Cardiovascular Topics

Correlation between maternally expressed gene 3 expression and heart rate variability in heart failure patients with ventricular arrhythmia

Ling Lin, Mei Hou, Ailing Yang, Yunfei Li, Rong Su, Li Li, Siyun Wu, Mingguo Zhang

Abstract

Aim: The aim of the study was to analyse the correlation between maternally expressed gene 3 (MEG3) expression and heart rate variability (HRV) in heart failure patients with ventricular arrhythmia (VA).

Methods: A total of 130 heart failure patients, treated from July 2018 to March 2021, were prospectively selected and divided into a non-VA group (n = 85) and a VA group (n = 45) according to the presence or absence of VA. The correlations of serum MEG3 expression and HRV with cardiac function indicators were investigated by Pearson correlation analysis. Receiver operating characteristic (ROC) curves were plotted to assess the predictive value of MEG3, HRV and their combination for the occurrence of heart failure complicated with VA.

Results: The VA group had a higher left atrial diameter (LAD) and left ventricular end-diastolic diameter (LVEDD) but lower left ventricular ejection fraction (LVEF) and ratio of mitral early diastolic peak velocity (E) to late peak atrial filling velocity (A) (E/A) than the non-VA group ($p < 0.05$). The serum MEG3 expression was negatively correlated with: standard deviation of the average RR intervals calculated over five-minute segments in the 24-hour record (SDANN), SDANN index, standard deviation of normal-to-normal RR interval (SDNN) index, percentage of differences between adjacent normal RR intervals exceeding 50 ms (PNN50), root mean square of successive difference (RMSSD), low frequency (LF), high frequency (HF), very low frequency (VLF), LVEF and E/A ($r < 0$, $p < 0.05$). The serum MEG3 expression was positively correlated with LAD and LVEDD ($r > 0$, $p < 0.05$). The areas under the ROC curves of MEG3, SDANN, SDANN index, SDNN index, PNN50, RMSSD, LF, HF, VLF and their combination for the prediction of the occurrence of heart failure complicated with VA were 0.812, 0.731, 0.737, 0.689, 0.860, 0.783, 0.791, 0.856, 0.769 and 0.966, respectively.

Conclusion: MEG3 combined with HRV can effectively predict the occurrence of heart failure complicated with VA.

The First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan Province, China

Ling Lin, PhD, linlingfahkmu@wl-asia.com
Mei Hou, MD
Ailing Yang, MD
Yunfei Li, MD
Rong Su, MD
Li Li, MD
Siyun Wu, MD
Mingguo Zhang, MD

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Heart failure is a cardiocirculatory disorder resulting from insufficient blood supply from the heart, which is the end stage of a variety of cardiovascular diseases.[1,2] Due to haemodynamic changes, pathological remodelling, neuroendocrine activation and electrolyte disturbance occur in the myocardial cells in the non-infarction zone following heart failure, which will develop into arrhythmia and pump failure if not treated promptly.[3]

Sudden deaths after five years of heart failure account for 30–50% of the total heart failure deaths, more than 80% of which are sudden cardiac death due to malignant ventricular arrhythmia (VA).[4] VA has a higher incidence rate, and its repeated attacks can further worsen the cardiac function, and raise the risk of sudden cardiac death.[5,6] Therefore, early detection and treatment of VA are of great significance for preventing sudden cardiac death and improving the prognosis of heart failure patients.

Heart rate variability (HRV), which refers to the variation in time between each heartbeat, is often used to measure the function and balance of the autonomic nerve. It can also reflect the severity and type of arrhythmia.[7] The heart is governed by autonomic nerves, and decreased HRV indicates enhanced sympathetic nerve function, decreased vagal activity and threshold of ventricular fibrillation, and myocardial electrical instability.[8]

Maternally expressed gene 3 (MEG3), a long, non-coding RNA (lncRNA), can be involved in the occurrence of cardiovascular diseases through regulating smooth muscle migration, angiogenesis, ventricular remodelling and apoptosis.[9] MEG3 is related to myocardial infarction, and down-regulating its expression can alleviate myocardial hypertrophy and myocardial damage in a rat model of myocardial infarction.[10] However, whether MEG3 expression is related to heart failure complicated with VA remains unclear.

