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RESEARCH ARTICLE

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Cardiovascular and respiratory consequences of bilateral involvement of the medullary intermediate reticular formation in syringobulbia

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Abstract We studied five patients with clinical and radiological evidence of syringobulbia (SB) to determine whether the distribution of lesions in relationship to the cardiorespiratory control networks in the medullary intermediate reticular zone (IRt) correlates with the presence of abnormalities in autonomic cardiovascular and respiratory control in these patients. All patients underwent high resolution MRI to characterize the size, volume and distribution of the SB lesions, cardiovascular autonomic function testing and polysomnography. One patient with bilateral IRt involvement at both the rostral and caudal medulla had orthostatic hypotension (OH), absent HR_{DB}, abnormal Valsalva ratio, exaggerated fall of BP during phase II and absent phase IV during VM, and a dramatic fall of BP during head up tilt; this patient also had severe obstructive sleep apnea (OSA) and exhibited BP drops during each respiratory effort. A second patient, with bilateral IRt involvement restricted to the caudal medulla, had less severe cardiovascular autonomic dysfunction but also exhibited severe OSA. The other three patients had small SB cavities sparing the IRt and had sleep apnea but no autonomic dysfunction. Autonomic dysfunction could not be related to the size of the syrinx or the degree of atrophy in the cervical spinal cord in any of the five patients. Bilateral involvement of the IRt by SB produces cardiovascular autonomic failure and sleep apnea. In patients with more restricted lesions, autonomic and respiratory dysfunction may be dissociated. Clinico-radiological correlations using high resolution MRI assessment of medullary lesions can provide insight into the central organization of cardiovascular and respiratory control in humans.

Key words syringobulbia · medulla · SDB · autonomic failure · intermediate reticular formation

Introduction

Syringobulbia (SB) can affect cardiovascular and respiratory functions [4, 5, 7, 11, 15–17, 19]. Involvement of cardiovascular and respiratory control networks in the intermediate reticular formation (IRt) of the medulla by the syrinx [8] may provide the substrate for the cardiorespiratory manifestations of the disease. The IRt extends from the nucleus tractus solitarius (NTS) to the

ventrolateral medulla (VLM), and contains propriobulbar and bulbospinal neurons that are critical for generation and integration of tonic and reflex cardiovascular and respiratory control mechanisms [1, 3, 9, 20]. Tonic activity depends on intrinsic pacemaker properties of specific groups of neurons and network interactions at the level of the IRt, whereas reflexes are initiated by inputs from baroreceptors, cardiac receptors and pulmonary receptors that relay in different subnuclei of the NTS. The outputs are mediated by cardiovagal neurons of the nucleus ambiguus; sympathoexcitatory neurons of the rostral VLM, and neurons of the ventral respiratory group (VRG); the VRG also contains neurons generating respiratory rhythm and drive [1, 3, 9, 20].

These areas may be affected in syringobulbia (SB), but the relationship between these lesions and the presence of cardiovascular and respiratory abnormalities in SB has not been systematically explored. We sought to determine the relationship between the distribution of lesions in syringobulbia and the abnormalities in cardiovascular and respiratory function in these patients, by using high resolution MRI and quantitative autonomic function testing. These results were previously presented in an abstract form [12].

Materials and methods

We studied 5 patients (4 men, 1 woman, ages 35 to 46 years) with clinical and radiological evidence of SB (Table 1). They had variable disease duration, variable involvement of cranial nerves and variable degrees of coexistent syringomyelia (SM). A disability status score (DSS, 0 = normal neurological examination, 9 = totally helpless and bedridden) based on Kurtzke's scale for multiple sclerosis [13] is included in Table 1. Patient 3 had a minimal disability, whereas the rest of the patients had marked paraparesis or quadriparesis ranging from relatively severe disability (patient 5) to restriction to wheelchair (patient 1). None of the patients complained of autonomic symptoms, and none suffered from pulmonary or heart disease. Baseline heart rate (HR), blood pressure (BP), and body mass index (BMI) are shown in Table 1. All patients signed an informed consent to undergo this study, according to institutional guidelines.

