IJC Heart & Vasculature 31 (2020) 100658

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.journals.elsevier.com/ijc-heart-and-vasculature

Correspondence

# Coronary microvascular dysfunction in patients with mild-to-moderate aortic stenosis – Insights from intracoronary acetylcholine testing

## 1. Background

Evaluation of patients with aortic stenosis represents a challenging task for the clinical cardiologist. The cause of the patient's symptoms is especially difficult to assess in cases of mild-to-moderate stenosis. It has been postulated that coronary microvascular dysfunction (CMD) may contribute to the clinical symptoms in patients with aortic stenosis (AS) [1]. This assumption is further supported by studies showing that increased extravascular pressure, increased left ventricular end-diastolic pressure (LVEDP) and microvascular remodeling are frequently found in patients with AS and contribute to the development of CMD [2,3]. Furthermore, studies showed that the severity of AS correlates with the decline in myocardial flow reserve [1,4], a mechanism regulated by the microvasculature. Recently, recommendations for the assessment of CMD have been published by the Coronary Vasomotion Disorders International Study Group (COVADIS), which not only include the measurement of coronary flow reserve or myocardial perfusion reserve but also intracoronary acetylcholine (ACh) spasm provocation testing [5]. To elucidate the connection between CMD and AS, we assessed the frequency of coronary microvascular spasm, a subtype of CMD, with ACh provocation testing in symptomatic patients with mild-to-moderate AS compared to a control group (see Fig. 1).

## 2. Methods

From 2013 to 2017 19 patients (mean age 77 ± 8, 53% male) were enrolled retrospectively. All procedures performed in this study were in accordance with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all participants included in the study.

Invasive coronary angiography, right heart catheterization and left ventricular (LV) pressure measurements were carried out to evaluate the severity of the AS. After exclusion of epicardial stenoses as well as high-grade AS (peak-to-peak gradient <40 mmHg, aortic valve area >1.0 $cm^2$ and normal systolic LV function), all patients underwent ACh provocation testing to assess coronary vasomotion. Provocation testing was carried out as described previously [5]. Coronary microvascular spasm, a subtype of CMD, was defined as ischemic ECG changes with reproduction of the patient's symptoms in the absence of epicardial spasm (<90% vasoconstriction) during ACh-testing. A group of ten patients without angina or dyspnoea symptoms served as a control group. This group included patients who underwent catheterization as diagnostic coronary angiography before surgical removal of atrial masses or patients with chest discomfort of unknown origin in whom a non-cardiac cause was identified after further diagnostic work-up.

Statistical analysis was carried out with SPSS Statistics 23.0 and a two-sided p-value of <0.05 was considered statistically significant. Results are expressed as mean ± standard deviation. The *t*-test was used to compare continuous variables. The Fisher-exact-test was used for categorical variables.

## 3. Results

Nine of the patients (47%) suffered from exercise-related dyspnoea, 3 (16%) reported dyspnoea at rest and 7 (37%) had a combination of dyspnoea at rest and during exertion. Exercise-related angina pectoris was seen in 2 patients (11%) whereas 3 (16%) suffered from angina symptoms at rest and 5 (26%) had a combination of both. No angina symptoms were reported in 9 patients (47%). The following echocardiographic data were obtained: left ventric-

*Abbreviations*: Ach, acetylcholine
AOA, aortic orifice area
AS, aortic stenosis
AV, aortic valve
CFR, coronary flow reserve
CMD, coronary microvascular dysfunction
COVADIS, coronary vaomotion disorders international study group
ECG, electrocardiogram
LCA, left coronary artery
LV, left ventricle
LVEDP, left ventricular end-diastolic pressure
LVEF, left ventricular ejection fraction
LVPSP, left ventricular peak systolic pressure
MPG, mean pressure gradient
MPRI, myocardial perfusion reserve index
NOCAD, non-obstructive coronary artery disease
NTG, nitroglycerine
PG, pressure gradient
RCA, right coronary artery
V, velocity
VTI, velocity time integral

