REVIEW

The cardiovascular effects of obstructive sleep apnoeas: analysis of pathogenic mechanisms

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The cardiovascular effects of obstructive sleep apnoeas: analysis of pathogenic mechanisms. M.R. Bonsignore, O. Marrone, G. Insalaco, G. Bonsignore. ©ERS Journals Ltd 1994.

ABSTRACT: Obstructive sleep apnoeas (OSA) exert immediate marked cardiovascular effects, and may favour the development of systemic and pulmonary hypertension in the long-term.

As for the pathogenesis of the acute cardiovascular changes, the first studies highlighted the role of OSA-induced hypoxia and mechanical changes. However, more recent work pointed to the role played by the arousal reaction terminating OSA, and to the activity of the autonomic nervous system during apnoea and inter-apnoeic phase.

As for the pathogenesis of chronic cardiovascular changes, recent findings suggest that the link between OSA and systemic hypertension may be through an abnormal function of the carotid body and underline the importance of chronic intermittent hypoxia *versus* continuous hypoxia in the development of stable systemic hypertension. On the other hand, OSA do not appear to enhance strongly the development of stable pulmonary hypertension.

In this review, we analyze OSA-induced cardiovascular changes with particular emphasis on to the interplay of the possible pathogenic mechanisms involved. Acute OSA-induced cardiovascular alterations during the apnoeic phase appear to result mainly from the mechanical effects of OSA, while during the interapnoeic phase they seem mostly determined by chemical factors (hypoxia, hypercapnia) and by the arousal reaction. In addition, the role of reflex changes elicited by resumption of ventilation should be reconsidered, since lung inflation seems to exert a positive effect on the cardiovascular changes occurring at the end of OSA. This would be in contrast with the inhibitory effects described as "lung inflation reflex", and deserves further study.
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Both the acute and long-term cardiovascular effects of obstructive sleep apnoeas (OSA) result from a multifactorial pathogenesis, and their study is complicated by the possibly contrasting effects of the different pathogenic factors involved. With respect to acute changes, OSA may elicit reflexes similar to those occurring during voluntary apnoea or diving [1], but such effects are modified by the mechanical effects of the intrathoracic pressure changes secondary to airway obstruction [2]. The responses to peripheral and central chemoreceptor activation by hypoxia and hypercapnia [3] are affected by the sleep state [4, 5], as well as the circulatory control [6, 7]. Parasympathetic tone is high during sleep [8], but the sympathetic system is activated during apnoeas [9] and is likely to be involved in OSA-induced cardiocirculatory changes. Finally, most OSA end with an arousal, which increases sympathetic activity, blood pressure, and heart rate [10, 11]. Therefore, OSA-induced acute circulatory changes should be considered as integrated responses to different pathogenic factors acting simultaneously or in rapid succession.

Concerning long-term changes, they are also the result of a multifactorial pathogenesis. Both pulmonary and systemic arterial hypertension in OSA patients may depend, directly or indirectly, on the effects of apnoeas, as well as on other factors, like obesity. In addition, the long-term cardiovascular effects of OSA are clinically relevant. Epidemiological studies have shown that OSA and systemic hypertension are often associated [12–21]. Even uncomplicated snoring may increase the risk for cardiovascular diseases [20, 22–26], possibly by potentiating the effect of other risk factors [27]. Since the prevalence of undiagnosed sleep-related disordered breathing may be higher than previously believed, especially in women [28], the acute and long-term cardiovascular effects of OSA are potentially major health problems, in addition to raising an interesting physiological puzzle.

OSA-related cardiovascular changes have been the subject of many reviews [15, 17, 19, 20, 29–35]. Attention to sleep medicine is increasing [36], and new data on the circadian behaviour of cardiovascular, hormonal, and nervous variables have recently been published. This widespread growth of interest has taken advantage of modern technology, since miniaturization of recorders

and development of software for computer analysis has allowed cardiovascular monitoring in ambulatory patients, without major alterations of their sleep pattern [37]. In addition, experimental models of OSA in animals have been established [38–41], and may help in the study of individual pathogenic factors, despite some limitations such as species differences, or experimental designs which do not entirely mimic human OSA.

This review is centred on the factors believed to play a role in the pathogenesis of OSA-induced acute and long-term circulatory changes. After discussing some aspects of cardiovascular regulation during sleep, we describe the time course of heart rate (HR), cardiac output (CO), pulmonary arterial pressure (PAP), and systemic arterial blood pressure (BP) during OSA, with special attention to the role of: 1) hypoxaemia and hypercapnia; 2) the mechanical effects of OSA; and 3) the arousals at the end of the apnoeic events. The importance of the sympathetic nervous system is highlighted, since it is normally involved in cardiovascular regulation during sleep [42], and may mediate the effects of OSA-induced hypoxia and arousals. Finally, the role of OSA in the pathogenesis of diurnal pulmonary and systemic hypertension is discussed.

The cardiovascular system in normal sleep

The cardiovascular changes normally occurring during human sleep were first related to the sleep phases in the 1960s [43, 44]. It was shown that during non-rapid eye movement (NREM) sleep, HR and CO decreased by 5–10% compared to wakefulness, and that the CO reduction might depend mainly on decreased HR, since stroke volume (SV) remained unchanged [44]. While PAP did not change significantly [45], BP decreased during sleep [46, 47], due partly to recumbency, and partly to sleep itself [48]. Muscle sympathetic nervous activity (SNA) also decreased progressively during NREM sleep [42, 49]. During rapid eye movement (REM) sleep, a highly variable haemodynamic pattern was reported [43, 44], together with evidence of peripheral vasoconstriction and increased sympathetic vasomotor activity [42, 44].

The sympathetic nervous system is believed to make an important contribution to cardiovascular homeostasis during the REM phase [50]. Recent studies in humans have shown that muscle SNA increased above the wakefulness level during tonic REM sleep [42, 49], and fell whenever muscle tone increased (REM twitches), concomitant with an increase in BP [42]. Increased muscle SNA and BP coincided with the phasic eye movements of REM sleep [10, 51], while muscle SNA tended to decrease as REM sleep duration increased [51]. Auditory stimuli causing arousals during NREM sleep also gave rise to a transient increase in muscle SNA and BP [10, 51]. It should be emphasized that muscle SNA, although physiologically important, is only part of total SNA. While muscle SNA is dominated by vasoconstrictor impulses [52], skin SNA shows different features, such as dependency on thermoregulation, coupling with inspiration, and increase with arousal stimuli [53]. Changes

in skin SNA during sleep have received much less attention than changes in muscle SNA. In normal subjects, skin SNA was reported to decrease during NREM sleep [44, 53], whereas variable changes were found during REM sleep [44, 53].

Further studies are needed to give a better understanding of the role of SNA during sleep and OSA, particularly since the sympathetic nervous system may, for the most part, regulate the distribution of peripheral blood flow rather than simply affecting total peripheral resistance during sleep. In cats, a profound vasodilation occurred during REM sleep, together with lack of sympathetic responses and of thermal regulation [6, 7]; however, this was accompanied by mesenteric vasodilation and iliac vasoconstriction [6]. Therefore, the analysis of cardiovascular regulation during sleep appears complicated, especially in humans where the distribution of blood flow is hard to investigate. Among the few areas studied, subcutaneous adipose tissue was shown to undergo vasodilation at the onset of deep NREM sleep, while its blood flow rate was stable during REM sleep [54]. Cerebral blood flow decreased during NREM and increased during REM sleep, possibly in relation to changes in brain metabolism [55, 56]. Intracranial blood flow velocity, measured by transcranial Doppler and corrected for $P_{ET}CO_2$, remained fairly constant during sleep in normal subjects [57].

The sleep state may also modify cardiovascular regulation through other mechanisms, directly or by modulating SNA. For example, experimental data suggest that the parasympathetic and sympathetic systems may variably interact during the different sleep phases [8]. In addition, the baroreceptor-cardiac reflex was shown to undergo resetting during sleep [46], while its sensitivity, inconsistently affected during NREM, increased during REM sleep [46, 58]. Thermoregulation, was found to be blunted during REM sleep in humans [59]. In summary, this brief description underlines the fact that sleep-related cardiocirculatory changes may result from complex adjustments involving different homeostatic mechanisms. Cardiovascular regulation in normal conditions appears to be affected mainly by the sleep phases, and by the related changes in activity of the autonomic nervous system [60].

