PREVENTION OF TAKOTSUBO CARDIOMYOPATHY THROUGH GENERALIZED ANXIETY DISORDER MANAGEMENT*:* A NOVEL PATHOPHYSIOLOGY REVIEW FROM NEUROENDOCRINAL ASPECT

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Abstract

Background: Takotsubo cardiomyopathy (TCM) is one of the cardiovascular diseases that often went misdiagnosed due to its similar features with other cardiovascular diseases such as coronary heart disease and acute coronary syndrome, but the pathophysiology of TCM remains unclear. It affects mostly women of older age, possibly due to the decreased cardioprotective effect of estrogen in older women. Patients who emerge with TCM usually have psychiatric history or triggered by psychological stresses that may alter their physiological work, hence it is termed "Broken heart syndrome". Generalized anxiety disorder (GAD) is one of the most common mental disorders that affects people in the world. Several literatures and studies showed that TCM patients have history of GAD and the associations are significant. Therefore, this review is made to prove the association between GAD and TCM through neuroendocrinal aspect.

Method: To approach wide and comprehensive review through studies that have been done about TCM and management of GAD in correlation with the topic of discussion, writers have reviewed 42 journals systematically and by using several inclusion and exclusion criteria, 35 journals are used as the data and source of this review. Those journals acquired from trusted, accredited, scientific online journal bases. Keywords being used were "Takotsubo cardiomyopathy", "Generalized anxiety disorder", "Neuroendocrine", "HPA axis", "Catecholamine", "Cortisol".

Result: GAD affects the hypothalamic-pituitary-adrenal axis (HPA axis) in elevating cortisol and catecholamine level and overactivates autonomic nervous system (ANS). In endocrinal pathway, the increase in epinephrine

and norepinephrine hormones levels targeting adrenoreceptors (ARs) in blood vessels and heart causes cardiotoxicity on cardiomyocytes. In neural pathway, GAD also affects neurotransmitters in the cortico-striato-thalamo-cortical (CSTC) loop, amygdala, locus coeruleus, and several autonomic neurons that regulate heart physiology. Excessive arousal from GAD causes ANS overactivation which causes sympathetic hypertonus response, which leads to TCM. Management of GAD may be an important part of TCM prevention, including pharmacological therapy with benzodiazepine and psychotherapy. The future healthcare worker are expected to understand and able to manage GAD as a prevention act of TCM.

Conclusion: TCM is one of acute cardiovascular diseases that is hard to diagnose because of the symptoms and pathophysiology that are not clear and usually associated with psychiatric problems. Several studies show that GAD has associations with TCM and known to be one of the risk factors. In neuroendocrinal aspect, GAD causes elevation of catecholamine and overactivation of ANS, which leads to TCM. Holistic management of GAD through psychotherapy and pharmacotherapy could be one effective act in preventing TCM.

Keywords : takotsubo cardiomyopathy, generalized anxiety disorder, neuroendocrine, HPA axis, catecholamine, cortisol.

BACKGROUND

Takotsubo cardiomyopathy (TCM) is a syndrome characterized by the dysfunction of transient systolic located at the apex of left ventricle.[1] After firstly discovered in Japan on 1990, TCM was being recognized widely. The word 'takotsubo' is derived from Japanese word which means 'octopus trap', because the clinical finding of the ventricle ballooning resembles the shape of a Japanese octopus trap, due to acute myocardial infarc without coronary artery spasm.[2] Even though this syndrome has been researched for 25 years, sources and literatures of TCM are still limited.[3] Many cases of acute or chronic reversible left ventricle dysfunction are still not able to be classified into the present cardiovascular diseases. The prevalence of TCM is higher in female compared to male, and the prevalence is found to be higher in postmenopausal female.[2] The symptoms of TCM generally occurs after a physical or psychological stress, but the etiology or definite cause of TCM is still remain unclear. Researchers predict that excessive catecholamine production might be the main pathological cause of this syndrome.[4] Another suspect factor found in two-thirds of all TCM patients is hyperexcitation of autonomic nervous system (ANS) that affects physical and psychological stressor immediately before the symptoms occured.

