Prognostic value of combined preoperative phase angle and handgrip strength in cardiac surgery

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Abstract

Objectives: Phase angle (PA) constitutes a bioelectrical impedance measurement, indicating cell membrane health and integrity, hydration, and nutritional status. Handgrip strength (HS) has been also associated with body composition, nutritional status, inflammation, and functional ability in several chronic diseases. Although their prognostic significance as independent biomarkers has been already investigated regarding the outcomes of a cardiac surgery, our study is the first one to assess the combined predictive value of preoperative PA and HS.

Design and methods: HS and PA measurements were performed preoperativelyin 195 patients undergoing cardiac surgery. The association ofthe combination of HS and PAwith all-cause mortality rates was the primary study outcome, while its association with the intensive care unit (ICU) length of stay(LOS) was the secondary one.

Results:PA was positively correlated with HS ($r=0.446$, $p<0.005$)and negatively with EuroSCORE II ($r = -0.306$ $p <0.005$). The combination of PA<5.15 and HS<25.5 was associated with higher one-year all-cause mortality (OR=9.28; 95% CI 2.50-34.45; $p=0.001$)compared to patients with PA>5.15 and HS>25.5, respectively.Patients with combined lower values of PA and HS (PA<5.15 and HS<30.7) were at higher risk of prolonged ICU LOS (OR=4.02; 95% CI 1.53-10.56; $P=0.005$)compared to those with higher PA-HS (PA>5.15-HS>30.7). The combination of PA-HS was also significantly linked with EuroSCORE II.

Conclusion: The combination of low preoperative PA and HS values was significantly associated with higher risk of all-cause mortality at 12 months and prolonged ICU LOS; thereby it might serve as a clinically useful prognostic biomarker after cardiac surgery procedures.

Introduction

Predictingpost-procedural morbidity and mortality remains challenging despite the development of many scoring systems and prognostic algorithms in cardiac surgery[1,2]. Hence, the assessment of novel biomarkers capable of guiding the modern physician in choosing the optimal, individualized, treatment for patients based on clinical prediction is of outmost importance[3].

The latest international guidelines support a more individualized patient management based on group discussion among cardiac specialists (i.e. “heart team”) and on the utilization of novel biomarkers such as frailty tests[4].Indicators of cellular integrity, functional capacity, and biological vulnerability have been recently proposed as preoperative risk factors associated with short- and long-term patient outcomes[5].In this context, phase angle (PA)[6]assessed with bioelectric impedance and handgrip strength (HS)[7]measured using a hand dynamometer emerge as valuable tools of promising cost-effectiveness with high reliability and accuracy, without posing a significant burden to the examiner. More specifically, PA, reflecting the resistance and reactance of cell membranes, and HS, reflectingthephysical performance, have been already associated with sarcopenia, systemic inflammation, and increased morbidity and mortality burden[8].

In this prospective study enrolling patients undergoing selective open-heart surgery, we examined whether the combination of PA and HS values was associated with higher rates of one-year mortality, early morbidityand higher intensive care unit (ICU) stay. Our aim was to investigate the role of PA and HS in predicting clinical outcomes and enhancing pre-operative risk stratification in cardiac surgery patients.

Materials-methods

Study population and Eligibility criteria

The study population comprised adult patients undergoing scheduled selective coronary artery bypass grafting (CABG) surgery, individual valve replacement or repair, or any combination of these procedures at the Cardio-Thoracic Surgery Department of AHEPA University Hospital between December 2018 and October 2019.

The exclusion criteria were: i. age <18 years, ii. hemodynamic instability requiring urgent surgery, iii. urgent surgery for aortic dissection, iv.any major adverse intra-operative outcome, v. congenital heart disease, vi. recent cardiac surgery during the prior three months, and vii. presence of any implantable device.The study protocol has been approved by the Scientific Board of AHEPA University Hospital as well as by Ethics Committee of the Aristotle University of Thessaloniki. Written informed consent was obtained pre-operatively from every participant.

