Am J Cardiovasc Dis 2020;10(3):150-163
www.AJCD.us /ISSN:2160-200X/AJCD0116955

Original Article

Right ventricular deformation and right ventricular-arterial coupling in patients with heart failure due to severe aortic stenosis undergoing TAVI: long-term results

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Received June 25, 2020; Accepted August 10, 2020; Epub August 15, 2020; Published August 30, 2020

Abstract: Aim: To evaluate the long-term prognostic significance of right ventricular (RV) deformation and RV-arterial coupling in a cohort of patients with heart failure (HF) due to severe aortic stenosis (AS) candidate for trans-catheter aortic valve implantation (TAVI). Methods: The study is a retrospective analysis of 56 patients undergoing echocardiography before TAVI execution. RV function was defined by tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC), peak systolic myocardial velocity by tissue Doppler imaging (RVSm) and RV longitudinal strain (RVLS). RV-arterial coupling were defined as TAPSE and RVLS normalized for systolic pulmonary artery pressure (sPAP) to obtain afterload-independent parameters: TAPSE/sPAP and RVLS/sPAP, respectively. All-cause mortality was the primary endpoint of survival analysis; composite of death and hospitalization for HF was the secondary endpoint. Results: All patients underwent TAVI from femoral access. Mean age was 81.6±6.3 years and left ventricular ejection fraction was preserved in most patients (51±15%). At 10 years, using Cox regression analysis adjusted for the parameters related to prognosis at univariate analysis, we found that only pre-procedural RVLS was independently associated with all-cause mortality (aHR 1.53, 95% CI 1.10-2.12, P=0.011). RVLS (aHR 7.542, 95% CI 1.325-42.921, P=0.023), sPAP (aHR 1.421, 95% CI 1.045-1.932, P=0.025), TAPSE/sPAP (aHR 4.977, 95% CI 5.425-21.99, P=0.044) and RVLS/sPAP (aHR 2.333, 95% CI 3.9677-12.999, P=0.046) were independently associated with the secondary endpoint. Conclusions: Among patients with HF due to severe AS undergoing TAVI, deformation imaging (i.e., RVLS) and RV-arterial coupling (i.e., TAPSE/sPAP and RVLS/sPAP) provide better risk stratification at long-term follow up of 10 years than other RV echocardiographic parameters.

Keywords: Right ventricular function, right ventricle longitudinal strain, trans-catheter valve implantation, heart failure, right ventricular-arterial coupling

Introduction

Trans-catheter aortic valve implantation (TAVI) was demonstrated to reduce mortality and morbidity in patients with severe aortic stenosis (AS), considered at prohibitive, high and intermediate surgical risk [1, 2]. Moreover, it was recently shown that TAVI is also a valid alternative to surgery in patients at low surgical risk [3, 4]. However, according to current guidelines, patients candidate for TAVI still have high rates of short- and long-term mortality, because of their comorbidities and procedure-related complications [5-9]. To now, there is no TAVI risk predicting model comparable to the Logistic EuroScore used in cardiac surgery, even if several clinical and procedural characteristics have been shown to affect the outcome after TAVI. Baseline cardiovascular characteristics (e.g., low left ventricular ejection fraction (LVEF), moderate-to-severe mitral regurgitation (MR)) and procedural complications (e.g., vascular complications, residual aortic regurgitation (AR), need for cardiac stimulation) are now recognized to play a central role in acute and early mortality. Regarding long-term mortality, non-

cardiac comorbidities (such as anemia, liver disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease) seem to be more important [2, 10]. Pre-procedural full echocardiographic assessment of patients with AS candidate for TAVI or surgery should be performed to identify anatomical and functional detailed features of the aortic valve, ascending aorta and LV [11-13]. Importantly, lack of knowledge does still exist about the role of right ventricular (RV) dysfunction. Given its particular position and shape, cardiovascular magnetic resonance (CMR) is the gold standard to evaluate RV volumes, mass and function, but it has limited availability [14-16]. For this reason, echocardiography is still the most used imaging technique in this field [17]. Tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE) estimate ventricular contractility which is less influenced by passive motion of the myocardium and loading conditions [18]. In particular, load-independent indices of RV function are able to determine RV-arterial coupling and can be obtained normalizing RV longitudinal systolic parameters to RV afterload (i.e., systolic pulmonary artery pressure (sPAP)) [19]. The idea that such parameters could be more efficacious prognostic markers in HF than other conventional echocardiographic parameters is now well recognized [20-22]. We aimed to assess the role of pre-procedural RV STE and RV-arterial coupling in predicting long-term outcome in patients with HF undergoing TAVI.

Materials and methods

Study population

The present study is a retrospective evaluation of a cohort of 56 patients with severe degenerative AS in tricuspid valves (valve area ≤ 1.0 cm^2 or peak velocity > 4 m/s) who were referred for TAVI between September 2009 and September 2012 at the Cardiology Department of the University Hospital ASST Spedali Civili of Brescia, Italy. Inclusion criteria were: diagnosis of severe degenerative AS and recent onset of symptoms and sign of HF not due to other concomitant conditions than AS; age > 18 years; adequate image quality for post-hoc analysis of STE measurements; planned TAVI with transfemoral access during hospitalization. Exclusion criteria were: concomitant diagnosis of coronary artery disease requiring revascularization during hospitalization for TAVI; idiopathic cardiomyopathy; history of pulmonary embolism; recent acute coronary syndrome or revascularization (in the previous 3 months); other life-threatening comorbidities with adverse prognosis at time of hospitalization for symptomatic AS; any disease causing precapillary pulmonary hypertension (PH). The study was carried out according to the principles of the Declaration of Helsinki and approved by local ethics committee; all patients provided written informed consent. TAVI was performed under general anesthesia. Patients underwent CoreValve implantation due to high/prohibitive risk for surgical operation.

