Acta Neurochir (2012) 154:2179–2185
DOI 10.1007/s00701-012-1515-x

CLINICAL ARTICLE

# The role of catecholamines in the pathogenesis of neurogenic pulmonary edema associated with subarachnoid hemorrhage

**Joji Inamasu · Keiko Sugimoto · Yasuhiro Yamada · Tsukasa Ganaha · Keisuke Ito · Takeya Watabe · Takuro Hayashi · Yoko Kato · Yukio Ozaki · Yuichi Hirose**

Received: 11 July 2012 / Accepted: 25 September 2012 / Published online: 9 October 2012


**Abstract**
*Background* Neurogenic pulmonary edema (NPE) occurs frequently after aneurysmal subarachnoid hemorrhage (SAH), and excessive release of catecholamines (epinephrine/norepinephrine) has been suggested as its principal cause. The objective of this retrospective study is to evaluate the relative contribution of each catecholamine in the pathogenesis of NPE associated with SAH.
*Methods* Records of 63 SAH patients (20 men/43 women) whose plasma catecholamine levels were measured within 48 h of SAH onset were reviewed, and the clinical characteristics and laboratory data of those who developed early-onset NPE were analyzed thoroughly.
*Results* Seven patients (11 %) were diagnosed with NPE on admission. Demographic comparison revealed that the NPE + group sustained more severe SAH than the NPE− group. Cardiac dysfunction was also significantly more profound in the former, and the great majority of the NPE+ group sustained concomitant cardiac wall motion abnormality. There was no significant difference in the plasma epinephrine levels between NPE+ and NPE− group (324.6±172.8 vs 163.1±257.2 pg/ml, $p$=0.11). By contrast, plasma norepinephrine levels were significantly higher in the NPE+ group (2977.6±2034.5 vs 847.9±535.6 pg/ml, $p$<0.001). Multivariate regression analysis revealed that increased norepinephrine levels were associated with NPE (OR, 1.003; 95 % CI, 1.002–1.007). Plasma epinephrine and norepinephrine levels were positively correlated ($R$=0.48, $p$< 0.001). According to receiver operating characteristic curve analysis, the threshold value for plasma norepinephrine predictive of NPE was 2,000 pg/ml, with an area under the curve value of 0.85.
*Conclusions* Elevated plasma norepinephrine may have more active role in the pathogenesis of SAH-induced NPE compared with epinephrine, although both catecholamines may be involved via multiple signaling pathways.

**Keywords** Catecholamine · Epinephrine · Neurogenic pulmonary edema · Norepinephrine · Subarachnoid hemorrhage

J. Inamasu (✉) · Y. Yamada · T. Ganaha · K. Ito · T. Watabe · T. Hayashi · Y. Kato · Y. Hirose
Department of Neurosurgery,
Fujita Health University School of Medicine,
1-84 Kutsukake,
Toyoake 470-1192, Japan
e-mail: inamasu@fujita-hu.ac.jp

K. Sugimoto
Department of Laboratory Medicine,
Fujita Health University School of Medicine,
Toyoake, Japan

Y. Ozaki
Department of Cardiology,
Fujita Health University School of Medicine,
Toyoake, Japan

## Introduction

Patients with subarachnoid hemorrhage (SAH) are frequently complicated by acute pulmonary dysfunctions, particularly neurogenic pulmonary edema (NPE) [1, 5–7, 11, 12, 20]. The *catecholamine storm* hypothesis, i.e., massive catecholamine release into the systemic circulation occurring immediately after aneurysmal rupture, has been proposed as the pathogenic mechanism of NPE [1, 11, 12, 20]. However, the hypothesis remains speculative since plasma catecholamine levels have rarely been measured in SAH patients

complicated by NPE [13]. At our institution, attempts have been made to measure plasma catecholamine levels in SAH patients shortly after admission [21, 22]. This retrospective study was conducted to evaluate the relative contribution of each catecholamine (epinephrine/norepinephrine) to the pathogenesis of SAH-induced NPE. SAH-induced NPE is known to exhibit temporal profiles with two peaks: early (within several hours) and late (within several days) after SAH onset [4]. In this study, we focused only on those who developed early-onset NPE. Because catecholamines in the systemic circulation are rapidly metabolized and their plasma levels decrease with time, only patients from whom blood samples were obtained within 48 h of SAH onset were included.

