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Chapter

Chronic Fatigue Stress and Sudden Death

Haiyan Zhu, Guoxin Han and Shuoshuo Li

Abstract

Stress refers to a series of neuroendocrine reactions, such as sympathetic nerve excitation and pituitary-adrenal cortex secretion increase, which occur when the body is stimulated by various stressors, and the changes of various functions and metabolism caused by these reactions. Chronic fatigue stress is a fatigue state caused by long-term physical and psychological stress. When the stress reaches a certain intensity or the individual is not well-tolerated, the body stability is impaired, resulting in various pathophysiological reactions leading to various diseases, such as stress hyperglycemia, stress cardiomyopathy, stress arrhythmia, stress ulcer hemorrhagic shock, or even stress ulcer hemorrhagic shock. Eventually lead to sudden death and other adverse events.

Keywords: chronic fatigue stress, epidemiology, sudden death, acute coronary syndrome, arrhythmia

1. Introduction

With the development of today's society, people's pace of work and life is accelerating, resulting in increasing physical and mental stress on people, the main productive forces of society. Long-term physical fatigue and excessive mental load, as well as consequent adverse emotions such as depression and irritability, constitute the unfavorable stress state that is currently common among people. The sudden death of young people caused by chronic fatigue stress is not uncommon, especially in the first-tier cities of developed countries. The early death of these lives not only brought huge disasters to their families, but also caused serious negative impacts on social production. It has created a huge medical and social burden. Chronic fatigue stress and sudden cardiac death in people will be introduced in this passage.

2. Epidemiology

According to the latest research survey, 80% of white-collar workers in China are in the state of overfatigue at present. About 95.7% of young people have died of fatigue-related fatal diseases [1]. According to statistics, the annual incidence of sudden death in Western European and American countries is 0.1–0.2%. According to the epidemiological survey in China, the annual incidence of sudden death in China is 4184 cases per 100,000 people, which is about 0.04% of the general population. Although it is lower than that in European and American countries, because of the large population base in our country, according to the national population of

1.3 billion, nearly 544,000 people die suddenly every year, with an average of about 1500 people per day [2]. Due to the immature pre-hospital first aid transfer system in the past, the success rate of rescue for sudden death outside hospital is <1%. Therefore, the mechanism of sudden death induced by chronic fatigue stress needs to be studied urgently.

3. Acute coronary syndrome and sudden death

The causes of cardiopulmonary arrest are mainly divided into two aspects: primary cardiopulmonary arrest and secondary cardiopulmonary arrest. Eighty percentage of the primary causes are sudden cardiac death, and the leading cause is acute coronary syndrome. Other causes were dilated cardiomyopathy, genetic disorders of rhythm and various types of cardiomyopathy (such as stress cardiomyopathy). The main causes of secondary cardiopulmonary arrest are accidental casualties such as electric shock, drowning, severe trauma, poisoning, etc. Acute coronary syndrome (ACS) is a common and serious cardiovascular disease. It is common in postmenopausal women, men and the elderly. High risk factors include smoking, hypertension, diabetes, hyperlipidemia, obesity and family history of coronary heart disease. Acute coronary syndrome (ACS) patients are usually characterized by paroxysmal anterior pain, chest tightness, suffocation and other symptoms, which can lead to arrhythmia, even heart failure, and ultimately cardiopulmonary arrest. The main mechanism is that after the occurrence of ACS, myocardial activity is more unstable than before, and myocardial autonomy will increase, which will lead to arrhythmia in patients. Abnormal phenomenon, after myocardial ischemia and reperfusion, myocardium will appear abnormal sympathetic nerve regeneration problems, myocardial damage, myocardial hypoxia and ischemia problems, make electrolyte ions imbalance, lead to acidosis, affect ECG activity, arrhythmia, and eventually lead to sudden death [3].