Data collecting and echocardiographic parameters

For each patient we collected pre-operative clinical and demographic characteristics (at time of hospitalization for TAVI): age, sex, body mass index (BMI), biochemical data, functional class (New York Hear Association, NYHA), clinical history and risk factors (i.e., hypertension, diabetes, coronary heart disease, COPD), preoperative cardiac surgery risk score assessed as Logistic EuroScore. We used all pre-operative echocardiographic images of study participants for post-hoc analysis of parameters. The echocardiographic evaluation was performed in a blinded way by two specialists and included mono- and two-dimensional evaluation, continuous Doppler, pulsed Doppler, TDI. All LV and RV parameters were evaluated and analyzed according to the more recent international standards defined by the American Society of Echocardiography and the European Association of Cardiovascular Imaging [17, 23]. LVEF was calculated using the Simpson's biplane method. The mean pressure gradient across the aortic valve was estimated using the simplified Bernoulli equation. Using Doppler echocardiography, peak aortic velocity, peak left ventricular outflow tract (LVOT) velocity, aortic and LVOT velocity time integral (VTI) and mean pressure gradient were determined [24]. The effective orifice area (EOA) was calculated from the continuity equation. MR, AR, and tricuspid valve regurgitation (TR) were evaluated using spectral and color-Doppler images and graded as trivial, mild, moderate, and severe, as recommended [25]. LV and RV diastolic function was obtained as the ratio of the early

and late diastolic trans-mitral and trans-tricuspidal flow velocities (LV E/A ratio and RV E/A ratio), by the deceleration time of the early diastolic trans-mitral and trans-tricuspidal flow velocity (LV E deceleration time, RV E deceleration time) [17, 26]. The sPAP was calculated by measurement of the TR velocity and estimation of the right atrial pressure by dimension and collapsibility of the inferior vena cava [17]. RV systolic quantitative parameters were consistent with current guidelines and acquired as follows: fractional area change (FAC), peak systolic myocardial velocity by TDI (RVSm), tricuspid annular plane systolic excursion by M-Mode (TAPSE), RV longitudinal strain (RVLS) [17]. FAC was computed as: (RV diastolic area-RV systolic area)/RV diastolic area × 100% [17]. Echocardiographic images for deformation analyses had been stored at a frame rate between 50 and 70 frames/sec, for at least three cardiac cycles. Loops were processed with an ad hoc software (EchoPAC BT12; GE Medical Systems), allowing offline STE analyses. For RVLS loops had been acquired using 4 chamber view, RV endocardial border was traced at the end-systolic frame and RV was partitioned into 6 standard segments at 3 levels (i.e., the basal, middle, and apical levels), correspondingly generating 6 time-strain curves. We calculated the global RVLS values by averaging the values computed at the segmental level, as recommended in the consensus document of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [27]. TAPSE/sPAP ratio and RVLS/sPAP ratio were derived as indexes of RV-arterial coupling to obtain afterload-independent parameters [19-22].

Follow-up and endpoint of the study

The follow-up was conducted either at the hospital during a routine clinical evaluation or by telephone contact with the patients, their relatives or family doctors, and was 100% complete. Long-term mortality included death for any cause. Readmission at follow-up included any episode of re-hospitalization for HF. The primary endpoint of the present study was long-term (10-year) mortality from any cause. Secondary endpoint was long-term freedom from cardiac events, defined as combined of death of any cause and HF readmission (combined endpoint).

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD). Frequencies are reported as number (%). We randomly selected 10 patients and evaluated intra-observer and inter-observer variabilities using Pearson's correlation coefficient (R), Bland-Altman with limit of agreement (LOA) statistics and intraclass correlation coefficient. Univariate analysis was performed to identify the correlates of RV dysfunction described as TAPSE < 17 mm or RVLS < median value (given the absence of consensus about a cut-off for normality in the general population): variables tested included those known to cause or contribute to RV dysfunction, including age, history of coronary artery disease, arterial pressure, LVEF, sPAP. Odds ratios (OR) and their 95% confidence intervals (CI) were computed by means of logistic models. Cumulative survival was calculated based on Kaplan-Meier estimates; the endpoint of survival analysis was all-cause death and combined endpoint of all-cause death and hospitalization for HF. Cox regression model was used for defining multivariate analysis with variables and survival (time-free event). All statistical analyses were performed using SPSS V.21 .0, IBM, Chicago, Illinois, USA), with a two-sided significance level of p 0.05.

Results

Patients population and echocardiographic measurements

56 patients were included in this retrospective analysis. Patients underwent TAVI during hospitalization and 50% of them were treated with 26 mm valve and other 50% with 29 mm valve, according to pre-operative evaluation. TAVI was performed by femoral access in all patients, so they were homogeneous under this point of view. Clinical and demographic characteristics of patients are listed in (**Table 1**). Mean age was 81.6±6.3 years and patients were at high risk for surgical replacement according to Logistic EuroScore (mean value more than 20%). Most patients had hypertension (70%) and coronary artery disease (50%). At time of evaluation most patients were hemodynamically stable (mean systolic pressure: 128 mmHg, mean diastolic pressure: 68 mmHg)

Table 1. Clinical features of patients population

Variable	Value (n=56)
Age (years)	81.6±6.3
Male gender	24 (42.9%)
Body mass index (kg/m^2)	26.6±4.6
Logistic EuroScore (%)	24.1±17.9
Creatinine clearance (mL/min)	47±22
Hemoglobin (g/dL)	11.8±2.2
NYHA Class III-IV	42 (75.0%)
Systolic arterial pressure (mmHg)	127.7±20.2
Diastolic arterial pressure (mmHg)	67.5±10.9
Hypertension	39 (69.6%)
Diabetes mellitus	16 (28.6%)
Coronary artery disease	28 (50.0%)
Chronic obstructive pulmonary disease	12 (21.4%)
Previous cardiac surgery	15 (26.8%)

NYHA, New York Heart Association.

and most had functional class NYHA III (41 patients, 73%).

Echocardiographic parameters are listed in **Table 2**. Patients had LV hypertrophy and the mean of values of LVEF was 51±15%, so no one of patients enrolled had severe systolic dysfunction (LVEF < 35%). Mean trans-aortic gradient was 51 mmHg; AR was mild in 32% of patients, moderate in 53% and severe only in 5% of patients. Concomitant MR was mild in 38% of patients, moderate in 62% and no one had severe MR. About TR, there was more heterogeneity: 50% of patients had mild TR, 27% moderate and 23% severe. Most patients had PH pre-TAVI (sPAP was 39±16 mmHg). Continuous Doppler on tricuspid valve showed reduced early diastolic flow (E/A < 1), with mean deceleration time 216±47 ms. Tricuspid annulus diameter, FAC, TAPSE, RVSm had normal values. Before TAVI we observed 42.9% (n=24) of prevalence of RV dysfunction detected by TAPSE < 17 mm.

