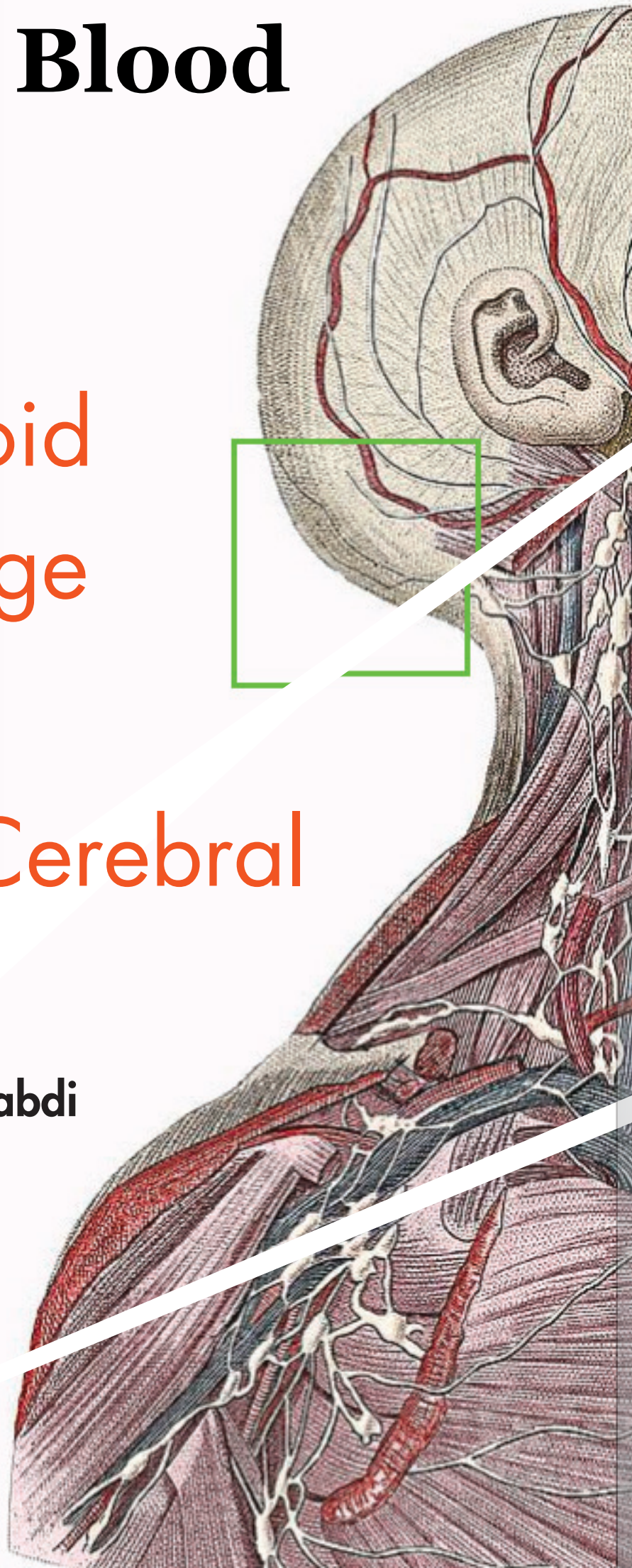


Title	Trends in blood pressure: following subarachnoid haemorrhage and preceding cerebral vasospasm
Authors	Abdulghani Binabdi, Ali
Publication date	2021
Original Citation	Abdulghani Binabdi, A. (2021) 'Trends in blood pressure: following subarachnoid haemorrhage and preceding cerebral vasospasm', UCC Student Medical Journal, Vol. 2, pp. 49-65. https://doi.org/10.33178/SMJ.2021.1.5
Type of publication	Peer-reviewed Article
Link to publisher's version	https://journals.ucc.ie/index.php/smj/article/view/4317/6477 - 10.33178/SMJ.2021.1.5
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Download date	2026-10-26 23:22:20
Item downloaded from	https://hdl.handle.net/10468/16557

Trends in Blood Pressure:

Following
Subarachnoid
Haemorrhage
and
Preceding Cerebral
Vasospasm

by Ali Abdulghani Binabdi





Abstract

Background

Trends in Blood Pressure (BP) following Subarachnoid Haemorrhage (SAH) have been reported in literature since 1982 (1). Recent studies suggest a correlation to the incidence of Cerebral Vasospasm (2, 3). This renders BP a candidate for possible early detection of Vasospasm. However, conflicting results regarding the nature and numerical of this correlation exist.

Objectives

To determine trends in BP following SAH in terms of Systolic (SBP), Diastolic (DBP) and Mean Arterial Pressure (MAP) and collaborate current literature evidence of their association to Cerebral Vasospasm.

Methods

Two databases (EBSCO Medline and PubMed) systematically reviewed using specified search criteria. Thirteen studies were portrayed, of which ten were accessible. Thorough critical appraisal of each paper was then manually performed using the CASP Cohort study checklist.

Results

A consistent pattern of change is seen through time in majority of studies with differences in the definite values of the BP variables. Collation of results showed a gradual rise in SBP followed by a plateau of $154.08 (\pm 10.79)$ mmHg on days 4-8 post-SAH. Variations exist with regards to the association with Cerebral Vasospasm: a third of the studies depicted a significant steeper rise in SBP in Vasospasm patients (1-3), another third conversely reported sudden drops in SBP (4-6), and one study concluded that MAP has no significant relation to Vasospasm (7).

Conclusion

A biphasic trend is expected following SAH with an initial gradual rise followed by a sustained hypertensive plateau. Considerable conflict exists in the nature of association between BP and Vasospasm. Further analysis of such beneficial predictive potential is recommended for advancement in Vasospasm and Neuro-Cardiogenic care.

