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### Heart and mind

Pedersen, S.S.; Kupper, N.; van Domburg, R.T.

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# Heart and mind: are we closer to disentangling the relationship between emotions and poor prognosis in heart disease?

Susanne S. Pedersen<sup>1,2\*</sup>, Nina Kupper<sup>1</sup>, and Ron T. van Domburg<sup>2</sup>

<sup>1</sup>CoRPS—Center of Research on Psychology in Somatic diseases, Tilburg University, Tilburg, The Netherlands; and <sup>2</sup>Department of Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands

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**This editorial refers to ‘Fear of dying and inflammation following acute coronary syndrome’<sup>†</sup>, by A. Steptoe et al., on page 2405**

‘A mental disturbance provoking pain, excessive joy, hope or anxiety extends to the heart, where it affects temper and rate’.

William Harvey, English physician, 1578–1657

The idea that emotions might be tied to coronary heart disease (CHD) is not new, but a strong and cumulative body of empirical evidence is now available to support this notion. Negative emotions [e.g. depression and the distressed (Type D) personality] have been implicated in the risk of incident CHD in apparently healthy individuals, the risk of mortality in patients with established CHD, or both, while positive emotions (e.g. optimism) seem to be protective for both incident CHD and its progression.<sup>1–3</sup> For sceptics, it might be tempting to dismiss this evidence arguing that these patients have more cardiovascular risk factors, more severe disease, or receive less than optimal treatment. However, these studies have been well controlled with statistical adjustment for traditional biomedical risk factors and indicators of disease severity, and patients have received state-of-the art treatment.<sup>4,5</sup>

In their seminal paper, Steptoe and colleagues demonstrate that one in five patients report intense distress and fear of dying at the time of admission for acute coronary syndrome (ACS), and that such emotions are linked to increased immune activation.<sup>6</sup> The odds of high tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) levels was 4.67 in patients with intense distress at the time of admission, controlling for pain intensity at the time of ACS, sociodemographic factors, medication, and clinical risk. Fear of dying was also associated with reduced daytime cortisol output, but not with heart rate variability (HRV) indices 3 weeks after the ACS event. TNF- $\alpha$  levels at the time of the ACS were associated with reduced high

frequency (HF)-HRV and root mean square of successive differences (RMSSD), and elevated low frequency (LF)-HRV at 3 weeks, while TNF- $\alpha$  levels were unrelated to 3 week cortisol output. These results are consistent with existing stress theory that acute fear is associated with increased pro-inflammatory cytokine levels, and that increased cytokine levels are linked to lower parasympathetic activity according to the cholinergic anti-inflammatory reflex,<sup>7</sup> but also to higher LF-HRV activity, which might suggest elevated sympathetic activity (Figure 1). Nevertheless, these results leave us with important questions unanswered with respect to potential differences in the acute vs. chronic physiological effects of fear of dying in combination with an acute cardiac event, which on its own can also induce pro-inflammatory cytokine activation.<sup>8</sup>

