Review Article

Cardiac rhythm disorders in obstructive sleep apnea

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: GR Geovanini; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Obstructive sleep apnea (OSA) is common among patients with cardiac rhythm disorders. OSA may contribute to arrhythmias due to acute mechanisms, such as generation of negative intrathoracic pressure during futile efforts to breath, intermittent hypoxia, and surges in sympathetic activity. In addition, OSA may lead to heart remodeling and increases arrhythmia susceptibility. Atrial distension and remodeling, that has been shown to be associated with OSA, is a well-known anatomical substrate for atrial fibrillation (AF). AF is the arrhythmia most commonly described in patients with OSA. Several observational studies have shown that the treatment of OSA with continuous positive airway pressure (CPAP) reduces recurrence of AF after electrical cardioversion and catheter ablation. There is also evidence that nocturnal hypoxemia, a hallmark of OSA, predicts sudden cardiac death (SCD) independently of well-established cardiovascular risk factors. Among patients with an implantable cardiac defibrillator, those with OSA have a higher risk of receiving treatment for life-threatening arrhythmias. Nocturnal hypoxemia may also increase vagal tone, which increases susceptibility to bradycardic and conduction rhythm disorders that have also been described in patients with OSA. In conclusion, there are several biological pathways linking OSA and increased cardiac arrhythmogenesis propensity. However, the independent association is derived from observational studies and the direction of the association still needs clarification due to the lack of large clinical trials. This review focuses on the current scientific evidence linking OSA to cardiac rhythm disorders and point out future directions.

Keywords: Arrhythmias; cardiac rhythm disorders; atrial fibrillation (AF); sudden cardiac death (SCD); bradycardia; obstructive sleep apnea (OSA); sleep-disordered breathing; sleep apnea

Submitted May 08, 2018. Accepted for publication Oct 21, 2018.
doi: 10.21037/jtd.2018.12.63
View this article at: http://dx.doi.org/10.21037/jtd.2018.12.63

Introduction

Obstructive sleep apnea (OSA) and cardiovascular diseases (CVD) commonly co-exist because of bi-directional mechanisms (1). Observational studies have shown that OSA is independently associated with CVD (1-3) and untreated OSA is associated with increased risk of cardiac events (4-6). In addition, OSA and CVD share several risk factors, including increasing age, sedentary life, and obesity, which help to explain the co-existence of both conditions in the same individuals. OSA is frequent in the general population, but it is strikingly common among patients with established hypertension (>30%) (7-9), heart failure (HF) (~40%) (10-12), and arrhythmias (~30%) (13-15). More than three decades ago, Guilleminault and colleagues reported a case series of 400 patients with OSA who underwent

24-hour Holter EKG. The authors showed that 48% had arrhythmias and conduction disturbances during sleep (16). Non-sustained ventricular tachycardia (VT), sinus arrest, and second-degree atrioventricular conduction block were the most significant rhythm disorders (16). Furthermore, among 50 patients who were treated with tracheostomy, the arrhythmias were resolved (16). Despite this compelling early evidence, OSA still remains largely underdiagnosed among patients with CVD (17). This may be partially explained by the perceived lack of studies clearly showing a causal relationship between OSA and CVD.

There is mounting evidence pointing that OSA may contribute to the development of cardiac rhythm disorders (13-17). For instance, treating OSA with continuous positive airway pressure (CPAP) reduced the frequency of ventricular premature beats during the sleep, in patients with heart failure (HF) (14). However, methodological limitations, such as the paucity of studies showing the clear mechanisms linking OSA and cardiac rhythm disorders, potential selection bias derived from observational studies, and lack of large randomized clinical trials are the main weakness of the field. Thus, the main goal of this article is to review the evidence that supports the hypothesis that OSA contributes to cardiac rhythm disorders development. To this end, we will first focus on the biological plausibility, by reviewing the potential mechanistic pathways linking OSA and cardiac arrhythmias. Among all arrhythmias, particular attention will be devoted to atrial fibrillation (AF). AF is the most prevalent arrhythmia worldwide (18) and is the arrhythmia most studied in association with OSA (19,20). In addition, attention will be devoted to the association between OSA and sudden cardiac death (SCD) (21). We have also combined several other arrhythmias potentially linked to OSA into a single topic. Finally, we will discuss future directions in the area. Due to the limited space, this review will not explore the link between central sleep apnea and arrhythmias, which frequently co-exist among patients with congestive HF (22,23).

