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Original Article

Association of Preoperative Sleep-Disordered Breathing With Functional Status After Septal Myectomy for Obstructive Hypertrophic Cardiomyopathy

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ABSTRACT

Background: Sleep-disordered breathing (SDB) is a risk factor for heart failure symptoms in patients with hypertrophic cardiomyopathy (HCM). However, the relationship between preoperative SDB and post-operative functional status after septal myectomy (SM) is unknown. In this study, we investigated the association of preoperative SDB with late self-reported health status among patients undergoing SM for obstructive HCM.

Methods: Prior to SM, an overnight pulse oximetry test was used to measure oxygen desaturation index (ODI), which indicates the average number of desaturation episodes with at least 4% of drops in oxygen level from baseline per hour of sleep. Patients reported postoperative function through a questionnaire-based survey completed 3-5 years following SM.

Results: We analyzed 264 patients who underwent transaortic SM from November 2005 through April 2016. On predischarge transthoracic echocardiography post-procedure, no significant difference was present in the extent of mitral valve regurgitation (P = 0.524), left ventricular outflow tract gradient (P = 0.405), or septal thickness (P = 0.744) related to ODI. At 3 to 5 years after their operation, 236 patients (89%) reported good or excellent health. Approximately 18%

RÉSUMÉ

Contexte : Les troubles respiratoires du sommeil (TRS) sont un facteur de risque d'insuffisance cardiaque chez les patients atteints de cardiomyopathie hypertrophique (CMH). Toutefois, la relation entre la présence préopératoire d'un TRS et le statut fonctionnel postopératoire après une myectomie septale (MS) est inconnue. Dans notre étude, nous avons examiné l'association entre les TRS préopératoires et le statut de santé à long terme, tel qu'autodéclaré par les patients ayant subi une MS dans le traitement de la CMH.

Méthodologie : Un test nocturne d'oxymétrie de pouls, réalisé avant la MS, a été utilisé pour déterminer l'indice de désaturation en oxygène (IDO), qui indique le nombre moyen d'épisodes de désaturation avec une baisse d'oxygène d'au moins 4 % sous le niveau de base, par heure de sommeil. Les patients ont rapporté leur fonction postopératoire au moyen d'un sondage sous forme de questionnaire, rempli de 3 à 5 ans après la MS.

Résultats : Les données de 264 patients ayant subi une MS transaortique entre novembre 2005 et avril 2016 ont été analysées. À l'échocardiographie transthoracique postopératoire réalisée avant le congé hospitalier, aucune différence significative liée à l'IDO n'a été notée quant à l'insuffisance de la valve mitrale (p = 0,524), au

Sleep-disordered breathing (SDB), especially obstructive sleep apnea (OSA), is an under-recognized risk factor for cardiovascular disease.¹ Patients with OSA present with transient hypoxemia during sleep, which triggers sympathetic activation

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See page 853 for disclosure information.

and systemic inflammation in response to increased oxidative stress. In previous studies, OSA has been associated with systemic hypertension, coronary artery disease, stroke, and death from cardiovascular disorders.²⁻⁴ OSA treated with continuous positive airway pressure (CPAP) is believed to reduce risks of fatal and nonfatal cardiovascular events.³

SDB is highly prevalent in patients with hypertrophic cardiomyopathy (HCM). Eleid and colleagues reported that 71% of HCM patients who were referred for nocturnal oximetry tests to evaluate SDB had abnormal results.⁵ In the general HCM population, exercise capacity is reduced in patients with SDB, as reflected by self-reported physical limitation in daily life and lower peak oxygen consumption during

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Ethics Statement: This study was approved by the Mayo Clinic Institutional Review Board. Informed consent was obtained from each patient.

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(n=48) and 8% (n=22) of the cohort continued to experience exertional dyspnea and chest tightness, respectively, on walking 2 blocks or less. A greater ODI was not an independent predictor of worse health status or residual symptoms.

Conclusions: Relief of left ventricular outflow tract obstruction in patients with obstructive HCM improves symptoms, with 89% of patients reporting good or excellent health. Preoperative SDB is not significantly associated with late functional status after septal myectomy.

cardiopulmonary exercise testing.⁶ However, whether SDB identified before septal myectomy (SM) impacts improvement in symptoms and functional status postoperatively is unknown. In this study, we investigated the possible association between SDB with self-reported late health status following SM for obstructive HCM.