3.1 Establishment of predictive and early warning model for acute coronary syndrome

Now that medical care has entered the era of big data, turning big data into scientific facts and knowledge is the future direction of medicine. The goal of big data analysis is to use data to generate predictions and make more reasonable plans and operational decisions. In this information age, research on big data support for acute coronary syndromes is still rare at home and abroad. Since there is no classification method to predict acute coronary syndrome, the two-category method is used to construct the predictive and early warning model of acute coronary syndrome. The aortic dissection is most easily misdiagnosed as acute chest syndrome with chest pain, so aortic dissection is chosen as a control group. This study systematically summarized the etiology, risk factors, risk stratification, treatment methods and prognosis of acute coronary syndrome in young people, and established a standardized early warning model to gain time for patients' rescue. A total of 58 variables were selected, 14 variables were deleted, and the missing values were >25%. The remaining variables are used to analyze the correlation between variables and ACS and AD, and the variables are filtered by feature selection before the model is built using machine learning algorithms. While maintaining the performance of the machine learning model, some of the most effective features were selected from the original data set to reduce the dimensions. Firstly, the indicators are normalized, and the recursive feature elimination method is adopted. The machine learning model method is used to select random

	Average error rate	Sensitivity	Specificity	Accuracy	AUC
Logistic	0.131	0.868(5.31e-04)	0.869(2.55e-03)	0.869(6.42e-04)	0.915(1.50e-04)
SVM	0.133	0.835(6.86e-03)	0.895(2.88e-03)	0.867(1.06e-03)	0.935(1.61e-04)
RF	0.093	0.913(3.60e-03)	0.902(7.66e-04)	0.907(1.36e-03)	0.964(5.94e-06)

Table 1.
Model evaluation indicators.

forests for feature selection. The results show that when the characteristic variable is 33, the prediction accuracy of the model is the highest. Among them, 13 variables are most closely related to AD and ACS, including plasma D-dimer, troponin T, creatine kinase, creatine kinase isoenzyme, aspartate aminotransferase, urea, platelet count, glucose, creatinine, serum albumin, total protein, direct bilirubin and sodium. The selection of these eigenvalues is based on their specific expression of different pathological processes for ACS and AD. The risk prediction model of young patients with acute chest pain was constructed by logistic regression, SVM method and random forest method. The model evaluation index was obtained by five-fold cross-validation. The prediction accuracy of the three classifiers was >85%. The risk prediction model constructed by the random forest algorithm is the most effective. Sensitivity, specificity and accuracy are all >90%. These results indicate that the random forest risk prediction model can distinguish between acute coronary syndrome and aortic dissection, and has a high recognition ability. According to the average accuracy rate and the average kappa value of the model evaluation index, the prediction model established by the random forest method has the best effect, and the accuracy rate reaches 90.17%. Therefore, the results of this study can achieve early, non-invasive, accurate and safe diagnosis and early warning of acute coronary syndrome. As a result of the updated criteria for assessing coronary stenosis, such as the non-invasive coronary angiography-based blood flow reserve fraction (FFRCT) assessment method, it is becoming a new non-invasive standard to evaluate the functional significance of coronary artery disease and determine whether the lesion leads to myocardial ischemia. We will introduce this method in the next study, comprehensively evaluate the correlation between stress indicators and non-invasive detection, and further evaluate the clinical value of GDF-15, catecholamine and HSP-70 (**Table 1**).

4. Stress and sudden death

Acute coronary syndrome (ACS) is a process of ischemic events caused by the formation of unstable plaques in the coronary artery. After the formation of atherosclerotic plaques, acute stress, such as fatigue, emotional excitement and infection, excites the sympathetic nervous system, promotes the release of inflammatory factors such as norepinephrine, adrenaline and dopamine, and acts on B receptor and a receptor in the body. The body, dopamine receptor, causes a series of reactions such as systolic peripheral blood vessels and visceral blood vessels of the body, leading to increased blood pressure, which causes unstable atherosclerotic plaques to become more vulnerable to rupture, forming coronary artery thrombosis, leading to severe reduction of distal blood supply to myocardial tissue, thus causing a series of clinical manifestations, including ventricular arrhythmia, cardiac insufficiency, shock, etc. Clinical manifestation. At the same time, a large amount of catecholamine release, resulting in increased blood pressure, accelerated heart rate, increased cardiac

