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Research Article
Effect of Chronic and Acute Psychological Stress and Fluoxetine on Biomolecules of Heart

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Abstract

Background and Objective: Evidence-based knowledge of depression reveals the existence of co-morbidity with a wide range of diseases including cardiac dysfunction. Molecular indications between depression and the risk of heart failure are required for clinical correlation. The objective of the study was to evaluate the effect of both acute, chronic psychological stress and stress treatment (fluoxetine) on heart structure and functional biomolecules. **Materials and Methods:** Mild chronic and acute stress paradigm of 8 weeks was performed and compared with untreated (control group) and mild heat stress with isoproterenol (1 mg kg^{-1} as per 8 week paradigm as negative control) in rats. Heart functionalities were checked by echocardiography and the level of monoamine oxidase enzyme activity was checked while heart failure molecular attribute was vested to Matrix Metalloproteinase (MMP). Contractility strength of left ventricular cardiac muscles strip along with caspase as an apoptotic attribute by western blotting was also carried out to strengthen the conclusion. **Results:** Results clearly showed the significant effects of psychological stress on heart functionalities (ejection fraction (%), heart rate, absolute heart mass, systolic and diastolic left ventricular pressure), MMP level, cardiac contractility and caspase expression ($p<0.05$ for all). The effect of fluoxetine treatment attenuated the contractility in terms of passive strength reaching to level of the control group only while there was a large difference between acute stress only and acute stress with fluoxetine treatment ($p<0.05$) but not reaching to level of the control group ($p<0.05$ for both). **Conclusion:** The effect of mental stress on organ functionality and structure is wide and conspicuous but was not perceptibly protected by the psychological treatment given in this study.

Key words: Antidepressant, anxiety, caspase, contractility strength, depression, heart failure, monoamine oxidase, stress

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

World Health Organization (WHO) fact sheet 2017 revealed the global scenario of cardiovascular diseases. A total of 17.9 million deaths were reported in 2016 due to cardiovascular diseases corresponding to 31% of all global deaths. Cardiovascular diseases retained their rank as number one as a primary reason for death. Among all deaths due to cardiovascular diseases the most contribution is from heart attack and stroke alone[1]. So, it is of utmost urgency to find the root cause and cure in this particular direction.

Many diseases have been attributed as coexistence with depression (or vice versa) like cardiovascular diseases[2], diabetes[3], kidney disease[4], arthritis[5], cancer[6]. There is the relation between/among depression and other non-communicable organ physiology dependent disease(s) and vice versa situation[7]. In a clinical study, supporting the above statement, it was found that out of 388 stable and hospitalized, adult subjects with cardiac complications 40% (i.e., 156 subjects) were suffering from clinical depression alongside. While non-minimal depression was observed in ~80% i.e. twice of the subjects (approximately 304 in number)[8]. In a recent study, repeated psychological stress (e.g., witnessing a traumatic event) to the animal (rat) developed depression and heart functionality disorder as co-morbidity. The researcher concluded that psychological stress i.e., witness of defeat showed consequently chronic impairment in cardiovascular functionalities[9].

Based on the above background this animal study was directed to evaluate the effect of both acute, chronic psychological stress and stress treatment (fluoxetine) on heart structure and functional biomolecules.

MATERIALS AND METHODS

Study area: The study was carried out at the Department of Coronary Disease, Qinghai Province Cardiovascular and Cerebrovascular Disease Specialist Hospital, Xining, Qinghai, China from 1 April, 2018-7 May, 2020.

Ethics approval and consent to participate: All the protocols of animal studies (given below) were presented to and got it approved by the institutional committee of Qinghai Province Cardiovascular and Cerebrovascular Disease Specialist Hospital, for ethics in animal experiments (ICEAE_2018/07/25_3, dated 15 July 2020). The study was carried out in compliance with the ARRIVE guidelines 2.0[10].

