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Ankle–Brachial Index and Ventricular–Arterial Coupling for the Assessment of Acute Left Ventricular Systolic Dysfunction

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Abstract

Background: The ankle–brachial index (ABI) has been extensively applied for the diagnosis and risk stratification of vascular disease. However, it can also provide information about the interaction between ventricular function and peripheral vascular compliance, defined as ventricular–arterial coupling (VAC), which has been extensively shown to predict the outcome of patients with heart failure (HF). So far, no study has addressed the use of ABI for the assessment and prognostic stratification of patients with acute decompensated left ventricular systolic dysfunction, which was the aim of our study. **Methods:** Patients hospitalized with acute HF and reduced left ventricular ejection fraction (EF < 50%) were prospectively included. Echocardiogram and ABI were performed after the resolution of the acute phase, before discharge, and on optimized medical therapy. Abnormal ABI was defined as values ≤0.90 or >1.4. Arterial and ventricular elastance and E_{es}/E_a (*i*VAC) were estimated from echocardiographic parameters. The normal range for *i*VAC was considered [0.5–1.0]. **Results:** We included 80 patients, of whom 81.3% were males, with a mean age of 67.98 ± 11.3 years. Among them, 57.5% were hypertensive, 32.5% were active smokers, 41.3% were hypercholesterolemic, 20% were diabetic and 11.3% had previous myocardial infarction. The mean ejection fraction was 36.8 ± 9.22%, stroke volume was 46.3 ± 14.3 mL, arterial elastance was (E_a) 2.48 ± 0.87 mmHg/mL and VA coupling was 0.64 ± 0.25. HF etiology was ischemic in 58 (72.5%) of the patients, of whom 31 displayed multivessel disease. Impaired ABI values were observed in 21 (26.3%) of the patients (≤0.90 in 11 patients and >1.4 in 10 patients). A significant non-linear (logistic) relationship was observed between ABI values and VA coupling (β = 1.07, $p = 0.007$), which became linear for *i*VAC ≥ 0.5 (β = 0.92, $p < 0.001$). A similar trend was observed in patients with ischemic (β = 1.06, $p < 0.001$) and non-ischemic etiology (β = 1.02, $p = 0.12$). Echocardiographic follow-up was available in 63 patients, as three died before re-assessment. At a median follow-up of 281.5 days, EF recovery was observed in 44 patients, and EF improvement in 76.2%. VA coupling was the only independent predictor of EF recovery (OR [95%CI] = 0.15 [0.03–0.69], $p = 0.015$ for *i*VAC < 0.5). **Conclusions:** Ventricular–arterial coupling can represent a useful tool for the prognostic stratification of patients hospitalized for acute decompensated left ventricular systolic dysfunction, with lower values being associated with worse outcomes. The ankle–brachial index is a widely available parameter displaying a good association with VAC; therefore, it could offer a faster bedside estimation of ventricular–arterial interaction. Future larger-scale studies are certainly needed to confirm our results and implement the use of the ABI in acute HF.

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Keywords: left ventricular dysfunction; ankle–brachial index (ABI); ejection fraction; elastance; blood pressure; stroke volume; outcomes

1. Introduction

Heart failure represents a broad spectrum of conditions with similar clinical presentation and treatment, but with enclosing different aetiologies and various phenotypes, thus translating into uncertain outcomes [1–3].

In particular very little is known, so far, about the predictors of left ventricular recovery in patients with heart failure and reduced ejection fraction (HFrEF).

Previous studies have pointed at the importance of defining the pathophysiological mechanisms underneath, or HF phenotypes, including left ventricular (LV) failure, vascular failure or their combination, for improving the management and prognostic stratification of these patients [4,5]. Several non-invasive parameters have been developed to provide an indirect estimation of pressure and volume data generally derived from heart catheterization, and they still represent the gold standard for the assessment of cardiovascular performance [6]. Nevertheless, echocardiographic-derived ventricular elastance (E_{es}) and arterial elastance (E_a) and their ratio, defined as ventricular–arterial coupling (VAC), have shown a strong association with clinical outcomes [7].

In addition, the evaluation of arterial stiffness has been proposed not only for measuring peripheral atherosclerosis (PAD), but also as an indicator of impaired vascular function in patients with HF [8–10].

The ankle-brachial index (ABI) currently represents one of the most largely available and cheap tools for vascular screening. Several studies have demonstrated a negative prognostic impact of extreme values of the ABI, with ABI < 0.9 indicating being diagnostic for PAD and ABI > 1.4 indicating pathological arterial stiffness [7,8].

However, despite PAD and altered values of ABI having been associated with an increased risk of cardiovascular events [11,12], few data have been reported about the use of the ABI for risk prediction in patients with HFrEF.

The aim of the present study was to assess the relationship of the ABI with other diagnostic parameters for the assessment and prognostic stratification of patients presenting with new-onset acute left ventricular dysfunction.

