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Arterial-Ventricular Coupling Impairment is Evidenced in Both Normal and Ischemic Subjects by Applying Cluster Analysis*

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Abstract— **INTRODUCTION: Left ventricular (LV) interaction with the arterial system (arterial-ventricular coupling, AVC) is a central determinant of cardiovascular performance and cardiac energetics. Stress Echocardiography (SE) constitutes a valuable clinical tool in both diagnosis and risk stratification of patients with suspected and established coronary artery disease. Cluster Analysis (CA), an unsupervised Machine Learning technique, defines an exploratory statistical method which can be used to uncover natural groups within data. OBJECTIVE: To evaluate the capacity of CA to identify uncoupled groups with ischemic condition based on SE baseline information. MATERIAL AND METHODS: CA was applied to SE data acquired at baseline and peak exercise (PE) conditions. Obtained clusters were evaluated in terms of coupling conditions and LV wall motility alterations. RESULTS: Inter cluster significant AVC differences were obtained in terms of baseline data and changes in wall motility, confirmed by CA applied to PE data. CONCLUSION: AVC impairment was evidenced in both normal and ischemic subjects by applying CA.**

I. Introduction

Preventive actions and effective treatment intervention have always been helpful when heart disease has been diagnosed at the preliminary stage [1]. In this sense, Stress Echocardiography (SE) constitutes a valuable clinical tool in both diagnosis and risk stratification of patients with suspected and established coronary artery disease (CAD) [2]. In addition, SE has exploded in its breadth and variety of application over the last years, employing a variety of technologies on patients that covers a wide range of disease severity and ages [3].

Cluster analysis (CA), an unsupervised Machine Learning (ML) technique, defines an exploratory statistical method which can be used to uncover natural groups (without being previously labeled) that would otherwise be undistinguishable by the application of traditional classification methods [2]. Accordingly, ML techniques offer the potential to interpret simultaneously multiple echocardiographic and clinical data in an efficient and automatic manner, thus contributing with valuable information related to patient's care [4]. CA particularly allows the segregation of similar cases without the restriction of an a priori diagnostic system, so the variables of interest corresponding to each group are strongly related to each other. [5]. As a result, a CA based model could analyze a variety of left ventricular descriptors to determine whether a patient presents a particular condition [4]. Due to CAD remains as one of the world's most influential causes of morbidity and mortality, its identification using modern approaches such us CA techniques is challenging [5].

It is well known that physiological SE is focused on left ventricular (LV) wall motion alterations to diagnose ischemic response to stress. The SE manifestation of ischemia (a transient regional imbalance between oxygen demand and supply) is represented by a stress-induced worsening of function in a LV region contracting normally at baseline. In several cases the evidence of ischemia only appears at high workloads, demanding an extra effort from the subject and thus incrementing the risk of suffering complications such us chest pain, tachyarrhythmia, dyspnea or abnormal blood pressure variations, among others. The Wall Motion Score Index (WMSI) reflects the magnitude of myocardial damage and total extent of wall motion abnormalities. While in a normal response a segment is normokinetic at rest and normal-hyperkinetic during stress, the ischemic response is characterized by a transition from normokinetic to dyssinergy [6]. On the other hand, LV interaction with the arterial system, termed arterial-ventricular coupling (AVC), is a determining factor of cardiovascular (CV) functioning and cardiac energetics. Appropriate matching at rest results in an optimal transfer of blood from the LV to the periphery towards energetic efficiency. During exercise, the purpose of CV system is to prioritize cardiac efficacy over energetic efficiency, thus AVC is reduced. In heart disease, a suboptimal coupling occurs, reflecting diminished CV performance of the failing heart [7].

Considering the above mentioned, the main objective of the present study was to explore CA based on left ventricular features, both obtained at rest and peak exercise (PE) from a standard SE protocol. To this end, LV parameters, coupling conditions and ventricular wall motility alterations were evaluated on the obtained clusterization, with the aim of analyze the capacity of SE baseline variables to provide valuable information in terms of the ischemic response addressed at high exercise loads.

II. Materials an Methods

A. Study Population

This study included patients referred for exercise echocardiography, evaluated at Stress Echocardiography Lab

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at Cardiocentro, Asociación Española of Montevideo, Uruguay. From that population, 567 participants, over 50 years of age, were selected based on clinical, echocardiographic and hemodynamic features. Height and weight were measured, and body mass index (BMI) and body surface area (BSA) were calculated. Systolic and diastolic blood pressure measurements (SBP and DBP, respectively) were performed using a sphygmomanometer, in accordance to the Guidelines of the European Society of Hypertension. This study was approved by an independent institutional review board. The research protocol was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and all subjects gave their written informed consent before inclusion into the study.