In this study, therefore, the association between MEG3 expression and HRV in heart failure patients with VA was analysed, aiming to provide references for disease assessment and prognostic prediction.

Methods

The sample size was calculated according to the equation in the 8th edition of *Epidemiology*:[11]

$$n = \frac{z^2 \times pq}{d^2},$$

where n is the sample size, p is the expected prevalence rate, q = 1–p, d is the allowable error, and a is the significance level.

The incidence rate of VA in China is approximately 30%. Therefore, the rate was set at 35%, a = 0.05 and d = 0.1 × q, yielding a sample size of 108. Finally, the sample size was set at 130, considering the rate of loss to follow up (20%).

A total of 130 heart failure patients treated in our hospital from July 2018 to March 2021 were prospectively selected and divided into a non-VA group (n = 85) and a VA group (n = 45) according to the presence or absence of VA. This study was approved by the Hospital Medical Ethics Committee.

Inclusion criteria were as follows: (1) patients who met the diagnostic criteria for heart failure[12] and VA,[13] (2) those who voluntarily signed the informed consent form, (3) those who were ranked in class II, III and IV based on the New York Heart Association (NYHA) cardiac function classification, and (4) those with normal coagulation function.

Exclusion criteria were as follows: (1) patients complicated with atrial flutter, atrial fibrillation, sick sinus syndrome, supraventricular tachycardia or other ectopic cardiac rhythms, (2) those with atrioventricular block of degree II or above, (3) those complicated with autonomic nerve disorders such as hypertension, menopausal syndrome or hyperthyroidism, (4) those who had undergone percutaneous coronary intervention or coronary artery bypass grafting, (5) those who used diazepam, propranolol, amiodarone or other drugs that affected the autonomic nerve function within one week before enrollment, (6) pregnant or lactating women, or (7) those with a duration of dynamic ECG recording of less than 22 hours.

For detection of serum MEG3 expression, fasting peripheral venous blood (4 ml) was drawn from each patient with heart failure, left standing for 30 minutes and centrifuged for 10 minutes (2 500 rpm, 6 cm in radius) to separate the serum. Then the serum sample was dispensed, numbered and stored in a refrigerator at –80°C for later testing.

Total RNA was extracted by TRIzol and reversely transcribed into cDNA using a reverse transcription kit (Nanjing Vazyme Biotechnology Co, Ltd, China). With the resulting cDNA as a template, polymerase chain reaction (PCR) amplification was performed using the Prism 7000 quantitative PCR system (Thermo Fisher Scientific, USA) and a 15-µl PCR system.

The relative expression of MEG3 was detected by $2^{-\Delta\Delta Ct}$, with β-actin as an internal reference. The primer sequences used were as follows: MEG3 F: 5'-CTGCCCATCTACACCTCACG-3′, R: 5′-CTTCTCCGCCGTCTGCGCTAGGGGCT-3′. β-actin F: 5′-CTCCATCCTGGCCTCCCTGT-3′, R: 5′-GCTGTCACCTTCACCGTTCC-3′.

For measurement of HRV, the time-domain indicators and frequency-domain indicators of HRV were recorded using a Qx-2000 dynamic ECG analyser and Marquette 12-lead synchronous ECG recorder (GE, USA), and the data were analysed and corrected by professional analysts. The time-domain indicators included standard deviation of the average RR intervals calculated over five-minute segments in the 24-hour record (SDANN), standard deviation of normal-to-normal RR interval (SDNN) index, SDANN index, root mean square of successive difference (RMSSD), and percentage of differences between adjacent normal RR intervals exceeding 50 ms (PNN50). The frequency-domain indicators included low frequency (LF), high frequency (HF) and very low frequency (VLF).

