Relation of Obstructive Sleep Apnea in Patients With a Coronary Chronic Total Occlusion to Coronary Collaterals and Mortality

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A chronic total occlusion (CTO) is frequently identified in patients undergoing coronary angiography. The prognostic implications of intermittent hypoxia from obstructive sleep apnea (OSA) on patients with a CTO, and effects on collateral recruitment are unknown. The aim of this study was to determine the prevalence, vascular effects, and prognostic implications of the presence of OSA in patients with a CTO. Patients with a CTO between July 2010 and December 2019 were reviewed. Electronic medical records were accessed to determine documented patient history of OSA, demographics, and clinical course. Patients with robust collateral recruitment were defined as Rentrop grade 2 or 3. A total of 948 patients were included in the study, of which 127 (13.4%) had a documented history of OSA. These patients were younger (67.0 years vs 70.6 years, $p < 0.01$), had a higher body mass index (29.6 kg/m^2 vs 26.7 kg/m^2, $p < 0.0001$), higher rates of hypertension (91.3% vs 83.2%, $p < 0.05$), higher rates of smokers (63.3% vs 49.0%, $p < 0.01$) and more use of β-blockers (79% vs 68.5%, $p < 0.05$) and statins (92.7% vs 82.1%, $p < 0.01$). A documented history of OSA was independently associated with robust collaterals (OR 3.0 95%CI 1.5 to 5.8, $p < 0.01$) and lower mortality (HR 0.3 95% CI 0.1 to 0.7, $p < 0.01$) with a mean survival of 10.8 years, as compared to 8.1 years (log rank $p < 0.0001$). In conclusion, in patients with a CTO, documented OSA is independently associated with more robust coronary collaterals and lower mortality. The possible cardioprotective implications of intermittent hypoxia in OSA, as well as treatment effect requires further investigation. **(Am J Cardiol 2021;148:30−35)**

A coronary chronic total occlusion (CTO) is the presence of a completely occluded coronary artery, angiographically appreciated as the presence of collaterals filling the occluded vessel.[1] A CTO is identified in almost 7% of patients presenting with an acute coronary syndrome, and 18% to 52% in patients with stable coronary artery disease (CAD).[2,3−6] The precise etiology and predictors of collateral recruitment and maturation, vital for the development of a CTO, remain uncertain.[7,8] However, one of the possible mechanisms by which this may occur is through ischemic preconditioning, whereby brief, intermittent ischemia, renders tissue, tolerant to subsequent ischemia.[9,10] Obstructive sleep apnea (OSA) is a chronic, sleep-related breathing disorder characterized by periodic obstruction of the pharyngeal airway during sleep, resulting in repetitive apneas.[11] The prevalence of OSA in CAD is 38% to 65%, significantly greater than in the general population.[12] The hallmarks of OSA, namely intermittent hypoxia and exaggerated intrathoracic pressure swings have acute and chronic effects on hemodynamics and cardiovascular function. Thus, it is plausible that concurrent presence of OSA may be associated with development of, and in turn prognosis in, patients with a CTO. We sought to determine the prevalence and prognostic implications of OSA in patients with a CTO and predictors of collaterals in this population.

Methods

We reviewed all patients undergoing coronary angiography at our tertiary center from July 2010 to December 2019. We identified patients who had a reported CTO in their angiography report through a commercially available reporting system (McKesson, Irving, Texas). Patients who had had a prior coronary artery bypass graft (CABG) were excluded from the analysis to allow characterization of native collaterals alone. Patients presenting with ST elevation myocardial infarction (STEMI), whereby acute recruitment of robust collaterals is associated with improved prognosis, were also excluded to focus on patients with chronically developed collaterals.[13] To ascertain whether patients had a coexistent diagnosis of OSA, electronic medical records and records from the hospital's sleep investigation laboratory were reviewed to identify a documented history of OSA. Procedural characteristics, in-hospital

