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Central periodic breathing during sleep in 74 patients with acute ischemic stroke - Neurogenic and cardiogenic factors

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Abstract: **OBJECTIVES :** The aims of our study were 1) to better characterize central periodic breathing during sleep (CPBS) and its clinical relevance in acute stroke, 2) to better define the role of brain damage in its pathogenesis. **METHODS :** We included 74 consecutive patients admitted within 96 hours after stroke onset. Stroke severity at admission, stroke outcome at discharge and stroke topography were assessed. ECG and transesophageal echocardiography were performed. Nocturnal breathing was assessed with an ambulatory device the first night after admission. CPBS severity was represented as absolute time and percentage of recording time. **RESULTS :** Age was 63 +/- 13 (25-82), 49 (66 %) were male. Thirty (41 %) patients showed CPBS during ≥ 10 % and 7 (9 %) during ≥ 50 % of recording time. CPBS severity was associated with age ($p = 0.017$), stroke severity ($p = 0.008$), ECG abnormalities ($p = 0.005$) and lower left ventricular ejection fraction ($p < 0.0001$). CPBS severity was higher in patients with extensive hemispheric strokes ($n = 6$, $p < 0.0001$), and lower in patients with partial strokes involving the left insula ($n = 5$, $p < 0.0001$) and the mesencephalon ($n = 5$, $p = 0.002$). **CONCLUSIONS :** CPBS is frequent in acute ischemic stroke and is associated with older age, stroke severity/extension, and lower left ventricular function. The lower occurrence of CPBS in left insular and mesencephalic stroke suggests a major role of distinct brain areas in the modulation of respiratory phenomena accompanying acute stroke.

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CENTRAL PERIODIC BREATHING IN 74 PATIENTS WITH ACUTE ISCHEMIC STROKE - NEUROGENIC VERSUS CARDIOGENIC FACTORS

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Abstract

Objectives: The aims of our study are 1) to better characterize central periodic breathing during sleep (CPBS) and its clinical relevance in acute stroke, 2) to better define the role of brain damage in its pathogenesis.

Methods: We included 74 consecutive patients admitted within 96 hours after stroke onset. Stroke severity on admission, stroke outcome at discharge and stroke topography were assessed. ECG and transesophageal echocardiography were performed. Nocturnal breathing was assessed with an ambulatory device the first night after admission. CPBS severity was represented as absolute time and percentage of recording time.

Results: Age was 63 ± 13 [25-82], 49 (66%) were male. Thirty (41%) patients showed CPBS during $\geq 10\%$ and 7 (9%) during $\geq 50\%$ of recording time. CPBS severity was associated with age ($p=0.017$), stroke severity ($p=0.008$), ECG abnormalities ($p=0.005$) and lower left ventricular ejection fraction ($p<0.0001$). CPBS severity was higher in patients with extensive hemispheric strokes ($n=6$, $p<0.0001$), and significantly lower in patients with partial strokes involving the left insula ($n=5$, $p<0.0001$) and the mesencephalon ($n=5$, $p=0.002$).

Conclusions: CPBS is a frequent phenomenon in acute ischemic stroke, and is associated with older age, stroke severity/extension, and lower left ventricular function. The lower occurrence of CPBS in left insular and mesencephalic stroke suggests a major role of distinct brain areas in the modulation of respiratory phenomena accompanying acute stroke, and emphasize the role of acute brain damage in their pathogenesis.

Introduction

Central periodic breathing (CPB) - or Cheyne-Stokes breathing, characterized by cyclic fluctuations in breathing drive in a gradual waxing-and-waning fashion [1] - result from a variety of conditions affecting the neuronal network involved in respiratory control.

CPB during wakefulness and/or sleep have been reported in patients with brainstem or bilateral extensive hemispheric stroke and impaired level of consciousness [2-4]. More recent studies in stroke patients report a variable prevalence (6-38%) for CPB during sleep (CPBS) [4-8], a spontaneous recovery of these breathing pattern after stroke [6,9,10] and an association with large ischemic lesions and poor functional outcome [11,12].

