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ORIGINAL RESEARCH

Circulating PGC-1α and MOTS-c Peptide as Potential Mitochondrial Biomarkers in Patients Undergoing Aortic Valve Replacement

María J Sánchez-Quintero[1–3,*], Andrea Iboleón[4,*], Laura Martín Chaves[1–3], Bárbara Pozo Vilumbrales[1,5], Ada DM Carmona-Segovia[1–3], Pilar Martínez López[1,6], Miguel Romero-Cuevas[1–3], Jorge Rodríguez-Capitán[1–3], Víctor M Becerra-Muñoz[1–3], Francisco Javier Pavón-Morón[1–3], Mora Murri[1,2,7,8]

[1]Instituto de Investigación Biomédica de Málaga y Plataforma en Nanomedicina (IBIMA Plataforma BIONAND), Málaga, Spain; [2]Unidad de Gestión Clínica Cardiología y Cirugía Cardiovascular, Hospital Universitario Virgen de la Victoria, Málaga, Spain; [3]Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Instituto de Salud Carlos III, Madrid, Spain; [4]Unidad Docente Multiprofesional de Atención Familiar y Comunitaria. Distrito de Atención Primaria Málaga-Guadalhorce, Málaga, Spain; [5]Department of Animal Biology, University of Málaga, Málaga, Spain; [6]Unidad de Gestión Clínica de Cuidados Críticos y Urgencias, Medicina Intensiva. Hospital Universitario Virgen de la Victoria, Málaga, Spain; [7]Unidad de Gestión Clínica de Endocrinología y Nutrición, Hospital Universitario Virgen de la Victoria, Málaga, Spain; [8]Centro de Investigación Biomédica en Red de la Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain

*These authors contributed equally to this work

Correspondence: Francisco Javier Pavón Biomédica de Málaga y Plataforma en Nanomedicina (IBIMA Plataforma BIONAND), Málaga, 29590, Spain, Email javier.pavon@ibima.eu; Mora Murri, Unidad de Gestión Clínica de Endocrinología y Nutrición, Hospital Universitario Virgen de la Victoria, Málaga, 29010, Spain, Email moramurri@gmail.com

Purpose: Aortic valve disease (AVD) is a common condition that leads to pressure and/or volume overload in the left ventricle. Aortic valve replacement is the standard treatment, as no pharmacological therapies are currently available. The incidence of AVD is increasing in developed countries, making the discovery of new biomarkers for early detection crucial. The importance of mitochondria in heart function is well established, and various cardiovascular pathologies are associated with mitochondrial dysfunction. In this cross-sectional study, we evaluated for the first time the role of mitochondria in AVD, aiming to identify new pathways involved in the disease and discover potential biomarkers.

Patients and Methods: We recruited 17 patients diagnosed with AVD and scheduled for aortic valve replacement, and 22 healthy controls. Plasma levels of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) and mitochondrial open reading frame of the 12S rRNA type-c peptide (MOTS-c) were measured by ELISA.

Results: We observed significantly reduced levels of both proteins in patients, suggesting that substantial mitochondrial dysfunction occurs in AVD patients, independent of sex or age, but directly related to the disease.

Conclusion: Mitochondria may represent a promising target for studying new pathways involved in AVD. We propose PGC1α and MOTS-c as potential plasma biomarkers for AVD detection. Further studies, including early-stage patients, are necessary to confirm the significance of our findings.