Acute cardiovascular changes in obstructive sleep apnoeas

Heart rate (fig. 1)

OSA-related HR changes are so characteristic that they may suggest the diagnosis of the OSA syndrome [61]. HR decreases during apnoeas and increases abruptly immediately post-apnoea [62], this pattern occurring cyclically during sleep [61]. ZWILLICH *et al.* [63] compared HR immediately before and at the end of apnoeas of different duration, and concluded that the development of bradycardia in OSA was directly related to apnoea length and arterial oxygen desaturation. The sleep phase seemed not to affect HR changes, since the profound bradycardia of REM sleep could be accounted for by more
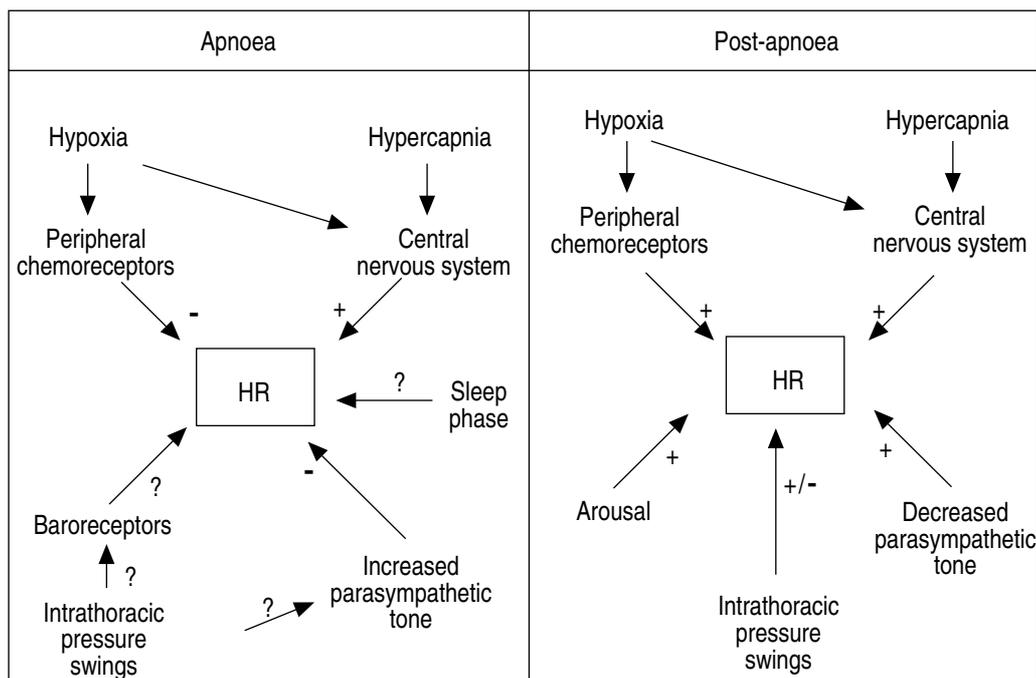
Fig. 1. – Schematic summary of the influence of various pathogenic factors on heart rate (HR) during apnoeas and immediate post-apnoea (details in the text).

prolonged and desaturating apnoeas than during NREM sleep. In awake OSA patients, ventilation with hypoxic mixtures increased HR. This study concluded that both apnoea and hypoxia contributed to the pathogenesis of bradycardia in OSA [63], in agreement with the classic studies on the pulmonary inflation reflex (hypoxia causes either bradycardia or tachycardia according to the absence or presence of ventilation, respectively) [64]. The role of OSA-induced progressive hypercapnia on HR was not examined [63], but experiments in normal subjects during wakefulness indicated that hypercapnia may slightly counteract both apnoea- and hypoxia-induced bradycardia [65]. In summary, in humans, the effect of apnoea on HR may be similar during wakefulness and sleep.

However, other studies have indicated that activation of peripheral chemoreceptors may not be the only factor responsible for the OSA-induced decrease in HR. Bradycardia only partially reverted following oxygen administration during OSA [61, 63]. In awake normal subject, the HR changes of OSA were mimicked by tidal breathing interrupted by recurrent apnoeas, but were unaffected by oxygen administration, suggesting that, during OSA, HR may be modulated mainly by other mechanisms [66]. Peripheral chemoreceptors could play a minor or no role in regulating HR during hypoxia, as indicated by the finding that ventilation with hypoxic mixtures in carotid body-resected awake humans caused tachycardia, as in normal subjects [67, 68]. In addition to stimulating peripheral chemoreceptors, hypoxia has central nervous system effects, suggesting that HR changes during OSA may be the result of the simultaneous activation of different reflex pathways. Indeed, hypoxia of peripheral chemoreceptors in conditions of constant ventilation caused bradycardia, whereas hypoxia of the cen-

tral nervous system increased sympathetic outflow and HR [69]. Moreover, in addition to this difference between central and peripheral responses, the peripheral (carotid and aortic) chemoreceptors could respond differently to hypoxia and hypercapnia [3], further complicating the analysis of the HR behaviour.

Furthermore, since respiratory efforts due to upper airway obstruction develop during OSA, HR may be affected, directly or indirectly, by mechanically-induced changes in other cardiovascular variables (for example, SV or BP) through baroreceptor activation. This hypothesis was tested by studying the HR response to phenylephrine during wakefulness and sleep in normotensive and hypertensive OSA patients [70], but the results did not confirm it. Although the cardiac baroreflex sensitivity differed between the two groups, the absolute and relative HR changes during the apnoeic cycle were similar in normotensive and hypertensive patients [70]. Therefore, the cardiac baroreflex did not explain OSA-induced bradycardia.

Increased parasympathetic tone appears to contribute to the bradycardiac response [71], since atropine prevented the decrease in HR during OSA [61, 63]. In OSA patients, the HR response to the Müller or Valsalva manoeuvre during wakefulness predicted the HR changes observed in OSA, whether or not concomitant hypoxaemia occurred [71]. OSA-induced HR changes may depend on the stimulation of upper airway receptors, possibly increasing parasympathetic efferent activity even in the absence of lung inflation and stretch receptor stimulation [72]. OSA patients responded with bradycardia to the Müller manoeuvre, whereas normal subjects did not, suggesting that upper airway obstruction may activate parasympathetic receptors at the site of airway collapse or distortion [72].

Respiratory sinus arrhythmia (higher HR during inspiration than during expiration) [73] can be demonstrated during OSA, suggesting that respiration modulates HR even during obstructed breathing [74]. This modulation could result from a direct central interaction between respiratory and cardiovascular control centres [75], or from activation of peripheral receptors indirectly increasing parasympathetic efferent activity [72].

Compared to the marked sinus arrhythmia found when examining the whole apnoea-interapnoeic phase cycle [61], HR changes during the apnoeic phase appear relatively small. Recently, it was suggested that HR may behave differently during OSA in NREM and REM sleep [76], thus challenging the conclusion reached by ZWILLICH et al. [63]. In NREM sleep, HR was lowest at the beginning and increased towards the end of apnoeas, whereas during REM sleep it progressively decreased during apnoeas. Whilst confirming the relationship between bradycardia and hypoxia, these results suggested an independent effect of the sleep phase on HR during OSA [76]. Other investigators found variable HR changes in OSA [77], or a modest trend to progressive bradycardia during NREM OSA [78].

Although OSA-induced HR changes may be modulated by different factors (apnoea, hypoxia, parasympathetic activity, sleep phase), an intact autonomic nervous system is necessary for HR changes to occur, since a stable HR was found during OSA in patients with autonomic dysfunction [61, 79, 80]. Spectral analysis may be employed to analyse the sympathetic-parasympathetic balance in relation to HR changes during sleep [81–84]. Unfortunately, HR in OSA does not vary in a sinusoidal fashion, which is a prerequisite of any method applying Fourier analysis [85]. The few published data have documented a high HR variability in OSA patients during sleep [86], and a phase difference between HR and BP changes, not supporting a major role for baroreflexes during OSA [87].

Post-apnoeic tachycardia also deserves comment. It may be an effect of hypoxia, increasing HR at the resolution of airway obstruction when the pulmonary inflation reflex is re-established [64]. In addition, the arousal reaction could increase HR by increasing SNA [10]. A decrease in parasympathetic tone may also occur, as suggested by the blunted respiratory sinus arrhythmia found immediately post-apnoea [74]. Therefore, a crucial role for the autonomic nervous system in the post-apnoeic phase seems likely. In OSA patients, post-apnoeic HR tended to be higher in REM than in NREM sleep, and peak HR significantly correlated with the HR response to the Valsalva manoeuvre [76]. In snorers, the smallest post-apnoeic increase in HR was found in the patients with the highest apnoea-hypopnoea index (AHI), suggesting that the HR response to apnoeas may reflect the degree of "brainstem arousability" [88]. The intriguing hypothesis that subcortical arousals may be important in the pathophysiology of OSA-related HR changes needs further evaluation, but is supported by another study in normal subjects, reporting that stimuli insufficient to cause electro-encephalographic (EEG) arousals did increase HR and BP [11].

It would be interesting to transform the increasing knowledge on the autonomic nervous system during sleep into clinically useful information. An alternative approach may include studying the responses of OSA patients to autonomic stress tests (AST), although their standardization is difficult. Abnormal responses to AST were more frequently found in OSA patients than in snorers, especially when nocturnal oxygen desaturations were severe [89]. Because the subjects studied were young and without any known cause of autonomic dysfunction, these results imply that abnormal autonomic responses may be very common in the whole population of OSA patients [89], supporting the hypothesis that OSA may reset the threshold of cardiovascular adaptation through chronic autonomic overstimulation.

