was carried out that included a baseline measurement and a period after induced hypertension. During the recordings, MCAv was obtained using unilateral TCD (Multi-Dop T, DWL, Singen, Germany), non-invasive ABP using photoplethysmography (Nano System, ADInstruments Inc., Oxford, UK), invasive ABP using arterial cannula in the radial artery, and ICP using either a Codman Microsensor ICP Transducer (Integra LifeSciences, Princeton, New Jersey, USA) or a Spiegelberg external ventricular drain combined with an ICP sensor (Spiegelberg, Hamburg, Germany).

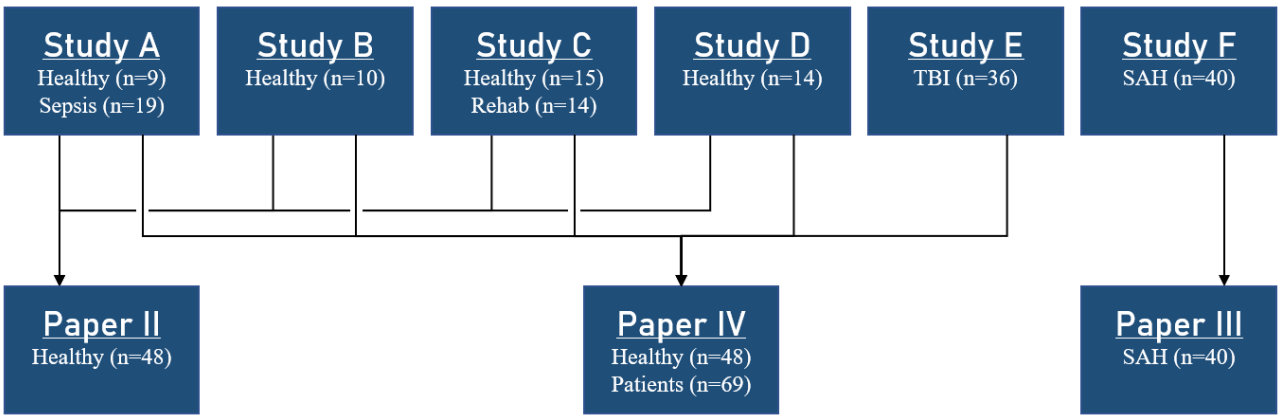

Figure 4 – The population investigated in this thesis was assembled from six different studies [61,65–69]. *Paper II* included healthy volunteers from *Study A-D*; *Paper III* included patients with SAH from *Study F*; and *Paper IV* included both healthy volunteers and patients from *Study A-E*. Rehab: patients admitted to neurorehabilitation unit; TBI: traumatic brain injury; SAH: aneurysmal subarachnoid haemorrhage.

9.3 Data collection and processing

Study A and B recorded ABP invasively in the radial artery, and MCAv was recorded by TCD-insonation [65–67]; *Study C, D, and E* all used non-invasive recordings of ABP with photoplethysmographic continuous beat-to-beat measurement, and MCAv by TCD-insonation [61,68,69]; *Study F* recorded ABP both invasively in the radial artery and non-invasively using

photoplethysmographic continuous beat-to-beat measurement, and when available also ICP to calculate CPP, and MCAv by TCD-insonation.

The measurements were all recorded using LabChart (ADInstruments, Sidney, Australia) and extracted into tab-delimited files in 1,000 Hz. For TFA analyses, the measurements were averaged using the 'cyclic measurement'-function in LabChart before extraction. Any artefacts were removed before the calculation of Mx, and for TFA, only periods without artefacts were used. Mx was calculated by averaging epochs throughout the period; the epochs were only included if 50% of the expected blocks were present, and the blocks were only included if 50% of the raw measurement was available for averaging (for details, see *'clintools'-package*, page 22).

9.4 Terminology

Mx and TFA were used when referred to the generic indices. The suffix 'c' refers to the indices calculated using CPP calculated by subtracting ICP from invasive ABP (i.e. Mxc and TFAc); the suffix 'a' refers to the indices calculated using invasive ABP (i.e. Mxa and TFAa); and the prefix 'n' refers to the indices calculated using non-invasive ABP (i.e. nMxa and nTFAa).

9.5 Statistical analyses

The statistical analyses were carried out using the most recent stable version of R (R Core Team, Vienna, Austria) available at the time of the analyses. Normal distributed continuous data are presented as mean and standard deviations (SD) or mean and 95% confidence intervals (CI), while non-normal distributed continuous data are presented as median and interquartile range (IQR) or median and range. Categorical and dichotomous data are presented as n and percentage.

Reliability was assessed by ICC and Bland-Altman plots. ICC was calculated using the 'irr'-package [70], and Bland-Altman plots were created using the 'blandr'-package [71]. Validity was assessed using ROC analysis and carried out using the 'pROC'-package [72].

9.6 'clintools'-package

The initial investigation on how to calculate Mx showed that every step from raw data to the final Mx-value seemed to influence the results. Thus, we developed an open-source publicly available R-package named '*clintools*' [1]. The aim was to simplify the process, increase the methodological reproducibility, and provide publicly available source code. Two functions – the *'clinmon'*-function

and the *'TFA'*-function – from the '*clintools*'-package are used in the papers included in this thesis (The publicly available documentation is provided as supplemental material in this thesis, see *Package 'clintools'*, page 150).

The 'clinmon'-function

The *'clinmon'*-function uses the raw waveform recording to output multiple indices and information about the recording. Apart from the required raw recording, a data frame containing which periods should be deleted and a data frame containing which periods should be analysed is needed. The latter can be used if a recording consists of multiple periods of interest. The default settings include a block length of 3 seconds; an epoch length of 60 seconds; no overlapping calculations; and quality control with requirement of 50% blocks in each epoch and 50% raw data in each block before removal from analysis. Apart from Mx (i.e. Mxc and Mxa), the output data frame include multiple indices depending on the data: the estimated cardiac output (COest) [73]; the optimal cerebral perfusion pressure (CPPopt) [74]; the cardiovascular resistance index (CVRi) [75]; the diastolic flow index (Dx) [26]; the Gosling index of pulsatility (PI) [76]; the pulse wave amplitude (PWA) [77]; the Pourcelot's resistive (resistance) index (RI) [78]; and Systolic flow index (Sx) [25]. Furthermore, the output data frame also includes the number of epochs and blocks, and percentage of missing data.

The *'clinmon'*-function and ICM+ have two different thresholds for missing data. ICM+ only removes an epoch if 50% of the raw data is missing, and the *'clinmon'*-function removes a block if 50% raw data is missing and then an epoch if 50% of the blocks are missing. These differences in quality control explains the minor difference between ICM+ and the *'clinmon'*-function and resulted in an absolute median difference in Mx of 0.02 (IQR: 0.01-0.03) when investigating 76 recordings from *Study F*. Nonetheless, the reliability of the *'clinmon'*-function was excellent (ICC agreement: 1.00 (95% CI 0.98 to 1.00); n = 76) when comparing it to the ICM+ software (Cambridge Enterprise, Cambridge, United Kingdoms).

The 'TFA'-function

The *'TFA'*-function uses either the raw waveform recording, or the default beat-to-beat averaged recording. The function is created to replicate the MatLab-code developed by Prof. David Simpson

explicitly to follow the recommendations from the white paper providing detailed recommendations on how to calculate TFA [32].

The *'TFA'*-function showed perfect reliability for the parameters related to dynamic cerebral autoregulation compared to the MatLab-code (ICC agreement; Normalised gain, non-normalised gain and phase in the low-frequency domain: 1.00 (95% CI 1.00 to 1.00); Recordings compared = 53).

10 SUMMARY OF FINDINGS

10.1 Paper I

Aim

The aim of this systematic review was to investigate the current knowledge of reliability and validity of Mx.

Summary of results

One hundred twenty-eight studies were included from a search strategy initially yielding 6,580 publications. This study found no consensus in the approach of how to calculate Mx. Predominantly blocks of 10 seconds, epochs of 300 seconds, and no overlapping feature was applied, but the approaches varied throughout the literature (**Figure 5**). There was also no consensus on how to deal with artefacts or which method should be used for pre-processing.

Repeatability was assessed in four and reproducibility in three studies, whereas one study investigated both. Repeatability ranged from poor to excellent, and the only study reporting excellent repeatability used comparators with overlapping recordings [79]. The reproducibility ranged from poor to good, and the mean ICC was moderate at best.

Validity evaluated as diagnostic and prognostic performance was assessed in fifteen studies each. Actual diagnostic performance as investigated by reporting AUC was evaluated only in patients with stroke. Mx presented with moderate accuracy. However, multiple studies showed a statistically significant difference between healthy volunteers and patients. The prognostic performance of Mx ranged from chance-result to moderate accuracy, depending on the illness.

Main findings

- The optimal approach for calculating Mx is currently unknown, and no consensus on the approach has been established.
- The reliability of Mx is highly variable.
- The discriminatory and prognostic performance of Mx is highly variable

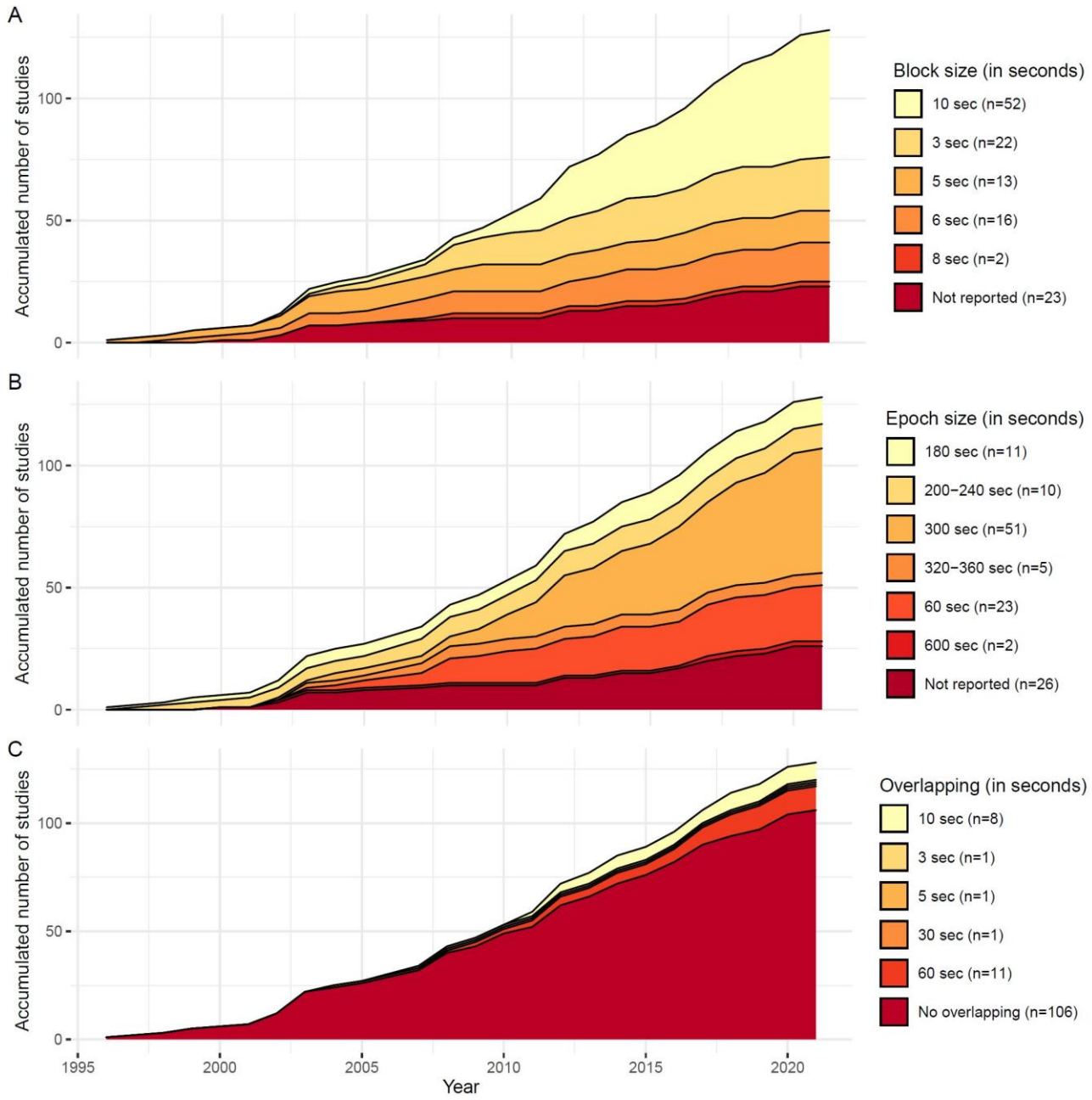

Figure 5 – The accumulated number of studies *(y-axis)* throughout the years *(x-axis)* and the selected (**A**) length of blocks, (**B**) length of epochs, and (**C**) the number of seconds the period for calculating the epochs was moved before a new calculation *(Figure from **Paper I**)*.

10.2 Paper II

Aim

The aim of this paper, based on data from Study A to D, was to assess the reliability of Mx by investigation of Mxa in healthy volunteers. This was addressed by evaluating reliability between different approaches, the stability over time, and the influence of recording length and artefacts on Mxa.

Summary of results

In 62 recordings from healthy volunteers, Mxa was highly dependent on the approach, as the approach with the shortest blocks and epochs generally resulted in higher values. The approach with the shortest blocks (3 seconds) showed poor to good reliability when comparing them with the other approaches (**Figure 6**). The stability, assessed by comparing the first and last half of a recording, showed poor to moderate reliability, i.e. questionable stability (**Figure 7**). Comparing the full recording with shorter segments showed a drop in reliability when the segments were at least 5 minutes shorter than the full recording, and simulated artefacts of less than 10% of the full duration showed overall acceptable reliability compared to the optimal recording.

Main findings

- The chosen approach for processing the measurements highly affects Mxa.
- Mxa has poor to moderate stability when comparing the first and last half of a recording.
- Mxa is influenced by approach, recording length, and artefacts.

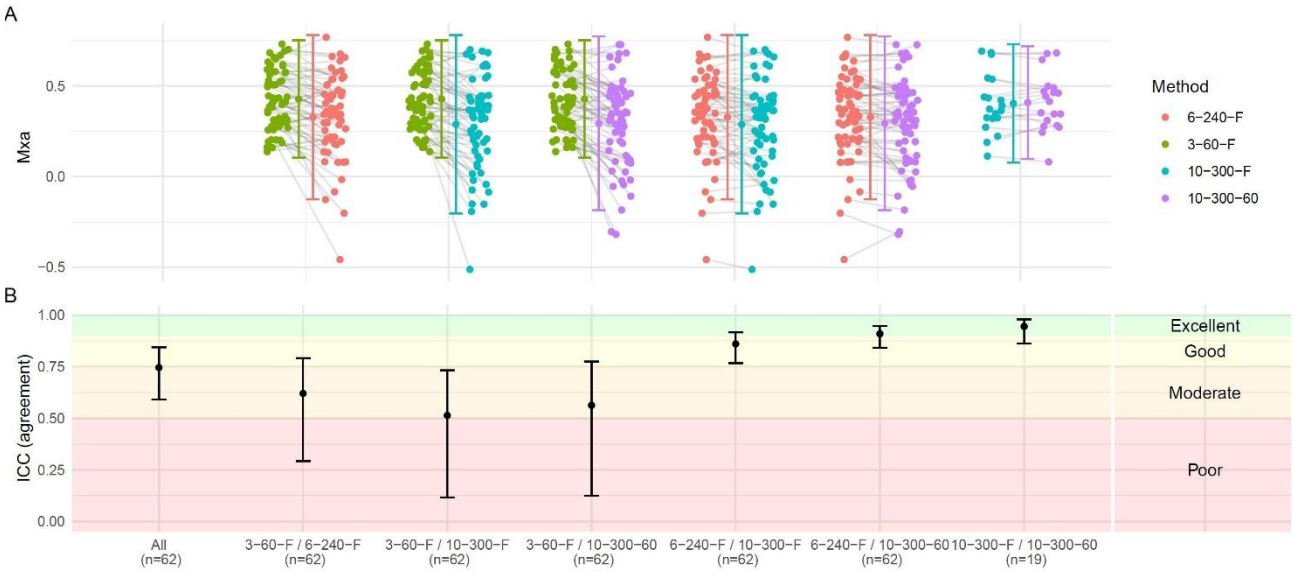

Figure 6 – Mxa for different approaches with (**A**) pairwise comparison of every participant in every column, and (**B**) the reliability, i.e. comparability, between the approaches. *(Figure from **Paper II**)*

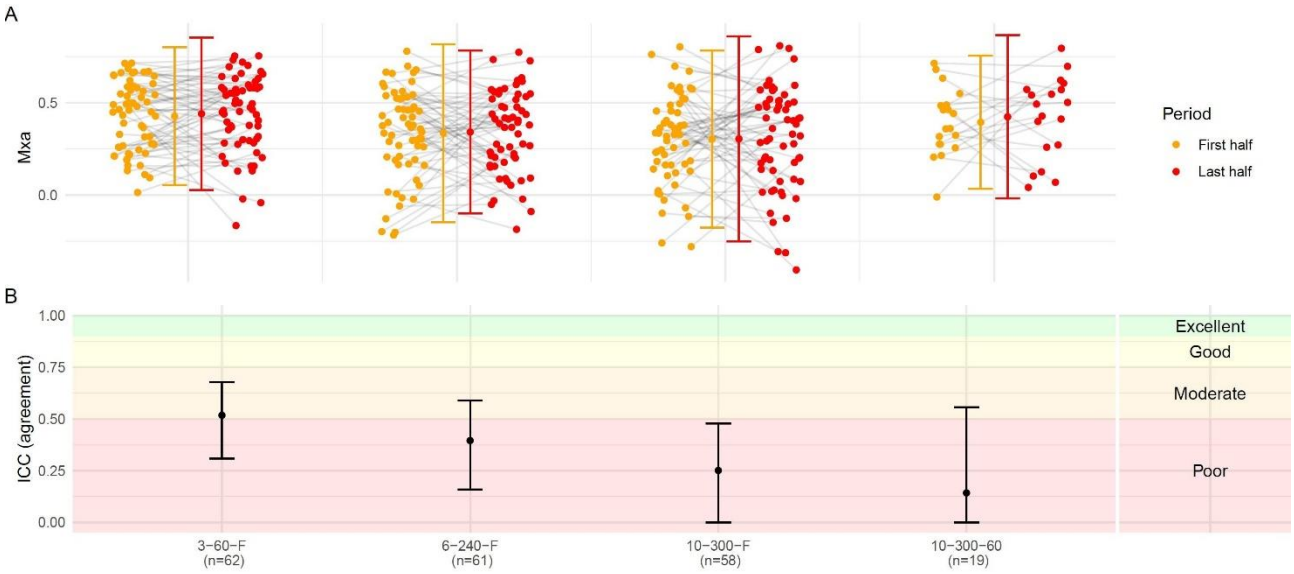

Figure 7 – Mxa for each approach (*columns*) and comparison of the first and last half of a recording with (**A**) the results from the first and last half of every recordings, and (**B**) the reliability, i.e. stability, between the first and last half *(Figure from **Paper II**)*.

10.3 Paper III

Aim

The aim of this paper, based on *Study F*, was to assess the reliability of Mx and TFA when using different measurements of pressure input. This was addressed by comparing Mx and TFA based on recordings with simultaneous measurements of at least two of the following: non-invasive ABP, invasive ABP, and CPP (derived from subtracting ICP from invasive ABP).

Summary of results

In 95 recordings from 39 participants with SAH, Mxc was on average lower than both Mxa and nMxa. The overall reliability showed poor to good reliability with similar results during pairwise comparison of Mxc, Mxa, and nMxa (**Figure 8**). In 99 recordings from 39 participants, the TFA normalised and non-normalised gain showed good to excellent reliability, while phase showed moderate to good reliability when comparing TFAc to TFAa. However, comparisons of nTFA with both TFAa and TFAc showed poor reliability for all the measures.

Main findings

- The measure of pressure input for Mx influences the results.
- Invasive ABP results in the highest Mx-values.
- TFAa-based measures of dynamic cerebral autoregulation are comparable TFAc-based measures.
- nTFA showed poor reliability when compared to both TFAa and TFAc.

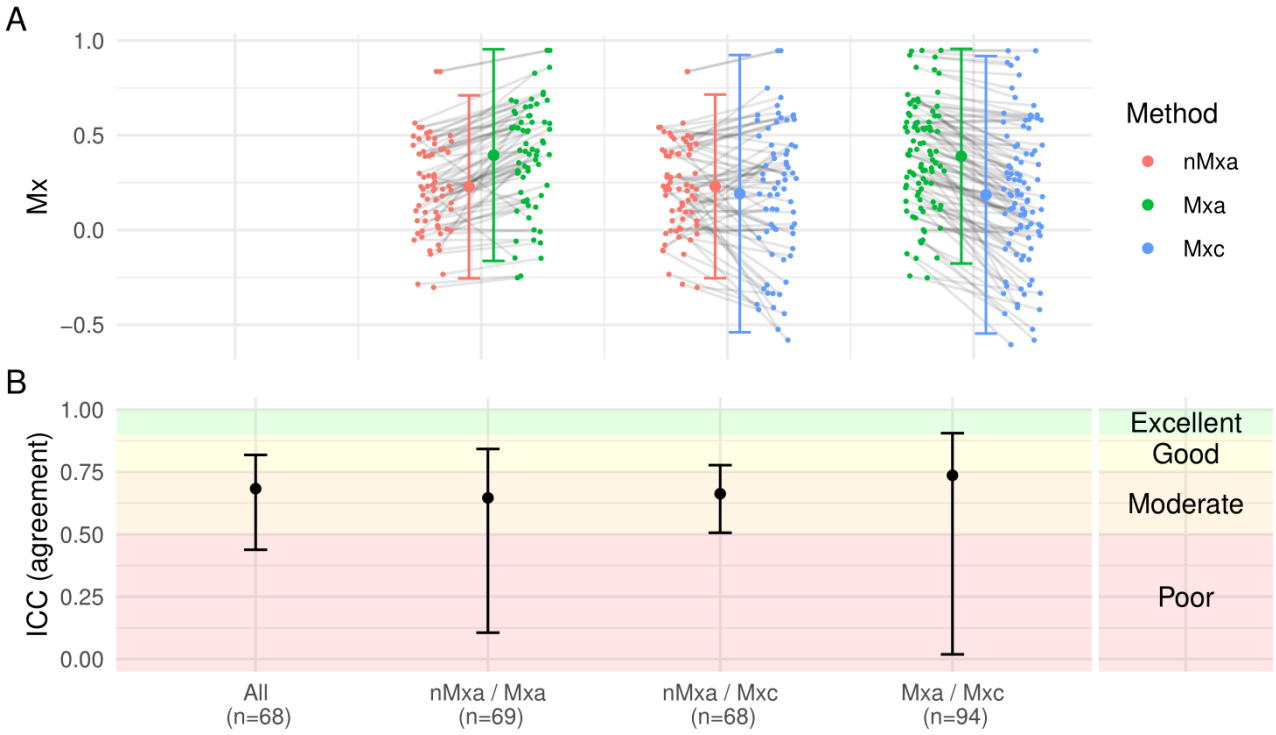

Figure 8 - The reliability of Mx depending on the pressure measurement (**A**) with every pressure measurement, and (**B**) the reliability, i.e. comparability, between the compared pressure measurements. ICC: Intraclass correlation coefficient *(Figure from **Paper III**)*.

10.4 Paper IV

Aim

The aim of this paper, based on data from *Study A to E*, was to assess the diagnostic and prognostic performance of Mx through evaluation of different approaches for calculation Mxa. The diagnostic performance of Mxa compared healthy volunteers to patients with sepsis, with TBI, and who were admitted to a neurorehabilitation unit. The prognostic performance of Mxa was investigated using mortality for patients with sepsis and with TBI, and functional outcome in patients with TBI. Furthermore, we investigated if the approach could result in a difference in interpretation for physiological interventions or comparisons between the group.

Summary of results

Mxa was at best 'no better than chance' to discriminate healthy volunteers from patients with sepsis, patients with TBI, or patients admitted to a neurorehabilitation unit. Healthy volunteers, on average, showed higher Mxa than both patients with TBI and those admitted to neurorehabilitation. This raises doubt to the interpretation that Mxa should be higher during impaired autoregulation (**Figure 9**). Similarly, the prognostic performance of Mxa was 'no better than chance' for mortality in patients with sepsis and TBI and functional outcome in patients with TBI. We noted that statistical significance depends critically on the approach for the comparisons between different groups and before and after physiological interventions (**Figure 10**).

Main findings

- Mxa could not discriminate between healthy volunteers and patients with sepsis, with TBI, and those admitted to a neurorehabilitation unit.
- Mxa could not predict mortality in patients with sepsis and patients with TBI or functional outcome in patients with TBI.
- Statistical significance can be achieved by changing the approach for calculation of Mx.

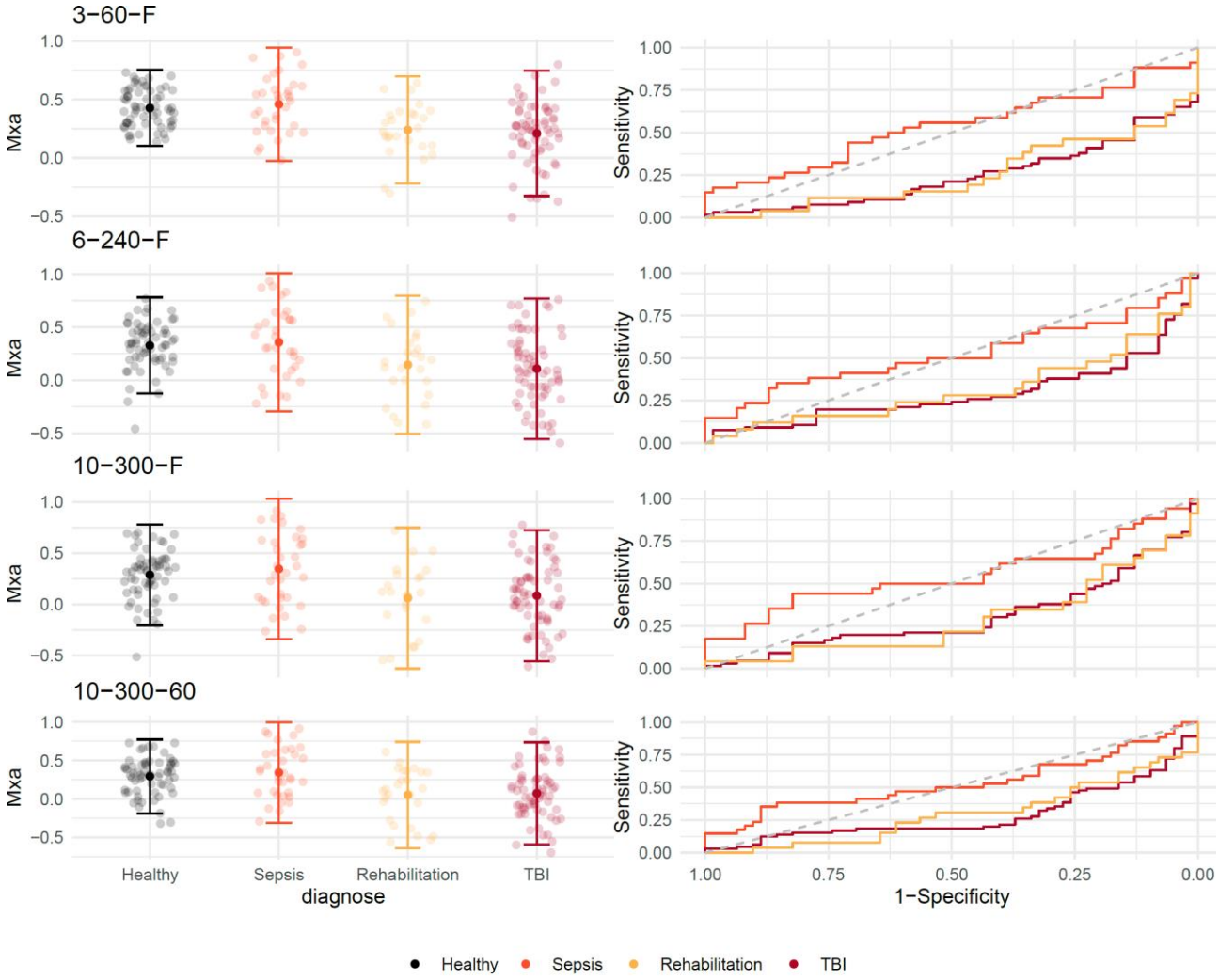

Figure 9 – The average and confidence interval for Mxa for each population (*left column*), and a receiver operating characteristics curve for each of the populations with healthy volunteers as comparators (*right column*). This is investigated for each of the common approach to calculate Mxa (*rows*) *(Figure from **Paper IV**)*.

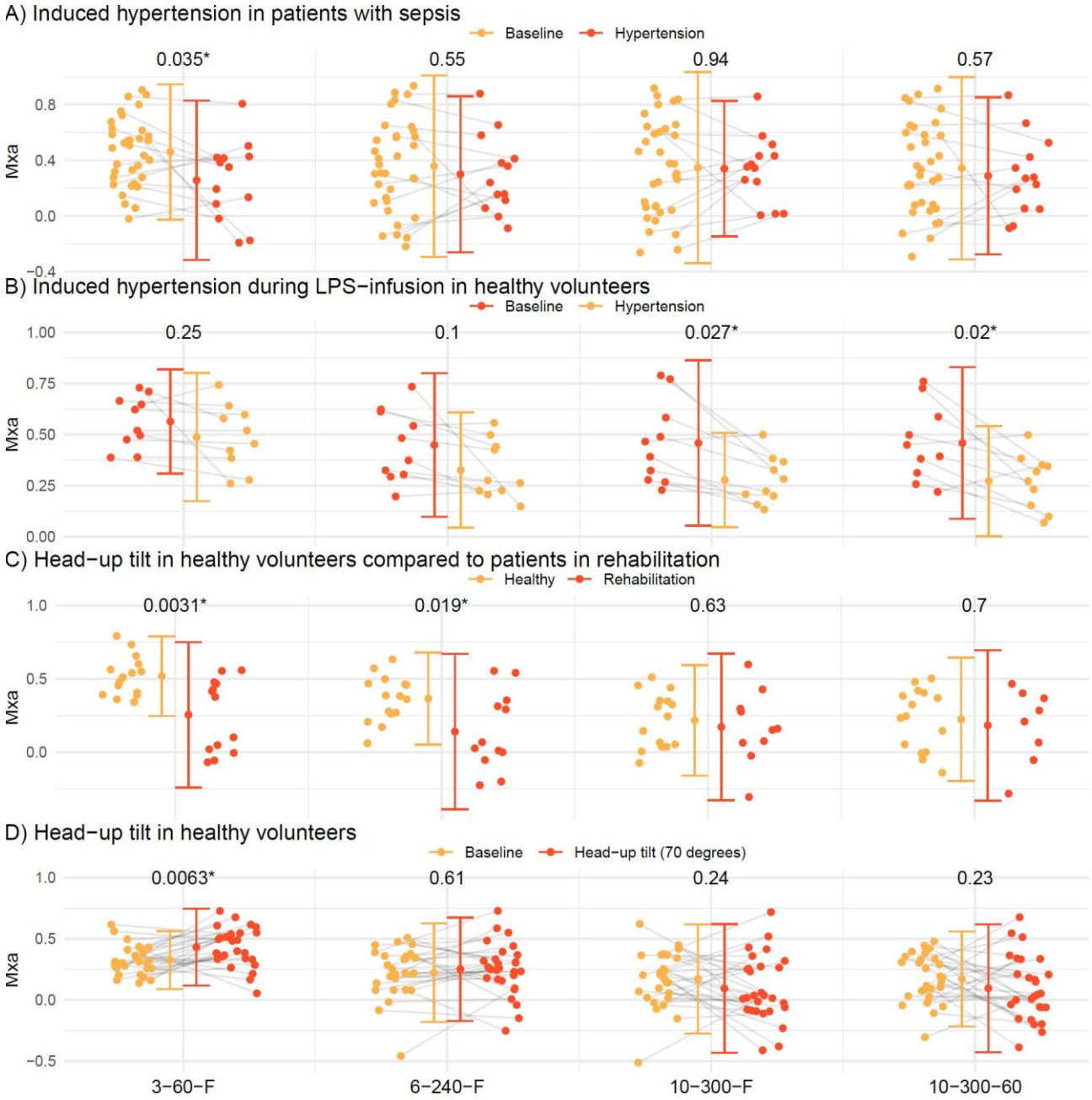

Figure 10 – Investigation of different comparisons (*rows*) and the statistical significance based on each approach (*columns*). (**A**) Induced hypertension in patients with sepsis is only significantly associated with a decrease in Mxa if 3-60-F was chosen. (**B**) Induced hypertension during lipopolysaccharide (LPS)-infusion in healthy volunteers only significantly reduced Mxa if 10-300-F and 10-300-60 were chosen. (**C**) Mxa during head-up tilt is only significantly higher when choosing 3-60-F and 6-240-F. (**D**) Head-up tilt was only associated with a significant increase if 3-60-F was chosen *(Figure from **Paper IV**)*.

11 DISCUSSION

11.1 Principal findings

Mx has been calculated and reported from recordings carried out in both healthy volunteers and in many different patient populations [Paper I]. Even though some approaches for calculating Mx are predominant in the literature, no consensus has been reached [Paper I].

In accordance with previous studies assessing the reliability of non-overlapping recordings [80–82], we found that the stability of Mxa between two consecutive stable periods was poor to moderate [Paper II]. Furthermore, the approach to calculating Mx highly influences the results, where the most comparable approaches were those using comparable lengths of blocks and epochs [Paper II]. Similarly, comparing different measurements of input pressure, i.e. non-invasive ABP, invasive ABP, and CPP, the reliability was moderate at best [Paper III].

In terms of diagnostic performance of Mx, we found an accuracy 'no better than chance' when comparing healthy volunteers with patients with sepsis, TBI, and those admitted to neurorehabilitation [Paper IV]. The prognostic performance of Mx has previously been shown to range from moderate to good accuracy, including the ability to predict both functional outcome and all-cause mortality in patients with TBI [Paper I]. The prognostic performance in our cohort was as for the diagnostic performance 'no better than chance' [Paper IV].

The reliability between different approaches to calculate Mx ranged from poor to excellent [Paper II]. Furthermore, we found that the chosen approach could influence the statistical significance between groups or even when addressing the effect of a physiological intervention [Paper IV].

11.2 Discussion of findings

Mx uses two simultaneously recorded waveform data for the calculation; one is MCAv, and the other is a measurement of input pressure. MCAv is recorded using TCD predominantly with insonation through the transtemporal window [83], using either a handheld probe or one mounted on a headband. TCD has in multiple settings been used as a surrogate of CBF and is interpreted as such for the calculation of Mx. The first measure of Mx, the TCD measurements, has questionable

reliability [84] and reproducibility of the MCAv measurements when measuring with two separate operators or on two separate days is comparable to what we have seen with Mx [85,86].

