INTRODUCTION
Sleep apnea syndrome (SA) is a common breathing disorder that affects 5% of the North American adult population, with men being affected almost twice as much as women [1]. The condition has well defined associations with increased cardiovascular morbidity and mortality, arrhythmia, daytime hypersomnolence, motor vehicle accidents and neurocognitive dysfunction; but despite this it is grossly under-diagnosed [2-8].

The diagnosis is suspected by history and often body habitus but requires confirmation with a formal sleep study. Polysomnography is the gold-standard study for diagnosis of SA. It determines the severity of SA by measuring the apnea-hypopnea index (AHI), which is the number of apneic and hypopneic episodes that occur during the course of one hour [9,10].

The mechanisms linking SA with cardiac arrhythmias remain somewhat speculative and controversial. We have recently published our speculations on what we consider the most relevant mechanisms linking both conditions [11]. Some of these possible links are:

1. **Impaired autonomic nervous control** has been demonstrated in patients with obstructive SA (OSA), manifest as increased sympathetic tone and/or decreased parasympathetic tone. Decreased baroreflex sensitivity, reduced vagal input, and impairment of the parasympathetic components of heart rate variability have been demonstrated in patients with SA [12,13].

2. A persistent **increase in sympathetic tone**, as occurs in OSA, has been shown to generate abnormal electrical remodeling of the atrium, facilitating supraventricular arrhythmias, and atrial fibrillation in particular [14]. Specifically, electrical remodeling may create some degree of interatrial block (IAB), contributing to the genesis of atrial arrhythmias [15]. Our group recently demonstrated the high prevalence of IAB in 180 patients referred to the Sleep Disorder Clinic. IAB was more prevalent in patients with severe SA (AHI > 30) compared with controls (34.7% SA vs. 0% controls, p <0.001) [15].

3. A strong association between **SA and hypertension** has been extensively reported [6,16] and the association between hypertension and AF is also well recognized [17,18]. Although purely speculative, the link between OSA and AF could merely be the distortion of the atrial anatomy that occurs during hypertension (Figure 1).
The recognition of the mechanisms that possibly link SA are multifactorial and do not depend only on autonomic imbalance. Pulmonary hypertension as well as direct effect of intermittent hypoxia and hypercapnea may also play a role [19].

The purpose of the following lecture is to review the association between SA and cardiac arrhythmias including supraventricular arrhythmias (predominantly AF), bradyarrhythmias and ventricular arrhythmias. Special emphasis will be given to the role of pacemakers and cardiac resynchronization therapy for the treatment of SA.

SLEEP APNEA & ATRIAL FIBRILLATION

The first comments on the association between AF and SA were derived from epidemiological studies. A sub-study of the Sleep Heart Health Study [20] compared a group with AHI > 30 vs. a group without OSA. They included 566 patients who underwent continuous electrocardiographic monitoring during polysomnography, showing that AF occurred in 5% of those with severe SA and only 1% of those without SA. Adjusting for confounding factors, patients with OSA had four times the odds of experiencing atrial fibrillation (OR 4.02; 95% CI 1.03-15.74, p=0.003) [20].

The polysomnographic ECG recording maybe helpful to detect AF or bradyarrhythmias, but quite frequently other types of monitoring are required to assess the presence of AF or to confirm a possible rhythm disorder [21].

The proportion of patients with OSA was significantly higher in a group of 151 patients with AF (49%) than in high-risk cardiovascular patients without AF (32%) [22].

Twenty-seven patients with untreated OSA had a higher risk of AF recurrence in one year after cardioversion compared to 79 patients without diagnosed OSA (80% at 1 year, p<0.013) [23].

The increased risk of AF among individuals with OSA may account, at least in part, for the significantly increased risk of stroke among patients with OSA (HR 1.97; 95% CI, 1.12 to 3.48) [19].

Recently, OSA and obesity have been found to be independent predictors of new onset AF in patients < 65 years old. For body mass index (per 1 Kg/m2, HR 1.07, 95% CI 1.05-1.10) and for decrease in nocturnal oxygen saturation (per 0.5 U log change, HR 3.29, 95% CI 1.35-8.04) [24].

A high SA profile identified by the Berlin questionnaire has been associated with AF recurrence after a pulmonary vein association in 210 consecutive patients (OR 4.53, CI: 1.21-16.87, P = 0.02) [25].

The association between SA and AF is evident. The mechanisms involved are multiple but we are able to speculate on the drivers (Figure 2). It remains unknown whether the correction of gasometric parameters by CPAP (the cornerstone of care for SA) would induce reversal of changes in the anatomical substrate and ultimately reduce AF recurrences.
It is clear that a detailed interrogation of sleeping patterns (e.g., snoring) and daytime sleepiness is needed in order to consider this entity when interviewing a patient with paroxysmal AF. Treating the sleeping disorder may positively influence long-term follow-up of patients with paroxysmal (or lone) AF, decreasing the risk of recurrence. It seems reasonable to use CPAP in addition to an antiarrhythmic strategy in order to maintain sinus rhythm in patients with concomitant SA.