Therefore the psychiatric and psychological problems have significant roles in the pathogenesis of common cardiovascular diseases, including TCM.[5] Research by Mayer et al. explained that stress have important role in TCM initiation. Release of stress hormones such as noreepinephrine increases acute phase of TCM. One of the psychological stressors that could trigger TCM is generalized anxiety disorder (GAD).[6]

GAD is a chronic and persistent fear that has multifactorial causes. It is difficult to control, and usually comorbid with nonspecific physical and psychological symptoms.[7] Chronic GAD disrupts social life and performances.[8] The prevalence of GAD in female is twice higher than in male.[7]

According to a research conducted by Summers et al. from 25 patients with TCM, 56% had history of anxiety.[9] Society believes that in general, cardiovascular disease is not affected by GAD, but with other factors, such as obesity, dietary, low quality of sleep, etc. Nevertheless, in fact, GAD is one of the major risks that could trigger TCM. Therefore, this literature review is made to give a contribution for healthcare workers in the future cardiovascular studies.

METHOD

To approach a comprehensive review through studies about TCM and management for GAD correlated to the topic that discussed in this paper, writers have reviewed 42 journals systematically. 35 journals are used as the base of data and discussion of this review, fulfilling criterias these journals are published within 10 years, concentrating in correlation between GAD and TCM specifically. 7 journals are not used because of the topic is not significant and specific with topic of discussion in this paper, and some of these journal put correlation towards another cardiovascular disease or psychiatric disorder. These journals are obtained from Google Scholar, The New England Journal of Medicine, Journal of the American College of Cardiology, PubMed, and other online journal sites. Keywords being used for this review were: “Takotsubo cardiomyopathy”, “Generalized anxiety disorder”, “HPA Axis”, “Neuroendocrine”, “Catecholamine”, “Cortisol”.

RESULT AND DISCUSSION

Takotsubo Cardiomyopathy

Takotsubo Cardiomyopathy (TCM) – known as “Broken Heart Syndrome” – cause related to physical and physicological stress.[10] TCM is characterized by balooning of left ventricle apex, mimicking the shape

of Japanese octopus trap.[3] Templin et al. have researched 1750 patients and found 4 types of TCM: Apical TCM (81.7% patients), midventricular form (14.6% patients), basal form (2.2%), and focal form (1.5% patients) (Figure 1).[3]

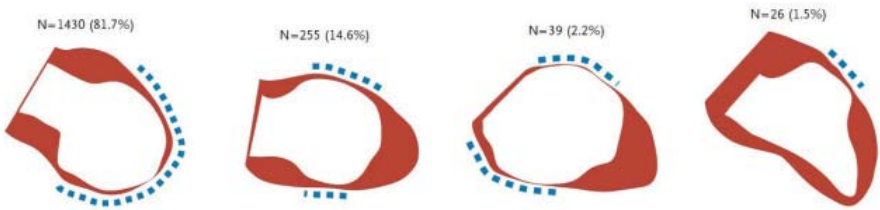

Figure 1. *Takotsubo Cardiomyopathy* (TCM) types, L-R : apical ballooning, apical-midventricular ballooning, basal ballooning, focal ballooning[3].

Minneapolis Heart Institute have conducted research in 337 patients, 10% of the patients have not experienced stress, 40% have experienced it, and 50% have experienced physical stressor.[12] Anger/frustation, job/financial problems, grief / loss, interpersonal conflicts, and panic/fear/anxiety are some psychological stressors that would cause TCM. While the physical stressor that have ever been reported are like laryngeal obstruction from tumor, gastric ulcer with hemorrhage, subarachnoid hemorrhage, diverticulitis with septic shock, diabetic gastroparesis, etc.[12]

Prevalence of this case depends on age and genders. In the United States and Europe, prevalence of TCM case is 90% in postmenopausal female (age 65-70 years old) and ±10% in male.[12] The extreme difference of prevalence between male and female is still not clearly understood. Apparently, male are exposed by physical stressor more often than female and have developed mechanisms to overcome the stressors. Density of adrenergic receptor in cardiomyocyte membrane is found higher in male compared to female. Higher recpetor density improves defense to excessive catecholamine exposure because saturation of receptor takes longer time in male than female, but this speculation is still not validated.[1]

Deshmukh et al. found that female age >55 years old have 4.8 higher risk for TCM compared with female age <55 years old and have 10.7 higher risk compared with males with the same age group. Female age <55 years old have 1.9 higher risk compared with males with the same age group. But prevalence in male group did not associated with age. [1]