In both patients with and without stroke, CPBS has been linked to increased respiratory CO₂ sensitivity [13,14] and left ventricular dysfunction [15,16]. CPBS has also been reported in patients with unilateral lesions of variable topography without disturbed level of consciousness or overt heart failure [4,10,17]. Although these observations clearly suggest a major role of distinct brain areas in the regulation of respiratory response to ischemic brain damage, the mechanisms leading to CPBS in association with a new-onset ischemic brain lesion remain poorly known.

Following a preliminary retrospective observation on three patients (University Hospital of Berne) [10], we performed a systematic and prospective assessment of CPBS in a new larger series of patients with the aim 1) to better characterize this breathing pattern and its clinical relevance in acute stroke, 2) to better define the role of brain damage in its pathogenesis.

Methods

Patients. Seventy-four consecutive adult patients with first-ever acute ischemic stroke were prospectively included. The study design was approved by the local ethical committee, and written informed consent was obtained from patients or relatives. Patients with very

severe strokes (National Institutes of Health Stroke Scale [18] [NIHSS]>20), intracerebral/subarachnoid haemorrhage, coma/stupor, life-threatening medical conditions were excluded.

Clinical and radiological evaluation. Cardiovascular risk factors including family history, arterial hypertension (defined as BP >140/90 mmHg measured ≥ 3 times prior to stroke), diabetes (defined as fasting glucose level >140 mg/dl), smoking status, hypercholesterinemia (defined as cholesterol level >250 mg/dl), obesity (defined as Body-Mass-Index (BMI) ≥ 25 kg/m²) and previous history of heart failure/coronary heart disease were assessed.

Clinical stroke assessment included NIHSS and modified Rankin disability Scale [19] at hospital discharge.

An ECG was performed on admission, Holter ECG and transesophageal echocardiography during the hospitalization.

Stroke topography was assessed in the acute phase according to clinical and radiological criteria by CT scan examination and/or MR imaging. A detailed topographic description of the ischemic region according to clinically identifiable subtypes [20] and vascular territories [21] was performed.

Nocturnal breathing. Overnight respirography was performed with a validated [9] portable device (Autoset® Embletta PDS, ResMed) during the first night after admission. The recording was considered to be successful if ≥ 60 minutes with nasal flow and at least one chest band signal were present. The analysis was performed automatically and corrected manually according to previously described standard criteria [5]. Chaotic signals automatically scored from the computer as events were carefully checked manually, and, if not clearly classifiable, were not considered as respiratory events and excluded. Apnea was defined by a cessation of oro-nasal airflow ≥ 10 seconds, hypopnea by a reduction of oro-nasal airflow ≥ 10 seconds by $\geq 50\%$, or $\geq 30\%$ when associated with an oxygen desaturation $\geq 4\%$. Apnea-hypopnea-index (AHI)

was defined by the mean number of apneas and hypopneas per hour, apnea-index (AI) by the mean number of apneas per hour between lights off and on. Sleep apnea was defined by $AHI \geq 10/h$, mild by $AHI 10-30/h$, moderate-severe by $AHI >30/h$. A differentiation between obstructive (OAI) and central (CAI) apnea-index was undertaken according to standard criteria. The percentage of time with oxygen saturation $<90\%$, as well as the oxygen-desaturation-index (ODI) were calculated. The magnitude of the oxygen desaturation considered for ODI was $\geq 4\%$. Body position was not monitored. CPBS was defined as ≥ 3 cycles of regular crescendo-decrescendo-breathing associated with reduction of $\geq 50\%$ in nasal airflow and respiratory effort lasting ≥ 10 seconds [1,22,23]. A cycle was defined from the end of one apnea/hypopnea to the end of the next. The periodic pattern of CPBS had to be recognized visually in both the nasal pressure and the respiratory effort signal in order to prevent over-interpretation of the data. Episodes with reduced airflow but clearly maintained respiratory effort were classified as obstructive, and not as central periodic breathing. Severity of CPBS was represented as absolute time and as percentage of total recording time. No patients received oxygen or sedative medication in the hours before or during the recording.