## Materials and methods

### Patients

Between April 2010 and March 2012, a total of 114 patients with aneurysmal SAH were admitted to our institution. Brain computed tomography (CT) and chest X-rays were obtained immediately for those suspected of having SAH. Clinical criteria for NPE included the presence of crackles that suggested fluid in the lungs and presence of frothy pink tracheal fluid [12]. Radiographic criteria for NPE included sharply defined pulmonary markings accompanied by blurring or haziness of the perivascular outlines and loss of demarcation of hilar shadows [12]. All chest X-rays were interpreted by board-certified emergency medicine physicians. Patients who fulfilled both clinical and radiographic criteria were diagnosed with NPE. Among the 114 SAH patients, ten (9 %) were diagnosed with NPE at the time of admission. Forty-eight patients without NPE were excluded from analysis since measurement of plasma catecholamines were not completed within 48 h of SAH onset. Three patients with NPE complicated by severe hypotension who had received IV catecholamines before blood sample collection ($n$=3) were also excluded. Therefore, a total of 63 patients (55 %) were included into analysis. All 63 patients underwent bedside two-dimensional echocardiography to evaluate the presence of concomitant cardiac wall motion abnormality (WMA), using a General Electric Vivid 7 (GE Healthcare, Tokyo, Japan). WMA was evaluated using the American Society of Echocardiography 16 segment model [9, 22]. Cardiac function was represented by left ventricular ejection fraction (LVEF). All electrocardiograms and echocardiographs were interpreted by board-certified cardiologists. Demographic data and outcomes of patients were retrieved by reviewing charts and the institutional database. The study protocol was approved by our institution's internal review board.

### Plasma catecholamine measurement

In accordance with the inclusion criteria, only blood samples collected within 48 h of SAH onset were analyzed. Plasma epinephrine and norepinephrine levels were measured by high-performance liquid chromatography (SRL, Tokyo, Japan). In addition, plasma levels of troponin I and brain natriuretic peptide (BNP) were measured by standard chemiluminescence immunoassay and immunoradiometric assay [18].

### Clinical management

All SAH patients underwent either surgical or endovascular obliteration of an aneurysm within 48 h of SAH onset, unless they were extremely hypotensive or they had sustained irreversible brainstem damage. Those who sustained NPE were sedated, intubated and managed with a ventilator with minimal positive end-expiratory pressure. Dopamine was used as the primary IV vasopressor. The use of norepinephrine was avoided as much as possible since it may exacerbate hemodynamic instability [7]. Neither α-blockers nor β-blockers to attenuate possible adverse effects of increased plasma catecholamine levels were routinely used in our institution. For removal of subarachnoid clots, an intraventricular catheter was placed in patients who underwent clipping and a lumbar catheter was placed in those who underwent coiling of an aneurysm. Other postoperative management included administration of IV fasudil hydrochloride (Asahi-Kasei Pharma, Miyazaki, Japan), low-molecular weight dextran, and albumin to attenuate vasospasm. Although central venous catheters were placed routinely, pulmonary artery catheters were rarely placed. For patients with symptomatic vasospasm, the triple-H therapy was initiated. However, for patients with NPE, efforts were made to keep them *normovolemic* instead of *hypervolemic* to avoid its exacerbation. Brain CT scans were obtained routinely on day 1, 2, 7, and 14 of admission. For the evaluation of delayed cerebral infarction due to vasospasm, CT scans obtained on day 14 were used.

### Statistical analysis

The 63 patients were dichotomized based on the presence of NPE. For comparison between NPE+ and NPE− groups, Fisher's exact test was used for categorical variables and the unpaired $t$-test for continuous variables. Multivariate logistic regression analysis was used to identify clinical variables predictive of NPE. Linear regression analysis was employed to evaluate the association between plasma epinephrine and norepinephrine levels. A receiver operating characteristic (ROC) curve was created for plasma norepinephrine levels. From the ROC curve, we derived optimal

threshold values to distinguish between NPE+ and NPE− groups by seeking the best tradeoff between the highest possible sensitivities and specificities of the threshold values. JMP (SAS Institute, Cary, NC, USA) was used for statistical analysis. Data are indicated by mean ± SD, and $p<0.05$ was considered statistically significant.

