

Psychocardiology: the spectrum of stress in the genesis of heart disease: a point of view

Horst J Koch

Department of Psychiatry and
Psychotherapy, HELIOS Clinic Aue –
Academic Hospital of the Technical
University Dresden, Aue, Germany

Abstract: Psychiatric disease, particularly depression and stress disorders, worsens the outcome of cardiovascular disease by about a factor of two to three. Conversely, heart disease can also cause or aggravate affective disorders in the person concerned. Although this mind–heart interaction has been known since the 1930s, many questions about the underlying mutual pathophysiology remain. Apart from psychological stress models, inflammatory or psychoimmunology processes and metabolic or endocrinological mechanisms may be involved, as might lifestyle and drug treatments. Takotsubo, or broken-heart cardiomyopathy, which frequently occurs in response to stressful events, and post-myocardial infarction depression may serve as paradigms in seeking to understand the pathological basis of the mind–heart relationship.

Keywords: broken-heart cardiomyopathy, takotsubo, post-infarction depression, mind–heart interaction, pathophysiology

Introduction

There is no doubt that psychiatric syndromes such as depression, stress disorders and schizophrenia increase the risk of heart and cardiovascular disorders such as coronary heart disease, with odds ratios of 1.5 to 2.7 reported for depression in epidemiological studies.¹ As a consequence, the clinical outcomes can be worse, and this corresponds to increased mortality.^{2–6} This important negative impact of depression on mortality has been known since 1937.⁷ A recent study of more than 4000 patients suffering from depression and myocardial infarction found that, if not treated adequately, the depression tripled patients' risk of dying following heart attack.⁸ Similarly, anxiety spectrum disorders (eg, panic disorder, post-traumatic stress disorder, generalized anxiety) – both with and without depressive symptoms – significantly increase the risk of heart attack.⁹ The psycho–cardiovascular interaction is reciprocal; that is, psychiatric disorders deteriorate cardiovascular disease and vice versa. Two extreme examples of such mind–heart interactions are “takotsubo,” or broken-heart syndrome, and post-myocardial infarction depression.

The mind–heart interaction – the relationship between the heart and the mind – is complex and far from being completely understood. Hypothetical pathophysiological mediating links may help to approach the problem, but one should be very cautious to explain individual disorders by means of these hypothetical models. Some of these plausible and helpful hypotheses are summarized in Table 1. It is not possible to ascertain and distinguish pathophysiological associations for each individual, as every patient has their own medical history and diagnostic findings must be evaluated for each patient. Hence, physicians should strive for individual medical

Correspondence: Horst J Koch
Department of Psychiatry and
Psychotherapy, HELIOS Clinic Aue –
Academic Hospital of the Technical
University Dresden, Gartenstraße 6,
D-08280 Aue, Germany
Tel +49 03 771 581 509
Email horst.koch@helios-kliniken.de

Table 1 Potential pathophysiological links between psychological disorders and cardiovascular disease^{2–5,10,11,15,63–77}

Etiological factor	Associated mechanisms
Transient insulin resistance	Hypercortisolemia during depression, increased risk of developing diabetes
Visceral overweight	Diabetes, MS, hypercortisolemia
Arterial hypertonia	Overweight, diabetes, “vascular depression” (association between MS and depression)
Low birth weight	Depression, heart disease, possibly mediated by programming the HPA-axis
Metabolic syndrome	Lifestyle, nutrition, medication (eg, antipsychotics, antidepressants)
Hyperlipidemia	High TGL, low HDL during depression, suicide and possibly hypocholesterolemia, vascular depression
Reduced MTHFR activity	Depression, hyperhomocysteinemia, possibly dementia
Serotonin transporter polymorphism	Depression, increased platelet function and cardiovascular risk
Norepinephrine transporter	Reduced function in heart failure and possible involvement in depression (particularly anhedonia)
Autonomic dysregulation	Increased sympathetic tone with tachycardia, reduced heart rate variability, risk of arrhythmia, increased QT variability
Endocrinology	Activation of HPA axis (hypercortisolemia, stress), hypothyreosis
Lack of omega-3 fatty acids	Unbalanced diet, lifestyle
Inflammation	CRP, IL-6, TNF- α , viral disease, PNI, cholinergic anti-inflammatory reflex
Reactive oxygen species	Calcium homeostasis and contractile dysfunction, cellular damage
Drugs	Weight, MS, diabetes, depletion of neurotransmitter stores, hypertonia, risk of bleeding (SSRIs can cause gastrointestinal bleeding)
Compliance/Lifestyle	General risk, self-medication, addiction, lack of training, smoking habits
Pain localization and perception and focus of attention	Syndrome X (angina with normal coronary vessels), panic attacks
Cardiological interventions	Anxiety (especially during procedure), unrealistic expectations (cognitive dissonance)