Cardiac arrhythmias could contribute to increase cardiovascular risk in OSA patients [34]. Besides the sinus arrhythmia already described [61], both bradyarrhythmias (sinus pauses, A-V block of variable degree) and tachyarrhythmias (premature ventricular contractions, ventricular tachycardia) were reported in OSA patients during sleep, but, in the same patients, electrophysiological studies were normal during the daytime [90]. OSA-related disturbances in cardiac rhythm may depend both on the high nocturnal parasympathetic tone (especially for bradyarrhythmias), and the recurrent falls in arterial oxygen saturation (Sa_{O_2}). An important role for hypoxaemia was suggested by the increased frequency of premature ventricular complexes found in severe OSA with very low nocturnal Sa_{O_2} [34, 91, 92]. Conversely, nocturnal oxygen administration in patients with OSA and chronic obstructive pulmonary disease (COPD) improved OSA-dependent bradycardia, but had no effect on supraventricular or ventricular arrhythmias [93]. However, these results may not be generally applicable to the whole OSA population. Most investigators agree that arrhythmias in OSA disappeared after tracheostomy [90], or under therapy with nasal continuous positive airway pressure (nCPAP) [34].

Cardiac output (fig. 2)

Knowledge of the time course of cardiac output (CO) when sleep is disturbed by repeated upper airway obstruction is clinically important, since alterations in cerebral or myocardial blood flow may contribute to increase the risk for cardiovascular disease in snorers compared to the general population [23–25]. The velocity of carotid [94] and intracranial blood flow [57] was found to decrease in OSA, more than could be accounted for by the increased P_{ETCO_2} during apnoeas [57]. Preliminary data have suggested that cerebral blood flow velocity increased during OSA, but fell rapidly to the initial value post-apnoea, implying that such chronic strain of the brain vessels might lead to microangiopathic vascular lesions [95]. The pathophysiological consequences of these findings are still undefined, as is the relationship between cerebrovascular disease and OSA.

Similarly, coronary blood flow was never measured during OSA, but myocardial oxygen consumption ($M\dot{V}_{O_2}$)
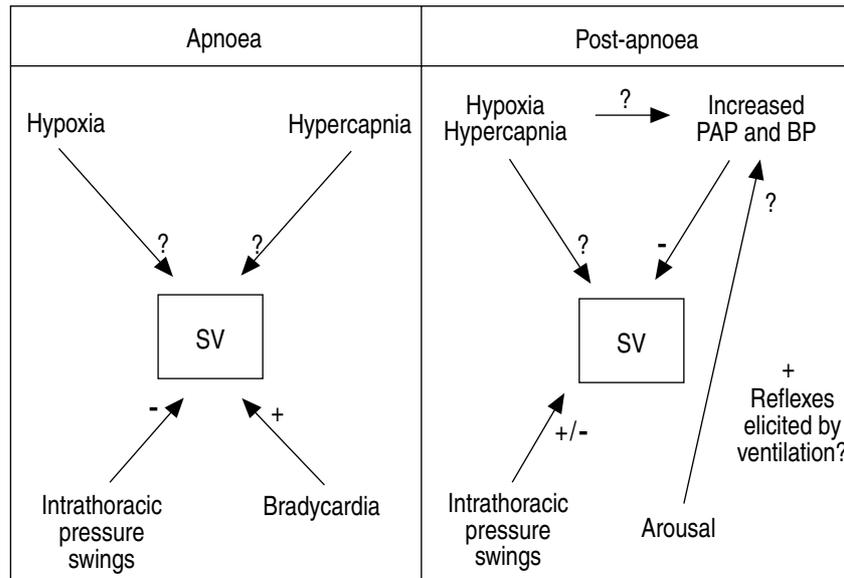
Fig. 2. – Schematic summary of the influence of various pathogenic factors on right and left ventricular stroke volume (SV) during apnoeas and immediately post-apnoea (details in the text). PAP: pulmonary artery pressure; BP: systemic arterial blood pressure.

was estimated, based on the time course of haemodynamic variables during apnoeas [91]. OSA-induced bradycardia may limit M$\dot{V}$O$_2$, but the post-apnoeic increase in HR and systemic BP are likely to increase M$\dot{V}$O$_2$. Therefore, on theoretical grounds, OSA may significantly reduce myocardial blood flow supply and/or increase demand [91]. Left ventricular (LV) ejection fraction decreased in some OSA patients both during exercise and REM sleep, together with evidence of myocardial hypoperfusion at thallium scintigraphy, suggesting that REM sleep could be as stressful as exercise in OSA [96]. However, no conclusion can be drawn until more data become available on this issue.

Besides these uncertainties concerning the time course of cerebral and myocardial blood flow during apnoeas, measuring total blood flow (CO) in OSA also raises problems. The thermodilution method provides average data over several cardiac cycles and requires measurements in triplicate for validation of results. Since OSA patients show recurrent apnoeas of relatively short duration, it is not surprising that some studies found no significant change in CO during apnoeas or interapnoeic phases [97, 98]. Another study reported that CO decreased during apnoeas, more in REM than in NREM sleep, and increased in the interapnoeic periods [99], but no conclusion could be drawn on such variable results.

Application of beat-by-beat methods during OSA has improved our knowledge of the time course of CO, calculated as stroke volume (SV) times heart rate (HR). Most techniques providing beat-by-beat data are noninvasive, but artifacts caused by lung inflation and/or body movements may prevent data collection during the interapnoeic phase [100, 101]. Thoracic electrical impedance [76, 100], echocardiography [101], and, more recently, continuous measurement of left ventricular volume [102] and of blood velocity in the pulmonary artery to estimate right ventricular stroke volume (RVSV) [78] were employed in OSA. CO was found to be well-maintained during NREM OSA (fig. 2), since HR and SV underwent reci-

procal changes during the apnoeic phase without significant effects on CO [76, 78, 102]. CO decreased during apnoeas in REM sleep, since HR progressively fell during apnoea and SV remained at the pre-apnoeic level ([76], Bonsignore, unpublished observations). Interestingly and unexpectedly, CO was found to decrease post-apnoea (fig. 2), due to a decrease in SV not compensated for by the post-apnoeic increase in HR [78, 102]. This conclusion was reached by two studies using unrelated methodologies to monitor left ventricular stroke volume (LVSV) and RVSV, respectively, and appeared at variance with previous data [99]. The post-apnoeic decrease in LVSV coincided with an abrupt increase in end-systolic LV volume and BP [102]. The post-apnoeic decrease in RVSV was explained as possibly resulting from a limitation of RV diastolic filling or from increased pulmonary vascular resistance caused by lung expansion [78]. In fact, most of the post-apnoeic decrease in RVSV occurred at maximal inspiration [78] (fig. 3). During post-apnoea, it
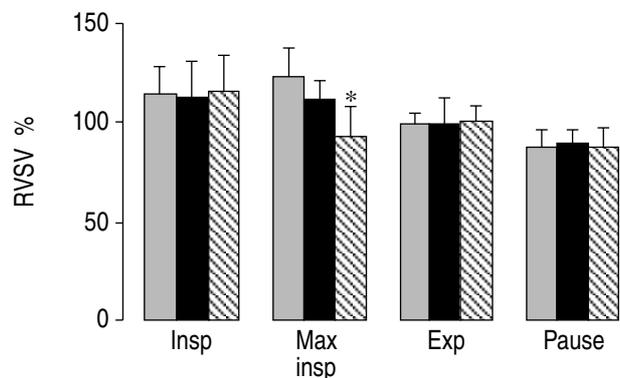

Fig. 3. – Distribution of right ventricular stroke volume (RVSV) (% of mean value for each apnoeic phase±SD) in the respiratory cycle before, during and after obstructive apnoeas □ : pre-apnoea; ■ : apnoea; ▨ : post-apnoea. Insp: inspiration; Max insp: maximal inspiration; Exp: expiration; pause: late expiration, when oesophageal pressure is stable.

is likely that the autonomic nervous system is simultaneously affected by different factors, *i.e.* hypoxia, arousal, and lung inflation, and changes in SNA may contribute to acutely decrease SV immediately post-apnoea. However, the data available during OSA indicate that muscle SNA, after a progressive increase during apnoeas, fell abruptly at resumption of ventilation [9], probably because of both increased oxygen tension [9] and the pulmonary inflation reflex [64]. The post-apnoeic decrease in SV seemed to occur at the same time that muscle SNA decreased, but the relationship between changes in SNA and SV during OSA has not been investigated. Interestingly, preliminary data suggest that skin SNA, evaluated from changes in finger plethysmographic volume, increased at the resumption of ventilation after OSA [53], raising the question of the relative pathophysiological significance of muscle and skin SNA changes during apnoeas. Insufficient data are available at present to provide any answer.

The arousal reaction seems to play a minor role in the post-apnoeic decrease in CO, for LVSV did not change after isolated arousals, whereas delaying the resumption of ventilation delayed the post-apnoeic LVSV fall [103]. The post-apnoeic decrease in RVSV and LVSV was documented only during NREM OSA [78, 102], but preliminary data indicate that it may also occur in REM OSA, as well as at the resolution of partial airway obstruction during snoring (fig. 4) (Bonsignore, unpublished observations). Whatever the mechanism(s) responsible, the SV changes immediately post-apnoea suggest an effect of reflex adjustments originating from lung inflation [104].

This issue deserves further study, to define the pathophysiological aspects, as well as its clinical relevance in OSA patients and snorers.

