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Non-Invasive Hemodynamic Monitoring in TAVI-Patients Reveals More Pronounced Early in-Hospital Circulatory Recovery for Low-Gradient Aortic Stenosis

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Abstract

Background: Little is known about differences and changes in hemodynamic in patients with Low-gradient (LG) and Non-Low-Gradient (NLG-) Aortic valve Stenosis (AS). Our current observation reveals such specific changes using the non-invasive NICaS® electrical bio-impedance monitoring system.

Aim: Primary goal was to illustrate possible differences in subgroups of LG-AS and NLG-AS patients and to discriminate post-procedural adaptive mechanisms for the two subgroups.

Methods and findings: In 99 unselected patients subjected to TAVI, NICaS® measurements were performed at baseline, 6 to 8 hours after TAVI and before discharge. 46 patients had a mean pressure gradient <40 mmHg corresponding to a LG-AS. Primary endpoint was defined as the change in cardiac index between the LG-AS and NLG-AS group at discharge. Cardiac index increased in both groups as compared with baseline [from 2.52 ± 0.75 to 3.45 ± 1.15 L/min/m^2 (P=0.00014) in LG-AS and form 2.70 ± 0.97 to 3.08 ± 0.94 L/min/m^2 (P=0.0198) in NLG-AS]. Increase in cardiac index was more pronounced in LG-AS with a difference between the groups of 0.52 ± 0.32 L/min/m^2 (P=0.041) at discharge. Additionally, LG-AS patients showed higher increase in stroke volume index, cardiac power index, and Granov-Goor index and decrease of total peripheral resistance and total peripheral resistance index as secondary parameters. One limitation of our study is the observational design in a small cohort of patients. Therefore, larger trials are warranted to confirm our findings and to show whether there is prognostic relevance for long term outcomes of the different subgroups.

Conclusion: NICaS® monitoring represents an accurate non-invasive bedside-tool to discriminate adaptive circulatory changes in subgroups of aortic stenosis patients subjected to TAVI. Hemodynamic parameters recovered more effectively in LG-AS patients after procedure. Whether a measurement-guided approach might be used for tailored peri-procedural management and could have long-term prognostic influence for AS subgroups remains to be elucidated.

Keywords: Transcatheter aortic valve implantation; Non-invasive whole body electrical bio-impedance measurements; NICaS®; In-hospital hemodynamic outcomes

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Abbreviations

AS: Aortic Valve Stenosis; ANOVA: Analysis of Variance; BI: Basal Impedance; BP: Blood Pressure; CI: Cardiac Index; CO: cardiac output; CPI: Cardiac Power Index; GGI: Granov Goor Index; HR: Heart Rate; ICU: Intensive Care Unit; LOS: Length Of Stay; LG-AS:

Low Gradient Aortic Valve Stenosis; LVEF: Left Ventricular Ejection Fraction; NLG-AS: Non Low Gradient Aortic Valve Stenosis; MPG: Mean Pressure Gradient; RAAS: Renin Angiotensin Aldosterone System; RR: Respiration Rate; SI: Stroke Volume Index; STI: Systolic Time Intervals; STS: Society of Thoracic Surgeons; SV: Stroke Volume; TAVI: Transcatheter Aortic Valve Implantation; TPR: Total Peripheral Resistance; TPRI: Total Peripheral Resistance Index.

Introduction

Percutaneous, Transcatheter Aortic Valve Implantation (TAVI) is particularly appealing to Aortic Stenosis (AS) patients with advanced age and comorbidities whose outcome depends on less invasive surgical access and concomitant need of mechanical ventilation cardioplegia and heart-lung-machine [1,2]. Since the landmark PARTNER-trials, this less-invasive method has become an established alternative to conventional surgery in individuals at high surgical risk [3,4]. Meanwhile, several controlled trials and registries confirmed non-inferiority for TAVI in patients at intermediate and low risk as well [5,6].

Whereas beneficial outcome is proven for transfemoral TAVI, little is known about immediate and post-procedural hemodynamic changes compared to patients´ baseline status. This depends on the need of predominantly invasive measurement tools such as Swan-Ganz®- or PICCO® catheterisation systems. Information regarding baseline hemodynamics and changes after procedure may provide important information on TAVI scheduling and outcomes. Moreover, these parameters may offer an accurate tool for tailored peri- and post-procedural management and may influence outcomes of subgroups like patients with Low-Gradient (LG) and Non-Low-Gradient (NLG) AS in a different manner [7,8].

The NICaS® whole body electrical bio-impedance monitoring system provides an accurate and approved method to obtain hemodynamic parameters in an easy non-invasive manner and that can be used bedside at any time for repeated measurements [9-13].

Recently, we could demonstrate an improvement of hemodynamics in an unselected TAVI patients´ collective using the NICaS® system [14]. Nevertheless, this observation was not designed to discriminate changes within different subgroups with aortic valve stenosis.

Since there is proven accuracy for illustration of hemodynamic changes in patients measured with the NICaS®, the present prospective series aims to report on the ability to discriminate short-term hemodynamic outcomes in TAVI patients for subgroups with LG- and NLG-AS.

Materials and Methods

Patients

Over a period of 21 months, 100 unselected patients with severe symptomatic AS were scheduled to TAVI procedure after heart-team decision. Endovascular TAVI was applied in local anaesthesia and analgosedation without mechanical ventilation in all patients using the Medtronic Evolut R® (n=48), Edwards Sapien 3® (n=47) or Boston Scientific SYMETIS ACURATE neo™ TF® (n=4) system.

All comers were measured with the NICaS® system at baseline at the day before TAVI. Measurements were repeated after six to eight hours at the same day of TAVI procedure at the cardiology Intensive Care Unit (ICU) when patients were free of inotropics vasopressors or sedatives. A second in-hospital follow-up was performed at the day of discharge [mean hospital Length of Stay (LOS) 6.4 ± 1.2 days].