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course along with left ventricular function and biochemical results were reviewed. Left ventricular function was assessed by transthoracic echocardiography, or if not performed, then based on ventriculography at the time of the procedure. The presence and degree of collaterals were graded according to the Rentrop classification, where grade 0 = no filling of any collateral channel; grade 1 = filling of the side branches of the infarct related artery; grade 2 = partial filling of the epicardial vessel of the infarct related artery; grade 3 = complete filling of the epicardial vessel.[14] Patients with Rentrop grade 0 or 1 collaterals were defined as having poor collaterals, whilst those with Rentrop grade 2 or 3 were defined as robust collaterals. Angiographic determination of the collateral connection (CC) grade, which is based on the size of the collaterals, rather than their ability to opacify the epicardial vessel, was also assessed.[15] The donor vessel was defined as the epicardial vessel which provided the predominant collaterals to the occluded vessel. In patients with multiple CTOs, the subsequent angiographic and collateral data (i.e., Rentrop classification) referred to the vessel which corresponded to the greatest ischaemic territory, which in most cases was the left anterior descending (LAD) artery.[16–18] If no LAD CTO was present, then the vessel which had the more proximal location of the CTO was used.

Emergent indication for coronary angiography was defined as acute coronary syndrome, including unstable angina and non-ST elevation myocardial infarction or ventricular arrhythmia or cardiac arrest not fulfilling criteria for STEMI. Left ventricular impairment was defined as left ventricular ejection fraction (LVEF) ≤50% as determined by echocardiography or ventriculography. Valvular heart disease was defined as moderate or severe mitral or aortic valve disease as determined by echocardiography. CTO percutaneous coronary intervention (PCI) technical success was defined as <30% residual diameter stenosis within the treated segment and restoration of thrombolysis in myocardial infarction (TIMI) grade 3 antegrade flow. Management of the CTO was based upon both intention to treat (including patients who had attempted CTO PCI but was unsuccessful) as well as 'as treated' whereby patients' who had failed CTO PCI were stratified by subsequent management − CABG or medical management. Project approval by the local human ethics committee was obtained prior to data analysis.

Categorical variables were reported as percentages, whilst continuous variables were presented as means (± standard deviation) or as medians and interquartile ranges, depending on distribution of data. Comparisons between groups were performed using Pearson's chi square test for all categorical variables. Continuous variables were firstly assessed by the Shapiro-Wilk test to ascertain normality of distribution, after which, a student's T-test was used for normally distributed data, while the Mann-Whitney U test was used for continuous data not distributed normally. Multivariate logistic regression analyses were performed to determine variables associated with the recruitment of robust collaterals. Variables included in the model were those which had a correlation on univariate analysis with robust collateral recruitment, with entry and exit criteria of variables included in the model set at p <0.1. Cox regression analysis was performed to determine the independent predictors of mortality with entry set at p <0.05 and removal at p <0.1 from the model. Both multivariate models were built by forward linear regression. All data were analyzed at the patient level. All tests were 2-sided, and a p <0.05 was considered statistically significant. Analyses were performed using SPSS (version 24, IBM, New York, New York).

Results

A total of 948 patients with a CTO were identified, of which 127 (13.4%) had a documented history of OSA within their medical records, while 821 (86.6%) patients had no documented history of OSA. The mean age was 70.2 years (± 12.3) with 773 (81.5%) males. The indication for angiography was stable angina in 458 (48.3%) with the remaining 490 patients having emergent indications. The CTO vessel was the LAD in 224 (23.6%) patients, the left circumflex artery (LCx) in 197 (20.8%) patients, and the right coronary artery (RCA) in 527 (55.6%) patients. Two hundred and twenty patients (23.2%) had an attempt at CTO percutaneous coronary intervention (PCI), of which 185 (84.1%) achieved technical success. Two hundred and ninety-one patients (30.7%) underwent coronary artery bypass grafting, whilst 472 (48.8%) underwent medical management to the CTO, including PCI to a non-CTO lesion.

Baseline and angiographic differences between patients with documented OSA and those without OSA are summarized in Table 1. Patients with OSA were younger, had a higher body mass index (BMI), higher rates of hypertension, and higher rates of smokers compared to those without a history of OSA. With respect to medications at the time of angiography, patients with a documented history of OSA were more likely to be prescribed β blockers and statins. Patients with a documented history of OSA also had a significantly higher rate of robust collaterals compared to those without a documented history of OSA. There were no differences in the CCS or management strategies with respect to intention to revascularize the CTO, successful CTO revascularisation, or final management of the CTO (Table 2).