Literature Reviews

Introduction

Cerebral Vasospasm is defined as the narrowing of the large and medium intra-cranial arteries. It is a major complication following Subarachnoid Haemorrhage (SAH) occurring in up to half of successfully treated SAHs and is responsible for 20% of deaths and serious neurological deficit (8-10); and is still of unclear aetiology (11). Its incidence is sudden and usually presents within the first 4-9 days after SAH without any preceding signs or symptoms (12). Diagnosis is usually confirmed via the gold standard invasive CT angiography after which, various treatment approaches are initiated to salvage adequate cerebral perfusion (13). Several efforts have been made to identify potential factors that may be used for early detection of Vasospasm; however, it remains one of the major challenges in Neuro-intensive care (14). Recent trials include the use of continuous EEG monitoring, measuring CSF glutamate and serum S100 Biomarkers, regular Transcranial Doppler (TCD) ultrasonography imaging, or Motor Evoked Potentials (13, 15-17); none of which proved significant and practical enough for their application.

Fluctuations in Blood Pressure (BP) following SAH have been reported in early studies rendering them a candidate for possible detection of Vasospasm (1). A recent German study (2), targeted specifically at this association, reported spontaneous changes in BP as early as day 4 post-operation to be correlated with the incidence of vasospasm. Arterial BP is a routine measurement in all post-operative SAH patients, the presence of correlation with Vasospasm may suggest a non-invasive, easily accessible, and cost-effective strategy to sensitise healthcare and guide prophylactic measures. Detecting specific changes in either Systolic, Diastolic or Mean Arterial Pressure may also aid in the understanding of the underlying pathophysiology and development of new treatments (2).

Objectives

This systematic review seeks to condense and appraise existing literature on the relationship between BP and Cerebral Vasospasm following SAH through the following objectives:

1. Determine the trends in BP after SAH with regards to SBP, DBP, and MAP.
2. Analyse current evidence on the relationship of BP to the incidence of Cerebral Vasospasm

Methodology

Search Strategy

On the 3rd of January 2020, electronic searches were conducted in EBSCO MEDLINE and PubMed to retrieve all relevant articles that will achieve the objectives of this review.

The following search criteria was finalised:

- In EBSCO MEDLINE (<https://www.ebsco.com/products/research-databases/medline>) with the aid of MeSH Terms:
 - I. Blood Pressure
(MM "Blood Pressure+") OR
(MM "Arterial Pressure") OR (MM "Venous Pressure+") [All Fields]
AND
 - II. Subarachnoid Haemorrhage
(MM "Subarachnoid Hemorrhage+") OR (MM "Subarachnoid Hemorrhage, Traumatic")
[All Fields]

Initial search yielded 94 articles. 74 articles were obtained after application of language and human subject filters.

- In PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) with the aid of MeSH Terms:
 - III. Blood Pressure
Blood Pressure[Title/Abstract]
AND

IV. Subarachnoid Haemorrhage
Subarachnoid *morrhage[Title/
Abstract] OR "subarachnoid hem-
orrhage"[MeSH Terms]

Initial search yielded 674 articles. 472
articles were obtained after application of
language and human subject filters.

Equations generated by EBSCO MEDLINE and
PubMed are found in Appendix A.

Selection Criteria

Table 2 lists the inclusion and exclusion crite-
ria applied in this review.

Selection Process

Due to the limited number of results, the
timeframe for the published articles was not
restrained to avail all the relevant literature
possible.

Articles involving drug trials were excluded
to avoid the effect of drug therapy on the BP
trend observed. Articles that merely analysed
BP within the first 24 hours were excluded to
avoid unnecessary analysis not aiding Va-

sospasm prediction; along the same basis,
articles that initiated analysis more than 4
days after SAH were deemed inaccurate for
this review as uncertainty will retain on wheth-
er Vasospasm has already onset.

Thorough screening eventually yielded 5
articles from Medline and 12 from PubMed;
upon removal of duplicates, 13 articles were
drawn. Three of the resulting articles were
denied access and required paid subscrip-
tions, yielding a total of 10 articles for analy-
sis.