Keywords: aortic valve disease, biomarkers, mitochondria, PGC-1α, MOTS-c

Introduction

Aortic valve diseases (AVDs) are common valve lesions characterized by malfunction of the aortic valve, affecting more than 13% of the population over 75 years old.[1] Currently, the incidence of AVD is increasing in developed countries due to the aging population.[2,3] The pathophysiology of AVD includes angina, syncope, and dyspnea as late-stage symptoms, which occur after years of left ventricular overload. The lesions may be congenital, acquired, or a combination of both.[4] AVD encompasses aortic valve stenosis and aortic valve regurgitation. Degenerative calcific AVD is the most common

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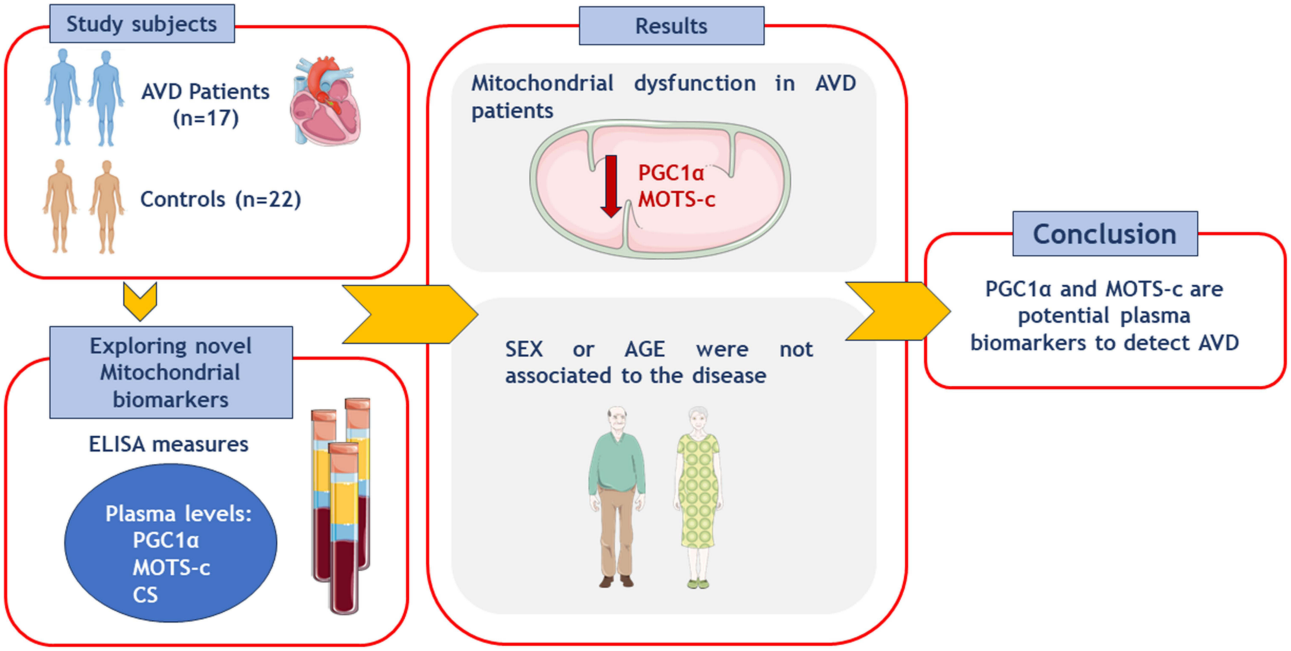
Graphical Abstract



cause of aortic stenosis,[5] leading to a narrowed aortic valve orifice. Due to mechanical stress, blood pressure increases, causing concomitant left ventricular pressure overload.[6] Aortic regurgitation, however, can result from AVD and/or abnormalities of the aortic root,[2] leading to both pressure and volume overload in the left ventricle. Currently, no pharmacological therapies are available for AVD, and transcatheter or surgical aortic valve implantation is the standard treatment, but only for appropriately selected patients.[6,7]

Various cardiac diseases are associated with mitochondrial dysfunction. For example, cardiac hypertrophy and heart failure are linked to uncontrolled production of reactive oxygen species (ROS).[8] Patients with pulmonary arterial hypertension show decreased activity of complexes I and III in the oxidative phosphorylation system.[9] Additionally, due to the high number of mitochondria in the heart, this organ is frequently affected by mitochondrial DNA (mtDNA) mutations, which can trigger the onset of several cardiovascular diseases such as cardiomyopathy, heart failure, arrhythmias, conduction defects, and vascular pathologies.[10,11] A role for mitochondria in AVD has also been described in the literature.[12] Studies have shown that various pathophysiological mechanisms involving mitochondria contribute to AVD, including oxidative stress and mitochondrial antioxidant capacity,[13] hydrogen sulfide metabolism in mitochondria,[14] mitochondrial calcium signaling,[15] and hypoxia signaling leading to mitochondrial dysfunction.[1] Impaired mitochondrial dynamics have also been implicated in AVD.[16]

