Significance and Determinants of Plasma Apelin in Patients With Obstructive Hypertrophic Cardiomyopathy

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Background: Recent studies suggest apelin has multiple protective effects in some cardiovascular diseases. However, there are few data concerning apelin levels in patients with obstructive hypertrophic cardiomyopathy (OHCM) or the relationship between apelin levels and severity of OHCM.

Methods: We studied 88 patients with OHCM and 32 control subjects with matched age and sex distribution. Complete medical history was collected and related examinations were performed. Cardiac magnetic resonance (CMR) and echocardiography were employed to characterize cardiac morphology and function. Plasma apelin was measured by enzyme-linked immunosorbent assay (ELISA).

Results: Plasma apelin levels were significantly lower in patients with OHCM than those in control subjects (96.6 ± 34.3 vs. 169.4 ± 62.5 µg/L, p < 0.001). When patients with OHCM were divided into two groups according to the mean value of plasma apelin, patients with lower apelin levels (plasma apelin ≤ 96.6 µg/L) had greater septal wall thickness (SWT; 25.6 ± 5.5 vs. 23.2 ± 4.3 mm, p = 0.035) and less right ventricular end-diastolic diameter (RVEDD; 20.4 ± 3.3 vs. 23.0 ± 3.6 mm, p = 0.001). Consistently, plasma apelin levels were inversely correlated with SWT (r = −0.334, p = 0.002) and positively correlated with RVEDD (r = 0.368, p < 0.001). Besides, plasma apelin levels were inversely correlated with Ln (NT-proBNP) (r = −0.307, p = 0.008) and positively correlated with body mass index (BMI; r = 0.287, p = 0.008). On multivariate analysis, the SWT was independently associated with decreasing plasma apelin, while the RVEDD was independently associated with increasing plasma apelin.

Conclusion: Plasma apelin levels are significantly lower in patients with OHCM than those in control subjects (96.6 ± 34.3 vs. 169.4 ± 62.5 µg/L, p < 0.001). When patients with OHCM were divided into two groups according to the mean value of plasma apelin, patients with lower apelin levels (plasma apelin ≤ 96.6 µg/L) had greater septal wall thickness (SWT; 25.6 ± 5.5 vs. 23.2 ± 4.3 mm, p = 0.035) and less right ventricular end-diastolic diameter (RVEDD; 20.4 ± 3.3 vs. 23.0 ± 3.6 mm, p = 0.001). Consistently, plasma apelin levels were inversely correlated with SWT (r = −0.334, p = 0.002) and positively correlated with RVEDD (r = 0.368, p < 0.001). Besides, plasma apelin levels were inversely correlated with Ln (NT-proBNP) (r = −0.307, p = 0.008) and positively correlated with body mass index (BMI; r = 0.287, p = 0.008). On multivariate analysis, the SWT was independently associated with decreasing plasma apelin, while the RVEDD was independently associated with increasing plasma apelin.

Keywords: apelin, obstructive hypertrophic cardiomyopathy, septal wall thickness, myocardial hypertrophy, right ventricular end-diastolic diameter
INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a primary inherited myocardial disorder characterized by asymmetrical left ventricular hypertrophy (LVH), with a prevalence of 1:500 in the general population (1). Notably, about 70% of patients with HCM have left ventricular outflow tract (LVOT) obstruction, which is called obstructive hypertrophic cardiomyopathy (OHCM) (1). The presence of LVOT obstruction prominently aggravates clinical symptoms of HCM, such as dyspnea, chest pain and syncope. The LVOT obstruction is often attributed to septal hypertrophy and systolic anterior motion of the mitral valve, and the former is the pathological basis of OHCM (2). However, there are few findings concerning circulating biomarkers that can reflect the severity of LVH in OHCM.

Apelin is an endogenous peptide isolated from bovine stomach extracts (3). Recent studies have shown that apelin has diverse protective effects in many cardiovascular diseases, such as heart failure, systemic and pulmonary arterial hypertension and ischemic-reperfusion lesion (4, 5). Of note, Scimia et al. reported that apelin administration blunts progression to cardiac hypertrophy induced with transverse aortic constriction in mice (6). And our previous study found that apelin could inhibit angiotensin II-induced myocardial hypertrophy (7). These findings suggest that apelin may have some effects on LVH in patients with OHCM. Currently, however, there are few studies concerning the relationship between apelin levels and characteristics indicating severity of OHCM. In this study, we sought to investigate apelin levels in patients with OHCM compared with control subjects and their association with clinical and cardiac morphological characteristics of patients.