Animals: A total of 68 Sprague-Dawley (SD) rats, weight ranging from 200-290 g was procured from Shanghai Experiment Animal Research Center, China. Animals were acclimatized in a new laboratory for 15 days under standard conditions as per directions given by animal care laws of China.

Psychological stress

Chronic unpredicted mild stress: The chronic and unpredicted mild stress depression model was referred to from the literature[11]. In this model, rats were given stress for a total of 8 weeks with 4 cycles of 2 weeks each. After completion of each stress cycle, one day of "no stress" exposure was given. The unpredictable pattern decided given in Table 1 assuring not repeating the stressor on the same day of the cycle.

Acute stresses model for depression: Following stresses were exposed to animals i. Forced Swim stress (FS) apparatus is of glass (25×15×25) filled with ice-cold water temperature 5±3 up to the height of 15 cm and the animal was forced to swim in water for 10 min, ii. immobility of rat as stress for 10 min with standard immobility cage, iii. animal upside-down suspension stress through the tail (50 cm height) for 10 min. Each stress was given twice a day (8 hrs interval). The acute stressors exposure design is expressed in Table 2.

Heart stress leading to failure: The stress to heart was selected (1 mg mL^{-1} for 28 days) as per experimental requirements which is low and chronic injury exposure to heart to compare the heart functions and biochemicals with

Table 1: Chronic unpredictable mild stress exposure design

	Days													
Cycle	1	2	3	4	5	6	7	8	9	10	11	12	13	14
C_1	TC	NS	FO	WD	LD	NS	UB	LD	WD	TC	FL	UB	FO	FL
C_2	FO	WD	NS	UB	TC	FO	WD	FL	LD	UB	NS	TC	FL	LD
C_3	WD	FL	LD	NS	FO	TC	LD	UB	FO	WD	TC	FL	NS	UB
C_4	LD	FO	WD	TC	NS	UB	FL	WD	NS	LD	UB	FO	TC	FL

C: Cycle of 2 weeks, C1-4: 1-4 Cycles, WD: Water deficit, TC: Tilted cage, LD: Light and dark, UB: Uncomfortable bedding, FO: Foreign object, FL: Flashing light, NS: No stress

Table 2: Acute stress exposure design

	Days													
Cycle	1	2	3	4	5	6	7	8	9	10	11	12	13	14
C_1	TS	NS	FS	NS	IM	NS	NS	TS	NS	FS	NS	IM	NS	TS
C_2	No exposure to stressors													
C_3	No exposure to stressors													
C_4	TS	NS	FS	NS	IM	NS	NS	TS	NS	FS	NS	IM	NS	TS

C: Cycle of 2 weeks, C1-4: 1-4 cycles, FS: Forced swim, TS: Tail suspension, IM: Immobility, NS: No stress

Table 3: Isoproterenol (1 mg kg^{-1}) injection planning for 8 weeks

	Days													
Cycle	1	2	3	4	5	6	7	8	9	10	11	12	13	14
C_1	IP	NI	IP	NI	IP	NI	NI	IP	NI	IP	NI	IP	NI	IP
C_2	No stress week cycle													
C_3	No stress week cycle													
C_4	IP	NI	IP	NI	IP	NI	NI	IP	NI	IP	NI	IP	NI	IP

C: Cycle of 2 weeks, C1-4: 1-4 cycles, IP: Isoproterenol (1 mg kg^{-1}), NI: No injection

Table 4: Planning of animal groups and treatment

Groups	Numbers of rats	Study	Drug treatment	Abbreviation
I	6	Control	N/A	C
II	6	Heart stress leading to failure	N/A	HS
III	14	Mild stress	N/A	MS
VI	14	Mild stress with standard antidepressant treatment	Fluoxetine as a standard drug in a drinking water bottle (0.1 mg mL^{-1} to deliver 10 mg/kg/day p/o from day 1 of the second cycle (C2) end of the fourth cycle (C4) except days of water deprivation	MSF
V	14	Acute stress	N/A	AS
VI	14	Acute stress with standard antidepressant treatment	Fluoxetine as a standard drug in a drinking water bottle (0.1 mg mL^{-1} to deliver 10 mg/kg/day p/o from day 1 of the second cycle (C2) end of the fourth cycle (C4) except days of water deprivation	ASF

N/A: Not applicable

chronic and acute stress treated animal groups. The planning of isoproterenol is given in Table 3. The experimental design of animal grouping is given in Table 4.