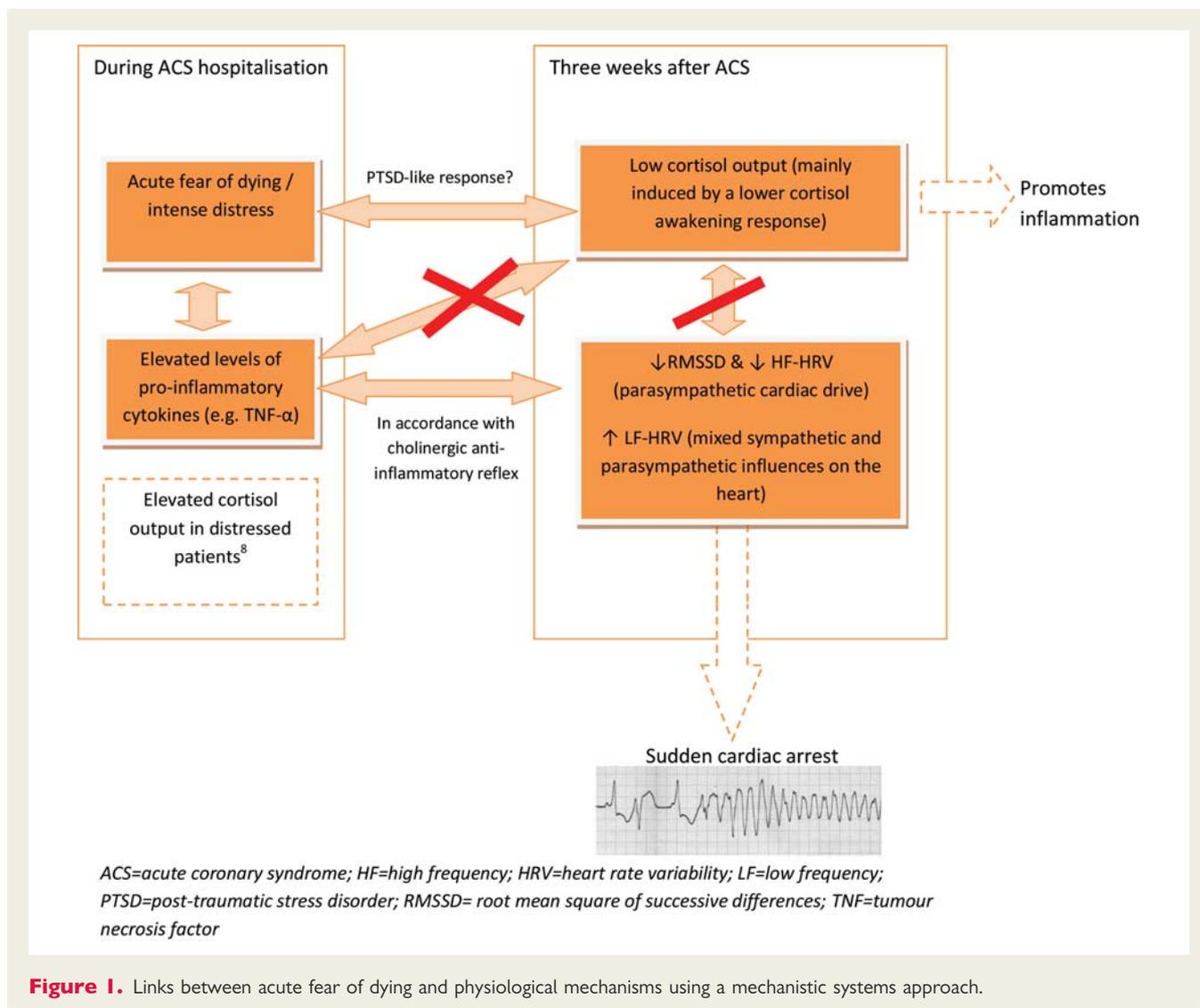
It is difficult to interpret daytime cortisol output, as it may differ as a function of the duration (acute vs. chronic) and the type (acute fear, post-traumatic stress, Type D personality) of stressor. Steptoe and colleagues focused on an acute stressor (i.e. fear of dying) at the moment of admission for ACS which was associated with reduced daytime cortisol output 3 weeks after the index event.<sup>6</sup> In a previous study of patients admitted for ACS, Steptoe and colleagues found that the magnitude of the cortisol awakening response (i.e. increase in cortisol following awakening) was elevated in Type D patients as compared with non-Type D patients, while there was no difference between depressed vs. non-depressed patients.<sup>9</sup> Typically, in response to acute fear as well as to acute physiological stress (i.e. ACS), both pro-inflammatory cytokines and cortisol (also stimulated by the pro-inflammatory cytokines) increase,<sup>10</sup> while post-stressor fear may be associated with low cortisol response.<sup>10</sup> How can we then explain the decreased cortisol output 3 weeks after heightened fear of dying? The answer may be found in the literature on post-traumatic stress disorder (PTSD). PTSD is prevalent in 25% of patients

