Psychophysiological concepts of stress induced cardiomyopathy with broken heart syndrome as a paradigm

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Summary
Psychiatric disease, particularly depression and stress disorders, worsen the outcome of cardiovascular disease substantially. Although this mind-heart interaction is known since the 1930s, many questions with regard to the underlying pathophysiology remain to be answered. Apart from psychological stress and psychiatric disease, inflammatory or psychoneuroimmunological processes, metabolic or endocrinological mechanisms may be involved as are lifestyle and effects of drug treatment. The takotsubo or broken heart cardiomyopathy, which can be regularly referred to stressful event, may serve as paradigm to understand pathological base of the mind-heart relation.

INTRODUCTION

There is no doubt that psychiatric disorders such as depression or schizophrenia increase the risk of heart and cardiovascular disorders such as coronary heart disease. As a consequence, the clinical outcome is worse corresponding to an overall excess letality [1-4]. Interestingly, this negative important impact of depression on mortality is already known since 1937 [5]. In a recent study which included more than 4000 patients suffering from depression and myocard infarction the factor depression triplicated the risk of dying after the heart attack, if inadequately treated [6]. Similarly, anxiety spectrum disorders (panic disorder, post traumatic stress disorder, generalized anxiety), both with or without depressive symptoms, increase significantly the risk of heart attacks [7]. Obviously, the psychocardiovascular interaction is reciprocal, i.e. psychiatric disorders deteriorate cardiovascular disease and vice versa. Two extreme poles of these interactions are the takotsubo cardiomyopathy or broken heart syndrome on the one hand and the post-infarct depression on the other hand. The review will focus on the neurobiology models of psychocardiology and only glance on coping strategies, which are important to explain aftermaths of stress or anxiety.

The mind-heart interaction, i.e. the relation between heart and soul, is complex and by far not completely understood. Hypothetical pathophysiological mediating links may help to approach the problem, although individualized allocations should be expressed with caution. Some of these plausible and helpful hypotheses are summarized on Tab. 1 – next page.

It is not possible to distinguish and ascertain pathophysiological associations for each patient, as a clear diagnostic and therapeutic concept is essential for the patient. However, Bradford-Hill
### Table 1. Potential pathophysiological links between psychological disorders and cardiovascular disease [1, 2, 9, 13, 55, 56]

<table>
<thead>
<tr>
<th>Etiological factor</th>
<th>Associated mechanisms</th>
</tr>
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<tbody>
<tr>
<td>Transient insulin resistance</td>
<td>Hypercortisolemia during depression, risk factor diabetes</td>
</tr>
<tr>
<td>Visceral overweight</td>
<td>Diabetes, MS, hypercortisolemia</td>
</tr>
<tr>
<td>Arterial hypertonia</td>
<td>Overweight, diabetes, «vascular depression» (association between MS and depression)</td>
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<tr>
<td>Low birth weight</td>
<td>Depression, heart disease (HPA-axis?)</td>
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<tr>
<td>Metabolic syndrome</td>
<td>Lifestyle, nutrition, medication (e.g. antipsychotics, antidepressants)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>High TGL, low HDL during depression, suicide and hypcholesterinemia?, vascular Depression</td>
</tr>
<tr>
<td>Reduced MTHFR activity</td>
<td>Depression, hyperhomocysteinemia, dementia?</td>
</tr>
<tr>
<td>Serotonin transporter polymorphism</td>
<td>Depression, increased platelet function and cardiovascular risk</td>
</tr>
<tr>
<td>Autonomic dysregulation</td>
<td>Increased sympathetic tone with tachycardia, reduced heart rate variability, risk of arrhythmia, increased QT-variability,</td>
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<tr>
<td>Endocrinology</td>
<td>Activation of HPA-axis (hypercortisolemia, stress), hypothyreosis</td>
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<tr>
<td>Lack of ω-3 fatty acids</td>
<td>Unbalanced diet, life style</td>
</tr>
<tr>
<td>Inflammation</td>
<td>CRP, CRP, IL 6, TNFa, viral disease, PNI, &quot;cholinergic anti-inflammatory reflex&quot;</td>
</tr>
<tr>
<td>Reactive oxygen species</td>
<td>Calcium homeostasis and contractile dysfunction, cellular damage</td>
</tr>
<tr>
<td>Drugs</td>
<td>Weight, MS, diabetes, depletion of neurotransmitter stores, hypertonia, risk of bleeding (SSRI)</td>
</tr>
<tr>
<td>Compliance / lifestyle</td>
<td>General risk, self-medication, addiction, lack of training, smoking habits</td>
</tr>
<tr>
<td>Pain localization and perception and focus of attention</td>
<td>Syndrome X (Angina with normal coronary vessels), panic attacks</td>
</tr>
<tr>
<td>Cardiological interventions</td>
<td>Anxiety (especially during procedure), unrealistic expectations (&quot;cognitive dissonance&quot;)</td>
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<tr>
<td>Reduced heart rate variability</td>
<td>Autonomous changes before treatment of depression or anxiety disorders and aftermath of treatment</td>
</tr>
</tbody>
</table>

