Culprit versus non-culprit lesion related adverse cardiac events in patients with obstructive sleep apnoea

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ABSTRACT

Background In patients with obstructive sleep apnoea (OSA), the relative contribution of culprit versus non-culprit lesions to subsequent major adverse cardiac events (MACE) after acute myocardial infarction (AMI) remains unknown. Elucidating this relationship will shed light on the contributions of OSA to the advancement of coronary artery disease.

Methods In a cohort of 105 patients who underwent an overnight sleep study after AMI, 98 were diagnosed with OSA (Apnoea–Hypopnoea Index (AHI) ≥5). The clinical outcomes at 5-year follow-up were determined. MACE was defined as a composite of cardiac death, reinfarction and repeat revascularisation. A culprit lesion was defined as the lesion involved in the initial AMI, and a non-culprit lesion as any lesion in the entire coronary tree outside the culprit lesion.

Results Eighteen patients (median AHI: 28.1) developed MACE, of whom 12 presented with reinfarction and 6 with repeat revascularisation for stable angina. There was no cardiac death. Based on repeated coronary angiography, the MACE was related to the culprit lesion in 4 patients and the non-culprit lesion in 12 patients. The lesion responsible for the MACE was indeterminate in 2 patients, as coronary angiography was declined. The median duration from index AMI to culprit lesion-related and non-culprit lesion-related MACE were 10.5 and 20 months, respectively.

Conclusions The incidence of MACE among patients with OSA and AMI was 18.4%, and most of the events were related to non-culprit lesions rather than the culprit lesion during the initial AMI.

INTRODUCTION

The role of obstructive sleep apnoea (OSA) as an emerging cardiovascular risk factor is increasingly recognised.[1][2] Intermittent hypoxaemia during sleep triggers a cascade of reactions including sympathetic activation, endothelial dysfunction and systemic inflammation.[3] Collectively, these responses promote vascular atherosclerosis. Epidemiological evidence shows that patients with acute coronary syndrome have a high prevalence of OSA.[4][5] Moreover, patients with untreated OSA have a higher risk of developing major adverse cardiac events (MACE) compared with those without OSA.[2][6][7]

Percutaneous coronary intervention (PCI) with stent implantation has been established as the standard treatment for patients presenting with acute myocardial infarction (AMI). Compared with fibrinolytic therapy, PCI is associated with a higher rate of successful reperfusion and fewer bleeding complications.[8][9] However, the subsequent occurrence of in-stent restenosis/thrombosis in the culprit lesion and the progression of non-culprit lesions remain major limitations of PCI; these events often manifest as myocardial ischaemia that warrants repeat revascularisation. A multicentre study investigating the natural history of acute coronary syndrome treated with PCI found that both culprit and non-culprit lesions contributed to MACE to a similar extent (12.9% vs 11.6%) at 3-year follow-up.[10] However, it remains unknown if this finding applies to patients with OSA.

Culprit lesion in-stent restenosis/thrombosis and non-culprit lesion disease progression are due to different mechanisms. Therefore, identifying their respective contributions to subsequent MACE will shed light in the mechanisms of OSA on coronary artery disease. To the best of our knowledge, no such information is available in the literature. In this study, we examined the clinical outcomes of OSA patients who underwent PCI for a first AMI, and the relative contribution of culprit versus non-culprit lesions to MACE at 5-year follow-up.

METHODS

Study design and patient population

This was a post-hoc analysis of a cohort study of 105 patients who presented with ST-segment elevation AMI and who underwent an overnight sleep study during their index admission. The original study investigating the prevalence of OSA among patients presenting with AMI and the effect of OSA on microvascular perfusion following primary PCI has been published.[4] As reported previously, patients aged 21–80 years who were admitted to our institution with ST-segment elevation AMI and had undergone a PCI were eligible. Exclusion criteria included known OSA, intubation and mechanical ventilation, electrical instability with ventricular arrhythmia, cardiogenic shock, previous coronary artery bypass surgery, previous PCI to the target vessel and inability to give informed consent.

