Cardiology Research and Practice

Effect of Stress in Autonomic and Cardiovascular Systems

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Cardiology Research and Practice
Volume 2020, Article ID 7986249, 9 pages
https://doi.org/10.1155/2020/7986249

Review Article

Effect of Stress on Autonomic and Cardiovascular Systems in Military Population: A Systematic Review

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Received 14 December 2019; Accepted 24 July 2020; Published 11 August 2020

Academic Editor: Anne Knowlton

Stress is regulated by the autonomous nervous system, increasing the sympathetic modulation when a threat is perceived. A multifactorial response usually leads to significant behavioural modifications and alterations on homeostasis and physical and psychological status. Moreover, stress is an emotional response that can lead to psychosocial and psychophysiological adversity. Regarding military population, military operations and combat exposure are important stressors that influence acute and chronic stress response in soldiers, affecting their performance and health. A bibliographic search was carried out between April and May 2019, focusing on recent studies (2013–2019) that analysed psychophysiological response, stress, stress regulation, heart rate, heart rate variability, and posttraumatic stress disorder in military population. Autonomic and cardiovascular chronic stress seems to be modulated by experience and previous specific training of each military unit. Physical exercise, music embedded with binaural beat technology, bidirectional sensory motor rhythm training, heart rate variability biofeedback, and transcutaneous vagal nerve stimulation are the main techniques applied to balance stress and to recover body homeostasis. Since military population are usually exposed to multiple stressors, knowing previous training and experience, together with developing techniques to balance stress, is the main practical application in this field of study to balance autonomic and cardiovascular systems.

1. Introduction

Stress is a multifactorial response that leads to significant behavioural modifications and alterations on homeostasis and physical and psychological status. The stress response is regulated by the autonomous nervous system, increasing the sympathetic modulation when a threat is perceived and causing increases in the physiological response (heart rate, blood pressure, breathing frequency, glucose levels, etc.). When stressors disappear, the parasympathetic modulation increases, returning the organism to the homeostasis state [1]. Stress has become a challenge for humans because of its negative physiological and psychological implications [2], which are normally related to cardiovascular diseases [3]. A chronic activation of the autonomous sympathetic nervous system could trigger acute heart diseases and hypertension [4].

In this line, posttraumatic stress disorder (PTSD) is one of the most common postdeployment chronic stress diseases [5] and usually happens after a war deployment and the highly stressful events that military personnel have to cope with. PTSD reduces the quality of life by a hyperarousal state that influences autonomic modulation. In fact, PTSD was prospectively associated with heart disease mortality among

veterans free of heart disease at baseline [6]. Stress should be trained and monitored during military rehearsal: heart rate (HR) is one of the most used indexes to measure stress response, although heart rate variability (HRV) (variability of the time between R waves of the electrocardiogram or RR intervals) is more sensitive to cardiac autonomic modulation changes [7].

While there have been systematic reviews on PTSD among military and ex-military personnel, there are no systematic reviews in the acute and chronic stress response of military population and its effect on the cardiovascular and autonomic nervous system. Then, we proposed the present research with the aim to analyse the effect of acute, chronic, and regulation stress methods of soldiers in their cardiovascular and autonomic nervous system.

2. Materials and Methods

2.1. Search Strategy. The bibliographic search was carried out between April and May 2019. The electronic databases such as Web of Science, EBSCOHost, SCOPUS, and PubMed identified studies published between January 2013 and May 2019. The keywords used were as follows: "heart rate," "heart rate variability," "autonomic modulation," "stress," "military," "combat," "soldier," "PTSD," and "Armed forces." The reference lists of included studies were checked for further relevant papers.

2.2. Inclusion Criteria. Inclusion criteria for the systematic review were as follows: (1) studies measuring psychophysiology response, stress, stress regulation, heart rate, heart rate variability, and PTSD; (2) studies focusing on military samples exposed to stressful situations; (3) studies published between 2013 and 2019; (4) studies published in English; and (5) the design of the studies met the level 2 (prospective cohort study and retrospective study), according to the guidance of The Journal of Bone and Joint Surgery level of evidence grading tool [8].

2.3. Selection Criteria. A total of 959 papers were retrieved from the above bibliographic searches, and 433 papers were removed after publishing period inclusion criteria. Eighty-one papers were removed as duplicates, and 422 were rejected after reviewing paper titles and abstracts. The final 23 papers were read to be considered relevant to the search criteria and appropriate for assessing our research objective (Figure 1). Reviews were used for the introduction section.

2.4. Exclusion Criteria. Exclusion criteria were as follows: (1) reviews, PhD dissertations, conference proceedings, abstracts, unpublished studies and books, study cases, and papers not in English.

3. Results and Discussion

The general definition of "stress" focuses on acute intense situations as in the fight-or-flight response presented in military population during combat and combat simulation.

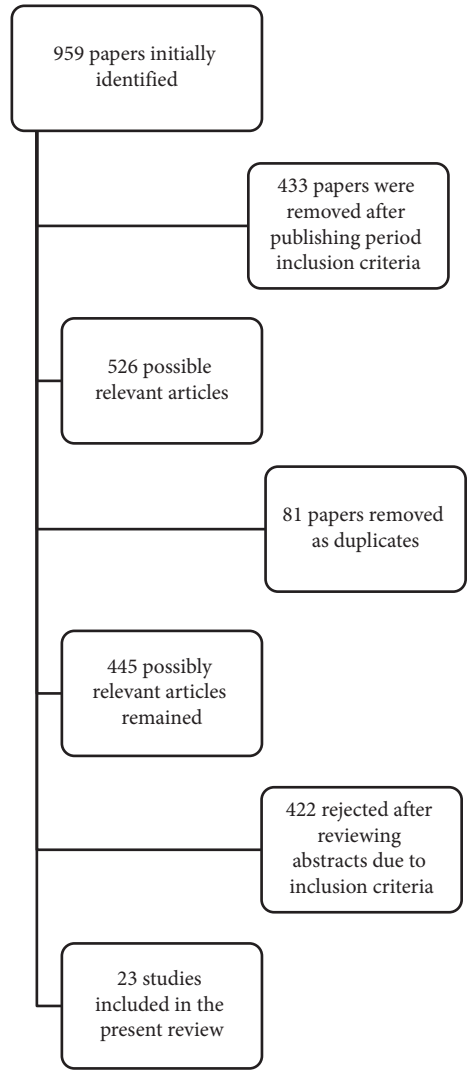

Figure 1: Flowchart of study search.

However, the brain, as the central organ managing stress, since it perceives what is threatening, as well as the behavioural and physiological responses to the stressor, leads to adaptations (i.e., "allostasis") but also contributes to pathophysiology ("allostatic load/overload") when overused and dysregulated [9]. Thus, when the stressor keeps affecting the psychophysiological response over time, the stress response becomes chronic.

3.1. Stress Response in the Military Population. Regarding military population, military operations and combat training simulation exposure are important stressors that influence chronic stress response in soldiers, affecting their performance and physical integrity and health.

Paratroopers are a military corps that suffers the stress of parachute jumping and combat. Regarding the parachute jump, two studies have analysed the effects of chronic stress response comparing experienced and novice paratrooper. In the first study, the psychophysiological response and specific motor skills of 17 novel and 23 expert warfighters before and

after a tactical combat parachute jump were analysed [10]. They found a 1.7% greater increase in HR, 38.7% in salivary cortisol, 52.5% in creatine kinase, and 188.9% in lactate in novel paratrooper compared to expert ones. However, in any case, fine motor skills and muscle performance were affected. In the second study, conducted by the same research group, the psychophysiological response of 11 sports parachute jumps, 8 manual tactical parachute jumps, and 4 tandem pilot and 4 tandem passengers parachute jumps was compared. In this case, only the 4 tandem passengers were novice with the rest of the paratroopers having more than 30 jumps experience. It was found that novice parachute jumpers presented a higher psychophysiological stress response before and after the parachute jumps than the experienced jumpers. Also, they presented a large anticipatory anxiety response before the jump, but it was decreased afterwards [11]. In the case of parachute jumps, it seems that experience modulates chronic stress response, reducing the psychophysiological and cardiovascular anticipatory and during the task responses, although it does not seem to affect specific performance.

Infantry units and other ground forces usually use simulated combat as training for real combat situations. Within these methods, new operation theatres, such as close-quarter combat, underground operations, or urban combat, examples of asymmetrical combat, are defined as highly stressful combat situations in which there are a large number of uncontrolled threats (urban areas, the presence of civilians in the battlefield, and unstructured and undefined battlefield [12]). Chronical exposure to this kind of stressors can drive soldiers to PTSD or other diseases. The effect of chronic stress on soldier's performance has been studied compared with nonelite soldier with less or no previous exposure to different combat situations. The effect of combat stress on psychophysiological responses and performance of elite and nonelite infantry soldiers was analysed during a tactical combat developed in urban area [13]. They found the elite soldiers presented a significantly higher lactate concentration after combat than nonelite soldiers (3.8 ± 1.5 vs. 6.6 ± 1.3 mmol/L). Nonelite soldiers had a higher heart rate before and after the simulation than elite soldiers (82.9 ± 12.3 vs. 64.4 ± 11 bpm, pre nonelite and elite, respectively; 93.0 ± 12.8 vs. 88 ± 13.8 bpm post nonelite and elite, respectively). Also, elite soldiers presented higher muscular strength than nonelite before and after the combat simulation. Nonetheless, cortical arousal was not significantly modified in any group. In a subsequent study, the effect of combat stress on psychophysiological response attention and memory of experienced and novel infantry soldiers during urban combat was analysed [14]. They found a significant increase in the low-frequency domain and a significant decrease in the high-frequency domain of the heart rate variability of experienced and highly trained soldiers. Also, they found that experienced had significantly higher values in blood lactate, blood glucose, blood oxygen saturation, rated perceived exertion, heart rate, and cognitive and somatic anxiety. However, the postmission questionnaire showed that experienced soldiers presented a higher negative effect on memory probably due to the highest psychophysiological activation, which seems to be related to chronic stress exposure.

