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Research paper

Change in Systemic Arterial Pulsatility index (SAPi) during heart failure hospitalization is associated with improved outcomes☆

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ABSTRACT

Study objective: To identify Change in Systemic Arterial Pulsatitlity index (ΔSAPi) as a novel hemodynamic marker associated with outcomes in heart failure (HF).
Design: The ESCAPE trial was a randomized controlled trial.
Setting: The ESCAPE trial was conducted at 26 sites.
Participants: 134 patients were analyzed (mean age 56.8 ± 13.4 years, 29 % female).
Interventions: We evaluated the change in SAPi, (systemic pulse pressure/pulmonary artery wedge pressure) obtained at baseline and at the final hemodynamic measurement in the ESCAPE trial.
Main outcome measures: Change in SAPi, (ΔSAPi), was analyzed for the primary outcomes of death, heart transplant, left ventricular assist device (DTxLVAD) or hospitalization, (DTxLVADHF) and secondary outcome of DTxLVAD using Cox proportional hazards regression.
Results: Median change in SAPi was 0.81 (IQR 0.20–1.68). ΔSAPi in uppermost quartile was associated with reductions in DTxLVADHF (HR 0.55 [95 % CI 0.32, 0.93]). ΔSAPi in the uppermost and lowermost quartiles combined was similarly associated with significant reductions in DTxLVADHF (HR 0.62 [95 % CI 0.41, 0.94]). ΔSAPi higher than 1.17 was associated with improved DTxLVADHF. ΔSAPi was also associated with troponin levels at discharge (regression coefficient $p = 0.001$) and trended with 6-minute walk at discharge (Spearman correlation $r = 0.179$, $p = 0.058$).
Conclusion: ΔSAPi was strongly associated with improved HF clinical profile and adverse outcomes. These findings support further exploration of Δ SAPi in the risk stratification of HF.

1. Introduction

Systemic Arterial Pulsatility index (SAPi) is a novel hemodynamic index associated with adverse outcomes among patients with advanced heart failure [1]. SAPi is calculated as the ratio of systemic pulse pressure to pulmonary artery wedge pressure (PAWP). Among patients with heart failure with reduced ejection fraction (HFrEF) in the ESCAPE trial, SAPi above the median threshold of 2.57, obtained prior to the removal of the pulmonary artery catheter (PAC) was significantly associated with improved outcomes [1]. SAPi is a proxy for ventriculo-arterial coupling (VAC) and constitutively incorporates markers that reflect left ventricular contractile efficiency as well as the characteristic impedance of the

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; CI, cardiac index; IQR, interquartile range; LVSWI, left ventricular stroke work index; LVAD, left ventricular assist device; PAC, pulmonary arterial capacitance; PADP, pulmonary arterial diastolic pressure; PASP, pulmonary arterial systolic pressure; PAWP, pulmonary artery wedge pressure; PP, pulse pressure; RAP, right atrial pressure; ROC, receiver operating characteristic; RV, right ventricle; SAPi, systemic arterial pulsatility index; SBP, systolic blood pressure; VAC, ventriculo-arterial coupling.

☆ This study was undertaken in Charlottesville, Virginia.

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arterial system (afterload). Patients with acute decompensated heart failure requiring hospitalization have suboptimal VAC hemodynamics. In this context, patients in acute decompensated heart failure may conceptually be considered to be hemodynamically at their lower limit of left ventricular contractile reserve [2,3]. When treatment for heart failure is instituted (with afterload reduction and congestion relief with diuretics), especially during this "vulnerable phase", a proportion of heart failure patients' contractile reserve may improve [3], while others, despite treatment with guideline directed medical therapy, may continue to deteriorate to require advanced heart failure therapies. Determining the optimal timing for such therapies along with risk stratification is challenging and requires nuanced incorporation of multi-modality assessments using a combination of clinical, biomarker, hemodynamic and imaging parameters [4]. Thus, identification of high-risk patients likely to experience adverse outcomes or who may require escalation of advanced heart failure therapies, is key to improving outcomes among patients hospitalized with acute decompensated heart failure. We sought to expand upon our prior work in the impact of SAPi on patient outcomes and theorized that the change in SAPi from baseline to discharge (ΔSAPi) may separately serve as a predictor of survival. In the present study, we hypothesized that ΔSAPi would be associated with adverse outcomes in advanced heart failure patients undergoing pulmonary artery catheter monitoring in the ESCAPE trial. We theorized that SAPi used in this way would provide a proxy measure of "VAC reserve".