(MS metabolic syndrome, TGL triglyceride, MTHFR methylene tetrahydrofolate reductase, HPA hypothalamic-pituitary-adrenal, CRP C-reactive protein, IL interleukin, TNF tumor necrosis factor, PNI psychoneuroimmunology)

causative criteria may be substantiated epidemiologically for most of the suggested etiological mechanisms [8]. In everyday psychiatric practice we have to deal with ECG, clinical laboratory and weight controls, particularly to safeguard drug treatment and improve compliance of patients on the one hand. On the other hand psychiatrists are regularly asked for consultation in case of palpitations and reasonable suspicion for somatoform disorders. Mind-heart interaction really starts prior to evident cardiovascular or psychiatric disease. Anxiety, depression and corresponding personalities tend to be anxious and worried about heart attacks or pain [9]. Hermann-Lingen and Buss [10] showed that anxiety, depression and type D personality (chronic depressive mood) are associated, physiological and psychological patho-mechanisms (e.g. autonomic nervous system, endocrinology) being etiologically important. On the contrary, Myrtek [11] carved out that Type A behavior (competitive drive, enhanced aggressiveness, impatience and sense of time urgency) is not – as could be prima facie expected – a risk factor for coronary heart disease compared to Type B behavior (relaxed and less hurried). In fact, Type A is slightly protective corresponding to an active lifestyle with much less risk factors such as serious overweight or smoking. We should not forget that modern cardiovascular diagnostic and interventional procedures – although absolutely beneficial – may cause anxiety and some kind of cog-
nitive dissonance or disappointment due to unrealistic expectations [12].

One interesting mechanism of mind-heart interaction in chronic heart failure is psychoneuroimmunology (PNI), particularly the so-called CAR or “cholinergic anti-inflammatory reflex” [13]. Cytokines such as interleukin-6 can stimulate the sympathetic nervous system, are increased during stress and correlate to ventricular dysfunction. Cholinergic activity, on the contrary, reduces this negative escalation, and mediates feedback loops - cytokines stimulate parasympathetic outflow leading to a decelerated inflammation process [14]. In this regard also reactive oxygen species (ROS) are discussed both in cardiac and psychiatric disorders [15, 16]. Another exciting field of future research in this respect are epigenetic phenomena, which are involved in the pathology of both psychiatric and cardiac diseases and may be an additional link of mind-heart-interaction [17, 18]. Generally, DNA methylation, histone modification and micro-RNA alterations respond rapidly to environmental stress both in neuropsychiatric and cardiovascular disorders.

**PRINCIPLES OF COPING STRATEGIES**

“It is our attitude towards events, not the events themselves, which we can control” is a famous quote of Epictetus 2000 years ago. And he continues to say that only our attitude makes an event dangerous or harmless. This co-inci-dence and interaction of personal and environmental determines, whether an event is a stressor or not and whether we need to cope with an event [19]. Early coping theories were developed by psychoanalytical scientists in the 1930ies and 1940ies by Otto Fenichel, Karen Horney or Heinz Hartmann but thorough discussion of this issue is by far beyond the aim of this review. For, sure, the research of Lazarus and co-workers in the 1960ies [20] is a milestone with regard to stress models and coping concepts, leading finally to the transactional stress model. Quintessence of this model are primary appraisal, secondary appraisal and re-appraisal, which are lead to 3 basic coping techniques, namely problem-focused, emotion-focused or appraisal-focused coping [21]. The concept of coping is historically relat-ed to concept of resilience, i. e. the capability to deal stress and strive for education and success. Again, both personal and environmental factors – often the attitude of the family - are important. Emmy Werner [22] was one of the first scientists who used this term to characterize 1/3 of Hawaiian children stemming from poor families who, nevertheless, were successful in life.