Estrogen induce transcription of cardioprotective factors such as heat shock protein and natriuretic peptide that protect the heart from the toxic effect of catecholamin, elevation of calcium ion level, and reduce oxidative stress.[13] After menopause, this protective mechanism declined and cause higher susceptibility for female in catecholamine level increase that associated with stress. [14]

Patients usually come to emergency unit with chest pain accompanied with dyspnea. The symptoms and diagnostic criteria of TCM are hard to be distinguished from acute coronary syndrome (ACS). 1-3% patients that come to hospital with ACS symptoms are found having TCM and have been treated with aspirin and anticoagulant drug.[11,12] Lyon et al. categorize TCM cases as two main types: primary and secondary TCM. Main reason of patients with primary TCM come to hospital is acute heart problems, stress triggering factors are hard to be identified, previous medical condition might be the risk factors of catecholamine level elevation. Patients with secondary TCM have been hospitalized because of other medical condition. Excessive catecholamine that induce TCM is because of complication of patient's primary condition or the medication itself. [15]

There are no world concensus that can be used for TCM. Researchers from Mayo Clinic in America has made diagnostic criteria of TCM[16]:

1. Transient hypokinesis, akinesis, or dyskinesis in the left ventricular mid segments with or without apical involvement; regional wall motion abnormalities that extend beyond a single epicardial vascular distribution; and frequently, but not always, a stressful trigger.
2. The absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
3. New ECG abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.
4. The absence of pheochromocytoma and myocarditis.

But these criteria only exclude the possibility of other disease and lead the diagnosis to TCM.[17] The prognosis is highly dependent on other non-heart disease.[18] Eventhough the complication and pathophysiology of TCM is still not clearly understood, the mortality rate is high. Identification of pathophysiology which are related to the mechanism of TCM can improve the treatment of the disease.[11]

Generalized Anxiety Disorder as Takotsubo Cardiomyopathy Risk Factor

Psychiatric problems are one of the most common health problems. Psychiatric problems include disturbance in mood, emotion, psychotic,

etc. Generalized Anxiety Disorder (GAD) shows up as a respond to some stressors or threats from the patients themselves. GAD characterized as chronic and nonspecific arousal and worry that related to potential threat in the future.[19] GAD could disrupt individuals by altering their social roles in life as human being or disrupt the physical and medical condition.

Prevalence of GAD in U.S population reach 3.1% in 2014 and occur during 5.7% of patient's entire life,[7] and one of the most common psychiatric problem in the world. Generally, female experienced anxiety more than male because female are more susceptible to stressor and male have better coping mechanisms.

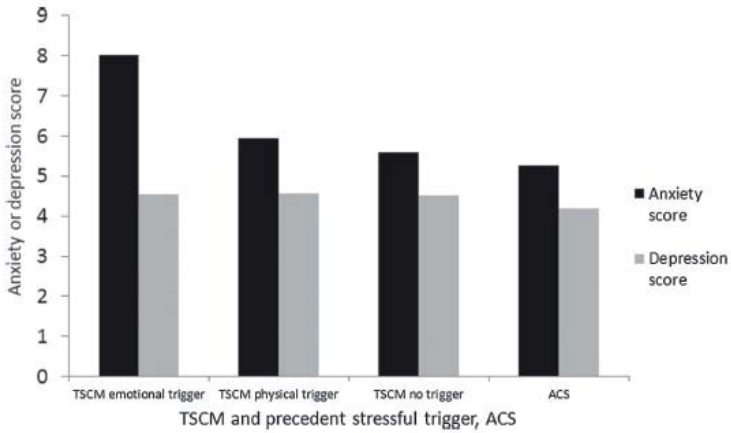

Figure 2. Anxiety and depression mean score in TCM patients with different triggers compared to acute coronary syndrome (ACS) patients using Hospital Anxiety and Depression Scale. Anxiety score found to be higher in all situations and more significant associated to TCM (p-value TCM vs. ACS; anxiety=0.06 , depression=0.61). TSCM, *Takotsubo Cardiomyopathy;* ACS, *Acute Coronary Syndrome*[21].