Multivariate analysis was performed to determine the independent predictors of robust collaterals with variables which had a correlation with robust collaterals on univariate analysis of p <0.10, included in the model, namely, a documented history of OSA, β-blocker therapy, a history of hypertension, and BMI. The independent predictors or robust collaterals were a documented history of OSA (odds ratio [OR] 3.0 95% confidence interval [CI] 1.5 to 5.8, p <0.01), whilst a history of hypertension (OR 0.4 95% CI 0.2 to 0.7, p <0.01) and β blockers (OR 0.5 95% CI 0.3 to 0.8, p <0.01) were associated with poorer collaterals, while BMI was not independently associated with robustness of collaterals. Cox regression analysis was performed to determine the independent predictors of mortality. The variables included in the model were age, history of OSA, male sex, multiple CTOs, Rentrop grade, history of diabetes mellitus, BMI, indication for diagnostic angiography,

Table 1
Baseline characteristics in patients with and without a documented history of OSA

Variable	Obstructive sleep apnea		p value
	YES n = 127	NO n = 821	
Age (years)	67 (± 14.1)	70.6 (± 12.0)	<0.01
Men	108 (85%)	665 (81%)	0.27
BMI *(kg/m²)*	**29.6 (26.2 − 33.6)**	**26.7 (24.0 − 29.9)**	**<0.0001**
Hypertension	**116 (91%)**	**672 (83%)**	**<0.05**
Hypercholesterolaemia	111 (87%)	647 (81%)	0.07
Smoker			**<0.01**
Never	**44 (37%)**	**385 (51%)**	
Former	**59 (49%)**	**260 (34%)**	
Current	**17 (14%)**	**110 (15%)**	
Diabetes Mellitus	49 (39%)	277 (35%)	0.39
Previous AMI	49 (39%)	256 (32%)	0.12
LVEF *(%)*	55 (40 − 55)	55 (40 − 60)	0.93
LV Impairment	59 (48%)	363 (46%)	0.76
Valvular Heart Disease	10 (9%)	96 (14%)	0.20
Emergent Indication for angiogram	58 (46%)	432 (53%)	0.14
Number of CTOs			0.49
1	103 (81%)	677 (82%)	
2	21 (16%)	135 (16%)	
3	3 (2%)	9 (1%)	
CTO artery			0.12
Left anterior descending	26 (20%)	198 (24%)	
Left circumflex	20 (16%)	177 (22%)	
Right	81 (64%)	446 (54%)	
CTO of stented vessel	11 (9%)	41 (5%)	0.09
Stenosis in Donor Artery *(%)*	50 (30 - 72.5)	50 (30 - 75)	0.81
Rentrop			**<0.001**
0/1	**11 (9%)**	**154 (19%)**	
2	**75 (59%)**	**500 (61%)**	
3	**41 (32%)**	**167 (20%)**	
Collateral Connection Score (CCS)			0.46
0	6 (5%)	55 (7%)	
1	27 (21%)	201 (24%)	
2	94 (74%)	565 (69%)	
Medications			
Aspirin	109 (88%)	670 (86%)	0.57
P2Y12 Inhibitor	78 (63%)	458 (59%)	0.39
Beta Blockers	**98 (79%)**	**534 (68%)**	**<0.05**
ACE-I/ARB	76 (61%)	488 (63%)	0.77
Nitrates	30 (24%)	145 (19%)	0.14
Statin	**115 (93%)**	**640 (82%)**	**<0.01**

ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; AMI = acute myocardial infarction; BMI = body mass index; CTO = chronic total occlusion; LV = left ventricular; LVEF = left ventricular ejection fraction.
Bold values are significant p<0.05.