This higher sympathetic activation before and during the combat was also found during urban combat simulation when comparing light infantry soldiers [15], more experienced in asymmetrical combat, with heavy infantry soldiers, less accustomed to close-quarter combat. Moreover, light infantry showed lower metabolic, cardiovascular, and anxiogenic responses before and after the combat simulation than heavy infantry. Nevertheless, fine motor skill measured by time of ammunition of a pistol magazine was similar in both groups before (39.25 ± 7.62 and 35.38 ± 8.19 s for light and heavy infantry, respectively) and after combat (31.58 ± 5.12 and 28.79 ± 4.77 s for light and heavy infantry, respectively). However, when comparing elite vs. nonelite soldiers during close-quarter combat [15], these same researchers found that the higher metabolic, cardiovascular, and anxiogenic responses viewed in elite soldiers supposed a significant loss in the fine motor skill after the combat manoeuvre (−8.34% vs. −11.23% of change in gun reloading time of elite group and novel group ($p < 0.05$)). These differences between studies may lean on the greater training and experiences of heavy infantry compared to nonelite soldiers despite the differences in the task specificity. Finally, a study comparing experienced soldiers and civilians psychophysiological and memory responses during an underground combat simulation, with interference of night-vision systems use or not, and previous fire situation or not, showed that, before the simulation, soldiers' sympathetic modulation was greater than civilians and that all groups increased their psychophysiological response and deteriorated their memory and time consciousness after simulation [16]. However, the civilian control group presented the highest number of incorrect answers on the postmission memory recall questionnaire (73% vs. 47.5, 65 and 57.8% for the soldiers' groups). Thus, it seems that experience disposes soldiers towards better self-confidence and readiness despite the effect on chronic stress that increased the anticipatory higher metabolic, cardiovascular, and anxiogenic response previous to combat. This activation seems to lead to a better fine motor skill. Nevertheless, this higher level of self-confidence and readiness does not translate into better physical performance when compared with nonelite soldiers or civilians.

Several studies have analysed stress response, mainly through questionnaires, heart rate (HR), or heart rate variability (HRV) in military population. In all cases, HR and/or HRV measures were included to evaluate stress. Mostly, male population was used, although in three cases [14, 16, 17] female soldiers were also examined. Only one study included a control group in the experimental design [14]. Standard methods using specific software for HRV analysis were implemented in almost all studies. In the majority of the selected studies, stress responses were investigated during ground operations, except one study that focused on air force soldiers in which HR and perceived stress augmented after a combat jet manoeuvre in professional pilots [18] and four studies in which participants were engaged in parachute jumps [10, 11, 19, 20].

Generally, researchers were interested in analysing acute stress responses in terms of different levels of expertise [10, 11, 13, 16]. In one of these studies, HR augmented after a parachute jump in both novice and experienced warfighters, although the psychophysiological response was higher in the less experienced group, which had less self-confidence, and more somatic anxiety with higher blood lactate levels [10]. There were no differences when examining parachute jump modalities, among sport parachute jump, manual tactical parachute jump, tandem pilots, and tandem passengers, but they were when considering the experience of the jumpers. The less experienced jumpers had a higher psychophysiological response and higher values of anxiety before the jump [11]. Underground operations also produced a stress response (blood lactate, blood oxygen saturation, rated perceived exertion, heart rate, cognitive and somatic anxiety, and sympathetic modulation) in soldiers with different experimental conditions of fire night vision, with no differences between the groups with different equipment, but a negative effect on memory modulated by previous experience [16]. Combat stress was also addressed in elite and nonelite soldiers, with higher values of heart rate for nonelite in pre- and postmeasures, but similar cortical arousal values [13].

Researchers also focused on studying units with different training backgrounds [14, 15, 21]. In one of these studies, hypoxia induced different cognitive performances for different tasks, according to the job profile (transport pilots, fighter pilots, helicopter pilots, and transport aircrew). Although HR increases due to a lower blood oxygen saturation, hypoxia did not affect HR and HRV differently when the groups were compared [21]. Light infantry and heavy infantry units have been assessed in combat simulation: light infantry training background involved a different stress response with less anxiety and lower metabolic and cardiovascular stress, both before and after the combat manoeuvre [15]. Highly trained soldiers (5.9 ± 0.8 years) had a higher stress response than lower trained soldiers (3.9 ± 3 years), with more cognitive and memory impairment and a higher physiological activation [14].

In the cases where a single task was analysed [10, 11, 13, 15, 16, 19, 20, 22, 23], data collection was performed during 2 occasions of the selected task, i.e., before and during/after. One of the studies monitored stress during four consecutive days, finding higher stress after a simulated air accident manoeuvre, with questionnaire and HRV analysis [17]. Regarding the acute stress responses in the parameters measured, a reduction in high-frequency HRV with a concurrent increase in low-frequency HRV was identified [14, 15, 19, 20, 22, 23]. Moreover, experienced soldiers presented lower HR values during a stressful situation [10, 13, 16] compared to their less experienced counterparts, or no significant changes after a parachute jump [11]. In contrast, the single study that included a control group noted a significant decrease in all the variables evaluated during HRV analysis [14].

Table 1 shows a summary of the articles related to stress response in the military population that met the level 2 (prospective cohort study and retrospective study), according to the guidance of The Journal of Bone and Joint Surgery level of evidence grading tool [8]:

3.2. Regulation of Stress Methods. Stress as an emotional response with adaptive function can lead to psychosocial and psychophysiological adversity. It is directly linked with a dysregulation of the autonomic nervous system, which leads to a disruption of body homeostasis and may lead to pathological conditions and syndromes due to either acute or chronic psychophysiological changes. Since no one is stranger to stress and its effects, recently, authors have tried to identify new mechanisms and intervention programs in order to improve stress management.

Physical exercise, when correctly periodized and regularly practiced, can modify the cardiac autonomic balance by increasing the parasympathetic activity and decreasing the sympathetic activity, promoting the autonomic nervous system function to meet the demands of the cardiovascular system, thus, HRV. Authors found just after 12 weeks significant increases in the vagal tone, thus increases in the parasympathetic activity, consequence of high-intensity exercise programs intervention, and however, greater significant increases and peak vagal tone was obtained at 20-week intervention program [24]. In comparison with other modalities of physical exercise, those in which the workload is interval and intense are those which have greater benefit in the autonomic nervous system and vagal tone as in sport modalities like Judo [25].

Despite physical exercise, the use of technology for stress treatment and management is largely extended. The use of music embedded with binaural beat technology (BBT) with a focus on the theta brainwave frequency was studied, as an effective, noninvasive tool with great potential on stress reduction and management. Subjects, under the intervention program (PTSD diagnosed soldiers), presented increased parasympathetic activation and decreased sympathetic response, showing greater self-reported relaxation, after using this technology [26]. In another research study, a noninvasive acoustic stimulation in PTSD patients showed improvements in SDNN, HF, LF, and systolic and diastolic blood pressure and reduction in C-reactive protein (CRP), angiotensin II to angiotensin 1–7 ratio, and interleukin-10. It was based on real-time translation of dominant brain frequencies into audible tones of variable pitch and timing to support the autocalibration of neural oscillations. PTSD symptomatology, insomnia, depressive mood, and anxiety were reduced after 6-month intervention program [27]. The increasing and growing interest in the application of psychophysiological signals and biofeedback is clear.

Bidirectional sensory motor rhythm training (SMR) and heart rate variability biofeedback were used, which allowed subjects after 21 training sessions, to control their SMR frequency bidirectionally, showing significant improvements in stress management [28]. However, no significant effects were seen in sleep quality improvement, possibly explained since bidirectional training does not result in the same neuroplastic changes seen with unidirectional training, due to the constant changing contingencies (i.e., up vs. down

Table 1: Summary of articles about stress response in military population.

Authors and year	Study title	Participants	Aim of study/assessment	Main outcomes
Clemente-Suárez et al. (2016) [10]	Experience modulates the psychophysiological response of airborne warfighters during a tactical combat parachute jump	40 male warfighters divided in two groups: novels ($n = 17$) and experts ($n = 23$)	To analyse the effect of experience in the psychophysiological response and fine motor skills of novel and expert parachute warfighters during a combat	Experience influences the psychophysiological response. Novel paratroopers were more affected than experts
Clemente-Suárez et al. (2017) [11]	Psychophysiological response in parachute jumps, the effect of experience and type of jump	27 male airborne brigade in parachute jump (n: 11; 41.0 ± 9.7 years), manual tactical parachute jump (n: 8; 33.1 ± 5.3 years), tandem pilots (n: 4; 35.5 ± 3.0 years), and tandem passengers (n: 4; 28.5 ± 5.4 years)	To analyse the effect of experience and jump on the psychophysiological response	Novice parachute jumpers had higher values of stress than the experienced jumpers, and a large anticipatory anxiety response before the jump
Clemente-Suárez and Robles-Pérez (2013) [12]	Mechanical, physical, and physiological analysis of symmetrical and asymmetrical combat	20 soldiers from the Spanish Army and Spanish Forces and Security Corps (34.5 ± 4.2 years; 176.4 ± 8.4 cm; 74.6 ± 8.7 kg; 63.3 ± 8.0 kg muscular mass; 7.6 ± 3.2 kg fat mass)	To analyse physical, mechanical, and physiological parameters during symmetrical and asymmetrical combat simulations	Asymmetrical combat showed higher maximum speed, number of sprints, sprint distance, and average heart rate. Symmetric combat presented a higher number of impacts and training load
Tornero-Aguilera et al. (2017) [13]	Effect of combat stress in the psychophysiological response of elite and non-elite soldiers	40 warfighters divided in two groups: elite (n: 20; 28.5 ± 6.38 years) and nonelite (n:20; 31.94 ± 6.24 years)	To analyse the effect of combat stress in the psychophysiological responses of elite and nonelite soldiers	Elite soldiers had higher muscular strength than nonelite in all tests (before and after the combat simulation), while cortical arousal was not modified significantly in both groups
Tornero-Aguilera et al. (2018) [14]	Use of psychophysiological portable devices to analyse stress response in different experienced soldiers	49 soldiers of Spanish Army (19 men and 1 woman; 34.5 ± 4.2 years; 176.4 ± 8.4 cm; 74.6 ± 8.7 kg; 63.3 ± 8.0 kg muscular mass; 7.6 ± 3.2 kg fat mass)	To analyse the effect of experience and training in psychophysiological response and attention and memory of soldiers in combat	The most experienced soldiers presented higher physiological activation as well as cognitive and memory impairment than lower experienced soldiers, and memory function was modulated by the type of external stimulus
Sánchez-Molina et al. (2018) [15]	Assessment of psychophysiological response and specific fine motor skills in combat units	31 male soldiers of the Spanish Army, 19 nonexperienced soldiers (30.2 ± 5.25 years, 9.95 ± 5.17 years of experience) and 12 experienced soldiers (34.5 ± 4.85 years, 14.58 ± 4.87 years of experience)	To analyse the psychophysiological response and specific motor skills in an urban combat simulation with two infantry units with different previous training and experience	A combat simulation changed the psychophysiological basal state and unbalanced the sympathetic-vagal interaction, but motor skills were not affected after the combat
Tornero-Aguilera and Clemente-Suárez (2018) [16]	Effect of experience, equipment and fire actions in psychophysiological response and memory of soldiers in actual underground operations	Fifty-four professional soldiers of the Spanish Army (mean age 30.60 ± 4.6 years; 8.85 ± 4.1 years of experience) and 16 were civilians (mean age 26 ± 3 years)	To analyse the effect of underground operations on the psychophysiological and memory response of soldiers depending on the previous experience and the use of nocturne vision systems	The underground operation produced a significant increase in blood lactate, blood oxygen saturation, rated perceived exertion, heart rate, cognitive and somatic anxiety, and sympathetic modulation in all groups

Table 1: Continued.