Recruited patients were scheduled to undergo an overnight sleep study using a portable diagnostic device between day 2 and 5 after their primary PCI. Discharge medications were prescribed according to international guidelines. All patients underwent a transthoracic echocardiogram before discharge from the hospital. The study was approved by the local institutional review board (Domain Specific Review Boards. Reference: DSRB-C/06/389), and all of the patients provided written informed consent.

Overnight sleep study

Sleep studies were performed using a level 3 portable diagnostic device (Somte; Compumedics, Australia). The parameters measured included nasal airflow (nasal cannula), thoracoabdominal movements (inductive respiratory bands), arterial oxygen saturation (pulse oximetry), snoring episodes (derived from the integrated pressure transducer), limb movements, electrocardiogram and body position (continuous actigraphy). This system has been validated against 12-channel 'in-hospital' polysomnography for quantifying sleep disordered breathing.[11]

Outputs from the portable diagnostic device were analysed by two investigators who were blinded to the demographic and clinical characteristics of the patients. An apneic episode was defined as the cessation of airflow for more than 10 s and hypopnoea as a reduction in airflow of more than 50% for more than 10 s. An event was also considered to be a hypopnoea when there was a reduction in airflow that did not reach the 50% criteria but was associated with an arterial oxygen desaturation of more than 3%. Apnoeas were classified as obstructive if there was paradoxical thoracoabdominal movement and as central if there was no thoracoabdominal movement. The Apnoea–Hypopnoea Index (AHI) was calculated as the number of apneic plus hypopneic episodes that occurred per hour of recording time in bed. Recording started at the point at which respiration settled to a rhythmic, stable pattern, and ended either at the waking time recorded by the subject or the point at which the thoracoabdominal tracings became disturbed, consistent with wakefulness. For this post-hoc analysis, OSA was defined as AHI ≥5.

Long-term clinical outcomes

The 5-year follow-up data of the patient cohort were collected for this post-hoc analysis. Clinical outcomes were collected by a dedicated research assistant via telephone calls and/or clinic chart reviews, and all of the information was entered. MACE included cardiac death, reinfarction and repeat revascularisation.

Culprit versus non-culprit lesion related MACE

Culprit lesion-related MACE was defined as an event (defined above) that occurred due to the same lesion that caused the initial AMI. Culprit lesions were always treated with PCI and stent implantation. Non-culprit lesion-related MACE was defined as an event that occurred due to any lesion in the coronary tree that was not the culprit lesion (figure 1). The above classification required angiographic documentation during the

subsequent admission for MACE. The index coronary angiography during the initial AMI and the subsequent coronary angiography during the MACE were compared side-by-side by an experienced cardiologist.

Statistical analyses

The demographic and clinical characteristics of the study subjects measured by categorical variables are summarised using frequencies and percentages. For continuous variables, the mean and SD, or the median and range are used to describe the distribution of the data.

RESULTS

Clinical characteristics and sleep study results

Among the 105 patients who underwent an overnight sleep study, 98 were diagnosed with OSA, and all had reached the 5-year follow-up. MACE occurred in 18 OSA patients (18.4%), and they formed the study population of this post-hoc analysis. None of these 18 patients had presented with the symptoms of daytime sleepiness or received continuous positive airway pressure or any other treatments for OSA.

The baseline demographic and clinical characteristics of the 18 patients are shown in table 1. The median AHI was 28.1 (range 6.4–73.4). All of the patients were men except one, and there was a high prevalence of existing cardiovascular risk factors. The angiographic and procedural characteristics of the patients are shown in table 2. The infarct-related artery was successfully opened in all patients, each of whom received at least one coronary stent.

