General Psychiatry

Mental stress, atheroma, myocardial ischaemia and injury: the link is inflammation

Hean Teik Ong ,[1] Jinghong Chen [2,3]

To cite: Ong HT, Chen J. Mental stress, atheroma, myocardial ischaemia and injury: the link is inflammation. *General Psychiatry* 2023;**36**:e101282. doi:10.1136/gpsych-2023-101282

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gpsych-2023-101282).

Received 08 August 2023
Accepted 20 November 2023

[1]Cardiology, HT Ong Heart Clinic, Georgetown, Penang, Malaysia
[2]Editorial Office of General Psychiatry, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[3]Shanghai Key Laboratory of Psychotic Disorders, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Correspondence to
Dr Hean Teik Ong;
ongheanteik@gmail.com

Dr Jinghong Chen;
chenjh_008@hotmail.com

ABSTRACT

Increasing observational and experimental trial data have shown that mental stress can lead to an increase in adverse clinical cardiovascular events. Mental stress affects the heart by inducing ischaemia and precipitating myocardial infarction (MI) or direct myocardial injury. Mental stress leads to systemic inflammation. Inflammation is known to cause rapid atheromatous plaque progression, instability and thrombosis—the classic type 1 MI. Inflammation can also lead to type 2 MI or myocarditis and injury. The published data linking systemic inflammation, mental stress and cardiovascular disease will be reviewed to establish the linkage between mind and heart, thereby highlighting the importance of holistically managing the patient, not only addressing separate organ systems. Finally, recent trial evidence showing the value of anti-inflammatory drugs in cardiovascular and mental conditions will be briefly considered.

INTRODUCTION

A large amount of data from both observational and experimental studies has shown that mental stress can increase the risk of clinical cardiovascular events by precipitating myocardial infarction (MI) or causing myocardial injury and damage.[1] To understand how mental stress can cause MI and myocardial injury, it is essential to recall the latest Fourth Universal Definition of MI that was published in 2018 by a joint task force of the European Society of Cardiology, American College of Cardiology, American Health Association and World Heart Federation.[2] The document classified MI into five types. The most common form of MI, due to acute plaque rupture and consequent coronary thrombosis, is labelled as type 1 MI. Type 2 MI occurs when the MI is secondary to an ongoing systemic disease such as severe hypertension, tachycardia, sepsis or shock. Type 2 MI must be distinguished from direct myocardial damage, where the insult is caused by a non-ischaemic condition, now labelled as myocardial injury (figure 1). Mental stress can lead to direct myocardial injury, as in Takotsubo cardiomyopathy, also known as broken heart syndrome, because it often occurs after a stressful or emotional event. Mental stress can also accelerate plaque progression, instability and thrombosis (type 1 MI). Furthermore, mental stress can precipitate systemic disease conditions, which then cause type 2 MI. Thus, mental stress can result in adverse clinical cardiovascular events by precipitating either type 1 or type 2 MI, as well as producing direct myocardial injury.

This article reviews the observational studies and experimental trials linking mental stress with myocardial ischaemia and adverse cardiovascular events. It then looks at the relationship between cardiovascular disease and systemic inflammation. Inflammation has been found to be fundamental to rapid plaque progression, which invariably precedes plaque rupture and coronary thrombosis. There is also increasing evidence indicating that inflammation is the underlying pathophysiology in mental stress-induced direct myocardial injury. Furthermore, in many mental diseases, systemic inflammation has also been found to be present, supporting that inflammation could be the common pathophysiology linking mental stress with cardiovascular events. By recognising the link between mental stress, inflammation and cardiovascular events, clinicians could better manage cardiovascular and mental diseases by offering behavioural or anti-inflammatory treatment in addition to the usual cardiovascular and psychiatric drugs or other interventional treatment strategies.

MENTAL STRESS AND CARDIOVASCULAR EVENTS

Observational studies

Observational studies linking mental stress with cardiovascular disease have been available for some time. A prospective cohort study of 7052 participants in a community health survey over a 12-year follow-up in Norway found that 6.1% of those reporting health anxiety as assessed by the Whiteley

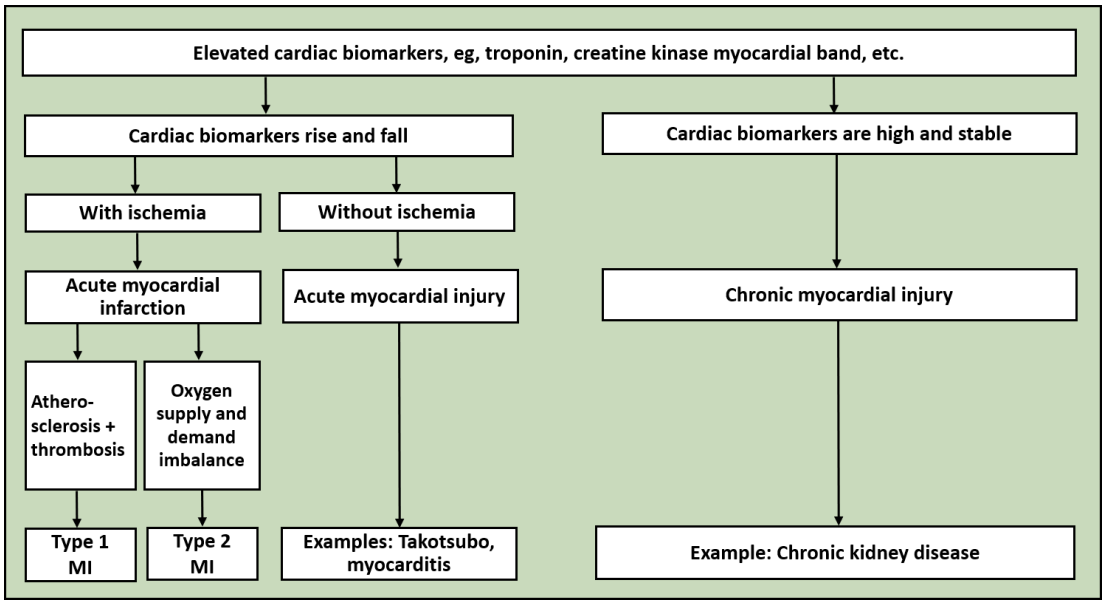

Figure 1 Differences in definition and diagnosis between type 1 and type 2 myocardial infarctions (MIs): acute and chronic myocardial injury*. *Modified from Figure 6, Fourth Universal Definition of Myocardial Infarction. Thygesen *et al*.[2]

Index developed clinical ischaemic heart disease (IHD), compared with 3.0% of those without health anxiety (hazard ratio (HR): 2.12, 95% confidence interval (CI): 1.52 to 2.48).[3] Anxiety can also adversely affect traditional cardiometabolic risk (CMR) factors such as systolic and diastolic blood pressure, fasting cholesterol and triglycerides, fasting glucose, body mass index and erythrocyte sedimentation rate. In a cohort of 1561 middle-aged American men followed up over 40 years, those with neuroticism and worry on the Whiteley Index had a worse CMR profile than those without such anxious features.[4] The higher the level of neuroticism and worry, the higher the overall CMR scores and the higher their likelihood of having over six CMR markers. In the China Kadoorie Biobank Study, among 486 541 participants, the overall prevalence of major depression was 0.61% (n=2972).[5] Over a median follow-up of 7.2 years, the incidence of IHD was 8.76 per 1000 person-years in those with major depression in the preceding 12 months, compared with 7.21 per 1000 person-years in those without (HR: 1.32, 95% CI: 1.14 to 1.53). Even the presence of depressive symptoms alone without major depression significantly increased the incidence of IHD (HR: 1.13, 95% CI: 1.04 to 1.23).

