Changes in heart rate during obstructive sleep apnoea

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ABSTRACT: The mechanisms behind the decrease in heart rate during apnoeas in patients with obstructive sleep apnoea (OSA) are little known. Recent findings in animal experiments indicate that stimulation of the upper airway activates postinspiratory and cardiac vagal neurones in the medullary respiratory centre, causing alterations in heart rate and respiratory rhythm.

Since OSA leads to a collapse of the airway and consequent stimulation of upper airway receptors, we studied the interrelations between heart rate and respiratory rhythm during apnoea and during negative intrathoracic pressure generated by the Mueller manoeuvre (MM).

Fifteen patients with OSA (apnoea hypopnoea index (AHI) $45\pm28\cdot h^{-1}$) were studied by polysomnography, during a MM and a Valsalva manoeuvre, each of 15 s duration. The heart rate decrease (ΔHRA) and the increase in total respiratory cycle duration (TOT) were evaluated during apnoea in non-rapid eye movement (REM) sleep.

Patients with OSA demonstrated a decrease in heart rate during apnoea (-14.4 ± 9.0 beats·min^{-1}), and during MM (-11.5 ± 13.5 in OSA *vs* 3.1 ± 7.8 beats·min^{-1} in a control group). TOT increased during apnoea (4.6 ± 3.1 s). There was a significant correlation between ΔHRA and AHI ($r=-0.64$) as well as between ΔHRA and increase in TOT($r=0.62$).

These findings indicate that upper airway obstruction may cause an activation of receptors at the site of airway collapse or distortion leading to changes in heart rate and respiratory rhythm.
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Obstructive sleep apnoea (OSA) is characterized by recurring upper airway collapse with ongoing respiratory effort, causing apnoea, and a fall in oxygen saturation. The decrease in heart rate during apnoea has long been recognized and is of some diagnostic importance in OSA; the mechanisms behind this decrease are, however, little understood [1, 2]. Recent animal studies suggest that the stimulation of receptors in the upper airway activates postinspiratory neurones in the medullary respiratory centre, causing alterations in heart rate and respiratory rhythm [3, 4]. OSA leads to collapse of the upper airway and, therefore, stimulates upper airway receptors [5, 6].

Since the Mueller manoeuvre (MM) mimics negative intrathoracic pressure caused by obstructive apnoea and leads to upper airway obstruction [6, 7], we compared heart rate changes during the MM with heart rate and total respiratory cycle duration (TOT) changes during apnoea. Comparable changes in heart rate during apnoea and MM, as well as between heart rate and TOT during apnoea would support the hypothesis that these changes are caused by activation of neurones in the medullary respiratory centre due to upper airway obstruction.

Subjects and methods

Fifteen consecutive patients aged 53 ± 8 yrs, with documented OSA, were studied (table 1). OSA was diagnosed when the apnoea hypopnoea index (AHI) was ≥ 10. The patients were required to have a normal exercise electrocardiogram, *i.e.* ST segment depression <0.1 mV, while achieving at least 75% of maximal heart rate. Thus, coronary heart disease was unlikely. No patient showed clinical evidence of polyneuropathy. Patients no. 6, 8, 9 and 12 had systemic hypertension, patient no. 1 was on treatment with calcium antagonists and patients no. 8 and 11 were on low-dose beta-blockade before and during the study. Patient no. 10 was the only female. The control group consisted of 15 healthy subjects, taken from our clinic staff, with no history of sleep disorders. These controls were comparable to the OSA patients (table 2 and 3). Informed consent was obtained from all subjects.

On two consecutive nights, the patients underwent polysomnography with electroencephalography, electro-oculography, electromyography of the submandibular muscles and electrocardiography. Respiration was monitored by oral and nasal thermistors and effort was

recorded by abdominal and thoracic strain gauges. Arterial oxyhaemoglobin saturation was measured by ear oximetry (Ohmeda, Biox 3700e). Parameters were registered on a polysomnograph (Nihon, Kohden), with a paper speed of 10 mm·s^{-1}, and subsequently evaluated [8]. An apnoea was scored as mixed if there was a cessation of airflow associated with an absence of ventilatory effort for at least 10 s, followed by continued absence of airflow despite the resumption of ventilatory effort. The percentage of mixed apnoeas in relation to all apnoeas was calculated.