Materials and Methods

Patient population and data collection

This study was approved by the Mayo Clinic Institutional Review Board. Informed consent was obtained from each patient. We identified adult patients aged 18 years and older who underwent transaortic SM for obstructive HCM at Mayo Clinic in Rochester, Minnesota from November 2005 through April 2016. We included patients who underwent overnight pulse oximetry tests prior to SM (median 6 days [interquartile range: 2-55]) and responded to follow-up surveys 3-5 years after the procedure. In all analyzed patients, overnight oximetry was performed on room air without assisted breathing devices. The oxygen desaturation index (ODI) was calculated as the average number of drops in oxygen saturation (at least 4% from baseline) per hour of sleep.7 Patients with ODI equal to or greater than 5 were considered to have SDB. These patients were further stratified into 2 groups, as follows: mild SDB, with ODI from 5 to 15; and moderate or severe SDB, with ODI > 15.

Postoperative physical function was evaluated through questionnaire-based surveys at 3 and 5 years after SM. The same protocol was used at 3 years and 5 years. Because the time interval between the 2 surveys was relatively short, we analyzed results from the first survey response for each patient; only results at 3 years were included if patients responded to both surveys. Patients were queried regarding their perceived general health and whether their physical activity was limited by persistent shortness of breath and/or exertional chest tightness since hospital dismissal. Questions about perceived general health and residual chest tightness were formatted using a 5-point response scale (Supplemental Appendix S1), and dyspnea on exertion was assessed using a 4-point response scale. We excluded patients who did not complete all 3 survey items. Patients were considered to be markedly limited by gradient de la voie d'éjection du ventricule gauche (p = 0,405), ou à l'épaisseur du septum (p = 0,744) des patients. Trois à cinq ans après l'intervention chirurgicale, 236 patients (89 %) ont rapporté être en bonne ou en excellente santé. Environ 18 % (n = 48) et 8 % (n = 22) des patients de la cohorte présentaient encore une dyspnée à l'effort et une oppression thoracique, respectivement, après une marche de deux coins de rue ou moins. Un IDO plus élevé ne constituait pas un facteur prédictif indépendant pour un état de santé plus défavorable ou pour la présence de symptômes résiduels.

Conclusions : Le traitement d'une obstruction du sang par le ventricule gauche chez les patients présentant une CMH obstructive permet d'améliorer leurs symptômes, et 89 % des patients rapportent par la suite être en bonne ou en excellente santé. Les TRS préopératoires ne sont pas associés de manière significative au statut fonctionnel postopératoire après une myectomie septale.

dyspnea and/or chest tightness if they experienced such symptom(s) when walking at a normal pace for 2 blocks or less. Patients who did not acknowledge having exertional dyspnea or chest tightness were considered to be asymptomatic. The complete questionnaire used for follow-up has been detailed elsewhere, and the response rate of the entire survey is 68%.⁸ Our primary outcomes of interest were self-rated health status and levels of physical activity after hospital dismissal.

Baseline demographics and comorbidity profiles were obtained from medical records. Pre- and postoperative hemodynamic data were gathered from the most recent transthoracic echocardiograms prior to SM, and the early postoperative transthoracic echocardiogram before hospital dismissal. Measurements of the left ventricular (LV) ejection fraction (EF), resting left ventricular outflow tract (LVOT) gradient, septal thickness, extent of mitral valve regurgitation, right ventricular systolic pressure, LV end-diastolic dimension, and LV mass were collected.

Statistical analysis

Continuous variables and categorical variables are presented as median (interquartile range [IQR]) and count (percentile), respectively. To assess the association of ODI with baseline characteristics and hemodynamic features, we used the Spearman correlation test for continuous variables, and univariate logistic regression for binary variables. Assessment of general health and exertional symptoms were modeled as binary outcomes, which were regressed on ODI with multivariable logistic regression, with adjustment for age at surgery, sex, and baseline body mass index (BMI). Risk factors for persistent exertional symptoms were identified using univariate logistic regression models.