The second measure used for Mx, perfusion pressure, in itself seems more reliable [87–89]. However, our unpublished findings suggest photoplethysmography in patients with SAH is not a reliable measure of actual invasively measured ABP (see *14.6 Reliability of non-invasive arterial blood pressure measurement*, page 170). Nonetheless, CPP, invasive ABP, and non-invasive ABP have all been used to calculate Mx, but when defining the methodology and interpreting the results, the differences of Mx depending on the pressure measurement are seldom mentioned. In 2003, Czosnyka et al. [90] and Schmidt et al. [91] showed that Mxa was 0.15 higher than Mxc. Schmidt et al. used this information to suggest the dichotomisation between intact and impaired autoregulation was 0.15 higher than the commonly used 0.30 [91,92]. Only a few have since used this proposed threshold [93–95], and two of them even used non-invasive ABP as their pressure measurement (nMxa) [94,95]. Unfortunately, nMxa is generally more comparable with Mxc and not 0.15 higher [Paper III][29,91].

The idea of a threshold between intact and impaired autoregulation depending on the Mx value seems flawed. In healthy volunteers, mean nMxa and Mxa were reportedly higher than both the conventional threshold of 0.3 and the threshold proposed by Schmidt et al. [Paper II][11,96,97]. Furthermore, Mx has in patients with severe TBI and mixed populations of acute brain injury been reported with an average that was lower than both thresholds [69,98,99], even when only including those with an unfavourable outcome [99,100]. Thus, uncritical use of the threshold would lead to the conclusion that cerebral autoregulation of healthy volunteers, as reported in some studies, is more impaired than that of patients with severe acute brain injury as reported in other studies (**Figure 11**).

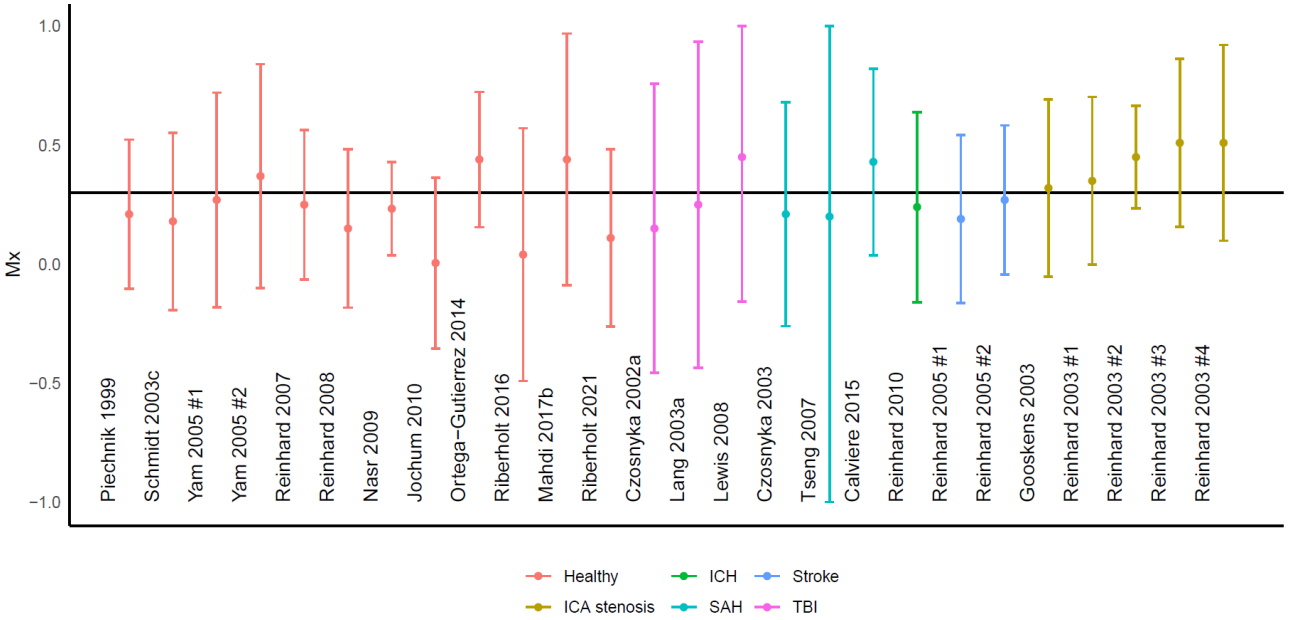

Figure 11 – An overview of some of the results from previous studies stratified by study and diagnosis (colour) [11,14,26,61,69,82,90,92,96,97,101–110]. A black horizontal line depicting the conventional threshold between intact and impaired cerebral autoregulation of 0.3. There is no apparent difference between healthy volunteers and patients with acute brain injury. For the studies with multiple presented values the first, the left, the baseline, or the ipsilateral is chosen. ICH: Intracerebral haemorrhage; ICA: internal carotid artery; SAH: subarachnoid haemorrhage; TBI: traumatic brain injury.

In general, patients with acute brain injury should have a higher risk of impaired cerebral autoregulation than healthy volunteers. One explanation of the apparent paradox could be that Mx depicts the raw relationship between CPP and MCAv and does not include any potential confounders [111]. Especially, $PaCO_2$ influences Mx [110,112,113], and comparison without 'accounting for differences in $PaCO_2$' has been coined pointless [16]. The exact formula for 'accounting for differences' is unknown; however, one study in healthy volunteers suggested that a change of 1 kPa in end-tidal CO_2 causes a 0.2 unit change in Mx [110]. Nonetheless, age [11,96], positive end-expiratory pressure (PEEP) in mechanical ventilation [114], posture [61,69,82,115,116], and side of insonation also influences Mx [11,96,97,103,117,118].

The approach for pre-processing and calculating Mx introduces multiple unnecessary additional confounders [Paper II][61]. Mx is affected by the length of blocks, epochs, and whether overlapping recordings are used [Paper II]. Shorter blocks have been shown to both increase and decrease Mx [Paper II][61]. Furthermore, the reliability between these different approaches is moderate at best [Paper II][61]. Moreover, the optimal duration of a recording has been proposed to be 6 minutes, which led to stabilisation of nMxa [119], and the reliability when comparing short recordings with

longer recordings is also questionable [Paper II]. Multiple studies have used shorter recordings [11,105,120–122], thus rendering their derived Mx values unstable.

Hitherto, the process of validating Mx as a measure of cerebral autoregulation has been uncoordinated. A high Mx was initially reported as a predictor of an unfavourable functional outcome in patients with severe TBI [25]. The literature is jammed with correlations, most predominantly correlation coefficients used to show that Mx is correlated with physiological interventions, other indices, and outcomes [Paper III]. The use of correlation coefficients to validate Mx is at best inaccurate, and probably even outright faulty [Paper III]. For calculation of a correlation coefficient, both sets of data need to be independent, homoscedastic, and continuous [48,123]. Unfortunately, at least one of these assumptions is not fulfilled in the majority of these analyses [25,30,101,120,121,124–140].

It appears that in the past, significantly different values when stratifying for the functional outcome has been enough to incite the introduction of a new measure of cerebral autoregulation [139]. The lack of an actual gold standard has led authors to experiment and use these indices prematurely without thorough systematic evaluation [Paper I]. The tedious methodological evaluation of biomarkers is necessary, and we, as researchers, must ensure that the biomarkers we use are valid and reliable at a minimum [37,42].

The overall confidence in Mx as a measure of cerebral autoregulation seems primarily based on flawed correlation analyses. Even if they were carried out without violating the assumptions, Fleming and DeMets have summarised another potential issue: “A correlate does not a surrogate make” [40]. If Mx is a biomarker of an unalterable independent prognostic marker, such as age [11,96], a higher Mx in patients would indeed correlate with outcome, but would likely underperform as a surrogate marker of interventional effects.

Overall, Mx is not readily measurable nor easily interpretable. Furthermore, Mx shows questionable reliability and validity. Hence, Mx does not fulfil any of the requirements for a valid biomarker of biological processes [37,42]. In summary, I would refrain from using Mx as a measure of cerebral autoregulation in future studies. Furthermore, I would recommend those who are not convinced of

this recommendation to at least follow the guidelines in **Paper I** and use the *'clintools'*-package when calculating Mx [1].

In comparison with Mx, the reliability between TFAc and TFAa is substantially higher [Paper III]. Furthermore, there is a peer-review consensus on how to calculate TFA and how to interpret the findings [32]. However, the above-presented systematic evaluation has not been carried out for TFA. Thus, there are still multiple known and unknown confounders that have not been systematically addressed. The known issues include the reliability, the length of recording, and reference values [32,79,81,96,119,141,142]. Our unpublished results suggest the diagnostic performance of TFAa measures show low to moderate accuracy to distinguish between healthy volunteers and patients with acute brain injury. However, the TFAa measures also presented with equally unsatisfactory prognostic performance as seen with Mxa (see *14.7 Diagnostic and prognostic performance of transfer function analysis (TFA)*, page 172). Thus, the jury is still out to whether TFA is a useful measure of dynamic cerebral autoregulation.

11.3 Strengths and limitations

The strengths of the papers included in this thesis are the systematic evaluation of Mx as a biomarker. This, together with the creation of a publicly available R-package for the calculation of Mx and TFA, increases the reproducibility of the findings. The pitfalls of Mx were identified through a systematic review, with all available peer-reviewed data, and after that investigated by combining data from many previous studies [61,65–69]. However, the use of previously collected data also limits our ability to address issues beyond what the data could provide. Longer recordings from more healthy volunteers and different patient categories would increase the quality. Furthermore, as we have no gold standard measure of dynamic cerebral autoregulation, we are confined to critically evaluate the discrepancy in the literature, being thus unable to provide a final and exact recommendation on how to calculate dynamic cerebral autoregulation in the future. Another limitation is the use of healthy volunteers as comparators for diagnostic performance. The ideal comparators are patients with similar symptomatology but without the investigated diagnosis. The systematic review is limited by only having searched two databases, and did not include grey literature; thus, we cannot be sure that we have included all research. Due to the sample size of the studies the imprecision of the estimates is high. Finally, the conclusions are limited by being based

on the specific patient populations, but before any systematic investigation in other patient populations it would be an illusion to think that it would perform any differently.

11.4 Perspectives

We are currently in a so-called ‘reproducibility crisis’ [143,144]. A thorough investigation of previous findings must be carried out to ensure researchers in the future do not waste their time on these and similar issues. The methodology outlined in this thesis and the related papers can act as a template for investigating biomarkers in the future. Thus, ideally, any research should start by collecting all available evidence through a systematic review. Then, we should critically investigate reliability, including repeatability, reproducibility, susceptibility to confounders, and stability. Finally, we should investigate the diagnostic and prognostic performance. However, such investigations are tedious, time-consuming, and the findings might be unpopular to the researchers submerged into the field.

As for measures of cerebral autoregulation, no single bedside measure of cerebral autoregulation seems to be superior, as they all have some limitations. For instance, the autoregulatory index (ARI) has poor reproducibility [80] and PRx has only moderate accuracy for predicting all-cause mortality in patients with severe TBI [145]. Maybe it is time to go back to the drawing board and imagine find possible techniques to measures cerebral autoregulation.

12 CONCLUSIONS

Mx is a widely used, unreliable, and invalid measure supposed to depict dynamic cerebral autoregulation. The lack of consensus in the literature on how to calculate Mx renders previously collected data incomparable. There is no sound evidence for Mx even being a measure of dynamic cerebral autoregulation, and this interpretation should be avoided going forward. In one study, TFA shows better reliability than Mx but has yet to undergo similar investigation as outlined in this thesis.

Epilogue

In *"The Emperor's New Clothes"* written by Hans Christian Andersen, the first to blurt out the truth about the emperors' gown was a child. This innocent outbreak led everyone to realise they had been fooled. In relation to Mx being a measure of cerebral autoregulation, am I the child or is there something overlooked in passing to suggest I am just a fool?

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14 APPENDICES

14.1 Paper I

Reliability and validity of the mean flow index (Mx) for assessing cerebral autoregulation in humans: A systematic review of the methodology

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Reliability and validity of the mean flow index (Mx) for assessing cerebral autoregulation in humans: A systematic review of the methodology

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Abstract

Cerebral autoregulation is a complex mechanism that serves to keep cerebral blood flow relatively constant within a wide range of cerebral perfusion pressures. The mean flow index (Mx) is one of several methods to assess dynamic cerebral autoregulation, but its reliability and validity have never been assessed systematically. The purpose of the present systematic review was to evaluate the methodology, reliability and validity of Mx.

Based on 128 studies, we found inconsistency in the pre-processing of the recordings and the methods for calculation of Mx. The reliability in terms of repeatability and reproducibility ranged from poor to excellent, with optimal repeatability when comparing overlapping recordings. The discriminatory ability varied depending on the patient populations; in general, those with acute brain injury exhibited a higher Mx than healthy volunteers. The prognostic ability in terms of functional outcome and mortality ranged from chance result to moderate accuracy.

Since the methodology was inconsistent between studies, resulting in varying reliability and validity estimates, the results were difficult to compare. The optimal method for deriving Mx is currently unknown.

Keywords

Mean flow index, systematic review, autoregulation, methodology, reliability, validity, confounders, Mx

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Introduction

Cerebral autoregulation serves to keep cerebral blood flow (CBF) relatively constant within a wide range of cerebral perfusion pressures (CPP) through adaptive changes in cerebrovascular resistance.[1] Conceptually, cerebral autoregulation may be viewed as both a static and dynamic phenomenon, of which the former refers to the cerebrovascular adaptations to a steady-state change in CPP, while the latter refers to the acute cerebrovascular changes during a sudden, either spontaneous or induced, change in CPP.[1,2]

In 1996, Czosnyka and co-workers introduced the mean flow index (Mx) as a measure of dynamic cerebral autoregulation in the time domain. Mx can be measured at the bedside as the correlation between spontaneous fluctuations in CPP and cerebral blood flow velocity in the middle cerebral artery (MCAv)

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measured by transcranial Doppler. Thus, an increase in Mx indicates worsening of cerebral autoregulation, whereas a decrease indicates improvement.[2] In the initial studies, each raw recording of simultaneous values of CPP and MCAv was averaged and then split into *blocks* which were gathered into *epochs*, for which Pearson's correlation coefficient was calculated, ranging from −1 to 1. Mx was subsequently obtained by averaging the correlation coefficients from every epoch throughout the recorded period of interest (Figure 1). CPP was later replaced with arterial blood pressure (ABP), creating an alternative to the original Mx, coined *Mxa*.[3]

Since their inception, both Mx and Mxa have been used to assess dynamic cerebral autoregulation in several studies with a variety of patients categories, and for some of these, a poor outcome has been linked to more profoundly disturbed autoregulation.[4] However, the specific methodology varies between studies, and the reliability and validity of Mx and Mxa have never been assessed systematically. Conceivably, even small changes in the measurement approach and underlying calculations may lead to markedly different results, both for the resulting strength of autoregulation and for its association with clinical outcomes.[5]

In the present study, we provide a systematic review of the existing literature on the assessment of dynamic cerebral autoregulation by Mx and Mxa, focusing on the methodological approach and measurement reliability, as well as their validity for predicting clinical outcomes.

Methods

This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PRISMA checklist available in Supplemental Material),[6] using the methodology outlined in the Cochrane Handbook for Systematic Reviews,[7] and was registered on PROSPERO (protocol id: CRD42020164028, Januray 8, 2020) prior to initiation. The protocol was updated on November 20, 2020 in order to specify how reliability and validity were defined and how these data were extracted. Manuscripts that reported calculations of Mx, Mxa,

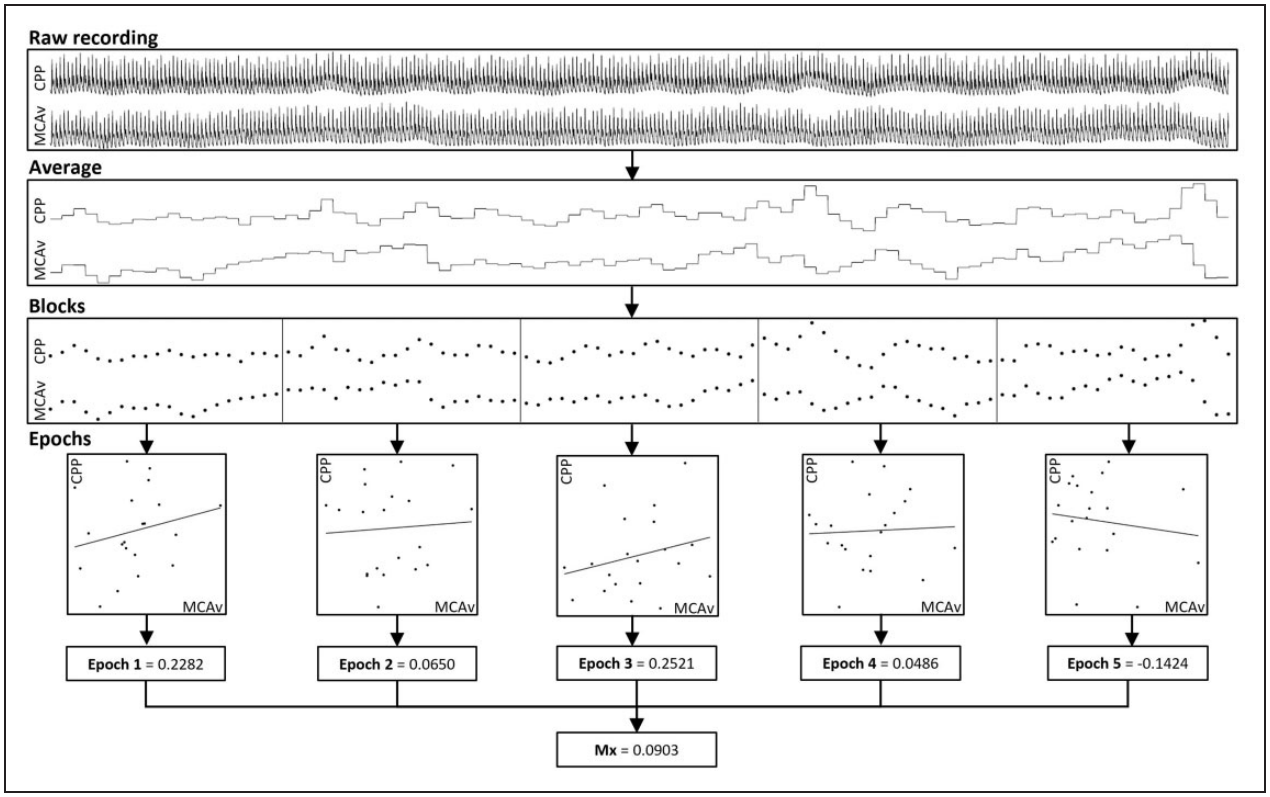

Figure 1. Overview of the general methodology of generating the mean flow index (Mx). The raw recording (1st row) is averaged into blocks (2nd row). The values from the blocks are then split into epochs (3rd row), and a Pearson's correlation coefficient is calculated for every epoch (4th row), and the average of the correlation coefficient from the epochs (5th row) generates one mean flow index (6th row).
CPP: cerebral perfusion pressure; MCAv: middle cerebral artery velocity; Mx: mean flow index.

or both based on original data from human subjects or simulation studies were included (Supplemental Material).

Search strategy

MEDLINE, PUBMED, and EMBASE from January 1, 1996 up until February 14, 2021, were searched using commonly used synonyms of Mx. The EMBASE search string read as follows: "(Mxa OR Mx OR (Flow index)) AND (cerebral OR brain OR MCA OR (Middle cerebral artery)) AND (autoregulation OR (blood flow))". The databases were initially searched January 31, 2020, and with a second search on February 14, 2021 to update the results. Furthermore, the reference lists of included papers and review articles were browsed for additional relevant publications.

Study selection

Two authors (MHO and CGR) screened titles and abstracts retrieved by the search strategy using the web and mobile screening app Rayyan,[8] and reports that were deemed irrelevant were excluded. Subsequently, full-text versions of potentially relevant reports were reviewed and included if they calculated Mx, Mxa, or both from original data from human subjects. At all stages of screening, any disagreement about inclusion was discussed, and if consensus was not reached, a third author (RMGB) decided whether to include the specific report. The abstracts where full-text were not available were only excluded after the primary investigator was contacted three times and did not provide a full-text manuscript published or non-published.

Data extraction

Data on methodology were extracted independently by two authors (MHO and CGR) and included patient or volunteer population, interventions if any, the method for recording arterial blood pressure, level of the transducer, insonation side (right, left or bilateral; or ipsi- or contralateral to the injured hemisphere), method of carbon dioxide measurement, terminology of the index from the article, the time resolution of recordings, recording length, number of recordings, preprocessing, whether calculations were overlapping, and the approach to creating blocks and epochs. Furthermore, measurement results from the manuscript were extracted in studies in relations to reliability, and validity.

Terminology

Mean flow index (Mx). In the following, Mx refers to the mean flow index as a unifying concept, Mxc refers to the index calculated as the correlation between CPP (usually calculated from invasive measurement of both ABP and ICP) and mean flow velocity, Mxa to the correlation between invasively measured ABP and mean flow velocity, and nMxa to the correlation between non-invasively measured ABP and mean flow velocity.

Reliability. Reliability was divided into repeatability (ability to replicate the same results in identical settings) and reproducibility (ability to replicate the same results in the same subject under changing conditions)[9] and reported using the intraclass correlation coefficient (ICC) and a Bland-Altman plot, with limits of agreement (LOA). Repeatability also was assessed by including studies addressing the internal consistency, referring to the stability on a group level, during identical settings.[10] The ICC was interpreted using the 95% confidence interval (CI), if available, and interpreted as defined by Koo et al. to indicate poor (<0.5), moderate (0.5–0.75), good (0.75–0.9), and excellent reliability (>0.9).[11] When possible, we have reported the specific type of ICC since ICC-agreement refers to the agreement between the two 'raters', and ICC-consistency refers to how consistent the difference between 'raters' is.[12] Studies that reported Spearman's or Pearson's correlation coefficient only were not included in the results section, as the assumptions, requirements and pitfalls of these analyses were seldom reported.[13,14]

Validity. The validity of Mx was assessed by the discriminatory and prognostic ability. The discriminatory ability was defined as the ability of Mx to distinguish different patient categories from healthy volunteers, while the prognostic ability was defined as the ability to predict a defined clinical outcome or event. Validity reported using receiver operating characteristics curve with the use of the confidence limits for the area under the curve (AUC) was as toss-up (chance result, ~ 0.5), low accuracy (0.5–0.7), moderate (0.7–0.9), and high accuracy (>0.9).[15] If AUC was not available, the group-specific results were presented.

Statistics

All statistical analyses were carried out using R 4.0.2 (R Core Team (2020), Vienna, Austria). Normally distributed data are presented as mean and standard deviation (SD), while non-normally distributed data are presented with median and interquartile range (IQR). If relevant raw or aggregated data were available, these were used in calculations. P-values <0.05 were considered significant.

Results

The search strategy resulted in identification of 6,580 publications, of which 312 were duplicates. After abstract and full-text screening, 128 studies reporting the Mx in humans were included (Figure 2). The authors of abstract where full-text was not available did not provide any additional published or non-published full-text manuscripts or data; hence only published peer-reviewed articles were included. Of these, 83 (65%) included patients with acute brain injury (including TBI: 45; aneurysmal subarachnoid haemorrhage (aSAH): 5; intracerebral haemorrhage (ICH): 2; ischaemic stroke or stenosis: 18; and mixed populations of acute brain injury: 11), while 32 (32%) included healthy volunteers either alone or as controls. Mxc was reported in 48 studies, Mxa in 46 studies, and nMxa in 41 studies. Forty-seven studies dichotomised Mx, with 0.3 being the predominant threshold between impaired and intact cerebral autoregulation ($n = 23$; Supplemental Material), while the remaining studies included Mx as a continuous measure.

Methodology

Comparisons between different measures of Mx. Five studies provided head-to-head comparisons between different measures of Mx, all in patients with traumatic brain injury (TBI). Four studies compared overall differences, where two studies reported that Mxa was higher than Mxc (mean difference, 0.15 ($n = 145$)[16] and 0.22 ($n = 288$)[17]) one reported that Mxa was higher than nMxa (mean difference 0.08 (95%CI: 0.11–0.04))[18]; and one reported that nMxa was slightly higher than Mxc (mean difference, 0.01, limit of agreement, ± 0.36).[19] Mxc increased significantly during so-called plateau waves of increased ICP in TBI patients, but the increase was not significant for Mxa (Mxc baseline: 0.12 ± 0.40, ICP increase: 0.47 ± 0.47; Mxa baseline: 0.21 ± 0.34, ICP increase: 0.28 ± 0.42).[20]

Pre-processing. 48 of 128 (38%) of the articles described an approach for pre-processing; thus, 11 studies applied low-pass filters, high-pass filters, or both to data, 8 studies used spectral filtering, two studies used a Fourier transform algorithm, and 27 studies used either manual or automatic artefact removal. Several different methods were used to remove artefacts, and none of the studies addressed the influence artefact removal have on data quality. One study, however, showed an increase in nMxa with increasing noise,[21] and one study defined an upper limit of 10% for the numbers of artefacts acceptable before exclusion[22] (Supplemental Material).

Calculation. All studies but two[22,23] created blocks without overlaps. The duration of blocks varied between 3 and 10 seconds, with 10 seconds being the most predominant (Figure 3(a)). Epoch sizes ranged from

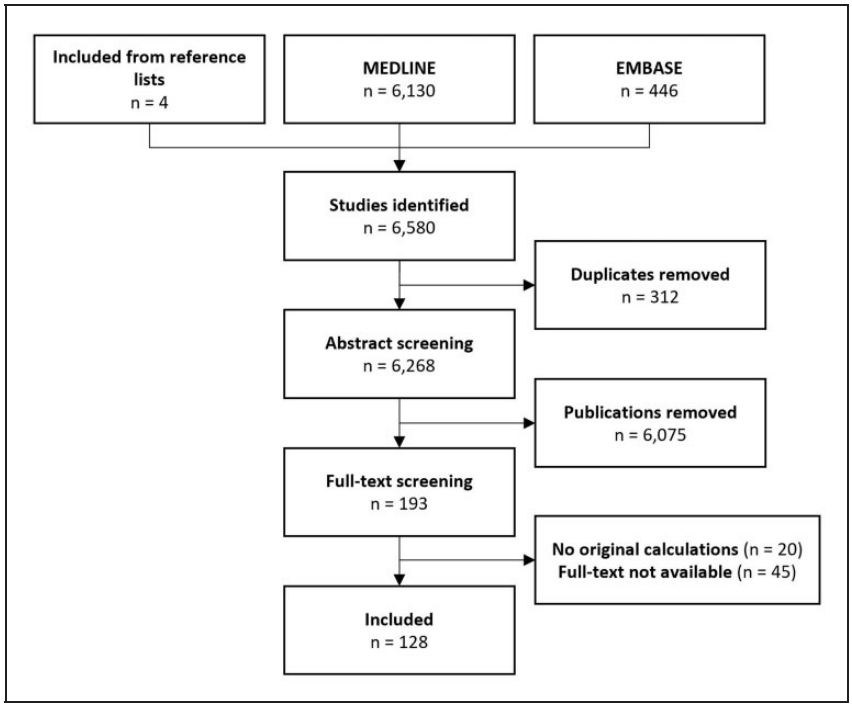

Figure 2. CONSORT Flow diagram. Forty-five abstracts did not have an accompanying full-text manuscript; none of the corresponding authors of these abstracts provided such full-texts after up to three attempts at contact.

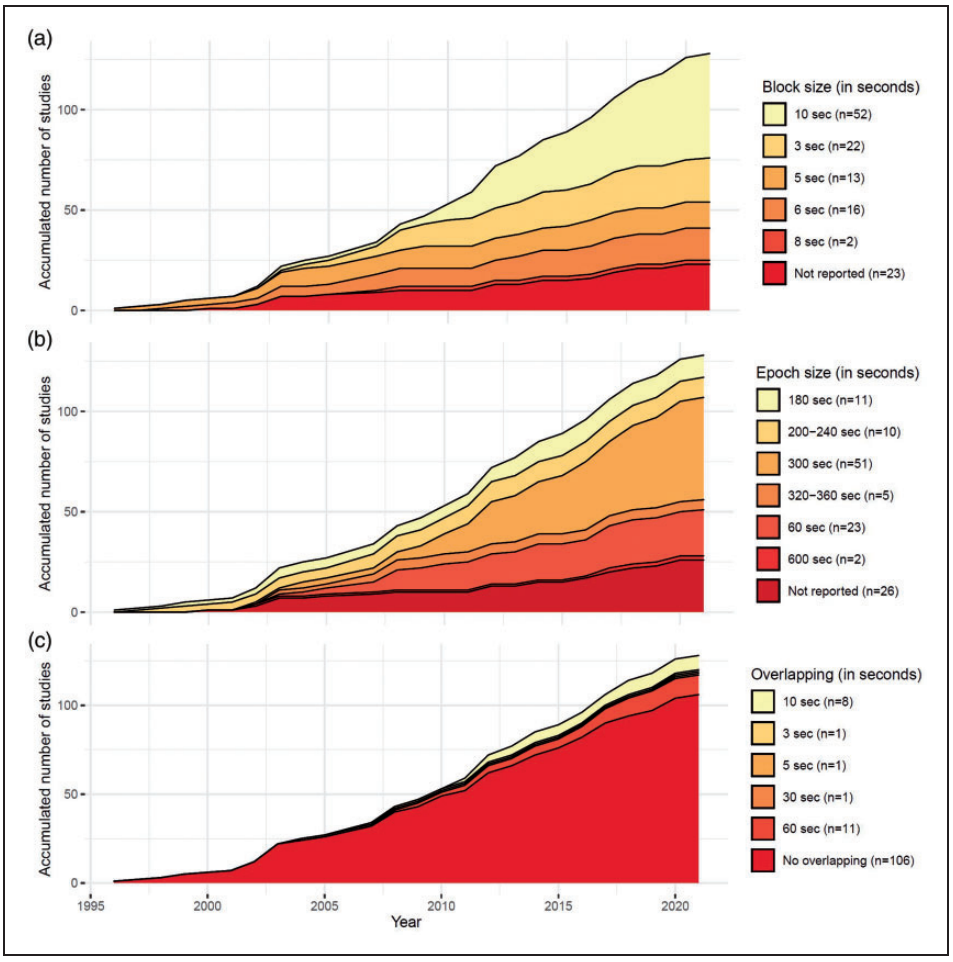

Figure 3. Accumulated methodology from the included studies. (a) Block size; (b) Epoch size; (c) use of overlap and interval between epochs.

10 to 60 blocks, with 30 blocks for a total of 300 seconds being the predominant choice (n = 50) (Figure 3(b)). The epochs overlapped in 21 studies, typically by 1 to 6 blocks (for a total of 3 to 60 seconds) between each new calculation (Figure 3(c)).

Reliability

The reliability of Mx was assessed in eight studies, four of which reported data on repeatability, three on reproducibility, and one on both.

Repeatability. In one study, 10-minute recordings were obtained in 37 patients with ischaemic stroke and 51 healthy volunteers. The aim of this study was to assess the agreement between the first part of a 10-minute recording and the full recording for deriving nMxa; a difference of 0.02 ± 0.19 and an ICC-agreement of 0.93 (95%CI: 0.90–0.96) was found.[24] However, another study including 167 recordings from patients with transient ischaemic attack used a similar methodology with the comparison of the first and last half of a 10-minute recording with the full recording showed a significant difference between the full recording and the last half for both sides.[25] Comparing two consecutive 5-minute recordings, in 46 healthy volunteers, resulted in an ICC of 0.39 (95%CI: 0.08-0.63) for the native recordings.[26] In another study, repeated recordings were obtained in twenty healthy volunteers during 60 s of sitting and 60 s of free-standing. The ICC-agreement between two consecutive sessions where the participants were sitting was reported to be <0, while an ICC-agreement of ~0.75 was reported for the standing position.[27] Recordings were obtained for 16 minutes without any interventions in 10 healthy volunteers through simulations, and nMxa was found to stabilise after 6 minutes when it was calculated by including one more minute for every calculation from 1 to 16 minutes.[28]

Reproducibility. The four studies assessing reproducibility all included healthy volunteers. In a study on 19 participants, Ortega-Gutierrez et al. obtained

recordings 17 (IQR 5–27) days apart and calculated ICC for nMxa based on 10-min recordings. ICC was 0.46 (95%CI: 0.02–0.75) when based on insonation of the left and 0.42 (95%CI: −0.34–0.73) when based on the right MCA.[29] Similarly, Riberholt et al. measured Mx 23 ± 3 days apart in 14 persons, both in supine position and during head-up tilt for 5 minutes each. These authors compared ICC-agreement for different block and epoch sizes and found 3-second blocks, with 20 blocks in an epoch to provide the best reproducibility in the supine position (3-second blocks: 0.55 (95% CI: 0.04–0.82); 5-second blocks: 0.22 (95%CI: −0.32–0.66); 10 second blocks: 0.21 (95%CI: −0.33–0.65)), as well as during head-up tilt (3-second blocks: 0.46 (95% CI: −0.05–0.79); 5-second blocks: 0.57 (95%CI: 0.10–0.84); 10 second blocks: 0.21 (95%CI: −0.38–0.61)).[5]

Finally, Lorenz et al. assessed the reproducibility of nMxa by comparing a model of poor insonation quality, in which aluminium foil was placed between the probe and the skin to reduce the signal power,[26] with the native recording in two studies of healthy volunteers, reporting ICCs of 0.62 (n = 45; 95%CI: 0.39–0.78)[30] and 0.45 (n = 41; 95%CI: 0.16–0.67) respectively.[26]

Validity

Thirty studies evaluated the validity of Mx in terms of discriminatory and/or prognostic ability.

Discriminatory ability. Fifteen studies were identified. In patients with SAH (n = 15), Mxc was higher in patients with vasospasm compared to their baseline measurement (baseline: 0.21 ± 0.24; vasospasm: 0.46 ± 0.32),[31,32] and nMxa was higher than nMxa in healthy controls (patients, n = 30, 0.43 ± 0.2; controls, n = 9, 0.02 ± 0.1).[33] Higher values of Mx in different patient populations compared to healthy control groups were also obtained in patients with alcohol withdrawal syndrome (patients, n = 20, 0.16, SE: 0.05; controls, n = 20, 0.00 SE 0.04),[34] obstructive sleep apnoea (patients, n = 11, 0.41 ± 0.13; controls, n = 9, 0.23 ± 0.10),[35] schizophrenia (patients, n = 21, 0.40; controls, n = 23, 0.26),[36] and intracerebral haemorrhage (patients, n = 12, 0.41 ± 0.27; controls, n = 7, 0.17 ± 0.13),[37] whereas patients admitted to a neurorehabilitation unit showed lower values of nMxa compared to healthy controls (patients, n = 14, 0.04, SE: 0.07; healthy, n = 15, 0.35, SE: 0.07; $p < 0.01$).[38] In contrast, no differences were found in patients with migraine compared with healthy volunteers[39,40] (19 patients vs. 75 healthy volunteers: mean nMxa 0.29 ± 0.17 vs. 0.27 ± 0.17[39]; 22 patients vs. 22 healthy volunteers: mean nMxa 0.24 vs. 0.26)[40]) patients with a brain tumour vs. healthy volunteers (12 patients vs. 12 healthy volunteers: mean nMxa 0.45 ± 0.10 vs. 0.36 ± 0.18[41]) and critically ill patients with compared to without sepsis (52 septic vs. 40 non-septic: Mean nMxa 0.33 (IQR: 0.08–0.58) vs. 0.31 (IQR: 0.04–0.59)[23])

Tang et al. reported a reduction in Mxa after compared with before stenting of the internal carotid artery (25 patients; before stent, 0.42 ± 0.16; after stent, 0.21 ± 0.09),[42] whereas successful recanalization after thrombectomy was not associated with any change (10 patients; successful recanalization: 0.50 ± 0.24; no recanalization: 0.45 ± 0.24).[43] Two studies examined nMxa as a diagnostic marker of stroke, using healthy volunteers as controls (stroke = 32 vs. healthy volunteers = 59[44]; stroke = 37 vs. healthy volunteers = 51[24]) reporting an AUC of 0.709 (0.604–0.799)[44] and 0.719 (0.613–0.810), respectively.[24] However, none of these studies provided further data on the performance of Mx to diagnose stroke, such as cut-off values or predictive values.