Mitochondria possess their own genetic material, comprising 37 genes, including those involved in oxidative phosphorylation as well as genes encoding transfer RNA (tRNA) and ribosomal RNA (rRNA). A regulatory peptide named mitochondrial open reading frame of the 12S rRNA type-c (MOTS-c), encoded by mitochondrial 12S rRNA, was recently discovered.[17] MOTS-c has been extensively studied as a mitokine, a signaling molecule that communicates mitochondrial stress in affected tissues to distant cells or tissues.[18] Several studies have demonstrated the protective role of MOTS-c in cardiovascular diseases. MOTS-c prevents the development of heart failure, alleviates diabetic myocardial injury, and repairs myocardial damage in diabetic rats.[19–21] Another crucial player in mitochondrial function is peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α), a protein encoded by the PPARGC1A gene in humans. PGC1α is a master regulator of mitochondrial biogenesis[22–24] and is highly expressed in cardiac cells. PGC1α plays a protective role in certain cardiac diseases, such as myocardial ischemia/reperfusion (I/R) injury, by reducing

mitochondrial membrane potential and, consequently, oxidative stress in mitochondria.[25] PGC1α is also involved in the cardioprotective effects of tilianin and syringin in diabetic cardiomyopathy.[26]

There remain significant knowledge gaps in the diagnosis and treatment of AVD. For instance, these include the criteria for surgical intervention in asymptomatic patients, the assessment of severity in cases of aortic stenosis with low flow and low gradient, and the correlation between symptoms and valvular disease in patients with comorbidities that mimic valvular disease symptoms. In the present study, we focused on late-stage patients to expand our understanding on the involvement of mitochondria in AVD, a topic that is still poorly explored in the literature. Given their reported protective roles in other cardiovascular diseases, we measured plasma levels of PGC1α and MOTS-c as markers of mitochondrial function. To the best of our knowledge, this is the first study to assess these mitochondrial markers in the context of AVD. Additionally, we analyzed citrate synthase (CS) levels, an important mitochondrial enzyme commonly used as a quantitative marker for the presence of intact mitochondria. Considering the urgency of identifying early signs of the disease in asymptomatic patients, our ultimate goal is to discover or suggest new biomarkers for AVD diagnosis.

Materials and Methods

Ethics Statements

The present study was approved by the Regional Ethics Committee (Málaga Provincial Research Ethics Committee, Málaga, Spain) (code: 1981-N-21), in agreement with the World Medical Association Declaration of Helsinki. All participants were properly informed about the procedures, the aim of the study and privacy rights. Signing a written informed consent form was a requirement for all participants.

Participants and Patient Recruitment

This cross-sectional study comprised a total of 39 participants, categorized into two groups: a) Disease group or AVD group; and b) Healthy Control (HC) group. The AVD group consisted of 17 patients with AVD (9 men and 8 women), who were evaluated at Hospital Universitario Virgen de la Victoria (Málaga, Spain). All patients were indicated for aortic valve replacement. The clinical evaluation included blood test, electrocardiogram, echocardiogram and invasive coronarography. Clinical data of patients are summarized in Table 1. Patient eligibility criteria were defined as follows: 1) Patients with significant AVD, including stenosis and/or regurgitation, with at least one reaching a severe degree, who present with clinical indications for surgical intervention; 2) Age greater than 65 years; 3) Absence of mitochondrial pathology or comorbidities that could affect plasma levels of the mitochondrial proteins studied: PGC1α, MOTS-c, and CS. The control group consisted of 22 healthy individuals (12 men and 10 women) who attended for a routine blood test.