Abbreviations: CRP, C-reactive protein; HDL, high-density lipoprotein; HPA, hypothalamic–pituitary–adrenal; IL, interleukin; MS, metabolic syndrome; MTHFR, methylene tetrahydrofolate reductase; PNI, psychoneuroimmunology; SSRIs, selective serotonin reuptake inhibitors; TGL, triglyceride; TNF- α , tumor necrosis factor- α .

and psychotherapeutic approaches. However, Bradford Hill causation criteria may be substantiated epidemiologically for most of the suggested etiological mechanisms.^{5,10}

In everyday psychiatric practice, we have to deal with electrocardiography (ECG), clinical laboratory results, and weight control, particularly to safeguard drug treatment and improve patient compliance. In addition, we are regularly asked to consult in case of palpitations and/or reasonable suspicion of somatization. Mind–heart interaction really starts prior to evident cardiovascular or psychiatric disease. Patients with anxiety, depression, and/or corresponding personality disorders tend to be worried about heart attacks and/or pain.¹¹ Herrmann-Lingen and Buss¹² showed that anxiety, depression, and Type D personality (ie, chronic depressive mood) are associated, with physiological and psychological patho-mechanisms (eg, the autonomous nervous system, the endocrine system) being etiologically important. In contrast, Myrtek¹³ determined that Type A behavior (ie, competitive drive, enhanced aggressiveness, impatience, and sense of time urgency) is not – as could be *prima facie* expected – a relevant risk factor for coronary heart disease compared with Type B behavior (relaxed and less hurried). In fact, Type A behavior is slightly protective against heart disease, as it corresponds with an active lifestyle

with many fewer risk factors such as obesity and smoking. Finally, it should not be forgotten that modern cardiological diagnostic and interventional procedures, although absolutely beneficial, may cause patients anxiety and some kind of cognitive dissonance or disappointment due to unrealistic expectations.¹⁴

One interesting mechanism of mind–heart interaction in chronic heart failure is psychoneuroimmunology, particularly the so-called cholinergic anti-inflammatory reflex.¹⁵ Cytokines such as interleukin 6 can stimulate the sympathetic nervous system and are increased at times of stress; this rise in cytokines correlates to ventricular dysfunction. In contrast, cholinergic activity reduces this negative escalation, and – mediated via feedback loops – the cytokines stimulate parasympathetic outflow, leading to a decelerated inflammation process.¹⁶ Reactive oxygen species are also discussed in this regard, both in cardiac and psychiatric disorders.^{17,18} Epigenetic phenomena are another exciting field of future research in this respect; these are involved in the pathology of both psychiatric and cardiac diseases and may be an additional link in the mind–heart interaction.^{19,20} Generally, DNA methylation, histone modification and micro-RNA alterations respond rapidly to environmental stress, both in neuropsychiatric and cardiovascular disorders.

Takotsubo cardiomyopathy, or broken-heart syndrome, as a paradigm of mind–heart interaction

Although much has been learned about the relationship between psychiatric disorders or stress and heart disease, it is difficult to discern underlying pathophysiological factors, and sometimes such investigation proves fruitless. Takotsubo cardiomyopathy (and post-myocardial infarction depression, which is discussed further on) may serve as a pathophysiological paradigm to determine physiological mechanisms.