Prognostic ability. Fifteen studies were identified. Five studies of patients with severe TBI were conducted by the research group that originally introduced Mx,[2] and potentially with some overlap between patients.[45–49] The authors reported lower values of Mxc in those with a favourable (Glasgow outcome scales (GOS) of 4–5) than in those with a poor outcome (GOS 1-3)[45–49]; in one study (n = 151) Mxa was also measured and did not differ between outcome groups (favourable 0.16 ± 0.24; unfavourable 0.23 ± 0.21; p = 0.08).[48] Four studies also from this research group calculated AUC to assess the prognostic value of Mxc for functional outcome using the same dichotomisation of GOS.[50–53] In these studies an AUC between 0.593 (n = 37; p = NS[52]) and 0.658 (n = 300; 95%CI: 0.595–0.722[50]) was reported for Mxc, while an AUC between 0.620 (n = 300; 95%CI: 0.555-0.685[50]) and 0.704 (n = 37; p = NS[52]) was reported for Mxa. The AUC for the relationship between Mxc and fatal outcome, defined as 6 month all-cause mortality, also varied between 0.608 (n = 37; p = NS[52]) and 0.628 (n = 300; 95%CI: 0.550-0.70[50]) while that of Mxa showed an AUC from 0.565 (n = 300; 95%CI: 0.584-0.714[50]) to 0.616 (n = 37; p = NS[52])

In contrast to TBI, Mxc appeared not to differ between survivors and non-survivors after aSAH (alive: n = 30, 0.04 ± 0.11; dead: n = 7, 0.06 ± 0.10).[54] Two studies of overlapping cohorts with acute brain injury (approximately half with TBI and 15% with aSAH) reported a lower Mxa in those who survived (n = 6; 0.03 ± 0.21) than in those who did not survive until discharge from hospital (n = 0.28 ± 0.40),[55] with an AUC of 0.80 (n = 41).[56] Finally, a higher nMxa increased the odds of postoperative cognitive dysfunction in 82 elderly patients (>65 years of age)

undergoing major non-cardiac surgery (POCD, OR: 1.44, 95%CI: 1.05–1.95),[57] and predicted sepsis-associated encephalopathy in a population of septic patients (n = 100, AUC: 0.65, 95%CI: 0.53–0.76).[22]

Discussion

Based on 128 studies in healthy humans and a large variety of patient populations, the findings of this systematic review indicate that the methodology for assessing cerebral autoregulation by Mx varies markedly regarding signal processing, and the calculation of Mx. Repeatability and reproducibility varied from poor to excellent in the relatively few studies that have addressed this. Indeed, many studies provided insufficient information regarding signal processing, including artefact handling and calculations, and no attempt to generalise reporting of the findings have hitherto been made.

In terms of signal processing, the process of transforming the raw recording into Mx varies greatly in terms of removal of artefacts, pre-processing, block size, epoch size, and epoch overlaps. Only one study mentioned the maximum amount of artefacts which could be accepted,[22] even though both TCD and ABP (invasive and non-invasive) recordings are prone to artefacts. The necessary pre-processing mentioned is either manual or automated, which both could introduce bias if not standardised between studies. The actual effect of including or omitting artefacts was quantified in one study using an artificial source of noise, which showed decrease Mx with increasing amounts of noise.[21] Furthermore, the differences in block and epoch size have not been investigated in full, although one study does show a substantial variation in reproducibility when comparing different methods.[5]

A consensus regarding recording length is clearly required before repeatability and reproducibility of Mx in different patient populations can be formally compared, and before its actual discriminatory and predictive ability in individual patients can be determined. This is further complicated by the lack of consensus for a threshold that identifies impaired dynamic cerebral autoregulation.[58] More than one-third of the studies mention a threshold between intact and impaired cerebral autoregulation, with the primary threshold being 0.30. However, this is primarily based on the Mxc from group-specific observations in patients with TBI. While cerebral autoregulation is widely accepted to be impaired in most of these patients, it should also predominantly be intact in healthy volunteers. One study with 56 healthy volunteers reported an average nMxa of 0.44, and the average nMxa in healthy volunteers has been reported to range from 0.00[34] to 0.44[29] in comparable cohorts.; thus, with a threshold of 0.30, it may be inferred that many healthy volunteers would also be classified as having impaired cerebral autoregulation. However, besides using non-invasive rather than invasive blood pressure recording, signal processing, notably with regard to block and epoch numbers and lengths, as well as the length of recordings, practically renders these findings incomparable. It is still possible that a threshold of impaired cerebral autoregulation can be defined, but the intrapopulation (SD of ~0.2) and interpopulation variation in healthy volunteers is worrisome, not only in terms of reliability and validity but also in the interpretation of Mx as an index of dynamic cerebral autoregulation. The ICC in itself is affected by variation, where the same absolute difference between comparators influences the results differently, depending on the variation in the data. Thus, a difference of 0.1 might result in a 'large' drop in ICC in a population with small variation, while the same difference in a population with large variation might result in a negligible change in ICC. The questionable reliability could primarily be an effect of a smaller variation in the investigated populations of healthy volunteers. The variation limits the usefulness of Mx clinically, or even as an outcome in studies. If the variation of Mx reflects the actual variation of cerebral autoregulation, even standardisation might not increase its usefulness. This variation seen for Mx and other indices of cerebral autoregulation, and the fact that reference values of intact autoregulation for these indices have not yet been identified, might be due to the fact that these are merely simplified quantifications of a complex physiological mechanism.[59]

Despite the inconsistent methodology, Mx was generally reported to be higher in patients than in healthy controls, thus suggesting worse dynamic cerebral autoregulation in the former. The usefulness of Mx, and other indices of autoregulation, is highly dependent on the discriminatory and prognostic ability. Only two studies, however, utilised prediction modelling, where nMxa was found to have a low to moderate accuracy at diagnosing stroke. Since the actual discriminatory accuracy was not assessed, this limits the interpretation and clinical application of Mx even as a group-based index. The interpretation of individual measures of impaired autoregulation in comparison with healthy volunteers has also not been assessed. Furthermore, the utilisation of individual thresholds for identifying impaired cerebral autoregulation requires excellent reliability, since individual variation when assessing repeatability or reproducibility might change the interpretation. The repeatability varied from poor to excellent, with one study reporting excellent[24] and the two other reporting poor to good

Table 1. Recommendations of methodology and reporting.

Design	Recommendation	Explanation/comment
Reporting	Report characteristics of variables measured below	Facilitates transparency and attempts at reproducing observations.
Naming convention	Mxc – CPP/MCAv Mxa – invasive ABP/MCAv nMxa – non-invasive ABP/MCAv	Uniform naming convention depending on the variables recorded to calculate Mx.
Length of recording	>6 minutes	Fluctuations in calculations are minimised with recordings longer than 6 minutes[28]; however, for optimal results, we suggest even longer recordings, optimally at least 30 minutes.
Side of measurement	Bilateral with respect to injured (ipsilateral) or non-injured (contralateral) side	Pathophysiological implications.
CO_2 measurement	$ETCO_2$ or $PaCO_2$	Direct effect on autoregulation and possibly Mx.
Resolution	>100 Hz	Optimised chance of identifying artefacts.
Data handling		
Artefact deletion	Delete from nadir to nadir	When a pulsation is affected by artefacts, targeted deletion of the artefact may affect block variables.
Block size	–	We do not have a final suggestion on block size.
Epoch size	–	We do not have a final suggestion on epoch size.
Overlapping	No overlapping	Used in most studies.
Software for calculation	–	We do not have a final suggestion on software, which should be utilised when calculating the mean flow index, we do however suggest utilization of an R-package (clintools; https://cran.rstudio.com/web/packages/clintools/index.html), which could help uniform the methodology.
Results		
Mean flow index	Average (SD)	The primary methodology for presenting the mean flow index is, and should be, average and standard deviation
Other variables	Number of recordings Recording length Missing data	Multiple studies do not present sufficient information about how the mean flow index was calculated, and it could increase transparency to include a number of recordings, recording length and missing data.
Interpretation	Continuous	We still do not have a clear cut off between intact, affected, and/or impaired autoregulation, why we recommend a continuous interpretation of the results.

repeatability.[26,27] The reproducibility, assessed in healthy volunteers also shows variation with poor to good reliability,[29,30] depending on methodology.[5] The questionable repeatability and reproducibility of Mx, might be explained partly by the length of the recordings, where one study sought to identify the potential cut-off where Mx would stabilize.[28] The actual block and epoch size are not described in the study, but the authors conclude that recordings shorter than six minutes should not be utilized. Nonetheless, all but one[29] of the studies addressing reliability used recordings shorter than these six minutes as at least one of the comparators,[5,24–27,30] and one study even used 60 s recordings.[27] This may have contributed to the poor repeatability.

The above-mentioned inconsistencies and shortcomings of Mx methodology are also likely to explain the differing conclusions of the prognostic ability of both Mxc and Mxa, which has been most extensively investigated in patients with severe TBI.[45–49,60] The accuracy of Mx in these studies ranges from chance-result to moderate in prediction of unfavourable functional outcome or mortality. Similar accuracy is reported in prediction of sepsis-associated encephalopathy (low to

moderate accuracy),[22] and mortality in a mixed population of acute brain injury (moderate accuracy).[56] While this may simply be interpreted to reflect that impaired cerebral autoregulation is a poor prognostic marker, no firm conclusion can currently be drawn in this regard from Mx-based studies.

Apart from the importance of standardising recording length, signal processing, and Mx calculations in future studies, future systematic investigation of potential confounders and covariates is equally important. In our opinion, the most important covariates are the measures used to calculate Mx, i.e. ABP, ICP, and MCAv.[16–20] Other previously highlighted confounders and covariates include age,[29,61] the side of insonation relative to a given intracerebral focus,[29,34,39,61–63] $PaCO_2$,[64–66] use of positive end-expiratory pressure (PEEP) in mechanically ventilated patients,[67] and posture.[5,27,38,68,69] Especially $PaCO_2$ or $ETCO_2$ should be measured as part of a study as it is an important covariate, but their exact influence on Mx is still unclear.[64–66] These should, however, be investigated using standardised methodology before any firm conclusions can be drawn.

The International Cerebral Autoregulation Research Network (CARNet) have previously addressed issues similar to those outlined in the present paper with the assessment of dynamic cerebral autoregulation by transfer function analysis.[70] No gold standard measure of dynamic cerebral autoregulation has been identified as all the hitherto identified measures have their own limitations. Transfer function analysis for instance also present with questionable reliability and no apparent reference values.[24,26,29,70,71] CARNet subsequently published a white paper with the purpose of standardising the assessments in studies that use this method and provided recommendations for design, artefact handling, data reporting, and calculation.[59] We suggest a similar standardisation for future studies that assess dynamic cerebral autoregulation by Mx and related indices in the temporal domain (Table 1).

The majority of the studies investigating Mx and related indices are carried out by one research group or in collaboration with them; we are therefore aware that the current knowledge of Mx, as well as the conclusions drawn in this review, might be subject to bias.

It must, however, be noted that according to our findings, the shortcomings of Mx cannot be resolved by standardisation alone. Because the methodology varied so markedly in previous studies, the actual physiological and clinical relevance of Mx is practically unknown. As described by Colli et al.,[9] *phase 0* in diagnostic research is to address the validity and reliability of the test, and the currently available studies do not fully answer this question. Some knowledge of the range and variation in healthy volunteers, including potential confounders *(Phase I)*, and the ability to distinguish patients with or without disease *(Phase IIa)* has been obtained, but the next feasible step should be to further investigate the reliability and validity of Mx.

Conclusion

According to this systematic review, the methodology and interpretation of Mx and related indices in previous studies is markedly inconsistent and often insufficiently reported, thus leading to highly variable reliability. Consequently, and despite being based on firm physiological principles, the optimal method for deriving Mx is currently unknown. It also remains to be established to which extent it provides meaningful clinical information in various clinical populations and healthy volunteers, both in terms of dynamic cerebral autoregulation, as well as diagnosis and prognostic stratification.

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Authors' contributions

All authors deisgned the study; MHO and CGR carried out the selection and extraction; MHO wrote the first draft; all others revised and accepted the final version.

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Supplemental material

Supplemental material for this article is available online.

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Supplemental Material

NB. The references in this document corresponds to all included papers, but not all of them are cited in the main manuscript, hence, the numbers do not correspond.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	#1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	#2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	#3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	#3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	#4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	#4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	#4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	#4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	#4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	#4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	#4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	#5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	#5

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	#5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	#6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Suppl. Mat
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	#6-9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	#10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	#11-12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	#12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	#1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Supplemental material

Methodology

Variable explanation

Study	The identification name of the study, *e.g. "Czosnyka 1996"*
Pop. (n):	Type of population, and the number of every type included. *e.g. "TBI (20)"*
Type	Studies are defined as either observational (*"Obs"*), physiological (*"Phys"*). Physiological studies require an intervention, while observational have none.
Press.	The pressure variable is correlated with MCAv, *i.e. "CPP" or "ABP".*
ABP	The invasiveness of the measurement of ABP. *i.e. "Inv." is invasive, while "Non" is non-invasive.*
Lvl.	The level of the ABP transducer, *e.g. "heart"*
Side	Side of insonation, *i.e., "bilat" (bilateral), "uni" (unilateral), "ipsi" (ipsilateral) or "contra" (contralateral)*
CO_2	CO_2 measurement and type, *e.g. "$ETCO_2$"*
Name	The name of the index used in the article, *e.g. "Mx"*
Length	The length and frequency of recordings, *e.g. "20-120m / day"*
N / patient	Number of recordings per patient, *e.g. "4"*
Res	Which resolution was the data recorded, *e.g. "20 Hz"*
Pre-proc.	The type of pre-processing, *e.g. "high pass filtered 0.003 Hz"*
B/E	The length of blocks (seconds) and epochs (number of blocks), *e.g. "5/36"*
Overlap	Overlapping calculation of index in seconds, *e.g. "3 sec"*

Table 1 – Methodology

Study	Pop. (n)	Type	Press.	ABP	Lvl.	Side	CO_2	Name	Name	Length	N / patient	Res	Pre-proc.	B/E	Overlap
[1] Czosnyka 1996	TBI (82)	Obs.	CPP	inv.	-	-	-	Mx	Mx	20-120 min / day	-	-	Spectral filtration of MCAv	5/36	-
[2] Czosnyka 1997	TBI (82)	Obs.	CPP	Inv.	-	-	$ETCO_2$ (3)	Mx	Mx	20-120 min / day	4 (range 2-7)	50Hz	-	5/40	-
[3] Czosnyka 1998	TBI (82-107)	Obs.	CPP	Inv	-	-	-	Mx	Mx	20-120 min / day	-	-	-	6/40	-
[4] Czosnyka 1999	TBI (98)	Obs.	CPP	Inv	-	-	-	Mx	Mx	20-240 min / day	-	50Hz	Fourier transform algorithm	6/40	-
[5] Piechnik 1999	Healthy (14)	Obs.	ABP	Non	Heart	bilat	-	Mx	nMxa	-	1	50Hz	Spectral filtration	5/36	-
[6] Czosnyka 2000	TBI (175)	Obs.	CPP	Inv	-	-	-	Mx	Mx	20-240 min / day	-	-	-	-/-	-
[7] Czosnyka 2001	TBI (187)	Obs.	CPP	Inv.	-	ipsi	-	Mx	Mx	20-120 min / day	3.4	-	Spectral filtration	6/40	-
[8] Czosnyka 2002a	TBI (188)	Obs.	CPP	-	-	-	-	Mx	Mx	30-120 min	-	-	-	-/-	-
[9] Czosnyka 2002b	Ventricular dilation (35)	Obs.	CPP (lumbar ICP)	Non	-	-	-	Mx	Mx	> 50 min	-	-	-	5/60	-

Supplemental material

Study	Pop. (n)	Type	Press.	ABP	Lvl.	Side	CO_2	Name	Name	Length	N / patient	Res	Pre-proc.	B/E	Overlap
[10] Lang 2002	TBI (17)	Phys.	CPP	Inv.	-	bilat	$PaCO_2$ 4.7-5.1 kPa.	Mx	Mx	35-50 min	-	-	-	-	-
[11] Schmidt 2002a	TBI (135) Stroke (10)	Phys.	CPP	-	-	-	$PaCO_2$	Mx	Mx	6 min	-	-	-	10/60	-
[12] Schmidt 2002b	TBI (96)	Obs.	CPP	Inv.	-	bilat	$PaCO_2$ 3.5 - 4 kPa	Mx	Mx	20-120 min	Median 3 (range 1-11)	30Hz	-	5/36	-
[13] Czosnyka 2003	TBI (243) SAH (15) Carotid artery stenosis (38) Hydrocephalus (35) Healthy (14)	Obs.	CPP	Inv. Inv. Inv. Non Non	-	Ipsi to ICP bilat	$PaCO_2$	Mx	Mx Mx Mx nMxa nMxa	20-120 min / day	-	-	-	6-10/30-60	-
[14] Gooskens 2003	ICA stenosis (38)	Phys.	ABP	Non	Heart	bilat	$ETCO_2$	Mx	nMxa	20 min	-	50Hz	Low pass filtration (25Hz)	5/36	-
[15] Lang 2003a	TBI (25)	Obs.	ABP	Inv.	-	bilat	CO_2 Constant	Mx	Mxa	18 min	4 per patient	57.4 Hz	-	-	-
[16] Lang 2003b	TBI (40)	Obs.	ABP	Inv.	-	bilat	-	Mx	Mxa	174 sec	-	57.4 Hz	-	-	-
[17] Lang 2003c	TBI (37)	Obs.	ABP CPP	Inv.	-	bilat	CO_2 Constant	Mx-ABP Mx	Mxa Mx	174 sec	-	57.4 Hz	-	-	-
[18] Reinhard 2003	ICA stenosis (150)	Obs.	ABP	Non	Heart	bilat	$ETCO_2$	Mx	nMxa	565±65 sec	1	100 Hz	Spectral filtration (>0.05 Hz or >0.15 Hz) and 5 or 10 sec blocks[1]*	3/20	-
[19] Schmidt 2003a	TBI (135) Haemorrhagic stroke (10)	Obs.	CPP	Inv.	-	Ipsi to ICP	$PaCO_2$	Mx	Mx	20-120 min	-	25-50 Hz	-	10/36	-
[20] Schmidt 2003b	TBI (96)	Obs.	CPP	Inv.	-	bilat	$PaCO_2$ 3.5–4 kPa	Mx	Mx	20-120 min	3 (range 1-11) days	30 Hz	-	5/36	-
[21] Schmidt 2003c	Healthy (44)	Obs.	ABP	Non	Heart	Bilat	-	Mx	nMxa	10 min	1	50 Hz	-	6/40	-
[22] Steiner 2003	TBI (20)	Obs.	CPP	Inv.	-	Bilat	$PaCO_2$	Mx	Mx	-	1	30 Hz	-	6/60	
[23] Minhas 2004	ICA stenosis (40)	Phys.	ABP	Inv.	-	Bilat	$PaCO_2$	Mx	Mxa	45 min	1	-	Average	5/60	-
[24] Reinhard 2004	ICA senosis undergoing CEA (41) or SPAC (17)	Phys.	ABP	Non	Heart.	Bilat	$ETCO_2$	Mx	nMxa	> 20 min	2	100 Hz	-	3/20	-
[25] Soehle 2004	SAH (32)	Obs.	ABP	Inv.	-	Bilat	$PaCO_2$ Stable	Mx	Mxa	20 min	> 1	50 Hz	-	5/60	5 sec
[26] Reinhard 2005	Stroke (62) Healthy (25)	Obs.	ABP	Non	Heart.	Bilat	$ETCO_2$	Mx	nMxa	10 min (587±61 sec)	2	100 Hz	-	3/20	-
[27] Yam 2005	Healthy (32)	Obs.	ABP	Non	-	Bilat	-	Mx	nMxa	174 sec	-	57.4 Hz	-	-	-
[28] Eide 2007	TBI (76)	Obs.	CPP	Inv.	-	-	-	Mx	Mx	5-391 min / day	3,4	-	-	6/40	-
[29] Haubrich 2007	NPH (9) post-traumatic hydrocephalus (6) IIH (5)	Phys.	CPP	Non	Heart	Left MCA and right PCA	-	Mx	nMx	> 10 min	1	50 Hz	-	-	-
[30] Lavinio 2007	TBI (10)	Obs.	CPP	Inv. Non	Heart	Bilat	-	Mx nMxa	Mx nMx	30 min / day	4.8	50 Hz	-	8/40	-
[31] Lewis 2007	TBI (151)	Obs.	CPP ABP	Inv.	-	Ipsi to ICP probe	-	Mx Mxa	Mx Mxa	10-180 min / day	3.3	-	Low-pass filter	6/60	3 sec
[32] Lorenz 2007	Healthy (46)	Obs.	ABP	Non	-	Bilat	-	Mx	nMxa	10 min	1	100 Hz	-	3/20	-
[33] Reinhard 2007	Migraine (19) Healthy (75)	Obs.	ABP	Non	Heart	Bilat	$ETCO_2$	Mx	nMxa	580 ± 67 sec	1	100 Hz	Fourier transform algorithm	3/20	-

[1] Discarded because data did not change

Supplemental material

Study	Pop. (n)	Type	Press.	ABP	Lvl.	Side	CO_2	Name	Name	Length	N / patient	Res	Pre-proc.	B/E	Overlap
[34] Tseng 2007	SAH (35)	Phys.	CPP	-	-	Bilat	-	Mx	Mx	240 min	1	-	-	6/40	-
[35] Czosnyka 2008	TBI (50)	Obs.	CPP	Inv.	-	Ipsi to ICP probe	$PaCO_2$ 28–35 mmHg	Mx	Mx	20-120 min / day	Up to 3		Patients with good quality signals where included	6/40	-
[36] Lewis 2008	TBI (22)	Obs.	ABP	Inv.	-	Bilat	$ETCO_2$	Mx-ABP	Mxa	200 sec	1 or 2 measures	57.4 Hz	-	-	-
[37] Lorenz 2008	Neurologic -good insonation (45) Neurologic -poor insonation (30)	Phys.	ABP	Non	-	Bilat	-	Mx	nMxa	13 min	3 times 4 times	-	-	3/20	
[38] Pfister 2008	Sepsis (16)	Obs.	ABP	Inv.	-	Bilat	$PaCO_2$	Mx	Mxa	60 min	1	-	-	10/30	60 sec
[39] Reinhard 2008a	ICA stenosis (165)	Phys.	ABP	Non	-	Bilat	$ETCO_2$	Mx	nMxa	10 min	1	-	-	3/20	-
[40] Reinhard 2008b	MCA Stroke (18) Healthy (71)	Phys.	ABP	Non	-	Bilat	$ETCO_2$	Mx	nMxa	10 min	3	-	-	3/20	-
[41] Reinhard 2008c	Healthy (60)	Phys	ABP	Non	-	Uni	$ETCO_2$	Mx	nMxa	17 min	1	-	-	3/20	-
[42] Tang 2008	ICA stenosis (21)	Phys	ABP	Inv.	-	-	-	aMx	Mxa	864 ±14.8 sec	1	100 Hz	-	3/20	-
[43] Zweifel 2008	TBI (298)	Obs.	CPP	Inv.	-	-	-	Mx	Mx	300 sec	1	-	-	8/40	-
[44] Altamura 2009	Stroke (6) Healthy (12)	Obs.	ABP	Non	-	Bilat	$ETCO_2$	Mx	nMxa	10 min	1	-	-	3/20	-
[45] Nasr 2009	Obstructive sleep apnea syndrome (11) Healthy (9)	Obs.	ABP	-	-	Uni	$ETCO_2$	Mx	Mx	15 min	1	-	Spectral filtration	5/36	-
[46] Schmidt 2009	TBI (210)	Obs.	CPP	Inv.	-	Ipsi	$PaCO_2$	Mx	Mx	20-120 min	3.5	25–50 Hz	Low-pass filter 0.15 Hz	5/60	-
[47] Steiner 2009	Sepsis (23)	Obs.	ABP	Inv.	-	Bilat	$PaCO_2$	Mx	Mx	60 min	1-4	-	-	10/30	60 sec
[48] Brady 2010	Cardiopulmonary bypass (55)		ABP	Inv.	-	Bilat	PaCO2	Mx	Mx	100.5 ±25.9 min	1	60 Hz	high pass filtered 0.003 Hz	10/30	No
[49] Joshi 2010	Cardiopulmonary bypass (138)	Obs.	ABP	Inv.	-	-	$ETCO_2$	Mx	Mx	74.1 ± 30.6 min	1	60 Hz	high pass filtered 0.003 Hz	10/30	No
[50] Jochum 2010	Alcohol withdrawal syndrome (20) Healthy (20)	Phys.	ABP	Non	-	Bilat	$ETCO_2$	Mx	Mx	20 min	2	-	-	3/20	No
[51] Reinhard 2010	ICH (26)	Obs.	ABP	Non	-	Bilat	$ETCO_2$	Mx	Mx	8-10 min	3	-	-	3/20	-
[52] Zweifel 2010a	Head injured (29)	Obs.	CPP	Inv.	-	Uni	CO_2 3.5–4.5 kPa	Mx	Mx	34 min	2.9	50 Hz	Removed artefacts	10/30	-
[53] Zweifel 2010b	SAH (27)	Obs.	CPP	Inv.	-	-	$PaCO_2$	Mx	Mx	73.5 ±20.5	1	50 Hz	Excluded patients with poor quality. Removed artefacts	10/30	-
[54] Burkhart 2011	Elective major surgery (104)	Obs	ABP	Non	-	Bilat	$ETCO_2$	Mx	Mx	> 25 min	1	30 Hz	Removed artefacts	10/30	60 sec
[55] Haubrich 2011	TBI (30)	Phys.	CPP	Inv.	-	Bilat	$ETCO_2$	Mx	Mx	50 min	1	30 Hz	-	10/24	-
[56] Nasr 2011	IDDM (60) Healthy (9)	Phys	ABP	Non	Heart.	Uni	-	Mx	Mx	10-20 min	1	-	-	10/30	10 sec
[57] Radolovich 2011	Severe TBI (293)	Obs.	CPP	Inv.	-	Uni.	CO_2 3.5–4.5 kPa	Mx	Mx	10-180 min	3 (range 1–13)	30-70 Hz	The artefacts were cleaned manually	10/30	-
[58] Sorrentino 2011	TBI (248)	Obs.	CPP ABP	Inv.	-	-	CO_2 4–5 kPa	Mx Mxa	Mx Mxa	20-120 min	3	30–70 Hz	-	10/30	10 sec
[59] Stüer 2011	AVM (12) Control (15)	Obs.	ABP	Inv.	-	Laser Doppler	$PaCO_2$	Mx	Mx	-	1	1 Hz	-	3/20	-

Supplemental material

Study	Pop. (n)	Type	Press.	ABP	Lvl.	Side	CO_2	Name	Name	Length	N / patient	Res	Pre-proc.	B/E	Overlap
[60] Budohoski 2012a	TBI (300)	Obs.	CPP ABP	Inv.	-	Uni	$PaCO_2$ 4.5-5 kPa	Mx Mxa	Mx Mxa	10-60 min	>1	50 Hz	Removed artefacts	10/30	10 sec
[61] Budohoski 2012b	TBI (201)	Obs.	CPP	Inv.	-	Uni	$PaCO_2$ 4.5-5 kPa	Mx	Mx	10-180 min	2.4 times	-	automated artefact removal process as well as manual correction	10/30	10 sec
[62] Haubrich 2012	TBI (29)	Phys.	CPP	Inv.	-	Bilat.	$ETCO_2$ $PaCO_2$	Mx	Mx	50 min	1	30 Hz	-	10/24	-
[63] Joshi 2012	Cardiopulmonary bypass (232)	Obs.	ABP	Inv.	-	Bilat	$PaCO_2$	mean velocity index	mean velocity index	235 ±114 min	1	-	Low pass and High pass filtering	10/30	-
[64] Lewis 2012a	TBI (187)	Obs.	-	-	-	-	-	Mx	Mx	-	2.2 times	-	-	-	-
[65] Lewis 2012b	TBI (187)	Obs.	CPP	-	-	-	-	Mx	Mx	5 min	2.8 times	-	-	10/30	-
[66] Ono 2012a	LVAD (15) CABG (10)	Obs.	ABP	Inv.	-	Bilat	$PaCO_2$	Mx	Mx	>55 min	1	58 Hz	-	10/30	-
[67] Ono 2012b	Cardiopulmonary bypass (234)	Obs.	ABP	Inv.	-	Bilat	$PaCO_2$ 5.3 ±0.5 kPa	Mx	Mx	110-114 min	1	-	Low pass and High pass filtering	10/30	-
[68] Reinhard 2012a	Ischemic stroke (45)	Obs.	ABP	Non	-	Bilat	-	Mx	Mx	10 min	2	-	-	-	-
[69] Reinhard 2012b	Ischemic stroke (45) Age matched controls (45)	Obs.	ABP	Non	-	Bilat	$ETCO_2$	Mx	Mx	10 min	2	-	-	3/20	-
[70] Schmidt 2012	TBI (210) Stroke (28)	Obs.	CPP	Inv.	-	Ipsi	$PaCO_2$ 30-40 mmHg	Mx	Mx	20-120 min	3.4 times	25-50 Hz	Low-pass filter	-	-
[71] Schramm 2012	Sepsis (30)	Obs.	ABP	Inv.	-	Bilat.	$PaCO_2$ 4.7-6.0 kPa	Mx	Mx	60 min	4	-	-	6/30	-
[72] Zheng 2012	Liver transplant (9)	Phys.	ABP	Inv.	-	-	$ETCO_2$ 35-45 mmHg	Mx	Mx	5 min	1	1-60 Hz	-	10/30	60 sec
[73] Easly 2013	Cardiopulmonary bypass (109)	Obs.	ABP	Inv.	-	Bilat.	$PaCO_2$ 40 ±4 mmHg	Mx	Mx	80±29 min	1	100 Hz	Low pass filter	10/30	10 sec
[74] Mezei 2013	Multiple sclerosis (30) Healthy (10)	Phys.	ABP	Non	-	Bilat	-	Mx	Mx	45 min	2	-	-	3/20	-
[75] Ono 2013	Cardiopulmonary bypass (70)	Obs.	ABP	Inv.	-	Bilat	-	Mx	Mx	107±49 min	1	60 Hz	-	10/30	-
[76] Schramm 2013a	Renal failure (20)	Phys	ABP	Inv.	-	Uni	$PaCO_2$ 35-45 mmHg	Mx	Mx	45 min	2	-	-	6/30	-
[77] Schramm 2013b	ARDS (20)	Obs.	ABP	Inv.	-	Bilat	$PaCO_2$ 5.4-6 kPa	Mx	Mx	-	1	30-70 Hz	-	6/30	-
[78] Angarita-Jaimes 2014	Healthy (13)	Phys.	ABP	Non	-	Uni	$ETCO_2$	Mx	Mx	7 min	1	200 Hz	-	-	-
[79] Lewis 2014	TBI (21)	Obs.	CPP	Inv.	-	Ipsi to ICP probe	-	Mx	Mx	-	1.4	-	Filter 0.05 Hz	10/30	10 sec
[80] Nasr 2014	Carotid stenosis (45) Healthy (10)	Obs.	ABP	Non	-	Uni	No	Mx	Mx	10-20 min	1	-	-	-	-
[81] Ortega-Gutierrez 2014	Healthy (53)	Obs.	ABP	Non	Heart	Bilat	-	Mx	Mx	10 min	1	100 Hz	Visual inspection	3/20	-
[82] Petersen 2014	SAH (7) Ischemic stroke (4) ICH (3)	Obs.	ABP	Inv. Non	-	Uni	-	Mx	Mx	10 min	1	100 Hz	-	3/20	-

Study	Pop. (n)	Type	Press.	ABP	Lvl.	Side	CO_2	Name	Name	Length	N / patient	Res	Pre-proc.	B/E	Overlap
	Cerebral vasoconstriction syndrome (1)														
[83] Rhee 2014	Premature infants (179)	Obs.	ABP	Inv.	Umbilical cord	Uni	$PaCO_2$ Constant	Mx	Mx	60 min	10	200 Hz	Artefact removal	10/30	60 sec
[84] Schramm 2014	Prostatectomy (23)	Obs.	ABP	Inv.	Heart	Uni	$ETCO_2$	Mx	Mx	10 min	1	-	-	6/30	-
[85] Varsos 2014	TBI (280)	Obs.	CPP	Inv.	Heart	Uni	-	Mx	Mx	10-60 min	-	50 Hz	-	10/30	-
[86] Calviere 2015	SAH (30) Healthy (9)	Obs.	ABP	Non	Heart	Uni	-	Mx	Mx	20–30 min	10	-	-	5/36	-
[87] Highton 2015	TBI (11) SAH (6) ICH (10)	Obs.	ABP	Inv.	-	Ipsi to ICP probe	-	Mx	Mx	60 min	1	125 Hz	Cubic spline interpolation. Artefacts removed by interpolation	10/30	-
[88] Hori 2015	Cardiopulmonary bypass (64)	Obs.	ABP	Inv.	-	Bilat.	$PaCO_2$	Mx	Mx	Median: 111 min (IQR: 75-148)	1	60 Hz	-	10/30	-
[89] Liu 2015	TBI (288)	Obs.	CPP ABP	Inv.	-	Bilat	-	Mxc Mxa	Mxc Mxa	20-60 min	2.9	100 Hz	Artefacts were removed	10/30	-
[90] Haubrich 2016	TBI (22)	Obs.	-	Inv.	-	Bilat	PaCO2	Mx	Mx	20 min	4	30Hz	-	-	-
[91] Lewis 2016	TBI (24)	Obs.	CPP	-	-	Uni	-	Mx	Mx	-	-	-	-	10/30	-
[92] Liu 2016	TBI (24)	Obs.	CPP ABP	Inv.	-	Uni	-	Mxc Mxa	Mxc Mxa	-	1.3	-	-	10/30	-
[93] Riberholt 2016	TBI (8) Haemorrhagic stroke (5) Anoxic (1) Healthy (15)	Phys.	ABP Estimated CPP	Non	Heart	Uni	-	Mxa Mxc	Mxa Mxc	30 min	1	1000 Hz	-	10/30	-
[94] Schmidt 2016a	TBI (20) SAH (4) ICH (10) Ischaemic stroke (6) Encephalitis (1)	Obs.	CPP	Inv.	-	Ipsi	$PaCO_2$	Mx	Mx	60 min	3.2	25 Hz	-	10/30	60 sec
[95] Schmidt 2016b	TBI (15) SAH (4) Ischaemic stroke (5) ICH (8)	Obs.	CPP	Inv.	-	Ipsi	$PaCO_2$ Constant	Mx	Mx	60 min	3	25-50 Hz	-	5/60	-
[96] Zhang 2016	TBI (31)	Phys.	CPP	Inv.	-	Bilat.	$ETCO_2$ Constant	Mx	Mx	60 min	1	-	Spectral filtration	6/-	-
[97] Chi 2017	Stroke (32) Healthy (59)	Obs.	ABP	Non	-	Uni.	$ETCO_2$ Stable	Mx	Mx	25 min	1	50 Hz	-	3/20	-
[98] Goettel 2017	Non-cardiac surgery (82)	Obs.	ABP	Non	-	Bilateral.	$ETCO_2$	MxA	MxA	Median 261 min (IQR 205–331)	1	0.1 Hz	-	-	60 sec
[99] Kermorgant 2017	Healthy (12)	Phys.	ABP	Non	-	Uni	-	Mxa	Mxa	-	2	-	Specific signal filtering	10/60	-
[100] Ku 2017	Schizophrenia (21) Healthy (23)	Obs.	ABP	Non	-	Bilat	$ETCO_2$ Stable	Mx	Mx	15 min	1	50 Hz	-	3/20	-
[101] Lee 2017	ICH (12) Healthy (7)	Obs.	ABP	Non	-	Bilat.	-	Mx	Mx	11.5 ±3.9 min	1	512 Hz	-	6/10	-
[102] Mahdi 2017a	Healthy (10)	Obs.	ABP	Non	-	Bilat	$ETCO_2$	Mx	Mx	18 min	5	125 Hz	Median filter and linear interpolation	-	30-150
[103] Mahdi 2017b	Healthy (18)	Obs.	ABP	Non	Heart	Uni	-	Mx	Mx	6 min	1	-	Median filter, 4th-order Butterworth filter	-	-

