Reflections on the past four decades of mental stress research in autonomic cardiology

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This commentary with some reflections and summary of my experience in the field of mental stress research is my contribution to celebrate the thirtieth anniversary of *Clinical Autonomic Research*, a journal that, over the past years, has become the benchmark publication for all those interested in the autonomic nervous system, regardless of their primary medical specialty, which, in my case, is cardiology.

In 1977, after 4 years of postgraduate research and clinical training with Prof. Stevo Julius in the Hypertension Division of the University of Michigan Medical Center, I returned to the Baker Medical Research Institute and the Alfred Hospital in Melbourne, Australia, where I worked as a clinical cardiologist and established a cardiovascular neuroscience laboratory.

In my early clinical practice in Melbourne, I remember being struck by how the presentation of patients with myocardial infarction or ventricular arrhythmias was sometimes precipitated by emotional turmoil. I saw patients in whom a heart attack had been triggered by armed robbery, assaults, and even an owner's racehorse winning by a “nose”. With this clinical exposure, I was pleased to accept, in 1985, an invitation to participate in what I anticipated would be an influential national panel to explore the relationship between mental stress and heart disease. I was, however, not ready for the opening statement of the meeting chair (whose name I won't say): “There is no evidence that stress causes heart disease, nor will there ever be”. I was disappointed though not discouraged, as of course this could not be true—where was his crystal ball?—although the statement did capture the pessimism that was common in the cardiology of that era.

Faced with this setback, I applied my newly established noradrenaline spillover methodology [4] to the stress-heart question, tapping into research opportunities that are open to a cardiologist, by studying cardiac sympathetic responses to mental stress. I conducted this research in a cardiac catheterization laboratory, using an infusion of tritiated noradrenaline to measure the release of this catecholamine from sympathetic nerves by isotope dilution, with sampling from the coronary sinus of the heart. This was to make these noradrenaline release measurements specific to the cardiac sympathetic nerves, all done during exposure of the research participants to laboratory mental stress (Fig. 1a) [4]. As approved by my institutional ethics committee, the applied stressor was 10 min of difficult mental arithmetic, just to exceed the volunteer's arithmetic competence, and paced by a metronome. An extra tweak was provided, for the mathematically gifted by telling the participant they were wrong... when they were indeed right! In a typical experiment, we measured adrenaline secretion by the adrenal medulla, noradrenaline release from the cardiac sympathetic nerves and the sympathetic nerves of the whole body, noradrenaline and adrenaline plasma concentrations sampled from an antecubital vein, and sympathetic outflow firing using microneurography in the innervation of the skeletal muscle vasculature in the leg.

The theory at the time was that mental stress responses were “adrenergic, not noradrenergic”. This idea came from the standard stress research protocol of the day, measuring plasma catecholamine concentrations in a forearm antecubital venous blood sample, where the plasma adrenaline concentration was found to rise with mental stress, but with plasma noradrenaline concentration changing little, if at all. I was not sure what “adrenergic, not noradrenergic” meant, but it turned out not to be true. Adrenaline secretion did increase, but there was an accompanying sympathetic response, which was highly regionalized, highest (very

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Fig. 1 Cardiac noradrenergic spillover, increased sympathetic outflow, and stress-induced ischemic heart disease. **a** Assessment of sympathetic nervous outflow to the heart, from the measurement of cardiac noradrenaline spillover (outward flux of noradrenaline from the sympathetic nerves of the heart). During constant rate infusion of tritiated noradrenaline into a peripheral vein, and blood sampling from the coronary sinus and brachial or radial artery, cardiac noradrenaline spillover is calculated at steady-state by the principle of isotope dilution, according to the formula $[(NA_{CS} - NA_A) + (NA_A \times EX_{3HNA})] \times CSPF$. In simple terms, the method determines net noradrenaline overflow from the heart, corrected for noradrenaline uptake from plasma during transit of blood through the heart, since noradrenaline flux is bi-directional. The tracer provides the noradrenaline uptake value [4]. NA_{CS} coronary sinus plasma noradrenaline concentration, NA_A arterial plasma noradrenaline conc., EX_{3HNA} cardiac extraction tritiated noradrenaline from plasma, $CSPF$ coronary sinus plasma flow, SCV superior coronary vein, MCV middle coronary vein. **b** An Australian fire team captain in a moment of exhaus-