2. Methods

We included in this observational registry patients hospitalized in a single center from 1 June 2022 to 15 April 2026 and presenting with: (1) first episode of acute decompensated HF; (2) reduced or mid-range ventricular function (defined as EF $< 50\%$), either for ischemic or non-ischemic etiology (i.e., chronic coronary syndrome presenting with left ventricular dysfunction, tachycardiomyopathy, first diagnosis of other cardiomypathies). Patients with prior cardiovascular history (previously hospitalized for HFrEF or dilated cardiomyopathy), acute myocardial infarction or severe valvular disease at admission were excluded. Patients with a known history of peripheral arterial disease or symptoms suggestive of claudicatio intermittens were also excluded.

All the patients started with guideline-directed medical therapy to reduce fluid overload, including diuretics, mineralocorticoid receptor antagonists (MRAs), renin–angiotensin system inhibitors (RASIs), beta blockers, sodium–glucose co-transporter 2 inhibitors (SGLT2Is) and angiotensin receptor/neprilysin inhibitors (ARNIs), when applicable. HF therapies were titrated to the maximum tolerated dose.

When adequate compensation was achieved, all the patients underwent coronary angiography to better define the etiology of LV dysfunction. In cases of significant coronary artery disease (at least 1 vessel stenosis >70%), ischemic etiology was considered and percutaneous coronary intervention (PCI) could be performed within the same procedure, according to the operator's discretion. A written informed consent was obtained from all patients. All demographic and clinical data were collected in a dedicated database. Hypertension was defined as systolic pressure > 140 mmHg and/or diastolic pressure > 90 mmHg or if the individual was taking antihypertensive medications. Diabetes mellitus was defined as previous diagnosis, specific treatment administration (oral drug or insulin), fasting glycemia > 126 mg/dL or HbA1c > 6.5%. Chronic renal failure was considered for history of renal failure or an admission-estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 by MDRD (Modification of Diet in renal Disease) formula. Hypercholesterolemia was defined for values of fasting total cholesterol > 200 mg/dL or HDL cholesterol < 40 mg/dL, or specific treatment administration. Previous smokers were considered following over a 30-day discontinuation [13].

Biomarkers were measured at admission for the evaluation of blood cell count, hepatic and renal function, metabolic profile, cardiac troponins (highly sensitive Troponin T) and N-terminal pro-B-type natriuretic peptide (NT-proBNP). The methods for blood samples collection and processing have been previously reported [14].

2.1. Transthoracic Echocardiogram

Routine transthoracic echocardiogram was performed with a Philips Epiq7 machine by experienced physicians, differing from ABI operators. Parasternal long- and short-axis, as well as apical, views were obtained, and systolic and diastolic diameters and volumes were measured. LV ejection fraction (EF) was calculated using the modified biplane Simpson's method, where a reduced EF was considered below 50%. Diastolic dysfunction was graded according to mitral inflow velocities (E/A ratio), whereas tricuspid annular plane systolic excursion (TAPSE) was used to measure right ventricular function.

Mitral and aortic valve stenosis and regurgitation were assessed by visual color Doppler evaluation and continuous Doppler flow measurement.

The stroke volume (SV) was calculated as the difference between end-diastolic (EDV) and end-systolic (ESV) volumes, with arterial elastance (Ea) as the ratio between systolic blood pressure (SBP) and SV, and *i*VAC, the inverse of VAC, as the ratio between ventricular elastance (Ees) and E_a, which was simplified as SV/ESV, in accordance with Chen et al.'s single beat formula [15]. The normal range for *i*VAC was considered: [0.5–1.0].

2.2. Ankle–Brachial Index (ABI) Measurement

The ABI was measured in all the patients before discharge with a single instrument, the WatchBP Office ABI instrument (Colpharma Srl, Parma, Italy). Two trained operators (MV, FP) strictly applied the pre-defined protocol for patients' positioning and cuffs application. First, the dominant arm was identified by performing 3 repeated measures of blood pressure (BP) in both arms of supine patients. Thereafter, the cuffs were applied to the dominant arm and same-side ankle, immediately proximal to the malleoli, and 3 measurements of the BP were obtained. The average of the 3 measures was taken into account. Systolic and diastolic blood pressure, heart rate and the ABI were automatically provided by the instrument. A diagnosis of peripheral arterial disease (PAD) was made for ABI ≤ 0.90, although an impaired ABI was also considered in cases of values >1.4, according to the literature [16].

2.3. Study Endpoints and Long-Term Follow-Up

Follow-up was performed from electronic notes of out-patients visits and echocardiographic reports for the longest time available. In cases where no data were reported, a telephone contact was attempted.

The primary study endpoint was to define the relationship between the ABI and ventricular performance parameters. Primary clinical endpoint was LV function recovery, which was defined as EF ≥ 50% or an increase of ≥50% from baseline, over a 30-day follow-up. The secondary endpoint was EF improvement, defined as a ≥10-point absolute increase and a second EF > 40%.