Table 1 Clinical Variables of Each Group

	Healthy Controls		AVD Patients		p value	p value	p value
	Men	Women	Men	Women	Disease group	Sex	Interaction
N	12	10	9	8	–	–	–
Age	69.2 ± 4.9	70.3 ± 6.6	73.1 ± 1.7	73.5 ± 2.4	0.024	0.490	0.942
GFR (mL/min/1.73m2)	72 ± 13	68 ± 16	63 ± 17	72 ± 17	0.674	0.627	0.290
Creatinine (mg/dL)	1.0 ± 0.2	0.9 ± 0.2	1.2 ± 0.3	0.8 ± 0.2	0.651	<0.001	0.134
Urea (mg/dL)	43 ± 9	41 ± 10	47 ± 10	47 ± 11	0.129	0.860	0.707
LVEF (%)	–	–	55.3 ± 11.9	61.3 ± 8.3	–	–	–
IS (mm)	–	–	14.9 ± 2.5	14.0 ± 2.2	–	–	–
LVTD (mm)	–	–	49.2 ± 4.8	45.5 ± 7.5	–	–	–
AVA (cm^2)	–	–	0.9 ± 0.2	0.7 ± 0.2	–	–	–
AVmean (mmHg)	–	–	34 0.0 ± 12.1	46.8 ± 11.2	–	–	–
AVmax (mmHg)	–	–	59.5 ± 24.4	76.5 ± 18.4	–	–	–

Abbreviations: N, Number of subjects; AVD, Aortic valve diseases; GFR, Glomerular filtration rate; LVEF, Left ventricular ejection fraction; IS, Interventricular septum; LVTD, Left ventricle telediastolic diameter; AVA, Aortic valve area; AVmean, Aortic valve mean gradient; AVmax, Aortic valve maximum gradient.

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Healthy controls were matched for sex and age, and were recruited at a primary care center (Centro de Salud Colonia Santa Inés, Málaga, Spain). The eligibility criteria included: 1) Age greater than 65 years; 2) Absence of cardiovascular or mitochondrial pathologies.

Sample Collection and Biochemical Determinations

Samples were collected from patients at the time of surgery. A total of 3 mL of peripheral venous blood were collected from patients and controls after fasting 12-hour overnight. Samples were centrifugated at 2200 g during 15 minutes at 4 ° C. Plasma was separated in aliquots and immediately frozen at −80 °C until their analysis. Plasma was collected from each participant and glomerular filtration rate (GFR), creatinine and urea were determined by standard enzymatic methods, using the hospital analyses service.

Determination of Circulating Mitochondrial Markers

To explore the role of mitochondria in AVD we selected three key proteins involved in mitochondrial activity, PGC1α, MOTS-c and CS, and we analyzed their plasma levels in patients. Quantitative measurement of PGC1α, MOTS-c and CS were performed in plasma from patients and controls using ELISA Kits from MyBioSource (San Diego, CA, USA), following manufacturer´s instructions. Absorbance at 450 nm was read in a microplate reader, and the concentrations of targets were calculated. The intra-assay coefficient of variation was less than 10%, while the inter-assay coefficient of variation was less than 12%. The selected ELISA kits have high sensitivity and excellent specificity for detection of PGC1α, MOTS-c and CS, respectively, and they are specific enzyme immunoassay techniques for the in vitro quantitative measurement of these markers in human serum or plasma.

Statistical Analysis

The results are expressed as either mean values ± standard deviation (SD), or median and interquartile range (IQR), unless otherwise stated. The normality of the datasets was assessed with the Kolmogorov–Smirnov test. Post-hoc power analysis for two-way Mann–Whitney tests assessing plasma levels of PGC1α, MOTS-c, and CS was conducted using G*Power (version 3.1.9.4). For each marker, the recruited sample size, observed mean values, SD, and $\alpha = 0.05$ were considered.

