Normalized Left Ventricular Workload Using Phase-Contrast Magnetic Resonance Imaging in Patients with Aortic Stenosis

J. Garcia, Z. Keshavarz-Motamed, R. Capoulade, F. Le Ven, L. Kadem, E. Larose and P. Pibarot

Abstract -- **Aortic stenosis (AS) severity contributes to the left ventricle (LV) deterioration due to the aortic valve narrowing and the alteration of systemic hemodynamic load. This load increment may also increase the LV stroke work (SW) which represent the required energy to deliver the blood at ejection. In this study, SW was derived from in-vivo cardiovascular magnetic resonance (CMR) velocity measurements (n=57) using a lumped-parametric model. Furthermore, normalized SW (N-SW) was evaluated as AS severity parameter. SW differentiated from normal flow (>35 mL/m^2) and low flow (<35 mL/m^2) states (p<0.05). N-SW showed a good association with valve effective orifice area (EOA, r=-0.5, p<0.001) and valvulo-arterial impedance (ZVA, r=0.65, p<0.001). A severity threshold for N-SW (1.5 cJ/mL) was found using an EOA=1 cm^2 as AS severity marker. CMR-derived SW and N-SW may be useful to the assessment and grading of AS patients.**

I. INTRODUCTION

Aortic stenosis (AS) is a complex disease that often involves concomitant arterial diseases [1]–[3]. Under this condition, the left ventricle (LV) faces a double load imposed by the AS and the arterial load contributing to the deterioration of the LV function [4]. Furthermore, this double load may increases the LV stroke work (SW) which is the energy that the LV delivers to the blood at ejection, and the potential energy necessary to overcome the viscoelastic proprieties of the myocardium itself.

Transthoracic Doppler-Echocardiography (TTE) is the primary imaging technique to assess and grade AS severity [5], [6]. In addition, cardiovascular magnetic resonance (CMR) imaging has emerged as an accurate alternative to corroborate AS severity when uncertain or discordant results are obtained at TTE [7]–[9]. This challenging situation is often presented in patients with severe AS, reduced low flow (stroke volume indexed < 35 mL/m^2), low transvalvular pressure gradient (<40 mmHg) and preserved ejection fraction (> 50%). It has been reported that up to 35% of AS patients may present these hemodynamic characteristics which are also associated with poor prognosis (< 50 % at 3-year follow-up) [10]–[12]. A comprehensive assessment of LV hemodynamic load may be crucial to early identify patients at risk. In particular, SW has been shown to be effective characterizing the LV loads and consequently patient's outcome by assessing the inotropic state of AS [13]–[15]. Traditional TTE and CMR imaging methods fail to estimate the LVSW which is typically measured invasively by cardiac catheterization and may cause cerebral embolism [16]. However, we recently introduce and validate a simple lumped-parameter model able to evaluate LVSW using TTE/CMR measurements [17], [18]. We hypothesized that LVSW, as calculated by our model using CMR in-vivo data, may detect LV load alterations due to AS severity.

Thus, this study aims to: 1) evaluate in-vivo this previously introduced lumped-parameter model to describe the ventricular-valvular-arterial interaction to estimate LVSW using CMR phase-contrast flow measurements in AS patients, and 2) assess normalized LVSW (N-SW), representing the energy required by the LV to eject 1 mL of blood through the valvulo-arterial system, in the same population.

II. METHODS

Lumped-parameter model

This model (Fig. 1) includes three different sub-models: 1) LV model; 2) AS model; 3) systemic circulation model. It only requires few non-invasively measurements from CMR (valve effective orifice area [EOA] and aortic cross-sectional area of the aorta (AAo) at sino-tubular junction), and systolic pulse pressure at rest measured by sphygmomanometer. Normalized LVSW is given by:

$$\text{N-SW} = \text{LVSW} / \text{SV} \qquad (1)$$

where SV is the stroke volume.