The cardiac function, including left atrial diameter (LAD), left ventricular end-diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF) and ratio of mitral early diastolic peak velocity (E) to late peak atrial filling velocity (A) (E/A) were detected using an iE33 full-digital colour cardiac ultrasound diagnostic machine equipped with an X3-1 array real-time three-dimensional (3D) cardiac ultrasound transducer (frequency: 1.9–3.8 MHz), TomTec ultrasound image processing workstation and 4D right ventricular function software (Philips, USA).

Statistical analysis

The SPSS 25.0 software package (IBM Inc, USA) was used for statistical analysis. Normally distributed data are described as mean ± standard deviation and were compared between two groups by the independent-samples t-test. Count data are expressed as percentage and were compared between two groups by the chi-squared test. Pearson's correlation analysis was performed. The predictive values were assessed using receiver operating characteristic (ROC) curves. A p-value < 0.05 was considered statistically significant.

Table 2. Time-domain indicators of HRV (mean ± SD)

Group	n	*SDANN (ms)*	*SDANN index (ms)*	*SDNN index (ms)*	*PNN50 (%)*	*RMSSD (ms)*
Non-VA	85	75.30 ± 3.55	74.27 ± 4.02	36.34 ± 2.59	17.56 ± 1.73	18.18 ± 1.82
VA	45	71.89 ± 3.51	70.52 ± 3.37	34.41 ± 2.86	14.25 ± 2.39	16.06 ± 1.58
t		5.219	5.206	3.898	9.032	6.578
p		0.000	0.000	0.000	0.000	0.000

HRV: Heart rate variability; PNN50: percentage of differences between adjacent normal RR intervals exceeding 50 ms; RMSSD: root mean square of successive difference; SDANN: standard deviation of the average RR intervals calculated over five-minute segments in the 24-hour record; SDNN: standard deviation of normal-to-normal RR intervals; VA: ventricular arrhythmia.

Table 1. Clinical data and serum MEG3 expression in the two groups (n, mean ± SD)

Group	n	*Male/female*	*Mean age (years)*	*Age distribution (n) Young/middle-aged/elderly*	*Duration of heart failure (months)*	*Body mass index (kg/m²)*	*Cardiac function II/III–IV*	*MEG3*
Non-VA	85	46/39	56.84 ± 5.28	19/40/26	31.05 ± 5.62	23.46 ± 2.15	48/37	1.04 ± 0.12
VA	45	24/21	57.16 ± 4.96	10/23/12	30.95 ± 4.85	23.96 ± 2.08	25/20	1.27 ± 0.21
χ^2/t		0.007	0.336	0.300	0.101	1.276	0.010	7.845
p		0.932	0.738	0.764	0.920	0.204	0.920	0.000

MEG3: maternally expressed gene 3; VA: ventricular arrhythmia.

Results

Out of 130 heart failure patients involved in the study, there were 70 males and 60 females. Among them, 29 cases were in the age range of 32–44 years (young), 63 cases were in the range of 45–64 years (middle-aged) and 38 cases were in the range of 65–77 (elderly). The mean body mass index was 23.58 (19.5–26.8) kg/m^2. The young patients had 15 cases in NYHA class II and 14 cases in class III–IV. The middle-aged patients had 36 cases in NYHA class II and 27 cases in class III–IV. The elderly patients had 22 cases in NYHA class II and 16 cases in class III–IV.

The young patients had a mean heart failure duration of 29 months (three to 73 months). The middle-aged patients had a mean heart failure duration of 32 months (five to 75 months). The elderly patients had a mean heart failure duration of 33 months (three to 80 months). No statistically significant differences were found in gender, age, duration of heart failure, body mass index and classification of cardiac function between the non-VA and VA groups or between different age groups ($p > 0.05$). The serum MEG3 expression was significantly higher in the VA group than that in the non-VA group ($p < 0.05$) (Table 1).

The time-domain indicators SDANN, SDANN index, SDNN index, PNN50 and RMSSD in the VA group were lower than those in the non-VA group ($p < 0.05$) (Table 2). For the frequency-domain indicators of HRV, the VA group had a lower LF, HF and VLF than the non-VA group ($p < 0.05$) (Table 3).

