Structural Heart

The Journal of the Heart Team

ISSN: 2474-8706 (Print) 2474-8714 (Online) Journal homepage: https://www.tandfonline.com/loi/ushj20

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To cite this article: Tiffany Mathieu, Virginia Nguyen, Claire Cimadevilla, Maria Melissopoulou, Isabelle Codogno, Constance Verdonk, Xavier Duval, Sarah Tubiana, Dimitri Arangalage, Alec Vahanian & David Messika-Zeitoun (2017) Prognostic Value of Combination of Hemodynamic Parameters in Asymptomatic Aortic Valve Stenosis—The COFRASA/GENERAC Study, Structural Heart, 1:1-2, 75-80, DOI: 10.1080/24748706.2017.1327734

To link to this article: https://doi.org/10.1080/24748706.2017.1327734

Accepted author version posted online: 09 May 2017.
Published online: 09 Jun 2017.

STRUCTURAL HEART
2017, VOL. 1, NOS. 1–2, 75–80
https://doi.org/10.1080/24748706.2017.1327734

ORIGINAL RESEARCH

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Prognostic Value of Combination of Hemodynamic Parameters in Asymptomatic Aortic Valve Stenosis—The COFRASA/GENERAC Study

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ABSTRACT

Background: Whether risk-stratification in aortic valve stenosis (AS) should rely on a single hemodynamic parameter or a combination of hemodynamic parameters is still debated. We aimed to evaluate the prognostic value of mean pressure gradient (MPG), aortic valve area (AVA), and the dimensionless index (DI) in patients with AS and to test whether their combination provides additional prognostic information.

Methods: We enrolled 319 asymptomatic patients with AS (90 mild, 173 moderate, and 56 severe AS). All patients were prospectively followed on a yearly basis and AS-related events (sudden death, heart failure, or new onset of AS-related symptoms) were collected.

Results: After a mean follow-up of 3.1±1.7 years, an AS-related event occurred in 84 patients (26%). When considered in isolation, after adjustment for age, sex, history of coronary artery disease, valve anatomy, and left ventricular ejection fraction, each parameter (MPG, AVA, and DI) independently predicted the occurrence of AS-related events (all $p<0.0001$). When considered in combination, MPG and AVA ($p=0.0009$ and $p<0.0001$ respectively) or MPG and DI ($p=0.0001$ and $p<0.0001$ respectively) remained independent predictors of outcome. Results were sustained after exclusion of 31 patients (10%) with discordant grading.

Conclusion: In a large prospective cohort of asymptomatic patients with a wide range of AS severity, AVA, MPG, and DI were all important prognostic factors. More importantly, irrespective of the presence of patients with discordant grading, MPG and either the AVA or the DI provided complementary prognostic information. Our results show that these hemodynamic parameters should be considered in combination in the clinical management of AS patients.

ARTICLE HISTORY Received 24 March 2017; Revised 27 April 2017; Accepted 1 May 2017

KEYWORDS Aortic stenosis; aortic valve area; mean pressure gradient; dimensionless index; prognosis

Introduction

Aortic valve stenosis (AS) is the most common valvular heart disease in Western countries and its prevalence is going to dramatically increase with the ageing of the population.[1,2] There is currently no medical therapy that can prevent AS progression and aortic valve replacement (AVR) is the only approved treatment for AS. AVR is recommended in patients with severe AS and either symptoms or left ventricular (LV) dysfunction.[3,4] Accurate AS grading is therefore crucial in the clinical decision making process of patients with AS.

Echocardiography is the reference method for the assessment of AS severity and mainly relies on the aortic valve area (AVA), the peak velocity (PV), the mean pressure gradient (MPG) and the dimensionless index (DI).[5] Thresholds for severe AS have been defined and validated in outcome studies for each parameter.[6] However, whether risk-stratification in AS should rely on a single hemodynamic parameter or a multi-parametric approach (combination of hemodynamic parameters) is debated and the literature conflicting.[6,7]

These uncertainties are an important limitation in the clinical management of AS patients. In an ongoing prospective cohort of AS patients, we aimed to evaluate the respective prognostic value of the different AS hemodynamic parameters and to test whether their combination provides additional prognostic information.

