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Transcatheter Aortic Valve Implantation Reduces Sympathetic Activity and Normalizes Arterial Spontaneous Baroreflex in Patients With Aortic Stenosis

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Objectives This study sought to measure muscle sympathetic nerve activity (MSNA) in patients with aortic stenosis (AS) before and after transcatheter aortic valve implantation (TAVI) and to compare MSNA with that of control patients.

Background TAVI is an emerging therapeutic option in patients with severe AS at high risk of open heart surgery. Whether patients with AS have increased sympathetic activity remains to be established, and the effects of TAVI on the sympathetic nervous system are also unknown.

Methods We prospectively enrolled 14 patients with severe symptomatic AS treated by TAVI. Fourteen control patients matched for age, body mass index, and unscathed of AS were also included. All patients underwent MSNA and arterial baroreflex gain assessment at baseline and 1 week after TAVI for AS patients.

Results Patients with AS had lower blood pressure (BP) levels, a significant increase in MSNA (61.0 ± 1.7 burst/min vs. 55.4 ± 1.4 burst/min; $p < 0.05$), and a decrease in arterial baroreflex gain (2.13 ± 0.14% burst/mm Hg vs. 3.32 ± 0.19% burst/mm Hg; $p < 0.01$) compared with matched control patients. The TAVI procedures induced an increase in BP associated with a significant decrease in MSNA (from 61.0 ± 1.7 burst/min to 54.1 ± 1.0 burst/min; $p < 0.01$) and was associated with a significant increase in arterial baroreflex gain (from 2.13 ± 0.14% burst/mm Hg to 3.49 ± 0.33% burst/mm Hg; $p < 0.01$).

Conclusions We report for the first time, through direct measurement of nerve activity, that patients with AS have increased sympathetic nervous system activity associated with a decrease in sympathetic baroreflex gain and that TAVI normalizes these parameters. This study provides evidence of a new beneficial effect of TAVI, namely, normalization of sympathetic nervous system hyperactivity.
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In developed countries, aortic stenosis (AS) is the most prevalent of all valvular heart diseases (1,2). Symptomatic patients have a dire outlook, with three-fourths dying within 3 years of symptom onset. Surgical aortic valve replacement is currently the gold standard treatment for patients with severe symptomatic AS (3,4). However, 33% of all patients 75 years and older with severe AS are not surgical candidates (5). In this context, transcatheter aortic valve implantation (TAVI) is an emerging therapeutic option in patients with AS at high risk of open heart surgery (6–9).Whether patients with AS have increased sympathetic activity remains to be established. As AS worsens, cardiac output is reduced, and this situation may increase sympathetic nervous system (SNS) activity as in patients with chronic heart failure (CHF). An increase in SNS activity may trigger or exacerbate many of the pathophysiological features associated with AS such as cardiac hypertrophy and decreased peripheral perfusion (mediated by both low cardiac output and systemic vasoconstriction). Moreover, sympathetic outflow stimulates renin release from the kidney and potentiates the described mechanisms (fluid and sodium retention promoting pulmonary congestion but also systemic vasoconstriction or cardiac failure). Finally, sympathetic stimulation increases heart rate, which shortens the diastolic filling period and may increase the risk of cardiac ischemia. Thus, increased SNS activity may represent an important risk factor for the progression and prognosis of AS patients. Sympathetic activation has been identified in patients with multiple cardiovascular conditions (i.e., arterial hypertension, CHF). In most cases, SNS activation is a marker of a poor prognosis, and therapeutic interventions leading to a decrease in SNS activity are usually associated with a beneficial outcome (i.e., beta-blockers in heart failure, hypertension, or ischemic heart disease). Until now, it has remained unknown whether sympathetic tone is increased in patients with AS, and, if so, which mechanisms are involved. Moreover, the effect of AS treatment on autonomic tone has never been studied adequately because sympathetic nerve activity and related reflexes have not been directly measured in this pathological condition. This question is clinically relevant because identification of increased sympathetic tone in AS patients could explain the progression and prognosis of this condition. Finally, it could be assumed that AS treatment that alleviates the obstruction of blood flow and eliminates afterload mismatch may normalize sympathetic activity and improve the prognosis of patients (9,10).