Critical appraisal and analysis

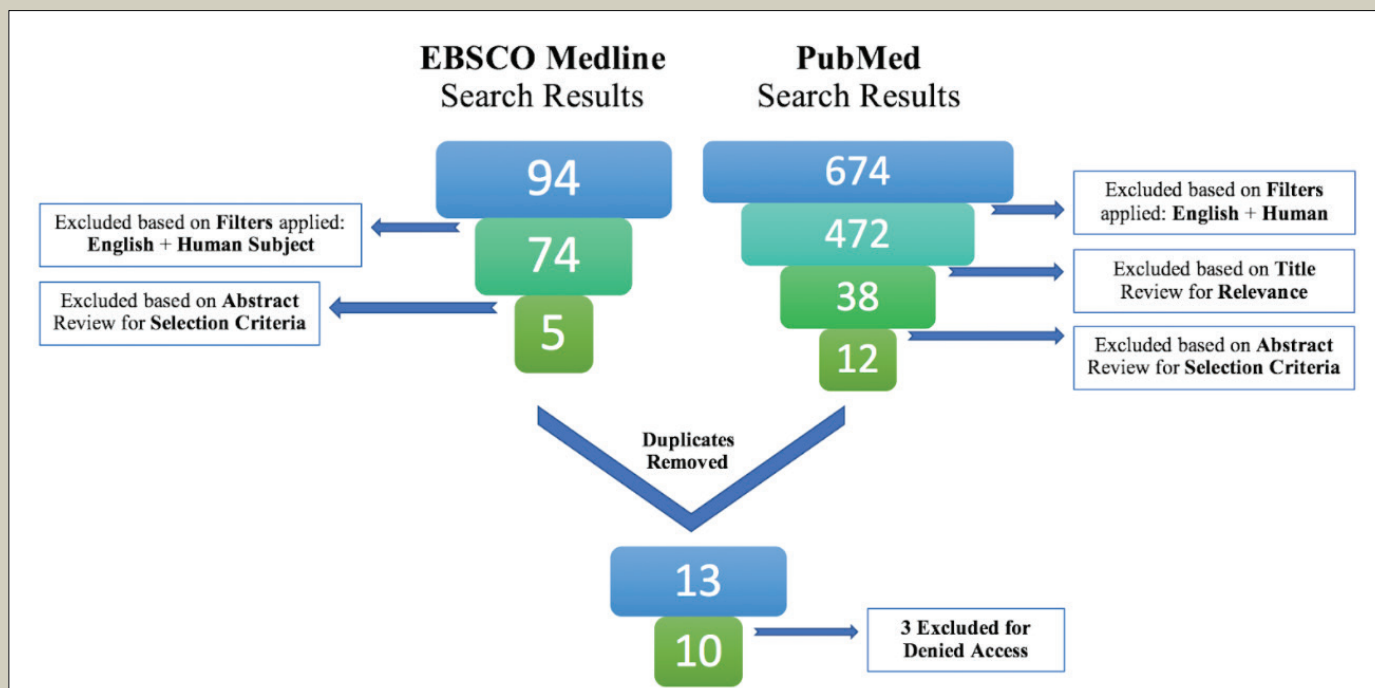
The 10 articles were then thoroughly read and
critically appraised using the CASP Cohort
Study checklist (20). Although the tool does
not provide quantitative analysis to papers’
validity, its use was preferred as it avails the
option to annotate and encourage reasoning
for each analytic answer to the paper’s ac-
curacy and findings. It is also appropriate for
cohort studies given that all our search results
have a cohort study design.

*Table (4) found in Appendix B summarizes the
Yes/No answers to the CASP checklist for the
10 reviewed articles.*

Inclusion Criteria	Exclusion Criteria
Studied SAH patients	Involved drug trials
Recorded BP measurements of either SBP, DBP or MAP as a variable	Evaluated unconscious/comatose/vegetative patients
Conducted on human population	Analysed BP before the incidence of SAH
Available in English	Analysed ≤24 hrs of BP after SAH
	Started BP analysis > 4 days after SAH onset
	Not accessible even through the UCC portal
	Studies conducted on animal populations

Table 2: Inclusion and Exclusion Criteria

Literature Reviews



Data of daily BP measurements provided by 3 studies was extracted and inputted into an Excel spreadsheet for production of a collated line graph and to facilitate visual and mathematical analysis of BP trends (refer to Figure 2 in Section 4.2).

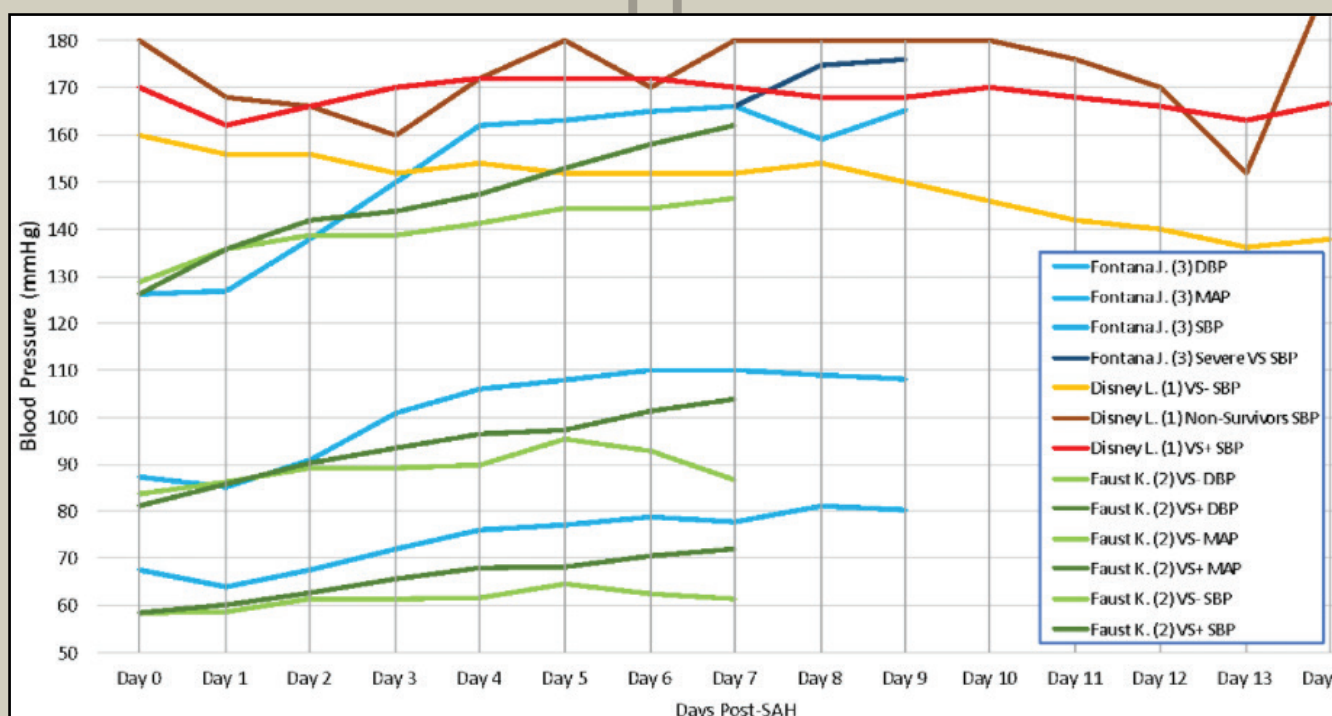
Results

Summary table of results

Refer to Appendix C

Presentation of results

All 10 articles analysed BP trends after SAH to an extent: 3 of which provided daily readings (extrapolated into the results line graphs, Fig.2 (1-3)), 2 emphasised specific changes in SBP (5) or MAP (21) in terms of magnitude and frequency, and 7 attempted to analyse BP in terms of prediction of Cerebral Vasospasm (1-7). Analysis and results of 2 studies focused on presenting the complexity, variability and Time-Frequency analysis of BP and did not provide absolute BP values (18, 19); hence, they were not very specific to the objective of



