Cardiac diastolic function and hypercapnic ventilatory responses in central sleep apnoea

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Cardiac diastolic function and hypercapnic ventilatory responses in central sleep apnoea. P. Solin, D.M. Jackson, T. Roebuck, M.T. Naughton. ©ERS Journals Ltd 2002.
ABSTRACT: Hyperventilation is the key factor contributing to the development of idiopathic nonhypercapnic central sleep apnoea (ICSA), where left ventricular systolic function is normal. ICSA is reported to occur in 20% of patients with left ventricular diastolic dysfunction, in whom elevated pulmonary vascular pressures and resultant increased pulmonary vagal afferent traffic may contribute to hyperventilation. The contribution of the two potential mechanisms responsible for the hyperventilation seen in the following ICSA was measured: 1) left ventricular diastolic dysfunction-induced pulmonary hypertension; and 2) increased peripheral and central hypercapnic ventilatory responses (HCVR).

The pulmonary artery pressure, left ventricular diastolic function and chemosensitivity to hypercapnia were measured during wakefulness in 16 subjects with ICSA.

All subjects had systolic pulmonary artery pressures <3.99 kPa (<30 mmHg) and only four had diastolic dysfunction. All subjects had elevated peripheral and central HCVR compared with historical normal control subjects. Diastolic dysfunction correlated with increasing age but not with HCVR or markers of central sleep apnoea severity.

Idiopathic nonhypercapnic central sleep apnoea is likely to be dependent upon raised hypercapnic ventilatory responses, and not pulmonary hypertension due to left ventricular diastolic dysfunction.
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Periodic breathing, or nonhypercapnic central sleep apnoea (CSA), is triggered by oscillations in respiratory drive induced by hyperventilation during non-rapid eye movement (NREM) sleep when respiratory control is under a chemically-controlled, negative-feedback loop [1]. The most common form of CSA is seen in subjects with congestive systolic heart failure (CHF), and is termed Cheyne-Stokes respiration (CSA). However, CSA also occurs in the absence of systolic heart failure, and is termed "idiopathic central sleep apnoea" (ICSA) [2].

The two apnoea conditions can be clearly distinguished by the apnoea and ventilatory cycle length, and the ventilatory:apnoea length ratio measured on the polysomnograph [3, 4]. Compared with CHF-CSA, ICSA is characterised by a shorter apnoea and ventilatory cycle length (35 *versus* 70 s, respectively), shorter ventilatory length (14 *versus* 43 s, respectively) and lower ventilatory:apnoea length ratio (0.66 *versus* 1.65, respectively) [3].

The pathogenesis of the hyperventilation, underlying both forms of CSA, is thought to relate to either: 1) increased pulmonary vascular pressures and resultant increased pulmonary vagal afferent nerve activity; or 2) a primary abnormality of central and/or peripheral hypercapnic ventilatory responses [1, 5–8].

Past studies have demonstrated that raised pulmonary vascular pressures increase pulmonary vagal afferent-nerve activity and minute ventilation, thereby allowing the carbon dioxide tension in arterial blood (Pa,CO$_2$) level to fall below the apnoea threshold, provoking cyclic central apnoeas [9–13].

Furthermore, the hyperventilation/apnoea cycle length is inversely correlated with cardiac systolic function [3, 4]. In patients with systolic heart failure, a significant correlation was found between pulmonary capillary wedge pressure and both the Pa,CO$_2$ level and the severity of CHF-CSA, consistent with this hypothesis [14]. Moreover, severe CSA has been reported in ≤29% of patients with primary pulmonary hypertension [15]. A common cause of pulmonary hypertension in the absence of systolic heart failure is diastolic dysfunction, a condition in which there is an elevation of end-diastolic pressure for a given end-diastolic volume [16, 17]. However, pulmonary hypertension, or markers thereof have not been studied systematically in subjects presenting with ICSA.

