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ORIGINAL ARTICLE

Myocardial fibrosis detected with Gadolinium Delayed Enhancement in Cardiac Magnetic Resonance Imaging and Ventriculoarterial Coupling alterations in patients with Acute Myocarditis

Christina Chrysohoou, MD [a,*], Christos Konstantinos Antoniou, MD [a], Arthur Stillman, MD [b], Osalewa Lalude, MD [b], Travis Henry, MD [b], Stamatios Lerakis, MD [b]

[a] *First Department of Cardiology, Athens Medical School, Athens, Greece*
[b] *Emory University Hospital, Atlanta, GA, USA*

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Abstract *Background:* The delayed Gadolinium Myocardium Enhancement (DGE) extent on Cardiac Magnetic Resonance (CMR) correlates with biomarkers of myocardial injury in patients with acute viral myocarditis and is an independent predictor of adverse cardiovascular outcome. Ventriculoarterial Coupling (VAC) is related to both the cardiovascular work output and energy efficiency and can be noninvasively assessed. In this work, we aimed to evaluate alterations in VAC indices in correlation with DGE in patients with acute myocarditis.
Methods: Fifty-seven patients (mean age 42 (18) years old, 58% male, 19% had hypertension, 9% coronary artery disease and 2% diabetes mellitus) with diagnosed acute myocarditis were enrolled. All patients underwent comprehensive echocardiographic evaluation with a VAC value calculation and CMR imaging within a 24-hour period.
Results: The mean ejection fraction was 42±18%; 49% had preserved systolic function. DGE was noted in 56% of patients. When stratified by EF (preserved or reduced), those with an EF>50% had significantly smaller ventricles and a lower VAC, closer to the values that maximize the stroke work and energy efficiency ($p=0.002$ for end diastolic diameters, 0.001 for VAC, 0.01 for distance from 0.7 and 0.5 and 0.056 for distance from 1). No difference in DGE prevalence was noted ($p=0.34$). DGE-based stratification did not reveal any difference

* Corresponding author.
E-mail address: chrysohoou@usa.net (C. Chrysohoou).
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in the EF or VAC values between groups. Multi-adjusted regression analysis showed that EF was a significant predictor of VAC alterations.
Conclusion: In acute myocarditis patients, DGE is related to neither EF nor VAC; however, EF significantly affects the VAC status. Further studies are needed to investigate the potential quantitative, rather than qualitative, relationships between these variables.

1. Introduction

Myocarditis is an inflammatory disease of the heart muscle that is diagnosed by established histological, immunological, and immunohistochemical criteria.[1] It is implicated in sudden death cases in young adults (8.6%—12%[2,3]) and in 9% to 16% of newly onset dilative cardiomyopathy (DCM) cases.[4,5] cMRI is the most promising imaging technique for the early diagnosis of myocarditis,[6—10] providing both anatomical data and histological insights.[11] The use of enhancement agents, such as gadolinium DTPA (Gd), has significantly improved tissue contrast, leading to more advanced tissue characterization[12] and allowing for a correct diagnosis in up to 78% of patients with EMB-proven disease.[7,13]

In an effort to express the interplay between the heart and vessels and determine the implications of this interplay on organ perfusion, the concept of ventriculoarterial coupling has gained attention.[14—16] The coupling status indicates whether, for a given contractility, maximal stroke work is achieved and may also assess the efficiency of cardiac function.[17] Given that tissue perfusion relies on both the pressure reached and volume pumped,[18,19] their combined effect is described by stroke work, and it follows that VAC optimization may contribute to improved organ perfusion and, potentially, function.[15] Indeed, increased VAC values have been associated with a worse prognosis in chronic heart failure,[19] while theoretical and experimental studies[15—17,20] have shown that work maximization occurs at VAC values near 1 and efficiency optimization at values within the 0.5—0.7 range.