For cardiac function indicators, the VA group had a higher LAD and LVEDD but lower LVEF and E/A than the non-VA group ($p < 0.05$) (Table 4). The serum MEG3 expression was negatively correlated with SDANN, SDANN index, SDNN index, PNN50, RMSSD, LF, HF, VLF, LVEF and E/A ($r < 0$, $p < 0.05$), and positively correlated with LAD and LVEDD ($r > 0$, $p < 0.05$) (Table 5, Fig. 1).

Table 3. Frequency-domain indicators of HRV (mean ± SD, m^2/Hz)

Group	n	*LF*	*HF*	*VLF*
Non-VA	85	10.33 ± 1.61	9.29 ± 1.19	18.97 ± 2.82
VA	45	8.65 ± 1.58	7.53 ± 0.95	16.18 ± 2.00
t		6.393	8.556	5.888
p		0.000	0.000	0.000

HF: high frequency; HRV: heart rate variability; LF: low frequency; VA: ventricular arrhythmia; VLF: very low frequency.

Table 4. Cardiac function indicators (mean ± SD)

Group	n	*LAD (mm)*	*LVEDD (mm)*	*LVEF (%)*	*E/A*
Non-VA	85	35.29 ± 2.62	46.33 ± 2.20	67.61 ± 8.29	0.76 ± 0.22
VA	45	38.44 ± 3.85	50.21 ± 5.60	61.74 ± 6.91	0.58 ± 0.17
t		5.516	5.636	4.062	4.925
p		0.000	0.000	0.000	0.000

E/A: Ratio of mitral early diastolic peak velocity to late peak atrial filling velocity; LAD: left atrial diameter; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; VA: ventricular arrhythmia.

Table 5. Results of correlation analysis between MEG3 and HRV and cardiac function [*r* (*p*)]

Index	*MEG3*	*LAD*	*LVEDD*	*LVEF*	*E/A*
MEG3	–	0.173 (0.025)	0.402 (0.000)	–0.156 (0.043)	–0.189 (0.016)
SDANN	–0.281 (0.001)	–0.151 (0.045)	–0.174 (0.025)	0.263 (0.001)	0.151 (0.043)
SDANN index	–0.220 (0.012)	–0.156 (0.038)	–0.183 (0.019)	0.174 (0.025)	0.144 (0.044)
SDNN index	–0.241 (0.006)	–0.149 (0.047)	–0.171 (0.026)	0.226 (0.005)	0.312 (0.000)
PNN50	–0.452 (0.000)	–0.250 (0.002)	–0.219 (0.006)	0.157 (0.042)	0.154 (0.041)
RMSSD	–0.332 (0.000)	–0.235 (0.004)	–0.246 (0.002)	0.215 (0.007)	0.210 (0.008)
LF	–0.386 (0.000)	–0.273 (0.001)	–0.332 (0.000)	0.149 (0.045)	0.178 (0.021)
HF	–0.261 (0.003)	–0.334 (0.000)	–0.242 (0.003)	0.250 (0.002)	0.303 (0.000)
VLF	–0.250 (0.004)	–0.163 (0.031)	–0.164 (0.031)	0.221 (0.006)	0.241 (0.003)

E/A: Ratio of mitral early diastolic peak velocity to late peak atrial filling velocity; HF: high frequency; HRV: heart rate variability; LAD: left atrial diameter; LF: low frequency; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; MEG3: maternally expressed gene 3; PNN50: percentage of differences between adjacent normal RR intervals exceeding 50 ms; RMSSD: root mean square of successive difference; SDANN: standard deviation of the average RR intervals calculated over 5-minute segments in the 24-hour record; SDNN: standard deviation of normal-to-normal RR intervals; VLF: very low frequency.

