Obstructive sleep apnea, atrial fibrillation, and erectile dysfunction: are they only coexisting conditions or a new clinical syndrome? 
The concept of the OSAFED syndrome

Filip M. Szymański, Bartosz Puchalski, Krzysztof J. Filipiak

Department of Cardiology, Medical University of Warsaw, Warszawa, Poland

KEY WORDS
atrial fibrillation, erectile dysfunction, OSAFED, obstructive sleep apnea

ABSTRACT
Patients rarely suffer from only 1 disease. Most of them have several conditions with common risk factors and etiology, and which often increase the severity of each other. The phenotypes linked to 1 condition are often linked to many others. We describe 3 patients with obstructive sleep apnea (OSA), atrial fibrillation (AF), and erectile dysfunction (ED), all of which are highly prevalent in the general population. OSA is one of the most common sleep disorders, affecting approximately 24% of men and 9% of women between 30 and 60 years of age. AF is one of the most common arrhythmias, present in approximately 2% of the population, and erectile dysfunction can be found in 18% to 40% of the male population older than 20 years. The presence of these 3 conditions in the same patient may be not only a coincidence but rather a new clinical syndrome. We present data which allow one to consider OSA, AF, and ED as parts of a clinical syndrome: OSAFED (obstructive sleep apnea, atrial fibrillation, and erectile dysfunction), with a larger effect on the cardiovascular risk profile than those 3 conditions taken alone. Introducing the OSAFED acronym into everyday clinical practice would have the tremendous advantage of reminding health care workers to screen every patient with either OSA, AF, or ED for the remaining 2 diseases. This would result in an early diagnosis and break the vicious circle of mutual disease exacerbation.
them with his physician, as he linked them to his age and medications. Unfortunately, during his hospitalization he was not investigated for ED.

The next patient was an obese 57-year-old man referred to the cardiologist for erectile dysfunction. He complained of severe difficulties, for the past 6 months, in achieving and maintaining erections. Further examination revealed that he was also snoring loudly and irregularly.

On a physical examination, we observed obesity (BMI, 40.2 kg/m$^2$), a short neck with a large circumference (47 cm), an arterial blood pressure of 148/95 mmHg, and, upon auscultation, an irregular heart rhythm. He never experienced heart palpitations or any other signs of AF. We observed AF during the ECG, which was further confirmed with 24-hour ambulatory ECG monitoring (5 h/day of AF). During polysomnography, we observed an AHI of 11.4/h and a mean night-time blood oxygen saturation of 94.6%.

He was diagnosed with mild OSA, instructed to reduce his body mass and refrain from sleeping on his back, and given advice on the use of sleep medication and to avoid drinking alcohol before sleeping. ED drugs were also recommended.

Currently, as cardiologists in an aging society, we scarcely meet patients with only 1 disease. Most of our patients suffer from several conditions with shared risk factors, etiology, and which often increase the severity of each other. Phenotypes that are linked to 1 condition are often linked to many others.

We describe here 3 clinical conditions: obstructive sleep apnea (OSA), atrial fibrillation (AF), and erectile dysfunction (ED). Further investigation revealed that he had been having problems with erections for over 5 years but never spoke about them with his physician, as he linked them to his age and medications. Unfortunately, during his hospitalization he was not investigated for ED.

The next patient was an obese 57-year-old man referred to the cardiologist for erectile dysfunction. He complained of severe difficulties, for the past 6 months, in achieving and maintaining erections. Further examination revealed that he was also snoring loudly and irregularly.

On a physical examination, we observed obesity (BMI, 40.2 kg/m$^2$), a short neck with a large circumference (47 cm), an arterial blood pressure of 148/95 mmHg, and, upon auscultation, an irregular heart rhythm. He never experienced heart palpitations or any other signs of AF. We observed AF during the ECG, which was further confirmed with 24-hour ambulatory ECG monitoring (5 h/day of AF). During polysomnography, we observed an AHI of 11.4/h and a mean night-time blood oxygen saturation of 94.6%.