Statistics. Statistical analysis was performed with SPSS software package 12.0. Continuous data were presented as mean and standard deviation, categorical data as numbers and percentage. Student's unpaired t-tests were used for comparison of patients groups and for testing of continuous variables. Categorical data were compared with the Mann-Whitney rank-sum tests or the χ^2 tests. Correlations were calculated using the Pearson's coefficient. A p-value <0.05 was considered to be statistically significant. Multiple stepwise regression models with entry value set to 0.05 and removal value set to 0.1 in the univariate analysis were tested using stroke outcome (mRS) as dependent variable. Duration and severity of CPBS and stroke severity on admission (NIHSS) were candidate predictors.

Results

Clinical data. Seventy-four adult patients with first-ever acute ischemic stroke were included, three underwent systemic thrombolysis. The main characteristics of all patients are summarized in table 1.

Cardiological data. ECG abnormalities (Sinus brady-/tachycardia, ST-segment/T-waves abnormalities, AV-blocks of different degree) were found in 41 (55%) patients, 10 patients (13%) had atrial fibrillation. Transesophageal echocardiography was performed in 55 (74%) patients, left ventricular ejection fraction (LVEF) was $61\pm 9\%$ [33-80]. Eighteen (33%) patients had a LVEF $<60\%$, six (11%) patients $<50\%$.

Radiological data. The stroke was localized on the right side in 40 (54%) patients and on the left side in 34 (46%) patients. Sixty-one (82%) patients had an hemispheric stroke and 13 patients (18%) a brainstem stroke. In fifty-five (74%) patients the ischemic lesion was localized in the middle cerebral artery territory, in six patients (8%) in the posterior cerebral artery territory. There were no strokes in the anterior cerebral artery territory. The most representative detailed stroke topographies and the corresponding respiratory parameters and CPBS severity are shown in table 3.

Respirographic data. Respirography was performed 45 ± 26 hours [4-96] after stroke onset. CPBS was found in 53 (72%) patients, in 30 (41%) patients during $\geq 10\%$ and in seven (9%) patients during $\geq 50\%$ of recording time, by a mean total recording time of 598 ± 150 minutes [0-776]. The main respiratory results are summarized in table 1. Sleep apnea (defined as $AHI > 10/h$) was found in 41 (55%) patients ($AHI 33\pm 19/h$ [11-82], $OAI 5\pm 9/h$ [0-57], $CAI 12\pm 14/h$ [0-61], $ODI 27\pm 21/h$ [5-84]). Severity of CPBS correlated with severity of sleep apnea ($r=0.755$, $p<0.0001$), central apneas ($r=0.798$, $p<0.0001$), and oxygen desaturations ($r=0.661$, $p<0.0001$).

Patients with CPBS were older, had a higher occurrence of ECG abnormalities on admission, and a lower LVEF compared to patients without CPBS (table 2). Accordingly, severity of CPBS correlated with age ($r=0.280$, $p=0.017$), stroke severity on admission ($r=0.309$, $p=0.009$), occurrence of ECG abnormalities ($r=0.337$, $p=0.005$), and lower LVEF ($r=-0.542$, $p<0.0001$). Conversely, there was no significant correlation between the pre-stroke cardiovascular risk factors (positive family history for cardiovascular disease, arterial hypertension, diabetes, smoking, hypercholesterinemia, obesity, history of heart failure/coronary heart disease) and CPBS severity. No significant correlation between CPBS severity and stroke outcome at discharge was found after taking into account stroke severity on admission.