Another well-designed study from Sweden looked at 136 637 patients diagnosed with stress-related disorders, comparing them with 171 314 unaffected siblings and 1 366 370 matched unexposed people from the general population.[6] During up to 27 years of follow-up, cardiovascular disease crude incidence was 10.5 per 1000 person-years in stress-exposed patients, 8.4 per 1000 person-years in their unaffected siblings and 6.9 per 1000 person-years in matched unexposed individuals. In the first year after the diagnosis of stress-related disorder, the incidence of cardiovascular disease was significantly higher in patients than in their unaffected siblings (HR: 1.64, 95% CI: 1.45 to 1.84). Comparing patients diagnosed with stress-related disorders with a population-matched cohort, cardiovascular disease incidence was similarly significantly raised during the subsequent year (HR: 1.71, 95% CI: 1.59 to 1.83).

Between 75% and 87% of strokes are ischaemic in origin. Since the pathogenesis of cerebral ischaemia is similar to myocardial ischaemia, it is not surprising that mental stress can increase acute strokes.[7–9] INTERSTROKE is an international retrospective case-controlled study in 32 countries that recruited 13 462 patients who had a stroke and compared them with 13 488 matched controls.[10] Stress level was higher in younger people (mean age 57.5 years vs 62.6 years) and in those with better education (post-secondary 33.7% vs 23.9%). Stress level was also higher in high-income countries compared with low- and middle-income countries, showing that income and education do not ameliorate stress levels. Increased acute stroke was associated with increased stress at home (odds ratio (OR): 1.95, 95% CI: 1.77 to 2.15) or at work (OR: 2.70, 95% CI: 2.25 to 3.23) and after recent stressful life events (OR: 1.31, 95% CI: 1.19 to 1.43), such as major family conflict, marital separation or divorce, death of spouse and violence. The study also found that having a higher locus of control at home was associated with reduced stroke (OR: 0.73, 95% CI: 0.68 to 0.79). Although those with high home-related or work-related stress levels have a higher incidence of strokes, among these patients, those with higher control over their home or work circumstances had a lower incidence of strokes compared with those with lower control. Thus, it appears that stress is not reduced by education or income but can be reduced by increasing the ability to control home or work circumstances.

A prospective population-based cohort study from 21 countries recruited 118 706 participants; based on their

responses to entry questionnaires, their stress levels were classified as high, moderate, low or no stress.[11] Over a median follow-up of 10.2 years, after adjustment for multiple factors, compared with those with no stress, the risk of coronary heart disease was higher in those with high stress (HR: 1.24, 95% CI: 1.08 to 1.42), medium stress (HR: 1.15, 95% CI: 1.04 to 1.26) and even low stress (HR: 1.09, 95% CI: 1.01 to 1.18). Moreover, the risk of cardiovascular disease was higher in those with high stress (HR: 1.22, 95% CI: 1.08 to 1.37) and the risk of stroke increased with high stress (HR: 1.30, 95% CI: 1.09 to 1.56). All-cause death increased with high stress (HR: 1.17, 95% CI: 1.06 to 1.29), medium stress (HR: 1.19, 95% CI: 1.11 to 1.27) and even low stress (HR: 1.09, 95% CI: 1.03 to 1.16).

If mental stress is associated with an increased risk of cardiovascular diseases, does its opposite, optimism and physical activity, have any association with cardiovascular health? A meta-analysis of 15 studies including 229 391 participants with a mean follow-up of 13.8 years looked at the association of optimism with cardiovascular events and total mortality.[12] Optimism was associated with a reduced risk of cardiovascular events (relative risk (RR): 0.65, 95% CI: 0.51 to 0.78) and a reduced risk of total mortality (RR: 0.86, 95% CI: 0.80 to 0.92). While mental stress increases adverse cardiovascular events, there is ample evidence that a positive mental outlook promotes cardiovascular health.[13 14] A prospective cohort study of 487 334 Chinese adults aged 30–79 years followed up for a mean of 7.5 years showed that more physical activity was associated with lower risk of vascular events; HR for the top versus bottom quintile of physical activity was 0.77 (95% CI: 0.74 to 0.80).[15] Both occupational and non-occupational physical activities are protective against adverse cardiovascular events. Another report of 3099 Italians aged over 65 years showed that compared with those with low physical activity, participants reporting high physical activity had a lower risk of adverse cardiovascular outcomes (HR: 0.48, 95% CI: 0.27 to 0.86).[16] Even muscle-strengthening exercises appear to reduce the risk of cardiovascular events and other non-communicable diseases.[17] Patients should be encouraged to avoid mental stress and increase optimism, aerobic and muscle-strengthening exercises to improve their overall and cardiovascular health.

EXPERIMENTAL STUDIES

Although observational studies can show the association between stress and adverse clinical cardiovascular outcomes, they cannot prove causation. However, we now have increasing experimental studies to establish the link between mental stress, myocardial ischaemia and subsequent cardiovascular events. There have been few reports of trials of mental stress-induced myocardial ischaemia (MSIMI) due to technical challenges, as the methods for inducing mental stress and the manner of diagnosing objective myocardial ischaemia are yet to be standardised.

A meta-analysis of MSIMI in patients with coronary artery disease (CAD) in 2014 found only five trials, including a total of 555 patients, with follow-ups ranging from 35 days to 8.8 years.[18] The presence of MSIMI increased the subsequent development of cardiac events or total mortality (RR: 2.2, 95% CI: 1.59 to 3.15). Another meta-analysis in 2020 analysed 20 studies of MSIMI in patients with CAD.[19] This paper studied the prevalence of MSIMI, the factors associated with it and the methods used in diagnosing the disease. Out of 3164 studied patients with CAD, 902 had MSIMI, giving an overall prevalence of 32% (95% CI: 26% to 38%). Patients with a previous MI or coronary artery bypass graft were more likely to have MSIMI. Mental stress was induced by 5 minutes of one or more activities such as mental arithmetic, public speaking or anger recall. Using more than one method to produce mental stress resulted in a higher prevalence of MSIMI.