Therefore, the authors hypothesised that previously unrecognised or asymptomatic elevations in pulmonary vascular pressures, due to left ventricular diastolic dysfunction, may contribute to the genesis of ICSA, separately or in addition to elevated HCVR. Accordingly, the prevalence of left ventricular diastolic dysfunction and pulmonary hypertension, and the

relationship between diastolic dysfunction and ventilatory responses to CO_2, were determined in a group of subjects with ICSA free of systolic heart failure.

Methods

Subjects

Sixteen adult subjects, aged 18–75 yrs, were selected on the basis of the following: 1) at least two of the following clinical features: snoring, witnessed apnoea, excessive daytime sleepiness, restless sleep, nocturnal dyspnoea or choking, 2) central sleep apnoea during NREM sleep, 3) awake P_{a,CO_2} of $\leqslant 45$ mmHg. On the basis of echocardiography, subjects were divided into those with normal (no diastolic dysfunction group) and those with abnormal diastolic function as defined below. All patients had normal systolic function.

Exclusion criteria included symptoms, signs, or evidence of renal, neurological or respiratory disease. The study was approved by the Alfred Hospital Ethics Committee and all subjects provided informed written consent.

Echocardiography

Echocardiography was performed during wakefulness in the supine position after 15 min of quiet rest, by qualified and experienced operators, and reported by a cardiologist, both blinded to the sleep-study results. To confirm accuracy, all measurements were re-read by a second and senior echocardiographer, also blinded to the results of polysomnography.

Left-ventricular measurements. Left-ventricular fractional shortening, size and wall thicknesses were calculated from M-mode (or movement) measurements from the parasternal (long or short axis) view. M-mode measurements are made from a single narrow ultrasound beam to depict a one-dimensional slice of the target structure. Left-ventricular hypertrophy was defined as diastolic septal and posterior wall thickness of >1.2 cm.

Pulmonary pressure measurement. Doppler ECG was used to estimate pulmonary artery systolic pressure [18]. By measuring the maximum tricuspid regurgitation velocity (from either the apical or parasternal window) and adding an estimated right-atrial pressure of 1.33 kPa (10 mmHg), an estimate of right-ventricular systolic pressure was made. This value was assumed to equal pulmonary artery systolic pressure in the absence of pulmonary stenosis or right-ventricular outflow obstruction. Pulmonary hypertension was defined as pulmonary artery systolic pressure >4.66 kPa (>35 mmHg) [18, 19].

Diastolic-function measurement. Peak early (E) and atrial contraction (A) left-ventricular inflow velocities at the tips of the mitral valve, as well as deceleration time (DT) and isovolumetric relaxation time (IVRT) were measured according to standard criteria [20]. DT

was defined as the time for peak early filling velocity to fall to baseline values, and IVRT was defined as the time from aortic-valve closure to the onset of mitral-valve inflow.

Diastolic dysfunction was defined on the basis of a reversed E:A ratio (E:A <1.0). Pathological diastolic dysfunction was differentiated from age-related diastolic dysfunction (fig. 1). Pathological diastolic dysfunction was defined as a reversed E:A ratio in combination with a prolonged DT and/or IVRT, according to Mayo Clinic guidelines [20]. Prolongation was defined as an absolute DT >240 ms and IVRT >110 ms [20, 21].

