LA SLEEP APNEA: FATTORE DI RISCHIO CARDIOVASCOLARE

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Epidemiologia della sleep apnea

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Definizione:

L’apnea ostruttiva (OSA) del sonno è una ripetitiva, completa (apnea) o parziale (ipopnea) ostruzione della porzione collassabile delle alte vie respiratorie durante il sonno.

La sindrome dell’apnea ostruttiva del sonno (OSAS) è associata ad eccessiva sonnolenza diurna, fatica cronica, russamento notturno, frequenti risvegli notturni.
L’apnea ostruttiva del sonno fa parte dei cosiddetti disturbi respiratori del sonno (SDB: sleep disordered breathing) che comprendono le apnee ostruttive e le apnee centrali con il respiro di Cheyne-Stokes

Non c’è un gold standard per la diagnosi di OSA e la poli-sonno-grafia è stata usata come standard di riferimento per la diagnosi.

Obstructive sleep apnoea syndrome is a clinical disorder marked by frequent pauses in breathing during sleep usually accompanied by loud snoring. These pauses cut off the oxygen supply to your body for a few seconds and halt the removal of carbon dioxide. As a result of this, your brain briefly wakes you up, re-opens the airways and re-starts breathing. This can occur many times during the night and makes proper sleep impossible. During the day you may experience excessive daytime sleepiness, difficulty in concentrating or headaches. At night, snoring is the most common feature.

Obstructive sleep apnoea syndrome is diagnosed through polysomnography, a method of recording body activity during sleep; and pulse oximetry, which measures the amount of oxygen in the blood at any time. Obstructive sleep apnoea syndrome is not a life-threatening condition in itself, but it can result in serious problems such as cardiovascular and cerebrovascular diseases. The disease can impact on the quality of life, but can be easily managed. One of the treatments is continuous positive airway pressure, which forces air through a mask into the airways so that they do not close.

WHO 2009

La poli-sonno-grafia misura diverse variabili del sonno una delle quali è l'indice di apnea-ipopnea (AHI: apnea- hypopnea index) o l'indice di disturbo respiratorio (RDI: respiratory disturbance index):

AHI: la somma delle apnee ed ipopnee per ora di sonno.
Apnea è definita l'assenza di flusso d'aria per ≥ 10 sec
Ipopnea è definita la riduzione dello sforzo respiratorio con una riduzione della saturazione di ossigeno > 4%

RDI: la somma delle apnee ipopnee ed eventi respiratori anormali per ora di sonno.