Authors and year	Study title	Participants	Aim of study/assessment	Main outcomes
Hormeño-Holgado et al. (2019) [17]	Psychophysiological response of air mobile protection teams in an air accident manoeuvre	12 male and 1 female soldiers from an air security force unit of the Spanish Air Force (32.4 ± 8.0 years; 7.2 ± 4.8 years of experience)	To study the psychophysiological response of an air security force in a simulated air accident in a hostile area and its subterfuge to a safe area	An air accident manoeuvre of three nights and four days caused a higher sympathetic nervous system modulation and increased stress, muscle strength, and dehydration
Hormeño-Holgado and Clemente-Suárez (2019) [18]	Effect of different combat jet manoeuvres in the psychophysiological response of professional pilots	29 fighter pilots of the Spanish Air Forces (28.3 ± 7.4 years)	To analyse the effect of air combat manoeuvres (defence and attack) on the psychophysiological response of air combat fighter pilots	The defensive manoeuvre produced a significant decrease in forced vital capacity and an increase in heart rate, stress, and exertion in both manoeuvres
Clemente-Suárez et al. (2017) [19]	Psychophysiological response and fine motor skills in high-altitude parachute jumps	16 veteran male soldiers of the Spanish Army with more than 200 parachute jumps experience 8 high-altitude low-opening (32.6 ± 7.7 years) and 8 high-altitude high-opening (30.3 ± 5.6 years)	To analyse the psychophysiological response and specific fine motor skill of an experienced jumper in high-altitude low-opening and high-altitude high-opening parachute jumps	High-altitude low-opening and high-altitude high-opening jumps produced a significant increase in CK, lactate, and RPE and a decrease in glucose. High-altitude high-opening decreased cortical arousal and presented a higher sympathetic modulation and a higher HR during the jump than high-altitude low-opening
Clemente-Suárez et al. (2016) [20]	Psychophysiological response in an automatic parachute jump	We analysed 38 male sport active soldiers of Spanish Army (25.6 ± 5.9 years; 172.3 ± 4.7 cm; 70.3 ± 4.9 kg; 23.8 ± 0.5 BMI) with an average of 44.7 ± 82.1 civil and military parachute jumps	To analyse modifications in blood oxygen saturation, heart rate, cortisol, glucose, lactate, creatine kinase, muscle strength, cortical arousal, autonomic modulation, and anxiety before and after an automatic open parachute jump	An automatic parachute jump increased physiological and cortical response and decreased somatic anxiety of participants
Bustamante-Sánchez et al. (2019) [21]	Psychophysiological response of different aircrew in normobaric hypoxia training	22 male pilots (10 helicopter pilots, 7 transport aircrew, 3 transport pilots, and 3 fighter pilots) from the Spanish Air Forces	To study the effect of hypoxia training in cortical arousal, autonomic modulation, muscle strength, and cognitive function	Hypoxia produced an increase in perceived stress and effort, a higher heart rate, and a decreased function of breathing muscles. Working memory and pattern recognition were impaired after hypoxia exposition. Aircrew groups performed differently in cognitive tests, suggesting differences in their previous training
Delgado-Morerno et al. (2017) [22]	Combat stress decreases memory of warfighters in action	Twenty male soldiers from the Spanish Army (35.4 ± 6.2 years; 179.9 ± 7.0 cm; 82.3.8 ± 10.5 kg; BMI: 25.7 ± 2.6; 14.6 ± 6.4 years of experience)	To analyse the effect of combat stress in the psychophysiological response and attention and memory of warfighters in a simulated combat situation	Combat stress increased the psychophysiological response and caused a selective decrease of memory, depending on the dangerous or harmless nature of the stimulus
Gamble et al. (2018) [23]	Different profiles of decision making and physiology under varying levels of stress in trained military personnel	26 male active duty US Army Infantrymen (age = 30.73 ± 7.71 years)	To examine the relationship between decision making and physiology under varying levels of stress in trained military personnel	Participants performed worse in the high-stress condition, and heart rate variability measurements could help to measure the adaptive response when danger is imminent

Table 2: Summary of articles about stress regulation.

Authors and year	Study title	Sex/participants/age	Aim of study/assessment	Main outcomes
Grant et al. (2018) [24]	The difference between exercise-induced autonomic and Fitness changes measured after 12 and 20 weeks of medium-to-high intensity military training	154 healthy recruits (male = 89, female = 65, age = 20.91 ± 1.29 with a body mass index of 22.85 ± 2.78 kg/m^2)	To compare the physical fitness, based on VO2max and exercise-induced cardiac autonomic changes, measured by heart rate variability of 12 weeks with 20 weeks of training in the South African National Defence Force	Cardiorespiratory fitness (VO2max) did not increase during the 12- to 20-week period although heart rate and sympathetic cardiac control decreased with a simultaneous increase in vagal cardiac control
Campos et al. (2018) [25]	Influence of autonomic control on the specific intermittent performance of judo athletes	Sixteen judo athletes of both sexes (12 men and 4 women, age of 19.6 ± 2.9 years, body mass of 67.9 ± 12.1 kg)	To verify the correlation between heart rate variability at rest with performance in the special judo fitness test	The rates of vagal tone in the time domain of resting heart rate variability correlated positively with the performance of judo athletes (number of throws)
Gantt et al. (2017) [26]	The effect of binaural beat technology on the cardiovascular stress response in military service members with postdeployment stress	74 military service members with a complaint of continued stress following a deployment	To assess the efficacy of embedded theta brainwave frequency in music using binaural beat technology compared to music alone on the cardiovascular stress response in military service members with postdeployment stress	Participants who used music with embedded binaural beat technology displayed a decrease in sympathetic responses and an increase in parasympathetic responses, while participants who used music alone had the opposite effect
Tegeler et al. (2017) [27]	Successful use of closed-loop allostatic neurotechnology for post-traumatic stress symptoms in military personnel: self-reported and autonomic improvements	Eighteen service members or recent veterans (15 active duty and 3 veterans, most from special operations, 1 female, age = 40.9 ± 6.9 years) and symptoms of posttraumatic stress disorder from 1 to 25 years	To document changes in self-reported symptoms, autonomic, and functional measures after use of a closed-loop acoustic stimulation neurotechnology	There were significant improvements in multiple measures of heart rate variability in both time and frequency domains
Binsch et al. (2017) [28]	No effects of successful bidirectional SMR feedback training on objective and subjective sleep in healthy subjects	62 participants, all military working at the Dutch Ministry of Defence	To analyse to what extent participants could gain voluntary control over sleep-related parameters and secondarily to assess possible influences of this training on sleep metrics	After the training, the heart rate variability values improved, but no effects were found on sleep spindles, actigraphy, sleep diaries, and self-reported sleep quality
Wahbeh et al. (2016) [30]	Mechanistic pathways of mindfulness meditation in combat veterans with posttraumatic stress disorder	102 combat veterans with posttraumatic stress disorder	To evaluate the effect of two common components of meditation (mindfulness and slow breathing) on potential mechanistic pathways	Meditation helped to improve posttraumatic stress disorder and related symptoms, although there were no different effects between groups
Hourani et al. (2016) [31]	Toward preventing post-traumatic stress disorder: development and testing of a pilot predeployment stress inoculation training program	351 active duty male Marines scheduled for imminent deployment for combat operations	To design, develop, and evaluate a predeployment stress inoculation training preventive intervention to enable deploying personnel to cope better with combat-related stressors and mitigate the negative effects of trauma exposure	The predeployment stress inoculation training protected against post-traumatic stress disorders among Marines without baseline mental health problems. This strategy could be used as a potential preventive strategy in the military personnel

Table 2: Continued.

Authors and year	Study title	Sex/participants/age	Aim of study/assessment	Main outcomes
Lamb et al. (2017) [32]	Non-invasive vagal nerve stimulation effects on hyperarousal and autonomic state in patients with posttraumatic stress disorder and history of mild traumatic brain injury: preliminary evidence	Participants diagnosed with posttraumatic stress disorder ($n = 12$, 30.4 ± 5.4 years) and healthy combat controls ($n = 10$, age $= 29.7 \pm 7.0$ years)	To evaluate noninvasive vagal nerve stimulation on hyperarousal and autonomic state in patients with posttraumatic stress disorder	The stimulation improved the vagal tone and moderated the autonomic response to startle and stress in this population

required) [28]. However, other simpler interventions have proven efficiency on the reduction of global PTSD symptoms with a high degree of adherence to the program, like the self-controlled HRV biofeedback 4-week intervention program [29], or relaxation and personal perception intervention programs, such as mind fullness, breathing techniques, the combination of both, and sitting quietly form [30]. In addition, the PRESIST program, also noninvasive and based on a sum of the aforementioned research studies [31] and consisting of (i) educational materials on combat and operation stress control, (ii) copying skills training involving focused and relaxation breathing exercises with biofeedback, and (iii) exposure to video multimedia stress environment to practice knowledge and skills learned in the aforementioned steps (i) and (ii), showed a protective effect on PTSD development and stress management, thus being a potential preventive strategy tool.