Intra-observer and inter-observer variabilities

Intra-observer and inter-observer variabilities for our measures, obtained from 10 patients of study population, are summarized in **Table 3** and Supplementary Figure 1. The intra-class correlation coefficients for RVLS was 0.891 (95% CI 0.721-0.960, P < 0.001) for intra-observer variability and 0.827 (95% CI 0.519-0.939, P=0.001) for inter-observer variability. With Bland-Altman plots we found the following bias: for intra-observer variability -0.75% (range from -5.13% to 3.63% for 95% LOA) and for inter-observer variability -0.31% (from -7.13% to 6.50% for 95% LOA).

Correlates of RV dysfunction

We tested clinical and echocardiographic variables in multivariate analysis for evaluating factors associated with RV dysfunction at baseline, expressed as TAPSE < 17 mm and RVLS < median value of our cohort (> -17%) (**Table 4**). For TAPSE, we found significant relations with: gender (OR 0.235, 95% CI 0.076-0.727, P=0.012), coronary artery disease (OR 2.8, 95% CI 0.617-5.251, P=0.049), previous cardiac surgery (OR: 5.923, 95% CI 1.582-22.172, P=0.008), and sPAP (OR 2.600, 95% CI: 1.2-6.333, P=0.042). A weak correlation was found with LV mass (OR 1.007, 95% CI 1.000-1.014, P=0.050), not maintained after indexation for body surface area. No correlation was observed between TAPSE and sPAP in our cohort, nor between TAPSE and grade of TR or tricuspid annulus diameter. Predictors of reduced RVLS were found to be: hypertension (OR 0.290, 95% CI 0.085-0.985, P=0.047), coronary artery disease (OR 2.800, 95% CI 0.617-5.251, P=0.049), previous cardiac surgery (OR 3.882, 95% CI 1.056-14.276, P=0.041), sPAP (OR 3.622, 95% CI 0.988-12.333, P=0.007).

Long-term outcomes

The mean follow-up length in the overall population was 8.5±0.5 years. During follow-up, 46 patients died (82% of our cohort). At univariate analysis predictors of survival were (**Table 5**): low grade of TR (HR 0.585, 95% CI 0.392-0.875, P=0.009), tricuspid annulus diameter (HR 0.929, 95% CI 0.882-0.978, P=0.005); TAPSE (HR 0.943, 95% CI 0.890-0.999, P= 0.047), TAPSE/sPAP (HR 0.195, 95%CI 0.050-0.765, P=0.019), RVLS (HR 1.140, 95% CI 1.072-1.213, P < 0.001), RVLS/sPAP (HR 11.432, 95% CI 2.837-46.070, P=0.001). The Kaplan-Meier curve of 10-year survival according to RVLS value in our cohort is presented in **Figure 1** (chi-square 7.8, log-rank; P=0.05). We performed a Cox regression multivariable analysis, adjusted for the parameters related to prognosis at univariate analysis, and we found that only RVLS was independently associate with all-cause mortality (adjusted HR 1.53, 95% CI 1.10-2.12, P=0.011).

Table 2. Echocardiographic characteristics of patients population

Variable	Value (n=56)
Aortic annulus diameter (mm)	22.8±2.0
Sinus of Valsalva diameter (mm)	32.9±3.6
Tubular tract diameter (mm)	36.0±3.4
LA antero-posterior diameter (mm)	45±8
LA area (cm^2)	26±10
EDD (mm)	55±11
IVS (mm)	14±2
PWT (mm)	15±3
LV mass (g)	348.3±110.8
LV mass index (g/m^2)	198.8±54.5
EDV (mL)	114±50
ESV (mL)	54±31
LVEF (%)	51±15
Peak transaortic gradient (mmHg)	86±24
Mean transaortic Gradient (mmHg)	51±17
Aortic regurgitation	
- trivial	21 (37.5%)
- mild	18 (32.1%)
- moderate	14 (25.0%)
- severe	3 (5.4%)
Mitral regurgitation	
- trivial	0 (0.0%)
- mild	21 (37.5%)
- moderate	35 (62.5%)
- severe	0 (0.0%)
Tricuspidal regurgitation	
- trivial	0 (0.0%)
- mild	28 (50.0%)
- moderate	15 (26.8%)
- severe	13 (23.2%)
sPAP (mmHg)	39.1±15.7
RV E (m/s)	0.34±0.14
RV A (m/s)	0.5±0.2
RV E/A	0.9±0.9
RV DT (ms)	216±47
Tricuspid anulus diameter (mm)	34.9±6.6
IVC diameter (mm)	18.4±4.7
FAC (%)	35.8±13.4
RVLS (%)	-17.6±4.8
TAPSE (mm)	18.6±4.8
RVSm (m/s)	0.1±0.03
TAPSE/sPAP (mm/mmHg)	0.50±0.23
RVLS/sPAP (%/mmHg)	-0.48±0.23

A, late diastolic flow velocity; DT, deceleration time; E, early diastolic flow velocity; EDD, end-diastolic diameter; EDV, end-diastolic volume; ESV, end-systolic volume; FAC, fractional area change; IVC, inferior vena cava; IVS, interventricular septum thickness; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; PWT, posterior wall thickness; RV, right ventricular; RVLS, right ventricular longitudinal strain; RVSm, peak systolic myocardial velocity by TDI; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

The combined endpoint was reached by 82% of patients. At univariate analysis the predictors were (**Table 6**): grade of TR (HR 0.634, 95% CI 0.427-0.942, P=0.024), tricuspid annulus diameter (HR 0.929, 95% CI 0.882-0.978, P=0.037); TAPSE/sPAP (HR 0.193, 95% CI 0.048-0.775, P=0.020), RVLS (HR 1.23, 95% CI 1.058-1.192, P < 0.001), sPAP (HR 1.020, 95% CI 1.001-1.040, P=0.042), RVLS/sPAP (HR 12.3, 95% CI 2.9-52.031, P=0.001). Even for this endpoint, we performed a multivariable Cox regression analysis, adjusted for the parameters related to prognosis at univariate analysis, and we found correlations with RVLS (adjusted HR 7.542, 95% CI 1.325-42.921, P=0.023), sPAP (adjusted HR 1.421, 95% CI 1.045-1.932, P=0.025), TAPSE/sPAP (adjusted HR 4.977, 95% CI 5.425-21.99, P=0.044), RVLS/sPAP (adjusted HR 2.333, 95% CI 3.9677-12.999, P=0.046). **Figure 2** shows the Kaplan Meier curves of survival free from the composite endpoint according to these four parameters.