He was diagnosed with mild OSA, instructed to reduce his body mass and refrain from sleeping on his back, and given advice on the use of sleep medication and to avoid drinking alcohol before sleeping. ED drugs were also recommended.

Currently, as cardiologists in an aging society, we scarcely meet patients with only 1 disease. Most of our patients suffer from several conditions with shared risk factors, etiology, and which often increase the severity of each other. Phenotypes that are linked to 1 condition are often linked to many others.

We describe here 3 clinical conditions: obstructive sleep apnea (OSA), atrial fibrillation (AF), and erectile dysfunction (ED). Further investigation revealed that he had been having problems with erections for over 5 years but never spoke about

FIGURE 1 Example of polysomnography results of a patient with severe obstructive sleep apnea

Abbreviations: bpm – beats per minute, SpO$_2$ – oxygen saturation
data which allow one to consider OSA, AF, and ED as one clinical syndrome: OSAFED (obstructive sleep apnea, atrial fibrillation, and erectile dysfunction), which may have a bigger impact on the cardiovascular risk profile than those 3 conditions taken separately.

Obstructive sleep apnea OSA is one of the most common types of sleep disorder. Breathing disorders during sleep affect approximately 24% of men and 9% of women between the age of 30 and 60 years. OSA is defined as a repetitive interruption of ventilation during sleep caused by the collapse of the pharyngeal part of the airway. Pharyngeal airway collapse may be due to muscle weakness, bone and soft tissue abnormalities such as enlarged tonsils or adenoids, or fat tissue deposits around the neck, which narrow the pharyngeal lumen. The most typical patient presenting with OSA is an obese, middle-aged man with daytime somnolence. Further investigation often reveals hypertension, sometimes in its resistant form, cardiac arrhythmias, nocturnal angina, and loud snoring. Unfortunately, OSA is a condition often forgotten in everyday clinical practice and deserves special consideration.

Because of the anatomical and physiological mechanisms of OSA, its prevalence rises with age and body mass. OSA is definitely associated with weight. The prevalence of OSA has been proven to rise 4-fold with each standard deviation of the body mass index (BMI). In morbidly obese patients, with a BMI of ≥60 kg/m², the prevalence of OSA is over 90%. The risk of developing OSA is increased by weight gain. A 10% weight gain is associated with a 32% increase in the AHI and is increased by weight gain. A 10% weight gain causes a 6-fold increase in the risk for developing moderate-to-severe OSA. Furthermore, not only is obesity a risk factor for OSA, but also OSA represents a risk factor for obesity. Patients with OSA have reduced physical activity, exercise performance, energy metabolism, and motivation along with excessive daytime sleepiness. Reduced physical activity is associated with a reduction in inflammation marker levels, and this reduction, without an alteration in caloric intake, promotes weight gain. Conversely, weight loss alleviates the severity of OSA. Each 10% reduction in body mass reduces the AHI by 26%. However, even successful weight loss after bariatric surgery does not fully cure OSA, which suggests that other mechanisms, besides fat tissue accumulation, are responsible for both conditions. In patients with OSA, alterations in the vascular system occur more often than in the general population. Ongoing inflammation, sympathetic activation, and oxidative stress all contribute to the development of endothelial dysfunction, which is responsible, for instance, for atherosclerosis. Endothelial function is impaired in OSA patients, but can be improved by CPAP therapy. OSA is also associated with an increased inflammatory response and platelet activation and aggregation and, therefore, a more active coagulation. The close association between OSA, obesity, and endothelial dysfunction obscures the specific effects on cardiovascular risk of each condition or their synergistic effect.

OSA is important in initiating the development of cardiac and vascular disease, and in patients with established cardiovascular disease, it accelerates disease progression. Its treatment can result in clinical improvement and a reduction in cardiovascular event rate and mortality. The conditions most often associated with OSA include: hypertension, heart failure, coronary artery disease, myocardial infarction, stroke, arrhythmias, and pulmonary arterial hypertension.

