Coronary and sympathetic responses to core hypothermia: answers and questions

It is a time-honoured clinical observation that in patients with coronary heart disease exposure to cold environments may trigger the development of anginal attacks, thereby aggravating the unbalanced condition of coronary perfusion already displayed by these subjects. It is also believed that the pathophysiological mechanism leading to the acute myocardial ischaemic event is represented by a decrease in coronary blood flow induced by the sudden exposure to cold environmental temperatures.

Cardiovascular and adrenergic effects of core hypothermia

In this issue of Clinical Science, a study by Frank and co-workers [1] is an important step forward in our understanding of the coronary and myocardial responses (and related mechanisms) to hypothermia. The new major findings provided by the study [1] can be summarized as follows. First, in young healthy subjects, a reduction in core temperature by 1°C, achieved by systemic infusion of cold saline, elicited an increase in coronary perfusion coupled with a tachycardic and a pressor response (mainly systolic), thereby resulting in an increase in the heart rate–pressure product and myocardial oxygen demand. Secondly, these marked systemic and coronary haemodynamic responses are accompanied by a consistent increase in circulating plasma noradrenaline and adrenaline levels. Finally, administration of a $\beta$-adrenergic blocker abolished the observed tachycardic response, and also attenuated the concomitantly reported increase in plasma catecholamines and systolic blood pressure.

As properly discussed by Frank et al. [1], these three sets of data lead to the conclusion that cold exposure does not cause coronary vasoconstriction, but rather vaso-dilatation. They also show that a reduction in core temperature increases cardiac work and markedly stimulates the release of the adrenergic neurotransmitters at the level of both peripheral nerves and the adrenal medulla, suggesting that a neuro-adrenergic activation is responsible for some of the cold-induced haemodynamic effects (tachycardia and systolic blood pressure increase). This conclusion is strengthened by the evidence that acute $\beta$-blockade abolishes or attenuates the heart rate, blood pressure and catecholamine responses to cold stimuli.

Outstanding questions

As often happens in research, the findings provided by a well-designed and accurately performed study raise a number of intriguing questions. This is also the case for the present investigation [1], which raises at least three questions. Do the results apply to patients with coronary heart disease? Would the coronary and sympathetic responses to core hypothermia described in young subjects be affected by the aging process? Do the study’s findings rule out the pathophysiological participation of neurohumoral and vasoactive systems, other than the neuro-adrenergic one, in coronary responses to cold exposure?

The first question has been already addressed by Frank et al. [1] by quoting the results of a previously published study [2] showing that cold exposure triggered coronary vasodilatation in healthy subjects, but coronary vasoconstriction in patients with ischaemic heart disease. It should be noted, however, that other evidence of the differential effects of a given stimulus in healthy and diseased coronary vessels have been shown. It has been shown, for example, that immersion of the face in cold water (the so-called ‘diving reflex’) may cause a different degree of coronary vasoconstriction in patients with coronary artery disease, according to the less or more marked degree of the impairment in resting myocardial perfusion [3]. It has also been shown that acute cigarette smoking, which is known to cause a marked increase in blood pressure and heart rate mediated by a sympathetic stimulation [4], while not inducing a substantial change in coronary blood flow in healthy subjects, elicits coronary vasoconstrictor effects in patients with ischaemic heart disease [5,6]. It would be thus of major clinical relevance to investigate the sympathetic and coronary vasomotor responses to core hypothermia in patients with coronary artery stenosis of different angiographic severity.

It will also be of major clinical relevance to examine how aging affects the coronary and adrenergic responses to core hypothermia, given the evidence that elderly individuals: (i) display an age-related increase in cardiovascular sympathetic drive [7], (ii) are characterized by an endothelial dysfunction which may impair the coronary vasomotor responses to hypothermic stimuli [8], and (iii) show a functional impairment in the vascular, as well as the sympathetic, components involved in the thermoregulatory process [9].

Finally, the evidence provided by the study by Frank et al. [1] that acute blockade of $\beta$-adrenergic receptors attenuates, but not completely normalizes, the coronary blood flow responses to core hypothermia, suggests that neurohumoral, as well as vasoactive systems other than the adrenergic one, participate in the phenomenon. These may include endothelial function, given the evidence that
a hypothermic stimulus impairs the vascular responses to bradykinin and acetylcholine [10] and inhibits nitric oxide synthesis [11]. They may also include, however, the renin–angiotensin system and specifically angiotensin II, whose circulating levels display a 10-fold increase during cold exposure [12]. Because angiotensin II affects directly and indirectly, i.e. through an interaction with the sympathetic neurotransmission, the vasomotor tone [13], it is possible to speculate that this substance may be indeed involved. Therefore the evaluation of the effects of drugs interfering with the renin–angiotensin system (angiotensin-converting-enzyme inhibitors or angioten-
sin-II-receptor blockers) on the coronary, as well as on the adrenergic, responses to core hypothermia should be worthy of future investigations.

A final comment should be made on the way through which the Authors have assessed the neuroadrenergic function in their patients, performing the assay of arterial and venous noradrenaline levels. Although technical and ethical considerations have probably precluded Frank et al. [1] from carrying out a more ‘regional’ evaluation of the adrenergic responses (for example, performing venous blood sampling from the coronary sinus and thus calculating the artero-venous difference in noradrenaline), this approach would have allowed the effects of core hypothermia and β-adrenergic blockade on the net release of noradrenaline in the coronary vascular regions to be assessed. It is indeed well established that there are profound differences in adrenergic drive in the different vascular districts and that systemic noradrenaline levels do not necessarily reflect regional sympathetic drive [14]. Despite this limitation, the study by Frank and co-workers [1] provides important and new information, which expands our knowledge on an issue with relevant pathophysiological and clinic implications.

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REFERENCES


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