MRI and lesion characterization

We used high resolution and 3-D thin-slice MRI techniques with an automated image analysis system to characterize the size, volume and distribution of the SB lesions. The scans were acquired on a 1.5 T GE Sigma Horizon scanner (GE Medical Systems, Milwaukee, WI) using a 3D (three dimensional)/SPER/60 volume acquisition in the axial plane. TR/TE = 20 ms/3 ms, number of excitations = 2, 60 slices; slice thickness = 1.5 mm; matrix = 256 × 192; FOV = 24 × 18 cm; scan time = 6 min, 12 s.

Tracing the outline of both the medulla and the lesion with the image analysis system (SPGR, GE Medical Systems, Milwaukee, WI) allowed calculation of the area in mm^2, which could then be multiplied by the 1.5-mm thickness of each slice to approximate volume. Size of the syrinx was expressed as a percentage of volume of the medulla. Reconstructions were matched to tyrosine hydroxylase (TH) stained sections of the normal human medulla at the same level to plot the distribution of the lesions in relationship to the IRt.

Autonomic function testing

All patients underwent autonomic testing, including heart rate (HR) and systolic (SBP) and diastolic (DBP) blood pressure responses to deep breathing (DB), Valsalva maneuver (VM) and head-up tilt (HUT). Continuous electrocardiogram (ECG) was recorded via two surface electrodes placed on the chest. Arterial pressure was continuously monitored via an indwelling 20 g intraarterial catheter inserted in the radial artery, and connected to a disposable pressure transducer (Ohmeda, model DT-6012).

Respiratory sinus arrhythmia

Patients rested in a supine position for 3 minutes prior to testing. The first run was obtained during baseline conditions with normal breathing. The next run recorded subject deep breathing at a frequency of 6 cycles per minute, obtained by following instructions from the operator. An epoch of 1 minute was analyzed. A plot of R-R intervals versus time was displayed on the equipment screen. The following algorithm was used to analyze R-R variation: (RR maximal – RR minimal) × 100/RR mean (the difference between the shortest and the longest RR intervals during 1 minute given in percent of the mean of all maximal and minimal peaks). Recording was made on an electromyograph Keypoint (Medtronic, Minneapolis, MN). Reference values for sinus arrhythmia were obtained from Stålberg and Nogués [21].

Valsalva maneuver

The maneuver was performed in the supine position by blowing into a device connected to a standard manometer. Subjects were trained to maintain an expiratory pressure of 40 mmHg for 15 s. Following a training period, each subject performed two Valsalva maneuvers sep-

Table 1 Patient population

Patient	Age/Sex	Disease duration (yrs.)	BMI	SM	Chiari malf.	Cranial Nerve Involv.	DSS	HR (bpm)	BP (mmHg)
P1	39/M	10	26.9	Yes	Yes	IX, X, VIII	7	80	130/80
P2	42/M	29	19.9	Yes	Yes	IX, X, VIII	5	92	100/80
P3	35/W	5	23.5	Yes	No	V, VIII	2	80	110/70
P4	46/M	35	28.1	Yes	No	VIII	5	82	110/70
P5	41/M	18	26.3	Yes	No	VIII, X	4	100	120/80

M male; *F* female; *BMI* body mass index; *SM* syringomyelia; *Chiari malf.* Chiari malformation; *Cranial Nerve Involv* Cranial Nerve Involvement; *DSS* Disability status score; *HR* heart rate; *BP* blood pressure

arated by a rest period of at least two minutes. Blood pressure during early and late Phase II and Phase IV of the Valsalva maneuver was continuously monitored via the intraarterial line. Care was taken that the pressure rose sharply at the onset and fell abruptly at the termination of the strain period. The Valsalva ratio (VR) was calculated by dividing the longest RR interval after the strain, by the minimal RR variation during the strain [VR = max HR of II/min HR of IV]. Normal values were obtained from Stålberg and Nogués [21].

Head-up tilt

Patients underwent head up tilt up to 70 degrees within 4 s, with continuous monitoring of HR and BP for five minutes.

Respiratory function testing

All patients underwent respiratory function testing. Vital capacity (VC), forced expiratory volume in one second (FEV_1) and FEV_1/FVC ratio were obtained with a Fleisch Pneumotach. Maximum static mouth pressure at residual volume and total lung capacity were measured using a SCUBA-type mouthpiece according to the protocol of Black and Hyatt [2]. Reference values were calculated following the guidelines of Vinken et al. [23].