Details of the MACE of the 18 patients are shown in table 3. The adverse events were attributed to culprit lesions in four patients (22.2%) and non-culprit lesions in 12 patients (66.7%). The remaining two patients presented with reinfarction. The 12-lead electrocardiography of these two patients did not reveal ischaemia in any specific territory. They declined coronary angiography, and the location of the lesion responsible for the MACE was indeterminate.
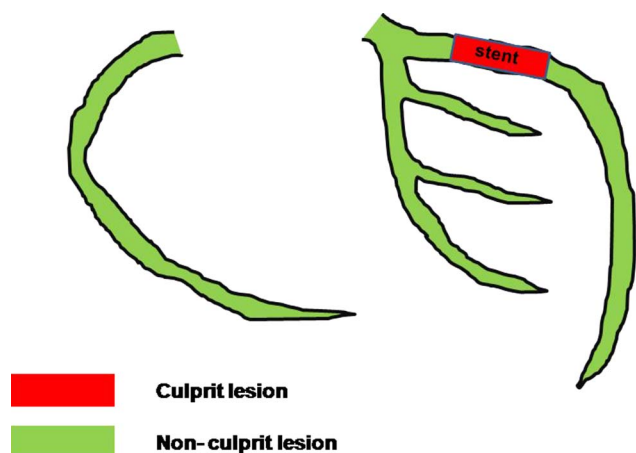
Figure 1 Definitions of culprit lesion and non-culprit lesion.

Table 1 Demographic and clinical characteristics of the patients

Characteristics	Overall (n=18)
Mean age in years (SD)	55.6 (9.2)
Male sex, n (%)	17 (94.4)
Smoking, n (%)	10 (55.6)
Hypertension n, (%)	9 (50.0)
Diabetes mellitus, n (%)	8 (44.4)
Hypercholesterolemia, n (%)	15 (83.3)
Family history of coronary artery disease, n (%)	4 (22.2)
Mean height in metre (SD)	1.67 (0.06)
Mean weight in kg (SD)	69.6 (9.8)
Mean body mass index in kg/m^2 (SD)	24.9 (2.9)
Mean systolic blood pressure in mm Hg (SD)	139 (29.6)
Mean diastolic blood pressure in mm Hg (SD)	88 (19.9)
Previous myocardial infarction, n (%)*	1 (5.6)
Previous stroke, n (%)*	2 (11.1)
Previous percutaneous coronary intervention, n (%)*	1 (5.6)
Chronic renal failure, n (%)	0 (0)
Location of infarction, n (%)	
Anterior	10 (55.6)
Non-anterior	8 (44.4)

Table 2 Angiographic and procedural characteristics of the patients

Characteristics	Overall (n=18)
Culprit vessel, n (%)	
Left anterior descending artery	10 (55.6)
Left circumflex artery	0 (0)
Right coronary artery	8 (44.4)
Culprit lesion site, n (%)	
Proximal	10 (55.6)
Mid	6 (27.8)
Distal	2 (11.1)
Door-to-balloon time, median (min)	71
Symptom-to-balloon time, median (min)	225
Peak creatine kinase, median (U/L)	2731
Mean left ventricular ejection fraction (%) (SD)	46 (11)
Mean time from PCI to sleep study, hour (SD)	40 (16)
Mean time from admission to sleep study (SD)	41 (16)
Baseline TIMI flow, n (%)	
0	15 (83.3)
1	1 (5.6)
2	2 (11.1)
3	0 (0)
Final TIMI flow, n (%)	
2	0 (0)
3	18 (100)
Ostial lesion, n (%)	2 (11.1)
Bifurcation lesion, n (%)	3 (16.7)

PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

Coronary angiography showed significant in-stent restenosis in all the four patients who presented with culprit lesion-related MACE. Among these four patients, three presented with stable angina and the in-stent restenosis was treated with PCI. One patient presented with reinfarction after the index procedure. Due to the presence of concomitant residual lesions in other arteries, the patient underwent coronary artery bypass surgery. The median duration from index AMI to MACE was 10.5 months. An example of culprit lesion-related MACE is shown in figure 2.

Among the 12 patients with MACE related to non-culprit lesions, nine presented with reinfarction. All were treated with repeat revascularisation with either PCI or coronary artery bypass grafting. The remaining three patients presented with stable angina and all were treated with PCI. All of the non-culprit lesions in these 12 patients were located in non-infarct related coronary arteries. The median duration from index AMI to adverse event was 20 months. An example of non-culprit lesion-related MACE is shown in figure 3.