2. Materials and methods

2.1. Study design and outcomes

The ESCAPE trial was a clinical trial evaluating the efficacy of pulmonary arterial catheterization in patients with congestive heart failure [5]. To evaluate the relationship between ΔSAPi, with clinical outcomes in the ESCAPE database, we calculated SAPi both at baseline and at the final hemodynamic measurement prior to the removal of the PAC. The range in the two temporal measurements in SAPi is what we refer as the delta SAPi (ΔSAPi). Previous studies have reported the methods of measurement of the hemodynamics in the ESCAPE trial in more detail [5]. For this analysis, SAPi was assessed at baseline and final hemodynamic measurement as (Systolic Blood Pressure − Diastolic Blood Pressure) / PAWP. Blood pressure measurements were performed using cuff brachial artery blood pressure. PAWP was obtained via Swan-Ganz catheter. It is noted that pulmonary artery pressure measurements may be inaccurate with Swan-Ganz catheters. We then stratified ΔSAPi into quartiles and these quartiles were analyzed for association with adverse outcomes. We determined the association of ΔSAPi with the six-month primary outcome of death (D), heart transplant (Tx) or left ventricular assist device (LVAD) and heart failure rehospitalization (HF), (DTxLVADHF), as well as the secondary outcome of death, transplant, or LVAD (DTxLVAD). The ESCAPE trial was conducted in accordance with the ethical standards stipulated in the 1964 Declaration of Helsinki and its later amendments. This analysis used the de-identified publicly available data from the National Heart, Lung, and Blood Institute data repository.

2.2. Statistical analysis

Analyses of categorical variables were conducted using the parametric Chi-square test. The permutation Chi-square test was used for categorical variables with low frequencies. The Kruskal Wallis test was used to test for differences in continuous variables. Categorical variables are presented as frequencies with percentages, whereas continuous variables are described using medians and interquartile ranges (IQR). Survival analysis and Kaplan-Meier plots are used to show differences in adverse events between groups with stratification based on key predictor variables. The log rank test was used to show differences between groups. Univariate Cox proportional hazards regression and multivariable logistic regression were used to model associations of multiple independent variables of interest with the endpoints of interest during follow-up. Receiver operating characteristic curves (ROC) were constructed based on logistic regression results. Linear regression and Spearman correlation were used to evaluate association with laboratory values. An alpha value of 0.05 was used for statistical significance. Statistical analysis was conducted using R (v4.0.3; R Core Team 2020).

3. Results

3.1. Baseline characteristics and ΔSAPi

The ESCAPE database had 134 patients with complete invasive hemodynamics needed for the determination of ΔSAPi and was used in the present analysis. The mean age of the study cohort was 56.8 ± 13.4 years, and 29 % were female. As shown in Fig. 1, the distribution of ΔSAPi was approximately symmetrically distributed. The median ΔSAPi was 0.81 (IQR 0.20–1.68). The distribution of baseline demographic characteristics and hemodynamic characteristics based on ΔSAPi quartiles and above or below the median are shown in Table 1.

3.2. Composite heart failure outcome by ΔSAPi groups

Survival free of transplantation, LVAD, and heart failure hospitalization by quartile of ΔSAPi is shown in Fig. 2. There was segregation of this outcome based on quartiles with best outcomes noted in the highest quartile.

3.3. Comparison with pulmonary artery wedge pressure and systemic pulse pressure

As the SAPi is the quotient of the systemic pulse pressure and PAWP, the associations of each of these parameters with the clinical outcome was also assessed (Table 2). No significant associations were observed.

3.4. Survival free of LVAD and transplantation by highest quartile of ΔSAPi

Survival free of transplantation and LVAD comparing the highest quartile of ΔSAPi compared to the lower 3 quartiles is shown in Fig. 3a. The best survival outcomes were observed in patients with ΔSAPi in the highest quartile ($p = 0.04$). However, this trend was not reflected in the Cox proportional hazards model (Table 2a).