Results

Patient characteristics

Among the 264 patients included in the analysis, the ODI ranged from 0 to 52.6; 153 patients (58.0%) had SDB with an ODI Greater than or equal to 5, and in 53 (20.1%), SDB was moderate/severe with an ODI > 15. Preoperatively, 10 of the 53 patients received CPAP treatment. Four of them did

Variable	Overall (N $= 264$)	Normal $(n = 111)$	Mild SDB $(n = 100)$	Moderate/Severe SDB ($n = 53$)	Р					
Age at surgery, y	58.0 (49.0, 66.0)	55.0 (43.0, 63.5)	60.5 (50.8, 67.0)	59.0 (54.0, 69.0)	< 0.001					
Male	138 (52.3)	52 (46.8)	58 (58.0)	28 (52.8)	0.163					
NYHA class III/IV	231 (87.5)	93 (83.8)	88 (88.0)	50 (94.3)	0.040					
Body mass index, kg/m ²	29.4 (26.3, 33.4)	28.2 (25.1, 31.5)	29.8 (27.5, 33.6)	32.1 (28.3, 35.4)	< 0.001					
Diabetes	23 (8.7)	7 (6.3)	8 (8.0)	8 (15.1)	0.159					
Hypertension	138 (52.3)	55 (49.5)	51 (51.0)	32 (60.4)	0.057					
Dyslipidemia	176 (66.7)	71 (64.0)	65 (65.0)	40 (75.5)	0.034					
Atrial fibrillation	52 (19.7)	16 (14.4)	21 (21.0)	15 (28.3)	0.014					
Coronary artery disease	38 (14.4)	15 (13.5)	12 (12.0)	11 (20.8)	0.096					
Myocardial infarction	7 (2.7)	2(1.8)	1 (1.0)	4 (7.5)	0.019					

Table 1. Baseline characteristics of patients undergoing septal myectomy for obstructive hypertrophic cardiomyopathy, stratified by the severity of sleep-disordered breathing (SDB)

Values represent the median (interquartile range) for continuous variables and count (%) for categorical variables. Boldface indicates significance. NYHA, New York Heart Association.

not comply with or could not tolerate the therapy, and only 6 patients were using CPAP at the time of evaluation for SM. Baseline characteristics are presented in Table 1. The median (IQR) age of the entire cohort was 58.0 years (49.0-66.0), and patients with SDB tended to be older (P < 0.001). There was no sex-related difference in SDB prevalence. A greater ODI was significantly related to higher prevalence of severe heart failure symptoms (P = 0.040); 83.8% of patients without SDB, 88.0% of patients with mild SDB, and 94.3% of those with moderate/severe SDB were in New York Heart Association (NYHA) class III or IV prior to SM. Compared to those with a normal ODI, patients with an abnormal ODI had greater BMI (P < 0.001). The prevalence of obesity (BMI > 30.0 kg/m^2) was 37.8% (n = 42), 47.0% (n = 47), and 58.5% (n = 31) in patients with normal, mild, and moderate/ severe SDB, respectively. Additionally, SDB was significantly correlated with the presence of dyslipidemia (P = 0.034) and myocardial infarction (P = 0.019), which affected 66.7% (n = 176) and 2.7% of patients (n = 7), respectively. Diabetes, hypertension, and coronary artery disease were slightly more prevalent in patients with moderate/severe SDB, but these associations did not reach statistical significance. Atrial fibrillation, present in 19.7% of the entire cohort, was recorded in 28.3% of the patients with moderate/severe SDB, compared to 14.4% in normal patients (P = 0.014).

Hemodynamic features

The median (IQR) LVEF was 71.0% (68.0%-75.0%) prior to SM (Table 2). Resting LVOT gradient was not related to the severity of SDB (P = 0.285), but the interventricular septum was thicker in patients with a greater ODI (P = 0.017). Similarly, a greater ODI was linked to increased LV mass (P < 0.001), and this association remained significant after indexing to body surface area (P = 0.011). The severity of mitral valve regurgitation did not significantly differ across the strata (P = 0.462), but right ventricular systolic pressure was higher in patients with moderate/severe SDB (median [IQR], 40.5 mm Hg [30.5-47.5]) as compared to the others (P = 0.008).