Beat-by-beat analysis of SV has provided information about the mechanical effects of OSA on the circulation. Intrathoracic pressure influences SV by affecting cardiac filling pressure (preload), and transmural PAP and BP (afterload) [2]. Moreover, mechanical changes affect the heart indirectly through the ventricular interdependence mechanism: since the septum is common to both ventricles, it can be shifted by increased filling of one ventricle, thus decreasing the filling of the other [105]. During normal breathing, inspiration increases RVSV and decreases LVSV slightly, the opposite occurring in expiration. These small, respiratory-dependent variations become marked oscillations during airway obstruction [2]. Echocardiographic monitoring has documented decreased LV diastolic dimensions and left ventricular collapse during OSA [101]. Beat-by-beat analysis of LVSV relative to intrathoracic pressure during OSA has revealed that LVSV was stable at oesophageal pressures (Poes) $\geq$-10 cmH$_2$O, but decreased linearly at Poes <-10 cmH$_2$O [100]. Subsequent studies reported that LVSV changes during OSA could be accounted for not only by changes in Poes, but also by HR changes during apnoea, SV at onset of apnoea, and age [76]. SV changes did not correlate with Sao$_2$ changes, suggesting that SV during OSA may be affected more by mechanical events than by hypoxaemia [76].

Mechanically-induced RV changes are opposite to LV changes [2], and RV enlargement was found during OSA
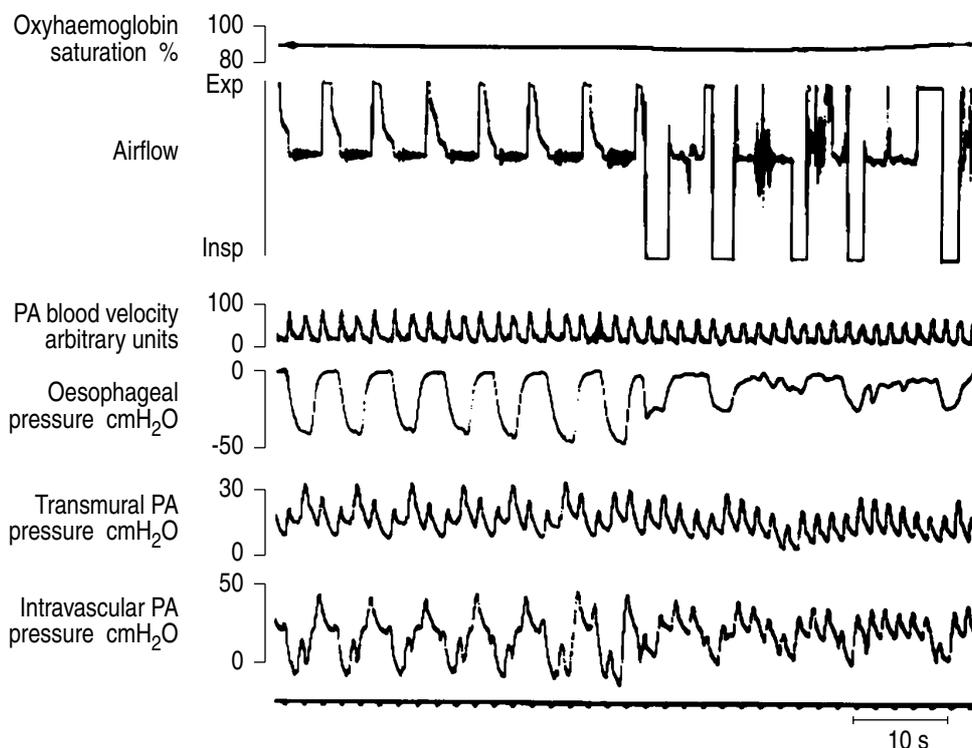

Fig. 4. – Resolution of partial airway obstruction during snoring followed by a decrease in right ventricular stroke volume, as estimated by integration over time of the pulmonary arterial (PA) blood velocity signal. Snoring (left half of figure) is characterized by partial airway obstruction, indicated by marked oesophageal pressure (Poes) swings with inspiratory limitation of airflow. At resolution of snoring, Poes swings decrease and inspiratory flows increase. Meanwhile, the amplitude of the pulmonary arterial (PA) blood velocity signal decreased, suggesting reduction of right ventricular stroke volume, similar to what can be observed at the resolution of obstructive sleep apnoea.. Exp: expiration; Insp: inspiration.

[101]. Because venous return at low intrathoracic pressures may be limited by collapse of the great veins at the entrance of the chest [106–109], the relationship between RVSV and Poes was studied in a small sample of OSA patients [110]. Preliminary data suggested that RVSV may decrease at low Poes, supporting the hypothesis of a limited venous return at low intrathoracic pressure [107]. However, an effect of increased RV afterload in limiting RVSV at low intrathoracic pressure could not be excluded [110].

It is uncertain whether myocardial contractility is acutely affected by apnoeas [29, 35], but OSA-related SV changes can, for the most part, be explained by mechanical effects [76, 111]. In isolated cardiac fibres, both hypoxia and hypercapnia decreased maximum force and velocity of shortening [112], but regulation of myocardial contractility in the intact animal is more complex [113]. On one side, myocardial contractile strength decreased during hypoxia, possibly due to a carotid chemoreceptor-induced negative inotropic effect [114]. On the other hand, hypoxia of the central nervous system increased cardiac contractility by eliciting a strong sympathetic discharge, and this central response would override the inhibitory effect of carotid body stimulation [69]. The predominance of central over peripheral effects was also suggested by the unchanged cardiac and coronary haemodynamics found during hypoxia in sinoaortic-denervated dogs [115].

If an acute decrease in cardiac contractility during OSA is uncertain, chronic right and/or left ventricular dysfunction can occur in OSA patients [35], and improve under nCPAP treatment [116, 117]. Therefore, chronic recurrence of OSA, through many possible pathophysiological mechanisms, may adversely affect cardiac function [35]. However, no evidence for LV dysfunction was found in OSA patients, even when selecting a group with severe disease (AHI >40·h^{-1} with marked nocturnal falls in Sao$_2$) [118]. Therefore, the direct role of OSA in the pathogenesis of acute or chronic cardiac dysfunction remains controversial.

Pulmonary arterial pressure (fig. 5)

The first studies on the pulmonary circulation in OSA described the large oscillations in PAP caused by the intrathoracic pressure swings, and reported that mean PAP increased immediately post-apnoea [62, 119]. Other investigations reported only maximal PAP values attained during sleep, and suggested that OSA may cause nocturnal pulmonary hypertension [97]. PAP behaviour during OSA was better evaluated by calculating transmural PAP (PAPtm), *i.e* intravascular PAP minus intrathoracic pressure, that is the true distending PAP [120]. During NREM sleep, systolic and diastolic PAPtm decreased slightly at the beginning of OSA, then increased at the end of the apnoeic phase, and were high at the resumption of ventilation [120]. Increased PAP during OSA could result either from mechanical events [98], or from hypoxic vasoconstriction. A significant inverse correlation between PAPtm and Sao$_2$ was found in most OSA patients, suggesting that hypoxia plays a part in the pathogenesis of nocturnal pulmonary hypertension [120]. This hypothesis was further tested by evaluating the effect of oxygen administration on PAPtm during OSA [121]. If hypoxia contributed to OSA-induced pulmonary hypertension, PAPtm would be lower when nocturnal Sao$_2$ was maintained at values ≥90%. However, in most patients, oxygen administration affected neither mean PAPtm, nor the amplitude of PAPtm swings [121]. As possible explanations, prolongation of OSA by supplemental oxygen might increase CO$_2$ retention compared to OSA while breathing room air. CO$_2$ may counteract the effects of oxygen, by constricting pulmonary vessels [122]. Alternatively, PAPtm remained high because the oscillations of PAPtm were dependent on the intrathoracic pressure swings and unaffected by oxygen. PAPtm during oxygen administration decreased in only two patients, both showing a minor increase in transcutaneous carbon dioxide tension (Pco$_2$) and being the youngest among the patients studied. This suggests that structural pulmonary
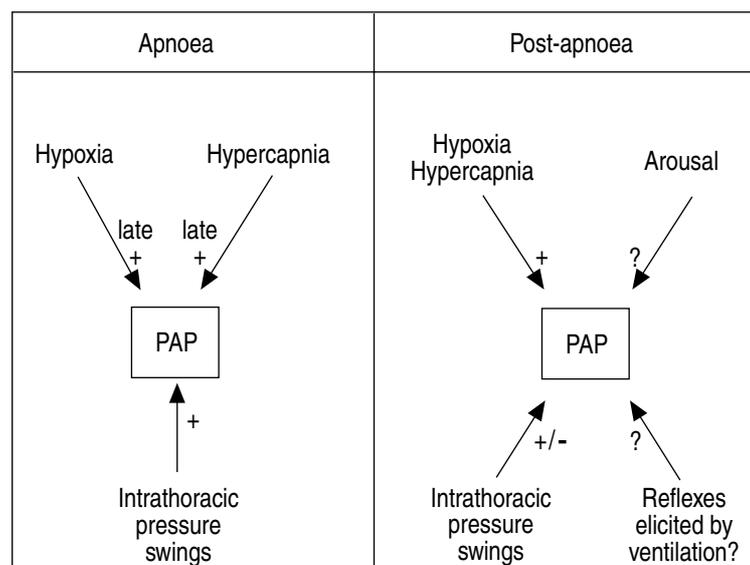

Fig. 5. – Schematic summary of the influence of various pathogenic factors on pulmonary arterial pressure (PAP) during apnoeas and immediately post-apnoea (details in the text).

vascular changes may influence the pulmonary haemodynamic response to OSA [121]. An additional possibility was that pulmonary hypoxic vasoconstriction may develop slowly, requiring repetitive and profound desaturations to significantly increase PAPtm [121].

