ORIGINAL ARTICLE

# Pulmonary Edema and Cardiac Dysfunction Following Subarachnoid Hemorrhage

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**ABSTRACT:** ***Background:*** Pulmonary edema (PE) can occur in the early or late period following subarachnoid hemorrhage (SAH). The incidence of each type of PE is unknown and the association with ventricular dysfunction, both systolic and diastolic, has not been described. ***Methods:*** Retrospective chart review of 178 consecutive patients with SAH surgically treated over a three-year period. Patients with pulmonary edema diagnosed by a radiologist were included. Early onset SAH was defined as occurring within 12 hours. Cardiac function at the time of the PE was analyzed using hemodynamic and echocardiographic criteria of systolic and diastolic dysfunction. Pulmonary edema was observed in 42 patients (28.8%) and was more often delayed (89.4%). Evidence of cardiac involvement during PE varied between 40 to 100%. ***Results and conclusions:*** Pulmonary edema occurs in 28.8% of patients after SAH, and is most commonly delayed. Cardiac dysfunction, both systolic and diastolic, is commonly observed during SAH and could contribute to the genesis of PE after SAH.

**RÉSUMÉ: Œdème pulmonaire et dysfonction cardiaque suite à une hémorragie sous-arachnoïdienne.** ***Introduction:*** L'œdème pulmonaire (OP) peut survenir précocement ou tardivement après une hémorragie sous-arachnoïdienne (HSA). L'incidence de chaque type d'OP est inconnue et l'association à une dysfonction ventriculaire tant systolique que diastolique n'a jamais été décrite. ***Méthodes:*** Nous avons révisé les dossiers de 178 patients consécutifs atteints de HSA traitée par chirurgie sur une période de trois ans. Les patients ayant présenté un OP diagnostiqué par un radiologiste ont été inclus dans l'étude. L'OP était considéré comme précoce s'il survenait dans les 12 heures de l'HSA. La fonction cardiaque au moment de l'OP a été analysée au moyen des critères hémodynamiques et échocardiographiques de la dysfonction systolique et diastolique. Un OP a été observé chez 42 patients (28,8%) et il était souvent tardif (89,4%). La fréquence de manifestations d'atteinte cardiaque pendant l'OP variait de 40% à 100%. ***Résultats et conclusions:*** Un OP survient chez 28,8% des patients suite à une HSA et il est souvent tardif. On observe fréquemment une dysfonction cardiaque tant systolique que diastolique pendant l'HSA, ce qui pourrait contribuer à la genèse de l'OP après l'HSA.

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Pulmonary edema (PE) is a recognized complication of major neurological events including subarachnoid hemorrhage (SAH).[1-4] Usually known to occur in the hours following SAH, a delayed form has also been reported.[3,5] Clinical observations and experimental studies have produced conflicting data on the mechanisms of PE following SAH. The cardiogenic component in PE's pathogenesis remains incompletely understood. Electrocardiographic modifications and pathological changes in myocardium that develop in the setting of SAH have been described. However, few reports have detailed hemodynamic data and wall motion abnormalities observed during episodes of PE occurring in humans. The goal of this study is to describe the incidence of early and delayed PE following SAH, to demonstrate the possible existence of a cardiogenic component in both types of PE and to reveal the existence of both systolic and diastolic myocardial dysfunction. To our knowledge this is the first study to document the incidence of PE in a large population of patients with SAH and to address the issue of diastolic function in patients with PE in the setting of SAH.

## Population and Methods

Retrospective chart review of all patients with aneurysmal SAH operated at the "Hôpital Notre-Dame" from April 1998 to April 2001 was performed. Initial medical management included a normal saline to maintain normovolemia, a perfusion of beta-

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blockers to maintain systolic blood pressure below 150 mm Hg and calcium channel blockers to prevent vasospasm. Chest radiographs were done routinely at admission unless the patient's clinical presentation stressed the need for an urgent surgical intervention. In these circumstances the chest X-ray was delayed after the surgery and performed in the recovery room. Postoperatively, chest radiographs were done daily while patient was intubated or during the first three postoperative days if patient was extubated rapidly after surgery. Afterwards, chest radiographs were done when clinically indicated, at the discretion of attending intensivist.