Based on PPDGJ-III, one of the diagnostic point of GAD was patients must show anxiety as a primary symptoms that free floating and not limited or prominent on particular situations. GAD still could be the primary diagnosis as long as the other symptoms last in days such as depression, but did not complete the episode criteria of depression, phobia anxiety, panic disorder, or obsessive compulsive disorder,[20] so the diagnostic scope of GAD was large and universal.

On cardiovascular disease, depression was more often being associated as a risk factors than anxiety. But study of Goh et al. that used Hospital Anxiety and Depression Score (HADS) questionnaire showed that anxiety score of patients with TCM are higher and more significant compared with depression compared with sample group ACS (mean value HADS of anxiety in TCM=6.7±4.7 vs ACS=5.4±3.4, p=0.06, depression in TCM=4.3±3.7 vs ACS=4.0±3.1, p=0.61) (Figure 2). The research also test the higher risk of TCM in persons with anxiety compared with depression. On univariat regression analysis showed that TCM has significant association with anxiety (OR=1.09 (1.01-1.17), 95% CI, p=0.022) and has unsignificant association with depression (OR=1.02 (0.95-1.10), 95% CI, p=0.56). To demonstrate whether increase per units of anxiety and depression also increase the risk of TCM, the data was studied more further in multivariat regression analysis. Proven that anxiety has significant association with TCM (adjusted OR=1.13 (1.01-1.26), 95% CI, p=0.03) and depression has nonsignificant association (adjusted OR=0.94 (0.83 -1.05), 95% CI, p=0.29).[21]

Table 1. Emotional Stress Prevalence In TCM

Emotional Stressor	**Dias et al.**[24] (n = 78)	**Eitel et al.**[25] (n=256)
Family / friend / pet death or sickness	6 (7,7%)	20 (7,8%)
Interpersonal conflict	5 (6,4%)	15 (5,9%)
Panic / Fear / Anxiety	5 (6,4%)	10 (3,9%)
Career and Workplace Problems	2 (2,6%)	5 (2,0%)
Bad News	1 (1,3%)	6 (2,3%)

Study by Christensen et al. through comparison between TCM sample group and ST-elevation myocardial infarc (STEMI) growup using Major Depression Indeks (MDI) test and Anxiety Subscale of Hopkin's Symptoms Checklist (ASS), measuring p-values using Wilcoxon-Mann-Whitney test shows that anxiety has higher significance with TCM compared to depression (TCM vs STEMI; ASS p=0.007; MDI p=0.72).[22]

Another study by Delmas et al. to identify psychological factor that affects TCM and compared to ACS sample group. It shows that percentage of GAD found higher in TCM patients compared to ACS (26% vs. 6%; p=0.01).[23] Study by Summers et al. shows that anxiety has significant association with TCM compared to STEMI patients according to psychiatric disorder history of patients (anxiety in TCM=56%; in STEMI=12%; p=<0.01).[9]

Anxiety become one of risk factor that cause TCM by environmental stressior that could affect a person psychological state. GAD could be triggered because of anxious feeling toward life situation in several aspects such as politics, social, economy, health, family, and more. Studies show that the highest TCM prevalence is TCM that triggered by emotional condition (43%). Patient with emotional triggered TCM have higher mean anxiety score compared to patients with TCM that triggered with non-emotional factor or ACS patients (p=0.05).[21]Research shows that mostly TCM patients has psychiatric history before, and GAD would increase the risk of TCM, especially in post-menopausal women.

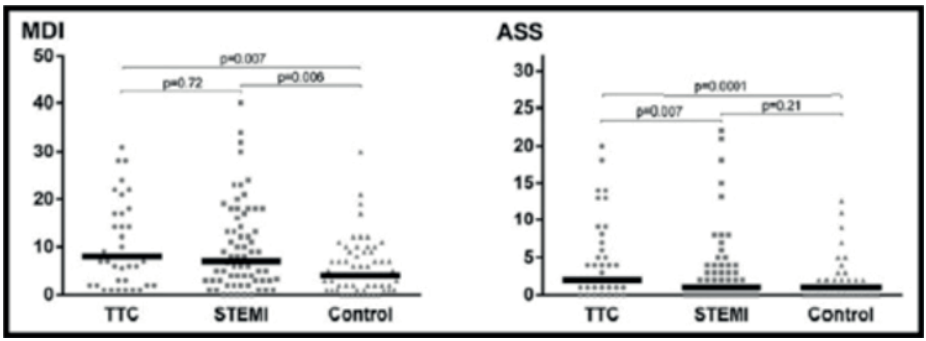

Figure 3. Scatter-plot diagram for MDI and ASS result from three groups of research subject. Bold line showing median and p-value shows association significancy with Wilcoxon-Mann-Whitney test. MDI, *major depression index*; ASS, *anxiety subscale of Hopkin's symptoms checklist*; TTC, *takotsubo cardiomyopathy*; STEMI, *ST-elevation myocard infarc*[22].