Abbreviations and Acronyms

AS = aortic stenosis
CHF = chronic heart failure
DBP = diastolic blood pressure
MAP = mean arterial blood pressure
MSNA = muscle sympathetic nerve activity
SNS = sympathetic nervous system
TAVI = transcatheter aortic valve implantation
TF = transfemoral

The present study was undertaken to determine whether AS is associated with an increase in sympathetic nerve activity as assessed directly by muscle sympathetic nerve activity (MSNA) recording. Thus, we aimed to investigate the role of sympathetic baroreflex function in the genesis of this elevated sympathetic tone. Finally, we also assessed MSNA and calculated sympathetic baroreflex function in AS patients before and after TAVI as well as in a control group of patients (without AS) matched for age and body mass index.

Methods

Patients. Between January and April 2011, we prospectively enrolled in this study high-risk patients with severe symptomatic AS (aortic valve area <1 cm^2 or 0.6 cm^2/m^2 of body surface area) treated by TAVI at the Rangueil University Hospital, Toulouse, France. Patients were considered at high risk of surgery on the basis of clinical judgment after multidisciplinary evaluation including cardiologists (interventional and noninterventional), cardiovascular surgeons, cardiovascular anesthesiologists, and geriatricians and on a quantitative assessment of the expected operative mortality by the Logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) (11) and on the Society of Thoracic Surgeons score (12). Patients treated by TAVI were selected following the recommendations of the position statement from the European Association for Cardio-Thoracic Surgery/European Society of Cardiology/European Association of Percutaneous Cardiovascular Interventions (4) and had a logistic EuroSCORE $>20\%$ or a Society of Thoracic Surgeons score $>10\%$, or other risk factors not covered by scores such as chest radiation, porcelain aorta, and liver cirrhosis. Extreme frailty precluding any invasive intervention, comorbidities limiting life expectancy to <1 year, coagulopathy, sepsis including active endocarditis, active digestive bleeding, and recent (<30 days) ST-segment elevation myocardial infarction were considered exclusion criteria for this study. At admission, all patients underwent coronarography and transthoracic echocardiography with measurement of all conventional parameters.

Control patients matched for age, body mass index, and without AS were also included.

The research protocol complies with the Declaration of Helsinki and was approved by the Toulouse University Hospital Human Research and Ethics Committee. Informed written consent was obtained from all participants.

Transfemoral TAVI. The retrograde transfemoral (TF) approach was used as the first option whenever possible. Both devices currently available during the study were implanted: the Edwards XT valve delivered by its NovaFlex catheter requiring a 16- or 18-F sheath (Edwards Lifesciences Inc., Irvine, California) and the third-generation Medtronic CoreValve ReValving System requiring an 18-F

sheath (Medtronic, Minneapolis, Minnesota). Procedures were performed in a catheterization laboratory, with patients under general anesthesia, with fluoroscopic and transesophageal echocardiography guidance. Details of patient selection for TAVI, choice of the device, access site selection, choice of surgical cutdown or percutaneous approach with pre-closing of the femoral artery were previously published (8), as well as technical aspects of the implantations (4,13–16).

Alternative approaches. The transapical approach was proposed when the TF approach was contraindicated with the Edwards prosthesis, most of the time because of unsuitable femoroiliac arterial anatomy for retrograde access. Procedures were performed in a catheterization laboratory, following technical standards previously detailed (4,17,18), using the ES valve and Ascendra system (Edwards Lifesciences Inc.). When the TF approach was contraindicated with the Medtronic CoreValve device and the left subclavian arterial anatomy was deemed suitable after appropriate screening, a left subclavian Medtronic CoreValve implantation was performed as previously described (19).