Blood pressure trends following SAH

The majority (62.5%) of the studies reported rises in SBP and an equivalent reported MAP but only a minority (25%) reported DBP trends. Each variable differs significantly between the studies with SBP ranging between 126.04mmHg (2) and 180mmHg (1) on Day 0 (day of SAH), MAP between 81.25mmHg (2) and 122.824mmHg (4), and DBP between 58.32mmHg (2) and 67.76mmHg (3) (refer to Fig.2).

Fontana et al. (3) and Faust et al. (2) agree that a gradual rise is seen amongst the BP variables as the days progress after SAH, while Disney et al. (1) depict that an initial fall is seen in Day 1 followed by a gradual rise to Day 8 and a subsequent gradual fall afterwards. The plateau seen between Day 4 and 7 is consistent with the findings of Teping et al. (21) where Endogenous Persistent Hypertension of MAP > 117.16 ($\pm$ 9.92) mmHg was noted at a greater frequency in Phase 2 of their study period (Days 4-14). Tabuchi et al. (5), on the other hand, annotated spontaneous falls in SBP defined as drops of > 40 mmHg mostly seen in Days 2-5 and Days 7-17; both of which are inconsistent with the line graphs illustrated.

Blood pressure and cerebral vasospasm prediction

The correlation between BP and Cerebral Vasospasm was depicted in all but one study (21) which analysed Delayed Cerebral Ischaemia without specifying if associated to Vasospasm or not. One third of the studies (1-3) agree that a significant steeper rise in SBP is seen in Vasospasm patients. This is seen as early as Day 3 by Disney et al. (1), who also emphasise that the increase in BP precedes the onset of clinical symptoms; Day 6 (SBP) and Day 4 (MAP) by Faust et al. (2), who also claim that >20% rise in MAP provides a Positive Predictive Value (PPV) of 86%. Fontana et al. (3) illustrated a secondary Norepinephrine (NE) independent rise in SBP seen in patients with severe global Vasospasm as shown between Days 8-9 in Figure 2.

In contrast, another third of these studies

demonstrated a drop in BP as a predictor of vasospasm (4-6). Yarlagadda et al. (6) reported that a drop of SBP below 130 mmHg in Day 5 post-SAH is associated with death (OR=6.7) which coincides within the "clinical window" of Cerebral Vasospasm. Tabuchi et al. (5) evoke that 70.4% of the spontaneous falls in SBP recorded were significantly associated with symptomatic Vasospasm, 22% of which occurred before the incidence. Roederer et al. (4), however, only elicit the association of MAP on Day 1 post-SAH and claim that MAP of 107.524mmHg (CI=2.99-27.72) has a better PPV and sensitivity than TCD imaging in predicting Vasospasm. Placek et al. (18) and Soehle (19) report opposing results arguing an increase or decrease in complexity of BP during Vasospasm. In contrast to all of the other studies, Kirkness et al. (7) concluded that MAP (both level and variability) measured over 4 days has no significant relation to Vasospasm.

Discussion

Blood pressure trends following SAH

Trends in BP following SAH have been elicited across clinical and physiological studies since the early 1980s and as shown by this review, BP fluctuations are inevitable and vary despite rigorous control (1). In this discussion, the time period following SAH is divided into 2 phases as done by Teping et al. (21) to facilitate analysis: Phase 1 (Day 0-3), and Phase 2 (Days 3-14). A conflict is seen from Day 0 of Phase 1 between the results of Disney et al. (1) and the results of Fontana et al. (3) and Faust et al. (2) (Fig.2) where the former claim a significantly higher SBP that remains at a mean SBP of (156 $\pm$ 3.02) mmHg throughout the first phase. The 3 eventually conjoin at the start of Phase 2 with a noticeable steeper rise in Fontana et al. (3).

Given the limitations of the study by Disney et al. (1) in neglecting vital confounding consideration such as Vasopressor Therapy, application of Nimodipine, history of hypertension, sedation level etc. and the fact that only 24% of the proposed sample had available records

Literature Reviews

gives a potential for sampling and confounding bias. It is also worth noting the age of the study (1989) which although limits its available technology, sets a basis for all present studies in SAH and BP association.

The steeper and more pronounced rise between Days 1-5 seen in Fontana et al. (3) can be explained by its strict yet plausible control in its study design; it is the only prospective study and controlled for all aforementioned confounding including the restriction of standard Nimodipine prophylaxis (22). As one of the most recent available research, with its multi-level quality assurance in terms of comprehensive measure of exposure and outcome and analytical testing, its relevance and viability are greatly strengthened. The only limitations encountered were the relatively small sample and the undisclosed mode of treatment.

Despite the relatively less pronounced rise seen with Faust et al. (2), it provides a more accurate reflection of the actual ICU setting, where prophylactic Nimodipine is applied and various covariables matched for to ensure reliability. The study provides promising results in predicting Vasospasm as will be seen in the next section. The sample was larger and included patients from both surgical and endovascular SAH treatment, providing significant level of evidence. Both studies (2,3) provide substantial evidence for a relatively normotensive BP on Day 0 that rises within the next few days to reach a plateau of (154.08 ± 10.79) mmHg between Days 4-8. Disney et al. (1) also remains within proximal statistical range throughout this period.