https://doi.org/10.1016/j.ijcha.2020.100658

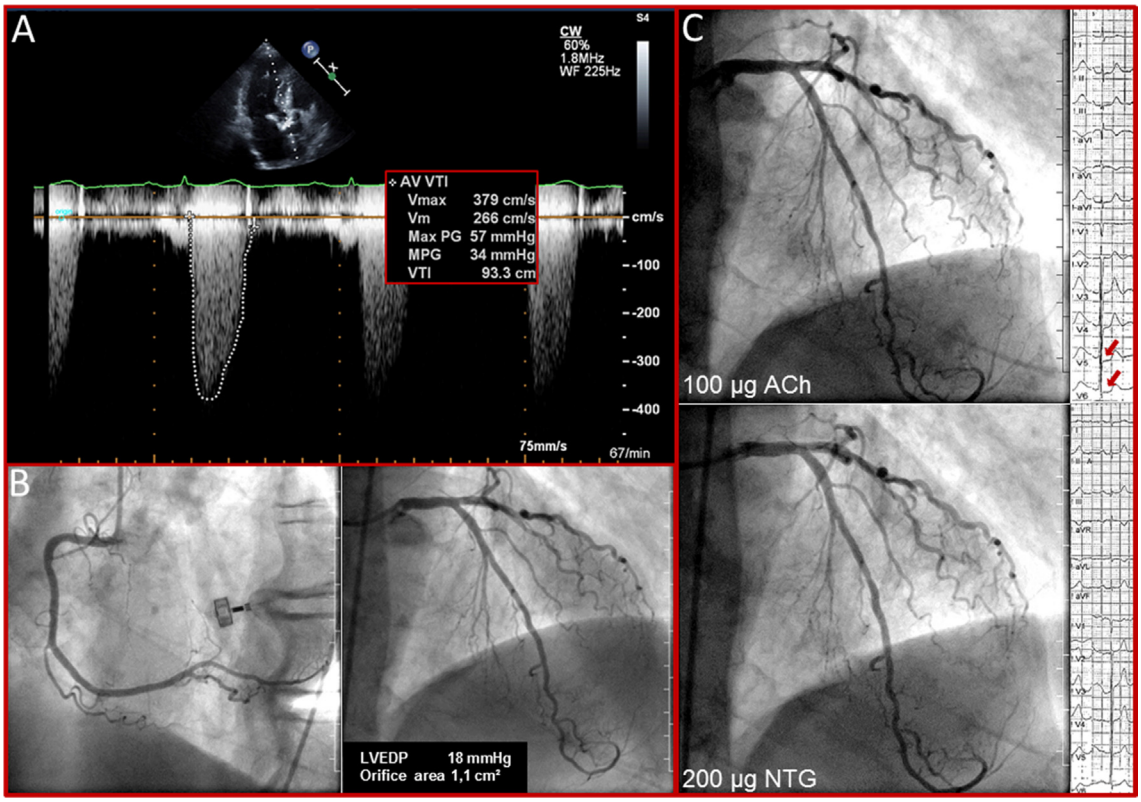


**Fig. 1. Representative case of an 84-year old man with exercise-related dyspnea and anginal symptoms at rest. Diagnostic assessments revealed a moderate aortic stenosis and microvascular spasm induced by acetylcholine provocation testing.** Echocardiography - to assess the severity of the aortic stenosis - showed a $V_{max}$ of 379 cm/s and a mean pressure gradient (MPG) of 34 mmHg **(A)**. Coronary angiography revealed unobstructed coronary arteries (RCA and LCA), a left ventricular end-diastolic pressure of 18 mmHg and a calculated aortic orifice area of 1.1 $cm^2$ **(B)**. The aortic stenosis was thus considered moderate. Additional assessment of coronary vasomotion was carried out with acetylcholine testing **(C)**. After intracoronary (i.c.) administration of 100 µg the patient reported a reproduction of his usual symptoms and ischemic ECG-changes (red arrows) without significant epicardial vasoconstriction could be observed (**C, upper panel**). Subsequent i.c. administration of 0.2 mg nitroglycerine (NTG) led to a resolution of the symptoms and normalization of the ECG (**C, lower panel**). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ular ejection fraction (LVEF) (mean 63 ± 9%), interventricular septum (median 13 ± 2.3 mm), left ventricular posterior wall diameter (median 9.8 ± 2.4 mm), Pmean 28 ± 12 mmHg, Vmax (mean 3.2 ± 0.6 m/s) and aortic orifice area (AOA) (median 1.1 ± 0.2 $cm^2$).