B. Exercise Protocol and Data Acquisition

All patients were supervised by a cardiologist during the entire study. Symptoms including chest pain, palpitations and New York Heart Association (NYHA) functional class were documented. After remaining at rest for 5-10 minutes, individuals sat on a semisupine graduated cycle ergometer (Bike EL of General Electric) and were continuously monitored (Astrand protocol). Each subject experimented an effort at constant speed, with load increments of 150-300 kgm/min every 2 minutes (25W-50W), until 100% of maximal HR (220 bpm minus age) was achieved or limiting signs (muscular fatigue or CV symptoms) were observed. The data acquisition process continued until baseline values of arterial pressure and heart rate were restored [8]. Two-dimensional echocardiography (Vivid S70 ultrasound system; GE Medical Milwaukee, Wisconsin, USA; with a 3.0 MHz transducer) in combination with 12-lead electrocardiographic (ECG) monitoring were performed in all individuals. Systolic and diastolic brachial blood pressure values (SBD and DBP, respectively) jointly with ECG recordings were obtained in each stage of the test. Additionally, aortic pressure waveform was obtained by means of the Sphygmocor Xcell® device (AtCor Medical, Sidney, Autralia). The echocardiographic images were acquired in the parasternal long-axis, short-axis, and apical four, two, three and five chambers, during baseline and peak of stress stages. Images were evaluated using the semiquantitative technique, with a 4-point scale model of 17 LV segments. A wall motility score index was calculated by adding the single segment scores, divided by the number of interpretable segments. Left ventricular end-diastolic and end-systolic volumes (ESV and EDV, respectively) were evaluated with the biplane Simpson method. The endocardial border was traced, excluding the papillary muscles. The frame with the smallest left ventricular cavity was considered to be the end-systolic frame [16]. ESV and EDV were then corrected by BSA (ESVI and EDVI, respectively).

Non-ischemic SEs were defined as having no evidence of myocardial ischemia on the SE. The existence of wall motion abnormalities was determined by WMSI, assessed at baseline and during PE. Presence of myocardial ischemia was then determined by means of the increment of WMSI, between maximum load and rest (ΔWMSI>0) [9]. Only subjects who were able to finish the protocol at higher loads were considered for evaluation data.

C. Left Ventricular Function Parameters

The LV pressure vs. volume loop was reconstructed in terms of the obtained echocardiographic and aortic pressure values. Instantaneous ventricular volume variation was obtained from the echocardiographic images, by means of a frame by frame analysis of the ventricular chamber, averaging the volumes obtained automatically in 4 and 2 cameras. LV pressure variations were estimated from the aortic pressure variations during the ejection period.

In order to characterize the interplay between the heart and arterial system, AVC was calculated, as the ratio between arterial elastance (E_A) and end systolic left ventricular elastance (E_{LV}). E_A quantifies the workload imposed on the ventricle by the arteries (a measure of afterload) while E_{LV} constitutes a load-independent measure of cardiac performance. As a result, the coupling ratio describes how LV vs afterload interaction is able to modify cardiovascular reserve, cardiac performance and peripheral hemodynamics [7]:

$$E_A = \frac{ESP}{SV};\ E_{LV} = \frac{ESP}{ESV - V_0};\ AVC = \frac{E_A}{E_{LV}}, \qquad (1)$$

where SV is the stroke volume (EDV-ESV) and ESP is the end systolic pressure, which was obtained from the aortic pressure waveform in terms of the ventricular volume variations. V_0 is the theoretical volume when no ventricular pressure is generated, which was assumed (in this study) to be negligible compared with ESV.

C. Machine Learning Analysis

Unsupervised cluster analysis is a technique that allows subjects to be segregated into groups, without previous labelling. Firstly, data was normalized, allowing variables to follow a uniform scale. Secondly, Principal Component Analysis (PCA) technique was applied to the dataset, for dimensionality reduction. Thirdly, subject's similarities were computed in terms of distance measures between variables (eg. Euclidean distance), by means of the CA k-means technique [2]. The optimal number of clusters was determined using the Siluette Coefficient.

Two different types of clusterization were carried out. Firstly, the cluster model was constructed strictly based on baseline variables, in terms of the following SE descriptors: Age, Weight, BMI, BSA, SBP, DBP, ESVI, EDVI, HR. This are the parameters usually obtained by a SE protocol. After the application of the CA procedure, LV function of each obtained cluster was evaluated, both at baseline and considering the corresponding PE values of each participant, by means of HR, E_{LV}, E_A and AVC. Finally, subjects that developed exercise induced ischemia (an increase of WSMI) were identified in each group.