Discussion

The main finding of this study is that pre-operative careful and comprehensive evaluation of RV function (including deformation) and RV-arterial coupling can predict long-term outcomes of patients with HF and AS who are candidate for TAVI. Death for any cause was independently predicted by RVLS, while the composite endpoint of death and HF hospitalization was independently associated to each one of RVLS, sPAP, TAPSE/sPAP and RVLS/sPAP. Our patients were homogeneous regarding their demographic characteristics, aortic valve grade of degeneration, LVEF, type of intervention (all patients had femoral access), so these parameters were not related to long-term incidence of events. Indeed, all patients in our cohort had LV hypertrophy and a mean LVEF of 51±15%, so no one of patients enrolled had severe systolic dysfunction (LVEF < 35%). Recently, Sultan et al. found that TAPSE/sPAP quartiles have a linear relationship with 2-year all-cause mortality after TAVI in a larger population with similar characteristics to ours [28]. Our study is the first with a so long follow-up (8.5±0.5 years), and the results are even more important because of the recent moving to treatment with TAVI from higher to lower-risk groups, which have a longer life-expectancy [3, 4]. These results highlight the importance of RV function assessment by different methods for better

Table 3. Intraobserver and interobserver variabilities using Bland-Altman statistics, intraclass correlation coefficient (ICC) and Pearson's correlation coefficient (R)

Intra	Measure 1	Measure 2	Bland-Altman (95% CI)	ICC (95% CI)	R
RVLS (%)	-17.3±4.6	-16.6±5.1	-0.75% (-5.13%-3.63%)	0.891 (70.721-0.960), P < 0.001	0.9, P=0.04
Inter	Measure 1	Measure 3	Bland-Altman (95% CI)	ICC (95% CI)	R
RVLS (%)	-17.3±4.6	-17.1±4.1	-0.31% (-7.13%-6.50%)	0.827 (0.519-0.939), P=0.001	0.7, P=0.03

Two specialists reviewed the images of 10 randomly selected patients; both specialists performed RVLS measure; the first performed 2 measurements (Measure 1 and 2) for evaluating the intraobserver variability, the second specialist performed only one measure (Measure 3), that was compared with Measure 1 for the interobserver variability.

Table 4. Independent predictors of reduced TAPSE < 17 mm and RVLS > -17%

Clinical and demographic characteristics	TAPSE < 17 mm			RVLS > -17%		
	OR	95% CI	P	OR	95% CI	P
Age	1.04	0.947-1.134	0.44	0.94	0.85-1.03	0.18
Sex (male vs female)	0.24	0.076-0.727	0.01	1.00	0.14-1.22	0.11
Body mass index	1.01	0.899-1.137	0.85	1.00	0.89-1.12	0.99
NYHA class	1.81	0.595-5.517	0.30	0.57	0.19-1.66	0.30
Hypertension	0.39	0.122-1.259	0.12	0.29	0.085-0.985	0.05
Diabetes mellitus	1.50	0.467-4.816	0.50	0.70	0.22-2.26	0.55
Coronary artery disease (yes vs no)	2.80	0.617-5.251	0.05	2.80	0.62-5.25	0.05
Logistic EuroScore	1.02	0.985-1.049	0.30	1.02	0.99-1.05	0.21
COPD	2.22	0.60-8.104	0.23	2.40	0.63-9.16	0.20
Previous cardiac surgery	5.92	1.58-22.17	0.01	3.88	1.06-14.28	0.04
Creatinine clearance	0.98	0.95-1.00	0.17	1.00	0.98-1.03	0.72
Hemoglobin	0.90	0.69-1.15	0.40	1.18	0.88-1.57	0.26
Systolic arterial pressure	1.00	0.97-1.029	0.89	1.02	0.99-1.05	0.24
Diastolic arterial pressure	0.98	0.93-1.031	0.45	1.06	1.01-1.12	0.02
Echocardiographic measurements	OR	95% CI	P	OR	95% CI	P
Aortic annulus diameter	1.32	1-1.75	0.05	0.96	0.74-1.25	0.77
Sinus of Valsalva diameter	1.02	0.872-1.18	0.84	0.94	0.81-1.10	0.44
Tubular tract diameter	1.14	0.964-1.352	0.13	0.99	0.85-1.16	0.91
LA antero-posterior diameter	1.06	0.96-1.16	0.24	1.04	0.95-1.14	0.40
LA area	0.95	0.839-1.073	0.40	1.19	0.95-1.50	0.13
EDD	1.03	0.96-1.091	0.36	1.02	0.96-1.08	0.45
IVS	1.01	0.76-1.337	0.96	1.01	0.77-1.33	0.95
PWT	1.02	1.053-1.914	0.22	1.14	0.90-1.44	0.27
LV mass	1.01	0.99-1.014	0.05	1.00	0.99-1.01	0.29
EDV	1.01	0.99-1.02	0.29	1.01	0.99-1.02	0.44
ESV	1.03	0.998-1.062	0.06	1.02	0.99-1.04	0.16
LVEF	0.99	0.957-1.029	0.67	0.99	0.95-1.03	0.58
Peak trans-aortic gradient	1.00	0.972-1.019	0.69	1.01	0.98-1.03	0.41
Medium trans-aortic gradient	1.00	0.965-1.035	0.98	1.02	0.99-1.06	0.19
Aortic regurgitation	1.19	0.724-1.941	0.50	0.97	0.59-1.58	0.90
Mitral Regurgitation	0.67	0.322-1.390	0.28	1.21	0.59-2.46	0.59
sPAP	2.60	1.200-6.333	0.04	3.62	0.988-12.333	0.01
Tricuspid regurgitation	1.63	0.84-3.180	0.15	1.31	0.68-2.52	0.41
Tricuspid annulus diameter	1.08	0.99-1.182	0.08	0.93	0.85-1.01	0.08

EDD, end-diastolic diameter; EDV, end-diastolic volume; ESV, end-systolic volume; IVS, interventricular septum thickness; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; PWT, posterior wall thickness; sPAP, systolic pulmonary artery pressure.