Data extraction

On admission, demographic, anthropometric and clinical data [age, gender, and body mass index (BMI), type of surgery, EuroSCORE II, left ventricular ejection fraction (LVEF) and comorbidities] were recorded for each individual. Hospitalization data such as cardiopulmonary bypass (CPB) time, duration of mechanical ventilation, occurrence of post-operative complications, length of stay in the Intensive Care Unit (ICU) and postoperative length of hospital stay were also noted.

PA was measured using bioelectrical impedance method on the first pre-operative day by a blinded researcher trained in this technique. A simple quadrupole measurement was applied to the right side of the body using four-surface electrodes (QuadScan 4000, Bodystat, Isle of White, UK).Thereby, resistance (restriction of current flow) and reactance (capacitance of cell membranes to block current) were measured. The primary 50 kHz resistance and reactance data were used to calculate PA (tangent of reactance / resistance X 180°, divided by p and expressed in degrees).

HSwas also assessed preoperatively using a portable hydraulic dynamometer (Takei 5001 GripA, Takei Scientific Instruments CO, Japan). The HS test was performed in the sitting position, having their elbow flexed at 90°, whilst pressing the dynamometer with the dominant hand at full force for three seconds. After three repetitions of the test with an interval of one minute to avoid fatigue, the best performance was recorded in kilograms (kg).

Outcomes of interest

Primary study outcome wasdeemed all-cause mortality, as assessed at last available telephonic follow-up oras determined by electronic medical health records. The length of ICU stay was considered as the secondary study outcome.

Statistical analysis

Continuous variables are presented with mean and standard deviation (SD) or with median and intra-quartile range (IQR) depending on data normality. Categorical variables are presented with frequencies (n) and percentages (%). Regularity of data distribution was checked using the Kolmogorov-Smirnov test.

The correlation of PA and HSwith outcomes of interest was performed via t-test or Mann Whitney test for independent samples. Logistic regression was performed to detect the independent effect of demographic and clinical indicators on the outcomes of interest.The predictive value of PA and HS was evaluated through receiver operator characteristics (ROC) analyses and calculated Areas Under the Curve (AUC).Cut-off points of PA and HS that maximize sensitivity and specificity for risk stratification were evaluated via calculating Positive Predictive Value (PPV) and Negative Predictive Value (NPV). All statistical analyses were performed with the statistical package SPSS version 21 (IBM Corporation, Somers, NY, USA). The p-value of less than 0.05 was defined as the level of statistical significance.

Results

Our study included 195 patients with a mean age of 67 years (SD: 9 years) of whom 150 were men (76.9%) and 45 women (23.1%). 90 patients suffered from coronary artery disease (46.2%), 87 (44.6%) from valvular disease and 18 from both (9.2%).Median EuroSCORE II was equal to 2.6%(0.6–15.5) (Table 1). PA was positively correlated with HS ($r = 0.446$ $p < 0.005$) and negatively with EUROSCORE II ($r = -0.306$ $p < 0.005$) (Table 2).

Table 1
Demographic and clinical characteristics of the study population

Age (years)	**67.18 ± 9.14**
Male gender (%)	150(76.9)
Body Mass Index (kg/m^2)	27.75 ± 4.34(18.1–39.6)
Cardiopulmonary bypass time (minutes)	114.5(23–290)
Coronary Artery Disease/ Valvular disease / both (%)	90(46.2)/87(44.6)/18(9.2)
Type II diabetes mellitus (%)	89(45.6)
Chronic kidney disease (%)	66(33.8) 9
Euroscore II (units)	2.6 (0.6–15.5)
Phase angle (°)	5.52 ± 1.47(2.7–16.0)
Handgrip strength (calf circumference)	27.48 ± 9.16(5–51)
Postoperative infections (%)	22(11.3)
Intensive Care Unit stay over 1 day (%)	99(50.8)
Mechanical ventilation over 1 day (%)	51(26.2)
In-hospital postoperative stay more than 7 days (%)	147(75.4)
Postoperative complications (reopening, pulmonary embolism, peripheral thrombosis, septic condition, in-hospital mortality) (%)	51(26.2)
All-cause mortality (%)	27(13.8)
Quantitative variables are recorded as mean ± standard deviation or median (interquartile range), while qualitative as n (%).	