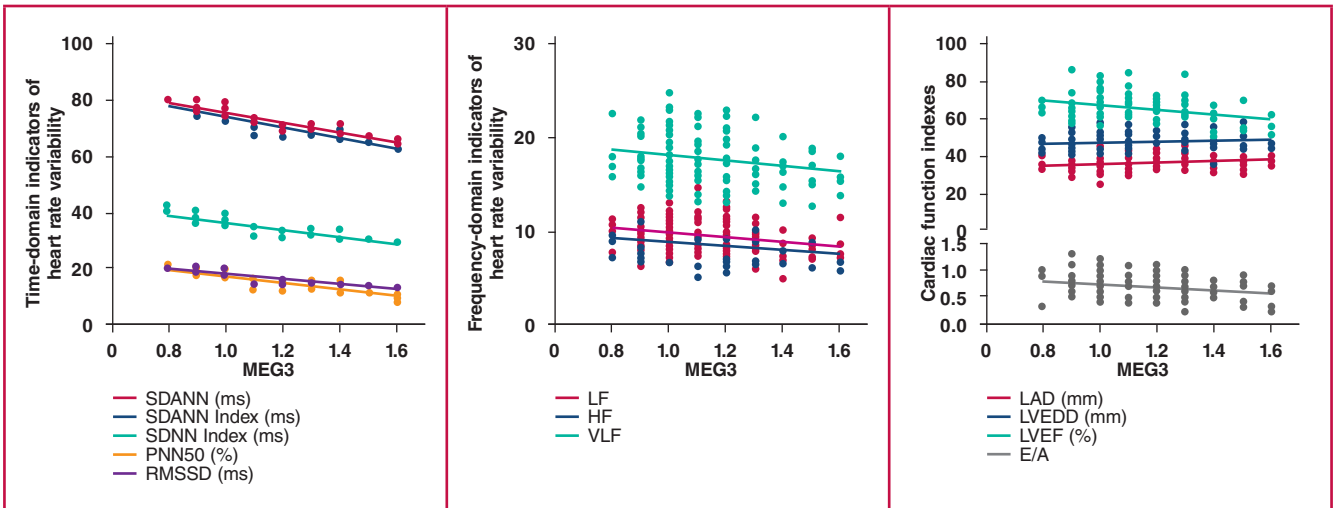

Fig. 1. Results of correlation analysis between MEG3 and other indicators. MEG3: maternally expressed gene 3.

Table 6. Predictive values of MEG3, HRV and their combination for occurrence of heart failure complicated with VA

Indicator	Cut-off point	Standard error	p	Area under the curve	95% CI Lower limit	95% CI Upper limit
MEG3	1.146	0.043	0.000	0.812	0.727	0.897
SDANN (ms)	73.526	0.044	0.000	0.731	0.645	0.817
SDANN index (ms)	73.415	0.043	0.000	0.737	0.652	0.822
SDNN index (ms)	35.428	0.049	0.000	0.689	0.593	0.786
PNN50 (%)	15.953	0.038	0.000	0.860	0.785	0.935
RMSSD (ms)	17.152	0.040	0.000	0.783	0.704	0.862
LF (m^2/Hz)	9.623	0.038	0.000	0.791	0.716	0.866
HF (m^2/Hz)	8.152	0.032	0.000	0.856	0.793	0.919
VLF (m^2/Hz)	17.562	0.040	0.000	0.769	0.690	0.849
Combination	–	0.014	0.000	0.966	0.939	0.993

HF: High frequency; HRV: heart rate variability; LF: low frequency; MEG3: maternally expressed gene 3; PNN50: percentage of differences between adjacent normal RR intervals exceeding 50 ms; RMSSD: root mean square of successive difference; SDANN: standard deviation of the average RR intervals calculated over 5-minute segments in the 24-hour record; SDNN: standard deviation of normal-to-normal RR intervals; VA: ventricular arrhythmia; VLF: very low frequency.

With the presence or absence of VA in heart failure as an independent variable (no = 0, yes = 1), and MEG3 and HRV indicators as dependent variables, the ROC curve was plotted. The results showed that the areas under the ROC curves (AUC) of MEG3, SDANN, SDANN index, SDNN index, PNN50, RMSSD, LF, HF, VLF and their combination for the prediction of the occurrence of heart failure complicated with VA were 0.812, 0.731, 0.737, 0.689, 0.860, 0.783, 0.791, 0.856, 0.769 and 0.966, respectively (Table 6, Figs 2, 3).