GAD in TCM pathophysiology review from neuroendocrinal aspect

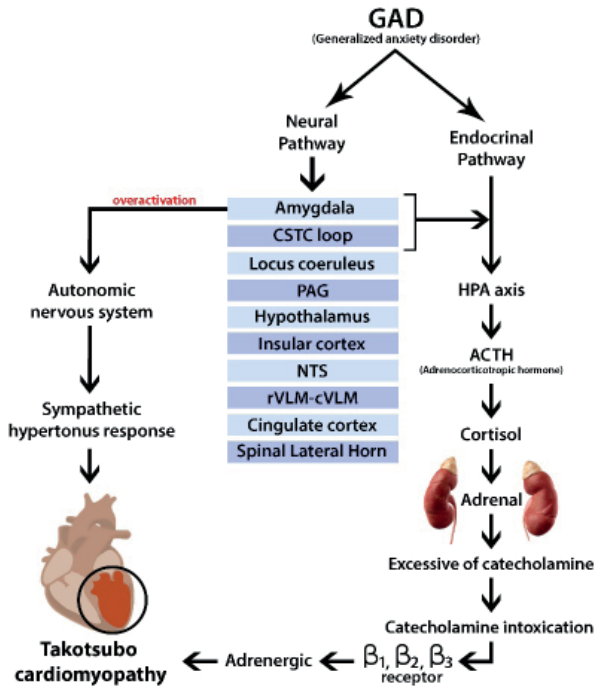

Figure 4. GAD in TCM pathophysiology review through neuroendocrinal aspect. GAD, generalized anxiety disorder; CSTC, cortico-striato-thalamo-cortical; PAG, periaqueductal grey; NTS, nucleus tractus solitarii; rVLM, rostral ventral lateral medulla; cVLM, caudal ventral lateral medulla; HPA, hipotalamus-pituitari-adrenal; ACTH, adrenocorticotropic hormone.

GAD neuroendocrinal mechanism divided into two pathways (Figure 4). Amygdala-centered pathway aroused by neurotransmitter, causing response in hypothalamus that would secrete adrenocorticotropin hormone (ACTH) and arouse adrenal gland produce cortisol and catecholamine as a physiologic response towards external stressor. Cortico-striato-thalamo-cortical (CSTC) loop pathway aroused by neurotransmitter would cause anxiety disorder response such as catastrophic though and obsessive-compulsive. Both of these pathways causing anxiety response physiologically.[26]

GAD also affects ANS through causing exceeds activation from amygdala to locus coeruleus (LC) where LC is one of the main part in brain that regulates cardiovascular system through ANS. If there are overactive LC due to anxiety, this cause risk increase of atherosclerosis, cardiac ischemia

increase, elevation of blood pressure, decrease of heart rate variability (HRV), risk of myocardial infarction, even sudden death.[26]

GAD also arouse another part in brain such as periaqueductal grey (PAG) that modulate fight-or-flight response, hypothalamus and integration with paraventricular nucleus (PVN) in stress response, insular cortex, rostral ventral lateral medulla-caudal ventral lateral medulla (rVLM-cVLM) as central cardiovascular regulator, cingulate cortex regulate integration of autonomic, affection, and cognition, nucleus tractus solitarii (NTS) that regulates baroreceptor integration, and spinal lateral horn as spinal cord effector from sympathetic activities. Arousal due to GAD would overactivate ANS, causing sympathetic hypertonus response, and progressing to TCM. [27]