CTO revascularizaton, and left ventricular impairment. The independent predictors of mortality were older age (hazard ratio [HR] 1.6 for every 10 years of age 95% CI 1.4 to 1.9, p <0.0001), a history of diabetes mellitus (HR 1.8, 95% CI: 1.2 to 2.5, p <0.01), and left ventricular impairment (HR 2.3, 95% CI 1.6 to 3.4, p <0.0001). Meanwhile, a documented history of OSA was associated with a significant reduction in mortality (HR 0.3, 95% CI 0.1 to 0.7, p <0.01), as was CTO revascularization (HR 0.5, 95% CI 0.4 to 0.8, p <0.01), while male sex, multiple CTOs, Rentrop grade, BMI, and indication for angiography were not independently associated with mortality. Patients with a documented history of OSA had a mean survival of 10.8 years, as compared to 8.1 years for patients without a documented history of OSA (p <0.01) (Figure 1).

Discussion

In patients with a coronary CTO, a documented history of OSA was conservatively identified in 14.1% of patients and was associated with robust coronary collaterals and lower mortality. The prevalence of OSA in patients with stable coronary disease is common, and likely underreported, with a cross-sectional study of 772 patients finding mild-to-severe OSA in 38.9% of patients with stable coronary disease.[19] Whilst this was higher than in the present study, this may reflect differing populations of all-comers with CAD as compared to only patients with a CTO in the current study. Alternatively, this may be due to the methods of diagnosis of OSA, whereby the former study performed polysomnography in all patients, the current study utilized medical records to determine the diagnosis of OSA.

Table 2
Management of patients with a CTO stratified by history of OSA.

Variable	Obstructive sleep apnea		P value
	YES n = 127	NO n = 821	
CTO revascularization (ITT)	77 (60.6%)	434 (52.9%)	0.1
Successful CTO revascularization (PCI or CABG)	70 (55.1%)	406 (49.4%)	0.23
Management			0.66
CTO PCI	27 (21.2%)	158 (19.2%)	
CABG	43 (33.9%)	248 (30.2%)	
Medical management	36 (28.3%)	246 (30.0%)	
PCI to non donor vessel	9 (7.1%)	90 (11.0%)	
PCI to donor vessel	12 (9.4%)	79 (9.6%)	
Final management of CTO			0.49
CTO PCI	27 (21.3%)	158 (19.2%)	
CABG	43 (33.9%)	248 (30.2%)	
Medical management	57 (44.9%)	415 (50.5%)	

CABG = coronary artery bypass grafting; CTO = chronic total occlusion; ITT = intention to treat; PCI = percutaneous coronary intervention.

There is an increasing evidence that OSA is associated with the development of CAD, as a result of increased oxidative stress, poorly controlled hypertension, increased sympathetic nervous system activity, and endothelial dysfunction.[20] Furthermore, in patients with stable CAD undergoing PCI, the presence of OSA is associated with poorer prognosis.[21] However, in the setting of a CTO, we found that a diagnosis of OSA was independently associated with robust coronary collaterals. These findings are similar to a previous small study of 34 patients with a CTO, of whom 15 had polysomnographically confirmed sleep apnea (apnea-hypopnea index >10/hr), whereby patients with OSA were also found to have more robust coronary collaterals.[22] This cardioprotective mechanism may be driven by intermittent hypoxia, the hallmark of OSA, resulting in upregulation of transcription factors associated with collateral development, including vascular endothelial growth factor (VEGF) and hypoxia inducible factor 1α (HIF-1α).[23,24] Meanwhile, the complex interplay between OSA and generation of reactive oxygen species (ROS), and the so-called "redox window," whereby an equilibrium of oxidative and reductive factors are necessary for the maturation of collaterals is also likely implicated in this association.[8,25]

Patients with a CTO and concurrent diagnosis of OSA were younger, had a higher BMI and were more likely to have a history of hypertension, and smoking history. Despite the close relationship between OSA and development of systemic hypertension, patients with a documented history of hypertension are less likely to have robust collaterals, related to endothelial dysfunction.[26–28] This was observed in the current study, where a history of hypertension was independently associated with poorer collaterals. It is possible that the putative advantage of intermittent hypoxia may override any disadvantage of systemic hypertension on collateral maturation in patients with OSA. A documented history of OSA was associated with greater usage of β-blocker therapy, which may be attributed to higher rates of atrial fibrillation, although this was not assessed in our current study.[29] Clinical studies have previously suggested a lower resting heart rate is associated with more robust collaterals, possibly due to prolonged diastolic time and promotion of endothelial shear stress, although whether exogenous beta blockers have similar effects has been controversial.[30–32] The present study suggested that the use of beta blockers was independently associated with poorer collateral recruitment. Invasive studies have previously suggested that acute administration of β blockers is associated with a reduction in collateral flow.[32,33] The mechanism for this is believed to be an increase in coronary collateral resistance or a reduction in oxygen demand associated with a decrease in rate-pressure product.[34] Furthermore, patients with OSA were more likely to be taking statins, which has also been independently associated with more robust collaterals, although this was not seen in the present study.[35]