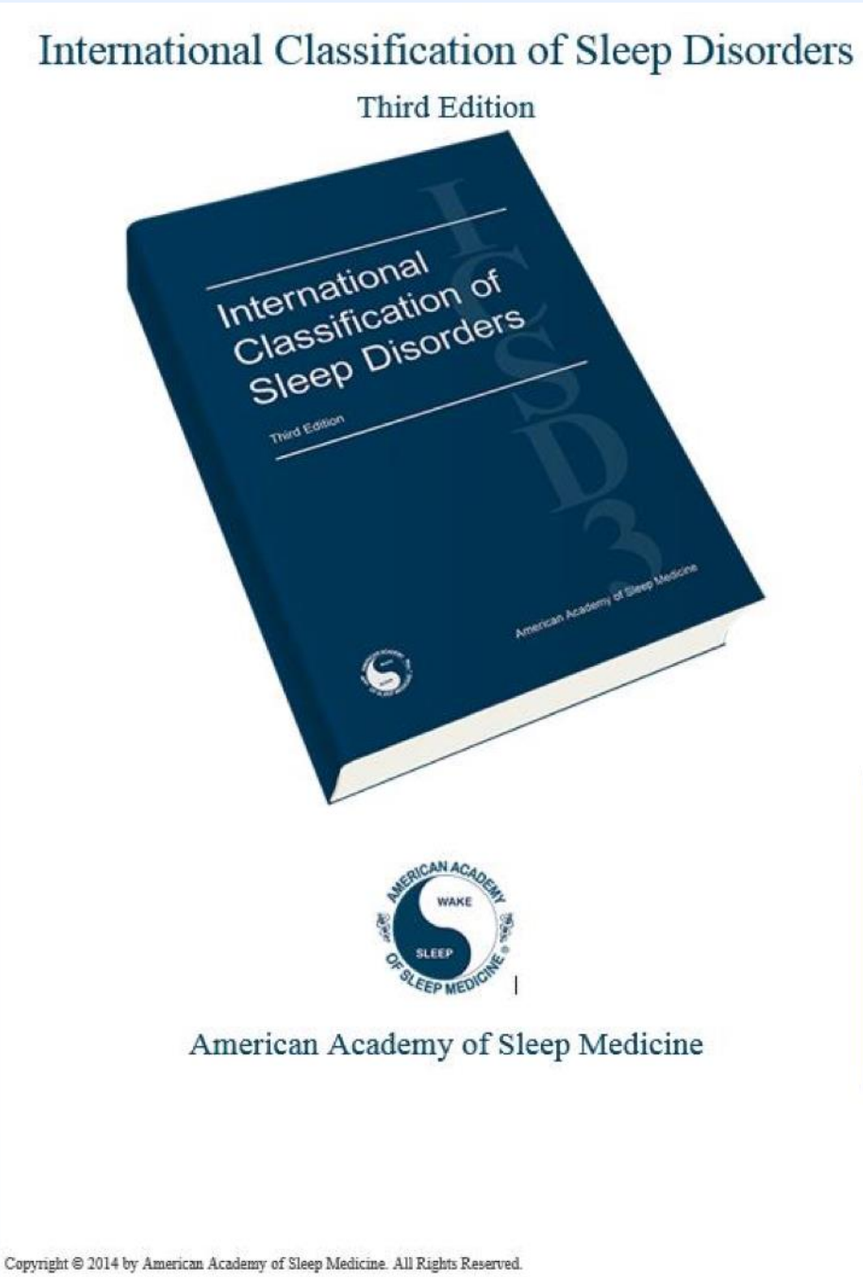
Spesso i due termini vengono usati in maniera interscambiabile.

L’AHI è stato ampiamente utilizzato per la diagnosi di OSA, sebbene con differenti livelli di cut-off, spesso determinati in modo non chiaro o arbitrario

Generalmente un AHI di più di cinque eventi per ora di sonno è considerato anormale ed il paziente è considerato un soggetto con disordini del sonno.

La gravità dell’indice correla con la presenza e gravità delle malattie metaboliche e cardiovascolari associate e con la sopravvivenza

Polysonnography in patients with obstructive sleep apnoea in an evidence based analysis (2006)



Demographics

OSA can occur in any age group. Estimates of prevalence are very dependent on how sleep related respiratory events are defined, as well as their frequency and other criteria used to define disease. Nevertheless, general population-based studies from a number of countries indicate that OSA associated with daytime sleepiness occurs in 3% to 7% of adult men and 2% to 5% of adult women.

However, because many individuals with OSA do not endorse daytime sleepiness, the prevalence of the disease is likely much higher. A major study yielded prevalence rates as high as 24% in men and 9% in women using only an apnea-hypopnea index (AHI) criterion of ≥ 5/hour, although addition of a daytime sleepiness criterion reduced these estimates to 4% in males and 2% in females.

In Italia si può stimare che milioni di persone siano affette da OSA e di questi circa 2.000.000 presentano un quadro conclamato

Ogni MMG (1500 assistiti)

ha ~50-60 pazienti OSA

- ISTAT, 14° Censimento Generale della Popolazione
- Young T et al, NEJM, 1993; 328: 1230-1235
- Punjabi NM. Proc Am Thorac Soc 2008, 5(2):136-143
- D. Croce et al 2006