In endocrine system, due to sudden response or severe emotional stress, autonomic system neurons become active, increasing sympathetic nerves activity and adrenomedullary hormones. Norepinephrine secretion from medullary adrenal gland, cardiac and extracardiac sympathetic nerves targetting adrenoceptors (ARs) in blood vessel and heart. Due to increase in norepinephrine and epinephrine levels that circulate in heart and increase in these hormone secretions and decrease in sympathetic neuron hormones uptake could cause cardiotoxicity in cardiomyocyte through ARs occupation. Density and/or distribution difference and downstream signaling difference on myocardial βARs (β1-AR, β2-AR, β3-AR) could contribute not only to TCM, but also each contractile pattern. Hyperkinetic of left ventricle base caused by β1-AR. β3-AR is stimulated due to high concentration of catecholamine, cause negative inotropic effect. β3-AR function as barrier and causing negative inotropic effect to protect heart from overstimulation caused by catecholamine. Even so, overactivated β3-AR/Gi on heart apex would cause decrease myofibril fraction volume, increasing myocardial fibrosis, denser capillary blood vessel except in arteriol.[28,29]

Reversible coronary microvascular dysfunction especially in arteriol due to high sympathetic tonus in resting period, along with decrease in coronary vascular resistance and worsened stress response.[28] Rijinierse et al. found that hyperemia myocard blood flow has association with non-infarc cardiomyopathy innervation, so it could be concluded that microvascular dysfunction could be one of major factor that associated with the intact of sympathetic neurons.[30] Due to stress response, increase in catecholamine level cause elevation of oxygen demand in cardiomyocyte and trigger oxidative stress; accelerate positive feedback that could weakened myocard. In postmenopausal women, diminished estrogen effect could accelerate cental

nervous system and cardiomyocyte response toward stress. Microvascular dysfunction in female would cause myocard ischemia as a response toward mental stress.[31]

GAD management as TCM prevention act

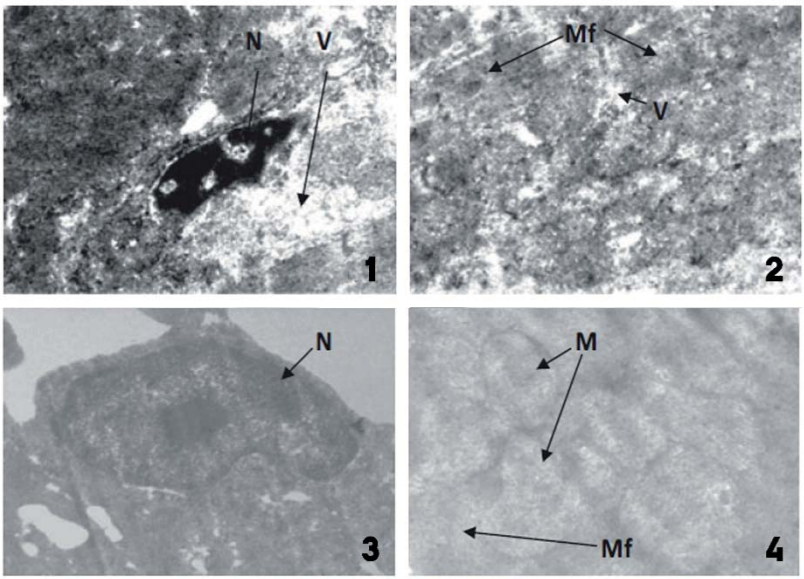

Figure 5. Picture 1 and 2 showing nucleus abnormalities and myofibril damage after doxorubicin administration (10mg/kg). Picture 3 and 4 showing cardioprotective effect after alprazolam administration (1mg/kg). N, nucleus; V, extensive vacuolization; Mf, myofibril; M, mitochondria[33].

Anxiety management is an important key in preventing TCM cases. If anxiety doesn't treated well, it could increase the risk of TCM and worsened patient prognosis due to increase of stress and mental burden.

Holistic and comprehensive GAD management with pharmacology and psychotherapy intervention is a preventive act and could make TCM prognosis better. Pharmacological therapy that used to manage GAD is benzodiazepines, Selective Serotonin Reuptake Inhibitors (SSRIs), tricyclics, and tetracyclics.[32]

Most used benzodiazepines are alprazolam (Xanax) and lorazepam (ativan).[32] Alprazolam often given as the first choice of benzodiazepines for patients with cardiovascular disease history. Anwar et al. conducted a research in alprazolam's effect for anxiety and cardiomyopathy in mice that

induced by doxorubicin. Administration of 10mg/kg doxorubicin show abnormalities in nucleus and myofibril damage in mice, and after given alprazolam, it shows cardioprotective effect using electron microscope shows normal nucleus shape and normal myofibril structure. It is proven that alprazolam administration through oral route with dosage 1 mg/kg is the effective dose that could diminish the effects caused by doxorubicin (Figure 5). Evaluation of alprazolam's cardioprotective effect by measuring serum lactate dehydrogenase (LDH) and tissue malondialdehyde (MDA).