Arrhythmogenesis

OSA is characterized by recurrent episodes of partial or complete upper airway occlusion during sleep (24). Several of the potential mechanisms linking OSA to arrhythmias overlap with the pathways relating OSA with other CVD (4-6). The primary potential mechanisms linking OSA and arrhythmias are: (I) excessive negative intrathoracic pressure swings that occur during futile efforts to breath against the occluded airway; (II) arousals from sleep at the end of obstructive events; (III) intermittent asphyxia characterized by hypoxia and hypercapnia. These three primary mechanisms occurring during sleep trigger a cascade of intermediate mechanisms that may augment acutely and chronically the propensity to arrhythmia (25-27). The two most studied pathways linking OSA and arrhythmias are intermittent hypoxia and sympathetic over activity (21,25-27). Increased sympathetic tone occurs during each episode of upper airway obstruction and sympathetic over activation remains during the wakefulness period in patients with OSA (21,28,29). Sympathetic discharges may trigger atrial activity abnormalities (30). In addition to acute mechanisms occurring during each obstructive event, OSA may lead to heart remodeling, that in turn, increases the propensity to cardiac arrhythmias. For the sake of clarity, we have divided the potential mechanisms linking OSA and arrhythmogenesis in subheads.

Heart remodeling

Atrial distension and remodeling are the anatomical substrates of atrial arrhythmias, in particular AF (31-33). In turn, OSA has been associated with atrial remodeling (34). For instance, OSA was associated with atrial conduction abnormalities related to connexin dysregulation and fibrosis in a rat model of repetitive obstructive events triggered by closing the airway at the end-expiration (35). Cardiac chambers distension and remodeling in patients with OSA may occur because of several mechanisms, including increased cardiac transmural pressure, surges in sympathetic activity and blood pressure that occur during each obstructive event (24). Cardiac over load may be also observed during the wakefulness due to sympathetic over activity that may contribute to high blood pressure (24). Atrial electromechanical alterations associated with increased risk of AF, including interatrial and intra-atrial electromechanical delay, as well as prolongation of P-wave dispersion have been observed in patients with moderate-to-severe OSA (34). Moreover, shortening of the atrial effective refractory period triggered by generation of negative intrathoracic pressure was observed in a pig model of OSA (36). Intrathoracic pressure shifts and surges in blood pressure lead to not only atrial consequences, but also ventricular hypertrophy and increased propensity to arrhythmias (37,38). Pathological left ventricular hypertrophy has been associated with sudden death (39).

Autonomic imbalance

The autonomic nervous system (ANS) modulates cardiac arrhythmogenesis (40-42). However, the role of ANS imbalance generating arrhythmias is still not fully understood, particularly because ANS modulation plays a different role according to specific arrhythmias (40). For instance, both sympathetic and parasympathetic activation may trigger AF. In contrast, sympathetic stimulation is pro-arrhythmic, whereas parasympathetic activation is anti-arrhythmic for ventricular fibrillation (VF) (40). In addition, an animal model showed that the stimulation of the right and the left vagus nerve has differential effects on atrioventricular conduction and heart rate (41). In this complex mechanistic scenario, the sympathovagal imbalance has been noted to be the key trigger in cardiac arrhythmogenesis in OSA patients (42). Increased sympathetic tone and decreased parasympathetic tone have been reported in patients with OSA (42,43). However, increased vagal tone has also been described in OSA patients (43). During each obstructive event, patients with OSA frequently have relative bradycardia due to surges in vagal tone, triggered by the diving reflex (43). Several studies have evaluated OSA patients using indirect measures of ANS activity, in particular heart rate variability (HRV) (42-45). A typical pattern of bradycardia-tachycardia represents the variation of cardiac ANS with bradycardia while apneic event and tachycardia at the end of apneic event (44,45). However, HRV should be interpreted with caution due to potential confounding effects of age, sex, and disease severity with HRV measures (46-48).