One patient died before onset of TAVI procedure due to low-output heart failure and was excluded from analysis. Thus, 99 patients left to be analysed for hemodynamic outcomes at the day of procedure and before discharge.

Additionally, the last 48 of the 99 included all-comers were assessed for baseline quality of life (QoL) using the EQ-5D-5L questioner [14,15]. Patients were called by phone to report on clinical outcomes after 3 months.

Ethics committee approval

The analysis was approved by the local Ethics Committee complying with the Declaration of Helsinki. All patients gave written informed consent for participation and anonymized data publication. Trial Registration Number 105/18, date of ethical approval 1st of November 2018.

NICaS® device and procedure

The NICaS® whole body electrical bio-impedance monitoring system (NIMedical, Israel Advanced Technology Industries, Hertzliya Pituach 4676672, Israel) is a FDA and European CE-sign approved non-invasive hemodynamic monitoring tool. Using a combination of pulse contour analysis and the Granov-Goor Index (GGI) based on the Systolic Time Intervals (STI) which similarly to Left Ventricular Ejection Fraction (LVEF)-can assess cardiac function and provide information on several circulatory parameters and volume status.

NICaS®-measurement procedure and validation studies compared to Swan-Ganz- and PICCO®- catheterisation techniques were reported recently [9-13].

In all of the 99 patients at least four consecutive measurements were carried out to achieve valuable results for each time point (mean number of consecutive measurements for baseline 4.8 ± 0.12 after procedure 5.1 ± 0.9 and before discharge 4.5 ± 1.6). Outliers within the consecutive measurements >20% were eliminated to achieve accurate means (3.9% of all measurements).

Study objectives

The purpose of this investigation was to prospectively validate in-hospital hemodynamic improvement after TAVI by repeated bedside non-invasive monitoring and to illustrate possible differences in subgroups of LG-AS and NLG-AS patients [7,8]. Primary goal was to discriminate post-procedural adaptive mechanisms for the two subgroups. Investigators obtaining NICaS® measurements were blinded to baseline TTE parameters while echo-cardiographers operators and ICU physicians were blinded to NICaS® results. Thus, NICaS® results did not influence TAVI scheduling or post-procedural management up to discharge illustrating hemodynamics only based on usual care principals.

Independently, we aimed to prospectively analyse mid-term clinical outcomes in TAVI procedure survivors after 3 month based on the EQ-5D-5L- Score [15,16].

Statistical analysis

Categorical variables are presented as counts and percentages. Continuous variables following a normal distribution are presented as mean+standard deviation. Variables were assessed for normal distribution with the Anderson-Darling test.

Primary endpoint was defined as the baseline-adjusted effect of between-group comparisons (LG-AS vs. NLG-AS) for changes in Cardiac Index (CI) at discharge. Sample size was calculated for an independent t-test of the means post-therapy with $\alpha=0.05$. All tests were performed two-sided and p values <0.05 were considered as statistically significant. Data were analysed by Friedman´s ANOVA for comparison across multiple groups processing the data by the SPSS (version 15, SPSS Inc., Chicago, IL, USA) software package.

With a sample size of 46 per group, a relative effect of 80% of the standard deviation is detectable with a power of 80%. Thus, with an a priori estimated standard deviation of 0.1 L/min/m^2, a difference 0.3 L/min/m^2 is detectable for the primary endpoint change in CI which we consider as clinically relevant.

Results

Clinical characteristics

Patients' baseline characteristics with regard to age, gender, body-mass-index clinical symptoms and baseline echocardiographic parameters are summarized in **Table 1**.

Baseline Transthoracic Echocardiography (TTE) revealed a mean AV pressure gradient (MPG) <40 mmHg in 46 patients (46.6%) corresponding to a LG-AS [1]. On average, LG-AS patients were older and had a higher BMI.

Mean ICU-LOS was 2.6 ± 0.9 days and mean hospital LOS was 6.4 ± 1.2 days without difference for the two subgroups.

TTE was performed on all patients before discharge despite of cardiac symptoms. In no patient, more than of first degree residual prosthesis regurgitation was detectable while mild regurgitation (I°) was observed only in 21 of the 99 patients (21.2%).

Results of all NICaS® measurements for the overall TAVI population are presented in **Table 2** while the two subgroups are reported in **Table 3** (LG-AS) and **Table 4** (NLG-AS).

Impact of TAVI procedure on hemodynamic parameters in the overall population

In the overall population, there was no significant change in resting Heart Rate (HR) resting Respiration Rate (RR) Stroke Volume (SV) diastolic and mean arterial blood pressure (BP) at discharge as compared to baseline. Significant increase was observed for cardiac output (CO), CI, cardiac power index (CPI) and Systolic Arterial Blood Pressure (sBP) as well as reduction of Total Peripheral Resistance (TPR) and Total Peripheral Resistance Index (TPRI) prospectively confirming the results of our recently reported TAVI series. Additionally, the increase of Stroke Index (SI) and Garnov-Goor-index (GGI) and reduction of Basal Impedance (BI) reached statistical significance.

Significant decrease of SV, SI, GGI and diastolic arterial BP (dBP) was obtained 6 to 8 hours after TAVI, when patients were free of inotropics and vasopressors. All of these parameters recovered up to discharge **(Table 2).**

Impact on change in CI in the LG- and NLG-AS subgroups (primary endpoint)

When comparing discharge to baseline, there was an increase in CI detectable for both TAVI subgroups. CI increased from 2.52 ± 0.75 to 3.45 ± 1.15 L/min/m^2 (P=0.00014) in the LG-AS group

Table 1 Characteristics of study subjects.

Parameters	All patients scheduled to TAVI procedure	Patients with NLG-AS	Patients with LG-AS
Subjects (n)	99 (100 %)	53 (53.5/100%)	46 (46.5/100%)
Male/female	54 (54.5%)/45 (45.5%)	28 (52.8%)/25 (47.2%)	29 (63%)/17 (37%)
Age	82.4 ± 4.7	80.1 ± 2.9	83.2 ± 3.8
Body mass index (kg/m^2)	27.8 ± 5.3	26.6 ± 5.5	28.1 ± 5.2
Functional NYHA Class			
NYHA Class I	3(3.03%)	2 (3.77%)	1 (2.17%)
NYHA Class II	27(27.3%)	15 (28.3%)	12 (26.1%)
NYHA Class III	60(60.6%)	33 (62.3%)	27 (58.7%)
NYHA Class IV	9 (9.09%)	3 (5.66%)	6 (13.0%)
Angina	32(32.3%)	20 (37.7%)	12 (26.1%)
Syncope	11(11.1%)	3 (5.66%)	8 (17.4%)
Baseline echocardiographic values			
LVEF (%)	48.6 ± 9.4	49.6 ± 8.7	39.6 ± 9.1
AV velocity max (cm/sec)	376.4 ± 62.2	396.4 ± 41.7	283.4 ± 33.5
AV gradient max (mmHg)	69.3 ± 18.7	72.9 ± 19.8	61.2 ± 11.6
AV gradient mean (mmHg)	37.9 ± 13.4	46.9 ± 5.2	29.2 ± 7.5
AV opening area (cm^2)	0.80 ± 0.16	0.73 ± 0.13	0.84 ± 0.15

Table 2 Parameter changes due to early impact after TAVI (6 to 8 hours) and at discharge (6.4 ± 1.2 days) as compared to baseline in the overall patient population.

Parameters	Measurement changes compared to baseline				
	Baseline	6-8 h after TAVI	P value	Before discharge (6.4 ± 1.2 days)	P value
Resting Heart Rate (HR); (bpm)	76.27 ± 16,98	77.81 ± 16,51	0.31863	75.88 ± 17,30	0.85089
Resting Respiration Rate (RR); (min)	**18.31 ± 4,54**	18.91 ± 4,69	0,23601	18.52 ± 4.87	0.75026
Stroke Volume (SV); (mL)	71.16 ± 23,45	63.86 ± 21.73	0.00026	76.15 ± 24.83	0.05104
Stroke Index (SI); (mL/m²)	36.75 ± 12.31	33.87 ± 12.34	0.00784	40.41 ± 13.41	0.01535
Cardiac Output (CO); (L/min)	5.06 ± 1.86	4.84 ± 1.84	0.25187	5.77 ± 1.57	0.00078
Cardiac Index (CI); (L/min/m²)	2.64 ± 0.89	2.58 ± 0.94	0.58371	3.25 ± 1.05	0.000009
Cardiac Power Index (CPI); (w/m²)	0.53 ± 0.19	0.46 ± 0.19	0.00107	0.64 ± 0.22	0.000013
Garnov-Goor-index (GGI); (LVSF)	11.68 ± 4.19	10.48 ± 3.38	0.00230	13.02 ± 4.22	0.00799
Total Peripheral Resistance (TPR); (dn*s/cm5)	1521.42 ± 546.69	1568.27 ± 615.35	0.46251	1290.33 ± 466.13	0.000665
Total Peripheral Resistance Index (TPRI); (dn*s/cm5*m²)	2821.16 ± 965.68	2923.70 ± 1149.9	0.39492	2403.17 ± 878.98	0.001002
Systolic Arterial BP; (mmHg)	125.69 ± 22.34	129.39 ± 22.60	0.15477	131.77 ± 19.98	0.008283
diastolic arterial BP; (mmHg)	68.68 ± 14.96	60.03 ± 12.83	0.0000007	66.42 ± 12.43	0.085448
mean arterial BP; (mmHg)	87.68 ± 10.01	85.75 ± 13.65	0.06123	87.58 ± 11.90	0.35324
Basal Impedance (BI); (ohm)	361.69 ± 69.68	370.14 ± 70.56	0.19625	348.57 ± 62.09	0.021672
Significant P values for changes at the two time points after TAVI are outlined in cursive characters.					

Table 3 Parameter changes due to early impact after TAVI (6 to 8 hours) and at discharge (6.4 ± 1.2 days) as compared to baseline in patients with LG-AS.

Parameters	Measurement changes compared to baseline				
	baseline	6-8 h after TAVI	P value	before discharge (6.4 ± 1.2 days)	P value
Resting heart rate (HR); (bpm)	77.33 ± 16.94	80.18 ± 17.40	0.26663	74.59 ± 18.65	0.42806
Resting respiration rate (RR); (/min)	18.65 ± 4.70	19.76 ± 5.20	0.13605	17.87 ± 5.07	0.47490
Stroke volume (SV); (mL)	69.15 ± 23.38	63.14 ± 20.55	*0.01390*	76.17 ± 23.96	0.06725
Stroke index (SI); (mL/m²)	34.70 ± 12.83	32.03 ± 11.44	0.06020	40.23 ± 13.01	*0.01779*
Cardiac output (CO); (L/min)	4.98 ± 1.68	4.76 ± 1.47	0.34177	5.82 ± 1.37	*0.00594*
Cardiac index (CI); (L/min/m²)	2.56 ± 0.75	2.52 ± 0.69	0.54744	3.45 ± 1.15	*0.00014*
Cardiac Power Index (CPI); (w/m)	0.50 ± 0.18	0.44 ± 0.17	*0.02542*	0.67 ± 0.24	*0.00016*
Garnov-Goor-Index (GGI); (LVSF)	10.85 ± 4.11	10.26 ± 3.26	0.27003	13.11 ± 4.70	*0.00969*
Total Peripheral Resistance (TPR); (dn*s/cm5)	1495.76 ± 437.75	1615.42 ± 617.97	0.19659	1250.39 ± 431.70	*0.00782*
Total Peripheral Resistance index (TPRI); (dn*s/cm5*m²)	2850 ± 839.31	3030.33 ± 1180.19	0.32325	2378.70 ± 863.48	*0.00949*
Systolic arterial BP; (mmHg)	125.87 ± 23.70	129.27 ± 22.27	0.48555	131.37 ± 20.87	0.09206
Diastolic arterial BP; (mmHg)	68.59 ± 11.74	59.04 ± 12.74	*0.000031*	67.98 ± 11.17	0.72638
Mean arterial BP; (mmHg)	87.66 ± 15.73	82.45 ± 15.89	0.05147	89.11 ± 16.91	0.53427
Basal impedance (BI); (ohm)	362.83 ± 58.10	375.48 ± 63.66	0.23149	348.98 ± 60.66	0.06036
Significant P values for changes at the two time points after TAVI are outlined in cursive characters.					

Table 4 Parameter changes due to early impact after TAVI (6 to 8 hours) and at discharge (6.4 ± 1.2 days) as compared to baseline in patients with NLG-AS.

Parameters	Measurement changes compared to baseline				
	baseline	6-8 h after TAVI	P value	before discharge (6.4 ± 1.2 days)	P value
Resting Heart Rate (HR); (bpm)	75.36 ± 17.16	75.75 ± 15.56	0.83089	77 ± 16.14	0.5192
Resting Respiration Rate (RR); (/min)	18.02 ± 4.42	18.17 ± 4.09	0.82669	18.34 ± 4.63	0.6030
Stroke Volume (SV); (ml)	72.91 ± 23.59	64.49 ± 22.89	*0.00660*	76.13 ± 25.79	0.3519
Stroke Index (SI); (mL/m²)	38.53 ± 11.66	35.13 ± 13.13	*0.00784*	40.57 ± 13.87	0.3038
Cardiac Output (CO); (L/min)	5.12 ± 2.01	4.92 ± 2.13	0.47314	5.73 ± 1.74	*0.0431*
Cardiac Index (CI); (L/min/m²)	2.70 ± 0.97	2.64 ± 1.13	0.68184	3.08 ± 0.94	*0.0198*
Cardiac Power Index (CPI); (w/m)	0.55 ± 0.20	0.48 ± 0.20	*0.01853*	0.62 ± 0.20	*0.0220*
Garnov-Goor-Index (GGI); (LVSF)	12.40 ± 4.17	10.66 ± 3.50	*0.00249*	12.94 ± 3.79	0.3375
Total Peripheral Resistance (TPR); (dn*s/cm5)	1543.70 ± 629.56	1527.34 ± 616.01	0.85352	1325 ± 495.56	*0.0280*
Total Peripheral Resistance Index (TPRI); (dn*s/cm5*m²)	2796.13 ± 1070.74	2831.15 ± 1126.16	0.82897	2424.42 ± 899.92	*0.0385*
Systolic Arterial BP; (mmHg)	125.57 ± 21.31	129.49 ± 23.06	0.19501	132.11 ± 19.38	*0.0446*
Diastolic Arterial BP; (mmHg)	68.77 ± 10.97	60.89 ± 12.97	*0.00061*	65.08 ± 13.40	0.0631
Mean Arterial BP; (mmHg)	87.70 ± 17.09	83.75 ± 18.69	0.09832	87.42 ± 15.57	0.5534
Basal Impedance (BI); (ohm)	360.70 ± 78.91	365.51 ± 76.36	0.55729	348.21 ± 63.88	0.1484

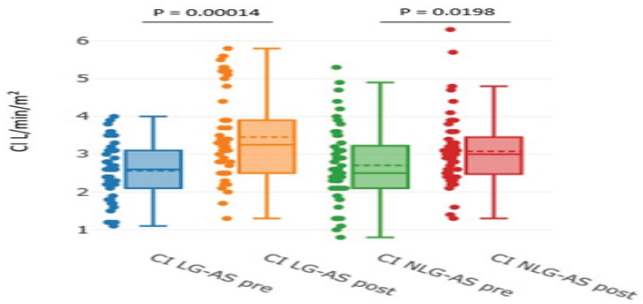
and form 2.70 ± 0.97 to 3.08 ± 0.94 L/min/m² (P=0.0198) in the NLG-AS group **(Tables 3 and 4, Figure 1).** The effect was more pronounced in the LG-AS group than in patients with NLG-AS showing a significant difference between the two groups of 0.52 ± 0.32 L/min/m² (P = 0.041 for baseline-adjusted between-group comparison at discharge) for the primary endpoint **(Figure 2).**

Subgroup impact on CO, CPI and GGI

When comparing discharge to baseline, there was a more pronounced increase in CO from 4.98 ± 1.68 to 5.82 ± 1.37 L/min (P=0.0059) and in CPI from 0.50 ± 0.18 to 0.67 ± 0.24 w/m² (P=0.00016) in the LG-AS group with P = 0.037 for CO and P=0.001 for CPI for baseline-adjusted between-group comparison at discharge **(Tables 3 and 4, Figures 3 and 4).** Interestingly, no significant changes of GGI could be observed in the NLG-AS group and the overall significant effect was mainly driven by an increase in the LG-AS group (10.85 ± 4.11 to 13.11 ± 4.70; P=0.0097) **(Figure 5).**

Whereas CO did not change immediately after TAVI (6-8 hours), there was a decrease of CPI in both groups as compared to baseline (P=0.025 for LG-AS and P=0.019 for NLG-AS) but without significant difference for baseline-adjusted between-group comparison.

Early significant decrease in GGI was observed in the NLG-AS group only (P=0.0025) **(Tables 3 and 4).**

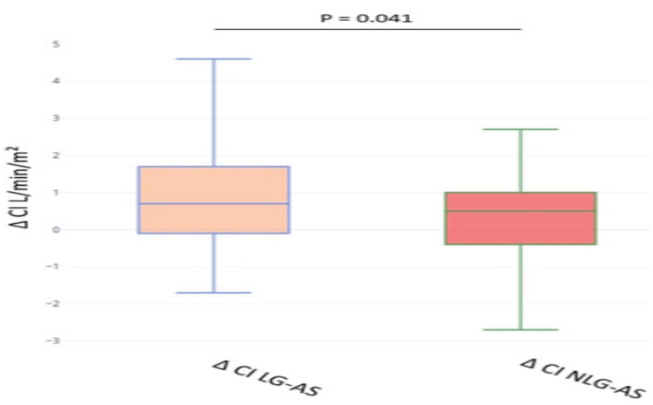


Compared with baseline, CI increased in both groups from 2.52 ± 0.75 to 3.45 ± 1.15 L/min/m² (P = 0.00014) in the LG-AS group and form 2.70 ± 0.97 to 3.08 ± 0.94 L/min/m² (P=0.0198) in the NLG-AS group respectively. No significant early change (6-8 h after TAVI) was observed in both groups as compared to baseline. Bar graphs represent mean, upper and lower quartile and scatter with outliers within 5th/95th percentile.

Figure 1 Impact on Cardiac Index (CI) at discharge (post; 6.4 ± 1.2 days) compared to baseline (pre) in the LG-AS vs. NLG-AS subgroups.

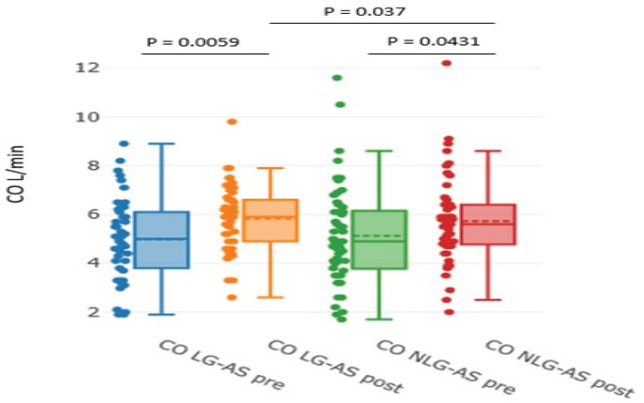
Subgroup impact on TPR and TPRI

TPR and TPRI significantly decrease in both LG-AS and NLG-AS patients when compared to baseline **(Tables 3 and 4)**. This effect was more pronounced in the LG-AS with a TPR decrease from



Compared with baseline, CI increased in both groups from 2.52 ± 0.75 to 3.45 ± 1.15 L/min/m² (P = 0.00014) in the LG-AS group and form 2.70 ± 0.97 to 3.08 ± 0.94 L/min/m² (P=0.0198) in the NLG-AS group respectively. No significant early change (6-8 h after TAVI) was observed in both groups as compared to baseline. Bar graphs represent mean, upper and lower quartile and scatter with outliers within 5th/95th percentile.

Figure 2 Comparison of absolute changes in CI in the LG-AS vs. NLG-AS from baseline to discharge (6.4 ± 1.2 days after TAVI) as primary endpoint.

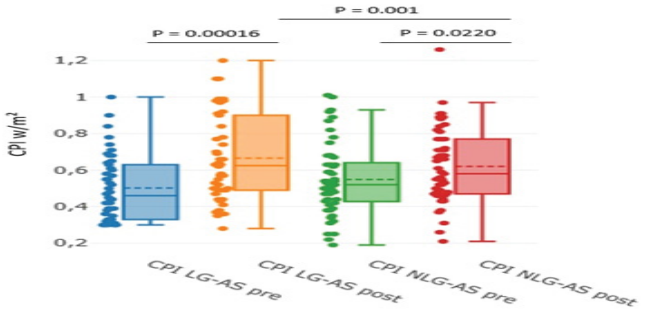


Increase in CI was more pronounced in the LG-AS group than in patients with NLG-AS showing a significant difference between the two groups with a Delta of 0.52 ± 0.32 L/min/m² (P = 0.041 for baseline-adjusted between-group comparison at discharge) for the primary endpoint.

Figure 3 Impact on Cardiac Output (CO) at discharge (post; 6.4 ± 1.2 days) compared to baseline (pre) in the LG-AS vs. NLG-AS subgroups.

1495.76 ± 437.75 to 1250.39 ± 431.70 dynes*s/cm^5 (P=0.0078) corresponding to a total peripheral resistance index TPRI decrease from 2850 ± 839.31 to 2378.70 ± 863.48 dynes*s/cm^5/m^2 (P=0.0095) at discharge compared to baseline with P = 0.014 for TPR and P=0.019 for TPRI for baseline-adjusted between-group comparison at discharge **(Figures 6 and 7).**

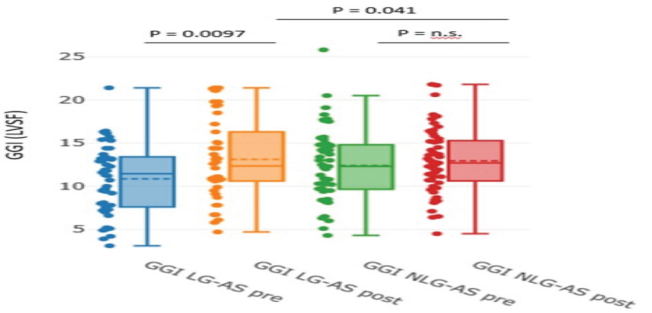
No early changes were detectable for same day after TAVI (6-8 hours) results in both subgroups **(Tables 2-4).**



CPI increased in both groups from 0.50 ± 0.18 to 0.67 ± 0.24 w/m² (P=0.00016) in the LG-AS group and form 0.55 ± 0.20 to 0.62 ± 0.20 L/min (P=0.022) in the NLG-AS group respectively. The increase was more pronounced in LG-AS than in NLG-AS patients (P=0.001 for baseline-adjusted between-group comparison at discharge). CPI significantly decreased 6-8 h after TAVI in both groups as compared to baseline but without significant difference for baseline-adjusted between-group comparison.

Bar graphs represent mean, upper and lower quartile and scatter with outliers within 5th/95th percentile.

Figure 4 Impact on Cardiac Power Index (CPI) at discharge (post; 6.4 ± 1.2 days) compared to baseline (pre) in the LG-AS vs. NLG-AS subgroups.



GGI only increased in LG-AS patients from 10.85 ± 4.11 to 13.11 ± 4.70 (P = 0.0097) at discharge. At discharge, NLG-AS recovered to nearly the same level after initial significant drop down 6 to 8 hours after TAVI form 12.40 ± 4.17 over 10.66 ± 3.50 (P= 0.0025) to 12.94 ± 3.79 (P = 0.34). GGI increased significantly in LG-AS vs. NLG-AS patients with P = 0.001 for baseline-adjusted between-group comparison at discharge. No significant CPI drop down was observed 6-8 h after TAVI in the LG-AS group as compared to baseline.

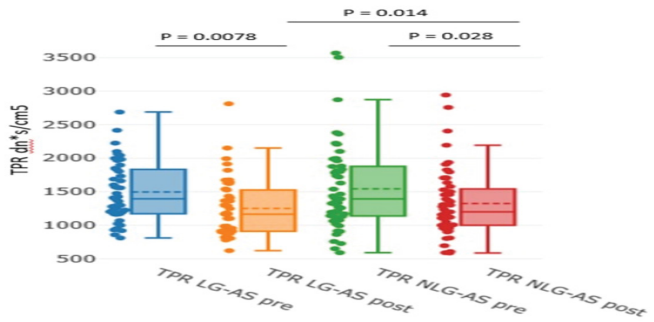
Bar graphs represent mean, upper and lower quartile and scatter with outliers within 5th/95th percentile.

Figure 5 Impact on Garnov-Goor Index (GGI) at discharge (post; 6.4 ± 1.2 days) compared to baseline (pre) in the LG-AS vs. NLG-AS subgroups.

Subgroup impact on SV and SI

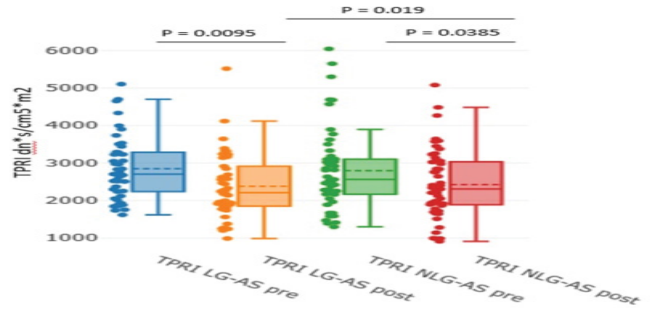
SI did significantly improve in LG-AS patients at discharge as compared to baseline (34.70 ± 12.83 to 40.23 ± 13.01 mL/m^2; P=0.018) with only a numerical increase of SV. In NLG-AS, SV and SI only recovered to nearly the same level.

Immediately after TAVI (6-8 hours), significant decrease in SV and



When comparing discharge with baseline, TPR decreased from 1495.76±437.75 to 1250.39 ± 431.70 dynes*s/cm5 (P = 0.0078) in the LG-AS and from 1543.70 ± 629.56 to 1325 ± 495.56 dynes*s/cm5 (P=0.028) in the NLG-AS group. The decrease was more pronounced in LG-AS than in NLG-AS patients (P=0.014 for baseline-adjusted between-group comparison at discharge). No significant change was observed in both groups 6-8 h after TAVI.
Bar graphs represent mean, upper and lower quartile and scatter with outliers within 5th/95th percentile.

Figure 6 Impact on Total Peripheral Resistance (TPR) at discharge (post; 6.4 ± 1.2 days) compared to baseline (pre) in the LG-AS vs. NLG-AS subgroups.



When comparing discharge with baseline, TPRI decreased from 2850 ± 839.31 to 2378.70 ± 863.48 dynes*s/cm5*m^2 (P = 0.0095) in the LG-AS and from 2796.13 ± 1070.74 to 2424.42 ± 899.92 dynes*s/cm5*m^2 (P=0.0385) in the NLG-AS group. The decrease was more pronounced in LG-AS than in NLG-AS patients (P=0.019 for baseline-adjusted between-group comparison at discharge). No significant change was observed in both groups 6-8 h after TAVI.
Bar graphs represent mean, upper and lower quartile and scatter with outliers within 5th/95th percentile.

Figure 7 Impact on Total Peripheral Resistance Index (TPRI) at discharge (post; 6.4 ± 1.2 days) compared to baseline (pre) in the LG-AS vs. NLG-AS subgroups.

SVI was observed in the NLG-AS group, while impact on these parameters was not so pronounced (SV) or insignificant (SVI) in the LG-AS group **(Tables 3 and Table 4).**

Impact on BP

In the overall population, there was only significant changes of sBP on non-invasive BP readings detectable at discharge compared to baseline with an increase of systolic values from 125.69 ± 22.34 to 131.77 ± 19.98 (P=0.008) **(Table 2).** This effect was mainly driven by the increase in the NLG-AS group (125.57 ± 21.31 to 132.11 ± 19.38; P=0.045).