Materials and methods

Study design

Asymptomatic patients with at least mild degenerative AS enrolled between November 2006 and February 2014 in our ongoing prospective cohort COFRASA/GENERAC (clinicalTrial.gov number NCT 00338676 and NCT00647088) aiming at evaluating the determinants of AS occurrence and progression, constituted our study population. Exclusion criteria were AS due to rheumatic valve disease or radiotherapy, previous infective endocarditis, more than mild associated valvular disease and severe respiratory or renal insufficiency (creatinine clearance ≤ 30 ml/min). All patients underwent a comprehensive clinical

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and TTE evaluation at study entry. Asymptomatic patients had to be free of dyspnea angina and syncope. Coronary artery disease (CAD) was defined as a history of angina, coronary angioplasty, coronary artery bypass or myocardial infarction. Occurrence of AS-related events (sudden death, congestive heart failure or new onset of symptoms (dyspnea, angina, or syncope)) was prospectively recorded. Our regional ethics committee approved the study and all patients gave written informed consent.

Transthoracic echocardiography

A comprehensive TTE was performed at baseline, AS severity was evaluated based on PV, MPG, AVA and AVAi (AVA indexed to body surface area) calculated using the continuity equation as recommended by current guidelines.[8] Mild AS was defined by an AVA between 1.5 and 2.0 cm^2 (or a MPG /PV <20 mmHg or < 3.0m/s respectively) and moderate AS by an AVA between 1.0 and 1.5cm^2 (or a MPG between 20 and 40mmHg or a PV between 3.0 and 4.0m/s). Finally severe AS was defined by an AVA <1.0cm^2 (or a MPG >40mmHg or PV >4.0m/s). The dimensionless index (DI) (ratio of the left ventricular outflow tract (LVOT) /transvalvular aortic valve time-velocity integral) was also calculated and we divided our population into 3 groups of AS severity according to the DI as proposed (DI >0.25, 0.20–0.25 and <0.20).[6] Discordant grading was defined by an AVA <1.0cm^2 and a MPG < 40mmHg or an AVA ≥1.0cm^2 and a MPG ≥ 40mmHg. Cine loops of apical 4-, 3- and 2-chamber, parasternal long-axis, and short-axis views were obtained and the LVEF was determined visually or using the Simpson method. LVEF ≥ 50% was considered normal. Short-axis view in systole was used to assess aortic valve anatomy (bicuspid or tricuspid valve).

Statistical analysis

Continuous variables were expressed as mean ± SD and categorical variables as number of patients (percentage). Correlation between hemodynamic parameters was evaluated using linear and non-linear regressions and the model providing the best fit was retained. Prognostic value of hemodynamic parameters was analyzed overall, in the subset of patients with moderate to severe AS and in the subset of patients with severe AS. Event-free survival was assessed using the Kaplan-Meier analysis. Comparison of event-free survival according to AS severity groups was performed by log-rank test. Cox proportional-hazard analyses evaluated the predictive value of hemodynamic parameters for event-free survival in univariate analysis and multivariate analysis after adjustment for age, sex, history of CAD, valve anatomy (bicuspid or tricuspid aortic valve) and LVEF. The survival-based c-statistic with the [95% confidence interval (CI)] was calculated with the R software packages to evaluate the added prognostic-value of the MPG in severe AS subgroup (AVA<1.0cm^2 or DI<0.25) and other analysis were performed using JMP (version 9.0) software (SAS institute, Cary, North Carolina, USA). A p value <0.05 was considered statistically significant.

Results

Baseline characteristics

Between November 2006 and February 2014, 338 patients were prospectively enrolled. Ten patients (3%) were excluded due to left ventricular dysfunction (LVEF<50%), 9 patients (3%) were either lost to follow-up or refused to remain in the study and thus 319 patients constituted our study population. Baseline characteristics of the study population are presented in the Table. Briefly, mean age was 73±10 years, 229 (72%) were male and 97 (30%) had a history of CAD. Mean LVEF was 64±3% and 69 patients (22%) had a bicuspid aortic valve. Mean AVA was 1.35±0.40 cm^2 and based on AVA, 90 patients (28%) had a mild AS, 173 patients (54%) had moderate AS and 56 patients (18%) had severe AS. MPG was 26±16 mm Hg and mean DI 0.31±0.09. An excellent correlation between the DI and both the AVA and the MPG was observed (r=0.85 and r=0.82, both P<0.0001) whereas correlation between AVA and MPG was slightly lower (r=0.76, P<0.0001). As shown in figure 1, correlation between MPG and both the AVA and the DI were exponential whereas correlation between AVA and DI was linear. All clinical characteristics but sex were not different between groups of AS severity (Table 1).