## Results

### Demographics

The 63 SAH patients consisted of 20 men and 43 women with a mean age of 64.3±10.7 years (range, 36–87). The interval between SAH onset and completion of blood sample collection/echocardiogram was 16.5±11.4 h. For obliteration of a ruptured aneurysm, 39 patients underwent clipping, 17 underwent coiling, and the other 7 were treated conservatively. Seven of the 63 patients (11 %) exhibited clinical/radiographic signs of NPE. Comparison of demographics (Table 1) revealed that the NPE+ group sustained more severe SAH than the NPE− group, as represented by a significantly higher frequency of patients with World Federation of Neurosurgical Societies score of grade III-V ($p=0.04$). Cardiac damage was also more severe in the NPE+ group, as represented by significantly higher plasma troponin I levels (1.86±2.23 vs 0.09±0.11 ng/ml, $p=0.002$) and lower LVEF (47.9±13.4 % vs 66.6±7.8 %, $p<0.001$). By contrast, there was no significant intergroup difference in the plasma levels of BNP (177.4±187.1 vs 106.9±102.4 pg/ml, $p=0.15$). The frequency of WMA was also significantly higher in NPE+ group (86 % vs 20 %, $p=0.001$). The inpatient mortality rate was significantly higher in NPE+ group (57 % vs 14 %, $p=0.02$). The frequency of delayed cerebral infarction related to vasospasm was 50 % in NPE+ group ($n=4$) vs 18 % in NPE group ($n=51$), and the difference was not statistically significant ($p=0.18$). Another four patients in the NPE+ group and five patients in the NPE− group died of initial brain damage within 7 days of SAH onset, in whom evaluation for the presence of delayed cerebral infarction was not conducted.

### Multivariate logistic regression analysis

Clinical variables evaluated included age, sex, location of ruptured aneurysm (anterior vs posterior circulation), and plasma epinephrine and norepinephrine levels. Multivariate logistic regression analysis showed that plasma norepinephrine levels (OR, 1.003; 95 % confidence interval, 1.002–1.007; $p=0.044$) correlated with NPE (Table 2). However, the other variables evaluated, including plasma epinephrine levels, did not correlate with NPE.

### NPE and plasma catecholamine levels

There was no significant difference in the plasma epinephrine levels between NPE+ and NPE− group (324.6±172.8 vs 163.1±257.2 pg/ml, $p=0.11$) (Fig. 1a). By contrast, plasma norepinephrine levels in NPE + group were significantly higher than those in NPE− group (2977.6±2034.5 vs 847.9±535.6 pg/ml, $p<0.001$) (Fig. 1b).

### Association between epinephrine and norepinephrine levels

Linear regression analysis revealed that there was a positive correlation between plasma epinephrine and norepinephrine levels ($R=0.48$, $p<0.001$) (Fig. 2).

### ROC analysis

ROC analysis revealed that the threshold value for plasma norepinephrine predicting NPE was 2,000 pg/ml (Fig. 3).

**Table 1** Comparison of demographic variables and outcomes between SAH patients with and without neurogenic pulmonary edema

| | NPE+ ($n=7$) | NPE− ($n=56$) | $p$ |
|---|---|---|---|
| Age (years) | 67.1±6.2 | 64.0±11.1 | 0.48 |
| Male vs female | 1:6 | 19:37 | 0.42 |
| WFNS SAH grade (I-II vs III-V) | 0:8 | 23:33 | 0.04[a] |
| Aneurysm location (ant. vs post.) | 6:1 | 52:4 | 0.46 |
| Treatment (clipping vs coiling vs conservative) | 5:0:2 | 34:17:5 | NA |
| Echographic wall motion abnormality | 6 (86 %) | 11 (20 %) | 0.001[a] |
| Left ventricular ejection fraction (%) | 47.9±13.4 | 66.6±7.8 | <0.001[a] |
| ECG abnormality | 6 (86 %) | 42 (75 %) | 0.88 |
| Cardiac arrhythmias | 3 (43 %) | 12 (21 %) | 0.34 |
| Plasma troponin I level (ng/ml) | 1.86±2.23 | 0.09±0.11 | 0.002[a] |
| Plasma brain natriuretic peptide level (pg/ml) | 177.4±187.1 | 106.9±102.4 | 0.15 |
| Infarction related to vasospasm[b] | 2/4(50 %) [b] | 9/51 (18 %)[b] | 0.17 |
| Inpatient death | 4 (57 %) | 8 (14 %) | 0.02[a] |