Further characteristics of patients and the control group are presented in table 1. There were no significant differences between the two groups regarding demographic and risk factor data, apart from the fact that the group of patients with aortic stenosis was older (77 ± 8 vs. 67 ± 5 years, p = 0.002).

Patients with AS showed a significantly higher LVEDP (17 ± 5 vs. 7 ± 2 mmHg, p = <0.001) as well as a significantly higher Pmean (19 ± 11 vs. 3 ± 1 mmHg, p = <0.001) than the control group. The AOA, calculated by the Fick method, was significantly smaller in patients with aortic stenosis compared to the control group (1.3 ± 0.3 vs. 2.4 ± 0.2 $cm^2$, p = <0.001). Cardiac output did not statistically differ between groups (4.4 ± 1.3 vs. 4.9 ± 0.5 l/min., p = 0.24).

During ACh provocation testing, coronary microvascular spasm could be diagnosed in 12 (63%) of the 19 patients. Patients with mild-to-moderate AS exhibited significantly more often a pathological response to ACh-testing compared to the control group (63 vs. 10%, p = 0.008).

## 4. Discussion

Under healthy conditions, the microvasculature regulates myocardial perfusion in response to an increased oxygen demand. Consequently a reduced coronary flow reserve (CFR), indicating an impaired vasodilator capacity of the microvasculature, serves as a marker for CMD in patients with unobstructed coronary arteries [6]. However, it has been suggested that impaired microvascular vasodilation represents only one subtype of CMD. Indeed, coronary microvascular spasm has been described as another form of CMD [7]. Furthermore, a considerable number (30–40%) of patients with AS and non-obstructive coronary arteries has been described to suffer from angina pectoris [8,9]. It has been shown that a reduced CFR [2,10] and a reduced myocardial perfusion reserve index (MPRI) [1] is a frequent finding in patients with AS, indicating that angina symptoms in these patients are related to an impaired function of the coronary microvasculature.

While it is hypothesized that a reduced vasodilation during hyperaemia can cause exercise-related angina and/or dyspnoea symptoms, coronary artery spasm may lead to attacks of angina or dyspnoea at rest, symptoms that were frequent (42 and 53%, respectively) in our patients. Indeed, during spasm the oxygen supply to the myocardium is decreased, leading to myocardial ischemia and consequently anginal symptoms [11]. Frequently, microvascular spasm and reduced microvascular vasodilator capacity occur together [12,13] resulting in the occurrence of symptoms at rest and during exercise. The presence of CMD has been explained by an elevated shear stress to the vessels of the microvasculature, resulting from an increased LVEDP as well as LV hypertrophy [2]. Additionally, it is known that an increase in left ventricular peak systolic pressure (LVPSP) and LV mass leads to an increase in oxygen demand of the myocardium [14]. Julius et al. proposed that myocardial ischemia in patients with severe

**Table 1**
Characteristics of patients with mild-to moderate aortic stenosis (AS) and the control group.

| | Mild-to-moderate AS | Control group | p-value |
|---|---|---|---|
| n | 19 | 10 | |
| Male sex n (%) | 10 (53) | 5 (50) | 0.99 |
| Age years (mean, SD) | 77 ± 8 | 67 ± 5 | <0.005 |
| LVEF % (mean, SD) | 73 ± 9 | 70 ± 4 | 0.33 |
| CVRF n (%) | | | |
| Arterial Hypertension | 15 (79) | 7 (70) | 0.66 |
| Diabetes mellitus | 7 (37) | 2 (20) | 0.43 |
| Dislipidemia | 12 (63) | 3 (30) | 0.13 |
| Positive family history | 10 (58) | 2 (20) | 0.13 |
| Smoking | 2 (11) | 4 (40) | 0.14 |
| Invasive measurements (mean, SD) | | | |
| LVEDP (mmHg) | 17 ± 5 | 7 ± 2 | <0.001 |
| CO (l/min) | 4.4 ± 1.3 | 4.9 ± 0.5 | 0.24 |
| Peak-to-peak gradient (mmHg) | 19 ± 11 | 3 ± 1.1 | <0.001 |
| Aortic orifice area ($cm^2$) | 1.3 ± 0.3 | 2.4 ± 0.2 | <0.001 |

Data are presented as mean ± standard deviation (SD). A p-value of <0.05 was considered statistically significant.
AS, aortic stenosis; CO, cardiac output; CVRF, cardiovascular risk factors; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end-diastolic pressure.