Patients were included in the study if they had diagnosis of PE during their hospitalization. The diagnosis of PE was based on the interpretation of the chest radiographs reviewed and confirmed by a radiologist. Clinical findings supporting the diagnostic imagery were not essential for diagnosis of PE since signs and symptoms are greatly variable and unspecific. The time period between the SAH, the PE and the surgery was noted.

Exclusion criteria were the following: 1) inadequate chest radiographs defined as poor inspiration, 2) lung infiltrates diagnosed as lung infection or aspiration, 3) patients with unstable angina or recent myocardial infarction, valvular disease, or known cardiac insufficiency. Although patients with controlled arterial hypertension, arrhythmia, or coronary artery disease may be at higher risk for cardiac decompensation in the setting of acute SAH, patients with stable conditions under medical treatment and documented normal myocardial function were not excluded from the study. If a patient presented more than one episode of PE, each episode was studied separately. Early onset has been defined as PE occurring in the first 12 hours after SAH.

Myocardial function was assessed using hemodynamic criteria suggestive of systolic or diastolic dysfunction. The following variables were defined as abnormal based on established criteria:[6] central venous pressure (CVP) >15 mm Hg, pulmonary capillary wedge pressure (PCWP) >15 mm Hg, mean pulmonary arterial pressure (MPAP) >25 mm Hg, the ratio of mean arterial pressure (MAP) on MPAP <4[7,8](normal value >4) expiratory end tidal $CO_2$ ($ETCO_2$) <25 mm Hg, cardiac index (CI) <2.5 L/min/$m^2$ or reduction of 40% or more of the initial value. All intraoperative and postoperative hemodynamic evaluations were reviewed by an intensivist and cardiac anesthesiologist expert and with Board Certification in perioperative echocardiography. Data were collected within a six-hour period before or after initial chest radiograph with signs of PE. The echocardiographic exams were performed either by an anesthesiologist expert or a cardiologist expert with National Board Certification. Systolic dysfunction was evaluated using two-dimensional (2D) observations of wall motion abnormalities classified as normal, akinetic, hypokinetic or dyskinetic.[9] The ejection fraction was estimated using fractional area change measured using a transgastric mid-papillary view.[10] No contrast agents were necessary to evaluate ventricular function. This measure has been validated.[11,12] Diastolic function was evaluated according to the Canadian consensus.[12]

## Results

A total of 385 consecutive patients admitted between April 1998 and April 2001 with confirmed SAH either by lumbar puncture or positive computed tomogram scan were retrospectively studied. Among these, 296 cases were secondary to ruptured aneurysms: 118 underwent endovascular treatments and 178 underwent surgical interventions. Forty-two patients (28.8%) were included in the present study for a total of 47 episodes of PE (Figure 1). Demographic variables are presented in Table 1.

Delay between SAH and PE onset are presented in Table 2. Five cases had an early onset (10.6%) and 42 a delayed onset (89.4%). Delay between SAH and aneurysm surgery was <24 hours in 29 cases (62%), 24 to 48 hours in nine cases (19%), 48 to 72 hours in one case (2%), 72 to 96 hours in four cases (8.5%). In four cases (8.5%) delay was more than four days due to delayed patient consultation or delayed hospital transfer.

In the intraoperative setting, using the hemodynamic criteria, abnormal values were observed between 58.3% and 100% (Table 3). From the 47 PE episodes studied, 43 (91.5%) satisfied at least one criterion and 24 (51.1%) satisfied at least two criteria. In the four cases not having satisfied any criterion, only the CVP and $ETCO_2$ were available in the charts. At the moment of radiographic diagnosis of PE, abnormal values were observed between 50% and 94.7% (Table 4), at least one criterion was satisfied in 27 (57.5%) cases and two or more were satisfied in 16 (34.0%) cases. In the 20 cases not having satisfied a criterion, the CVP was the only available data in 13 cases and no data was available in seven cases.