*ECG* electrocardiogram, *GCS* Glasgow Coma Scale, *NA* not applicable; *NPE* neurologic pulmonary edema, *SAH* subarachnoid hemorrhage, *WFNS* World Federation of Neurosurgical Societies

[a]Statistically significant

[b]Patients who died of primary brain damage within 7 days of SAH onset were excluded from analysis

**Table 2** Multivariate logistic regression analysis to identify clinical variables predictive of neurogenic pulmonary edema associated with SAH

| Clinical variables | OR | 95 % CI | *p* |
|---|---|---|---|
| Age | 0.953 | 0.801–1.133 | 0.585 |
| Male sex | 0.011 | 0.000–2.672 | 0.108 |
| Ant. circulation aneurysm | 0.133 | 0.001–16.109 | 0.410 |
| Epinephrine (pg/ml) | 1.000 | 0.992–1.008 | 0.989 |
| Norepinephrine (pg/ml) | 1.003 | 1.002–1.007 | 0.044[a] |

*CI* confidence interval, *OR* odds ratio, *SAH* subarachnoid hemorrhage, *WFNS* World Federation of Neurosurgical Societies

[a] Statistically significant

The area under the curve (AUC) value, sensitivity, specificity, and *p* value were 0.85, 71 %, 95 %, and 0.002, respectively.

## Discussion

NPE occurs relatively frequently after SAH, with a reported incidence of 2–29 % [1, 5–7, 11, 12, 20]. Although excessive release of catecholamines into the systemic circulation after an acute increase in intracranial pressure has been implicated as the principal cause of SAH-induced NPE [1, 11, 12, 20], measurement of plasma catecholamine levels has rarely been conducted in a systematic manner [13]. The relative contribution of each catecholamine, i.e., epinephrine vs norepinephrine, in the pathogenesis of NPE has also been unclear. In this study, a significant increase in plasma norepinephrine levels was observed in SAH patients complicated by NPE, and the results are in line with the *catecholamine storm* hypothesis [1, 11, 12, 20]. Since plasma epinephrine and norepinephrine levels were positively correlated (Fig. 2), most SAH patients complicated by NPE exhibited a concomitant increase in epinephrine and norepinephrine levels. Multivariate logistic regression analysis revealed that elevated plasma levels of norepinephrine, but not of epinephrine, were correlated with NPE (Table 2). ROC analysis demonstrated that a threshold value for NPE existed for norepinephrine, with high AUC, sensitivity, and specificity values (Fig. 3). These results suggest that norepinephrine plays a more pivotal role in the pathogenesis of SAH-induced NPE compared with epinephrine, although both catecholamines may be involved.

The pathogenesis of NPE is multifactorial and may involve several signaling pathways. Most importantly, $\alpha_1$-adrenoceptor stimulation is responsible for increased permeability and capillary pressure of the pulmonary microvasculature [10, 16, 17]. In addition, $\beta_1$-adrenoceptor stimulation seems to result in overperfusion of the lungs because of increased right ventricular systolic pressure and also contributes to edema [17]. The fact that landiolol, a selective $\beta_1$-antagonist, is effective in ameliorating experimental pulmonary edema, supports the role of the $\beta_1$-adrenoceptor in the pathogenesis of NPE [24]. This is in contrast to the function of the $\beta_2$-adrenoceptor, which promotes clearance of the accumulated alveolar fluid [3]. It is reasonable to