Hypercapnic ventilatory response

Central (medullary) chemosensitivity to carbon dioxide (CO_2) was calculated by measuring the ventilatory response to progressive hypercapnia, based on the rebreathing method presented by READ [22]. In brief, awake subjects rebreathe a mixture comprising 7% CO_2, 50% oxygen (O_2), 43% nitrogen (N_2) for $\leqslant 4$ min, during three runs separated by 20-min rest
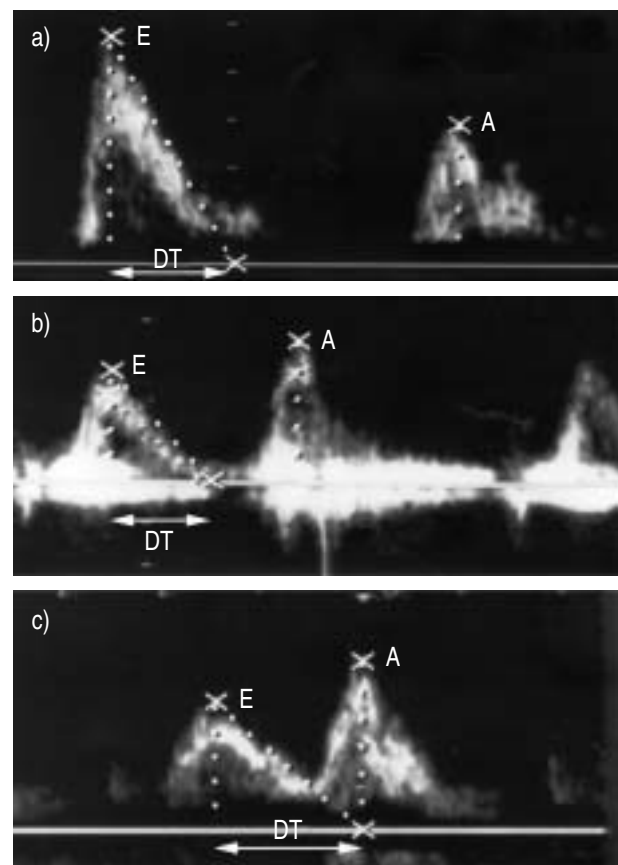

Fig. 1. – Typical examples of early (E): atrial (A) contraction ratio and deceleration time (DT) measured by echocardiography. a) Normal diastolic function with a large early inflow phase (E) followed by a smaller atrial contraction phase (A). b) Age-related diastolic dysfunction with small (E) and large (A) phase (reversed E:A ratio) but normal DT. c) Pathological diastolic dysfunction with reversed E:A ratio and prolonged DT.

intervals. Tidal volume and end-tidal CO_2 tension (PET,CO_2) were measured continuously, and the slope described by this relationship was calculated by least-squares linear regression. The numerical average of the slopes from each of the three runs was taken as the ventilatory response, and expressed as $L \cdot min^{-1}$ divided by the change in PET,CO_2 in mmHg ($L \cdot min^{-1} \cdot P$ET,CO_2 $mmHg^{-1}$). Normal values for the authors' laboratory were age-dependent with a mean of 2.37 (range 0.89–3.95) $L \cdot min^{-1} \cdot P$ET,CO_2 $mmHg^{-1}$ [8].

Peripheral (carotid body) chemoreceptor sensitivity was tested awake by the ventilatory response to transient hypercapnia using the single-breath technique, as described by McCLEAN et al. [23]. Individual tidal breaths and PET,CO_2 were measured continuously. Once stable ventilation was confirmed, subjects inhaled a single tidal breath of a mixture containing 13% CO_2, 21% O_2, 66% N_2, and the raised PET,CO_2 plateau for this breath was identified. Typically, a transient increase in ventilation is seen within 20 s of the inhalation. The single-breath HCVR is therefore defined as the maximal increase in ventilation divided by the change in PET,CO_2, expressed in $L \cdot min^{-1} \cdot$ PET,CO_2 $mmHg^{-1}$. At least five runs were performed, each separated by 4 min of rest, with the numerical average taken as the single-breath HCVR. Normal values for the authors' laboratory are a mean of 0.25 (range 0.00–0.51) $L \cdot min^{-1} \cdot P$ET,CO_2 $mmHg^{-1}$ [8].

Spirometry (Masterlab, Jaeger, Hoechberg, Germany) was measured within 2 weeks of polysomnography. Arterial-blood gas tensions were measured (Model 865, Ciba Corning Diagnostics Corp., Medfield, MA, USA) on the night of polysomnography from a radial artery sample taken whilst the subject was supine, awake, and rested for $\geqslant 10$ min.