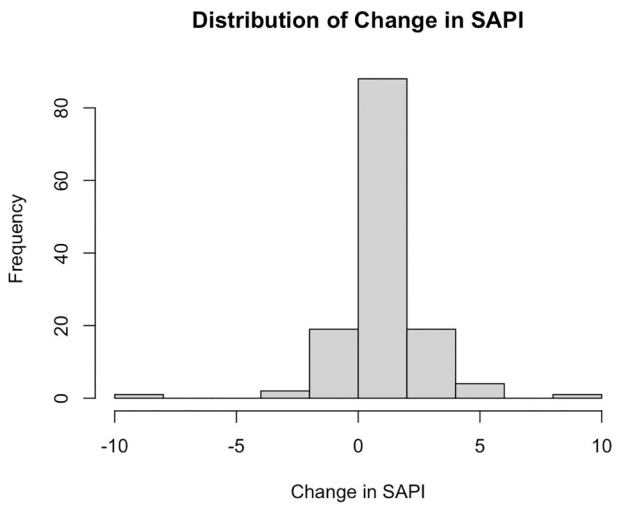

Fig. 1. Histogram of ΔSAPi distribution. The histogram showing the distribution of the delta change in systemic artery pulsatility index (ΔSAPi).

Table 1
Baseline demographic and hemodynamic characteristics by ΔSAPi quartile.[a]

	ΔSAPi Q1 (≤0.20)	ΔSAPi Q2 (0.20–0.81)	ΔSAPi Q3 (0.81–1.68)	ΔSAPi Q4 (≥1.68)	p-Value
Age	59 (53–68)	58 (46–63)	54 (44–63)	59 (50–68)	0.3
BMI	27.5 (24.1–33.6)	28.2 (24.3–33.8)	25.7 (23.2–32.5)	25.6 (22.6–29.0)	0.61
Sex	9 (36)	9 (37.5)	11 (50)	10 (42)	0.93
Race					**0.002**
White	27 (79.4)	23 (70)	12 (36.4)	16 (47.1)	
Black	5 (14.7)	10 (30.3)	13 (39.4)	9 (26.5)	
Other	2 (5.9)	0	8 (24.2)	9 (26.5)	
Diabetes	8 (24.2)	11 (34.4)	12 (36.4)	10 (30.3)	0.73
Atrial fibrillation	10 (29.4)	13 (39.4)	6 (18.2)	8 (23.5)	0.25
Ischemic cardiomyopathy	23 (67.6)	18 (54.5)	15 (45.5)	16 (47.1)	0.24
Non-ischemic cardiomyopathy	11 (32.4)	15 (45.5)	18 (54.5)	18 (52.9)	0.24
Hypertension	16 (47.1)	18 (54.5)	19 (57.6)	15 (44.1)	0.66
SBP (baseline)	110 (97.3–119.5)	101 (90–114)	105 (98–118)	110 (98.3–119.8)	0.29
DBP (baseline)	64 (58–72.8)	65 (60–71)	70 (63–74)	71 (61.3–80)	0.07
SBP (discharge)	106.5 (90.3–110)	98 (91–102)	102 (94–119)	108 (97.3–118.5)	0.053
DBP (discharge)	60 (52.5–68)	62 (55–70)	60 (54–66)	59 (49.3–67)	0.53
PP (discharge minus baseline)	-3 (−7.8–5.8)	0 (−5–7)	9 (2–15)	12 (9–23)	**<0.001**
Heart rate	82 (69.3–87.8)	81 (72–93)	80 (75–93)	74 (66–82.8)	**0.035**
LVEF	20 (15.3–23.5)	20 (15–25)	15 (15–20)	20 (15–24.3)	0.33
PAWP (mmHg, baseline)	22 (15–27.3)	28 (20–36)	24 (20−30)	23 (20–29.8)	0.09
PAWP (mmHg, discharge)	20 (16–24.8)	19 (16–22)	16 (15–19)	11 (9–13.8)	**<0.001**
ΔPAWP (mmHg, discharge minus baseline)	0 (−2.8–4)	-5 (−12-(−1))	-9 (−13-(−5))	−12.5 (−17-(−7.3))	**<0.001**
PASP (mmHg, baseline)	50 (40–61.3)	60 (44.3–68)	56 (46–64)	57 (46.3–64)	0.26
PASP (mmHg, discharge)	48 (38.5–60)	48 (39–54)	44 (38–50)	37 (30.5–45)	**0.003**
PADP (mmHg, baseline)	23.5 (18.5–28.5)	29.5 (20.8–37.8)	25 (24–35)	25 (21.8–34.5)	0.076
PADP (mmHg, discharge)	24 (18.5–26)	20 (17–25)	23 (17–25)	15.5 (13–19.5)	**<0.001**
Mean RAP (mmHg, baseline)	10 (6–13)	12 (8–18.3)	14 (9–19)	12 (7.3–18.8)	0.054
Mean RAP (mmHg, discharge)	10 (7–12)	10 (6–15.5)	9 (5–11)	5.5 (2.8–8)	**0.001**
SVR (wood units, baseline)	1210 (917–1514)	1546 (1249–1796)	1304 (1151–1906)	1499 (1135–1898)	0.11
SVR (wood units, discharge)	1083 (838.5–1373)	1050.5 (872.2–1212.8)	1153 (766.5–1488.5)	1096 (754–1515)	0.96
LVSWI (g/m^2, baseline)	20.3 (15.2–27.4)	15.5 (12.2, 20.3)	15 (12.9, 20.4)	19.3 (13, 26)	0.07
LVSWI (g/m^2, discharge)	23.6 (18, 27.6)	21.8 (14.9, 25.6)	21.2 (16.4, 28.8)	25.8 (20.7, 32.1)	0.09
CI (L/min/m^2, baseline)	2.1 (1.7–2.5)	1.9 (1.6–2.2)	1.8 (1.5–2.1)	1.8 (1.5–2.2)	0.19
CI (L/min/m^2, discharge)	2.4 (2–2.8)	2.3 (2–2.6)	2.3 (1.8–2.7)	2.3 (1.9–2.7)	0.95