2.4. Statistical Analysis

Statistical analysis was performed using SPSS 23.0 statistical package. Continuous data were expressed as mean ± SD and categorical data as percentage. Patients were grouped according to ABI tertile values. Analysis of variance (ANOVA) and the chi-square test were used for continuous and categorical variables, respectively. Best-fitting curve analysis and linear regression analysis were performed to evaluate the relationship between ABI and echocardiographic parameters, E_a, *i*VAC and NT-proBNP. Multivariable forward conditional logistic regression analysis was run to identify the independent predictors of LV function recovery. A p value < 0.05 was considered statistically significant.

As the present study represented an exploratory analysis, with no pre-existing data in the literature, the sample size calculation could not be anticipated.

3. Results

We included 80 patients, of whom 81.3% were males and with a mean age of 67.98 ± 11.3 years. Patients were divided according to tertiles values of the ABI (<0.99, $n = 27$; 0.99–1.18, $n = 28$; ≥1.18, $n = 25$).

The flow chart of the study, containing the criteria for inclusion and exclusion and the follow-up procedures, is displayed in Figure 1.

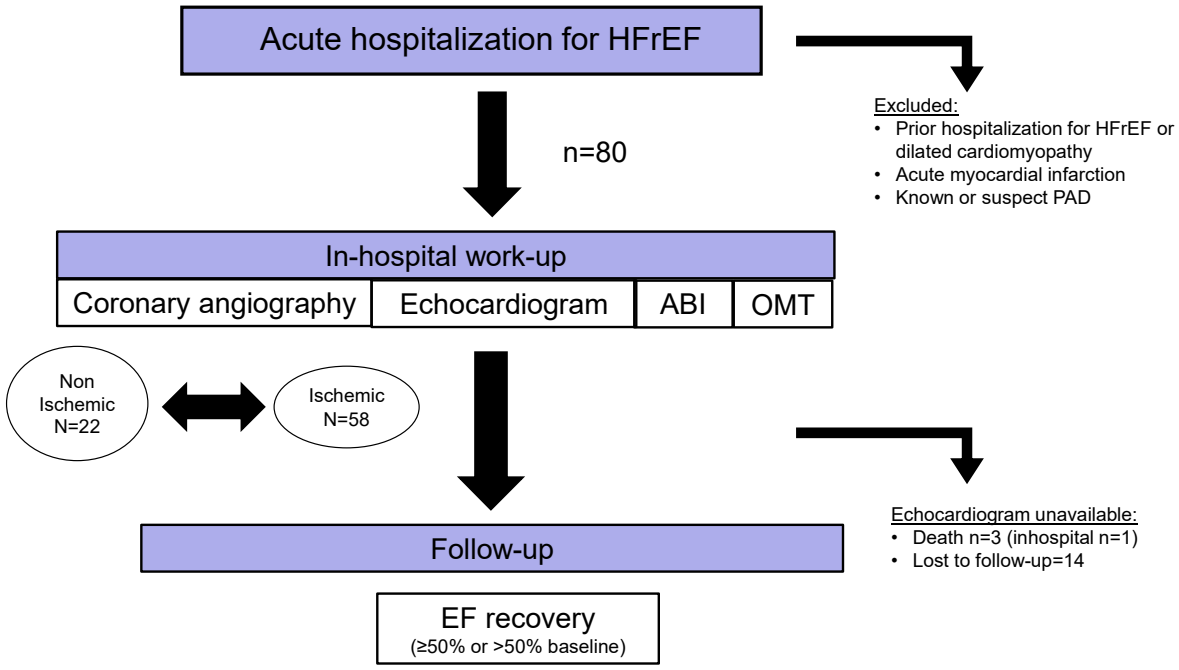


Figure 1. Flow chart for the study protocol and analysis.

Baseline characteristics, main cardiovascular risk factors, and chemistry and echocardiographic parameters are shown in Table 1. In particular, we observed a significant association of ABI values with age ($p = 0.03$) and an inverse relationship with the use of calcium antagonists at admission ($p = 0.04$).

Table 1. Clinical and demographic features according to ankle–brachial index (ABI).