DISCUSSION

PCI with stent implantation is the standard therapy for patients presenting with AMI.[8][9] Elucidating the patterns of subsequent MACE is crucial in advancing our understanding of the effect of OSA on coronary artery disease. In the present cohort of patients with untreated OSA, the incidence of MACE at 5-year follow-up was 18.4%. In contrast to a previous study suggesting a similar contribution of culprit and non-culprit lesions, in patients with OSA, 22% of the MACE were related to culprit lesions and 66% were related to non-culprit lesions. Our findings suggest that OSA has a greater effect on the progression of non-culprit lesions than culprit lesions and stent-related complications.

Despite recent advances in stent design and adjunct pharmacological therapy, long-term clinical outcomes following AMI remain unsatisfactory. In the Drug Elution and Distal Protection in Acute Myocardial Infarction (DEDICATION) trial, the incidence of major adverse events at 3-year follow-up was as high as 18.2%.[12] Consequently, much effort has been focused on investigating the role of non-traditional cardiovascular risk factors in determining the outcomes of AMI patients. With regard to OSA, an early study by Peker et al[13] found OSA to be an independent predictor of cardiovascular mortality at 5-year

Table 3 Details of the 18 patients who developed MACE

Patient number	Index culprit vessel	AHI	MACE	MACE culprit vessel	MACE time (months)	Treatment	Outcomes
1	LAD	24.10	Reinfarction	RCA	53	PCI	Alive
2	LAD	19.70	Reinfarction	RCA	65	PCI	Alive
3	LAD	71.60	Reinfarction	RCA	5	PCI	Dead*
4	RCA	8.60	Reinfarction	LAD	66	PCI	Alive
5	LAD	52.80	Stable angina-PCI	LCx	16	PCI	Alive
6	RCA	48.10	Reinfarction	Indeterminate	63	Medical	Alive
7	RCA	55.90	Stable angina-PCI	LAD	3	PCI	Alive
8	RCA	28.10	Reinfarction	Indeterminate	64	Medical	Alive
9	LAD	47.60	Stable angina-PCI	LAD	6	PCI	Alive
10	LAD	26.90	Stable angina-PCI	LCx	57	PCI	Alive
11	LAD	73.40	Stable angina-PCI	LAD	8	PCI	Alive
12	LAD	6.40	Reinfarction	LAD	19	CABG	Alive
13	LAD	50.50	Reinfarction	LCx	29	PCI	Alive
14	RCA	9.00	Reinfarction	LAD	7	CABG	Alive
15	LAD	11.30	Stable angina-PCI	LAD	13	PCI	Alive
16	RCA	25.10	Reinfarction	LAD	24	PCI	Alive
17	RCA	36.00	Reinfarction	LAD	1	CABG	Alive
18	RCA	45.50	Reinfarction	LAD	5	CABG	Alive