Study population

Eight (8) healthy control subjects (25% female, age = 34 ± 8 years) and 49 patients (37% female, age = 63 ± 16 years) with mild to severe AS (0.60 cm^2 ≤ EOA ≤ 1.79 cm^2)

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underwent CMR scans. AS patients were graded by EOA as indicated by AHA guidelines [6]. All subjects were graded by normal (SVi > 35 mL/m^2) and low flow (SVi < 35 mL/m^2). Systolic pulse pressure (PP=systolic – diastolic pressure) and mean arterial pressure (MAP) at rest was taken previous to CMR examination. A third of patients had bicuspid aortic valve. All subjects provided written informed consent under the supervision of the local IRB.

CMR imaging

CMR imaging was performed with the use of a 1.5 T scanner (Philips Achieva, Philips Healthcare, Best, The Netherlands). Standard LV and aortic examination were performed. Aortic cine images were used to measure the ascending aorta (AAo) diameter. In addition, through-plane phase-contrast imaging was performed in the LVOT upstream from the aortic valve annulus plane and in the vena contracta position (AoVC) [8], [9]. Velocity flow imaging parameters consisted of: TR/TE of 4.60-4.92/2.76-3.05 ms, flip angle 15°, 24 phases, pixel spacing 1.32–2.07 mm, slice thickness 10 mm and acquisition matrix of 256 x 208.

CMR measurements

For each patient, mean pressure gradient (MPG) was determined by simplified Bernoulli formula:

$$MPG = 4 \times Vmax^2 \qquad (2)$$

where Vmax is the maximum through-plane velocity at AoVC. Valve EOA was calculated using jet shear layer detection method from velocity field at AoVC plane [19], [20]. Stroke volume (SV) was estimated from the LVOT plane using integration method during systole. Systemic arterial compliance was calculated by

$$SAC = SVi / PP \qquad (3)$$

where SVi is the indexed SV to body surface area. Systemic vascular resistance was given by

$$SVR = (80 \times MAP) / CO \qquad (4)$$

where CO is the cardiac output. Global (valvulo+arterial) LV load was estimated by the valvulo-arterial impedance as follows:

$$ZVA = (Systolic\ pressure + MPG) / SVi \qquad (5)$$

AS severity classification was based on the EOA: normal (EOA > 2 cm^2), mild (1.5 < EOA < 2 cm^2), moderate (1.0 < EOA < 1.5 cm^2) and severe (EOA < 1.0 cm^2). Measurements were compared by 2-tailed Student t-test or one-way ANOVA. Associations between parameters and LVSW were assessed by Pearson's correlations

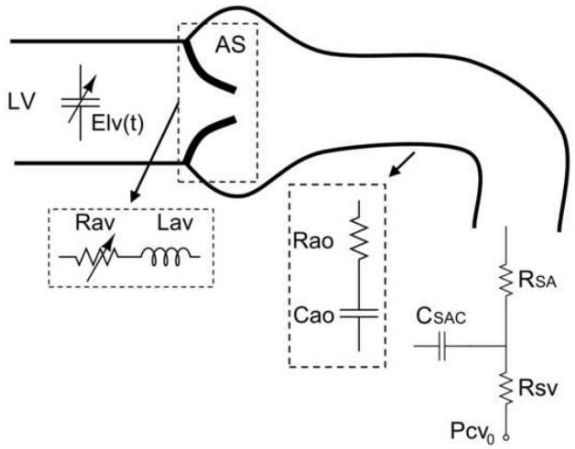

Figure 1. Lumped-parameter model used to simulated left-sided heart in presence of aortic stenosis and/or systemic arterial hypertension. LV: left ventricle; AS: aortic stenosis; Elv (t): normalized time-varying elastance; Rav: variable aortic resistance; Lav: aortic valve inductance; Rao: aortic resistance; Cao: aortic compliance; C_{SAC}: systemic compliance; R_{SA}: systemic resistance; P_{CV0}: central venous pressure. For specific values please see references [17] and [18].