Concerning stroke topography, CPBS was much more frequent/severe in total anterior circulation strokes (TACS), especially left-sided ($p<0.0001$). CPBS was more frequent in patients with stroke in the frontal/prefrontal region, deep MCA territory, right insula, and thalamic/hypothalamic region, the difference in CPBS severity compared to other stroke topographies did not reach however statistical significance. Patients with strokes in the mesencephalic ($n=5$) and left insular region ($n=5$) had a significantly lower severity of sleep apnea (both topographies $p<0.0001$), central apneas (both topographies $p<0.0001$), and CPBS (mesencephalic $p=0.002$, left insular region $p<0.0001$, respectively) compared to patients with other stroke localizations, despite the absence of significant differences in stroke severity, cardiovascular risk factors and left ventricular function. A summary of sleep apnea/CPBS severity according to stroke topography is reported in table 3.

Discussion

The aim of our study was to describe characteristics and clinical relevance of CPBS in acute ischemic stroke, and to better define the role of brain damage in its pathogenesis. Our main results are:

- 1) CPBS is frequent in the first few days after acute ischemic stroke,
- 2) CPBS is associated with a) older age, b) ECG abnormalities and c) lower left ventricular function.
- 3) occurs more frequently in patients with (left-sided) severe/extensive hemispheric strokes, and remarkably less frequently in patients with strokes involving the left insular or mesencephalic region.

1) Frequency of CPBS in acute ischemic stroke

CPBS was found in 53 (72%) patients, in 30 (41%) during $\geq 10\%$ of recording time.

In previous studies investigating breathing disorders during sleep in the very early stroke phase (≤ 72 hours after stroke onset) performed with different portable devices [6,11,12,24] or with full polysomnography [7], CPBS was observed in 23-38% of patients [7,11,12,24], and was present during $\geq 10\%$ of recording time in 12-28% of patients [6,24]. In contrast, in the studies performed with full polysomnography during the subacute stroke phase (after a mean time of 9 to 44 days after stroke) [4,5,16], lower frequencies of CPBS (6-19%) were reported. Parra et al. [6] showed an improvement of CPBS after 3 months. Only in one study performed with full polysomnography [8] after a mean time of 12 days after stroke CPBS was documented during $\geq 10\%$ of recording time in 37% of patients. However, this higher frequency of CPBS might be explained by the fact that 70% of these patients underwent polysomnography early (< 10 days) following stroke and that $> 50\%$ of them had coronary heart disease or congestive heart failure.

Thus, the high frequency of CPBS in our study may be in part explained with the short latency between stroke onset and respirography. In addition, the methodology used in the recording of nocturnal breathing (highly sensitive XactTrace sensor) may have contributed to these results. The left ventricular function was similar or higher in our series compared to previous studies [4,16] and may not explain the higher CPBS frequency found. Our patients

were in part younger and had milder strokes compared to previous studies [4-7,11,12,16,24] and to a general stroke population [25,26] despite the absence of major differences in cardiovascular risk profile or stroke topography. However, considering that CPBS has been described in association with large and severe strokes [11,12], the younger age and the milder stroke severity are very unlikely to explain the higher CPBS frequency observed in our series.

2) CPBS and left ventricular function

We found an association of CPBS with age, ECG abnormalities and lower left ventricular function in patients with acute ischemic stroke. In our series, although only six (11%) out of 55 patients undergoing echocardiography had a LVEF <50%, we observed a significant inverse linear correlation between CPBS severity and LVEF. Our results suggest an association between CPBS severity and lower LVEF even in the absence of a cardiac dysfunction. Similarly, Nopmaneejumruslers et al. [16] found a significant association between CPBS and reduced (<40%) LVEF after stroke, but also a normal LVEF in 14 patients with CPBS, which could not be explained by the authors.