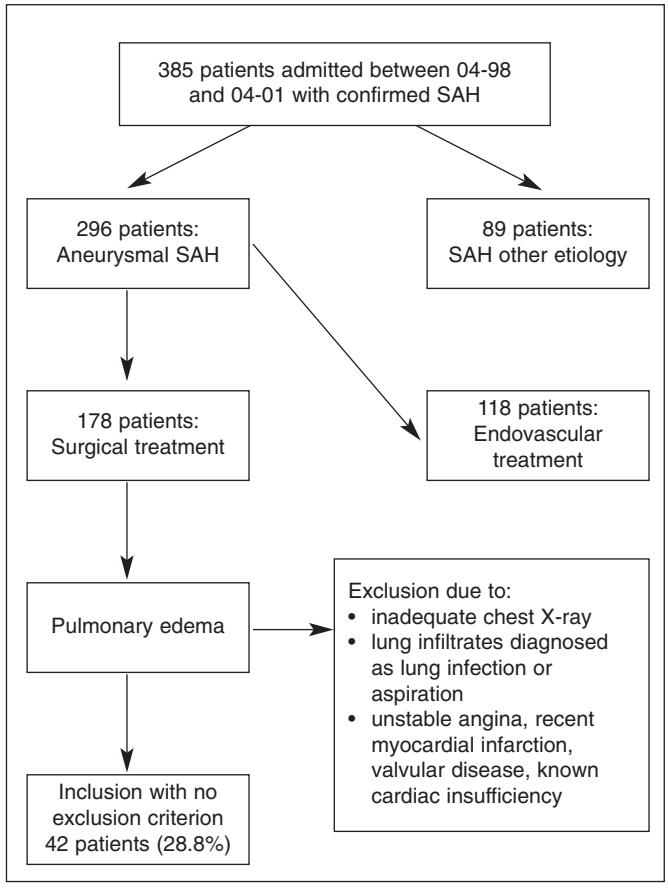


***Figure 1:*** *Algorithm for patients' distribution.*



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**Table 1: Demographic variables.**

| Characteristics | |
|---|---|
| Sex | M: 14 |
| | F: 28 |
| Age | Mean 51.8 |
| | Range: 33-79 |
| Coronary artery disease | 2 |
| Systemic hypertension | 15 |
| Arrhythmia | 1 |
| Smoking | 20 |
| Hunt & Hess grade | Good (grades 1-2): 13 |
| | Fair (grade 3): 13 |
| | Poor (grades 4-5): 16 |

**Table 2: Delay between subarachnoid hemorrhage and pulmonary edema onset.**

| Delay between SAH and PE onset (in days) | Number of episodes |
|---|---|
| [0-0.5[ | 5 |
| [0.5-1[ | 1 |
| [1-2[ | 10 |
| [2-3[ | 8 |
| [3-4[ | 11 |
| [4-5[ | 6 |
| 5 and more | 6 |

Abbreviations: SAH=subarachnoid hemorrhage; PE=pulmonary edema.

**Table 3: Intraoperative hemodynamic evaluation.**

| Abnormal variable | Data available (Number of cases) | Criterion satisfied (Number of cases) | % |
|---|---|---|---|
| CVP >15 mm Hg | 24 | 14 | 58.3 |
| PCWP >15 mm Hg | 4 | 3 | 75.0 |
| MPAP >25 mm Hg | 24 | 14 | 58.3 |
| Ratio MAP/MPAP <4 | 24 | 24 | 100.0 |
| $EtCO_2$ <25 mm Hg | 47 | 28 | 59.6 |

Abbreviations: CVP=central venous pressure; PCWP=pulmonary capillary wedge pressure; MPAP=mean pulmonary artery pressure; MAP=mean arterial pressure; $EtCO_2$=End-tidal carbon dioxide.

In some patients, the hemodynamic findings were by themselves diagnostic of myocardial involvement. In other cases, the anesthesiologist or intensivist requested that an echocardiographic exam be done to confirm the suspected cardiac dysfunction. An echocardiographic exam was performed in 20 cases of PE. Eight patients (40%) showed a local and/or global diminished left ventricular systolic function. Of the two exams that were done before pulmonary deterioration, one showed apical hypokinesis. One case that was investigated the following day of PE diagnosis had hypokinetic and akinetic segments. Cases investigated more than two days after onset of pulmonary deterioration showed no wall motion abnormality. Left ventricular ejection fraction was normal (>50%) in three cases that had segmental hypokinesis and one case with diffuse hypokinesis. Left ventricular ejection fraction was mildly (40 to 50%) diminished in one case with hypokinetic and akinetic segments and severely (<30%) diminished in one case with hypokinetic segments and another with akinetic segments. In one case, hypokinesis was found on echocardiography but left ventricular ejection fraction was not reported during the exam.