Heart rate and TOT during 10 randomly selected apnoeas in sleep stage I–IV were analysed. The difference in heart rate during apnoea (ΔHRA) was calculated by subtracting heart rate immediately before apnoea from heart rate at the end of apnoea. Heart rate was averaged over three cardiac cycles. The difference in TOT (ΔTOT) was calculated by subtracting TOT immediately before apnoea from TOT at the beginning of apnoea. TOT was averaged over three respiratory cycles derived from abdominal or thoracic effort tracings.

Table 1. – Patient data

Pt no.	Age yrs	Weight kg	Broca	Sao$_2$m %	Sao$_2$b %	AHI ·h^{-1}	ΔTOT s	ΔHRB ·min^{-1}	ΔHRV ·min^{-1}	ΔHRM ·min^{-1}	TN s	ΔHRA ·min^{-1}	VE ·24 h^{-1}	Mixed %
1	53	95	110	57	95	53	6.2	-5	20	11	35	-25	912	32
2	59	80	107	85	96	10	1.8	-3	24	4	24	-10	8	5
3	41	96	137	69	94	73	7.9	-10	20	-30	23	-10	0	30
4	50	96	123	66	93	65	7.3	0	15	-30	31	-31	9	2
5	61	86	123	70	96	33	5.2	-5	10	-12	22	-15	695	71
6	61	78	100	90	96	19	4.5	-4	12	-9	21	-13	6	53
7	51	140	159	52	96	82	8.1	-8	8	-33	28	-35	7	80
8	58	85	127	36	97	58	8.3	-8	4	-12	33	-15	3996	67
9	54	73	100	78	96	19	3.5	0	5	5	23	-8	2	1
10	55	80	121	85	94	28	2.0	-17	7	-27	30	-15	1	34
11	43	98	136	85	95	29	1.7	0	10	-14	13	-8	0	31
12	60	83	119	78	95	33	1.4	-3	6	-9	22	-7	3	3
13	35	89	107	66	96	57	9.5	0	15	-5	43	-14	7	20
14	50	75	99	79	94	15	0.2	-2	8	-3	40	-4	0	7
15	58	73	104	71	94	25	1.0	0	4	-8	31	-7	11	0
Mean	53	88	118	71	95	43.4	4.6	-4.3	11.2	-11.5	28	-14.4	377	29.1
±SD	7.8	16.6	16.9	14.5	1.2	27.2	3.1	4.8	6.3	-13.5	8	9.0	1040	27.5

Broca: Broca-index; Sao$_2$m: minimal arterial oxygen saturation during apnoea; Sao$_2$b: basal arterial oxygen saturation; AHI: apnoea hypopnoea index; ΔTOT: difference in total respiratory cycle duration during apnoea; ΔHRB: difference of heart rate during breathholding; ΔHRV: difference of heart rate during Valsalva manoeuvre; ΔHRM: difference of heart rate during Mueller manoeuvre; TN: duration of apnoea in non-REM sleep; ΔHRA: difference of heart rate during apnoea in non-REM sleep; VE: ventricular ectopic beats; Mixed: percentage of mixed apnoeas.

Table 2. – Control group

Subject no.	Age yrs	Weight kg	Broca	Sao$_2$b %	HR ·min^{-1}	ΔHRB ·min^{-1}	ΔHRV ·min^{-1}	ΔHRM ·min^{-1}
1	42	92	116	96	68	-15	32	5
2	66	78	130	96	75	-2	8	-1
3	51	55	96	95	84	-1	16	-2
4	54	79	108	96	62	-5	21	6
5	47	74	100	98	85	-2	38	-1
6	44	80	119	96	85	0	27	0
7	32	75	92	96	86	0	35	-3
8	43	75	119	98	71	-2	40	10
9	57	80	106	99	74	-3	9	5
10	39	71	101	96	92	-1	25	14
11	50	98	122	97	87	2	35	20
12	35	83	97	97	80	4	10	-11
13	50	83	115	97	78	-4	24	5
14	36	92	121	97	82	2	17	4
15	26	86	100	97	66	6	28	-5
Mean	45	80.0	110	96.8	78	-1.4	24.3	3.1
±SD	10.4	10.2	11.5	1.1	8.7	-4.8	10.6	7.8

For abbreviations see legend to table 1.