MATERIALS AND METHODS

Study Population

The protocol of this study was approved by Fuwai Hospital (Beijing, China) ethics committee and complied with the Declaration of Helsinki. The informed consents were obtained from all participants.

We enrolled patients with OHCM who were evaluated in Fuwai Hospital (Beijing, China) from October 2015 to October 2016. The diagnosis of OHCM was based on a maximum left ventricular (LV) wall thickness ≥ 15 mm (or ≥ 13 mm with an unequivocal family history of HCM) and the presence of LVOT obstruction, as measured by echocardiography or cardiac magnetic resonance imaging (CMRI), in the absence of other cardiac or systemic diseases capable of producing comparable magnitude of hypertrophy (8). Evaluation of patients included complete medical history, physical examination, 12-lead electrocardiography, 24-h ambulatory electrocardiographic monitoring, transthoracic echocardiography, blood examination, CMRI, and coronary angiography.

Patients with coronary artery disease (epicardial coronary stenosis > 70% on coronary angiography, previous myocardial infarction, bypass surgery, or percutaneous coronary intervention), renal dysfunction, liver diseases, or permanent mechanical device implantation were excluded. Finally, a total of 88 patients with OHCM were recruited in the present study.

Thirty-two asymptomatic subjects with matched age and sex distribution of the OHCM patients were invited to participate as controls after detailed clinical and cardiac examination.

Measurement of Plasma Apelin and N-Terminal pro-B-Type Natriuretic Peptide Levels

Fasting venous blood samples of patients with OHCM were collected in tubes containing EDTA within 2 days of echocardiography and 1 week of CMRI examination. Fasting blood samples of control subjects were collected at the same day of echocardiography examination. Blood samples were subsequently centrifuged for 15 min at 3,000 g. Then plasma was collected and stored at −80°C until assay. Plasma concentration of apelin was measured by a commercial enzyme-linked immunosorbent assay (ELISA) kit for human apelin (RayBiotech, Inc., Norcross, GA, United States) according to the manufacturer’s instructions. This kit is designed to target the C-terminus of the 77-aa apelin peptide and therefore is expected to detect all active forms of apelin, including apelin-36, apelin-31, apelin-28, and apelin 13. The intra-assay coefficient of variation was <10% and the inter-assay coefficient of variation was <15%. The lower and upper limit of detection was 0.1 and 1,000 µg apelin/L, respectively. NT-proBNP was measured using an electrochemiluminescent immunoassay (Elecys proBNP II assay, Roche Diagnostics, Mannheim, Germany) by the clinical chemistry department of our hospital.

Echocardiography

Standard transthoracic M-mode, 2-dimensional, and pulse-wave and continuous-wave Doppler images were obtained with an iE33 Color Doppler Ultrasound System (Philips Healthcare, Andover, Massachusetts). All measurements were analyzed following the guidelines of the American Society of Echocardiography (9). The peak velocity across the LVOT was measured and the peak pressure gradient was estimated using the simplified Bernoulli equation. The presence of LVOT obstruction was defined as an instantaneous peak Doppler LVOT gradient ≥ 30 mm Hg at rest or during physiological provocation, such as Valsalva maneuver, standing, and exercise.

Cardiac Magnetic Resonance Imaging

CMRI was performed using a 1.5-T speed clinical scanner (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany). The imaging protocol and analysis have been described previously (10). All MR image analysis was performed using a commercial software (Medis Medical Imaging systems, Netherlands) by a single experienced observer who was blinded to the patients’ clinical and procedural data. Endocardial and epicardial contours of the LV myocardium (excluding papillary muscles) were manually traced at end-diastole and end-systole on each LV short-axis cine image. LV end-diastolic volume, LV
end-systolic volume, LVEF, stroke volume, cardiac output, and LV mass (LVM) were then calculated in a standard fashion. LVM was derived by multiplying LV myocardial volume measured at end-diastole with the specific gravity of myocardium (1.05 g/ml). The LV end-diastolic diameter, septal wall thickness and right ventricular end-diastolic diameter were traced and measured from the short-axis views at end-diastole.