Monoamine oxidase (MAO)-A/B level estimation in brain: Active enzyme solution from brain homogenate along with non-specific substrate 30 µL of 2 mM kynuramine di-hydrobromide was added in the absence/presence of specific inhibitors (clorgyline for MAO-A and deprenyl for MAO-B at their IC_{100} concentration) for 30 min. The sample was analyzed with a fluorescence spectrophotometer (F-7100, Hitach High-Tech Solutions Corporation, Fukuoka-shi, Fukuoka, Japan) with 315 nm as excitation wavelength and 380 as emission wavelength to detect the fluorescent product of enzyme reaction 4-hydroxyquinoline. The specific activity of MAO-A/B is the number of µM of product formed/ min of reaction/ mg of proteins[12].

Matrix metalloproteinase (MMP) activity: Rats were euthanatized with inhaled isoflurane (Sigma Chemical Co., USA) and proteins extracted from minced brain tissue were separated by sodium dodecyl polyacrylamide gel electrophoresis (SDS-PAGE, Rockland Immunochemicals, Inc. Limerick, PA, USA) standard procedure. The enzyme in the gel was made active and started degrading gelatin after incubation with development buffer (50 mM Tris pH 7.4, 10 mM $CaCl_2$, 0.02% sodium azide) for 36 hrs at room temperature. MMPs activity i.e., gelatin hydrolysis corresponding band separated gelatinase (MMPs) in the gel was made conspicuous by staining with 0.1% coomassie brilliant blue and destaining (ethanol: acetic acid: water: 5:10:85). The intensity of the stained band around the enzyme was measured for quantification to present enzyme activity using densitometry (ImageQuant, Molecular Dynamics, New York, NY, USA). Recombinant MMP2 of 10 ng/10 µL was also loaded in parallel well as a positive control standard to confirm system performance and quantification of MMPs enzyme in the extract[13].

Heart muscles strength: The isolated striped muscle was attached to the length controller by piercing the hook and fixed by glue at one end. Another end was glued to the force

transducer. Resting force (F_R) of the cardiac muscle/cell was observed and recorded at 2 µm sarcomere length. Muscles were placed in a washing buffer (relaxing buffer devoid of K_2EGTA content) for 5 min then in the activation solution (washing buffer supplemented with 5 mM CaEGTA) to record its active force (Fa)[14].

Western Blot analysis apoptotic signals detection: The SDS PAGE separated proteins (20 µg) extracted from the minced brain were electroblot transferred to the blotting membrane of polyvinylidene difluoride (Millipore, Bedford, MA, USA) and blocked with Blot analysis apoptotic signals detection apparatus for 45 min at 25°C. After blocking the membrane was incubated with mouse anti-caspase 3 antibodies (1:1000 dilution), Santa Cruz Biotechnology (Dallas, Texas, USA) for 18 hrs at 4 then exposed to biotinylated IgG antiserum (Kirkegaard Perry Laboratories, MD, USA) and horseradish peroxide derivatized biotin ligand i.e., streptavidin (Zymed Laboratories, CA, USA) for 2 hrs each at 1:3000 dilution. The visualization blot was possible after exposure with chromogen DAB using densitometry (ImageQuant, Molecular Dynamics, New York, NY, USA)[15].