The purpose of the study was to examine the association between cMRI findings suggestive of permanent cardiac injury (presence of DGE) and non-invasively calculated VAC values[21,22] in patients with acute myocarditis, diagnosed non-invasively by the use of Lake Louise criteria.[7]

2. Methods

2.1. Sample

All consecutive patients admitted to our institution (Emory University Hospital, Atlanta, Georgia) from April 2010 to April 2014 were screened for clinically suspected myocarditis based on criteria proposed by the working group of the European Society of Cardiology on myocardial and pericardial diseases.[10] Those considered to be at high clinical suspicion of myocarditis were submitted to cMR imaging in addition to undergoing the standard echocardiographic assessment. Lake Louise criteria[7] were then applied to diagnose acute myocarditis. Both studies were performed no more than 24 hours apart, with the cardiac ultrasound performed immediately after the initial assessment. In total, 57 patients fulfilled the study admission criteria.

2.2. Measurements

Patients underwent an echocardiographic evaluation, in which the cardiac chamber dimensions, stroke volume (SV), and ejection fraction (EF) were measured. An EF$\geq$50% was considered to signify preserved systolic function.[23] Measurements were taken in accordance with the guidelines issued by the American Society of Echocardiography and the European Society of Cardiology.[24,25] Furthermore, VAC was measured by using the non-invasive, single beat calculation method introduced by Chen et al[21] to calculate the left ventricular end-systolic elastance (Ees) and by calculating arterial elastance (Ea) as:

$$E_a = \frac{0.9 \times \textit{Brachial Systolic Blood Pressure}}{\textit{Stroke Volume}}$$

VAC was then calculated as[16]:

$$VAC = \frac{E_a}{E_{es}}$$

The distance of the calculated VAC from critical values of 1 (stroke work maximization), 0.7 and 0.5 (efficiency optimization) was determined by means of the following equation:

$$VAC_{distance} = |X - VAC|$$

with 1, 0.7 and 0.5 substituted for X in turn.

A CX-50 cardiac ultrasound system (Philips Healthcare, Andover, Massachusetts) equipped with pulse wave tissue Doppler imaging technology was used for all studies.

A Siemens 1.5 Tesla nuclear MRI scanner was used for all cMRI scans. Gd-DTPA was employed as the contrast medium. Scans were performed in accordance with the protocols issued by the Society for Cardiovascular Magnetic Resonance.[26]

2.3. Statistical Analysis

Continuous variables are presented as the mean $\pm$ standard deviation when normally distributed and as the median (25^{th} and 75^{th} quartile) when not. Qualitative variables are presented as absolute and relative frequencies. Student's

t-test was used to assess differences in all cases of parametric variables with known normal distributions, with X^2 substituted for non-parametric values. In the case of VAC and VACdistance, however, due to the non-normality of the distributions, the independent samples Mann − Whitney U test was used.[27] A p-level $\leq$0.05 was considered statistically significant.

Multi-adjusted regression analysis was performed to study the relationship between VAC and DGE, allowing for adjustments for age, body mass index (BMI), normalized left ventricular chamber dimensions, coronary heart disease, hypertension, and EF. Furthermore, regression analysis was stratified according to EF status (reduced or preserved). The normality of the distribution of all of the explanatory variables (VAC, VAC1, VAC07, VAC05) was first examined by means of the Kolmogorov-Smirnov criterion. Given that all of the variables were found to be significantly (positively) skewed, they were log-transformed, and subsequent tests demonstrated the adequate normality of the new distributions. Scatterplots were drawn to assess the linearity between each log-transformed explanatory variable and each independent variable and to thus verify the adequacy of applying linear regression.

3. Results

The baseline demographics of patients are shown in Table 1. Fifty-eight percent were male and 49% had a preserved systolic function. Ventricular dimensions, normalized by BSA, were found to be generally within the normal range, as suggested by the study of Lang et al., as was the case with the VAC values.[15] In addition, 56% displayed DGE in the cMRI scan.

