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# CARDIOVASCULAR DYNAMICS AND ADRENERGIC RESPONSES OF THE RAINBOW TROUT *IN VIVO*

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## SUMMARY

Cardiac output and dorsal aorta, ventral aorta, caudal artery, caudal vein, and subintestinal vein pressures have been directly measured in intact unanaesthetized trout. Cardiac output ($\dot{Q}$) averaged 36·7 ml/kg.min. The pressure drop across the systemic vascular resistance ($R_s$) was approximately twice that across the gill resistance ($R_g$), and a significant positive pressure persisted in the venous system. $\alpha$-Adrenergic blockade revealed a considerable endogenous vasomotor tone resulting from latent adrenergic constriction of $R_s$. Intravenous adrenaline caused a pressor response throughout the circulatory system which has been analysed in detail with the aid of previous studies on isolated parts of the trout circulation. The complex and variable form of the pressor response reflected differential contributions from changes in $\dot{Q}$, $R_g$, and $R_s$. Increases in $R_s$ ($\alpha$-receptor activation) were the principal cause of all pressor responses. $R_g$ usually declined slightly due to passive dilation and/or $\beta$-receptor stimulation, but occasionally increased due to $\alpha$-receptor activation. The cardiac response reflected a varying balance between a direct $\beta$-stimulatory effect of adrenaline on $\dot{Q}$ and an indirect passive inhibition of $\dot{Q}$ by the increase in peripheral resistance. Both effects were mediated through changes in stroke volume. Occasional tachycardia or more frequent reflex bradycardia were minor components of the cardiac response. The *in vivo* actions of other adrenergic agents have been similarly analysed.

## INTRODUCTION

Cardiovascular dynamics under various 'stressing' conditions (exercise, hypoxia, anaemia, anaesthesia, haemorrhage, CO-poisoning) have been studied in greater detail in the salmonids than in any other type of teleost (e.g. Randall, Smith & Brett, 1965; Randall & J. Smith, 1967; Randall & L. Smith, 1967; Holeton & Randall, 1967*a*; Stevens & Randall, 1967*a*; Cameron & Davis, 1970; Holeton, 1971; Wood, 1974*b*; Kiceniuk & Jones, 1977; Smith, 1978). Autonomic influences, especially changes in plasma catecholamines and/or sympathetic activity, have been widely invoked to explain the observed responses. While it is known that blood levels of adrenaline and noradrenaline increase during stress in salmonids (Fontaine, Mazeaud & Mazeaud, 1963;

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Nakano & Tomlinson, 1967; Mazeaud, Mazeaud & Donaldson, 1977), there is almost no information on the *in vivo* cardiovascular actions of catecholamines in these fish. Indeed the only such study remains the work of Randall & Stevens (1967), who recorded changes in dorsal aortic blood pressure and heart rate in Pacific salmon following intravenous adrenaline. Their conclusions were necessarily tentative, as changes in dorsal aortic blood pressure can result from actions at many sites.

The interpretation of cardiovascular responses in the intact teleost is a complex task. As well as directly modifying branchial ($R_g$) and systemic ($R_s$) vascular resistances in the same or opposite directions, a drug will probably also change blood pressures and thus introduce passive alterations in these resistances, may alter cardiac output ($\dot{Q}$), stroke volume, or both, by direct or indirect pathways, may change the resistance of the venous segment, and may bring into play compensatory adjustments to oppose the direct action of the drug. Ideally, direct measurements of blood pressure on either side of $R_g$ and $R_s$, cardiac output, and instantaneous heart rate (and thus stroke volume) are desirable. Knowledge of the active and passive responses of isolated vascular beds and the heart *in vitro* will further aid interpretation. Recently we have recorded such information for adrenergic and cholinergic effects in perfused branchial and systemic preparations of the rainbow trout (Wood, 1974*a*, 1975, 1976, 1977; Wood & Shelton, 1975; Wood, McMahon & McDonald, 1978), while other workers have reported on the isolated trout heart (Bennion, 1968; Gannon & Burnstock, 1969; Gannon, 1971). In the present study, all of the desired *in vivo* measurements have been performed in intact, unanaesthetized trout. The objective was to provide a detailed cardiovascular analysis of adrenergic effects *in vivo* by integrating the present *in vivo* findings with the previous *in vitro* data. A subsequent report will deal with cholinergic effects (C. M. Wood & C. Shelton, in preparation).

## MATERIALS AND METHODS

Rainbow trout (*Salmo gairdneri*; 100–725 g) were acquired, maintained, and acclimated to $14{\cdot}5 \pm 1{\cdot}5$ °C as described previously (Wood, 1974*a*). Sixty-nine animals were employed in the present study. Data on other aspects of cardiovascular function (Mayer waves) in this same group of animals have been reported elsewhere (Wood, 1974*b*).

### I. *Operative procedures*

Fish were anaesthetized with 1:15000 MS-222 on an operating table at the acclimation temperature. Cannulae were implanted in the buccal cavity, ventral aorta, dorsal aorta, caudal artery, caudal vein, and subintestinal vein, and a flow probe was placed around the ventral aorta. All trout were fitted with buccal, dorsal aorta, and subintestinal vein cannulae; the other catheters and the flow probe were added in various combinations. All blood vessel catheters were filled with Cortland saline (Wolf, 1963) containing 20 I.U./ml of sodium heparin (Sigma).

The buccal cavity was cannulated with Portex PP200 as described by Holeton & Randall (1967*a*) in order to monitor ventilation. The dorsal aorta was cannulated at the level of the first gill arch by the method of Smith & Bell (1964); a regular poin

no. 22 needle joined to PP50 was used in small fish ( < 200 g) and a Huber point no. 21 with PP60 in larger ones. In a few fish the ventral aorta was cannulated through the median ventral surface of the isthmus (Holeton & Randall, 1967*a*). More frequently, the ventral aorta was directly exposed by dissection and cannulated in an anterior direction with the sharpened tip of PP50 which had been softened by gentle heating and pulled to about two-thirds of its normal diameter. The elasticity of the vessel wall prevented leakage, and the cannula was held in place by a PP190 sleeve via which it was led through the body wall. The wound in this and other incisions was tightly closed with silk sutures. Results with the two techniques were comparable, but the latter proved more durable. The caudal artery and caudal vein were cannulated in the peduncle with a regular point no. 22 needle bent at 120° and attached to PP50 (Wood & Randall, 1971). It was not possible to cannulate both the caudal artery and the caudal vein in the same fish. The subintestinal vein was exposed by dissection in the ventral pelvic midline, cannulated anteriorly with 1 cm of PP10 attached to a length of PP90, and tied off posteriorly in a procedure similar to that of Randall & Stevens (1967). This cannula served mainly for injection.

The ventral aorta was exposed and fitted with a Biotronex cuff type electromagnetic flow probe for direct measurement of cardiac output ($\dot{Q}$). For valid flow records, it was essential that the extremely elastic vessel wall be in contact with the probe throughout the cardiac cycle. The probe was positioned as far anteriorly as possible at the point where the ventral aorta leaves the pericardial cavity and runs dorsally for a short distance. This location also allowed the probe to lie flat against the underlying tissue so that its lead could be passed out of the incision anteriorly along the isthmus without a bend and be firmly sutured to adjacent muscles. Probe apertures of 1·0, 1·5 and 2·0 mm were used for fish of (approximately) 150–300, 300–500 and 500–725 g. The separate earth lead of the probe was sutured into the ventral body wall posterior to the heart. Flow probe implantation necessitated rupture of the anterior end of the pericardium and transection of the pectoral girdle. Experimental flow data were only taken from animals in relatively good condition as judged from ventilation and the form of the flow trace (see below). Values for other cardiovascular parameters in these trout were comparable to those in fish not bearing probes. Implantation of both a flow probe and a ventral aorta catheter proved impractical in fish of the size used here. Thus aortic pressures and flows could not be recorded simultaneously.

### II. *Experimental chambers*

After operation the animal was placed in a shielded Perspex chamber (volume = 1·8 or 5·1 l for fish respectively less than or greater than 450 g) served by a flow-through aerated water supply of $\approx$200 ml/100 g.min at 14·5 $\pm$ 1·5 °C. To avoid tangling and displacement of the many catheters and leads, the fish was immobilized on a pegboard restraint placed on the bottom of the chamber (Davis & Cameron, 1971), which restricted all but ventilatory movements. A recovery period of at least 6 h was allowed, and data were taken up to 6 days post-operatively.

