Denervation supersensitivity to noradrenaline in resistance vessels in denervated canine myocardium

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Abstract:

Cannon’s law states that a chronically denervated structure is supersensitive to the neurotransmitter it is normally regulated by. However, the present consensus is that myocardial arteriolar resistance vessels are not supersensitive to noradrenaline following chronic sympathetic denervation of the heart. We present an extended interpretation of results of a published study in which the volume of distribution of radiolabeled hydroxyephedrine and blood flow were measured in innervated and denervated regions of the same canine heart using positron emission tomography. For a given amount of noradrenaline, myocardial blood flow was lower in denervated than innervated myocardium, indicating denervation supersensitivity. This finding has implications for patients with cardiac autonomic neuropathy.

Abbreviations used in this article:

HED – hydroxyephedrine; MBF – myocardial blood flow; PET – positron emission tomography; and Vd – volume of distribution
Introduction:
It is well established that activation of α-adrenergic receptors causes an increase in coronary vascular resistance [1-4]. Noradrenaline released from sympathetic nerve terminals as well as exogenously administered noradrenaline administration cause coronary vasoconstriction mediated by α adrenergic receptors, coronary vasodilation mediated by β-adrenergic receptors, and coronary vasodilatation secondary to metabolic autoregulatory mechanisms accompanying an increase in heart rate and myocardial contractility. Chronically denervated organs are supersensitive to the neurotransmitter by which they are normally regulated – “Cannon’s Law” [5]. As Cannon’s law applies particularly to heart rate and contractility effects [6, 11], it is not easy to study whether it also applies to coronary vascular responses as these are concomitantly affected by changes in heart rate and myocardial contractility. Additional difficulty arises from the fact that myocardial vascular resistance is heterogeneous so that if only global values are calculated, false conclusions could be drawn. In this paper, we present our reinterpretation of data from a study published recently by Rimoldi et al [7] in which the required discrete measurements were made in canine hearts with chronic regionally denervated myocardium.

Methods:
The methods of the published paper:
The paper by Rimoldi et al [7] was published in a nuclear medicine journal so that the discussion presented here (which we think is of clinical importance) was not addressed earlier. The authors were able to make measurements of myocardial blood flow (MBF) with positron emission tomography (PET). The intact dogs (n = 9) were sleeping under a dose regime of α-chloralose less than that required for surgical anaesthesia, the sedation being required so that the animal rested without motion, other than respiration, within the PET scanner. Rimoldi et al [7] measured the heterogeneity of MBF as well as sympathetic innervation. MBF was measured with oxygen-15-labeled water (H_2^{15}O). The radioisotope ^{11}C-hydroxyephedrine (^{11}C-HED) is handled by cells in the same way as noradrenaline; sympathetic innervation was estimated from the volume of distribution (Vd) of ^{11}C-HED. As the study protocol did not include the administration of a β-adrenergic antagonist, we needed to consider theoretical arguments presented below.

Theoretical considerations:
The methods used by Rimoldi et al [7] provided data on differences in the amount of noradrenaline as well as blood flow in different parts of the myocardium. As the perfusion pressure is the same everywhere (the different parts are in the same heart), blood flow is inversely related to resistance to flow. If there were no sympathetic vascular tone or if the vasoconstrictor and vasodilator effects of α and β adrenergic receptors...
respectively were equal, then, a statistically significant relationship between content of norepinephrine and myocardial blood flow would not be expected. If β-adrenergic tone dominated over α-adrenergic tone, a positive correlation between local noradrenaline content and blood flow would be expected. On the other hand, if α-adrenergic vasoconstrictor tone predominated, there would be an inverse relationship between local noradrenaline content and blood flow.