Statistical analysis: The results presented were mean of 6 or 14 experimental points with the standard error of the mean (mean±SEM). After statistical evaluation, the decision of significance was made by using Tukey's test of analysis of variance i.e., analysis of variance (ANOVA) to compare all groups with each other at $p<0.05$[16].

RESULTS

Hemodynamic indices: In echocardiography different parameters were studied in control (C, n = 6), heart stress leading to failure (HS n = 6), mild stress (MS, n = 14), mild stress with fluoxetine treatment 10 mg/kg/day (MSF, n = 14), acute stress (AS, n = 14), acute stress with fluoxetine treatment 10 mg/kg/day (ASF, n = 14) group of rats. Almost all parameters were affected by both mild and acute stresses. Even in some cases e.g., Ejection Fraction (EF) of AS group, Absolute Heart Mass (AHM) of MS and AS group, Left Ventricular Systolic Pressure (LVSP) of MS and AS group showed value statistically same that of HS group. The rats of the C group showed EF 82.43±2.30%, AHM 2.13±0.09 g and heart rate 368.24±8.83 beats min^{-1} (Table 5). In the case, of EF (%) of the HS, AS and ASF group, the rats showed lower values than those of the C group (57.91±1.43, 69.91±2.46 and 68.75±1.42%) which are statistically significant ($p<0.05$).

MAO-A and MAO-B activity: Homogenized brain extract adjusted to 20 µg mL^{-1} protein content was checked for MAO-A (Fig. 1a) and B (Fig. 1b) isoforms expressed in the different parts of the brain depending upon emotional exposure. Results showed clearly that injury to the heart in the HS group has shown value higher than C group which is by chance from a statistics point of view. It was found interesting to note that MAO-A activity was found significantly high ($p<0.001$) in case of MS and insignificantly high in case AS while MAO-B activity was found to be more in the case of AS group although the value activity in MS was also higher than C and HS but significantly lower than AS. Antidepressant treatment was not able to reduce the level of MAO-A either in mild and acute stress. On the other side, the MAO-B level was significantly reduced by antidepressant treatment in the acute stressed group (ASF) even statistically equal to the normal group of animals (C).

Matrix metalloproteinase (MMP): Taking intensity of recombinant MMP 10 ng in the zymography as 100% the intensities of all groups of rats were observed. HS group showed a very high MMP level even more than standards

Table 5: Hemodynamic indices of different groups of animals

				Left ventricular pressure		Pressure differential	
Groups	EF (%)	AHM (g)	HR (beats min^{-1})	LVSP (mm Hg)	LVDP (mm Hg)	+dp/dt_{max} (mm Hg s^{-1})	-dp/dt_{max} (mm Hg s^{-1})
C	82.43±2.30	2.13±0.09	368.24±8.83	78.34±1.90	6.52±0.17	980.39±17.93	973.94±13.17
HS	57.91±1.43^{W}	1.72±0.07^{W}	490.34±16.44^{W}	61.65±2.06^{W}	10.91±0.39^{W}	514.66±13.96^{W}	384.52±15.63^{W}
MS	72.47±1.93^{Wx}	1.85±0.06^{Wx}	400.54±11.59^{Wx}	65.00±1.69^{Wx}	7.89±0.24^{WX}	638.55±19.49^{WX}	543.27±13.33^{WX}
MSF	75.67±3.87^{wXy}	2.04±0.04^{wXy}	379.41±7.51^{wXy}	74.65±0.96^{wXY}	6.25±0.19^{wXY}	724.42±12.88^{WXY}	745.30±28.37^{WXY}
AS	69.91±2.46^{Wxy}	1.75±0.06^{Wxy}	438.02±9.92^{Wxy}	59.99±3.03^{Wxy}	8.53±0.24^{WXy}	611.21±16.96^{WXy}	592.15±32.48^{WXy}
ASF	68.75±1.42^{Wxz}	1.82±0.04^{Wxz}	350.48±15.69^{Wxz}	71.11±2.21^{wxZ}	7.72±0.21^{WXz}	793.54±23.82^{WXZ}	726.07±30.28^{WXZ}