### III. *Recording techniques*

All of the catheters were 45 cm in length and connected to either Sanborn 267 BC or Statham P23 DC transducers; the pressure signals were amplified by Sanborn

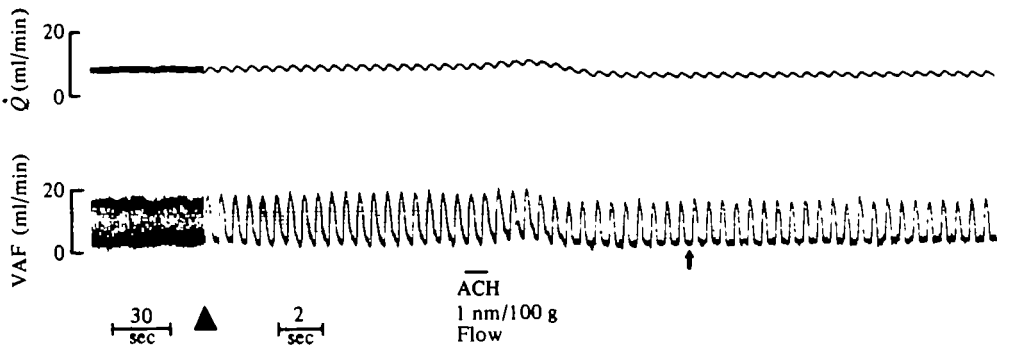


Fig. 1. Original records of ventral aortic flow (VAF = phasic flow) and mean cardiac output ($\dot{Q}$ = mean flow) illustrating the method used to determine flow zero *in vivo*. Injection of ACH (1 nmole/100 g) into the subintestinal vein reduced cardiac stroke volume so that the phasic flow trace became horizontal (= zero flow, arrow) during diastole. ▲ = change in recorder speed. Weight = 285 g.

350–1100 C carrier pre-amplifiers. Simultaneous records of phasic and mean blood flows were taken at frequency responses of 20 and 0·5 c/s respectively on a Biotronex BL410 system. Instantaneous heart rate was obtained by triggering a linear output rate-meter from a blood pressure or flow signal. All measurements were displayed on a Sanborn 6-channel chart recorder writing on rectangular co-ordinates.

Flow probes were calibrated using isolated segments of ventral aorta perfused at known flow rates with heparinized trout blood or Cortland saline. There were no significant differences in probe sensitivity to the two perfusates. Because of the lack of space around the aorta, mechanical occluders could not be used to establish zero flow, so the method of Jones *et al.* (1974) was adopted. Subintestinal injection of acetylcholine chloride (1 nmole/100 g) reduced cardiac stroke volume so that the phasic flow trace became horizontal between systoles (Fig. 1). That this levelling represented a true flow zero could be confirmed by temporarily stopping the heart with 10–32 nmole/100 g acetylcholine, though the latter procedure was performed only occasionally when zero was in doubt. The flow trace zero was determined periodically with 1 nmole/100 g acetylcholine throughout an experiment, followed by a recovery period of at least 15 min before any experimental treatment.

## IV. *Drugs*

Drugs were administered on a body weight basis in a volume of 0·05 ml saline/100 g. Injections were made through short sidearms on the pressure measuring cannulae and a brief pressure surge on the record accurately marked the point of injection. Unless otherwise stated, drugs were injected via a single rapid infusion (< 1 s) into the subintestinal vein. Drugs were kept in the dark at room temperature and renewed every 1–2 h because of their lability. The following agents were used: l-adrenaline bitartrate (AD), l-noradrenaline bitartrate (NAD), l-isoprenaline bitartrate (ISO) l-phenylephrine hydrochloride (PHE), yohimbine hydrochloride, propranolol hydrochloride, acetylcholine chloride (ACH), atropine sulphate (all Sigma) and phenoxybenzamine hydrochloride (Smith, Kline and French).

## RESULTS

### I. *Basic cardiovascular parameters*

In trout in relatively good condition with normal heart rates (> 60/min), ventral aortic flow, though extremely pulsatile, did not fall to zero between systoles (Figs. 1, 2A, B). Only in trout with low or irregular heart beats (usually in poor condition) were zero flows detected. After periods of activity, mean ventral aortic flow ($= \dot{Q}$) was elevated up to 2-fold by increases in stroke volume with little or no change in heart rate (Fig. 2C). Similarly as fish tended to become progressively anaemic over several days after setting up (haematocrit falling from 15–25% to 5%, there were 2- to 4-fold increases in $\dot{Q}$ with only slight (< 10%) increases in cardiac rate. The relationship between body weight and resting cardiac output, taken at the highest haematocrit observed in each fish, is shown in Fig. 3. Both this relationship ($r = 0{\cdot}78$, $P < 0{\cdot}001$) and the scatter in it were largely due to variations in stroke volume rather than rate.

Ventilatory interactions on the ventral aortic flow trace were frequently seen. The phenomenon consisted of an initial small negative component, reducing the normal flow at that point in the cardiac cycle (and occasionally causing reversals), followed by a larger positive component augmenting the flow. A 'scalloping' pattern resulted on the trace as the interaction gradually drifted through the flow cycle due to the difference between cardiac and respiratory rates. Fig. 2A presents one of the most pronounced examples seen of the phenomenon, and Fig. 2B a more normal record, though in all cases, the basic pattern was identical. Flow changes were associated in a fixed way with the breathing movements. The negative component was always concurrent with the buccal pressure peak, and the positive component with the down-stroke of the buccal pressure and its following lower plateau. If the heart stopped, these flow changes associated with breathing gradually disappeared over 3–4 breathing cycles as the ventral aorta became depleted of blood. It seems likely therefore that this interaction is not an artifact caused by breathing-induced displacement of the probe, but rather a real effect causing a moderate net increase in blood propulsion, as in some elasmobranchs (Johansen, Franklin & Van Citters, 1966). The mechanism may be direct mechanical compression of the ventral aorta by the branchial muscles, an aspiratory effect of external water pressure reversal, or a direct alteration of $R_g$ (Hughes, 1972).

Cardiovascular and ventilatory parameters recorded from resting trout are summarized in Table 1. The relatively low haematocrits reflected blood loss both during and after surgery (normal haematocrit = 20–40%). The pressure gradients across various parts of the circulation derived from simultaneous measurements on each side of the resistance in question are listed separately because these values differ slightly from the gradients which can be calculated from the mean blood pressure data from all the animals. The pressure drop across the gills was approximately one half that across the systemic circulation, and a significant positive pressure persisted in the caudal vein. Only a very slight pressure drop occurred along the length of the dorsal aorta (dorsal aorta *v.* caudal artery) as would be expected in a large conducting artery, and pressure changes at the two points were always identical (Fig. 4A, C). In