Baseline Clinical Characteristics	I Tert ($n = 27$)	II Tert ($n = 28$)	I Tert ($n = 25$)	p Value
Age (mean ± SD)	70.2 ± 9.8	63.5 ± 10.4	70.5 ± 12.6	0.03
Male Sex (%)	77.8	82.1	84	0.57
Hypertension (%)	51.9	67.9	52	0.97
Hypercholesterolemia (%)	33.3	57.1	32	0.97
Active Smokers (%)	22.2	42.9	32	0.34
Diabetes mellitus (%)	25.9	7.1	28	0.89
Renal failure (%)	11.1	21.4	4	0.47
History of MI (%)	11.1	14.3	8	0.74
Previous PCI (%)	14.8	14.3	8	0.47
Therapy at admission				
ACE inhibitors (%)	18.5	28.6	24	0.64
ARB (%)	22.2	14.3	8	0.15
Beta blockers (%)	29.6	32.1	24	0.66
Nitrates (%)	0	0	4	0.20
Calcium antagonists (%)	25.4	21.4	4	0.04
Diuretics (%)	22.2	32.1	20	0.87
Statins (%)	29.6	21.4	16	0.24
ASA (%)	29.6	25	28	0.89
P2Y12 inhibitor (%)	3.7	0	8	0.44
Therapy at discharge				
ACE inhibitors (%)	37	53.6	44	0.6
ARB (%)	25.9	3.6	24	0.81
Beta blockers (%)	88.9	92.9	88	0.93
OAC (%)	33.3	17.9	32	0.89
Calcium antagonists (%)	7.4	3.6	4	0.57
okDiuretics (%)	81.5	71.4	88	0.58
Statins (%)	59.3	89.3	76	0.15
ASA (%)	66.7	78.6	80	0.27
P2Y12 inhibitor (%)	55.6	67.9	68	0.35
SGLT2-I (%)	40.7	39.3	40	0.96
ARNI (%)	33.3	28.6	40	0.63
MRA (%)	70.4	64.3	76	0.67
Main chemistry				
Glycemia (mg/dL ± SD)	126.7 ± 31.1	125.8 ± 38.5	149.2 ± 67.3	0.15
Creatinine (mg/dL ± SD)	1.14 ± 0.42	1.1 ± 0.31	1.06 ± 0.26	0.65
Platelets (10^3/μL; mean ± SD)	265.5 ± 71	265.5 ± 119	223.6 ± 56	0.16
Hemoglobin (g/dL ± SD)	14.7 ± 1.6	14.9 ± 1.7	14.5 ± 1.7	0.65
LDL cholesterol (mg/dL ± SD)	87.1 ± 37.5	100.8 ± 49	96.5 ± 38.3	0.48
NT-proBNP	7269 ± 6738	4868 ± 8636	5175 ± 5410	0.58
Echocardiographic parameters				
Septum thickness (mm ± SD)	10.4 ± 1	10.3 ± 1.8	11.3 ± 1.7	0.39
EDV (mL ± SD)	133.7 ± 44	133.2 ± 61.6	136 ± 57.9	0.98
Stroke volume (mL ± SD)	43.9 ± 12.6	47 ± 13.2	47.7 ± 17.4	0.66
Ejection fraction (% ± SD)	34.5 ± 9.5	38.2 ± 10.3	35.8 ± 9.2	0.36
TAPSE (mm ± SD)	20.6 ± 3.9	21.3 ± 4.5	20.5 ± 2.5	0.69
E_a (mmHg/mL ± SD)	2.4 ± 1.18	2.47 ± 0.67	2.57 ± 0.66	0.78
VAC (mean ± SD)	0.59 ± 0.23	0.67 ± 0.24	0.64 ± 0.28	0.64

Table 1. *Cont.*

Baseline Clinical Characteristics	I Tert (n = 27)	II Tert (n = 28)	I Tert (n = 25)	p Value
Coronary angiography				
Coronary artery disease (%)	66.7	71.4	80	0.29
Multivessel disease (%)	46.2	32.1	40	0.65
Percutaneous intervention (%)	70	76	70	0.99

Mean EF was 36.8 ± 9.22%, SV 46.3 ± 14.3 mL, E_a 2.48 ± 0.87 mmHg/mL and *i*VAC 0.64 ± 0.25. *i*VAC in normal range was observed in 49 patients (61.25%), whereas 21 patients (26.25%) had *i*VAC values < 0.5.

HF etiology was ischemic in 58 (72.5%) of the patients, of whom 31 (38.8%) displayed multivessel disease and 47 (58.8%) underwent PCI.

Impaired values of the ABI were observed in 21 (26.3%) of the patients (<0.90 in 11 patients and >1.4 in 10 patients).

Table 2 displays the results of the regression analysis between the ABI and other parameters.

Table 2. Coefficient for linear regression analysis between ankle–brachial index (ABI), echocardiographic parameters and biomarkers.

ABI		
Variable	**Unstandardized B 95% Confidence Interval**	**β; p Value**
Age	−5.05; 18.9	0.12; 0.25
Body weight	−11.1; 25.2	0.09; 0.44
Hemoglobin	−2.26; 1.44	−0.05; 0.66
Creatinine	−0.49; 0.24	−0.08; 0.49
NT-proBNP	−0.15; 359	−0.19; 0.21
Ejection fraction	−10.8; 9.9	−0.009; 0.94
Stroke volume	−13.5; 21.3	0.55; 0.66
EDV	−57.4; 67.8	0.19; 0.87
E_a	−0.53; 1.47	0.11; 0.35
E_{es}	−4.7; 3.46	−0.36; 0.77
VAC (overall)	−0.23; 0.11	−0.6; 0.71
VAC (≥0.5)	0.89; 0.94	0.92; <0.001
VA coupling		
Age	−14.6; 7.4	−0.08; 0.52
Body weight	−23.5; 9.9	−0.10; 0.42
Hemoglobin	−1.65: 1.48	−0.013; 0.92
Creatinine	−0.44; 0.1	−0.15; 0.22
NT-proBNP	−13,925; 6618	−0.12; 0.48
Ejection fraction	29.03; 37.4	0.89; <0.001
Stroke volume	−2.28; 24.8	0.19; 0.10
EDV	−169.8; −85.2	−0.58; <0.001
E_a	−1.28; 0.13	−0.19; 0.11
E_{es}	−12.5; −8.54	−0.78; <0.001