MSNA assessment. All patients underwent MSNA recording before and a week after TAVI. MSNA assessment was performed with patients in the supine position under carefully standardized conditions. MSNA allows a direct and dynamic evaluation of post-ganglionic SNS activity. As previously described (20), MSNA was recorded by a tungsten microelectrode (shaft diameter, 200 μm) inserted selectively in sympathetic efferent fibers around the peroneal nerve. A subcutaneous reference electrode is inserted 2 to 3 cm away from the recording microelectrode (Fig. 1). Once positioned, the recording microelectrode allows the collection of the electrical activity of sympathetic contingent, which appears as a sequence of electrical bursts. In the absence of sensory stimuli and muscle movement, the potential difference measured between the 2 microelectrodes is the sum of the electrical activity of orthosympathetic fibers of the peripheral muscle vessels. The neural signal is amplified, filtered, rectified, and integrated to obtain a neurogram identifying trains of SNS discharge visualized as a sequence of bursts (Fig. 1D). SNS activity can then be expressed as bursts per min. Heart rate was measured continuously by electrocardiography (AD Instruments, Castle Hill, New South Wales, Australia). Blood pressure (BP) was measured continuously using the Finometer system (Finapress Medical System BV, Amsterdam, the Netherlands). Oxygen saturation was monitored with a pulse oximeter (AD Instruments), and respiratory rate was assessed continuously with a thoracic belt (Pneumotrace II, UFI, Morro Bay, California).

Arterial baroreflex gain determination. The spontaneous arterial baroreflex gain was calculated during the MSNA exploration. Assessment of spontaneous arterial baroreflex

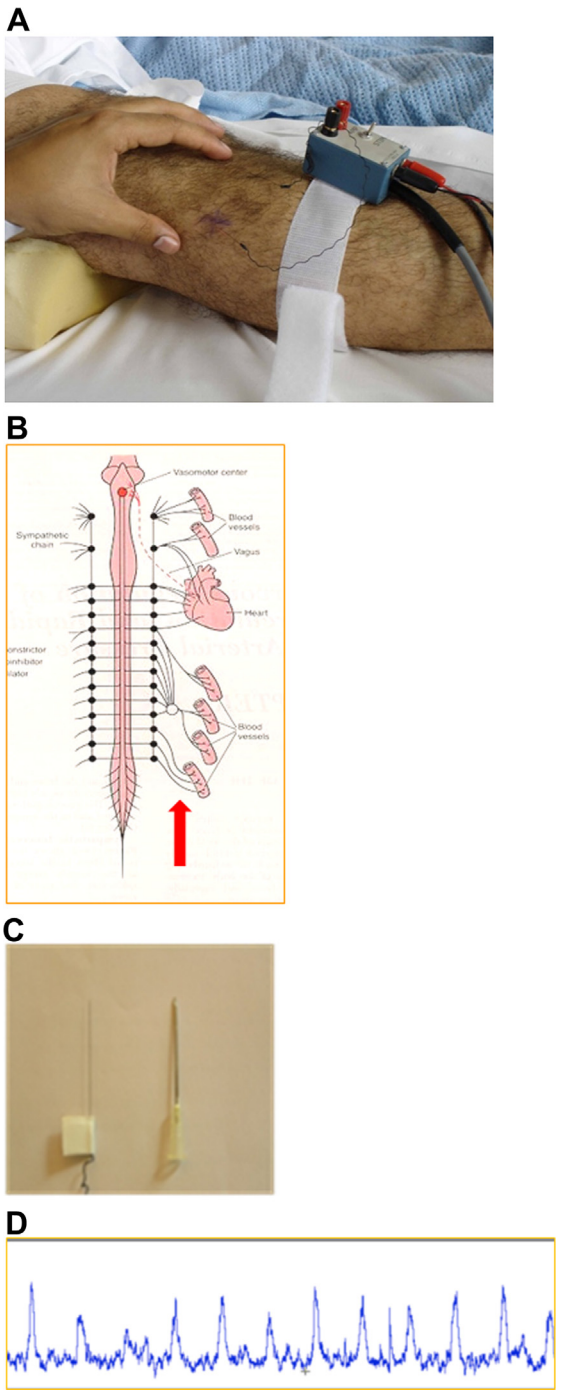

Figure 1. Microneurography Recording

The different steps of microneurography recording are shown. The objective is to record the electrical depolarization of sympathetic nervous system fiber contained in fibular nerves. **(A)** Demonstration of recording electrode inserted in the muscle fascicle of the peroneal nerve plus a reference electrode inserted 2 or 3 cm away. **(B)** Microneurography as a recording of sympathetic muscular and vascular efference. **(C)** Microneurographic needle electrode **(on the left)** compared with a 30-gauge needle. **(D)** Example of a microneurographic recording of sympathetic nervous system activity as a sequence of bursts.

