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REVIEW

Review on depression and coronary heart disease

Dépression et pathologie coronarienne : une revue

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Summary The impact of psychological factors on somatic disorders – and vice versa – and the involvement of biological mechanisms in psychic disorders have generated considerable interest in recent years, notably thanks to cutting-edge investigation techniques (immunohistochemistry, functional imaging, genetics, etc.). In the field of psychosomatics, coronary heart disease (CHD) is a frequent co-morbidity of mental disorders, particularly mood disorders. Indeed, there is a bidirectional relationship between CHD and mood disorders, with a strong co-occurrence of the two diseases accompanied by a reciprocal worsening of the prognosis for the two conditions. Various epidemiological studies have shown that depression is a psychic risk factor for CHD and that CHD is present in almost 30% of patients with affective disorders. In this review of the literature, we tackle the crucial question of the diagnosis of depression during myocardial infarction. This clinical approach is essential given the underevaluation of this psychic problem. Then, various psychological, biological and genetic arguments are presented in support of the hypothesis that various aetiological mechanisms of the two disorders are partly shared. We finally deal with the treatment of depression in the context of CHD with its pharmacological and psychological specificities. In conclusion, this review reiterates the need for a multidisciplinary approach, which is necessary to understand, diagnose and then treat this frequent co-morbid condition of heart disease and depression.

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Abbreviations: CHD, coronary heart disease; HPA, hypothalamohypophysoadrenal; HRV, heart rate variability; ROS, reactive oxygen species.

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MOTS CLÉS

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Résumé L'influence de facteurs psychologiques promoteurs d'affections somatiques ainsi que réciproquement l'implication de mécanismes biologiques dans les maladies psychiques suscitent actuellement un réel intérêt, notamment grâce aux techniques d'investigation performantes (immunohistochimie, imagerie fonctionnelle, génétique, etc.). Or dans le domaine de la psychosomatique, les maladies cardiovasculaires en general et les affections coronariennes plus particulièrement représentent une fréquente co-morbidité des troubles mentaux, notamment dans les troubles de l'humeur. En effet, coronaropathies et troubles de l'humeur entretiennent des relations bidirectionnelles avec une forte co-occurrence des deux pathologies accompagnée d'une aggravation mutuelle du pronostic des deux affections. Divers travaux épidémiologiques démontrent que la dépression constitue précisément, d'une part, un facteur de risque psychique de coronaropathie tandis que, d'autre part, les pathologies coronariennes s'accompagnent chez près de 30% de sujets de troubles affectifs. À partir d'une récente revue de la littérature, les auteurs abordent la question cruciale du diagnostic de la dépression au décours d'un accident cardiaque, approche clinique essentielle du fait de la sous-évaluation de cette problématique psychique. Puis divers arguments psychologiques, biologiques et génétiques sont exposés, soutenant l'hypothèse de mécanismes étiologiques partiellement communs aux deux affections. Enfin les auteurs s'intéressent à l'aspect thérapeutique de la dépression dans un contexte de maladie coronarienne avec ses spécificités pharmacologiques et psychologiques. En conclusion cette revue rappelle la nécessaire collaboration transdisciplinaire nécessaire à la compréhension, au diagnostic, puis au traitement de la fréquente comorbidité cardiaque et dépressive.
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Background

The supposed links between affections of the mind and the body have given rise to many questions and debates. The field of psychosomatics may shed light on the impact of psychic equilibrium on the psychodynamic and biological aspects of physical health. This discipline explores the measurable organic consequences of psychological factors in the aetiology. For example, the stress reaction experienced by a subject exposed to a stressful environment is a model of a psychosomatic phenomenon. This normal adaptive response to stress may sometimes become excessively intense or excessively long and trigger physiological modifications that are harmful for the body. In the field of somatic disease, could the fact of developing a depressive state, which is a major factor of stress, lead to physiopathological alterations at the origin of heart disorders? Today, although the precise nature of the links between depression and coronary heart disease (CHD) has not yet been clearly established, these links are being highlighted more and more frequently, first of all from an epidemiological point of view and then with regard to the aetiological and clinical aspects in patients with this worrying co-morbidity. In addition, for many years, the psychosomatic approach has led to better understanding of the bidirectional impact of emotional disorders on cardiac disease and vice versa. Different studies have underlined the impact of certain psychic dimensions in heart disease, in particular the importance of depression, which is frequently discovered in patients with coronary artery disease. Surprisingly, despite progress in theoretical knowledge on this issue, detecting an episode of depression in patients with a heart condition is not always easy for the clinician. We tackle here all of the epidemiological aspects of the links between depression and CHD; we also cover the clinical specificities

