Can a single vasodilator be responsible for both coronary autoregulation and metabolic vasodilation?

J. D. Laird, P. N. Breuls, P. van der Meer, and J. A. E. Spaan

Summary

To test the hypothesis that both coronary autoregulation and metabolic vasodilation can be mediated by the same substance, we have analysed measured autoregulation curves with the aid of a simple mass balance model. In an open-chest dog preparation, increasing the heart rate by pacing results in a nearly parallel shift of the autoregulation curve to a higher flow (Q) level. We assume a unique relationship between vascular conductance and interstitial concentration of a vasodilating substance [A]. Applying a compartmental mass balance, it is possible to predict with a minimum of assumptions the increase of flow between two points with increased production but having the same vasodilator concentration. The simple result of this analysis is: ΔQ = Δproduction/[A]. If the vasodilator concentration varies by more than a factor 2 between low and high conductance points, the autoregulation curve cannot shift in a parallel fashion as a result of an increased production rate, but rather will become less and less steep. We conclude that a single vasodilator cannot be responsible for both autoregulation and metabolic vasodilation unless complex assumptions are made, for which there is as yet no experimental support.

Introduction

Adenosine is well documented to be a potent vasodilator of the coronary vascular bed. By far the greatest body of evidence supporting the adenosine hypothesis relates to its role under conditions of ischaemia and/or hypoxia as well as with variations in metabolic state (Berne, 1). However, an equally plausible argument can be made for the possible role of adenosine in autoregulation. In this paper we will, with the aid of a simple model, examine whether such a unifying role attributable to a single vasodilator can be consistent with the experimentally observed behaviour of the coronary vascular bed under conditions of varying perfusion pressure (autoregulation) and altered oxygen consumption (metabolic vasodilation).
The observation

Figure 1 shows a measured pressure-flow diagram taken at two different heart rates. Two distinct and remarkable features of these data are pertinent to our present discussion: (1) At a constant heart rate and aortic pressure (not shown), the flow is nearly constant over a wide range of perfusion pressure (autoregulation), and (2) the vasodilation associated with an increase in heart rate results in an essentially parallel shift upwards in flow (metabolic vasodilation). Can these observations be rationalized with a model which assumes both effects to be mediated by adenosine or for that matter any other single vasodilating substance?

The model

The potency of adenosine as a vasodilator is known to be dose related (Schrader, 7; Olsson, 3; Kroll, 2) and moreover there is evidence that the receptor site is located on the outside of the resistance vessels (Olsson, 4), exposed to the chemical environment of the interstitial space. It is thus important to systematically consider the determinants of the interstitial concentration of the vasodilating substance, denoted by $[A_i]$. The vasodilator is assumed to be “produced” or released by the myocardial cells and in the case of adenosine this has been well documented (Rubio, 6). The vasodilator, so produced, is “dumped”, as it were, into the interstitial space. The final concentration in the steady state will be determined by the balance between this production rate and the rate of “disappearance”. In the simplest of models there are three routes by which adenosine or any other vasodilator can be removed from the interstitium, namely (1) chemical degradation to an inactive form, (2) re-uptake into the myocardial cell, and last but certainly not least, (3) washout. Degradation and re-uptake can, for our purposes, be conveniently lumped together, since their rates...