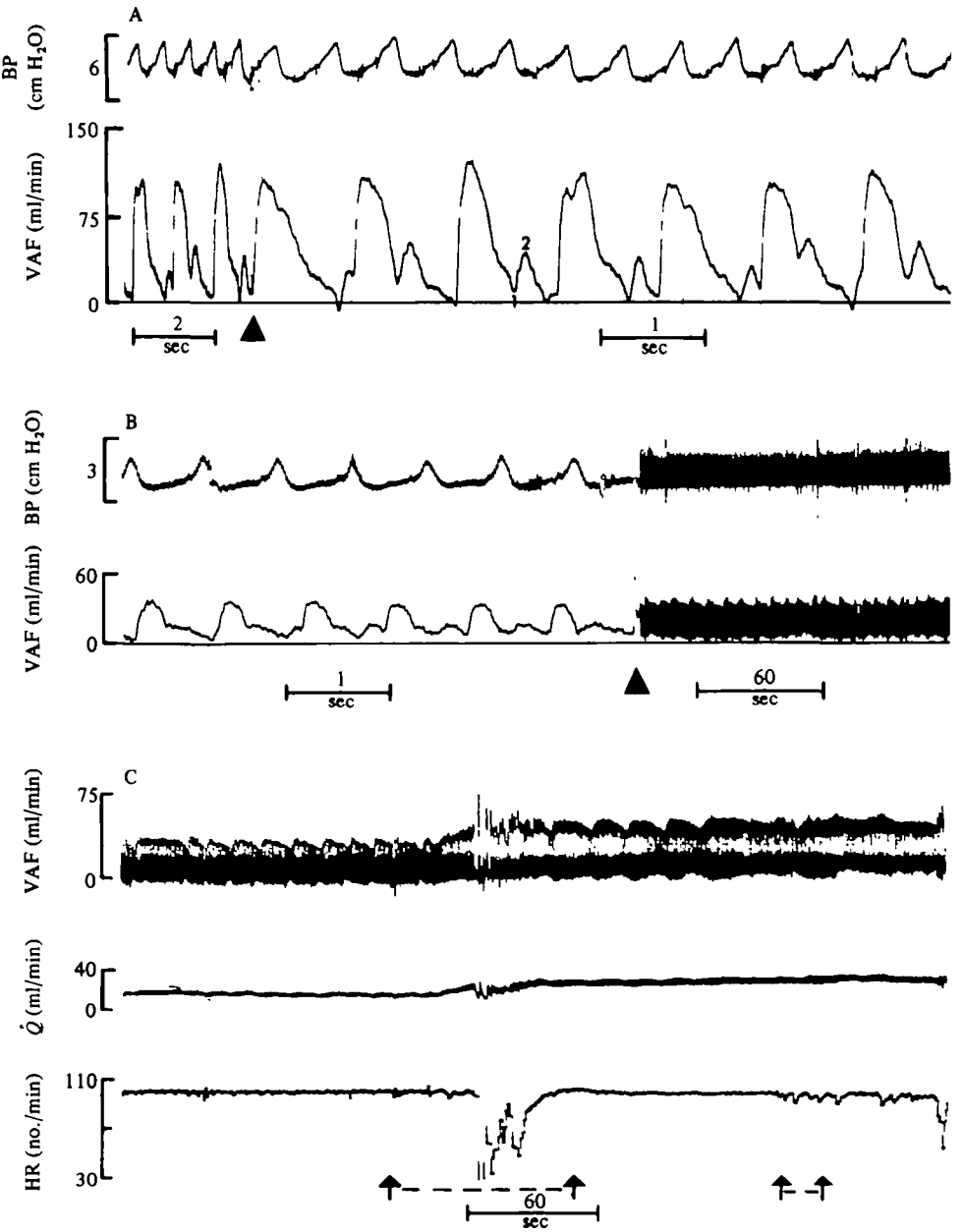


Fig. 2. Original records of ventral aortic flow and other parameters. VAF = ventral aortic flow; BP = buccal pressure; $\dot{Q}$ = mean cardiac output; HR = instantaneous heart rate; ▲ = change in recorder speed. (A) Pronounced interaction between ventilation and VAF. Numbers 1 and 2 indicate respectively the negative and positive components of the interaction. Note the constancy of position of these events relative to the BP trace and occasional reversals (flow less than zero) caused by the negative component. Weight = 718 g. (B) Interaction of more normal magnitude. Note 'scalloping' pattern on the VAF trace (at slow chart speed) caused by the interaction. Weight = 543 g. (C) Typical effects of struggling activity on $\dot{Q}$. Arrows indicate two periods of activity. Note the large increase in $\dot{Q}$ (via stroke volume) occurring during and after the struggling, with no increase in HR. Weight = 681 g.

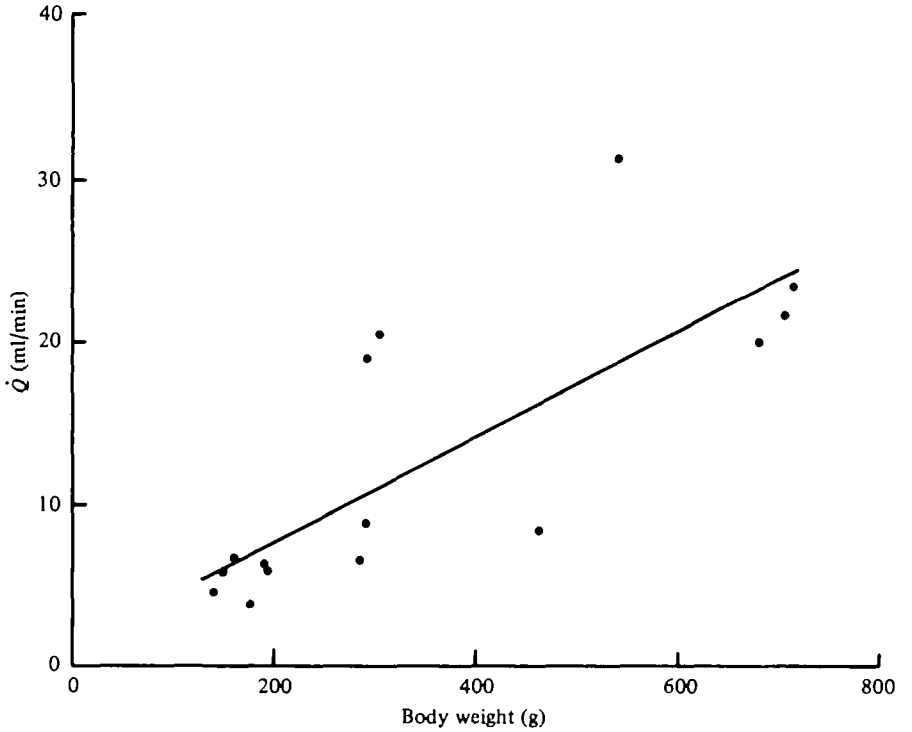


Fig. 3. Relationship between mean cardiac output ($\dot{Q}$, ml/min) and body weight (W, g) in 15 resting trout. The equation of the regression line is $\dot{Q} = 0{\cdot}032W + 1{\cdot}45$ ($r = 0{\cdot}78$, $P < 0{\cdot}001$).

Table 1. *Cardiovascular and respiratory parameters in resting trout: means* ± 1 S.E. ($N$)

| | | |
|---|---|---|
| Ventral aortic pressure (cm $H_2O$) | Systolic | 58·0 ± 3·3 (14) |
| | Diastolic | 34·7 ± 2·3 (14) |
| | Mean | 42·5 ± 2·4 (14) |
| Dorsal aortic pressure (cm $H_2O$) | Systolic | 40·6 ± 1·1 (58) |
| | Diastolic | 31·4 ± 0·9 (58) |
| | Mean | 34·5 ± 0·9 (58) |
| Caudal artery pressure (cm $H_2O$) | Systolic | 39·1 ± 1·9 (17) |
| | Diastolic | 30·4 ± 1·6 (17) |
| | Mean | 33·3 ± 1·7 (17) |
| Caudal vein pressure (cm $H_2O$) | — | 5·6 ± 0·4 (23) |
| Pressure gradients (cm $H_2O$) | Ventral aorta–dorsal aorta | 12·6 ± 1·5 (11) |
| | Dorsal aorta–caudal artery | 2·0 ± 0·2 (17) |
| | Dorsal aorta–caudal vein | 26·2 ± 1·6 (18) |
| Cardiac output (ml/kg.min) | — | 36·67 ± 3·93 (15) |
| Cardiac stroke volume (ml/kg.beat) | — | 0·462 ± 0·047 (15) |
| Heart rate (beats/min) | — | 78·6 ± 1·6 (62) |
| Pressure pulsatility (pulse/mean) | Ventral aorta | 0·52 ± 0·04 (14) |
| Pressure pulsatility (pulse/mean) | Dorsal aorta | 0·27 ± 0·03 (58) |
| Pressure pulsatility (pulse/mean) | Caudal artery | 0·26 ± 0·04 (17) |
| Flow pulsatility (pulse/mean) | Ventral aorta | 1·89 ± 0·16 (14) |
| Buccal pressure amplitude (cm $H_2O$) | — | 2·00 + 0·11 (53) |
| Ventilation rate (breaths/min) | — | 92·9 ± 1·7 (52) |
| Haematocrit | — | 16·5 ± 1·1 (30) |

Note: mean arterial pressures have been calculated as (1 systolic + 2 diastolic)/3 (Burton, 1972).

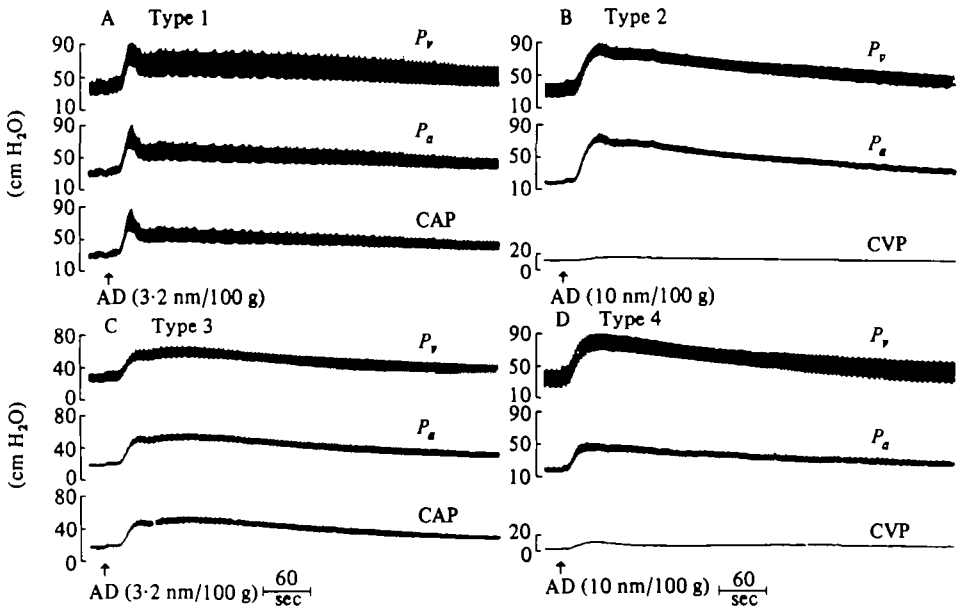


Fig. 4. Original records showing pressor responses of (A) type 1, (B) type 2, (C) type 3, and (D) type 4 in response to subintestinal injection of AD in four different fish. $P_v$ = ventral aortic pressure; $P_a$ = dorsal aortic pressure; CAP = caudal artery pressure; CVP = caudal vein pressure.

a few trout with chronically high dorsal aortic blood pressure (45–60 cm $H_2O$), caudal vein pressure was also elevated (10–15 cm $H_2O$), and reached these levels in all fish during struggling or drug induced pressor events (Fig. 4B, D). In undisturbed fish, subintestinal vein pressures were within 1 cm $H_2O$ of caudal vein pressures, but responded only slowly during pressor events elsewhere in the animal (probably due to the occlusive nature of the cannulation). Pressure pulsatility in the ventral aorta was considerably lower than flow pulsatility, reflecting the considerable compliance of the ventral aorta. Pressure pulsatility was approximately halved beyond the gills in the dorsal aorta and was identical at the two ends of this conducting vessel. The venous pressure was non-pulsatile.