Diagnostic techniques for detecting myocardial ischaemia include electrocardiography, echocardiography, single-photon emission computed tomography (CT) or radionuclide ventriculography. Ischaemia has been diagnosed by a decrease in left ventricular function, wall motion abnormalities (WMAs), ST depression or myocardial perfusion defects. Using different diagnostic techniques and measurements has produced different prevalence rates for MSIMI. The highest rate for MSIMI was found with WMA (51%) and echocardiography (41%). The researchers found that using two diagnostic techniques and measurements detected significantly more cases of MSIMI than using only one. The authors concluded that MSIMI is widespread, but standardisation of the diagnostic methodology is needed to study the topic properly.

A more recent report in 2021 pooled two prospective cohort studies enrolling 918 patients with CAD; it focused on subsequent cardiovascular outcomes in patients with MSIMI compared with those exhibiting conventional stress-induced ischaemia.[20] In their sample, 16% had MSIMI, 31% had conventional stress-induced myocardial ischaemia and 10% had both. Median follow-up was 5 years, and the primary endpoint was a composite of cardiovascular death or non-fatal MI, with a secondary endpoint of heart failure hospitalisation. The primary endpoint was 6.9 per 100 patient-years in those with MSIMI and 2.6 per 100 patient-years for those without MSIMI (HR: 2.5, 95% CI: 1.8 to 3.5). The secondary event rate was 12.6 per 100 patient-years for those with MSIMI and 5.6 per 100 patient-years for those without MSIMI (HR: 2.0, 95% CI: 1.5 to 2.5). In comparison, the primary endpoint event rate was 4.8 per 100 patient-years in those with conventional stress-induced ischaemia and 2.5 per 100 patient-years for those without it (HR: 2.0, 95% CI: 1.5 to 2.8). For the secondary endpoints, event rates in those with and without conventional stress-induced ischaemia were 8.4 and 5.6, respectively (HR: 1.6, 95% CI: 1.3 to 2.0). It appears that MSIMI is worse than conventional stress-induced ischaemia when predicting future adverse cardiovascular events in patients with CAD.

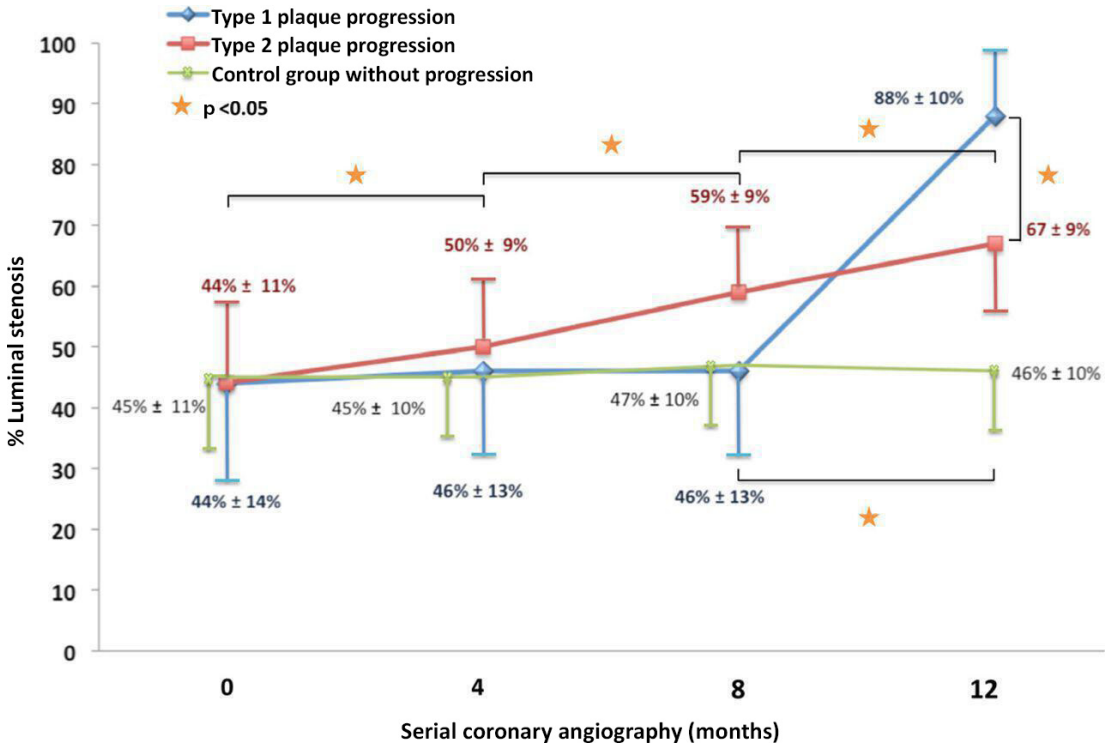

Figure 2 Plaque progression, not the percentage of stenosis, determines the clinical event.* With type 1 plaque progression, the stenosis did not change in the first three measurements, but a sudden marked increase was observed between the third and fourth measurements: 71% of the patients developed ACS. With type 2 plaque progression, stenosis increased constantly throughout all intervals: 14% of the patients developed angina. In the control group with no significant plaque progression, no ACS was found: only 2% of the patients developed angina. It is not the degree of stenosis at any one time but the rate of future plaque progression that determines adverse clinical events. *Adapted from Yokoya *et al*[24] and Ahmadi *et al*.[25] ACS, acute coronary syndrome.

In the above study, the risks posed by the presence of MSIMI were even more clearly shown if patients with no ischaemia were taken as the control group. While the primary event rate was 2.3 per 100 patient-years in the no-ischaemia control group, the conventional stress-induced ischaemia group had an event rate of 3.1 (HR: 1.4, 95% CI: 0.9 to 2.1), the MSIMI group had an event rate of 4.8 (HR: 2.0, 95 % CI: 1.1 to 3.7), and the group with both conventional stress and MSIMI had a primary event rate of 8.1 (HR: 3.8, 95% CI: 2.6 to 5.6). Patients with MSIMI are thus at higher risk of adverse events than those with conventional stress-induced ischaemia, and the prognosis is the worst for patients with both conventional and mental stress ischaemia. The relatively low incidence of adverse cardiovascular events in patients with conventional stress-induced ischaemia, although surprising to some, has also been shown in a prospective randomised, single-centre trial of 535 patients with CAD followed up for a mean of 10 years.[21] Among the patients with chronic CAD with multivessel disease, those with and without a baseline positive conventional stress test ischaemia had similar survival-free cardiovascular event rates (HR 1.0, 95% CI: 0.80 to 1.27). Thus, by using only the standard conventional stress test techniques, many patients at high risk of CAD adverse events can be missed. Even if patients cannot be formally tested for MSIMI, alert clinicians should look for its presence during history intake to identify this vulnerable group and then arrange for more intensive therapy.