Finally, other methods such as transcutaneous vagal nerve stimulation (tVNS) have presented significant positive effects on systems underlying emotional dysregulation, thus improving global stress and PTSD symptoms [32], where high-frequency heart rate variability during a tilt-table procedure derived from an electrocardiogram, and skin conductance changes in response to acoustic startle while viewing emotional images, resulted in improvements in the vagal tone and moderation of autonomic response, consistent with modulation of autonomic state and response to stress. However, the use of this technology may not be accessible for everyone, thus simpler approaches which have shown significant improvement in stress management and reduction as well as PTSD global symptoms [32].

Table 2 shows a summary of the articles related to methods to regulate the stress that met the level 2 (prospective cohort study and retrospective study), according to the guidance of The Journal of Bone and Joint Surgery level of evidence grading tool [8]:

4. Conclusions

Soldiers' autonomic and cardiovascular chronic stress seems to be modulated by experience and previous specific training, but its magnitude can be dependent on the task performed (e.g., fine motor skills or cardiometabolic performance) and on the type of units and the specific stressors that are exposed (e.g., paratroopers or infantry).

Physical exercise, music embedded with binaural beat technology, bidirectional sensory motor rhythm training, heart rate variability biofeedback, and transcutaneous vagal nerve stimulation are the main techniques applied to modify the cardiac autonomic balance by increasing the parasympathetic activity, thus balancing stress and reaching body homeostasis with basal levels of stress.

This information could help to improve the training guidelines to follow in different military populations to adapt better to the contexts of stress that affect both autonomic and cardiovascular systems that the soldiers must face during their job. Moreover, the information of this study could help to recognize the different strategies to reduce the posttraumatic stress that veteran soldiers have to face once they have finished their professional life.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Hindawi
Cardiology Research and Practice
Volume 2020, Article ID 4150291, 5 pages
https://doi.org/10.1155/2020/4150291

Review Article

The Brain-Heart Connection in Takotsubo Syndrome: The Central Nervous System, Sympathetic Nervous System, and Catecholamine Overload

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Received 20 December 2019; Accepted 13 February 2020; Published 9 March 2020

Guest Editor: Vicente Javier Clemente-Suárez

Takotsubo syndrome (TTS), also known as stress cardiomyopathy, is a type of acute heart failure syndrome triggered by intense psychological or physiological stress. TTS typically manifests as acute chest pain, dyspnea or syncope that mimics an acute myocardial infarction but does not involve coronary artery obstruction. The current understanding of the pathogenesis of TTS suggests that sympathetic nervous system (SNS) activation plays a central role. Specifically, stress can activate the SNS and lead to the over-release of catecholamine, which have toxic effects on myocardial tissue when present at excessive levels. However, the brain changes associated with TTS and the connection between the brain and the heart in patients with this disease remain unclear. In recent years, several published reports have revealed the role of this brain-heart connection in the pathogenesis of TTS. This review summarizes recent studies regarding SNS activation, catecholamine overload, and the brain-heart connection in patients with TTS from both pathophysiological and mechanistic aspects.

1. Introduction

Takotsubo syndrome (TTS), which is also known as stress cardiomyopathy, is an acute syndrome that is induced by psychological or physiological stress and characterized by acute reversible heart failure [1]. TTS typically manifests as the acute onset of chest pain, dyspnea, or syncope, and may even present as ventricular arrhythmia or cardiogenic shock in severe cases [2]. Initially, it may be difficult to distinguish TTS from acute myocardial infarction (AMI), as the electrocardiogram (ECG) of a patient with TTS would display an ST-segment elevation with or without an elevated troponin or creatine kinase-MB (CK-MB) level [3]. However, most patients with TTS do not present with coronary artery occlusion, and such cases are also characterized by reversible left ventricular dysfunction [3].

TTS was first described by Sato et al. in a report of five cases [4]. In that series, the first case involved a 64-year old woman with significant symptoms and ECG changes consistent with AMI. However, her coronary arteries were normal, and apical ballooning gave the appearance of a traditional Japanese pot called a "Takotsubo." She additionally presented with marked abnormalities in ventricular motion that were visible on left ventriculography, which disappeared after 2 weeks [5]. These interesting cases were first reported only in Asia, and the disease attracted gradual attention as western countries began to report similar cases in the late 1990s [6]. In 2006, the American Heart Association (AHA) officially conferred the name "stress cardiomyopathy" on this condition [7]. In 2015, however, the European Society of Cardiology (ESC) proposed to abandon "cardiomyopathy" in favor of the original term, takotsubo syndrome (TTS), in light of recent basic and clinical research [1].

As noted above, the number of reported cases of TTS worldwide increased gradually. Current epidemiological data indicate that TTS patients account for 1–3% of all cases of suspected AMI, and 90% of affected patients are

postmenopausal women [8–10], consistent with the observation that women older than 55 years have a 10-fold greater risk of TTS than men of the same age and a five-fold greater risk than younger women [11]. In the United States, TTS accounts for 0.02% of hospitalizations and has an in-hospital mortality rate of approximately 2% [11, 12]. Despite some severe and potentially fatal complications, including heart failure, cardiac shock, and malignant arrhythmias, the prognosis of TTS is generally favorable [13].

2. The Role of Stress and Catecholamines in Takotsubo Syndrome

Although the pathophysiological mechanism of TTS is incompletely understood, the syndrome is generally considered a complex and systemic cardiovascular system reaction caused by acute and severe psychological or physiological stimulation [1]. Stress events are considered both a hallmark of TTS and the most important general trigger. The results of the Comorbidity Frequency in the Takotsubo Syndrome (COUNTS) study indicated that emotional and physical stress were the triggers in 39% and 35%, respectively, of 1109 patients with TTS and that 24% of affected patients had mental disorders [14]. Moreover, Summers et al. reported in 2010 that many women with TTS had a history of chronic anxiety before onset [15]. In patients, physical stress may be related to basic disease. For example, the COUNTS study found as many as 15% of patients with TTS had pulmonary vascular disease, while 7% had nervous system disease (subarachnoid hemorrhage was most common) and 1% had experienced trauma [14]. Another study identified complications such as malignant tumors, chronic kidney diseases, and connective tissue diseases as the strongest predictors of death in patients with TTS [16].

In the current concept of TTS, increasing sympathetic nervous system (SNS) activity plays a central part in the disease pathogenesis. A stress event triggers SNS activation, leading to the release of catecholamines. A recognizable emotionally or physiologically triggering event and excess catecholamines release have been identified in most cases of TTS [17–20]. In 2005, Wittstein et al. observed significantly higher levels of catecholamines in patients with TTS than in patients with Killip class III myocardial infarction [21]. However, this finding has not been duplicated by other studies, possibly because of limitations of the methodology or number of cases. In a 2009 study, Madhavan et al. did not identify elevated plasma catecholamines concentrations but did detect an interesting marked increase in plasma noradrenaline concentrations at the onset of TTS in a cohort of 15 patients [22]. In 2008, Kume et al. observed elevated noradrenaline concentrations in the coronary sinuses of patients with TTS [23]. Although these studies suggest an association between SNS activation and TTS, the plasma catecholamines concentration is not necessarily related to local myocardial sympathetic regulation [24].

Despite the abovementioned conflicting results, TTS has been induced in several clinical cases by the intravenous injection of catecholamines. In 2017, Kido and Guglin analyzed 157 cases of drug-induced TTS and found that 68.2% were catecholamines-related, while 8.9% appeared to be associated with chemotherapy-induced coronary vasospasm [25]. In addition, Abraham et al. revealed in 2009 that the intravenous administration of epinephrine or beta-receptor agonists could induce all the characteristic features of TTS, including an elevation of cardiac isoenzyme levels, rapidly reversible cardiac dysfunction, and QTc interval prolongation [26]. Notably, some studies of pheochromocytoma and other diseases associated with the excess release of catecholamines have provided evidence supporting the abovementioned observations. For example, Giavarini et al. observed 140 consecutive patients with pheochromocytomas and paragangliomas (PPGL) and considered that the latter condition may present as acute catecholamine cardiomyopathy (ACC) in 11% of cases (excluding patients who died from undiagnosed tumors) [27, 28]. Several studies of animal models of TTS have led to similar conclusions [29]. Immobilization stress can provoke apical ballooning of the left ventricle in rats, while alpha- and beta-receptor blockade can attenuate this ballooning [30, 31].

Mechanistically, the transient left ventricle dysfunction observed in TSS may represent the toxic effect of an excess of catecholamines on the myocardium. At doses above normal physiological levels, catecholamines can disrupt the calcium-regulatory system by stimulating β-adrenoceptors and consequently downregulating the expression of genes encoding calcium-regulatory protein [32]. Sarcoplasmic-Ca^{2+}-ATPase (SERCA2a) gene expression is downregulated with the upregulation of sarcolipin, while phospholamban is dephosphorylated. The consequent increase in the phospholamban/SERCA2a ratio leads to contractile dysfunction via decreased affinity for Ca^{2+} [33]. In patients with acute-phase TTS, the histopathological features of this contractile dysfunction include regional inflammatory cell infiltration, enhanced fibrosis, and contraction bands [34].

3. Activation of the Sympathetic Nervous System (SNS) in Takotsubo Syndrome

Other aspects of SNS activation have also been observed in patients with TTS. As mentioned above, 90% of patients with TTS are postmenopausal women. During this unique period of life, a decrease in estrogen levels weakens the parasympathetic nerve stabilization in the hypothalamic autonomic center, which increases the reactivity of the SNS to activation. We believe that this increased reactivity may at least partly explain why TTS most frequently affects postmenopausal women. Interestingly, a study of 33894 patients with TTS (88.9% women) found that the prevalence of diabetes mellitus was lower than the prevalence in a general population of participants in the National Health and Nutrition Examination Survey (NHANES) [35]. We hypothesize that the autonomic neuropathy induced by diabetes mellitus results in a disconnection between the brain and heart disconnection and thus could conceivably alleviate the characteristic effect of an adrenergic storm of the myocardium in TTS.