**Statistical Analysis**

Continuous variables are expressed as mean ± SD or median [interquartile range (IQR)], according to their normality. Categorical variables are shown as frequencies (percentages). Comparisons of continuous variables between two groups were assessed using independent Student’s t-test or Mann-Whitney U-test depending on the distribution of variables. The chi-square test was used for comparisons between categorical variables.

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**Table 1** | Baseline characteristics of patients with OHCM and control subjects.

| Variable                  | Patients with OHCM (n = 88) | Control subjects (n = 32) | P-value |
|---------------------------|-----------------------------|---------------------------|---------|
| Apelin (µg/L)             | 96.6 ± 34.3                 | 169.4 ± 62.5              | <0.001  |
| Age (years)               | 48.8 ± 13.1                 | 46.8 ± 5.9                | 0.262   |
| Male, n (%)               | 57 (65%)                    | 21 (66%)                  | 1.000   |
| BMI (kg/m²)               | 25.9 ± 3.4                  | 26.9 ± 5.8                | 0.230   |
| Systolic blood pressure, mmHg | 120.6 ± 15.9              | 116.9 ± 11.7              | 0.240   |
| Diastolic blood pressure, mmHg | 74.0 ± 9.8                  | 75.3 ± 8.5                | 0.508   |
| Heart rate, beats/min     | 72.6 ± 10.8                 | 67.9 ± 6.7                | 0.013   |
| Dyspnea, n (%)            | 71 (81%)                    | 0 (0%)                    | <0.001  |
| Atrial fibrillation, n (%)| 15 (17%)                    | 1 (3%)                    | 0.066   |
| Hypertension, n (%)       | 21 (24%)                    | 0 (0%)                    | 0.001   |
| Hyperlipidemia, n (%)     | 35 (40%)                    | 13 (41%)                  | 1.000   |
| Diabetes mellitus, n (%)  | 7 (8%)                      | 0 (0%)                    | 0.187   |
| Current smokers, n (%)    | 26 (30%)                    | 8 (25%)                   | 0.819   |

**Table 2** | Characteristics of patients with obstructive hypertrophic cardiomyopathy according to plasma apelin levels stratified by mean value.

| Variable                  | Plasma apelin (µg/L) | P-value |
|---------------------------|----------------------|---------|
| Age (years)               | 49.0 ± 12.8          | 48.5 ± 13.6 | 0.835   |
| Male, n (%)               | 31 (65%)             | 26 (65%) | 1.000   |
| BMI (kg/m²)               | 25.5 ± 3.7           | 26.4 ± 2.9 | 0.215   |
| Systolic blood pressure, mmHg | 119.9 ± 16.7         | 121.5 ± 15.1 | 0.660   |
| Diastolic blood pressure, mmHg | 73.7 ± 9.9           | 74.4 ± 9.7 | 0.769   |
| Heart rate, beats/min     | 73.2 ± 8.1           | 71.9 ± 13.4 | 0.597   |
| NYHA functional class III or IV, n (%) | 16 (33%) | 6 (15%) | 0.053   |
| Chest pain, n (%)         | 20 (42%)             | 17 (43%) | 1.000   |
| Family history of HCM, n (%) | 3 (6%)                | 5 (13%) | 0.458   |
| Atrial fibrillation, n (%)| 9 (19%)              | 6 (15%) | 0.778   |

**Echocardiography**

| Septal wall thickness (mm) | Left atrium diameter (mm) | LV end-diastolic diameter (mm) | LV ejection fraction (%) | Mitral regurgitation* |
|---------------------------|---------------------------|--------------------------------|-------------------------|-----------------------|
| 22.9 ± 5.2                | 41.1 ± 6.5                | 42.2 ± 5.2                     | 69.0 ± 4.8              | 62 (72%)              |
| 8.6 ± 0.9                 | 32.6 ± 3.0                | 47.4 ± 3.5                     | 65.3 ± 3.4              | 0 (0%)                |
| <0.001                    | <0.001                    | <0.001                         | <0.001                  | <0.001                |