Stratifying the analysis by EF>50%, no differences were observed between groups regarding gender, presence of hypertension, CAD and DM (p-values 0.53, 0.48, 0.51, 0.34, respectively). The DGE frequencies were 52% in the EF<50% group and 61% in the EF>50% group (p=0.34). No statistically significant differences were noted regarding BMI and age difference (p=0.43 and p=0.27, respectively). The normalized LV end diastolic diameter and VAC-related parameters, however, showed a statistically significant divergence between groups, with coupling values that were significantly lower in the preserved systolic function group (p=0.001 − Table 2). Regarding parameters with non-Gaussian distributions, statistically significant differences were found in the cases of VAC and a VAC distance from 0.7 and 0.5 (p<0.01 in all cases), while a borderline deviation was noted in the case of the distance from 1 (p=0.056).

When the presence of DGE was used for stratification, significant relationships were noted between the presence of DGE and either EGE or T2 enhancement (X^2 p=0.005 and p=0.001, respectively). No differences were noted regarding age, CAD, DM presence, LV dimensions, EF (treated as a continuous variable), VAC value or VAC distance from 1, 0.7, or 0.5 (Table 3).

Multi-adjusted regression analysis with log-transformed VAC as a dependent variable revealed that the model could account for approximately 52% of the observed VAC variability, and the significance level was <0.001. Of the input variables, however, only BMI and EF were statistically significant (B=0.004 and B=-0.003, respectively), with DGE having a p value of approximately 0.06 (Table 4). For log-transformed VAC0.7 as a dependent variable, the findings displayed similar significance, with the BMI p reduced to 0.041 and DGE p to 0.131, while EF maintained its significance (p=0.02). In the case of log-transformed VAC0.5, our model had a statistically significant predictive power, with BMI and EF reaching significance (p=0.025 and p=0.011, respectively) and DGE having a p of 0.09.

No significant model predictive power was noted in the VAC1 case (p=0.33). Finally, the model lacked predictive power in all per EF stratum analyses.

Table 1 Baseline demographics of the study sample (n=57).

Parameter	
Age (years)	42.16 (17.88)
Gender (% male)	58
BMI (kg/m^2)	29.2 (8.8)
Hypertension (%)	19
Coronary artery disease (%)	9
Diabetes mellitus (%)	2
Systolic BP (mmHg)	109 (24.8)
Diastolic BP (mmHg)	71 (17.4)
Left ventricular end diastolic diameter (mm) by BSA (m^2)	2.66 (0.59)
Ejection fraction, %	42 (18)
EF>50% (n, %)	28, 49%
Ees	2.12 (0.99)
Ea	2.10 (1.13)
VAC	1.04 (0.40)
VAC distance 1	0.25 (0.1, 0.4)
VAC distance 0.7	0.27 (0.10, 0.51)
VAC distance 0.5	0.47 (0.24, 0.71)
DGE (n, %)	32, 56%

Data are presented as the mean (standard deviation), frequencies, or in the case of the VAC distances, as the median (25th − 75th percentiles) due to non-normal distributions (see "Statistical Analysis").

Table 2 Left ventriculoarterial coupling parameters according to the left ventricular ejection fraction distribution.

Parameter	EF<50	EF>50	p (t-test)
Left ventricular end diastolic diameter (mm) by BSA	2.96	2.35	0.002
Ees	2.23	2	0.4
Ea	2.60	1.58	0.001
Parameter	**EF<50**	**EF>50**	**p (Mann-Whitney U-test)**
VAC	1.24	0.83	<0.001
VAC1	0.37	0.22	0.056
VAC07	0.55	0.19	<0.001
VAC05	0.74	0.33	<0.001

BSA: body surface area; Ees: Ventricular elastance; Ea: arterial elastance.

Table 3 Differences in DGE-based stratification.

Parameter	DGE absence	DGE presence	p (t-test)
EF	0.39	0.44	0.33
Parameter	**DGE absence**	**DGE presence**	**p (Mann-Whitney U-test)**
VAC	1.12	0.97	0.51
VAC1	0.36	0.24	0.3
VAC07	0.45	0.31	0.44
VAC05	0.62	0.47	0.51

EF: ejection fraction; VAC: ventriculoarterial coupling.