As noted above, the ECG characteristics observed in TTS patients are very similar to those in AMI patients. In both

conditions, the most common manifestations are T-wave inversion, large upright peaked T-waves and QT interval prolongation. Possibly, the ECG changes observed in TTS may reflect the disturbance of the sympathetic nerve terminals [36]. In a review of the 24-hour ambulatory electrocardiograms of TTS patients with apical ballooning at 2 and 3 days and 3 months, Ortak et al. observed that the indices of heart rate variability (HRV) were significantly depressed, suggesting a decrease in cardiac parasympathetic activity [37]. Akashi et al. reached a similar conclusion when exploring the standard deviation of the mean cycle lengths of normal-normal R-R (NN) intervals over 24 h (SDNN). In that study, the 24-h standard deviation of the mean value of the difference between NN intervals for each 5-min segment (SDANN) had improved significantly at 3 months post-onset in patients with TTS [38]. Nuclear imaging may provide more evidence supporting a role of the SNS in TTS. For example, an earlier study revealed that a decrease in ^{123}I-metaiodobenzylguanidine uptake on single-photon-emission computed tomography was indicative of cardiac sympathetic hyperactivity in patients with TTS [39].

4. Brain-Heart Connection in Takotsubo Syndrome

Stress is a physiological response mediated by both the central nervous system and SNS. The limbic system, neocortex, spinal cord, reticular formation, and brainstem are fundamental anatomic structures in the stress response [40]. In this response, the main neuroendocrine changes that occur in response to strong stimulation include an intense excitation of the locus coeruleus-adrenomedullin axis and hypothalamus-pituitary-adrenocortical (HPA) axis [41].

The locus coeruleus is situated in the posterior area of the rostral pons in the lateral floor of the fourth ventricle and serves as the central site of noradrenergic neurons in the brain stem and sympathetic adrenomedullin system. The locus coeruleus can receive afferent signals from the amygdala, hypothalamus, and cingulate gyrus and is related to excitement and alertness during stress. Moreover, this brain structure can cause emotional reactions such as tension and anxiety, which can trigger noradrenergic responses. The locus coeruleus also regulates the acute response of the body to stress by maintaining a state of alertness that is conducive to coping with environmental changes. Activation of the locus coeruleus induces the secretion of norepinephrine by adrenal medullary chromaffin cells, which in turn stimulates the HPA axis [42, 43].

The sympathetic nerve descends through the cranial and sacral spinal cord. Sympathetic preganglionic neurons are located in the lateral gray column between the spinal levels of T1 and L2. These neurons form synapses with postganglionic neurons and then interact with the myocardium and coronary circulation along the epicardial vessels. The sympathetic nerve endings activate the α and β postsynaptic adrenergic receptors by releasing noradrenaline into the synaptic space [44].

Stress is also regulated by the HPA axis, which is also known as the limbic system-hypothalamus-pituitary-adrenal axis (LHPA axis). This axis is centered around the paraventricular nucleus, which comprises the hypothalamus, adenohypophysis, and adrenal cortex. Notably, cortisol synthesis in the adrenal cortex is the downstream result of HPA axis activity. Cortisol, a major stress hormone, can act on many tissues, including the brain, and the combined functions of the sympathetic nerve and cortisol can promote the synthesis and secretion of adrenaline and noradrenaline in the adrenal medulla. The hypothalamus is connected physically to the amygdala and hippocampus, among other structures, and these nuclei can also stimulate the HPA axis via these physical links.

Recently, increasing interest has been directed toward the brain and neural changes observed in patients with TTS. In 2014, Suzuki et al. used (99 m)Tc ethyl cysteinate dimmer single-photon-emission computed tomography to measure the cerebral blood flow (CBF), a widely accepted index of brain activity, in patients during the acute and chronic phases of TTS. In the acute phase, the researchers observed a marked increase in CBF in the brainstem, hippocampus, and basal ganglia, which was accompanied by a significant decrease in CBF in the prefrontal cortex [45]. Both the basal ganglia and hippocampus are components of the limbic system, which is associated with emotion and sympathetic activation, while the brainstem contains the sympathetic central nucleus and the origins of descending sympathetic nerves. In 2017, Klein et al. similarly demonstrated specific homogeneous anatomical and neurophysiological features in brain regions mainly associated with the control of heart functions in patients with TTS [46]. In 2018, Hiestand et al. used magnetic resonance imaging to reveal structural and connective differences in the limbic networks of TTS patients and healthy subjects. Specifically, patients with TTS had a cortex over the limbic region and significantly reduced connectivity in the autonomic nervous system, including the left amygdala, both hippocampi, the left superior temporal pole, and right putamen [47]. Moreover, a recently published study similarly reported reduced functional connectivity in the limbic systems of patients with TTS patients relative to healthy individuals [48]. As noted above, the proportion of individuals with mental disorders was found to be higher among patients with TTS than in a general population. Therefore, primary structural alterations in the autonomic nervous systems of TTS patients may reduce control in this region.

5. Conclusions and Perspectives

In this review, we have presented the findings of recent studies concerning the potential pathophysiologic and mechanistic roles of SNS activation, catecholamine overload, and the brain-heart connection in patients with TTS. The mechanisms by which an excess of catecholamines induce direct and indirect myocardial damage have been clarified gradually over time, and the role of the SNS in the pathogenesis of TTS has become clear. Notably, several recently published reports revealed that stress-related structures in the brain undergo anatomical and neurophysiological changes during the onset of TTS, suggesting that stress-induced

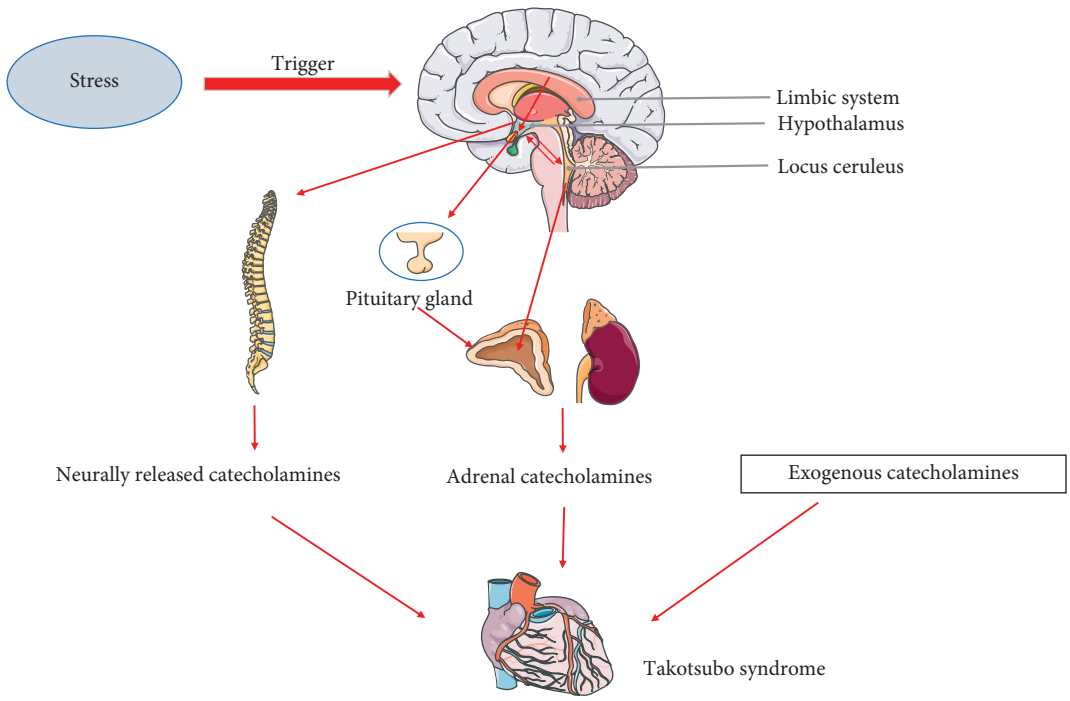

Figure 1: The possible brain-heart connection in the pathogenesis of TTS. The stress-induced alterations in the central nervous system may activate the SNS and thus cause TTS.

alterations in the central nervous system may activate the SNS and thus cause TTS (Figure 1). However, these studies all featured a cross-sectional design. Additional randomized prospective trials and new interdisciplinary approaches are required to further investigate the role of the central nervous system and the brain-heart connection in the pathogenesis of TTS.

Conflicts of Interest

The authors declare no conflicts of interest.

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Hindawi
Cardiology Research and Practice
Volume 2020, Article ID 5695723, 9 pages
https://doi.org/10.1155/2020/5695723

Review Article

The Nrf-2/HO-1 Signaling Axis: A Ray of Hope in Cardiovascular Diseases

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Received 5 September 2019; Revised 28 December 2019; Accepted 7 January 2020; Published 30 January 2020

Guest Editor: Vicente Javier Clemente-Suárez

Cardiovascular disease, which can lead to angina and shortness of breath, remains one of the most serious threats to human health. Owing to its imperceptible symptoms, it is difficult to determine the pathogenesis and treatment methods for cardiovascular disease. Nuclear factor erythropoietin-2-related factor 2/heme oxygenase 1 (Nrf2/HO-1) is a protein found in all cells of the human body. It is activated, transferred to the nucleus, and bound to DNA by antioxidant response elements (AREs). As a regulator of the antioxidant system, it upregulates the expression of HO-1 to reduce oxidative stress. Nrf2/HO-1 also has the ability to modulate calcium levels to prevent ferroptosis, pyroptosis, autophagy, programmed cell necrosis, alkaliptosis, and clockophagy. In view of the importance of Nrf2/HO-1 in the regulation of homeostasis, this review summarizes current research on the relationship between cardiovascular disease and Nrf2/HO-1. Normal cardiovascular diseases, such as viral myocarditis and myocardial ischemia-reperfusion injury, have been treated with Nrf2/HO-1. Rheumatic heart disease, cardiac tumors, arteriosclerosis, arrhythmia, hypertensive heart disease, and myocardial infarction have also been treated during experiments. Research has demonstrated the clinical application of Nrf2/HO-1 in pediatric cardiovascular disease; further clinical trials will help elucidate the potential of the Nrf2/HO-1 signaling axis.