Lazarus and Folkman [21] postulated 5 emotion-focused coping strategies, which may still be of clinical relevance in practice: disclaiming, escape-avoidance, accepting responsibility or blame, exercising self-control and positive re-appraisal. Should a psychosomatic disease occur – e. g. heart disease caused by stress – we deal with some kind of maladaptive coping strategy, which is not uncommon in emotional-focused approaches. The patient did not have the resources to use such as the appraisal-focused or problem-focused coping strategy, i. e. he was not able to modify his way of thinking in time (“his attitude”) or deal with problem and learn suitable skills to solve the underlying conflict. Although well-being is maintained transiently – some kind of facade or pseudo-therapy is established – the problem remains “undercov er” virulent and causes heart disease. Avoidance and escape behavior are often associated with maladaptive coping techniques, which are frequently involved in the development of depre-sions [23, 24].

**THE TAKOTSUBO CARDIOMYOPATHY OR BROKEN-HEART SYNDROME AS A PARADIGM OF MIND-HEART INTERACTION**

Although we have learned much about the relation between psychiatric disorders or stress and heart disease, it is difficult and sometimes in vain to discern underlying pathophysiological factors. The takotsubo cardiomyopathy may serve as pathological model to allocate physiological mechanisms. The broken-heart syndrome (stress-induced cardiomyopathy, ampulla cardiomyopathy) was first characterized in Japan roughly 20 years ago by Sato et al. 1990 [25] and a year later by Dote and colleagues [26]. In a population admitted to hospital due to risk of myocard infarction, takotsubo-like presentation may occur in some 7 to 8% [27]. The typical pa-
Patient, frequently postmenopausal women, is referred to the department of cardiology due to strong suspicion of myocardial infarction (ST-elevation) or acute coronary syndrome without concomitant stenoses and – at the most – slight elevation of the cardiac laboratory panel. The Japanese name takotsubo derives from bulgy pot with bottle neck 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 [28-34]. Embolic events, or heart failure, ventricular wall damage may occur and worsen the outcome. Standard diagnostic approaches (ECG, clinical laboratory, echocardiography, coronary angiography, possibly cardiac NMRI) have to be done to ascertain the syndrome.

Almost as a rule, intense, mostly emotional - occasionally somatic- stress precedes the acute disorder, which leads to acute adjustment disorder with anxious-depressive syndromes or every now and then panic-like attacks with hyperventilation [35-38]. The syndrome needs an interdisciplinary approach, combining treatment of heart failure and psychiatric disorder. First, patients should be treated as having myocardial infarction until the opposite – namely takotsubo – is proven in order to avoid tissue damage. Platelet aggregation inhibitors (e. g. acetylsalicylic acid, ASS) and, if necessary, anticoagulation (heparin, warfarin) are recommended [39]. β-blockers should reduce sympathetic tone and are also used – with ASS – for maintenance treatment. ACE-inhibitors or AT-II-1 antagonists are indicated according to left-ventricular dysfunction and may be supplemented by aldosterone antagonists later on. Of course, in case of severe heart failure intensive care unit therapy including intraaortal pumps is indicated. β-agonists, nitrates, sotalol or amiodarone should be given with caution due to sympathetic tone QTc-interval prolongation [29, 39].

**PATHOPHYSIOLOGICAL MODEL OF THE TAKOTSUBO CARDIOMYOPATHY**

Most clinicians admit spasms of the epicardiac coronary vessels or impaired microcirculation and overstimulation of the heart due increased catecholamine levels [26, 28, 37, 40, 41]. The common underlying psychological factor is stress with activation of the HPA-axis and hypercortisolemia. Indeed, catecholamine levels are raised by a factor 2 to 3 [37]. In addition, hormonal balance or fatty acid metabolism may play an etiological role [42]. In this context one should not forget that catecholamine activity is not uniformly distributed in the heart muscle. On the contrary, noradrenaline infused to dogs shows a gradient from the base (high) towards the apex (low) corresponding to an analogue innervations pattern and the density of beta-receptors decreases from apex to base [43-45]. Following adrenaline infusion, the overall contractility is more pronounced the apex. If we consider the heart being an inverted cone, we can derive from the (simplified) Laplace law (Wall tension = transmural Pressure * radius) that the effect of catecholaminergic overstimulation may be emphasized in the apical region [57] which favors myocardial hypoxia – or increase of oxygen demand – in the apex. This lack of oxygen then may cause wall dyskinesia.