Polysomnography

All patients underwent polysomnography with continuous monitoring of HR and BP. Patients were studied in a darkened, sound-attenuated room for one night, employing conventional leads for EEG, EOG, EMG (chin and tibialis anterior muscles), and ECG recordings. Rubber bellows placed at the maximal excursion abdominal site with a piezoelectric respiratory effort transducer (piezoelectric respiratory effort transducer Grass F-RCTA) served to transduce respiratory movements to pressure changes, while surface electrodes were also used to record EMG intercostal activity. Airflow was monitored by nasal and oral thermistors and snoring by a microphone. Oxygen saturation (SaO_2) was monitored with an ear oxymeter (Ohmeda Biox 3700e, Datex-Ohmeda, Finland). A Grass model 8 Plus EEG/Polysomnograph (Grass Instruments Co., Quincy, MA) was employed at chart speeds of 5-, 10-, and 15-mm/s. A slower chart speed (2.5 mm/s) was also used to assess blood pressure changes during respiratory events. Patients were videotaped during polysomnography recording [6].

The number and duration of central and obstructive apneas as well as hypopneas were calculated. Central sleep apnea (CSA) was defined as cessation of airflow during sleep lasting 10 s or longer. Obstructive sleep apnea (OSA) was defined as cessation of airflow for at least 10 s in spite of persistent respiratory efforts. Hypopneas were defined as a 50 % decrease in airflow associated to a reduction of at least 4 % in oxygen saturation (SaO_2) without complete cessation of breathing. Classifying hypopneas as central or obstructive was not possible as the use of nasal and oral thermistors precluded this determination and more reliable techniques such as inductance plethysmography or intraesophageal balloons to obtain information about respiratory effort were not employed. In order to quantify respiratory pauses during sleep, the apnea index (AI = number of apneas-hypopneas per hour of sleep) was calculated. The HR and BP responses during apneas were assessed [10, 22, 24] by means of an intraarterial recording.

Results

Distribution of lesions

MRI findings in all patients are shown in Fig. 1, which displays tracings of sections of the medulla from rostral to caudal. Patient 1, with involvement of the caudal medulla only, and Patient 2, with involvement of both the caudal and the rostral medulla, both demonstrated the lesions in the area corresponding to the IRt, as de-