1. Introduction

Cardiovascular disease is the most serious threat to the health and quality of life of humans. In 2016, an estimated 17.9 million people died of cardiovascular disease, accounting for 31 percent of all deaths worldwide. Currently, the World Health Organization (WHO) Cardiovascular Disease Program works to prevent, manage, and monitor cardiovascular disease globally. Identifying potential functional mechanisms and effective therapeutic drugs to reduce the incidence, prevalence, and mortality of cardiovascular disease has become a universal concern. One approach to preventing pathophysiological and biochemical damage is to use the body's own self-defense mechanism. The autonomic nervous system (ANS), formerly known as the vegetative nervous system, is a controlling system that largely acts unconsciously and regulates bodily functions. It plays an important role in maintaining and regulating homeostasis, indicating that dysfunction of the ANS caused by oxidative stress induces inflammation and exaggerates oxidative stress. Several cytokines triggered by the ANS are involved in the process of self-defense. When nuclear factor erythropoietin-2-related factor 2 (Nrf2) is activated in the nucleus, it turns on the production of antioxidant enzymes such as catalase, glutathione (GSH), and superoxide dismutase (SOD). These antioxidant enzymes neutralize up to one

million free radicals per second. This is an effective approach for reducing oxidative stress, inflammatory response, necrosis, apoptosis, ferroptosis, alkaliptosis, and clockophagy.

The presence of three branches—the sympathetic nervous system, the parasympathetic nervous system, and the enteric nervous system, which constitute the ANS—inside the human body helps trigger vital pathways, such as the Nrf2/HO-1 pathway, when an organism suffers from oxidative stress. The oxidative stress secondarily triggers the synapses. Inhibitory and excitatory synapses between neurons control the internal system by releasing cytokines, which may lead to the activation of relevant pathways. On activation of the Nrf2/HO-1 pathway, the ANS is gradually modified to adapt to the following organ process. Through inflammation and oxidative stress, the ANS helps restore homeostasis. Hence, the effects of the ANS are associated with the Nrf2/HO-1 pathway.

Nrf2 is a critical redox-sensitive transcription factor. It is activated to improve the oxidative stress state of the body, promote cell survival, and maintain the redox homeostasis of cells by regulating the induced expression of phase-II detoxifying enzymes and antioxidant enzymes [1]. Nrf2 protein is expressed in various tissues of the body (such as liver, kidney, spleen, and heart), and contains seven structural domains (Neh1–Neh7). Kelch-like ECH-associated protein-1 (Keap1) has two characteristic domains, namely, the dimerized domain of broad complex-tramtrack-bric-a-brac (BTB) and the double glycine repeat (DGR). The association between Nrf2 and Keap1 is realized through its N-terminal Neh2 domain, which interacts with DGR and negatively regulates Nrf2 function. When cells are attacked by reactive oxygen species (ROS) or electrophiles, Nrf2 dissociates from Keap1 and is rapidly transferred to the nucleus. Phosphorylated Nrf2 forms a heterodimer with Maf protein and then combines with antioxidant response elements (AREs), which activate the expression of heme oxygenase 1 (HO-1) [2]. In addition, various protein kinases, such as mitogen activated protein kinases (MAPKs), protein kinase C (PKC), and (phosphoinositide 3-kinase (PI3K), participate in the regulation of Nrf2 transcriptional activity by inducing phosphorylation of Nrf2. The specific signal transduction is depicted in Figure 1.

HO-1 is an important endogenous antioxidant and constitutes an important defense system. Activated by Nrf2, HO-1, and its metabolites, including CO, Fe^{2+}, and biliverdin, can prevent excessive oxidation of lipids and proteins by scavenging hydroxyl-free radicals, singlet oxygen, and superoxide anions, and play an effective role in anti-inflammation, antioxidation, and anti-apoptosis [3]. Our previous studies have demonstrated that HO-1 plays a regulatory role in the induction of anti-inflammatory cytokines and adjustment in T-helper 1/T-helper 2 (Th1/Th2) and Th17/Treg ratios of immune cells [4] by activating p55/tumor necrosis factor receptor 1 (TNFR-1), p38 MAPK, and PI3K/AKT signaling axes [4, 5]. Jin et al. demonstrated that HO-1 exerts a cardioprotective effect in simulated H9C2 cells in vitro [5, 6]. Chen et al. have shown that HO-1 can reduce the amount of mitochondrial oxidation products by inducing autophagy to protect the heart [6, 7]. Available evidence indicates that HO-1 protects the systolic function of the heart and improves blood supply to target organs.

This review summarizes the important protective role of the Nrf2/HO-1 signaling axis in cardiovascular diseases. Newly discovered alkaliptosis and clockophagy not only reveal a new form of cell death but also have important implications for the prevention and treatment of biological abnormalities. Through analysis of its mechanism and specific application in disease, the Nrf2/HO-1 signaling axis provides novel insights and directions for the clinical targeted treatment and prevention of cardiovascular diseases.

2. Functional Regulation of the Nrf2/HO-1 Signaling Pathway

2.1. Nrf2/HO-1 Signaling Axis in Regulating Internal Flow of Calcium Ions. Under normal circumstances, the distribution of ions inside and outside the cell membrane is in a stable state. An excessive Ca^{2+} influx may lead to an excessive Ca^{2+} concentration in the mitochondria, Ca^{2+}–dependent degradation enzyme activation, and apoptosis induction, resulting in oxidative stress and dysfunction of cells.

Jin et al. found that rutaecarpine can increase the transcriptional activity of Nrf2 and Nrf2 target genes, HO-1 and NAD(P)H quinone oxidoreductase 1 (NQO1), thereby promoting the phosphorylation of AKT and Ca^{2+}/calmodulin-dependent protein kinase-II (CaMKII) [8]. Li et al. demonstrated that $HgCl_2$ increases the expression of Nrf2, HO-1, and NQO1, and induces apoptosis by inducing Na^{+}/Ca^{2+} overload and ATPase inactivation in mice, providing a new idea for studying the regulatory effect of Ca^{2+} ions and the molecular regulation of the Nrf2-mediated antioxidant pathway [9]. Guidarelli et al. found that inhibiting excessive Ca^{2+} influx into the mitochondria could prevent arsenite-induced cardiolipin oxidation and DNA single strand breakage, which in turn inhibits the survival signal of Nrf2 [10]. The research has demonstrated that the Nrf2/HO-1 signaling pathway is a typical antioxidant pathway and has the potential to alleviate cardiac disorders.

2.2. Nrf2/HO-1 Signaling Axis in Mitochondrial Oxidative Stress. During ischemia, mitochondrial electron transfer dysfunction and ROS accumulation lead to protein degradation, which then leads to mitochondrial dysfunction. The opening of mitochondrial membrane channels destroys the integrity of the mitochondrial membrane. ATP deficiency, intracellular Ca^{2+} overload, and autophagy insufficiency eventually lead to cardiac apoptosis and death.

Chen et al. showed that the potential of the mitochondrial membrane is higher than normal levels, and the mitochondrial ROS level is abruptly reduced during ischemia-reperfusion injuries [7]. Under the influence of oxidative stress, mtDNA mutations easily occur in the mitochondria, thus altering the permeability of the cell membrane [11]. Experimental studies conducted by Zhang et al. have shown that the activation of Nrf2 can reduce the

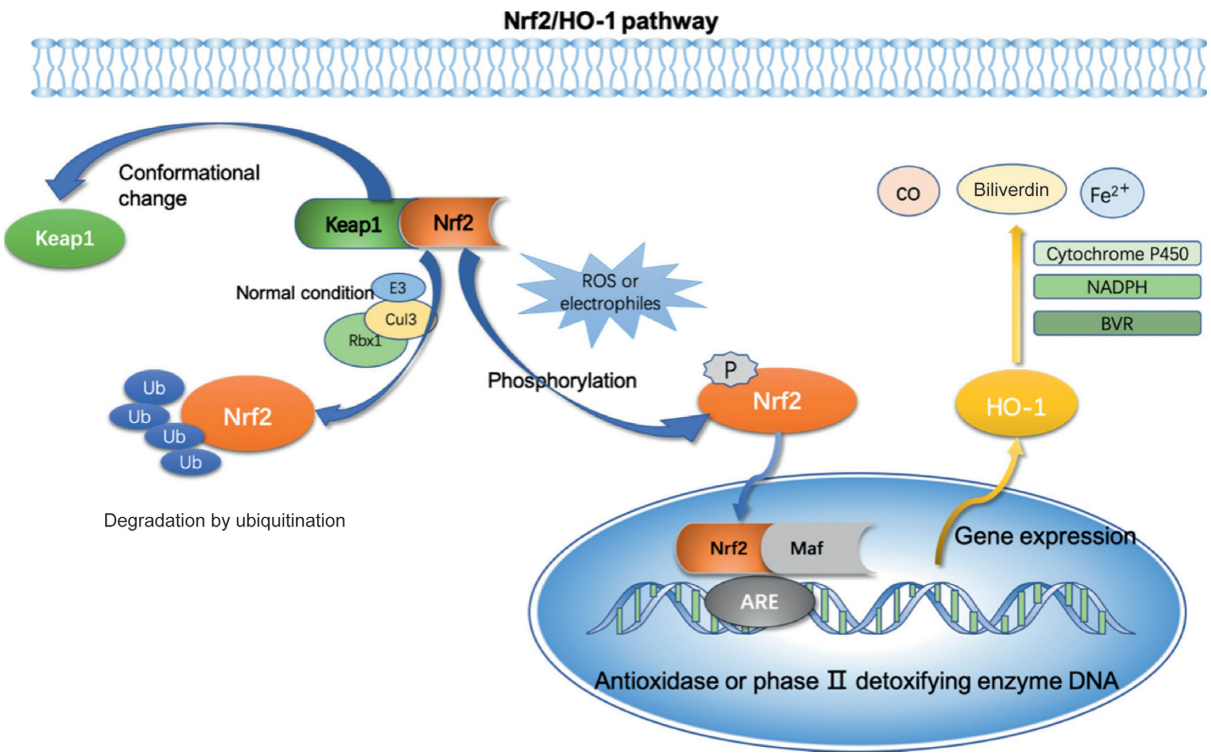

Figure 1: Specific signal transduction of the Nrf2/HO-1 signaling axis.

degree of oxidative stress in the mitochondria and can reduce the oxidative stress and inflammatory response of vascular endothelial cells [12]. Therefore, drugs targeting oxidative stress and mitochondrial dysfunction could be used for the treatment of cardiovascular diseases in the future.