Outcome

Mean follow-up was 3.1±1.7 years. An AS-related event occurred in 84 patients (26%), 81 patients developed

Table 1. Characteristics of the population according to aortic valve stenosis (AS) severity groups defined by aortic valve area (AVA).

Variable	Overall (n=319)	Mild AS AVA >1.5cm^2 (n=90)	Moderate AS 1.0cm^2≤AVA<1.5cm^2 (n=173)	Severe AS AVA<1.0cm^2 (n=56)	P value
Age, year	73±10	73±9	73±10	75±10	0.12
Male gender	224 (70%)	68 (76%)	130 (75%)	31 (55%)	0.02
Hypertension	235 (70%)	64 (71%)	123 (72%)	37 (66%)	0.73
Atrial fibrillation	19 (6%)	5 (6%)	9 (5%)	5 (9%)	0.26
Diabetes	80 (25%)	23 (26%)	48 (28%)	9 (16%)	0.21
History of coronary artery disease	97 (30%)	30 (33%)	55 (32%)	12 (21%)	0.27
Bicuspid aortic valve	69 (22%)	12 (17%)	42 (61%)	15 (22%)	0.06
Aortic valve area, cm^2	1.35±0.40	1.84±0.28	1.27±0.16	0.82±0.12	<0.0001
Mean pressure gradient, mmHg	26±16	15±5	25±10	49±21	<0.0001
Mean pressure gradient > 40 mmHg	47 (15%)	0	11 (6%)	36 (64%)	<0.0001
Peak velocity, m/sec	3.18±84	2.51±40	3.16±55	4.34±90	<0.0001
Peak velocity > 4m/sec	43 (13%)	0	9 (5%)	34 (61%)	<0.0001
Dimensionless index	0.31±0.09	0.42±0.08	0.29±0.05	0.20±0.04	<0.0001
Dimensionless index < 0.20	31 (10)	0	2 (1)	29 (52)	<0.0001
Left ventricular ejection fraction, %	64±3	64±3	64±3	64±4	0.77

Note. Data are expressed as mean±SD, or number (percentage).

symptoms (71 dyspnea, 9 angina, and 1 syncope) and three patients died suddenly; five events occurred in the subset of mild AS, 42 in the subset of moderate AS and 37 in the subset of severe AS based on AVA. All these 84 patients had severe AS at the time of occurrence of the event. A surgical or transcatheter aortic valve replacement was performed in 71 patients; 10 patients (12%) remained under medical therapy because of high surgical risk or patients' preference. Nineteen patients also died from non-AS–related cause and were censored at the time of death.

Univariate analysis

Aortic valve area

AVA was significantly smaller in patients who presented an AS-related event compared to those who remained free of AS-related events (1.04±0.28 cm^2 vs. 1.46 cm^2±0.38, p <0.0001). Event-free survival curves according to groups of AS severity were also significantly different (p<0.0001) (Figure 2A). Event-free survival at 2 and 5 years was 100% and 90% in patients with mild AS, 89% and 67% in patients with moderate AS and 55% and 16% in patients with severe AS respectively. In univariate analysis, AVA was significantly associated with outcome (p <0.0001).

Mean pressure gradient and peak velocity

Due to co-linearity between MPG and PV (R=0.95) only the MPG was considered in the following analysis. Based on MPG, 141 patients (44%) had mild AS, 131 patients (41%) moderate AS and 47 patients (15%) severe AS. Event-free survival was significantly different according to AS severity groups, (p<0.0001) (Figure 2B). Event-free survival rates at 2 and 5 years were 99% and 95% in patients with mild AS, 85% and 49% in patients with moderate AS and 49% and 7% in patients with severe AS respectively. In univariate analysis, MPG was predictive of outcome (p<0.0001).