Polysomnography

Overnight polysomnography was recorded on a computerised system (Somnostar®; SensorMedics Corp., Anaheim, CA, USA). Standard techniques and scoring criteria were used for the manual determination of sleep stages [24]. Electrocardiogram and cardiac frequency were recorded continuously from precordial lead II. Arterial O_2 pulse saturation (Sp,O_2) was measured by an ear oximeter, and the averaging time of the oximeter was set at 3 s. Chest and abdominal movements were monitored using respiratory effort bands calibrated for phase (Respez; EPM Systems, VA, USA). Oronasal airflow was monitored by thermocouples (Pro-Tech Services, WA, USA). A central apnoea was defined as an absence of airflow for $\geqslant 10$ s, associated with an absence of chest or abdominal movement. Central hypopnoea was defined as a reduction in airflow for $\geqslant 10$ s, associated with a 2% fall in the arterial O_2 saturation (Sa,O_2) and in-phase chest and abdominal movement with no increase in the submental electromyogram (EMG) or snoring. Obstructive apnoea was defined as an absence of airflow for $\geqslant 10$ s, despite continued out-of-phase chest and abdominal movements. Obstructive hypopnoea was defined as a reduction in airflow for $\geqslant 10$ s

associated with a 2% fall in Sa,O_2 despite continued out-of-phase chest and abdominal movements, or snoring. A mixed apnoea was defined as absence of oronasal airflow associated with central followed by obstructive components. The apnoea/hypopnoea index (AHI) was defined as the total number of apnoeas and hypopnoeas divided by the total sleep time, and expressed as the number of events·h^{-1}. CSA was defined as the central apnoeas occuring on average $\geqslant 5 \cdot h^{-1}$, $\geqslant 75\%$ of all apnoeas being purely central in origin, and $\geqslant 50\%$ of apnoeas and hypopnoeas being purely central.

Cycle length was measured from the first breath following an apnoea to the end of the following apnoea and comprised the ventilatory phase and apnoea phase. Ventilatory length was measured from the beginning of inspiration at the end of an apnoea to the end of expiration following the hyperpnoeic phase. Apnoea length was taken as the difference between cycle length and ventilatory length. Circulation time from lung to peripheral chemoreceptor was estimated by the lung-to-ear circulation time. This was measured as the time from the first breath following a central apnoea to the subsequent nadir of Sp,O_2, measured by ear oximetry, using an amplified scale on a high-resolution screen. Ten consecutive central apnoeas were used for measurements, and these were taken from stage 2 sleep to minimise the effect of changes in sleep state between wakefulness and stage 1.

Statistical analysis

Data is presented as mean±SEM. Unpaired t-tests were used for comparisons between the two groups. Correlations utilised the Pearson's least-squares method. A p=0.05 was considered to be significant.

Results

Sixteen subjects (14 male) with ICSA were studied (table 1). All subjects had normal left-ventricular fractional shortening (>28%) and systolic-contractile function. All patients had normal pulmonary pressures on ECG. Four male subjects had reversed E:A ratios indicative of left-ventricular diastolic dysfunction. All four with left-ventricular diastolic dysfunction had systemic hypertension diagnosed previously and, of these, three were taking antihypertensive tablets for $\geqslant 1$ yr. These four were amongst the six oldest patients in this sample. Of these four, two had a prolonged DT, indicating that left-ventricular diastolic dysfunction was due to a structural cause and could not be attributed to age alone (one subject had mild aortic regurgitation with mild atrial dilation, not apparent on clinical examination, and the other had left-ventricular hypertrophy). The other two subjects with left-ventricular diastolic dysfunction but normal DT and IVRT had no evidence of left-ventricular hypertrophy, indicating that the left-ventricular diastolic dysfunction was due to age alone.