CARDIOVASCULAR DISEASE AND INFLAMMATION

When thrombosis occurs at the site of an unstable atheromatous plaque in a coronary artery, total occlusion can develop, leading to severe ischaemia with myocardial cell death and resulting MI—now classified in the Fourth Universal Definition as type 1 MI.[2] A debate has erupted about whether more severe stenosis causes more frequent MIs since some studies suggest that the mildly stenotic lipid-rich plaque with thin caps is more likely to rupture, leading to thrombosis and MI.[22 23] This matter is now resolved by recalling the seminal work on plaque progression from Japan (figure 2).[24 25] Patients with plaque progression of over 15% on four serial angiograms performed in a year were selected from a database of about 15 000 patients. This study showed that some plaques do not progress (control group), while some do not progress for a period and then suddenly and rapidly progress in size (type 1 progression). Others grow and progress gradually (type 2 progression). It is the type 1 progression that accounts for most of the adverse cardiovascular events. In the type 1 plaque progression group, 71% of patients developed unstable angina or MI; in contrast, the type 2 plaque progression group had no MIs

and only 14% experienced angina.[24] Meanwhile, in the control group with no plaque progression, only 2% developed angina.[25] As shown in figure 2, at the time of the fourth angiogram, patients with type 1 plaque progression had a mean stenosis of 88%, and those with type 2 had a mean stenosis of 67%. However, at the time of the third angiogram, patients with type 1 plaque progression had a mean stenosis of only 47%, while patients with type 2 plaque progression had more severe stenosis with a mean of 59%. It is not the degree of stenosis of the plaque at any one time that is important, but its rate of progression that correlates with adverse clinical events.

It is now increasingly clear that inflammation plays a major role in coronary atheroma progression. In patients with unstable angina, inflammation-induced neutrophil activation was found in the blood of the aorta as well as the coronary vascular bed far from the site of the culprit plaque.[26] This shows that vulnerable plaque rupture is not a local event but the result of generalised inflammation in the body. The relationship between inflammation and plaque progression was elegantly demonstrated in a prospective study of patients with angina waiting for coronary angioplasty over a mean period of 4.8 months.[27] Of all 124 patients, 35 (28%) experienced atheroma plaque progression during that period. Inflammatory markers such as neopterin, high-sensitivity C reactive protein (CRP), matrix metalloproteinase-9 and soluble intercellular adhesion molecule 1 were significantly elevated in the patients with stenosis progression compared with those with no progression. The study suggests that the presence of inflammatory molecules and cells determines whether a plaque will progress and become unstable to cause adverse clinical cardiovascular events. Therefore, it is the plaque inflammatory mechanism involving endothelial and macrophage activation, not the degree of stenosis, that predicts plaque progression and myocardial vulnerability.

Today, the relationship between stenosis, plaque vulnerability and clinical events has been established. It is not the degree of stenosis that is important, but the amount of inflammation in the plaque.[28 29] The more inflammation associated with the atheromatous plaque, the more it is likely to progress and rupture, resulting in thrombosis and unstable clinical coronary events. During the acute event, the culprit plaque is expected to be severely stenosed, but prior to the event, an angiographic coronary study cannot predict whether any plaque will subsequently progress and rupture. Mental stress is increasingly reported to be involved in the pathogenesis of atherosclerosis by causing increased vascular inflammation that leads to more rapid plaque progression, ending in thrombosis, MI and adverse clinical cardiovascular events.[30 31]

In addition to plaque thrombosis, mental stress can cause direct myocardial injury. As shown in figure 1, it is essential to distinguish type 2 MI from acute myocardial injury. In type 2 MI, a systemic condition results in reduced coronary blood flow, causing ischaemia and damage to the myocardium.[32] In contrast, in myocardial injury from myocarditis, troponin elevation is not due to ischaemia but results directly from muscle damage brought on by toxins, infection, vaccination or other inflammatory stimuli.[33–36] Takotsubo cardiomyopathy is the classic situation of mental stress-induced myocardial injury and damage.[37] Initially thought to be due to an excessive sympathetic drive related to mental stress, it is increasingly being acknowledged that the pathogenesis of Takotsubo cardiomyopathy is an inflammatory process.[38] Compared with matched controls, a study of 55 patients with Takotsubo cardiomyopathy showed elevated serum monocyte and inflammatory marker levels. With multiparametric cardiac resonance imaging, these patients were found to have myocardial macrophage inflammatory infiltrate, confirming that Takotsubo cardiomyopathy is indeed a disease of myocardial inflammation.[39] Inflammation plays a primary pathophysiological role in Takotsubo cardiomyopathy and other types of myocarditis and is likely to be of primary importance in all types of mental stress-induced myocardial injury.[40]

MENTAL STRESS AND INFLAMMATION

With the above strong medical evidence linking mental stress to cardiac disease and cardiac disease to inflammation, the final piece of the jigsaw is to look for trial evidence linking mental stress to systemic inflammation. Its discovery would assist in establishing the link between systemic inflammation, mental stress and cardiovascular events. Evidence linking mental stress to inflammation was found in a study of 293 healthy people, selected from a pool of 6088, who had baseline health screening for cancer with a positron emission tomography (PET)/CT scan of the brain.[41] The amygdala is the region of the brain involved in emotional stress. Over a follow-up of 3.7 years, baseline amygdala activity was associated with increased bone marrow activity ($r=0.47$; $p<0.001$), arterial inflammation ($r=0.49$; $p<0.001$) and cardiovascular events (HR: 1.59, 95% CI: 1.27 to 1.98; $p<0.001$). This interesting report points to a strong linkage between mental stress, inflammation and increased cardiovascular events.