A significant non-linear (logistic) relationship was observed between ABI values and VA coupling (β = 1.07, p = 0.007; R^2 = 0.005), that became linear for *i*VAC ≥ 0.5 (β = 0.92, p < 0.001, Figure 2).

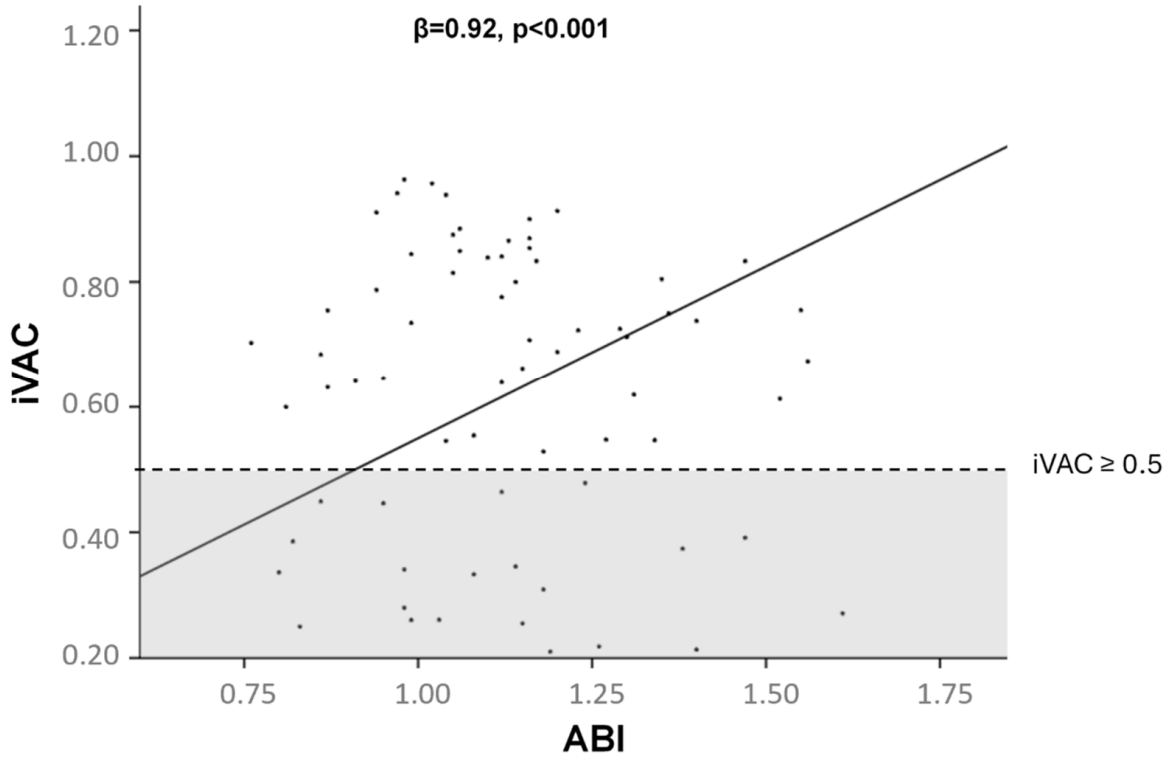


Figure 2. Linear regression analysis between ventricular–arterial coupling (VAC) and ankle-brachial index (ABI) (for VAC ≥ 0.5).

A similar trend was observed in patients with ischemic (β = 1.06, $p < 0.001$) and non-ischemic etiology (β = 1.02, $p = 0.12$).

No relationship was observed between the ABI or *i*VAC and pre-discharge NT-proBNP (Table 2).

At follow-up, 3 patients died before a new evaluation was performed (1 patient in-hospital), and for other 14 survivors, no echocardiogram was repeated, resulting in 63 (78.8%) of the patients available for an echocardiographic follow-up, At a median follow-up of 281.5 days [96–448], EF recovery was observed in 44 patients (67%) and EF improvement in 48 patients (76.2%). As shown in Figure 3A, a trend of a higher rate of recovery was observed in patients across tertile values of the ABI (71.4% vs. 72.7% vs. 92.9%, $p = 0.16$), whereas the rate of recovery was significantly lower in patients with *i*VAC < 0.5 (61.1% vs. 91.2%, $p = 0.014$; Figure 3B).

Similar results were obtained for EF improvement across tertile values of the ABI (76.2% vs. 86.4% vs. 92.9%, $p = 0.18$) and in patients with low *i*VAC (72.2% vs. 94.1%, $p = 0.04$).