contractility, increased oxygen demand, excitation of sympathetic nerve receptors, increased coronary artery tension, on the contrary, oxygen supply seriously reduced, affecting blood flow shear stress, accelerating the formation of plaque, leading to plaque rupture, which can trigger the occurrence of arrhythmia and arrhythmia. Platelet aggregation [4]. Inflammatory factors play an important role in the process of stimulation and promotion. In addition, stress can aggravate the severity of acute coronary syndrome, because stress hyperglycemia can lead to glycosylation of low density lipoprotein in blood and transform into foam cells, accelerate coronary atherosclerosis [5–8]. It can also affect the occurrence and development of acute coronary syndrome from the aspects of endothelial dysfunction, insufficient collateral filling, abnormal coagulation mechanism, vasculitis, oxidative stress and increased myocardial oxygen consumption. At the same time, when acute coronary syndrome occurs, the more extensive the myocardial injury is, the more severe the stress is.

Protective inflammatory factors play an important role in the formation of unstable atherosclerotic plaque in coronary artery, besides the involvement of endothelial cells and lipids. A large number of experimental and clinical studies have confirmed the role of inflammatory factors in it. A meta-study found that Bootcov et al. first published a literature report on the structure and function of GDF-15 protein in Proceedings of the National Academy of Sciences of the United States of America in 1997 [9]. Later studies found that GDF-15 is a stress response protein, which is highly expressed in the prostate and placenta under physiological conditions, and weakly expressed in most other tissues, including heart tissue, but under pathological and environmental stresses such as ischemia-reperfusion injury. GDF-15 is abundantly expressed in cardiac myocytes under conditions of injury, cardiac hypertension, heart failure and atherosclerosis, and plays a regulatory role in the structure and apoptotic process of cardiac myocytes [10, 11]. At the same time, GDF-15 is closely related to inflammation. It is an endogenous anti-inflammatory factor, which promotes the repair and survival of infarcted myocardium, inhibits leukocyte infiltration, and inhibits the activation of macrophages and the occurrence of inflammation [12]. In addition, some studies have found that GDF-15 may be related to the basic pathology of cardiovascular diseases. Long-term physical and mental stress can lead to the exhilaration of neuroendocrine system, the increase of corticotropin secretion, and the hyperfunction of sympathetic-adrenal medullary system and pituitary-adrenal cortex system, resulting in the excessive release of adrenaline and noradrenaline, which has an impact on hemodynamics, hemorheology, lipid metabolism and peripheral blood vessels. Increased resistance, increased blood viscosity, increased cardiac load, increased myocardial oxygen consumption and myocardial ischemia are a series of factors that together lead to the occurrence of ACS [13]. Heat shock protein 70 (HSP-70) is a kind of stress protein widely existing in bacteria and mammals. It is a group of proteins that increase rapidly in cells when stimulated by heat, ischemia, hypoxia or metabolic toxicants. According to its molecular weight, it can be divided into HSP30, HSP60, HSP70, HSP90 and so on. Heat shock protein-70 was expressed in normal cells and maintained normal physiological activity, but was low in normal tissues. HSP70 is highly induced during stress. It can mediate the occurrence of vascular inflammation through inflammatory reaction and immune response, destroy vascular endothelium and promote the formation and development of atherosclerosis. At the same time, it can stimulate the expression level of inflammatory factors such as IL-6 to increase the immune response and increase the instability of atherosclerotic plaque. Its serum expression level is correlated with ACS [14]. In recent years, more attention has been paid to its pathophysiological significance.