4. Discussion

In this work, the relationship between the presence of Delayed Gadolinium Enhancement (DGE) and Ventriculoarterial Coupling Values in patients with diagnosed acute myocarditis was studied. It was hypothesized that inasmuch as DGE is a herald of fibrosis and necrosis of myocardial tissue,[7,28] for processes in common with chronic heart failure (condition with known derangements in VAC status[16]), a negative relationship between its presence and VAC status might be detectable. The utilization of imaging criteria for diagnosing myocarditis[7] allowed the completion of a relatively simple protocol within 24 hours from patient presentation. The main finding of this work was that despite the presence of DGE in the majority of studied patients, no statistically significant relationship was noted with VAC status, at least upon qualitative assessment of the former.

In recent years, there has been a shift in diagnosis of acute myocarditis from performing endomyocardial biopsy (EMB) (Dallas criteria[29]) to applying cardiac magnetic resonance imaging (cMRI),[7] given the difficulties and complications of EMB.[30,31] cMRI has the potential to diagnose and differentiate between different aspects of the disease.[7,11,32,33]

More specifically, T2 weighted sequences demonstrate edema, T1 based sequences with early Gd enhancement – EGE – detect vasodilation and increased permeability,[11,32] and T1 based sequences with delayed Gd enhancement – DGE – reveal necrosis/fibrosis.[33] DGE has also been found to correlate with troponin-T increases in acute myocardial inflammation.[34] Although several patterns of signals have been described,[11,32,35,36] the "Lake Louise criteria"[7] remain the gold standard for non-bioptic myocarditis diagnosis and were employed in the present study.

The multitude of variables affecting the function of the cardiovascular system has led to efforts to describe it in a less analytical but more concise way.[14,16,37] It was determined that the arterial elastance (Ea), defined as the ratio of aortic end-systolic pressure to stroke volume,[15] could be the vascular link to assess cardiovascular performance in terms of energy transfer and efficiency.[15,20] The cardiac link was the end-systolic left ventricular elastance (Ees), defined as the slope of the end-systolic pressure-volume relationship of the ventricle, in a classic pressure-volume loop.[16,37] Conceptually, both parameters express pressure alterations per unit volume change. Their ratio (Ea/Ees) constitutes the ventriculoarterial coupling.

Table 4 Multi-adjusted linear regression analysis results for ventriculoarterial coupling (VAC), VAC0.7 and VAC0.5.

	Model for VAC			Model for VAC 0.7			Model for VAC 0.5		
	B-coefficient (SE)	Beta (standardized coefficient)	p	B-coefficient (SE)	Beta (standardized coefficient)	p	B-coefficient (SE)	Beta (standardized coefficient)	p
Age per 1 year	<0.001 (0.001)	0.030	0.86	<0.001 (0.001)	0.066	0.71	<0.001 (0.001)	0.030	0.86
Body Mass Index per 1 kg/m^2	0.004 (0.002)	0.377	0.025	0.004 (0.002)	0.356	0.041	0.004 (0.002)	0.377	0.025
Normalized LV diastolic diameter, per 1 mm/m^2	0.026 (0.037)	0.145	0.49	0.033 (0.038)	0.192	0.39	0.025 (0.037)	0.144	0.5
Ejection fraction, per 1%	−0.003 (0.001)	−0.536	0.011	-0.003 (0.001)	−0.51	0.020	−0.003 (0.001)	−0.537	0.011
History of CAD, *y* vs. *n*	−0.033 (0.047)	–	0.5	−0.054 (0.049)	–	0.28	−0.032 (0.047)	–	0.5
History of hypertension, *y* vs. *n*	0.014 (0.038)	–	0.72	0.005 (0.039)	–	0.9	0.014 (0.038)	–	0.73
DGE, *y* vs. *n*	−0.054 (0.028)	–	0.06	−0.045 (0.029)	–	0.13	−0.054 (0.028)	–	0.06

LV: left ventricle; CAD: coronary artery disease; DGE: delayed gadolinium enhancement; VAC: ventriculoarterial coupling. Explanatory variables have been log-transformed to achieve normality of distribution.

