Original Article

Improved Exercise Tolerance, Oxygen Delivery, and Oxygen Utilization After Transcatheter Aortic Valve Implantation for Severe Aortic Stenosis

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ABSTRACT

Background: Transcatheter aortic valve implantation (TAVI) represents an effective therapeutic procedure, particularly in patients with severe aortic stenosis. We hypothesized that the decreased afterload induced by TAVI would improve exercise capacity by enhancing oxygen uptake in working muscles.

Methods: A standardized exercise test was performed in patients with severe aortic stenosis the day before TAVI and within 5 days thereafter. The main study endpoint was the workload achieved during a 5-minute standardized exercise test. Using electrical cardiometry and near-infrared spectroscopy, we explored and compared the changes in cardiac index (CI), as well as muscular and cerebral tissue oximetry, during the 2 exercise tests.

RÉSUMÉ

Contexte : Le remplacement valvulaire aortique par cathéter (TAVI) représente une procédure thérapeutique efficace, en particulier chez les patients présentant une sténose aortique sévère. Nous avons émis l'hypothèse que la diminution de la postcharge induite par le TAVI améliorerait la capacité à l'effort en favorisant la consommation d'oxygène des muscles travaillant.

Méthodes : Un test d'effort standardisé a été réalisé chez des patients souffrant de sténose aortique sévère la veille de l'intervention TAVI et dans les 5 jours qui ont suivi. Le principal critère d'évaluation de l'étude était la charge de travail atteinte lors d'un test d'effort standardisé de 5 minutes. En utilisant la cardiométrie électrique et la spectroscopie proche infrarouge, nous avons exploré et comparé les

Aortic stenosis (AS) is the most prevalent valvular disease in developed countries and affects up to 5% of people over the age of 75.[1] Along the pathophysiological time course of AS, the initial increase in afterload is compensated by left ventricular concentric hypertrophy that allows adaptation of the cardiac output (CO) to varying metabolic needs.[2] At later stages, the remodeled left ventricle is no longer able to compensate for the increased hemodynamic load that results from progressive aortic valve obstruction as well as atherosclerosis and medial elastocalcinosis.[3] These morphologic

changes are associated with limited exercise capacity, reflecting the inability to generate sufficient CO to match oxygen consumption within working skeletal muscles.[3]

In this study, we hypothesized that the immediate reduction in hemodynamic load following transcatheter aortic valve implantation (TAVI) would result in improved exercise capacity owing to increased tissue oxygen availability. Therefore, we undertook a prospective study aiming to (i) describe the changes in exercise capacity occurring before and shortly after TAVI and (ii) compare—pre- vs post-TAVI—systemic hemodynamic parameters and tissue oxygen utilization using electrical cardiometry (EC) and near-infrared spectroscopy (NIRS).

Methods

This was a single-center prospective study. All patients with severe AS undergoing TAVI between January 2017 and September 2018 at the Geneva University Hospitals, Switzerland, were eligible for inclusion. Patients who were unable to perform the exercise stress test, who had structural

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Results: Thirty patients completed the study protocol. Compared with the pre-TAVI period, patients achieved a higher median workload after TAVI (316 Joules [interquartile range {IQR}: 169−494] vs 190 Joules [IQR: 131−301], *P* = 0.002). Baseline CI increased from 2.5 l/min per m^2 (IQR: 2.1−2.9) to 2.9 l/min per m^2 (IQR: 2.5−3.2; *P* = 0.009), whereas CI at the end of the exercise test increased from 4.5 l/min per m^2 (IQR: 3.4−5.3) to 4.7 l/min per m^2 (3.4−6.4; *P* = 0.019). At the end of the exercise test, cerebral tissue oximetry increased from 70% (IQR: 65−72) to 74% (IQR: 66−78), and muscle tissue oximetry increased from 62% (IQR: 58−65) to 71% (65−74; *P* = 0.046 and *P* < 0.001, respectively).

Conclusions: Early improvement of exercise capacity after TAVI is associated with increased CI and better oxygen utilization in the brain and skeletal muscles.

changements de l'index cardiaque (IC), ainsi que l'oxymétrie des tissus musculaires et cérébraux, pendant les 2 tests d'effort.