EF: Ejection fraction, HR: Hear rate, AHM: Absolute heart mass, LVSP: Left ventricular systolic pressure, LVDP: Left ventricular diastolic pressure. Results are presented mean±SEM of control (C, n = 6), heart stress leading to failure (HS n = 6), mild stress (MS, n = 14), mild stress with fluoxetine treatment 10 mg/kg/day (MSF, n = 14), acute stress (AS, n = 14), acute stress with fluoxetine treatment 10 mg/kg/day (ASF, n = 14). W: Significant difference of mean concerning C, X: Significant difference of mean concerning HS, Y: Significant difference of mean concerning MS, Z: Significant difference of mean concerning AS while their lower case represents a non-significant difference at $p<0.05$

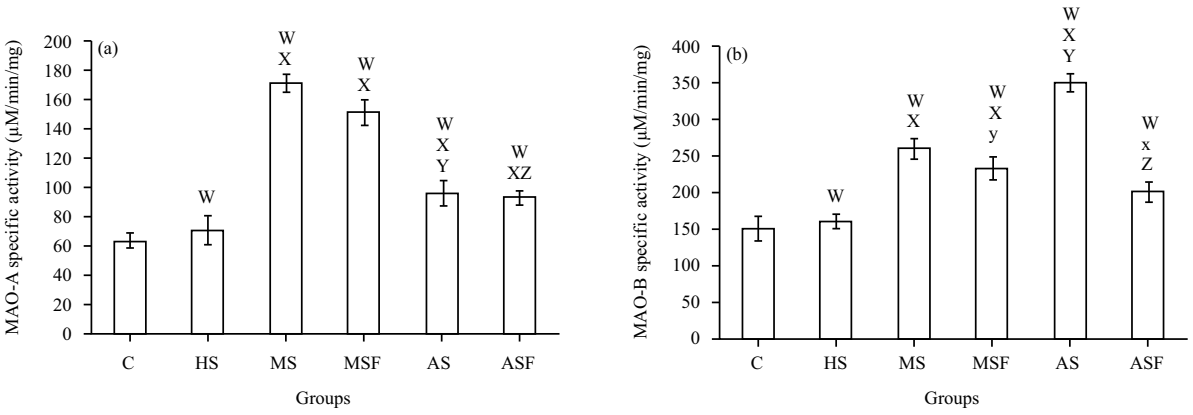

Fig. 1(a-b): Monoamine oxidase activity

(a) MAO-A and (b) MAO-B activity in brain homogenate soluble proteins. Results are presented as mean±SEM of control (C, n = 6), heart Stress leading to failure (HS, n = 6), mild stress (MS, n = 14), mild stress with fluoxetine treatment 10 mg/kg/day (MSF, n = 14), acute stress (AS, n = 14), acute stress with fluoxetine treatment 10 mg/kg/day (ASF, n = 14). W represents a significant difference of mean concerning C, X represents a significant difference of mean concerning HS, Y represents a significant difference of mean concerning MS, Z represents a significant difference of mean concerning AS while their lower case represents a non-significant difference at $p<0.05$

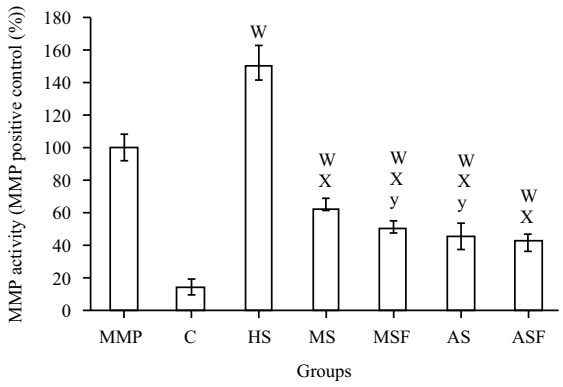

Fig. 2: MMP (%) activity by zymography densitometer intensity taking standard MMP activity intensity as 100%