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gain was performed as described previously (21). Briefly, over a 3- to 5-min resting period, diastolic blood pressure (DBP) values of individual heart beats were grouped in intervals of 2 mm Hg, and for each interval, the percentage of diastoles associated with a sympathetic burst was plotted against the mean of the pressure interval (threshold diagram). Muscle sympathetic bursts were advanced by 1.3 s to compensate for the baroreflex delay. The baroreflex gain was defined as the absolute value of the slope of the regression line.

Follow-up. In-hospital clinical, biological, and transthoracic echocardiography follow-up were performed before discharge. Thirty-day follow-up was active, and information was obtained for all survivors by medical visit or direct contact with their cardiologist. All events and values were prospectively site recorded. Because of the publication of the Valve Academic Research Consortium consensus report during analysis of this study, we decided to retrospectively readjudicate events according to these harmonized endpoint definitions (22).

Statistical analysis. The amplitude of each burst was determined and sympathetic activity was calculated as bursts per min. MSNA-related data were collected by F.D., A.V., and M.L., sampled by a research assistant, and analyzed blindly by investigators. Measurements of MSNA and spontaneous arterial baroreflex and hemodynamic parameters of the 2 periods (before and after TAVI) were compared using a Wilcoxon test (matched, nonparametric). Parameters determined for TAVI patients were compared with those for control patients with a Wilcoxon test (matched, nonparametric). Testing was 2-sided, and results are presented as the mean ± SEM. Statistically significant differences are reported for p values <0.05. Statistical analyses were performed with Graphpad Prism 5.0 (Graphpad Software, La Jolla, California).

Results

Clinical characteristics. We enrolled 14 consecutive high-risk patients with a diagnosis of AS treated by TAVI.

Table 1. Patient Baseline Clinical Characteristics

Measurements	Control Patients (n = 14)	Patients (n = 14)
Male	10 (71)	8 (57.1)
Age, yrs	80.0 ± 3.8	84.3 ± 2.1
Body mass index, kg/m^2	24.2 ± 1.9	25.3 ± 1.6
NYHA functional class		
II	11 (78.6)	2 (14.3)*
III	0 (0)	4 (28.6)†
IV	0 (0)	8 (57.1)†
Symptoms		
Angina	0 (0)	5 (35.7)†
Syncope	0 (0)	1 (7.1)
Left ventricular ejection fraction, %	59.7 ± 1.2	50.4 ± 4.7
Hemoglobin, g/dl	12.1 ± 0.8	11.8 ± 0.6
Creatinine clearance, ml/min	68.5 ± 6.3	62.2 ± 5.8
Treatments at exploration time		
Beta-blockers	2 (14.3)	4 (28.6)
ACEi + AT1 receptor blocker	6 (42.8)	3 (21.4)

Values are n (%) or mean ± SEM. *p < 0.01 versus control patients. †p < 0.05 versus control patients.
ACEi = angiotensin-converting enzyme inhibitor; NYHA = New York Heart Association.

During the same period, 14 control patients matched for age, body mass index, and without AS were prospectively included. The demographic characteristics of the 2 populations did not significantly differ (Table 1) except for AS-related symptoms, with angina and dyspnea being more prevalent and severe in AS patients.