**Results:**

It was found that local MBF in various regions within innervated tissue was inversely related to $^{11}$C-HED; i.e., higher the local noradrenaline content, less the blood flow. The regression equation for this inverse relationship between MBF and the Vd of $^{11}$C-HED is as follows: $\text{MBF} = 1.772 - 0.01 \times \text{Vd of HED}$; $r = 0.72$, $P = 0.02$. This relationship was then compared with that in the denervated part of the heart, where, again, an inverse relationship was found: $\text{MBF} = 1.363 - 0.03 \times \text{Vd of HED}$; $r = 0.80$, $P = 0.01$. A comparison of the two regression lines by analysis of covariance indicated that the positions of these lines were significantly different ($F = 10.8$, $P = 0.005$); i.e., myocardial blood flow for a given Vd of HED was lower in denervated tissue compared to innervated tissue.

**Discussion:**

The interpretation presented here takes into account the theoretical considerations alluded to above. The inverse relationship between MBF and the Vd of $^{11}$C-HED is interpreted as indicating vasoconstriction mediated by α-adrenergic receptors outweighs vasodilation mediated by β-adrenergic receptors in both innervated and denervated myocardium. We assume, in the unfortunate absence of results following administration of a β-adrenergic antagonist, that the proportion of β to α effects are similar in the two situations, and that the lower MBF for a given amount of noradrenaline is caused by the supersensitivity of coronary resistance vessels to noradrenaline. An alternative explanation might be that a β-adrenergic vasodilatory contribution to the relationship between norepinephrine content in sympathetic postganglionic neurons and MBF in the innervated tissue disappears in denervated tissue due to downregulation of β-adrenergic receptors. However there is no evidence of downregulation according to the results of study of the distribution of the β-adrenergic receptor ligand, $^{11}$C-CGP 12177 [7], a finding similar to that of Van der Vusse et al [8].

Supersensitivity has been denied in the case of coronary vasculature in chronic regionally denervated hearts because the application of noradrenaline did not alter pressor responses in isolated epicardial arteries [9]. However, epicardial arteries are not resistance vessels and would be subject to the in vitro changes caused by the perfusion conditions. The only study we could identify from amongst similar studies of resistance vessels...
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was a paper suggesting increased MBF in response to intracoronary norepinephrine after ventricular sympathectomy [10]. However, this may have been secondary to the increased inotropic effect and increased demand for flow accompanying administration of norepinephrine.

Classic studies of cardiac denervation have involved a surgical technique [6, 11-13] that removed sympathetic as well as parasympathetic innervation (as is also the case in transplanted hearts). In such chronically denervated preparations, the increased response to noradrenaline is a well accepted phenomenon: a tachycardic response is certainly present [6] and so is an increase in myocardial contractility [11], both confirmed in the study by Drake et al [12]. The heightened contractility response was confirmed using the alternative method of selective regional sympathetic denervation with phenol [9]. This method [14] also revealed supersensitivity of the shortening effect of noradrenaline on effective refractory period [15-17]. Supersensitivity following chronic sympathetic denervation of the heart is not accompanied by upregulation of ß-adrenergic receptors [7, 8, 17]. Supersensitivity has been ascribed to lack of reuptake of norepinephrine from denervated myocardium following degeneration of sympathetic postganglionic neurons [13]. Thus, an increase in tissue noradrenaline has a greater effect on the adrenergic receptors in target tissues. Hammond et al [18] also think that adrenergic denervation supersensitivity in the myocardium depends on a post-receptor mechanism but that it is not linked with increased cyclic AMP production. It would be extraordinary if supersensitivity of the heart rate response [6] and of the contractility response [11, 13], which are present, was not accompanied by supersensitivity of arterioles in the same tissue. We are not aware of an exception to Cannon’s law of denervation.

The clinical implication of our interpretation, if correct, is that a heightened vasoconstrictor response to noradrenaline (circulating noradrenaline and or noradrenaline diffusing from neighbouring innervated regions [17]) reaching chronically denervated myocardial resistance vessels would increase the susceptibility of denervated myocardium (for example in patients with cardiac autonomic neuropathy [19-20] or patients with transplanted hearts) to ischemia.

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Conflict of interests: none declared

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