Results are mean±SEM of control (C, n = 6), heart stress leading to failure (HS n = 6), mild stress (MS, n = 14), mild stress with fluoxetine treatment 10 mg/kg/day (MSF, n = 14), acute stress (AS, n = 14), acute stress with fluoxetine treatment 10 mg/kg/day (ASF, n = 14). W represents a significant difference of mean concerning C, X represents a significant difference of mean concerning HS, Y represents a significant difference of mean concerning MS, Z represents a significant difference of mean concerning AS

MMP in the zymography. Although the stress mild (MS) or acute (AS) was showing significantly higher MMP activity than control, respective antidepressant treatment was not able to reduce (statistically) the MMP level (Fig. 2).

Cardiac strength: Cardiac muscles were checked for their strength in the activation solution having 5 mM Ca^{2+} and active force (F_a) was determined in force transducer. The value of C was found to be 23.48±1.9 kN $m^{2\ -1}$. Stress to the heart via isoproterenol (HS) and psychological (mild and acute, MS and AS) reduced the active stress significantly. While the AS group showed F_a statistically equivalent to HS. Interestingly, it was a dilemma to decide the efficacy of fluoxetine in case of mild treatment as the MSF group showed F_a in significantly lower than the C group and insignificantly higher than the MS group (Fig. 3a) but MS and C difference were significant ($p>0.05$). The result of Fig. 3b represents passive force (F_p) of optimal length muscle in which F_p of C was 2.64±0.09 kN $m^{2\ -1}$. The Fp value of HS, MS and AS was significantly lower than C suggesting all the stresses were affecting the F_p property of the heart muscle. AS group showed a reduction in passive force equivalent to HS suggesting the effect of acute stress equivalent to isoproterenol in this particular muscle parameter. While treatment to Acute stressed group (ASF) significantly changed the F_p status (in comparison to AS) close to but was significantly lower than C. Simultaneously F_p MSF reached the value equivalent to C and higher than MS although the level of F_p in MS was much higher than AS.

Caspase expression: The result of Fig. 4 showing caspase expression in the blot for various groups of rats. The result of Fig. 5 is the relative intensity of the blot relative to Glyceraldehyde 3-Phosphate Dehydrogenase (GAPDH). Caspase was found significantly high in the HS, MS and AS groups representing the effect of every stress on caspase expression. In this study ASF group was able to reduce the caspase expression to the level of the C group even the reduction was not significant in comparison to the AS group, creating an intermediate level of decision.