Table 2
Correlation of the PA indicator with HS and EuroScore II

Correlation Indicators		PA		
		Correlation Coefficient	p-value	N
Spearman 's rho	HS	0.446	**< 0.005**	195
	EUROSCORE II(%)	-0.306	**< 0.005**	195

Regarding the primary study outcome, 27 patients (13.8%) died from any cause after one-year follow-up. PA, HS and their combination had a significant yet fair predictive value for all-cause mortality; PA: AUC (95% CI) 0.657 (0.54–0.77); p = 0.009, HS: AUC (95% CI) 0.659 (0.5–0.78); p = 0.008, and their combination: AUC (95% CI) 0.671 (0.56–0.78); p = 0.004 (Table 3).

Table 3
ROC analysis of the PA and HS indicators and their combination in relation to mortality and ICU stay

Predictors	Variable	AUC(95%CI)*	p-value	Cut-off point	Sensitivity	Specificity	PPV*	NPV*
PA †	**Mortality**	**0.657** (0.54–0.77)	0.009	5.15	67%	61%	21%	92%
	ICU LOS	**0.600** (0.52–0.68)	0.016	5.15	56%	70%	65%	60%
HS†	**Mortality**	**0.659** (0.55–0.78)	0.008	25.5	67%	63%	22%	92%
	ICU LOS	**0.586** (0.51–0.67)	0.040	30.75	71%	47%	57%	60%
	ICU LOS							
Combination† PA/HS	**Mortality**	**0.671** (0.56–0.78)	0.004	**5.15/25.5**	67%	62%	22%	92%
	ICU LOS	**0.597** (0.52–0.68)	0.019	**5.15/30.75**	63%	59%	61%	60%

†Lower values indicate a poor outcome

*AUC: Area Under the Curve; CI: confidence interval; PPV: positive prognostic value; NPV: negative prognostic value

The PA-HS combination had a significant effect on mortality occurrence [p = 0.009]. Patients with PA < 5.15 and HS < 25.5 were 5 times more likely to die [5.13 (1.84–14.27); p = 0.002] when compared to those with PA > 5.15 – HS > 25.5 (Table 4). The multivariate analysis, presented in Table 5, yielded that female gender [0.27 (0.08–0.94); p = 0.040], Euroscore II [1.59 (1.17–2.14); p = 0.003] and the combination of PA-HS [p = 0.005] had an independent effect on mortality. Regarding the PA-HS combination,patients with PA < 5.15 and HS < 25.5 were 9.3 times more likely to die [9.28 (2.50-34.45); p = 0.001] in relation to those with PA > 5.15 - HS > 25.5 (Table 5).

Table 4
Univariate logistic regression of all-cause mortality with the combination of PA and HS

	OR	95% CI		p-value
Combination PA-HS				0.009
PA > 5.15 –HS > 25.5	1.00 (reference)			–
PA > 5.15 –HS < 25.5	1.62	0.38	6.99	0.514
PA < 5.15 –HS > 25.5	1.39	0.33	5.95	0.655
PA < 5.15 –HS < 25.5	5.13	1.84	14.27	0.002

Table 5
Multivariate logarithmic regression of all-cause mortality with the combination of PA and HS adjusted to clinical indicators

Variables	OR	95% CI		p-value
Female Gender	0.27	0.08	.94	0.040
Age	1.00	0.94	1.05	0.869
Diabetes II	0.85	0.31	2.30	0.746
Chronic Kidney Disease	0.53	0.19	1.50	0.233
EuroscoreII	1.59	1.17	2.14	0.003
Ejection Fraction	0.96	0.91	1.02	0.226
Combination PA-HS				0.005
PA > 5.15 –HS > 25.5	1.00 (reference)			–
PA > 5.15 –HS < 25.5	2.97	0.57	15.41	0.195
PA < 5.15 –HS > 25.5	1.65	0.34	8.02	0.533
PA < 5.15 –HS < 25.5	9.28	2.50	34.45	0.001