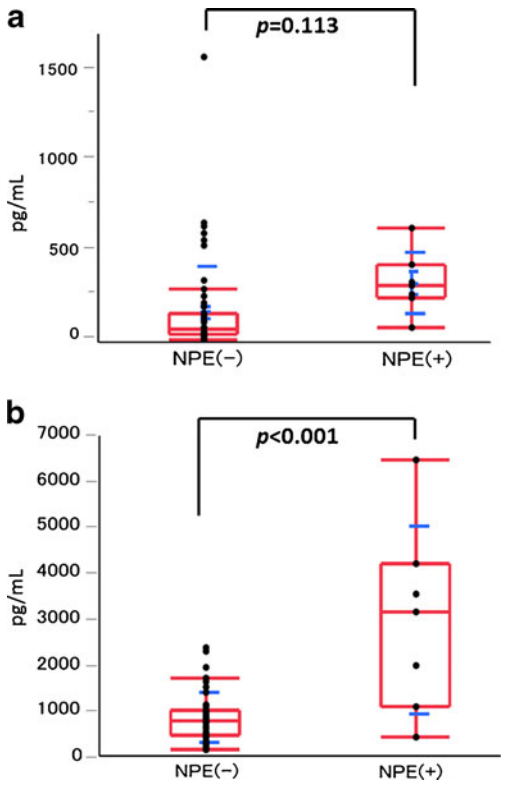


**Fig. 1** There was no significant difference in the plasma epinephrine levels between patients with (NPE+) and without (NPE−) neurologic pulmonary edema ($p$=0.11) (**a**). By contrast, plasma norepinephrine levels in the NPE+ group were significantly higher than the NPE− group ($p$<0.001) (**b**)

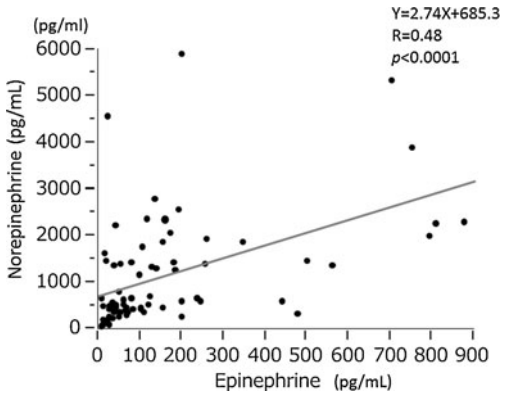


**Fig. 2** Linear regression analysis revealed that there was significant correlation between plasma epinephrine and norepinephrine levels ($R$= 0.48, $p$<0.001)

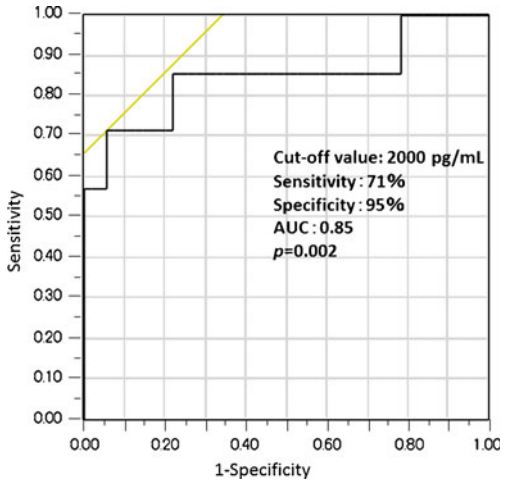


**Fig. 3** The ROC curve was created for plasma norepinephrine levels. From the ROC curve, optimal threshold value to distinguish between patients with and without NPE was derived. The threshold value for norepinephrine was 2,000 pg/ml. The area under the curve value and *p* value was 0.85 and 0.002, respectively

hypothesize that NPE develops more frequently in the presence of both increased epinephrine and norepinephrine levels. For example, patients with pheochromocytoma with predominant epinephrine secretion (which actually secretes both epinephrine and norepinephrine in high concentration) experience pulmonary edema more frequently than those with predominant norepinephrine secretion [8, 15]. In a rat model of spinal cord injury, NPE develops only when both plasma epinephrine and norepinephrine levels are substantially increased [19]. Considering these findings, the use of α-blockers and/or β-blockers, neither of which were used in this study, may be a reasonable option in the acute management of SAH-induced NPE to attenuate the adverse effects of increased plasma catecholamine levels [10]. Recently, IV phentolamine, a nonselective α-blocker used for pheochromocytoma patients in hypertensive crisis, is shown to attenuate NPE caused by a ruptured arteriovenous malformation [2].