2.3. Nrf2/HO-1 Signaling Axis in Ferroptosis. It was previously thought that almost all regulated cell death in mammalian cells resulted from the activation of caspase-dependent apoptosis [13]. However, Stockwell et al. challenged this view by discovering regulated nonapoptotic cell death pathways. Erastin, a RAS-selective lethal compound, can trigger a unique iron-dependent nonapoptotic cell death by accumulating ROS; this type of cell death was defined as "programmed iron necrosis" [14]. Iron death is driven by the lipid peroxidation pathway, mainly through the iron metabolism and GSH depletion pathways.

Nrf2 can produce an effect on the heme-binding ferrous content by regulating intracellular heme synthesis and metabolism [15]. The most important effect is the regulation of the expression of HO-1 [16]. Nrf2 can also maintain the stability of intracellular active iron by regulating its storage and release. Human ferritin can be divided into ferritin heavy chain (FTH1) and ferritin light chain (FTL). The FTH1 gene is the target gene of Nrf2. FTH1 can oxidize Fe^{2+} to Fe^{3+} and store it. Activated Nrf2 regulates not only iron homeostasis by increasing iron storage but also the expression of the membrane iron transporter (FPN1) to regulate iron ions in and out of cells. FPN1 is the only protein that can transfer iron ions out of cells. Recent studies have also shown that Nrf2 activation can upregulate the expression of genes involved in iron metabolism and ROS metabolism.

By injecting mice with doxorubicin (DOX), Fang et al. demonstrated that ferroptosis is associated with cardiomyopathy [17]. They also discovered that HO-1 is activated at a higher rate in diseased mice than in control mice. Based on these studies, we suggest that the effect of the Nrf2/HO-1 signaling pathway in cardiovascular diseases may be linked to ferroptosis.

2.4. Nrf2/HO-1 Signaling Axis in Pyroptosis. Pyroptosis, characterized by caspase-1 dependence and the release of a large number of pro-inflammatory cytokines, is a newly identified type of programmed cell death. The morphological characteristics, occurrence, and regulatory mechanisms of pyroptosis are different from those of other cell death modes such as apoptosis and necrosis.

The inflammatory response involved in pyroptosis is closely related to the Nrf2/HO-1 signaling axis. Zhao et al. found that downregulation of the Nrf2/HO-1 pathway in neuroblastoma cells activated cell pyroptosis and increased oxidative stress-induced toxicity [18]. The cyclooxygenase-2 inflammatory signaling cascade pathway, as summarized by Kobayashi et al., confirmed that the downstream product of the cyclooxygenase-2 pathway binds to Keap1, thereby activating Nrf2 and promoting inflammation regression [19]. Zhang et al. recently demonstrated the effective regulation of HO-1 in reducing inflammation and oxidative stress [4, 19]. Furthermore, Chen et al. found that the lipopolysaccharide-induced AMPK/Nrf2/CXC chemokine receptor 2 axis can

promote the recruitment of neutrophils to the heart, significantly reducing myocardial dysfunction in mice [20]. Therefore, Nrf2 upregulates neutrophils activity, alleviating lipopolysaccharide-induced cardiac pyroptosis. The evidence implies a protective function of upregulating the Nrf2/HO-1 axis in cardiovascular diseases.

2.5. Nrf2/HO-1 Signaling Axis in Autophagy. Autophagy is the process of phagocytosis of cytoplasmic proteins or organelles and their inclusion into vesicles. These vesicles then fuse with lysosomes to form autophagy lysosomes, which is followed by degradation of the contents of the lysosomes for realization of the metabolic needs of the cell and for the renewal of some organelles. It is a dynamically regulated self-digestion process and an endogenous protective mechanism that inhibits myocardial and vascular injury by reducing the release of interstitial vesicles.

There have been multiple reports on the effects of Nrf2-induced autophagy. Inoue et al. found that, under iron deficiency conditions, the body activates Nrf2 expression by regulating the p62/SQSTM1/sequestosome-1 signal during autophagy [21]. Yao et al. demonstrated that activation of the Nrf2-ARE signaling pathway promotes autophagy in vascular smooth muscle cells and alleviates vascular calcification in high phosphoric conditions [22]. Previous studies have shown that, under oxidative stress, autophagy processes compensate each other to promote cell survival [22]. Recently, it has been found that Nrf2 mRNA levels increased during hepatitis C virus replication, suggesting that the protein kinase RNA-like endoplasmic reticulum kinase axis controls the transcription of antioxidant genes [23].

Based on these reports, we speculate that high levels of cellular stress, especially with the induction of Nrf2, may activate other forms of autophagy to improve cell survival. Now that evidence suggests that Nrf2 signals activate cell survival programs by degrading tumor suppressors and activating oncogenic signals [23], it is reasonable to assume that induction of the Nrf2/HO-1 signaling axis could be a new and efficient clinical treatment method for cardiovascular diseases, especially cardiac tumors and ischemia-reperfusion diseases.

2.6. Nrf2/HO-1 Signaling Axis in Programmed Cell Necrosis. Necrosis was recognized as an unregulated form of cell death, but a growing number of studies have shown that necrosis is a highly regulated process. Programmed cell necrosis is a type of necrosis. Adameova et al. found that in the absence of lethal stress or injury, programmed necrosis of cardiomyocytes is a major factor that may induce cardiovascular diseases [24]. Zhu and Sun stated that programmed cell necrosis plays a crucial role not only in heart homeostasis but also in the pathogenesis of cardiovascular diseases [25]. de Souza Prestes et al. demonstrated that patients with cardiovascular diseases have a higher level of methylglyoxal (MG), which can be controlled by the Nrf2/HO-2 signaling axis and converted to D-lactic acid [26]. Moreover, the increase in MG content is closely related to cell necrosis [26]. These data indicate that Nrf2/HO-1 is associated with programmed cell necrosis.

2.7. Nrf2/HO-1 Signaling Axis in Alkaliptosis. Recently, new forms of nonapoptotic regulated cell deaths (RCD), such as alkaliptosis, have been studied. Alkaliptosis is a unique pH-dependent form of RCD driven by intracellular alkalinization [27]. Song et al. showed that JTC801 can induce a pH-dependent cell death in human pancreatic cancer cells by activating NF-κB [28]. This form was found to be distinct from ferroptosis, necroptosis, and autophagy, and was defined as alkaliptosis. As we have pointed above, NF-κB is closely related to Nrf2/HO-1 signaling axis. Therefore, we suggest that alkaliptosis and Nrf2/HO-1 signaling axis are related.

Although NF-κB inhibitors can inhibit alkaliptosis [29], no effect of Nrf2 knockout alters JTC801-induced cell death [28]. However, as pathological significance of alkaloptosis and its core effector molecules are still being studied, the specific relationship is not yet clear. In addition, Song et al. are focusing on pancreatic cancer rather than cardiovascular disease, and the study has limitations. Therefore, based on the close relationship between Nrf2/HO-1 and NF-κB, we hypothesize that Nrf2/HO-1 causes cardiovascular diseases through alkalinization.

2.8. Nrf2/HO-1 Signaling Axis in Clockophagy. Disruption of circadian rhythms exacerbates disease pathogenesis. Profiling of mice genes showed that 43% of all protein-coding genes display a biological rhythm, mostly in an organ-specific manner [30]. de la Sierra et al. have demonstrated that clockophagy is associated with hypertension [31], which indicates that clockophagy has a link with cardiovascular diseases. Melissa et al. found that the circadian regulation of protein expression plays a significant role in the cellular response to oxidative stress. They also concluded that the different levels of lipid peroxidation and protein oxidation in the day indicate circadian oscillations of oxidative stress responses. This rhythmicity of antioxidant levels can be exploited for a more precise targeting of ROS [32]. Yang et al. indicated that clockophagy is the endogenous oscillating mechanism, as it controls various cellular processes, including iron metabolism, oxidative stress, and cell death [33]. Liu et al. demonstrated that clockophagy, namely, the selective autophagic degradation of the circadian clock regulator aryl hydrocarbon receptor nuclear translocator-like protein/brain and muscle ARNT-like 1 (ARNTL/BMAL1), promotes ferroptosis in vitro and in vivo [34]. In other words, clockophagy-mediated ARNTL degradation promotes lipid peroxidation and subsequent ferroptosis. These studies indicate that an all-new type of selective autophagy can promote ferroptosis via the Egl 9 homolog 2-hypoxia-induced factor 1A (EGLN2-HIF1A) pathway. As ferroptosis can have an effect on cardiovascular diseases, it is closely related to clockophagy; we suggest that there is a relationship between cardiovascular diseases and clockophagy.

3. Clinical Research in Pediatric Cardiovascular Diseases

3.1. Viral Myocarditis. Viral myocarditis refers to an infectious cardiomyopathy, which can be localized to myocardium or diffuse inflammatory disease caused by viral infection. Viral myocarditis is usually caused by enteroviruses, including Coxsackie virus B (CVB). Patients suffering from viral myocarditis show symptoms such as chest pain, rapid or abnormal heart rhythms, and shortness of breath.

According to Song et al., ulinastatin (UTI) protects against CVB3-induced acute viral myocarditis through Nrf2 activation [35]. Furthermore, Ai et al. revealed that Nrf2 pathway is downregulated because of the upregulation of the 12/15-lipoxygenase (12/15-LO), which can be inhibited by baicalein through reducing inflammatory cytokine production and oxidative stress [35, 36]. Conversely, Wang et al. have demonstrated that the immune and inflammatory processes can also function as a trigger for the activation of Nrf2 [37].

The Nrf2 pathway has not yet been systematically researched in the context of the treatment of viral myocarditis; further research will reveal the effects of this pathway.

3.2. Rheumatic Heart Disease (RHD). Common in remote communities, RHD is a disease involving severe damage to the human heart caused by rheumatic fever. RHD often develops from untreated streptococcal infection, leading to an inflammatory condition.

Similar to RHD, rheumatic arthritis (RA) also results in immune activation, inflammation, and oxidative stress [38]. In response to oxidative stress, the activation of Nrf2/HO-1 exhibits anti-inflammatory and antioxidative effects in animal and human models of RA [39].

Although there are few studies investigating the function of Nrf2 in RHD, with numerous reports regarding Nrf2 functioning in the anti-inflammatory process, we can reasonably speculate that the Nrf2 pathway plays an important role in recovery from RHD.