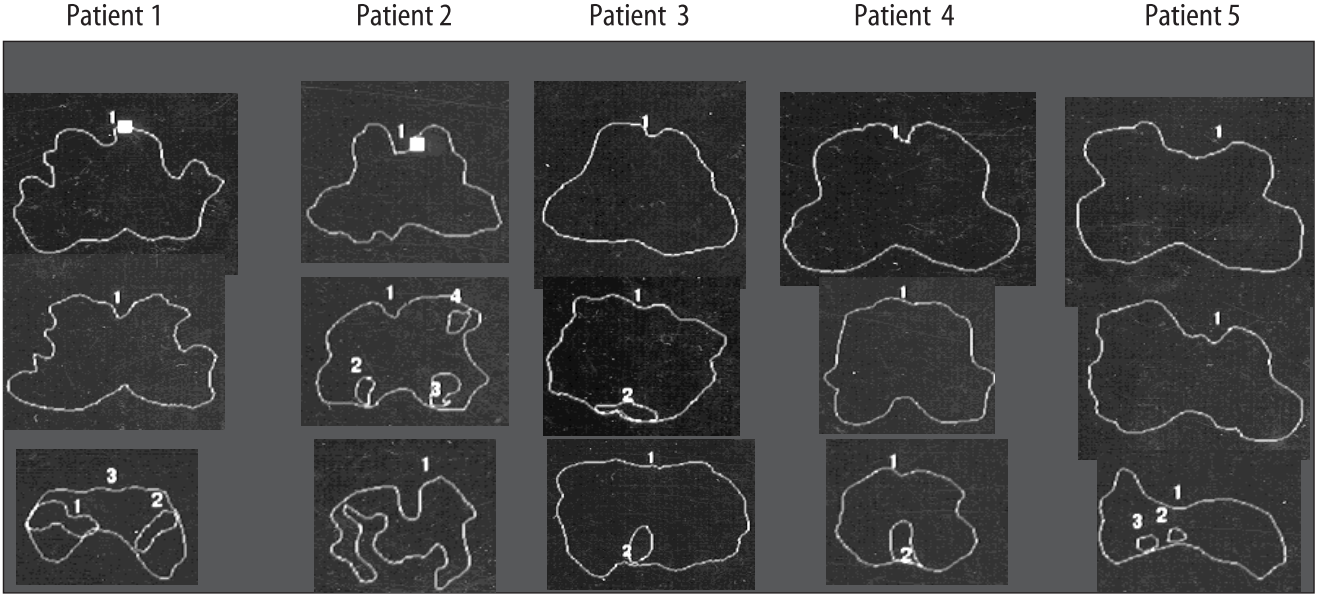

Fig. 1 MRI findings in the five patients. Tracings of transverse 1.5-mm thick sections of the medulla are displayed from rostral to caudal. Note the bilateral involvement of the IRt in the caudal medulla of Patient 1, and in both caudal and rostral medulla in Patient 2. Patients 3–5 had small lesions restricted to the dorsal medulla. Note the distortion of the medulla in Patient 5

fined by overlapping with reconstruction of the medulla stained for tyrosine hydroxylase. Patients 3, 4, and 5, with involvement primarily of the caudal medulla, had no involvement of the IRt.

Cardiovascular responses

Patients 1 and 2, with bilateral involvement of the IRt, had impaired HR response to DB and VM (Fig. 2). The responses were normal in the patients without IRt involvement. Patient 2, with bilateral involvement of the IRt at the caudal and rostral medulla, had not only profound orthostatic hypotension, but also impaired compensatory tachycardia during head-up tilt. The other patients had normal responses.

The cardiovascular responses during the VM are shown in Fig. 3. Patients 1 and 2, with involvement of the IRt, had a marked decrease of arterial pressure during early and late Phase II and impaired overshoot in Phase IV. Patient 3, with a small cavity in the dorsal portion of the caudal medulla, had normal responses. Patients 4 and 5, with small lesions in the caudal medulla, exhibited profound fall of systolic blood pressure during early and late Phase II, but normal Phase IV overshoot. The Valsalva ratio was reduced in Patients 1, 2, and 4 (Fig. 3).

Polysomnography

Maximal duration of hypopneas varied in the five patients between 25 and 160 s, of OSA between 15 and 125 s, and of CSA between 15 and 65 s. SaO_2 dropped during prolonged events in Patients 1 and 2, to values of 64 and 20 % respectively. Patient 1 showed periodic leg movements throughout the night, both during REM and non-REM sleep (periodic limb movement index = 360/hour of sleep). Patient 2 had marked motor activity and agitation during prolonged obstructive episodes. Patient 1 showed surges of BP at the end of each obstructive apnea, whereas patient 2 had drops in BP with each respiratory effort.

A follow-up polysomnography with continuous positive airway pressure (CPAP) was done on Patient 1. The sleep efficiency rose in the second study, and stages 3 and 4, which were absent in the first polysomnography, rose to 29 and 31 % in the second study. Patient 5 showed a moderately increased apnea index (26.4), while Patients 1 and 2 had severe SDB (AI > 50) (Fig. 3). Hypopneas were the respiratory events more frequently found. Obstructive events were more common than central ones.

Relationship among autonomic and respiratory dysfunction and syrinx size

The relationship between the severity of cardiovascular and respiratory dysfunction and size of the medullary