**SLEEP APNEA & BRADYARRHYTHMIAS.**

1. The role of Atrial Overdrive Pacing (AOP) for the treatment of SA.

Initial isolated case reports hinted at an association between SA and bradyarrhythmias. Zwillich et al. [26] have found a close relationship between SA and bradycardia. There was a significant association between bradycardia and the apnea length (p<0.01) as well as with increased oxyhemoglobin desaturation (p<0.01). Several case reports were published since then with similar observations, however, the Sleep Heart Health Study, which is the largest epidemiologic study involving patients with sleep apnea, did not demonstrate an increased incidence of bradycardia among patients with SA [20].

This resulted in many groups investigating the role of pacemakers as a potential treatment for SA - more than 10 well-conducted randomized trials addressing this issue have been published in the last 5 years. The main hypothesis was that suppressing periods of bradycardia associated with apnea may reduce the autonomic imbalance associated with SA, thereby improving the respiratory condition [27-29]. We recently published a meta-analysis of all randomized trials on atrial overdrive pacing (AOP) for the treatment of SA (11 studies) that showed that the use of AOP reduced the AHI by - 4.65 episodes per hour (95% confidence interval [CI], -8.27 to -1.03, p = 0.01) [30]. Although statistically significant, the reduction in AHI seen with AOP is substantially less than with the current standard treatment for severe SA; CPAP. The American Academy of Sleep Medicine classifies SA severity based on the AHI into mild (AHI 5-14.9), moderate (AHI 15-29.9) and severe (AHI 30 or greater) [10]. A reduction in AHI of 5 might thus be adequate to change severity grading of a patient’s SA, but it would not provide adequate treatment for moderate or severe SA. Thus, despite reaching statistical significance, the reduction of the AHI by less than 5 episodes per hour is unlikely to have much clinical significance or to justify the use of AOP solely to treat SA [30] (Figure 3). Floras and Bradley [31] still believe in a possible physiological benefit of pacing by improving cardiac output leading to reduction of lung-chemoreceptor circulation time and left ventricular filling pressure, which may stabilize breathing and prevent the hyperventilation that initiates central SA. According to this, they favor pacing in patients with central sleep apnea and heart failure, and they speculate that biventricular pacing (also known as cardiac resynchronization therapy may result in larger benefit. Based on the results of this meta-analysis, AOP should not be considered an alternative to CPAP in the treatment of patients with SA.
2. The role of Cardiac Resynchronization Therapy (CRT) for the treatment of SA

A subgroup of patients with central SA and repetitive episodes of bradycardia may represent a subgroup of benefit; however, this hypothesis deserves further investigation. CRT appears somewhat more promising and there is limited evidence from some small studies of clinical significant improvement with the use of CRT in patients with central SA, heart failure and depressed left ventricular ejection fraction (LVEF) [32, 33]. It remains uncertain whether the benefit is driven by improving lung circulation times, reducing periods of apnea or by improving the LVEF by resynchronizing the ventricles. Further studies are on-going to answer this question.

SLEEP APNEA & VENTRICULAR ARRHYTHMIAS

The relationship between SA and ventricular arrhythmias is less well defined than for atrial or bradycardia. With recent data, however, it is becoming clearer that there exists an association between SA and ventricular arrhythmias, including ventricular tachycardia, ventricular fibrillation and sudden cardiac death (SCD).

A sub-study of the Sleep Heart Health Study has demonstrated a significant association between SA and ventricular arrhythmia. Comparison of a group of 228 patients with SA to a group of 338 patients without SA found that over 25% of the patients with SA experienced ventricular ectopy and 5% experienced Non-Sustained Ventricular Tachycardia (NSVT) during sleep while establishing that overall, adjusting for confounders, SA is associated with a three-fold increase in the risk of NSVT (OR 3.40; 95% CI 1.03-11.20, p=0.004) [20].

SA has been previously linked to SCD in a study that showed that CPAP decreased the incidence of SCD in patients with SA. In a long-term study of 107 patients (mean follow-up 7.5 years), 0% of CPAP-compliant patients experienced SCD compared to 7% of patients who were not being treated with CPAP [34]. Gami et al. demonstrated that patients with SA were more likely to die from SCD during the night (between 12 AM and 6 AM (RR 2.57, 95% CI 1.87-3.52, p=0.01)). This is in contrast with a nadir in the incidence of mortality from cardiovascular causes in patients without SA during the same time period. It is speculated that this peak in nocturnal SCD among SA patients can be attributed to exposures to hypoxemia, hypertensive surges and autonomic imbalances occurring during sleep in patients with SA [35].

The prevalence of SA has been shown to be 50% or higher in patients with symptomatic heart failure and depressed left ventricular ejection fraction (LVEF), asymptomatic systolic dysfunction, and diastolic dysfunction [36-38]. These clinical parameters correspond to the populations of patients currently receiving implantable cardioverter defibrillators (ICDs) for the prevention of SCD due to ventricular arrhythmias [39, 40]. Patients receiving ICDs are patients having survived ventricular tachycardia or ventricular fibrillation (secondary prevention) and patients with prior myocardial infarction (MI) and advanced left ventricular dysfunction (primary prevention) [41-43]. Our group has reported a prevalence of SA of 20% in a retrospective study of SA in patients with ICDs. The bias introduced by the retrospective nature of our study may lead us to underestimate the real prevalence of this association [44]. Grimm et al. prospectively explored a similar population and noted a prevalence of 62% (44% CSA, 18% OSA) [44].