*II. The effects of adrenaline (AD) on blood pressure*

Subintestinal injection of AD, a dual $\alpha$- and $\beta$-adrenergic agonist, caused dose-dependent pressor events in the ventral aorta, dorsal aorta, and caudal vein (Fig. 4) with a threshold of 10–100 pmole/100 g. The maximum of the dose/response curve lay beyond the tolerance of the animal, for doses $\geqslant$ 32 nmole/100 g caused arterial pressure rises over 100 cm $H_2O$ and branchial haemorrhage. The form of the pressor response varied considerably both between and within fish from day to day, but remained reasonably consistent within a dose/response curve determined on a single animal over several hours. Four basic response configurations (for convenience labelled types 1, 2, 3 and 4) were identified in an analysis of 104 AD induced pressor events in 11 fish fitted with patent dorsal and ventral aortic catheters (Figs. 4, 5).

Type 1 responses (Figs. 4A, 5A) were the commonest (32%). Here dorsal aortic ($P_a$) and ventral aortic ($P_v$) pressures increased rapidly by similar amounts to a distinct

initial peak, followed by a sharp drop, a definite plateau, and a final gradual decline. Type 2 responses (28%; Figs. 4B, 5B) were initially the same, but the plateau was reduced or non-existent so that the sharp decline was immediately followed by a gradual decline. Type 3 responses (26%; Figs. 4C, 5C) were also initially the same, but both $P_a$ and $P_v$ continued to increase more gradually to a much later peak or plateau before a final gradual decline. Type 4 responses were the rarest (14%; 2 animals only); there was a single peak followed by a monophasic gradual decline in both $P_a$ and $P_v$. However, the elevation of $P_v$ was much greater (up to 2 times) than that of $P_a$. In all four types, the caudal vein pressure increased to a maximum of 20 cm $H_2O$ with a peak coincident with or slightly later than that in $P_a$ (Fig. 4B, D).

III. *The effects of AD on cardiac output*

Simultaneous measurements of ventral aortic flow and $P_a$ were made during 42 AD-induced pressor events in eight fish. In the commonest pattern (Fig. 6A), there was an initial slight increase in $\dot{Q}$ followed by a fall close to or below the original baseline as $P_a$ rose. Finally $\dot{Q}$ rose again above baseline as the initial pressor peak subsided. This sequence was always associated with a type 1 or 2 response in $P_a$. Less frequently, a similar pattern lacking the final increase in $\dot{Q}$ occurred, always in conjunction with a type 2 response (Fig. 6B). In other preparations, a decrease in $\dot{Q}$ was completely dominant, commencing at the start of the pressor response and persisting throughout it (Fig. 6C). The associated pressor response was again type 2. In a very few cases a flow increase was completely dominant, $\dot{Q}$ increasing steadily during the pressor event (Fig. 6D). The accompanying $P_a$ rise seemed to resemble type 4, although the lack of $P_v$ measurements made this conclusion tentative.

The variability in the $\dot{Q}$ response was due to differing balances between a flow increasing effect and a flow decreasing effect. The former most probably represented a direct stimulatory action of AD on the heart and the latter a passive reduction in $\dot{Q}$ due to the elevated peripheral resistance against which the heart must pump during pressor events. On this basis, an analysis of the four types of pressor response to AD was feasible.

IV. *Analysis of the haemodynamic response to AD*

In this analysis, the trout circulation is considered as two resistances ($R_g$ and $R_s$) perfused in series at variable flow ($\dot{Q}$) by the heart. Two ratios are useful in separating various components of the response: (i) mean $P_v$/mean $P_a$ is essentially independent of $\dot{Q}$ and entirely dependent on $R_g/R_s$ (i.e. $P_v/P_a = 1 + R_g/R_s$). (ii) Mean $\Delta P_v$/mean $\Delta P_a$ (relative to pre-injection baseline) at constant $\dot{Q}$ will equal 1·0 if only $R_s$ increases, will exceed 1·0 if both $R_g$ and $R_s$ increase, and will be less than 1·0 if $R_g$ decreases while $R_s$ increases. However increases or decreases in $\dot{Q}$ will tend respectively to raise or lower $\Delta P_v/\Delta P_a$ in addition to those changes caused by alteration of $R_s$ and $R_g$. Very small pressure changes, reflecting injection volume effects, occurred over the first 0–20 s in all response types. Changes in $\Delta P_v/\Delta P_a$ were erratic and unreliable during this period and so have been neglected in the analysis.

(i) *Type* 1 (Fig. 5A). $P_v/P_a$ steadily decreased during the initial pressor peak, indicating a fall in $R_g/R_s$. As $\Delta P_v$ and $\Delta P_a$ were of similar size, this largely reflected

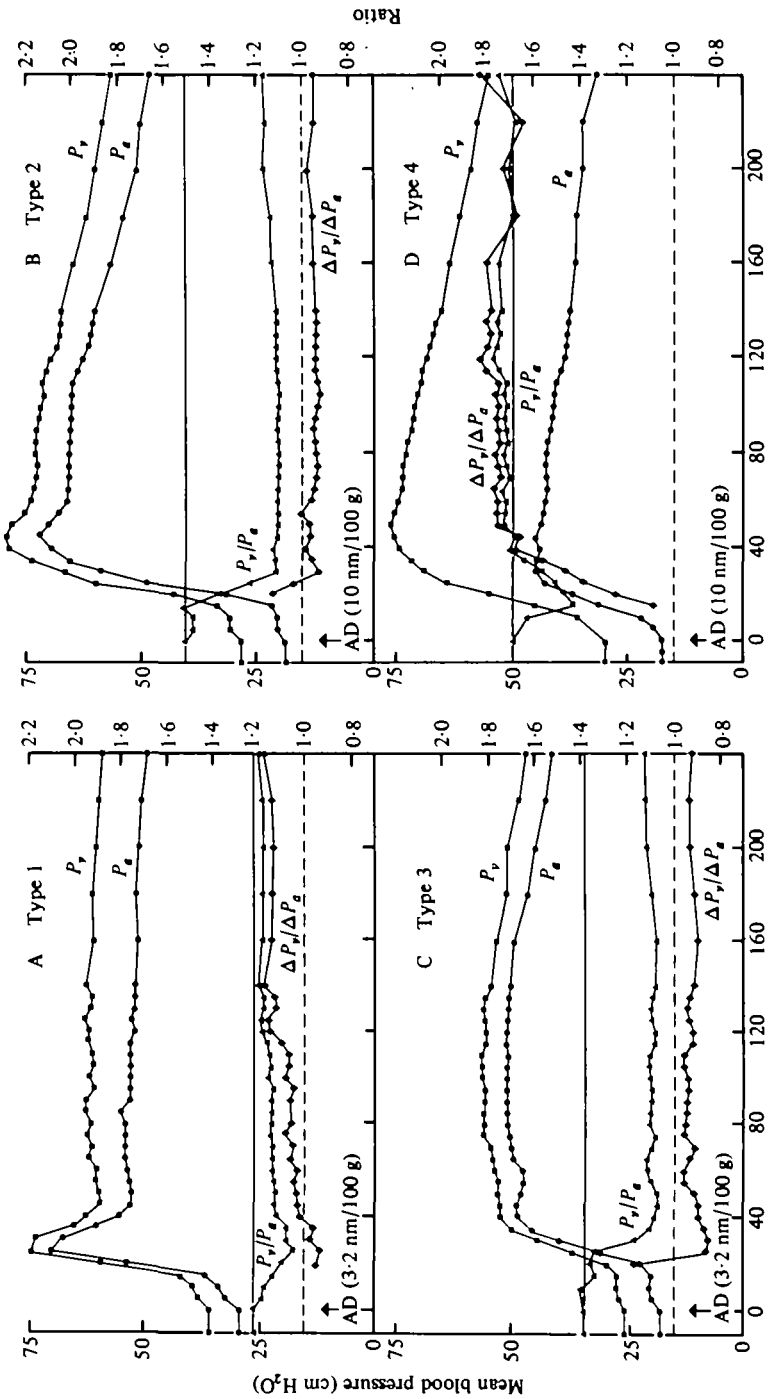


Fig. 5. Analyses of pressor responses to AD of (A) type 1, (B) type 2, (C) type 3, and (D) type 4 in terms of mean pressures (1 systolic + 2 diastolic)/3, $\Delta P_v/\Delta P_a$ and $P_v/P_a$. Data from same respective parts of Fig. 4. Broken line indicates a ratio of 1·0, a value of importance in the $\Delta P_v/\Delta P_a$ analysis. Solid line indicates original value of $P_v/P_a$ before injection of AD, a value of importance in the $P_v/P_a$ analysis. See text for details. Abbreviations as in Fig. 4.