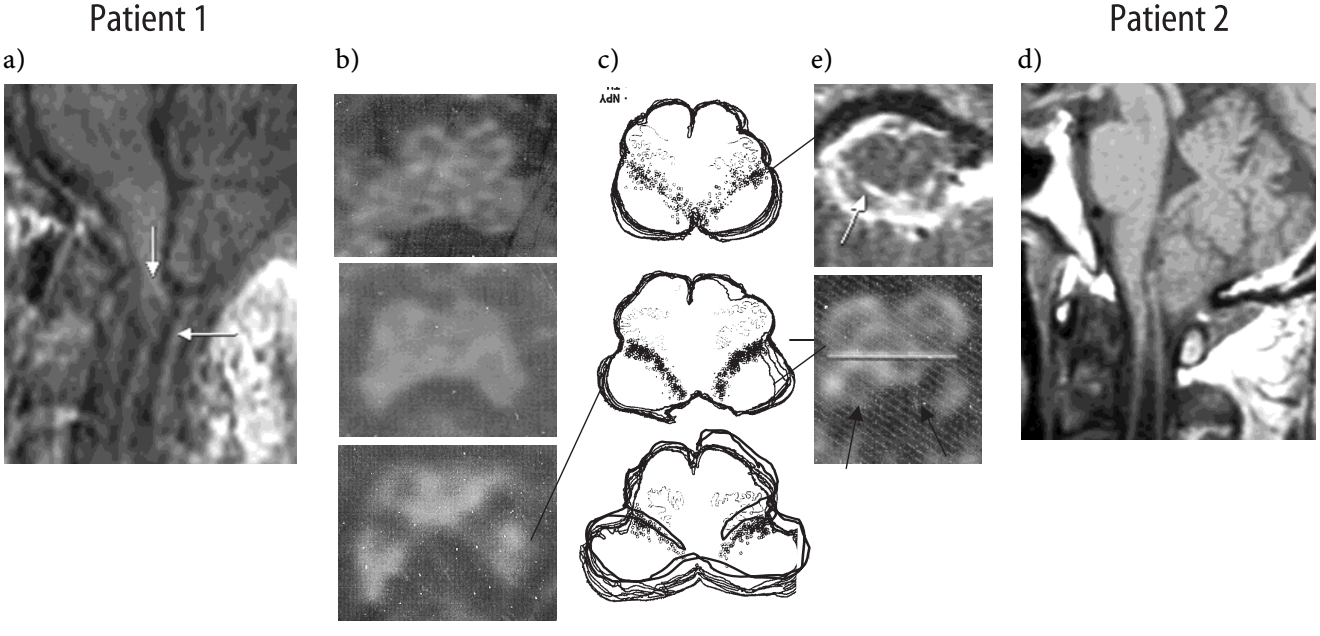

Fig. 2 Left panel: Sagittal (**a**) and transverse (**b**) sections of the medulla in Patient 1 in comparison with the distribution of tyrosine hydroxylase (TH) in corresponding sections (**c**). Right panel: Sagittal (**d**) and transverse (**e**) sections of the medulla in Patient 2 in comparison with the distribution of tyrosine hydroxylase (TH) in corresponding sections (**c**)