Résultats : Trente patients ont terminé le protocole d'étude. Par rapport à la période pré-TAVI, les patients ont atteint une charge de travail médiane plus élevée après le TAVI (316 Joules [intervalle interquartile (IIQ) : 169-494] contre 190 Joules [IIQ : 131-301], *p* = 0.002). L'IC de base est passé de 2,5 l/min par m^2 (IIQ : 2,1-2,9) à 2,9 l/min par m^2 (IIQ : 2,5-3,2 ; *p* = 0.009), tandis que l'IC à la fin du test d'effort est passé de 4,5 l/min par m^2 (IIQ : 3.4-5.3) à 4,7 l/min par m^2 (3,4-6,4 ; *p* = 0,019). À la fin du test d'effort, l'oxymétrie du tissu cérébral est passée de 70 % (IIQ : 65-72) à 74 % (IIQ : 66-78), et l'oxymétrie du tissu musculaire est passée de 62 % (IIQ : 58-65) à 71 % (65-74; *p* = 0,046 et *p* < 0,001, respectivement).

Conclusions : L'amélioration précoce de la capacité d'exercice après le TAVI est associée à un IC accru et à une meilleure utilisation de l'oxygène au niveau du cerveau et des muscles squelettiques.

heart disease other than AS, who had unstable ischemic heart disease requiring combined percutaneous coronary intervention, or had a previous intervention on the aortic valve were excluded. The local ethics committee had approved the Geneva TAVI registry, which is part of a Swiss prospective registry (NCT01368250). All patients provided written informed consent for participation. The TAVI procedure has been previously described in detail, and the exercise test was part of the routine pre-intervention workup.[4]

The exercise test was performed the day before TAVI and 3 to 5 days post-TAVI. It was conducted according to a standardized protocol using a leg ergometer (THERA-Trainer mobi 540, Medica Medizintechnik, Hochdorf, Germany) designed for disabled persons. The test entailed a 2-minute warm-up, a 5-minute incremental exercise, and a 5-minute recovery period. The patients were instructed to pedal at a regular pace (>50 cycles/min) while the ramp resistance was gradually increased to achieve their safe limit of exercise capacity. The test was interrupted whenever the patient felt exhausted (Borg dyspnea scale >5/10), experienced chest pain, dizziness, hypotension, or a decrease in pulsed oxygen saturation (SpO$_2$, ≥3%).

Patients were equipped with a multiparameter hemodynamic monitor (Philips IntelliVue X2, Amsterdam, Netherlands) to measure mean arterial pressure (MAP), heart rate (HR), SpO$_2$, and respiratory rate (RR) every minute. Stroke volume was measured by EC to analyze the changes in transthoracic impedance created by pulsatile blood flow (ICON, Osypka Medical, La Jolla, CA).[5] Four skin sensors were placed on the left side of the neck and thorax, and a current field was longitudinally applied across the left part of the chest by means of a constant low-amplitude, high-frequency alternating current. Stroke index (SI), cardiac index (CI), and systemic oxygen delivery index (DO$_2$I) were derived using standard formulas:

$$SI = \text{stroke volume} / \text{body surface area};$$

$$CI = SI \times HR; \text{ and}$$

$$DO_2I = 1.39 \times Hb \text{ (hemoglobin)} \times SpO_2 \times CI.$$

Using the NIRS Foresight device (CAS Medical Systems, Branford, CT), changes in cerebral and muscular tissue oximetry (ctSO$_2$ and mtSO$_2$, respectively) were continuously monitored. One NIRS emitter-detector pair was placed over the left prefrontal lobe, and a second NIRS emitter−detector pair was placed over the soleus muscle of the right calf to assess cerebral and muscular tissue oxygenation, respectively. The differences in the intensity of near-infrared waves emitted at 4 different wavelengths by a laser source are analyzed at a scanning frequency of 100 Hz. Differences in their respective absorptions by oxygenated and reduced hemoglobin are derived using algorithms based on the Lambert−Beer law.[6]

These hemodynamic and oxygen-delivery data were recorded at rest (baseline) and at the end of the exercise test. Baseline clinical characteristics as well as outcomes and complications of TAVI were recorded for all patients according to the Valve Academic Research Consortium definitions.[7]

The main study endpoint was the maximal workload (W) displayed in Joules (J) on the ergometer at the end of the exercise test. To assess the functional responsiveness to TAVI, and considering a minimum clinically important difference (MCID) in physical performance for submaximal exercise tests,[8,9] patients were categorized as "low-responders" or "high responders" if the post-TAVI gain in W was ≤ or > 25%, respectively, of pre-TAVI values. Secondary endpoints were the changes in respiratory and hemodynamic variables (RR, SpO$_2$, HR, MAP, SI, and CI) as well as in DO$_2$I, ctSO$_2$, and mtSO$_2$.