Study	Pop. (n)	Type	Press.	ABP	Lvl.	Side	CO_2	Name	Name	Length	N / patient	Res	Pre-proc.	B/E	Overlap
[104] Rivera-Lara 2017	Comatose patients (33)	Obs.	ABP (MAP)	Inv.	Heart	Bilat.	-	Mx	Mx	-	1.3 times	-	Excluded CBFV less than 25 cm/s	10/30	-
[105] Uryga 2017	Healthy (39)	Obs.	ABP	Non	Heart	Left	$ETCO_2$	Mx	Mx	31 min	1	200 Hz	Visual inspection	10/30	-
[106] Zeiler 2017	TBI (37)	Obs.	CPP ABP	Inv.	-	Left	-	Mx Mx-a	Mx Mx-a	60-120 min	1	50 Hz	-	10/30	60 sec
[107] Chi 2018	Stroke (37) Non-stroke (51)	Obs.	ABP	Non	-	-	$ETCO_2$	Mx	Mx	10 min	1	50 Hz	Manual inspection and linear interpolation	3/20	-
[108] Crippa 2018	Sepsis (100)	Obs.	ABP	Inv.	-	Left	$PaCO_2$	Mxa	Mxa	13 [10–18] min	1	50 Hz	Automatically (through script) and manually. >10% artefacts were excluded	10[2]/-	-
[109] Ortega-Gutierrez 2018	Cerebral ischemia (1)	Obs.	ABP	-	-	Bilat.	-	Mx	Mx	-	3	-	-	-	-
[110] Riberholt 2018	Acquired brain injury (14)	Phys.	ABP	Non.	-	-	-	Mxa Mxc	Mxa Mxc	5 min	2	1000 Hz	Artefacts were removed	10/30	-
[111] Uryga 2018	SAH (57)	Obs.	ABP	Inv.	-	Uni	-	Mxa	Mxa	30 min	6	200 Hz	Artefacts removed using customised algorithms or manually	10/30	10 sec
[112] Zeiler 2018a	TBI (347)	Obs.	ABP	Inv.	Tragus	Right	-	Mx_a	Mx_a	61 min (range: 30-195)	1.2	50 Hz	Artefacts removed using manual and automatic	10/30	60 sec
[113] Zeiler 2018b	TBI (40)	Obs.	CPP ABP	Inv.	-	Ipsi	-	Mx Mx_a	Mx Mx_a	30-60 min	1.5	50 Hz	Artefacts were removed	10/30	10 sec
[114] Zeiler 2018c	TBI (347)	Obs.	CPP ABP	Inv.	-	-	-	Mx Mx_a	Mx Mx_a	61 min (range: 30-195)	1.2	50 Hz	Artefacts were removed	10/30	60 sec
[115] Cardim 2019	Shoulder surgery (23)	Obs.	ABP	Non	Auditory meatus	Ipsi to surg.	$ETCO_2$	Mxa	Mxa	Phase A: 5.40 ± 1.60 Phase B: 5.30 ± 1.50	1	100 Hz	Manual artefact removal	10/-	-
[116] Gollion 2019	Migraine (22) Healthy (22)	Obs.	ABP	Non	-	Right	$EtCO_2$	Mx	Mx	30 min	1	-	-	10/30	-
[117] Kermorgant 2019	Healthy (12)	Obs.	ABP	Non	-	Right	-	Mxa	Mxa	150 min	3	-	Specific signal filtering	10/30	-
[118] Zeiler 2019	TBI (10)	Obs.	ABP	Inv.	-	Bilat	-	Mx_a	Mx_a	180-240 min	1	100 Hz	Data was artefact cleared	10/30	60 sec
[119] **Cornejo 2020**	Septic (52) Non-septic (40)	Obs.	ABP	Inv.	Heart	Uni	$PaCO_2$	Mxa	Mxa	-	1	50-100 Hz	-	10[2]/-	-
[120] **Heckelmann 2020**	TBI (5) SAH (2) ICH (1)	Obs.	ABP	Inv.	-	Uni	-	Mxa	Mxa	16-84 min	1	200 Hz	-	10/30	30 sec
[121] **Lee 2020**	Transient Ischemic Attack (453)	Obs.	ABP	Non	-	Bilat	-	Mx	Mx	10 min	1	100-200 Hz	-	-	-
[122] **Liu 2020a**	TBI (34)	Obs.	ABP	Inv.	Heart	Bilat	-	Mx	Mx	>30 min	4	50-100 Hz	Manual removal of artefacts	10/30	-
[123] **Liu 2020b**	Cardiopulmonary bypass (226)	Obs.	ABP	Inv.	-	Bilat	$PaCO_2$	Mx	Mx	-	1	128 Hz	Manual removal of artefacts	10/30	-
[124] **Meyer 2020**	Stroke (20)	Obs.	ABP	Inv.	-	Bilat	$PaCO_2$	Mxa	Mxa	45 minutes	Max 4	-	-	6/50	-
[125] **Pochard 2020**	Acute brain injury (15)	Obs.	CPP	Inv.	Heart	Bilat	-	Mx	Mx	-	-	250 Hz	-	10/30	-
[126] **Crippa 2021**	TBI (154)	Obs.	CPP	Inv.	Heart	Uni	-	Mx	Mx	26 [21–37] min	1	50 Hz	Manual removal of artefacts	10/30	-
[127] **Janzarik 2020**	Brain tumor (12) Healthy (12)	Obs	ABP	Non	Heart	Bilat	-	Mx	Mx	10 min	1	100 Hz	-	-	-

[2] Created with 50% overlap

Study	Pop. (n)	Type	Press.	ABP	Lvl.	Side	CO_2	Name	Name	Length	N / patient	Res	Pre-proc.	B/E	Overlap
[128] **Riberholt 2021**	Healthy (14)	Obs.	ABP	Non	Heart	Uni	-	Mxa	Mxa	10 min.	1	1000 Hz	Manual artefact removal	3-10/20-30	-

Supplemental material

Reliability and validity

Variable explanation

Study	The identification name of the study, *e.g. "Czosnyka 1996"*
Pop. (n):	Type of population, and the number of every type included. *e.g. "TBI (20)"*
Reliability	Results from studies which look at the reliability of the mean flow index.
Validity	Results from studies which look at the validity, defined by any discriminatory ability or as an outcome predictor.
Dichotomization	This depicts if differentiation between intact or impaired autoregulation was interpreted as a dichotome value instead of a continuous value. The name used for the 'impairness' and the threshold are depicted.

Table 2 – Reliability and validity

Study	Pop. (n)	Reliability	Validity	Dichotomization
[1] Czosnyka 1996	TBI (82)	-	-	Impaired >0
[2] Czosnyka 1997	TBI (82)	-	-	-
[3] Czosnyka 1998	TBI (82-107)	-	-	-
[4] Czosnyka 1999	TBI (98)	-	-	-
[5] Piechnik 1999	Healthy (14)	-	-	-
[6] Czosnyka 2000	TBI (175)	-	Favourable vs. Unfavourable ($p < 0.001$)	-
[7] Czosnyka 2001	TBI (187)	-	Favourable (-0.06 ±0.26) vs. Unfavourable (0.15 ±0.31; $p < 0.00002$)	-
[8] Czosnyka 2002a	TBI (188)	-	Favourable (-0.06 ±0.26) vs. Unfavourable (0.15 ±0.31; $p < 0.00002$)	Disturbed > 0.23
[9] Czosnyka 2002b	Ventricular dilation (35)	-	-	Disturbed > 0.4
[10] Lang 2002	TBI (17)	-	-	Failure > 0.3
[11] Schmidt 2002a	TBI (135) Stroke (10)	-	-	Disturbed > 0.2
[12] Schmidt 2002b	TBI (96)	-	-	-
[13] Czosnyka 2003	TBI (243) SAH (15) Carotid artery stenosis (38) Hydrocephalus (35) Healthy (14)	-	Vasospasm (0.46 ±0.32) vs. Baseline (0.21 ±0.24; $p = 0.021$)	Disturbed > 0.2
[14] Gooskens 2003	ICA stenosis (38)	-	-	-
[15] Lang 2003a	TBI (25)	-	-	Failure > 0.3
[16] Lang 2003b	TBI (40)	-	-	Impaired > 0.3
[17] Lang 2003c	TBI (37)	-	-	Failure > 0.3
[18] Reinhard 2003	ICA stenosis (150)	-	-	-
[19] Schmidt 2003a	TBI (135) Haemorrhagic stroke (10)	-	-	Passive dependence >0
[20] Schmidt 2003b	TBI (96)	-	-	-
[21] Schmidt 2003c	Healthy (44)	-	-	Abnormal > 0.45
[22] Steiner 2003	TBI (20)	-	-	Impaired >0
[23] Minhas 2004	ICA stenosis (40)	-	-	Impaired > 0.4
[24] Reinhard 2004	ICA senosis undergoing CEA(41) or SPAC (17)	-	-	-

Study	Pop. (n)	Reliability	Validity	Dichotomization
[25] Soehle 2004	SAH (32)	-	Vasospasm (0.46 ±0.32) vs. baseline (0.21 ±0.24; p = 0.021)	-
[26] Reinhard 2005	Stroke (62) Healthy (25)	-	-	-
[27] Yam 2005	Healthy (32)	-	-	-
[28] Eide 2007	TBI (76)	-	Favourable (-0.18 (-0.68-0.25)) vs. Unfavourable (0.06 (-0.67-0.80); p<0.001)	-
[29] Haubrich 2007	NPH (9) post-traumatic hydrocephalus (6) IIH (5)	-	-	Disturbed >0.4
[30] Lavinio 2007	TBI (10)	-	-	-
[31] Lewis 2007	TBI (151)	-	Mx - Favourable (-0.07 ±0.21) vs. Unfavourable (0.12 ±0.24; p = 0.007) Mxa - Favourable (0.16 ±0.24) vs. Unfavourable (0.23 ±0.21; p = 0.08)	-
[32] Lorenz 2007	Healthy (46)	Native recording (ICC 0.39 (0.08-0.63)) Poor insonation (ICC 0.45 (0.16-0.67))	-	-
[33] Reinhard 2007	Healthy (75) Migraine (19)	-	Patient vs. Healthy (p = NS)	-
[34] Tseng 2007	SAH (35)	-	-	Impaired > 0.3
[35] Czosnyka 2008	TBI (50)	-	Favourable (-0.12 ±0.28) vs. Unfavourable (0.21 ±0.35; p = 0.0062)	-
[36] Lewis 2008	TBI (22)	-	-	-
[37] Lorenz 2008	Neurologic -good insonation (45) Neurologic -poor insonation (30)	Native recording (ICC 0.62 (0.39-0.78)) Poor insonation (ICC 0.64 (0.42-0.79))	-	-
[38] Pfister 2008	Sepsis (16)	-	-	Disturbed > 0.3
[39] Reinhard 2008a	ICA stenosis (165)	-	-	Impaired > 0.46
[40] Reinhard 2008b	MCA Stroke (18) Healthy (71)	-	-	-
[41] Reinhard 2008c	Healthy (60)	-	-	-
[42] Tang 2008	ICA stenosis (21)	-	Before stent (0.42 ±0.16) vs. After (0.21 ±0.09)	-
[43] Zweifel 2008	TBI (298)	-	-	-
[44] Altamura 2009	Stroke (6) Healthy (12)	-	-	Exhausted > 0.46
[45] Nasr 2009	Obstructive sleep apnea syndrome (11) Healthy (9)		Patients (0.41 ±0.14) vs. Healthy (0.23 ±0.10; p = 0.009)	Disturbed > 0.3
[46] Schmidt 2009	TBI (210)	-	-	-
[47] Steiner 2009	Sepsis (23)	-	-	-
[48] Brady 2010	Cardiopulmonary bypass (55)	-	-	-
[49] Joshi 2010	Cardiopulmonary bypass (138)	-	-	Impaired > 0.4
[50] Jochum 2010	Alcohol withdrawal syndrome (20) Healthy (20)	-	Patients (0.16 SEM 0.05) vs. Healthy (0.00-0.01 SEM 0.04)	-
[51] Reinhard 2010	ICH (26)	-	-	-
[52] Zweifel 2010a	Head injured (29)	-	-	-
[53] Zweifel 2010b	SAH (27)	-	-	Impaired > 0.15
[54] Burkhart 2011	Elective major surgery (104)	-	-	-
[55] Haubrich 2011	TBI (30)	-	-	Impaired > 0.3
[56] Nasr 2011	IDDM (60) Healthy (9)	-	-	Impaired > 0.3
[57] Radolovich 2011	Severe TBI (293)	-	-	-
[58] Sorrentino 2011	TBI (248)	-	Fatal outcome (>0.3; Sens 36%; Spec 81%) Unfavourable outcome (>0.3; Sens 71%; Spec. 57%)	Impaired > 0.3
[59] Stüer 2011	AVM (12) Control (15)	-	-	-
[60] Budohoski 2012a	TBI (300)	-	Mx - Unfavourable outcome (AUC 0.658 (0.595-0.722))	-

Study	Pop. (n)	Reliability	Validity	Dichotomization
			Mx - Fatal outcome (AUC 0.628 (0.550-0.705)) Mxa - Unfavourable outcome (AUC 0.620 (0.555-0.685)) Mxa - Fatal outcome (AUC 0.565 (0.484-0.645))	
[61] Budohoski 2012b	TBI (201)	-	Unfavourable outcome (AUC 0.649 (0.584-0.714), P < .001) Fatal outcome (AUC 0.606 (0.518-0.695), P = .003)	Impaired > 0.2
[62] Haubrich 2012	TBI (29)	-	-	Distrubed > 0.25
[63] Joshi 2012	Cardiopulmonary bypass (232)	-	-	-
[64] Lewis 2012a	TBI (187)	-	-	-
[65] Lewis 2012b	TBI (187)	-	-	-
[66] Ono 2012a	LVAD (15) CABG (10)	-	-	Impaired > 0.4
[67] Ono 2012b	Cardiopulmonary bypass (234)	-	-	Impaired > 0.4
[68] Reinhard 2012a	Ischemic stroke (45)	-	-	-
[69] Reinhard 2012b	Ischemic stroke (45) Age matched controls (45)	-	-	-
[70] Schmidt 2012	TBI (210) Stroke (28)	-	-	-
[71] Schramm 2012	Sepsis (30)	-	-	Impaired > 0.3
[72] Zheng 2012	Liver transplant (9)	-	-	Impaired > 0.4
[73] Easly 2013	Cardiopulmonary bypass (109)	-	-	Impaired > 0.4
[74] Mezei 2013	Multiple sclerosis (30) Healthy (10)	-	-	-
[75] Ono 2013	Cardiopulmonary bypass (70)	-	-	-
[76] Schramm 2013a	Renal failure (20)	-	-	Impaired > 0.3
[77] Schramm 2013b	ARDS (20)	-	-	Impaired > 0.3
[78] Angarita-Jaimes 2014	Healthy (13)	-	-	-
[79] Lewis 2014	TBI (21)	-	-	-
[80] Nasr 2014	Carotid stenosis (45) Healthy (10)	-	-	Impaired > 0.45
[81] Ortega-Gutierrez 2014	Healthy (53)	Test-retest left-nMxa (ICC: 0.456 (95% CI 0.15 to 0.748)) Test-retest right-nMxa (ICC: 0.416 (95% CI: -0.34 to 0.726))	-	-
[82] Petersen 2014	SAH (7) Ischemic stroke (4) ICH (3) Cerebral vasoconstriction syndrome (1)	-	-	-
[83] Rhee 2014	Premature infants (179)	-	-	-
[84] Schramm 2014	Prostatectomy (23)	-	-	Impaired > 0.3
[85] Varsos 2014	TBI (280)	-	-	-
[86] Calviere 2015	SAH (30) Healthy (9)	-	Patient (0.43 ±0.2) vs. Healthy (0.023 ± 0.1; p = 0.003)	-
[87] Highton 2015	TBI (11) SAH (6) ICH (10)	-	-	Impaired > 0.3
[88] Hori 2015	Cardiopulmonary bypass (64)	-	-	-
[89] Liu 2015	TBI (288)	-	-	-
[90] Haubrich 2016	TBI (22)	-	-	-
[91] Lewis 2016	TBI (24)	-	-	-
[92] Liu 2016	TBI (24)	-	-	-
[93] Riberholt 2016	TBI (8) Haemorrhagic stroke (5)	-	Patient (0.04 ±0.07) vs. Healthy (0.35 ±0.07; p < 0.01)	-

Study	Pop. (n)	Reliability	Validity	Dichotomization
	Anoxic (1) Healthy (15)			
[94] Schmidt 2016a	TBI (20) SAH (4) ICH (10) Ischaemic stroke (6) Encephalitis (1)	-	Unfavourable outcome (AUC 0.80; cut-off 0.2)	-
[95] Schmidt 2016b	TBI (15) SAH (4) Ischaemic stroke (5) ICH (8)	-	Survivors (0.03 ± 0.21) vs. Non-survivors (0.28 ± 0.40; p = 0.04)	-
[96] Zhang 2016	TBI (31)	-	-	-
[97] Chi 2017	Stroke (32) Healthy (59)	-	Stroke (AUC 0.709 (0.604–0.799); p < 0.05)	-
[98] Goettel 2017	Non-cardiac surgery (82)	-	POCD (OR 1.44; 1.06-1.95; p = 0.02) POCD (0.52 (0.41–0.64)) vs. no-POCD (0.43 (0.34–0.55); p = 0.2)	-
[99] Kermorgant 2017	Healthy (12)	-	-	Impairment >0.45
[100] Ku 2017	Schizophrenia (21) Healthy (23)	-	Patients (0.399) vs. Healthy (0.257; p = 0.036)	-
[101] Lee 2017	ICH (12) Healthy (7)	-	Patients (0.41 ±0.27) vs. Healthy (0.17 ±0.13; p = 0.044)	-
[102] Mahdi 2017a	Healthy (10)	Point of stabilisation 6 minutes	-	Failure > 0.3
[103] Mahdi 2017b	Healthy (18)	Sitting – ICC < 0 Standing – ICC ~0.75	-	-
[104] Rivera-Lara 2017	Comatose patients (33)	-	-	-
[105] Uryga 2017	Healthy (39)	-	-	-
[106] Zeiler 2017	TBI (37)	-	Mx - Unfavourable outcome (AUC 0.593 p=0.495) Mx - Fatal outcome (AUC 0.608 p=0.506) Mxa - Unfavourable outcome (AUC 0.704 p=0.213) Mxa - Fatal outcome (AUC 0.616 p=0.403)	-
[107] Chi 2018	Stroke (37) Non-stroke (51)	10 min (first half and full; ICC 0.93 (0.90-0.96)	Stroke (rec. 5 min; AUC 0.714 (0.607–0.805)) Stroke (rec. 10 min; AUC 0.719 (0.613–0.810))	-
[108] Crippa 2018	Sepsis (100)	-	Alive (0.27 (− 0.02–0.62)) vs. Dead (0.43 (0.23–0.63); p = 0.12) SABD (AUC: 0.65 (0.53–0.76); p < 0.01; cut-off 0.18 (Sens 79%, Spec 47%))	Impaired > 0
[109] Ortega-Gutierrez 2018	Cerebral ischemia (1)	-	-	-
[110] Riberholt 2018	Acquired brain injury (14)	-	-	-
[111] Uryga 2018	SAH (57)	-	Alive (n=30; 0.04 ± 0.11) vs. Dead (n=7; 0.06 ± 0.10; p = NS).	Impaired > 0
[112] Zeiler 2018a	TBI (347)	-	-	-
[113] Zeiler 2018b	TBI (40)	-	-	-
[114] Zeiler 2018c	TBI (347)	-	Unfavourable outcome (AUC 0.640 p = 0.001); Fatal outcome (AUC 0.614, p = 0.010)	-
[115] Cardim 2019	Shoulder surgery (23)	-	-	Failure > 0.3
[116] Gollion 2019	Migraine (22) Healthy (22)	-	Patient (0.24 ±0.22) vs. Healthy (0.26 ±0.13; p = 0.58)	Disturbed > 0.3
[117] Kermorgant 2019	Healthy (12)	-	-	Altered > 0.3
[118] Zeiler 2019	TBI (10)	-	-	-
[119] Cornejo 2020	Septic (52) Non-septic (40)	-	Septic Mxa 0.33 (0.08–0.58) vs. non-septic Mxa 0.31 (0.04-0.59)	Impaired > 0.3
[120] Heckelmann 2020	Acquired brain injury (8)	-	-	

Study	Pop. (n)	Reliability	Validity	Dichotomization
[121] Lee 2020	Transient Ischemic Attack (167 optimal quality)	Right 10 min recording 0.27 (0.16–0.44) 1st 5 min recording 0.33 (0.15–0.46) 2nd 5 min recording 0.34 (0.16–0.51) Left 10 min recording 0.32 (0.16–0.49) 1st 5 min recording 0.38 (0.15–0.50) 2nd 5 min recording0.38 (0.20–0.53)	-	
[122] Liu 2020a	TBI (34)	-	-	-
[123] Liu 2020b	Cardiopulmonary bypass (226)	-	-	-
[124] Meyer 2020	Stroke (20)	-	Succesful recanalization (0.50 ±0.20) vs. no recanalization (0.45 ±0.24)	Impaired > 0.3
[125] Pochard 2020	Acute brain injury (15)	-	-	Impaired > 0.3
[126] Crippa 2021	TBI (154)	-	-	Altered > 0.3
[127] Janzarik 2021	Brain tumor (12) Healthy (12)	-	MCA: Patient Mx 0.45 ±0.10 vs healthy Mx 0.36 ±0.18	-
[128] Riberholt 2021	Healthy (14)	Supine Mxa 3s blocks ICC 0.53 (0.04; 0.82) Supine Mxa 5s blocks ICC 0.22 (-0.32; 0.66) Supine Mxa 10s blocks ICC 0.21 (-0.33; 0.65) HUT Mxa 3s blocks ICC 0.46 (-0.05; 0.79) HUT Mxa 5s blocks ICC 0.57 (0.10; 0.84) HUT Mxa 10s blocks ICC 0.15 (-0.38; 0.61)	-	-

Abbreviations

ABP	Arterial blood pressure
ARDS	Acute Respiratory Distress Syndrome
AUC	Area under the curve
AVM	Arteriovenous malformation
CABG	coronary artery bypass grafting
CEA	carotid endarterectomy
CPP	Cerebral perfusion pressure
$ETCO_2$	End-tidal carbon dioxide
HUT	Head-up tilt
ICA	Internal carotid artery
ICC	Intraclass correlation coefficient
ICH	Intracerebral haemorrhage
IDDM	Insulin dependent diabetes mellitus
IIH	Idiopathic intracranial hypertension
LVAD	Left Ventricular Assist Device
MCAv	Middle cerebral artery velocity
NPH	Normal-pressure hydrocephalus
$PaCO_2$	Partial arterial pressure of carbon dioxide
POCD	Postoperative cognitive dysfunction
Pop.	Population
SABD	Sepsis-associated brain dysfunction
SAH	Subarachnoid haemorrhage
SPAC	stent-protected angioplasty of the carotid artery
TBI	Traumatic brain injury

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14.2 Paper II

Reliability of the mean flow index (Mx) for assessing cerebral autoregulation in healthy volunteers

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ORIGINAL ARTICLE

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Reliability of the mean flow index (Mx) for assessing cerebral autoregulation in healthy volunteers

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Abstract

Background: Mean flow index (Mxa) for evaluating dynamic cerebral autoregulation is derived using varying approaches for calculation, which may explain that the reliability ranges from poor to excellent. The comparability, repeatability, stability, and internal consistency of approaches have not previously been assessed.

Methods: We included 60 recordings from resting healthy volunteers and calculated Mxa using four different approaches: three without overlapping calculations, using intervals for averaging wave-form data (blocks) of 3, 6, and 10 s, and correlation periods (epochs) of 60, 240, and 300 s (3–60–F, 6–240–F, and 10–300–F); and one using 10-second blocks, 300 s epochs, and overlaps of 60 s (10–300–60). The comparability between the approaches was assessed using Student's *t* test, intraclass correlation coefficients (ICC), and Bland–Altman plot.

Results: Overall, 3–60–F resulted in a higher Mxa than the other indices ($p < 0.001$, for all). The reliability when comparing all the approaches ranged from moderate to good (ICC: 0.68; 95%CI: 0.59–0.84), which was primarily due to similarities between 10–300–F and 10–300–60 (ICC: 0.94; 95%CI: 0.86–0.98). The reliability when comparing the first and last half was poor for 10–300–F and ranged from poor to moderate for the other approaches. Additional random artifacts resulted in poor reliability for 10–300–F, while the other approaches were more stable.

Conclusions: Mxa in general has a low sensitivity to artifacts, but otherwise seems highly dependent on the approach, with a repeatability that is moderate at best. The varying accuracy and precision renders Mxa unreliable for classifying impaired cerebral autoregulation when using healthy adults for comparison.

KEYWORDS
autoregulation, mean flow index, methodology, Mx, reliability

1 | INTRODUCTION

Dynamic cerebral autoregulation is a physiological mechanism that serves to dampen changes in cerebral blood flow (CBF) secondary to acute fluctuations in cerebral perfusion pressures (CPP) through compensatory adjustments in cerebrovascular resistance (Strandgaard & Paulson, 1984). It may be assessed in humans through a wide array of transcranial Doppler ultrasound (TCD)-based methods, of which the mean flow index (Mx) was introduced by Czosnyka et al., 1996. Mx was initially calculated as a correlation coefficient between CPP and middle cerebral artery velocity (MCAv) (Czosnyka et al., 1996). As an alternative approach, arterial blood pressure (ABP), measured invasively or noninvasively, has replaced ICP in patients and healthy volunteers where the latter is not readily available for the determination of CPP; the resulting measure is then typically coined Mxa (Zeiler et al., 2017). Mx and Mxa range from −1 to 1; high values are interpreted as inefficient dynamic cerebral autoregulation, and vice versa for low values. The most commonly used threshold for preserved versus impaired cerebral autoregulation is 0.3 (Czosnyka et al., 1996).

The reliability of Mxa has previously been assessed in healthy volunteers in several studies, which have reported highly variable repeatability and reproducibility ranging from poor to excellent (Chi et al., 2018; Lee et al., 2020; Lorenz et al., 2007; Mahdi, Nikolic, Birch, Olufsen, et al., 2017), and from poor to good (Lorenz et al., 2008; Ortega-Gutierrez et al., 2014; Riberholt et al., 2021), respectively. As a potential explanation, these studies utilized short recordings, often shorter than 6 min, the minimum duration necessary for Mxa to stabilize according to one study (Mahdi et al., 2017). There are, furthermore, substantial differences in the approaches used to derive Mxa in the different studies, and there is currently no consensus on how to derive the most reliable value.

In the present study, we sought to assess the reliability of Mxa in resting healthy volunteers by measuring repeatability, stability, and internal consistency when exposing the same dataset to four different widely used approaches, with varying length of blocks, epochs, and recording length, and with the introduction of random artifacts.

2 | METHODS

2.1 | Ethical approval

The present work is based on data from four studies, previously published elsewhere (Berg et al., 2012, 2013; Riberholt et al., 2016, 2021), which were all approved by either the Scientific-Ethical Committee of Copenhagen and Frederiksberg Municipalities (file numbers H-A-2009–020 and H-2–2010–04) or the Regional Ethical Committee of the Capital Region of Copenhagen (file numbers H-3–2013–024 and H-16042103), and conformed to the standards set by the Declaration of Helsinki. No new ethical approval was necessary to conduct the present retrospective study. All subjects provided oral and written informed consent prior to inclusion. This study describes novel analyses of selected data from these studies to address an independent working hypothesis. The data and analyses that support the findings of this study can be shared upon reasonable request by contact to the corresponding author of this study and the original studies.

2.2 | Subjects and recordings

This study encompasses recordings from a total of 48 healthy volunteers, with 62 individual baseline periods, which was defined as periods before any interventions were initiated. Subject and recording characteristics are provided in Table 1.

2.3 | Data collection

Studies A and *B* recorded invasive ABP in the left radial artery and MCAv by TCD insonation in healthy volunteers while lying supine with a slight elevation of the head (20°) (Berg et al., 2012, 2013). *Studies C* and *D* recorded ABP noninvasively with photopletysmographic continuous beat-to-beat measurement, and MCAv measured by TCD in the healthy volunteers while lying supine without head elevation (Riberholt et al., 2016). *Study D* recorded the same healthy volunteers twice separated by an interval of 23 ± 3 (mean, SD) days (Riberholt et al., 2021). Further details on data collection are described in full in the original publications.

2.4 | Data processing

The recordings were extracted from LabChart into a tab-delimited file in the original resolution of 1,000 Hz and visually inspected for artifacts. The artifacts were deleted by removing a period that started and ended in a curve nadir. To ensure sufficient quality of the calculations, blocks were omitted from the analysis if 50% of the raw measurements were missing, and similarly epochs were omitted if more than 50% of the blocks were missing. Mxa or nMxa was calculated using the clinmon function from the publicly available R package "clintools" v. 0.8.0 (Olsen & Riberholt, 2021).

2.5 | Assessment of reliability

Reliability of Mxa and nMxa was assessed by comparing four different approaches, which pragmatically were chosen as

TABLE 1 Study characteristics

	Study A ($n = 9$)	Study B ($n = 10$)	Study C ($n = 15$)	Study D ($n = 14$)	All ($n = 48$)
Age – years ±SD	23 ± 2	23 ± 2	31 ± 13	28 ± 9	27 ± 9
Male – n (%)	9 (100%)	10 (100%)	7 (47%)	5 (36%)	31 (65%)
Recordings – n	9	10	15	28	62
Recording length – min ±SD	20.0 ± 1.8	17.9 ± 1.8	4.9 ± 0.4	5.2 ± 0.2	9.3 ± 6.5
Recordings longer than 15 min – n	9	10	0	0	19
Heart rate – min^{-1} ±SD	60 ± 9	58 ± 10	62 ± 8	63 ± 9	61 ± 9
Mean arterial pressure – mmHg ±SD	88 ± 6	84 ± 4	76 ± 13	66 ± 9	75 ± 12
Middle cerebral artery velocity – ^{cm}/s ±SD	68 ± 11	71 ± 12	64 ± 18	75 ± 10	71 ± 13
Artifacts percentage – median (IQR)	0.1 (0–0.4)	0.5 (0.1–2.4)	0.1 (0–2.6)	2.2 (0.1–5.6)	0.45 (0–4.4)
Approach	Mxa	Mxa	nMxa	nMxa	—
3–60–F – mean ±SD	0.44 ± 0.15	0.58 ± 0.11	0.51 ± 0.15	0.32 ± 0.12	0.43 ± 0.16
6–240–F – mean ±SD	0.38 ± 0.15	0.48 ± 0.11	0.39 ± 0.28	0.22 ± 0.20	0.33 ± 0.23
10–300–F – mean ±SD	0.35 ± 0.18	0.45 ± 0.14	0.36 ± 0.29	0.17 ± 0.22	0.29 ± 0.25
10–300–60 – mean ±SD	0.36 ± 0.16	0.44 ± 0.15	0.38 ± 0.30	0.17 ± 0.19	0.29 ± 0.24

Abbreviation: nMxa, ABP is measured noninvasively.

the four most common approaches in the literature (Riberholt et al., 2021), here designated *3–60–F*, *6–240–F*, *10–300–F*, and *10–300–60*. In 3–60–F, 3-second blocks and 60-second epochs, that is, 20 blocks in every epoch, without overlaps were used; while 6-second blocks and 240-second epochs without overlaps were used in 6–240–F, 10-second blocks and 300-second epochs without overlaps were used in 10–300–F, and 10-second blocks and 300-second epochs with 60-second overlaps were used in 10–300–60. Only recordings longer than 15 min were used to compare 10–300–F and 10–300–60, since shorter recordings would not "activate" the overlapping feature in 10–300–60.

For each of these approaches, repeatability was measured by comparing the first with the last half of recordings (Figure 1A), and by comparing recordings longer than 15 min with shorter segments of the same recording (Figure 1B). The latter was simulated by consecutively comparing the result from the full 15-minutes with that of the same recording with a 1-minute shorter duration (always removing the excess recording from the end), which was then repeated until recording length was 5 min.

The stability was assessed by introducing random artifacts of varying length (1–5 s) occupying a varying percentage (5%–50%) of the recording (Figure 1C). During these analyses, the quality restrictions in percentage available data, described above, was ignored. Each recording underwent one hundred imputations with randomly deleted periods for each artifact, length, and percentage of the total recording. Manually identified artifacts were always deleted before analysis, since inclusion of those in the analysis would introduce further bias.

2.6 | Statistical analysis

All statistical analyses were carried out using R 4.0.2 (R Core Team (2020), Vienna, Austria). If not specified, normally distributed data are presented as mean (±SD), while non-normally distributed data are presented as median (IQR). Paired Student's *t* test was applied to compare groups, and p values are presented after Bonferroni correction. Reliability was calculated using the two-way mixed-effects single measurement absolute agreement intraclass correlation coefficient (ICC), and classified as poor (<0.5), moderate (0.5–0.75), good (0.75–0.9), or excellent (>0.9) with reference to both the lower and upper confidence limits (Koo & Li, 2016). Furthermore, Bland–Altman plots with the limits of agreement (LOA) were generated to quantify differences (Bland & Altman, 1986). Error bars in the figures represent the 95% confidence interval (95%CI).