*Died of liver failure at 3 months after the MACE.
AHI, apnoea–hypopnoea index; CABG, coronary artery bypass grafting; LAD, left anterior descending artery; LCx, left circumflex artery; MACE, major adverse cardiac event; PCI, percutaneous coronary intervention; RCA, right coronary artery.
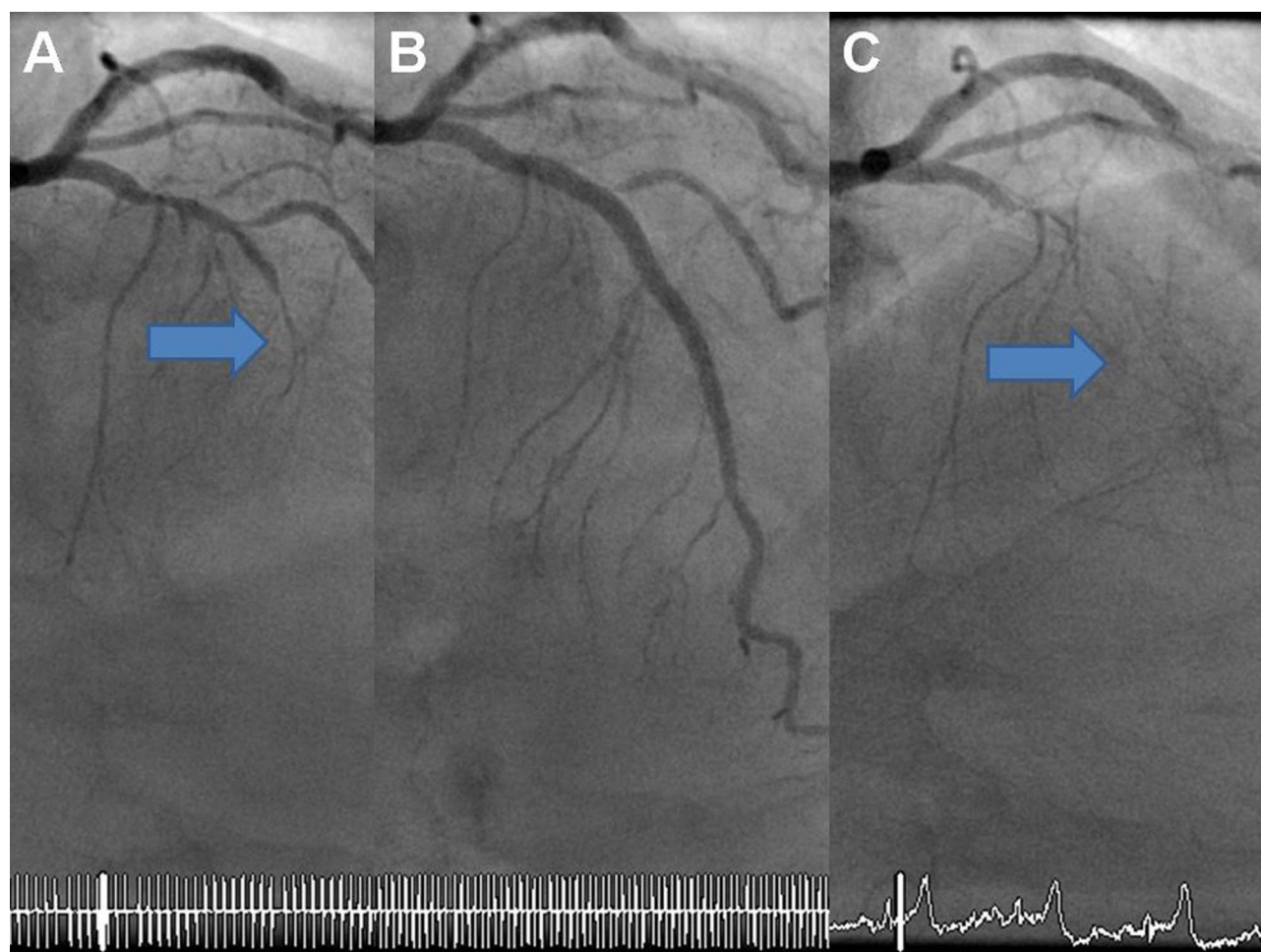
Figure 2 An example of culprit lesion related major adverse cardiac event. (A) This patient presented with anterior myocardial infarction due to occlusion of the left anterior descending artery (arrow). (B) The patient was treated with coronary stent implantation. (C) The patient developed chest pain 8 months later. Repeat coronary angiography showed 100% in-stent restenosis (arrow).

follow-up in patients with stable coronary artery disease. More recently, OSA was reported to be an independent predictor of MACE in patients with acute coronary syndrome.[6][7] However, these studies are limited by their relatively short follow-up duration and failure to determine the relative contributions of culprit versus non-culprit lesions to MACE.