In a preliminary investigation to assess the feasibility and safety of the physiological measurements (n = 15), patients achieved a mean (±SD) W of 168 (±73) J before TAVI and 207 (±55) J after TAVI. The 23% gain in W between the 2 measurement periods largely exceeded the MCID for changes in similar aerobic tests.[10] Hence, to detect a mean difference of 39 J between pairs, we estimated a required sample size of 30 participants to achieve a power of 80% and a level of significance of 5%.

Stata 15 (StataCorp, College Station, TX) was used for statistical analysis. Patient characteristics were expressed as median and interquartile range 25%−75% for continuous
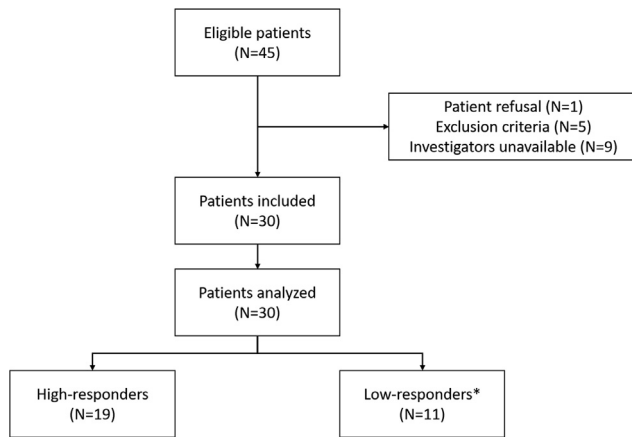
Figure 1. Flow chart. * < 25% exercise load increase (post- vs pre-transcatheter aortic valve implantation).

variables. Categorical variables were expressed as frequency (%). Overall variations in continuous variables were assessed using Friedman's test. Difference between medians was calculated using a Wilcoxon signed-rank test, and results were given as median and interquartile range. The Kruskal-Wallis test was used when more than 2 groups were compared. The Mann-Whitney U test was used to test for significance in subgroup analysis, and a quantile regression was performed to estimate 95% confidence intervals. The relationship between the changes in W and in hemodynamic response between the 2 exercise tests was analyzed using Pearson coefficients ($r < 0.2$, 0.2–0.4, 0.41–0.6, 0.61–0.8, and > 0.8, corresponding to poor, moderate, good, very good, and excellent correlation, respectively). A P value of < 0.05 was considered statistically significant.

Results

Over a 21-month period, 45 patients were considered for inclusion, and 30 were finally analyzed (Fig. 1). Study patients had a median age of 86 years (79–89), and a median EuroScore of 7.9 (5.3–14.4); women and men were equally distributed, with a median hospital stay of 6 days (Table 1).

Patients achieved a higher median W after TAVI (316 J [169–494] vs 190 J [131–301]; $P = 0.002$), whereas the duration of the exercise test was similar (300 seconds [300–300] vs 300 seconds [240–324], $P = 1.000$). Eleven patients (37%) were categorized as low-responders and 18 (63%) as high-responders. Similar demographic, clinical, biological, and interventional characteristics were found in the 2 subgroups (Table 1). There was no difference in exercise capacity between these subgroups in the pre-TAVI period ($P = 0.590$).

The results of hemodynamic as well as systemic and regional oxygen delivery variables before and after TAVI are summarized in Table 2. Resting SpO$_2$, SI, CI, and DO$_2$I were all significantly higher in the post-TAVI period (with a median increase of 2%, 24%, 16%, and 24%, respectively), whereas MAP was lower (with a median decrease of 10%). Baseline ctSO$_2$, HR, and RR were unchanged. Between the pre- and post-TAVI periods, there was a significant increase in the differences in SpO$_2$, ctSO$_2$, and mtSO$_2$ at

baseline vs at the end of the exercise test (Supplemental Table S1).