of an episode of depression in patients with CHD and we present the principal aetiological mechanisms revealed to date, before dealing with the different management strategies for depression in patients with CHD.

CHD and depression: epidemiology of a co-morbidity

The significant prevalence of depression in cardiovascular disease in general and coronary artery disease in particular is a frequent phenomenon [1]. Several studies (Table 1) have shown a rather high incidence of episodes of depression, characterized by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria, ranging from 15% to 30% in the aftermath of a coronary event. These figures need to be compared with the mean annual prevalence of episodes of depression in the population at large, which is about 7%.

In a bidirectional manner, depression is an independent risk factor of cardiovascular co-morbidity [2]. Compared with the population at large, people with characterized depression frequently develop cardiovascular disease due to psychological, behavioural and biological mechanisms. The multicentre INTERHEART study reported the impact of psychic disease on coronary artery disease and the importance of psychosocial stress (a notion that includes depression), which puts it in third place in the league table of risk factors (with an odds ratio of 2.67) for developing cardiovascular disease [3], after the apolipoprotein B/apolipoprotein A1 ratio and smoking but in front of diabetes, arterial hypertension and abdominal obesity. Intense and chronic stress lead to anxiety or depression disorders. Consequently, a certain number of patients with heart disease had experienced mood disorders beforehand, whereas

Table 1 Prevalence of depression in coronary heart disease.

Published studies	Number of subjects	Mean age (years)	Symptoms of depression (%)	Depression characterized by DSM IV-TR criteria (%)
Myers et al., 2012 [5]	632	52	27.8	NA
Davidson et al., 2010 [47]	453	25–93	24.0	17.0
Ziegelstein et al., 2000 [48]	204	60	17.2	15.2
Frasure-Smith et al., 1995 [4]	222	60	30.6	16.0

DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; NA: not available.

others developed heart disease and the episode of depression occurred during the evolution of their disorder; these epidemiological aspects thus justify specific attention.

In addition, major depression worsens the cardiovascular prognosis, particularly for coronary artery disease, by significantly increasing the risk of recurrent coronary artery disease. The relative risk of death in depressed patients during the 18 months following the cardiac event is twice that in non-depressed patients [4]. Recent studies have also shown the harmful nature of depression after myocardial infarction in terms of rehospitalization and of greater difficulty in stopping smoking or getting access to cardiac rehabilitation, which is particularly beneficial in this context [5].

All of these epidemiological aspects underline the frequent co-occurrence of depression and heart disease and clinicians should investigate the presence of depression in patients with heart disease.

Depression in CHD patients: specific clinical aspects

The diagnosis of an episode of characterized depression in the context of CHD remains a complex question, requiring a specific approach from the clinician, who often focuses on the somatic environment and does not spontaneously consider a psychiatric approach. Given the sometimes sudden onset of a cardiovascular event, the normal psychological reaction to disease requires the patient to adapt, which leads to a certain physiological depression in mood, the time to come to terms with the possible loss related to the disease and the sometimes very much changed future prospects for life. Usually, the potential problems due to adaptation should resolve in a few weeks with no amplification of thymic phenomena. In certain cases, patients fail to recover their normal mood to such a degree that authentic depression progressively develops. The diagnosis will be relatively easy if this state of characterized depression takes on a classical clinical presentation, combining over several weeks the three key elements of sadness, ideomotor slowing and somatic signs (modification in sleep and appetite, the existence of various functional disorders). Nonetheless, the clinical picture is often incomplete: first of all, the patient is particularly preoccupied by the somatic aspects of the heart condition and cannot think about a psychic problem that he was probably unaware of; and then the symptoms of depression develop insidiously, in an almost masked form, essentially appearing as extreme fatigue, which makes it dif-