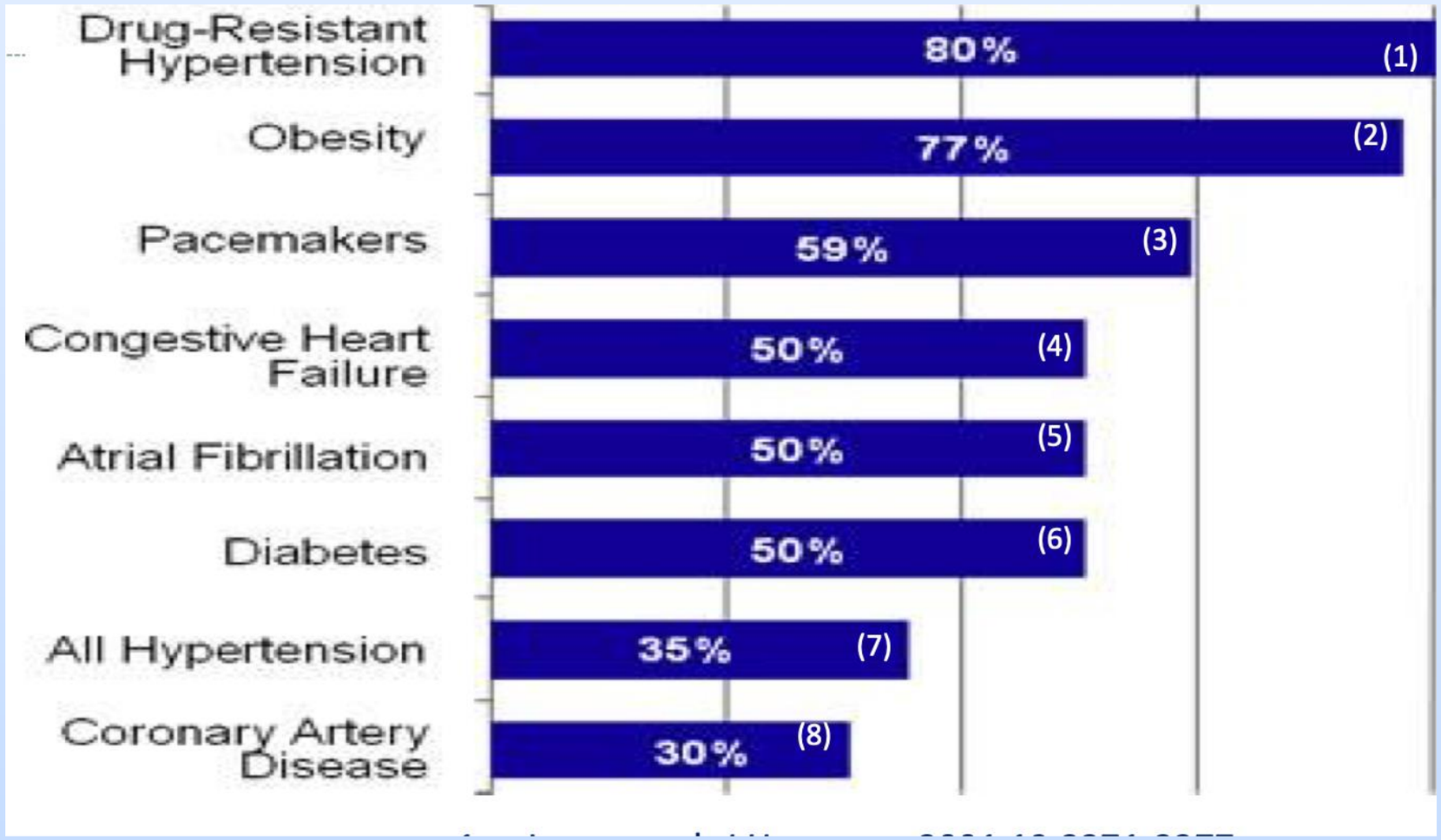
Le apnee ostruttive nel sonno (OSA) sono una patologia cronica con elevata prevalenza e rilevanti implicazioni economiche e sociali, ancora sotto-diagnosticata e sotto-trattata.

Molti studi hanno mostrato che l'apnea ostruttiva del sonno (OSA) è associata a *diabete*, *dislipidemia*, *ipertensione*, *ictus cerebrale, vari disordini cardiovascolari* (*ischemia miocardica, infarto, depressione del tratto ST notturna, scompenso cardiaco, disturbi del ritmo cardiaco e della conduzione)* e molti ricercatori ritengono che questi disordini cardiovascolari siano conseguenze dell'OSA.