**CMR imaging**

| Septal wall thickness (mm) | RV end-diastolic diameter (mm) | Left atrium diameter (mm) | Left atrium volume (ml/m²) | LV end-diastolic diameter (mm) | LV end-diastolic volume (ml) | LV end-diastolic volume index (ml/m²) | LV mass (g) | LV mass index (g/m²) | LV ejection fraction (%) | Cardiac index (L/mm²) | P-value |
|---------------------------|--------------------------------|---------------------------|----------------------------|-------------------------------|-----------------------------|--------------------------------------|-------------|----------------------|------------------------|------------------------|---------|
| 25.6 ± 5.5                | 20.4 ± 3.3                     | 43.4 ± 7.8                | 115.8 ± 43.6              | 45.7 ± 4.6                    | 135.6 ± 34.3               | 75.9 ± 17.8                           | 163.6 ± 73.2 | 92.5 ± 41.2           | 64.6 ± 9.5            | 3.3 ± 1.0              | 0.640   |
| 23.2 ± 4.3                | 23.0 ± 3.6                     | 42.5 ± 6.7                | 122.2 ± 42.3              | 45.4 ± 6.1                    | 137.3 ± 27.5               | 75.1 ± 15.0                           | 153.7 ± 53.2 | 85.1 ± 30.7           | 65.3 ± 8.0             | 3.3 ± 0.8             | 0.001   |
| 0.035                     | 0.001                          | 0.582                      | 0.497                     | 0.819                         | 0.803                       | 0.825                                 | 0.492        | 0.372                | 0.709                 | 0.862                 |
RESULTS

Clinical and echocardiographic characteristics of the study population are presented in Table 1. There were 88 patients with OHCM and 32 control subjects. The mean age of OHCM patients was 48.8 ± 13.1 years, and 57 (65%) of them were male. Plasma apelin levels were significantly lower in patients with OHCM than those in control subjects (96.6 ± 34.3 vs. 169.4 ± 62.5 µg/L, \( p < 0.001 \); Figure 1). Twenty-three (24%) of patients with OHCM had hypertension and 7 (8%) had diabetes. There were 88 patients with OHCM and 32 control subjects. The mean age of OHCM patients was 48.8 ± 13.1 years, and 57 (65%) of them were male. Plasma apelin levels were significantly lower in patients with OHCM than those in control subjects (96.6 ± 34.3 vs. 169.4 ± 62.5 µg/L, \( p < 0.001 \); Figure 1). Twenty-three (24%) of patients with OHCM had hypertension and 7 (8%) had diabetes.

Echocardiographic data showed that patients had significantly greater septal wall thickness (22.7 ± 5.2 vs. 8.6 ± 0.9 mm, \( p < 0.001 \)). The LVOT gradient at rest was 78.5 ± 39.1 mmHg. These data indicated the patients suffered from severe left ventricular hypertrophy and LVOT obstruction, whereas control subjects did not have cardiac abnormity.

Table 2 shows characteristics of patients with OHCM according to plasma apelin levels stratified by mean value.

| TABLE 3 | Correlation between clinical characteristics and plasma apelin levels of patients with obstructive hypertrophic cardiomyopathy. |
| Variable | Correlation coefficient (\( r \)) | \( P \)-value |
|----------------|-----------------|----------|
| Septal wall thickness (mm) | −0.334 | 0.002 |
| RV end-diastolic diameter (mm) | 0.368 | <0.001 |
| BMI (kg/m\(^2\)) | 0.287 | 0.008 |
| Ln (NT-proBNP) | −0.307 | 0.008 |

Abbreviations as in Tables 1, 2.

Patients with lower apelin levels (plasma apelin ≤ 96.6 µg/L) had greater septal wall thickness than those with higher apelin levels (plasma apelin > 96.6 µg/L; 25.6 ± 5.5 vs. 23.2 ± 4.3 mm, \( p = 0.035 \)). In contrast, the right ventricular end-diastolic diameter was greater in patients with higher apelin levels (23.0 ± 3.6 vs. 20.4 ± 3.3 mm, \( p = 0.001 \)). Besides, there were marginally more patients suffering from heart failure of NYHA functional class III or IV in lower apelin group (33 vs. 15%, \( p = 0.053 \)). Interestingly, the apelin levels of patients with higher apelin were still lower than those of control subjects (125.4 ± 20.4 vs. 169.4 ± 62.5 µg/L, \( p < 0.001 \); Supplementary Figure 1).