Postoperatively, the LVEF of the entire cohort decreased to a median (IQR) of 68.0% (64.0%-71.0%) (P = 0.077). Both the septal thickness (median [IQR], 15.0 mm (12.0-18.0), P = 0.668) and the LVOT gradient at rest (median [IQR], 0.0 mm Hg (0.0-9.0), P = 0.423) were comparable between patients with vs without SDB. The LV end-diastolic dimension was slightly larger in patients with SDB (P = 0.011). But the LV mass (P = 0.099) as well as the LV mass index (P = 0.508) were independent of the ODI. Patients with moderate/severe SDB seemed to have higher right ventricular systolic pressure postoperatively, but this association was not statistically significant (P = 0.075).

Perceived health following SM

Perceived general health since surgery was good, very good, or excellent in 89.4% of the cohort (n = 236; Fig. 1). Presence of preoperative SDB did not significantly correlate with physical capacity following myectomy. As shown in Table 3, perceived general health was not related to ODI (odds ratio [OR] [95% confidence interval {CI}]), 0.995 (0.947, 1.045), P = 0.828). Accounting for age and sex, patients having a greater ODI were less likely to be asymptomatic during follow-up (OR [95% CI], 0.967 [0.940, 0.995], P = 0.022). But after further adjusting for baseline BMI, ODI was no longer a significant predictor of residual symptoms (P = 0.096). Similarly, a greater ODI was not an independent risk factor for marked limitation due to either exertional dyspnea (OR [95% CI], 1.000 [0.962, 1.040], P = 0.980) or chest tightness (OR [95% CI], 1.020 (0.967, 1.075), P = 0.468).

Discussion

SDB may complicate the clinical management of several cardiovascular diseases including HCM. In this study, we investigated the possible association between SDB (measured by ODI) and self-rated health post-procedure in patients undergoing SM for obstructive HCM. We found that the extent of LVOT gradient relief early postoperatively before hospital dismissal was generally comparable throughout the ODI spectrum. Important to note is that 3-5 years following SM, having SDB preoperatively was not an independent predictor of perceived health status and late physical capacity.

Treating SDB with CPAP may lead to reverse cardiac remodeling.⁹ In HCM patients with drug-refractory symptoms, CPAP has been proposed as an alternative to SM. Sengupta et al. reported 4 HCM patients who were treated with CPAP for drug-refractory symptoms, and all experienced improvement in exertional symptoms during the study observation period.¹⁰ However, significant LVOT obstruction (gradient > 30 mm Hg) remained in 2 of the 3 patients with LVOT gradients > 30 mm Hg prior to CPAP therapy. On

Table 2.	Preoperative and postoperative	hemodynamics of patients	s undergoing septal mye	ectomy for obstructive	hypertrophic ca	rdiomyopathy
stratified	by the severity of sleep-disorde	red breathing (SDB)				