An example of a patient with PE who developed hemodynamic instability intraoperatively is shown in Figure 2. This was a 37-year-old woman with no past medical history of cardiac disease who presented with a SAH. The CT scan done at her arrival showed massive SAH with intraventricular flooding and PE was present on the chest radiograph performed at admission. No cardiomegaly was noted. The intraoperative hemodynamic tracing showed a heart rate from 88 to 96 beats/min, systolic and diastolic arterial pressure from 94 to 104 and 51 to 59 mm Hg, elevated systolic and diastolic pulmonary artery pressure with a mean value above 25 mm Hg and a ratio of MAP to MPAP of 1.9. This was associated with a V wave on the pulmonary artery tracing. With transesophageal echocardiography, there was no significant mitral regurgitation with color Doppler. On pulse wave Doppler, a significant E (90 cm/sec) to A (30 cm/sec) ratio and a short deceleration time (140 msec) was present, consistent with abnormal diastolic function. In addition, she had severe apical akinesis and diffuse mid-papillary hypokinesis.

## Discussion

It has been previously described that PE most often developed within minutes to a few hours after an acute central nervous system insult.[1,3,5,13-15] However PE may have a delayed onset and develop within the first few days of the insult.[3,5,16] Our results support the existence of a more common delayed type of PE with an incidence of 89%.

**Table 4: Hemodynamic evaluation at the moment of radiographic diagnosis of pulmonary edema.**

| Abnormal variable | Data available (Number of cases) | Criterion satisfied (Number of cases) | % |
|---|---|---|---|
| CVP >15 mm Hg | 40 | 21 | 52.5 |
| PCWP >15 mm Hg | 12 | 10 | 83.3 |
| MPAP >25 mm Hg | 19 | 13 | 68.4 |
| Ratio MAP/MPAP <4 | 19 | 18 | 94.7 |
| CI <2.5 L/min/$m^2$ or reduction of 40% or more from initial value | 8 | 4 | 50.0 |

Abbreviations: CVP=central venous pressure; PCWP=pulmonary capillary wedge pressure; MPAP=mean pulmonary artery pressure; MAP=mean arterial pressure; CI=cardiac index.