Assessment of hemodynamic parameters, sympathetic nerve activity, and sympathetic baroreflex function. Baseline characteristics of AS and control patients are presented in Table 1. Patient characteristics before and after TAVI are presented in Table 2. DBP and mean arterial blood pressure (MAP) were lower in patients with AS before TAVI. Baseline MSNA was increased in AS patients compared with control patients (61.0 ± 1.7 burst/min vs. 55.4 ± 1.4 burst/min, p < 0.05). The spontaneous sympathetic arterial baroreflex gain was significantly decreased in AS patients

Table 2. Effect of TAVI on Hemodynamic Parameters, Sympathetic Activity, and Arterial Baroreflex

Measurements	Control Patients (N = 14)	Before TAVI Procedure (N = 14)	After TAVI Procedure (N = 14)
Blood pressure, mm Hg			
Systolic	124.0 ± 5.0	111.7 ± 4.7*	125.3 ± 5.1
Diastolic	63.6 ± 3.3	53.2 ± 2.5*	64.3 ± 3.5†
Mean	83.7 ± 2.5	74.0 ± 2.8*	84.5 ± 3.2†
Heart rate, beats/min	77.1 ± 4.8	71.3 ± 3.0	76.7 ± 4.4
Oxygen saturation, %	93.8 ± 0.5	93.9 ± 0.6	93.6 ± 0.7
MSNA, bursts/min	55.4 ± 1.4	61.0 ± 1.7*	54.1 ± 1.0‡
Arterial baroreflex gain, %burst/mm Hg	3.32 ± 0.19	2.13 ± 0.14§	3.49 ± 0.33‡

Values are mean ± SEM. *p < 0.05 versus control patients. †p < 0.05 versus before TAVI procedure. ‡p < 0.01 versus before TAVI procedure. §p < 0.01 versus control patients.
MSNA = muscle sympathetic nerve activity; TAVI = transcatheter aortic valve implantation.

before TAVI compared with controls (2.13 ± 0.14 vs. 3.32 ± 0.19; $p < 0.01$) (Fig. 2, Table 2).

Effect of TAVI. In patients with AS, TAVI had an expected effect on hemodynamic parameters with an increase in DBP and MAP (Table 2). At the cardiac level, aortic valve area and cardiac output improved, whereas the mean gradient decreased (Table 3). Despite a trend toward a decrease, levels of brain natriuretic peptide levels were not significantly different after TAVI (550 ± 153 pg/ml vs. 496 ± 121 pg/ml; NS). TAVI decreased MSNA significantly from 61.0 ± 1.7 bursts/min to 54.1 ± 1.0 bursts/min ($p < 0.01$) (Table 2). Moreover, TAVI increased the sympathetic arterial baroreflex gain from 2.13 ± 0.14 to 3.49 ± 0.33 ($p < 0.01$) (Fig. 2, Table 2). No differences were found between patients treated with an Edwards or CoreValve prosthesis. In AS patients after TAVI, BP, MSNA, and sympathetic arterial baroreflex gain were not different compared with control patients, suggesting that TAVI normalizes SNS activity. There were no significant changes in beta-blocker and/or angiotensin-converting enzyme inhibitor/AT1 blocker therapy in the AS group after TAVI.