Metabolic and mitochondrial markers were analyzed using non-parametric statistical procedures due to their non-normal distribution. Specifically, the Mann–Whitney *U*-test was used to assess differences between two groups, and the Kruskall-Wallis test was applied to assess differences among more than two groups.

Two-way analysis of covariance (ANCOVA) was performed to evaluate the main effects and interaction of independent factors [sample group (HC and AVD) and sex (men and women)] on PGC1α, MOTS-c and CS levels while controlling for age. Since PGC1α, MOTS-c, and CS concentrations exhibited a positively skewed distribution and did not pass the normality test, the raw data were log10-transformed to meet the parametric assumptions of ANCOVA. The estimated marginal means and 95% confidence interval (95% CI) of the log10-transformed PGC1α, MOTS-c and CS concentrations were back-transformed and displayed in the figures. Sidak's test was used for post-hoc pairwise comparisons.

A logistic regression model was developed to differentiate between HC and AVD based on PGC1α, MOTS-c, and CS concentrations. Receiver operating characteristic (ROC) analysis was performed to evaluate the model's accuracy using the area under the curve (AUC) along with estimates of sensitivity and specificity.

Spearman correlation (rho) tests were calculated to assess the association between age and the concentrations of these analytes.

All statistical analyses were conducted using the PSPP (GNU software) and GraphPad Prism (GraphPad Software, San Diego, CA, USA) programs. A p-value less than 0.05 was considered statistically significant.

Results

Characteristics of Subjects

We recruited 9 male and 8 female AVD patients, all of whom were indicated for surgical intervention. Additionally, we recruited 22 subjects as the control group. Demographic and clinical characteristic of subjects are detailed in Table 1. None of the controls presented cardiovascular issues or mitochondrial diseases. Age was slightly lower in controls respect to AVD patients. The observed difference is, however, clinically irrelevant, although is considered in further statistical analysis. Regarding the biochemical parameters, we measured GFR, creatinine and urea levels in blood. Results showed no significant differences between groups in GFR and urea levels. However, creatinine showed significant lower values in women. In the cardiac evaluation of the patients, we measured the left ventricular ejection fraction (LVEF), interventricular septum thickness (IS), left ventricular end-diastolic diameter (LVED), aortic valve area (AVA), aortic valve mean gradient (AVmean), and aortic valve maximum gradient (AVmax). The mean values of AVA, AVmean, and AVmax were calculated considering only patients with stenosis, that was observed in 5 men and 6 women. Additional data related to the clinical characteristics of the studied patients are presented in Table S1.

Decreased Levels of Circulating PGC1α, and MOTS-c in AVD Patients

When plasma levels of potential mitochondrial markers were analyzed, we found that AVD patients exhibited significantly lower levels of PGC1α and MOTS-c compared to healthy controls (Figure 1a and b). However, no statistical differences were observed in plasma levels of CS between AVD patients and the control group (Figure 1c). The achieved statistical power for PGC1α, MOTS-c and CS were 0.9999, 0.9997 and 0.0519, respectively. Since the reported decline in PGC1α with age could act as a confounding factor, particularly in our older patient population, we performed a correlation analysis between age and PGC1α levels. We observed that only the healthy control group showed a negative correlation between PGC1α levels and age ($r = -0.4935$, $p = 0.0230$), whereas no correlation was found in the patient group ($r = -0.1366$, $p = 0.6120$).

Mitochondrial Proteins Concentration Based on Sample Group and Sex

To assess whether sex or age affect to the levels of the mitochondrial markers, values of plasma concentration of PGC1α, MOTS-c and CS were analyzed using a two-way ANCOVA, with sample group and sex as factors, while controlling for age. The statistical analysis found a main effect on the interaction between groups (HC and AVD patients) and mitochondrial proteins PGC1α and MOTS-c (Figure 2a and b, respectively), but not CS (Figure 2c). In contrast, no effect was found when the interaction between age and mitochondrial proteins were analyzed. Finally, no interaction was found between sex and mitochondrial proteins.