While changes in dBP were not significantly different in both groups from baseline to discharge, dBP decreased in both groups immediately after TAVI procedure **(Tables 3 and 4).**

Changes in left ventricular ejection fraction

Left ventricular ejection fraction (LVEF) results obtained with the Simpson´s method were available from TTE in all patients at baseline and at discharge. While overall baseline LVEF was 46.3 ± 9.4%, LG-AS patients had significant lower LVEF than NLG-AS patients (38.3 ± 5.1% vs. 54.2 ± 8.7%, P=0.013). When comparing discharge to baseline, there was no significant change in the LVEF for the two subgroups with a not mentionable numerical decrease in the NLG-AS group and a slight numerical increase in the LG-AS group **(Table 5).**

Impact on QoL in a subgroup of the overall patients´ collective (n= 41) at 3 months follow-up

41 of 48 patients (85.42%) completed the EQ-5D-5L questioner for baseline and at 3 months follow-up. Three patients died within the 3 months follow-up and four patients refused to provide phone call based information.

Baseline EQ-5D-5L Score was 53.05 ± 17.87 with an overall increase to 60.61 ± 16.29 (P=0.0046) at 3 months. **(Figure 8a)** Increase in EQ-5D-5L Score of ≥ 5 point was documented in 27 of the 41 obtained reports at 3 months. Only four patients reported deterioration of ≥ 5 points while 10 remained unchanged (0 to + 4 points) **(Figure 8b).** However, the seven patients should be considered for analysis as non-survivors (n=3) and by assuming deterioration for those refused to report on QoL (n=4).

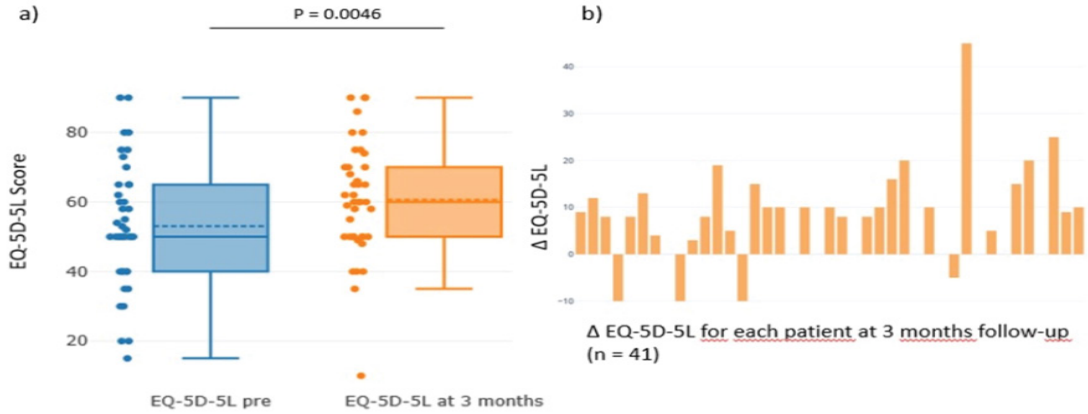
We do not report on subgroup analysis for LG- and NLG-patients due to less than half of the overall patients available to baseline and 3 months follow-up reports. Nevertheless, two of the four deteriorated patients had an LG-AS (MPG 32 and 30 mmHg) and the other two NLG-AS (MPG 46 and 49 mmHg). This was also the case for the four patients refusing to provide information on phone call (n=2, MPG 30 and 36 mmHg; n=2, MPG 48 and 58 mmHg). Two of the three non-survivors belonged to the LG-AS group (MPG 35 and 30 mmHg) and one to the NLG-AS-group (MPG 52 mmHg).

Discussion

Although beneficial TAVI outcomes are reported throughout

Table 5 Changes of Left Ventricular Ejection Fraction (LVEF) after TAVI at discharge (6.4 ± 1.2 days) as compared to baseline in the overall patient's population and for the two subgroups (NLG- and LG-AS).

Parameters	All patients scheduled to TAVI procedure	Patients with NLG-AS	Patients with LG-AS	P value NLG/LG
Subjects (n)	99 (100 %)	53 (53.5%)	46 (46.5%)	
LVEF (%)baseline	46.3 ± 9.4	54.2 ± 8.7	38.3 ± 5.1	0.013
LVEF (%) at discharge (6.4 ± 1.2 days)	47.6 ± 10.2	52.8 ± 9.4	42.6 ± 6.5	0.026
P value pre/post	0.673	0.231	0.096	



(a) Baseline EQ-5D-5L Score was 53.05 ± 17.87 with an overall increase to 60.61 ± 16.29 (P=0.0046) at 3 months follow-up. (b) Only 4 of the 41 patients available to follow-up reported deterioration of health status. (a) Bar graphs represent mean, upper and lower quartile and scatter with outliers within 5th/95th percentile. (b) and absolute changes in the EQ-5D-5L Score for each patient at 3 months as compared to baseline.

Figure 8 Changes in EQ-5D-5L Score in the overall TAVI population for the prospectively analysed survivors at 3 months.

the whole spectre of heterogeneous groups summarized under the term "severe symptomatic AS", little is known about their baseline circulatory characteristics or post-procedural and long term hemodynamic treatment response [7,8]. Several investigations reported on impact of either LG or Low Flow (LF) parameters as well as impaired LVEF on outcomes after TAVI. Nevertheless, outcome data remain partly inconsistent when based on TTE measurements alone or when taking only one of such subgroup-defining criteria into account [17-20]. Thus, providing individualized information on various hemodynamic parameters in AS might give additional information for patients´ selection and post-procedural management thereby defining subgroups that might benefit most.

The present series was designed to prospectively illustrate the impact on various haemodynamic parameters immediately after treatment and before discharge compared to patients' baseline status and to discriminate possible differences in LG-AS and NLG-AS with primary focus on changes in CI as primary endpoint.

The present results revealed an increase in CO, CI and CPI and reduction in TPR and TPRI as a positive hemodynamic response in the overall TAVI population. Additionally, there was an increase in Stroke Index (SI) and Garnov-Goor-index (GGI) - as a correlate for LV systolic function.