Table 5. Cox proportional hazard model for all-cause mortality; variable adjusted included each one of variables related to the endpoint at univariate analysis

	Unadjusted			Adjusted		
	HR	95% CI	P	HR	95% CI	P
Tricuspid regurgitation	0.585	0.392-0.875	0.009	0.471	0.17-1.30	0.147
Tricuspidal annulus diameter	0.929	0.882-0.978	0.005	1.023	0.87-1.20	0.781
FAC	0.986	0.964-1.008	0.209	0.6	0.89-1.2	0.89
RVLS	1.140	1.072-1.213	< 0.001	1.53	1.10-2.12	0.011
TAPSE	0.943	0.890-0.999	0.047	1.154	0.92-1.43	0.201
sPAP	1.017	0.998-1.037	0.086	-	-	-
TAPSE/sPAP	0.195	0.050-0.765	0.019	0.019	0.00023-1.64	0.082
RVsm	0.001	0.000-10.817	0.137	0.6	0.13-1.06	0.12
RVLS/sPAP	11.432	2.837-46.070	0.001	0.5	0.6-0.99	0.14

FAC, fractional area change; RVLS, right ventricular longitudinal strain; RVSm, peak systolic myocardial velocity by TDI; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

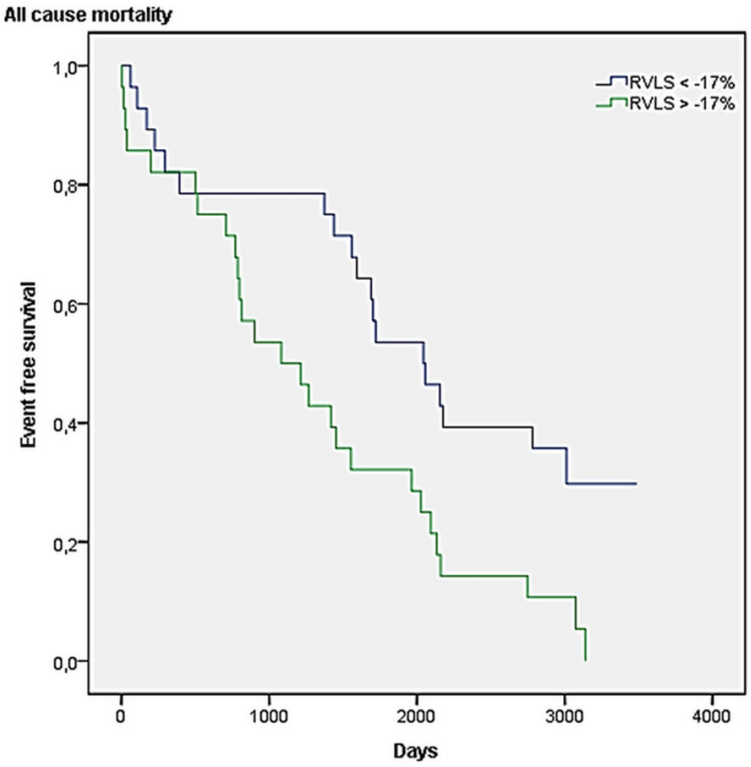


Figure 1. Kaplan-Meier 10-year survival curves according to RVLS value in our cohort (chi-square 7.8, log-rank P=0.05).

stratification of prognosis of patients admitted for HF due to severe AS and candidate for TAVI.

As well known, TAPSE and RVSm reflect the function of the basal segment of the RV free wall, which is assumed to represent RV global function; for the same reason, given the base-apex motion gradient of right fibers, they are mostly load-dependent. This could be an important limitation for these parameters in predicting long-term prognosis when regional dysfunction is supposed and, moreover, when a reduction in RV afterload is forecast, such as after TAVI [29]. In other previous studies we demonstrated the superiority of RVSm compared with TAPSE and FAC in predicting prognosis of patients with chronic HF [30, 31]. Indeed, in 31 patients with HF with no or mild RV dysfunction we correlated all echocardiographic parameters with the CMR-calculated RVEF, stroke volume, end-diastolic volume, and end-systolic volume and we found that, given the importance of longitudinal deformation of RV fibers in whole RV function, there was a strongest correlation between RVLS and not only RVEF, but also RV volumes [32]. In addition, RVLS is an independent predictor of first HF hospitalization and death for any cause in patients with asymptomatic left-sided structural heart disease at 5-year follow-up [33]. PH itself is an accepted predictor of poor outcome both after cardiac surgery and TAVI [34, 35]. Gerges et al. analyzed RV function in patients with HF and PH, and demonstrated that TAPSE/sPAP, which is validated against invasive hemodynamics [19], was a predictor of combined pre-capillary

Table 6. Cox proportional hazard model for all-cause mortality + heart failure hospitalization; variable adjusted included each one of variables related to the endpoint at univariate analysis

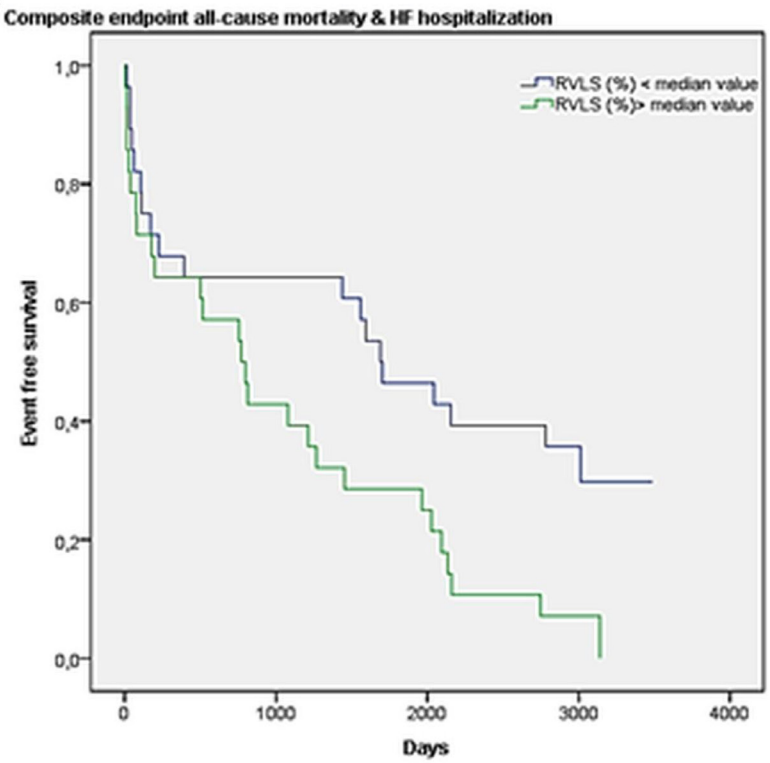
	Unadjusted			Adjusted		
	HR	95% CI	P	HR	95% CI	P
Tricuspid regurgitation	0.634	0.427-0.942	0.024	5.412	0.54-54.24	0.151
Tricuspidal annulus diameter	0.929	0.882-0.978	0.037	1.514	0.985-2.326	0.059
FAC	0.986	1.058-1.192	0.340	-	-	-
RVLS	1.23	1.058-1.192	< 0.001	7.542	1.325-42.921	0.023
TAPSE	0.953	0.899-1.009	0.100	-	-	-
sPAP	1.020	1.001-1.040	0.042	1.421	1.045-1.932	0.025
TAPSE/sPAP	0.193	0.048-0.775	0.020	4.977	5.425-21.99	0.044
RVsm	0.001	0.000-10.817	0.400	-	-	-
RVLS/sPAP	12.3	2.9-52.031	0.001	2.333	3.9677-12.999	0.046