The plasma apelin levels with respect to presence or not of clinical characteristics in the patients with OHCM were depicted in Supplementary Table 1. There were no significant differences in the plasma apelin levels between OHCM patients with hypertension, diabetes mellitus, hyperlipidemia, and patients without these cardiovascular risk factors.

The correlations between clinical characteristics and apelin levels in the patients with OHCM are shown in Table 3. Plasma apelin levels were inversely correlated with septal wall thickness (SWT; \( r = −0.334, p = 0.002 \); Figure 2A) and Ln (NT-proBNP) \( (r = −0.307, p = 0.008) \). In contrast, plasma apelin levels were positively correlated with right ventricular end-diastolic diameter (RVEDD; \( r = 0.368, p < 0.001 \); Figure 2B) and body mass index (BMI; \( r = 0.287, p = 0.008 \)). In multiple linear regression analysis, SWT was independently associated with decreasing apelin values, whereas RVEDD was independently associated with increasing apelin values (Table 4).

DISCUSSION

Although recent studies have unraveled that apelin may have multiple protective effects against development of several cardiovascular diseases (4, 11), there are few data on the plasma apelin levels in patients with OHCM or potential relations between apelin levels and clinical variables that reflect severity
of the disease. For the first time, the present study revealed that plasma apelin levels were decreased in patients with OHCM. Furthermore, the septal wall thickness (SWT) was independently and inversely associated with plasma apelin levels, while the right ventricular end-diastolic diameter (RVEDD) was positively associated with plasma apelin levels.

HCM, particularly OHCM, is the most common inherited cardiomyopathy and the most common cause of sudden death in young people. So far, it is not difficult to diagnose OHCM in patients with obvious clinical symptoms using echocardiography and cardiac magnetic resonance imaging. Previous studies showed that existing biomarkers of cardiovascular diseases, such as cardiac troponin and N-terminal proB-type natriuretic peptide (NT-proBNP), could be employed to assess the severity of OHCM in terms of myocardial damage and heart failure (12). With regard to medical treatment, beta-blockers and non-dihydropyridine calcium channel blockers have long been “first line” pharmacotherapy in OHCM (13). Recently, mavacamten, a myosin adenosine triphosphatase (ATPase) inhibitor, markedly reduced post-exercise LVOT gradient and gave rise to symptoms improvement in patients with OHCM (14). However, mavacamten also showed several adverse effects. For instance, it led to too much decrease of LVEF and stress cardiomyopathy in some patients within 30 weeks (14). There might be more patients suffering dramatic LVEF reduction and stress cardiomyopathy if mavacamten is taken for a long time in a large population. Hence, there is still a great need to comprehensively identify the mechanism of OHCM so that optimal therapeutic measures may be found.

Since its discovery in 1998, apelin has attracted intense interest (15). Apelin is highly expressed in the heart and plays an important role in the regulation of cardiovascular functions, including inotropic, vasodilator, and diuretic (5). It has been reported that plasma apelin levels are decreased in several cardiovascular diseases. Our previous work revealed that plasma apelin concentration was reduced following acute coronary syndrome (ACS) and remained low to 6 months (16). This reduction of apelin may be in part due to elevated filling pressure in the LV after ACS (16, 17). Chong et al. investigated 202 patients with chronic heart failure secondary to LV systolic dysfunction and 22 control subjects, and observed that plasma apelin concentrations were decreased in patients (18). Furthermore, Chandrasekaran et al. reported similar observations and they found decrease of plasma apelin was owing to a reduction of myocardial apelin production (19). Considering the positive inotropic and vasodilative effects of apelin, the down-regulation may be an upstream event of heart failure. A variety of hypotheses have been proposed to explain why apelin levels are reduced in heart failure. The major mechanism may be that apelin is down-regulated by excessively activated renin–angiotensin system (11). Our data showed that plasma apelin levels were significantly decreased in patients with OHCM compared with control subjects. The mechanism that leads to reduction of apelin in patients with OHCM may be similar to that in heart failure with reduced LVEF, or due to its unique pathological changes of myocardium. Based on cardio-protective actions of apelin, potential benefits of apelin in treating acute heart failure have been assessed. Evidence from animal study indicated that exogenous administration of apelin improved LV systolic function in dogs with advanced heart failure (20). Additionally, Japp et al. performed a study in 18 patients with heart failure and 26 control subjects, and found that acute apelin administration in humans causes peripheral and coronary vasodilatation and increases cardiac output (21).