The presence of a documented history of OSA was independently associated with lower mortality in patients with a coronary CTO, irrespective of revascularisation strategy, age and left ventricular dysfunction, with patents with a CTO having a 70% reduced risk of mortality. This protective effect of OSA with respect to developing collaterals may explain the paradoxical finding of a survival advantage in older patients with OSA, who may have developed protective collaterals.[36] It is possible that intermittent hypoxia and resultant ischemic preconditioning are protective against future cardiovascular events. This is particularly relevant, as any potential advantage of OSA with respect to mortality cannot simply be explained by demographic

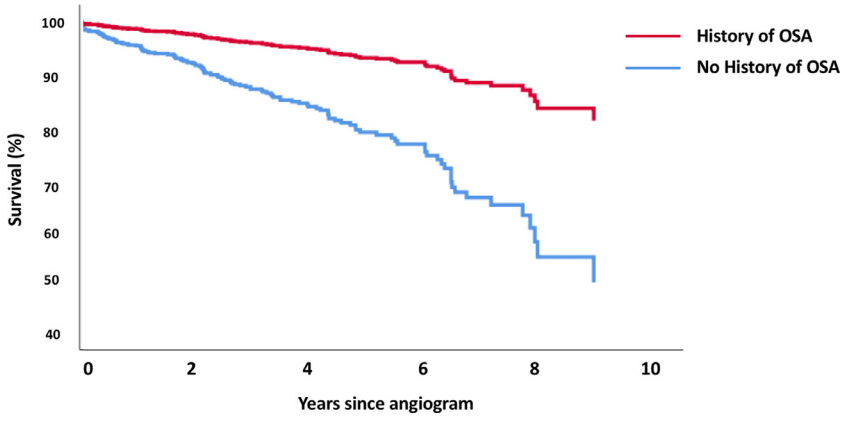

Figure 1. Survival in patients with and without documented OSA following diagnosis of a CTO on coronary angiography.

variations. Whilst the presence of a CTO has been associated with poorer prognosis, including mortality, recent data from randomised trials have not shown an improvement in mortality with percutaneous revascularization.[37] Non-randomised trials have consistently shown that compared to either medical management, or failed CTO PCI, revascularization is associated with a significant improvement in survival.[38–40] Future studies assessing the implications of a concurrent diagnosis of OSA in patients with CTO and, indeed, stable coronary disease should be considered. Furthermore, the effect of treatment of OSA should also be prospectively studied to ascertain whether the apparent protective effect of OSA remains.

Although this is the largest study of patients with a CTO to assess the prognostic implications of concurrent diagnosis of OSA, given this is a single-center retrospective study, there are inherent limitations. Most importantly, OSA diagnosis was based on medical records, which, although are reliable, presumably underestimates the prevalence of OSA.[41] Furthermore, we were unable to ascertain the impact of severity or treatment on patients with OSA. Given the known challenges of positive airway pressure treatment, we speculate that many patients would be receiving nil or suboptimal therapy. These confounders may have significant implications for effect, and in particular the protective effect of collaterals may be lost with more severe or untreated OSA. These factors underline the importance of further prospective research into the cardiovascular implications of OSA in patients with stable coronary disease and CTOs.