Discussion

Berier *et al.*[14] found that the mortality rate of hospitalised patients with heart failure was linearly related to HRV, and high HRV would increase the risk of death. Xie *et al.*[15] reported that HRV could be used to effectively determine whether obstructive sleep apnoea syndrome was accompanied by arrhythmia, which had a close correlation with the level of inflammatory factors and polysomnography parameters in patients. However, the association between HRV and heart failure with VA has been rarely reported in China and foreign countries.

In this study, the SDANN, SDANN index, SDNN index, PNN50, RMSSD, LF, HF and VLF in VA group were all lower than those in the non-VA group, suggesting that the heart failure patients with VA had decreased HRV, significant impairment of the vagus nerve and increased tension of the sympathetic nerve.

The possible reasons are as follows. (1) Following VA, intracellular oxidative stress can be activated, leading to long-term chronic inflammation in the myocardial cells, resulting in cardiac structural changes and ventricular remodelling, and weakening the cardiac diastolic and systolic function.[16] (2) As VA occurs, a large number of inflammatory cells and inflammatory factors will be released, thereby activating the renin–angiotensin–aldosterone system and reducing HRV. (3) VA can reduce the cardiac output and ejection fraction, so a series of feedbacks such as compensatory activation of the cardiac sympathetic nervous system will be generated to increase cardiac output and maintain normal demand.[17,18] Vagus nerve stimulation can lead to decreased myocardial contractility, myocardial conduction velocity and heart rate, thus reducing the threshold of ventricular fibrillation and HRV.

Located on chromosome 14q32, MEG3 is a tumour suppressor in normal human tissues, which not only regulates malignant behaviour of tumour cells, such as invasion, migration and proliferation, but also contributes to cardiac fibrosis and induces myocardial damage, thereby mediating cardiac remodelling and apoptosis.[19] Wei *et al.*[20] found that the plasma MEG3 level rose in patients with acute myocardial infarction, and its specificity and sensitivity were 81.58 and 85.29%, respectively, in predicting the occurrence of acute myocardial infarction.

In an animal experiment, Zhou *et al.*[21] reported that MEG3 knockout could relieve hypoxia-induced myocardial damage through regulating the expression of miR-325-3p. Piccoli *et al.*[22]

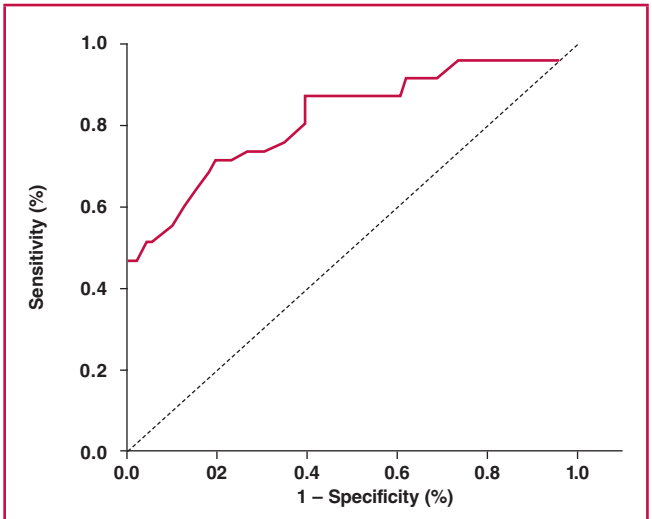

Fig. 2. ROC curve of MEG3 for predicting the occurrence of heart failure complicated with VA. MEG3: maternally expressed gene 3; ROC: receiver operator characteristic; VA: ventricular arrhythmia.