Oxidative stress and inflammation

OSA is a natural model of intermittent hypoxia, a well-known mechanism for the production of reactive oxygen species (ROS) (49). Oxidative stress was associated with autonomic dysfunction and hypertension in animal models (50). Similarly, in humans, OSA patients excessively generate ROS from leukocytes that have been ameliorated by the treatment of OSA patients with CPAP (51). However, there are some methodological limitations on these studies, such as observational design, small sample size, and inclusion of subjects with comorbidities (49-51). Thus, more research is needed to establish the effect of OSA treatment on oxidative stress. In the same context, intermittent hypoxia triggers inflammation (52). Inflammatory biomarkers have also been associated with OSA (53-55). Several inflammatory biomarkers such as C-reactive protein, interleukin-6, interleukin-8, tumor necrosis factor-alpha, and adhesion molecules have been associated with OSA (55). CPAP therapy has shown to decrease both inflammation and oxidative stress levels in OSA patients (56,57). On the other hand, there is increasing evidence that systemic inflammation plays a key role in AF development and also contributes to AF persistence (58). ROS also plays a role in producing arrhythmic substrate, especially in conditions such as diabetes and hypertension (59). Therefore, oxidative stress and inflammation contribute to increased arrhythmogenesis propensity (58,59) and they are mechanisms linked to OSA pathogenesis (49-57). These mechanistic pathways are potential therapeutic targets for reducing arrhythmias in OSA patients.

Atrial fibrillation (AF)

OSA has been associated with atrial perturbations that increase AF development susceptibility (*Table 1*) (25,26,34,36). In the Sleep Heart Health Study (SHHS) a multicenter, community-based with more than 6,000 participants, a cross sectional study showed that sleep-disordered breathing was independently associated with a four folder higher odds of AF compared to those without sleep-disordered breathing (60). Gami and colleagues studied consecutive patients undergoing electrical cardioversion for AF, who were compared to consecutive patients referred to a general cardiology practice, but without AF (61). They noted that the proportion of patients with OSA was higher in AF group compared to patients from a general cardiology practice (61). The odds ratio for the association between OSA and AF was 2.2 (61). Furthermore, another study showed that after a successful electrical cardioversion, untreated OSA was associated with a higher recurrence rate of AF than patients without OSA (62). AF recurrence was also more common after catheter ablation in patients with OSA (51%) than without OSA (30%) (63). Observational prospective studies are in line with these findings showing that OSA treatment with CPAP decreased the necessity of anti-arrhythmic drugs use as well as AF recurrence (64,65). Interestingly, the hazard ratio (HR) for AF recurrence after catheter ablation was higher for OSA severity (HR =2.61) than for left atrial volume measurement (HR =1.11), which is a well-recognized factor associated with AF development (65). In addition, the

Table 1 The main studies reporting on the association between OSA and arrhythmias