The objective of this study was to determine how often events occur at the sites of non-culprit lesions as opposed to the sites of previously treated culprit lesions. There are fundamental differences in the pathophysiological mechanisms of in-stent restenosis versus the progression of de novo lesions. In-stent restenosis is a vascular response to endothelial injury inflicted by stent struts during stent deployment, involving smooth muscle cell proliferation and the formation of neointimal hyperplasia.[14][15] In contrast, the progression of de novo lesions is related to overall atherogenesis risk including inflammation, lipid accumulation and endothelial dysfunction.[16][17] When observing the contributions of the two different lesion types to MACE rates in patients with acute coronary syndrome, the PROSPECT study found that culprit and non-culprit lesions each accounted for half of all 3-year major adverse cardiovascular events observed (cumulative 3-year event rates of 20.4%).[10]

To the best of our knowledge, the present study is the first to report the relative contributions of culprit and non-culprit lesion to MACE in OSA patients who have undergone PCI. We

found that the ratio of culprit versus non-culprit lesion related events was 1:3. In this study population, there was no incidence of stent thrombosis. However, the small sample size precludes definite conclusions on this infrequent adverse event.

A major strength of this study is the long follow-up period. All previous studies on the effect of OSA on patients with coronary artery disease have reported in-hospital or short-term follow-up. A short-term follow-up duration is barely long enough to evaluate stent-related complications and inadequate to detect the progression of de novo lesions. The 5-year follow-up period of the present study allowed accurate interrogation of the pattern of MACE in PCI-treated AMI patients. Unlike other studies, our study recruited a homogenous sample, with all of the patients presenting with ST-segment elevation AMI.

The culprit and non-culprit lesion-related MACE showed different time patterns. The median duration from index procedure to event was 10.5 months for the culprit lesion related events and 20 months for the non-culprit lesion related events. This is in accordance with the pathophysiological mechanism for progression to manifestation of the respective lesion types. The peak incidence of in-stent restenosis has been documented as between 9 months and 1 year,[15] corresponding to the time taken for complete neointimal proliferation. Although the exact timing for the progression of a de novo coronary lesion from
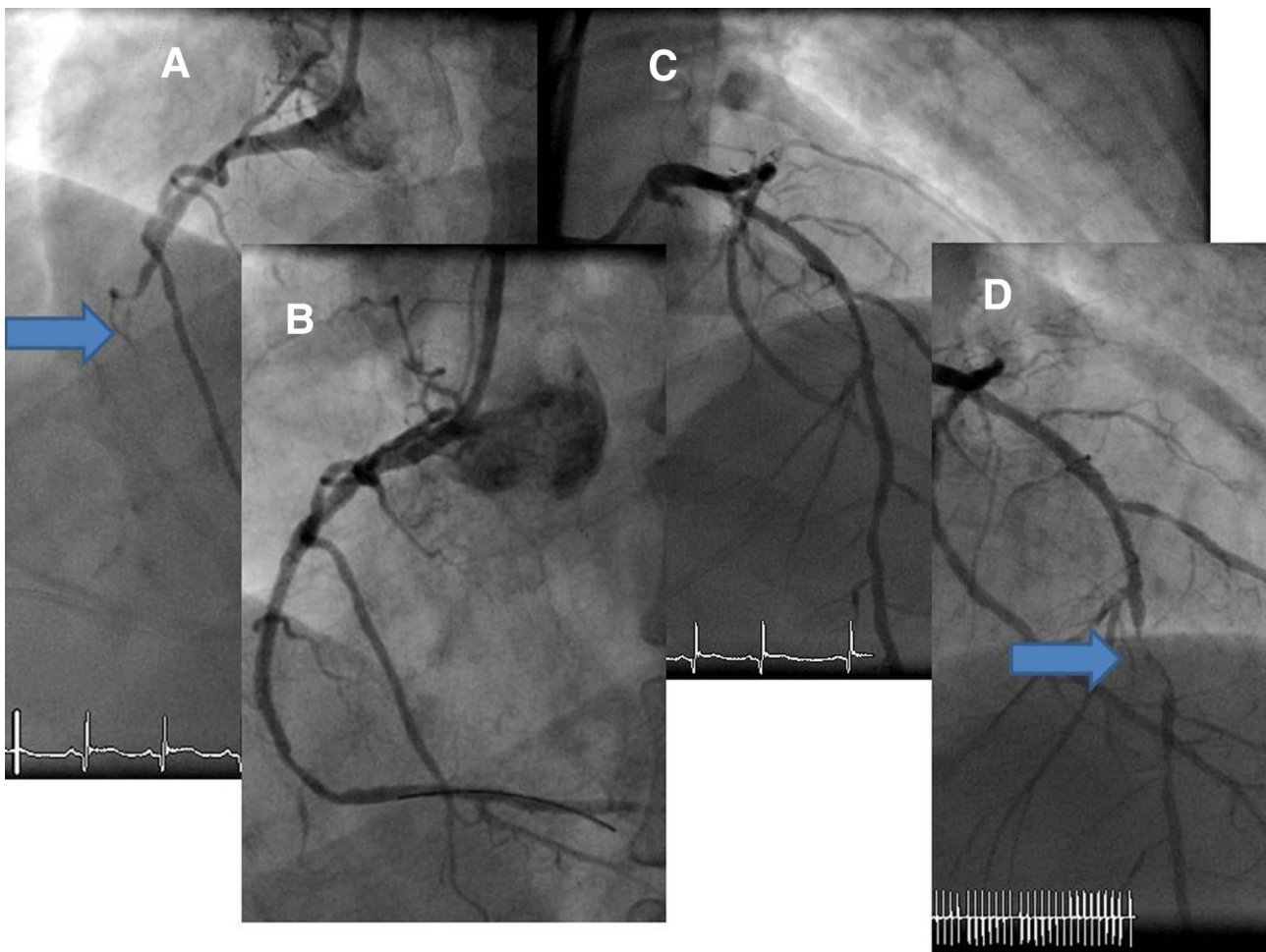
Figure 3 An example of non-culprit lesion-related major adverse cardiac event. (A) This patient presented with inferior myocardial infarction due to occlusion of the right coronary artery (arrow). (B) The patient was treated with coronary stent implantation. (C) At the time of the first infarction, the left anterior descending artery showed minor disease at the midsegment. (D) The patient presented with myocardial infarction 24 months later due to progression of the lesion at the left anterior descending artery (arrow).