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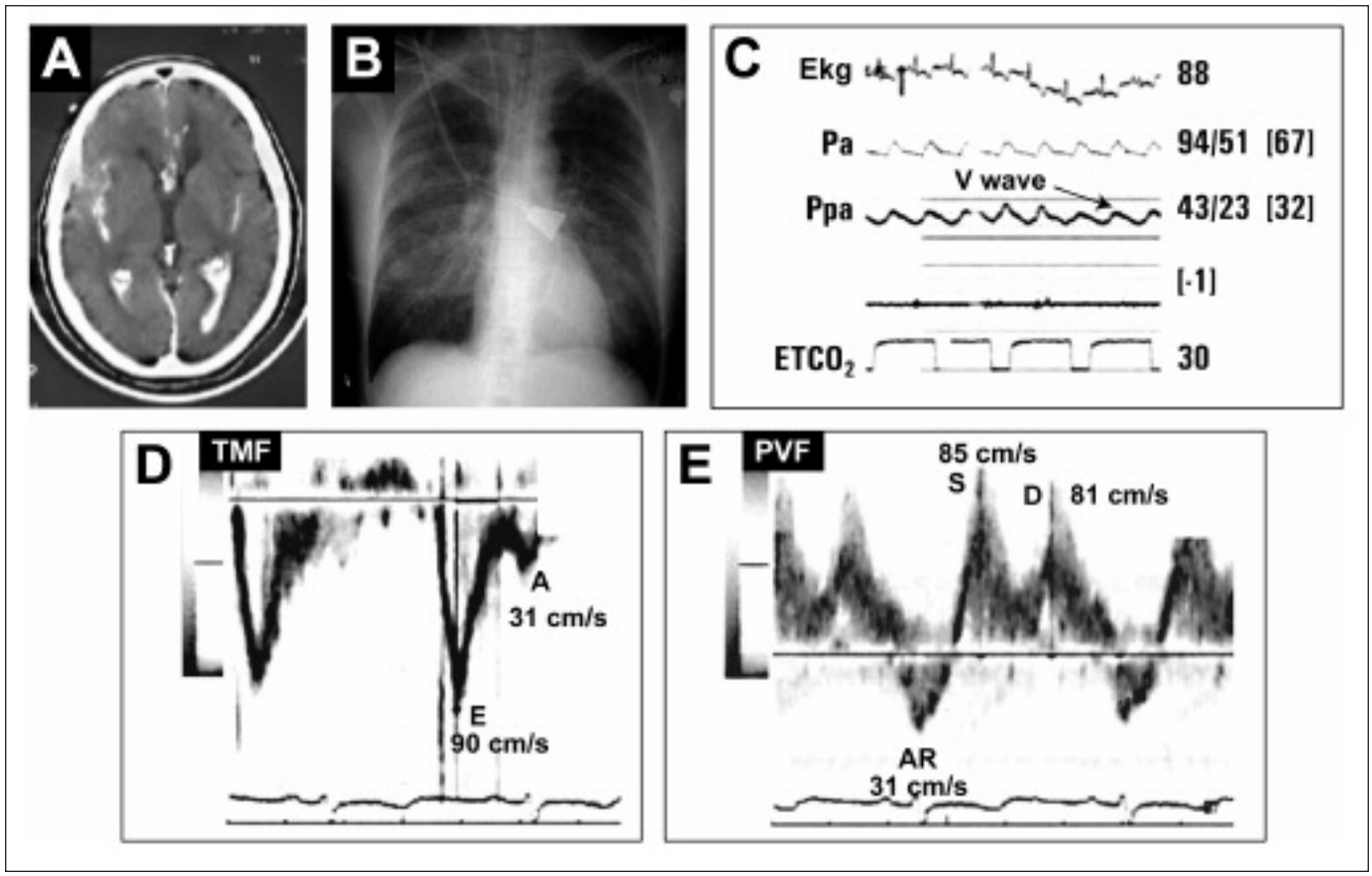


***Figure 2:*** *A 37-year-old woman with subarachnoid hemorrhage. The patient's head CT-scan showed intraventricular bleeding (A) and pulmonary edema is seen on the chest radiograph (B). The hemodynamic tracing shows a heart rate of 88 beats/min, systolic and diastolic arterial pressure of 94 and 51 mm Hg, systolic and diastolic pulmonary artery pressure of 43 and 23 mm Hg with a prominent V wave (C). Transmitral flow Doppler velocities of the mitral valve inflow reveals a high E/A ratio (D) and the systolic "S" to diastolic " D" ratio of the pulmonary venous flow is close to 1 (E). These features are consistent with abnormal diastolic function and elevated filling pressure. There was no significant mitral regurgitation with color Doppler (data not shown). (AR: atrial reversal, EKG: electrocardiogram, $ETCO_2$: end-tidal carbon dioxide, Pa: arterial pressure, Ppa: pulmonary artery pressure).*

The mechanisms of pulmonary edema occurring after a central nervous system lesion are partially understood. Four primary forces determine fluid movement through the capillary membrane: capillary pressure, interstitial fluid pressure, plasma colloid osmotic pressure, and interstitial fluid colloid osmotic pressure. Controversial evidence in current literature brought authors to believe that the PE found in these patients may be due to a spectrum of hemodynamic and permeability mechanisms (Figure 3). The term neurohemodynamic pulmonary edema has been proposed.[17] This is supported by various authors that suggest simultaneous hydrostatic and permeability mechanisms.[3,4,18-21] A summary of the various mechanisms proposed in case reports and retrospective studies from human literature is presented in Table 5.

Many case reports supporting the hydrostatic mechanism have been published. However, only a few retrospective studies supporting or refuting this hypothesis can be found in the literature. Our observations show that a significant proportion of patients with PE in the setting of SAH have an abnormal hemodynamic profile suggesting myocardial dysfunction which might contribute to a raised hydrostatic pressure.