Dimensionless index

Based on DI, 227 (71%) had a DI>0.25, 61 (19%) had a DI between 0.20 and 0.25 and 31 (10%) had a DI<0.20. Event-free survival was significantly different according to groups of AS severity (p<0.0001) (Figure 2C). Event-free survival rates at 2 and 5 years were 95% and 76% in patients with a DI > 0.25, 79% and 46% in patients with a DI between 0.25 and 0.20 and 31% and 0% in patients with a DI<0.20 respectively. In univariate analysis DI was predictive of AS-related events (p<0.0001).

Multivariate analysis—Complementary prognostic value of hemodynamic parameters

After adjustment for age, sex, history of CAD, aortic valve anatomy ((bicuspid or tricuspid aortic valve) and LVEF, all three hemodynamic parameters were independent predictors of outcome (all p<0.0001). When MPG and AVA were entered into the model, both parameters were independent predictors of outcome (p=0.0009 and p<0.0001 respectively). Similar results were observed when MPG and DI were considered (p=0.0001 and p<0.0001 respectively). Excluding patients with CAD did not change our conclusion (all p<0.001)

Most of the AS-related events (79 (94%)) occurred in the 229 patients with moderate or severe AS (mean AVA 1.16 ±0.25cm2, MPG 31±17 mmHg and DI 0.27±0.07). In this subset, both MPG and AVA remained independent predictors of outcome in multivariate analysis (p=0.003 and p=0.001

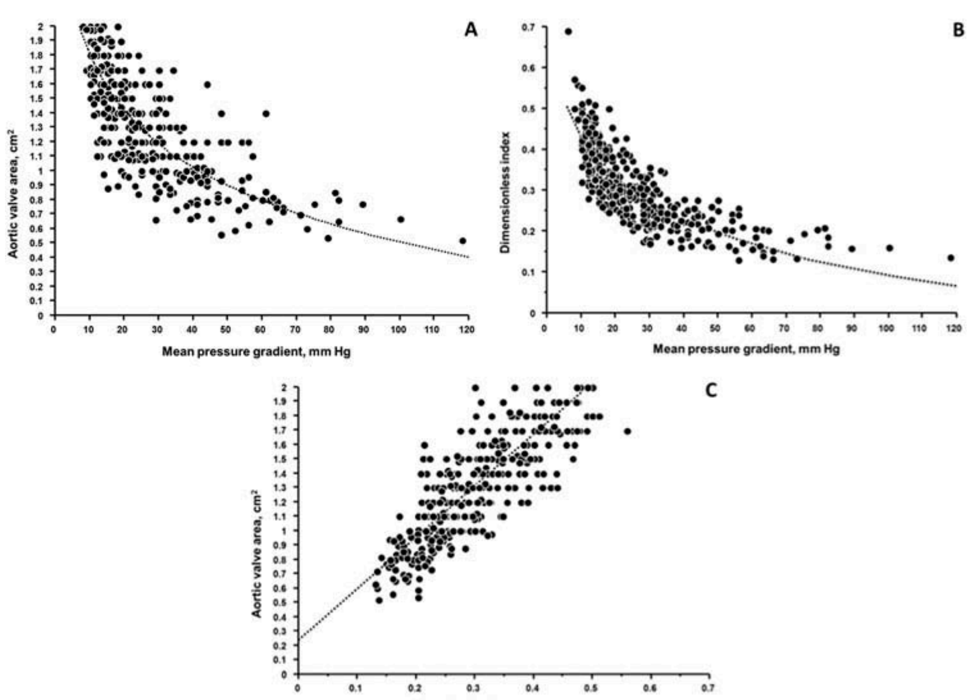

Figure 1. Correlations between (A) the mean pressure gradient (MPG) and the aortic valve area (AVA), (B) the MPG and the dimensionless index (DI) and (C) the AVA and the DI in 319 asymptomatic patients with at least mild AS. The dotted line corresponds to the regression curve providing the best fit.