In the multivariable regression analysis (including age, calcium antagonists at admission, impaired ABI, ischemic etiology, use of beta blockers and statins, inverse VA coupling), *i*VAC < 0.5 was the only independent predictor of EF recovery (OR [95%CI] = 0.15 [0.03–0.69], $p = 0.015$).

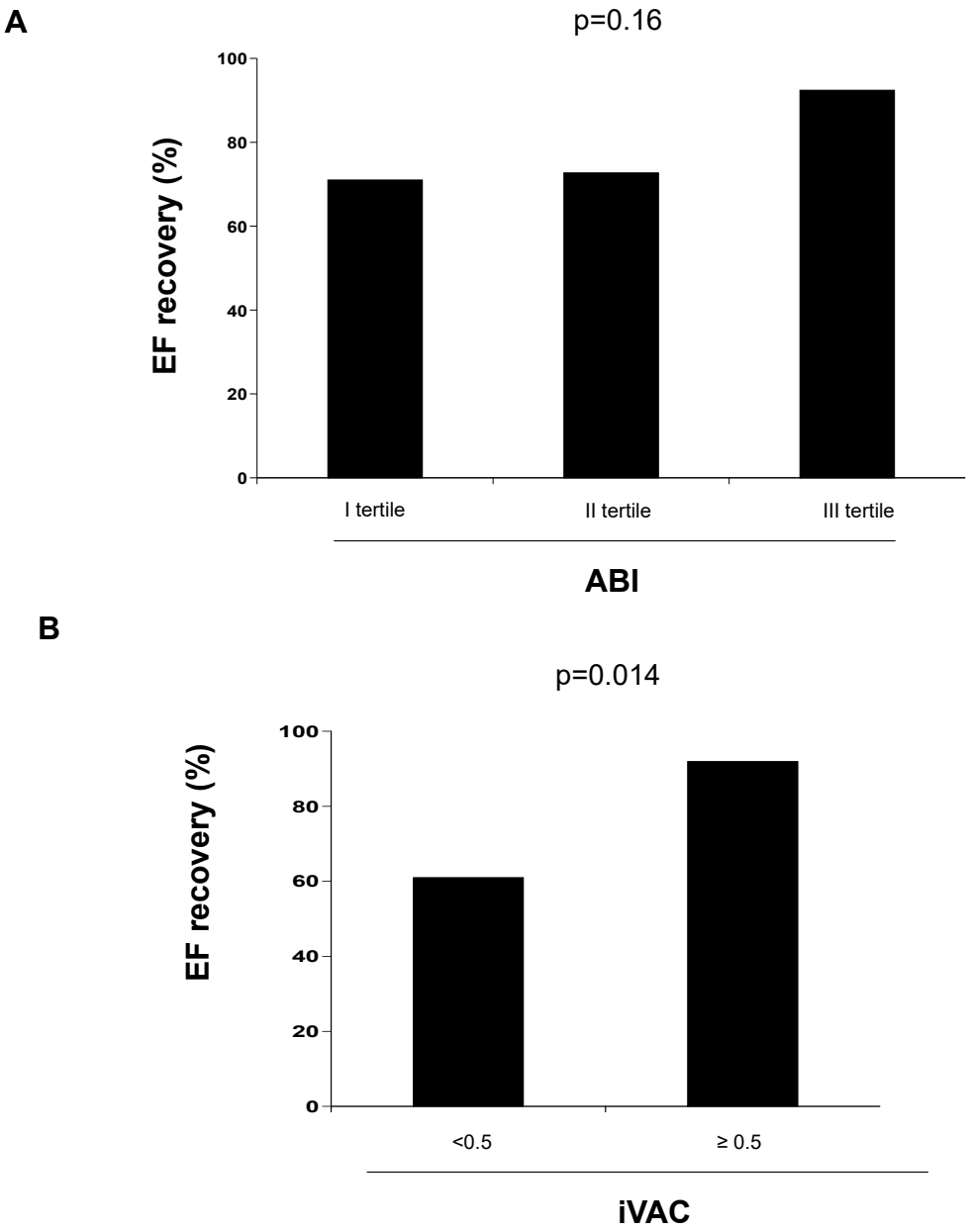


Figure 3. Left ventricular function recovery according to tertile values of the ankle–brachial index (ABI, (**A**) upper graph) or ventricular–arterial coupling (VAC) values ((**B**), lower graph).

4. Discussion

The present study represents the first attempt to evaluate the relationship between the ABI and other non-invasive parameters of ventricular function with prognosis in patients hospitalized for acute HF and EF < 50%. We observed a significant direct relationship between the ABI and *i*VAC and lower rates of EF recovery in patients displaying lower values of the ABI and *i*VAC, although only the latter emerged as an independent predictor of left ventricular function improvement.