ficult to return to the previous state [6]. It therefore seems important to adopt a dimensional analysis of the depression by seeking the circadian component, with increased sadness in the morning, the absence of vitality or simply asthenia, accompanied by a substantial improvement in these symptoms at the end of the day. Indeed, these semiological circadian variations may be the only signs that suggest a diagnosis of depression. In the same way, particular attention should be paid to sleep with regard to both quality and quantity, as depression is almost systematically accompanied by sleep disorders: insomnia in 80% of cases and hypersomnia more rarely. Although depression is sometimes difficult to identify, cardiologists and general practitioners must be encouraged to seek expert advice in cases of doubt about the diagnosis. Clinicians must really bear in mind the potential severity of this co-morbid association, as it very seriously worsens the prognosis in terms of suicide. A recent study showed that women in particular showed a significantly greater risk of suicide in depression associated with coronary artery disease [7]. In order to optimize screening for affective disorders, certain cardiology or cardiac rehabilitation units routinely use standard self-questionnaires, such as the Hospital Anxiety and Depression scale [8], which give an overall idea of the severity of the anxiodepressive episodes sometimes found in patients with heart disease; obviously, these questionnaires do not replace the clinical interview and are not standardized automatic providers of psychiatric diagnoses but they do reveal certain emotional disorders and may confirm a clinical impression or simply facilitate discussions between the doctor and the patient on this very sensitive issue of depression in the wake of a cardiac event. As the epidemiological and clinical reality of depression during a cardiac event is now accepted, the nature of the aetiological links between depression and CHD needs to be considered from a psychological, behavioural and even biological point of view.

Presumed common mechanisms shared by depression and CHD

The impact of stress

From a psychological point of view, several authors have raised the question of the role of stress factors and the level of adaptation to stressful stimuli. Indeed, the way in which a factor of stress is first perceived and then managed conditions not only the cognitive, behavioural and emotional responses but also the neurohumoral response, leading to

biological reactions likely, in the long term, to tire the body and foster the onset of cardiovascular disease or to accelerate its evolution [9]. The type A personality profile defined in the 1960s illustrates quite well the psychosomatic transition from a psychosocial phenomenon to biological consequences [10]. This type A personality brings together three criteria: intense activity, a desire to do things quickly and combativeness that may lead to hostile attitudes in order to reach fixed objectives. Several studies have shown that people with this type of personality are more likely to develop coronary artery disease [11,12]. In addition, the behaviour pattern of type A people confers great vulnerability to depression, which Consoli et al. [13] considered one explanation for the very high risk of heart disease in these subjects. Many victims of myocardial infarction have this type of personality or something very similar, which destabilizes them with regard to both the heart and the thymus. In addition, certain factors of stress may require radical adaptation, which may be costly from a psychosomatic point of view. Such factors include losses (mourning, retirement, unemployment) or painful socioprofessional situations (social isolation, lack of recognition at work). Indeed, several studies have shown that these events, which have a strong emotional component and are likely to lead to mood disorders, are able to trigger an adverse coronary event [14].

Behavioural and psychological features

Besides the influence of psychological factors, it seems necessary to underline the behavioural impact of depression on the negative evolution of heart disease. Indeed mood disorders are sometimes the cause of psychobehavioural disturbances, such as a loss of interest in carrying out simple tasks (meals, physical activity), which explains the poor lifestyle habits of depressed patients, who cannot summon up enough energy or motivation to consider stopping smoking, changing to a well-balanced diet or maintaining regular physical activity [15]. Depression may occur at any time during a person's history of coronary artery disease and is a behavioural factor in the development or aggravation of heart disease as the patient adopts a prolonged sedentary lifestyle, experiences a decline in psychological and physical motivation and tends not to respect the therapeutic regimen. To underline the impact of behavioural disturbances, we can quote the study of Raikkonen et al., who showed that depressive symptoms may be a predictive factor for the development of metabolic syndrome, especially among middle-aged women [16]; metabolic disturbances then contribute to the onset of CHD.