Table 3. – Comparison between patient and control group (mean±SD)

	OSA patients	Controls	p
Age yrs	53±7.8	45±10.4	0.02*
Broca	118±16.9	110±11.5	0.14
HR b·min⁻¹	79.9±14.1	78±8.7	0.78
Weight kg	88±16.6	80±10.2	0.17
ΔHRB ·min⁻¹	-4.3±4.8	-1.4±4.8	0.2
ΔHRV ·min⁻¹	11.2±6.3	24.3±10.6	0.002*
ΔHRM ·min⁻¹	-11.5±13.5	3.1±7.8	0.008*
Sao₂b %	94.9±1.2	96.8±1.1	0.01*

OSA: obstructive sleep apnoea. For further abbreviations see legend to table 1. *: denotes significant differences.
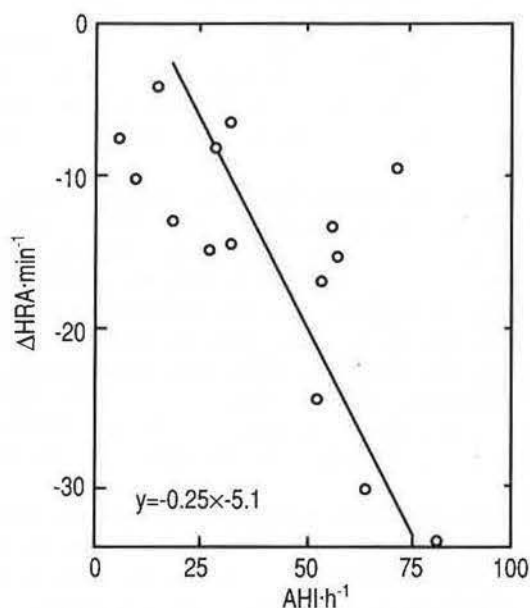

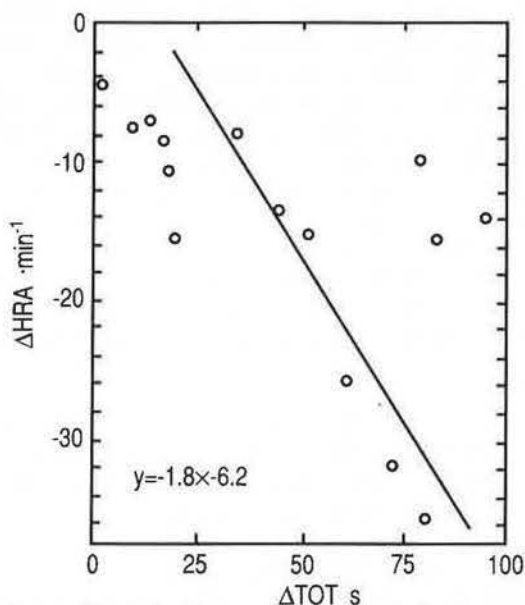Fig. 1. – Correlation between the decrease in heart rate during apnoea (ΔHRA) and the apnoea hypopnoea index (AHI) in OSA patients (n=15).

Fig. 2. – Correlation between the decrease in heart rate during apnoea (ΔHRA) and the difference in total respiratory cycle duration (ΔTOT) in OSA patients (n=15).

All respiratory manoeuvres were performed in a sitting position, at end-expiration, during quiet breathing. Heart rate was evaluated by electrocardiogram and oxygen saturation was measured transcutaneously, as described above. The Mueller manoeuvre was performed by inspiring with constant effort against a closed tube with a distally mounted pressure gauge, enabling the subject to control the pressure generated [9]. The manoeuvre was standardized by requiring an inspiratory effort of 5 kPa for 15 s. For the Valsalva manoeuvre, a positive pressure of 5 kPa was to be attained for the same period. Breath-holding lasted for 15 s. Several manoeuvres were performed before measurement was made in order to allow each subject to become accustomed to the procedure. A 24 h Holter electrocardiogram (Tracker, Reynolds), spirometry and two-dimensional M-mode echocardiogram were performed in all patients. The Broca index was calculated as weight·100/ (height-100).