Data shown that decrease in serum LDH and MDA are significant in mice after administrating alprazolam before and after administration of doxorubicin (Table 2).

Table 2. Evaluation of alprazolam cardioprotective effect by serum LDH and MDA measurement in DOX-induced cardiomyopathy in mice

Groups	n	Treatment	Doses (mg/kg)	LDH (IU/L)	MDA (nmoles/mg protein)
1	8	0.5% CMC	(1 mL/kg)	53.39 ± 2.58	0.40 ± 0.03
2	8	DOX	10	295.83 ± 13.04**	1.38 ± 0.08**
3	8	ALP + DOX + ALP	0.5 + 10 + 0.5	101.10 ± 1.80**##	1.30 ± 0.18**
4	8	ALP + DOX + ALP	1 + 10 + 1	78.56 ± 1.77**##	0.73 ± 0.13##
5	8	ALP + DOX + ALP	2 + 10 + 2	57.02 ± 2.06##	0.58 ± 0.04##
6	8	ALP per se	2	58.88 ± 1.67##	0.81 ± 0.07##

All values are expressed as mean ± SEM.

DOX was administered intravenously while alprazolam was administered by oral route. Treatment duration = 14 days (7 days' pre-treatment + 7 days' post-treatment).

n, number of animals; CMC, carboxymethylcellulose; DOX, doxorubicin; ALP, alprazolam; LDH, lactate dehydrogenase; MDA, malondialdehyde; TBARS, thiobarbituric acid reactive substance.

*P < 0.05, **P < 0.01, and ns (nonsignificant), vs. Group I (Normal); ##P < 0.01, #P < 0.05, ns (nonsignificant), vs. Group II (Toxic control), significant by ANOVA followed by Dunnett's *t*-test.

Administration of doxorubicin reduced the number of open arm entries and time spent in open arm in the EPM on first day (i.e on day 8 of treatment) although it was significant (p<0,005). On seventh day (i.e on day 14 of treatment), the number of open arm entries were significanly reduced, which indicating anxiety. Alprazolam administration (0.5, 1 and 2 mg/kg p.o.) significantly reversed the reduction in the number of open arm entries and time spent in open arm, whereby it shown that anxiety symptoms are treated (Table 3).[33] SSRIs usage in TCM patients should be avoided instead, because it's ineffective compared to tricyclics and according to research by Dias et al. shows that SSRIs could increase mortality in hospitalized patients and decrease left ventricular ejection fraction (LVEF) (OR 7,6; 95% CI 1,1-50,3; P = 0,01).(34) Administration of fluoxentine and citalopram on animal trials show decrease in heart contractility and creasing heart beat due to type L Na+ and Ca2+ canal activation.[34]

Table 3. Evaluation of alprazolam in anxiolytic effect on mice on day 8 (pre-treatment) and day 14 (post-treatment) using open and closed arm maze

			On day 8		On day 14	
Groups	Treatment	Doses (mg/kg)	No. of open arm entries	Time spent in open arm	No. of open arm entries	Time spent in open arm
1	0.5% CMC	(1 mL/kg)	3.0 ± 0.57	20.28 ± 2.60	31.28 ± 8.64	7.91 ± 1.58
2	DOX	10	0.71 ± 0.35	7.5 ± 4.15	8.46 ± 2.57[a]	3.0 ± 0.95
3	ALP + DOX + ALP	0.5 + 10 + 0.5	3.5 ± 0.84[d]	30 ± 8.67[d]	29.87 ± 5.81[a]	13.29 ± 3.57
4	ALP + DOX + ALP	1 + 10 + 1	3.85 ± 0.45[ns]	32.37 ± 3.8[ns]	52.28 ± 2.23[ns]	14.87 ± 2.55[a]
5	ALP + DOX + ALP	2 + 10 + 2	3.28 ± 0.77[d]	32.87 ± 7.38[ns]	32.16 ± 4.68[a]	13.79 ± 1.86[a]
6	ALP per se	2	3.14 ± 0.82[d]	28.37 ± 4.85[a]	30.84 ± 4.39[a]	13.87 ± 5.64[a]

All values are expressed as mean ± SEM.