3 | RESULTS

Overall, 3–60–F resulted in a higher Mxa than the other approaches ($p < 0.001$, for all), while 6–240–F yielded a

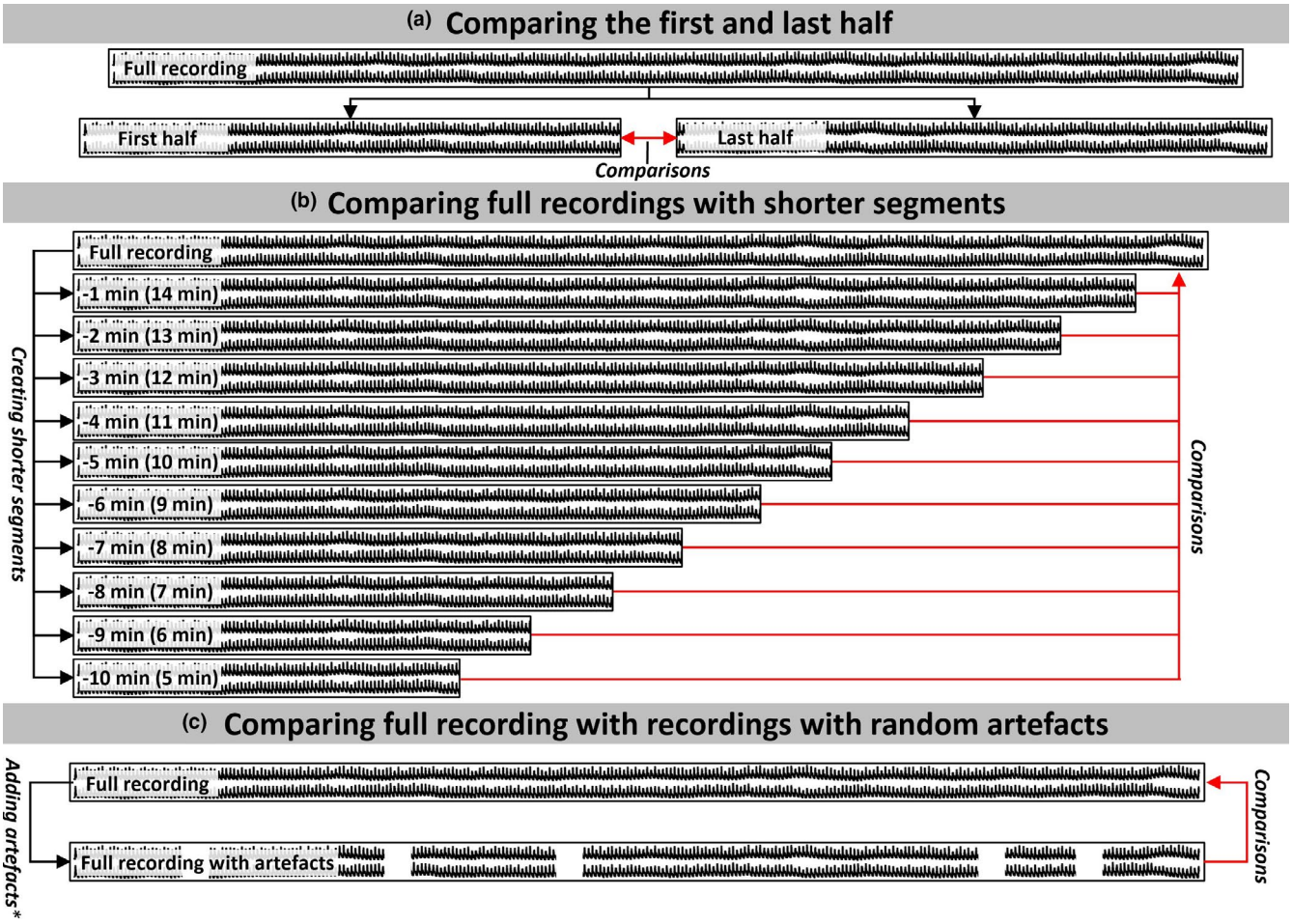

FIGURE 1 The approaches for assessing reliability were a comparison between (a) the first and last half of a recording; (b) comparing the full recordings with shorter segments of the same recording; and (c) the full recording and the same recording with random artifacts. The red arrows depict how the comparisons were carried out. * We calculated the addition of artifacts of varying length and percentage using 100 random artifact-periods for each recording and chose the median Mxa-value generated for comparison

higher Mxa than 10–300–60 ($p = 0.03$), and the Mxa resulting from 10–300–F did not differ significantly from that of 10–300–60 or 6–240–F (Figure 2A). The reliability when comparing all the approaches ranged from moderate to good (ICC: 0.68; 95%CI: 0.59 to 0.84), which could be primarily credited to the similarities between 10–300–F and 10–300–60 (ICC: 0.94; 95%CI: 0.86 to 0.98) (Figure 2B). This similarity was also reflected in the Bland–Altman plot, which showed almost no systematic bias when 10–300–F and 10–300–60 were compared (bias: 0.01; LOA: −0.16 to 0.17). Comparison of 3–60–F with 10–300–F (bias: 0.14; LOA: −0.21 to 0.49) and 3–60–F with 10–300–60 (bias: 0.13; LOA: −0.19 to 0.45) resulted in wider LOA and a systematic bias with 3–60–F being higher in general. Similarly, 6–240–F was higher than 10–300–F (bias: 0.04; LOA: −0.20 to 0.28) and 10–300–60 (bias: 0.03; LOA: −0.15 to 0.22), but lower than 3–60–F (bias: −0.10; LOA: −0.40 to 0.20) (Figure S1).

The four approaches showed similar mean and standard deviation when comparing the first and last half of the recordings (first vs. last; 3–60–F: 0.43 ±0.19 vs. 0.44 ±0.21; 6–240–F: 0.34 ±0.24 vs. 0.34 ±0.22; 10–300–F: 0.30 ±0.24 vs. 0.30 ±0.28; 10–300–60: 0.39 ±0.18; 0.42 ±0.22) (Figure 3A). The reliability ranged from poor to moderate for 3–60–F (ICC: 0.52; 95%CI: 0.31 to 0.68), 6–240–F (ICC: 0.40; 95%CI: 0.16 to 0.59), and 10–300–60 (ICC: 0.14; 95%CI: −0.34 to 0.56), and was poor for 10–300–F (ICC: 0.25; 95%CI: −0.01 to 0.48) (Figure 3B). The narrowest LOA was found with 3–60–F (3–60–F, bias: −0.01; LOA: −0.39 to 0.37; 6–240–F, bias: −0.01; LOA: −0.51 to 0.49; 10–300–F, bias: −0.01; LOA: −0.64 to 0.62; 10–300–60, bias: −0.03; LOA: −0.55 to 0.49) (Figure S2).

Mxa calculated from 15-minute recordings ($n = 18$; 3–60–F: 0.51 ±0.15; 10–300–F: 0.40 ±0.16; 10–300–60: 0.40 ±0.16) did not differ from that of the shorter recordings (Figure 4A). The reliability was good to excellent when comparing the first 13 and 14 min of the recordings with the full 15 min for all three approaches, while 10–300–F and 10–300–60 showed poor to good reliability when including nine minutes or less to compare

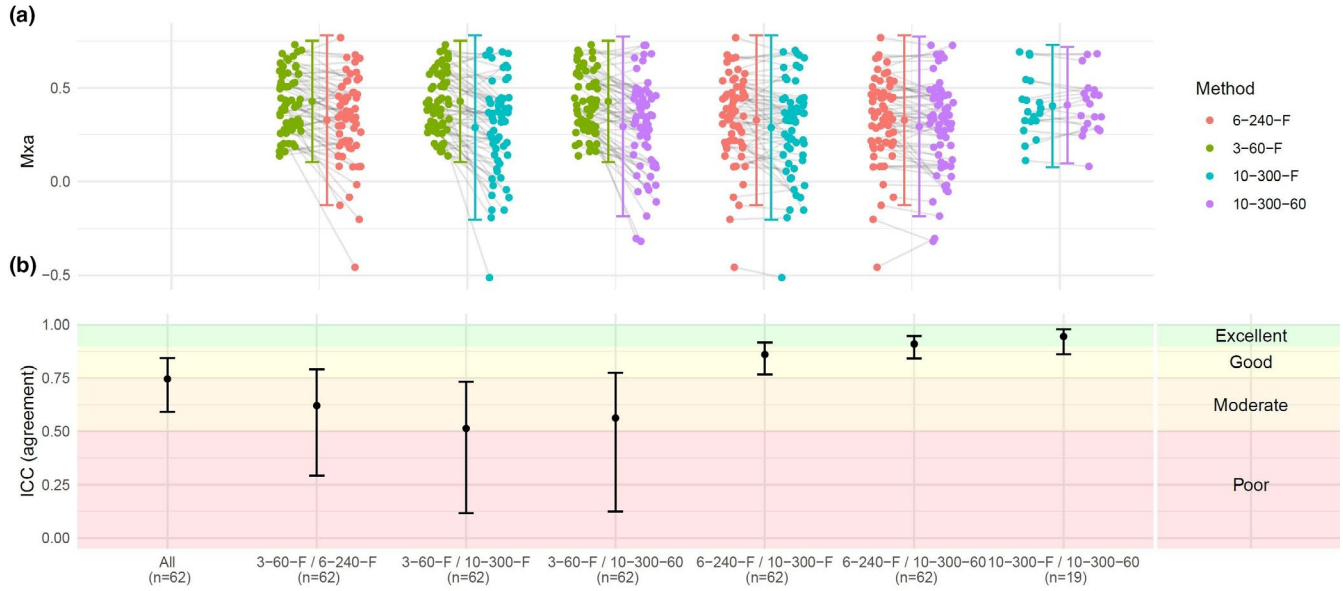

FIGURE 2 Comparison between the same recording using different approaches. (a) The recording assessed with different approaches showing the Mxa for every participant, with gray lines depicting the relationship between the results gained from the left and right approach for each comparison. (b) The ICC when comparison all approaches, and between each. ICC, Intraclass correlation coefficient

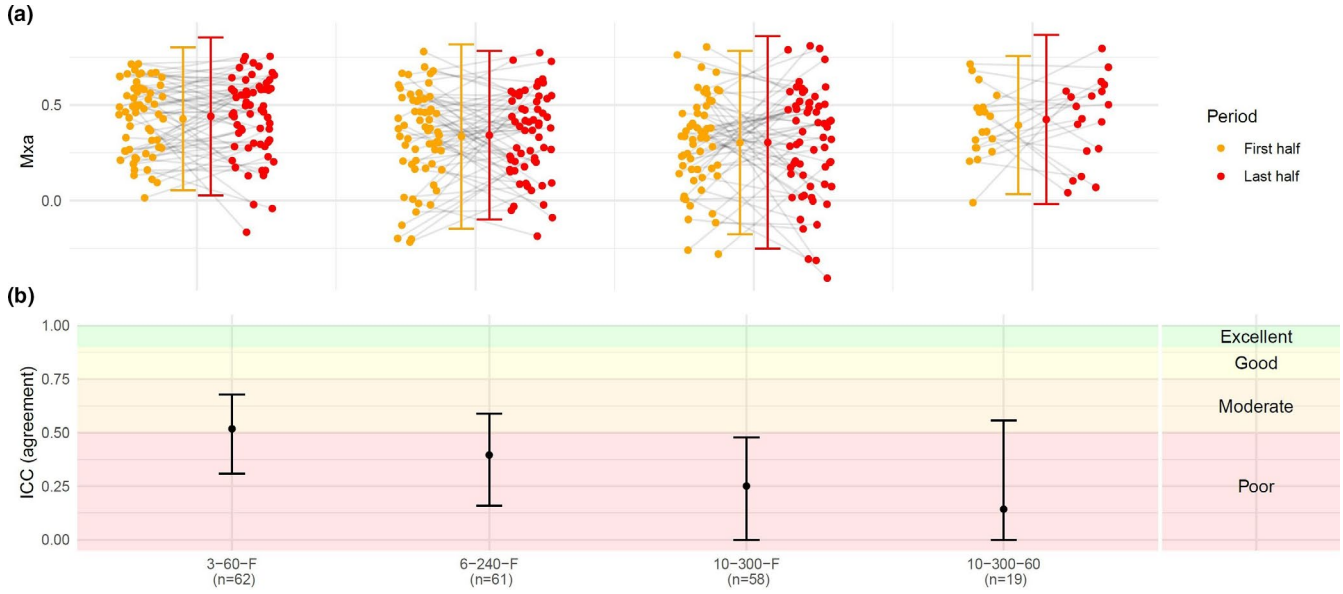

FIGURE 3 Comparison between the first and last half of a recording with different approaches. (a) The Mxa for the first and last half of the recordings, with grey lines depicting the relationship between the results gained from the first and last half. Only recordings with at least two epochs were included in analysis of 10–300–60, that is a duration of more than 6 min (n=19). (b) The ICC for each approach. ICC, Intraclass correlation coefficient

with the full 15 min (Figure 4B). The absolute difference between the full 15 min and the shorter recording decreased when increasing the recording length of the comparator (Figure S3).

The addition of artifacts without quality control showed that increasing percentage and length of artifacts lowered the reliability for all the approaches. Overall, any additional artifacts resulted in poor reliability for 10–300–F; for 6–240–F and 3–60–F, respectively, poor reliability was identified after the addition of 25% and 40% artifacts. 10–300–60 was more robust and together with 3–60–F showed excellent reliability after the addition of 5% artifacts. 6–240–F and 10–300–F showed moderate reliability at best, when only 5% of artifacts were added (Figure 5).

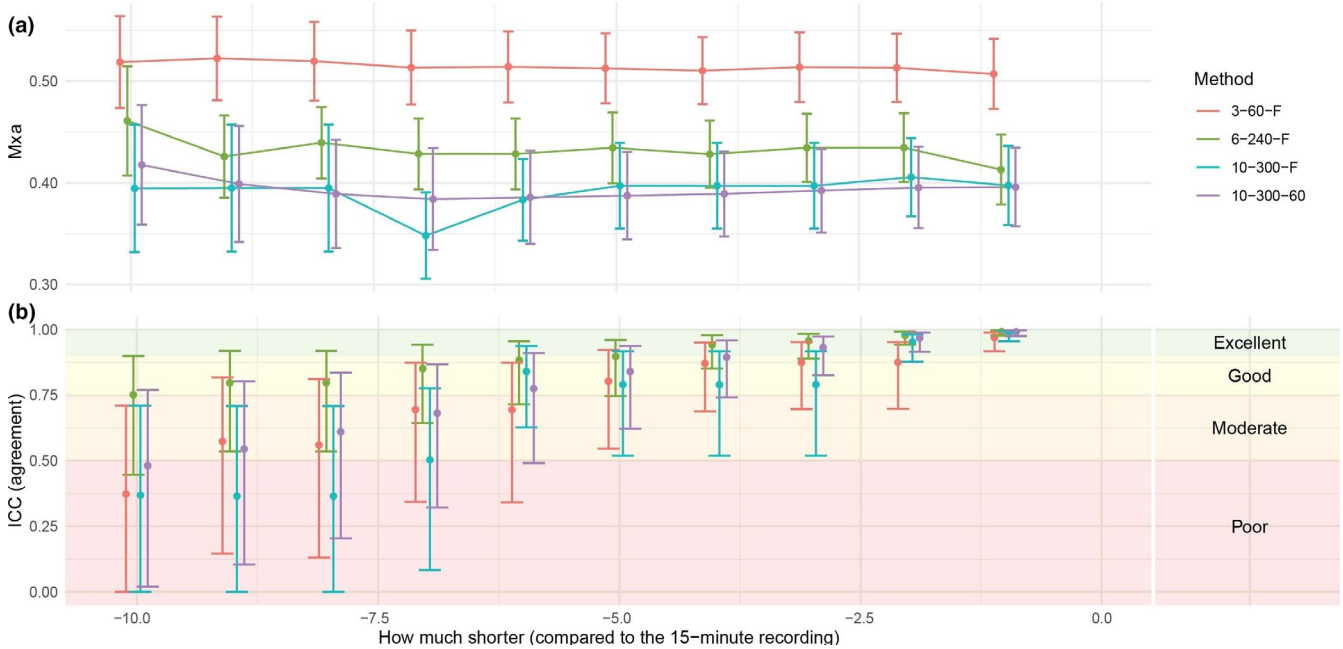

FIGURE 4 Comparison between the full 15-minutes and shorter segments of the same recording for each approach (colors). The figures presents (a) the Mxa for the recordings of different lengths; (b) The ICC for each approach (colors) and for each segment which is compared to the full 15-minutes. ICC, Intraclass correlation coefficient

4 | DISCUSSION

The findings of this study highlight that a given Mxa value depends greatly on the methodological details, including the length of blocks and epochs. This is the first study to compare values of Mxa resulting from different approaches; although this measure appears to be robust towards artifacts, other of our findings question its reliability. The healthy volunteers had an average Mxa close to the usual threshold for impaired cerebral autoregulation of 0.3, which is somewhat high, but comparable to previous reports (Ortega-Gutierrez et al., 2014; Reinhard et al., 2007; Yam et al., 2005).

In this study, we compared four commonly used approaches to data collection and calculation. Although reliability was good to excellent for comparisons between three of the approaches (6–240–F, 10–300–F and 10–300–60), it deteriorated to a result reliability between poor and good for comparison with 3–60–F, which is the second most widely used approach in the literature. The findings indicate that Mxa is strongly influenced by changes in the length of blocks and epochs, and that comparison of Mxa between studies with different methodology is problematic. This issue is also reflected in the substantial bias with wide LOA in Bland–Altman plots. 3–60–F, in general, resulted in higher Mxa values than other approaches; more than 50% of measurements in healthy volunteers (who should exhibit intact autoregulation) were higher than 0.30, a commonly applied threshold for identifying impaired cerebral autoregulation (Altamura et al., 2009; Czosnyka et al., 2003; Kermorgant et al., 2019; Mahdi, Nikolic, Birch, & Payne, 2017; Nasr et al., 2011, 2014; Schmidt et al., 2003). One possible explanation for the higher Mxa in 3–60–F is that each 3-second block is affected by respiratory waves, and that the impact of this is lessened when longer block sizes are used (Czosnyka et al., 2003). Even though 3–60–F resulted in the highest Mxa, dichotomization between intact and impaired cerebral autoregulation in the other approaches still seem inappropriate. This difference between 3–60–F and the other approaches questions both if the estimate of cerebral autoregulation is comparable, and maybe more important if studies which utilize different approaches are comparable.

Previous studies have assessed the repeatability by comparing the first and last half of recordings, reporting poor to moderate repeatability (Lorenz et al., 2007, 2008). This pattern applies to all approaches in the present study. As an exception from the rule, one previous study showed excellent repeatability of Mxa when the first or last half of a recording was compared with the full recording of 10 min (Chi et al., 2018). This excellent reliability when comparing overlapping segments, is only reproduced in our data when comparing 14- with the full 15-minute recording. Across approaches, a marked reduction in reliability is observed at 9 min, and at 5 min the reliability of all approaches is poor. 3–60–F presents the best overall reliability for all recording lengths, which corresponds to simply removing one epoch for every minute the recording is shortened. This stresses that a higher number of epochs for the same recording increases the stability of Mxa. 3–60–F seems the least susceptible to variations

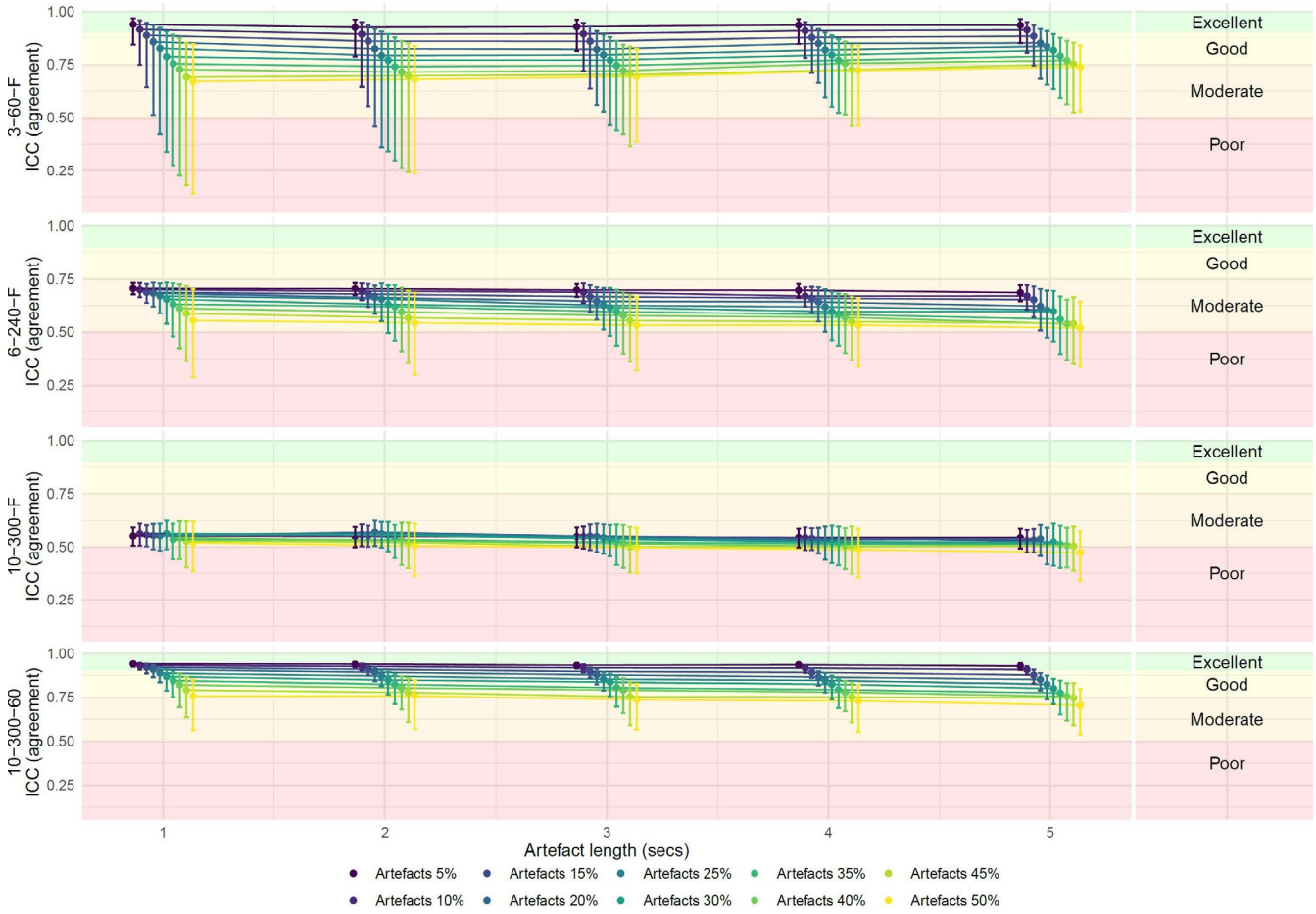

FIGURE 5 The ICC for each approach when comparing artifacts with a length between 1 and 5 s (x-axis), and between 5% and 50% of the recording (colors). ICC, Intraclass correlation coefficient

in shorter recordings, which primarily is due to the shorter epochs, why utilization of 6–240–F, 10–300–F, 10–300–60 is only recommended when using substantially longer recordings. Our findings of poor to moderate repeatability is comparable to previous reports of other indices for dynamic cerebral autoregulation, including index of autoregulation and transfer functions analysis (Brodie et al., 2009; Gommer et al., 2010).

The stability of Mxa assessed when adding random artifacts shows decreasing reliability with the best reliability for 3–60–F and 10–300–60. The length and number of artifacts did not seem to affect 10–300–F as much as the three other approaches, which exhibited poor reliability even after adding only 5% artifacts. The number of blocks and epochs seems to be an important factor for reliability for Mxa.

The internal consistency refers to the stability of Mxa on a group level and ignores the individual variations (Bannigan & Watson, 2009). The internal consistency of Mxa is primarily related to the length of blocks and epochs. In contrast, the recording duration and amount of artifacts appear to be less critical.

4.1 | Strength and limitations

The main strength of this study is the use of clinically relevant data and strict criteria for assessing reliability defined as repeatability, stability, and internal consistency. Since the data were collected for another purpose unintentional confounder might be present. We did not include all the approaches described in the literature for this analysis, but nonetheless believe that the chosen examples underline the influence of details in the approach used to generate Mxa. As another limitation, the variation in recording length between the studies pooled in this study may have affected some of the reliability measures. Finally, this study was designed neither to interpret the clinical relevance nor the difference between groups of Mxa in clinical studies.

5 | CONCLUSION

According to the present findings, the reliability of Mx, in our example Mxa, as a generic index is questionable. While

being relatively insensitive to artifacts, the calculation of Mxa is highly dependent on the underlying approach, notably recording length, and the length and number of blocks and epochs. We suggest that caution is warranted for the comparison of Mxa reported by different studies. The varying accuracy and precision, furthermore, renders Mxa unreliable for classifying impaired cerebral autoregulation using healthy adults for comparison.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

AUTHOR CONTRIBUTIONS

MHO, CR, KM, and RMGB designed the study; CR, RRP, and RMGB collected the data; MHO did the analyses and wrote first draft; all authors revised and approved final version.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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14.3 Paper III

Reliability of cerebral autoregulation using different measures of pressure in patients with subarachnoid haemorrhage

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Manuscript submitted for publication

Reliability of cerebral autoregulation using different measures of perfusion pressure in patients with subarachnoid haemorrhage

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Short title: Reliability of dynamic cerebral autoregulation

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Keywords: autoregulation, mean flow index, Mx, reliability, transfer function analysis

Word Count: 2,599**. Number of Figures:** 3; **Number of Tables:** 1; **Number of References:** 47

Abstract (200 words)

Background

Dynamic cerebral autoregulation to spontaneous fluctuations in cerebral perfusion pressure (CPP) is often assessed by transcranial Doppler (TCD) in the time domain, yielding primarily the mean flow index (Mx), or in the frequency domain using transfer function analysis (TFA), yielding gain and phase. For both domains, the measurement of blood pressure is critical. This study assessed the inter-method reliability of dynamic cerebral autoregulation using three different methods of pressure measurement.

Methods

In 39 patients with aneurysmal subarachnoid haemorrhage, non-invasive arterial blood pressure (ABP), invasive ABP (measured in the radial artery) and CPP were recorded simultaneously with TCD. Intraclass correlation coefficient (ICC) was used to quantify reliability.

Results

Mx was higher when calculated using invasive ABP (0.39; 95% confidence interval (95%CI): 0.33;0.44) compared to non-invasive ABP and CPP. The overall ICC showed poor to good reliability (0.65; 95%CI: 0.11;0.84; n=69). In the low frequency domain, the comparison between invasively measured ABP and CPP showed good to excellent (normalised gain, ICC: 0.87, 95CI: 0.81;0.91; n=96; non-normalised gain: 0.89, 95%CI: 0.84;0.92; n=96) and moderate to good reliability (phase, ICC: 0.69, 95%CI: 0.55;0.79; n=96), respectively.

Conclusions

Different methods for pressure measurement in the assessment of dynamic cerebral autoregulation yield different results and cannot be used interchangeably.

Trial registration: clinicaltrials.gov (NCT03987139; 14 June 2019)

Introduction

Acute fluctuations in cerebral perfusion pressure (CPP) challenge the requirement for a constant cerebral blood flow (CBF). Dynamic cerebral autoregulation dampens these changes by adjusting the cerebrovascular resistance and can be assessed in humans through several (most commonly) transcranial Doppler ultrasound (TCD)-based methods (Claassen *et al.*, 2021). Many of these involve CPP measurements, which necessitates the measurement of intracranial pressure (ICP) and arterial blood pressure (ABP). The latter has often been measured either invasively or non-invasively as a surrogate of CPP (Petersen *et al.*, 2014; Claassen *et al.*, 2015; Olsen *et al.*, 2022).

Results from studies using different pressure measurements are readily compared in the literature, even though the influence of the chosen method for measurement of perfusion pressure is not fully understood (Olsen *et al.*, 2022). Dynamic cerebral autoregulation to spontaneous CPP fluctuations may be assessed in either the time domain investigating changes in signal over time, yielding measures such as the mean flow index (Mx) (Czosnyka *et al.*, 1996), or in the frequency domain investigating the distribution of the signal within different frequency bands, often by transfer function analysis (TFA), which yields the metrics gain, phase, and coherence (Claassen *et al.*, 2015).

In the present study, we sought to assess the reliability of Mx and TFA when using non-invasive ABP, invasive ABP, and CPP (calculated by subtracting ICP from invasive ABP) in patients with aneurysmal subarachnoid haemorrhage (SAH).

Methods

The present work was a prospective controlled intervention study designed to evaluate the effects of noradrenaline-induced hypertension in patients admitted to the neurointensive care unit (neuro-ICU) with SAH. This work comprised exploratory analyses of selected data and addressed an independent working hypothesis. The study was registered at clinicaltrials.gov (NCT03987139, 14 June 2019) and approved by the Regional Ethical Committee of the Capital Region of Denmark (H-19017185, 28 May 2019), and by The Danish Data Protection Agency (P-2019-87, 14 May 2019). Oral and written informed consent was obtained from next-of-kin. The data underlying the findings of this study can be shared upon reasonable request and only after approval from corresponding author and relevant regulatory authorities.

Subjects and recordings

Adults (≥ 18 years old) admitted to the neuro-ICU with SAH and treated with an external ventricular drain were eligible for inclusion. The exclusion criteria were conservative treatment of the aneurysm, expected death within 48 hours from admission, and acute or chronic diseases associated with impaired cerebral autoregulation (e.g. previous ischaemic stroke, sepsis within a year before admission, diabetes mellitus with organ manifestation, or traumatic brain injury). For inclusion in the present study, at least one autoregulation measurement, either baseline or induced hypertension, with simultaneous recording for more than five minutes of at least two of the three pressure measurements (i.e. non-invasive ABP, invasive ABP or CPP (calculated by subtracting ICP from invasive ABP)) was required. This study included recordings from 40 participants. Subject and recording characteristics are provided in **Table 1**. The study was performed as a before-and-after study with two repeated autoregulation assessments, and both recordings were included for this study if they met the above-mentioned requirements.

Transcranial doppler

For each TCD session, an insonation probe (DWL, Atlanta, Georgia, USA) was kept stable by a LAM rack (DWL, Atlanta, Georgia, USA)**.** There were no changes to the transcranial Doppler settings, and the patients did not change position during recordings. Middle cerebral artery flow velocity (MCAv) was measured through the ipsilateral transtemporal window using MultiDop T digital (DWL, Atlanta, Georgia, USA) (Newell & Aaslid, 1992). ICP was measured using either a Codman Microsensor ICP Transducer (Integra LifeSciences, Princeton, New Jersey, USA) or a Spiegelberg external ventricular drain combined with an ICP sensor (Spiegelberg, Hamburg, Germany). Arterial blood pressure was measured invasively through a radial artery catheter and/or non-invasively by photoplethysmography (Nano System, ADInstruments Inc., Oxford, UK). The recordings were synchronised using an analogue-to-digital converter from AD Instruments and synchronised in LabChart (LabChart ver. 8.10.05, ADInstruments Inc., Oxford, UK).

Data processing

Calculation of Mx. Raw waveform data of TCD, ICP, and ABP were extracted from LabChart into a tab-delimited file in the original resolution of 1,000 Hz. The recordings were visually inspected for artefacts. Artefacts in any recording modalities resulted in the removal of a period surrounding that artefact, always starting and ending with a curve nadir for the specific recording modality. Mx was calculated by averaging waveform data into blocks, which were then grouped into epochs, where a correlation coefficient was calculated. All the correlation coefficients were then averaged into one Mx-value for the full recording period. To ensure sufficient quality of the calculations, blocks were omitted from the analysis if more than 50% of the raw measurements were missing, and epochs were omitted if more than 50% of the blocks were missing. Mx was calculated using the '*clinmon*'-function from the publicly available R package 'clintools' v. 0.8.2 (Olsen *et al.*, 2021). We have validated the

'*clinmon*'-function by comparing the results when calculating Mx using the ICM+ software which was used to develop Mx. This validation shown nearly perfect reliability (Intraclass correlation coefficient (ICC)-agreement: 1.00 (95%CI: 0.98;1.00); Recordings compared = 76; data not shown).

Calculation of TFA metrics. Raw waveform data were averaged using the 'cyclic measurement'-function in Labchart and extracted in the original resolution of 1,000 Hz. The recordings were visually inspected for artefacts; only continuous periods without any artefacts were extracted in order to avoid interpolation as a potential confounder (Claassen *et al.*, 2015), resulting in shorter recording periods. The TFA metrics were calculated using the '*TFA*'-function from the publicly available R package '*clintools*' v. 0.8.2 (Olsen *et al.*, 2021).

We have validated the '*TFA*'-function by comparing the results when calculating TFA using the publicly available MatLab-code from David Simpson (Claassen *et al.*, 2015). This validation showed perfect reliability (ICC-agreement; Normalised gain, non-normalised gain and phase in the low-frequency domain: 1.00 (95%CI: 1.00;1.00); Recordings compared = 53; data not shown). This script follows the recommendations including application of a coherence threshold identified using 95% confidence limits based on degrees of freedom. The package follows the recommendation where all frequencies with low magnitude-squared coherence are excluded from averaging when calculating the mean values of gain and phase across the bands below this threshold (Claassen *et al.*, 2015).

Terminology and interpretation

Mx: nMxa is used when ABP was measured non-invasively, whereas Mxa is used for the invasively measured ABP and Mxc for the index calculated using CPP. Mx was interpreted as a continuous measure ranging from -1 to 1, with higher values indicating less effective cerebral autoregulation and vice versa (Czosnyka *et al.*, 1996; Olsen *et al.*, 2022).

TFA: nTFA is used for non-invasively measured ABP, TFAa for invasively measured ABP, and TFAc for CPP. Specifically, gain and phase in the low frequency (LF) range from 0.07-0.20 Hz

(Claassen *et al.*, 2015) were interpreted to reflect dynamic cerebral autoregulation, with higher gain and/or lower phase indicating less efficacious autoregulation and *vice versa* (Zhang *et al.*, 1998; Claassen *et al.*, 2015). Gain wil be presented as both normalised gain and non-normalised gain.

Assessment of reliability

The reliability of Mx and TFA was assessed by comparing the different values based on CPP, MAP, and nMAP. For Mx, the analyses were carried out for four different approaches, which were pragmatically chosen because they were the most common approaches in the literature (Olsen *et al.*, 2022). The primary assessment was pragmatically chosen as Mx calculated using 3-second blocks and 60-second epochs (3-60-F). Exploratory assessments of Mx was 6-second blocks and 240-second epochs (6-240-F), 10-second blocks and 300-second epochs (10-300-F), and 10-second blocks and 300-second epochs with 60-second overlaps (10-300-60). The primary assessment for the TFA metrics was normalised gain, non-normalised gain and phase for the low frequency domain.