The ankle–brachial index (ABI) represents a cheap, widely available and easy-to-obtain method for assessing the performance of the arterial system by providing information about the arterial compliance or stiffness, the endothelial function and the likelihood of peripheral arterial disease [11,16].

The use of the ABI for the screening and prognostic stratification of patients with and without established cardiovascular disease has been extensively demonstrated. In the large

cohort of the Atherosclerosis Risk in Communities (ARIC) study [17], lower ABI values were associated with the risk of coronary artery disease and stroke in asymptomatic patients. Moreover, a large-scale meta-analysis reported a two-fold increased risk of 10-year mortality and major cardiovascular events in patients with ABI < 0.9 [18].

We also previously reported elevated rates of abnormal ABI values (21.5% ABI < 0.9) among patients with acute myocardial infarction with no history of peripheral arterial disease [19], a parameter that has been associated with worsened outcomes in patients undergoing percutaneous interventions [20]. Nevertheless, few studies have evaluated the role of the ABI in addressing the prognosis of patients with LV dysfunction.

Indeed, several efforts have been accomplished in recent years to identify non-invasive bedside parameters, allowing us to stratify the risk of patients with HFrEF, that still display an extremely elevated mortality, despite the improvements made in pharmacological therapies and mechanical support devices [21–23].

In particular, BNP and NT-proBNP are indicated in the guidelines of several HF societies as a Class I recommendation for the diagnosis and therapeutic management of patients with acute and chronic HF, with both among patients with reduced and preserved EF. In fact, several studies have confirmed a higher risk of re-hospitalization and long-term mortality for patients not achieving a significant reduction in NT-proBNP after volume unloading and optimization of medical therapy [24].

Large interest has also been dedicated to the echocardiographic estimates of cardiac and vascular mechanics, representing valid surrogates of cardiac heart catheterization, which still represents the gold standard for a complete definition of pressure–volume curves and cardiac index [25,26]. Among them, arterial elastance (E_a) is an indicator of vascular stiffness and peripheral resistances, while ventricular elastance (E_{es}) informs us about LV contractility as a load-independent measurement, whereas VA coupling (VAC) reflects the mutual interaction and energetic efficiency of the myocardial contraction being transferred to the vascular system.

Previous studies have confirmed a strict association between VAC and E_a and established cardiovascular risk factors, showing that lifestyle improvement could lead to a reduction of these parameters and a more efficient cardiac mechanical performance [27].

Moreover, VAC can be extremely useful in HF phenotyping, providing important pathophysiology insights that can prompt the discrimination among the broad spectrum of HF etiologies [28].

In addition, impaired or uncoupled VAC has emerged as a strong predictor of cardiovascular risk, disease progression and mortality in both patients with reduced and preserved EF [25]. In the STANISLAS cohort, Holm et al. found a significant relationship between HF biomarkers, including NT-proBNP and VAC, mainly derived from lower values of E_a, possibly indicating a compensatory vascular response to left ventricular remodeling and overload [29].

The ankle–brachial index, similarly to E_a, reflects the peripheral arterial pressure derived from the interaction between systolic contraction and vascular stiffness, thus potentially informing us about the hemodynamic status and the interaction between the heart and arterial system. However, being a more rapid, bedside and universally available parameter, it does not require dedicated instruments or a trained professional. In fact, several studies have suggested that lower ABI values could predict cardiovascular mortality and the development of future HF [8,30]. Comparable results were observed by Newman et al., reporting that an ABI < 0.9 was associated with 1.61-fold increase in the risk of incident HF compared with an ABI ≥ 0.9 in patients without prior coronary heart disease [31].

However, these studies only focused on chronic HF, whereas no study so far has evaluated the role of the ABI in patients with acute HfrEF: neither its relationship with VAC and other echocardiographic parameters, nor its predictive role for LV function recovery.

In the present study, we first systematically measured ABI values in patients with new-onset acute HF and reduced or mid-range EF, treated with optimal medical therapy and/or revascularization, that were followed up for over 30 days to assess LV function recovery.

In our study, 26.3% of patients without PAD displayed impaired ABI values, suggesting that this cheap, bedside parameter could reflect the activation of the mechanisms for vascular compensation in the presence of left ventricular dysfunction. In fact, we observed a significant association between the ABI and *i*VAC, fitting a linear relationship for non-extreme values ($iVAC \geq 0.5$). However, at multivariable analysis, only *i*VAC emerged as an independent predictor of EF improvement, with higher values being associated with better outcomes.

Our results confirm the previous literature, documenting the prognostic role of non-invasive estimates of ventricular–arterial interaction. As in our observation, Lin et al. recently documented a non-linear association between VAC and the risk of HF, stroke and all-cause mortality among 38,144 participants included in the UK Biobank registry and undergoing cardiac magnetic resonance [32]. They observed the strongest association for patients with VAC values in the 4th quartile, although in this registry, the inverse of our formula (E_a/E_{es}) was applied.