Using data from over 140 000 participants in the UK Biobank, the association between circulating CRP with anxiety and depression was tested.[42] There was a clear association between higher CRP levels and both higher depression and anxiety scores, with the association being stronger with depression and among women than men. Genetic analysis of the biodata showed that people with genetically predicted higher interleukin (IL)-6 activity were at increased risk of depressive symptoms, again suggesting that inflammation was involved in mental disorders. A meta-analysis of 41 studies on anxiety, posttraumatic stress and obsessive-compulsive disorders looked at the relationship of prolonged mental stress with chronic inflammation as measured by cytokines and CRP.[43] Proinflammatory cytokines, especially IL-1β and IL-6, are significantly higher in patients who are anxious

Table 1 Abnormal inflammatory markers in myocardial injury (myocarditis) and ischaemia

Clinical condition	Abnormal inflammatory markers	References
Myocardial injury (myocarditis)	↑ CRP ↑ IL-1, IL-6, IL-15 ↑ TNF-α ↑ IL-33 receptor sST ↑ Chemokines ↑ Matrix metalloproteinase	36 39 56
Unstable angina	↓ Neutrophil myeloperoxidase ↑ CRP	26
Coronary progression	↑ IL-1, IL-6, IL-18 ↑ Neopterin ↑ CRP ↑ Matrix metalloproteinase ↑ Soluble intercellular adhesion molecules	27 29

Reference numbers refer to references in the text.
CRP, C reactive protein; IL, interleukin; TNF-α, tumour necrosis factor-α.

compared with healthy controls, again pointing to an essential role of inflammation in these disease conditions.

Neuroimaging using PET, magnetic resonance imaging and magnetic resonance spectroscopy has shown that brain regions such as the basal ganglia, cortical reward, amygdala, insula and anterior cingulate cortex are affected by the introduction of peripheral inflammatory stimuli.[44] These studies confirm that inflammation is an intrinsic part of neuropsychiatric disease conditions. Mental diseases are thus more than conditions where the patient's thinking faculties are impaired. The absence of structural anatomical abnormalities obscures the fact that there is actually inflammation throughout the body of patients with mental disease. The systemic inflammation present with mental stress and disease, therefore, can lead to myocardial ischaemia and injury with resulting adverse clinical events.

Table 2 Abnormal inflammatory markers in major anxiety and depressive disorders

Mental condition	Abnormal inflammatory markers	References
Anxiety disorders	↑ IL-1β, IL-6, IL-2 ↑ TNF-α ↑ CRP	42 43
Depressive disorders	↑ CRP ↑ TNF-α ↑ IL-1, IL-6, IL-18	44 63–65

Reference numbers refer to references in the text.
CRP, C reactive protein; IL, interleukin; TNF-α, tumour necrosis factor-α.

ANTI-INFLAMMATORY DRUGS IN CARDIOVASCULAR AND MENTAL DISEASES

If inflammation is intrinsically involved in the pathogenesis of atheromatous plaque progression and plaque instability leading to MI, anti-inflammatory drugs should have a role to play in cardiovascular therapeutics. A study of canakinumab, a monoclonal antibody targeting IL-1β, was carried out on 10 061 patients with a prior MI and a CRP above 2 mg/L.[45] Canakinumab at 50 mg, 150 mg or 300 mg was given subcutaneously every 3 months. The primary endpoint was non-fatal MI, non-fatal stroke or cardiovascular death. After a median follow-up of 3.7 years, the primary endpoint event rate per 100 patient-years was 4.5 in the placebo group, 4.11 in the 50 mg canakinumab group (HR: 0.93, 95% CI: 0.80 to 1.07; p=0.300), 3.86 in the 150 mg canakinumab group (HR: 0.85, 95% CI: 0.74 to 0.98; p=0.021) and 3.90 in the 300 mg canakinumab group (HR: 0.86, 95% CI: 0.75 to 0.99; p=0.031). Therefore, while canakinumab did reduce cardiovascular events, the results were not particularly promising.

After an unsuccessful trial with methotrexate, cardiologists may have finally found the right anti-inflammatory therapy for IHD in colchicine. Among 4745 patients enrolled in a study within 30 days after an MI, the composite primary endpoint was significantly reduced by 0.5 mg colchicine once daily (HR: 0.77, 95% CI: 0.61 to 0.96; p=0.02), after a median of 22.6 months.[46] Moreover, in a study of stable chronic coronary disease, a small trial of 532 patients with a median follow-up of 3 years found that 0.5 mg daily colchicine significantly reduced the primary endpoint composite of acute coronary syndrome, cardiac arrest or stroke (HR: 0.33, 95% CI: 0.18 to 0.59; p<0.001, number needed to treat (NNT) 11).[47] The value of colchicine in chronic coronary disease was further confirmed in a larger trial of 5522 patients followed up for 28.6 months.[48] The composite primary endpoint was again very significantly reduced by a low dose of 0.5 mg daily colchicine (HR: 0.69, 95% CI: 0.57 to 0.83; p<0.001). Composites of the primary endpoint, including MI and revascularisation, were also significantly reduced. These findings strongly suggest that a low dose of colchicine (0.5 mg daily) is helpful in reducing adverse cardiovascular events for patients with recent MI and for those with stable coronary disease.

For mental diseases such as depression, anxiety, bipolar disorder, autism, schizophrenia, post-traumatic stress, addiction and obsessive-compulsive disorder, major inflammatory markers, including tumour necrosis factor-α (TNF-α) and IL-6, have been found to be elevated.[49 50] Patients in remission from atypical depressive symptoms had lower levels of TNF-α and IL-6 compared with those with no remission.[51] However, well-conducted, large-scale trials with long follow-up on anti-inflammatory drugs are

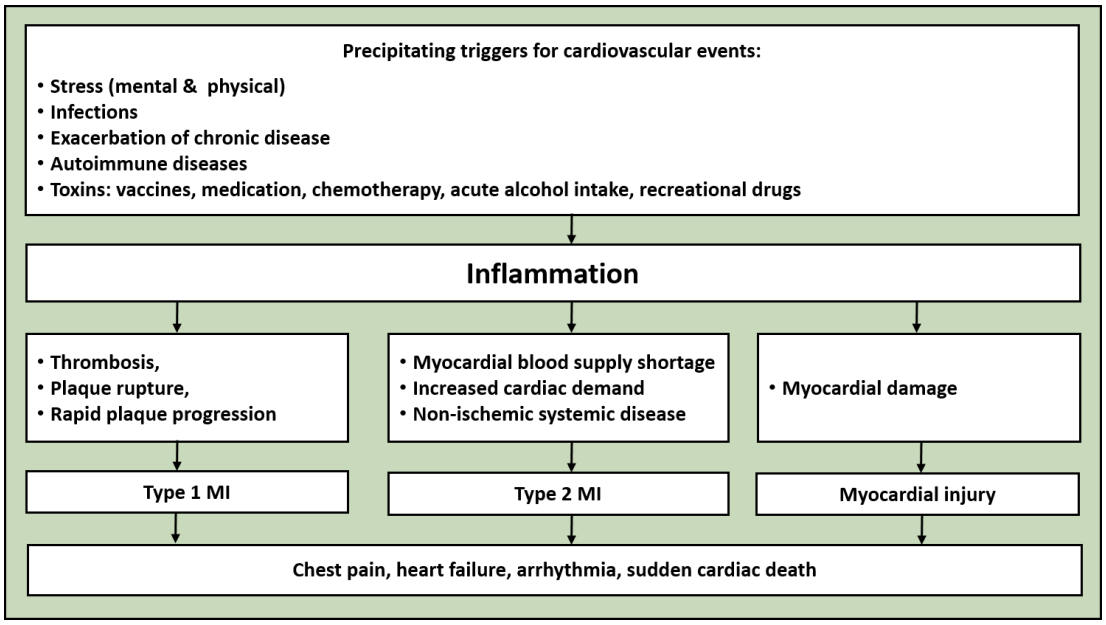

Figure 3 Inflammation leads to adverse cardiovascular outcomes by causing acute type 1 and type 2 myocardial infarctions (MIs) and myocardial injury.