Aritmie notturne si verificano icon un'incidenza fino al 50% nei pazienti con OSA:

- *tachicardie ventricolari non sostenute e sostenute*
- *arresti sinusali*
- *blocchi atrio-ventricolari*
- *fibrillazione atriale*
- *la più comune è l'aritmia sinusale notturna che è stata proposta come indicatore di OSA o alto rischio di OSA*

Prevalence of SDB in cardiovascular diseases



Associazione tra OSAS e malattie cardiovascolari

Un eccesso di mortalità cardiovascolare è stata più volte riportata in coorti longitudinali di popolazioni cliniche e non cliniche con OSAS[1] [2].

Nonostante la presenza di fattori confondenti come l'età, il sesso, l'obesità, vi è una crescente evidenza della stretta correlazione tra malattie cardiovascolari ed OSAS[3]

1) McNicholas WT, Bonsignore MR. Sleep apnoea as an independent risk factor for cardiovascular disease: Current evidence, basic mechanisms and research priorities. *Eur Respir J* 2007; 29: 156–178.

2) Marin JM, Carrizo SJ, Vicente E, *et al.* Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005; 365: 1046–1053.

3) Baguet JP, Barone-Rochette G, Tamisier R, *et al.* Mechanisms of cardiac dysfunction in obstructive sleep apnea. *Nat Rev Cardiol* 2012; 9: 679–688.

Il rischio di aritmie in pazienti con OSAS è correlato alla sua gravità, poiché la maggior parte dei pazienti con aritmie significative hanno una forma di malattia da moderata a severa.

Hersi A.S. Obstructive sleep apnea and cardiac arrhythmias. Ann Thorac Med 2010; 5(1):10-17

The Association Between Obstructive Sleep Apnea and Arrhythmias

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Pathophysiology

Over the years, attempts have been made to determine how arrhythmias develop in OSA patients. In OSA, the frequent collapse of the airway causes oxyhemoglobin desaturation, which leads to persistent inspiratory efforts made against a collapsed airway, often resulting in the patient's arousal from sleep [1].

One hypothesis is that OSA has reduced blood oxygen and increased carbon dioxide levels due to problems with the baroreflex and chemoreflex activity, leading to the activation of the sympathetic nervous system, causing electrical remodeling of the heart [7-10]. This remodeling can lead to arrhythmia development [1,7-10].

Another hypothesis is that co-existing hypertension in OSA patients may be responsible for the development of AF. Past studies have shown a strong association between OSA and hypertension, as well as hypertension and AF. Hypertension has been shown to cause atrial remodeling. Similarly, in OSA patients with hypertension, it is hypothesized that persistent inspiratory efforts made against a collapsed airway cause dramatic shifts in intracardiac pressures, leading to the activation of atrial ion channels, thus creating an acute change in cardiac chamber dimensions [11-12]. This change in size can lead to AF development [11-12].

The third hypothesis is the OSA effect of applying negative intrathoracic pressure on both atrial and ventricular free walls, which will lead to cardiac stretching thus activating cardiac ion channels, causing a change in cardiac chamber size, which can lead to arrhythmias [13].

The fourth hypothesis is related to OSA causing hypoxemia that stimulates the vagal nerve, leading to cardiac vagal reflex activation. In approximately 10% of OSA patients, the resulting hypoxemia activates the cardiac vagal reflex, leading to the development of bradyarrhythmias even in the absence of cardiac conduction disease [14].