3.3. Cardiac Tumors. Cardiac tumors are primary or secondary tumors that form in the heart. Whether the tumor is benign or malignant, it causes problems because of its location and size, which is large enough to be discovered by echocardiogram. Many patients have no symptoms; however, if blood flow is blocked, it results in shortness of breath.

Nrf2 pathway can be "fine-tuned" by microRNA (miRNA) to regulate antioxidant defense enzymes and counteract oxidative stress [40]. Furthermore, while studying sulforaphane, Bose et al. found that Nrf2 can be activated to protect heart from DOX toxicity, whereas DOX is functioning synergistically with sulforaphane [41]. Therefore, we can hypothesize that Nrf2 has a significant effect on cardiac tumors.

In future, methods for studying miRNAs and cardiac tumors will be developed, which could reveal the potential of the Nrf2 pathway for the treatment of cardiac tumors.

3.4. Myocardial Infarction (MI). MI occurs when the blood flow to the heart is insufficient, and it causes damage to cardiac muscles. MI is often caused by high blood pressure and myocarditis, and results in abnormal heart rate, sudden breathlessness, and extreme fatigue. MI, which is difficult to treat, has gradually become one of the most severe diseases worldwide.

According to Lian et al., in addition to downregulating the expression of several inflammatory factors and activating apoptosis-related proteins, MI model of rats having progressive nephropathy activate the renin-angiotensin-aldosterone system (RAAS), which is simultaneously connected with the defective Nrf2 pathway [42]. Hence, restoration of Nrf2 may have a positive influence on the RAAS. Furthermore, based on the consideration that Nrf2 reduces oxidative stress and that tetrahedral DNA nanostructures (TDNs) are biologically safe, Zhang et al. have discovered that TDNs can activate the Nrf2 pathway to improve the outcome after a myocardial infarction injury, by being transferred into the nucleus and upregulating genes involved in antioxidative mechanisms [43]. Ren et al. also discovered a pathway which cooperates with Nrf2 to maintain sufficient oxygen availability [44].

An increasing amount of research has been published to support the theory that Nrf2 pathway can be used in the recovery of MI. It is believed that a simplified method for utilizing the Nrf2 pathway will soon be applied to clinical settings.

3.5. Myocardial Ischemia Reperfusion Injury (MIRI). MIRI is an adverse cardiovascular condition caused by blood rushing back to the heart after a period of no blood flow. The lack of blood results in a shortage of oxygen and nutrients, which are necessary for heart functioning, whereas the return of blood flow causes inflammation and damage.

In MIRI, Nrf2 downregulates the inflammatory factor myeloperoxidase (MPO) and simultaneously upregulates the levels of antioxidants, such as SOD and glutathione peroxidase (GPx), to counter inflammation and oxidative stress. Jakobs et al. demonstrated that Nrf2 is maintained in the reduced state to increase the expression of antioxidative enzymes by thioredoxin-1 (Trx-1), and in turn, Nrf2 regulates the activation of Trx-1 through two AREs [45]. As demonstrated by Chen et al., Nrf2 is able to not only function after inflammation and oxidative stress but also after reperfusion injury, via activation by trigger factors such as emulsified isoflurane (EI) [46].

Though Nrf2 has a mostly indirect effect on MIRI, its potential for recovery from myocardial damage must not be neglected. When used with other clinical treatments, the Nrf2 pathway can significantly reduce inflammation and oxidative stress, thereby alleviating MIRI. However, the trials are still in the animal testing phase, and more experiments are required to prove Nrf2 as a therapeutic strategy.

3.6. Atherosclerosis (AS). Atherosclerosis is a disease that hardens and narrows the arteries, risking reduced blood

Table 1: Functional effects of the Nrf2/HO-1 signaling axis in cardiovascular diseases.

Cardiovascular disease	Effects	Reference
Viral myocarditis	Reduces inflammatory cytokine production and oxidative stress	[36]
	Reduces CVB3-induced myocarditis by activating GSK-3β	[37]
Rheumatic heart disease (RHD)	Inhibits signal transducer	[39]
Cardiac tumors	Regulates antioxidant defense enzymes and counteracts oxidative stress	[40]
	Reduces toxicity with sulforaphane	[41]
Myocardial infarction (MI)	Involved the renin-angiotensin-aldosterone system	[42]
	Upgrades antioxidant genes	[43]
Myocardial ischemia reperfusion injury (MIRI)	Regulates the activation of thioredoxin-1 (Trx-1) through two antioxidant response elements	[45]
	Regulates ROS levels	[46]
Atherosclerosis (AS)	Strengthens antioxidative potential and alleviates inflammation	[47]
	Enhances the expression of HO-1	[48]
	Mediates atherosclerosis by saturated fatty acids	[49]
Arrhythmia	Produces antioxidant enzymes to reverse oxidative damage	[52]
	Activates the NO pathway	[53]
Hypertensive heart disease	Reverses the mitochondrial apoptosis effect	[54]
	Downregulates TGF-1/Smads in myocardial remodeling	[55]
	Promotes lipolysis enzymatic activity	[56]

flow. AS usually results from damage of the endothelium from high blood pressure, smoking, and high cholesterol. If allowed to worsen, AS can lead to cardiovascular diseases.

Yang et al. demonstrated that the leaf extract of *Nelumbo nucifera* (NLE) possesses anti-atherosclerosis properties. The supplementation of NLE also increases the expression of Nrf2 and its downstream targets [47]. Hence, using NLE to upregulate the function of Nrf2 can be developed into a rational treatment for atherosclerosis. Li et al. put forward a similar method by utilizing bisdemethoxycurcumin (BDMC), extracted from turmeric, to enhance the expression of HO-1 [48]. In Nrf2/HO-1-dependent manner, BDMC provides cardioprotection and can be used in clinical treatments. Girona et al. have found that Nrf2 is activated by palmitate, and may represent a new mechanism of mediating atherosclerosis via saturated fatty acids [49]. AS has been shown to be triggered by multiple mechanisms. However, with the discovery of the Nrf2/HO-1 signaling axis, more targeted treatment for patients is possible.

3.7. Arrhythmia. Abnormal conduction by the heart can cause tachycardia, bradycardia, and arrhythmia. Arrhythmias are particularly common in patients with heart disease and often occur during anesthesia, surgery, or after surgery. Stress, smoking, drinking, excessive fatigue, and serious insomnia often result in arrhythmia.

Studies have shown that excessive ROS not only cause arrhythmia but also cause inflammatory body infiltration and activate autoimmunity [50], which may further damage cardiomyocytes. In addition, Dai et al. pointed out that long-term arrhythmia may cause or enhance fibrosis-induced chronic cardiomyopathy [51], which may lead to severe long-term damage in patients.

However, the exploration of the Nrf2/HO-1 axis has revealed a possible solution. Dong et al. showed that when Nrf2 expression is inhibited in H9C2 cells, aldehydes no longer stimulate the production of enough antioxidant enzymes to reverse the oxidative damage, leading to a greatly increased incidence of arrhythmias [52]. On the contrary, Enayati et al. found that *Potentilla reptans* extract directly enhances endogenous antioxidant defense of cardiomyocytes and indirectly activates the NO pathway through the Nrf2/HO-1 signaling axis, thereby relieving arrhythmia and myocardial infarction [53].

The activation of the Nrf2 signaling pathway can inhibit oxidation and reduce the production of free radicals, thereby reducing the oxidative damage to the myocardium. Research so far is restrained to cellular and animal experiments. Hopefully, Nrf2-based therapies will be tested in human clinical trials in the near future.

3.8. Hypertensive Heart Disease. Hypertensive heart disease results from the failure to control long-term hypertension, which leads to defects in the heart structure. Some studies show that 70% of heart failures are caused by high blood pressure. At the same time, high blood pressure may cause coronary heart disease, atrial fibrillation, and other cardiac complications, finally resulting in heart failure.

Previous studies have proposed that mitochondrial dysfunction may contribute to the development of cardiovascular diseases, such as hypertensive heart disease [54]. According to our theory summarized above, the Nrf2/HO-1 signaling axis may reverse the effect of mitochondrial apoptosis, thus slowing down the disease process, and could be used as a therapy to alleviate hypertensive heart disease. Furthermore, Wang et al. revealed that rosuvastatin can improve cardiac function and reduce hypertrophy by regulating the interaction between Nrf2 and Smads [55]. Upregulation of the Nrf2/ARE/HO-1 pathway and downregulation of the transforming growth factor 1 (TGF-1)/Smads pathway play important roles in myocardial remodeling.

A recent study by Biernacki et al. found that inhibition of lipolysis by fatty acid amide hydrolase inhibitors can

increase enzymatic activity and nonenzymatic antioxidant activity in rats, whereas Nrf2 expression is significantly downregulated [56]. Clinical trials have just started, and the specific treatments are now in the molecular and animal testing phases. Therefore, treatments involving the upregulation of Nrf2 expression will improve hypertensive heart disease by promoting lipolysis in the near future (Table. 1)

4. Conclusions

The Nrf2/HO-1 signaling pathway is a multi-organ protection pathway, with an antioxidative function, playing a role in eliminating environmental and endogenous stressors from the body, thus delaying the progress of related diseases. This pathway has become a popular target for research on the occurrence and development of oxidative stress-related diseases. This has a complex regulatory mechanism in oxidative stress-related diseases. It plays a role in reducing mitochondrial damage, and regulating Ca^{2+} influx, programmed cell death, autophagy, and cell pyroptosis and ferroptosis. Latest research also suggests two new processes in which the Nrf2/HO-1 axis is involved: alkaliptosis and clockophagy. Through in-depth research and exploration of the mechanisms, good theoretical support for the therapeutic application of Nrf2/HO-1 in clinical practice can be provided. Hopefully, the diseases mentioned above may well have a new therapy in the future.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

Xueyan Zhang, Yihan Yu, and Hanyu Lei contributed equally to this article.

Acknowledgments

This research was funded by the National Key Research and Development Program of China (2018YFA0108700 and 2017YFA0105602), NSFC Projects of International Cooperation and Exchanges (81720102004), National Natural Science Foundation of China (81570279, 81974019, and 81970248), the Research Team Project of Natural Science Foundation of Guangdong Province of China (2017A030312007), and the National Training Program of Innovation and Entrepreneurship for Undergraduates (GS201910533060).

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