Atrial fibrillation AF is one of the most common arrhythmias. AF affects approximately 2% of the population, and its prevalence increases with age. This arrhythmia affects 0.5% of people aged from 40 to 50 years, and 5% to 15% of those aged 80 years. Because of a better life expectancy, the number of patients presenting with AF is greater every year. Body mass correlates with AF. About one fourth of AF patients is obese, and the mean BMI of this population is 27.5 kg/m², which is classified as overweight. This arrhythmia is very important in clinical practice. Not only does it decrease the quality of life, but also it has a large financial burden on society. Hospital stays, procedure and medication costs, together with the costs of absences from work represent significant expenditure. It is also important to note that AF markedly affects general health and increases cardiovascular risk, doubling the risk of death. This arrhythmia also affects the risk for thromboembolic events. It is estimated that 1 in 5 strokes is caused by AF. This includes ischemic and hemorrhagic strokes as well as intracerebral bleeding, regardless of their severity – from those that cause no persistent impairment to those that result in long-term disability or death. AF also is responsible for a large fraction of hospitalizations. The increased activation of the coagulation process contributes to systemic embolic events. Low-grade inflammation and endothelial dysfunction, both present in AF patients, have the same effect. It is estimated that AF accounts for one-third of hospital admissions for cardiac arrhythmias. AF aggravates the course of acute coronary syndromes, heart failure, and ventricular dysfunction.

Cognitive dysfunction and dementia often affect AF patients. It is suggested that this is caused by asymptomatic cerebral embolic events in the absence of an overt stroke. AF-related symptoms, risk of death, frequent hospitalizations, and poor general health quality contribute negatively to the quality of life. Moreover, patients with AF have reduced exercise capacity and are more likely to suffer from depression and impaired sleep quality, all of which are risk factors for cardiovascular disease.
**FIGURE 2**  Clinical findings in obstructive sleep apnea, atrial fibrillation, and erectile dysfunction (OSAFED)

**Abbreviations:** AF – atrial fibrillation, CVD – cardiovascular disease, ED – erectile dysfunction, OSA – obstructive sleep apnea

**Erectile dysfunction**  ED is the inability to achieve or maintain an erection long enough to engage in sexual intercourse. This affects approximately from 18% to 40% of men older than 20 years. In Poland, ED affects about 11% of men between the ages of 50 and 59 years, 4% between the ages of 30 and 49 years, and 3% between the ages of 18 and 24 years. The prevalence of the condition increases with age and depends on many health-linked and psychosocial factors. Conditions that are associated with ED are diabetes mellitus, hypertension, coronary artery disease, obesity, difficult micturition, low socioeconomic status, a sedentary lifestyle, smoking, depression, subjectively reported premature ejaculation, low libido, and irregular coitus. The lowest prevalence of ED is noted in men who have no chronic medical conditions and follow healthy lifestyles. ED can be perceived as both a risk factor and a clinical manifestation of progressive atherosclerosis.

ED is common in obese patients, even if they are young. It was shown that, among of men aged 20 to 45 years, obesity results in an odds ratio of 2.74 (95% confidence interval [CI], 1.1–6.8) for ED. Obese men, independently of age, report less sexual desire (OR 1.48; CI 1.14–1.90). However, approximately one-third of obese men with ED can regain sexual functions after 2 years of a healthy lifestyle, for instance, the Mediterranean diet and regular exercise. In hypertensive patients with poor arterial blood pressure control ED occurs more often than in patients with well-controlled arterial blood pressure. Diabetes – alone or in the presence of hypertension – increases the odds of ED.