Several authors have studied the various effects SAH might have on the myocardium. This represents a spectrum of disease from cellular changes to increased enzymes such as Creatine Kinase isoenzyme Muscle-Brain (CK-MB) and troponin, electrocardiographic changes, hemodynamic and echocardiographic abnormalities. Evidence supports catecholamine surge mediated by the sympathetic system as primary contributor to myocardial damage.[19,22-26] In several studies, all myocardial cells had changes in their ultra-structure varying from mild cell disruption to cell death.[24,27-29] This cellular disruption supports the idea that a certain quantity of myocardial cell abnormality is required for a clinical manifestation to occur.

This cardiac multifocal myocytolysis is supported by numerous reports of elevated CK-MB concentrations measured in SAH patients.[22,23,25,30-32] The CK-MB release was found to increase progressively as left ventricular performance decreased.[31] The incidence of myocardial damage is further



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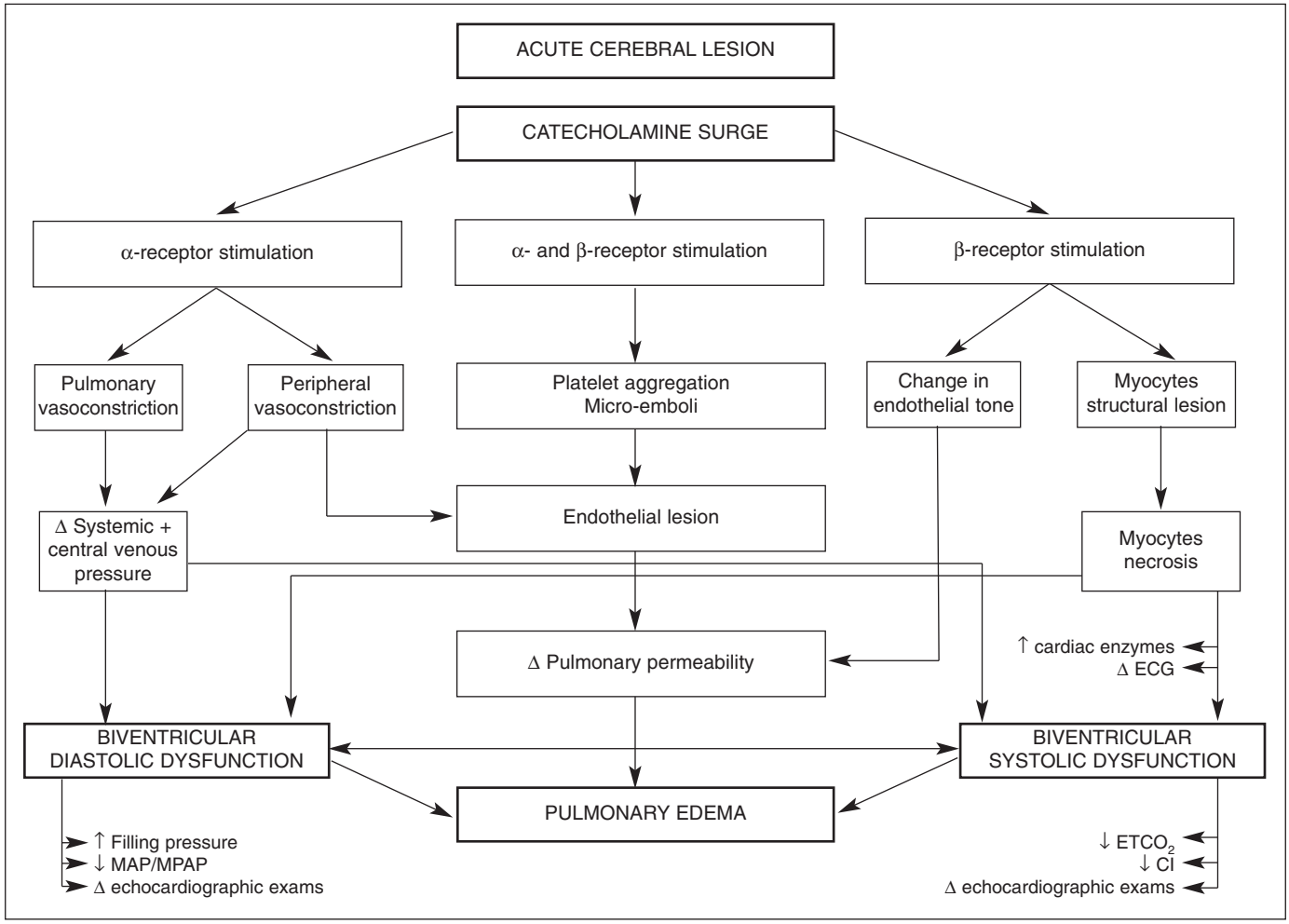