III. RESULTS

Baseline characteristics for healthy controls and AS patients are summarized in Table 1. Age, MPG, EOA, and SAC had a significant difference ($p<0.05$) when comparing healthy controls and AS patients.

A moderate correlation was found between SW and body surface area ($r=0.35$, $p<0.05$) and ascending aorta diameter ($r=0.3$, $p<0.05$). When comparing normal flow and low flow groups for SW a significant difference ($p<0.005$) was found (Fig. 2).

N-SW correlation analysis led to moderate correlations for age ($r=0.35$, $p<0.05$) and SVR ($r=0.31$, $p<0.05$) and to good correlations for EOA ($r=-0.5$, $p<0.001$), SAC ($r=0.68$, $p<0.001$) and ZVA ($r=0.68$, $p<0.001$). For N-SW an ANOVA Tukey's post-hoc analysis comparing healthy controls and AS severities (mild, moderate and severe), as given by EOA grading, led to a significant difference ($p<0.005$) between groups (Fig. 3). From EOA vs. N-SW regression analysis a 1.5 cJ/mL threshold was found for an EOA = 1 cm^2, indicating a severe AS. This threshold was used to divide AS patients into two groups (<1.5 cJ/mL and >1.5 cJ/mL which indicates LV load increase due to AS). A

significant difference ($p<0.001$) was found between both groups (Fig. 4).

Table 1. Baseline characteristic data

	Healthy Subjects (n=8, mean ± SD)	AS Patients (n=49, mean ± SD)
Patient description		
Age	34 ± 8	63 ± 16*
Sex (female %)	25	63
Body surface area (m^2)	1.93 ± 0.26	1.82 ± 0.19
Valve hemodynamics		
Mean transvalvular gradient (mmHg)	5 ± 1	21 ± 11*
Effective orifice area (cm^2)	2.67 ± 0.47	1.18 ± 0.28*
Aortic diameter (mm)	31 ± 4	32 ± 4
LV function and geometry		
Left ventricle mass index ($g/m^{2.7}$)	52 ± 14	49 ± 52
Left ventricular ejection fraction (%)	66 ± 4	66 ± 5
Vascular Hemodynamics		
Systemic arterial compliance ($mL.m^{-2}.mmHg^{-1}$)	1.17 ± 0.32	0.78 ± 0.26*
Systemic vascular resistance ($dyne.s.cm^{-5}$)	1335 ± 284	1801 ± 774
Systolic arterial pressure (mmHg)	116 ± 10	128 ± 22
Diastolic arterial pressure (mmHg)	77 ± 5	71 ± 11
Mean arterial pressure (mmHg)	90 ± 7	90 ± 13
Valvulo arterial impedance (mmHg)	3.35 ± 0.71	3.66 ± 0.85
Vascular Hemodynamics		
Stroke work (J)	1.06 ± 0.33	1.28 ± 0.21
Normalized stroke work (cJ/mL)	1.29 ± 0.23	1.69 ± 0.12

***: $p<0.05$ with healthy.**

IV. DISCUSSION

In this study we showed that LVSW and N-SW can be non-invasively derived from CMR flow velocity measurements using a simple lumped-parameter model. The main findings were: 1) LVSW may differentiate low flow conditions from normal flow in patients with AS; 2) N-SW showed to be strongly associated with AS severity markers such as EOA, ZVA, SAC and SVR; 3) A severity threshold was proposed (N-SW>1.5 cJ/mL) for differentiating severe AS load increment from moderate and/or normal load.