Table 1. – Subject characteristics, lung function and polysomnography

	ICSA		p-value
	No diastolic dysfunction	Diastolic dysfunction	
Subject characteristics			
Subjects (females) n	12 (2)	4 (0)	
Diagnosed hypertension (treated)	5 (3)	4 (3)	
Age yrs	45.3±2.9	59.0±2.0	NS
Body mass index (kg·m^{-2})	31.8±1.5	29.4±2.6	NS
Lung Function			
Awake pH	7.40±0.01	7.41±0.01	NS
Awake P_{a,CO_2} mmHg	41.2±1.2	41.0±1.5	NS
Awake P_{a,O_2} mmHg	73.4±2.1	74.6±4.2	NS
Awake S_{a,O_2} %	96.6±0.4	97.3±1.2	NS
FEV1 % pred	112±5	109±8	NS
FVC % pred	107±4	97±5	NS
FEV1/FVC % pred	104±4	111±3	NS
Polysomnography			
TST min	302±19	278±39	NS
Sleep efficiency %	77±5	77±4	NS
Stages 1 & 2 % sleep period time	60±3	56±6	NS
Stages 3 & 4 % sleep period time	8±2	6±3	NS
REM % sleep period time	12±3	16±3	NS
Apnoea hypopnoea index n·h^{-1}	29±6	24±5	NS
Movement arousal index n·h^{-1}	23±5	15±5	NS
Mean overnight S_{p,O_2} %	95±1	95±1	NS
TST with S_{p,O_2} <90% %	9.1±7.9	1.2±0.9	NS

Data are presented as mean±SEM, unless otherwise stated. S_{a,O_2}: arterial oxygen saturation; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; S_{p,O_2}: pulse oxygen saturation; TST with S_{p,O_2} <90% %: total sleep time with pulse oxygen saturation <90%; P_{a,CO_2}: carbon dioxide tension in arterial blood; P_{a,O_2}: oxygen tension in arterial blood; REM: rapid eye movement; ICSA: idiopathic nonhypercapnic central sleep apnoea; % pred.: % predicted.

There were no differences between the diastolic dysfunction and nondiastolic dysfunction groups in terms of age, body mass index, arterial blood gases, and spirometry (table 1). Similarly, sleep duration and staging, arousals, AHI markers of oxygenation (mean S_{p,O_2} and mean percentage of total sleep time spent with S_{p,O_2} <90%) and apnoea-ventilation cycle lengths were not statistically different between the two groups (table 2). Moreover, both single-breath and rebreathe HCVR were similar in the two groups. Examples of ICSA with and without diastolic dysfunction are shown in figure 2.

Diastolic dysfunction correlated with increasing age (r=-0.56, p=0.025) (fig. 3), but not with HCVR (rebreathe HCVR: r=0.18, p=0.59; single-breath: HCVR r=0.43, p=0.18) or markers of CSA severity (AHI: r=-0.04, p=0.90; arousals: r=-0.11, p=0.68; mean S_{p,O_2}: r=-0.08, p=0.97; and mean percentage of total sleep time spent with S_{p,O_2} <90%: r=0.15, p=0.59).

Table 2. – Echocardiography, hypercapnic ventilatory responses (HCVR) and central sleep apnoea (CSA) cycle characteristics

	ICSA		p-value
	No diastolic dysfunction	Diastolic dysfunction	
E:A ratio[#]	1.37±0.09	0.84±0.02	
E:A ratio (range)	1.00–2.11	0.78–0.88	
Highest systolic P_{pa} mmHg	18	26	
Rebreathe HCVR[¶]	3.56±0.39	3.01±0.26	NS
Single-breath HCVR[¶]	0.54±0.11	0.61±0.09	NS
VL s	14.0±1.1	16.2±1.5	NS
AL s	17.6±1.1	18.7±2.3	NS
Cycle length s	31.5±2.1	34.9±3.4	NS
VL:AL ratio	0.79±0.04	0.88±0.08	NS
Circulation time s	12.3±1.0	12.9±1.8	NS

Data are presented as mean±SEM unless otherwise stated. E:A ratio: left-ventricular inflow velocity of early:atrial contraction phase; P_{pa}: pulmonary artery pressure; VL: ventilatory length; AL: apnoea length; [#]: normally >1.0; [¶]: expressed in L·min^{-1} mmHg^{-1} and tidal carbon dioxide tension (P_{ET,CO_2}) mmHg^{-1}.