OSA during NREM sleep recurs with relatively constant characteristics in each patient, making the analysis of a slow effect of hypoxia difficult. In a dog model of OSA by repetitive airway obstructions of different duration, cardiovascular changes were analysed over a wide range of Sao_2 values [39]. At the release of airway occlusion, PAP progressively increased as Sao_2 decreased, but oxygen administration prevented the occurrence of the pulmonary hypertensive peaks [39]. Therefore, this study concluded that hypoxia was the major cause of OSA-related nocturnal increases in PAP. In OSA patients, similar results were obtained by comparing PAPtm during NREM and REM sleep in the same subjects [123]. At similar Poes values, PAPtm was higher during REM than NREM OSA, and the difference could be related to the more profound falls in Sao_2 observed during REM sleep [123]. Therefore, the role of hypoxia in the pathogenesis of nocturnal pulmonary hypertension in OSA patients is well-documented on both experimental and clinical grounds.

Nevertheless, OSA-induced mechanical changes may also affect the pulmonary circulation [98]. The analysis of PAPtm and pulmonary flow (RVSV) during NREM OSA suggested that pulmonary vascular resistance (PVR) increased at low intrathoracic pressures, because PAPtm increased as Poes decreased, but RVSV might decrease at low intrathoracic pressure (see previous section) [110]. This increase in PVR could not be ascribed to lung volume changes, absent during apnoeas, but may reflect the effects of low intrathoracic pressure on the left heart. Limitation of LV filling and emptying at low intrathoracic pressures [2, 101] could at least contribute to increase PVR during OSA by increasing pulmonary venous pressure and blood volume, as suggested in a recent review [35]. This hypothesis is further supported by the high pulmonary arterial wedge pressure documented during OSA [124], and by the possible, albeit infrequent, clinical presentation of OSA as nocturnal pulmonary oedema [125]. Thus, mechanical changes affect PVR during the apnoeic phase, while the pulmonary hypertensive peaks seem to be related mostly to hypoxaemia, since they occur when intrathoracic pressure returns towards normal values and are blunted by oxygen administration [39].

However, hypoxia may not be the only pathogenic factor responsible for the post-apnoeic increase in PAPtm. At the resolution of OSA, the similar behaviour of the pulmonary and systemic circulations (decrease in RVSV [78] and LVSV [102], and increase in pulmonary and systemic vascular resistance) may lead to the hypothesise that a generalized cardiovascular reflex may also play some role. The data available would not confirm the hypothesis of major, reflex-induced pulmonary circulatory changes, since PAP increased similarly during OSA in patients with or without the Shy-Drager syndrome [126]. However, studying reflex mechanisms is difficult, especially for the pulmonary circulation which can only be approached invasively. Preliminary results obtained during repetitive airway obstruction in dogs suggested that an α-adrenergic pathway through the carotid body played only a minor role in the pathogenesis of pulmonary hypertension [127]. On the other hand, in anaesthetized dogs, stimulation of peripheral chemoreceptors may inhibit hypoxic pulmonary vasoconstriction, whereas sympathetic activation would reduce pulmonary vascular tone during both hypoxia and hyperoxia [128]. At present, the available data do not allow the role of the autonomic nervous system in modulating the responses of the pulmonary circulation during OSA to be defined. Hopefully, future studies will investigate this issue.

Systemic arterial pressure (fig. 6)

The time course of changes in systemic arterial blood pressure (BP) during OSA is similar to that of PAP: BP is lowest at the beginning of OSA and increases towards the end of the apnoeic phase, the highest values being recorded during post-apnoea [62]. OSA patients show a high BP variability during sleep [86, 87], and the normal nocturnal decrease in BP can be prevented by the continuous recurrence of OSA [129]. As a result, mean 24 h BP is often increased in OSA patients, even when they are normotensive during wakefulness, and this may entail a higher cardiovascular risk [130, 131]. However, development of systemic hypotension during OSA has also been reported, especially in older patients [77, 132–134], and is currently ascribed to reduced sympathetic responsiveness to hypoxia in the elderly [135]. Systemic hypotension during OSA may favour occurrence of a stroke by decreasing cerebrovascular perfusion pressure [132], extending the hypothesis that nocturnal cerebrovascular accidents in OSA patients may be caused by the hypocapnia and cerebral vasoconstriction occurring during the hyperventilation periods [136].

Despite the variable time course of BP during apnoeas, the mechanical effect of airway obstruction is recognizable as pulsus paradoxus, coincident with Poes nadirs [101] or mouth pressure changes [137]. Pulsus paradox, *i.e.* a marked inspiratory decrease in BP, reflects the decrease in LVSV at low intrathoracic pressure [2]. Experimental data suggest that carotid and aortic baroreceptors are differently activated during obstructed breathing or the Müller manoeuvre [138]. During inspiratory efforts, carotid (extrathoracic) baroreceptors were exposed to a lower transmural pressure than aortic (intrathoracic) baroreceptors, and afferent activity from the carotid baroreceptors correspondingly decreased, while that of aortic baroreceptors was unchanged [138]. Therefore, it is possible that mechanically-induced BP oscillations during OSA may be, at least partly, buffered by the differential activation of the baroreceptors.

True hypertensive peaks occur in OSA at resumption of the ventilation, while the intrathoracic pressure swings decrease in amplitude. Since LVSV decreased during post-apnoea despite normalization of intrathoracic pressure [102], the post-apnoeic increase in BP cannot be ascribed to an increase in CO, as previously believed
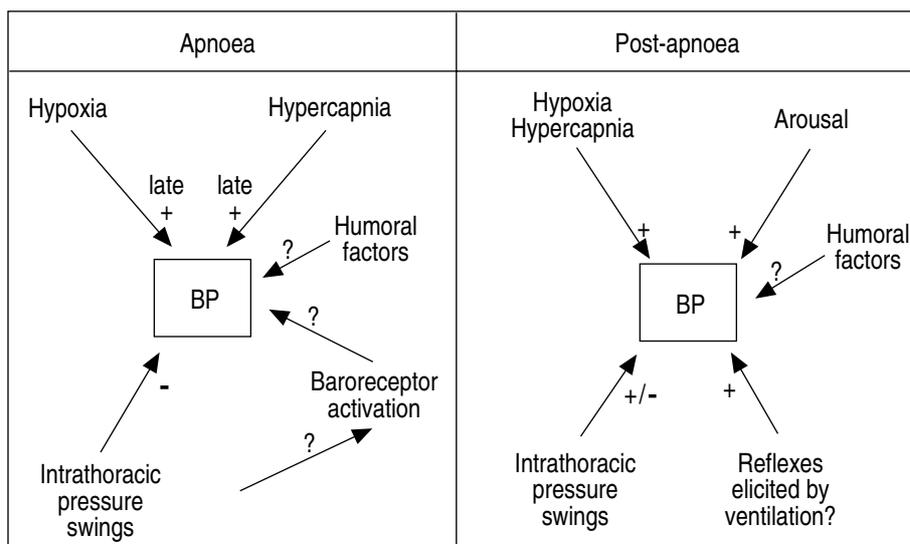
Fig. 6. – Schematic summary of the influence of various pathogenic factors on systemic arterial blood pressure (BP) during apnoeas and immediately post-apnoea (details in the text).

[29, 31]. In addition, this hypertensive response requires an intact autonomic nervous system, being absent in OSA patients with the Shy-Drager syndrome or transplanted heart [77, 126]. Various factors appear to contribute to its pathogenesis (fig. 6): hypoxia and hypercapnia, the arousal reaction, and OSA-induced changes in sympathoadrenal activity. However, the relative role of each of these possible causes is controversial.

The BP response to hypoxia is mediated by the activation of the carotid body [67, 68] and by SNA. In awake normal subjects, hypoxia increased muscle SNA, in turn causing peripheral vasoconstriction [139], while baroreceptor activation, at least partly, counteracted these hypertensive effects [140]. Hypoxia increased BP during both breathhold and ventilation [141, 142], despite SNA inhibition by ventilation [139]. During OSA, the relatively small and delayed BP increase of the apnoeic phase appears similar to the slow BP rise during breath-holding [141], modified by the beat-by-beat oscillations dependent on the obstructed respiratory efforts [101]. During post-apnoea, the brisk BP peak may still be an effect of hypoxia, potentiated, however, by the arousal reaction [11, 143], or by a yet undefined reflex elicited by the resumption of ventilation [103, 126]. Several data support a role for hypoxia during post-apnoea. Firstly, oxygen desaturation during OSA is universally found to correlate with the post-apnoeic BP increase, although the slope of this relationship is highly variable among OSA patients [91]. Secondly, the increase in BP was prevented by oxygen administration in a human model of recurrent apnoeas during wakefulness [144], and in experimental studies mimicking OSA in dogs [39]. Thirdly, observations during sleep at high altitude indicated that periodic breathing is characterized by a fall in Sao_2 and an increase in BP synchronous with breathing (Insalaco, unpublished observations) (fig. 7). A similar pattern was described in a patient with central alveolar hypoventilation and nocturnal periodic breathing [145].