Impact on rhythm: a decrease in heart rate variability

Heart rate variability has generated considerable interest and several studies have investigated the physiopathology of links between depression and heart disease. Heart rate variability (HRV) indicates the level of homeostasis between the sympathetic and parasympathetic systems in the regulation of the heart rate and involves several cholinergic and monoaminergic neurotransmitters [10]. HRV is an important indicator of prognosis in the wake

of myocardial infarction, in the same way as age, left-ventricular ejection fraction or the frequency of arrhythmia. A decrease in heart rate variability is pathological, as shown by the increased risk of sudden postinfarction death in patients with reduced HRV. This reduction in HRV was also more often found in depressed patients than in control subjects [17]. This suggests that decreased HRV exposes patients with simultaneous coronary artery disease and major depression to ventricular arrhythmia and excess mortality.

Inflammation, oxidative stress and activation of the HPA axis in depression and cardiac co-morbidities

The inflammatory hypothesis as a common physiopathological pathway in mood disorders and cardiovascular disease is being put forward more and more frequently. Indeed, by carefully examining the biological phenomena encountered in heart disease and depression, similar consequences seem to occur in both, in particular a major inflammatory reaction [18] and oxidative stress. Among the biological mechanisms described in the physiopathology of depression, the inflammatory hypothesis is becoming more and more solid. Increased concentrations of blood markers of inflammation (interleukin-1, interleukin-6, tumour necrosis factor- α) [19,20] have been found in both depression and heart disease. A parallel decrease in serum concentrations of omega-3-type polyunsaturated fatty acids with anti-inflammatory properties has also been observed in depression and cardiovascular disease [21].

Actually, oxidative stress related to inflammatory phenomena is frequently described in most psychiatric disorders, with increased membrane lipid peroxidation mediated by reactive oxygen species (ROS). These damaging ROS are generated through both aerobic metabolic physiological processes and physiopathological processes, which may be ischaemic, inflammatory or caused by psychological stress due to depression, for example. The hypothesis that inflammatory and oxidative stress are factors in both mood disorders and CHD seems to be growing stronger [22].

Furthermore, cardiovascular co-morbidities of affective disorders are usually associated with hyperactivation of the hypothalamohypophysoadrenal (HPA) axis. During an episode of characterized depression, which in itself is a major factor of stress, the HPA axis is strongly activated; an increase in serum concentrations of cortisol urinary derivatives indicate the initiation of anti-inflammatory processes that try to restore the disturbed homeostasis. This chronic hypercortisolaemia could induce glucid and lipid metabolism, leading to increased amounts of visceral fat and insulin resistance, both of which contribute to the development of metabolic syndrome through the activation of proinflammatory mediators [23]. The stimulation of the HPA axis could thus correlate with the development of atherosclerosis and show another biological similarity between mood disorders and CHD [10].

Sympathetic hyperactivity and disturbances in platelet reactivity

Studies have revealed an increase in plasma concentrations of noradrenaline [24] during episodes of characterized depression, in the same way that clinical observations show a faster heart rate in depressed subjects than in control subjects. This excessive stimulation of the sympathetic system develops and aggravates coronary artery disease via a double deleterious effect on heart function itself and on platelet aggregation, which is diminished. The harmful effect of depression on coronary artery disease could also be due to dysfunction of the platelet system. Platelets contain serotonin receptors and play a role in both haemostasis and coronary vasoconstriction via this monoamine; platelet hyperactivation encountered in depression could thus lead to an increased coronary risk or amplify the pathology once present by promoting ischaemic mechanisms [25]. The sympathetic pathway could therefore contribute to the development of heart disease in depressed patients without heart disease and worsen the cardiovascular prognosis in patients already weakened by coronary artery disease.