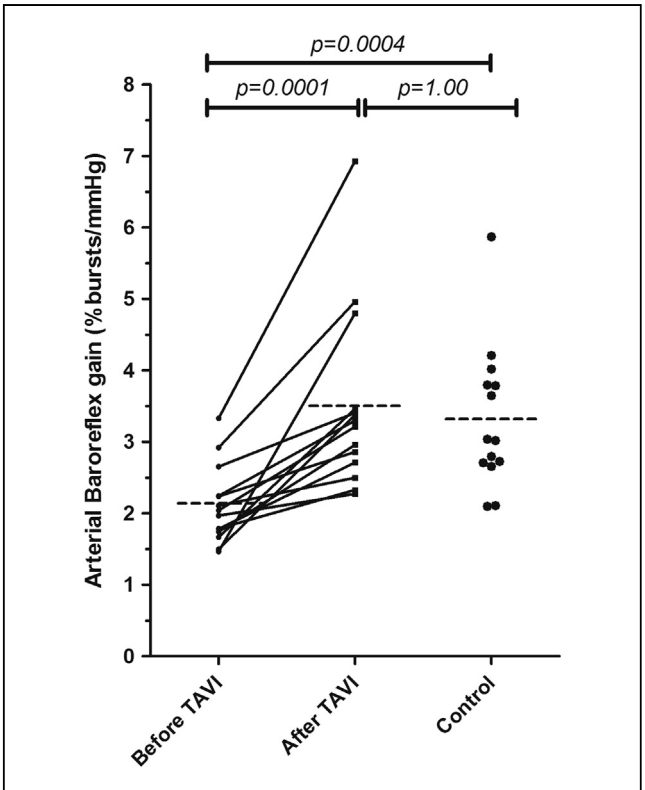

Figure 2. Individual Arterial Baroreflex Gain (%Bursts/mm Hg) in Patients Before and After TAVI and in Control Patients

The arterial baroreflex gain evaluates the modification of sympathetic nervous system activity consecutively to spontaneous diastolic arterial blood pressure variation. Transcatheter aortic valve implantation (TAVI) restores arterial baroreflex gain.

Table 3. Effect of TAVI on Hemodynamic Parameters Assessed by Echocardiography

Measurements	Before TAVI Procedure (N = 14)	After TAVI Procedure (N = 14)
Aortic valve area, cm^2	0.66 ± 0.04	1.55 ± 0.11*
Indexed aortic valve area, cm^2/m^2	0.39 ± 0.03	0.90 ± 0.07*
Maximum volume, m/s	4.65 ± 0.20	2.45 ± 0.08†
Mean gradient, mm Hg	56.0 ± 4.5	12.85 ± 0.79†
Velocity time integral left ventricular outflow tract, cm/s	19.5 ± 1.6	19.8 ± 1.6
Left ventricular end-diastolic volume, ml	94.2 ± 10.5	90.6 ± 8.4
Left ventricular end-systolic volume, ml	45.3 ± 10.6	37.6 ± 7.6*
Left ventricular ejection fraction, %	50.4 ± 4.7	61.3 ± 4.6
Cardiac output, l/min	3.13 ± 0.24	4.22 ± 0.42*

Values are mean ± SEM. *$p < 0.05$ versus before TAVI procedure. †$p < 0.01$ versus before TAVI procedure.
TAVI = transcatheter aortic valve implantation.

Procedural characteristics and 30-day follow-up are shown in Table 4.

Discussion

The novel and important finding of this study is that SNS activity is increased and arterial baroreflex is impaired in AS patients. We also showed that TAVI normalizes SNS activity and restores arterial baroreflex gain. We can hypothesize that decreased arterial baroreflex gain contributes to increased MSNA in AS patients and that TAVI normalizes SNS activity through enhancement of arterial baroreflex gain. Hence, the progression and prognosis in AS patients could be related to both hemodynamic impairment and also sympathoexcitation and additional impairment of

Table 4. Procedural Characteristics and 30-Day Outcome (N = 14)

Approach	
Transfemoral	11 (79)
Transapical	2 (14)
Left subclavian	1 (7)
Prosthesis	
Edwards Sapien	10 (71)
Medtronic CoreValve	4 (29)
Device success	13 (93)*
Mortality	
Intraprocedural	0
30-day all cause	0
30-day cardiovascular	0
Combined safety endpoint (at 30 days)†	1 (7)‡

Values are n (%). *1 patient with post-implantation moderate paravalvular regurgitation at discharge. †Combined safety endpoint: composite of all-cause mortality, major stroke, major vascular complication, life-threatening bleeding, acute kidney injury stage III, periprocedural myocardial infarction, repeat procedure for valve-related dysfunction. ‡1 major vascular complication.

baroreflex restraint of sympathetic tone. This autonomic dysfunction provides a further possible explanation for the high incidence of sudden death, mortality, or morbidity observed in AS patients but also insight into additional benefits of TAVI.

Determinant of SNS hyperactivity during AS. In this study we examined the effect of TAVI on SNS activity in AS patients. There are 3 key observations. First, MSNA was higher in AS patients than in control patients; this provides evidence of the first time that central sympathetic outflow to the skeletal muscle is increased in AS patients. Second, MSNA decreased to control patient level after successful treatment with TAVI. Finally, sympathetic baroreflex function was significantly impaired in AS patients but normalized with treatment of AS by TAVI.