Compared with pre-TAVI testing, the post-TAVI exercise test was characterized by significant increases in median SpO$_2$, CI, DO$_2$I, ctSO$_2$, and mtSO$_2$, whereas HR, MAP, and RR did not differ between the 2 periods (Table 2).

The changes in exercise W between pre-and post-TAVI periods correlated with the changes in CI and in DO$_2$I between these study periods ($r = 0.60$ and 0.63, respectively).

After TAVI, high-responders presented lower HR and RR, as well as higher MAP and ctSO2 at rest, compared with low-responders (Supplemental Table S2). As shown in Figure 2, at the end of the exercise test, high-responders presented larger increases in the following: HR (+33 beats per minutes [26–37] vs +6 beats per minute [4–10], $P < 0.001$); CI (+3.1 l/min per m^2 [1.8-–4.3] vs +0.8 l/min per m^2 [0.2–1.2], $P < 0.001$); DO$_2$I (+524 ml/min per m^2 [318–756] vs +120 ml/min per m^2 [24–208], $P < 0.001$); and ctSO$_2$ (+4% [2–6] vs +1% [1–2], $P = 0.001$).

Discussion

In this prospective clinical study, the main functional benefit of TAVI was expressed by the patient's ability to increase their exercise W by more than 60%, within days after the procedure. Reducing the left ventricular afterload with TAVI in patients with severe AS was associated with increased CO and systemic O$_2$ delivery, which in turn facilitated tissue oxygen uptake both in working skeletal muscles and in the brain, as reflected by higher regional tissue oximetric values. In the early seventies, Lee et al. reported similar systemic hemodynamic improvements with reduced ventricular preload that closely matched the exercise-induced increase in oxygen consumption in 12 patients, 3 to 6 months following surgical aortic valve replacement.[11]

As a maximal cardiopulmonary exercise test was deemed inappropriate and potentially dangerous in elderly patients with severe symptomatic AS,[12] we performed a submaximal bicycle exercise test that was safely conducted in all patients. As it integrates cardiopulmonary and musculoskeletal systems functioning, this test appears suitable for baseline screening, follow-up assessment, and research purposes, particularly among frail subjects.[13]

With NIRS, the differences in optical absorption spectra between oxygenated and deoxygenated hemoglobin/myoglobin states were continuously analyzed, assuming an arterial-to-venous ratio of 25:75 that enabled a valuable estimation of the regional DO$_2$/VO$_2$ balance without requirement for baseline calibration.[6] Hence, during the exercise stress test, the changes in ctSO$_2$ and mtSO$_2$ reflected the acute adaptation of cerebral and muscular oxidative activities along the enhanced regional blood flow.[14,15]

With EC, the changes in blood conductivity generated during each cardiac cycle were analyzed using a modified thoracic impedance algorithm to assess the changes in cardiac stroke volume. For CO measurements, the gold standard thermodilution method with a pulmonary artery catheter was considered too invasive and even hazardous in patients with critical AS. Despite its inability to accurately measure the absolute CO values, the EC technique offered the advantages of being noninvasive, being operator independent, and

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Table 1. Patients and procedural characteristics based on Valve Academic Research Consortium-2 recommendations