With regard to the secondary study outcome, the PA-HS combination was significantly associated with prolonged stay in the ICU [p = 0.002]. Patients with PA < 5.15 and HS < 30.7 were 4times more likely to stay in the ICU for more than 1 day [4.14 (1.95–8.80); p = 0.001] in comparison with those havingPA > 5.15 – HS > 30.7 (Table 6). PA, HS and their combination had also a significant yet poor predictive value for the prolonged stay in the ICU; PA: AUC (95% CI) 0.600 (0.52–0.68); p = 0.016, HS: AUC (95% CI) 0.586 (0.51–0.67); p = 0.040, and their combination: AUC (95% CI) 0.597 (0.52–0.68); p = 0.019 (Table 3).

Table 6
Univariate logistic regression of prolonged stay in the ICU with the combination of PA and HS

	OR	95%CI		p-value
Combination PA-HS				0.002
PA > 5.15 –HS > 30.7	1.00 (reference)			–
PA > 5.15 –HS < 30.7	2.01	0.93	4.36	0.076
PA < 5.15 –HS > 30.7	3.97	1.27	12.43	0.018
PA < 5.15 –HS < 30.7	4.14	1.95	8.80	< 0.005

Multivariate analysis for the prediction of prolonged ICU stay demonstrated that female gender [0.35 (0.15–0.83); p = 0.017], EuroSCORE II [1.71 (1.27–2.30); p < 0.005], left ventricular ejection fraction [1.05 (1.01–1.10); p = 0.018] and the combination of PA-HS [p = 0.038] were independent predictors.Regarding the combination of indicators, patients with PA < 5.15 and HS < 30.7 were found to be 4 times more likely to stay in the ICU for more than 1 day [4.02 (1.53–10.56); p = 0.005] compared to those with PA > 5.15 - HS > 30.7 (Table 7).In order to observe the relationship between the PA-HScombination and the standard EuroSCORE II risk index, an analysis of variance (ANOVA) was performed, showing a statistically significant difference in EuroSCORE II values among individuals with PA < 5.15 - HS < 25.5 compared to those with PA > 5.15 - HS > 25.5 in mortality (Table 8).

Table 7

Multivariate logistic regression of prolonged stay in the ICU with the combination of PA-HS adjusted to clinical indicators

Variables	OR	95% CI		p-value
Female gender	0.35	0.15	0.83	0.017
Age	1.03	0.99	1.07	0.152
Diabetes II	1.57	0.81	3.06	0.182
Chronic Kidney Disease	0.54	0.26	1.12	0.096
Euroscore II	1.71	1.27	2.30	< 0.005
Ejection Fraction	1.05	1.01	1.10	0.018
Combination PA-HS				0.038
PA > 5.15 –HS > 30.7	1.00 (reference)			–
PA > 5.15 –HS < 30.7	2.19	0.90	5.32	0.084
PA < 5.15 –HS > 30.7	2.97	0.85	10.46	0.090
PA < 5.15 –HS < 30.7	4.02	1.53	10.56	0.005

Table 8

EUROSCORE II relationship with PA-HS combination index Dependent variable: EUROSCORE II (%)

(I) Combination PA-HS(mortality)	(J) Combination PA-HS(mortality)	Sig.
below 5.15 – below 25.5	below 5.15 – above 25.5	1.000
	above 5.15 – below 25.5	0.558
	above 5.15 – above 25.5	**< 0.001**
below 5.15 – above 25.5	above 5.15 – below 25.5	1.000
	above 5.15 –above 25.5	0.119
above 5.15 – below 5.5	above 5.15 –above 25.5	0.932

Discussion

The results of this prospective observational study suggest the potential prognostic value of the combined preoperative PA-HS measurement as a new biomarker for predicting one-year mortality in cardiac patients undergoing selective cardiac surgery. According to our analyses, patients having a combination of low PA and HS values were 5 times more likely to die and 4 times more likely to remain in the ICU for more than one postoperative day, thus increasing postoperative morbidity and the likelihood of complications. Furthermore, the EuroSCORE II index, an internationally established risk index for death after cardiac surgery, was associated with the combination of PA-HS. To our knowledge, this is the first study examining whether the combination of PA and HS values is associated with one-year mortality rates and early morbidity in patients undergoing cardiac surgery, and could thereby enhance their pre-operative risk stratification.