Although these observations favoured a major role for hypoxia, the results of other studies gave rise to different conclusions. BP increased similarly during NREM OSA whether the patients were breathing room air or oxygen-enriched air to maintain Sao_2 ≥90% [146]. Conversely, BP did not change when the same patients breathed a hypoxic mixture under nCPAP (Sao_2 at 80% but no apnoeas) [146]. These results suggest that hypoxia was not the only cause of OSA-induced systemic hypertension. Such a conclusion, however, was recently questioned, because the flow of oxygen administered was relatively low, and perhaps insufficient to prevent the BP increase [39]. Another study compared BP during OSA while the patients were breathing room air, oxygen-enriched air, or under nCPAP, and found similar mean or maximal BP values under the three conditions [147]. BP correlated with apnoea length and the maximal post-apnoeic HR increase, suggesting that the arousal reaction at the end of OSA may be more important than hypoxia in the pathogenesis of the post-apnoeic BP peaks [147]. RINGLER et al. [146] similarly reported that BP increased significantly after arousals. On the other hand, the increase in BP during nocturnal periodic ventilation at high altitude seemed to occur irrespective of EEG and electromyographic (EMG) signs of arousals (Insalaco, unpublished observations). Therefore, while results of some studies strongly support the hypertensive role of hypoxia, other studies point to the arousal reaction as an equally important cause of the nocturnal hypertensive peaks. Preliminary data comparing OSA and arousals in the same subjects have suggested that OSA-induced BP changes may differ in magnitude and time course from arousal-induced BP changes [143]. BP increased more in OSA than in isolated arousals [143]. In addition, BP increased after EEG changes in induced arousals, but before EEG changes during OSA, suggesting that arousals may potentiate the OSA-related effects of hypoxia [143].

It has long been known that BP increases during sleep after EEG arousals (K-complexes) [10, 39], and upon awakening [148]. However, the role of arousals as a
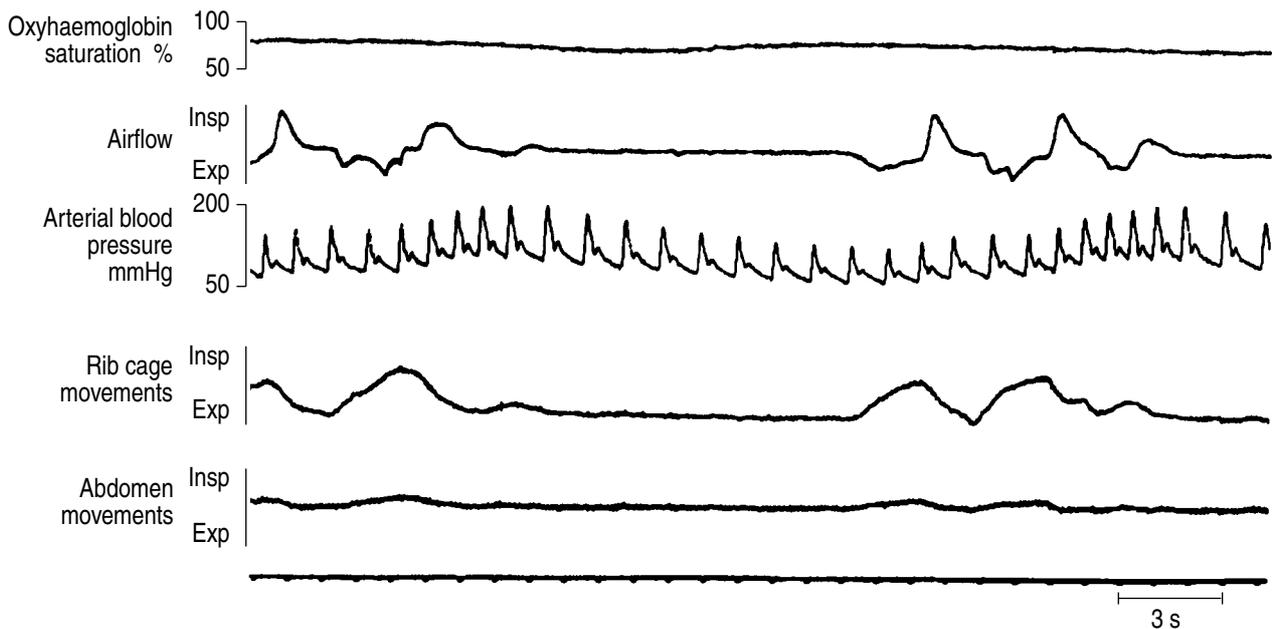
Fig. 7. – Periodic breathing during sleep at high altitude (5,050 m). Note the increase in systemic arterial blood pressure and heart rate during ventilation. Insp: inspiratory; Exp: expiration.

cause of BP changes has been reassessed recently by systematically analysing the cardiovascular response of normal subjects to graded arousal stimuli during sleep [11]. Changes in the EEG pattern were detected at 1 s intervals by computer analysis. As expected, arousal stimuli increased BP during both NREM and REM sleep, and usually caused EEG changes. However, stimuli insufficient to cause EEG changes also increased BP, suggesting that subcortical arousals may play an important role in OSA-induced cardiovascular changes, and that cardiovascular variables may be more sensitive indicators of sleep disruption than EEG [11]. The same group reported intriguing results in a patient with narcolepsy and periodic leg movements during sleep [149]. In this patient with no nocturnal hypoxaemia, BP increase coincided with arousals, but the BP changes during sleep persisted under temazepam treatment despite the disappearance of EEG signs of arousals [149]. Subcortical arousals may have been responsible for such BP changes, but this hypothesis should be substantiated before drawing any conclusion.

Concerning the mechanism by which arousals increase BP, the sympathetic nervous system is believed to play a central role. When arousal stimuli were delivered to normal subjects, muscle SNA always increased before BP elevations during sleep but after EEG changes [10], leading to the conclusion that cortical activation is necessary for the cardiovascular response to arousals to occur [10]. These findings were in agreement with some data obtained in OSA patients [143], but not with the evidence of subcortical arousals provided by other investigators [11, 149]. The same arousal stimuli delivered during wakefulness, instead, evoked no cardiovascular response [10, 11]. Methodological differences may explain the variability of results, for example concerning the type and intensity of the arousal stimuli used. However, a

major cause of discrepancy could be that, despite the fact that scoring rules for EEG arousals have recently been published [150], criteria for the identification of very short arousals (<3 s in duration) are still lacking. This field is in rapid evolution, and more definite data and criteria are to be expected in the future. In summary, the available results indicate that both hypoxia and arousals probably contribute to the pathogenesis of post-apnoeic hypertensive peaks. However, the role of arousals in OSA needs further clarification because, if arousals increase BP through increased SNA, this is hard to reconcile with the sudden decrease in muscle SNA described at the resumption of the ventilation after OSA [9]. One possibility is that arousals affect both skin and muscle SNA [52, 53], but no data are available at present on this issue.

The role of progressive hypercapnia in OSA-induced BP changes is traditionally considered minor compared to that of hypoxia, but experimental results on the cardiovascular effects of CO_2 deserve some comment. Hypercapnia strongly potentiated the cardiovascular effect of hypoxia during both breathholding and ventilation [142], and the release of catecholamines induced by hypoxia [151, 152]. Studies on muscle SNA, during either voluntary apnoea or ventilation with various gas mixtures in humans, confirmed the synergistic effect of hypoxia and hypercapnia in increasing SNA and BP [139, 153]. In addition, the increase in SNA and the hypertensive response to hypercapnia were insensitive to the feed-back mechanisms activated by the baroreceptor stimulation [140]. Instead, the increased SNA and the hypertensive response to hypoxia were selectively inhibited by baroreceptor stimulation [140]. Therefore, the role of hypercapnia in SNA and BP regulation during OSA, possibly overlooked compared to that of hypoxia [154], may be an important part of the cardiovascular response to OSA.

Besides the increased SNA documented in OSA [9], increased catecholamine release, synergistically induced by hypoxia and hypercapnia [151, 152], may contribute to OSA-induced BP changes. Sleep fragmentation can also increase sympathoadrenal activity, since sympathetic blockade decreased BP more in REM-sleep-deprived rats than in controls [155]. Many groups have addressed the question of whether circulating or excreted catecholamines were affected by OSA [156–164]. Although most investigators agree on an increased catecholamine release in OSA patients, major differences were reported: most studies did not measure catecholamines in control subjects [156, 158, 162], some reported only the changes observed under nCPAP therapy [159, 160, 162], while the relationship between catecholamine release and the severity of sleep respiratory disturbances was variable [158, 160, 161, 164]. Concerning OSA-related acute BP changes, no correlation between nocturnal BP and catecholamine release was demonstrated [158, 164]. These results, together with the variable reports on the effects of nCPAP on catecholamine levels, do not allow for a definite role to be attributed to catecholamines in the pathogenesis of OSA-induced BP changes. Nevertheless, they emphasize that sympathoadrenal function is heightened in OSA, in agreement with the increased SNA shown in OSA patients not only during the night, but also during the daytime [9].