Discussion

Nonhypercapnic CSA occurs frequently in subjects with CHF-CSA, and less frequently in subjects without known systolic heart failure, where it is called ICSA. The pathogenesis of hyperventilation, the hallmark feature of both types of CSA, has previously been attributed to either increased pulmonary vagal afferent-nerve activity due to pulmonary hypertension [9, 11–14] or increased ventilatory responses to CO_2 [5–8].

Subjects with CHF-CSA are thought to have both mechanisms operating [6–8, 14]. However, although it is thought that elevated HCVR is the major pathogenic factor in subjects with ICSA, the possibility of underlying cardiac dysfunction and pulmonary hypertension has not been systematically excluded.

The current study indicates that ICSA is a disorder associated with normal pulmonary artery pressures and can occur independently of left-ventricular diastolic function. Only four subjects had diastolic dysfunction and none of these had pulmonary hypertension, indicating that the severity of diastolic dysfunction was mild. Moreover, there were no significant differences in central or peripheral HCVR between groups with and without diastolic dysfunction. Given that the HCVR measured in the current study were similar to those measured by XIE et al. [5] and were elevated compared with the normal control values from the laboratory [8], it follows that elevated HCVRs are pathognomonic for the development of ICSA. Therefore, the independent contribution of left-ventricular diastolic dysfunction and associated pulmonary vagal afferent-nerve activity to the generation of ICSA is negligible or nonexistent. This is also consistent with the previous observation of CHF-CSA despite surgical-vagal denervation [25].

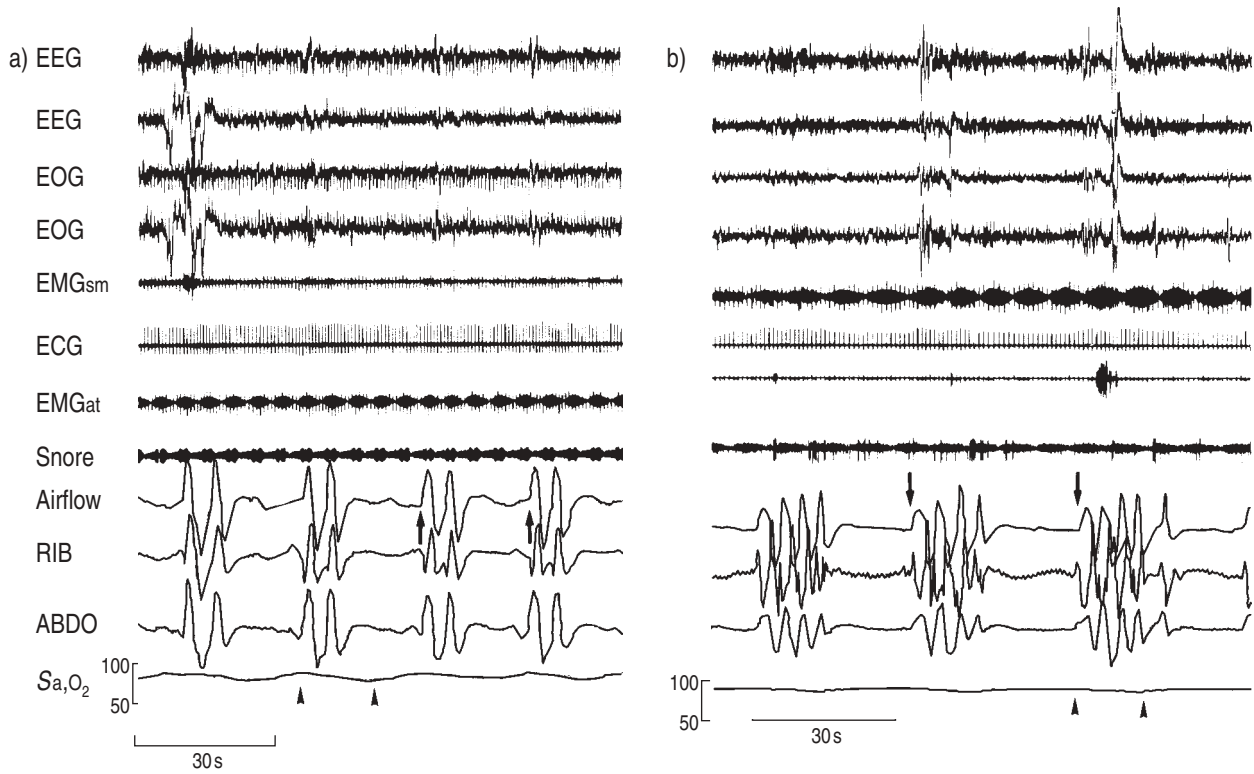Prior studies of subjects with ICSA have defined