Characteristic	All (N = 30)	Low-responders* (n = 11)	High-responders (n = 19)	P
Age (y)	86 (79−89)	86 (79−88)	85 (81−90)	0.880
BMI (kg/m^2)	26.6 (22.5−32.0)	25.0 (20.9−29.7)	27.4 (22.5−32.4)	0.464
Sex (female)	15 (50)	4 (36)	11 (58)	0.264
Ischemic heart disease	18 (60)	5 (45)	13 (68)	0.224
Congestive heart failure	7 (23)	3 (27)	4 (21)	0.703
Hypertension	23 (77)	8 (73)	15 (79)	0.703
Diabetes mellitus	7 (23)	4 (36)	3 (16)	0.207
Chronic renal failure	14 (47)	7 (64)	7 (34)	0.163
Cerebral vascular disease	7 (23)	3 (27)	4 (21)	0.703
Peripheral vascular disease	5 (17)	3 (27)	2 (11)	0.244
Chronic obstructive pulmonary disease	6 (20)	2 (18)	4 (21)	0.852
STS risk score	6.0 (3.3−7.6)	6.1 (4.0−13.4)	5.8 (3.2−6.5)	0.254
EuroScore	7.9 (5.3−14.4)	7.3 (5.2−16.1)	8.5 (5.3−14.4)	0.846
Left ventricular ejection fraction (%)	65 (55−65)	65 (55−65)	65 (53−65)	0.852
Hemoglobin (g/l)	128 (117−138)	127 (115−140)	128 (117−132)	0.590
Creatinine (μmol/l)	86 (78−104)	97 (77−113)	84 (78−101)	0.344
Frailty parameters				
Gait speed (m/s)	0.8 (0.7−0.9)	0.8 (0.7−0.9)	0.7 (0.5−1.1)	0.463
Grip strength (kg)	24 (21−31)	22 (21−28)	26 (20−33)	0.355
Unintentional weight loss	5 (17)	2 (18)	3 (16)	0.868
Recent fall	14 (47)	5 (46)	9 (47)	0.921
Poor mobility	4 (13)	1 (9)	3 (16)	0.673
Serum albumin (g/l)	43 (40−43)	41 (36−44)	43 (40−43)	0.632
MMSE	29 (26−30)	29 (28−30)	27 (25−30)	0.150
Procedural aspects				
Duration of intervention (min)	101 (78−131)	110 (100−160)	86 (71−131)	0.085
Correct device performance	29 (97)	10 (91)	19 (100)	0.189
Overall device success	28 (91)	10 (91)	18 (95)	0.691
Valve model (Evolut-R/ Evolut-Pro/ Edwards)	16 (53)/ 12 (40)/ 2 (7)	5 (46)/ 4 (36)/ 2 (18)	11 (58)/ 8 (42)/ 0 (0)	0.366
Clinical outcome				
Hospital length of stay (d)	6 (5−8)	5 (5−15)	6 (5−7)	0.931
Complications at discharge	10 (33)	4 (36)	6 (32)	0.792
New permanent pacemaker implantation	6 (20)	1 (9)	5 (26)	0.264
Stroke and transient ischemic attack	1 (3)	1 (9)	0 (0)	0.189
Acute kidney injury	0 (0)	0 (0)	0 (0)	N/A
Bleeding	5 (17)	2 (18)	3 (16)	0.868
Vascular complication	2 (7)	1 (9)	1 (5)	0.691

Data are presented as number (%) or median (interquartile range: 25%−75%).

BMI, body mass index; MMSE, mini mental state examination; N/A, not applicable; STS, Society of Thoracic Surgeons.

*< 25% exercise load increase (post- vs pre-transcatheter aortic valve implantation).

having a fast response time for detection of acute hemodynamic changes.[16] The combined application of EC and NIRS allowed trend monitoring of both circulatory blood flow and tissue O_2 utilization and provided some insight into flow-metabolic coupling during a submaximal exercise test.[5,17]

In this study, the frail phenotype of elderly patients with severe AS was characterized by poor exercise tolerance that was

Table 2. Hemodynamic and tissue oximetric data at baseline and at the end of the exercise test, before and after TAVI

	Global	Baseline			At end of exercise test		
	P^*	Pre-TAVI	Post-TAVI	$P^\dagger$	Pre-TAVI	Post-TAVI	$P^\dagger$
HR (bpm)	0.001	71 (65−76)	71 (65−76)	0.578	95 (78−104)	94 (85−102)	0.422
MAP (mm Hg)	0.038	94 (82−103)	85 (78−92)	0.023	111 (89−127)	107 (94−116)	0.405
SpO$_2$ (%)	0.047	96 (96−98)	98 (96−99)	0.010	96 (94−97)	99 (97−100)	0.001
RR (cpm)	0.228	15 (12−21)	14 (12−20)	0.931	25 (22−28)	23 (19−26)	0.256
SI (ml/m^2)	< 0.001	33 (31−42)	41 (37−46)	0.006	47 (40−52)	54 (43−63)	0.032
CI (l/min per m^2)	< 0.001	2.5 (2.1−2.9)	2.9 (2.5−3.2)	0.009	4.5 (3.4−5.3)	4.7 (3.4−6.4)	0.019
DO$_2$I (ml/min per m^2)	< 0.001	403 (357−500)	501 (373−578)	0.008	750 (564−902)	816 (646−1073)	0.008
ctSO$_2$ (%)	< 0.001	71 (66−76)	68 (65−76)	0.442	70 (65−72)	74 (66−78)	0.046
mtSO$_2$ (%)	0.032	68 (61−70)	63 (61−69)	0.026	62 (58−65)	71 (65−74)	< 0.001