In patients with a coronary CTO, a concurrent diagnosis of OSA is independently associated with more robust coronary collaterals, and subsequently independently associated with reduced mortality. The cellular processes and mechanism by which collaterals are recruited and mature require further investigation, and may include hypoxia mediated endothelial activation, reactive oxygen species formation, and upregulation of transcription factors implicated in collateral recruitment. The apparent protective effect of OSA on mortality in patients with CTO also requires further investigation to identify the underlying mechanisms of a "sleep apnea collateral paradox." Further studies should be performed to ascertain the pathophysiological basis of these findings and to determine the therapeutic and management implications for patients with OSA.

Authors' Contribution

Usaid K Allahwala: conceptualization, methodology, investigation, writing - original draft; Peter A Cistulli: conceptualization, resources, writing - review & editing; Avedis Ekmejian: investigation, writing - review & editing; Nadeem Mughal: investigation, writing - review & editing; Hasthi U Dissanayake: conceptualization, writing - review & editing; Michael Ward: supervision, writing - review & editing; James C Weaver: supervision, writing - review & editing; Ravinay Bhindi: supervision, methodology, writing - review & editing

Disclosures

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1. Allahwala UK, Brilakis ES, Byrne J, Davies JE, Ward MR, Weaver JC, Bhindi R. Applicability and interpretation of coronary physiology in the setting of a chronic total occlusion. *Circ Cardiovasc Interv* 2019;12:e007813.
2. Allahwala UK, Jolly SS, Dzavik V, Cairns JA, Kedev S, Balasubramanian K, Stankovic G, Moreno R, Valettas N, Bertrand O, Lavi S, Velianou JL, Sheth T, Meeks B, Brilakis ES, Bhindi R. The presence of a CTO in a non-infarct-related artery during a STEMI treated with contemporary primary PCI Is associated with increased rates of early and late cardiovascular morbidity and mortality: the CTO-TOTAL Substudy. *JACC Cardiovasc Interv* 2018;11:709–711.
3. Christofferson RD, Lehmann KG, Martin GV, Every N, Caldwell JH, Kapadia SR. Effect of chronic total coronary occlusion on treatment strategy. *Am J Cardiol* 2005;95:1088–1091.
4. Fefer P, Knudtson ML, Cheema AN, Galbraith PD, Osherov AB, Yalonetsky S, Gannot S, Samuel M, Weisbrod M, Bierstone D, Sparkes JD, Wright GA, Strauss BH. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. *J Am Coll Cardiol* 2012;59:991–997.
5. Grantham JA, Marso SP, Spertus J, House J, Holmes DR Jr., Rutherford BD. Chronic total occlusion angioplasty in the United States. *JACC Cardiovasc Interv* 2009;2:479–486.
6. Jeroudi OM, Alomar ME, Michael TT, El Sabbagh A, Patel VG, Mogabgab O, Fuh E, Sherbet D, Lo N, Roesle M, Rangan BV, Abdullah SM, Hastings JL, Grodin J, Banerjee S, Brilakis ES. Prevalence and management of coronary chronic total occlusions in a tertiary Veterans Affairs hospital. *Catheter Cardiovasc Interv* 2014;84:637–643.
7. Allahwala UK, Kott K, Bland A, Ward M, Bhindi R. Predictors and prognostic implications of well-matured coronary collateral circulation in patients with a chronic total occlusion (CTO). *Int Heart J* 2020;61:223–230.
8. Allahwala UK, Khachigian LM, Nour D, Ridiandres A, Billah M, Ward M, Weaver J, Bhindi R. Recruitment and maturation of the coronary collateral circulation: Current understanding and perspectives in arteriogenesis. *Microvasc Res* 2020;132:104058.
9. Billah M, Ridiandries A, Allahwala U, Mudaliar H, Dona A, Hunyor S, Khachigian LM, Bhindi R. Circulating mediators of remote ischemic preconditioning: search for the missing link between non-lethal ischemia and cardioprotection. *Oncotarget* 2019;10:216–244.
10. Chen W, Gabel S, Steenbergen C, Murphy E. A redox-based mechanism for cardioprotection induced by ischemic preconditioning in perfused rat heart. *Circ Res* 1995;77:424–429.
11. Osman AM, Carter SG, Carberry JC, Eckert DJ. Obstructive sleep apnea: current perspectives. *Nat Sci Sleep* 2018;10:21–34.
12. Javaheri S, Barbe F, Campos-Rodriguez F, Dempsey JA, Khayat R, Javaheri S, Malhotra A, Martinez-Garcia MA, Mehra R, Pack AI, Polotsky VY, Redline S, Somers VK. Sleep apnea: types, mechanisms, and clinical cardiovascular consequences. *J Am Coll Cardiol* 2017;69:841–858.
13. Allahwala UK, Weaver JC, Nelson GI, Nour D, Ray M, Ciofani JL, Ward M, Figtree G, Hansen P, Bhindi R. Effect of recruitment of acute coronary collaterals on In-hospital mortality and on left ventricular function in patients presenting with ST elevation myocardial infarction. *Am J Cardiol* 2020;125:1455–1460.
14. Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. *J Am Coll Cardiol* 1985;5:587–592.

