A Painful Sleep Apnea

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BACKGROUND: Obstructive sleep apnea (OSA) is largely recognized as an independent risk factor for coronary artery disease (CAD), its prevalence is higher in the acute phase of ischemic heart disease and the risk of developing ischemic myocardial injury is greater in presence of this syndrome. OSA seems to exacerbate ischemic nocturnal events, to impair coronary blood flow (CBF) response to myocardial energy demand, to increase myocardial vascular resistance and to negatively impact outcomes of percutaneous coronary intervention (PCI)

CASE REPORT: We reported the case of 57-years-old man with multiples cardiovascular risk factors and previous history of severe CAD, who presented multiples relapses of in-stent restenosis and failure in percutaneous procedures; because of overweight, snoring and nocturnal pains referred occurring simultaneously of respiratory apneic events, he underwent to an overnight sleep screening, resulting positive for obstructive sleep apnea.

CONCLUSIONS: OSA, likewise others chronic inflammatory states, could be responsible for negative outcomes of PCI(in-stent proliferation restenosis) due to abnormal inflammatory state, coronary microvascular dysfunction secondary to vascular remodeling, and thus ineffectiveness of coronary blood flow (CBF) response to myocardial work.
Obstructive sleep apnea (OSA) is a common sleep disorder breathing (SDB) frequently found in general population and even higher in cardiovascular patients. OSA seems to be strongly related to coronary artery disease (CAD), its prevalence is very high in coronary patients and negatively affects short and long-term prognosis following the acute phase of ischemic heart disease (IHD). Sudden death for cardiovascular causes seems to be 2-fold higher in apneic patients than in general population, mainly occurring between midnight and 6 a.m. contrary to control population in which mainly occurs between 6 a.m. and 12 p.m.

Nowadays, evidences support OSA to be an independent risk factor for CAD, and in this context its presence seems to exacerbate nocturnal ischemic events (both thoracic pain and ST-segment modifications), that occurs mainly in the early morning (5.00 to 7.00 a.m.) and it seems that coronary blood flow (CBF) response to the increased myocardial O2 demand is impaired. Moreover, OSA seems to be linked to negative outcomes following percutaneous coronary intervention (PCI).

**CASE PRESENTATION**

A 57-years old man smoker, diabetic, dyslipidemic, with a family history of ischemic heart disease (IHD), presented to our hospital for anterior ST-segment elevation Myocardial Infarction (STEMI). He was given Clopidogrel 75 mg, Acetylsalicylic Acid 75 mg, Ramipril 10 mg, Atenolol 50 mg × 2, Atorvastatin 40 mg, Nitroglycerin at need.

His medical history was marked by myocordial infarction (MI) in 2005 treated by PCI on left anterior descending artery (LAD) and marginal coronary artery, followed by in-stent restenosis 2 years later in both arteries and treated with intra-stent implantation.

Coronary artery angiogram revealed a multitruncular coronary artery disease: chronic occlusion of right coronary artery (RCA) and marginal artery; sub-occlusion of LAD due to a proliferative in-stent restenosis. Both LAD and marginal artery were treated with active balloon, with a successfully result (Figures 1A, 1B, 1C).

Echocardiography post-catheterization showed a left ventricle ejection fraction (LVEF) of 35-40% with hypokinesia in lateral, inferior, and infer-lateral territories.

Another coronary catheterization performed 48 hours later showed an occlusion of the marginal artery, so that medical treatment was chosen regardless marginal and RCA arteries.

Echocardiography performed before patient hospital discharge showed a promising evolution with a LVEF of 45% with anterolateral akinesia. The Cardiovascular magnetic resonance (CMR) showed ischemic lesions in inferior and lateral territories but with normal EF.

Medical treatment at the discharge consisted of: Clopidogrel 75 mg, Acetylsalicylic Acid 75 mg, Ramipril 5 mg, Atenolol 50 mg, Atorvastatin 80 mg, Metformine 500 mg × 2, Esomeprazole 40 mg.

Two weeks later, Mr. T. was hospitalized again because of persistence of thoracic pain at rest. An additional PCI was performed on the LAD with kissing on the LAD and the diagonal branch. Medical treatment at the discharge was unchanged except switch Clopidogrel 75 mg with Ticagrelor 90 mg.

Nevertheless, because of persistence of thoracic pain, myocardial scintigraphy was performed two months later, showing extensive ischemia in antero-lateral, infero-lateral and inferior territories (Figure 2) although the LVEF and volumes were normal both at physical exertion and rest.