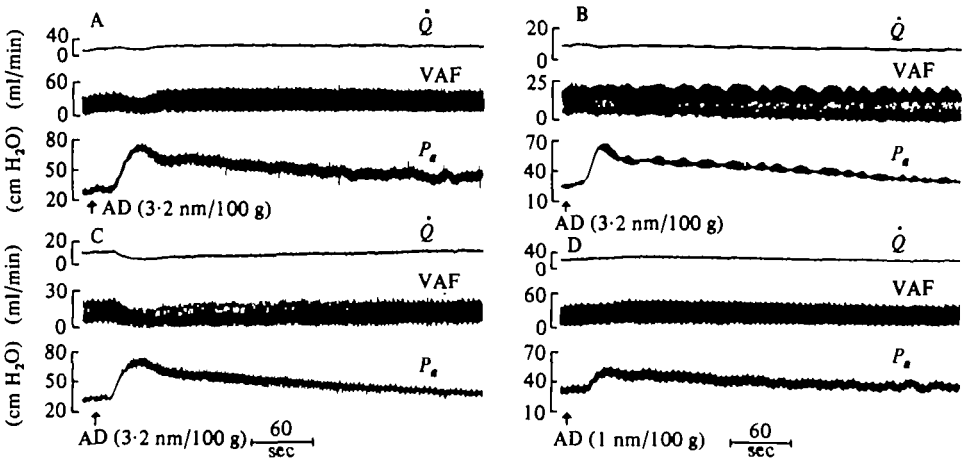


Fig. 6. Original records showing four different patterns of response in ventral aortic flow (VAF) and mean cardiac output ($\dot{Q}$) in response to subintestinal injections of AD. (A) and (D): weight = 543 g; (B) weight = 285 g; (C) weight = 305 g.

an increase in $R_s$, though an accompanying decrease in $R_g$ may also have occurred (i.e. $\Delta P_v/\Delta P_a < 1$). During this period, $\dot{Q}$ probably falls passively (e.g. Fig. 6A). The initial pressor peak declines as the maximum effect of AD on $R_s$ passes, and $\Delta P_v/\Delta P_a$ rises above 1·0 due largely to the later increase in $\dot{Q}$ (Fig. 6A), which now plays a significant role in the pressor event. As the persistent effect of AD on $R_s$ (and perhaps $R_g$) gradually declines, and $P_v/P_a$ returns towards its original level, the elevation of $\dot{Q}$ compensates for the decline in $R_s$, resulting in a plateau of pressure maintained for some time.

(ii) *Type* 2 (Fig. 5B). The events during the initial pressor peak are similar to those in Type 1 (rise in $R_s$, possible fall in $R_g$, and passive decrease in $\dot{Q}$). However, unlike type 1, $\Delta P_v/\Delta P_a$ does not rise after the pressor peak, indicating that there is no later elevation of $\dot{Q}$ (e.g. Fig. 6B, C). Consequently, there is no pressor plateau. In the example shown, $P_v/P_a$ remains at a minimum for some time, and thus the increase in $R_s$ is well maintained, resulting in only a slowly declining pressor effect. In other type 2 responses $P_v/P_a$ returned towards the original level more rapidly, and the pressure fell more rapidly.

(iii) *Type* 3 (Fig. 5C). The analysis of this type is uncertain because no clear-cut examples of it were seen in the trout in which both $P_a$ and $\dot{Q}$ were measured. The events may be similar to those of type 2, except that the constrictory effect of AD on $R_s$ develops more slowly, causing a later peak or plateau in pressure. The great similarity in the $P_v/P_a$ and $\Delta P_v/\Delta P_a$ changes between types 2 (Fig. 5B) and 3 (Fig. 5C) supports this interpretation. Alternatively, or in addition, the later pressure peak could result from a pronounced late rise in $\dot{Q}$ as in type 1.

(iv) *Type* 4 (Fig. 5D). This form obviously differs considerably from types 1, 2 and 3. There is an initial fall in $P_v/P_a$ of uncertain genesis (fall in $R_g$ and/or rise in $R_s$), but by the pressure peak this ratio returns to its original level. Meanwhile $\Delta P_v/\Delta P_a$ steadily increases, which probably reflects a progressive elevation of $\dot{Q}$ throughout the period (e.g. Fig. 6D). The $\dot{Q}$ elevation partially accounts for the much

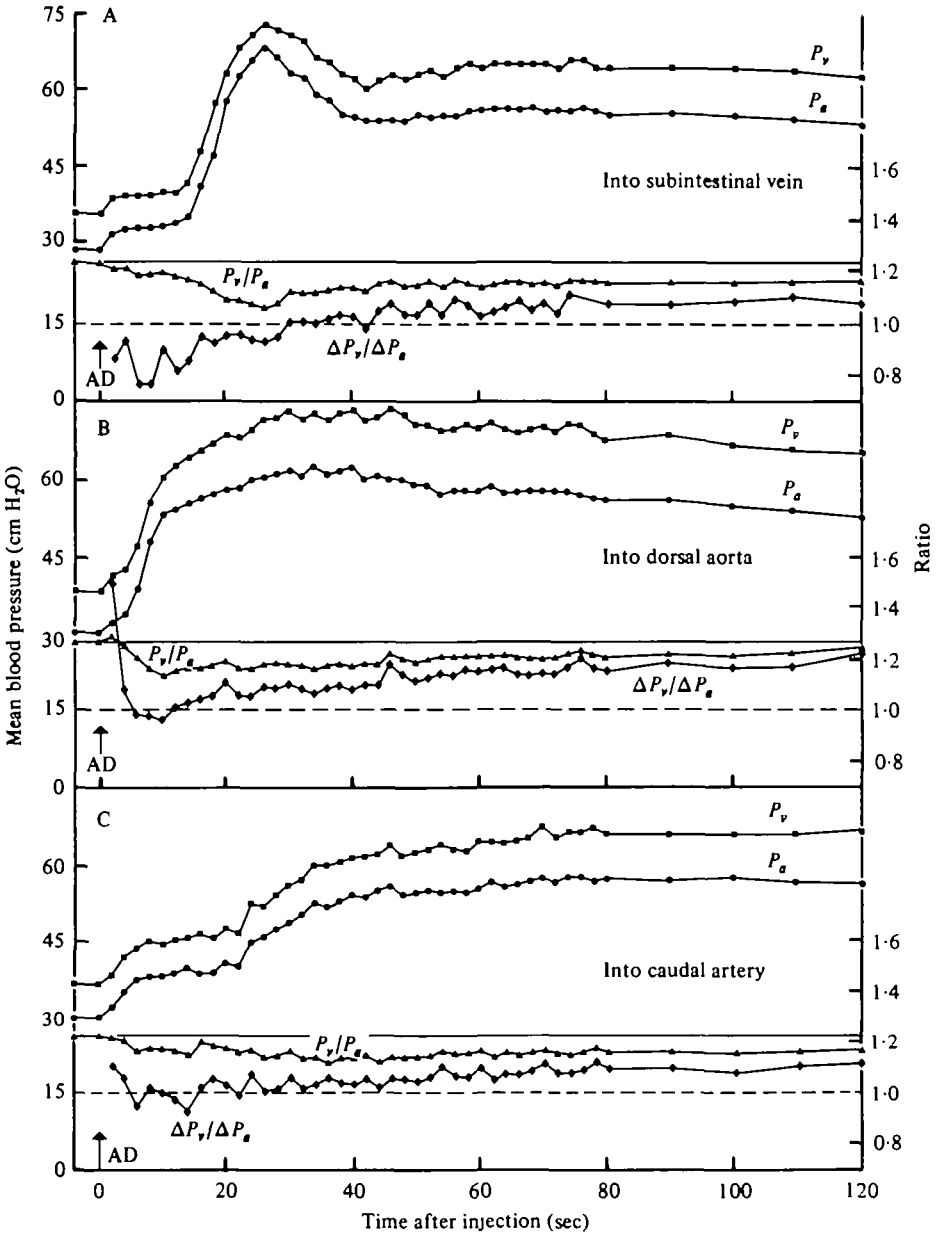


Fig. 7. Pressor responses in ventral ($P_v$) and dorsal aortic ($P_a$) pressures to injections of AD (3·2 nmole/100 g) into (A) the subintestinal vein, (B) the dorsal aorta; and (C) the caudal artery of the same fish. Analyses in terms of mean pressures, $\Delta P_v/\Delta P_a$, and $P_v/P_a$. See Fig. 5 for details. Weight = 380 g.

greater pressure rise in the ventral aorta than in the dorsal aorta. However an increase in $R_v$ must also occur because $P_v/P_a$ rises above its initial level while $\Delta P_v/\Delta P_a$ stays well above 1·0.

Injection of AD into different points in the circulation, so that it reached various sites in different sequence, also aided interpretation. Similar results were obtained

three such experiments, all on fish showing type 1 responses (e.g. Fig. 7). Subintestinal injection of AD caused a classical type 1 response with a delay of 14 s until the start of the pressor peak (Fig. 7A). This latency presumably represents the time for the drug to reach and constrict $R_s$. Prior to and during the initial pressure rise, there was a slight decrease in $P_v/P_a$ and a $\Delta P_v/\Delta P_a$ of less than 1·0, indicating a definite reduction in $R_v$. When AD was injected into the anterior dorsal aorta (pressure measured from the caudal artery; Fig. 7B), the pressor response commenced almost immediately, $\Delta P_v/\Delta P_a$ did not fall significantly below 1·0, and the absolute decline in $P_v/P_a$ was smaller than with subintestinal administration. These effects reflect AD immediately constricting $R_s$ without an effect on $R_v$. Injection of AD into the caudal artery (pressure measured from the anterior dorsal aorta; Fig. 7C) caused an initial small pressor effect, probably due to a local effect of AD on $R_s$ in the caudal region only. There followed a more pronounced pressure rise after 22 s due to a delayed action of AD on $\dot{Q}$ and/or $R_s$ after passage through the venous circulation, heart and gills.