Spontaneous blood pressure increases (SBI) as well as prolonged Endogenous Persistent increases (EPI) are seen by Teping et al. (21) - detected across all phases but predominantly during Phase 2. The quality assurance strategies with regards to visual cross-checking for artefacts, frequent exposure measure, comprehensive confounding analysis and evidential exclusion criteria avail a significant result that cannot be overlooked. In addition

to its alignment to the results above in terms of temporal distribution of BP rises, Teping et al. (21) evoke a disparity in BP regulation that was merely hypothesised in other studies (1-3); The difference in timing seen in SBI and EPI suggests that the initial response to demand and the capacity to sustain this response are not necessarily interchangeable. On the contrary, sudden falls (rather than rises) in SBP are depicted by Tabuchi et al. (5) predominantly in Phase 2. However, considering that only 41.6% of their sample experienced these falls and given the old sample set (1987-1996) relative to the date of the study (2006), the low prevalence and historical changes in management and recording of data provide an unavoidable level of inaccuracy. It is also worth noting that the biological plausibility of the study is based on non-human experiments. Nevertheless, since the hypotensive effect is claimed to be seen even after aggressive volume resuscitation, analysis of falls is recommended to be in consideration in future research.

Blood pressure and cerebral vasospasm prediction

With regards to Cerebral Vasospasm prediction, promising results are seen by Disney et al. (1), Faust et al. (2) and Fontana et al. (3); a statistically significant rise in SBP is associated with Vasospasm in all three. Faust et al. (2) studied a German sample of 98 patients and was particularly targeted at finding the predictive value of BP changes to Vasospasm incidence. It concluded that a 20% elevation in MAP is sufficient to sensitise care into anticipating Vasospasm. However, the study was limited to retrospective analysis and matching for confounding factors, confounding randomisation in future prospective studies is recommended to increase diagnostic specificity.

A year later, Fontana et al. (3) revealed similar promising results, also in a German sample of 61 patients, with higher accuracy through eliminating most potentially influencing variables. Given the various limitations of Disney et al. (1) aforementioned, a similar significant result was still elicited, in addition to associat-

ing unstable varying BP to mortality. (refer to brown line in Fig.2)

Meanwhile, Yarlagadda et al. (6), Tabuchi et al. (5), and Roederer et al. (4) conversely display a drop in BP as a predictor of Vasospasm. Despite the high odds ratio ($OR=6.7$) portrayed by Yarlagadda et al. (6), it is worth mentioning that the study focused on other exposures of cardiovascular abnormalities and its measurement of outcome was not sufficiently accurate in identifying Vasospasm. For example, treatment of Vasospasm or head CT evidence of cerebral infarction are not necessarily indicative of Vasospasm as defined in this study. BP was also only measured 3 times during the 5-Day study period.

In support of this drop in pressure relationship, 22% of Tabuchi et al. (5) reported drops in BP happened prior to the incidence of symptomatic vasospasm, however, only 5.5% are stated by the study to be within 6 hrs and considered causative. Nonetheless, to our analysis, a significant association is considered whether causative or not. However, the aforementioned critical analysis in the accuracy of this study must be noted. (refer to the last paragraph of Section 5.1)

A relatively new study (2014) analysing the viability of using automated physiologic data to predict Vasospasm in the ICU setting also supported the drop in pressure hypothesis and associated an MAP of 107.524mmHg on Day 1 to Vasospasm compared to 122.874mmHg in Non-Vasospasm patients (4). The study had extensive analytic statistical and validation techniques and an apt consideration of confounding variables. However, the 3-day study period was insufficient, only high-grade patients were recruited and no plausible physiologic evidence is available for the relationship of Vasospasm with BP on first day following SAH. Kirkness et al. (7) had similar MAP values for a similar study period (4 Days) yet concluded that there is no significance between MAP and Vasospasm. This is in agreement to the current available evidence aforementioned that Vasospasm is usually onset

Day 4 post-SAH (12).

Limitations of study

This review was limited by the number of available literature examining the trends of BP following SAH. Denied access to 3 additional studies found may have restricted vital evidence. The use of only 2 databases also provides possibility of non-accessed literature.

Conclusion

Despite the inconsistent absolute values of BP variables, it is rational to conclude that a biphasic trend is expected following SAH with an initial gradual rise during the first 4 days followed by a sustained hypertensive plateau fluctuating depending on severity and prognosis. With regards to Cerebral Vasospasm, considerable conflict is depicted in literature on whether spontaneous rises or falls in BP are associated with Vasospasm incidence; with the former showing greater significance in recent literature. Nevertheless, the presence of a correlation and potential prediction is almost ascertained; further analysis of such beneficial predictive potential is hence required for further advancement in Vasospasm and Neuro-Cardiogenic care.

Literature Reviews

Appendix A

EBSCO MEDLINE Generated Equation
((MM "Blood Pressure+") OR (MM "Arterial Pressure") OR (MM "Venous Pressure+")) AND ((MM "Subarachnoid Hemorrhage+") OR (MM "Subarachnoid Hemorrhage, Traumatic"))
PubMed Generated Equation
(Blood Pressure[Title/Abstract] AND (Subarachnoid *morrhage[Title/Abstract] OR "subarachnoid hemorrhage"[MeSH Terms]))