mild to significant varies widely and remains incompletely understood, in clinical practice, the timing is usually longer than the duration of in-stent restenosis.

Confirmations of the results of this study in a larger cohort would have substantial implications for healthcare. The current risk stratification for patients admitted with AMI is imperfect. Our findings suggest that by performing an overnight sleep study during the index admission, it may be possible to identify high-risk patients who are likely to have worse long-term prognoses related to the progression of non-culprit de novo lesions. Although not targeted at AMI patients, continuous positive airway pressure treatment for OSA has been shown to have beneficial effects on long-term cardiovascular outcomes. Studies evaluating the effectiveness of continuous positive airway pressure treatment on the progression of de novo lesion using intravascular ultrasound are warranted.

Study limitations

As the sample size of this study was relatively small, the findings are only intended for hypothesis generating. We are unable to determine the effect of OSA on late lumen loss following stent implantation due to a lack of planned repeat angiography. Data on OSA-related symptoms were not captured. However, the relation between OSA and cardiovascular disease does not seem

to be associated with the presence of OSA symptoms. Patients who were sick and intubated were excluded as they were unable to obtain written informed consent. It is conceivable that the effect of OSA would have been even more pronounced if all of the patients admitted for ST-segment elevation AMI comers had been included. This study was conducted in a multi-ethnic Asian country. There is evidence that the mechanism of OSA may differ between Asians and Caucasians. OSA in Asians is mainly due to craniofacial skeletal restriction, whereas in Caucasians it is more related to obesity.[18] The mean body mass index of our Asian study population (approximately 25 kg/m^2) was different from that of Western patients. Hence, whether the results can be generalised to the western population remains unclear.

CONCLUSION

In conclusion, 18.4% of the OSA patients who underwent PCI treatment for AMI had developed MACE at 5-year follow-up. In contrast to a previous study that found that culprit and non-culprit lesions contributed similarly to MACE, among the OSA patients in this study, culprit lesions contributed to 22% and non-culprit lesions to 66% of the MACE. Based on the results of this post-hoc analysis, future large-scale studies examining the effects of different OSA severities on the progression of

culprit and non-culprit lesions, as well as the potential therapeutic role of continuous positive aiway pressure are warranted.

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