Secondly, subjects clusterization was performed strictly on terms of the SE peak exercise descriptors (same baseline parameters were considered). The main idea of this action was to determine if subjects separated by means of baseline variables suffered a reclassification based on PE information (interchange of individuals between clusters). Basically, the capacity of baseline data to differentiate groups of

participants (prior of being submitted to an exercise test) was assessed.

D. Statistical Analysis

Continuous variables were expressed as mean ± SD. The Games-Howell test was used to compare the mean values of different groups. The two-proportion z-test was used to evaluate proportional changes of baseline values as a consequence of exercise. Statistical significance was assigned to $p < 0.05$.

III. Results

Considering the parameters selected for CA, three clusters of individuals were obtained. Similar aspects of CV function were found in two of them, so they were unified in a unique group. Table I describes the demographic characteristics of the two remaining subsets (cluster 1, C1; cluster 2, C2). Significant differences were found in age, height, BMI, blood pressure and HR ($p<0.05$) but not in weight.

TABLE I. Demographics and Clinical characteristics. Values are expressed as mean±standard deviation. C1: Cluster 1, C2: cluster 2. * P < 0.05 with respect to C1.

Demographic and Clinical Data		
Parameter	**C1**	**C2**
#	**456**	**111**
Age [years]	60.5±10.7	54.6±14.0 *
Height [m]	168.5±9.6	174.0±6.8 *
Weight [kg]	80.8±16.2	82.9±12.9
BMI [cm²/kg]	28.4±4.4	27.3±4.0 *
SBP [mmHg]	125.2±17.7	116.3±17.8 *
DBP [mmHg]	79.8±10.7	73.0±9.6 *

Table II shows the hemodynamic variations of both clusters, obtained from baseline features analysis. The corresponding variations of each group during exercise are expressed as percentages of increment. When baseline results are compared, clustering phenotyping shows that C1 subjects are characterized by greater HR, E_{LV} and E_A and a lower AVC with respect to C2 ($p<0.05$). On the other hand, when percentage variations of the same parameters are analyzed, C2 showed higher positive increments except in AVC which turned to be negative (a decrease).

In Table III, the baseline clustering results are analyzed in terms of WMSI variations. As can be seen, C2 showed a higher percentage of subjects that manifested a positive variation of WMSI (ischemic condition). The same analysis can be visualized in terms of PE data. In this case, a similar trend is observed in C2 with respect to C1, with a higher percentage of individuals with an increment of WMSI during exercise. This result is in accordance with the separation performed by CA using information of the participants at rest.

TABLE II. Hemodynamic Parameters at baseline and at Peak Execise (PE), HR: Heart Rate [bpm], ESP: End Systolic Pressure [mmHg], $E_{LV}I$: Left Ventricular Elastance [mmHg/ml], E_AI: Arterial Elastance [mmHg/ml], AVC: Arterial-Ventricular Coupling. Suffix "I": indexd by Body Surface Area. [a,b] P<0.05 was considered as statiscially significant (Games-Howell test and z-test respectively)

Hemodynamic Parameters Variation (Baseline Descriptors Based Clustering)			
Parameter	**Condition**	**C1 (456)**	**C2 (111)**
HR	**Baseline**	84.4±13.0	75.7±12.9 [a]
	PE increase [%]	71.6	93.3 [b]
$E_{LV}I$	**Baseline**	8.3±3.1	4.2±1.2 [a]
	PE increase [%]	112.9	148.2 [b]
E_AI	**Baseline**	4.3±1.1	3.1±0.7 [a]
	PE increase [%]	50.2	64.7 [b]
AVC	**Baseline**	0.6±0.2	0.8±0.3 [a]
	PE increase [%]	-23.5	-24.5

TABLE III. Analysis of the obtained clusters (C1, cluster 1, C2 cluster 2) based on baseline features in terms of Wall Motion Score Index (WMSI) variations

Assessment of Ischemic Condition after Clusterization			
Condition	**Motility Score**	**C1**	**C2**
Baseline Features	**Subjects # (567)**	**456 (80.4%)**	**111 (19.6%)**
	ΔWMSI=0 (Normal) [#]	398 (87.2%)	93 (83.8%)
	ΔWMSI>0 (Ischemic) [#]	58 (12.8%)	18 (16.2%)
Peak Exercise Features	**Subjects # (567)**	**448 (79.0%)**	**119 (21.0%)**
	ΔWMSI=0 (Normal) [#]	404 (90.2%)	87 (73.1%)
	ΔWMSI>0 (Ischemic) [#]	44 (9.8%)	32 (26.9%)

When subject's reclusterization was analyzed, it was verified that 13 from the 18 subjects with increased WMSI that were classified in terms of baseline based features effectively belonged to the 32 subjects with increased WMSI, which were classified using PE data. Finally, Table IV shows the corresponding AVC values, assessed for each subgroup obtained in Table III.