Genetic markers of vulnerability to depression and cardiovascular disease

Several authors have shown that depression and cardiovascular disease share common genetic mechanisms, particularly with regard to inflammation pathways and oxidative stress. For example, it has been shown that the length of telomeres (genetic markers of oxidative stress, that trigger cell death when the length reaches a critical threshold) measured in circulating leukocytes diminishes in both major depression and coronary artery disease, illustrating in both cases the impact of oxidative stress at the initial level of the genetic machinery [26,27]. In unipolar depression, Teyssier et al. demonstrated a strong correlation between the leukocyte expression of two candidate genes (p16^{INK4a} and STMN1, which are biomarkers of human aging and telomere dysfunction) and the depression scores in depressed patients and controls, sustaining the hypothesis of shared fundamental mechanisms in psychiatric and somatic diseases, particularly metabolic and cardiovascular diseases [28]. In addition, a recent study has shown that the omega-3 fatty acid synthesis pathway is impaired in characterized depression, with a fall in the expression of the candidate genes for this metabolic pathway, showing disturbances in the synthesis of these anti-inflammatory and cardioprotective fatty acids [29]. Moreover, it seems that these two diseases share another genetic vulnerability that could modulate their development. In a study of 977 patients with cardiopathy, McCaffery et al. revealed the influence of a single nucleotide polymorphism in the gene coding for Willebrand factor in the onset of depression secondary to heart disease [30]. These data should be considered along with the inflammation mechanisms, endothelial dysfunction or even altered platelet aggregation mentioned above but confirmed by genetic arguments showing physiopathological links that could lead to depression in heart disease and vice versa. In addition, in a genetic study in 30,000 twins, Kendler et al. showed the rather marked impact of coronary

artery disease on the onset of major depression [31]. Using the results of the Wellcome Trust Case Control Consortium (WTCCC) genome-wide association study, Torkamani et al. analysed the genetic relationships between seven diseases and showed significant robust correlations between bipolar disorders, diabetes type 2 and CHD [32]. There is thus a recent accumulation of genetic arguments that illustrate the mechanisms presumably shared by mood disorders and CHD.

The disturbance of circadian rhythms

Clinicians and researchers are showing an interest in the study of rhythms in mood disorders; particularly the effect of circadian rhythms on depression [33]. Indeed, the clinical presentation of characterized depression is not linear but often follows the circadian cycle, from classical morning sadness to improved mood in the evening, without forgetting disturbances in the sleep-waking cycle that are an almost consistent finding and, from a biological point of view, alterations in the secretion of biochemical mediators (cortisol, thyroid-stimulating, melatonin, etc.). The therapeutic manipulation of these rhythms thanks to light therapy or even sleep deprivation in certain clinical situations bears witness to the reality of this concept in depression. Several studies have shown different alterations in these rhythms characterized by advanced stages of clinical and biological phenomena (shorter latency to the onset of paradoxical sleep, early secretion of cortisol and melatonin). Currently, the theoretical model of the influence of circadian rhythms in the development of episodes of depression still seems imperfect and brings together extremely complex genetic, neurobiological and endocrinological variables. Here again, concerning this issue, there seems to be a group of similar phenomena in depression and heart disease. Adverse coronary events often seem to follow a circadian cycle, with a greater frequency of events in the early morning [34]. Various hypotheses have been put forward, including the influence of the genetic internal clock, which is of paramount importance, as is the case with mood disorders [35]. Various fundamental studies have shown that many of the genes involved in heart and aorta function have a circadian expression [36] and that disturbances in circadian rhythms cause histopathological modifications with fibrosis in animals. Finally, one team also demonstrated in "cardiomyopathic" Syrian hamsters that a decrease in the amplitude of central temperature variations was predictive of death 8 weeks later [37], which illustrates the impact of circadian dysregulation on heart function. Although it is impossible to establish absolute links between cardiovascular disease and depression via a dysfunctioning circadian system, it is well known that circadian desynchronization leads to both affective disorders and cardiac complications. In addition, the management of somatic or psychic disorders using an approach involving rhythms has the advantage of being a global approach. This endorses educational therapies based on promoting a balance between the biological and social life (healthy sleeping pattern, balanced alternation between work, physical activity, leisure, etc.), These strategies to fight against decompensated stress have been proved to be beneficial in both the somatic and psychological realms.

All of these psychological, behavioural and physiopathological arguments that link depression and heart disease in a reciprocal manner should lead clinicians to pay careful attention to the psychic symptoms of patients with CHD, in order to identify possible constituted affective disorders and to determine the appropriate therapeutic strategies.