Data are presented as median (interquartile range: 25%−75%).

bpm, beats per minute; CI, cardiac index; cpm, counts per minute; ctSO2, cerebral tissue oximetry; DO2I, indexed oxygen delivery; HR, heart rate; MAP, mean arterial pressure; mtSO2, muscular tissue oximetry; RR, respiratory rate; SI, stroke index; SpO2, pulsed oxygen saturation; TAVI, transcatheter aortic valve implantation.

* Overall variation according to Friedman's test.

† Difference between medians according to Wilcoxon signed-rank test.
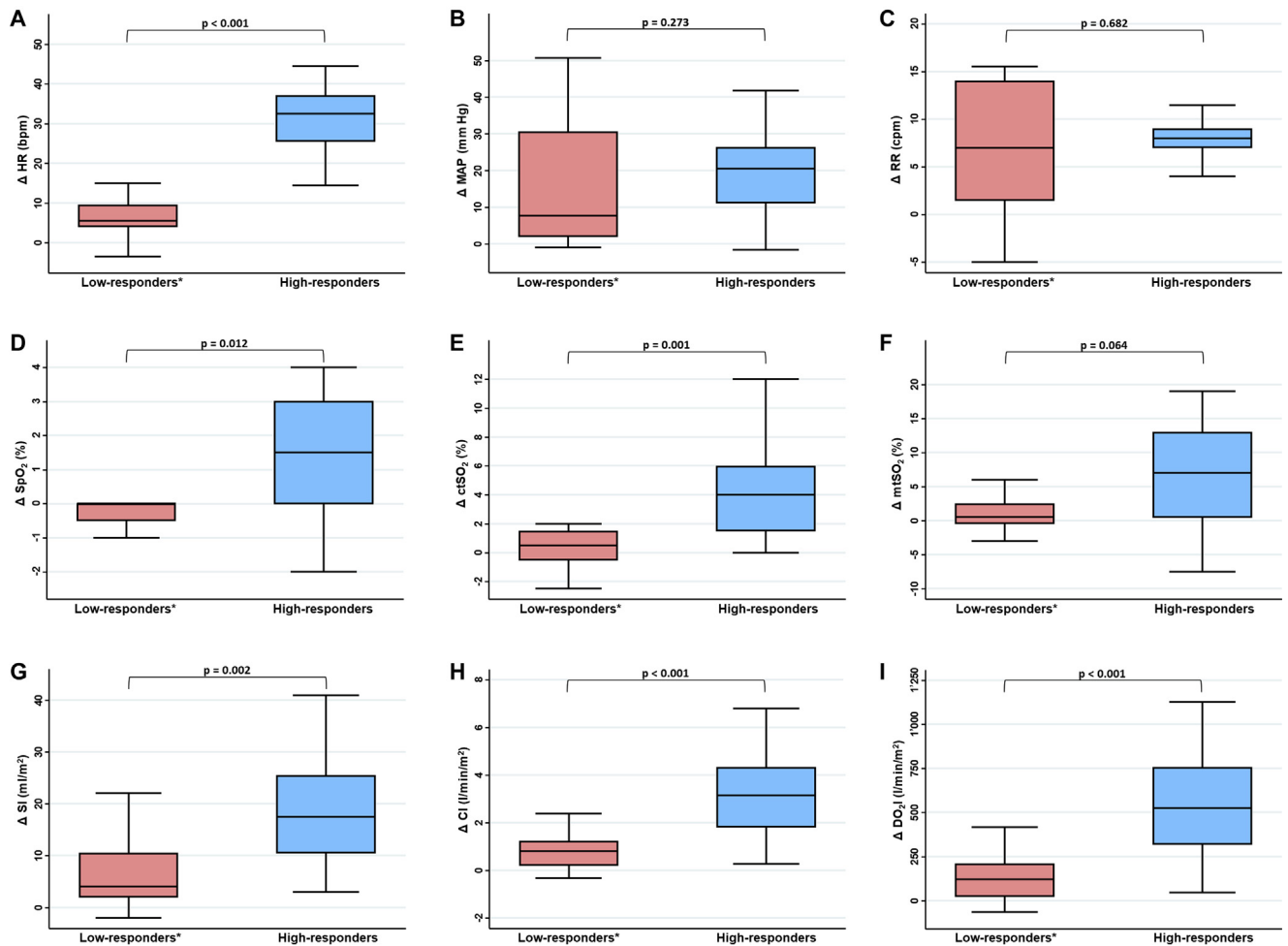
Figure 2. Differences at the end of the exercise test between low- and high-responders after transcatheter aortic valve implantation (TAVI). (**A**) heart rate (HR); (**B**) mean arterial pressure (MAP); (**c**) respiratory rate (RR); (**D**) pulsed oxygen saturation (SpO$_2$): (**E**) cerebral tissue oximetry (ctSO$_2$); (**F**) muscular tissue oximetry (mtSO$_2$); (**G**) stroke index (SI); (**H**) cardiac index (CI); (**I**) indexed oxygen delivery (DO$_2$I). * < 25% exercise load increase (post- vs pre-TAVI).