First author, year of publication (ref)	Arrhythmia type	Study design	Sample size	Study population characteristic	CPAP (yes/no)	Main outcomes
Mehra *et al.*, 2006 (60)	AF	Observational, longitudinal	3,295	SDB (49% female, mean age: 70 years, and BMI: 30); non-SDB (53% female, mean age: 69 years, and BMI: 28)	No	AF was more common in SDB than in non-SBD (4.8% *vs.* 0.9%; P=0.003); adjusted OR for AF in SDB compared to non-SDB (OR =4.0)
Gami *et al.*, 2004 (61)	AF	Observational, prospective	524	AF (mean age: 71 years, 64% male, and BMI: 29) *vs.* general cardiology (mean age: 68 years, 58% male, and BMI: 29)	No	OSA was higher in AF than in general cardiology (49% *vs.* 32%; P=0.0004); adjusted OSA for association AF and OSA (OR =2.2)
Kanagala *et al.*, 2003 (62)	AF	Observational, prospective	OSA (n=39); control (n=79)	OSA (mean age: 65y, 81% male and BMI: 37) *vs.* control (mean age: 67 years, 65% male, BMI:30)	Yes (n=12)	12-months AF recurrence after cardioversion higher in OSA non-treated (82%) *vs.* OSA treated (42%) *vs.* control (53%)
Neilan *et al.*, 2013 (63)	AF	Observational, prospective	Total (n=720); OSA (n=142)	Total cohort (mean age: 56 years, 74% male, persisted AF: 65%, prior AF ablation: 24%, and heart failure: 30%)	Yes (n=71)	AF recurrence after catheter ablation (51% in OSA *vs.* 30% in non-OSA) and (68% in non-treated *vs.* 35% treated pts)
Fein *et al.*, 2013 (64)	AF	Observational, prospective	Total (n=426); OSA (n=62); CPAP users (n=32)	PVI(+)/OSA(+)/CPAP (+) [mean age: 57 years, 77% male, BMI: 29]; PVI(+)/OSA(–)/CPAP (–) [mean age: 59 years, 72% male, BMI: 30]; PVI(–)/OSA(+)/CPAP(+) [mean age: 55 years, 73% male, BMI: 31]; PVI(+)/OSA(–)/CPAP(–) [mean age: 59 years, 72% male, BMI: 30]	Yes	AF-free survival rate after PVI in CPAP users *vs.* CPAP nonusers (72% *vs.* 37%, P=0.01) and non-OSA (67%).
Naruse *et al.*, 2013 (65)	AF	Observational, prospective	Total (n=153); OSA (n=116); CPAP (n=82)	Patients underwent PVI (mean age: 60 years, 84% male, BMI: 25, paroxysmal AF: 54%, LA volume: 61, LVEF =66)	Yes	AF recurrence after ablation (Cox regression for concomitant OSA HR =2,61 and for left atrial volume HR =1.11)
Mehra *et al.*, 2006 (60)	Complex ventricular arrhythmias	Observational, longitudinal	3,295	SDB (49% female, mean age: 70 years, and BMI: 30); non-SDB (53% female, mean age: 69 years, and BMI: 28)	No	NSVT more frequent in SDB than in non-SBD (5.3 *vs.* 1.2%; P=0.004); adjusted OR (OR =3.4) for SBD group compared to non-SDB
Gami *et al.*, 2013 (15)	SCD	Observational, prospective	10,701	Pts underwent PSG from 1987 to 2003; average follow-up: 5.3 years	No	SCD was best predicted by age >60 (HR =5.53), AHI >20 (HR =1.60), mean nocturnal O_2sat <93% (HR =2.93), and lowest nocturnal O_2sat<78% (HR =2.60)
Gami *et al.*, 2005 (66)	SCD	Observational, retrospective	Total (n=112); OSA (n=78)	Pts undergone PSG and death certificate of SCD; OSA group (mean age: 70 years, 82% male, BMI =34) *vs.* non-OSA group (mean age: 67 years, 62% male, BMI: 31)	No	Among OSA patients, RR =2.57 for SCD; SCD from midnight to 6 am occurred in OSA *vs.* non-OSA (46% *vs.* 21%; P=0.01) and 16% of general population (P<0.001)

Table above shows articles relating OSA and AF, as well as OSA and ventricular arrhythmias. OSA, obstructive sleep apnea; AF, atrial fibrillation; SDB, sleep-disordered breathing; BMI, body mass index; OR, odds ratio; VT, ventricular tachycardia; NSVT, non-sustained ventricular tachycardia; PVI, pulmonary vein isolation; CPAP, continuous positive airway pressure; HR, hazard ratio; LA, left atrial; LVEF, left ventricle ejection fraction; complex ventricular arrhythmias, bigeminy or trigeminy or quadrigeminy or NSVT; SCD, sudden cardiac death; PSG, polysomnography; RR, relative risk; AHI, apnea hypopnea index, Pts, patients.

ORBIT-AF registry, with more than 10,000 participants, almost 2,000 subjects had OSA (13). AF patients with OSA had worse symptoms and higher risk of hospitalization than those without OSA (13).

