

**AN OVERVIEW OF THE INTRINSIC CONTROL MECHANISMS
IN THE CORONARY TREE OF TROUT ISOLATED HEART**

Tariq Mustafa
Institute of Biology, SDU, Odense University,
Campusvej 55, DK-5230 Odense M, Denmark;
45 + 66502736; tariq@biology.sdu.dk

Claudio Agnisola
Department of General and Environmental Physiology,
University of Naples, Naples, Italy

EXTENDED ABSTRACT ONLY – DO NOT CITE

Background and Aims

Coronary blood flow is strictly regulated *via* changes in coronary resistance in relation to the metabolic demands of myocardium (Berne, 1964). This capacity to adjust blood flow to myocardial metabolic requirements remains unaltered in isolated preparation such as the perfused intact coronary system and vascular rings which are devoid of extrinsic control mechanisms i.e. sympathetic nerves and circulating agonists. This suggests the existence of intrinsic vasomotive mechanisms located in the endothelium and vascular muscle cells of the coronaries. Their role in the control of coronary blood flow in mammals (Levick, 1991) is well established but comparable information on non-mammalian species like fish is scanty.

So far in mammalian and fish species mostly coronary ring preparations are employed to study the vasomotive regulatory mechanisms. Recently, it is becoming evident that various regulatory factors affect the coronary microvascular resistance with differing sensitivities as the receptor distribution along the coronary tree is not homogenous (Chilian, 1997). The aims of this report are to describe (i) the pressure dependence of coronary resistance; and (ii) autacoid (i.e. prostanoids, adenosine/Ado and endothelial-derived nitric oxide/EDNO) mediated vasodilative mechanisms in the trout coronary system.

Methods

The preparation was allowed to perfuse with saline until coronary resistance became stable, the basal flow was measured and the perfusion was shifted to the drug-containing perfusate. Coronary flow (CF, ml min⁻¹) was determined according to the method described by Agnisola *et al.* (1996), modified to generate a computer-driven recording. The effects on coronary resistance (CR) are presented as the percentage change from the basal coronary resistance. The one-way analysis of variance (ANOVA) was used for statistical comparisons and Tukey's or Dunnett's *post-hoc* tests for multiple comparisons were used as appropriate, using GraphPad software, San Diego, USA.

Results and discussion

Unlike the ring preparations the intact coronary tree of a non-working trout heart employed in this study had an intact endothelium, resistance vessels and a continuous luminal pressure. A positive autoregulatory index (ArI) was observed in the pressure range of 2.5-3.5 kPa, suggesting the existence of an active vasomotive response probably involving local regulatory mechanisms (Agnisola *et al.*, 1996). Among prostanoids: prostacyclin (PGI₂), defibrotide (which increases the release of endogenous PGI₂), prostaglandin E₂ and 12-HETE elicited dose dependent decreases in the trout coronary resistance. The effect of adenosine on the coronary system of trout was biphasic: at 10⁻⁸ M there was a significant vasoconstriction, which was replaced by a vasodilation at higher concentrations (45% at 10⁻⁵ M). When adenosine perfusion was preceded with the perfusion of the adenosine aspecific inhibitor theophylline, both vasoconstrictory and vasodilatory responses were inhibited (Mustafa & Agnisola, 1998).

The use of specific adenosine agonists, 2-chloroadenosine: *CADO* (A₁), 5'-N-cyclopropyl-carboxyamidoadenosine: *NECA* (A₂), 5'-N-cyclopropyl-carboxyamidoadenosine: *CPCA* (A₂) suggested the presence of both A₁ and A₂ adenosine receptors in trout coronary. The response of A₁ and A₂ agonists in the trout coronary was successfully antagonised by selective A₁-adenosine antagonist 8-phenyltheophylline and A₂-adenosine antagonist 3,7-dimethyl-1-propargylxanthine (DPMX). Perfusion of the coronary tree with 2x10⁻⁵ M 8-bromo-cAMP (stable analogue of cAMP) or forskolin (adenyl cyclase activator) caused a significant vasodilation suggesting the involvement of A₂-receptor mediated adenylyl cyclase system.

L-arginine (L-arg, 10^{-8} M) caused a vasodilative response, which was inhibited by nitric oxide synthase inhibitors (Mustafa et al., 1997). Perfusion with L-arginine and adenosine both brings about increases in nitric oxide release by 25%, which were inhibited by the use of respective antagonists, i.e. *N*-nitro-L-arginine (L-NA) and theophylline respectively. This result was confirmed by the measurement of nitrate (NO_2^-) release as an index of nitric oxide (NO) synthesis in the coronary perfusate (Mustafa & Agnisola, 1998). Involvement of flow dependent decreases in CR via stretch receptors and nitric oxide possibly initiated by adenosine was also investigated. Perfusion with L-NA in presence of Ado minimises the Ado mediated vasodilation. When the flow was held constant the Ado response is halved compared to the Ado response at constant pressure where any change in CR will result in a change in the perfusion flow (Mustafa & Agnisola, 1998).

Conclusion

In an intact perfused coronary system of trout intrinsic vasodilative control mechanisms including the auto-regulatory (pressure), prostanoids (PGI_2 , PGE_2 , and 12-HETE), adenosine and nitric oxide mediated responses are present.

References

- Agnisola, C., Mustafa, T., Hansen, J.K. (1996). Autoregulatory index, adrenergic responses, and interaction between adrenoreceptors and prostacyclin in the coronary system of trout. *J. Exp. Zool.* 275:239-248
- Berne, R.M. (1964). Regulation of coronary blood flow. *Physiol. Rev.* 44:1-29
- Chilian, W. (1997). Local control of coronary vascular resistance. XXXIII international Congress of Physiological Sciences. St. Petersburg, Russia, Abstract No. L063.27
- Levick, J.R. (1991). *An introduction to cardiac Physiology.* London. Butterworth.

- Mustafa, T., Agnisola, C., Hansen J.K. (1997). Evidence for NO-dependent vasodilation in the trout (*Oncorhynchus mykiss*) coronary system. J. Comp. Physiol. 167:98-104
- Mustafa, T., Agnisola, C. (1998). Vasoactivity of adenosine in the trout (*Oncorhynchus mykiss*) coronary system: involvement of nitric oxide and interaction with noradrenaline . J. Exp. Biol. 201:3075-3083