For simplicity, the preceding analyses have incorporated the venous segment into $R_s$. However, injection of AD into the caudal vein in a few trials resulted in an immediate small rise in venous pressure (5–10 cm $H_2O$) before systemic pressor events occurred. Thus the normal pressor response in the caudal vein (e.g. Fig. 4B, D) must reflect a direct venoconstrictory action of AD as well as $\dot{Q}$ elevation.

*V. Analysis of the cardiac events accompanying the AD pressor response*

Occasionally, pressor doses of AD caused a slight tachycardia ($\approx$ 10%) but more usually there was either no change in rate or a bradycardia of variable degree and duration. Fig. 8A shows a well-defined example. After the muscarinic cholinergic antagonist atropine (100 nmole/100 g), the bradycardia was severely reduced or abolished and the pressor response to AD either unaffected or potentiated (Fig. 8B). Atropine itself generally had no effect on heart rate but tended to reduce $\dot{Q}$ by a depressant effect on stroke volume (C. M. Wood and G. Shelton, in preparation). However, atropine did not affect the pattern of $\dot{Q}$ alteration associated with a particular type of pressor response. Thus in Fig. 9, the initial slight increase, the decrease during the peak of the pressor event, and the final pronounced rise in $\dot{Q}$ persisted after atropine, but the slight bradycardia was abolished. From experiments of this nature it was evident that relative to stroke volume alterations, bradycardia usually had only a small effect on the overall $\dot{Q}$ changes caused by AD. Use of the $\beta$-adrenergic antagonist propranolol proved uninformative (see below). The $\alpha$-adrenergic antagonist yohimbine (100 nmole/100 g) had negligible effect on resting $\dot{Q}$ but blocked pressor responses to AD (see below); formerly pressor doses of AD (now subthreshold) which had previously reduced $\dot{Q}$ now either stimulated $\dot{Q}$ or had no effect.

VI. *Other adrenergic agonists*

(i) *Noradrenaline.* NAD, the other naturally occurring $\alpha$- and $\beta$-adrenergic agonist, caused dose-dependent pressor events in the ventral aorta, dorsal aorta, and caudal vein (Fig. 10) with a similar threshold and slope to the dose/response curve as with

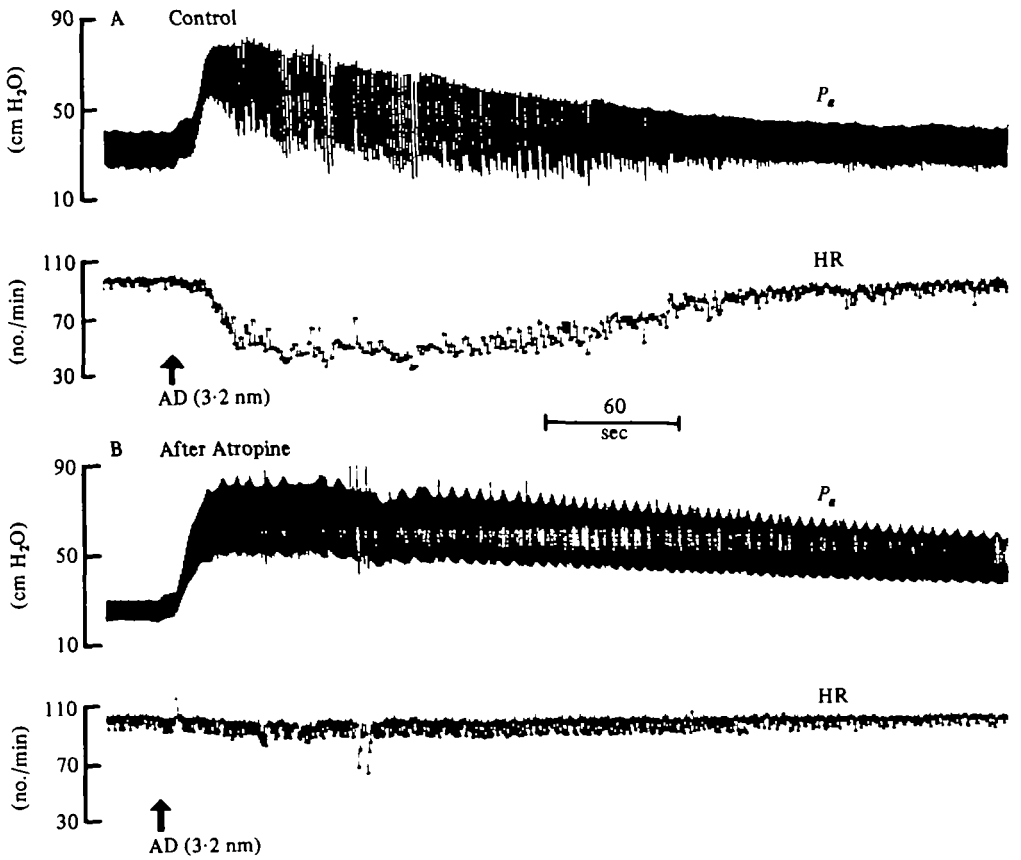


Fig. 8. Original records showing a pronounced bradycardia during a pressor response to AD and the effect of atropine (100 nmole/100 g) on the phenomenon. Note the virtual abolition of the bradycardia and potentiation of the pressor response by atropine. $P_a$ = dorsal aortic pressure; HR = instantaneous heart rate.

AD. Heart rate effects and the influence of atropine on NAD responses were also similar. NAD responses were always type 2, even in fish showing other type responses to AD (e.g. Fig. 10). In the only two fish tested for $\dot{Q}$ changes, NAD caused a decrease in $\dot{Q}$ during the pressor peak followed by a return to baseline; $\dot{Q}$ responses to AD were identical in these animals. However, in many experiments in which only pressure was measured, the increase in pulse pressure in both $P_v$ and $P_a$ with NAD was much less than with AD. This may indicate that NAD is less effective in stimulating stroke volume (and therefore $\dot{Q}$), thereby explaining the predominance of type 2 responses (see section IV(ii) above).

Pressor potency comparisons between NAD and AD were performed in seven animals by the dose/response curve method of Furchgott (1967). Overall, NAD was slightly less potent (Table 2). The results were surprisingly variable but demonstrated a consistent trend: whether NAD was more or less potent than AD in an individual fish, its potency relative to AD was always greater in raising $P_a$ than in raising $P_v$.

(ii) *Isoprenaline.* ISO (1–10 nmole/100 g), a selective $\beta$-agonist, produced a biphasic effect, first raising and then lowering both $P_a$ and $P_v$ by small amounts (1–10 c