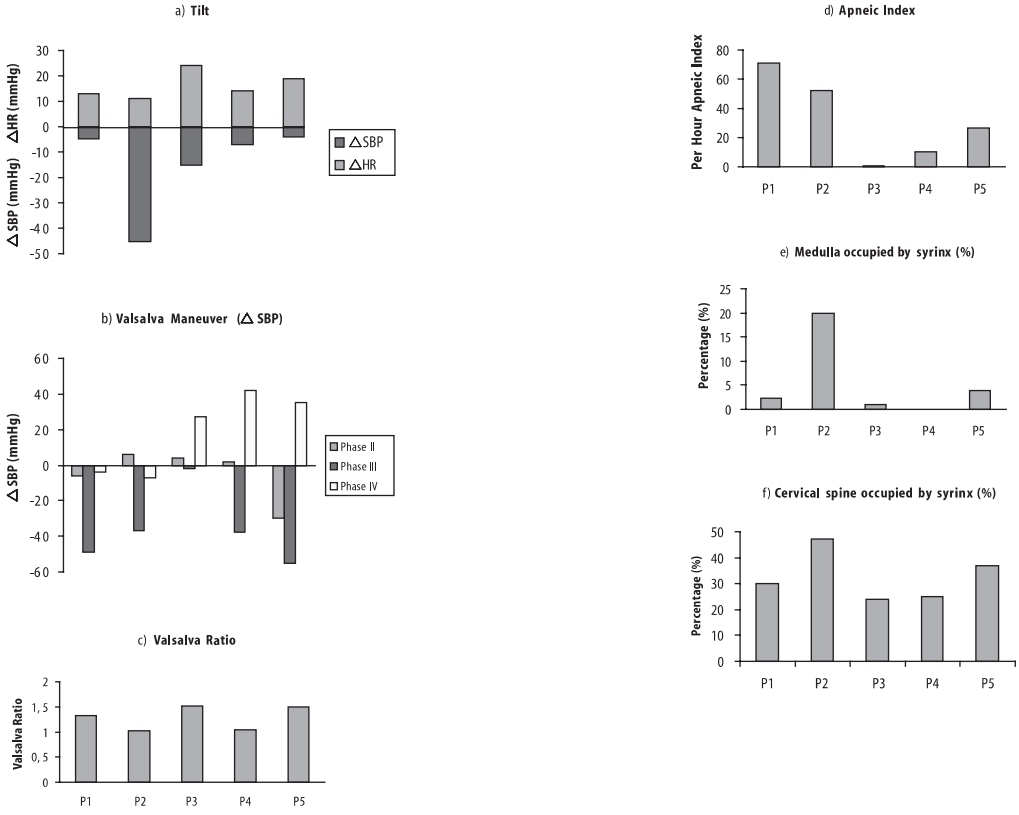

Fig. 3 Relationship between cardiovascular and respiratory findings and syrinx size in the 5 patients. **a** Change in SBP and heart rate (HR) during head-up tilt (HUT). Note the profound fall of SBP with blunted HR in Patient 2. **b** Change in systolic blood pressure (SBP) during Phase II and IV of the Valsalva maneuver (VM). Both marked reduction in early and late Phase II and absent Phase IV overshoot are seen in Patients 1 and 2. Patients 4 and 5 had preserved Phase IV. **c** Valsalva Ratio. **d** Apnea Index (AI). Note the severity of sleep apnea in Patients 1 and 2. Syrinx size expressed as percentage of volume in the medulla (**e**) and cervical spinal cord (**f**). Patients 1 and 2 with larger syrinx size had larger cardiovascular and respiratory abnormalities. Note the lack of relationship between the size of the cervical syrinx and the severity of the abnormalities

and cervical syrinx were assessed in all patients. Patient 2, with the largest medullary syrinx, exhibited, in addition to the severe cardiovascular abnormalities described above, the highest apneic index. Patient 1, with bilateral involvement of the IRt at the caudal medulla, also had a high apneic index. Patient 5 had large medullary and spinal syrinxes, and also had an elevated AI. No clear relationship existed between the size of the cervical syrinx and the severity of cardiovascular and respiratory failure in any of the patients (Fig. 3).

Patient 1 and 2 had severe fluctuation of SBP during episodes of sleep apnea and Patient 2 experienced progressive oxygen desaturation during an episode of sleep apnea (Fig. 4).

Discussion

Our results indicate that bilateral involvement of the IRt by syringobulbia produces cardiovagal and adrenergic vasomotor failure, in addition to affecting respiratory control. This is consistent with abundant experimental evidence of the critical role of this area in regulating tonic and reflex cardiorespiratory activity [1, 9]. Involvement of cardiovagal neurons of the nucleus ambiguus [1] likely explains the impaired HR responses to DB and VM observed in the two patients with bilateral involvement of this region. Bilateral involvement of the rostral IRt, containing the C1 adrenergic and the glutamatergic sympathoexcitatory bulbospinal neurons controlling tonic and reflex vasomotor activity [1, 3], is likely to explain the severe OH and blood pressure changes during the VM observed in Patient 2, who had bilateral involvement of this region. Interruption of descending sympathoexcitatory pathways may have contributed to the exaggerated fall of BP in phase II in Patients 4 and 5.