Several studies have suggested that apelin is involved in myocardial hypertrophy (1). Szokodi et al. reported that apelin gene expression was markedly down-regulated in cultured neonatal rat ventricular myocytes subjected to mechanical stretch and in vivo in two models of ventricular hypertrophy (17). Furthermore, apelin was found to ameliorate high fat diet-induced cardiac hypertrophy (22). In addition, our previous data showed that apelin could inhibit myocardial hypertrophy induced by angiotensin II in neonatal rat ventricular cardiomyocyte (7). Another study performed in 232 hypertensive patients without concomitant diseases affecting cardiovascular functions indicated that plasma apelin levels in hypertensive patients were significantly lower than those in controls (23).
And previous studies surmised that atrium produces most of apelin in the heart (4, 11). In the present study, we found that plasma apelin levels were inversely associated with septal wall thickness (SWT) in patients with OHCM. By contrast, the LV mass was not independently associated with apelin levels. Therefore, our novel findings indicated that septal wall, rather than other segments of LV, is a determinant of plasma apelin in patients with OHCM. A study with human plasma and heart tissues by Foldes et al. raised the possibility that apelin may be produced predominantly in the atria (24). However, Foldes et al. determined apelin-36 levels, while our kit can detect all active forms of apelin, including apelin-36, apelin-31, apelin-28, and apelin 13. Apelin fragments other than apelin-36 might be produced predominantly in the septal wall. The pathological septal hypertrophy might retard apelin expression, or otherwise, reduction of apelin promotes pathogenesis of septal hypertrophy in OHCM. Further experiment is necessary to elucidate how apelin is reduced in OHCM.

Hitherto, there were scarce data regarding the role of apelin in right ventricle (RV). In a recent study concerning right ventricular function in pulmonary hypertension, Frump et al. demonstrated that apelin are also expressed in RV (25). Apelin was decreased in RV failure but not in adaptive RV remodeling, indicating protective effects of apelin against RV failure development (25). In the current study, we observed that plasma apelin was positively associated with right ventricular end-diastolic diameter (RVEDD) in patients with OHCM. Given that the OHCM patients in our study did not have RV failure, the change of apelin in relation to RVEDD may be an adaptive regulation to improve RV function. Thus, our data also suggested beneficial effects of apelin in RV. Further work is necessary to investigate the role of apelin in structural and functional remodeling of RV.

This study has some limitations that warrant discussion. First, lower plasma apelin levels in patients with OHCM compared with those in control subjects may be confounded by hypertension or diabetes, which were only in patients group. However, further analysis showed that the presence of hypertension and diabetes or not did not affect apelin levels in patients with OHCM. Second, the study population all had left ventricular outflow tract (LVOT) obstruction. Therefore, the findings of this study do not apply to patients without LVOT obstruction. Additionally, this is a cross-sectional study, which renders conclusions about the causality of demonstrated relations impossible.

CONCLUSION
Plasma apelin levels are reduced in patients with OHCM. The apelin levels are inversely related to SWT and positively related to RVEDD.

DATA AVAILABILITY STATEMENT
The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT
The studies involving human participants were reviewed and approved by the Ethics Committee of Fuwai Hospital (Beijing, China). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS
ZJ, JY, and SQ contributed to the conception and design. CY, CZ, and RJ contributed to the manuscript writing. CY, CZ, JY, and SQ contributed to the provision of study materials or participants, collection, and assembly of data. All authors contributed to the data analysis and interpretation, and approval of final version of the manuscript.

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SUPPLEMENTARY MATERIAL
The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.904892/full#supplementary-material

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