15. Werner GS, Ferrari M, Heinke S, Kuethe F, Surber R, Richartz BM, Figulla HR. Angiographic assessment of collateral connections in comparison with invasively determined collateral function in chronic coronary occlusions. *Circulation* 2003;107:1972–1977.
16. McEntegart MB, Badar AA, Ahmad FA, Shaukat A, MacPherson M, Irving J, Strange J, Bagnall AJ, Hanratty CG, Walsh SJ, Werner GS, Spratt JC. The collateral circulation of coronary chronic total occlusions. *EuroIntervention* 2016;11:e1596–e1603.
17. Gould KL, Nakagawa Y, Nakagawa K, Sdringola S, Hess MJ, Haynie M, Parker N, Mullani N, Kirkeeide R. Frequency and clinical implications of fluid dynamically significant diffuse coronary artery disease manifest as graded, longitudinal, base-to-apex myocardial perfusion abnormalities by noninvasive positron emission tomography. *Circulation* 2000;101:1931–1939.
18. Hernandez-Pampaloni M, Keng FY, Kudo T, Sayre JS, Schelbert HR. Abnormal longitudinal, base-to-apex myocardial perfusion gradient by quantitative blood flow measurements in patients with coronary risk factors. *Circulation* 2001;104:527–532.
19. Alonderis A, Varoneckas G, Raskauskiene N, Brozaitiene J. Prevalence and predictors of sleep apnea in patients with stable coronary artery disease: a cross-sectional study. *Ther Clin Risk Manag* 2017;13:1031–1042.
20. Tietjens JR, Claman D, Kezirian EJ, De Marco T, Mirzayan A, Sadroonri B, Goldberg AN, Long C, Gerstenfeld EP, Yeghiazarians Y. Obstructive sleep apnea in cardiovascular disease: a review of the literature and proposed multidisciplinary clinical management strategy. *J Am Heart Assoc* 2019;8:e010440.
21. Zhang JJ, Gao XF, Ge Z, Jiang XM, Xiao PX, Tian NL, Kan J, Lee CH, Chen SL. Obstructive sleep apnea affects the clinical outcomes of patients undergoing percutaneous coronary intervention. *Patient Prefer Adherence* 2016;10:871–878.
22. Steiner S, Schueller PO, Schulze V, Strauer BE. Occurrence of coronary collateral vessels in patients with sleep apnea and total coronary occlusion. *Chest* 2010;137:516–520.
23. Lavie L, Kraiczi H, Hefetz A, Ghandour H, Perelman A, Hedner J, Lavie P. Plasma vascular endothelial growth factor in sleep apnea syndrome: effects of nasal continuous positive air pressure treatment. *Am J Respir Crit Care Med* 2002;165:1624–1628.
24. Lavie L, Lavie P. Molecular mechanisms of cardiovascular disease in OSAHS: the oxidative stress link. *Eur Respir J* 2009;33:1467–1484.
25. Lavie L. Oxidative stress in obstructive sleep apnea and intermittent hypoxia−revisited−the bad ugly and good: implications to the heart and brain. *Sleep Med Rev* 2015;20:27–45.
26. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *JAMA* 2000;283:1829–1836.
27. Koerselman J, de Jaegere PP, Verhaar MC, van der Graaf Y, Grobbee DE, Group SS. High blood pressure is inversely related with the presence and extent of coronary collaterals. *J Hum Hypertens* 2005; 19:809–817.
28. Olsen MH, Wachtell K, Meyer C, Hove JD, Palmieri V, Dige-Petersen H, Rokkedal J, Hesse B, Ibsen H. Association between vascular dysfunction and reduced myocardial flow reserve in patients with hypertension: a LIFE substudy. *J Hum Hypertens* 2004;18:445–452.