Another coronary angiogram revealed significant residual stenosis on LAD when evaluated by the fractional flow reserve (FFR) method. Because of multiples and severe coronary lesions difficult to revascularize by PCI, the possibility to revascularize efficiently at least the LAD and the circumflex arteries, the persistence of symptoms, the patient was offered a coronary artery by passes as the best therapeutic strategy. The patient refused this option.

One year later, because of persistent pains, a new coronary angiogram confirmed the lesions and a new myocardial scintigraphy evidenced contractile dysfunction on lateral and inferior territories. A PCI was attempted to treat the chronic total occlusion but failed.

Because of overweight, snoring and nocturnal pains, he underwent an overnight sleep study for the detection of obstructive sleep apnea. Nocturnal chest pains occurred simultaneously to obstructive respiratory events. The test was positive for obstructive sleep apnea, with an apnea-hypopnea index (AHI) of 23 per hour of sleep and a desaturation index of 21 per hour of sleep. The patient refused further investigations regarding the sleep apneas syndromes.

**DISCUSSION**

In this case report, two aspects deserve to be analyzed: multiple in-stent restenosis and above all nocturnal thoracic pains simultaneously to obstructive sleep apnea.

The medical history was heavily marked by frequently in-stent proliferation and failure in percutaneous procedures: this could be explained by the abnormal inflammation response found in OSA condition, promoting thrombosis and early neo-intimal hyperplasia following PCI. Indeed, OSA has been suggested as an independent risk factor for negative angiographic outcomes after PCI, as
shown in Yumino et al’s study, OSA is associated with a higher binary restenosis rate, and higher luminal late loss after percutaneous procedures.

This tendency to develop in-stent restenosis could be explained by the abnormal oxidative stress as well as the inflammatory response linked to the apneic events, promoting local inflammation and thus in-stent proliferation.

Secondly, during an obstructive apneic event, several hemodynamic changes in myocardial flow and perfusion occur.

Throughout the obstructive apneic event, similarly to a physical effort, myocardial energy demand increases secondary to both hemodynamic and metabolic changes. The rise both in heart rate and blood pressure due to the abnormal adrenergic system activation results in an increasing in myocardial consumption. Also the variations in intrathoracic pressure, due to persistent respiratory efforts against the occluded upper airways, are responsible for the increase in \( O_2 \) demand: increased difference between intra and extracardiac pressure and so, in the left ventricular transmural gradient, results in an increasing in LV wall tensions and again, in LV afterload.

On the other hand, during obstructive respiratory events, a transient mismatch between coronary blood flow (CBF) and myocardial work seems to occur.[14]

The imbalance between myocardial \( O_2 \) demand secondary to the increased LV afterload and myocardial \( O_2 \) supply secondary to the inadequate response of CBF to myocardial work, could reasonably explain the thoracic pains reported by patient during the apneic events.

Both LV compliance and LV end-diastolic volume decrease as consequence of increased venous return due to the negative intrathoracic pressure; this could lead to an increase in the LV end-diastolic pressure, in a reduction in the coronary AP and thus CBF, that could be inadequate to the increased myocardial work occurring throughout the obstructive event.

Nevertheless, this impairment in CBF could also bethe consequence of an increase in coronary vascular resistance. The increase in coronary vascular resistance is responsible for a reduction in CBF at maximal vasodilation, resulting in a dysfunction of coroary flow reserve (CFR= CBF at maximal vasodilation/ CBF at rest). Accordingly, Wang et al. show an inverse relationship between CFR and the severity of OSA and an increase odds of having low CFR as the AHI rises[15].

Maybe, the key linking OSA to microvascular dysfunction, expressed as an impaired CFR, is the inflammatory state. As well as high levels of C-reactive protein (CRP) are linked to lower CFR[17], and in OSA condition there are great plasma levels of CRP[18], inflammation could be responsible for the impairment of CFR observed in OSA state, likewise other chronic inflammatory diseases. Finally, increased coronary vascular resistance could be the consequence of vascular remodeling. In OSA condition, several mechanisms could be associated with vascular remodeling, as result of long-term vascular adaptation as explained in the following figure (Figure 3).

In conclusion, nocturnal thoracic pains occurring simultaneously to obstructive respiratory events could be the consequence of an
imbalance of O$_2$ supply and O$_2$ demand ratio, secondary to both an increased O$_2$ demand following LV increased afterload, and an impairment of CBF, due to both hemodynamics changes and microvascular dysfunction.

In-stent restenosis may be also the consequence of the inflammatory state linking to OSA condition.

CONFLICT OF INTEREST

There are no conflicts of interest with regard to the present study.

REFERENCES