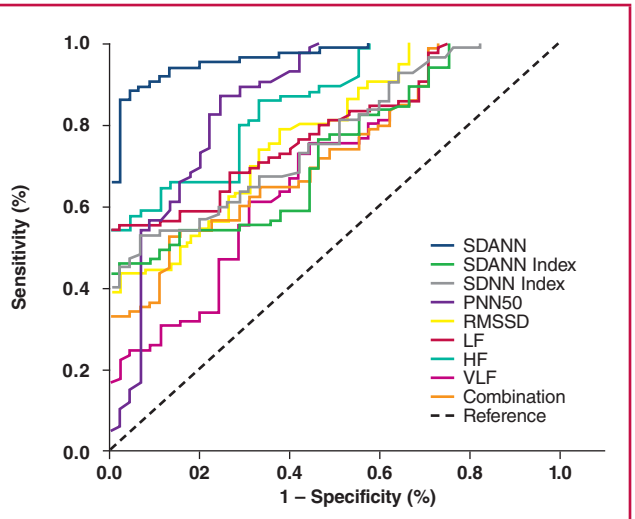

Fig. 3. ROC curve of HRV and combination for predicting the occurrence of heart failure complicated with VA. HRV: heart rate variability; ROC: receiver operator characteristic; VA: ventricular arrhythmia.

found in a cardiac remodelling experiment that inhibiting the MEG3 expression could block the induction of cardiac MMP-2 and down-regulate the TGF-β expression, thereby reducing cardiac fibrosis.

In our study, it was found that serum MEG3 expression was significantly higher in the VA group than in the non-VA group, and it was negatively correlated with time-domain and frequency-domain indicators of HRV, LVEF and E/A but positively correlated with LAD and LVEDD. It can be seen that MEG3 was associated with heart failure complicated with VA, and closely related to HRV and cardiac function of patients. The possible reason is that MEG3 is able to promote cardiac fibrosis and induce myocardial damage, and it is also implicated in cardiac remodelling.

Besides, the results of ROC curve analysis revealed that the AUC of the combination of MEG3, SDANN, SDANN index, SDNN index, PNN50, RMSSD, LF, HF and VLF was 0.966 in the prediction of the occurrence of heart failure complicated with VA, larger than that of any indicator alone. This demonstrates that MEG3 and HRV in heart failure patients should be closely monitored in the clinic, and we should be highly vigilant about increased MEG3 levels and decreased HRV in patients, and take targeted measures to prevent the occurrence of VA.

Furthermore, the mean age or age distribution of the non-VA and VA groups were not significantly different, so we postulated that age was not a risk factor for heart failure complicated with VA. Shade *et al*. generated a patient-specific computational heart model and found that QRS duration and age were not risk factors for postoperative VA.[23]

Conclusion

Our heart failure patients with VA had a significantly higher MEG3 expression and a lower HRV. MEG3 expression is closely associated with HRV and cardiac function. Furthermore, MEG3 combined with HRV can effectively predict the occurrence of heart failure complicated with VA.