TABLE IV. Analysis of the obtained clusters (C1, cluster 1, C2 cluster 2) based on baseline features in terms of Arterial Ventricular Coupling (AVC) variations. *P<0.05 was considered as statistically significant with respect to C1.

Assessment of Ischemic Condition after Clusterization			
Condition	**Coupling**	**C1 (#)**	**C2 (#)**
Baseline Features	**AVC (ΔWMSI=0)**	0.54±0.14 (398)	0.79±0.36 * (93)
	AVC (ΔWMSI>0)	0.70±0.30 (58)	0.92±0.32 * (18)
Peak Exercise Features	**AVC (ΔWMSI=0)**	0.37±0.11 (404)	0.57±0.32 * (87)
	AVC (ΔWMSI>0)	0.65±0.36 (44)	1.08±0.74 * (32)

The results show that AVC values were higher regarding an increment of WSMI (exercise induced ischemia), with respect of the groups of participants that not experimented a WMSI variation. When C1 and C2 clusters are compared, AVC is increased in C2 in any condition ($p<0.05$).

IV. Discussion

ML algorithms have the capability to differentiate cardiac structural and functional patterns that could be possibly ignored during the evaluation by the clinician, guiding the decision making process [4]. CA analysis can operationalize phenotyping approaches, insolating hidden prognostic

phenotypes not visualized by expert guidelines-based approaches [2]. Basically, the methodology analyzes the intrinsic structure within data and has been successfully applied in previous studies for detecting patient groups [5].

In the present study, CA (an unsupervised ML method) was applied to SE measurements. The identified clusters were then evaluated, both at rest and exercise, mainly in terms of arterial-ventricular coupling and wall motion abnormalities conditions. Firstly, the participants were clusterized based on baseline SE data and then using the corresponding PE data. The objective was to analyze the capacity of baseline descriptors to segregate subjects prior to the exercise test. The obtained findings show that the separation performed by CA when only baseline SE descriptors were considered, provided similar results to those obtained when CA was applied to PE data, specifically in terms of AVC alterations and presence of wall motion abnormalities (exercise induced ischemia).

Previous studies have demonstrated that the development and progression of heart failure with preserved ejection fraction are extensive and include abnormalities of myocardial and endothelial function, oxygen extraction, the autonomic nervous system and AVC [11]. Under normal conditions, AVC varies around 0.6 in humans, tending to optimize the overall metabolic efficiency. Exercise in healthy individuals elevates E_{LV} but reduces E_A (lowering AVC), thus suggesting a more efficient energy transfer from the LV to the periphery. On the other hand, increased values of AVC (towards AVC=1) indicate that LV is suboptimally coupled and the stroke work is being optimized [12]. In the present study, the obtained values of AVC were 0.54±0.14 in C1 and 0.79±0.36 in C2 in terms of the baseline features based CA analysis and no WMSI variations ($p<0.05$). Then, the obtained AVC values were higher (closer to an uncoupling condition) regarding a positive variation of WMSI. This condition implies that CA applied to SE baseline information was able to segregate uncoupled groups, among which the maximal uncoupling condition (AVC=1.08±0.74) was achieved in C2 jointly with an alteration of LV wall motility (as a consequence of exercise). This differentiation could be explained in terms of a reduced E_{LV} and a reduced E_A in this particular group. It is noteworthy the main determinants of the latter include HR, a resistive component (systemic vascular resistance), and a stiffness component [7].

A specific limitation of this study resides in the diagnosis of myocardial ischemia and, more specifically, the presence of stable CAD or acute coronary syndrome of or low/moderated risk, which could not be entirely assessed only by SE. Nevertheless, the sensitivity and specificity for the detection of ischemia of SE is (in general terms) 85%, where the assessment of sectoral alterations in contractility during stress and the evaluation of LVEF makes it possible to stratify the risk of presenting significant CAD. Moreover, a negative EE provides an excellent one-year prognosis [13]. In this sense, CA applied to anthropometric and baseline basic echocardiographic descriptors has demonstrated a capacity to discriminate groups with differentiated WMSI and AVC, prior to an exercise test.

To conclude, AVC impairment was evidenced in both normal and ischemic subjects through the application of CA. Further studies with a larger number of participants are needed to verify the clinical implications of the obtained results.

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