In addition, OSA may modify the release of other humoral factors exerting cardiovascular effects directly, or through changes in renal function and water-electrolyte homeostasis. Several studies have tested this hypothesis by measuring in OSA patients, both under baseline condition and during nCPAP, urinary flow and electrolytes [165], haematocrit [166, 167], proteinuria and albuminuria [168], plasma renin activity (PRA) and aldosterone [169–171], atrial natriuretic peptide (ANP) [172], and metabolites of thromboxane and prostacyclin [173]. In summary, their results indicate that urine output and electrolyte excretion are increased in OSA patients during sleep [165], probably *via* an augmented ANP release related to OSA-induced hypoxaemia and mechanical changes [172]. Increased haematocrit [166, 167] and low PRA [169, 170] indicated redistribution of liquids between the intra- and extravascular compartments, but circadian changes in PRA and aldosterone secretion were also demonstrated [171]. None of these complex alterations, however, was found to be directly related to OSA-dependent BP changes, although the release of ANP may exert a protective role against the development of systemic hypertension by promoting sodium excretion [172]. Interestingly, the ratio between urinary 6-keto prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$) and thromboxane-B_2, the stable metabolites of prostacyclin and thromboxane-A_2, respectively, increased under nCPAP, suggesting that release of vasoconstrictor prostaglandins may predominate in untreated OSA [173]. However, no correlation was found between this ratio and OSA severity or BP [173]. Arachidonic acid metabolites may affect the response to sympathetic stimulation, since the progressive increase in BP during repeated cold pressor test in humans could be related to reduced release of vasodilator prostaglandins [174]. These results, together with the relative decrease in the production of prosta-

cyclin found in OSA [173], suggest that arachidonic acid metabolites might intervene in modulating OSA-induced BP changes.

The role of OSA in diurnal pulmonary hypertension (fig. 8)

Since the first studies on OSA, it was hypothesized that the pulmonary hypertensive peaks continuously recurring during sleep may evolve into stable pulmonary hypertension [126]. This hypothesis was not confirmed, since right heart failure [175] or increased PAP during wakefulness [176, 177] were only found in a minority of OSA patients with diurnal hypoxaemia and/or hypercapnia. Nevertheless, although insufficient to independently cause pulmonary hypertension, OSA potentiated the pulmonary vascular effects of COPD in the "overlap syndrome" [178]. Right heart failure or pulmonary hypertension were found to develop at modest degrees of airway obstruction in the presence of OSA [175–177]. To account for the diurnal hypoxaemia often found in OSA patients, other possible pathogenic factors were investigated. Most studies failed to find a significant relationship between the severity of OSA and pulmonary hypertension [175–177], and suggested that obesity, causing a restricted ventilatory pattern, and/or reduced chemosensitivity with hypoventilation, may be responsible for daytime hypoxaemia and pulmonary hypertension in OSA patients. Conversely, KRIEGER *et al.* [179], while confirming the importance of impaired pulmonary function, found that the severity of OSA did contribute to the pathogenesis of daytime pulmonary hypertension, hypoxaemia and hypercapnia. However, treatment of OSA, either by tracheostomy [176] or long-term nCPAP [180], did not decrease diurnal PAP significantly, even when arterial blood gases improved [180]. The lack of statistical significance could be due to the small number of pulmonary hypertensive patients studied [176, 180]. Alternatively, treatment of OSA may act by preventing further increases in PAP, rather than by decreasing already elevated PAP levels [180]. Preliminary data suggest that some OSA patients may show a heightened pulmonary vascular responsiveness to hypoxia and hypercapnia, which may return to normal with long-term nCPAP [181].

Concerning the role of OSA in the development of right ventricular hypertrophy, controversial results have been reported so far. BERMAN *et al.* [182] found echocardiographic evidence of right ventricular hypertrophy in 71% of their unselected OSA patients. In another preliminary study, increased RV wall thickness and abnormal filling correlated to the severity of sleep-related respiratory disturbances [183]. HANLY *et al.* [118] found no evidence of right ventricular enlargement in snorers with or without OSA. These opposing conclusions may result from differences in the patients studied or in methods [184].

However, other factors could be involved in the pathogenesis of right ventricular hypertrophy. For example, genetic susceptibility may play some role, since it was reported that right ventricular hypertrophy developed in Sprague-Dawley rats, but not in Wistar rats, exposed to repeated intermittent hypoxia [40]. In addition, the chronic effects
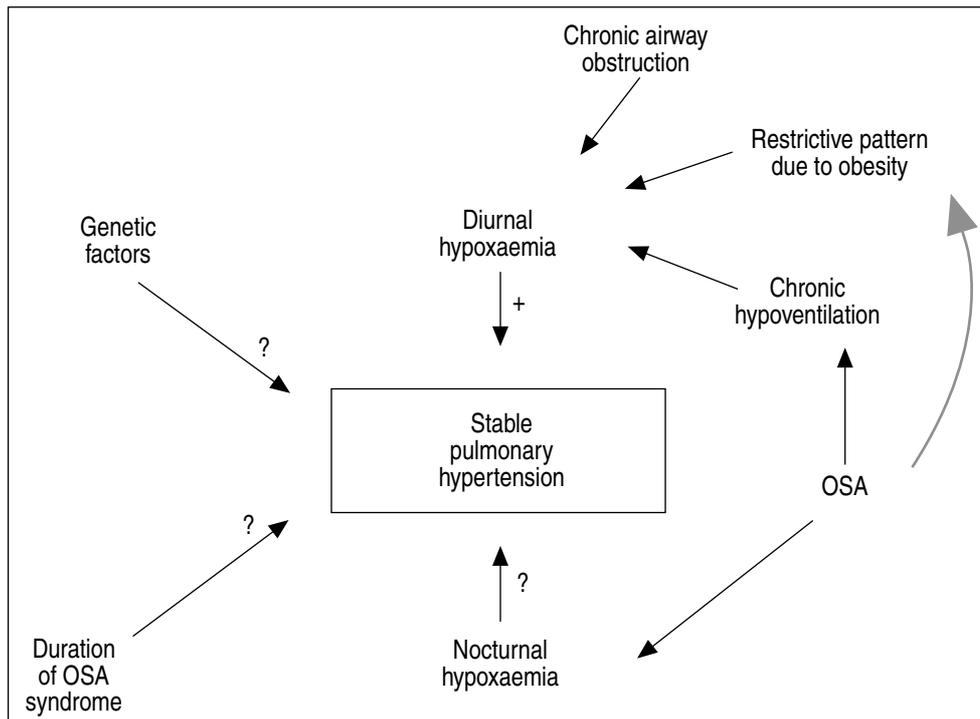
Fig. 8. – Schematic summary of the influence of various pathogenic factors in causing stable pulmonary hypertension in patients with the obstructive sleep apnoea (OSA) syndrome. The association between OSA and obesity is indicated by a hatched arrow (details in the text).

of OSA-dependent mechanical changes on the pulmonary circulation and on the right ventricle are unknown [179]. To summarize, there is general agreement that OSA does potentiate the effects of concomitant lung disease, whereas there is no conclusive proof that it independently causes stable pulmonary hypertension and/or right ventricular hypertrophy.

The role of OSA in diurnal systemic hypertension (fig. 9)

The hypothesis that OSA may favour the development of stable hypertension (HT) was advanced since the first studies in OSA patients [97], and was supported by the high prevalence of HT in OSA found by most, if not all, investigators [18, 21, 77, 134, 185–187]. In addition, it is possible that at least some hypertensive OSA patients become normotensive after tracheostomy [77, 176, 188–190] or nCPAP [33, 191], although some time may be necessary for OSA therapy to normalize BP. Even during sleep, nCPAP acutely decreased systolic BP, but did not affect diastolic BP in any sleep stage [192].

In order to understand the role of sleep-related respiratory disturbances in the pathogenesis of HT, the relationship between BP and snoring was examined [16, 22, 23, 187, 193–199], with variable results. Snoring was found to be directly related to diurnal [23] or nocturnal HT [134, 198], but most studies suggested that this relationship was indirect, mediated by age, cigarette smoking, or obesity [16, 22, 129, 187, 193, 194, 196, 197, 199, 200]. Prevalence of snoring was mostly assessed by questionnaire, and these results should be considered as only suggestive of an association between snoring and increased BP [26].

In studies on the relationship between nocturnal hypoxaemia and HT in snorers, obesity was found to be the factor most likely to be responsible for both snoring and nocturnal oxygen desaturations [16, 129, 194, 196], whereas the number of sleep-disordered breathing events and/or the degree of nocturnal hypoxaemia did not predict HT [187]. In OSA patients, obesity correlated strongly with HT [18, 187], even after chronic nCPAP therapy [201]. However, the issue is still unresolved, as some studies found that sleep-disordered breathing may contribute to HT in OSA patients [21, 196], even more than obesity [202]. On the other hand, no difference in sleep architecture, apnoea index, Sao_2 indices, or number of arousals was found between normotensive and hypertensive OSA patients [185].

The arguments in favour and against a role of OSA in the pathogenesis of HT were extensively reviewed [15, 17–20, 30, 33, 34], but no definite conclusion is presently available. A high prevalence of OSA was reported in hypertensive patients, although the degree of sleep-related respiratory disturbances in essential HT appeared low [12–14, 203–206]. Recent data have challenged the previously reported high prevalence of OSA in hypertensive patients, by reporting very few episodes of nocturnal hypoxaemia in a sample of such patients compared to age- and body mass index-matched controls [207]. The studies on hypertensive patients also left some questions unanswered, in particular on the possible role of the antihypertensive treatment in the pathogenesis of OSA [20].