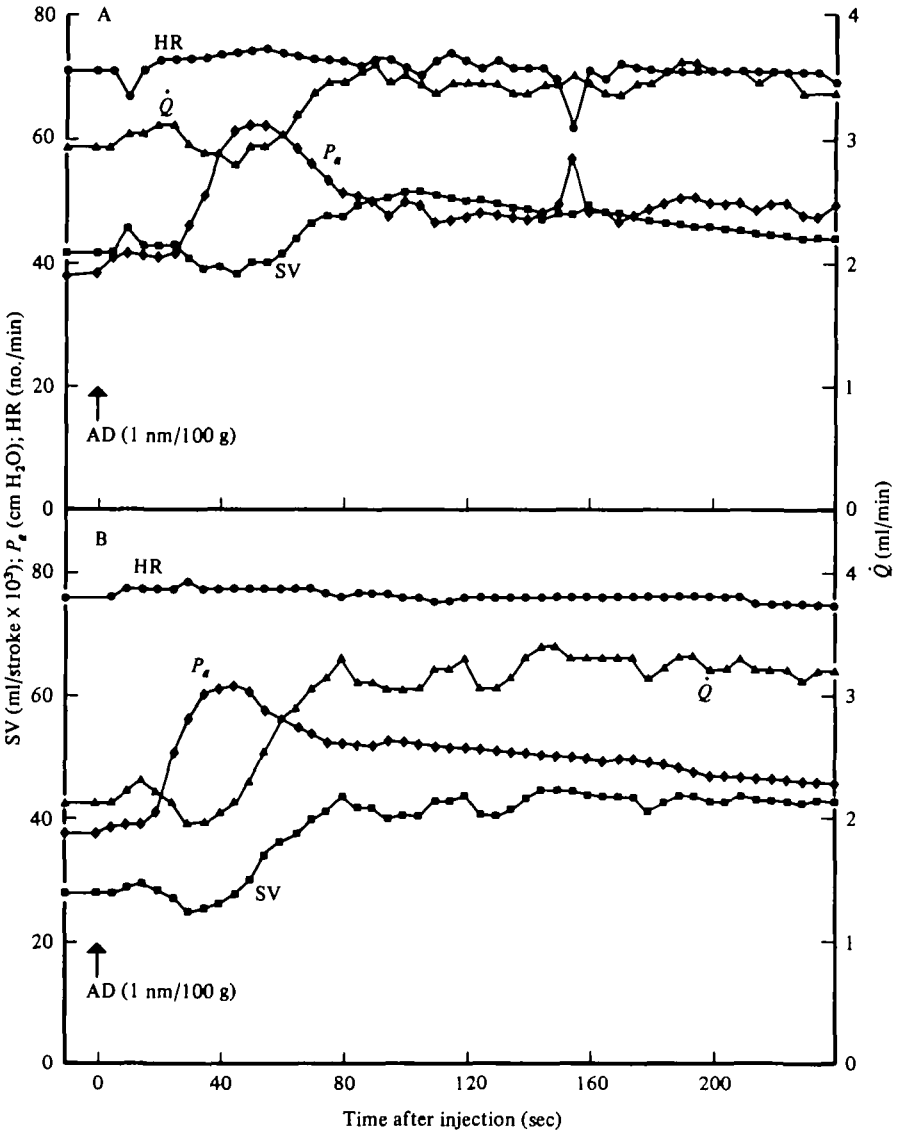


Fig. 9. Simultaneously recorded changes in mean cardiac output ($\dot{Q}$), stroke volume (SV), instantaneous heart rate (HR), and dorsal aortic blood pressure ($P_a$) in response to a subintestinal injection of AD (1 nmole/100 g) in a trout before (A) and after (B) atropine (100 nmole/100 g). Note persistence of basic changes in $\dot{Q}$ and SV but abolition of the slight bradycardia after atropine. Note also the very small initial increase in heart rate caused by AD both before and after atropine. Weight = 177 g.

$H_2O$; Fig. 11 A, B). In some fish the former influence dominated, and in others the latter. There was no effect on caudal vein pressure and heart rate either increased very slightly or remained unchanged. A rapidly developing tachyphylaxis to ISO (3–4 doses of 1–10 nmole/100 g produced complete desensitization) prevented accurate determination of threshold or dose/response relationships. Pressor events in $P_a$ and [redacted] were usually of similar size and associated with an increased pulse pressure (Fig.

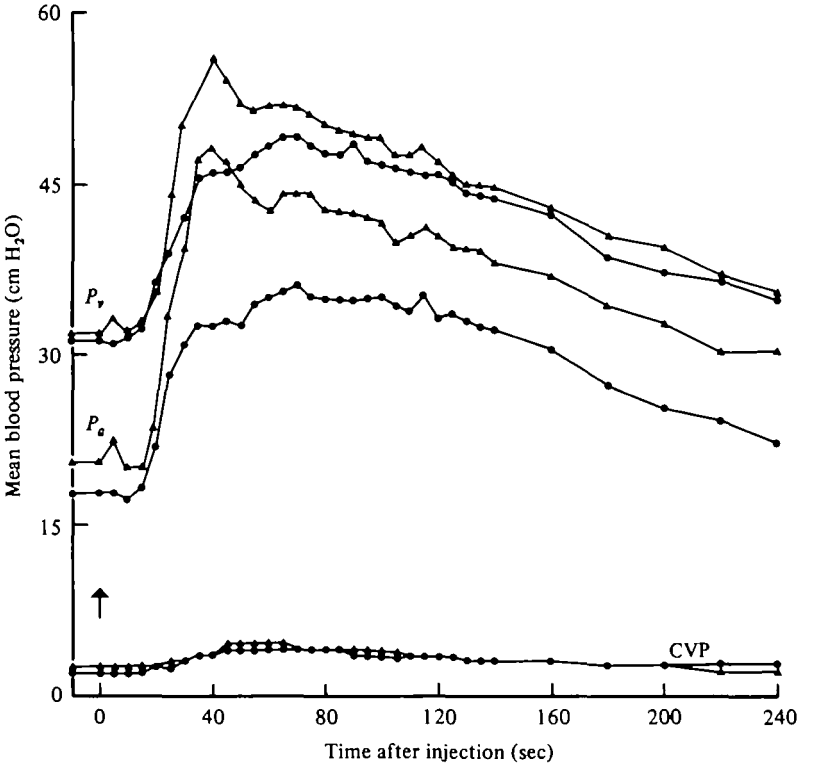


Fig. 10. A comparison of the pressor responses in mean ventral aortic ($P_v$), dorsal aortic ($P_a$), and caudal vein (CVP) pressures to subintestinal injections of AD (320 pmole/100 g; ●) and (NAD 320 pmole/100 g; ▲) in the same fish. The responses were of similar magnitude to the two agonists, but that to NAD was type 2, while that to AD was type 3. Note the greater decrease in the $P_v$–$P_a$ gradient caused by NAD.

Table 2. *A comparison of the pressor potency ratios (NAD/AD; AD = 1) determined simultaneously in the dorsal and ventral aortas, and a comparison of the ratios of the maximum pressure increases in the ventral and dorsal aortas respectively (max $\Delta P_v$/max $\Delta P_a$) caused by AD and NAD*

| | Pressor potency ratio | | Max $\Delta P_v$/max $\Delta P_a$* | |
|---|---|---|---|---|
| Fish | Dorsal aorta | Ventral aorta | AD | NAD |
| 1 | 1·635 | 0·337 | 1·738 | 1·005 |
| 2 | 0·346 | 0·153 | 1·064 | 1·005 |
| 3 | 2·424 | 1·563 | 1·012 | 0·888 |
| 4 | 0·286 | 0·224 | 1·014 | 0·884 |
| 5 | 0·388 | 0·372 | 0·970 | 0·951 |
| 6 | 0·586 | 0·272 | 1·122 | 0·963 |
| 7 | 0·529 | 0·417 | 1·055 | 0·926 |
| Mean | 0·885 | 0·477 | 1·139 | 0·946 |
| ±1 S.E. | ±0·309 | ±0·180 | ±0·101 | ±0·018 |

* Each value of max $\Delta P_v$/max $\Delta P_a$ represents the mean of 3–11 determinations at a variety of dose levels. Only responses in which the increases in both ventral and dorsal aortic pressures were greater than 5 cm $H_2O$ were used in calculating this mean.

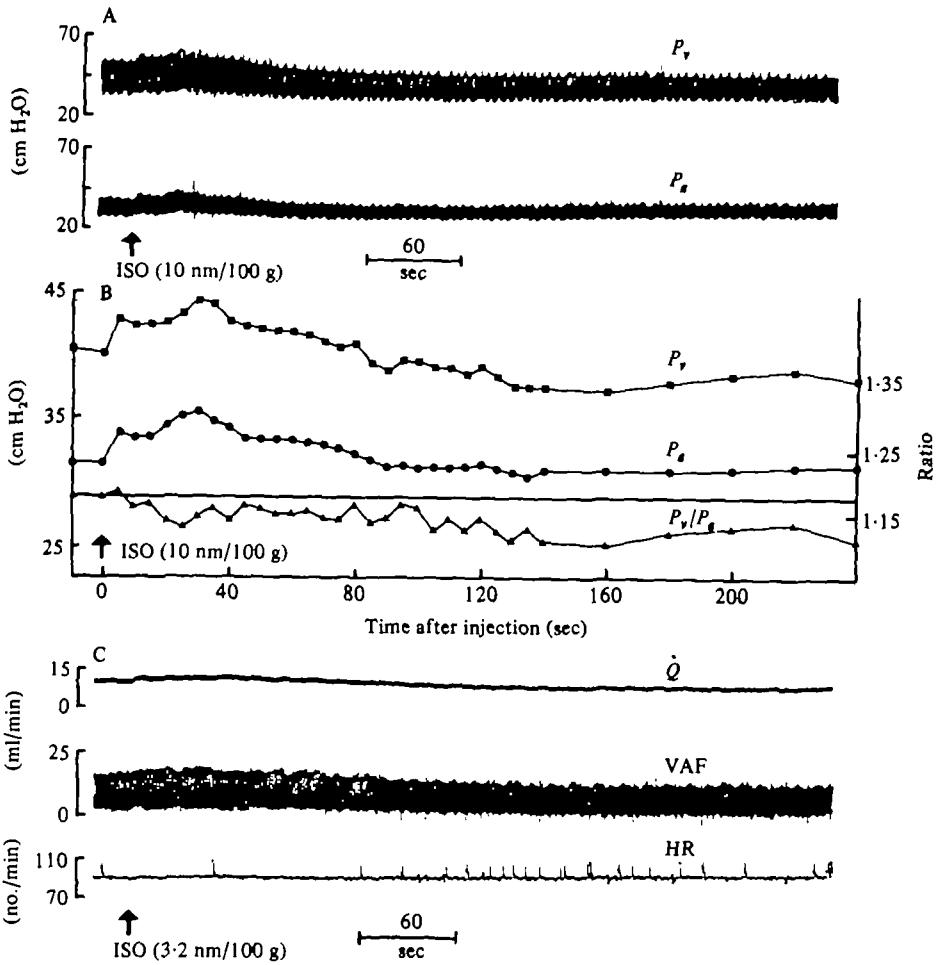


Fig. 11. (A) Original records of changes in ventral ($P_v$) and dorsal aortic ($P_a$) pressures in response to a subintestinal injection of ISO (10 nmole/100 g). Note the slight initial pressor response and the following depressor response and the associated changes in pulse pressure. (B) Analyses of (A) in terms of mean pressures and $P_v/P_a$ as in Fig. 5. (C) Original records of changes in ventral aortic flow (VAF) and mean cardiac output ($\dot{Q}$) in response to a subintestinal injection of ISO (3·2 nmole/100 g) in a different fish (weight = 291 g). Note the biphasic response in flow of similar form to that in pressures in (A). The constancy of instantaneous heart rate (HR) indicates that the observed changes in $\dot{Q}$ were due to alterations in stroke volume.