From the literature review, low PA is associated with nutritional risk, increased morbidity and mortality inimmunocompromised patients or patients with chronic kidney disease[8]. It has been particularly associated with poor functional status and worse prognosis in cancer patients[8]. PA is often lower than normal in diseased individuals, since infection, systemic inflammation or specific parameters of a disease may cause cell destruction and consequent reduction in PA[8,9]. PA is positively correlated with total body protein, muscle mass, offering a qualitative dynamic aspect of the body's functional state[10]. Moreover, low PA values have been associated with weakness, vulnerability (frailty) and mortality, regardless of age and other comorbidities[11,12].

According to the BICS (Bioimpedance in Cardiac Surgery) study enrolling 277 patients undergoing major cardiac surgery in Canada, PA can independently predict early and midterm mortality after major cardiac surgery[6]. A PA cutoff of < 4.5° had the highest predictive value for 1-year mortality, and every 1° decrease in PA conferred an almost 3-fold higher risk of mortality. Our analysis yielded a cut-off point of PA = 5.15° for the prediction of increased mortality and ICU stay. Additionally, PA has been suggested as a dynamic marker with the potential to respond to targeted interventions aiming to restore adequate nutritional status, increase physical activity, and optimize fluid status[6].

The measurement of HS is the most commonly used indicator for muscle function in several clinical conditions, as it is considered a strong indicator of functional capacity of the muscles as well as an indicative point of a patient'snutritional status. The correlation between nutritional status and HS is well documented[13,14]. Previous studies have also shown that HS was correlated with the severity of the disease, with aging and mortality in elderly individuals[15,16]. Particularly in cardiac surgery, HS has been well-recognized as a preoperative risk assessment tool since weak HS has been associated with 1-year and 30-day mortality, heart failure, kidney disease, malnutrition, and various frailty scales[17–19]. Hence, our study concurs with the growing body of literature regarding the poor outcomes of cardiac surgery patients with low preoperative PA and HS, and adds that their combined assessment might be an option to consider as a risk stratification tool.

Nevertheless, our study is subject to several limitations. The small sample size, the limited follow-up and the monocentric study design restrict the generalizability of our findings. However, PA and HS have not been sufficiently studied in the specific patient population; hence, our results seem to be promising for their utilization and could trigger future studies to combine these biomarkers and associate them with postoperative prognosis. Thereby, we could ultimately achieve a more detailed holistic risk stratification of patients undergoing cardiac surgery and possibly direct them towards other alternative treatments such as angioplasty, valvular replacement or optimal palliative care.

Conclusions

In this prospective observational study, the combination of low preoperative PA and HS values was significantly associated with higher risk of all-cause mortality at 12 months and prolonged ICU stay. Hence, these clinical biomarkers could serve as prognostic tools for assessing adverse clinical course after cardiac surgery procedures. Larger studies and randomized-controlled trials are needed to confirm these results.

Declarations

Ethics approval and consent to participate:

Study protocol has been approved by the Scientific Board of AHEPA University Hospital of Thessaloniki (reference number: 06/09/2018) and by the Ethics Committee of the Aristotle University of Thessaloniki (reference number: 21/11/2018). All methods were performed in accordance with the Declaration of Helsinki. All participants have provided written informed consent prior to study participation.

Consent for publication:

All participants have provided written informed consent for study publication.

Availability of data and materials:

The dataset supporting the conclusions of this article is available from Georgios Tagarakis (e-mail: gtagarakis@gmail.com) upon reasonable request and with permission of AHEPA University Hospital.

Competing interests:

None to declare

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Authors' contributions:

MP, ASP and DVM developed the draft of the manuscript and wrote the main text of the manuscript; EV and MP mainly contributed to the statistical analyses; EK, KA and AG revised and edited the manuscript; GT developed the concept and supervised the study progress; all authors have read and approved the final manuscript.

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