FAC, fractional area change; RVLS, right ventricular longitudinal strain; RVSm, peak systolic myocardial velocity by TDI; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

and post-capillary PH on univariate and multivariate analyses [36, 37]. O'Sullivan et al. enrolled 606 consecutive patients undergoing TAVI and pre-procedural right heart catheterization and demonstrated that, when compared with no PH, a higher 1-year mortality rate was observed in both pre-capillary and combined pre-capillary and post-capillary, but not isolated post-capillary PH patients [38]. Indeed, in the setting of HF, a growing evidence suggests the role of RV-arterial coupling in predicting early and long-term outcomes of patients, regardless of TAPSE, sPAP and RVEF [39, 40]. In patients with HF and both reduced and preserved LVEF, TAPSE/sPAP and RVLS/sPAP have shown to strongly predict long-term mortality and re-hospitalization [20-22]; more importantly, patients with preserved LVEF have less frequently RV dysfunction, but similar TAPSE/sPAP when compared with patients with reduced LVEF. Our findings are in line with recent evidences about the role of RV function and RV-arterial coupling in patients with HF and preserved LVEF [21]. Myocardial deformation imaging is more sensitive and specific than other methods in detecting RV global dysfunction, taking into account not only the basal-lateral segment; but, more important, this method is load independent, so it could maintain its value even after TAVI. Our findings highlight the importance of serial evaluation of RV function corrected for afterload, for early detection of pulmonary vascular remodeling leading to irreversible PH that could affect long-term prognosis of patients with AS. RVLS and RV-arterial coupling assessed as TAPSE/sPAP and RVLS/sPAP could detect the grade of global (rather than segmental) involvement of right chambers in chronic adaptation to AS and the grade of non-reversible cardio-pulmonary remodeling despite correction of severe AS by TAVI. These parameters, irrespective to other echocardiographic and clinical features, could reveal an important hemodynamic involvement so they should be periodically assessed during the echocardiographic follow-up of patients with severe AS without symptoms or evident PH. These results on composite endpoint including hospitalization for HF reaffirm, as expected, the role of both loading condition and RV contractility parameters on symptoms of congestion even after TAVI.

In the setting of cardiac surgery, the prognostic role of the preoperative RV dysfunction in predicting both early ad long-term outcomes have been widely underlined by several authors [41, 42]. The more, when compared with aortic replacement, TAVI results in better preservation of RV volumes and function [43], and also RV deformation [44]. In addition, RVLS was demonstrated to be more impaired after surgical replacement than TAVI in a small population of patients [45]. These evidences support the importance of carefully evaluating RV function before strategy decision in patients with severe AS. Patients with pre-existing RV dysfunction could have worse outcomes after aortic valve replacement because of the well-known impact of surgery on this chamber. Comparing traditional RV systolic parameters (TAPSE, FAC) with RVLS, Ternacle et al. found that 34% of patients