Fig. 2. – Typical examples of idiopathic nonhypercapnic central sleep apnoea (ICSA) a) with diastolic dysfunction and b) without diastolic dysfunction. Cycle length (top arrows) and circulation time measurements (bottom arrows) were similar in both groups. EEG: electroencephalogram; EOG: electrooculogram; EMGsm: submental electromyogram; ECG: electrocardiogram; EMGat: anterior tibialis electromyogram; Snore: snore microphone; Airflow: oronasal thermocouple; RIB: chest wall movement; ABDO: abdominal movement; Sa,O_2: oxygen saturation.

normal cardiac function based mainly upon clinical examination alone. In the original description of nonhypercapnic CSA, cardiac function was not objectively assessed [2]. In the studies of XIE and coworkers [5, 26, 27], cardiac disease was excluded in subjects with ICSA based upon clinical examination alone. Similarly, HALL et al. [4] excluded cardiac disease based upon clinical examination, yet measured cardiac

Fig. 3. – The relationship between age and diastolic function (early (E):atrial contraction (A) ratio) (r=-0.56, p=0.025). Open circles are those with diastolic dysfunction. Note that the four with diastolic dysfunction are amongst the oldest in this sample.

output to be normal by the Doppler technique in five of the 10 ICSA patients reported, without commenting upon diastolic function [4]. SOLIN et al. [3], who also studied 10 ICSA patients, excluded left-ventricular systolic dysfunction in all 10 subjects with a left-ventricular ejection fraction measured by technetium (^{99m}Tc) radionuclide radiography using the equilibrium method. However, left-ventricular diastolic function was not assessed. Therefore, until the present study, there has been insufficient evidence to state that ICSA subjects are free of diastolic dysfunction. As 40% of heart-failure patients with elevated pulmonary vascular pressures have normal systolic function [16, 17], the cause of CHF has been attributed to diastolic dysfunction, defined as an elevation of end-diastolic pressure for a given end-diastolic volume [16, 17, 28].

The authors aimed to determine whether there was a link between left-ventricular diastolic dysfunction and ICSA, based upon the following observations. First, subjects with ICSA often present with a past history of snoring, nocturnal choking, restless sleep and excessive daytime sleepiness, features that would suggest a previous history of obstructive sleep apnoea. Sleep studies of patients with ICSA often show an overlap of central, mixed and obstructive apnoeas, of varying proportions. The physiological consequences of obstructive sleep apnoea, namely hypoxaemia, systemic hypertension, myocardial hypertrophy and ischaemia, are well known causes of left-ventricular
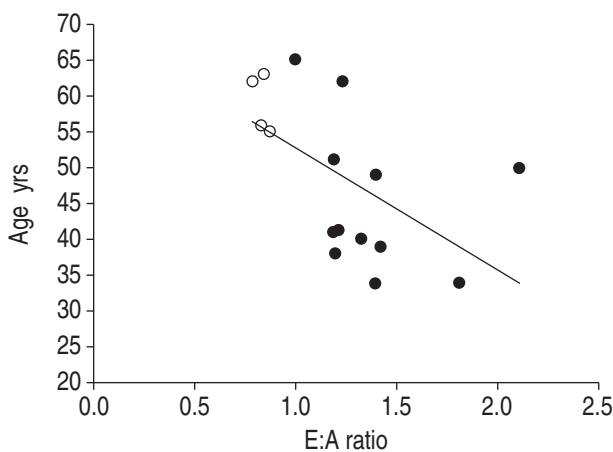
diastolic dysfunction [16, 17, 29], which can lead to increased pulmonary vascular pressures [28, 30]. It is therefore possible that years of obstructive apnoea may contribute to diastolic dysfunction, leading to pulmonary hypertension and the development of ICSA (similar to the development of CSA in CHF subjects with progressive systolic dysfunction). In addition, increasing age is an independent cause of diastolic dysfunction [20] and is associated with greater prevalence of central and obstructive sleep apnoea [31]. Secondly, CHAN *et al.* [32] observed that 35% of patients who had recovered from acute pulmonary oedema secondary solely to left-ventricular diastolic dysfunction had obstructive sleep apnoea, and a further 20% had nonhypercapnic CSA. Finally, severe CSA has been reported in $\leqslant 29\%$ of patients with primary pulmonary hypertension, with the speculative mechanism being attributed to pulmonary vagal afferent-nerve stimulation [15].