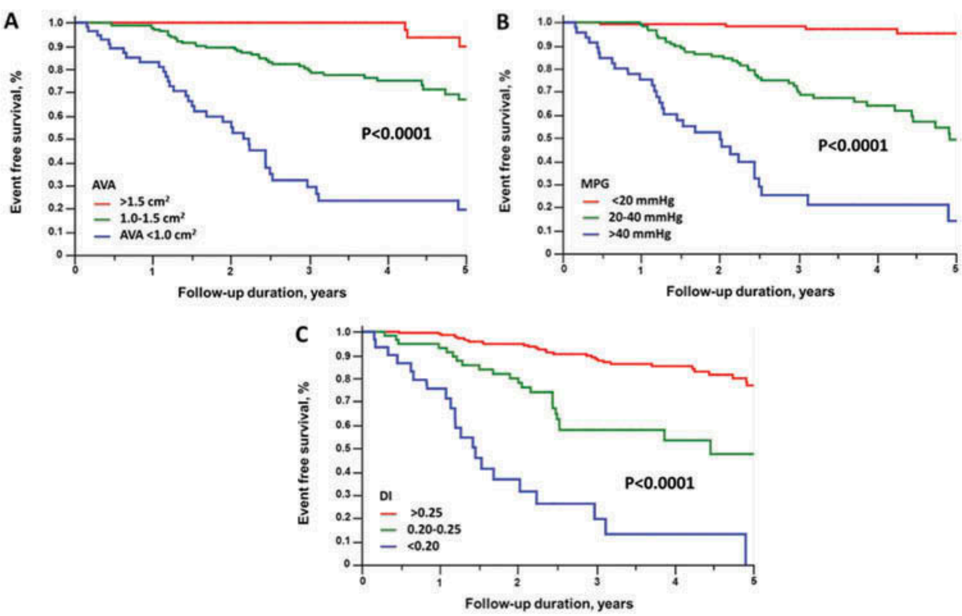

Figure 2. Event free survival of aortic valve stenosis (AS) related events (sudden death, congestive heart failure, or new AS related onset of symptoms (dyspnoea, angina or syncope)) according to (A) Aortic valve area (AVA) severity groups (AVA<1.0cm^2, AVA between 1.0 and 1.5cm^2 and AVA >1.5cm^2), (B) Mean pressure gradient (MPG) severity groups (MPG <20mmHg, MPG between 20 and 40mmHg and MPG >40mmHg) and (C) Dimensionless index (DI) severity groups (DI<0.20, DI between 0.20 and 0.25 and DI>0.25).

respectively). Same results were obtained with MPG and the DI (p=0.002 and p=0.0009 respectively).

When the analysis was restricted to the 56 patients (18%) with an AVA<1.0cm^2 or to the 92 patients (29%) with a DI ≤ 0.25, MPG remained a significant predictor of AS-related events (p=0.02 and p<0.0001 respectively). As illustrated in Figure 3, event-free survival was significantly different between patients with a MPG ≤ or > to 50 mmHg both in patients with an AVA <1.0cm^2 or a DI <0.25 (p=0.001 and p<0.0001 respectively). In those patients the survival c-statistic for the MPG was 0.67 [0.57–0.78] and 0.73 [0.63–0.82] respectively.

Similar results were obtained using AVAi instead of absolute AVA. In univariate and multivariate analysis, AVAi was an independent prognostic factor (both p<0.0001). When AVAi and MPG were considered in combination, both were independent predictors of outcome (p<0.0001 and p<0.0008) and among patients with an AVAi <0.6 cm/m^2 (N=97), MPG remained a significant predictor of outcome (p<0.0001).

Thirty-one patients (10%) had a discordant evaluation, 20 (6.5%) with an AVA <1.0 cm^2 and a MPG ≤ 40 mmHg, and 11 (3.5%) an AVA ≥1.0 cm^2 and a MPG > 40 mmHg. As a potential explanation for the independent predictive value of both AVA and MPG, the analysis was performed again after exclusion of these patients and the independent prognostic value of both MPG and AVA was sustained (p=0.004 and p<0.0001 respectively). Similar results were observed when MPG and the DI were considered (p=0.001 and p<0.0001 respectively).

