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An animal model of stress-induced cardiomyopathy utilizing the social defeat paradigm

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HIGHLIGHTS

- Social defeat serves as a useful animal model of stress-induced cardiomyopathy.
- Resident-intruder methodology for social defeat was utilized.
- Heart weight/body weight and left ventricle/body weight ratios of intruder rats increased.
- Heart lengths of intruder rats were elongated.
- Corticosterone and troponin I levels of intruder rats were elevated.

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ABSTRACT

Stress-induced cardiomyopathy (SIC) is a form of acute heart disease triggered by extreme psychological stress. In patients who develop SIC, the outward symptoms are almost indistinguishable from acute myocardial infarction (AMI). However, some important criteria differentiate patients with SIC from those with AMI. Patients with SIC: 1) experience some form of extreme psychological stress from minutes to hours before developing heart disease, 2) do not suffer from atherosclerosis or coronary artery obstruction, and 3) exhibit abnormal ballooning of the left ventricle. In the present study, the resident-intruder (RI) social defeat test was investigated as a potential rat model for stressed-induced cardiomyopathy. Adult Long-Evans rats were implanted with a biotelemetry transmitter for ECG recordings and habituated for two weeks. An intruder rat was placed in the cage of a resident rat behind a wire-mesh partition for 5 min. The partition was then removed for 5 min to allow direct contact between the intruder and resident rats. After this interval, the wire-mesh partition was replaced and the intruder rat remained behind the partition for an additional 50 min. Behavioral responses were noted and ECG recordings were collected during the entire 60-min testing period. Upon completion of the test, the intruder rat was removed from the cage of the resident rat and sacrificed. The heart was examined and blood was collected. Heart weight/body weight ratio, left ventricle/body weight ratio, heart length, plasma corticosterone levels, and plasma troponin I levels of intruder rats were significantly higher as compared to control rats. Intruder rats significantly increased their heart rate during the first 5 min of the RI test. It is concluded that the RI test to induce social defeat is a novel rodent paradigm for modeling stress-induced cardiomyopathy in the human.

1. Introduction

Current research in neurophysiology is revealing more evidence that negative psychological events have the potential to cause, in some cases, dramatic harm to human beings [1]. Stress-induced cardiomyopathy (SIC) is a form of acute heart disease triggered by extreme psychological stress. Reported cases of SIC have increased in frequency since the disease was first described in 1991 by Japanese cardiologist Dote and his colleagues [2]. In the *Journal of Cardiology*, Dote reported cases of patients with symptoms of acute heart disease involving an unusual dysfunction of the left ventricle (LV), which he described as myocardial stunning. This LV dysfunction, he noted, caused impaired systolic contraction (i.e., failure to adequately eject blood) due to a partial paralysis of the chamber walls and was reversible without residual damage to the tissue [3].

The disease characterized by Dote and his colleagues was later named Tako-tsubo (Japanese for "octopus trapping-pot"), since the stunned, dysfunctional LV balloons outward and physically resemble the silhouette of a Japanese octopus-trapping device [4]. In the literature, Tako-tsubo cardiomyopathy is synonymous with several other

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terms including SIC, apical ballooning syndrome, and broken heart syndrome [2]. Fortunately, SIC is easily reversible should treatment be given upon diagnosis. Within 7–37 days, a full recovery is evident in 96% of patients that receive appropriate medical care [5].

In patients who develop SIC, the outward symptoms are almost indistinguishable from acute myocardial infarction (AMI) [6,7]. However, several important criteria differentiate patients with SIC from those with AMI. First, all patients with SIC experience some form of extreme psychological stress from minutes to hours before developing heart disease [2]. Second, patients with SIC do not suffer from atherosclerosis or coronary artery obstruction common to most AMI patients. Third, abnormal LV ballooning due to hypokinesia (diminished contractility) or dyskinesia (paralysis of the myocardial wall muscle) of the apex is unique to SIC patients and does not occur during an AMI [8]. The ballooning exhibited in the LV of all human SIC patients is a result of visible wall motion abnormalities that decrease left ventricular functionality [9].

Although cardiac hypertrophy usually develops over a period of months or years in humans, one of the first studies to describe SIC in a population of patients in the United States noted that the time between the stressful event and the onset of cardiac symptoms ranged from minutes to hours [2].

Determination of heart rate variability (HRV) provides a better insight into the overall health and functionality of the heart than analyzing individual ECG recordings for arrhythmias [10]. In many cardiovascular disease states, HRV is markedly decreased below normal. To analyze HRV, a time-dependent analysis of changes in the R–R interval is commonly utilized. The standard deviation of the R–R interval, abbreviated SDNN, is well established as a reliable time-domain measure of HRV and can be calculated from ECG segments as short as 5 min. Thus, SDNN is an index of HRV, which is frequently used in patients to determine cardiovascular prognosis [11].