The central and peripheral hypercapnic-ventilatory responses measured in this study are similar to the findings of XIE *et al.* [5] who reported rebreathe and single-breath HCVR to be significantly greater (3.14 and 0.51 $L\cdot min^{-1}\cdot P\text{ET,CO}_2\cdot mmHg^{-1}$, respectively) than in normal controls (1.60 and 0.25 $L\cdot min^{-1}\cdot P\text{ET,CO}_2\cdot mmHg^{-1}$, respectively). Moreover, previous work by the authors [8] has suggested that peripheral (single-breath) ventilatory responses observed in ICSA patients are similarly elevated compared to that observed in patients with CHF-CSA and correlate significantly with the periodicity of central apnoeas. The central (rebreathe) ventilatory responses were elevated to a greater degree with CHF-CSA than ICSA and correlated inversely with the baseline $P\text{a,CO}_2$ level, suggesting that the greater central ventilatory response would predispose the individual to periodic breathing [5]. Thus, the authors believe that abnormalities of ventilatory responses underpin the development of periodic breathing, independent of vagal activity.

The main shortcomings of this study were three-fold. First, the small patient numbers are reflective of the rarity of ICSA. In the authors′ institution, ICSA occurs in approximately one in every 100 subjects who are referred with symptoms of obstructive sleep apnoea yet are free of symptoms of CHF. Therefore, a further 10 patients with mixed sleep apnoea (central apnoeas 50–75% of total apnoea score, and therefore not classified as ICSA) were studied (results not reported). Of this group, four out of 10 patients had left-ventricular diastolic dysfunction, of whom four were aged >50 yrs, three had long-standing treated hypertension, and the remaining patient was obese with a body mass index >36 $kg\cdot m^{-2}$. None had pulmonary hypertension. This would indicate that left-ventricular diastolic dysfunction occurs in a minority of patients with mixed sleep apnoea, where central events predominate, and is consistent with the conclusion that diastolic dysfunction and/or pulmonary hypertension is unrelated to the pathogenesis of central apnoeas.

A second potential shortcoming of this study was that diastolic function was measured by echocardiography when subjects were awake after 15 min of quiet rest, rather than during stage 1 and 2 NREM sleep, when central apnoea is most likely to occur. However, echocardiography remains the most effective noninvasive technique for estimation of diastolic dysfunction, and correlates well with invasive techniques [28]. Thirdly, pulmonary artery pressures during sleep were not directly measured. Whether the measurement of pulmonary artery pressures during sleep, either *via* echocardiography or invasively with pulmonary artery catheters, would have altered the outcome would need to be determined.

To conclude, idiopathic nonhypercapnic central sleep apnoea can occur in the absence of awake, left-ventricular diastolic dysfunction and pulmonary hypertension. This suggests that abnormal hypercapnic ventilatory responses are the primary factor responsible for the development of idiopathic nonhypercapnic central sleep apnoea. Therefore, in contrast to central sleep apnoea in congestive heart failure, idiopathic nonhypercapnic central sleep apnoea is unlikely to be related to elevated pressures at night. The factors responsible for the dysfunction of hypercapnic ventilatory responses remain to be determined.

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