Enhanced Responsiveness of the Coronary Blood Vessel of the Dog Heart-Lung Preparation to PGI2 after Chronic Chemical Sympathectomy

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Abstract—Chronic chemical denervation of the sympathetic nervous system with 6-OH dopamine resulted in an augmentation of the coronary blood flow (CBF) increase inherent in the canine heart-lung preparation, but not in an augmented accumulation of 6-keto PGF1α in the circulating blood. In denervated HLP, 6-keto PGF1α was lower and the vasodilator response to PGI2 larger at the start of the experiments. It was concluded that exaggerated increase in CBF was due to a potentiation of the vasodilator response to PGI2.

It is well known that the coronary blood vessels maintain a high level of vascular tone. However, in the heart-lung preparation (HLP), the coronary vascular tone, although initially high, is not maintained; the coronary blood vessels become maximally dilated after the lapse of an experimental period of 2–3 hr. A previous paper from this laboratory (1) demonstrated that this gradual increase in coronary blood flow (CBF) could be reversed with non-steroidal anti-inflammatory agents of widely-differing chemical structure. The relative potency of these agents for this effect corresponded roughly to that of cyclo-oxygenase inhibition of these compounds reported in the literature. Furthermore, analysis of prostaglandins (PGs) and related substances in the circulating blood of the preparation with gas chromatography-mass spectrometry (GC-MS) revealed an accumulation of 6-keto PGF1α at a time when the coronary blood flow of the preparation attained a steady high level. 6-Keto PGF1α is a stable metabolite of the potent coronary vasodilator prostacyclin (PGI2). After indomethacin, the level of this substance returned to the initial low level, together with the restitution of the initial low blood flow level, suggesting that PGI2 was responsible for the increase in CBF inherent in HLP.

In the present study, we attempted to clarify the role played by the sympathetic nervous system in the gradual increase in CBF inherent in HLP. For this purpose, the animals were chemically denervated with chronic administration of 6-hydroxydopamine (6-OH dopamine).

Mongrel dogs of either sex weighing between 6-15 kg were anesthetized with sodium pentobarbital (35 mg/kg) administered intraperitoneally. Heart-lung preparations were prepared according to the Kray-Mendez modifications of the original Starling method, the details of which were described in our previous publications (2–4). The heparinized blood obtained from other large dogs under slight thiopental anesthesia (20 mg/kg, i.v.) was used for priming of the extracorporeal circuit. Coronary sinus outflow was led out by a Morawitz cannula, measured with a square-wave electromagnetic flowmeter (Nihon Kohden MF26) with a cannulating-type flow probe (2 mm internal diameter) and returned to the preparation via the inferior vena cava. The total coronary blood flow was calculated as 10/6 of the...
coronary sinus outflow (5).

Chemical sympathectomy of the animals was conducted by injecting 6-OH dopamine intravenously in increasing doses every other day for 5 days, until the cumulative dose reached around 70 mg/kg. To avoid the acute toxicity of the substance, it was administered as two divided doses (1st day: 2+3, 3rd day: 5+15, 5th day: 15+30 mg/kg). 6-OH dopamine was dissolved in ascorbic acid. To check the completeness of the chemical denervation, tyramine was injected to the preparation up to the dose of 1 mg. No positive inotropic and chronotropic effect was observed.

For analysis of the 6-keto PGF₁α, blood samples were collected from the arterial side of the preparation into chilled test tubes and were centrifuged within 5 min to separate the plasma. The plasma was kept frozen at −80°C until further processing. 6-Keto PGF₁α was quantitated by GC-MS after extraction and purification with thin-layer chromatography as described by Miyazaki et al. (6).

As shown in Fig. 1 with a representative record, the gradual increase in CBF inherent in dog HLP was augmented in HLP prepared from the dogs subjected to chronic chemical sympathectomy as compared with that of the non-treated HLP. The initial level of CBF was a little higher in the treated HLPs than in the non-treated ones. Indomethacin was still effective in reversing the CBF increase in chemically denervated HLP. However, much larger doses were needed to produce effects of equal magnitudes (data not shown). It was found that the coronary vasodilator responses to PGI₂ were much greater at the start of the experiments in chemically denervated HLP as shown in Fig. 1.

The upper half of Fig. 2 summarizes the data on CBF, 6-keto PGF₁α in the circulating blood and the magnitude of vasodilator response to PGI₂ at the start of the experiments. The lower half illustrates the rate of increase in CBF and 6-keto PGF₁α at the stage of linear increase in these two parameters. As stated above, the initial CBF tended to be a little higher and the vasodilator response to PGI₂ at the start of the experiments was significantly larger (P<0.01) in

Fig. 1. A representative record showing the time course of the gradual increase in the coronary blood flow inherent in dog heart-lung preparation. The coronary vasodilatation induced by 10 μg of PGI₂ at the start of the experiments is also shown in this figure. Cor. F: coronary sinus outflow measured with a Morawitz cannula.
the chemically denervated HLP. The level of 6-keto PGF\(_{1\alpha}\) in the circulating blood at the start of the experiments was significantly lower (P<0.01) in the denervated HLP.

The rate of CBF increase inherent in HLP was found to be significantly larger (P<0.05) in denervated HLP than in innervated HLP as shown in this figure. Though a little higher in denervated HLP, the rate of increase in 6-keto PGF\(_{1\alpha}\): the rate of increase in 6-keto PGF\(_{1\alpha}\). Thus, it may be concluded that the augmentation induced by chronic chemical denervation of the gradual increase in CBF inherent in HLP was due not to the enhanced production of PG\(_{I_2}\), but to the enhanced reactivity of the coronary blood vessels to PG\(_{I_2}\). The fact that the initial level of 6-keto PGF\(_{1\alpha}\) was lower in the denervated HLP indicates that the sympathetic nervous system exerted a tonic accelerating influence on PG\(_{I_2}\) production in HLP at least at the initial stage. Enhanced vasodilator responsiveness of the coronary blood vessel to exogenous PG\(_{I_2}\) observed in denervated HLPs at the start of the experiments is compatible with the idea of tonic accelerating influence of the sympathetic nervous system on PG\(_{I_2}\) production, for it may be explained by the lesser preoccupancy of PG\(_{I_2}\) receptor by endogenous PG\(_{I_2}\) in sympathetically denervated HLP. Increased release of PGs by nerve stimulation and catecholamines readily occurs in a number of adrenergically innervated tissues including the heart (7) (for further references, see Hedqvist (8)). In most cases, the PG predominantly released is PG\(_{E_2}\) followed by PG\(_{F_2\alpha}\). However, a recent report by Wennmalm (9) indicated that PG\(_{I_2}\) was also released from the heart under these conditions. The initial level of CBF was not reduced despite a significantly lower level of 6-keto PGF\(_{1\alpha}\). This may also be explained by the enhanced responsiveness to PG\(_{I_2}\).

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