4.1 Analysis of relationship between stress and ACS

Forty patients with ACS were included in the case group, aged 29–85 years, including 28 males and 12 females. There were 17 cases of unstable angina and 23 cases of myocardial infarction. Forty healthy volunteers were selected from the physical examination center, aged 35–74 (52.53 ± 8.397), including 30 males and 10 females. The acute coronary syndrome was used as the catecholamine in the plasma of the case group and the healthy control group (46592.15 ± 30931.27, $p < 0.001$), GDF-15 (21.94 ± 14.23, $p = 0.007$), HSP-70 (369.56 ± 300.44, $p < 0.001$). Statistical analysis showed that the case group compared catecholamine in the control group (46592.15 ± 30931.27, $p < 0.001$), GDF-15 (21.94 ± 14.23, $p = 0.007$), HSP-70 (369.56 ± 300.44, $p < 0.001$). The level was significantly elevated ($p < 0.05$), which was statistically significant (**Table 2**).

4.2 The relationship between stress and the degree of coronary artery stenosis

Lesion vascular stenosis in the case group ACS patients was divided into <20 group, 20–39 group, <40 group according to Gensini score. Statistical analysis was performed on risk factors such as age, BMI, smoking history, history of hypertension, and stress and severity of diseased vessels. The results showed that serum stenosis >40 group GDF-15 serum levels were significantly higher than <20 group (324.27 ± 198.81 vs. 77.43 ± 699.22, $p = 0.03$), vascular stenosis >40 group serum catecholamines (adrenalin, norepinephrine, dopamine). The level was significantly higher than the <20 group (18.71 ± 7.32 vs. 18.6 ± 46.1, $p = 0.017$), the difference was statistically significant, and the other results were not statistically significant (**Table 3**).

With reference to domestic and foreign literature, the degree of coronary stenosis is evaluated by coronary artery lesion count and Gensini score in this study. It is found that the serum levels of GDF-15, HSP-70, catecholamine (adrenalin, norepinephrine, dopamine) in the ACS case group were higher than those in the control group, and it is speculated that the chronic fatigue stress indicators GDF-15, HSP-70, catecholamine (adrenalin, norepinephrine, dopamine) is associated with ACS. The research team further studied the relationship between these stress indicators and the severity of ACS. The study found that the elevated serum levels of GDF-15 were linearly related to the Gensini score. The correlation coefficient was 0.131 ($p > 0.05$), but the difference was not of statistical significance, which indicates that GDF-15 has a correlation with ACS, but there is no linear regression relationship. GDF-15 and vascular stenosis studies showed that serum levels of GDF-15 in the multivessel disease group were significantly higher than those in the single vessel disease group ($p = 0.035$, $p < 0.05$), and stenosis <40 group GDF-15 serum levels. Compared with the <20 group ($p = 0.033$, $p < 0.05$), serum GDF-15 levels increased with the

Group	GDF-15	HSP-70	Catecholamine
Case group	21.94 ± 14.23	369.56 ± 300.44	46592.15 ± 30931.27
Control group	7.059 ± 5.53	107.76 ± 54.23	5507.14 ± 2083.28
F	1.922	19.024	43.841
P	0.007※	<0.001※	<0.001※

※*P < 0.05 means statistically significant.*

Table 2.
Comparative analysis of stress indexes between case group and control group.

Parameter	<20分 (n = 3)	20–39分 (n = 5)	>40分 (n = 15)	P1	P2	P3
Age	46 ± 12.17	66.6 ± 9.40	63.93 ± 14.33	0.035	0.704	0.061
BMI	25.90 ± 1.46	25.95 ± 6.27	27.07 ± 5.83	0.990	0.720	0.742
Smoke	0.33	0.8	0.533	0.244	0.317	0.555
Hypertension	0.33	0.8	0.8	0.244	1.000	0.111
GDF-15	77.43 ± 699.22	400.98 ± 294.1	324.27 ± 198.81	0.318	0.515	0.035※
HSP-70	74453.4 ± 69224.2	45655.2 ± 45185.1	43978.25 ± 17068.4	0.496	0.902	0.119
Catecholamine	18.6 ± 46.1	19.94 ± 6.15	18.71 ± 7.32	0.317	0.741	0.017※

P1 stands for comparison between Gensini <20 and Gensini 20–39, P2 stands for comparison between Gensini 20–39 and Gensini <40, P3 stands for comparison between Gensini <20 and Gensini <40.
※P < 0.05 means statistically significant.