still unavailable, although numerous small studies have tested anti-inflammatory drugs in addition to conventional therapy for anxiety, depression and a variety of other conditions. Nevertheless, meta-analyses have suggested benefits for mental disorders with anti-inflammatory drugs. A Danish meta-analysis of anti-inflammatory medications in depression looked at 36 trials including about 10 000 patients.[52] Anti-inflammatory agents such as non-steroidal anti-inflammatory drugs (NSAIDs), cytokine inhibitors, glucocorticoids, statins and minocycline are useful in treating depression and improving depression scores and depressive symptoms. Another Chinese meta-analysis of 26 trials showed that anti-inflammatory agents, whether as monotherapy or add-ons to antidepressants, reduce depressive symptoms and produce higher response and remission rates.[53] In particular, NSAIDs, omega-3, statins and minocycline were all found to be effective.

INFLAMMATORY MARKERS LINK CARDIOVASCULAR AND MENTAL DISEASES

Although Takotsubo, or stress-induced cardiomyopathy, was first reported in Japan in the 1990s, a clear link between mental stress, atheroma, myocardial ischaemia and injury has eluded the medical fraternity for a long time.[54 55] Two major deficiencies exist in our previous understanding of cardiac diseases that have slowed our ability to see the link between mental stress and the heart. The first deficiency is that the distinction between myocardial ischaemia and injury was not clear, and the definition was not standardised until the important Fourth Universal Definition of MI in 2018.[2] We now know that there are two different ways the heart muscle can be damaged: by ischaemia, when the problem usually is due to atheromatous plaques or by direct heart muscle injury or myocarditis, a condition increasingly recognised during the coronavirus disease 2019 (COVID-19) pandemic.[36 56] The second deficiency lies in our inadequate understanding of atheroma progression and subsequent myocardial ischaemia. It is only recently that instead of plaque size or content, inflammation and plaque progression have been identified as the pivotal pathologies leading to MI and adverse clinical cardiac events.[25 28]

Studies experimentally inducing myocardial ischaemia or injury can result in morbidity and mortality, so these are faced with ethical and methodological obstacles in humans. Large animal models for studying coronary atheroma have limitations because animal models of mental stress—although a hot topic of research—may not accurately represent human stress since animals are highly adaptable to their environment.[57–59]

Although there have recently been several review articles on mental stress and cardiovascular disease, no new large prospective clinical studies of MSIMI have been reported.[60–62] The methodology for inducing mental stress and the method of diagnosing myocardial ischaemia have not been standardised. Reported trials included only between 35 and 660 patients, and the largest series reporting over 900 patients was only possible because of pooling together two different studies.[19 20]

Nevertheless, once sufficient evidence shows that inflammatory markers are elevated not only in cardiac conditions but also in mental disorders, the link between them will become clear.[44 63–65] As shown in tables 1 and 2, a large number of studies have shown that serum inflammatory markers are elevated in both mental and cardiac conditions.

A hypothesis of how clinical cardiovascular events from type 1 MI, type 2 MI or myocardial injury are precipitated by inflammation is shown in figure 3. Systemic inflammation can be induced by various conditions, including infections, vaccination, systemic toxins and excessive mental or physical stress. Inflammation produces a widespread severe systemic oxidative state, which overwhelms the body's anti-oxidant defences, resulting in systemic organ damage, including cardiovascular and mental diseases. Inflammation and oxidation can cause rapid plaque progression and thrombosis, with the resulting MI manifesting adverse clinical cardiovascular events.[66] The oxidative stress from inflammation can also cause direct myocardial injury, with myocarditis producing adverse clinical cardiovascular events.[67] Patients with psychiatric diseases such as depression, anxiety, bipolar disorder, post-traumatic stress disorders, addiction and schizophrenia can exhibit inflammatory cytokine signalling alterations and increased oxidative stress.[68] The close connection between mental stress and cardiovascular diseases through the common pathology of inflammation and oxidation is thus becoming more apparent.

CONCLUSION

The human body functions as a whole system, and disease in one organ system can affect another. Mental stress causes inflammation, which can then lead to cardiovascular events. Similarly, when MI occurs, anxiety and depression are often accompanying conditions, and patients suffering from these mental complications have a worse subsequent prognosis.[69–71] Even risk factors for cardiovascular events, such as hypertension and sleep quality, are affected by mental stress.[72 73] When systemic inflammation is precipitated, for example, by infection or autoimmune conditions, mental disease, cardiac disease or both can result. In summary, the focus of a good clinician should never be confined to one particular organ system but rather encompass the patient holistically, constantly aware of the possibility of interconnected disorders. This holistic approach is particularly important for patients with cardiovascular, neuropsychiatric and inflammatory diseases.

Twitter Jinghong Chen @CJH_gp

Contributors HTO and JC contributed equally to planning, conducting, reviewing and producing the reported work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests JC is Deputy Editor of *General Psychiatry*.

Patient consent for publication Not required.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Hean Teik Ong http://orcid.org/0000-0001-8429-7670
Jinghong Chen http://orcid.org/0000-0002-7428-9359