The frequency of NPE in our cohort of 114 SAH patients was 9 %, which is comparable with that reported in the literature [1, 7, 12]. According to the results of demographic comparison (Table 1), the NPE+ group sustained more severe SAH than the NPE− group, as expected. Similarly, cardiac dysfunction was also more profound in the NPE+ group, which was represented by the significantly higher plasma troponin I levels, higher frequency of WMA, and lower LVEF (Table 1). Interestingly, the great majority of the NPE+ group was complicated by concomitant WMA. The more disturbed cardiac function observed in the NPE+ group may be another sign of markedly increased plasma catecholamine levels in this group. The poorer outcomes in the NPE+ group, as represented by significantly higher inpatient mortality rate, may be attributable both to the worse initial SAH grade and higher incidence of cardiac dysfunction. The frequency of delayed cerebral infarction was also higher in the NPE+ group. Those who died within 7 days of SAH onset were excluded from evaluation, and because of the small number in each group, the difference might have failed to reach statistical significance. Although previous studies showed that ruptured posterior circulation aneurysms were risk factors for NPE [7, 12], the location of aneurysm was not associated with NPE in this study. The lack of statistical difference in this study may be attributable to the relatively small number of total SAH patients ($n$=63). Contrary to a previous study by Tung et al. [23], our results do not support an active role of BNP in the pathogenesis of SAH-induced NPE.

There are several limitations to this study. First, the study design is retrospective and only 55 % of total SAH patients were included. There may have been room for selection bias, since patients with obvious signs of NPE are more likely to undergo timely examinations and to be included in the study than those without NPE. Second, plasma catecholamines released into the systemic circulation after SAH are rapidly degraded and plasma levels decrease over time [14]. We attempted to reduce such time-related variability by our strict inclusion criteria (i.e., including only patients in whom blood sample collection had been conducted within 48 h of SAH onset). Nevertheless, the possibility that differences in the timing of sample collection may have influenced measurement results cannot be denied. Third, the association of plasma catecholamine levels with late-onset NPE, which develops several days after aneurysmal rupture, remains unclear. Because plasma catecholamine levels were measured only at the time of admission, we were unable to collect data on those who developed delayed-onset NPE. For the same reason, the chronological change of plasma catecholamine levels in each patient with early-onset NPE was not evaluated. Fourth, pulmonary artery catheters were rarely placed and hemodynamic parameters of the systemic and pulmonary circulation were not obtained. Therefore, to what degree concomitant SAH-induced cardiac dysfunction and/or WMA contributes to pathogenesis of NPE remains unclear: the possibility that increased afterload following norepinephrine-induced peripheral vasoconstriction causes acute left ventricular failure and elevation in pulmonary artery pressure, which subsequently leads to NPE, cannot be excluded. Finally, interaction between catecholamines and other vasoactive substances reported to have a role in the pathogenesis of NPE, such as endothelin-1 and nitric oxide [1, 19], was not evaluated in this study. Despite these limitations, this study is unique in that relative contribution of epinephrine and norepinephrine in the pathogenesis of SAH-induced NPE was evaluated for the first time, and we believe that it will provide a new insight into its pathogenesis. The possibility that the use of α-blockers and/or β-

blockers may improve the hemodynamic status and outcomes of NPE patients also needs to be evaluated further. Since the number of SAH patients complicated by NPE is relatively small, a multi-center study may be required to clarify the issue.

## Conclusions

Marked increase in plasma norepinephrine levels was observed in SAH patients complicated by NPE. Norepinephrine appears to play a more active role compared with epinephrine, although both catecholamines may be involved in the pathogenesis of SAH-induced NPE via multiple signaling pathways.