29. Tung P, Levitzky YS, Wang R, Weng J, Quan SF, Gottlieb DJ, Rueschman M, Punjabi NM, Mehra R, Bertisch S, Benjamin EJ, Redline S. Obstructive and central sleep apnea and the risk of incident atrial fibrillation in a community cohort of men and women. *J Am Heart Assoc* 2017;6:e004500.
30. de Marchi SF, Gloekler S, Meier P, Traupe T, Steck H, Cook S, Vogel R, Seiler C. Determinants of preformed collateral vessels in the human heart without coronary artery disease. *Cardiology* 2011;118:198–206.
31. Wright AJ, Hudlicka O. Capillary growth and changes in heart performance induced by chronic bradycardial pacing in the rabbit. *Circ Res* 1981;49:469–478.
32. Billinger M, Raeber L, Seiler C, Windecker S, Meier B, Hess OM. Coronary collateral perfusion in patients with coronary artery disease: effect of metoprolol. *Eur Heart J* 2004;25:565–570.
33. Kyriakides ZS, Kolettis T, Antoniadis A, Nikolaou N, Sbarouni E, Tzanalaridou E, Kremastinos DT. Beta-adrenergic blockade decreases coronary collateral blood flow in patients with coronary artery disease. *Cardiovasc Drugs Ther* 1998;12:551–559.
34. Sato M, Harding SE, Poole-Wilson PA. Beta-blockers, myocardial ischaemia and collateral circulation. *Eur Heart J* 2004;25:537–539.
35. Dincer I, Ongun A, Turhan S, Ozdol C, Ertas F, Erol C. Effect of statin treatment on coronary collateral development in patients with diabetes mellitus. *Am J Cardiol* 2006;97:772–774.
36. Lavie P, Lavie L. Unexpected survival advantage in elderly people with moderate sleep apnoea. *J Sleep Res* 2009;18:397–403.
37. Allahwala UK, Ward MR, Brieger D, Weaver JC, Bhindi R. Indications for Percutaneous Coronary Intervention (PCI) in Chronic Total Occlusion (CTO): have we reached a DECISION or do we continue to EXPLORE after EURO-CTO? *Heart Lung Circ* 2019;28:1484–1489.
38. Jang WJ, Yang JH, Choi SH, Song YB, Hahn JY, Choi JH, Kim WS, Lee YT, Gwon HC. Long-term survival benefit of revascularization compared with medical therapy in patients with coronary chronic total occlusion and well-developed collateral circulation. *JACC Cardiovasc Interv* 2015;8:271–279.
39. Choi SY, Choi BG, Rha SW, Baek MJ, Ryu YG, Park Y, Byun JK, Shim M, Li H, Mashaly A, Jang WY, Kim W, Choi JY, Park EJ, Na JO, Choi CU, Lim HE, Kim EJ, Park CG, Seo HS, Oh DJ. Percutaneous coronary intervention versus optimal medical therapy for chronic total coronary occlusion with well-developed collaterals. *J Am Heart Assoc* 2017;6:e006357.
40. George S, Cockburn J, Clayton TC, Ludman P, Cotton J, Spratt J, Redwood S, de Belder M, de Belder A, Hill J, Hoye A, Palmer N, Rathore S, Gershlick A, Di Mario C, Hildick-Smith D, British Cardiovascular Intervention Society, National Institute for Cardiovascular Outcomes Research. . Long-term follow-up of elective chronic total coronary occlusion angioplasty: analysis from the U.K. Central Cardiac Audit Database. *J Am Coll Cardiol* 2014;64:235–243.
41. Kelstrup AM, Juillerat P, Korzenik J. The accuracy of self-reported medical history: a preliminary analysis of the promise of internet-based research in Inflammatory Bowel Diseases. *J Crohns Colitis* 2014;8:349–356.