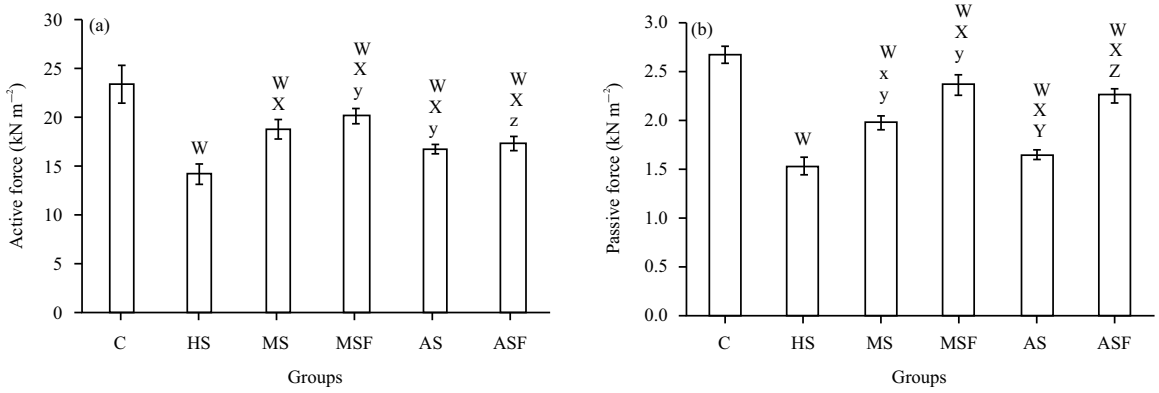

Fig. 3(a-b): Stress on the heart muscles

(a) Active stress and (b) Passive stress on the transducer with an optimal length of heart muscles. Results are represented as mean±SEM of control (C, n = 6), heart Stress leading to failure (HS n = 6), mild stress (MS, n = 14), mild stress with fluoxetine treatment 10 mg/kg/day (MSF, n = 14), acute stress (AS, n = 14), acute stress with fluoxetine treatment 10 mg/kg/day (ASF, n = 14). W represents a significant difference of mean concerning C, X represents a significant difference of mean concerning HS, Y represents a significant difference of mean concerning MS, Z represents a significant difference of mean concerning AS

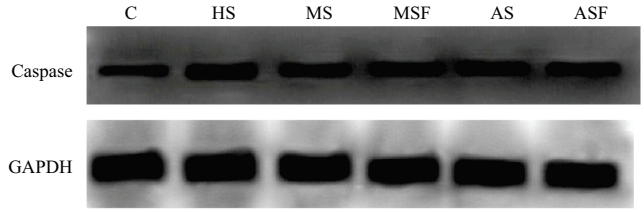

Fig. 4: Western blot image of caspase expression level

GAPDH: Glyceraldehyde 3-phosphate dehydrogenase

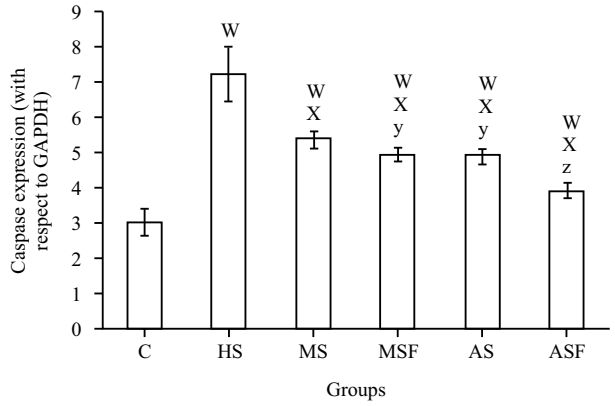

Fig. 5: Plot of the intensity of caspase expression in different animal groups relative to GAPDH intensity

Results are mean±SEM of control (C, n = 6), heart stress leading to failure (HS n = 6), mild stress (MS, n = 14), mild stress with fluoxetine treatment 10 mg/kg/day (MSF, n = 14), acute stress (AS, n = 14), acute stress with fluoxetine treatment 10 mg/kg/day (ASF, n = 14). W represents a significant difference of mean concerning C, X represents a significant difference of mean concerning HS, Y represents a significant difference of mean concerning MS, Z represents a significant difference of mean concerning AS. GAPDH: Glyceraldehyde 3-phosphate dehydrogenase

DISCUSSION

The study reported significant worst hemodynamic parameters for the HS, the MS, the MSF, the AS and the ASF groups than those of the C group. There are many clinical instances in which emotional stress reversibly affected the heart functioning e.g., left ventricle reported parameters out of optimal range in such cases with the unknown established mechanism(s)[17,18]. The treatment of isoproterenol affects hemodynamic parameters because it causes necrosis of heart tissue, which leads to stress to the heart.

The study reported improvement in the hemodynamic parameters of the rats of the MSF and the ASF groups than those of the HS group but improvement in the hemodynamic parameters were not equal to those of the C group. Fluoxetine is a Selective Serotonin Reuptake Inhibitor (SSRI) and has been reported to clinically affect the central nervous system based arousal (electroencephalogram) and SSRI responders were also in coordination with an autonomic nervous system based arousal (hemodynamic parameters)[19]. Fluoxetine treatment improves hemodynamic parameters. The study reveals the effect of the antidepressant drug (fluoxetine) on hemodynamic parameters.