Sympathetic activity may be increased in AS patients in association with decreased cardiac index and increased left ventricular volume or left ventricular hypertrophy. These modifications seen in patients with hypertrophic cardiomyopathy or CHF have been related to sympathetic activation in association with various hemodynamic and mechanical modifications (i.e., decrease in cardiac index, increase in left ventricular mass) (23). On the other hand, in AS patients, an increase in left ventricular or atrial pressure and even in pulmonary arterial pressure may inhibit sympathetic activity through cardiopulmonary mechanisms (i.e., Bezold-Jarich reflex). In this study, MSNA at rest was significantly increased in AS patients.

The strength of our study is the assessment of sympathetic nerve activity via direct recording by MSNA. Only a small number of clinical studies with few patients have investigated autonomic function in AS thus far. Although these studies underscore a potential role of increased SNS activity, some of them have drawbacks such as small sample size, inappropriate control subjects, or even the absence of any control. Some of these studies have used indirect SNS measurement techniques, such as heart rate variability (24), known to be influenced by other systems (i.e., nitric oxide release, temperature, thermoregulation) and do not reflect cardiac sympathetic nerve activity (25) and cardiac norepinephrine spillover (26). Plasma levels of norepinephrine may also be influenced by norepinephrine transporter function. Given that as much as 80% of neuronally released norepinephrine in the heart is taken up by the neuronal norepinephrine transporter, the heart is more susceptible than other organs to defects in norepinephrine transporter function (27). Other studies used myocardial scintigraphy with ^{123}I-metaiodobenzylguanidine, which is known to be less informative in patients, especially when they have severe left ventricular dysfunction (28–30). Overall, none of these studies directly assessed sympathetic nerve function or sympathetic baroreflex. Among tools able to measure SNS activity, MSNA remains the gold standard because of its low intervariability and intravariability as well as excellent reproducibility, as shown in studies performed in patients with various conditions (e.g., CHF [26,31], metabolic syndrome [32]). Moreover, available evidence indicates that indirect assessment of SNS activity cannot always be used to detect differences in sympathetic activity between patients and control subjects. Accordingly, our study allows us to draw a conclusion about increased SNS activity in AS patients.

Effects of TAVI on MSNA. Surgical aortic valve replacement may damage cardiac autonomic nerves, and the surgical procedure itself may influence sympathetic nerve activity. However, TAVI is less invasive than open surgery and therefore may minimally affect cardiac autonomic nerves. After TAVI, all patients showed a significant increase in aortic valve area and a significant decrease in the left ventricular/aortic pressure gradient, changes that indicate a successful hemodynamic outcome of TAVI. After a mean duration of a week, the elevated MSNA decreased significantly to the normal range. This suggests that TAVI appears to normalize increased levels of SNS activity in the short term. After TAVI, we observed an increase in MAP and DBP and a trend toward an increase in systolic BP. In an experimental model of aortic occlusion, it was shown that sustained increases in MAP induce increases in aortic depressor nerve activity, which persists after the return of MAP to control levels (33). These observations suggest that increased afterload in AS patients leads to a decrease in BP at the level of the aortic arch with a reduction of the depressor effect mediated by baroreceptor stimulation. After TAVI, the acute and sustained increase in arterial pressure may produce pressure-induced changes in afferent baroreceptor nerve activity and could explain the reduction of MSNA through a baroreflex-mediated mechanism. Hence, cardiac output and BP increase appear to be a major determinant of sympathetic activity. A reduction in afferent activity from the baroreceptor is considered a possible cause of sympathetic activation (34). In our study, AS patients had decreased spontaneous arterial baroreflex sensitivity and increased MSNA compared with control patients. In addition, after TAVI, arterial baroreflex gain increased (from 2.13 $\pm$ 0.14% burst/mm Hg to 3.49 $\pm$ 0.33% burst/mm Hg) and MSNA decreased to control levels (from 61.0 $\pm$ 1.7 bursts/min to 54.1 $\pm$ 1.0 bursts/min). Consequently, in patients with AS, decreased baroreflex sensitivity appears to be reversible. Furthermore, baroreceptor dysfunction may contribute to increased sympathetic activity in AS patients, and the reduction in SNS activity after TAVI may be related to the improvement of baroreflex gain. Baroreflex gain has been reported to be impaired in patients with AS (35), mitral stenosis (36), or CHF (37). Pharmacological intervention as well as cardiac transplantation leading to improvement of cardiac output reverses impaired arterial baroreflex gain; thus, a decrease in cardiac output may decrease afferent activity from the baroreceptor and increase SNS activity.