Appendix B

CASP Checklist Question (20)	Disney L. <i>et al.</i>	Faust K. <i>et al.</i>	Fontana J. <i>et al.</i>	Kirkness C.J. <i>et al.</i>	Placek M. <i>et al.</i>	Roederer A. <i>et al.</i>	Soehle M. <i>et al.</i>	Tabuchi S. <i>et al.</i>	Tening F. <i>et al.</i>	Yarlagadda S. <i>et al.</i>
1. Did the study address a clearly focused issue?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Was the cohort recruited in an acceptable way?	CT	Y	Y	CT	Y	N*4	Y	Y	Y	Y
3. Was the exposure accurately measured to <u>minimise</u> bias?	Y	Y	Y	Y	CT	Y	Y	Y	Y	CT
4. Was the outcome accurately measured to <u>minimise</u> bias?	Y	Y	Y	CT*1	CT	Y	CT	Y*5	Y	N
5. (a) Have the authors identified all important confounding factors?	N	Y	Y	Y	CT	Y	Y	Y	Y	Y
5. (b) Have they <u>taken</u> account of the confounding factors in the design and/or analysis?	N	Y	Y	Y	Y	CT	Y	CT	Y	Y
6. (a) Was the follow up of subjects complete enough?	N	Y	Y	Y	Y*3	Y	Y	Y	Y	Y
6. (b) Was the follow up of subjects long enough?	CT	Y	Y	N	CT	N	CT	Y	Y	N
7. What are the results of this study?										
	Refer to Table (3): SUMMARY OF RESULTS									
11. Do the results of this study fit with other available evidence?	Y	Y	Y	Y	CT	N	Y	Y*6	Y	N
12. What are the implications of this study for practice?	Refer to Table (3): SUMMARY OF RESULTS									
Y : Yes N : No CT : Can't Tell *1Qs maybe be tailored to Parent Study *2Not all results believed *4Only High-grade patients recruited *5Clearly defined; however, not Gold standard measure *6Evidence from Rat studies Other reasons for CT and N answers are explained in the Limitations section of the Summary of Results Table										

Appendix C

Table 3: SUMMARY OF RESULTS

Author (Year), Location, Title	Study Design, Sample Size / Selection	Methods	Key Findings	Strengths / Limitations	Future Research
Disney L. et al. (1989) <i>Alberta, Canada</i> Trends in Blood Pressure, Osmolality and Electrolytes after Subarachnoid Hemorrhage from Aneurysms (1)	Retrospective Cohort study N= 173 SAH Patients admitted to University of Alberta Hospitals or Royal Alexandra Hospital Inclusion: • 1971 – early 1987 • ≥ 2 days of Vital signs and Biochemical data available	Exposure: BP from Patients' charts (not every day available!) Outcome: Mortality – Death in Hospital Vasospasm – Delayed Neurological deterioration occurring > 4 days after SAH and associated with Angiographic Vasospasm	BP Trend: • Highest mean SBP on Day 0 = 163torr • Fell on Day 1, gradual rise to Day 8 the fell again • Considerable variation of SBP over time for Non-survivors Vasospasm: • Days 3-14: significantly higher SBP in Vasospasm group • Low BP = ½ incidence of VS • Difference increases progressively overtime • BP rise before Clinical onset of VS • Difference emphasized when categorized in comparison to Highest SBP on that day.	Strengths: • Biologically plausible evidence • Temporality established • Overall large sample size • Clearly defined outcome • Reasonable variation of sample (Gender, Age, Hunt & Hess grade on admission) Limitations: • No confounding factors considered • Not all days of data available • Only Surgical treatment • 173 patients from 721 had recorded data – sampling bias	

Literature Reviews

Table 3: SUMMARY OF RESULTS

Author (Year), Location,	Study Design, Sample Size	Methods	Key Findings	Strengths / Limitations	Future Research
Faust K. et al. (2014) Berlin, Germany Blood pressure changes after aneurysmal subarachnoid haemorrhage and their relationship to cerebral vasospasm and clinical outcome (2)	Retrospective Cohort study N= 98 Inclusion: - Aneurysmal SAH Exclusion: - No Angiogram to confirm diagnosis - Initial presentation of VS - No detected aneurysm as source of bleed - Received delayed aneurysmal disabling	Exposure: BP from Patients' charts For 8 Days Outcome: Vasospasm -33% narrowing of Cerebral vessels via Catheter Angiography on Day 7-9 Earlier if: - Delayed neurological deterioration not attributable to another source - TCD flow elevation (MCA>120cm/s, ΔMCA velocity 24hr>50, <u>Lindegaard index</u>>3) Clinical Outcome – Glasgow Clinical Outcome Scale <i>* <u>Lindegaard index</u>: the ratio between the mean flow velocity in the median cerebral artery and the mean flow velocity in the internal carotid artery</i>	BP Trend: - Daily data of DBP, MAP, SBP of available Vasospasm: - Days 1-8 = VS+ MAP $\uparrow$ 28% VS- MAP $\uparrow$ 3.5% - Statistical difference in MAP & DBP between VS+ & VS- on Day 4 - Statistical difference in SBP on Day 6 - Predominance in changes of DBP >20% spontaneous elevation in MAP might sensitize ICU for VS - Result unaffected by History of Hypertension, Age, Gender, Treatment modality - SAH severity (WFNS) did not correlate with BP	Strengths: - Confounding factors matched - Reflect real ICU situation - Temporality established - Supported by physiological evidence - Good sample size - Clearly defined outcome Limitations: - Not sufficient variation with regards to age - Regular Nimodipine may affect BP trend	Future Prospective studies randomizing variables (instead of matching)