11 A). The subsequent depressor effect was always slightly greater in $P_v$ than in $P_a$ and associated with a greater drop in systolic than in diastolic pressure. Consequently pulse pressure decreased, and $P_v/P_a$ fell below the original level (Fig. 11 B).

Stroke volume changes in $\dot{Q}$ accounted for most, if not all, of the pressor and depressor effects of ISO. In six of the seven ventral aortic flow records taken, ISO (1–10 nmole/100 g) caused a biphasic response in $\dot{Q}$ similar to that seen in blood pressures (Fig. 11 C). In the seventh, only a depression of stroke volume occurred. These declines in stroke volume explain the decreases in pulse pressure (Fig. 11 A, C). The consistent depression of $P_v/P_a$ during ISO responses can be explained by either

a relative increase in $R_s$ or decrease in $R_v$; from the actions of ISO on isolated branchial and systemic vascular beds (Wood, 1975, 1976) the latter appears far more probable.

(iii) *Phenylephrine.* PHE had no definite effect on blood pressure in doses up to 1 μmole/100 g, but tended to depress subsequent responses to AD, thereby confirming previous findings of non-specific effects only (Wood, 1974*a*, 1975, 1976; Wood & Shelton, 1975) in the trout.

VII. *Adrenergic antagonists*

(i) *Yohimbine.* This competitive α-adrenergic antagonist (100 nmole/100 g) caused a large, sustained (6–12 h) fall in blood pressure of similar magnitude in ventral and dorsal aortas. The mean pressure drop, measured in the latter, was 12·0 ± 1·3 (10) cm $H_2O$, or approximately 36%. There was negligible change in $\dot{Q}$ and heart rate, indicating that the depressor effect was largely due to a reduction in $R_s$. After yohimbine, $P_a$ and $P_v$ remained remarkably stable, even in the face of normal pressor stimuli (e.g. touching the skin, strong light), though the usual bradycardia elicited by such disturbances persisted. The AD and NAD dose response curves in both $P_v$ and $P_a$ were shifted to the right by 1–2 log units in a parallel fashion (Fig. 12A) characteristic of competitive antagonism (Ariens, 1964). Depressor effects of AD and NAD were never seen. After yohimbine, subpressor doses of AD either increased or had no effect on $\dot{Q}$; decreases in $\dot{Q}$ were only seen with high pressor doses after α-blockade.

(ii) *Phenoxybenzamine.* This non-equilibrium antagonist of α-adrenergic receptors (1 μmole/100 g) caused an immediate small pressor effect followed by a slow decline to pressures well below the original over the next 1–2 h. The final vasodepression (9·9 ± 2·8 (4) cm $H_2O$) was similar (30%) to that caused by yohimbine. A blockade of pressor responses to AD and external disturbance developed slowly over 1–2 h but then lasted 12–24 h. The AD dose/response curve was shifted to the right by 1–2 log units and slightly downwards at higher doses (Fig. 12B), an effect typical of non-equilibrium antagonism (Ariens, 1964).

(iii) *Propranolol.* Results with this competitive β-adrenergic antagonist were unsatisfactory because propranolol (10–100 nmole/100 g) severely reduced heart rate, stroke volume, $\dot{Q}$, and therefore arterial blood pressures, by an apparently non-specific depression of the heart (the cardiac effects of ACH were also reduced). This general cardiac depression by propranolol has also been seen in the trout heart *in vitro* (Bennion, 1968). Propranolol therefore reduced or abolished the stroke volume increase and occasional slight tachycardia caused by AD. Propranolol also inhibited the pressor response in $P_a$ to AD without a shift in the dose/response curve (Fig. 12C). The latter effect probably reflected non-competitive antagonism (Ariens, 1964) of the action of α-receptors, a phenomenon also seen in the isolated systemic circulation (Wood, 1976). Lower doses of propranolol (1 nmole/100 g) were without effect on the responses to AD.

## DISCUSSION

I. *Basic cardiovascular parameters*

The present ventral aortic flow records are the first direct measurements of $\dot{Q}$ in *S. gairdneri*. Table 3 compares these data with previous determinations in this and

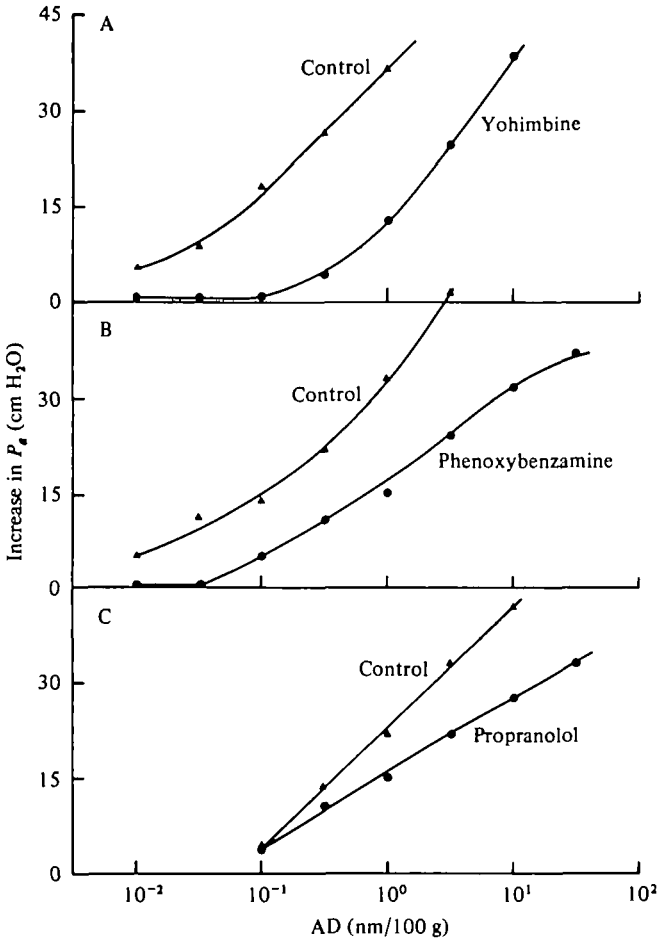


Fig. 12. The effects of (A) yohimbine (100 nmole/100 g), (B) phenoxybenzamine (1 μmole/100 g), and (C) propranolol (100 nmoles/100 g) on the pressor dose/response curve to AD in dorsal aortic pressure ($P_a$) in three different fish. Note the different types of effect on the dose/response curve produced by the three blocking agents.

other species. Directly measured $\dot{Q}$ in the trout was comparable to that in the jeju *Hoplerythrinus* but greater than that in the cods *Gadus* and *Ophiodon*. In all four species, ventral aortic flow was continuous throughout the cardiac cycle. Surgical stress and higher temperature probably elevated $\dot{Q}$ relative to previous studies on *S. gairdneri*. The present data lend some support to all the earlier Fick estimates with the exception of the very high value of Holeton & Randall (1967*b*).

The present $P_v$ and $P_{ct}$ data (Table 1) are in general agreement with earlier studies, while caudal vein pressures have not been reported previously. The positive variable venous pressure in trout may be significant in both passive distensibility of the systemic vasculature (see Wood, 1974*a*; Wood & Shelton, 1975) and in regulating $\dot{Q}$ via Starling's Law (Bennion, 1968).

Mean branchial ($R_g$ = 3·4 cm $H_2O$.min.100 g.ml$^{-1}$) and systemic ($R_s$ = 7·1 cm $H_2O$.100 g.ml$^{-1}$) vascular resistances can be calculated from the mean pressure

Table 3. *Cardiac outputs ($\dot{Q}$) in a number of intact, unanaesthetized teleosts determined by direct and indirect methods*

| Species | Temperature (° C) | Weight (g) | $\dot{Q}$ (ml/kg. min) | Determination | Method | Reference |
|---|---|---|---|---|---|---|
| *Salmo gairdneri* | 13–16 | 100–725 | 36·7 | Direct | Electro-/magnetic flowmeter | Present study |
| *S. gairdneri* | 4–8 | 200–400 | 7·6 | Indirect | Fick principle | Stevens & Randall (1967*b*) |
| *S. gairdneri* | 12–18 | 210–1100 | 65–100 | Indirect | Fick principle | Holeton & Randall (1967*b*) |
| *S. gairdneri* | 8–10 | 175–400 | 18·3 | Indirect | Fick principle | Cameron & Davis (1970); Davis & Cameron (1971) |
| *S. gairdneri* | 9–10·5 | 900–1500 | 17·6 | Indirect | Fick principle | Kiceniuk & Jones (1977) |
| *Ophiodon elongatus* | 13 | 1100–4000 | 5·9 | