

# Monitoring Hypervolemic-hemodilution And Hypertensive Therapy In Subarachnoid Hemorrhage

J Nates, M Jauss, S Singh, D Krieger

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## Abstract

**Introduction:** Prophylactic hypervolemic-hemodilution-hypertensive (HHH) therapy in subarachnoid hemorrhage (SAH) may be beneficial in reducing delayed ischaemia after early aneurysm clipping. The aim of this study was to assess the correlation among pulmonary artery catheter (PAC) measurements, effectiveness of HHH-therapy and mean flow velocity (MFV) in the middle cerebral artery (MCA) by transcranial Doppler.

**Methods:** We recorded Hunt-Hess classification, hematocrit, hemodynamic and PAC values, bilateral MFV in the MCA and Rankin scale in 37 ICU patients with SAH and no vasospasm (MFV <140 cm/s) receiving prophylactic HHH-therapy according to an Institutional protocol following early surgery. HHH-therapy efficacy was defined as high when systolic blood pressure (SBP) > 160 and wedge pressure (PCWP) > 12, moderate when only SBP > 160 or PCWP > 12, and ineffective when SBP < 160 and PCWP < 12. Fisher's t test and multiple regression analysis were used for data analysis, p < 0.05 was significant.

**Results:** An effective prophylactic HHH-therapy did not reduce occurrence of vasospasm. Outcome did not correlate with clinical state on admission or effectiveness of HHH-therapy. A constantly elevated systemic vascular resistance index (SVRI) was associated with a good outcome while the combination of high MFV in MCA and decline in SVRI with poor outcome (p < 0.05). Multiple regression analysis showed that SVRI and hematocrit explained 46% of variance of MFV in patients without vasospasm (MFV < 120 cm/s, n=16).

## Conclusion:

Our data demonstrate a correlation among SVRI, hematocrit and MFV. The differences in the outcome between the group where SVRI and MFV were moving in the same directions and the patient group where SVRI and MFV were moving in the opposite direction may be interpreted as early sign of vasospasm and may help to differentiate elevated MFV due to vasospasm (SVRI low) and elevated MFV due to effective HHH therapy (SVRI high). Differences in the outcome between the high and low SVRI may also be due to co-morbidities associated with low vascular resistance in the poor outcome group (e.g. sepsis, SIRS).

## INTRODUCTION

Prophylactic or therapeutic hypervolemic-hemodilution-hypertensive (HHH) therapy is used in subarachnoid hemorrhage (SAH) patients to reduce the damage produced by delayed ischaemia after early aneurysm clipping. Cerebral arterial vasospasm continues to be a major secondary medical complication of aneurysmal subarachnoid hemorrhage. Despite hypervolemic hemodilution, arterial hypertension, and other pharmacological therapy, morbidity and mortality due to vasospasm remain high<sup>(1,2,3,4)</sup>. Due to the high incidence of ischemic events after early intervention, there seems to be no significant difference in overall morbidity between patients who are treated with

early aneurysm surgery and those who have late surgery. Early surgery does not reduce the incidence of vasospasm, although the outcome is worse in the latter group<sup>(4,5)</sup>. Recent experience indicates that prophylactic HHH-therapy may be beneficial in reducing delayed ischemia after early aneurysm surgery<sup>(6,7)</sup>, however, some of these authors have expressed doubts in the ability to increase cerebral blood flow (CBF) using this therapy<sup>(8)</sup>.

HHH-therapy is usually considered a safe and effective modality for elevating and sustaining CBF after SAH and it is used to avoid hypotension and hypovolemia which, can exacerbate drops or reduce cerebral blood flow leading to

critical low perfusion pressures with potential ischemia and cerebral infarction. In combination with early aneurysm surgery, it might minimize delayed cerebral ischemia and an improved overall outcome has been reported (9). HHH-therapy has been favored also in patients after SAH with multiple un-ruptured aneurysms (10). There has been no human, prospective, randomized trial of HHH-therapy demonstrating that it improves the short or long-term neurological outcome or survival after subarachnoid hemorrhage (11). Nevertheless, there is strong evidence that HHH-therapy can reverse the delayed onset of profound neurological deficits by restoring blood flow to ischemic regions, and its prophylactic use can reduce the incidence and severity of strokes secondary to cerebral vasospasm (7,9,12,13,14,15).

The monitoring of HHH-therapy include, but is not limited to, daily bilateral monitoring of transcranial blood flow velocity, ECG, and patients' hemodynamics using continuous invasive arterial blood pressure and pulmonary artery catheter. The aim of this study was to assess the correlation among pulmonary artery catheter (PAC) measurements and the effectiveness of HHH-therapy, mean flow velocity (MFV) in the middle cerebral artery (MCA) by transcranial Doppler (TCD), and outcome by Rankin score at 1 month after discharge.

### MATERIALS AND METHODS

After approval by the Institutional Review Board of our Level I trauma center, a prospective observational study was conducted in 37 patients with diagnosis of SAH admitted to the 24 bed Neurosciences ICU. During their clinical course, we recorded Hunt-Hess classification, hemoglobin/hematocrit, hemodynamic values measured with pulmonary artery catheter, MFV in the MCA bilaterally by TCD, and outcome by Rankin scores at 1 month after discharge. A Multigon 500M unit, Yonkers, NY was used for TCD measurements. Hemodynamic values included, but were not limited to, cardiac output (CO), cardiac index (CI), systemic vascular resistance (SVR), systemic vascular resistance index (SVRI), pulmonary capillary artery occlusion pressure (PCOP) and central venous pressure (CVP).

Patients received prophylactic triple-H therapy according to the Institutional protocol following early surgery (targets: hematocrit 33 to 38%, pulmonary capillary wedge pressure or PCWP >12 and a systolic arterial pressure of 160-200 mm Hg (15). Four particular days were determined:

- First day of examination after SAH
- Day with maximum MFV value
- Day with minimum MFV value
- Last day of examination after SAH

Neurological findings were categorized as follows: (NNEXY1)

- Patients with normal neurological findings or a drowsy state of consciousness (no focal deficits and/or GCS=9)
- Patients with abnormal findings or a comatose state of consciousness (focal deficit and/or GCS=8)

Presence or absence of vasospasm during clinical course with respect to the maximum of the MFV in this group of patients was defined as followed (EINT1):

- Patients without vasospasm (bilateral =120 cm /s)
- Patients with focal vasospasm (unilateral >120 cm /s)
- Patients with global vasospasm (bilateral >120 cm /s)

The efficacy of triple-H therapy was evaluated on the day with the maximum of the MFV and on the day of the minimum of the MFV with respect to SBP and PCWP and categorized into 3 groups:

- Patients with effective triple-H therapy (SBP (160 and PCWP (12)
- Patients with moderate effective triple-H therapy (SBP (160 or PCWP (12)
- Patients with ineffective triple-H therapy (SBP <160 and PCWP <12)

Patients with a Rankin score of 1 to 3 were considered to have good outcome and with Rankin score 4 to 6 were considered to have poor outcome for the purposes of this study. Fisher's t test and multiple regression analysis were used for data analysis,  $p < 0.05$  was significant.

### RESULTS

Among the 37 patients included, there were 15 males and 22

females, age  $52.6 \pm 13.9$  (range 16.1-84.3). Their observation started  $3.08 \pm 2.31$  days after surgery and  $4.32 \pm 2.7$  days after SAH (range 1-12), and stopped on day  $8.38 \pm 2.97$  (range 4-18). The length of HHH-therapy was  $5.89 (\pm 2.62)$  days, with  $4.11 (\pm 2.37)$  pulmonary artery catheter days. The patients' Hunt and Hess classification and Rankin scores can be seen in tables 1-4.

**Figure 1**

Table 1: Presentation at admission - Hunt and Hess (HH)

| HH | Frequency | Percent |
|----|-----------|---------|
| 1  | 9         | 24.3    |
| 2  | 8         | 21.6    |
| 3  | 7         | 18.9    |
| 4  | 11        | 29.7    |
| 5  | 2         | 5.4     |

**Figure 2**

Table 2: Rankin-Score at discharge

| Rankin score | Frequency | Percent |
|--------------|-----------|---------|
| 1            | 3         | 8.1     |
| 2            | 7         | 18.9    |
| 3            | 13        | 35.1    |
| 4            | 6         | 16.2    |
| 5            | 1         | 2.7     |
| 6            | 7         | 18.9    |

There was no statistically significant correlation between admission score by Hunt and Hess classification and outcome as can be seen below in table 3.

**Figure 3**

Table 3. Correlation between Hunt and Hess (HH) classification and Rankin scores

| Admission Hunt and Hess | Outcome Rankin 1-3 | Outcome Rankin 4-6 | Died |
|-------------------------|--------------------|--------------------|------|
| 1 to 3                  | 17                 | 7                  | 3    |
| 4 to 5                  | 6                  | 7                  | 3    |

Fisher exact test - p value not significant

Only 28 patients received triple-H therapy (see table 4). Eight patients did not receive vasopressors because they were able to maintain the target values by themselves. One

patient did not have enough data to enter any hemodynamic analysis. A total of 6 (21.4% among the HHH therapy or 16.2% of all patients) patients died among the triple-H therapy group, 5 in the effective and 1 in the moderately effective groups.

**Figure 4**

Table 4. Efficacy of Triple-H therapy and Outcome by Rankin score

| Triple-H                | Outcome Rankin 1-3 | Outcome Rankin 4-6 |
|-------------------------|--------------------|--------------------|
| Effective               | 13                 | 10                 |
| Moderate or ineffective | 3                  | 2                  |

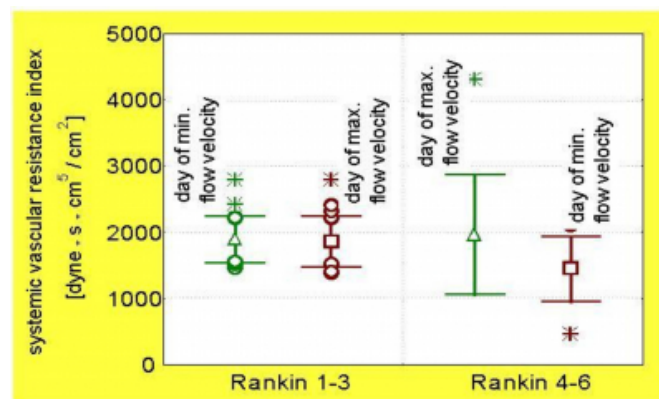
Fisher exact test - p value not significant

## SVR

When we considered the day with highest and lowest flow velocities, we found no differences between outcome groups for hemoglobin, central venous pressure, PCWP, cardiac index or systolic blood pressure. However, the SVRI did differ. A lower SVRI on the day with maximal MCA flow velocity was found among patients with poorer outcome ( $p < 0.05$ ) (see fig.1 below).

**Figure 5**

Fig 1. Changes of SVR according to outcome groups



MIN= minimum, MAX= maximum,  $p < 0.05$  for group effects (ANOVA with repeated measurements)

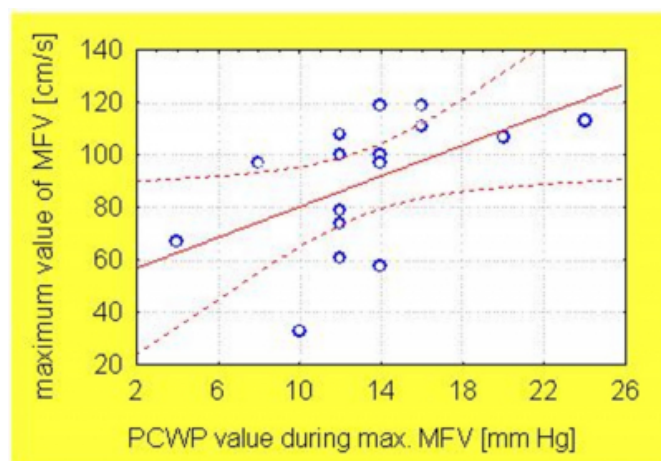
## MVF

Regression analysis of the dependence of MFV on hemodynamic parameters was performed using the day when minimum and maximum MFV occurred during the patient's clinical course. No regression model could be applied to the other days because of the large individual differences. For MFV range = 120 cm /s, we found that absolute MFV on the day with maximum MFV depends on PCWP; however,  $R^2$  was low 0,276 (fig. 2). The regression

model shown below explained only 27% of the variance of MFV. We found that in this group of patients, there was no parameter that determined absolute MFV on the day with minimum MFV.