Broken-heart syndrome (also called “stress-induced” or “ampulla” cardiomyopathy) was first characterized in Japan roughly 20 years ago by Sato et al²¹ and Dote et al.²² In a population admitted to hospital due to risk of myocardial infarction, 7% to 8% may show takotsubo-like symptoms.²³ The typical patient, frequently a postmenopausal woman, is referred to the cardiological department due to strong suspicion of myocardial infarction (ST-elevation) or acute coronary syndrome without concomitant stenosis and – at the most – slight elevation of the cardiac laboratory panel. The term “takotsubo” is from the Japanese word for a pot with a bottleneck to catch cuttlefish. The syndrome is defined by left-sided or biventricular apical akinesia with dynamic outflow obstruction. Clinically, angina pectoris, systolic heart murmur, cardiac failure, and arrhythmia may dominate the findings.^{24–29} Embolic events, heart failure, or ventricular wall damage may occur and worsen the outcome. Standard diagnostic procedures (ie, ECG, clinical laboratory tests, echocardiography, coronary angiography, and possibly cardiac nuclear magnetic resonance imaging) have to be done to confirm the diagnosis.

As a rule, intense, mostly emotional – occasionally somatic – stress precedes the acute disorder, which leads to acute adjustment disorder with anxious-depressive symptoms or occasionally panic-like attacks with hyperventilation.^{30–33} The syndrome requires an interdisciplinary approach, with treatment of both the heart failure and psychiatric disorder. First, until takotsubo is confirmed, patients should be treated for myocardial infarction to avoid tissue damage. Platelet aggregation inhibitors (eg, acetylsalicylic acid) and, if necessary, anticoagulants (eg, heparin, warfarin) are recommended.³⁴ Beta-blockers should reduce sympathetic tone and can be used with acetylsalicylic acid for maintenance treatment. Angiotensin-converting enzyme inhibitors or angiotensin II receptor type 1 antagonists are indicated for left-ventricular dysfunction and may be supplemented by aldosterone antagonists later on. Of course, in the case

of severe heart failure, intensive care unit therapy, including the use of intra-aortal pumps, is indicated. Beta-agonists, nitrates, methylxanthines, sotalol, or amiodarone should be administered with caution, due to increased sympathetic tone or possible QTc-interval prolongation.^{25,34}

Pathophysiological model of takotsubo cardiomyopathy

The exact pathophysiology underlying broken-heart syndrome is not known, but most clinicians speculate that spasms of epicardial coronary vessels, impaired microcirculation or overstimulation of the heart due increased catecholamine levels could cause the cardiomyopathy.^{22,24,32,35,36} The common underlying psychological factor is stress, with activation of the hypothalamic–pituitary–adrenal axis and hypercortisolemia. Indeed, catecholamine levels are raised by a factor of two to three.³² In addition, hormonal balance or fatty acid metabolism may play an etiological role.^{35,37}

In this context, one should not forget that catecholamine activity is not uniformly distributed in the heart muscle. Indeed, noradrenaline infusions in dogs have shown a gradient of activity, from the base (high) towards the apex (low), corresponding to an analog innervations pattern, and the density of beta-receptors decreases from apex to base.^{38–40} Following adrenaline infusion, the overall contractility is more pronounced in the apex. If we consider the heart as being an inverted cone, we can derive from the (simplified) Laplace law (wall tension \approx transmural pressure \times radius) that the effect of catecholaminergic overstimulation may be emphasized in the apical region,⁴¹ which favors myocardial hypoxia – or an increase of oxygen demand – in the apex. This lack of oxygen may hence be responsible for the wall dyskinesia. As we know that depression causes stress in the body, with increased levels of cortisol and catecholamines,⁴² stress-hormone flooding – subjective sadness is more important than the objective impact of the event – may explain the pathophysiology of broken-heart syndrome.

Post-myocardial infarction depression

Lett and colleagues⁴³ found that patients who develop a post-myocardial infarction depression are up to eight times more likely to experience complications and/or to die. Surprisingly, the severity of the depressive syndrome itself does not substantially influence the outcome and quality of life of persons concerned.⁴⁴ Indeed, even a slight depressive mood may impair the rehabilitation process and well-being

of the patient. Other studies have estimated the increased order of risk of mortality following myocardial infarction due to depression to be 1.5 to 3.0.^{45,46}

Post-myocardial infarction depression is observed in roughly 10% of patients, almost 40% of whom suffer depressive symptoms corresponding to Becks Depression Inventory scores greater than 10.⁴⁷ In most affected patients, the link between depression and worsened outcome of myocardial infarction is considered to be a psychological one, due to lack of vitality, stress due to diagnosis or treatment, and bereavement.^{48,49} Somatic complaints associated with depression appear to play a decisive role in the course of the infarction.⁵⁰ Further mechanisms, such as metabolic factors or cytokines, may also be involved but remain to be elucidated.