Therapeutic strategies

Although the scientific arguments in favour of the many links between depression and cardiovascular disease are accumulating, depression is still “underdiagnosed” in this specific somatic context because of insufficient therapeutic options. Concerning the pharmacological treatment of depression, tricyclic antidepressants, which cause potentially dangerous adverse effects (rhythm disorders), are no longer the molecules of choice in this context. Several studies have shown that the new generation of antidepressants, in particular selective serotonin reuptake inhibitors, are well tolerated, have a satisfactory efficacy-tolerance profile and are easy to use in patients with cardiovascular disease. In addition, these molecules show clinical efficacy, acting on physiopathological elements by improving endothelial function while reducing the concentration of inflammation markers (C-reactive protein, interleukin-6) [38]. In the same way, a meta-analysis by Mazza et al. showed that selective serotonin reuptake inhibitors used in the wake of an acute coronary syndrome led to fewer rehospitalizations [39]. It therefore appears important to underline the fact that antidepressants should be prescribed for a minimum of 6 months in the first episode of depression; this period can be extended in cases of recurrent episodes. Concerning the precautions of use, despite the remarkable acceptability of this new generation of antidepressants, particular attention must be paid to potential drug interactions between antidepressants and cardiovascular drugs, without forgetting to observe the metabolic pathways passing through p450 cytochromes; it is also necessary to take account of the potential lengthening of the QT interval on the electrocardiogram for certain molecules [40]. As a complement to the pharmacological treatment, any form of psychotherapy seems beneficial in that it allows the patient to speak to an attentive listener. However, in the scientific literature, only cognitive behavioural-type therapies have been evaluated in a standardized manner and have been shown to be of interest in heart disease. These pragmatic techniques for psychological support, which show a beneficial effect rather quickly, provide relevant help in stress management; on this subject, various studies have shown that a reduction in psychosocial stress could increase life expectancy after coronary artery bypass graft in victims of myocardial infarction [41]. Whatever the method employed, considerate empathy can certainly help the patient through possible reorganization of his/her existence and the frequent modifications in lifestyle, which are sometimes radical and difficult to accept (smoking cessation, diet changes, reconditioning to physical effort). These involve helping the patient to preserve the positive dynamic traits of his/her functioning while modifying in parallel the potentially dangerous negative aspects for the heart such as hostility, excessive pessimism or any attitude likely to trigger a harmful

psychobiological response to different factors of stress. It was thus shown that reducing inappropriate responses to factors of stress led to beneficial effects for both the heart and the psychological state [42]. Follow-up as an outpatient in a cardiac rehabilitation unit is an excellent way for patients to recover physical and psychic equilibrium by better understanding of their heart function, progressive reconditioning to effort, gradually learning the new rules for hygiene and diet and gaining access to professionals in psychological care [43,44]. Finally, particular attention should be paid to coronary patients with characterized depression who do not respond to medical treatments and psychotherapy, as several clinical trials have shown that resistance to treatment for depression is a risk factor for recurrent cardiovascular events and subsequent death [45,46].

Conclusion

Affective disorders in general and depression in particular are multifactorial conditions among which the somatic aspect is receiving more and more attention. Indeed, recent studies on mood disorders have confirmed the reality of a disease that affects the brain and the whole body via fundamental multidimensional processes that cause metabolic or cardiovascular diseases in particular [18]. We can therefore underline the fact that bidirectional epidemiological, biological and genetic phenomena closely concern the relationships between CHD and depression. These interconnected physiopathological events seen in both diseases bring support to the hypothesis that these two diseases partially share common mechanisms and lead us to focus our attention on the psychosomatic dimension. While medicine is being ceaselessly enriched with more and more effective technologies, the impact of psychological factors on the genesis, evolution and treatment of cardiovascular disease is establishing itself as a crucial element that should always be considered. And, whatever the aetiology, it clearly appears that depression darkens the prognosis in CHD and certainly requires a multidisciplinary approach so that the depressive co-morbidities of CHD can be diagnosed and then treated.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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