Statistical analysis

All statistical analyses were carried out using R 4.1.0 (R Core Team (2021), Vienna, Austria). Normally distributed data are presented as mean (±SD), while non-normally distributed data are presented as median (IQR). Reliability was calculated using the two-way mixed-effects, single measurement, absolute agreement intraclass correlation coefficient (ICC), and classified as poor (<0.5), moderate (0.5-0.75), good (0.75-0.9), or excellent (>0.9) with reference to both the lower and upper confidence limits (Koo & Li, 2016). Bland-Altman plots were used to quantify the difference (bias) and presented with limits of agreement (LOA) (Bland & Altman, 1986). Error bars in the figures represent the 95% confidence interval (95%CI).

Results

This study included 40 participants with SAH. We were able to calculate Mx for 95 periods from 39 participants (baseline: n=62; induced hypertension: n=33), and TFA for 99 periods from 39 participants (baseline: n=64; induced hypertension: n=35) (**Table 1**). The participants had higher invasive (mean: 88.9, 95%CI: 84.4;93.4) than non-invasive ABP (mean: 81.5, 95%CI: 75.7;87.4; *P*-value: 0.047) during baseline and comparable pressures during periods of induced hypertension (invasive ABP, mean: 93.1, 95%CI: 89.6; 96.5; non-invasive ABP: 95.1, 95%CI: 85.2;105.0; *P*-value: 0.70). The ICP was 8.6 (mean; 95%CI: 7.1;11.2) during baseline and 9.1 (95%CI: 6.7;11.5) during periods of induced hypertension.

Time domain measures

Mxc was 0.19 (mean; 95%CI: 0.11;0.26), Mxa was 0.39 (95%CI: 0.33;0.44), and nMxa was 0.23 (95%CI: 0.18;0.28). In the Bland-Altman plots, the smallest bias was observed between Mxc and nMxa (bias: -0.04; LOA: -0.54;0.46), while the bias was higher for comparison between Mxc and Mxa (bias: -0.20; LOA: -0.52;0.11) and between Mxa and nMxa (bias: 0.17; LOA: -0.17;0.51) (**Supplemental Material**). The overall ICC was 0.68 (95%CI: 0.44;0.82; n=68), with similar results when comparing nMxa with Mxa (ICC: 0.65; 95%CI: 0.11;0.84; n=69), nMxa with Mxc (ICC: 0.66; 95%CI: 0.51;0.78; n=68), and Mxa with Mxc (ICC: 0.74; 95%CI: 0.02;0.91; n=94) (**Figure 1**). The reliability of Mx was similar irrespective of block and epoch sizes, and regardless of measurement during baseline and induced hypertension (**Supplemental Material**).

Frequency domain measures (TFA)

The confidence intervals of gain and phase in the low frequency range were wider when measured by TFAc (non-normalised gain: 0.92, 95%CI: 0.78;1.06; normalised gain: 1.43, 95%CI: 1.22;1.63;

phase: -9.95, 95%CI: -19.2;-0.68) and TFAa (non-normalised gain: 0.83, 95%CI: 0.73;0.94; normalised gain: 1.33, 95%CI: 1.17;1.49; phase: 5.18, 95%CI: -1.36;11.7) than by nTFA (non-normalised gain: 0.40, 95%CI: 0.36;0.45; normalised gain: 0.67; 95%CI: 0.60;0.75; phase: 18.8, 95%CI: 10.6;26.9) (**Figure 2**). Both normalised and non-normalised gain in the low frequency range showed good to excellent reliability for the comparison between TFAc and TFAa (normalised gain: ICC: 0.87; 95%CI: 0.81;0.91; n=96; non-normalised gain: ICC: 0.89; 95%CI: 0.84;0.92; n=96). The ICC for phase when comparing TFAc with TFAa in the low frequency range was 0.69 (95%CI: 0.55;0.79; n=96) (**Figure 3**). Overall, the smallest bias and narrowest LOA were seen in the Bland-Altman plots when comparing TFAc with TFAa (**Supplemental Material**).

Discussion

The present study is the first to use simultaneous measurements of non-invasive ABP, invasive ABP, and CPP to assess the reliability of the two transcranial doppler derived parameters, Mx and TFA, for assessing dynamic cerebral autoregulation in patients with SAH.

We found that the Mx based on non-invasive and invasive blood pressure measurements alone were higher than the mean flow index incorporating ICP; this is in line with previous reports (Schmidt *et al.*, 2003*a*, 2003*b*; Petersen *et al.*, 2014; Liu *et al.*, 2015). The overall smaller difference between nMxa and Mxa is also in line with previous reports (Lavinio *et al.*, 2007; Petersen *et al.*, 2014). The lower confidence limit of all Mx comparisons (i.e. nMxa, Mxa, and Mxc) of reliability was located in the range of "poor reliability", except for the comparison between nMxa and Mxc. This raises doubts about the ability to directly compare results gained from nMxa, Mxa or Mxc. Our finding that the reliability of Mx is poor when calculated by different pressure measurements, as well as the fact that Mx in general has been reported as unreliable, unstable, highly influenced by recording length, and the choices made during preprocessing (Lorenz *et al.*, 2007*a*; Ortega-Gutierrez *et al.*, 2014*a*; Mahdi *et al.*, 2017*a*; Riberholt *et al.*, 2021), restricts the ability to collate previous literature, or even interpret the findings in relation to any physiological phenomenon.

The fact that more than 128 peer-reviewed articles have calculated Mx and interpreted this as cerebral autoregulation is based on previous publications describing the validity of Mx (Olsen *et al.*, 2022). Mx has been widely accepted as a measure of dynamic cerebral autoregulation partly due to its association with functional outcome in patients with severe traumatic brain injury (Czosnyka *et al.*, 1996), and due to its correlation with the rate of regulation (RoR) (Piechnik *et al.*, 1999; Lang *et al.*, 2002), pressure reactivity index (PRx) (Lang *et al.*, 2003*b*; Schmidt *et al.*, 2012; Zeiler *et al.*, 2017,

2018*a*, 2018*b*; Pochard *et al.*, 2020), autoregulation index (ARI) (Czosnyka *et al.*, 2008; Liu *et al.*, 2020), ABP (Crippa *et al.*, 2018), and carbondioxide (CO_2)-reacitivity (Zhang *et al.*, 2016). In our opinion, almost all of these correlations have been flawed due to suspected heteroscedasticity (Gollion *et al.*, 2019; Quispe Cornejo *et al.*, 2020), one of the comparators being categorical (Czosnyka *et al.*, 1996, 1997; Lang *et al.*, 2003*a*; Tang *et al.*, 2008; Reinhard *et al.*, 2012; Budohoski *et al.*, 2012; Schmidt *et al.*, 2016*a*, 2016*b*), or mathematical coupling (Aggarwal & Ranganathan, 2016; Schober & Schwarte, 2018). Indices such as RoR (Piechnik *et al.*, 1999; Lang *et al.*, 2002), PRx (Lang *et al.*, 2003*b*; Schmidt *et al.*, 2012; Zeiler *et al.*, 2017, 2018*a*, 2018*b*; Pochard *et al.*, 2020), ARI (Czosnyka *et al.*, 2008; Liu *et al.*, 2020), ABP (Crippa *et al.*, 2018), and CO_2 reactivity (Zhang *et al.*, 2016) all use the same data, increasing the risk that the correlation identified might be caused by interdependency of data, rather than physiological associations (Aggarwal & Ranganathan, 2016; Schober & Schwarte, 2018).

In contrast, the phase and gain in the low-frequency range in this material (normalised and non-normalised) showed higher reliabilty for the comparison of invasively measured ABP with CPP. The ICC for these comparisons ranged from good to excellent. However, comparison with non-invasively measured ABP yielded confidence limits in the area of poor reliability. Even though TFA metrics calculated using invasively measured ABP and CPP are comparable, TFA has its limitations. Thus, so far TFA has been reported to have poor repeatability and reproducibility, has been assigned no reference values, and furthermore has limited diagnostic usefulness (Lorenz *et al.*, 2007*b*; Ortega-Gutierrez *et al.*, 2014*b*; Claassen *et al.*, 2015; Chi *et al.*, 2018; Sanders *et al.*, 2018). Whether TFA can predict outcome more precisely than Mx needs further investigation.

As a methodological curiosity, it might be important to notice the generally high ICC for the TFA metrics when comparing TFAc and TFAa in all frequency ranges. Both methods use the invasive arterial blood pressure as a factor in the analysis, as the CPP is calculated by subtracting ICP from invasive ABP. If ICP is stable during measurements, this would explain the similar gain and phase values; however, the reason for the more tenous ICC values when comparing Mxa and Mxc remain elusive.

Strengths and limitations

This study applied the different methods for blood pressure measurement simultaneously, eliminating the risk of time-course effects between methods. A difference between invasive and non-invasive ABP is comparable with previous reports (Kim *et al.*, 2014). The open-source preprocessing (Olsen *et al.*, 2021) with a validated script ensured optimal transparency. A large sample size, with recording lengths above the minimum recommended, was included (Mahdi *et al.*, 2017*b*; Olsen *et al.*, 2022). The lack of a global standard bedside measure of cerebral autoregulation renders us unable to select one of the pressure measurement methods as the best. As the most significant limitation, we were not able to record all three pressure measurements in every patient. Moreover, the study investigated the reliability in patients with SAH which might restrict extrapolation of the results to patients with other types of acute brain injury. Finally, the ICC in itself is an arbitrary measure of reliability. It is highly dependent on how data are dispersed, where an outcome represented on a large scale with large variation will in general yield a higher ICC value than values with only a small dispersion (Müller & Büttner, 1994). This might be the case for some of the analysis in our SAH cohort and is, therefore, a limitation of ICC on the entire scale.

Conclusion

According to this study in patients with aneurysmal SAH, simultaneously measured non-invasive ABP, invasive ABP and CPP yields different results when calculating Mx or TFA measures for the evaluation of dynamic cerebral autoregulation. The reliability for the comparison of Mx measures was moderate at best, while the gain and phase in the low-frequency domain for TFA showed good reliability. We advice against using these measures interchangeably. Whether TFA is a better method than Mx for quantifying dynamic cerebral autoregulation needs further investigation.

Declarations

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Availability of data and material: Data will be made available upon reasonable request to the corresponding author, and provided regulatory approvals are obtained.

Code availability: R-code will be made available upon reasonable request to the corresponding author.

Authors' contributions: MHO, RMGB, SB, and KM designed the study; MHO did the interventions; MHO and TC collected the data; MHO and CGR handled and analysed the data; All authors critically revised and accepted the final draft for publication.

Ethics approval: This physiological study was approved by the Regional Committee on Health Research Ethics in the Capital Region in Denmark (H-19017185; 28 May 2019)

Consent to participate: Informed consent was obtained by the next-of-kin.

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Figure legends

Figure 1 – Reliability of Mx (3-60-F) by pressure measurement. (A) Individual-level values of Mx by pressure measurement. The grey lines depict the relationship between the results gained from the left and right approach for each comparison. Only results with corresponding measurements are presented. (B) ICC values.

ICC: Intraclass correlation coefficient.

Figure 2 – Individual-level TFA values by pressure measurement. Grey lines depict the relationship between the results for each of the different TFA metrics obtained by the left and right approach for each comparison. Only results with corresponding measurements are presented.

VLF: Very low frequency; LF: Low frequency; HF: High frequency; ABP: Arterial blood pressure; CBFv: Cerebral blood flow velocity.

Figure 3 – ICC by measurement approach. Green depicts the spectrum of excellent reliability, yellow of good reliability, orange of moderate reliability, and red of poor reliability.

VLF: Very low frequency; LF: Low frequency; HF: High frequency; ABP: Arterial blood pressure; CBFv: Cerebral blood flow velocity; ICC: Intraclass correlation coefficient.

Table 1 – Study characteristics

Participants *(n = 40)*	
Age (years) – median (IQR)	58 (51-64)
Male – n (%)	8 (20%)
Poor-grade SAH (WFNS 4-5) **-** n (%)	28 (70%)
Heart rate (min^{-1}) – mean ±SD	79.0 ± 23.6
Middle cerebral artery velocity ($^{cm}/s$) **–** mean ±SD	65.7 ± 25.5
Mean flow index (Mx)	
Recordings – n	95
Recording length baseline (min) – median (IQR)	27.3 (19.3-30.0)
Recording length induced hypertension (min) – median (IQR)	23.0 (17.0-27.6)
Artefacts (%)– median (IQR)	0.06 (0-0.13)
Transfer function analysis (TFA)	
Recordings – n	99
Recording length, baseline (min) – median (IQR)	24.5 (15.6-28.1)
Recording length, induced hypertension (min) – median (IQR)	19.9 (12.4-25.3)

SAH: aneurysmal subarachnoid haemorrhage;

WFNS: World Federation of Neurological Surgeons.

Figure 1 – Inter-method reliability of Mx

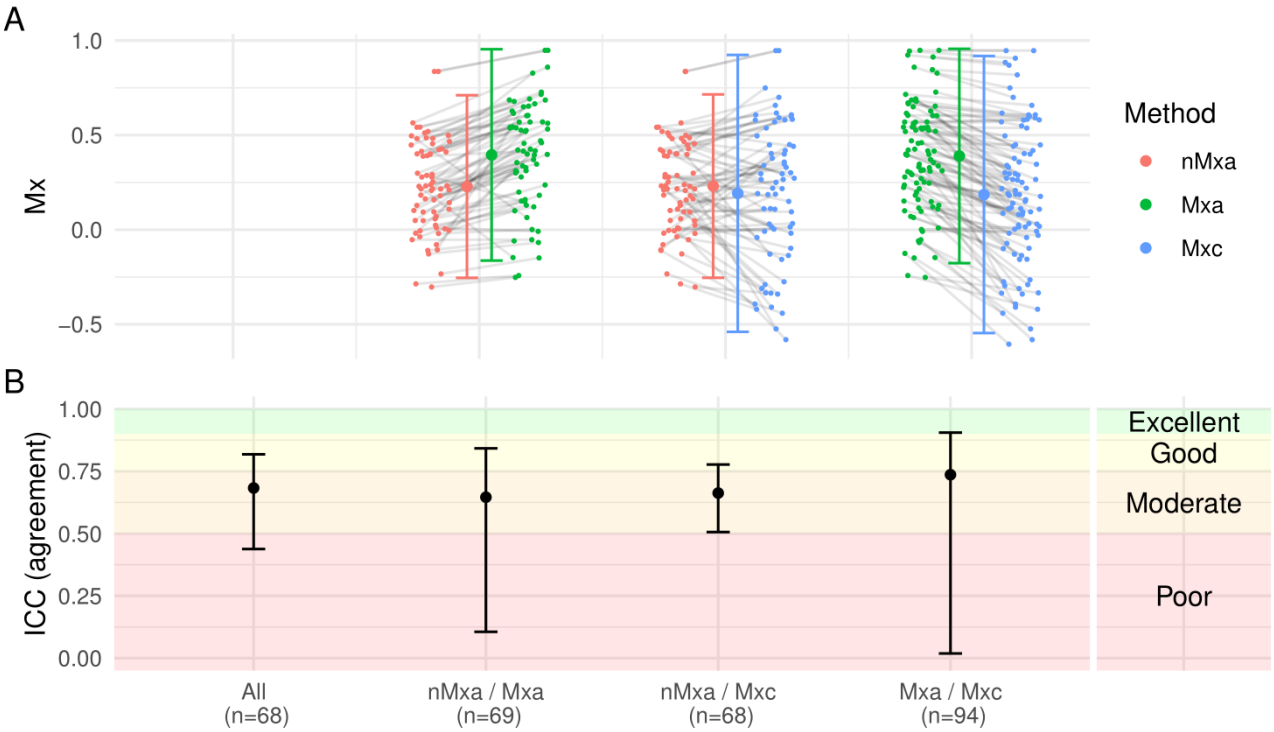


Figure 2 – TFA measures in individual participants

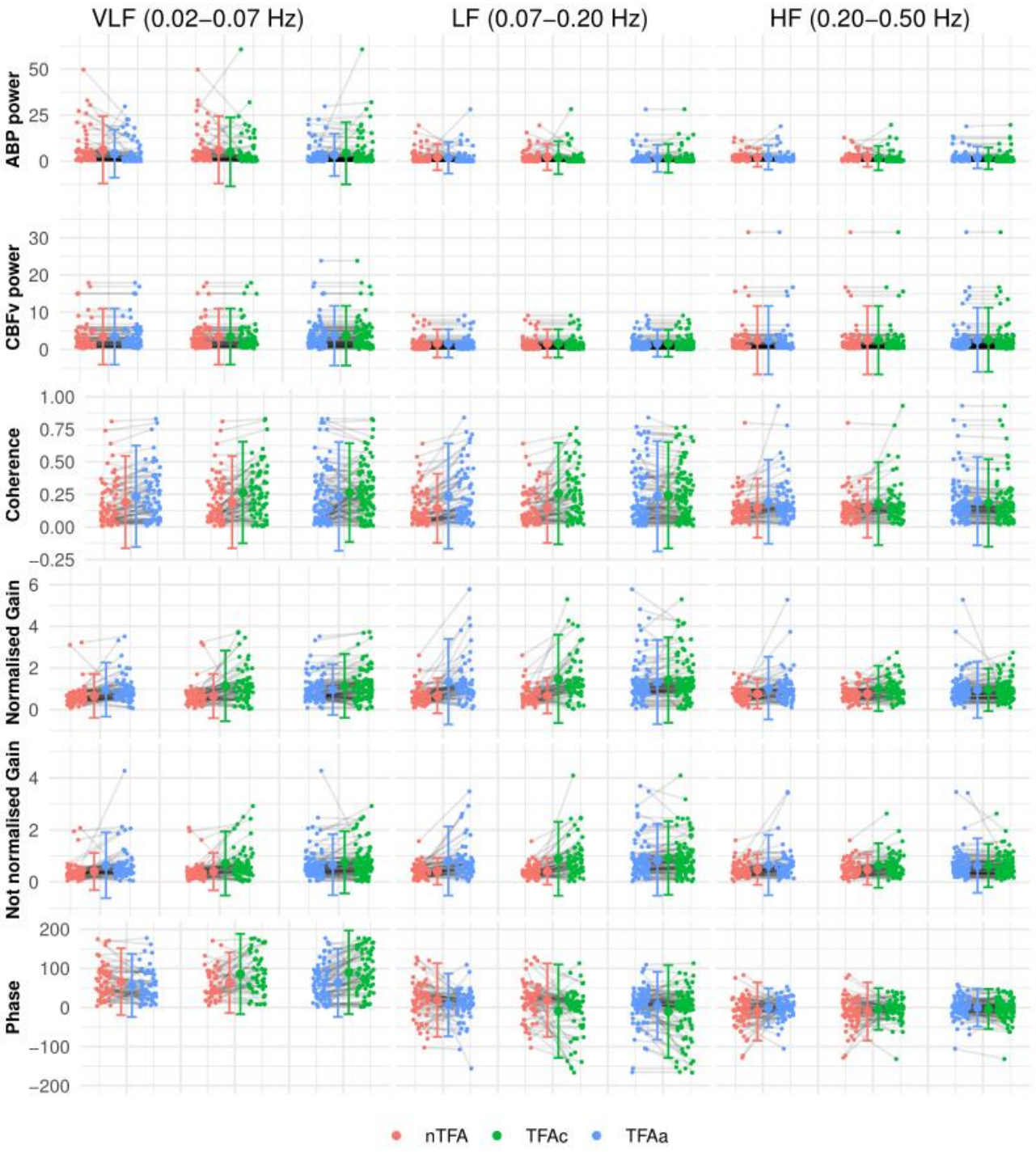
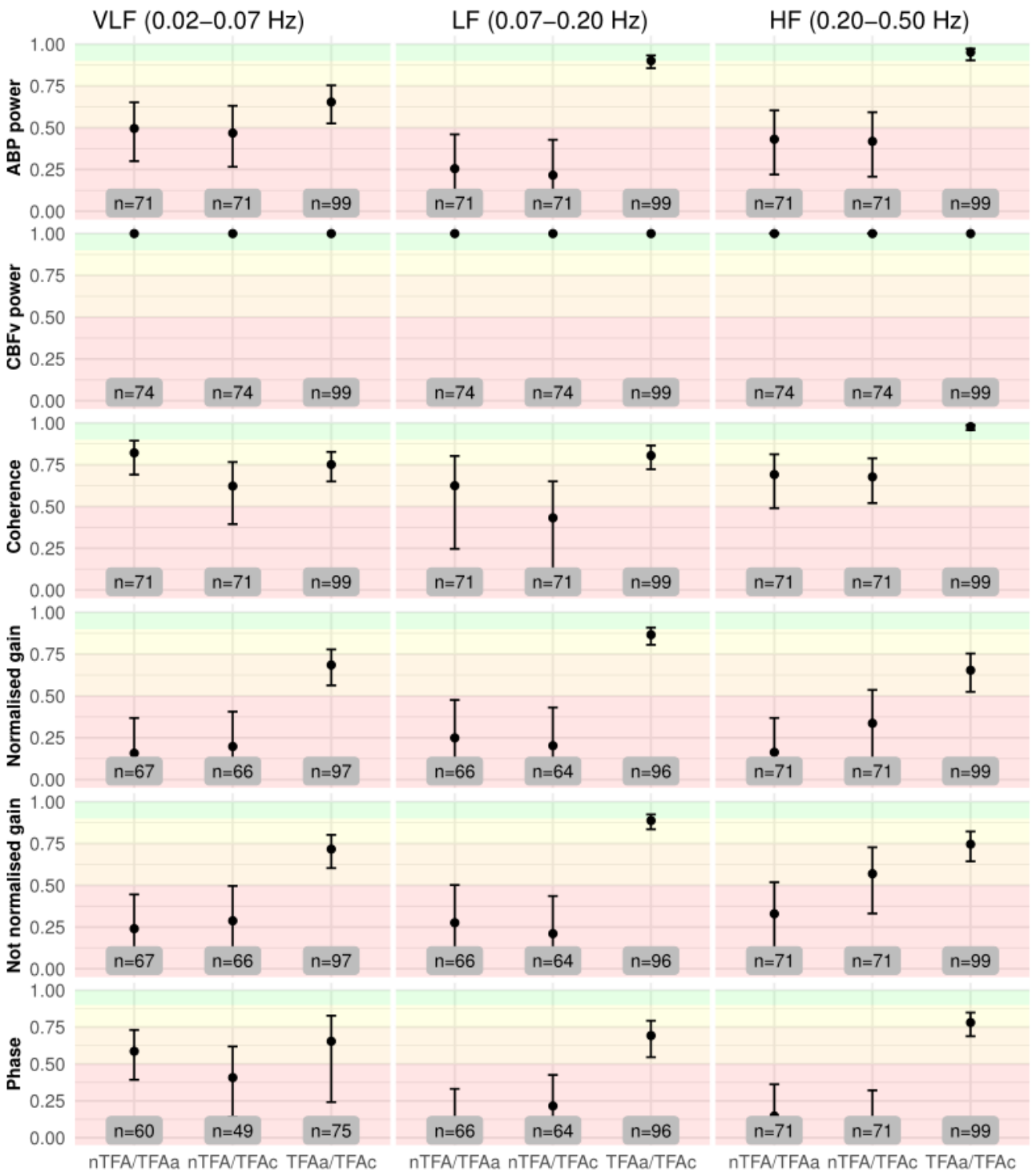


Figure 3 – Between-method reliability, TFA metrics



14.4 Paper IV

Diagnostic and prognostic performance of arterial pressure-derived mean flow index (Mxa): the influence of data pre-processing

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Diagnostic and prognostic performance of arterial pressure-derived mean flow index (Mxa): the influence of data pre-processing.

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Short title: Diagnostic and prognostic performance of Mxa

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Keywords: mean flow index, autoregulation, diagnostic tool, Mx, validity, biomarker

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Abstract (max 200 words)

The arterial blood pressure (ABP)-derived mean flow index (Mxa), calculated as the correlation between continuously recorded ABP and transcranial Doppler-derived mean cerebral blood flow velocity, is widely used for evaluating dynamic cerebral autoregulation. This study investigated how different data pre-processing approaches for calculating Mxa affected the diagnostic and prognostic performance of this measure. We included recordings from 48 healthy volunteers, 19 patients with sepsis, 36 with traumatic brain injury (TBI), and 14 admitted to a neurorehabilitation unit after severe non-traumatic or traumatic brain injury. Four different data pre-processing approaches were specified. The diagnostic (between healthy volunteers and patients) and prognostic performance (to predict death or poor functional outcome) of Mxa was assessed by area under the receiver-operating characteristic (AUROC) curves. AUROC generally indicated that regardless of pre-processing approach, Mxa was 'no better than chance' both for distinguishing between healthy volunteers and patient groups, and for predicting outcomes. Furthermore, changes in Mxa depended on the pre-processing approach during interventions in healthy volunteers and patients. Mxa depends heavily on data pre-processing approaches. No single approach emerged as superior for distinguishing between healthy volunteers and different patient groups, assessing the effect of interventions, or predicting mortality or functional outcome.

Introduction

Dynamic cerebral autoregulation dampens changes in cerebral blood flow during acute fluctuations in cerebral perfusion pressure (CPP) by adjusting cerebrovascular resistance[1]. The mean flow index (Mx) was introduced by Czosnyka et al. in 1996 as a time-domain-based measure of dynamic cerebral autoregulation[2]. Mx is based on the simultaneous recording of transcranial Doppler ultrasound (TCD)-measured mean flow velocity of the middle cerebral artery (MCAv) and either cerebral perfusion pressure (CPP) or, in the absence of intracranial pressure (ICP) measurement, arterial blood pressure (ABP)[3]. Before calculation of Mx or Mxa, data are commonly pre-processed by dividing recordings into blocks, collating blocks into epochs, and using different durations of overlaps, if any. Mx is then calculated as the mean of the repeatedly calculated correlation coefficients either between MCAv and CPP (Mx), whereas Mxa is similarly calculated as the mean correlation coefficient between MCAv and ABP (Mxa)[4]. Both Mx and Mxa range from -1 to 1; high positive values indicate impaired dynamic cerebral autoregulation, and conversely low values reflect more intact autoregulation[2]. The predominantly used threshold between preserved and impaired cerebral autoregulation is 0.3[5].

The diagnostic ability of Mxa has previously been assessed by averages between different patient groups; actual prediction modelling has only been reported for stroke patients with healthy volunteers as comparators, showing low (area under the curve, AUC 0.5-0.7) to moderate accuracy (AUC 0.7-0.9)[6,7]. The prognostic abilities of Mx and Mxa have been investigated in patients with traumatic brain injury (TBI), subarachnoid haemorrhage, and sepsis with results ranging from ‘no better than chance’ (AUC of 0.5) to moderate accuracy depending on the diagnosis and specific outcome[4,8–10].

In the present study, we compared four data pre-processing approaches that have commonly been applied according to the existing literature[5,11,12] with regard to their effect on the diagnostic and prognostic performance, respectively, of Mxa. We compared a group comprising healthy volunteers to groups comprising patients with sepsis, patients with TBI, and patients admitted to a neurorehabilitation unit after traumatic or non-traumatic brain injury, respectively. For the three patient categories, dynamic cerebral autoregulation has previously been reported to be impaired using other methods, such as thigh-cuff deflation and transfer function analysis[13–15]. Finally, we investigated how the different data pre-processing approaches affected the effect of various physiological interventions on Mxa, as well as the comparison of Mxa between groups.

Methods

Ethical approval

The present retrospective work is based on data from five studies, which have previously been published elsewhere[12,16–20], and describes entirely separate analyses to address an independent working hypothesis. All studies were approved by either the Scientific Ethical Committee of Copenhagen and Frederiksberg Municipalities or the Capital Region of Copenhagen (file numbers HA-2009020 and H-2201004, H-32013024, H-16042103, and H-16041794), and conformed to the standards set by the Declaration of Helsinki; no additional ethical approval was necessary for this retrospective study. Subjects or their next-of-kin provided oral and written informed consent prior to inclusion. The data underlying our findings can be shared upon reasonable request directed to the corresponding author of this and the original studies.

Subjects and recordings

The present study encompasses recordings from 48 healthy volunteers, in whom a total of 62 individual baseline periods were recorded; 19 patients with sepsis (34 individual baseline recordings); 36 patients admitted to an intensive care unit with severe TBI recorded a median of 12 (interquartile range, IQR: 11-16) days after the injury (66 individual baseline recordings); and 14 patients admitted to a neurorehabilitation unit 41 (standard deviation, SD: ±12) days after the injury with traumatic (57%) or non-traumatic brain injury (43%) (26 baseline recordings). Baseline recordings were defined as periods before any interventions were initiated. Characteristics of the recordings and studies are provided in **Table 1**.

Data collection

Studies A[16] and *B*[17,18] recorded invasive ABP in the left radial artery and MCAv by TCD-insonation in healthy volunteers and patients admitted to the intensive care unit with severe sepsis; all subjects were placed in the supine position with slight head elevation (20º). *Study C*[19], *D*[12], *and E*[20] recorded ABP non-invasively with photoplethysmographic continuous beat-to-beat measurement, and MCAv measured by TCD-insonation while lying supine without head elevation. Recordings from baseline sessions were extracted for all subjects. Recordings during physiological interventions were also extracted as follows:

- *Study A*: Induced hypertension during noradrenaline infusion[16];
- *Study B*: In the healthy volunteers - four hours after initiation of continuous lipopolysaccharide (LPS) infusion, (1) without and (2) with induced hypertension during noradrenaline infusion[18];
- *Study C*: Head-up tilt (80º)[19]; and
- *Study D*: Head-up tilt (70º)[12].

The data collection is described in full in the original articles[12,16–20].

Data pre-processing

Recordings were extracted from LabChart (ADInstruments, Sidney, Australia) into a tab-delimited file in the original resolution of 1,000 Hz and were visually inspected for artefacts; periods with artefacts were deleted, ensuring that such periods always started and ended in a nadir. Subsequently, recordings were divided into blocks and epochs using four different, commonly used pre-processing approaches from the literature[5,11,12], here designated *3-60-F*, *6-240-F*, *10-300-F*, and *10-300-60*. For these designations, the first number refers to the duration of each block in seconds, the second number is the duration of each epoch in seconds, and the third number is the duration of the overlaps in seconds, with F indicating an approach where overlaps were not used. To ensure sufficient quality of

the calculations, blocks were omitted from the analysis if 50% of the raw measurements were missing. Similarly, epochs were omitted if more than 50% of the blocks were missing. Mxa was subsequently calculated using the clinmon-function from the publicly available R-package 'clintools' v. 0.8.2[21]. Briefly, the clintools-package is a publicly available R-package. The packages has a clinmon-function, which generates results comparable to those generated using the ICM+ software (Cambridge Enterprise, Cambridge, United Kingdoms).

Diagnostic and prognostic performance

The diagnostic ability of Mxa was assessed by its ability to discriminate between healthy volunteers on one side and patients with sepsis, with severe TBI, and patients admitted to a neurorehabilitation unit, respectively. Its prognostic ability was assessed by the ability to predict mortality in patients with sepsis and TBI, and functional outcome for patients with TBI. All these assessments were based on baseline recordings alone.

Interventions

The effect on Mxa in the following four contexts (interventions, comparisons, and subjects) was calculated: (1) Induced hypertension by noradrenaline infusion compared with baseline in patients with sepsis (from *Study A*[16]); (2) Induced hypertension by noradrenaline infusion compared to baseline in healthy volunteers after LPS infusion (*Study B*[17,18]); (3) Head-up tilt (80^{o}) in healthy volunteers compared to head-up tilt in patients admitted to a neurorehabilitation (*Study C*[19]); and (4) the Head-up tilt (70^{o}) compared to the supine position in healthy volunteers (*Study D*[12]).

Statistical analysis

All statistical analyses were carried out using R 4.0.2 (R Core Team (2020), Vienna, Austria). Normally distributed data are presented as mean (±SD), while non-normally distributed data are presented as median (IQR). The validity of Mxa was assessed using receiver operating characteristics (ROC) curves and area under the curve (AUC). The analysis used higher Mxa as a predictor of the selected outcome. The AUC will be interpreted as representing 'no better than chance' (~0.5), low accuracy (0.5-0.7), moderate (0.7-0.9), and high accuracy (> 0.9)[22]. Students t test was used to compare groups, and p values calculated without correction for multiplicity. This correction would be relevant if we sought to determine actual significance levels. However, we wanted to exemplify what results could look like based on each approach. Hence, each individual p value is considered to represent the result of an analysis that could be carried out in a separate paper or study.

Results

Patients with sepsis had the highest Mxa compared to the other groups across the four approaches (3-60-F: 0.46 ±0.24; 6-240-F: 0.36 ±0.33; 10-300-F: 0.35 ±0.34; 10-300-60: 0.34 ±0.33), while healthy subjects (3-60-F: 0.43 ±0.16; 6-240-F: 0.33 ±0.23; 10-300-F: 0.29 ±0.25; 10-300-60: 0.29 ±0.24) exhibited higher values than both patients admitted to a neurorehabilitation unit (3-60-F: 0.24 ±0.23; 6-240-F: 0.15 ±0.33; 10-300-F: 0.06 ±0.34; 10-300-60: 0.05 ±0.35) and patients with TBI (3-60-F: 0.21 ±0.27; 6-240-F: 0.11 ±0.33; 10-300-F: 0.09 ±0.32; 10-300-60: 0.07 ±0.33) (**Figure 1, left column**). These patterns were also reflected in the prediction models, where the AUCs for the diagnostic ability of patients with sepsis ranged from 0.53 to 0.55, that of patients undergoing rehabilitation for acquired brain injury ranged from 0.25 to 0.32, and that of patients with TBI from 0.25 to 0.31 depending on the approach (**Figure 1, right column**). The ability of Mxa to predict mortality was best for 10-300-F in patients with sepsis (AUC: 0.59: 95% CI: 0.37-0.81) and 3-60-F in patients with TBI (AUC: 0.43: 95% CI: 0.25-0.60). The prognostic value to predict functional outcome in patients with TBI was best for 3-60-F (AUC: 0.48; 95% CI: 0.31-0.64) (**Figure 2**).

Induced hypertension resulted in a significant decrease in Mxa in patients with sepsis when analysed using 3-60-F (**Figure 3A**) but not with any other approach, while induced hypertension in healthy volunteers during LPS-infusion showed a significant decrease in Mxa for 10-300-F and 10-300-60, but not using 3-60-F and 6-240-F (**Figure 3B**). Mxa during head-up tilt in healthy volunteers was higher than patients in neurorehabilitation for 3-60-F and 6-240-F, while differences were non-significant for 10-300-F and 10-300-60 (**Figure 3C**). Finally, head-up tilt resulted in an increase in Mxa for healthy volunteers for 3-60-F, but not for the rest of the approaches (**Figure 3D**).

Discussion

This study used recordings from multiple studies to calculate Mxa for different patients and investigate Mxa as a diagnostic and prognostic tool. Mxa did not appear to consistently differentiate healthy volunteers from patients with sepsis, with TBI, and those admitted to rehabilitation after acute brain injury; the AUC values indicated 'no better than chance' at best. Similarly, Mxa could not predict mortality in patients with sepsis and TBI or functional outcome in patients with TBI. The approach of how Mxa was calculated affected the level of significance, thereby limiting the generalisability of Mxa.

Baseline Mxa was on average lower for patients with TBI compared to healthy volunteers, suggesting better autoregulation in patients with TBI. Cerebral autoregulation is commonly assumed to be intact in healthy volunteers[1,23], and should be comparably impaired in patients with acquired brain injury[24,25]. The present finding in itself questions the relevance of Mxa as a measure of dynamic cerebral autoregulation[2]. The present study is not the only one where Mxa in healthy volunteers is around 0.40 [26], nor where patients with TBI present with Mx or Mxa around 0.15[2,27]. The current understanding of Mxa thus conflicts with our findings, which also limits the usefulness of a pre-defined threshold for impaired autoregulation. Indeed, dichotomisation seems inappropriate for this purpose regardless of the chosen threshold. Thus, more than half of our healthy volunteers would have impaired cerebral autoregulation if the predominantly used threshold of 0.3 was used[5].

Mxa also showed chance-results at best in terms of predicting mortality in patients with sepsis and TBI and functional outcome in patients with TBI and. Previous studies have reported varying results in terms of the prognostic value of Mx and Mxa between chance-result and moderate accuracy[4,8,28,29]. This questions the value of cerebral autoregulation as a prognostic marker or rather,

as mentioned previously, the interpretation of Mxa as a measure of cerebral autoregulation. Thus, the physiological mechanism that Mxa is meant to depict is unclear. Moreover, the data pre-processing before calculation of Mxa directly affected the results, in that Mxa showed a significant change or difference for some approaches and not for others.

Biomarkers of biological processes should only be used as an endpoint in trials and studies if they are readily measurable, interpretable, reliable, and valid[30,31]. Mxa, which is closely related to Mx but based on ABP rather than CPP, is in principle readily measurable, but as shown in this and previous studies, the approaches to data pre-processing and calculation of Mx and Mxa vary between studies and may affect the results[5,11,12]. The repeatability and reproducibility of Mxa between measurement periods and approaches range from poor to moderate[11,12,26,32–34]; one study showing excellent reliability[7] used overlapping periods, which for mathematical reasons should yield an optimal reliability.

The use of a publicly available R-package and the large sample size is the two main strengths of the study. This study was however limited by the retrospective design. Another limitation is the use of recordings using both non-invasive, and invasive measurement of ABP. The potential difference between Mxa calculated using non-invasive and invasive ABP is not fully understood[35,36].

Conclusion

The results of this study, which used recordings from multiple studies to calculate Mxa as a measure of the strength of cerebral autoregulation for different groups of patients, indicate that the specific approach for data pre-processing strongly affects the results. The validity of Mxa as a diagnostic and prognostic tool appears to be questionable.

Conflict of Interest:

The authors have no conflict of interest to report.

Author contributions:

MHO, CR, KM and RMGB designed the study; CR, RRP and RMGB collected the data; MHO did the analyses and wrote the first draft; all authors revised and approved the final version.

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Table 1 – Study characteristics

		N	Age years ±SD	Male n (%)	Recordings n	Method
Study A[16]	Healthy	9	23 ±2	9 (100%)	9	Mxa
-	Sepsis	19	57 ±14	17 (89%)	34	Mxa
Study B[17,18]	Healthy	10	23 ±2	10 (100%)	10	Mxa
Study C[19]	Healthy	15	31 ±13	7 (47%)	15	nMxa
-	Rehabilitation	14	57 ±17	7 (50%)	26	nMxa
Study D[12]	Healthy	14	28 ±9	5 (36%)	28	nMxa
Study E[20]	TBI	36	44 ±18	10 (28%)	66	nMxa

Recordings are baseline periods without any interventions. N: number of patients; Mxa: Mx using invasively measured arterial blood pressure; nMxa: Mxa using non-invasively measured arterial blood pressure; TBI: traumatic brain injury.

Figure legends

Figure 1 – Mxa by pre-processing approach (one per row) and diagnostic group. Left column: Baseline recordings. Mean and 95% confidence interval is shown. Right column: Receiver operating curves for the discrimination of patient groups with healthy volunteers as the comparator (right column).

Figure 2 – The prognostic value of Mxa presented from baseline recordings grouped by outcome (left column) and data pre-processing approach (one per row), with receiver operating curves with a good outcome or survival as comparators, and the ability to increase Mxa to predict mortality or poor outcome in patients with sepsis and traumatic brain injury (TBI), respectively.

Figure 3 – For each of the four data pre-processing approaches, this figure presents the effect on Mxa of (A) induced hypertension (compared to baseline) in patients with sepsis; (B) induced hypertension (compared to baseline) in healthy volunteers after infusion of E.coli lipopolysachharide; (C) Mxa during head-up tilt for healthy volunteers and patients admitted to a neurorehabilitation unit, and (D) the effect of head-up tilt in healthy volunteers. P values were calculated using Student's t test.

Figure 1

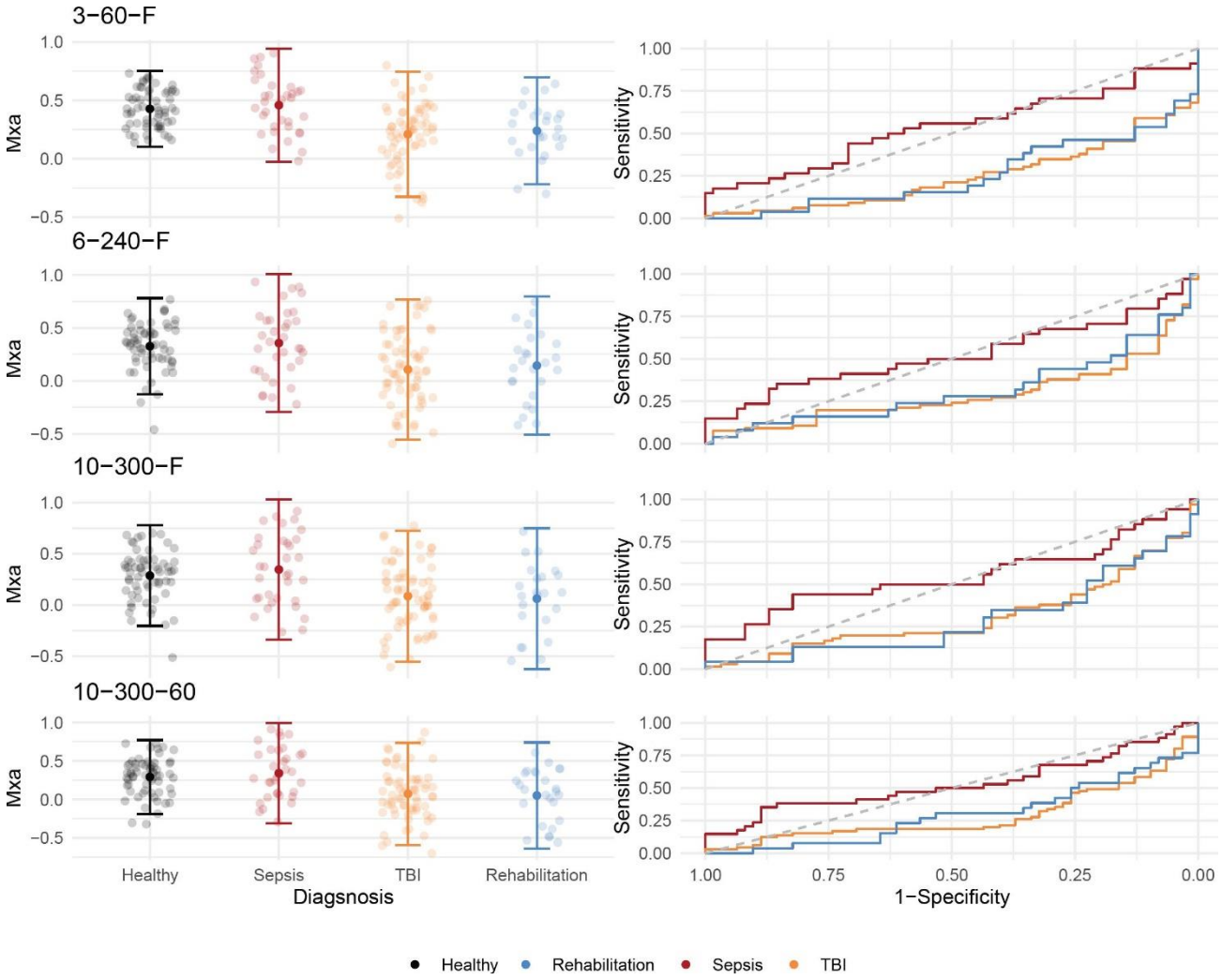

3−60−F
6−240−F
10−300−F
10−300−60
Mxa
Sensitivity
1−Specificity
Diagsnosis
Healthy
Sepsis
TBI
Rehabilitation
Healthy
Rehabilitation
Sepsis
TBI

Figure 2

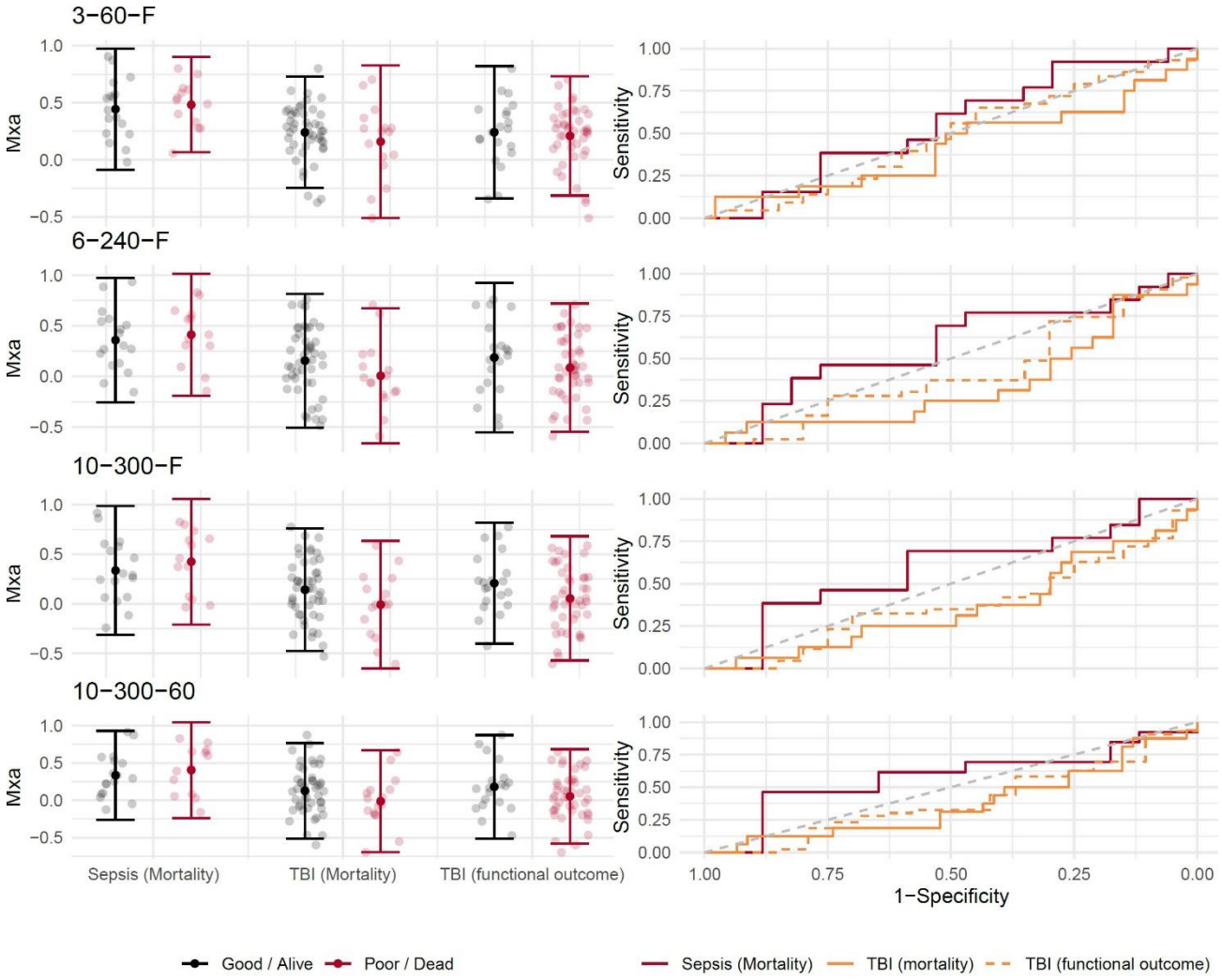
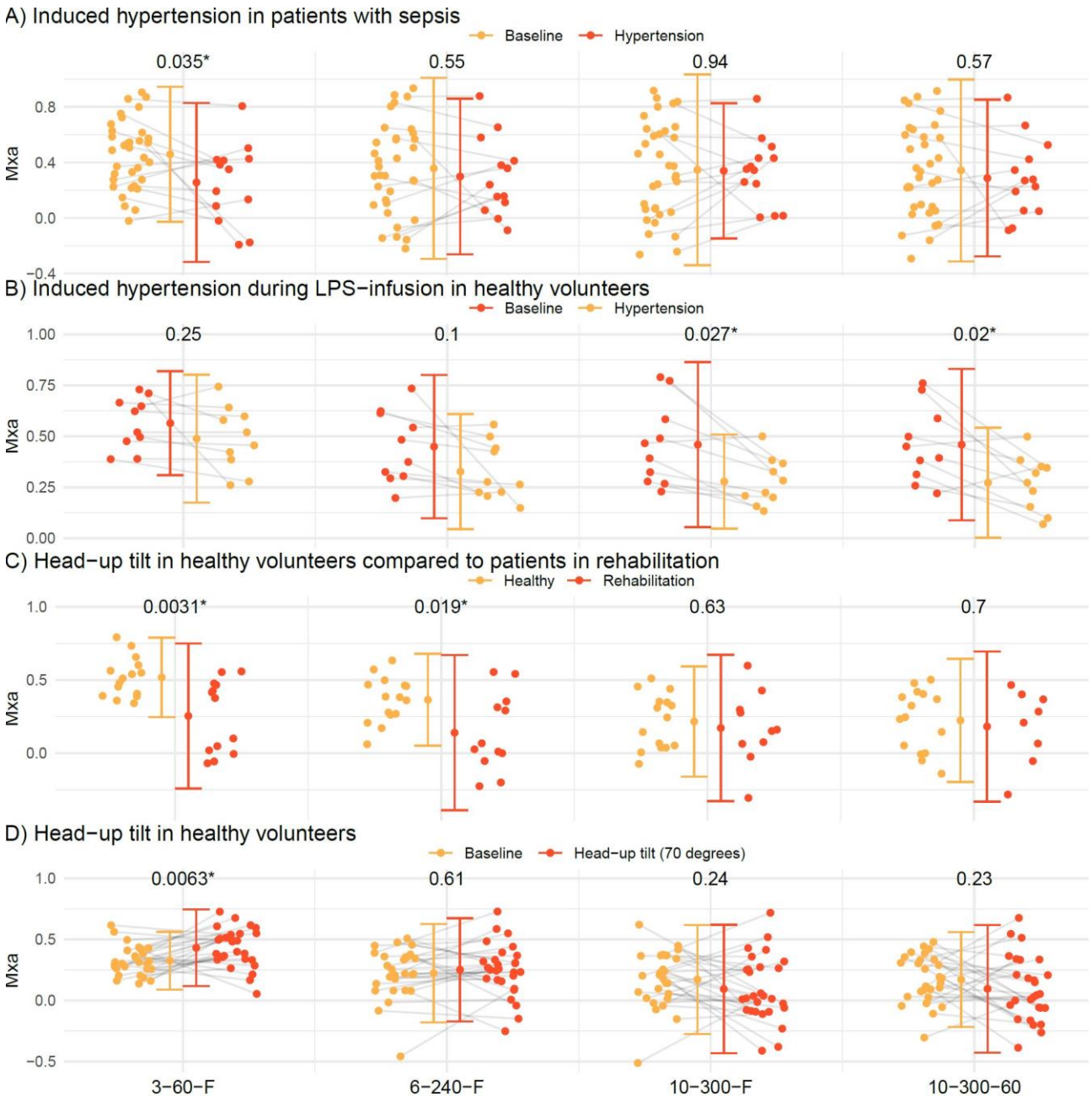

3−60−F
6−240−F
10−300−F
10−300−60
Mxa
Sensitivity
1.0
0.5
0.0
−0.5
1.00
0.75
0.50
0.25
0.00
Sepsis (Mortality)
TBI (Mortality)
TBI (functional outcome)
1−Specificity
Good / Alive
Poor / Dead
Sepsis (Mortality)
TBI (mortality)
TBI (functional outcome)

Figure 3


A) Induced hypertension in patients with sepsis
Baseline
Hypertension
0.035*
0.55
0.94
0.57
Mxa
B) Induced hypertension during LPS−infusion in healthy volunteers
Baseline
Hypertension
0.25
0.1
0.027*
0.02*
Mxa
C) Head−up tilt in healthy volunteers compared to patients in rehabilitation
Healthy
Rehabilitation
0.0031*
0.019*
0.63
0.7
Mxa
D) Head−up tilt in healthy volunteers
Baseline
Head−up tilt (70 degrees)
0.0063*
0.61
0.24
0.23
Mxa
3−60−F
6−240−F
10−300−F
10−300−60

14.5 Package ‘clintools’

Package 'clintools'

January 20, 2022

Type Package

Title Tools for Clinical Research

Version 0.9.2

Description Every research team have their own script for data management, statistics and most importantly hemodynamic indices. The purpose is to standardize scripts utilized in clinical research. The hemodynamic indices can be used in a long-format dataframe, and add both periods of interest (trigger-periods), and delete artifacts with deleter-files. Transfer function analysis (Claassen et al. (2016) <doi:10.1177/0271678X15626425>) and Mx (Czosnyka et al. (1996) <doi:10.1161/01.str.27.10.1829>) can be calculated using this package.

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URL https://github.com/lilleoel/clintools

BugReports https://github.com/lilleoel/clintools/issues

Depends R (>= 3.5.0)

Encoding UTF-8

Language en-US

LazyData true

RoxygenNote 7.1.1

Suggests knitr, rmarkdown

Imports signal (>= 0.7-6), xml2 (>= 1.3.2), lme4 (>= 1.1-27.1)

NeedsCompilation no

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R topics documented:

`clinmon` *Hemodynamic Indices Calculated From Clinical Monitoring (clinmon)*

Description

`clinmon()` uses a *continuous* recording and returns a dataframe with hemodynamic indices for every period, epoch or block depending on the input. Calculates `COest`, `CPPopt`, `CVRi`, `Dx`, `Mx`, `PI`, `PRx`, `PWA`, `RI`, and `Sx` (see *Hemodynamic indices*).

Usage

```
clinmon(df, variables,
trigger = NULL, deleter = NULL,
blocksize = 3, epochsize = 20,
overlapping = FALSE, freq = 1000,
blockmin = 0.5, epochmin = 0.5,
output = "period", fast = FALSE)
```

Arguments

`df`	Raw *continuous* recording with all numeric data and first column has to be time in seconds. (`dataframe`)
`variables`	Defining the type and order of the recorded variables as a list. Middle cerebral artery blood velocity (`'mcav'`), Arterial blood pressure (`'abp'`), cerebral perfusion pressure (`'cpp'`), intracranial pressure (`'icp'`), and heart rate (`'hr'`) is currently supported. *It is necessary that time is the first row*. (`list`)
`trigger`	Trigger with two columns: first is start, and second is end of periods to be analyzed. Every row corresponds to a period. Default is `NULL`, which results in analysis of the full dataframe. (`dataframe`)

deleter	Deleter with two columns: first is start and second is end of period with artefacts, which need to be deleted. Every row is a period with artefacts. Default is NULL. (dataframe)
blocksize	Length of a block, in seconds. Default is 3. (numeric)
epochsize	Size of epochs in number of blocks. Default is 20. (numeric)
overlapping	The number of block which should overlap when calculating correlation based indices, and remain blank if overlapping calculations should not be utilized. Default is FALSE. (numeric)
freq	Frequency of recorded data, in Hz. Default is 1000. (numeric)
blockmin	Minimum measurements required to create a block in ratio. Default is 0.5 corresponding to 50%. If the block holds less than the defined ratio the block will be omitted. (numeric)
epochmin	Minimum number of blocks required to create an epoch in ratio. Default is 0.5 corresponding to 50%. If the epoch holds less than the defined ration the epoch will be omitted. (numeric)
output	Select what each row should represent in the output. Correlation based indices are not presented when selecting blocks for every row. Currently 'block', 'epoch', 'period' or 'cppopt' is supported. Default is 'period'. (string)
fast	Select if you want the data to aggregated before analysis resulting in a faster, but perhaps more imprecise run, in Hz. Default is FALSE. (numeric)

Details

Using a *continuous* raw recording, clinmon() calculates hemodynamic indices for every period, epoch or block depending on the chosen output.

```
View(data)
```

time	abp	mcav
7.00	78	45
7.01	78	46
...	...	...
301.82	82	70
301.83	81	69

To calculate the indices insert the data and select the relevant variables.

```
clinmon(df=data, variables=c("abp","mcav"))
```

See **Value** for output description.

Value

Returns a dataframe with the results, with either every blocks, epochs or periods as rows, depending on the chosen output.

The columns of the output are:

- `period` - The period number corresponding to the row-number in the trigger file.
- `epoch` - The epoch number, or if `period` is chosen as output it reflects the number of epochs in the period.
- `block` - The block number, or if `period` or `epoch` is chosen as output it reflects the number of blocks in the `period` or `epoch`.
- `time_min` - The minimum time value or the `period`, `epoch` or `block`.
- `time_max` - The maximum time value or the `period`, `epoch` or `block`.
- `missing_percent` - The percentage of missing data in the `period`, `epoch` or `block`.
- `XX_mean` - The mean value of each variable for the `period`, `epoch` or `block`.
- `XX_min` - The minimum value of each variable for the `period`, `epoch` or `block`.
- `XX_max` - The maximum value of each variable for the `period`, `epoch` or `block`.
- `YY` - The indices in each column.

Hemodynamic indices

`COest` | **Estimated cardiac output:**

Required variables: `abp`, `hr`; *Required output:* `-`.

Estimated cardiac output (`COest`) is calculated by utilizing the method described by Koenig et al. [1]:

$$COest = PP/(SBP + DBP) * HR$$

PP: Pulse pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate.

`CPPopt` | **Optimal cerebral perfusion pressure:**

Required variables: `abp`, `icp`; *Required output:* `period`.

Optimal cerebral perfusion pressure (`CPPopt`) is calculated utilizing the method described by Steiner et al. [2]. The CPPopt return `NA` if CPPopt is the maximum or minimum CPP investigated. CPPopt is recommended to only be calculated after 'several hours' of recording:

$$CPPopt = The5mmHgCPPIntervalWithLowestMeanPRx$$

CPP: cerebral perfusion pressure; PRx: Pressure reactivity index.

`CVRi` | **Cardiovascular resistance index:**

Required variables: `abp`, `mcav`; *Required output:* `-`.

Cardiovascular resistance index (`CVRi`) is calculated utilizing the method described by Fan et al. [3]:

$$CVRi = meanABP/meanMCAv$$

ABP: arterial blood pressure; MCAv: middle cerebral artery blood velocity.

`Dx` | **Diastolic flow index:**

Required variables: `cpp`/`abp`, `mcav`; *Required output:* `epoch`, `period`.

Diastolic flow index (`Dx`) is calculated utilizing the method described by Reinhard et al. [4]:

$$Dxc = cor(meanCPP/minMCAv)$$

$$Dxa = cor(meanABP/minMCAv)$$

cor: correlation coefficient; CPP: cerebral perfusion pressure; ABP: arterial blood pressure; MCAv: middle cerebral artery blood velocity.

`Mx` | **Mean flow index:**
Required variables: `cpp`/`abp`, `mcav`; *Required output:* `epoch`, `period`.
Mean flow index (`Mx`) is calculated utilizing the method described by Czosnyka et al. [5]:

$$Mxc = cor(meanCPP/meanMCAv)$$

$$Mxa = cor(meanABP/meanMCAv)$$

cor: correlation coefficient; CPP: cerebral perfusion pressure; ABP: arterial blood pressure; MCAv: middle cerebral artery blood velocity.

`PI` | **Gosling index of pulsatility:**
Required variables: `mcav`; *Required output:* `-`.
Gosling index of pulsatility (`PI`) is calculated utilizing the method described by Michel et al. [6]:

$$PI = (systolicMCAv - diastolicMCAv)/meanMCAv$$

MCAv: middle cerebral artery blood velocity.

`PRx` | **Pressure reactivity index:**
Required variables: `abp`, `icp`; *Required output:* `epoch`, `period`.
Pressure reactivity index (`PRx`) is calculated utilizing the method described by Czosnyka et al. [7]:

$$PRx = cor(meanABP/meanICP)$$

cor: correlation coefficient; CPP: cerebral perfusion pressure; ICP: intracranial pressure.

`PWA` | **Pulse wave amplitude:**
Required variables: `cpp`/`icp`/`abp`/`mcav`; *Required output:* `-`.
Pulse wave amplitude (`PWA`) is calculated utilizing the method described by Norager et al. [8]:

$$PWA = systolic - diastolic$$

`RI` | **Pourcelots resistive (resistance) index:**
Required variables: `mcav`; *Required output:* `-`.
Pourcelots resistive (resistance) index (`RI`) is calculated utilizing the method described by Forster et al. [9]:

$$RI = (systolicMCAv - diastolicMCAv)/systolicMCAv$$

MCAv: middle cerebral artery blood velocity.

`Sx` | **Systolic flow index:**
Required variables: `cpp`/`abp`, `mcav`; *Required output:* `epoch`, `period`.
Systolic flow index (`Sx`) is calculated utilizing the method described by Czosnyka et al. [5]:

$$Sxc = cor(meanCPP/systolicMCAv)$$

$$Sxa = cor(meanABP/systolicMCAv)$$

cor: correlation coefficient; CPP: cerebral perfusion pressure; ABP: arterial blood pressure; MCAv: middle cerebral artery blood velocity.

References

1. Koenig et al. (2015) Biomed Sci Instrum. 2015;51:85-90. (PubMed)
2. Steiner et al. (2002) Crit Care Med. 2002 Apr;30(4):733-8. (PubMed)
3. Fan et al. (2018) Front Physiol. 2018 Jul 16;9:869. (PubMed)
4. Reinhard et al. (2003) Stroke. 2003 Sep;34(9):2138-44. (PubMed)
5. Czosnyka et al. (1996) Stroke. 1996 Oct;27(10):1829-34. (PubMed)
6. Michel et al. (1998) Ultrasound Med Biol. 1998 May;24(4):597-9. (PubMed)
7. Czosnyka et al. (1997) Neurosurgery. 1997 Jul;41(1):11-7; discussion 17-9. (PubMed)
8. Norager et al. (2020) Acta Neurochir (Wien). 2020 Dec;162(12):2983-2989. (PubMed)
9. Forster et al. (2017) J Paediatr Child Health. 2018 Jan;54(1):61-68. (PubMed)

Examples

```
data(testdata)
clinmon(df.data10, variables=c('abp','mcav','hr'), freq=10)
```

---

df.data1000 *Test-data - 1000 Hz*

Description

Recording with four columns: time (`t`), non-invasive arterial blood pressure (`abp`), middle cerebral artery velocity measured using transcranial Doppler (`mcav`), and heart rate (`hr`).

Usage

```
data(testdata)
```

Format

An object of class `"dataframe"`; an example of the usage in `clinmon`-function.

References

Olsen MH et al. (Unpublished data, 2020) (GitHub)

Examples

```
data(testdata)
variables <- c("abp","mcav","hr")
clinmon(df.data1000,variables,fast=50)
```

df.deleter *Test-deleter*

Description

Deleter dataframe with two columns: start (`start`) and end (`end`) of the deleter-period.

Usage

```
data(testdata)
```

Format

An object of class `"dataframe"`; an example of the usage in `clinmon`-function.

References

Olsen MH et al. (Unpublished data, 2020) (GitHub)

Examples

```
data(testdata)
variables <- c("abp","mcav","hr")
clinmon(df.data1000,variables,deleter=df.deleter,fast=50)
```

iscus *ISCUSFlex-values to dataframe (iscus)*

Description

`iscus()` is a function which converts XML files extracted from the Microdialysis-apparatur of ISCUSFlex apparatus to a dataframe.

Usage

```
iscus(filename)
```

Arguments

`filename`	path to the XML-file with the measurements

Value

Returns a dataframe with the measurements.

Examples

```
 ## Not run:
   iscus("C:/ISCUSfiles/7888e844-1c7a-40af-a3f2-3bb27a8dd9e5.xml")

## End(Not run)
```

---

ortable *Logistic regression table with Odds ratio (ortable)*

Description

ortable() is a small function which utilises the output from the glm-function to print a dataframe with odds ratio, confidence limits, and p-values.

Usage

```
ortable(x, d, d_p, intercept, simple)
```

Arguments

x	Utilises the output from a glm-function. (glm-output)
d	Refers to the number of digits for odds ratio and confidence intervals. Default is 2. (numeric)
d_p	Refers to the number of digits for odds ratio and confidence intervals. Default is 3. (numeric)
intercept	The intercept is presented in the table if TRUE. Default is FALSE. (boolian)
simple	Odds ratio and confidence intervals are merged into one column if TRUE. Default is TRUE. (boolian)

Value

Returns a dataframe with with odds ratio, confidence limits, and p-values.

Examples

```
df <- data.frame(outcome=sample(0:1, 100,replace=TRUE),
        var=sample(0:100,100,replace=TRUE))
ortable(glm(outcome ~ ., data=df))
```

PLR3000 *NeurOpticsTM PLR-3000 pupillometer file to dataframe (PLR3000)*

Description

PLR3000() is a function which converts the XLS file imported from the eurOpticsTM PLR-3000 pupillometer to a nested list with two dataframes.

Usage

```
PLR3000(filename = NULL, df = NULL)
```

Arguments

filename	path to the XLS-file with the measurements
df	the dataframe can also be used for the function if data is already imported.

Value

Returns a list with two dataframe, one with the measurements (pupils) and one with the markers (markers).

Examples

```
 ## Not run:
   PLR3000("C:/PLR3000/R_20200105_205901.xls")

## End(Not run)
```

rrGcomp *Relative risk derived by G-computation (rrGcomp)*

Description

rrGcomp() is a small function which generates population-level (marginal) relative risks derived by G-computation. For models with random effects mixed-effects generalized linear model with a logit link with adjustment for stratification variables will be used, while those without random effects a logistic regression will be used. The code is based on the method used in the paper by Dankiewicz et al. (2021) N Engl J Med. Jun 17;384(24):2283-2294. (PubMed

Usage

```
rrGcomp(df, outcome_col, group_col,
fixed_strata = NULL, random_strata = NULL,
nbrIter = 5000, conf_level = 0.95)
```

Arguments

df	the individual participant dataframe
outcome_col	column name for the outcome column
group_col	column name for the group column
fixed_strata	list of column names for the fixed effect stratification columns
random_strata	list of column names for the random effect stratification columns
nbrIter	number of iterations to be used in the G-computation. The original paper used 5000, which is also the default.
conf_level	the confidence level to be reported.

Value

Returns a list with relative risk (rr), simulated rr (simRR), lower- and upper confidence level (simLCL/simUCL), and the p-value (p_val)

Examples

```
df <- sRCT(n_sites=3,n_pop=50)
rrGcomp(df,"outcome","Var1","age","site",10)
```

---

sRCT *simulated Randomised Clinical Trial (sRCT)*

Description

sRCT() is a function which simulates a randomised clinical trial with a binary outome and returns a dataframe. This version is validated to be used for analysis of interaction in a factorial design.

Usage

```
sRCT(part_tbl = NULL, all_sizes = NULL,
n_pop = 100,n_sites = 1,design = c(2,2,2),
rrr = c(0.05,0.05,0), interaction = c(`1<-2` = 0.05, `1<>2` = -0.05),
strata_var = c("age","sex"), strata_site = T,
strata_risk = c(age=0.3,sex=0.5),
outcome_risk = 0.492)
```

Arguments

part_tbl	Here a participation data frame should be imported. [TODO: NOT FUNCTIONAL]
all_sizes	Size of blocks in allocation table. If left empty the three lowest possible block sizes will be randomly assigned.
n_pop	Number of participants included in the trial.

n_sites	Number of sites
design	Number of sites as a list where each element corresponds to an intervention and the number in the element is the number of groups. So for a 2x2 factorial design c(2,2) should be used. [TODO: THREE GROUPS]
rrr	relative risk reduction for each intervention so for the abovementioned 2x2 factorial desing with RRR of 0.05 and 0.10 we would use c(0.05,0.10).
interaction	Interaction between interventions with a named list. If intervention 2 increases the RRR of intervention 1 we would use 1<-2 = 0.05.
strata_var	Variable which would be used for stratification.
strata_site	If randomisation should be stratified by site
strata_risk	The frequency of a dichotomised strata. Named list where the name must correspond to a strata var.
outcome_risk	The baseline risk of the dichotomous primary outcome.

Details

The sRCT function is continuously being developed to answer specific questions in simulation studies. sRCT will be updated and tested for each specific question. For each update the function will be validated for the current purpose and all previous purposes. sRCT is not validated for all simulation studies

Value

Returns a dataframe with an individual participant data frame.

Examples

```
sRCT()
```

---

testdata10 *Test-data - 10 Hz*

Description

Recording with four columns: time (t), non-invasive arterial blood pressure (abp), middle cerebral artery velocity measured using transcranial Doppler (mcav), and heart rate (hr).

Usage

```
data(testdata)
```

Format

An object of class "dataframe"; an example of the usage in clinmon-function.

References

Olsen MH et al. (Unpublished data, 2020) (GitHub)

Examples

```
data(testdata)
variables <- c("abp","mcav","hr")
clinmon(df.data10,variables,freq=10)
```

TFA *Transfer function analysis of dynamic cerebral autoregulation (TFA)*

Description

`TFA()` calculates dynamic cerebral autoregulation trough a transfer function analysis from a *continuous* recording. This function follows the recommendations from Claassen et al. [1] and mimicks the matlab script created by David Simpsons in 2015 (Matlab TFA function). `TFA()` also includes the possibility to analyse raw recordings with application of cyclic (beat-to-beat) average with the possiblity of utilizing interpolation. (see **details**).