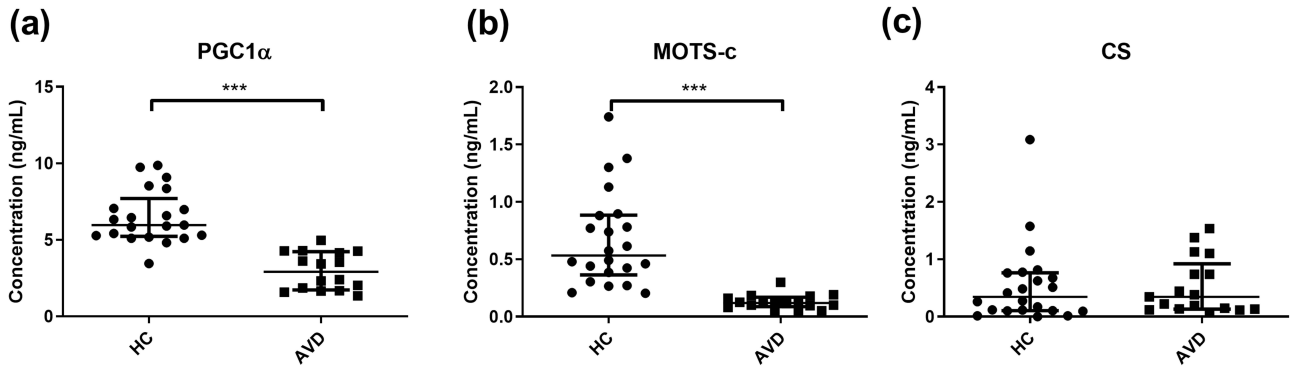

Figure 1 Plasma levels of PGC1α, MOTS-c and CS in controls and AVD patients. Plasma levels of PGC1α (**a**), MOTS-c (**b**) and CS (**c**) in controls and AVD patients. Median and IQR are represented. Mann–Whitney *U*-test was used for analysis and asterisks denote significant differences compared with healthy controls (***, p<0.0001).

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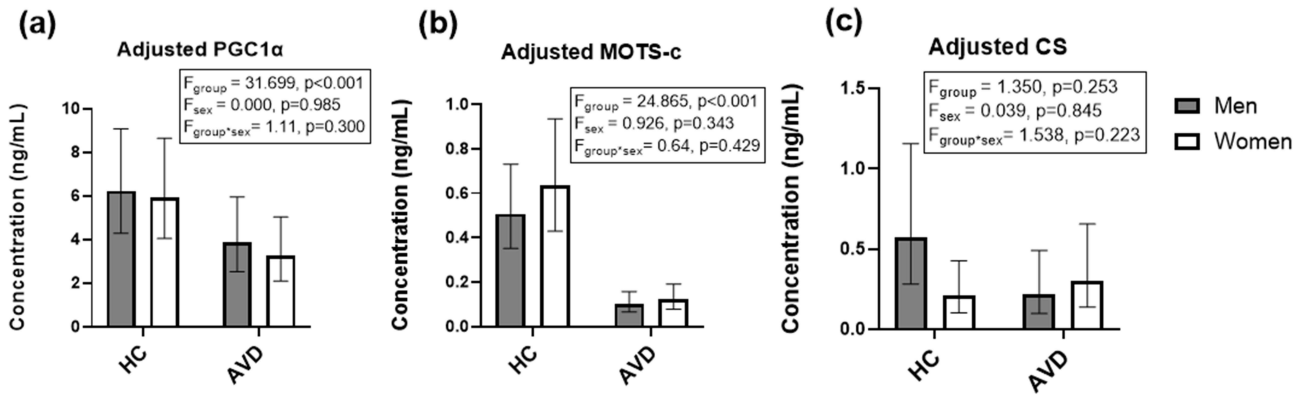

Figure 2 Plasma concentrations of PGC1α (a), MOTS-c (b) and CS (c) based on the sample group and sex factors. Plasma concentrations of PGC1α (**a**), MOTS (**b**) and CS (**c**) based on the sample group and sex factors. A two-way ANCOVA test was run with sample group (HC and AVD) and sex (men and women) as factors while controlling for age. The raw data were log10-transformed to meet the parametric assumptions of ANCOVA. The bars represent the estimated marginal means and 95% CI after back-transformation. F-statistics and p-values of ANCOVA are shown. N.s. denotes non-significant differences.