[a] Fisher's exact test was used to compute significance of race distribution among ΔSAPi quartiles.

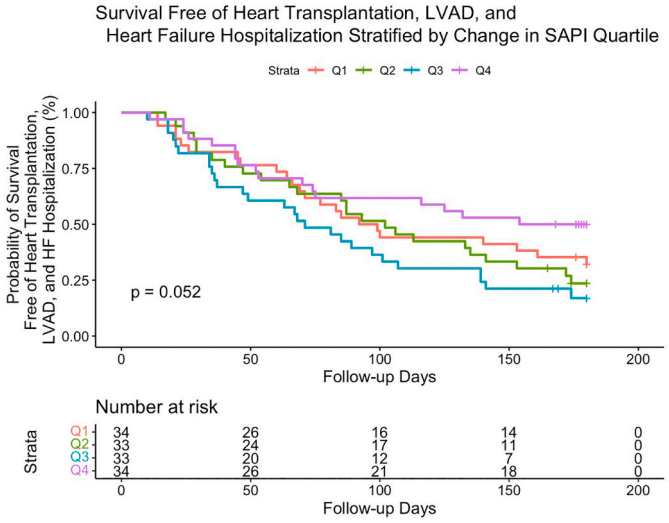

Fig. 2. Kaplan Meier survival curves for HF outcome stratified by ΔSAPi quartile. Survival free of transplantation, LVAD, and heart failure hospitalization stratified by ΔSAPi quartile.

3.5. *Composite heart failure outcome by highest quartile of ΔSAPi*

Survival free of transplantation, LVAD, and heart failure hospitalization comparing the highest quartile of ΔSAPi to the lower 3 quartiles is shown in Fig. 3b. The best composite heart failure outcomes were observed in patients with ΔSAPi in the highest quartile ($p = 0.02$). In a Cox proportional hazards model (Table 2a), ΔSAPi in the highest quartile was associated with the composite heart failure outcome (HR 0.55, 95 % CI 0.32–0.93, chi square statistic 4.92, $p = 0.03$). This was also reflected via logistic regression (odds ratio 0.33, 95 % CI 0.15–0.75) (Table 2b).

Table 2
Univariable Cox regression analyses and logistic models.