related to 3 main mechanisms[18−21]: (i) inability to increase CO owing to the obstructed aortic valve; (ii) blunting of the hyperemic muscular response owing to impaired endothelium function and sustained activation of the sympathoadrenergic and renin-angiotensin-aldosterone systems; and (iii) the chronic loss of muscle mass coupled with predominant fast-twitch skeletal muscle cells that are characterized by low mitochondria volume density and prone to fatigue during sustained or repeated contractions.[22] Besides muscle hypo-perfusion, the other key factor limiting exercise capacity was the impaired muscular oxidative capacity leading to earlier initiation of anaerobic metabolism during exercise. Previous studies have established a close relationship between oxygen availability in skeletal muscles and aerobic capacity in patients with heart failure, with lower mtSO$_2$ values being associated with low peak O$_2$ consumption and poor exercise tolerance.[23−26] In these patients, the limited increase in CO during exercise is preferentially distributed to active skeletal muscles, and despite elevated blood pressure, the cerebral blood flow is "sacrificed" as reflected by the lower ctSO$_2$ values.

In this study, TAVI-induced fall in left ventricular elastance resulted in more efficient myocardial working conditions that were translated into higher resting CI, SpO$_2$, and DO$_2$I, along with lower MAP. During the submaximal exercise test, higher Ws were paralleled by larger increases in CI, DO$_2$I, mtSO$_2$, and ctSO$_2$ compared with the pre-TAVI period. Coupling between systemic oxygen delivery and muscular performances was supported by the good correlation between TAVI-induced gain in DO$_2$I and exercise W. At the tissue level, the enhanced oxygen delivery in the working muscles and the brain both exceeded the metabolic needs and therefore resulted in higher mtSO$_2$ and ctSO$_2$ compared with the pre-TAVI period. Such improvements in oxygen perfusion and diffusion through the skeletal muscles are considered essential to support faster rates of oxidative phosphorylation and to reduce the reliance on anaerobic glycolysis.[27] Attenu-ation of sympathetic hyperactivity associated with higher resting CI after TAVI likely contributed to restoration of the hyperemic response to muscular contractions.[28]

Besides the procedural success (90%), we assessed the early functional success of TAVI by reporting the W gain during