3a) CPBS and stroke topography/type

In line with previous studies [4,11,12,17], we found that CPBS is much more frequent and severe in patients with TACS. CPBS was also more pronounced in strokes localized in distinct brain areas (table 3), although the difference to other topographies did not reach statistical significance. This observation suggests that brain lesions involving autonomic (insula) or volitional (prefrontal region, capsula interna, thalamus) structures participating to respiratory control may favour CPBS after stroke.

The most interesting, to our best knowledge unreported observation was the considerably lower frequency of central apneas and CPBS in patients with circumscribed (not extensive) strokes involving the left insula and the mesencephalon despite the absence of a

significant difference in stroke severity, demographics, cardiovascular risk profile and left ventricular function compared to other topographies.

The insula is with the amygdala, the hypothalamus, the periaqueductal grey (mesencephalon), and the ventrolateral medulla part of the central autonomic network [27], which plays a central role in the integration and processing of autonomic and behavioural information essential for survival [28]. Severe cardiovascular and autonomic disturbances have been reported in human and animals in association with insular lesions including stroke, predominantly on the right side [29-33]. Otherwise, left-sided insular strokes lead rather to a disturbed cardioinhibitory/cardioregulatory function with an autonomic shift toward a pro-arrhythmic condition [29].

Hence, we suggest - in analogy - that a shift in the autonomic (sympathetic-parasympathetic) balance may be responsible for the remarkably lower frequency of central apneas and CPBS in patients with circumscribed left insular (and mesencephalic) strokes. This hypothesis is supported by recent observations showing functional changes in brain areas responsible for autonomic respiratory control (including insula) in patients with sleep-disordered breathing [34].

Interestingly, extensive left hemispheric strokes (also involving the insula) presented with severe CPBS. The considerable variability in CPBS severity observed in patients with stroke of different extension involving the left insula may be in part explained by the complex somatotopic representation of the respiratory-related area in the insular cortex [35] and by the disruption of the insular afferent/efferent autonomic regulatory pathways leading - depending on its extension - to different changes in the respiratory patterns. However, probably due to our assessment methods, we could not identify further findings supporting this hypothesis. Obviously, considering the low sample size in the mentioned topographic subgroups, a type 1 error cannot be excluded. The observed associations between stroke in

distinct brain areas and severity of CPBS shall be regarded as hypothesis generating, and need to be confirmed in further studies including a larger number of patients.

3b) CPBS and stroke severity/outcome

Previous studies showed an association between CPBS, worse functional outcome, and increased mortality after stroke [12]. In our study we did not find - possibly due to the sample size and short observation time - this prognostic association after accounting for the initial stroke severity. Our results show that patients with an extensive unilateral hemispheric brain damage were more prone to develop central apneas and CPBS in the acute stroke phase. If CPBS may per se lead to a worse stroke evolution or (rather) represent a consequence of stroke in part related to its severity and extension, remains however still unclear. Considering that our patients mostly presented with mild-moderate strokes, extensive hemispheric strokes (TACS) might have been underrepresented in our series. This may be considered, along with the in part younger age of the patients compared to previous studies and to a general stroke population, as possible limitation of the study.

The fact that no PCO₂ measurement during the acute phase and no follow-up respirographies have been performed should be mentioned as further limitation of our study. These examinations might provide further useful information in understanding the pathophysiology of CPBS in acute stroke.

Our observations strongly emphasize the role of a central neurogenic component - in addition to the cardiac and pulmonary one - and the differential role of distinct brain areas in the pathogenesis of CPBS associated with acute ischemic brain damage, showing the tight link existing between brain, cardiovascular and respiratory system.

Further studies including a larger number of patients, PCO₂ measurements, follow-up respirographies and an assessment of autonomic function (or of its surrogate markers) are

needed to confirm our observations and to better define the pathophysiological background and the clinical implications of these findings.