Most studies listed above (13,60-65), are observational in design, have small sample size, or registries that report on the association between OSA and AF. Thus, a recent published meta-analysis explored whether treating OSA with CPAP in patients with AF reduces recurrence rates of AF after catheter ablation (19). After exclusions, a total of eight studies were identified with total of 4,516 participants with AF that were submitted to catheter ablation. Of these, 1,247 subjects were diagnosed with OSA, but only 698 were treated with CPAP. Among those eight studies included, there was only one small randomized clinical trial with 83 subjects (67). The eight studies included were published between 2003 and 2013, the majority were men, age ranged from 50 to 66 years. The use of CPAP was associated with 44% decreased risk for AF recurrence (P<0.001) (19). The overall effect size was in favor to CPAP users in association of AF recurrence, showing a relative risk (RR) of 0.56 and 95% CI (0.47–0.68) (19). Therefore, there is evidence that patients with OSA treated with CPAP have lower AF recurrence rates after catheter ablation than patients with OSA without treatment (19). However, the evidence is based mainly on observational studies (19). Thus, randomized clinical trials are needed to establish the causal relationship of AF recurrence and OSA and strength clinical practice recommendations for treating OSA in patients with AF.

SCD and ventricular arrhythmias

SCD, resulting from ventricular arrhythmias, mainly VF, is still a significant clinical problem with highly annual rates in US population (68). As previously discussed, OSA-related to hypoxia, sympathovagal imbalance, and mechanical effects of negative intrathoracic pressure on the ventricular free walls are the key factors generating cardiac electrical abnormalities and increasing arrhythmias susceptibility (21,24,26,37,38,42). The SHHS showed that complex ventricular arrhythmias (defined as bigeminy or trigeminy or quadrigeminy or non-sustained VT) were more common in subjects with sleep-disordered breathing compared to those without sleep-disordered breathing, respectively (25.0% *vs.* 14.5%, respectively, P=0.002) (60). These complex ventricular arrhythmias may trigger spontaneous cardiac impulse formation and predispose to cardiac electrical repolarization changes that facilitate initiation of VF, the main arrhythmia associated with SCD (69). The main studies pointing to an association between OSA and complex ventricular arrhythmias and SCD are summarized in *Table 1*.

The event peak of SCD is from 6 a.m. to noon and has a nadir from midnight to 6 a.m. in the general population (66). In contrast to the pattern observed in the general population, Gami and colleagues showed that patients with OSA had a peak of SCD during the sleeping hours (66). The increased morning risk of SCD in the general population may be explained by factors that predispose to ischemia and arrhythmias, such as increased sympathetic activity (70), increased coagulability (71), and electrophysiological abnormalities (72). On the other hand, OSA has been associated with systemic inflammation (53-55,73), endothelial dysfunction (73,74), hypercoagulability (75-78), and oxidative stress (49-51). Thus, it is reasonable that OSA facilitates arrhythmogenesis and may lead to SCD during sleep. In line with the hypothesis that OSA predisposes to SCD, a longitudinal study of more than 10,000 participants, followed during an average of 5.3 years, showed that OSA, specifically nocturnal hypoxemia, was independently associated with SCD, even after adjusting for well-established risk factors such as age, hypertension, coronary artery disease, HF, and ventricular ectopy (15). Therefore, this longitudinal study showed the independent association between OSA and SCD, after adjusting for traditional cardiovascular risk factors, highlighting that OSA increases the propensity of cardiac arrhythmogenesis (15). Furthermore, there is also evidence for the association between OSA and ventricular arrhythmias including ventricular ectopy, which is potential trigger for VT or VF (79). However, there is no clear evidence for the correlation between OSA severity and increased risk for VT or VF (79). However, the majority of the studies reporting the association between ventricular arrhythmias and OSA are among patients with HF. HF per se is a well-established risk factor for increased arrhythmogenesis susceptibility (80). Having this potential bias in mind, several studies showed that both central sleep apnea and OSA were independently associated with higher frequency of ventricular arrhythmias (15,66,81-83). OSA was also associated with appropriate therapy by implantable cardioverter-defibrillator (ICD) device (81-83). Bitter and colleagues showed that the time to first ventricular arrhythmias occurrence and to first appropriate ICD therapy were significantly shorter in patients with OSA compared to those without or with mild

OSA (81). Moreover, Serizawa and colleagues demonstrated that the presence of sleep-disordered breathing was common and an independent predictor of life-threatening ventricular arrhythmias in a HF population with ICD (82). The authors highlighted that these arrhythmias were more likely to occur during sleep (82). A higher incidence of appropriate ICD discharge was also shown in patients with sleep-disordered breathing and HF compared to those without sleep-disordered breathing and HF (83). However, some limitations merit consideration: only 17 patients were classified as having sleep-disordered breathing and of those 35% had central sleep apnea (83). Therefore, there is also a lack of studies with higher number of participants and longer follow-up period. Moreover, randomized studies evaluating the impact of OSA treatment are needed.