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the exercise test. As previously reported, the MCID in physical performance following various training modalities lies within a 5%−10% range and has been shown to help discriminate between nonresponders and responders. In consideration of some technical measurement errors, the learning effect with repeated testing, as well as the lack of current validation for the 5-minute low-grade exercise, we selected a higher cutoff, at 25% W gain, to discriminate between low and high-responders. Interestingly, the larger Ws sustained in high-responders were paralleled by greater exercise-induced systemic hemodynamic response (HR, CI), along with increased oxygen availability (DO_2I), whereas low-responders exhibited marginal increases in CI and in DO_2I. In line with these findings, an average 50% gain in walking distance has been reported at 6 months after TAVI using the 6-minute walk test. However, 25%−28% of patients also failed to exhibit functional improvement despite successful procedures, and these low-responders were at higher risk of mortality and adverse cardiovascular events over the ensuing 4 years.[29,30] In addition to muscular weakness, preexisting diastolic and systolic ventricular dysfunction likely influence the early physical performance following TAVI. The burden of myocardial fibrosis and scarring assessed by cardiac magnetic resonance and histopathologic examination has been shown to have a large impact on long-term survival, predict adverse reverse ventricular remodelling, and therefore limit functional recovery over 6−12 months after TAVI.[31,32]

Based on these results demonstrating exercise limitations related to muscle oxygen delivery, sedentary behavior, and frailty status, we hypothesize that hypoperfusion-related skeletal muscle abnormalities could be partially reversed with the initiation of an exercise intervention program to support enhanced muscular blood flow in the early period after TAVI. Indeed, in frail subjects and in patients with heart failure, exercise training combining different modalities (ie, endurance, resistance, stretching) and involving different muscle groups (respiratory and locomotor muscles) has been shown to induce sustained improvements in cardiopulmonary capacity that are associated with reduced muscle fatigability, increased lean muscle mass, and a "reversed" shift from fast-twitch glycolytic to slow-twitch oxidative fibers with increase muscular mass.[33] Preliminary data also suggest that implementation of an 8-week home-based program of combined endurance/resistance exercises within 6 months after TAVI results in improved peak oxygen uptake (mean gain of 25%) with a higher lactate threshold, greater muscle strength, and improved quality of life.[34] Likewise, Völler et al. reported that early post-TAVI initiation of a 3-week hospital-based cardiac rehabilitation program coupled with psychological support results in enhanced maximal exercise capacity (~30% W gain) and greater 6-minute walking distance (+11%).[35] This type of integrative rehabilitation approach would be particularly helpful in maintaining independence in daily life activities and promoting participation in sociocultural life in many of these frail patients.

The present study has several limitations. First, as an exploratory substudy, our small population sample did not allow a valuable analysis of factors implicated in the improved exercise tolerance following TAVI. Although high- and low-responders did not differ regarding age, presence of cardiopulmonary disease, and occurrence of periprocedural complications,

unrecorded markers of advanced myocardial fibrosis may preclude functional benefits in the early period following TAVI. Second, the functional and hemodynamic assessments were limited to the hospitalization period and were not repeated 3 or 6 months after TAVI. This valuable information would help to ascertain the early functional benefit of the TAVI procedure and evaluate the effects of drug intervention or rehabilitation programs in patients with an initially poor functional response. Third, given the absence of calibration and utilization of a different algorithm, NIRS tissue oximetric values obtained with different devices cannot be used interchangeably.[14] However, good repeatability within subjects (< 2.3%), particularly with the Foresight monitor, comes at the expense of low sensitivity.[36] Finally, the changes in transvalvular flow pattern before/after TAVI (turbulent/laminar) could potentially influence calculation of CO based on the changes in erythrocyte orientation during systole.[37] Teefy et al. recently reported clinically acceptable equivalence of EC compared to the thermodilution technique in nonobese patients with AS.[38] Following TAVI, the trend and changes in CI are more valuable data than absolute CI measurements, for clinical decision-making. Unfortunately, no study has provided trend analysis with comparative data between a reference dilution method and EC.

To the best of our knowledge, this is the first study that reports the early functional changes in patients treated with TAVI and describes the changes in systemic hemodynamics and tissue oxygen utilization based on noninvasive physiological monitoring tools during a standardized exercise test. Although exercise tolerance with systemic and muscular oxygen availability was improved in most patients within 3 to 5 days following TAVI, some patients failed to demonstrate early benefits. Further studies with larger numbers of patients are needed to confirm these results and establish the factors determining the lack of functional improvements.[39]

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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.2020.06.005.