(a)

	HR (95 % CI)	Chi-square	p-Value
Change in ΔSAPI (per 1 unit)	0.97 (0.86, 1.09)	0.33	0.6
Change in PAWP (per mmHg)	0.997 (0.97, 1.02)	0.07	0.8
Change in PP (per mmHg)	1.01 (0.996, 1.02)	1.67	0.2
ΔSAPI Upper Quartile: DTxLVAD	0.35 (0.12, 1.00)	3.82	0.05
ΔSAPI Upper Quartile: DTxLVADHF	0.55 (0.32, 0.93)	4.92	0.02
ΔSAPI Above ROC Threshold	0.64 (0.41–0.99)	4.05	0.04

(b)

Effect	Point estimate (odds ratio)	95 % Wald confidence limits
ΔSAPI Upper Quartile: DTxLVADHF	0.33	0.15, 0.75
ΔSAPI Above ROC Threshold	0.38	0.18–0.8

[a]Univariable Cox regression analyses. DTxLVADHF *PAWP* pulmonary artery wedge pressure, *PP* pulse pressure, Δ*SAPi* change in systemic arterial pulsatility. DTxLVAD and DTxLVADHF: ΔSAPI Q4 vs Q1-Q3. DTxLVADHF: ΔSAPI Above (vs. Below) ROC Threshold.
[b]Logistic models. DTxLVADHF: ΔSAPI Q4 vs Q1-Q3. ΔSAPI Above (vs. Below) ROC Threshold (ΔSAPI above (vs. below) the ROC threshold has an odds ratio of 0.38 associated with DTxLVADHF).

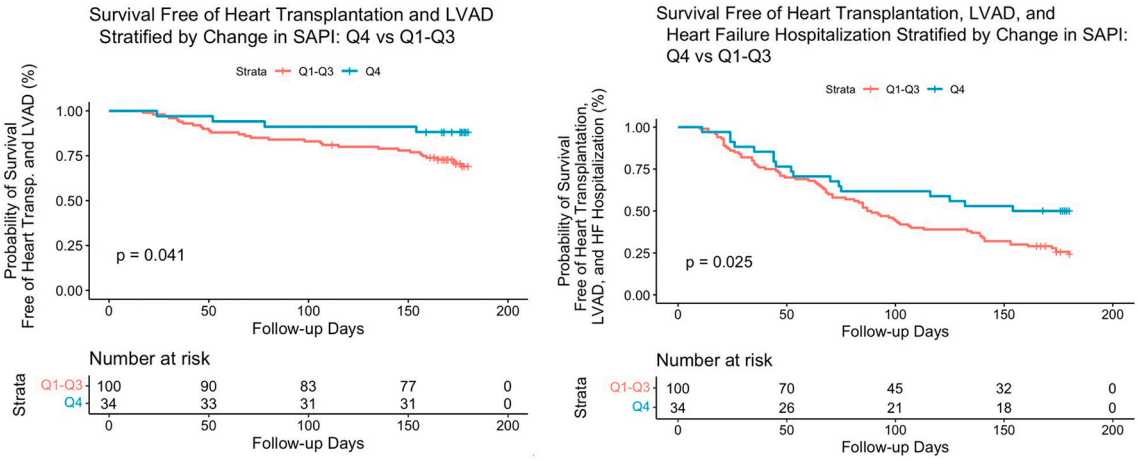

Fig. 3. (a) Kaplan Meier survival curves comparing the highest quartile of ΔSAPi to the Lower Quartiles. (b) Kaplan Meier Survival Curves for HF Outcome Comparing the Highest Quartile of ΔSAPi to the Lower Quartiles.

3.6. Receiver operating characteristic analysis

ROC analysis demonstrated that a ΔSAPi >1.177 (within Q3 range) predicted DTxLVADHF with 68.5 % sensitivity and 54.8 % specificity, and AUC 0.552 (Fig. 4a). DTxLVADHF comparing ΔSAPi above and below 1.177 is shown in Fig. 4b. The best composite heart failure outcomes were observed in patients with ΔSAPi above 1.177 ($p = 0.04$). In a Cox proportional hazards model (Table 2a), ΔSAPi above 1.177 was associated with composite heart failure outcome (HR 0.64, 95 % CI 0.41–0.99, chi square statistic 4.05, p = 0.04). This was also reflected via logistic regression (odds ratio 0.38, 95 % CI 0.18–0.8) (Table 2b).

3.7. Association with troponin levels

Ordinary linear regression demonstrated a significant association between ΔSAPi and discharge troponin levels (ΔSAPi coefficient 0.138, $p = 0.001$). However, there was no significant association between ΔSAPi and baseline troponin levels (ΔSAPi coefficient 0.004, $p = 0.126$).