AS and without LV hypertrophy could occur due to an increased LVED pressure and a high LVPSP [2], suggesting that the microvasculature is normal yet undersized for the requirement imposed by a severe narrowing of the aortic valve. This could also be observed in our patients, exhibiting significant greater LVEDP and LVPSP values than the controls. These alterations may lead to a high wall stress, alterations in the microvasculature and hence an increased susceptibility to microvascular spasm.

In contrast to previous studies reporting CFR abnormalities in patients with AS [2,10], our results showing a high frequency of coronary microvascular spasm in patients with mild-to-moderate AS are novel. This finding points towards the fact that in patients with AS not only the vasodilatory microvascular function may be impaired but that these patients may also suffer from an abnormal microvascular vasoconstrictor response.

A comprehensive assessment of CMD including spasm testing and assessment of CFR in patients with AS, should be considered in future trials. Such an approach has recently been labelled as interventional diagnostic procedure (IDP) [15].

The main limitation of this study is the small sample size, which should be considered when interpreting the results. Moreover, it is unclear whether our findings can be extrapolated to other patient cohorts with aortic stenosis, e.g. those with high-grade aortic stenosis. Nevertheless, we believe that our results can serve as the basis for future trial planning as well as supporting clinical management in similar patients encountered in everyday clinical practice.

In conclusion, ACh-induced CMD is frequently found in patients with mild-to-moderate AS and likely contributes to their clinical symptoms. Targeted treatment of CMD may be beneficial in patients with mild-to-moderate AS to improve symptoms and outcome.

## Declaration of Competing Interest

The authors declare no conflict of interest.

## Acknowledgements/Funding

This work was supported by Berthold-Leibinger-Foundation, Ditzingen, Germany and the Robert-Bosch-Foundation, Stuttgart.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100658.