References

1. Bozkurt B, Fonarow GC, Goldberg LR, *et al*. Cardiac rehabilitation for patients with heart failure: JACC Expert Panel. *J Am Coll Cardiol* 2021; **77**(11): 1454–1469.
2. Kamiya K, Sato Y, Takahashi T, *et al.* Multidisciplinary cardiac rehabilitation and long-term prognosis in patients with heart failure. *Circ Heart Fail* 2020; **13**(10): e006798.
3. Zhang D, Tu H, Wadman MC, *et al*. Substrates and potential therapeutics of ventricular arrhythmias in heart failure. *Eur J Pharmacol* 2018; **833**: 349–356.
4. Bjarnason-Wehrens B, Nebel R, Jensen K, *et al*. Exercise-based cardiac rehabilitation in patients with reduced left ventricular ejection fraction: The Cardiac Rehabilitation Outcome Study in Heart Failure (CROS-HF): A systematic review and meta-analysis. *Eur J Prev Cardiol* 2020; **27**(9): 929–952.
5. Santangeli P, Rame JE, Birati EY, *et al*. Management of ventricular arrhythmias in patients with advanced heart failure. *J Am Coll Cardiol* 2017; **69**(14): 1842–1860.
6. Nikoo MH, Naeemi R, Moaref A, *et al*. Global longitudinal strain for prediction of ventricular arrhythmia in patients with heart failure. *ESC Heart Fail* 2020; **7**(5): 2956–2961.
7. Koshy A, Okwose NC, Nunan D, *et al.* Association between heart rate variability and haemodynamic response to exercise in chronic heart failure. *Scand Cardiovasc J* 2019; **53**(2): 77–82.
8. Shanks J, Abukar Y, Lever NA, *et al*. Reverse re-modelling chronic heart failure by reinstating heart rate variability. *Basic Res Cardiol* 2022; **117**(1): 4.
9. Al-Rugeebah A, Alanazi M, Parine NR. MEG3: an oncogenic long non-coding RNA in different cancers. *Pathol Oncol Res* 2019; **25**(3): 859–874.
10. Gong L, Xu H, Chang H, *et al*. Knockdown of long non-coding RNA MEG3 protects H9c2 cells from hypoxia-induced injury by targeting microRNA-183. *J Cell Biochem* 2018; **119**(2): 1429–1440.
11. Shen HB, Qi XY. *Epidemiology* (8th EdN). Beijing: People's Medical Publishing House, 2013: 84–85. https://item.jd.com/12146375.html.
12. Van der Meer P, Gaggin HK, Dec GW. ACC/AHA Versus ESC guidelines on heart failure: JACC guideline comparison. *J Am Coll Cardiol* 2019; **73**(21): 2756–2768.
13. Al-Khatib SM, Stevenson WG, Ackerman MJ, *et al*. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm* 2018; **15**(10): e73–e189.
14. Besnier F, Labrunée M, Richard L, *et al*. Short-term effects of a 3-week interval training program on heart rate variability in chronic heart failure. A randomised controlled trial. *Ann Phys Rehabil Med* 2019; **62**(5): 321–328.
15. Xie JY, Liu WX, Ji L, *et al*. Relationship between inflammatory factors and arrhythmia and heart rate variability in OSAS patients. *Eur Rev Med Pharmacol Sci* 2020; **24**(4): 2037–2053.
16. Silva LEV, Lataro RM, Castania JA, *et al*. Nonlinearities of heart rate variability in animal models of impaired cardiac control: contribution of different time scales. *J Appl Physiol* 2017; **123**(2): 344–351.
17. Ling N, Li CL, Wang ZZ, *et al*. Heart rate variability in children with myocarditis presenting with ventricular arrhythmias. *Eur Rev Med Pharmacol Sci* 2018; **22**(4): 1102–1105.
18. Maagaard M, Eckerström F, Hjortdal VE. Cardiac arrhythmias and impaired heart rate variability in older patients with ventricular septal defects. *J Am Heart Assoc* 2021; **10**(17): e020672.
19. Zhang J, Liang Y, Huang X, *et al*. STAT3-induced upregulation of lncRNA MEG3 regulates the growth of cardiac hypertrophy through miR-361-5p/HDAC9 axis. *Sci Rep* 2019; **9**(1): 460.
20. Wei Y, Wang B. The expression levels of plasma dimethylglycine (DMG), human maternally expressed gene 3 (MEG3), and apelin-12 in patients with acute myocardial infarction and their clinical significance. *Ann Palliat Med* 2021; **10**(2): 2175–2183.
21. Zhou Y, Li X, Zhao D, *et al.* Long non-coding RNA MEG3 knockdown alleviates hypoxia-induced injury in rat cardiomyocytes via the miR-325-3p/TRPV4 axis. *Mol Med Rep* 2021; **23**(1): 18.
22. Piccoli MT, Gupta SK, Viereck J, *et al*. Inhibition of the cardiac fibroblast-enriched lncRNA MEG3 prevents cardiac fibrosis and diastolic dysfunction. *Circ Res* 2017; **121**(5): 575–583.
23. Shade JK, Cartoski MJ, Nikolov P, *et al*. Ventricular arrhythmia risk prediction in repaired tetralogy of Fallot using personalized computational cardiac models. *Heart Rhythm* 2020; **17**(3): 408–414.