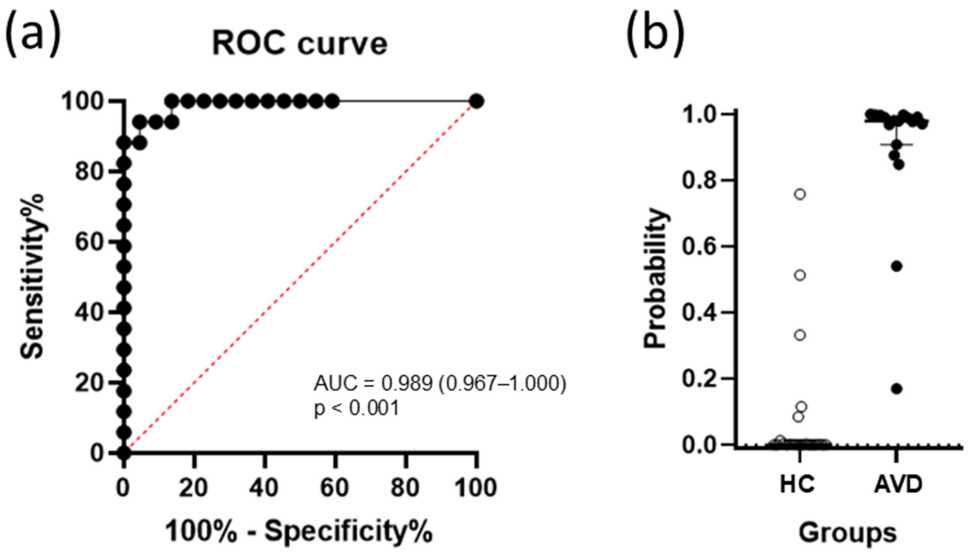

Figure 3 ROC analysis of the regression model. ROC curve analysis (**a**) and resulting probabilities (**b**) derived from a logistic regression model incorporating the concentrations of PGC1α, MOTS-c, and CS. The model demonstrated excellent predictive power, with an AUC of 0.989 ($p < 0.001$).

Mitochondrial Protein Concentrations as Potential Biomarkers to Differentiate AVD Patients

Since PGC1α, MOTS-c and CS concentrations were examined in HC and AVD patients and significant differences were observed, we examined their potential as biomarkers using a logistic regression model (Table S2). As expected, these proteins were identified as predictive variables to distinguish AVD patients from healthy subjects. Furthermore, the ROC analysis showed a significant AUC of 0.989 ($p < 0.001$) (Figure 3a) and revealed a high discriminatory power of the model (Figure 3b).

Discussion

AVD is a type of heart valve disease in which normal blood flow is compromised due to a damaged or diseased aortic valve. The pathology can develop over several years, but symptoms are often detected only in the later stages, when the disease becomes severe. In this study, our aim was to identify new potential targets for the assessment of AVD.

Mitochondrial dysfunction has been reported as relevant in various cardiovascular diseases.[8,11,27,28] Given the importance of mitochondria in these conditions, we sought to investigate their role in AVD. We selected PGC1α, MOTS-c, and CS as mitochondrial markers due to their relevance in mitochondrial function and their involvement in cardiovascular diseases.

Our results revealed a significant decrease in plasma levels of PGC1α in AVD patients compared to the control group, indicating mitochondrial biogenesis dysfunction. The decrease in PGC1α expression in various tissues with aging is well documented.[29–31] However, our patient and control groups were age-matched, and our statistical analyses showed that age only correlated with PGC1α levels in the HC group, not in the AVD group. Our findings suggest that the downregulation of PGC1α in AVD patients is independent of age, highlighting a dysregulation in mitochondrial biogenesis signaling as a potential disease mechanism in AVD.