Other arrhythmias

Bradycardic rhythm disorders have been associated with OSA (84-86). Sleep apnea–induced hypoxemia is a key mechanism leading to an increased vagal tone and bradycardic rhythm disorders (84-86). For instance, Zwillich and colleagues showed that oxygen supplementation eliminated bradycardia (84). However, in the SHHS, sleep-disordered breathing was not significant associated with bradycardic rhythms and conduction delay arrhythmias (60). One potential explanation for the weaker association between conduction delay arrhythmias and sleep-disordered breathing was related to differences in ANS responses that could be mitigated in older individuals (60). A previous European multicenter study demonstrated a high prevalence of OSA (~60%) among patients with long-term pacing independent of the indication for pacing (87). However, paced patients with OSA were less symptomatic than typical patients with OSA and the significance of such high association remains to be established (87). Similarly, atrioventricular conduction block has been reported to be common in patients with OSA (16,85,86). However, the independent association between OSA and atrioventricular conduction block was also not shown in the SHHS (60). Some case reports showed an association between OSA and atrioventricular block (88-90) that were resolved after CPAP therapy (91). However, the impact of OSA treatment on bradycardic rhythms is still unclear and relies on studies with a limited sample size (88-91). For instance, one study evaluated 23 moderate-to-severe OSA patients with insertable loop recorder during 16 months and reported that almost 50% had severe nocturnal bradycardic events (91). CPAP treatment for 8 weeks was associated with a significant decrease in the median number of bradycardic episodes per patient (91).

The effects of sleep disordered breathing on increased arrhythmias susceptibility may be bi-directional. For instance, atrial overdrive stimulation may reduce both central sleep apnea and OSA (92). The rationale behind the mechanisms is not fully understood. One plausible explanation is that increasing heart rate and cardiac output by atrial overdrive stimulation, would lead to reduction in circulation time, decrease in pulmonary congestion, and neck fluid accumulation (92,93). In turn, these mechanisms may contribute to the pathogenesis of central sleep apnea and OSA. A meta-analysis evaluating the effects of atrial overdrive pacing included a total of eight randomized trials with only 129 patients (92). It is important to point out that the participants had HF with predominance of central sleep apnea in 3 out of 8 studies. The pooled analyzes showed that atrial overdrive pacing reduced sleep apnea in patients with central sleep apnea-predominantly. However, no significant effects were observed in patients with OSA (92). Finally, OSA has also been common among patients with typical atrial flutter (94). However, in contrast to AF as previously described, OSA was not a predictor of arrhythmia recurrence after catheter ablation in patients with atrial flutter (94). This observation reinforces the need to clear elucidate the specificity of the association between OSA and each rhythm disorder.

Future directions

There is consistent evidence that nocturnal arrhythmias are common in patients with OSA. There are several biological pathways that may explain the link between OSA and increased cardiac arrhythmogenesis propensity. Intermittent hypoxia, intrathoracic pressure shifts, acting synergistically with increased sympathetic activation and blood pressure surges, play a key role in electromechanical cardiac abnormalities, increasing arrhythmias development susceptibility. However, the evidence of the beneficial effects of OSA treatment on arrhythmias is derived from observational studies and small sized clinical trials. Therefore, large randomized clinical trials are needed to point out future directions for treatment with evidence-based guidelines. In the precision medicine area, a better understanding of different OSA phenotypes and specific pathways, which contribute to cardiac electrical remodeling, may be important for targeting future therapy.

Acknowledgements

The authors thank the Lemann Foundation for supporting education in the research area. Dr. Geovanini was supported by the Lemann Foundation during her postdoctoral fellowship at Brigham and Women's Hospital-Harvard Medical School, Boston-MA, USA (from July 2015 to July 2017).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Geovanini GR, Lorenzi-Filho G. Cardiac rhythm disorders in obstructive sleep apnea. J Thorac Dis 2018;10(Suppl 34):S4221-S4230. doi: 10.21037/jtd.2018.12.63