REFERENCES

1 Bravo PE, Cappola TP. Mental stress induced myocardial ischemia. *JAMA* 2021;326:1803.
2 Thygesen K, Alpert JS, Jaffe AS, *et al*. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol* 2018;72:2231–64.
3 Berge LI, Skogen JC, Sulo G, *et al*. Health anxiety and risk of ischaemic heart disease: a prospective cohort study linking the Hordaland Health Study (HUSK) with the Cardiovascular Diseases in Norway (CVDNOR) project. *BMJ Open* 2016;6:e012914.
4 Lee LO, Grimm KJ, Spiro A III, *et al*. Worry, and cardiometabolic risk trajectories: findings from a 40-year study of men. *JAHA* 2022;11:e022006.
5 Liu N, Pan X-F, Yu C, *et al*. Association of major depression with risk of ischemic heart disease in a mega-cohort of Chinese adults: the China Kadoorie Biobank study. *J Am Heart Assoc* 2016;5:e004687.
6 Song H, Fang F, Arnberg FK, *et al*. Stress related disorders and risk of cardiovascular disease: population based, sibling controlled cohort study. *BMJ* 2019;365:l1255.
7 Sridharan SE, Unnikrishnan JP, Sukumaran S, *et al*. Incidence, types, risk factors, and outcome of stroke in a developing country. *Stroke* 2009;40:1212–8.
8 Thrift AG, Dewey HM, Macdonell RAL, *et al*. Incidence of the major stroke subtypes: initial findings from the North East Melbourne stroke incidence study (NEMESIS). *Stroke* 2001;32:1732–8.
9 Kuriakose D, Xiao Z. Pathophysiology and treatment of stroke: present status and future perspectives. *Int J Mol Sci* 2020;21:7609.
10 Reddin C, Murphy R, Hankey GJ, *et al*. Association of psychosocial stress with risk of acute stroke. *JAMA Netw Open* 2022;5:e2244836.
11 Santosa A, Rosengren A, Ramasundarahettige C, *et al*. Psychosocial risk factors and cardiovascular disease and death in a population-based cohort from 21 low-, middle-, and high-income countries. *JAMA Netw Open* 2021;4:e2138920.
12 Rozanski A, Bavishi C, Kubzansky LD, *et al*. Association of optimism with cardiovascular events and all-cause mortality: a systematic review and meta-analysis. *JAMA Netw Open* 2019;2:e1912200.
13 Kubzansky LD, Huffman JC, Boehm JK, *et al*. Positive psychological well-being and cardiovascular disease: JACC health promotion series. *J Am Coll Cardiol* 2018;72:3012–26.
14 Huffman JC. Optimism and health: where do we go from here *JAMA Netw Open* 2019;2:e1912211.
15 Bennett DA, Du H, Clarke R, *et al*. Association of physical activity with risk of major cardiovascular diseases in Chinese men and women. *JAMA Cardiol* 2017;2:1349–58.
16 Barbiellini Amidei C, Trevisan C, Dotto M, *et al*. Association of physical activity trajectories with major cardiovascular diseases in elderly people. *Heart* 2022;108:360–6.
17 Momma H, Kawakami R, Honda T, *et al*. Muscle-strengthening activities are associated with lower risk and mortality in major non-communicable diseases: a systematic review and meta-analysis of cohort studies. *Br J Sports Med* 2022;56:755–63.
18 Wei J, Rooks C, Ramadan R, *et al*. Meta-analysis of mental stress-induced myocardial ischemia and subsequent cardiac events in patients with coronary artery disease. *Am J Cardiol* 2014;114:187–92.
19 Zhang L, Bao Y, Wang X, *et al*. A meta-analysis on the prevalence, associated factors and diagnostic methods of mental stress induced myocardial ischemia. *J Transl Med* 2020;18:218.
20 Vaccarino V, Almuwaqqat Z, Kim JH, *et al*. Association of mental stress-induced myocardial ischemia with cardiovascular events in patients with coronary heart disease. *JAMA* 2021;326:1818–28.
21 Garzillo CL, Hueb W, Gersh B, *et al*. Association between stress testing-induced myocardial ischemia and clinical events in patients with multivessel coronary artery disease. *JAMA Intern Med* 2019;179:1345–51.
22 Niccoli G, Stefanini GG, Capodanno D, *et al*. Are the culprit lesions severely stenotic? *JACC Cardiovasc Imaging* 2013;6:1108–14.
23 Stone GW, Narula J. The myth of the mild vulnerable plaques. *JACC Cardiovasc Imaging* 2013;6:1124–6.
24 Yokoya K, Takatsu H, Suzuki T, *et al*. Process of progression of coronary artery lesions from mild or moderate stenosis to moderate or severe stenosis: a study based on four serial coronary arteriograms per year. *Circulation* 1999;100:903–9.
25 Ahmadi A, Leipsic J, Blankstein R, *et al*. Do plaques rapidly progress prior to myocardial infarction? The interplay between plaque vulnerability and progression. *Circ Res* 2015;117:99–104.
26 Buffon A, Biasucci LM, Liuzzo G, *et al*. Widespread coronary inflammation in unstable angina. *N Engl J Med* 2002;347:5–12.
27 Zouridakis E, Avanzas P, Arroyo-Espliguero R, *et al*. Markers of inflammation and rapid coronary artery disease progression in patients with stable angina pectoris. *Circulation* 2004;110:1747–53.