By defining the LG-AS group based on a MPG cut-of-consensus of <40 mmHg at baseline TTE, significant increase in CI was observed in both TAVI subgroups at discharge. The effect was more pronounced in the LG-AS group with a significant difference between the groups of 0.52 ± 0.32 L/min/m^2 (P=0.041 for baseline-adjusted between-group comparison at discharge) for the primary endpoint.

At discharge, LG-AS patients showed correspondingly higher increase in CO, CPI and a more pronounced decrease of Total Peripheral Resistance (TPR) and Total Peripheral Resistance Index (TPRI) as secondary parameters. Moreover, SVI and GGI did only significantly improve in LG-AS patients at discharge as compared to baseline, while in NLG-AS patients both parameters recovered to nearly the same level. Immediately after TAVI at a time when patients were at stabile conditions not requiring inotropic or vasopressor support, significant decrease in SV SVI CPI and GGI was observed in NLG-AS, while impact on these parameters was not so pronounced (SV, CPI) or insignificant (SVI, GGI) in LG-AS.

Causal increase in myocardial function and pro-adaptive haemodynamic changes are expectable in TAVI but difficult to be representatively illustrated. On the other hand, peri-procedural stressors, filling status and temporary periprosthetic regurgitation may negatively affect contractility and early post-procedural circulatory response in a different manner. Thus, such subgroup-specific characteristics of baseline status and - more important - different post-procedural circulatory adaptation may contribute to different outcomes. Eleid and co-workers focused on prognostic impact of stroke volume, gradient, and ejection fraction as individual baseline parameters in a large Meta-analysis of 16 TAVI studies [7]. In conclusion, low SI, LG, and low LVEF at baseline were each associated with higher 1-year mortality after TAVI. Although not representative, two of three of our non-survivers at 3 month QoL follow-up matched such baseline criteria with both LG and low LVEF as well as low SI.

Nevertheless, there is little insight, how parameters like SI CI or TPRI change after TAVI and whether and how changes may affect outcomes. Our data analysis revealed such different circulatory impact for LG- and NLG-AS patients after TAVI while both groups did not show early LVEF changes. Interestingly, LG-AS patients showed more pronounced circulatory recovery at discharge and blander early negative impact of peri-procedural stressors. It suggests that relief of flow resistance and pressure overload might be more important to early readjust circulation in LG-AS independently of changes in LVEF. Hence, increase in SI CPI and GGI might better reflect mobilisation of myocardial contractile reserve eventually resulting in down regulation of maladaptively

Table 6 Changes in cardiovascular medication during in hospital stay (n = 99 patients; 100%).

Changes in oral medication	Newly prescribed oral medication	
Beta-blockers	n= 8 (8.08%)	
Bisoprolol	6 (6.06%)	
Metoprolol	2 (2.02%)	
Angiontensin converting enzyme antagonists	n= 6 (6.06%)	
Ramipril	5 (5.05%)	
Perindopril	1 (1.01%)	
Angiotensin receptor blockers	n= 4 (4.04%)	
Candesartan	3 (3.03%)	
Valsartan	1 (1.01%)	
Diuretics	n= 9 (9.09%)	
Torasemide	6 (6.06%)	
Hydrochlorothiacide	3 (3.03%)	
Mineralocorticoid-receptor antagonists	n= 5 (5.05%)	
Spironolactone	3 (3.03%)	
Eplerenone	2 (2.02%)	
Sacubitril/Valsartan	n = 2 (2.02%)	
	Discontinued oral medication	
Beta-blockers	n= 6 (6.06%)	
Bisoprolol	3 (3.03%)	
Nebivolol	1 (1.01%)	
Metoprolol	2 (2.02%)	
Angiontensin converting enzyme antagonists	n= 4 (4.04%)	
Ramipril	3 (3.03%)	
Lisinopril	1 (1.01%)	
Calcium channel blockers	n= 2 (2.02%)	
Amlodipine	2 (2.02%)	
	Dose modification	
Beta blockers	n= 8 (8.08%)	
Bisoprolol up-titration	2 (2.02%)	
Bisoprolol down-titration	2 (2.02%)	
Nebivolol up-titration	1 (1.01%)	
Metoprolol down-titration	3 (3.03%)	
Calcium channel blockers	n= 6 (6.06%)	
Amlodipine down-titration	4 (4.04%)	
Lercanidipine up-titration	2 (2.02%)	
Transient use of intravenous diuretics after TAVI		
Furosemide	n=9 (9.09%)	(for a maximum of 3 days after TAVI)

activated intrinsic catecholamines and Renin-Angiotensin-Aldosterone-System (RAAS) corresponding to an increase in CI and decrease in TPRI.

Taking into account that all of our non-survivors and deteriorated patients at 3 months QoL follow-up did not improve due to CI SI CPI and TPRI, further investigations should be designed to focus on possible importance of such criteria for early post-procedural management, tailored medication, discharge planning and long term ambulatory outcomes.

Conclusion

NICaS® monitoring represents an accurate non-invasive bedside-tool for discriminating adaptive circulatory changes in subgroups of unselected patients subjected to TAVI. LG-AS patients seem to show more effective early hemodynamic recovery after procedure. Whether a measurement-guided approach might be used for tailored peri-procedural management and could have long-term prognostic influence remains to be elucidated.

Study Limitations

Even though our observation is consistent with expectable results in TAVI patients, one of our limitations is the observational design in a small cohort of patients. Therefore, larger trials are warranted to confirm our findings and to show whether there is prognostic relevance for long term outcomes of the different subgroups. There were few changes in baseline oral cardiovascular medication during in-hospital stay and 9 patients required application of intravenous diuretics after TAVI procedure **(Table 6).** Nevertheless, our observation was designed to describe subgroup changes based on established in-hospital periprocedural patients management, not guided and influenced by the NICaS® measurements.

Acknowledgements

Not Applicable.

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