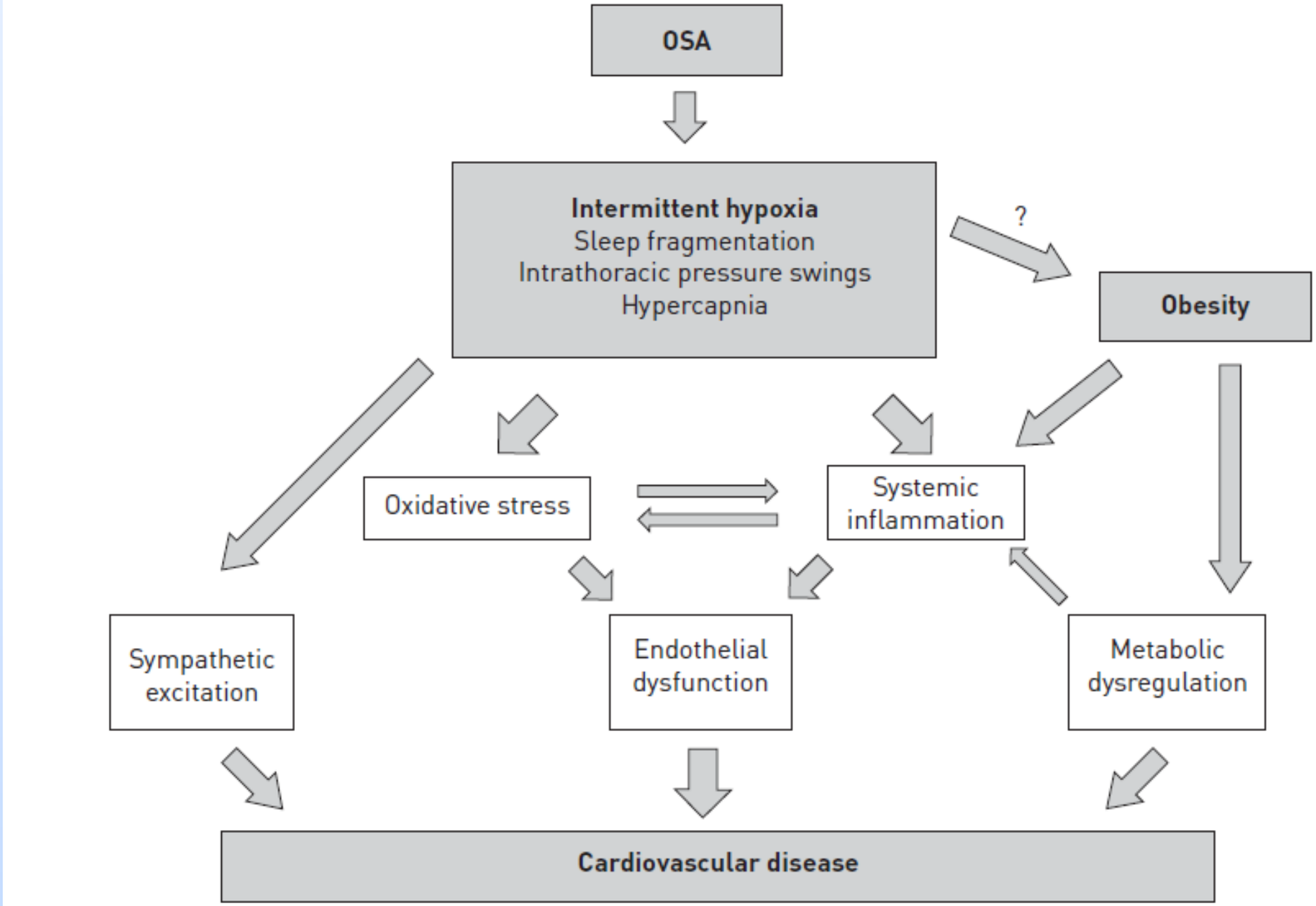

FIGURE 1 Main mechanisms linking obstructive sleep apnoea (OSA), intermittent hypoxia and cardiovascular diseases.

Levy P, Ryan S, Oldenburg O, Parati G. Sleep apnoea and the heart. Eur Respir Rev 2013; 22. 333-352

Rischio aritmico durante il sonno nella sleep apnea severa (Sleep Heart Health Study)

Table 1. Arrhythmia risk during sleep in severe sleep apnea (apnea–hypopnea index >30/h) in the Sleep Heart Health Study.

Arrhythmia type	OR (95% CI)		
	Unadjusted	*Adjusted for age, sex and BMI*	*Adjusted for age, sex, BMI and CAD*
Nonsustained VT	4.6 (1.5–14.6)	3.7 (1.1–12.2)	3.4 (1.0–11.2)
Complex ventricular ectopy	2.0 (1.3–3.0)	1.8 (1.2–2.8)	1.7 (1.1–2.7)
Atrial fibrillation	5.7 (1.6–20.5)	3.9 (1.0–14.9)	4.0 (1.0–15.7)

Data expressed as OR (95% CI).
AHI: Apnea–hypopnea index; CAD: Coronary artery disease; OR: Odds ratio; VT: Ventricular tachycardia.