**Figure 6**

Fig. 2: Regression model for absolute MFV value on day with maximal velocity by TCD. PCWP could be identified as a predictive factor for MFV; however, only 27 percent of the variance of MFV is explained by PCWP



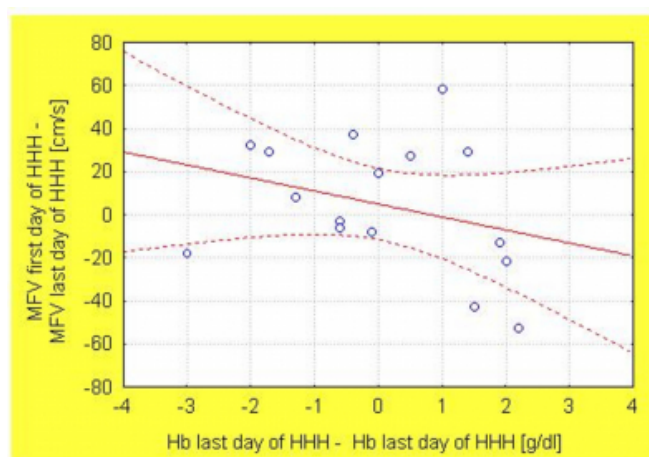
Cross-tabulation tests (Fisher exact test) revealed no significant relationship between Hunt and Hess classification at admission and outcome, sufficiency of HHH-therapy and vasospasm or outcome on the days with minimum and maximum MFV. There was neither a time effect nor a group effect for systolic blood pressure.

## HEMOGLOBIN

Stepwise regression by comparison of the first and the last HHH-therapy day, among the patients receiving prophylactic HHH-therapy and MFV <120 cm/second (16 patients), revealed a regression model with Hb as the independent variable; however, R2 was low (0,25) (figures 3 and 4).

**Figure 7**

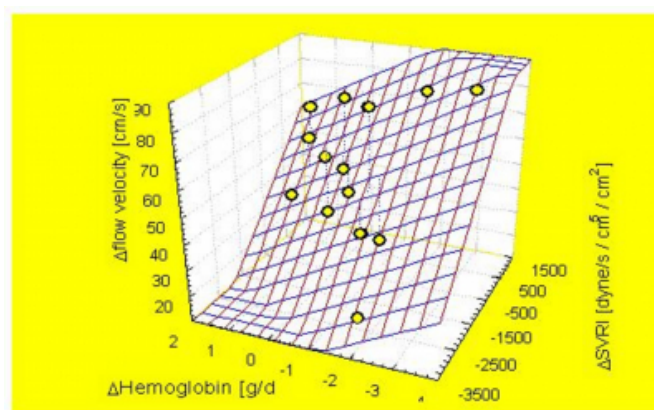
Fig. 3. Regression model comparing differences between first and last day of HHH -therapy and hemoglobin on the same days



## SVR, MFV AND HEMOGLOBIN

**Figure 8**

Fig. 4. Changes in MCA flow velocity in dependence of SVR and hemoglobin changes (by regression analysis).



3D Surface plot (SUB4B.STA 59v\*34c)  
 $z = 54,01309 + 0,01519 \cdot \text{DSVRI} + -8,30541 \cdot \text{HBQ}$

?= changes, SVRI= systemic vascular resistance index

## DISCUSSION

The most interesting and important findings of this study were the association between high SVR at the time of lowest MFV and low SVR at the time of highest MFV in the MCA. The latter associated with poor outcome measured by Rankin score (see graph 1). Until now, the manipulation of HHH-therapy has been based on maintaining the patient's euvolemic or hypervolemic status adding a vasopressor or an inotrope depending on the specific case. There is no consensus regarding what is the most important component

of HHH-therapy, hypervolemia, hemodilution or hypertension (3). Adequate response has been obtained using hypervolemia and hypertension without hemodilution (14), and no response has been obtained using only hypervolemia (8,<sub>16</sub>). This seems to support hypertension as the most important of the three components mentioned above; some authors believe hypertension is more important than hypervolemia (<sub>17</sub>). However in our experience, deficits in CBF can be reversed either by increasing the cardiac output using an inotrope like dobutamine, or increasing the mean arterial pressure with a vasopressor like norepinephrine (16).