General aspects of psychiatric pharmacotherapy in patients with concomitant cardiovascular disease

Although the author considers psychological support essential in case of myocardial infarction, only slight evidence exists for psychotherapeutic approaches.^{51,52} Moreover, in everyday practice, psychological services may be unavailable, although, if this is the case, they should be strived for in future. Of course, cardiologists should be trained to detect depressive mood and seek specialist help when it is noted, but unfortunately, long-term psychotherapies, which are certainly effective in the long run, cannot be carried out in intensive care units. However, a list of nearby psychotherapists should be kept at hand.

This section of the article focuses on pharmacological treatment, which should, of course, be incorporated into a good, communicative doctor–patient relationship. As physicians, we should never forget that it is better to prevent diseases by means of integrated lifestyle change programs than to correct lifestyle peccadilloes after onset of disease.⁵³ This insight holds for both affective and cardiologic disorders.

The principles of cardiologic treatment for takotsubo cardiomyopathy have been outlined in the previous section. However, treatment of simultaneous psychiatric disorders is mandatory to improve the outcome. There is no general treatment plan, as each case requires an individual approach, but individual aspects with regard to entity (eg, broken-heart syndrome, post-myocardial infarction depression), concomitant disease(s) (eg, diabetes, stroke), and severity (acute, chronic) must be considered. It would be foolhardy to insist on an active lifestyle, normal weight, and a mixed diet

rich in vitamins and unsaturated and/or omega-3 fatty acids if acute crisis intervention is indicated and, depending on the triggering factors, long-term psychotherapeutic care apart from medical intervention may be required. To objectively check the balance between the risk of adverse events and the risk of depression, one must keep in mind that antidepressant drugs – irrespective of class – improve the outcome and reduce overall mortality in myocardial infarction.⁵⁴ It is therefore wise to realistically discuss the issue with the patient or their attorney.

If antidepressant treatment should be necessary, selective serotonin reuptake inhibitors (eg, sertraline, citalopram) – compounds that also have some platelet anti-aggregating effects – are said to be safe and effective.^{55–57} Although safe with regard to cardiovascular disease, paroxetine (which has a half-life of about 16 hours) and fluoxetine (which has a half-life of about 5 days) may cause more pharmacological interactions – most important inhibition of CYP2D6 – mostly in elderly patients treated with polypharmacy. Mirtazapine, which has low risk of interaction, may be an alternative and patients may welcome its sleep-inducing effect. However, weight gain and glucose tolerance should be checked regularly and could in some patients limit its use.⁵⁸ Of course, regular ECG recordings (QTc-time) and tests of serum electrolytes (magnesium, sodium, potassium) should be part of the psycho-cardiovascular laboratory panel to minimize the risk of arrhythmia, which is low with therapeutic doses.

Drugs with noradrenergic mechanisms (eg, venlafaxine, bupropion, reboxetine) as well as the reversible monoamine-oxidase inhibitor moclobemide are prone to increase blood pressure, although the risk must be weighed against the clinical benefit.^{59,60} (Irreversible inhibitors such as tranylcypromine may not be suited due to the necessity of low tyramine diet.) Reboxetine, in particular, although possibly effective in post-myocardial infarction depression and which has low interaction potential, is no longer considered a first-choice drug. Regardless, regular blood pressure monitoring is advisable. Should antipsychotics be necessary – for example, in depression with paranoid symptoms – the lowest possible dose should be strived for. To date, the lowest risk with regard to metabolic syndrome or propensity towards ECG changes is carried by aripiprazole or asenapine.^{61,62} However, the risk of QTc-prolongations is lower than 0.05% in patients receiving therapeutic doses of risperidone, quetiapine, amisulpride, or olanzapine.⁵⁷ This risk may be manageable in clinical practice provided regular clinical laboratory tests and ECG recordings are warranted.

Conclusion

Mutual mind–heart interaction has a critical impact on the course of both cardiological and affective disorders. The treatment of depression or related syndromes improves the outcome of myocardial infarction or heart failure and saves lives, while good cardiovascular condition minimizes the risk of stress-induced affective disorders. We are beginning to understand the underlying pathophysiological common mechanisms involved, which may provide further approaches with regard to treatment and prevention of mind–heart disorders.

Disclosure

The author declares no conflicts of interest in this work.

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