Variable	Overall (N $= 264$)	Normal $(n = 111)$	Mild SDB $(n = 100)$	Moderate/Severe SDB ($n = 53$)	Р
Preoperative					
LVEF, %	71.0 (68.0, 75.0)	72.0 (68.5, 75.0)	72.0 (68.0, 75.0)	70.0 (66.0, 74.0)	0.089
Resting LVOT gradient, mm Hg	57.0 (25.0, 85.0)	58.0 (25.3, 85.0)	55.0 (24.0, 85.0)	49.5 (23.0, 85.0)	0.285
Septal thickness, mm	20.0 (17.0, 22.0)	19.0 (17.0, 22.0)	19.0 (17.0, 22.0)	21.0 (18.0, 24.0)	0.017
LV mass, g	275.0 (224.0, 344.3)	260.0 (211.8, 328.3)	279.5 (240.0, 350.5)	294.5 (250.0, 360.8)	< 0.001
LV mass index, g/m ²	140.0 (114.0, 173.8)	137.0 (106.5, 164.5)	139.5 (115.0, 172.5)	144.0 (128.0, 180.0)	0.011
LVEDD, mm	45.0 (41.0, 49.8)	46.0 (40.0, 49.0)	45.0 (42.0, 49.0)	44.0 (41.0, 50.0)	0.174
RVSP, mm Hg	34.0 (28.0, 41.0)	34.0 (28.0, 39.0)	32.0 (28.0, 41.3)	40.5 (30.5, 47.5)	0.008
MR, moderate or greater	128 (48.5)	57 (51.4)	44 (44.0)	27 (50.9)	0.462
Postoperative					
LVEF, %	68.0 (64.0, 71.0)	69.0 (65.0, 71.0)	67.0 (62.0, 70.0)	68.0 (64.0, 71.0)	0.077
Resting LVOT gradient, mm Hg	0.0 (0.0, 9.0)	0.0 (0.0, 9.0)	0.0 (0.0, 9.0)	0.0 (0.0, 9.0)	0.405
Septal thickness, mm	15.0 (12.0, 18.0)	14.0 (12.0, 18.0)	15.0 (12.0, 17.0)	15.0 (13.0, 18.0)	0.744
LV mass, g	236.0 (194.0, 289.0)	220.0 (189.0, 281.0)	253.0 (200.0, 294.0)	237.0 (202.0, 309.0)	0.099
LV mass index, g/m ²	119.0 (100.0, 143.0)	117.5 (97.8, 142.5)	123.0 (100.0, 141.0)	118.0 (105.5, 148.0)	0.508
LVEDD, mm	45.0 (41.0, 49.0)	44.0 (40.0, 48.0)	45.0 (42.0, 49.25)	45.0 (42.0, 50.0)	0.011
RVSP, mm Hg	36.0 (31.0, 43.0)	35.0 (30.0, 41.0)	35.0 (30.0, 41.0)	41.0 (32.0, 50.0)	0.075
MR, moderate or greater	22 (8.4)	13 (11.7)	7 (7.0)	2 (3.8)	0.524

Values are median (interquartile range) for continuous variables, and count (%) for categorical variables. Boldface indicates significance.

LV, left ventricular; LVEDD, LV end-diastolic dimension; LVEF, LV ejection fraction; LVOT, LV outflow tract; MR, mitral regurgitation; RVSP, right ventricular systolic pressure.

the contrary, findings of a nonsignificant association between the extent of abnormality during a preoperative nocturnal oximetry test and late postoperative functional status in the present study suggested that a history of preoperative SDB suggested by an abnormal overnight oximetry test may not be a crucial predictor of residual heart failure symptoms post-SM. The results suggest the importance of SM in treating HCM patients with advanced heart failure despite the presence of preoperative SDB. Although addressing SDB for the overall health of patients with obstructive HCM may be important, referral for SM should not be delayed for management of SDB. Presence of LVOT obstruction is an important predictor of symptom progression in patients with HCM.¹¹ For patients in whom septal reduction is advised, delaying surgery to relieve LVOT obstruction may result in advanced heart failure in approximately 5% per year.¹² Use of CPAP in a carefully selected subgroup of patients with both OSA and HCM may be effective, but the long-term benefit of CPAP therapy in relieving heart failure symptoms and improving LV function has not been established. Also important is recognition that the rate of long-term adherence to CPAP treatment varies widely, ranging from 46% to 83%.^{13,14} Indeed, in the present study, 40% of the patients



Figure 1. Late health status 3-5 years after septal myectomy for obstructive hypertrophic cardiomyopathy.

Table 3.	Odds ratio	(OR) of	late functional	status wit	h every	unit of	increase in	n oxygen	desaturation index
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	Model 1	Model 2	Model 2		
	OR (95% CI)	Р	OR (95% CI)	Р	
General state of health, good or better	0.995 (0.947, 1.045)	0.828	0.995 (0.946, 1.047)	0.851	
Asymptomatic	0.967 (0.940, 0.995)	0.022	0.976 (0.948, 1.004)	0.096	
Exertional dyspnea*	1.009 (0.973, 1.047)	0.621	1.000 (0.962, 1.040)	0.980	
Chest tightness*	1.025 (0.975, 1.078)	0.331	1.020 (0.967, 1.075)	0.468	

Model 1 was adjusted for age at surgery and sex. Model 2 was adjusted for age at surgery, sex, and body mass index using multivariate logistic regression models. Boldface indicates significance.

CI, confidence interval.

* Having shortness of breath or chest tightness on walking 2 blocks or less or climbing 1 flight of stairs or less.

discontinued CPAP therapy preoperatively due to poor tolerance.