The association between low SVR and poor outcome can not be explained by inadequate therapy because there was no difference in outcome between groups when stratified by effectiveness of therapy (table 4). A possible explanation is that most events of high MFV observed were partial products of HHH-therapy itself, but in those with low SVRI a true vasospasm may have occurred. Unfortunately, it is not possible to determine if high MFV is due to hyperperfusion as an effect of HHH-therapy due to vasospasm. We may have missed significant differences in CBF between these 2 groups because we did not perform angiograms or xenon scans to confirm the impact of the high MFV recorded. A second explanation could be the association of low SVR with systemic inflammatory reaction syndrome (SIRS), sepsis, lack of reactivity to vasopressors, and inability to compensate for the hemodynamic changes because of a poor cardiac function increasing the risk of stroke, severity of illness and risk of death. The impact on outcome of factors such as APACHE II score, SIRS, sepsis, and age among others has been noted in this population lately (17,<sub>18,19</sub>).

Several hemodynamic variables exist that might be helpful to control (i. e. pulmonary capillary wedge pressure, central venous pressure, mean arterial blood pressure, systolic arterial blood pressure, cardiac index, peripheral vascular resistance index). However, despite relevant changes to each of these variables in clinical course of HHH-therapy, we could identify only one hemodynamic value (pulmonary capillary wedge pressure) with some influence on MFV on the day where the maximum MFV value had been observed as shown in figure 2. Other factors might contribute to variation of MFV since the association of pulmonary capillary wedge pressure with MFV was only about 27%. Despite the exclusion of patients with MFV > 120 cm / s, a component of vasoconstriction of basal cerebral vessels cannot be excluded as well as post ischaemic hyperperfusion after remission of vasospasm since the diameter of MCA

could not be determined. Moreover the association of MFV and PCWP might reflect therapeutic efforts rather than a clear dependency of MFV from PCWP. Although the absolute value of MFV does not depend upon any hemodynamic variable, we found that changes in MFV during clinical course in a subgroup of patients with an MFV alteration of at least 15 cm /s were significantly (by 47 %) explained by changes in hemoglobin and changes in peripheral vascular resistance index as shown in fig. 4. It could be demonstrated that a decrease in hemoglobin, presumably due to hypervolemia and an increase of the SVR, probably due to vasopressors, leads to an elevation of MFV. During complete course of HHH-therapy (first day compared to last day) there was a (moderate) relationship of MFV changes and Hb changes. However, when comparing the first with the last day, the influence of SVRI could not be proved probably due to the fact that vasopressors were used less during the late clinical course when patients were about to recover and aggressive treatment no longer seemed necessary.

In summary, outcome did not correlate with clinical state on admission or effectiveness of HHH-therapy. A constantly elevated SVRI was associated with a good outcome while the combination of high MFV in MCA and low SVRI was associated with poor outcome ( $p<0.05$ ). Multiple regression analysis showed that SVRI and hematocrit explained 46% of variance of MFV in patients without vasospasm. These results suggest that, in addition to the already accepted variables (a hematocrit of 33-38%, a central venous pressure of 10-12 mm Hg, a pulmonary wedge pressure of 15-18 mm Hg and a systolic arterial pressure of 160-200 mm Hg)(13), SVR/SVRI might be of value to more appropriately adjust HHH-therapy.

Finally, we need a better understanding and monitoring of HHH-therapy, and development of guidelines to standardize its clinical application. It is possible that new therapies will be successfully introduced before well-controlled, prospective, randomized clinical trials of HHH-therapy are conducted (<sub>20,21</sub>).

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**Author Information**

**Joseph L. Nates, M.D, Assistant Professor**

Director Neurosciences ICU, Neurosurgery and Anesthesia/CCM, University of Texas Medical School-Houston

**Marek Jauss, M.D.**

Neurology, University of Giessen

**Sandip Singh, M.D.**

Anesthesia/CCM, University of Texas Medical School-Houston

**Derk Krieger, M.D.**

Neurology, University of Texas Medical School-Houston