tion and perhaps anguish. The incidence of stress (Takotsubo) cardiomyopathy increases during national disasters. After the catastrophic Black Saturday Melbourne forest fires, in February 2009, which encircled the city and caused 173 deaths, Takotsubo cardiomyopathy incidence spiked, both in civilians and in firefighters. **c** Sympathetic activation during a panic attack. A spontaneous panic attack in the laboratory in an unmedicated patient accompanied by a large increase in multiunit sympathetic burst size recorded in sympathetic fibers passing to the skeletal muscle vasculature of the leg, without an increase in sympathetic burst firing rate. **d** Coronary artery spasm during a panic attack. Coronary angiography performed on a patient who had frequent panic attacks usually provoking angina pain. A panic attack with angina occurred during the angiography. We noted a spasm in the left anterior descending coronary artery (upper panel). The administration of glyceryl trinitrate partly reversed the coronary spasm (lower panel). Sympathetic nerve recording was not performed in this patient

high indeed) for the heart, intermediate for whole-body sympathetic activity, and absent for muscle sympathetic activity. Unchanged antecubital venous noradrenaline concentrations resulted primarily from the lack of an increase in the sympathetic outflow to skeletal muscle vasculature. To my mind, the marked and preferential activation of the cardiac sympathetic outflow gave credence to the notion that mental stress could trigger cardiac catastrophes.

A second consideration was that the results seemed to challenge the historic formulation by Walter Cannon of the existence of a *sympathoadrenal system*, which provided a unified, homeostatic control mechanism, with the adrenal medullary secretion of adrenaline being accompanied by global activation of the sympathetic nervous system. We had found that in the iconic context in which this was proposed by Cannon, the “fight or flight” response, sympathetic

activation was regional rather than global, being most prominent in the sympathetic outflow to the heart, and absent in the sympathetic outflow to the skeletal muscle vasculature. I trod gently with this heresy, but, in subsequent years, Cannon's classic idea was to be deconstructed further, with a demonstration of the frequent mismatching of adrenal medullary and sympathetic nervous system responses [7].

I was pleased with this research, but, upon submission of a manuscript summarizing my results, the *American Journal of Psychiatry* did not share my enthusiasm. The editor thought the work was unsuitable for a psychiatry journal because it was physiology. One reviewer thought that simply measuring heart rate would be as instructive as this invasive research. Another was sure that venous antecubital plasma catecholamine measurements did validly measure human stress responses. Another journal, *Psychoneuroendocrinology*, was more welcoming and published my research findings [5]. That was in 1989, when *Clinical Autonomic Research* did not yet exist.

By 2001 it was no longer possible to maintain that stress does not cause heart disease. In that year, the September 11th terrorist attacks on the World Trade Center in New York were documented to increase defibrillation firing in people with implanted defibrillators. Earlier systematic evidence gathered at times of national disasters, including war, missile attacks on civilians, and earthquakes had strongly supported the link between stress and heart attack. Research linking mental stress to sudden death is often disputed because of disagreement over what constitutes stress, and whether stress can be accurately measured. Evidence that the incidence of sudden non-traumatic death markedly increases during earthquakes, with the 1994 Los Angeles earthquake providing a telling example [8], is free of this criticism, as here the existence of psychological stress is absolutely clear. The incidence of Takotsubo (i.e., stress-related) cardiomyopathy also increases during intense emotions, either positive [11, 12] or negative, including disasters of national span. After the catastrophic Black Saturday (February 7th, 2009) Melbourne forest fires, which encircled the city and caused 173 deaths, the incidence of Takotsubo cardiomyopathy spiked, both in civilians and in firefighters (Fig. 1b).