Discussion

In a large prospective cohort of asymptomatic patients with a wide range of AS severity, we evaluated the prognostic value of 3 hemodynamic parameters assessed using echocardiography, namely the aortic valve area, the mean pressure gradient and the dimensionless index. All 3 parameters were important prognostic factors in univariate analysis. More importantly, irrespective of the presence of patients with discordant grading, MPG and either the AVA or the DI was independent

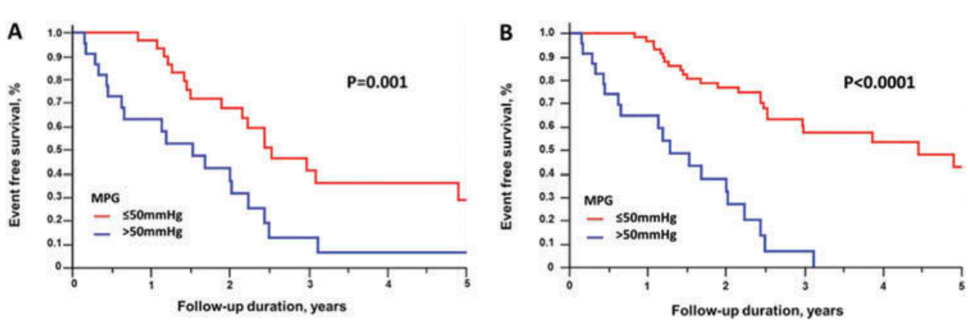

Figure 3. Event-free survival according to mean pressure gradient (MPG) below or above 50mmHg (A) in the subset of 61 patients with an aortic valve area (AVA) <1.0cm^2 or (B) in the subset of 92 patients with a dimensionless index (DI) ≤0.25.

predictors of outcome in multivariate analysis. Our results showed that hemodynamic parameters provide complementary prognostic information and that they should be considered in combination in the clinical management of AS patients.

Management of AS patients and thus the decision to intervene and perform AVR relies on the echocardiographic assessment of AS severity. Three parameters are routinely used, the couple MPG/PV, the AVA and the DI. Dedicated thresholds have been proposed but the classification has been recently turned upside down by the observation that the proposed thresholds do not fit together—discordant grading—and that an AVA of 1 cm^2 does not correspond to a PV of 4/sec or a MPG of 40 mm Hg despite a normal EF.[9,10] Several explanations have been proposed including error measurements and small body surface area but similar discrepancies were also observed using invasive assessment of AS severity instead of echocardiography.[11] In addition, the subdivision among AS patients with discordant grading of a subset with low flow—so called paradoxical low flow severe AS—makes this issue even more confusing.[12-14] Due to these uncertainties, the definition of severe AS has been questioned and the main parameter clinical on which management of AS patients' should rely on remains unclear. It is worth noting that over the last decade, thresholds to define severe AS have been modified (from 0.75/0.8 cm^2 to 1 cm^2 for the AVA and from 50 to 40 mm Hg for the MPG in Europe) with not much proof or validation data and some have suggested moving back AVA threshold to 0.8 cm^2 to achieve a better fit between parameters.[15]

Historically, the prognostic value of PV was first validated by Catherine Otto in her seminal study[16] and further confirmed by others.[17,18] A progressive decrease in event-free survival has been shown as peak velocity increases and has led to the definition of very severe AS above 5.5 m/sec.[19] The AVA was initially considered less significant but has recently gained attention with the emphasis on the discordant grading concept. AVA is now often regarded as the main parameter but its impact on outcome is less established. In a recent study, Maalouf et al. found that an AVA ≤ 1 cm^2 was the only independent measure of AS severity predictive of outcome under conservative management irrespective of functional status.[7] The DI is a simplified AVA calculation with no need for measurement of the LVOT diameter. Indeed, in contrast to the MPG or the PV which rely on a single measurement, calculation of the AVA requires 3 measurements (LVOT diameter, LVOT TVI and aortic TVI) all potentially affected by measurements errors. Despite being a classical marker of AS severity, the prognostic value of the DI was seldom evaluated. In a recent retrospective study, it has been shown that the DI was an independent predictor of outcome in asymptomatic patients diagnosed with at least mild AS.[6]