***Figure 3:*** *Pathophysiology of neurogenic pulmonary edema. (*Abbreviations: CI: cardiac index, ETCO2: end-tidal carbon dioxide, MAP/MPAP: ratio of mean arterial pressure to mean pulmonary arterial pressure (normal value > 4)).

supported by measurement of troponin I that has been found to reveal a higher incidence of myocardial injury than predicted by CK-MB in SAH patients and troponin I would be associated with a higher incidence of myocardial dysfunction.[33]

Electrocardiographic modifications are accounted for by activation of neural pathways and also by the presence of structural lesions.[25,27,30,32] Electrocardiographic abnormalities in patients with SAH are not specific and often transient. Echocardiographic studies have found wall motion abnormalities in 9% to 23% of SAH patients with electrocardiographic abnormalities.[34] These wall motion abnormalities are associated with T wave inversion and severe QTc prolongation, borderline CK-MB elevation (2% to 5%), and poor neurological grade.[30-32,34] Studies exploring left ventricular function during SAH are summarized in Table 6.

Our observations suggest that a cardiogenic component is present in a significant proportion of patients with PE following SAH. Abnormal hemodynamic variables obtained in this study were suggestive of myocardial dysfunction and confirmed by the echocardiographic findings.

Although we observed mostly systolic dysfunction, diastolic dysfunction is commonly present in patients with systolic dysfunction. So far, the presence of diastolic dysfunction has not been reported as a potential mechanism in PE associated with SAH. However it has been observed in up to 59% of hemodynamically unstable patients in the intensive care unit after cardiac surgery[35] and in unstable patients following SAH in whom transesophageal echocardiography was performed during episodes of hemodynamic instability. The extent to which diastolic dysfunction alone could contribute to PE in SAH is unknown.

There is growing interest in the appreciation of diastolic function. This interest is in part due to a widespread use of echocardiography which enables the noninvasive diagnosis of diastolic dysfunction. Diastolic dysfunction is likely to be an important contributor in >30% to 50% of patients presenting with PE.[36-38] It has been recognized to adversely affect outcome in patients with left ventricular[39-42] and right ventricular systolic dysfunction[43] and even in patients without left ventricular systolic dysfunction.[44]

The recognition of myocardial dysfunction in SAH patients might have important clinical significance. The existence of segmental or global wall motion abnormalities could facilitate the formation of thrombi that can embolize distally. Aggressive



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**Table 5: Summary of human studies concerning mechanisms contributing to pulmonary edema in patients with subarachnoid hemorrhage.**

| Authors | Type of study | Number of patients | Principal mechanism proposed[1] |
|---|---|---|---|
| Ducker 1968[46] | CR | 11 | NM |
| Ciongoli 1972[47] | CR | 3 | NM |
| Harari 1976[16] | CR | 5 | P |
| Kosnik 1977[48] | CR | 6 | HP |
| Wray 1978[14] | CR | 1 | HP+P |
| Carlson 1979[15] | CR | 1 | HP |
| Fein 1979[49] | RS | 24 | P |
| Eggleston 1982[50] | CR | 3 | NM |
| Fein 1982[2] | CR | 24 | P |
| Langerkranser 1982[51] | CR | 5 | HP |
| Melon 1985[52] | CR | 2 | P |
| Schell 1987[53] | CR | 1 | HP |
| Pender 1992[5] | CR | 4 | HP+P |
| Handlin 1993[22] | CR | 1 | HP |
| Mayer 1994[25] | CR | 5 | HP |
| Deehan 1996[54] | RS | 20 | HP |
| Smith 1997[55] | RS | 12 | HP |