In patients with ICDs, ventricular arrhythmias have been shown to occur significantly more often in patients with SA compared to those without (Arrhythmia Index (AI) = 20.9 ± 18.8/h vs. non-apnea-associated Arrhythmia Index (NAI) = 4.9 ± 3.3/h) [45].

In our study of 147 patients with new ICD implants, we found that SA was more frequently associated with appropriate ICD therapy (31% vs. 17%; p=0.09) and that the time to first appropriate therapy was shorter in patients with SA (8 vs. 12 months; p= 0.12) [44]. Figure 4 shows an example of an apneic episode in a patient with an ICD (Fig. 4 Panel A) and an electrogram recording of an appropriate ICD shock in a patient with severe SA (Figure 4, Panel B). These preliminary data establish the need for further validation in a larger prospective series.

The underlying pathophysiology connecting SA and ventricular arrhythmias remain somewhat speculative [11,19,46-48] but some considerations can be made:
1. SA has been linked to increased incidence of non-fatal cardiovascular events (non fatal MI, stroke, coronary insufficiency, revascularization) (OR: 3.17, 95% CI 1.12-7.51, p>0.05) [47]. This may represent an increased risk of post-MI associated arrhythmias and a long-term risk mediated by left ventricular function deterioration [3].

2. SA may have a detrimental effect on LV function. It is postulated that this effect could be mediated by increased negative intrathoracic pressure, intermittent hypoxia impairing cardiac contractility, and increased pulmonary artery pressure and/or myocardial ischemia. It is speculated that the deleterious effects on LVEF may lead to humoral and cellular changes, which may predispose to SCD. Continuous Positive Airway Pressure (CPAP) treatment has been shown to improve LVEF in a group of 24 patients with SA over a period of one month (25.0 ± 2.8 to 33.8 ± 2.4%, P<0.001) [49].

3. Premature ventricular contractions are common in hypertensive patients with LV hypertrophy (RR 8.9, p < 0.01) [50, 51]. Hypertension has a significant association with SA [6,11,16,19].

4. Intermittent hypoxemia is a consequence of SA. Acutely, severe hypoxic episodes can induce ventricular ectopy [52], a potential trigger for more complex ventricular arrhythmia. In the chronic setting, repetitive oxidative stress may induce ventricular remodeling predisposing to arrhythmia [47].

5. Impaired autonomic control as has been demonstrated in patients with SA [12,13], has deleterious effects on heart rate variability and coupling of cardiac and ventilatory inputs. Fluctuating autonomic activity caused by SA can also have effects on beat-to-beat changes in ventricular repolarization, which can predispose to ventricular arrhythmia [53].

6. The chronic elevation of sympathetic tone that has been observed in patients with SA [54] represents a major disturbance linked to an increased risk of SCD [55].

Although current data on the association between SA and ventricular arrhythmia are limited, it is clear that there exists an association and physicians should consider SA in patients at risk of SCD, particularly in patients with structural heart disease. Special consideration should be given to patients receiving an ICD. Recognition and treatment of SA has the potential to reduce therapies delivered by ICDs and limit triggers of ventricular arrhythmia. Research priorities in this field include further characterization of the association between SA and ventricular arrhythmia, elucidation of pathophysiological mechanisms and ultimately the development of clinical practice guidelines for physicians.

CONCLUSIONS
SA is associated with cardiovascular disease. By different mechanisms, SA has been found to be associated with coronary artery disease, heart failure, systemic hypertension, stroke and cardiac rhythm disturbances. The initial link was established for bradyarrhythmias and several case reports were published. Large epidemiological trials have failed to confirm this association; however, several well-conducted randomized trials on the role of atrial overdrive pacing have been reported. A recent meta-analysis from our group has demonstrated that despite a statistical significance, there is no clinical benefit driven from a systematic indication for pacing in patients with severe SA. Further studies are needed to confirm a possible benefit from CRT in patients with advanced heart failure, depressed LVEF and central SA.

The emphasis now is in recognizing the links between SA and cardiac arrhythmias. SA has been demonstrated to be associated with SA and to play a major role in the recurrence of AF. The role of SA as a trigger of malignant ventricular arrhythmias has been reported and recently investigated. Our preliminary retrospective data indicates that untreated SA maybe associated with increased appropriate discharges of the ICD and shorter time to first shock. These data may be confirmed by an on-going study at our institution.
REFERENCES

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- Adrian Baranchuk was born in Buenos Aires, Argentina, where he got his Cardiology and Electrophysiology training.
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- William F. McIntyre is a senior medical student in the class of 2010 at Queen’s University in Kingston, Ontario, Canada.
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