All variables were tested for normal distribution and are given as mean±SD [10]. For comparison of two groups the Mann-Whitney test was used. Correlations were calculated with Spearman's regression analysis. A p<0.05 was considered to be significant.

Results

With the exception of patients no. 4 and 15, who had mild obstructive airway disease, the spirometry was normal in all patients, as was the left ventricular end-diastolic diameter. There was a larger decrease in heart rate during MM and a smaller increase in heart rate during Valsalva manoeuvre in OSA patients as compared to the control group (tables 1–3). In all subjects, the respiratory manoeuvres led to an insignificant decrease in arterial oxygen saturation.

In patients with OSA, there was a significant correlation between the decrease in heart rate during MM and AHI (r=-0.53). A significant correlation was also found between ΔHRA and AHI (r=-0.64) and between ΔHRA and ΔTOT (figs 1 and 2, and table 4). There was no correlation between decrease in heart rate during apnoea and during MM. Patients no. 2, 4, 5, 9, 12, 13, 14 and 15 had <30% mixed apnoeas. When these patients were compared with the remaining patients there was no significant difference in AHI (p=0.3) and decrease in heart rate during MM (p=0.1) but there was in ΔHRA (p=0.05).

If a decrease in heart rateduring MM was considered to be a positive indication for OSA, there were three false negatives and eight false positives. Sensitivity was 80%, specificity 51%, positive predictive value 60% and negative predictive value 70%.

Patients no. 1, 5 and 8 demonstrated couplets and 11 patients had ventricular ectopic beats in the 24 h Holter electrocardiogram (table 1). There was no correlation between ventricular ectopic beats and changes in heart rate during respiratory manoeuvres.

Table 4. – Table of correlations

	ΔTOT	Sao$_2$m	ΔHRM	ΔHRV	ΔHRB	ΔHRA	VE	AHI
ΔTOT	1.00	-0.72*	-0.32	-0.13	-0.14	0.62*	0.38	-0.78*
Sao$_2$		1.00	0.19	0.04	0.18	0.56*	-0.57*	-0.71*
ΔHRM			1.00	0.13	0.47	0.42	0.09	-0.53*
ΔHRV				1.00	0.02	-0.19	-0.22	0.10
ΔHRB					1.00	0.20	-0.22	-0.16
ΔHRA						1.00	-0.10	-0.64*
VE							1.00	0.25

For abbreviations see legend to table 1.   *: denotes significant correlations.

Discussion

In spite of its use as a diagnostic aid [1, 2], the changes in heart rate during obstructive apnoea are not well understood. Several factors such as hypercapnia [11] and lung volume [12] may influence heart rate. Negative intrathoracic pressure during apnoea causes an increase in venous filling, which in turn decreases heart rate [9, 13]. In contrast, the decreased cardiac output during negative intrathoracic pressure stimulates peripheral baroreceptors [13, 14]. ZWILLICH et al. [15] studied six OSA patients and found that bradycardia became marked with increased apnoea length and oxygen desaturation. In four of their patients, administration of oxygen prevented bradycardia, although normal subjects did not have bradycardia during hypoxic hypopnoea. Evaluating nine OSA patients, HANLY et al. [16] could not confirm any significant influence of oxygen on bradycardia during apnoea or MM. Our findings are in accordance with those of Hanly et al. in that the decrease in heart rate observed during MM was not accompanied by a significant decrease in arterial oxygen saturation.