3.8. Association with 6-minute walk distance

Ordinary linear regression demonstrated a trend toward significance between ΔSAPi and discharge 6-minute walk distance (ΔSAPi coefficient 34.62, $p = 0.098$). Spearman correlation analysis confirms this trend toward significance ($r = 0.179$, $p = 0.058$). However, there was no significant association between ΔSAPi and baseline 6-minute walk distance (ΔSAPi coefficient 20.26, $p = 0.291$).

3.9. Association with VO2 max (maximal oxygen consumption)

Ordinary linear regression demonstrated no significant association between ΔSAPi and discharge VO2 (ΔSAPi coefficient 0.509, $p = 0.287$), and between ΔSAPi and baseline VO2 (ΔSAPi coefficient − 0.157, $p = 0.724$).

3.10. Association with brain natriuretic peptide (BNP)

Ordinary linear regression demonstrated no significant association between ΔSAPi and discharge BNP (ΔSAPi coefficient 102.09, $p = 0.301$), and between ΔSAPi and baseline BNP (ΔSAPi coefficient 184, $p = 0.136$).

4. Conclusions

In this study, we evaluated the association of ΔSAPi with adverse outcomes in the ESCAPE database. The findings of this study demonstrate that ΔSAPi is significantly associated with outcomes of DTxLVADHF and DTxLVAD over the 6 months of follow up. Importantly,

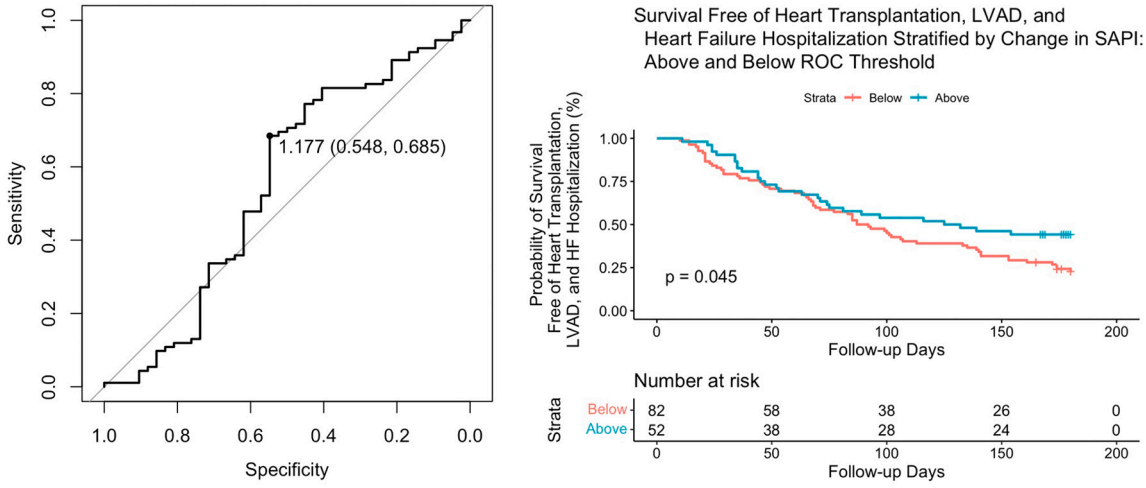

Fig. 4. (a) ROC analysis for optimal change in ΔSAPi. Receiver Operating Characteristic (ROC) for optimal change in ΔSAPi. ΔSAPi >1.177 predicted HF outcome with 68.5 % sensitivity and 54.8 % specificity. (b) Kaplan Meier Survival Curves for HF Outcome Comparing ΔSAPi Above and Below 1.177.

we observed that patients who had a change in SAPi below 1.17 from the baseline acute decompensated state to the final hemodynamic assessment (prior to the removal of the PAC) had worse adverse outcomes compared with those with ΔSAPi >1.17; the threshold change in ΔSAPi of 1.17 was selected based on the optimal ROC analysis. We further noted that patients who were in the lowest ΔSAPi quartile had the worst profile of clinical and hemodynamic indices (heart rate, pulmonary and right ventricular function hemodynamics, and discharge troponin) and a trend toward reduced functional status at discharge (6-minute walk). We additionally observed improved DTxLVAD and DTxLVADHF in the highest ΔSAPi quartile and a significant association between ΔSAPi and discharge troponin levels. Thus ΔSAPi may represent the magnitude of "VAC reserve" that may help identify patients who may require escalation of advanced heart failure therapies or close surveillance.

An acute decompensated heart failure state is a distinct phenotype that is associated with worse outcomes and portends a poor clinical trajectory [6,7]. This phenotype may signal a lower threshold of cardiac compensatory reserve, in the face of myocardial oxygen supply-demand mismatch [8]. The overarching goals of therapy in this acute vulnerable phase are to relieve congestion, improve the hemodynamic status and restore cardiac efficiency thereby ameliorating the negative downward spiral of reverse structural remodeling that ensues from the neurohormonal perturbations [9,10]. Given that the cardiovascular system is intrinsically pulsatile by constitution, high filling pressures and excessive systemic congestion have the net effect of attenuating systemic pulsatility [11]. On the basis of this rationale, we previously demonstrated that SAPi is associated with worse outcomes in heart failure patients [1]. More specifically, a higher SAPi (above median) of 2.57 was associated with improved outcomes. In the present study, we sought to incrementally advance the clinical application of this novel index by evaluating the association of the dynamic trajectory of ΔSAPi on clinical outcomes rather than a snapshot measurement. As hypothesized patients at high risk of short-term adverse outcomes had a diminutive range of ΔSAPi. In this context, a change in SAPi from baseline to when patient is clinically optimized could potentially serve as a hemodynamic biomarker of VAC reserve.

Importantly patients with lower ΔSAPi also had unfavorable hemodynamics overall including adverse right ventricular hemodynamic variables. For example, patients in the lower quartile ΔSAPi had higher right atrial pressures, mean pulmonary artery pressures and heart rates, all markers that have been associated with poor prognosis in heart failure [12–14]. Furthermore, patients with a low ΔSAPi had higher discharge troponin and a trend toward lower functional status as measured by discharge 6-minute walk distance. Lower discharge 6-minute walk distance and troponin elevation are both markers of poor prognosis in heart failure patients [15–18].

Cardiovascular pulsatility, enables the efficient delivery of blood flow to tissues and facilitates metabolic exchange at both the molecular and cellular levels [11,19,20]. In diminished pulsatile flow conditions, there is a heightened state of activation of neurohormonal pathways which promotes adverse structural remodeling [11], leading to worsening heart failure [21]. More recently a novel class of medications, sodium glucose co-transporter-2 (SGLT2) inhibitors, have been incorporated into the foundational therapies for heart failure [9,22,23]. The exact mechanisms by which these agents lead to improved outcomes in heart failure are not well elucidated, but there is evidence that these novel agents may improve pulsatile vascular function [24]. It is therefore intuitive that an increase in systemic pulsatility during therapy for acute decompensated heart failure could lead to favorable outcomes. Patients with a greater increase in ΔSAPi could be surmised to have a greater VAC coupling reserve and therefore likely to have a favorable clinical trajectory. Given that the risk of death is much more pronounced during the 'vulnerable phase,' [25] following the immediate hospitalization of acute decompensated heart failure, clinical tools aimed at enhancing risk stratification of patients at risk of adverse events in this proximate period of acute hospitalization are therefore needed [26]. Changes in ΔSAPi during therapy may need further exploration as a hemodynamic biomarker in acute decompensated heart failure.

In this post hoc study of the ESCAPE database, the cohort of patients in PAC was ~ half those in those enrolled in the entire trial, thus limiting the sample size and thus could be considered as hypothesis generating. Guideline directed medical therapies have significantly changed since the publication of the ESCAPE trial, and newer therapies such as angiotensin receptor/neprilysin inhibitor and SGLT2 inhibitors may have a profound effect on VAC mechanics. Even, so, the ESCAPE data base has a rich cohort of heart failure patients with invasive hemodynamic variables that are well phenotyped that could richly inform hemodynamic trajectories of advanced heart failure patients.

The Δ SAPi from baseline to final hemodynamic assessment was strongly associated with adverse clinical outcomes in advanced HF. ΔSAPi may lead to better risk stratification of patients undergoing invasive hemodynamic monitoring with advanced heart failure. ΔSAPi could serve as a hemodynamic biomarker for VAC in heart failure patients.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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