It has been theoretically predicted that when VAC equals 1, ventricular stroke work is maximized for a given contractility.[14] In this framework, the cardiovascular system can be thought of as an oscillator that reaches its resonance frequency (maximization of stroke work) when VAC equals 1. Further studies have established its role in assessing the energy efficiency of the cardiovascular system, which is optimized when VAC assumes values in the 0.5—0.7 range.[37,38] Finally, non-invasive calculations of both Ea and Ees has allowed for a prompt and reliable assessment of the VAC status.[21,22]

The aforementioned imaging and physiology approaches were combined in this work to evaluate the effect of myocarditis (DGE) on the function of the cardiovascular system (VAC).

DGE was present in 56% of our patients, suggesting a frequent chronic impact on the myocardium. Significant correlations were noted between the presence of DGE and either the EGE or T2 high intensity signal, as expected from the study protocol. Despite the above results, no differences were observed upon stratifying per presence of DGE regarding the ejection fraction or VAC value, either as an absolute number or as an indicator of the mechanical efficiency (distance from 1) and energy optimization (distance from either 0.7 or 0.5). This could be attributable to the crucial role of the ejection function on cardiovascular coupling, of which the presence of DGE is a surrogate. Given that no relationship was seen between DGE presence and EF, a more plausible explanation is that the lack of quantification of DGE may have blurred the relationship — that is, a smaller DGE volume would be associated with a relatively preserved EF and a larger volume with a reduced one, revealing the relationship between DGE and VAC.

By contrast, the ejection fraction displayed statistically significant relationships with the LV dimensions and VAC values, confirming its strong correlation with cardiovascular function as a whole. It is of note that although end systolic elastance was similar between groups (with a non-significantly higher value in the reduced EF group), arterial elastance was significantly higher in the reduced EF group, yielding significantly different VAC, VAC1, VAC0.7, and VAC0.5 values. It could be theorized that in the acute phase of the disease, homeostatic mechanisms (such as the neurohumoral axis) mobilize in the event of reduced EF, managing to maintain adequate hemodynamics at the cost of increased vascular stiffness (increased Ea) and reduced cardiovascular effectiveness and efficiency (VAC alterations), which prove deleterious if sustained (chronic heart failure).

The multi-adjusted regression analysis results of the log-transformed VAC relationships support our interpretation, given that despite including other clinically meaningful variables, EF maintained its significance in the model. A possible interpretation of the negativity of the B coefficient for EF is that as heart contractility improves, it can afford to function at levels optimizing its energy efficiency (0.5—0.7 range) rather than maximizing output (values approximately 1 — as work increases with increasing Ees, a healthier heart may have the same *absolute* work output as a failing one, even when not maximizing it *in relation to its contractility*[14]).

DGE was not found to be significantly related with shifts in VAC parameters; it should be noted, however, that DGE reached a 0.06 level of significance in the pooled analysis, necessitating further study by quantifying the cMRI findings to account for the differences in the DGE-positive subgroup (location and size of lesion).

Although BMI was found to significantly affect the VAC value, the absolute magnitude of the correlation reduces its clinical significance given that a VAC value shift of 0.4 (difference between preserved and reduced EF groups) requires a shift of 28 BMI units.

4.1. Limitations

This study has several limitations, including a small sample size that might preclude important relationships from reaching significance and the lack of a definite histological diagnosis. The lack of quantification of DGE may have had the strongest impact on our findings: a positive quantitative correlation between DGE and VAC shifts might assist in either predicting the cardiovascular functional status when assessing the cMRI findings or in inferring the presence of myocardial necrosis/fibrosis when measuring abnormal VAC values.

5. Conclusion

In conclusion, in this study, a relationship between DGE presence (qualitative) and VAC alterations in patients with acute myocarditis diagnosed by imaging criteria was not demonstrated ($p=0.06$). The strong relationship between EF and VAC status, however, was reproduced. Additional studies are necessary to clarify the DGE-VAC relationship, mainly by quantifying the volume (and/or location) of DGE observed and determining its form (potentially non-linear).

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Conflict of interest

Authors declare no conflict of interest.

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