Norepinephrine (NE) is hypothesized to play an integral role in the development of SIC [2]. It has been suggested that the initial surge of NE, released during a psychologically stressful experience, may lead to myocyte injury and dysfunction. Overstimulation of adrenergic receptors from excess NE at the neuromuscular junction may lead to the "neural stunning" and periodic LV akinesia in SIC [12]. Plasma NE levels in patients with SIC directly following acute stress are greater than the levels of NE in patients with an AMI [13].

Cortisol is also strongly implicated in the development and maintenance of SIC. It has been hypothesized that a potential dysregulation of glucose metabolism at the LV apex results in the observed partial paralysis of the chamber walls [12].

In addition to elevated NE and cortisol levels, plasma cardiac troponin I (TnI) has also been found to be increased in the blood of patients with SIC. Levels of plasma TnI are elevated in SIC patients slightly above healthy individuals, but not to the same extent observed in AMI patients [14].

Although SIC was first described as occurring primarily in older women, more recent reports recognize that it also occurs in men, and some studies have even reported a greater proportion of men than women in a group of patients treated for this disease [15–17]. For example, in the Park et al. [17] study, of the 92 patients admitted to the ICU for left ventricular apical ballooning over a 3 month period, 65 (71%) were men. Recent studies suggest that physical stressors are especially important in the occurrence of SIC in male adults [18]. The sympathetic activation caused by anger in men, such as emotional reactions while watching football matches, is also being studied for its relationship to acute heart disease [19].

In the past, animal models have been successfully utilized as a tool to mimic human cardiovascular disease and to study pathophysiological mechanisms in greater detail [20]. While several hypotheses exist, SIC is still largely uncharacterized and not well studied. Rats in particular are especially useful as animal models of human behavioral disease due to genetic similarity and closely related neurological and endocrine systems. Regarding SIC, a rat model has been proposed through the use of immobilization stress of female rats bound to wooden boards [4]. Although evidence of LV ballooning was induced by this technique, such a model is confounded by unrelated side effects pertaining to immobilization stress, such as stomach ulcers.

Since SIC results from acute and traumatic stress, a previously established paradigm of acute stress in lab rodents may be suitable for use as a SIC model. Specifically, the resident-intruder (RI) test is a classical paradigm that is commonly employed to facilitate aggression in resident rats and stress in intruder rats, mice and voles [21]. Sgoifo and his colleagues determined that social defeat through the RI test creates great instances of "heart rate accelerations," ventricular arrhythmias, and high plasma catecholaminergic responses in intruder rats [22].

An enlargement of the LV in the rat would parallel the characteristic "ballooning" demonstrated in the human associated with SIC. A normal HW/BW ratio in humans is approximately 5 g/kg, which is comparable to 2.5 mg/g in rats [23]. Since cardiac hypertrophy and symptoms of SIC occur within minutes to hours in humans, a rat model could be expected to develop SIC within 10–60 min of acute stress [2]. Similarly, in rats, ventricular weight-to-body weight (VW/BW) ratios have been determined to assess cardiac hypertrophy of the LV only [24]. VW/BW ratios are relevant in studies of cardiac diseases that affect the LV, such as SIC. In addition, the determination of lung weight-to-body weight (LW/BW) ratios provides insight into the cardiovascular health of animals [25]. High LW/BW ratios indicate pulmonary congestion, a severe consequence of heart disease and/or failure. In an animal model of SIC, a non-lethal disease, high LW/BW ratios would not be expected.

In a rat model of SIC, it is important that HR and HRV changes are monitored. This can be accomplished through biotelemetry, which involves the implantation of wireless biopotential transmitters into small animals, such as the rat. Biopotential transmitters monitor internal changes within the rat body and, via radio communication, deliver information in real time to a receiver for data storage. Continuous ECG recordings are commonly achieved via biotelemetry.

The purpose of the present study was to develop an animal model of SIC in the male Long-Evans rat through the psychological and physical acute stress of social defeat elicited by the RI paradigm. We hypothesized that the stress of the RI test could induce SIC in the intruder rat. In addition, we proposed that an examination of several parameters regarding the heart and blood constituents of intruder animals would indicate the viability of the test as a model of the disease.

2. Materials and methods

2.1. Animal housing and care

The Institutional Animal Care and Use Committee approved all animal procedures and NIH guidelines were followed. Fifteen male and three female Long-Evans rats (Harlan, Inc., Indianapolis, IN) were used in this study. Three male rats weighing between 250 and 274 g were designated as resident rats. Each resident rat was placed in a large cage (22" × 14" × 8") with granulated bedding, in a room separate from all other male rats, and was paired with one sterilized female rat (approximately the same age in days as the resident rats). The remaining twelve male rats were divided into two groups of 6 intruder and 6 intruder-control animals. Each group of animals (resident-female pairs, intruder rats, and intruder-control rats) was housed in a separate room.

2.2. Surgery and telemetry

Two weeks before the RI tests, CTA-F40 Data Sciences International (DSI) (St. Paul, MN) transmitters were implanted into the abdomen of the 6 intruder and 6 intruder-control animals for ECG recording. Each animal was anesthetized with an intraperitoneal injection using a 1:1