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Table 1. Main results of all patients

	All (n=74)
Male/female (%)	49/25 (66/34)
Age (years)	63±13 [25-82]
Body-mass-index (kg/m ²)	28±4 [20-39]
BMI >25 (%)	26 (35)
Arterial hypertension	36 (49)
Positive family history for vascular diseases	37 (50)
Diabetes	40 (54)
Smoking	31 (42)
Hypercholesterinemia	30 (40)
Coronary heart disease/heart failure	38 (51)
NIH Stroke Scale on admission	6±5 [0-20]
Modified Rankin Disability Scale at discharge	1.6±1.3 [0-5]
Apnea-hypopnea-index (/h)	20±20 [0-82]
Apnea-index (/h)	10±14 [0-70]
Obstructive apnea-index (/h)	3±7 [0-57]
Central apnea-index (/h)	7±12 [0-61]
Oxygen-desaturation-index (/h)	17±20 [0-84]
Total recording time (min)	598±150 [0-776]
CPBS duration (min)	102±155 [0-651]
CPBS severity, % of recording time (min)	16±22 [0-90]

Values are mean±SD [range in brackets] or numbers (% in brackets)

CPBS, central periodic breathing during sleep

Table 2. Selection of relevant demographic, cardiological and clinical stroke parameters in all patients with CPBS and in two subgroups of patient with CPBS severity of different degree compared to patients without CPBS

n=74	No CPBS (n=21)	CPBS (n=53)	CPBS severity	
			CPBS 10-50 % (n=23)	CPBS ≥50 % (n=7)
Age (years)	53±15 [25-82]	66±10 [45-82]*	67±11 [47-82]*	69±10 [52-79]*
History of hypertension	14 (67)	23 (44)	9 (39)*	3 (43)
Diabetes	9 (43)	30 (57)	12 (52)	6 (86)
CAD/HF	7 (37)	29 (55)	12 (52)	5 (71)
NIH Stroke Scale day1	6±4 [0-17]	6±5 [1-20]	5±5 [1-20]	11±8 [4-20]
mRS at discharge	1.6±1.6 [0-4]	1.7±1.3 [0-5]	1.5±1.0 [0-4]	2.7±2.0 [0-5]
LVEF	65±8 [55-80]	60±10 [33-77]	56±9 [33-70]*	50±4 [45-55]*
ECG abnormalities	7 (33)	33 (62)*	17 (74)*	5 (71)
AF on admission	2 (10)	7 (13)	4 (17)	2 (29)

Values are means±SD [ranges in brackets] or numbers (% in brackets)

CPBS, central periodic breathing during sleep; CAD, history of coronary heart disease; HF, history of heart failure; mRS, modified Rankin disability scale; LVEF, left ventricular ejection fraction; ECG abnormalities, electrocardiographic abnormalities on admission; CPBS, central periodic breathing during sleep

* **and bold** = statistically significant (p<0.05) compared to patients without CPBS

Table 3. Nocturnal breathing parameters and stroke topography (selection of most representative localizations regarding CPBS severity)

Stroke topography	N=74	AHI (/h)	CAI (/h)	CPBS%
TACS	6 (8)	41±35	17±23	54±39*
PACS	42 (57)	18±17	7±11	12±17
LACS	7 (9)	27±19	12±10	23±25
POCS	19 (26)	16±19	3±7	13±21
Frontal/precentral region (MCA)	10 (14)	30±20	17±16	19±19
Deep MCA	18 (24)	20±16	8±10	18±23
Right insula	5 (7)	17±12	8±7	12±8
Left insula	5 (7)	4±5*	1±1*	0±0*
Thalamus/hypothalamus	3 (4)	18±14	5±6	27±20
Pons	5 (7)	33±24	4±5	12±10
Mesencephalon	5 (7)	7±2*	1±1*	4±5*

Values are mean±SD or numbers (% in brackets)

AHI, Apnea-hypopnea-index; CAI, central apnea-index; CPBS%, central periodic breathing in sleep, % of total recording time

* **and bold** = statistically significant ($p < 0.05$) compared to strokes with different topography

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