A


Composite endpoint all-cause mortality & HF hospitalization
RVLS (%) < median value
RVLS (%)> median value
Event free survival
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0,6
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1000
2000
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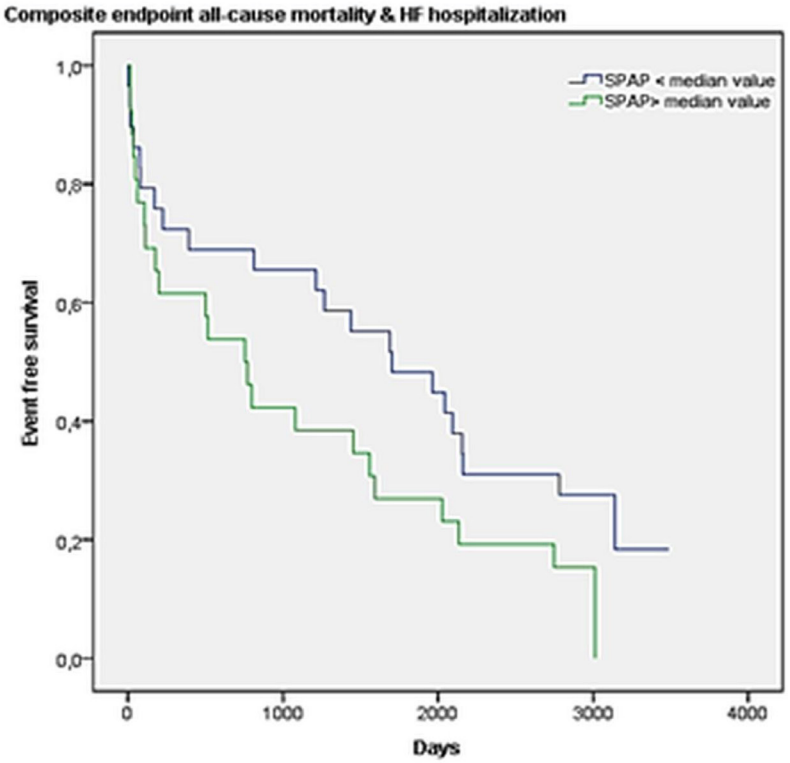
Composite endpoint all-cause mortality & HF hospitalization
SPAP < median value
SPAP> median value
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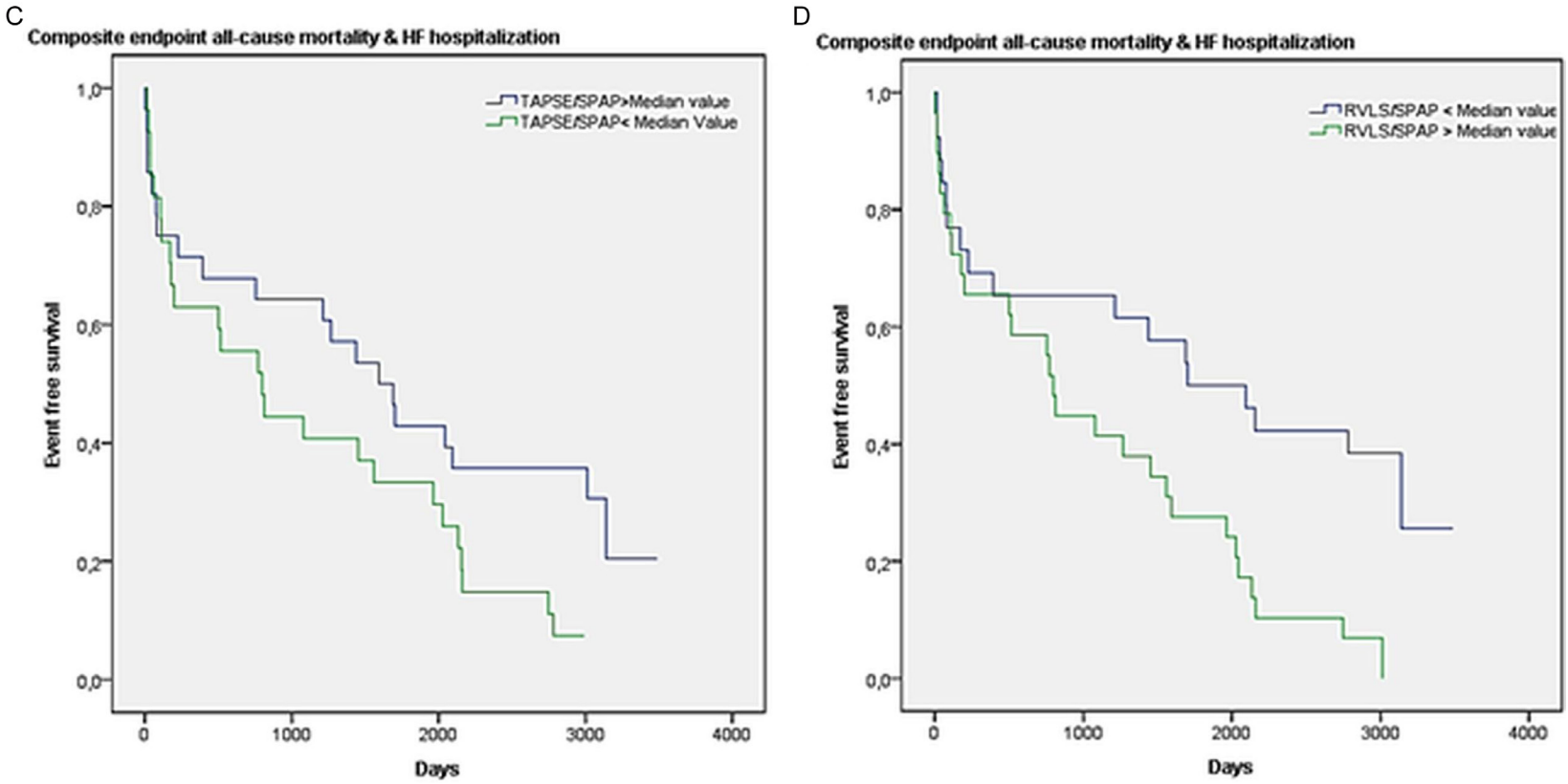

Figure 2. Kaplan-Meier 10-year curves of survival free of composite endpoint according to: (A) RVLS; (B) sPAP; (C) TAPSE/sPAP; (D) RVLS/sPAP.

with normal FAC but abnormal RVLS were at higher risk for post-operative mortality after surgical valve replacement, demonstrating that conventional parameters are less effective compared with STE [46]. Indeed, in another study of patients candidate for TAVI, RV function assessed using TAPSE and RVSm did not correlate with prognosis at a 2-year follow-up [47]. Conversely, CMR-derived RVEF has been demonstrated to have a significant prognostic value in severe AS, with both normal and low gradients [48]. In series of patients with low flow-low gradient AS and reduced LVEF, at multivariable Cox analysis stratified for the type of treatment (aortic valve replacement vs conservative) and adjusted for age, AS severity, previous myocardial infarction and LV longitudinal strain, RVLS > -13% was independently associated with all-cause mortality [49]. All these evidences support the idea that using more sensitive tools, a full assessment of RV function could be central in long-term risk stratification of patients candidate for TAVI (especially when trans-femoral approach is the final choice), given the less impact of the procedure on RV volumes and function themselves.

The present study has some limitations. It is a retrospective study of a small size cohort. Second, complete data about cardiovascular drugs before the procedure of TAVI are not available, so we cannot assess if therapies could affect echocardiographic measurements. Third, biomarkers of myocardial function or neurohormonal activation (such as natriuretic peptide) were not available, too.

In conclusion, in patients with HF due to severe AS candidate for TAVI the evaluation of RV function and RV-arterial coupling could add important prognostic information, similarly to what happens in all patients with HF without AS. This concept is important because of even more patients with not high surgical risk undergo TAVI, and have a long life expectancy. Our study is the first one with a so long follow-up. Deformation imaging allows a sensitive evaluation of RV function and RV-arterial coupling, and earlier identification of pulmonary remodeling leading to irreversible PH. The identification of RV involvement in patients with AS, irrespective to other echocardiographic and clinical features, could reveal most important hemodynamic alterations. Future larger studies are necessary to develop risk models for TAVI outcomes including RV function parameters.

Disclosure of conflict of interest

None.

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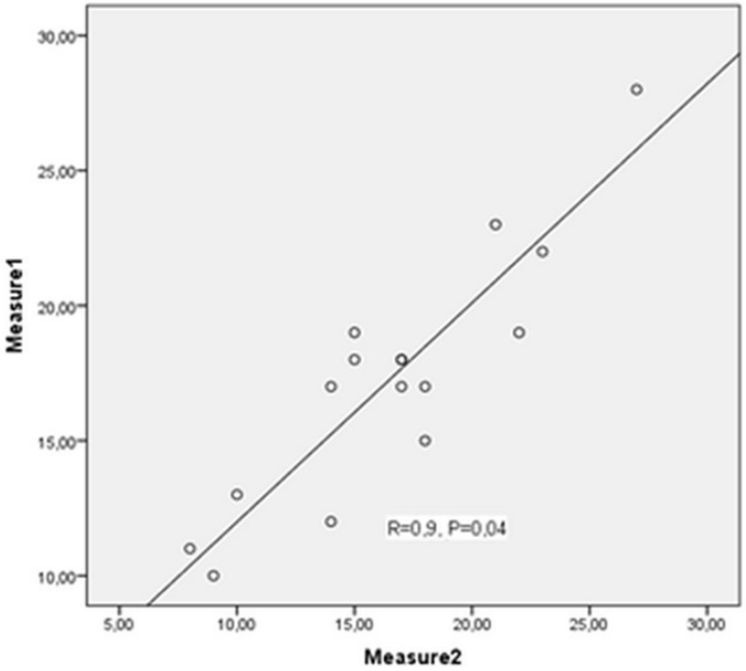
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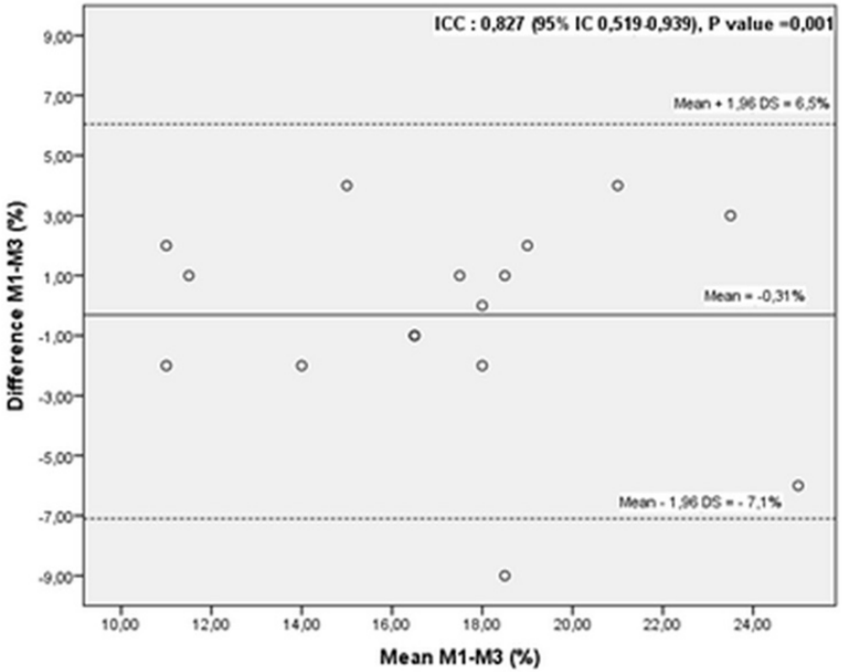
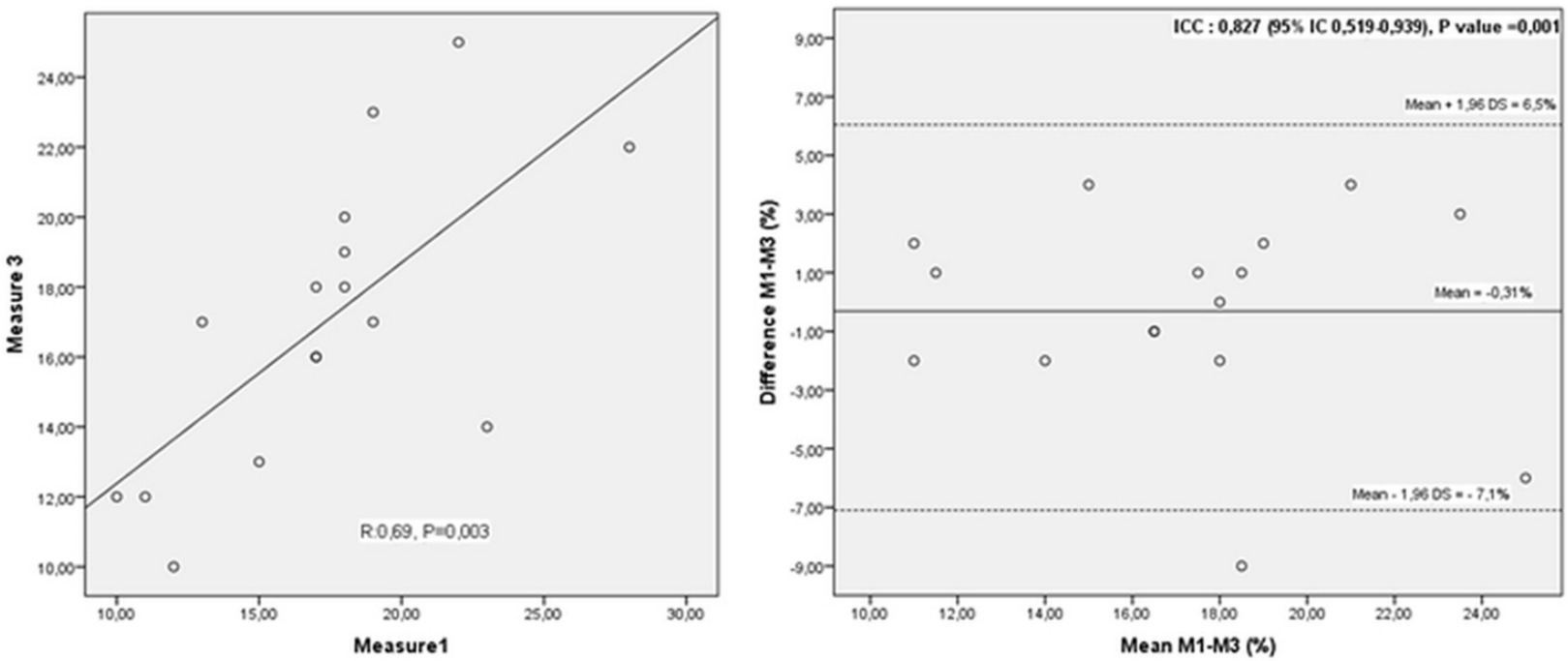

ICC : 0,827 (95% IC 0,519-0,939), P value =0,001
Mean + 1,96 DS = 6,5%
Mean = -0,31%
Mean - 1,96 DS = - 7,1%
Difference M1-M3 (%)
Mean M1-M3 (%)
9,00
7,00
5,00
3,00
1,00
-1,00
-3,00
-5,00
-7,00
-9,00
10,00
12,00
14,00
16,00
18,00
20,00
22,00
24,00



Supplementary Figure 1. Intraobserver and interobserver variability; scatterplots and Bland-Altman plots for measurements of RVLS. Pearson's correlation coefficient (R), intraclass correlation coefficient (ICC), and Bland-Altman bias with LOA are provided for intraobserver variability (upper two images) and for interobserver variability (lower two images).