People with panic disorder often fear that they have heart disease, because of the nature of their symptoms, but in the past, they were reassured that this is not the case. Contrary to this reassurance, my own extensive clinical experience with the management of patients with panic disorder attests that a range of cardiac complications can occur during panic attacks. Multifiber sympathetic nerve recordings document massive sympathetic stimulation in the skeletal muscle vascular outflow during panic attacks [2] (Fig. 1c). The consequences include, but are not limited to, atrial and ventricular arrhythmias, recurrent emergency room attendances with angina and electrocardiograph changes of ischemia,

coronary artery spasm documented in panic attacks occurring during coronary angiography (Fig. 1d), and myocardial infarction associated with coronary spasm and thrombosis [9]. Current epidemiological studies clearly indicate that patients with panic disorder have an increased risk of myocardial infarction and sudden death [1]. Activation of the sympathetic nervous system during panic attacks is a mediating mechanism. The contrast between this, and the absence of activation of the sympathetic outflow to skeletal muscle vasculature during experimental mental stress in the laboratory [7], was very evident at the time but remains unexplained.

I wondered whether the central venous catheter methodology used frequently by my group could be utilized to study brain neurotransmitters in patients with panic disorder. The clinical benefit of selective serotonin reuptake inhibitors (SSRI) implied that CNS serotonergic transmission could be defective in patients with panic disorder, but augmented by blocking the reuptake of the neurotransmitter with SSRI. We were unable to study patients during a panic attack, but with internal jugular venous sampling in the interim state, we found CNS serotonin turnover actually to be remarkably increased [6], rather than the expected reduction. This is congruent with the anxiogenic influence of serotonergic raphe neurons in experimental animals, but it is fair to say that our direct demonstration of increased CNS serotonin turnover has, so far, had no influence on the theories of CNS mechanisms of panic disorder.

Epidemiological research provides substantial support for the notion that behavioral and psychological factors may be important in the pathogenesis of essential hypertension. My research has focused on a search for stress biomarkers in patients with essential hypertension. My group did identify several of these biomarkers [3]. In essential hypertension, adrenaline is released as a co-transmitter from sympathetic nerves, which also occurs in experimental animals exposed to chronic mental stress [10]. The adrenaline appeared to be synthesized in situ, rather than extracted from plasma. In small subcutaneous veins of the forearm, biopsied in patients with hypertension as a source of sympathetic nerves, the adrenaline-synthesizing enzyme phenylethanolamine-N-methyltransferase (PNMT) was induced, an indicator of stress exposure. PNMT was absent in the biopsied veins of controls without hypertension [2, 3]. Also, in patients with essential hypertension, but not in healthy controls, microneurography recordings disclosed single sympathetic nerve fibers firing repeatedly within a cardiac cycle, in firing salvos. This appears to be a signature of mental stress exposure [2, 3].

The question of whether chronic mental stress causes hypertension was reviewed by the Specialist Medical Review Council, an Australian government-convened expert committee on which I served. Despite the challenging

medicolegal implications, the Council determined that stress, including stress in the workplace, is a proven cause of hypertension. This ruling was made official when published in the Australian Government Gazette on March, 27th 2002. This judgment was reached after consideration of the epidemiological evidence but, in particular, after a review of the specific stress biomarkers described above. Sometime later, the Australian government convened a second expert committee to advise the Specialist Medical Review Council and the ruling of the first expert committee was judged undesirable. Under the advice of this second committee, the Specialist Medical Review Council now determined that stress, including stress in the workplace, was not a cause of hypertension, this ruling duly being recorded in the Australian Government Gazette.

One thing is clear. Analysis of whether there is a causal relation of mental stress to cardiovascular disease remains an ideological battleground.

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Compliance with ethical standards

Conflict of interest The author declares that he has no competing interest.

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