Recently, REMMERS et al. [3] showed that stimulation of the superior laryngeal nerve by insufflation of smoke into the upper airway or application of water to the larynx activates postinspiratory neurones in the medullary respiratory centre. This causes prolongation of stage I expiration and TOT or even mixed and central apnoea - depending on the strength of the stimulus - and excites cardiac vagal motor neurones, leading to a reduction in heart rate [4, 17]. During obstructive apnoea the upper airway collapse begins at the oropharynx and progresses to the hypopharynx [6, 18]. Analogous to animal studies, the collapse of the upper airway during apnoea might activate pharyngeal receptors, thus causing bradycardia and increase in TOT or even central apnoea in OSA patients. The significant correlation between increase in TOT and decrease in heart rate during apnoea presented in this study is in accordance with this concept. Furthermore, patients with a higher rate of mixed apnoeas had a more pronounced ΔHRA. This is in accordance with the findings of ISSA and SULLIVAN [19]. They demonstrated that central and mixed apnoeas were eliminated and obstructive apnoeas did occur when upper airway collapse was prevented by intermediate levels of continuous positive airway pressure.

It has been shown in 123 OSA patients that there is a negative correlation between the AHI and the internal pharyngeal circumference [20]. In our study, patients with a higher AHI demonstrated a pronounced decrease in heart rate during apnoea. This might reflect a marked collapse of the pharynx and stimulation of receptors in patients with a narrowed upper airway.

In nearly all apnoeas heart rate reached a minimum towards the end of the apnoea and TOT a maximum at the beginning of the apnoea, thereafter decreasing. This is not in contradiction with the activation of postinspiratory neurones which mediate both bradycardia and increase in TOT, since increasing ventilatory effort at the end of an obstructive apnoea accelerates the respiratory rhythm. WILCOX et al. [21] demonstrated progressive respiratory muscle recruitment and a decrease in TOT towards the end of an obstructive apnoea.

Passive generation of negative intrathoracic pressure of 15 cmH$_2$O causes narrowing of the upper airway in supine normal subjects [22]. Active generation of negative intrathoracic pressure by graded inspiratory effort against a closed airway causes only minor narrowing of the upper airway in normal subjects [22] and in OSA patients [23]. However, a forced MM causes narrowing or closure of the upper airway as demonstrated by fluoroscopy, fibreoptic nasopharyngoscopy and computerized tomography in OSA patients [6, 7] and in normal subjects [24]. In the forced MM described in this study, the airway does not collapse as the negative intrathoracic pressure is transmitted to the pressure gauge, but distortion and narrowing of the pharynx leading to activation of pharyngeal receptors [17] is likely to be caused [6, 7, 24].

Since we did not visualize the upper airway during MM the extent of airway narrowing could not be related to changes in heart rate; this should be evaluated in further studies. Patients with OSA have a marked decrease in heart rate during MM whereas controls show a slight increase. This might be caused by a marked stimulation of pharyngeal receptors in the OSA patients during MM. In accordance with the findings, during obstructive apnoeas patients with a higher AHI demonstrated a pronounced decrease in heart rate during MM. This might reflect a marked stimulation of pharyngeal receptors in patients with higher AHI and narrowed upper airway. However, the time pattern of the repeated inspiratory efforts during

obstructive apnoeas is different from the sustained inspiratory effort of a MM. The decrease in heart rate during MM is of limited value as a simple screening test for OSA since the sensitivity and specificity are 80 and 51%, respectively.

It is well-known that heart rate response to Valsalva manoeuvre is impaired in decreased left ventricular function with increased pulmonary artery pressure [25]. Increased pulmonary artery pressure and ventricular arrhythmias often occur in patients with OSA [26, 27]. The changes in heart rate during Valsalva manoeuvre were less marked in OSA patients as compared to the controls.

In conclusion, OSA patients showed a pronounced decrease in heart rate during MM as compared to the control group. A significant correlation between heart rate decrease during MM, apnoea and AHI was demonstrated as well as between decrease in heart rate during apnoea and increase in TOT. This may be caused by excitation of postinspiratory and cardiac vagal neurones in the cardiorespiratory centre following stimulation of receptors at the site of airway distortion or collapse in OSA patients. Thus, decrease in heart rate during MM and during apnoea, increase in TOT during apnoea and the cessation of respiratory effort at the beginning of a mixed apnoea may be related to upper airway obstruction.

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