Fontana J. et al. (2015) Bochum, Germany The spontaneous rise after aneurysmal subarachnoid haemorrhage – A biphasic phenomenon (3)	Prospective Cohort study N= 61 Inclusion: - Aneurysmal SAH 18< Age <85 - Saccular aneurysm by DSA with chronologically defined onset Exclusion: - Non-aneurysmal SAH - Onset >24hrs - No or only thin clot on baseline CT (>20mm length)	Exposure: BP – Continuously monitored by intra-arterial catheter SBP, DBP & MAP for 9 Days Outcome: Vasospasm – DSA on Day 8±2 quantified as None, Mild, Moderate or Severe via DSA by measuring diameter relative to baseline angiogram on admission Angiography on Day 7-9 Clinical Outcome – modified Rankin Scale, National Institute of Health Stroke Scale, Glasgow Outcome Scale Extended at Discharge	BP Trend: - Daily data of DBP, MAP, SBP of available - Significant rise in all (P<0.0001) - Steepest rise between Days 1-5 Vasospasm: - Isolated secondary rise of SBP in severe VS global on Day 8-9 - Mean vessel diameter reduction = -21.3 (±23.30)% - Global VS significantly related to daily rise of DBP, SBP and strongly MAP - Steeper rise in patients with History of Hypertension - No significance of BP ad Gender, Aneurysm Location, NE application - Propofol had significant inhibitory influence on SBP - SBP rise sig. correlation to SAH severity by Hijdra score	Strengths: - Prospective - Confounding factors dissected including Nimodipine use - Continuous exposure monitoring - Multi-level quality checks - Outcome measured for inter-observer variability - Outcome sub-quantified relative to baseline of individual - Plausibility based on physiological evidence Limitations: - Small sample size - Most treated by Surgical clipping - Influence of NE doses cannot eventually be fully excluded
Kirkness C.J. et al. (2009) Seattle, USA Intracranial and Blood Pressure Variability and Long-Term Outcome After Aneurysmal Subarachnoid Hemorrhage (7)	Descriptive correlational analysis of physiological data gathered as part of a Randomized Clinical Trial N= 90 Inclusion: - Age ≥16 - Enrolled over a 2 year period	Exposure: BP – Continuously monitored by intra-arterial catheter connected to fluid-filled pressure transducers for 4 Days saved as 5-second means Variability calculated on 4 timescales: 5sec, 5min, 1hr, 2 hrs Outcome: Vasospasm – Defined by TCD criteria or other Clinical Outcome – trained interviewers using Glasgow Outcome Scale Extended 6 months after discharge	Faster variability correlates to better outcome BP Trend: - Avg. MAP over 4 days = (103.2±10.7)mmHg Vasospasm: - No significant association between MAP Level & variability and VS - Higher MAP level over 4 days associated with sig. lower odds of favourable outcome - No association between variability and Aneurysm location - Age inversely correlated with MAP - Women had greater 24hr MAP variability - MAP significantly correlated with anxiolytic, sedative, hypnotic dose (OR=0.2; p=0.02) & Corticosteroid dose (OR=0.39; p<0.001) - MAP 5sec variability significantly correlated with Antiarrhythmic, diuretic, vasodilator dose	Strengths: - Confounding factors analysed with statistical tests - Clearly explained method of exposure measurement Limitations: - Gender ratio imbalance - Unclear definition VS outcome - Interview questions accustomed to parent study

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Placek M. et al. (2015) Cambridge, UK Complexity of Cerebral Blood Flow Velocity and Arterial Blood Pressure in Subarachnoid Hemorrhage Using Time-Frequency Analysis (18)	Retrospective Cohort study N= 31 Inclusion: - Aneurysmal SAH - Admitted to Neuro Critical Care Unit of Addenbrooke's Hospital - Daily TCD monitoring	Exposure: BP – measured invasively by radial artery line Recorded simultaneously every 1 or 2 days for 20mins at a sampling frequency of 50Hz Outcome: Vasospasm - TCD criteria: - Mean FV >120cm/s - Lindgaard ratio >3	Vasospasm: - Onset of VS= 9±4 days - VS did NOT affect mean Time-Frequency Distribution measures of complexity of ABP - Reduction in complexity of ABP in early days after SAH - Gradual fall in ABP complexity before VS and rise during VS (p=0.002) - May serve as Early warning index of narrowing of cerebral arteries	Strengths: - Spatial and Temporal comparison of VS - Strong and Multivariate statistical analysis Limitations: - Analysis of study focused on time-frequency distribution and BP complexity and did not provide raw absolute BP data. - Gold standard CT not used - Small sample size - No VS- control group - No sufficient Confounding control	Whether analysis of complexity of CBFV and ABP with cerebral autoregulation assessment using Time-Frequency analysis can advance prediction of DCI
Roederer A. et al. (2014) Philadelphia, USA Prediction of Significant Vasospasm in Aneurysmal Subarachnoid Hemorrhage Using Automated Data (4)	Retrospective Cohort study N= 81 Inclusion: - Aneurysmal SAH 2001-2011 - Fisher Grade 3 or 4 Exclusion: - Delayed presentation >48hrs - Early VS (during first 2 days)	Exposure: BP – Continuously monitored by arterial lines for 3 Days Outcome: Vasospasm - Serial neurological exams - Daily TCD studies - Monitored every 1-3hrs for headache or clinical deterioration - Other diagnostic tests such as CT perfusion, Xenon CT, MR perfusion, cEEG available to help	Vasospasm: 43.2% of sample developed VS - MAP on Day 1 VS+= 107.524mmHg VS- = 122.874 mmHg (p=0.018; CI 2.99-27.72) - Better PPV & Sensitivity than TCD - All automated data variables measured deemed significant with VS (p<0.05) except CSF output	Strengths: - Patients well matched for clinical features - Different statistical & validation techniques for quality assurance - Useful as early warning Limitations: - Many exposure variables lead to reduced focus on MAP - Only high-grade patients – sample bias - Does not indicate anything about underlying cause - Timespan of 10 yrs – risk of historical bias - Lack of temporality	Exploration of tests to detect intellectual impairment with normal MMSE scores