The IRt also contains neurons of the ventral respiratory groups, including the pre-Bötzinger complex involved in respiratory rhythmogenesis, and inspiratory and expiratory neurons of the ambigual/retroambigual regions [9, 20]. Although bilateral involvement of this region could explain the abnormalities in respiratory rhythm seen in Patients 1 and 2, sleep apnea may also

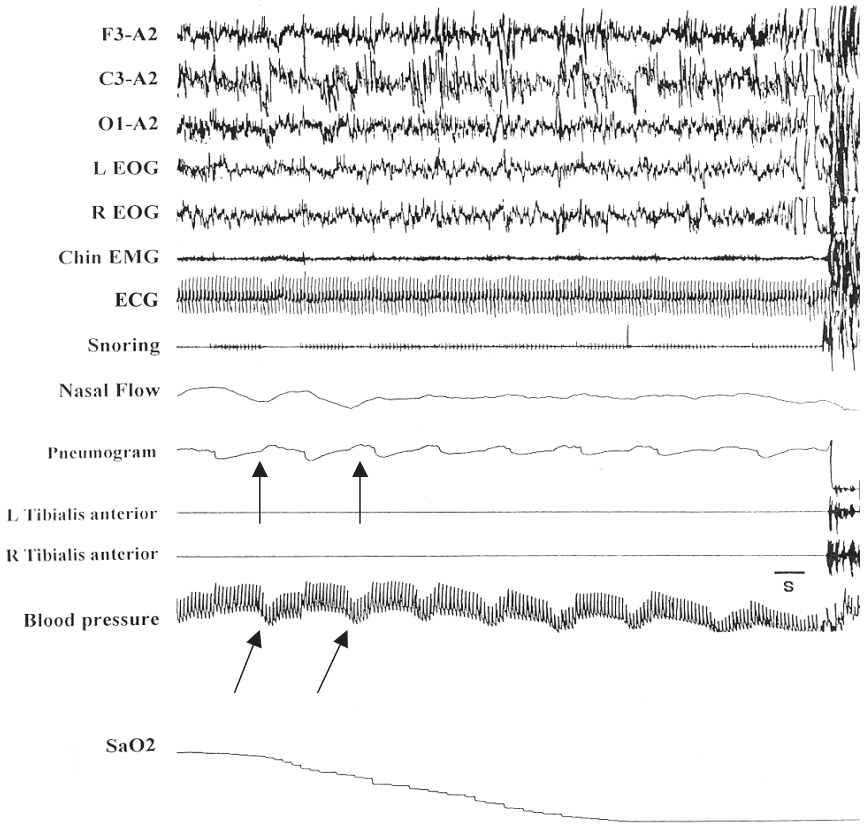

Fig. 4 Polysomnogram with continuous Blood pressure monitoring in Patient 2. Progressive oxygen desaturation. Note the occurrence of Blood pressure falls during the respiratory efforts (obstructive sleep apnea)

occur in the setting of sparing of the IRt, as observed in the other 3 Patients. This could represent interruption of descending bulbospinal pathways by the syrinx. Furthermore, evidence indicates that even unilateral focal lesions in the rostral ventrolateral medulla, including the IRt, result in sleep apnea and reduce chemosensitivity to CO_2 [14]. Finally, the abnormal cardiovascular response during episodes of sleep apnea in Patients 1 and 2 are consistent with evidence that the IRt contains interneuron networks that coordinate respiratory, cardiovagal and vasomotor functions [18]. The introduction of CPAP in one of the patients increased sleep efficiency and led to disappearance of marked BP oscillations associated with sleep apneas.

Although the main limitation of our present study is the small number of patients assessed, its most significant element was our ability to correlate cardiovascular and respiratory manifestations in SB with carefully analyzed lesions in the medulla, using three dimensional and high definition MRI and plotting their distribution to that of TH stained sections to identify the IRt. Several factors make it difficult to study the lower brainstem with neuroimaging: lesions are usually small and may be missed by using conventional MRI slides; the medulla may be markedly atrophied or deformed by the Chiari I anomaly; a distended IV ventricle or post-operative arachnoiditis could prevent reliable distinction between a small cavity from subarachnoid CSF; and the patients may find it difficult to remain still due to dyspnea, dysphagia, spasticity or flexor responses in the legs. Therefore, although our study can be considered preliminary, our ability to correlate the results of the autonomic and respiratory function tests with the distribution and volume of the syrinx allows us to suggest that bilateral IRt involvement provides a major anatomical substrate for cardiovascular autonomic failure and sleep apnea in SB.

In summary, our findings indicate that careful correlations among clinical, MRI, autonomic, and respiratory function tests could provide insight into the organization of medullary cardiorespiratory control in humans. Further studies with a larger number of patients and long-term follow-up are planned to extend and confirm these observations.

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