ED is not only important in terms of sexual life, it is also a significant marker of future adverse cardiac events. Cardiovascular disease and ED share risk factors, including age, hypertension, dyslipidemia, smoking, obesity, and diabetes. Patients with ED have a higher risk of cardiovascular disease (RR 1.48; 95% CI 1.25–1.74), coronary artery disease (RR 1.46; 95% CI 1.31–1.63), stroke (RR 1.35; 95% CI 1.19–1.54) and all-cause mortality (RR 1.19; 95% CI 1.05–1.34). ED usually precedes the onset of coronary artery disease symptoms by 2 to 3 years and the occurrence of adverse cardiovascular events by 3 to 5 years. ED is also a very important problem in patients with developed cardiovascular disease. In men, after myocardial infarction, both ED and anxiety associated with sexual activity are highly prevalent.

The association between ED and cardiovascular disease, especially coronary artery disease, is thought to be found in their common risk factors and in the state of the systemic blood vessels and in ongoing low grade inflammation. Patients with ED and cardiovascular disease tend to have endothelial dysfunction expressed by elevated levels of biomarkers and shown by the results of the physical examination. Increased circulating levels of inflammatory markers are noted in ED patients, as they are in cardiovascular disease. These factors can be responsible for the improper function of the penile corpora cavernosa and the onset of atherosclerosis – including the coronary arteries. The time interval between ED and cardiovascular disease symptoms may be partially explained by the differences in the lumen of the vessels.

**Common ground**  There are several links between the 3 conditions, summarized in **FIGURE 2**. These 3 health problems are frequent and likely to coexist, as in the 3 patients described in the beginning of the article. As noted above, obesity plays a major role in the development and in the course of OSA, AF, and ED. These are also associated with age. The connection between OSA and AF is well-described in numerous publications. The prevalence of OSA in consecutive AF patients is estimated to be over 40%, much more than in the general population. Complex pathomechanisms link both conditions. AF is partially a consequence of autonomic dysregulation, elevated sympathetic tone, oxidative stress, endothelial dysfunction, and left atrial stretch caused by arterial hypertension secondary to OSA. Atrial stretch causes aberrant conduction and, as a consequence, AF. OSA not only plays a part in the onset of AF, but also decreases the effectiveness of invasive AF treatment. Patients with OSA are overall more likely to experience the recurrence of AF after pulmonary vein isolation, as well as after pharmacological and electric cardioversion. As for OSA and ED, their concurrence is even more frequent. Almost 70% of male patients with OSA suffer from ED. The odds for ED, in patients who are at high risk of OSA according to the Berlin Questionnaire and the Epworth Sleepiness Scale are 55.71 (95% CI, 3.36–923.81; P = 0.005). AF, besides having a negative impact
on the overall quality of life, also hampers sexual activity in men. An important link between the single components of OSAFED is endothelial dysfunction. Patients with OSA tend to have lower levels of nitric oxide, which is responsible for vasodilatation and erection. Furthermore, the hypoxia which exists in OSA promotes the production of endothelin, a potent vasoconstrictor, which may act also on penile arteries. In fact, endothelial dysfunction is one of the most important mechanisms responsible for erectile dysfunction, which in many cases is one of its first manifestations – earlier, for instance, than coronary artery disease or cerebral artery disease. AF is also a risk factor for endothelial dysfunction. It is associated with impaired acetylcholine-mediated blood flow increase and reduced plasma nitrite/nitrate levels, and therefore associated with impaired blood flow and ED. Similarly, oxidative stress – one of the promoters of endothelial dysfunction – occurs in AF and OSA, promoting ED.

Of course, the most important issue in case of OSA, AF, and ED, is the cardiovascular risk associated with each of the diseases. It is unclear whether the increased cardiovascular risk found in patients with OSA, AF, and ED, is secondary to the sleep apnea, the arrhythmia, the sexual dysfunction – one of the promoters of endothelial dysfunction – occurs in AF and OSA, promoting ED.