Regarding the MOTS-c peptide, it has been previously reported as a mitokine, with a well-documented protective role in cardiovascular diseases, including the prevention of heart failure, alleviation of diabetic myocardial injury, and repair of myocardial damage.[19–21] Consistent with these findings, we observed a marked decrease in plasma MOTS-c levels in AVD patients, all of whom were scheduled for aortic valve replacement.

In terms of CS, we found no significant differences in circulating levels between AVD patients and controls. CS is a mitochondrial enzyme encoded by the nuclear genome and localized within the mitochondrial matrix, responsible for the condensation of acetyl-CoA and oxaloacetate to form citrate. Its levels or activity are commonly used as a marker of mitochondrial mass.[32–34] The similarity in CS plasma levels between AVD patients and controls suggests that the differences observed in PGC1α and MOTS-c are not due to alterations in mitochondrial mass, but rather to a failure to maintain normal levels of mitochondrial regulatory proteins in patients.

Although aortic stenosis tends to have a male predominance, men and women are equally represented among patients older than 75 years.[4] In our study, we found no sex-related differences in plasma levels of PGC1α or MOTS-c. Therefore, our findings suggest that the mitochondrial dysfunction observed in AVD patients is primarily related to the disease itself, with neither sex nor age playing a significant role in the development of this dysfunction.

Several limitations of this study should be acknowledged. Although the sample number was small, according to the post-hoc power analysis, our sample size was large enough to detect the dramatic decreased of PGC1α and MOTS-c plasma levels observed in AVD patients. Furthermore, the logistic regression model used in this study supports the conclusion that these proteins are predictive variables capable of distinguishing AVD patients from healthy subjects. However, a proper validation in an independent cohort would be desirable to confirm our results. Second, this is a cross-sectional study, and longitudinal studies are needed to better understand how these markers evolve with disease progression. Notably, we studied late-stage patients, all of whom were scheduled for aortic valve replacement. It would be valuable to recruit early-stage or asymptomatic patients to assess the potential of these mitochondrial proteins as biomarkers for the early diagnosis of AVD.

Conclusions

In conclusion, we have demonstrated that the significant decreases in plasma levels of PGC1α and MOTS-c peptide observed in AVD patients are not associated with age—at least within the age range of the patients included in this study—or sex. This suggests that the observed mitochondrial dysfunction is most likely linked to the disease itself. Further studies involving patients at earlier stages of the disease are needed to validate the relevance of our findings and to explore the potential role of PGC1α and MOTS-c peptide as biomarkers for aortic valve disease.

Abbreviations

ANCOVA, Analysis of covariance; ANOVA, Two-way analysis of variance; AUC, Area under the curve; AVA, Aortic valve area; AVDs, Aortic valve diseases; AVmax, Aortic valve maximum gradient; AVmean, Aortic valve mean gradient; CI, Confidence interval; CS, Citrate synthase; GFR, Glomerular filtration rate; HC, Healthy Control; IS, Interventricular septum thickness; I/R, Ischemia/Reperfusion; LVED, Left ventricular end-diastolic diameter; LVEF, Left ventricular ejection fraction; MOTS-c, Mitochondrial open reading frame of the 12S rRNA type-c; mtDNA, Mitochondrial DNA; PGC1α, Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; ROC, Receiver operating characteristic; ROS, Reactive oxygen species; rRNA, Ribosomal RNA; SD, Standard deviation; tRNA, Transfer RNA.

Data Sharing Statement

The data are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

Informed consent was obtained from all subjects involved in the study. The present study was approved by the Regional Ethics Committee (Málaga Provincial Research Ethics Committee, Málaga, Spain) (code: 1981-N-21), in agreement with the World Medical Association Declaration of Helsinki. All participants were properly informed about the procedures, the aim of the study and privacy rights.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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