Mehra R, Benjamin E, Shahar E *et al. Association of nocturnal arrhythmias with sleep-disordered breathing.The Sleep Heart Health Study. Am. J. Respir. Crit. Care Med. 173, 910–916 (2006).*

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Review

Epidemiology

The incidence and prevalence of OSA vary based on age in the general population. The prevalence is higher in the middle-aged and advanced age populations [2]. Based on an AHI of more than five, the prevalence ranges from 9%-38% and is higher in men than in women [2]. At an AHI of more than 15, the prevalence in the general adult population ranged from 6%-17% and was 49% in the advanced age group [2].

Atrial fibrillation (AF) has a prevalence of 9% in the 65 years and above population as compared to the 2% prevalence in the younger than 65 years population [3]. An estimated 2.7-6.1 million people in the United States have AF [3]. AF has more than 750,000 hospitalizations per year and

Prevalenza di OSA nella popolazione generale 9-38%

Prevalenza di FA
> 65 aa 9%,
< 65 aa 2%

TABLE 1: Summary of Incidence and Prevalence of OSA and Arrhythmias

OSA: obstructive sleep apnea; AF: atrial fibrillation, HF: heart failure; SAS: sleep apnea syndrome; SCD: sudden cardiac death; LVEF: left ventricular ejection fraction; AHI: apnea-hypopnea index

Mehra et al. [15]	566 patients	Study contained 228 patients with OSA and 338 patients without OSA. AF seen in 4.8% of patients. It was determined that severe OSA will have two to four higher chances of developing complex arrhythmias.	AF 2-4 X
Becker et al. [26]	239 patients	In about 30% of patients with sleep apnea, there is sinus arrest and AV block.	AV block 30%
Mooe et al. [20]	121 patients	AF in 32% of patients with AHI more than five. Furthermore, AF was found in 18% patients with AHI less than five.	AF 32%
Gami et al. [27]	10,701 patients	All patients had OSA. Compared to the general population SCD is prevalent in OSA patients.	SCD > in OSA
Gami et al. [28]	112 patients	All patients included suffered from SCD. There is a strong association between SCD and OSA.	

Treatment

There are no conclusive epidemiologic or longitudinal intervention studies that relate specifically to the prevalence, severity, and consequences of cardiac arrhythmias and the effects of OSA treatment [1]. Despite this, there have been many observations made from previous studies regarding the effectiveness of continuous positive airway pressure (CPAP) therapy for OSA patients and their therapeutic effect on arrhythmia incidence in the same patients. Based on the studies (see Table *2*), CPAP therapy had an effect on reducing the incidence and prevalence of cardiac arrhythmias in OSA patients.

Il maggior rischio di morte improvvisa (MI) nella popolazione generale si verifica al momento del risveglio dal sonno (tra le 6 e le 10 del mattino).
Nel 60-80% dei casi, la morte cardiaca improvvisa si manifesta nel contesto della malattia coronarica ed è provocata da una tachicardia ventricolare degenerante in fibrillazione ventricolare.

Nei pazienti con OSAS, la MI sembra verificarsi più comunemente durante il sonno. Gami e Coll. , in una revisione di 112 casi di MI in pazienti precedentemente sottoposti a polisonnografia ed affetti da OSAS, hanno trovato una maggiore incidenza di MI tra la mezzanotte e le 6 del mattino (rischio relativo = 2.57)[1]

1) Gami AS, Howard DE et Al. Day.night pattern of sudden death in obstructive sleep apnea. N Engl J Med 2005; 352:1206-1214

A pacemaker transthoracic impedance sensor with an advanced algorithm to identify severe sleep apnea: The DREAM European study

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BACKGROUND Sleep apnea (SA) is associated with cardiovascular diseases and is highly prevalent in patients with pacemakers (PMs).

OBJECTIVE To validate a transthoracic impedance sensor with an advanced algorithm (sleep apnea monitoring) for identifying severe SA.