DOX was administered intravenously while alprazolam was administered by oral route. Treatment duration = 14 days (7 days' pre-treatment + 7 days' post-treatment).

n, number of animals; CMC, carboxymethylcellulose; DOX, doxorubicin; ALP, alprazolam.

[a]$P < 0.05$, and ns (non significant), vs. Group I (Normal). [ns]$P < 0.01$, [d]$P < 0.05$, ns (non significant), vs. Group II (Toxic control), significant by ANOVA followed by Dunnett's t-test.

Psychotherapies such as Supportive Psychotherapy, Insight-Oriented Psychotherapy, Behaviour Therapy, Virtual Therapy, dan Cognitive Behaviour Therapy (CBT) are also importants in managing patients with GAD.[32] Suzuki et al. found that brain activation could trigger TCM but also could respond to repairment of heart. CBT or other psychotherapies could help or prevent prolonged psychological stress (Figure 6).[35] Fonzo et al found that CBT can decrease activation of amygdala, which could be concluded reducing of brain activity that stimulates GAD would be diminished and minimizing risk of TCM (Figure 7). [36]

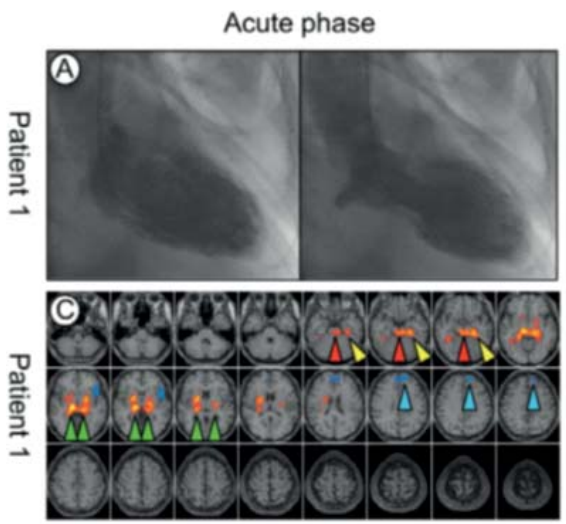

Figure 6. Brain activation site on TCM patient

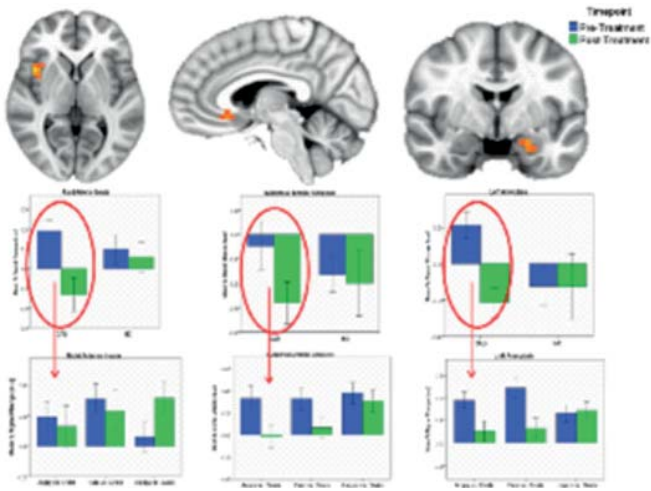

Figure 7. Effect of Cognitive Behavioral Therapy (CBT) in human brain by reducing brain activity.[36]

CONCLUSION

Conclusion

TCM is an acute heart disease that oftenly being underdiagnosed due to its symptoms that overlap with other heart disease and the pathophysiology of this disease remain unclear. People often judge that heart diseases were caused by unhealthy lifestyle, depression, and etc. GAD as one of the most common mental disorder, discovered in several studies as a risk factor in TCM. Through neuroendocrinal aspect review, GAD would cause increase in cathecolamine and excessive sympathetic nerve activation which led to TCM. A good and holistic GAD management, psychotherapy and pharmacotherapy usage would be an effective act of TCM prevention.

Conflict of Interest

Hereby, author declared that there are no conflict of intesert thorough the process of this review that would cause bias in the result of this review.

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