An important link between the single components of OSAFED is endothelial dysfunction. Patients with OSA tend to have lower levels of nitric oxide, which is responsible for vasodilatation and erection. Furthermore, the hypoxia which exists in OSA promotes the production of endothelin, a potent vasoconstrictor, which may act also on penile arteries. In fact, endothelial dysfunction is one of the most important mechanisms responsible for erectile dysfunction, which in many cases is one of its first manifestations – earlier, for instance, than coronary artery disease or cerebral artery disease. AF is also a risk factor for endothelial dysfunction. It is associated with impaired acetylcholine-mediated blood flow increase and reduced plasma nitrite/nitrate levels, and therefore associated with impaired blood flow and ED.

Similarly, oxidative stress – one of the promoters of endothelial dysfunction – occurs in AF and OSA, promoting ED.

The promotion of healthy lifestyles is unsatisfactory. Patients often do not know that their symptoms should be reported. OSAFED syndrome would remind health care workers to screen every patient with any of OSA, AF, or ED for the other 2 conditions, which would result in an early diagnosis and break the vicious circle of mutual disease exacerbation (Figure 3).

Conclusions The presence of untreated OSA, AF, or ED seems to decrease the efficacy of treatment of the other diseases. Given their prevalence and their effect on cardiovascular risk and long-term outcomes, the introduction of the OSAFED syndrome seems justified and necessary. Clinicians should assess individuals with any component of the OSAFED syndrome for the remaining ones. OSAFED can be a simple acronym, which will help remember an important connection and improve on the cardiovascular risk profile of many patients.
conference organized by the German Atrial Fibrillation Competence NETwork (AFNET) and the European Heart Rhythm Association (EHRA). Eur Heart J. 2007; 28: 2803-2817.
ARTYKUŁ POGŁĄDOWY

Obturacyjny bezdech senny, migotanie przedsionków i zaburzenia erekcji – tylko współistniejące schorzenia czy nowa jednostka chorobowa?  
Prezentowanie koncepcji zespołu OSAFED

Filip M. Szymański, Bartosz Puchalski, Krzysztof J. Filipiak
I Katedra i Klinika Kardiologii, Warszawski Uniwersytet Medyczny, Warszawa

SŁOWA KLUCZOWE
obturacyjny bezdech senny, migotanie przedsionków, OSAFED, zaburzenia erekcji

STRESZCZENIE
Większość pacjentów z chorobami układu krążenia zmaga się jednocześnie z kilkoma schorzeniami, które często mają wspólne czynniki ryzyka oraz etiologię, a w większości wypadków zaostrzają nawzajem swój przebieg. Fenotyp właściwy dla jednej choroby często występuje również w przypadku kilku innych jednostek. Poniżej prezentujemy opisy kliniczne przypadków pacjentów z obturacyjnym bezdechem sennym (obstructive sleep apnea – OSA), migotaniem przedsionków (atrial fibrillation – AF) i zaburzeniami erekcji (erectile dysfunction – ED). Te trzy schorzenia często występują w populacji ogólnej. OSA jest najczęściej występującym rodzajem zaburzeń oddychania w czasie snu, dotykającym około 24% mężczyzn i 9% kobiet w wieku od 30 do 60 lat. AF, jedno z najczęstszych zaburzeń rytmu serca obecne jest u około 2% populacji, a ED dotykają pomiędzy 18% a 40% mężczyzn powyżej 20. rż. Współwystępowanie tych trzech schorzeń u jednego pacjenta można uznać nie za przypadek, ale raczej za nowy zespół chorobowy. Poniżej prezentujemy dane, które pozwalają przypuszczać, że zespół (obstructive sleep apnea, atrial fibrillation, erectile dysfunction – OSAFED) może mieć istotniejszy wpływ na profil ryzyka sercowo-naczyniowego niż wszystkie trzy schorzenia z osobna. Wprowadzenie do praktyki klinicznej terminu OSAFED może przynieść jedną istotną zaletę – przypomnieć lekarzom praktykom o konieczności wykonywania u pacjentów z jedną ze składowych zespołu OSAFED badań mających na celu wykrycie pozostałych dwóch schorzeń, co wiąże się z wcześniejszą diagnozą i przerwaniem błędnego koła wzajemnego zaostrzania przebiegu opisanych schorzeń.