The improvement in the hemodynamic parameters due to the fluoxetine treatment was lower values in the ASF group than those of the MSF group. Fewer effect of fluoxetine treatment on acute stress condition than mild stress condition. The present study provided background data for the clinical practice that fluoxetine treatment would be more effective to improve hemodynamic parameters in the younger age patients than those of older age patients.

The study reported previously[19] an association between psychological stress and functional status of the heart of rats. Uninterrupted attempts are observed in the literature to find a key relation between psyche and cardio. One such effort to establish the level of neurotransmitters and neuropeptides in patients with stress-related cardio-myopathy was executed. As an instance serotonin (5-hydroxytryptamine) level was 2585 pg mL^{-1} in stressed cardiac patients and the same was 1308 pg mL^{-1} in patients with Killip Class III myocardial infarction i.e., not stressed while the normal value was 1004 pg mL^{-1}. Moreover, myocardial biopsy samples of the patients showed inflammatory cells and necrosis in heart muscles[18].

Fluoxetine treatment did not affect MAO-A in acute or mild stress. While it had been reduced the MAO-B level in the acute stress condition of the rat. The results of the MAO of the current study are parallel with those of the experimental study[12]. MAO-A and MAO-B are very closely associated with depression. Fluoxetine treatment can have a significant effect on depression.

In our experimental setup, fluoxetine showed no reduction in stress elevated MMPs level. This difference can be attributed to the mechanism of monocrotaline for MMPs which may be different from AS and MS in our study. MMPs have been reported to be over-expressed in failing heart clinically and pre-clinically. The result of similar behaviour is supported by hyperforin antidepressant treatment for vascular endothelial growth factor enhancement resulted in angiogenesis but cannot reduce the MMPs expression (mRNA) level[20]. Fluoxetine could be considered for down-modulation of MMPs.

The effect of fluoxetine treatment attenuated the contractility in terms of passive strength reaching to level of the C group only. Doxorubicin-induced heart failure models showed bias-ness with the decrease in active force rather than passive force in the myocardial cells[21] similarly psychological stress in this study showed more effect on passive force (F_p). Passive elasticity of heart muscle sarcomere related to titin protein[22] hence it may be possible that bias-ness of psychological treatment towards passive force has some interaction with titin.

In the limitation of the study, an experimental study and lack of human clinical trial. The sample size was small lead to type-I error. The lack of separate psychological versus physical stress and their impact upon cardiac function. This is seen with the seemingly significant increase in heart rate (the clinical parallel of this is seen in tachycardiomyopathy). These effects are even more difficult to dissect in small mammals such as rodents which have fast resting heart rates and the stress response is less compared to large mammals or indeed humans.

CONCLUSION

Depression itself is an origin point for many other non-communicable chronic and psychological diseases like heart failure, schizophrenia, Alzheimer's disease, kidney failure, diabetes and many more as human physiologies is being controlled by the central and peripheral nervous system. Results of the current study revealed the effect of chronic and/or acute stress, causing morbidity equivalent to targeted stress to the heart in some cases. Moreover, antidepressant treatment was also showing effects in curing or attenuating the consequences on heart physiology and anatomy in a few points of studies. This study can give a subtle recommendation of psychological balance for healthy life although further studies are still required.

SIGNIFICANCE STATEMENT

This is an animal study of the effects of psychological stress and an attempt to extrapolate these to the effects of depression. The study reported that the effect of mental stress on organ functionality and structure is wide and conspicuous but was not perceptibly protected by the psychological treatment. This study will help the researcher to uncover the critical areas of stress that many researchers were not able to explore. Thus, a new theory on stress management may be arrived at.

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