The negative impact of moderate to severe aortic regurgitation after TAVI on 1-year survival was recently described (38). In this study, we found that in the TAVI cohort, the only

patient without sympathetic baroreflex improvement was the one with moderate post-procedural aortic paravalvular regurgitation. The hemodynamic consequence of such leaks is particularly a decrease in DBP. In light of our results, we could assume that this condition would lead to a decrease in the depressor effect mediated by aortic baroreceptor stimulation. It may produce pressure-induced changes in afferent baroreceptor nerve activity and could explain the increase in MSNA via a baroreflex-mediated mechanism. Knowing the deleterious effect of SNA in other cardiovascular diseases such as hypertension and CHF, it could be the missing link between these significant regurgitations after TAVI and the associated poorer survival rate (38). However, our study does not allow us to draw conclusions from this single case observation, and this pathophysiological concept would need to be further evaluated.

Study limitations. Our findings do not indicate whether the excessive sympathetic activation occurring in AS is limited to the muscular vascular area only or whether it is generalized to the whole cardiovascular system. Evidence is available that under similar conditions such as CHF, sympathetic outflow is increased not only at the level of skeletal muscle but also in the coronary and renal circulation (39). Moreover, a significant positive correlation exists between spontaneous MSNA (expressed as the number of sympathetic bursts/min^{-1}) and both the spillover of norepinephrine from the heart and the concentration of norepinephrine in coronary sinus venous plasma, as demonstrated by Leimbach et al. (23) in 1992 in healthy subjects. Furthermore, a significant correlation between plasma norepinephrine levels and MSNA was demonstrated in heart failure subjects (23).

We have not assessed baroreceptor reflex function by using intravenous infusion of vasopressor and depressor agents. This technique cannot be used in patients with severe AS because of the high risk of hemodynamic failure after sodium nitroprusside or phenylephrine infusion. Moreover, this approach can be affected by long-term treatment. Finally, there are several limitations to the interpretation of sympathetic response to vasoactive drugs, among them nitroprusside inhibition of sympathetic neurotransmission (40) and unpredictable effects of cardiac loading conditions on low-pressure mechanoreceptor nerve firing. We have not investigated other reflexes such as chemoreflexes or muscular reflexes (i.e., metabomechanoreflexes). In this study, we cannot exclude that other mechanisms were involved in the increase in SNS activity such as renin-angiotensin system activation. Finally, further studies are needed to confirm whether MSNA decrease and sympathetic baroreflex gain increase after TAVI are maintained in the long-term.

Conclusions

We provide for the first time evidence via direct recording that SNA is increased in AS patients. Levels of SNS activity decreased to the normal range after TAVI, which increased cardiac output and sympathetic baroreflex function. These data illustrate the unknown effects of TAVI on SNA and baroreflex gain. Knowing that SNS hyperactivity and baroreflex dysfunction are prognostic of a poor outcome in various conditions (i.e., CHF, metabolic syndrome), our results provide insight and explanation about how TAVI, in addition to its hemodynamic effect, could reduce morbidity and mortality in AS patients. This opens the path for new research on autonomic markers as diagnostic, therapeutic, and prognostic tools for the management and follow-up of AS patients.

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Key Words: aortic stenosis ■ arterial baroreflex ■ sympathetic nervous system ■ transcatheter aortic valve implantation.