Abbreviations: CR=case report; RS=retrospective study; [1] HP=raised hydrostatic pressure; P=increased permeability; NM=no mechanism proposed.

hypertension-hypervolemia-hemodilution therapy might facilitate apparition of PE because patients with ventricular dysfunction do not tolerate increases in afterload. Such patients could be candidates for the use of inotropes such as dobutamine to improve cerebral perfusion. In these patients, intensive hemodynamic monitoring may be sought but 2D echocardiography should be obtained to evaluate both ventricular systolic and diastolic function.

There are some limitations to the present study. This study was retrospective and the selection and use of the various monitoring devices were not controlled for and could be subject to bias. Consequently, the real incidence of a cardiogenic component in PE occurring in SAH setting could be higher than reported if for instance 2D echocardiography was performed in all patients. The cardiac enzymes such as troponin are not measured routinely after SAH. There is also a time delay in the apparition of PE and cardiac dysfunction following SAH. Earlier echocardiographic exam could have detected a higher incidence of cardiac dysfunction.

The pulmonary artery catheter was not used in all patients. The routine use of this catheter in noncardiac surgery is controversial[45] and therefore used differently among clinicians. The timing of the echocardiographic exam was not controlled. Due to the reversibility of myocardial dysfunction, some exams performed later after the initial ictus might have shown normal myocardial function. We have seen patients with severe myocardial function in the operating room with significant improvement within 24 hours and complete normalization a week after hospitalization. Such reversibility of the echocardiographic observations might also be observed for the hemodynamic findings. Normal values observed six hours after obtaining the abnormal chest radiograph might represent re-

**Table 6: Summary of human studies concerning left ventricular performance in patients with subarachnoid hemorrhage.**

| Authors | Type of study | | | No. of Patients | Findings |
|---|---|---|---|---|---|
| | CR/CS | RS | PS | | |
| Pollick 1988[30] | - | 1 index case | 12 cases studied prospectively | 13 | Abnormal wall motion in 4 patients<br>Presence of thrombus in 2 patients |
| Davies 1991[34] | - | | | 45 | Abnormal wall motion in 4 patients |
| Handlin 1993[22] | X | - | - | 1 | Septal, apical, and lateral LV akinesis (LVEF 25%) |
| Kono 1994[56] | - | X | - | 12 | Abnormal wall motion in 12 patients<br>Group with ST-segment elevation had more hypokinesis at apex |
| Mayer 1994[25] | X | - | - | 5 | Abnormal wall motion in 5 patients (LVEF 16 to 35% initially)<br>Presence of apical thrombus in 2 patients |
| Pinto 1994[57] | X | - | - | 1 | Anterolateral, septal, apical hypokinesis (LVEF 25%) |
| Mayer 1995[32] | - | - | X | 57 | Abnormal wall motion in 5 patients (moderate to severe LVEF reduction). Presence of apical thrombus in 2 patients |
| Mayer 1999[31] | - | X | - | 72 | Abnormal wall motion in 9 patients |
| Sakka 1999[58] | X | - | - | 1 | Interventricular septum hypokinesis (LVEF 10%-12%) |
| Yasu 1999[59] | X | - | - | 1 | Anterolateral and inferior akinesis and apical hypokinesis (LVEF 54%) |
| Parekh 2000[33] | - | - | X | 39 | Abnormal wall motion in 5 patients (LVEF 25% to 50%) |

Abbreviations: LV=left ventricular; LVEF=left ventricular ejection fraction; CR=case report; CS=case series; RS=retrospective study; PS=prospective study.

normalization. In addition, PE could also be absent in patients with cardiac involvement. A prospective trial of consecutive patients with systematic and timely fashioned hemodynamic monitoring and 2D echocardiographic examination would provide a more accurate estimation of the incidence of systolic and diastolic dysfunction following SAH. Thus, further study is warranted to prospectively assess the incidence and mechanisms of PE and the importance of diastolic dysfunction in this condition.

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