Both SW and N-SW measurements may be useful in the clinical assessment of AS patients. SW showed to be able to detect flow state differences from AS patients (Fig. 2). Low flow population is clinically challenging because AS severity appears less severe that it is in the basis of EOA or MPG, as indicated by the guidelines [21]–[23]. In consequence, clinicians may mislead their assessment and not refer to a necessary surgery. Indeed, these patients typically are on a more advanced stage of AS severity [24]. However, the findings of this study must be carefully taken given the small number of patients (n=5) with low flow. In addition to aortic valve restriction, AS patients may have multiple factors altering LV load and systemic hemodynamics [25], [26]. In particular, the evaluated population of this study showed increased SAC, SVR, and ZVA. It should be notice that SW did not show any association with those parameters. However, when SW was normalized to the SV the association resulted statistically significant. This may be due to the fact that N-SW represents the global hemodynamic load imposed to the LV for ejecting a unit of blood volume. Since the isolated SW only represents the required LV work for heart beat.

Due to its invasive nature SW is not used in the clinical assessment of AS patients. However, the proposed approach opened a non-invasive option to assess it. The most used parameter to assess LV load in the clinical setup is the ZVA which represents the load imposed on the LV. Thus, the ZVA and the N-SW may be closely related, as shown by our findings ($r=0.65$, $p<0.001$). It is then important to define some important differences between these two parameters: 1) N-SW is not flow dependent as ZVA, and 2) N-SW determines the total mechanical load imposed to the LV while ZVA gives a global estimate. Thus ZVA may be less sensitive to assess AS patients with low flow states, as suggested by Lancelloti et al. [11]. One of the main contributions of this study is the introduction of a severity threshold for N-SW (1.5 cJ/mL). This threshold was derived from a linear regression analysis between EOA and N-SW and was estimated to match with an EOA = 1 cm^2, regardless the valve phenotype and flow state. However, further studies are needed to explore its diagnostic value.

V. CONCLUSIONS

The evaluated lump-parameter model used to estimate left ventricle hemodynamic load, SW and N-SW, may be useful to the assessment of AS severity in patients with low flow state. Furthermore, a severity threshold was derived for the assessment of AS severity, regardless valve phenotype and flow state, which may be useful for improving the stratification of AS patients.

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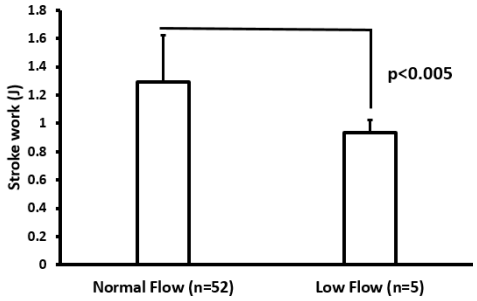

Figure 2. Left ventricle stroke work comparison between normal low (>35 mL/m^2) and low flow (<35 mL/m^2).

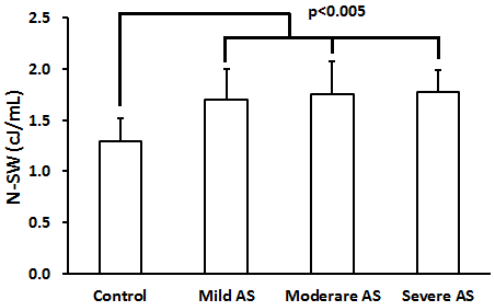

Figure 3. Group comparison for normalized left ventricle stroke work (N-SW) between healthy controls and mild aortic stenosis (AS), moderate AS, and severe AS.

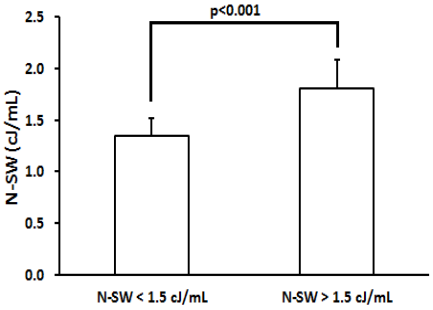

Figure 4. Normalized left ventricle stroke work (N-SW) comparison between N-SW > 1.5 cJ/mL and N-SW < 1.5 cJ/mL. N-SW threshold was obtained from EOA vs. N-SW linear regression using an EOA= 1 cm^2.

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