Despite the unresolved controversies, it is conceivable that OSA and HT might share common pathogenic factors (fig. 9). More specifically, it was recently proposed that abnormalities of the autonomic responses to
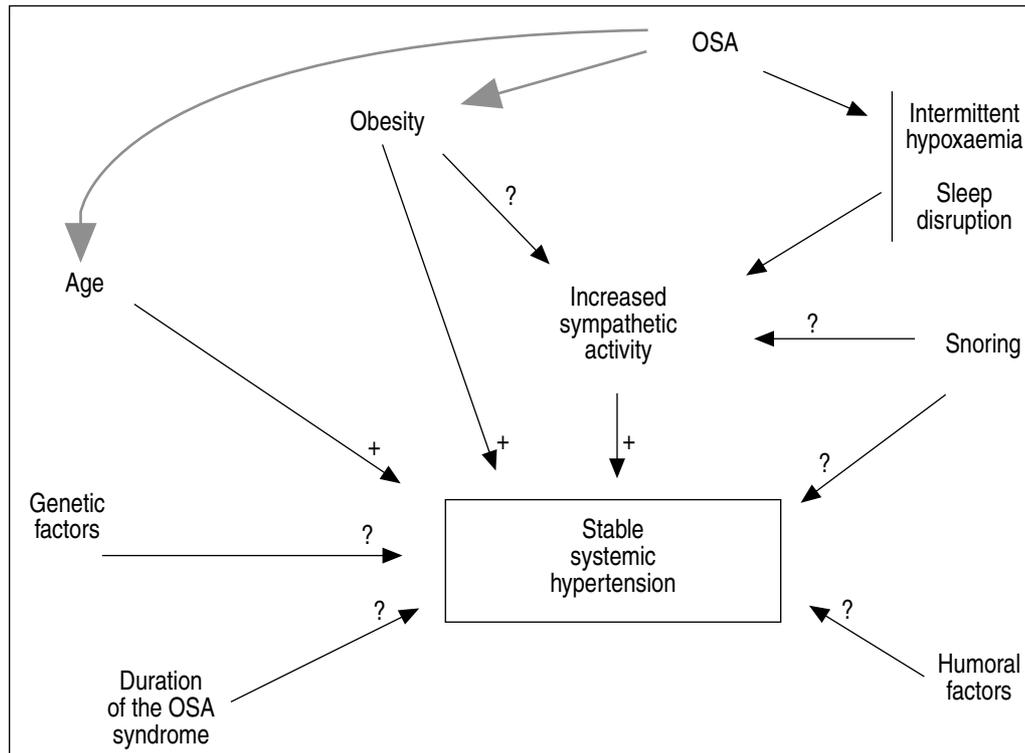
Fig. 9. – Schematic summary of the influence of various pathogenic factors in causing stable systemic hypertension in patients with the obstructive sleep apnoea (OSA) syndrome. The association between OSA and obesity or age is indicated by a hatched arrow (details in the text).

hypoxia [208] may be the link between OSA and essential HT [154]. Enlargement of the carotid body is commonly found in both essential HT and chronic hypoxia [209], but the anatomical features of the carotid bodies in OSA patients are unknown, as are the cellular mechanisms of carotid chemotransduction [3, 210]. However, hypoxia by itself does not appear to exert a strong hypertensive effect, since prevalence of HT is much higher in OSA patients than in patients with restrictive lung disease with comparable nocturnal falls in Sao$_2$ [211].

The evidence suggesting an abnormal chemoreceptor function in OSA and HT comes from different studies reporting variable results. Thus, the pathogenic role of altered chemotransduction is still an open question. In addition, there is no consensus on the abnormal cardiovascular and/or ventilatory response to hypoxia in both conditions. It was recently reported that OSA patients, either normotensive or hypertensive, develop a hypertensive response to hypoxia during wakefulness [212]. Such response, absent in controls, correlated with indices of severity of OSA, but not with daytime BP. However, no pressor response to hypoxia was found in another study on normotensive OSA patients [211].

The study reporting a significant pressor response to hypoxia in OSA patients found that, although the pressor and ventilatory responses were significantly related in the group of patients, they were found to be uncoupled in some cases [212]. The ventilatory response to hypoxia was reported to be decreased in normotensive OSA patients, possibly in relation to their increased upper airway resistance [213], whereas another study found that

it was higher in hypertensive than in normotensive OSA patients [214]. On the other hand, breathing 100% oxygen normally depressed ventilation in normotensive OSA patients, but had no effect on BP [213].

In borderline HT, hypoxia increased SNA, especially during breathholding, indicating an enhanced chemoreceptor reflex [215], whereas variable results were reported concerning the effect of hypoxia on ventilation [215, 216]. In patients with HT, breathing 100% oxygen decreased both ventilation and BP, indicating an increased resting ventilatory and circulatory chemoreceptor drive [213]. The ventilatory response to hypoxia was found to be increased in young hypertensives (age 20–41 yrs) but not in older groups [213]. These variable results, while supporting the hypothesis of an involvement of the carotid body in both OSA and HT, are far from conclusively proving any cause-effect relationship.

Support for the hypothesis that OSA may cause stable HT comes from experimental data obtained in carefully controlled studies in rats [41, 217, 218]. Repeated episodic hypoxia progressively increased BP [40], through activation of the carotid chemoreceptors [217] and increased SNA [218]. These experiments underlined that the intermittent occurrence of hypoxia may be the main factor in the pathogenesis of stable HT. Continuous hypoxia causes vasodilation, not vasoconstriction [40, 219], possibly explaining why stable HT is more common clinically in OSA patients than in patients with chronic pulmonary disease [211].

Intriguing results have been reported on the myocardial effects of hypoxia. Development of left ventricular

hypertrophy during hypoxia [220] occurred independent of HT in carotid body-denervated [217] or sympathetic-denervated [218] rats, suggesting that the myocardial effect of hypoxia might be direct, not through increased BP levels. These data may confirm the clinical finding that left ventricular hypertrophy is often found in OSA patients, irrespective of the presence of HT, and cannot be completely explained as an effect of obesity [221]. Persistently increased SNA [9] or the nocturnal hypertensive BP peaks [221] could partly account for it, but no correlation was found between left ventricular mass and severity of OSA [221]. These data were not confirmed by another study [117], but the possible effect of hypoxia on the myocardium deserves further investigation.

The link between OSA and HT could be through an increased sympathetic responsiveness. Persistently increased muscle SNA was demonstrated in OSA patients [9], and in essential HT [215]. Since increased SNA may mediate the effects of metabolic abnormalities, like hyper-insulinaemia [222], a direct or indirect role of obesity in both OSA and HT can be hypothesized [201]. Among other mechanisms by which OSA may contribute to the pathogenesis of HT, experimental data showed that REM sleep deprivation in rats affected sleep-dependent BP changes [223], but caused sustained HT only in rats with partial genetic predisposition to HT [155]. In humans, some relatives of hypertensive patients showed abnormal ventilatory responses to hypoxia or hyperoxia, whereas relatives of OSA patients responded normally to the same stimuli [213]. This field is mostly unexplored, but, as a possible hypothesis, genetic factors may be as important as hypoxia in the development of HT in OSA.

The "big picture"

What conclusions are possible on the pathogenesis of the acute and chronic cardiovascular changes commonly observed in OSA patients? This review of the literature indicates that despite the large amount of work already done, many questions are still unanswered, especially on the pathogenesis of OSA-induced chronic systemic hypertension. Instead, a "big picture" can at least be delineated for the acute haemodynamic changes occurring during sleep in OSA patients. We believe that such changes recognize a different pathogenesis according to the phase of the apnoeic cycle in which they occur (figs 1, 2, 6 and 7). During the apnoeic phase, the most impressive cardiovascular changes are determined by the mechanical effects of airway obstruction, whereas during the interapnoeic periods the role of chemical factors (hypoxia, hypercapnia) and of arousals, both acting through a complex activation of reflex circulatory adjustments, seems major compared to the role of mechanical effects. Interestingly, the pulmonary and systemic circulations are similarly affected by OSA, supporting the hypothesis that OSA may elicit generalized reflex changes. Another interesting point emerging from the available literature is that pulmonary inflation, commonly held as exerting a negative feed-back control on cardiovascular changes evoked by hypoxia, seems to exert a permissive role during OSA,

since the most dramatic hypertensive peaks occur at the resumption of the ventilation, and are coupled with a transient decrease in aortic and pulmonary flow. It is possible that lung volume changes temporally coincide with the effects of other factors, for example, the arousal reaction, but this hypothesis has not yet been tested. In addition, the large amount of data recently collected on SNA during sleep has mostly concerned muscle SNA, whereas analysis should include other areas, like the skin, in an effort to gain a comprehensive view of the entire sympathetic nervous system activity during OSA.

Concerning chronic cardiovascular changes in OSA patients, the "big picture" seems quite well drawn for the pathogenesis of stable pulmonary hypertension (fig. 8). Nevertheless, our limited knowledge of the natural history of the OSA syndrome warrants further longitudinal studies. At present, only a tentative scheme can be drawn on the pathogenesis of stable systemic hypertension (fig. 9), although the hypothesis of an abnormal chemoreceptor response to hypoxia seems very promising.

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