**Conflicts of interest** None.

## References


1. Baumann A, Audibert G, McDonnell J, Mertes PM (2007) Neurogenic pulmonary edema. Acta Anaesthesiol Scand 51:447–455
2. Davison DL, Chawla LS, Selassie L, Tevar R, Junker C, Seneff MG (2012) Neurogenic pulmonary edema: successful treatment with IV phentolamine. Chest 141:793–795
3. Groshaus HE, Manocha S, Walley KR, Russell JA (2004) Mechanisms of beta-receptor stimulation-induced improvement of acute lung injury and pulmonary edema. Crit Care 8:234–242
4. Hoff RG, Rinkel GJ, Verweij BH, Algra A, Kalkman CJ (2010) Pulmonary edema and blood volume after aneurysmal subarachnoid hemorrhage: a prospective observational study. Crit Care 14: R43
5. Inamasu J, Miyatake S, Tomioka H, Suzuki M, Nakatsukasa M, Maeda N, Ito T, Arai K, Komura M, Kase K, Kobayashi K (2009) Subarachnoid haemorrhage as a cause of out-of-hospital cardiac arrest: a prospective computed tomography study. Resuscitation 80:977–980
6. Inamasu J, Nakamura Y, Saito R, Kuroshima Y, Mayanagi K, Ohba S, Ichikizaki K (2002) Normokalemia and hyperglycemia in subarachnoid hemorrhage patients resuscitated from prehospital cardiopulmonary arrest. Resuscitation 54:255–258
7. Inamasu J, Nakatsukasa M, Mayanagi K, Miyatake S, Sugimoto K, Hayashi T, Kato Y, Hirose Y (2012) Subarachnoid hemorrhage complicated with neurogenic pulmonary edema and takotsubo-like cardiomyopathy. Neurol Med Chir (Tokyo) 52:49–55
8. Kaye J, Edlin S, Thompson I, Leedma PJ (2001) Pheochromocytoma presenting as life-threatening pulmonary edema. Endocrine 15:203–204
9. Khush K, Kopelnik A, Tung P, Banki N, Dae M, Lawton M, Smith W, Drew B, Foster E, Zaroff J (2005) Age and aneurysm position predict patterns of left ventricular dysfunction after subarachnoid hemorrhage. J Am Soc Echocardiogr 18:168–174
10. Lane SM, Maender KC, Awender NE, Maron MB (1998) Adrenal epinephrine increases alveolar liquid clearance in a canine model of neurogenic pulmonary edema. Am J Respir Crit Care Med 158:760–768
11. Macmillan CS, Grant IS, Andrews PJ (2002) Pulmonary and cardiac sequelae of subarachnoid haemorrhage: time for active management? Intensive Care Med 28:1012–1023
12. Muroi C, Keller M, Pangalu A, Fortunati M, Yonekawa Y, Keller E (2008) Neurogenic pulmonary edema in patients with subarachnoid hemorrhage. J Neurosurg Anesthesiol 20:188–192
13. Mutoh T, Kazumata K, Kobayashi S, Terasaka S, Ishikawa T (2012) Serial measurement of extravascular lung water and blood volume during the course of neurogenic pulmonary edema after subarachnoid hemorrhage: initial experience with 3 cases. J Neurosurg Anesthesiol 24:203–208
14. Naredi S, Lambert G, Edén E, Zäll S, Runnerstam M, Rydenhag B, Friberg P (2000) Increased sympathetic nervous activity in patients with nontraumatic subarachnoid hemorrhage. Stroke 31:901–906
15. Page LB, Raker JW, Berberich FR (1969) Pheochromocytoma with predominant epinephrine secretion. Am J Med 47:648–652
16. Rassler B, Reissig C, Briest W, Tannapfel A, Zimmer HG (2003) Pulmonary edema and pleural effusion in norepinephrine-stimulated rats—hemodynamic or inflammatory effect? Mol Cell Biochem 250:55–63
17. Rassler B, Reissig C, Briest W, Tannapfel A, Zimmer HG (2003) Catecholamine-induced pulmonary edema and pleural effusion in rats—alpha- and beta-adrenergic effects. Respir Physiol Neurobiol 135:25–37
18. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr (2002) Plasma brain natriuretic peptide concentration: impact of age and gender. J Am Coll Cardiol 40:976–982
19. Sedý J, Zicha J, Nedvídková J, Kunes J (2012) The role of sympathetic nervous system in the development of neurogenic pulmonary edema in spinal cord-injured rats. J Appl Physiol 112:1–8
20. Sugimoto K, Inamasu J, Hirose Y, Kato Y, Ito K, Iwase M, Sugimoto K, Watanabe E, Takahashi A, Ozaki Y (2012) The role of norepinephrine and estradiol in the pathogenesis of cardiac wall motion abnormality associated with subarachnoid hemorrhage. Stroke 43:1897–1903
21. Sugimoto K, Watanabe E, Yamada A, Iwase M, Sano H, Hishida H, Ozaki Y (2008) Prognostic implications of left ventricular wall motion abnormalities associated with subarachnoid hemorrhage. Int Heart J 49:75–85
22. Stevens RD, Nyquist PA (2007) The systemic implications of aneurysmal subarachnoid hemorrhage. J Neurol Sci 261:143–156
23. Tung PP, Olmsted E, Kopelnik A, Banki NM, Drew BJ, Ko N, Lawton MT, Smith W, Foster E, Young WL, Zaroff JG (2005) Plasma B-type natriuretic peptide levels are associated with early cardiac dysfunction after subarachnoid hemorrhage. Stroke 36:1567–1569
24. Uraoka M, Nakajima Y, Kurita T, Suzuki A, Takata K, Sato S (2010) Landiolol, an ultra-short acting beta$_1$-blocker, improves pulmonary edema after cardiopulmonary resuscitation with epinephrine in rats. J Anesth 24:67–72