Soehle M. et al. (2008) Cambridge, UK Variability and fractal analysis of middle cerebral artery blood flow velocity and arterial blood pressure in subarachnoid haemorrhage (19)	Retrospective Cohort study N= 31 Inclusion: • Aneurysmal SAH • Admitted to Neuro Critical Care Unit of Addenbrooke's Hospital	Exposure: BP – measured invasively by radial artery line Recorded simultaneously every other day for 20mins at a sampling frequency of 50Hz Outcome: Vasospasm • TCD criteria: ◦ Mean FV >120cm/s ◦ Lindegaard ratio >3 Clinical Outcome – Glasgow Outcome Scale by telephone interview 1 year after SAH	BP Trend: • Considerable amount of fluctuations in both FV & ABP after SAH • Variability more pronounced in FV Vasospasm: • Variability reduced in VS • High GOS (more favourable outcome) correlated with high standard deviation of ABP (p<0.05) • Decomplexification theory of illness may apply to SAH too	Strengths: • Blinded investigator for outcome • Temporal comparison of VS • Visual inspection for artefacts • Good analytic control for confounding Limitations: • Analysis of study focused on FV and BP variability and did not provide raw absolute BP data. • Gold standard CT not used • Small sample size	
Tabuchi S. et al. (2006) Yonago, Japan Relationship of hypotension and cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage (5)	Retrospective Cohort study N= 125 Inclusion: • Aneurysmal SAH • Jan 1987 – Nov 1996 • Head CT to diagnose SAH Exclusion: • Barbiturate Therapy • Continued administration of Vasopressor or Antihypertensive Therapy • Brain death	Exposure: BP – SBP & DBP measured every 2hrs by nurses using Riva Rocci manometer for >2 wks Continuous BP monitoring in severe grade patients Fall in BP: drop of >40mmHg in SBP of any 2 consecutive measurements Outcome: • Head CT in all patients every week for >2 months OR when there is an acute change Symptomatic Vasospasm: • Headache, confusion, disorientation, focal neurological deficit, decline in consciousness • CT scan confirm exclusion of other causes • Absence of other causes of decline e.g. electrolyte imbalance, hypoxia, seizure	BP Trend: • 41.6% experienced fall in BP at least once Vasospasm: • 54.4% of all patients experienced Symptomatic VS • Hypodense areas secondary to Delayed Cerebral Vasospasm in 48.1% of falls in BP • 70.4% of Falls in BP correlated to VS • 22% before Symptomatic VS • Only 5.5% within 6hrs of Symptomatic VS • Effect still seen after aggressive volume resuscitation • Falls in BP significantly higher in older patients, poor WFNS grade on admission • Falls in BP NOT related to gender, History of Hypertension, Aneurysm location, mode of treatment	Strengths: • Clearly defined outcome • Wide confounding analysis Limitations: • Gold standard for VS diagnosis not used • Sample is from a long period and relatively old to study – historical bias • Plausible evidence is of non-human experiments	Further investigation to characterize mechanisms & prevention of Falls in BP to understand the pathophysiology

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Teping F. et al. (2018) Aachen, Germany Spontaneous Elevation of Blood Pressure After SAH: An Epiphenomenon of Disease Severity and Demand, But Not a Surrogate for Outcome? (21)	Retrospective Cohort study N= 115 Inclusion: • Aneurysmal SAH • Jan 2011 – Dec 2014 Exclusion: • <18 yrs or >80 yrs • Died within first 96 hrs • Confounding comorbidities (listed) • Preconditions potentially influencing BP (listed)	Exposure: BP – Electronic patient record SBP, MAP & DBP every 15 mins Spontaneous Blood Pressure Increases (SBI) defined as rise of 25mmHg verified over consecutive readings Endogenous Persistent Hypertension (EPH) defined as persistent MAP > 160mmHg for at least 3hrs for 21 Days Outcome: Clinical Outcome – Glasgow Outcome Scale at Discharge	BP Trend: • Avg. MAP during SBI episode = 105.68 (± 10.7) mmHg • Avg. MAP during EPH episode = 117.16 (± 9.92) • Most frequent during Phase 2 (Days 4-14) ($p < 0.05$) • EPH during Phase 1 increase risk of DCI • EPH during Phase 2&3 reduce risk of functional DCI • Initial response to demand & ability to maintain response not interchangeable • SAH severity, Aneurysm location, treatment modality do NOT influence EPH • EPH more in older patients ($p < 0.001$)	Strengths: • Clearly defined exposures • Confounding factors dissected from study • Graphs visually cross-checked to exclude artefacts Limitations: • Not all results statistically significant • Gender ratio imbalance	
Yarlagadda S. et al. (2006) California, USA Cardiovascular Predictors of In-Patient Mortality After Subarachnoid Hemorrhage (6)	Prospective Cohort study N= 300 Inclusion: • Aneurysmal SAH • Feb 1999 – Nov 2003 • Age >21 • SAH diagnosed by CT or Lumbar puncture Exclusion: • History of Hypertension • Cardiomyopathy • LVEF <50% • SAH caused by trauma or mycotic aneurysm	Exposure: BP – SBP recorded once on Days 0,3,5 of study Outcome: Death caused by neurological deficit due to: • SAH only • Evidence of DCI • Worsening of neurological status • Imaging evidence of vasospasm by TCD or CT Angiography • Neurointerventional treatment for VS • Head CT evidence of Cerebral infarction	BP Trend: • On Day 1 SBP >180 mmHg associated with increased risk of death (OR=5.6; $p=0.008$) • On Day 5 SBP <130mmHg associated with death in clinical window of VS • Cardiac abnormalities contribute to morbidity and mortality after SAH Vasospasm: • Hypotension during the clinical window of VS is a risk of death	Strengths: • Multivariate regression analysis for confounding Limitations: • Data only taken 3 times; low frequency of exposure • Outcome may not always be due to VS • Many exposure variables lead to reduced focus on BP	Treatments that could potentially prevent neurocardiogenic injury such as Beta blockers should be studied in the current era of SAH therapy Further research required to determine relationship between cardiac abnormalities & neurological outcome are causal in nature

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