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\* Corresponding author: Tel: +31 13 466 2503, Fax: +31 13 466 2370, E-mail: [s.s.pedersen@uvt.nl](mailto:s.s.pedersen@uvt.nl)

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**Figure 1.** Links between acute fear of dying and physiological mechanisms using a mechanistic systems approach.

following ACS,<sup>11</sup> and the hypoactivity of the hypothalamic–pituitary–adrenal (HPA) axis and resulting low levels of cortisol are characteristic for PTSD.<sup>12</sup> Thus, fear of dying at the time of ACS may be a precursor for PTSD-like symptoms or acute stress disorder. In the current study, there was no association between acute fear and HRV 3 weeks later, suggesting that acute fear may not have chronic effects on LF- or HF-HRV. Previously, both negative emotions and HRV were shown to be independent predictors of 8-year mortality, and as such that HRV could not explain the link between emotions and prognosis.<sup>13</sup>

Consistent with findings on the link between emotions and prognosis in CHD patients,<sup>2,3</sup> these results show that emotions are also independently associated with biological pathways that have been implicated in CHD progression.<sup>14</sup> At the same time, the results reflect the complexity of the heart–mind relationship and the challenges ahead for translational cardiovascular medicine and behavioural cardiology. One of these challenges pertains to the ‘uncracked mystery of the chicken and the egg’ and disentangling cause and effect.<sup>15</sup> An acute cardiac event sets a cascade of

biological processes in motion, which includes a heightened immune response. At the same time, emotional states arising at the time of an acute cardiac event increase immune activation and may stay activated due to dysregulation of cortisol as an immune activity modulator when stress becomes chronic. Immune activation can also lead to depression referred to as sickness behaviour, but depression may also develop independently as a response to the acute cardiac event. As such, the various systems, including the HPA axis, the autonomic nervous system, and the immune system operate as a complex interactive network with feedback loops and mediators such as cortisol and cytokines enabling their up- and down-regulation.<sup>8</sup> To this complexity is further tied the influence of genetic make-up, developmental history, the behavioural state, and the psychological profile of the patient, with the cascade of events and the response of the various systems involved differing depending on the chronicity of the emotion.<sup>8</sup>

Despite the seminal findings of Steptoe and colleagues, they do not bring us closer to resolving the ‘chicken and egg mystery’, but

they do point towards an avenue worthwhile pursuing for the fields of translational cardiovascular medicine and behavioural cardiology. In the literature, there is a tendency to examine the association between emotions and one of the systems implicated in cardiovascular disease. Hence, it is commendable that Steptoe and colleagues opt for a mechanistic systems approach, with their results showing how psychological and biological factors interact in heart disease in complex and reciprocal ways.<sup>6</sup> Their findings favour that we pursue this avenue rather than opting for a 'mechanism of the month approach', which would represent an oversimplification of the reciprocal interactions between the heart, mind, and body. However, it is a pity that they have no information on cortisol output and HRV indices in close proximity to the acute event, as well as on inflammatory activity and the persistence of fear of dying at follow-up, such that acute and chronic and often contradictory effects could have been further disentangled.

In order to optimize the management and care of CHD patients, we need to acknowledge that emotions carry independent additional risk, with particular subsets of patients dying prematurely due to their psychological vulnerability. Physiological mechanisms may provide part of the answer to the vicious cycle linking emotions to incident CHD and its progression. Behavioural mechanisms should not be forgotten, as there is an urgent need for more effective lifestyle management in these patients, due to increases in the prevalence of obesity and diabetes, and no change in the proportion of patients who smoke, despite an increase in the prescription of cardioprotective drugs.<sup>16</sup> The issue of inadequate lifestyle management is unlikely to be resolved without attending to the emotions of our patients, as emotions such as depression play a pivotal role in compliance and adherence.<sup>17</sup> This suggests that the 'one size fits all approach' to intervention in CHD patients is unlikely to work and that a personalized medicine approach is warranted.

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