28 Ahmadi A, Argulian E, Leipsic J, *et al*. From subclinical atherosclerosis to plaque progression and acute coronary events: JACC state-of-the-art review. *J Am Coll Cardiol* 2019;74:1608–17.
29 Arnold N, Lechner K, Waldeyer C, *et al*. Inflammation and cardiovascular disease: the future. *Eur Cardiol* 2021;16:e20.
30 Yao BC, Meng LB, Hao ML, *et al*. Chronic stress: a critical risk factor for atherosclerosis. *J Int Med Res* 2019;47:1429–40.
31 Gao S, Wang X, Meng L-B, *et al*. Recent progress of chronic stress in the development of atherosclerosis. *Oxid Med Cell Longev* 2022;2022:4121173.
32 Coscia T, Nestelberger T, Boeddinghaus J, *et al*. Characteristics and outcomes of type 2 myocardial infarction. *JAMA Cardiol* 2022;7:427–34.
33 Liu C, Liu Y, Chen H, *et al*. Myocardial injury: where inflammation and autophagy meet. *Burns Trauma* 2023;11:tkac062.
34 Tschöpe C, Ammirati E, Bozkurt B, *et al*. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol* 2021;18:169–93.
35 Ammirati E, Moslehi JJ. Diagnosis and treatment of acute myocarditis: a review. *JAMA* 2023;329:1098–113.
36 Barmada A, Klein J, Ramaswamy A, *et al*. Cytokinopathy with aberrant cytotoxic lymphocytes and profibrotic myeloid response in SARS-CoV-2 mRNA vaccine-associated myocarditis. *Sci Immunol* 2023;8:eadh3455.
37 Boyd B, Solh T. Takotsubo cardiomyopathy: review of broken heart syndrome. *JAAPA* 2020;33:24–9.
38 Lyon AR, Citro R, Schneider B, *et al*. Pathophysiology of takotsubo syndrome: JACC state-of-the-art review. *J Am Coll Cardiol* 2021;77:902–21.
39 Scally C, Abbas H, Ahearn T, *et al*. Myocardial and systemic inflammation in acute stress-induced (Takotsubo) cardiomyopathy. *Circulation* 2019;139:1581–92.
40 Everett BM, Moorthy MV, Tikkanen JT, *et al*. Markers of myocardial stress, myocardial injury, and subclinical inflammation and the risk of sudden death. *Circulation* 2020;142:1148–58.
41 Tawakol A, Ishai A, Takx RA, *et al*. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. *Lancet* 2017;389:834–45.
42 Ye Z, Kappelmann N, Moser S, *et al*. Role of inflammation in depression and anxiety: tests for disorder specificity, linearity and potential causality of association in the UK Biobank. *EClinicalMedicine* 2021;38:100992.
43 Renna ME, O'Toole MS, Spaeth PE, *et al*. The association between anxiety, traumatic stress, and obsessive-compulsive disorders and chronic inflammation: a systematic review and meta-analysis. *Depress Anxiety* 2018;35:1081–94.
44 Felger JC. Imaging the role of inflammation in mood and anxiety-related disorders. *Curr Neuropharmacol* 2018;16:533–58.
45 Ridker PM, Everett BM, Thuren T, *et al*. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;377:1119–31.
46 Tardif J-C, Kouz S, Waters DD, *et al*. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019;381:2497–505.
47 Nidorf SM, Eikelboom JW, Budgeon CA, *et al*. Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll Cardiol* 2013;61:404–10.
48 Nidorf SM, Fiolet ATL, Mosterd A, *et al*. Colchicine in patients with chronic coronary disease. *N Engl J Med* 2020;383:1838–47.
49 Zhao H, Jin R, Hu J. Disturbed sensitive equilibrium led by stress-induced inflammation in psychiatric illness. *Gen Psychiatr* 2022;35:e100910.
50 Pitsavos C, Panagiotakos DB, Papageorgiou C, *et al*. Anxiety in relation to inflammation and coagulation markers, among healthy adults: the ATTICA study. *Atherosclerosis* 2006;185:320–6.
51 Liu H, Wu X, Wang Y, *et al*. TNF-A, IL-6 and hsCRP in patients with melancholic, atypical and anxious depression: an antibody array analysis related to somatic symptoms. *Gen Psychiatr* 2022;35:e100844.
52 Köhler-Forsberg O, N Lydholm C, Hjorthøj C, *et al*. Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: meta-analysis of clinical trials. *Acta Psychiatr Scand* 2019;139:404–19.
53 Bai S, Guo W, Feng Y, *et al*. Efficacy and safety of anti-inflammatory agents for the treatment of major depressive disorder: a systematic review and meta-analysis of randomised controlled trials. *J Neurol Neurosurg Psychiatry* 2020;91:21–32.
54 Matsuzaki M. Stress 'Takotsubo' cardiomyopathy: questions still remain. *Nat Clin Pract Cardiovasc Med* 2007;4:577.
55 Chahal GS, Polena S, Fard BS, *et al*. Takotsubo cardiomyopathy: case report and review of the literature. *Proc West Pharmacol Soc* 2008;51:48–51.
56 Wang DW. Chapter 7: clinical manifestations of and laboratory tests for myocarditis and fulminant myocarditis. In: *Fulminant myocarditis*. Springer Nature, 2023: 101–11.
57 Shin HS, Shin HH, Shudo Y. Current status and limitations of myocardial infarction large animal models in cardiovascular translational research. *Front Bioeng Biotechnol* 2021;9:673683.
58 Golbidi S, Frisbee JC, Laher I. Chronic stress impacts the cardiovascular system: animal models and clinical outcomes. *Am J Physiol Heart Circ Physiol* 2015;308:H1476–98.
59 Pesarico AP, Chagas PM, Nacher J. Editorial: animal models of stress - current knowledge and potential directions. *Front Behav Neurosci* 2021;15:655214.
60 Mehta PK, Sharma A, Bremner JD, *et al*. Mental stress-induced myocardial ischemia. *Curr Cardiol Rep* 2022;24:2109–20.
61 Vancheri F, Longo G, Vancheri E, *et al*. Mental stress and cardiovascular health-part I. *J Clin Med* 2022;11:3353.
62 Henein MY, Vancheri S, Longo G, *et al*. The impact of mental stress on cardiovascular health-part II. *J Clin Med* 2022;11:4405.
63 Yuan N, Chen Y, Xia Y, *et al*. Inflammation-related biomarkers in major psychiatric disorders: a cross-disorder assessment of reproducibility and specificity in 43 meta-analyses. *Transl Psychiatry* 2019;9:233.
64 Dowlati Y, Herrmann N, Swardfager W, *et al*. A meta-analysis of cytokines in major depression. *Biol Psychiatry* 2010;67:446–57.
65 Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med* 2009;71:171–86.
66 Zhong S, Li L, Shen X, *et al*. An update on lipid oxidation and inflammation in cardiovascular diseases. *Free Radic Biol Med* 2019;144:266–78.
67 Tada Y, Suzuki J-I. Oxidative stress and myocarditis. *Curr Pharm Des* 2016;22:450–71.
68 Casaril AM. Editorial: immune and oxidative pathways in psychiatric disorders. *Front Neurosci* 2022;16:1073757.
69 Feng HP, Chien WC, Cheng WT, *et al*. Risk of anxiety and depressive disorders in patients with myocardial infarction: a nationwide population-based cohort study. *Medicine (Baltimore)* 2016;95:e4464.
70 Liblik K, Mulvagh SL, Hindmarch CCT, *et al*. Depression and anxiety following acute myocardial infarction in women. *Trends Cardiovasc Med* 2022;32:341–7.
71 Santos J. Anxiety and depression after myocardial infarction: can inflammatory factors be involved. *Arq Bras Cardiol* 2018;111:684–5.
72 Cai L, Wei L, Yao J, *et al*. Impact of depression on the quality of sleep and immune functions in patients with coronary artery disease. *Gen Psychiatr* 2022;35:e100918.
73 Cai L, Liu Y, He L. Investigating genetic causal relationships between blood pressure and anxiety, depressive symptoms, neuroticism and subjective well-being. *Gen Psychiatr* 2022;35:e100877.

Ong graduated from the University of Malaya in 1983, obtained his Membership of the Royal Colleges of Physicians (MRCP) in the UK in 1987, and his Master of Medicine in Singapore in 1988. He has been elected as a Fellow of the Academy of Medicine Malaysia, the American College of Cardiology and the European Society of Cardiology. He is a consultant cardiologist at the HT Ong Heart Clinic, a visiting lecturer and examiner at RUMC in Penang and an examiner for the MRCP (UK) PACES postgraduate degree. The past few years of the COVID pandemic have made him realise the increasing role of myocarditis—in addition to myocardial ischemia—as the source of cardiovascular events. Moreover, the increase in suicides during the same period highlighted the vital role played by mental stress in cardiac disease. His main research interests include the field of heart disease, particularly myocarditis and mental stress.