In the present study, in a prospective cohort of asymptomatic patients with a wide range of AS severity, we show that all 3 parameters, AVA, PV and the DI, were powerful predictors of AS related-events (sudden death or need for AVR). A progressive event-free survival decrease as AS severity increased was observed for all 3 parameters. In patients with severe AS, event-free survival at 5 years was 16% based on AVA, 7% based on PV and 0% based on a DI < 0.20. We thus confirm the high AS-related event rate in patients with severe AS and extend these findings to parameters less validated such as the AVA and the DI. In contrast, the outcome of mild AS was remarkably good with a very low rate of events especially in the first 2 years. Outcome of moderate AS was intermediate. AS is a progressive disease and these patients need to be regularly followed and informed of the risk of developing severe AS and symptoms requiring an AVR. Rosenhek et al.[20] previously showed that the outcome of patents with moderate AS was worse than commonly assumed with, as in our study, a 50% event-free survival rate at 5 years based on PV. Although expected, the strong link between echocardiographic parameters of AS severity and outcome, whatever hemodynamic parameter is considered, is very reassuring for our clinical practice.

The most important aspect of our study was the evaluation of the prognostic value of a combination of these hemodynamic parameters. As previously mentioned most studies have emphasized the role of one hemodynamic parameter and have often disregarded the others. Our results clearly showed that in addition to AVA or to DI, MPG provides complementary prognostic information. This was true in the overall cohort and also in the subset of patients with moderate or severe AS. Furthermore, even in the subset of severe AS (AVA < 1cm^2 or DI < 0.25) the MPG provided complementary prognostic information as illustrated by the c-statistic value in these subgroups (0.67 and 0.73 respectively). Thus, MPG further refines the risk-stratification of patients with severe AS. The explanation may be related to the exponential relationship between the MPG and the AVA or the DI (Figure 1A and 1B). Among patients with severe AS, modest changes in AVA or DI are associated with much larger changes in MPG which provides a more discriminative value and translates into a complementary prognostic value. Thus, our results strongly support a multi-parametric evaluation of AS severity. It is worth noting that our finding of an independent prognostic value of both AVA and MPG was not related to the presence of patients with discordant grading as our results were sustained after exclusion of these patients.[21,22] In this regard, we found a better agreement between MPG and AVA than previously reported. Consequently, the prevalence of patients with discordant grading was remarkably low with only 6.5% presenting with an AVA < 1 cm^2 and a MPG < 40 mm Hg compared to up to 30% in some studies.[9] In the present study, all examinations were performed by a single operator (last author) with a special attention paid to LVOT measurements as well as recording the highest MPG in multiple views.[23,24]

The present study deserves several comments. First, it was a single center study. Nevertheless, it was a large and prospective study with a wide range of AS severity and predefined intervals of visit. Second, most of the patients were considered asymptomatic based on clinical judgment and no exercise test was performed. However, exercise testing is recommended in 'physically active' patients and the present study reflects real-life practice. Third, we did not consider AVR as an end-point. Although symptoms' assessment portends some degree of subjectivity, it reflects current clinical practice and aortic valve replacement is also influenced by both patients' and physicians' preference and possibly AS severity, before the occurrence of class I indications. In the present study, only AS-related events defined as sudden death or need for AVR (congestive heart failure or occurrence of symptoms due to AS) were considered prospectively and by a single experienced cardiologist. Finally, our aim was not to oppose the AVA and the DI, which are indeed close linked, but to show that a combination of MPG and either the AVA or the DI provides complementary prognostic information.

Conclusion

In a large prospective cohort of asymptomatic patients with a wide range of AS severity and age, we demonstrated that MPG, AVA and the DI were important prognostic factors. More importantly, our results clearly showed that they provide important complementary prognostic information and thus that MPG and AVA or DI should not be opposed but considered in combination. These findings strongly support a multi-parametric approach in the clinical management of AS patients.

Acknowledgments

We would like to specially thank the team of the Centre d'Investigation Clinique, Christophe Aucan from the Assistance Publique – Hopitaux de Paris Département de la Recherche Clinique et du Développement (DRCD), and Estelle Marcault from the Unité de Recherche Clinique Paris Nord for their help and support during all these years.

Funding

Drs. Virginia Nguyen and Tiffany Mathieu were supported by a grant from the Federation Française de Cardiologie; The COFRASA (clinicalTrial.gov number NCT 00338676) and GENERAC (clinicalTrial.gov number NCT00647088) studies are supported by grants from the Assistance Publique – Hôpitaux de Paris (PHRC National 2005 and 2010, and PHRC regional 2007).

Disclosure Statement

None of the authors has any conflict of interest or disclosure related to the present article.

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