Table 3.
Stress and known risk factors and severity of stenosis.

increase of coronary artery disease count and stenosis, GDF-15 level and coronary artery disease. There is a significant positive correlation between the number and the degree of stenosis Gensini score, which is consistent with the current research results related to GDF-15 and ACS. The meta-study found that GDF-15 is a stress-responsive protein, which represents the level of stress in the body. Through this study, it is found that the state of chronic fatigue stress is related to the severity of ACS. GDF-15 can be used as a potential indicator of risk classification and treatment prognosis. At the same time, the level of serum catecholamine (epinephrine, norepinephrine, dopamine) in the stenosis <40 group was significantly higher than that in the <20 group ($p = 0.017$, $p < 0.05$), indicating that the degree of vascular stenosis was correlated with the expression level of catecholamine. The more severe the vascular stenosis is, the higher the serum catecholamine level will be, which is closely related to the long-term chronic fatigue stress. Long-term stress leads to hyperactivity of the sympathetic-adrenal-pituitary neuroendocrine axis, which secretes a large number of catecholamine antibodies, resulting in their high expression in the body.

5. The pathogenesis of arrhythmia induced by chronic fatigue stress

Stress can cause a variety of arrhythmias, including tachyarrhythmias and bradyarrhythmias, including sinus arrhythmias, atrial arrhythmias and ventricular arrhythmias. It is closely related to stress intensity and basic heart disease. The mechanism of stress-induced cardiorespiratory arrest has been proved by some studies from the aspects of myocardial ischemia and the increase of ECG instability caused by autonomic nervous system. In the process of research, people have found important indicators and pathophysiological processes involved in stress-induced cardiopulmonary arrest, such as intracellular calcium homeostasis, central nervous system and so on. The arrhythmia caused by intracellular calcium homeostasis is still the focus of current research. When the human body is under fatigue stress for a long time, excessive production of highly active molecules such as reactive oxygen species (ROS) in mitochondria leads to a series of changes in myocardial ion channels leading to ventricular arrhythmia. The mutation of calmodulin gene induced by chronic fatigue stress may affect the structural changes of calmodulin, such as the increase of sulfhydryl group content. Both of them may increase the incidence of arrhythmia by influencing the function of calcium channel. In the pathological injury of myocardial ischemia or pressure overload, various signaling molecules and ionic mechanisms induce the increase of intracellular calcium level, while elevated calcium ion promotes the production of ROS. Too much ROS further increases the levels of calcium ion and ROS by triggering mitochondrial calcium signal and regulating calcium regulatory proteins, eventually forming positive feedback of calcium ion and ROS, causing myocardial fineness. Persistent cell damage and electrophysiological disorders [15]. At the same time, ROS can change the membrane lipid environment or activate signal transduction molecules such as protein kinase C and calmodulin-dependent protein kinase II. Thus, it can affect the phosphorylation of sodium channels, reduce the peak sodium current, and lead to arrhythmia. Activation of calmodulin-dependent protein kinase II can also phosphorylate subunits of Ca channel, opening L-type calcium channel. With the increase of calcium influx, delayed post depolarization and cardiac systolic dysfunction will eventually lead to arrhythmia. Young people under high intensity and high pressure under fatigue stress belong to the group at high risk of sudden death. Preventive measures should be taken in advance to provide an insurance for the people who are the backbone of society and make some contributions to the health of the main construction forces of the family and society.

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