Usage

```
TFA(df, variables,
trigger = NULL, deleter = NULL,
freq = 1000, fast = 50, raw_data = FALSE,
interpolation = 3, output = "table",
vlf = c(0.02,0.07),lf = c(0.07,0.2),
hf = c(0.2,0.5), detrend = FALSE,
spectral_smoothing = 3,
coherence2_thresholds = cbind(c(3:15),
c(0.51,0.40,0.34,0.29,0.25,0.22,0.20,0.18,
0.17,0.15,0.14,0.13,0.12)),
apply_coherence2_threshold = TRUE,
remove_negative_phase = TRUE,
remove_negative_phase_f_cutoff = 0.1,
normalize_ABP = FALSE,
normalize_CBFV = FALSE,
window_type = 'hanning',
window_length = 102.4,
overlap = 59.99,
overlap_adjust = TRUE,
na_as_mean = TRUE)
```

Arguments

df	Raw *continuous* recording with numeric data and first column has to be time in seconds. (dataframe)
variables	Definition of the type and order of recorded variables as a list. Middle cerebral artery blood velocity ('mcav') and arterial blood pressure ('abp') is currently supported. (list)
trigger	Trigger with two columns: first is start, and second is end of period to be analyzed. Every row is a period for analysis. Default is NULL, which results in analysis of the full dataframe. (dataframe)
deleter	Deleter with two columns: first is start and second is end of period with artefacts, which need to be deleted. Every row is a period with artefacts. Default is NULL. (dataframe)
freq	Frequency of recorded data, in Hz. Default is 1000. (numeric)
fast	Select if you want the data to aggregated resulting in a faster, but perhaps more imprecise run, in Hz. Default is 50 (numeric)
raw_data	Select TRUE if the data is raw and cyclic mean should be calculated. **NB:** this function have not been validated, why validated methods for calculating cyclic mean are preferred. Only 1 period can be analysed using raw_data. Default is FALSE (boolian)
interpolation	Select the number of beats which should be interpolated. Default is up to 3 beats and 0 results in no interpolation. (numeric)
output	Select what the output should be. 'table' results in a dataframe with values for the three frequencies defined by Claassen et al. [1]; 'long' results in a dataframe with the results in a long format; 'plot' results in a daframe which can help plot gain, phase and coherence; 'plot-peak' results in a dataframe, which can be used to validate the cyclic average, and 'raw' results in a nested list with results primarily for debugging. Default is 'table'. (string)
vlf, lf, hf, detrend, spectral_smoothing, coherence2_thresholds	See **TFA-parameters**
apply_coherence2_threshold, remove_negative_phase	See **TFA-parameters**
remove_negative_phase_f_cutoff, normalize_ABP	See **TFA-parameters**
normalize_CBFV, window_type, window_length, overlap	See **TFA-parameters**
overlap_adjust, na_as_mean	See **TFA-parameters**

Details

Using a *continuous* raw recording, TFA() calculates dynamic cerebral autoregulation trough a transfer function analysis. This function utilizes the recommendations from Claassen et al [1] and mimicks the matlab script created by David Simpsons in 2015.

```
View(data)
```

```
  time   abp   mcav
  7.00    78    45
  7.01    78    46
   ...   ...   ...
301.82    82    70
301.83    81    69
```

To calculate the variables insert the data and select the relevant variables.

```
TFA(df=data, variables=c("abp","mcav"))
```

See **Value** for output description.

Value

`TFA()` returns a dataframe depending on the output selected. `'table'` results in a dataframe with values for the three frequencies defined by Claassen et al. [1]; `'long'` results in a dataframe with the results in a long format; `'plot'` results in a daframe which can help plot gain, phase and coherence; `'plot-peak'` results in a dataframe, which can be used to validate the cyclic average, and `'raw'` results in a nested list with results primarily for debugging.

Some generic variables are listed below:

- `abp_power` - The blood pressure power measured in mmHg^2.
- `cbfv_power` - The cerebral blood flow velocity power measured in cm^2*s^-2
- `coherence` - Coherence.
- `gain_not_normal` - Not normalized gain measured in cm*s^-1*mmHg^-1.
- `gain_normal` - Normalized gain measured in %*mmHg^-1.
- `phase` - Phase measured in radians.

output = 'table':
Wide format output table with period, VLF, LF, and HF as columns, and the TFA-variables as rows.

```
period      variable   vlf    lf    hf
1          abp_power  6.25  1.56  0.21
1         cbfv_power  3.22  2.25  0.30
...              ...   ...   ...   ...
3        gain_normal  1.04  1.48  1.85
3              phase  53.0  25.4  9.38
```

output = 'long':
Long format output table which can be manipulated depending on the intended use, with period, interval, variables and values as columns.

```
 period  interval  variable    values
```

```
  1   hf        abp_power     6.25
  1   hf        cbfv_power    3.22
...   ...       ...            ...
  2   vlf       gain_norm     1.85
  2   vlf       phase         9.38
```

output = 'plot':

Plot format output table which can be used to draw figures with gain, phase and coherence depending on frequency.

```
period  freq  gain  phase  coherence
     1  0.00  0.16   0.00       0.04
     1  0.01  0.29   4.22       0.29
   ...   ...   ...    ...        ...
     2  1.55  1.15  -43.2       0.64
     2  1.56  1.16  -41.1       0.42
```

TFA-paramters

A series of parameters that control TFA analysis (window-length, frequency bands ...). If this is not provided, default values, corresponding to those recommended in the white paper, will be used. These default values are given below for each parameter.

- `vlf` Limits of *very low frequency* band (in Hz). This corresponds to the matematical inclusion of [X:Y[. Default is `c(0.02-0.07)`.
- `lf` Limits of *low frequency* band (in Hz). This corresponds to the matematical inclusion of [X:Y[. Default is `c(0.07-0.2)`.
- `hf` Limits of *high frequency* band (in Hz). This corresponds to the matematical inclusion of [X:Y[. Default is `c(0.2-0.5)`.
- `detrend` Linear detrending of data prior to TFA-analysis (detrending is carried out as one continuous trend over the whole length of the recording, not segment-by-segment). Default is `FALSE`.
- `spectral_smoothing` The length, in samples, of the triangular spectral smoothing function. Note that this must be an odd number, to ensure that smoothing is symmetrical around the centre frequency. Default is `3`.
- `coherence2_thresholds` The critical values (alpha=5%, second column) for coherence for a number of windows (first column, here from 3 to 15). These values were obtained by Monte Carlo simulation, using the default parameter settings for the TFA-analysis (Hanning window, overlap of 50% and 3-point spectral smoothing was assumed). These values should be recalculated for different settings. Note that if `overlap_adjust=TRUE`, the overlap will vary depending on the length of data. With an overlap of 60% (see below), the critical values increase by between 0.04 (for 3 windows) and 0.02 (for 15 windows). Default is cbind(c(3:15),c(0.51,0.40, 0.34,0.29,0.25,0.22,0.20,0.18,0.17, 0.15,0.14,0.13,0.12)).
- `apply_coherence2_threshold` Apply the thresholds given above to the TFA-estimates. All frequencies with magnitude-squared coherence below the threshold value are excluded from

averaging when calculating the mean values of gain and phase across the bands. Note that low values of coherence are not excluded in the average of coherence across the bands. Default is TRUE.

- remove_negative_phase Remove (ignore) negative values of phase in averaging across bands. Negative phase values are removed only for frequencies below the frequency given below, when calculating the average phase in bands. Default is TRUE.
- remove_negative_phase_f_cutoff The cut-off frequency below-which negative phase values are neglected (only if remove_negative_phase is TRUE). Default is 0.1.
- normalize_ABP Normalize ABP by dividing by the mean and multiplying by 100, to express ABP change in %. Note that mean-values are always removed from ABP prior to analysis. Default is FALSE.
- normalize_CBFV Normalize CBFV by dividing by the mean and multiplying by 100, to express CBFV change in %. Note that the band-average values of gain are always calculated both with and without normalization of CBFV, in accordance with the recommendations. Note also that mean-values are always removed from CBFV prior to analysis. Default is FALSE.
- window_type Chose window 'hanning' or 'boxcar'. Default is 'hanning'.
- window_length Length of the data-window, in seconds. Default is 102.4.
- overlap Overlap of the windows, in %. If overlap_adjust is TRUE (see below), then this value may be automatically reduced, to ensure that windows cover the full length of data. Default is 59.99% rather than 60%, so that with data corresponding to 5 windows of 100 s at an overlap of 50%, 5 windows are indeed chosen.
- overlap_adjust Ensure that the full length of data is used (i.e. the last window finishes as near as possible to the end of the recording), by adjusting the overlap up to a maximum value given by params.overlap. Default is TRUE.
- na_as_mean Changes all missing non-interpolated values to the mean value of the corresponding variable. This have not been adressed in the paper by Claassen, and to ensure the dataframes are not 'gathered' this should generate the most stable results. Default is TRUE.

References

1. Claassen et al. (2016) J Cereb Blood Flow Metab. 2016 Apr;36(4):665-80. (PubMed)

Examples

```
data(tfa_sample_data)
TFA(tfa_sample_data[,c(1:3)], variables=c("abp","mcav"), freq=10)
```

---

tfa_sample_data *TFA sample data*

Description

Dataframe with data provided by Prof. Simpsons, with time (t), arterial blood pressure (abp), left MCAv (mcav_l), right MCAv (mcav_r), and end-tidal CO2 (etco2).

Usage

```
data(tfa_sample_data)
```

Format

An object of class "dataframe"; an example of the usage in TFA-function.

Source

GitHub

References

- Simpsons D (2015) (Cerebral Autoregulation Research Network)
- Claassen et al. (2016) J Cereb Blood Flow Metab. 2016 Apr;36(4):665-80. (PubMed)

Examples

```
data(tfa_sample_data)
TFA(tfa_sample_data[,c(1:3)], variables=c("abp","mcav"), freq=10)
```

---

tfa_sample_data_1 *TFA sample data - 1*

Description

Dataframe with data provided by Prof. Simpsons, with time (t), arterial blood pressure (abp), left MCAv (mcav_l), right MCAv (mcav_r), and end-tidal CO2 (etco2).

Usage

```
data(tfa_sample_data)
```

Format

An object of class "dataframe"; an example of the usage in TFA-function.

Source

GitHub

References

- Simpsons D (2015) (Cerebral Autoregulation Research Network)
- Claassen et al. (2016) J Cereb Blood Flow Metab. 2016 Apr;36(4):665-80. (PubMed)

Examples

```
data(tfa_sample_data)
TFA(tfa_sample_data_1[,c(1:3)], variables=c("abp","mcav"), freq=10)
```

`tfa_sample_data_2` *TFA sample data - 2*

Description

Dataframe with data provided by Prof. Simpsons, with time (t), arterial blood pressure (abp), left MCAv (mcav_l), right MCAv (mcav_r), and end-tidal CO2 (etco2).

Usage

```
data(tfa_sample_data)
```

Format

An object of class `"dataframe"`; an example of the usage in `TFA`-function.

Source

GitHub

References

- Simpsons D (2015) (Cerebral Autoregulation Research Network)
- Claassen et al. (2016) J Cereb Blood Flow Metab. 2016 Apr;36(4):665-80. (PubMed)

Examples

```
data(tfa_sample_data)
TFA(tfa_sample_data_2[,c(1:3)], variables=c("abp","mcav"), freq=10)
```

Index

14.6 Reliability of non-invasive arterial blood pressure measurement

unpublished findings

Background

Invasively measured arterial blood pressure (ABP) is associated with complications, while non-invasively measure ABP is in general risk free. This study aimed to investigate the reliability of non-invasive ABP measured using photoplethysmography compared to invasive ABP measured through an arterial cannula in patients with aneurysmal subarachnoid haemorrhage (SAH).

Methods

In 30 patients with SAH, invasive and non-invasive ABP recorded were simultaneously. Reliability was assessed for mean, diastolic and systolic ABP separately using intraclass correlation coefficient (ICC) for both each full period and for each 3 second average.

Results

A median of 3 (interquartile range: 2-3.75) recordings were included for each participant. The full periods (n = 85) showed an ICC of 0.17 (95% confidence interval (CI): 0.00-0.36), 0.10 (95% CI: 0.00 to 0.31), and 0.16 (95% CI: 0.00 to 0.35) (**Figure 12**) for mean, diastolic, and systolic ABP, respectively. Three second averages (n = 33,786) for mean (ICC: 0.29; 95% CI: 0.28 to 0.31), diastolic (ICC: 0.18; 95% CI: 0.17 to 0.19), and systolic ABP (ICC: 0.27; 95% CI: 0.19 to 0.34) yielded similar findings (**Figure 13**).

Conclusions

Non-invasive ABP measurements showed poor reliability in patients with SAH and cannot be used interchangeably with invasive ABP in this population. Infections such as sepsis with cold fingers and localised oedema can be some important confounders.

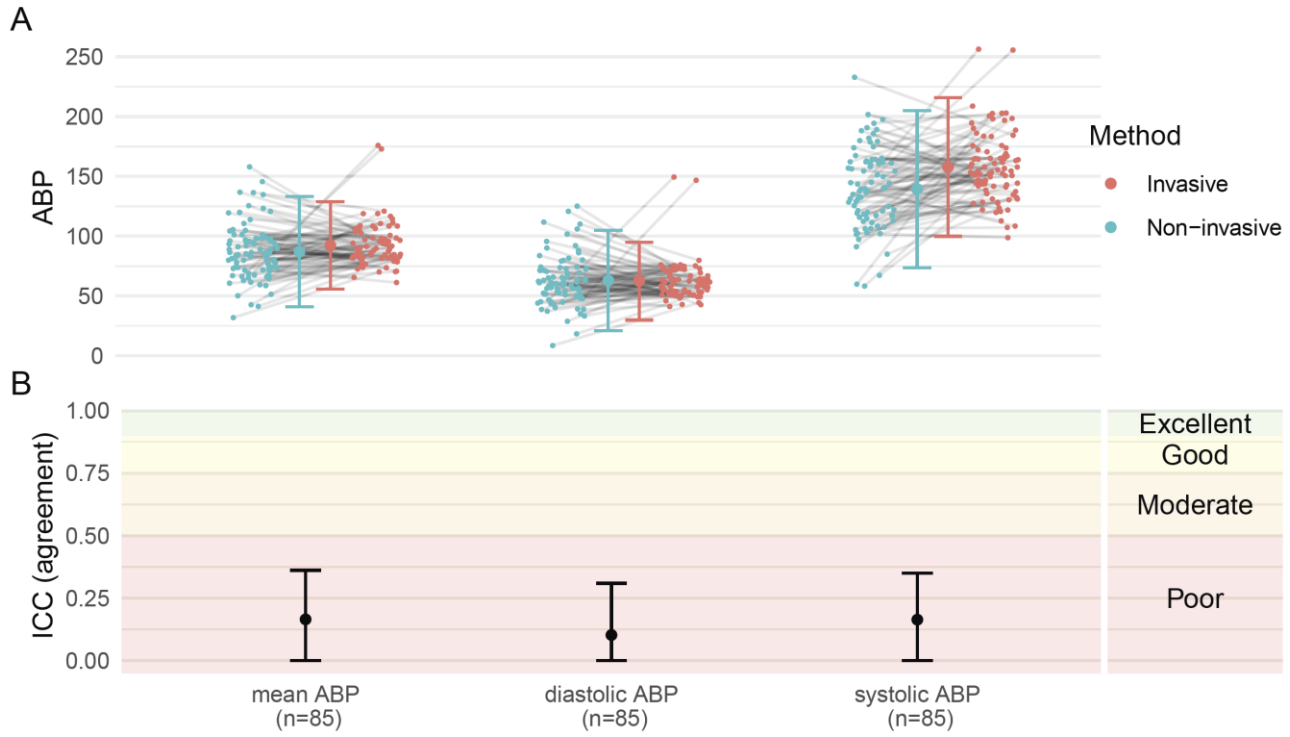

Figure 12 - The reliability of non-invasive ABP for mean, diastolic and systolic ABP for each period, (**A**) with every pressure measurement, and (**B**) the reliability, i.e. comparability, between the compared pressure measurements. ABP: arterial blood pressure; ICC: Intraclass correlation coefficient.

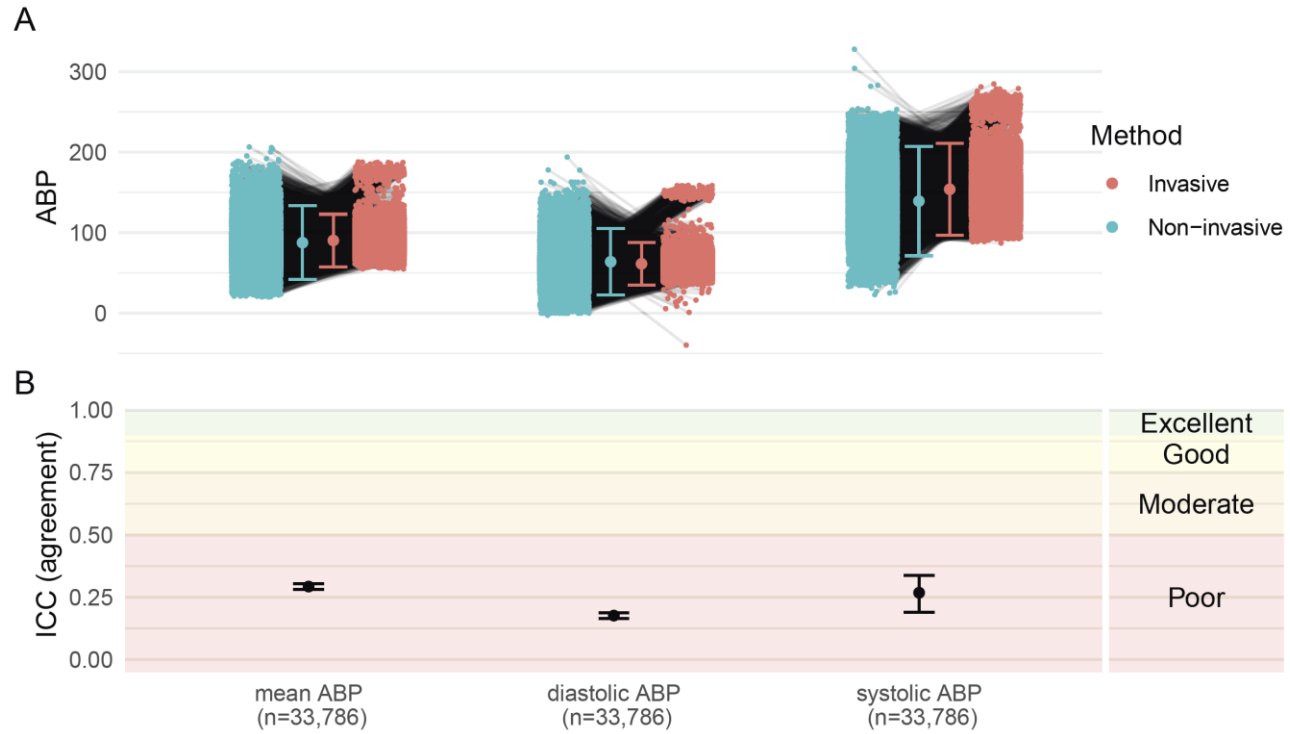

Figure 13 - The reliability of non-invasive ABP for mean, diastolic and systolic ABP for 3 second averages, (**A**) with every pressure measurement, and (**B**) the reliability, i.e. comparability, between the compared pressure measurements. ABP: arterial blood pressure; ICC: Intraclass correlation coefficient.

14.7 Diagnostic and prognostic performance of transfer function analysis (TFA)

unpublished findings

Background

Transfer function analysis (TFA) can be applied to simultaneously recorded arterial blood pressure (ABP) and middle cerebral artery velocity measurements. This analysis is widely used to assess dynamic cerebral autoregulation. The present study investigated whether different TFA measures differ between healthy volunteers and different patient, and furthermore whether populations TFA measures provide prognostic information in relation to functional outcome and/or mortality.

Methods

We included recordings from 48 healthy volunteers, 19 patients with sepsis, 36 patients with traumatic brain injury (TBI), 44 patients with aneurysmal subarachnoid haemorrhage (SAH), and 14 patients admitted to a neurorehabilitation unit after severe non-traumatic or traumatic brain injury. Normalised and non-non-normalised gain and phase in the low frequency domain was investigated as markers of dynamic cerebral autoregulation. The diagnostic (between healthy volunteers and patients) and prognostic performance (to predict death or poor functional outcome) of normalised and non-normalised gain was assessed by area under the receiver-operating characteristic (AUROC) curves.

Results

The diagnostic performance of normalised gain for TBI and SAH showed low to moderate accuracy, while non-normalised gain showed low to moderate accuracy for all the different patient populations. Phase showed low to moderate accuracy for sepsis and SAH (**Figure 14**). The prognostic performance for all the measures ranged from ‘no better than chance’ to low accuracy (**Figure 15**).

Conclusions

The diagnostic performance of TFA measures showed promise in being able to distinguish between healthy volunteers and those with acute brain injury. However, the TFA measures do not appear to be suitable for prognostication in any of the investigated patient populations.

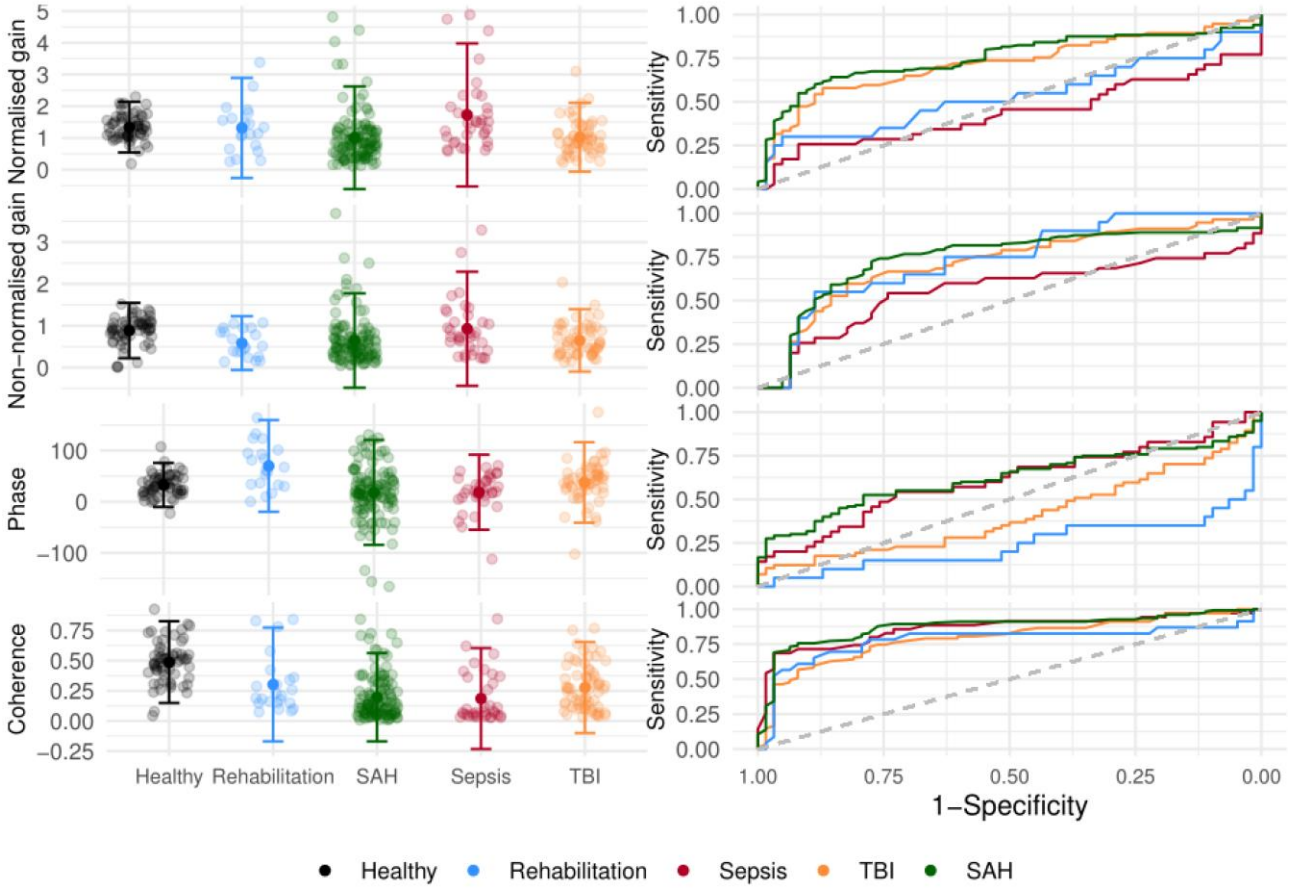

Figure 14 - The average and confidence interval for different TFA measures for each population (*left column*), and a receiver operating characteristics curve for each of the populations with healthy volunteers as comparators (*right column*).

Appendices

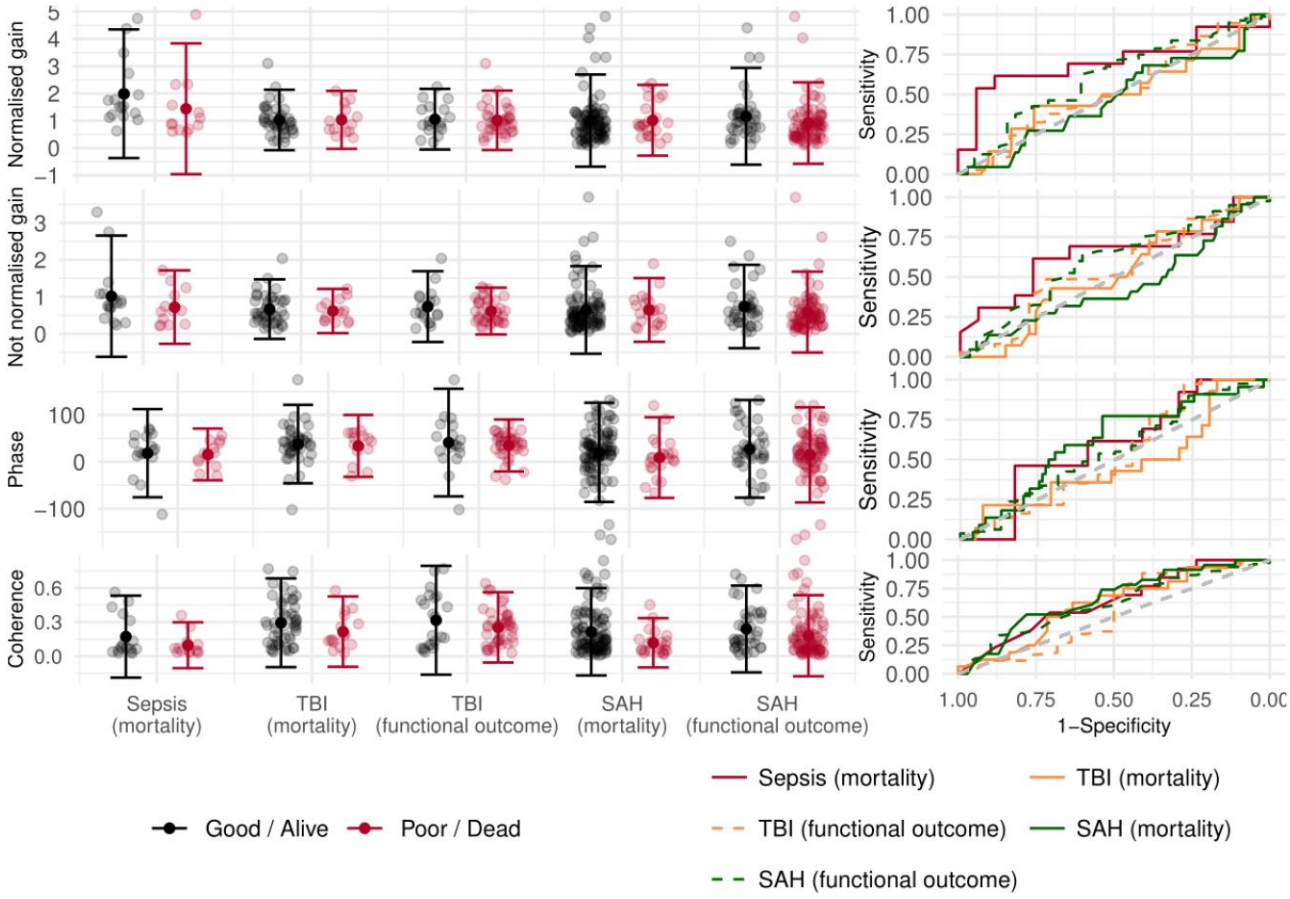

Figure 15 - The average and confidence interval for different TFA measures for each population (*left column*), and a receiver operating curves with a good outcome or survival as comparators, and the ability of TFA measures to predict mortality or poor outcome in patients with sepsis, subarachnoid haemorrhage (SAH), and traumatic brain injury (TBI), respectively. *(right column*).

14.8 Declarations of co-authorship

DECLARATION OF CO-AUTHORSHIP

The declaration is for PhD students and must be completed for each conjointly authored article. Please note that if a manuscript or published paper has ten or less co-authors, all co-authors must sign the declaration of co-authorship. If it has more than ten co-authors, declarations of co-authorship from the corresponding author(s), the senior author and the principal supervisor (if relevant) are a minimum requirement.

1. Declaration by	
Name of PhD student	Markus Harboe Olsen
E-mail	markus.harboe.olsen@regionh.dk
Name of principal supervisor	Kirsten Møller
Title of the PhD thesis	The mean flow index: the Emperor's new clothes?

2. The declaration applies to the following article	
Title of article	Reliability and validity of the mean flow index (Mx) for assessing cerebral autoregulation in humans: A systematic review of the methodology
Article status	
Published ☒ Date: 19.09.2021	Accepted for publication ☐ Date:
Manuscript submitted ☐ Date:	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	J Cereb Blood Flow Metab, 2022, **42,** 27–38, DOI: 10.1177/0271678X211052588

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A.** Has essentially done all the work (> 90 %) **B.** Has done most of the work (60-90 %) **C.** Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
1. Formulation/identification of the scientific problem	A
2. Development of the key methods	B

3. The PhD student's contribution to the article *(please use the scale A-F as benchmark)* Benchmark scale of the PhD-student's contribution to the article **A.** Has essentially done all the work (> 90 %) **B.** Has done most of the work (60-90 %) **C.** Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
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4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	B
5. Conducting the analysis of data	B
6. Interpretation of the results	B
7. Writing of the first draft of the manuscript	B
8. Finalisation of the manuscript and submission	B

Provide a short description of the PhD student´s specific contribution to the article.[i]

Markus Harboe Olsen (MHO) identified the issue, and all co-authors collaborated in the design of the study. MHO wrote initial draft of protocol, and conducted the majority of data collection, analyses, and interpretations. MHO wrote the initial draft, and all co-authors critically revised manuscript before submission.

4. Material from another thesis / dissertation[ii]	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	
If the article is part of another author's academic degree, please describe the PhD student´s and the author´s contributions to the article so that the individual contributions are clearly distinguishable from one another.	

5. Signatures of the co-authors[iii]				
	Date	**Name**	**Title**	**Signature**
1.	17.01.2022	Christian Gunge Riberholt	PT, PhD	

5. Signatures of the co-authors[iii]				
2.	28.01.2022	Jesper Mehlsen	MD	
3.	17.01.2022	Ronan MG Berg	MD, DMSc	
4.	28.01.2022	Kirsten Møller	MD, DMSc	
5.				
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7.				
8.				
9.				
10.				

6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.

Date: 28.01.2022

Principal supervisor:

7. Signature of the PhD student

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.

Date: 28.01.2022

PhD student:

Please learn more about responsible conduct of research on the Faculty of Health and Medical Sciences' website.

[i] This can be supplemented with an additional letter if needed.

[ii] Please see Ministerial Order on the PhD Programme at the Universities and Certain Higher Artistic Educational Institutions (PhD Order) § 12 (4):

"Any articles included in the thesis may be written in cooperation with others, provided that each of the co-authors submits a written declaration stating the PhD student's or the author's contribution to the work."

[iii] If more signatures are needed please add an extra sheet.

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Name of PhD student	Markus Harboe Olsen
E-mail	markus.harboe.olsen@regionh.dk
Name of principal supervisor	Kirsten Møller
Title of the PhD thesis	The mean flow index: the Emperor's new clothes?

2. The declaration applies to the following article	
Title of article	Reliability of the mean flow index (Mx) for assessing cerebral autoregulation in healthy volunteers
Article status	
Published ☒ Date: 17.05.2021	Accepted for publication ☐ Date:
Manuscript submitted ☐ Date:	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	Physiological reports, 2021, **9**, e14923, DOI: 10.14814/phy2.14923

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4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	C
5. Conducting the analysis of data	B
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7. Writing of the first draft of the manuscript	B
8. Finalisation of the manuscript and submission	B
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4. Material from another thesis / dissertation[ii]	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	
If the article is part of another author's academic degree, please describe the PhD student´s and the author´s contributions to the article so that the individual contributions are clearly distinguishable from one another.	

5. Signatures of the co-authors[iii]				
	Date	**Name**	**Title**	**Signature**
1.	17.01.2022	Christian Gunge Riberholt	PT, PhD	

5. Signatures of the co-authors[iii]				
2.	27.01.22	Ronni R. Plovsing	MD, PhD	
3.	27.01.2022	Kirsten Møller	MD, DMSc	
4.	17.01.2022	Ronan MG Berg	MD, DMSc	
5.				
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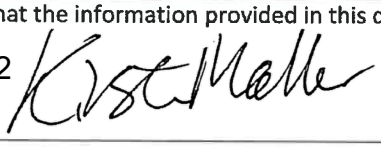
6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.

Date: 27.01.2022
Principal supervisor: 

7. Signature of the PhD student

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Date: 27.01.2022
PhD student: 

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E-mail	markus.harboe.olsen@regionh.dk
Name of principal supervisor	Kirsten Møller
Title of the PhD thesis	The mean flow index: the Emperor's new clothes?

2. The declaration applies to the following article	
Title of article	Reliability of cerebral autoregulation using different measures of perfusion pressure in patients with subarachnoid haemorrhage.

Article status	
Published ☐ Date:	Accepted for publication ☐ Date:
Manuscript submitted ☒ Date: 15.01.2022	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
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2. Development of the key methods	B
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5. Conducting the analysis of data	A
6. Interpretation of the results	B
7. Writing of the first draft of the manuscript	B
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5. Signatures of the co-authors[iii]				
	Date	**Name**	**Title**	**Signature**
1.	18.01.22	Tenna Capion	MD	Tenna Capion

5. Signatures of the co-authors[iii]				
2.	17.01.2022	Christian Gunge Riberholt	PT, PhD	
3.	17.01.2022	Søren Bache	MD, PhD	
4.	17.01.2022	Ronan MG Berg	MD, DMSc	
5.	27.01.2022	Kirsten Møller	MD, DMSc	
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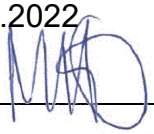
I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge. Date: 27.01.2022 Principal supervisor: 

7. Signature of the PhD student
I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge. Date: 18.01.2022 PhD student: 

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Name of principal supervisor	Kirsten Møller
Title of the PhD thesis	The mean flow index: the Emperor's new clothes?

2. The declaration applies to the following article	
Title of article	Diagnostic and prognostic performance of arterial pressure-derived mean flow index (Mxa): the influence of data pre-processing.
Article status	
Published ☐ Date:	Accepted for publication ☐ Date:
Manuscript submitted ☒ Date: 21.09.2021	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	

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2. Development of the key methods	B
3. Planning of the experiments and methodology design and development	B

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5. Conducting the analysis of data	B
6. Interpretation of the results	B
7. Writing of the first draft of the manuscript	B
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5. Signatures of the co-authors[iii]				
2.	27.01.22	Ronni R. Plovsing	MD, PhD	
3.	17.01.2022	Ronan MG Berg	MD, DMSc	
4.	27.01.2022	Kirsten Møller	MD, DMSc	
5.				
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10.				

6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.

Date: 27.01.2022
Principal supervisor:

7. Signature of the PhD student

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.

Date: 27.01.2022

PhD student:

Please learn more about responsible conduct of research on the Faculty of Health and Medical Sciences' website.

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