**GENERAL ASPECTS OF PSYCHIATRIC PHARMACOTHERAPY IN PATIENTS WITH CONCOMITANT CARDIOVASCULAR DISEASE**

The principles of cardiovascular treatment takostubo cardiomyopathy have been outlined in the previous section. However, treatment of simultaneous psychiatric disorders is unequivocally mandatory in order to improve the outcome. No general recipe for each patient can be given, but individual aspects with regard to entity (e. g. broken heart syndrome, postinfarct depression), concomitant diseases (diabetes, stroke) or severity (acute, chronic) must be considered. The author carries coals to Newcastle, if he insists on an active life style with normal weight and mixed diet rich in vitamins, unsaturated or Ω3- fatty acids. For sure, he also needs acute crisis intervention and, depending on the triggering factors, long-term psychotherapeutic care apart from medical interventions. In order to objectively check the balance between the risk of adverse events on the one hand and the risk of depression on the other hand, one must have
in mind that antidepressant drugs - irrespec-
tively which class is chosen – improve the outcome
and reduce overall mortality of myocardial in-
farction [46]. It is therefore wise to realistically
discuss the issue with the patient or his attor-
ney. SSRIs (e.g. sertraline, citalopram) are said
to be safe and effective, if antidepressant treat-
ment should be necessary [47-49]. Although safe
with regard to cardiovascular disease paroxetine
and fluoxetine may cause more pharmacological
interactions in the mostly elderly patients with
polypharmacy. Mirtazapine may be an alterna-
tive with low risk of interaction and patients
may welcome the sleep-inducing effect. How-
ever, weight gain and glucose tolerance should
be checked regularly and could in some patients
limit its use [50]. Of cause, regular ECG record-
ings (QTC-time) and serum electrolytes (magne-
sium, sodium, potassium) should be part of the
psycho-cardiovascular care to minimize the risk
of arrhythmia, which is indeed low in therapeu-
tic doses. One should keep in mind that drugs
with noradrenergic mechanisms (venlafaxine,
buproprion, reboxetine) and reversible monoam-
inoxidase inhibitors moclobemide (irreversible
inhibitors such as tranylcypromine may not be
suited due to the necessity of low tyramine diet)
are prone to increase blood pressure, although
the risk must be outweighed with clinical de-
mand [51, 52]. Anyway, regular blood pressure
controls are advisable. Should antipsychotics be
necessary, e.g. in depression with paranoid
symptoms, the lowest possible dose should be
strived for and the necessity of treatment should
be assessed at regular intervals. To date, the lo-
est risk with regard to metabolic syndrome or
propensity towards ECG changes may charac-
terize aripiprazole or asenapine [53, 54]. How-
ever, the risk of QTc-prolongations is lower than
0.05 % in patients receiving therapeutic doses of
risperidone, quetiapine, amisulpride or olanza-
pine [49]. This risk may be manageable in clin-
ical practice provided regular controls of clinical
laboratory and ECGs are warranted.

CONCLUSION AND CRITICAL APPRAISAL

We just begin to understand the pathophys-
iology of the heart-mind or mind-heart disor-
ders and there are evident limitations related to
theoretical foundations and to the focus of this
article. Particularly, many questions concerning
pathopsychology remain to be answered. There
is no doubt that psychotherapeutic approaches
based on stress and coping models must be in-
volved in treatment and care of those patients
who lack sufficient resilience to cope with life
events. Psychotherapeutic interventions are im-
portant, as functional coping strategies have
demonstrated to improve cardiovascular reha-
bilitation and the immune system patients with
stress-induced disorders. Further research is
essential with regard to pathophysiology and
pathopsychology, but it is our duty to struggle
for care in everyday practice.

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