Health-related quality of life can be significantly influenced by heart failure symptoms in patients with HCM. Previous series revealed that physical limitation as categorized by NYHA class was an independent risk factor for poor quality of life.¹⁵ Septal reduction therapy by myectomy ameliorates heart failure symptoms and can result in improved quality of life. Previously, Wells and colleagues reported improvement in physical capacity from NYHA class III/IV to class I/II in 96% of patients after SM for obstructive HCM.¹⁶ In a longer follow-up study, Nguyen et al. found that 80% of patients had improved perceived general health at a median follow-up of 5 years after SM.⁸ Our current investigation complements these findings, as 89% of patients reported good or excellent perceived health at 3-5 years after SM. The reasons for self-reported poor health are multifactorial. Previous studies have indicated the potential impact of SDB on quality of life. Poor quality of life has been linked to reduced sleep quality in HCM, independently of the presence of OSA.¹⁷ However, in our study, we did not observe a direct association between SDB and perceived general health.

Although LVOT obstruction is the primary cause of physical limitation in many patients with HCM, not all the patients experience complete relief of heart failure symptoms after gradient reduction by SM. As found in this study and a previous investigation,⁸ residual symptoms late postoperatively are rarely due to persistent LVOT obstruction. Compared to asymptomatic patients, symptomatic patients had a comparable postoperative LVOT gradient. Rather, we found that persistent symptoms after myectomy were associated with certain risk factors, such as greater BMI. This finding is in line with previous findings by Smith and colleagues, who found greater BMI to be an independent predictor of impaired exercise capacity in patients with obstructive HCM.¹⁸ Greater BMI is also a risk factor for reduced long-term survival in patients undergoing SM for obstructive HCM. However, despite the correlation between increased BMI and SDB, the latter is not a predictor of the length of survival post-procedure.

The impact of SDB on the physical fitness of patients with HCM is unclear. Indeed, BMI and SDB are closely tied and may interact with each other. Development of OSA increases the risk of subsequent weight gain and new-onset visceral obesity,^{19,20} and weight gain predicts an increase in the severity of SDB.²¹ Intentional weight loss has been linked to

improvement in OSA,²¹ and vice versa. Chin et al. suggested that correction of SDB by CPAP may reduce visceral fat accumulation.²² Our data confirm a strong correlation between BMI and SDB. After adjustment for age and sex, SDB remained significantly associated with late residual symptoms during follow-up. However, this association was significantly confounded by BMI. Despite the fact that losing weight is believed to increase fitness level, the effectiveness of CPAP in improving physical capacity in patients having SM requires further investigation.

Study Limitations

A limitation of this study is its reliance on overnight pulse oximetry as opposed to polysomnography, which is a more comprehensive assessment of SDB. Overnight pulse oximetry cannot be used to distinguish central and OSA. However, overnight pulse oximetry is relatively easily obtained, more affordable, and provides generally consistent results compared to polysomnography.^{5,6,23} Although polysomnography is more accurate in diagnosing SDB, we have previously shown that 96% of HCM patients with ODI greater than 5 on nocturnal oximetry were confirmed to have OSA by polysomnography.⁵

A second limitation of this study is that preoperative physical capacity was estimated subjectively by NYHA class, as opposed to an objective measure such as peak oxygen consumption from cardiopulmonary stress testing. In clinical practice, cardiopulmonary stress tests are not employed regularly for patients with obstructive HCM and typical symptoms, especially those with advanced limitations. Third, we do not have data on which patients with SDB were treated, and how SDB treatment may have affected subjective perceptions of health status at 3 to 5 years after SM. This study analyzed only those patients who survived 3-5 years after SM and responded to the follow-up surveys. Therefore, results may be susceptible to possible response and survivor bias. However, survivor bias is likely minimal, as the survival rate at 5 years following SM for obstructive HCM is approximately 95% at our clinic.²⁴

Conclusions

Moderate or severe SDB (ODI > 15) was present in 20.1% of patients undergoing SM for obstructive HCM. The extent of SDB was significantly associated with the severity of heart failure symptoms before the operation but did not correlate with self-reported late health status or exertional limitations 3-5 years following operation.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2022.06.010.