## References

[1] J.-H. Ahn, S.M. Kim, S.-J. Park, D.S. Jeong, M.-A. Woo, S.-H. Jung, S.-C. Lee, S.W. Park, Y.H. Choe, P.W. Park, J.K. Oh, Coronary microvascular dysfunction as a mechanism of angina in severe AS: prospective adenosine-stress CMR study, J. Am. Coll. Cardiol. 67 (2016) 1412–1422, https://doi.org/10.1016/j.jacc.2016.01.013.
[2] B.K. Julius, M. Spillmann, G. Vassalli, B. Villari, F.R. Eberli, O.M. Hess, Angina pectoris in patients with aortic stenosis and normal coronary arteries. Mechanisms and pathophysiological concepts, Circulation 95 (1997) 892–898, https://doi.org/10.1161/01.cir.95.4.892.
[3] K. Rajappan, O.E. Rimoldi, D.P. Dutka, B. Ariff, D.J. Pennell, D.J. Sheridan, P.G. Camici, Mechanisms of coronary microcirculatory dysfunction in patients with aortic stenosis and angiographically normal coronary arteries, Circulation 105 (2002) 470–476, https://doi.org/10.1161/hc0402.102931.
[4] W. Zhou, N. Bajaj, A. Gupta, Y.-P. Sun, S. Divakaran, C. Bibbo, J. Hainer, V. Taqueti, S. Dorbala, R. Blankstein, P. Shah, T. Kaneko, D. Adler, P. O'Gara, M. Di Carli, Coronary microvascular dysfunction, left ventricular remodeling, and clinical outcomes in aortic stenosis, J. Nucl. Cardiol. (2019), https://doi.org/10.1007/s12350-019-01706-y.
[5] P. Ong, A. Athanasiadis, G. Borgulya, H. Mahrholdt, J.C. Kaski, U. Sechtem, High prevalence of a pathological response to acetylcholine testing in patients with stable angina pectoris and unobstructed coronary arteries. The ACOVA Study (Abnormal COronary VAsomotion in patients with stable angina and unobstructed coronary arteries), J. Am. Coll. Cardiol. 59 (2012) 655–662, https://doi.org/10.1016/j.jacc.2011.11.015.
[6] P.G. Camici, F. Crea, Coronary microvascular dysfunction, N Engl. J. Med. 356 (2007) 830–840, https://doi.org/10.1056/NEJMra061889.
[7] P. Ong, B. Safdar, A. Seitz, A. Hubert, J. Beltrame, E. Prescott, Diagnosis of coronary microvascular dysfunction in the clinic, Cardiovasc. Res. (2020), https://doi.org/10.1093/cvr/cvz339.
[8] A.-H. Hakki, D. Kimbiris, A.S. Iskandrian, B.L. Segal, G.S. Mintz, C.E. Bemis, Angina pectoris and coronary artery disease in patients with severe aortic valvular disease, Am. Heart J. 100 (1980) 441–449, https://doi.org/10.1016/0002-8703(80)90655-9.
[9] O. Storstein, I. Enge, Angina pectoris in aortic valvular disease and its relation to coronary pathology, Acta Med. Scand. 205 (1979) 275–278, https://doi.org/10.1111/j.0954-6820.1979.tb06046.x.
[10] M.L. Marcus, D.B. Doty, L.F. Hiratzka, C.B. Wright, C.L. Eastham, Decreased coronary reserve: a mechanism for angina pectoris in patients with aortic stenosis and normal coronary arteries, N Engl. J. Med. 307 (1982) 1362–1366, https://doi.org/10.1056/NEJM198211253072202.
[11] M. Mohri, M. Koyanagi, K. Egashira, H. Tagawa, T. Ichiki, H. Shimokawa, A. Takeshita, Angina pectoris caused by coronary microvascular spasm, The Lancet 351 (1998) 1165–1169, https://doi.org/10.1016/S0140-6736(97)07329-7.
[12] A. Suda, J. Takahashi, K. Hao, Y. Kikuchi, T. Shindo, S. Ikeda, K. Sato, J. Sugisawa, Y. Matsumoto, S. Miyata, Y. Sakata, H. Shimokawa, Coronary functional abnormalities in patients with angina and nonobstructive coronary artery disease, J. Am. Coll. Cardiol. 74 (2019) 2350–2360, https://doi.org/10.1016/j.jacc.2019.08.1056.
[13] K. Ohba, S. Sugiyama, H. Sumida, T. Nozaki, J. Matsubara, Y. Matsuzawa, M. Konishi, E. Akiyama, H. Kurokawa, H. Maeda, K. Sugamura, Y. Nagayoshi, K. Morihisa, K. Sakamoto, K. Tsujita, E. Yamamoto, M. Yamamuro, S. Kojima, K. Kaikita, S. Tayama, S. Hokimoto, K. Matsui, T. Sakamoto, H. Ogawa, Microvascular coronary artery spasm presents distinctive clinical features with endothelial dysfunction as nonobstructive coronary artery disease, J. Am. Heart Assoc. 1 (2012), https://doi.org/10.1161/JAHA.112.002485 e002485.
[14] B.-E. Strauer, Myocardial oxygen consumption in chronic heart disease: Role of wall stress, hypertrophy and coronary reserve, Am. J. Cardiol. 44 (1979) 730–740, https://doi.org/10.1016/0002-9149(79)90295-9.
[15] T.J. Ford, B. Stanley, R. Good, P. Rocchiccioli, M. McEntegart, S. Watkins, H. Eteiba, A. Shaukat, M. Lindsay, K. Robertson, S. Hood, R. McGeoch, R. McDade, E. Yii, N. Sidik, P. McCartney, D. Corcoran, D. Collison, C. Rush, A. McConnachie, R.M. Touyz, K.G. Oldroyd, C. Berry, Stratified medical therapy using invasive coronary function testing in angina: the CorMicA trial, J. Am. Coll. Cardiol. 72 (2018) 2841–2855, https://doi.org/10.1016/j.jacc.2018.09.006.

Valeria Martínez Pereyra
Andreas Seitz
Heiko Mahrholdt
Raffi Bekeredjian
Udo Sechtem
Peter Ong [1,*]
*Robert-Bosch-Krankenhaus, Department of Cardiology, Auerbachstr. 110, 70376 Stuttgart, Germany*
* Corresponding author.
*E-mail address*: Peter.Ong@rbk.de (P. Ong)
Received 19 May 2020
Received in revised form 17 September 2020
Accepted 3 October 2020

[1] The last author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.