METHODS Patients with indications for PM (VVI/DDD) were enrolled regardless of symptoms suggesting SA. Severe SA diagnosis was acknowledged when the full polysomnography gave an apnea-hypopnea index (PSG-AHI) of ≥30 events/h. The PSG-AHI was compared with the respiratory disturbance index evaluated by the SAM algorithm (SAM-RDI) compiled from the device during the same diagnosis night, and the performance of the device and the SAM algorithm was calculated to identify patients with severe SA. The agreement between methods was assessed by using Bland and Altman statistics.

RESULTS Forty patients (mean age 73.8 ± 19.1 years; 67.5% men; body mass index 27.7 ± 4.4 kg/m^2) were included. Severe SA was diagnosed by PSG in 56% of the patients. We did not retrieve SAM-RDI data in 14% of the patients. An optimal cutoff value for the SAM-RDI at 20 events/h was obtained by a receiver operator characteristic curve analysis, which yielded a sensitivity of 88.9% (95% confidence interval [CI] 65.3%–98.6%), a positive predictive value of 88.9% (95% CI 65.3%–98.6%), and a specificity of 84.6% (95% CI 54.6%–98.1%) (n = 31). The Bland-Altman limits of agreement for PSG-AHI (in events per hour) were [−14.1 to 32.4].

CONCLUSION The results suggest that an advanced algorithm using PM transthoracic impedance could be used to identify SA in patients with PMs outside the clinic or at home.

KEYWORDS Bradycardia; Pacemaker; Minute ventilation; Sleep apnea; Sleep apnea diagnosis

ABBREVIATIONS **CI** = confidence interval; **NPV** = negative predictive value; **PM** = pacemaker; **PPV** = positive predictive value; **PSG** = polysomnography; **PSG-AHI** = apnea-hypopnea index evaluated by polysomnography; **SA** = sleep apnea; **SAM** = sleep apnea monitoring; **SAM-RDI** = respiratory disturbance index evaluated by the sleep apnea monitoring algorithm

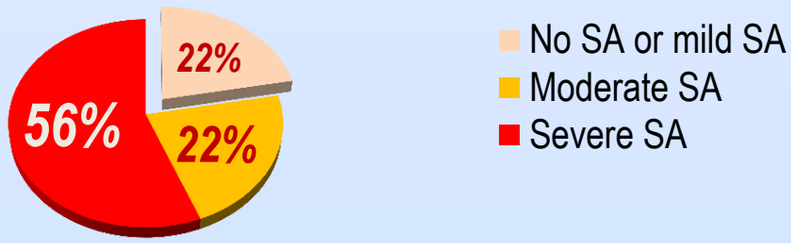
(Heart Rhythm 2014;11:842–848)

Defaye & al. Heart Rhythm 2014; 11: 842-8

AIAC
Associazione Italiana Aritmologia e Cardiostimolazione

Obiettivo primario:

validare l'utilizzo del segnale di impedenza transtoracica elaborato da un **algoritmo dedicato (SAM:** Sleep Apnea Monitoring) per identificare la **Sleep Apnea Severa** in una popolazione non selezionata di pazienti con indicazione all'impianto di pacemaker



Lo studio DREAM ha mostrato che un sensore di impedenza transtoracica con un algoritmo avanzato di detezione (SAM) può essere utilizzato per identificare pz. PM con SA severa

- Prevalenza di SA nei pazienti PM non-selezionati dello studio DREAM (valutata con PSG-AHI):
  - **78% SA moderata-severa**
  - **56% SA severa**
- **Un valore di cut-off ottimale pari a 20 eventi/h per l'indice SAM-RDI è stato validato per l'identificazione dei pz con SA severa, con valori di:**
  - **88.9% Sensibilità – 88.9% VPP**
  - **84.6% Specificità**

Conclusioni

1. Benché l'OSAS si presenti con sintomi prevalentemente respiratori, le sue più serie implicazioni sono cardiovascolari.

2. La severità dell'OSAS potrebbe essere meglio definita riferendosi ai suoi effetti cardiovascolari piuttosto che agli eventi respiratori.

3. Vi è una crescente messe di evidenze scientifiche che dimostrano l'associazione dell'OSAS con malattie strutturali cardiache e con un largo spettro di aritmie, comprendenti bradi-aritmie, fibrillazione atriale ed aritmie ventricolari.

4. L'OSAS può essere associata con un aumentato rischio di morte improvvisa notturna.