Further data indicated that VA uncoupling negatively affects the prognosis. In Sano et al., among 3239 patients with acute HF consequent to vascular dysfunction and blood pressure increase, the cardio-ankle vascular index could predict the risk of cardiac death or re-hospitalization at 1 year [33]. Similarly, Ky et al. showed that EDV and VA coupling, but not end-systolic elastance (E_{es}), were associated with worse prognosis among 466 patients with chronic systolic HF [34]. Similarly, in our population, lower *i*VAC was associated with a reduced likelihood of recovery, with a similar non-significant trend for lower tertile values of the ABI.

Indeed, HF encloses a broad spectrum of different phenotypes, potentially accounting for the differences observed in our study populations. In effect, abnormally low *i*VAC in our patients probably reflects an increase in E_a, which could be explained with the recruiting of the peripheral arterial response in a compensated setting, as compared to acute decompensated HF, as previously suggested by Holm et al. [29]. Indeed, the latter condition, known as vasoplegia, has also been associated with extremely negative consequences in patients undergoing cardiac surgery and cardiogenic shock [35,36].

The pro-inflammatory status of cardiac conditions, such as HF, could in fact promote the release of vasodilating factors, such as nitric oxide derivatives and cytokines, thus preventing the response of vascular resistances. Moreover, chronic adrenergic overstimulation could lead to the downregulation or desensitization of both myocardial β-receptors and α-adrenoreceptors [37].

A similar effect, indeed, could also be ascribed to HF therapy and especially for RASI and beta blockers, which were largely used in our population. Of note, in our population, patients with lower ABI values displayed a higher use of calcium antagonists at admission. However, these drugs were mostly discontinued at the time of hospitalization as a consequence of acute HF itself and were therefore not ongoing at the moment of assessment of both the ABI or VAC.

Furthermore, in these patients, the maintenance of ventricular E_{es} was achieved through a marked increase in the recruited volumes, as confirmed by the inverse linear relationship with EDV. Thus, it could be hypothesized that this shift downwards-right of the pressure–

volume curve could identify those patients with more advanced stages of left ventricular dysfunction, where recovery is more doubtful.

At present, the potential role of non-invasive hemodynamic estimates for tailoring a phenotype-guided therapy in HF patients, and especially in more critical cases, represents an appealing strategy that could better discriminate those patients achieving the greatest benefits from vasodilators and inotropes or requiring, conversely, vasopressors [7,25,36]. Nevertheless, these strategies for the VAC-guided management of patients in critical care units still need further large-scale validation and refining, while also accounting for the potential implementations derived from artificial intelligence and machine learning.

Indeed, should the significant relationship between VAC and the ABI, as reported in our study, be confirmed in larger dedicated trials, it could open new scenarios for the routine use of the ABI to assess HF hemodynamics. In this context, the ABI could potentially represent a more rapid, widely available and cost-effective bedside parameter, prompting echo-independent information for therapeutic guidance and prognostic stratification of critical patients.

5. Limitations

A first limitation of our study is represented by the large heterogeneity of our HF patients, including different etiologies and therapeutic management. In particular, the imbalance between ischemic and non-ischemic patients potentially hindered us from drawing significant conclusions, especially in the latter subgroup. In addition, the limited population included reduced the statistical power of our analysis. Nevertheless, we aimed at exploring a novel approach for the application of the ABI to a real-world cohort of patients with HFrEF/ HFmrEF, in the absence of similar studies in the literature, preventing a priori size-effect and sample size estimation.

Indeed, although functional testing could be performed during coronary angiography for the definition of epicardial or microvascular disease, according to clinical indications, non-invasive ischemia testing was not routinely performed in all the patients.

Another limitation can be represented by the lack of a complete follow-up in all the patients. Therefore, we cannot exclude better clinical outcomes for those survivors that did not require further controls. In fact, survival status was assessed in the complete cohort of patients.

In addition, we systematically measured NT-proBNP only during hospitalization, while lacking complete data at admission and in the long term. Therefore, we could not assess the prognostic impact of their relative changes and neither the relationship of post-discharge values with echocardiographic parameters nor that with the ABI.

Furthermore, only echocardiogram was applied to assess heart chamber volumes, potentially resulting in a less precise assessment than left ventriculography, and we did not assess other echocardiographic parameters as ventricular longitudinal strain or pulse wave velocity, which have been shown to display a good correlation with ventricular and arterial elastance. Finally, we did not systematically measure the cardio-ankle vascular index (CAVI) in all our patients, which could have certainly provided more information about the cardiovascular performance status, nor did we test the inter-operator reproducibility for ABI assessment, although the measurement was automatically performed with a single instrument.

6. Conclusions

Ventricular–arterial coupling can represent a useful tool for the prognostic stratification of patients hospitalized for acute decompensated left ventricular systolic dysfunction, with lower values being associated with worse outcomes. The ankle–brachial index is a largely

available parameter displaying a good association with VAC and could, therefore, offer a faster bedside estimation of ventricular–arterial interaction. Future larger-scale studies are certainly needed to confirm our results and implement the use of the ABI in acute HF.

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