## Comment

Inamasu and colleagues provide a retrospective study analysing the role of epinephrine and norepinephrine in the pathogenesis of pulmonary oedema after aneurysmal subarachnoid haemorrhage (SAH) in 63 patients.

Neurogenic pulmonary oedema presents a dangerous complication in the course of aneurysmal SAH and the pathogenesis of this kind of pulmonary oedema is still not completely understood. The presented study demonstrates the important role of norepinephrine in this disease and the less important role of epinephrine, even though a positive

correlation between epinephrine and norepinephrine levels has been shown by the authors. Thus, this study may present a further little step in understanding neurogenic pulmonary oedema after aneurysmal SAH.

On the other hand, we have to keep in mind the retrospective design of this study with the well-known shortcomings of such a study design. Further, and in my opinion most important, haemodynamic parameters of the systemic and pulmonary circulation have not been acquired. Thus, pulmonary oedema due to an increased afterload following induced peripheral vasoconstriction and acute left ventricular failure as a consequence of increased levels of norepinephrine cannot be excluded by the study presented.

Further studies should be performed to clear these questions.

Marcus Reinges
Giessen, GERMANY

Neurogenic pulmonary edema (NPE) may complicate subarachnoid haemorrhage (SAH) in a significant percentage of patients, approximately 10 % according to the literature and the experience reported in this article. Nonetheless, it is has been shown that NPE occurs in more than 70 % of fatal cases of SAH [1]. This can be attributed to the severity of the bleeding, but it is possible and even likely that the relevance of NPE as a direct cause of death is underestimated.

The formation of edema has been alternatively attributed to an increase in capillary hydrostatic pressure secondary to a left ventricle performance deterioration due to the effects of catecholamines on peripheral circulation or to a direct, non-hydrostatic effect on the pulmonary capillary permeability induced by cathecolamines. This is an important issue with implications in the choice of medications that, however, is not addressed by this study. Nevertheless, in this clear and concise article Inamasu and co-workers demonstrated that the norepinephrine serum level represents an independent predictor of NPE. They also identified a cut-off value, thus providing a potential serum biomarker for the diagnosis of NPE. Further studies on this topic are necessary, but warranted by the importance of the question.

1. Muroi C, Keller M, Pangalu A, Fortunati M, Yonekawa Y, Keller E (2008) Neurogenic pulmonary edema in patients with subarachnoid hemorrhage. J Neurosurg Anesthesiol 20:188–192

Alfredo Conti
Messina, ITALY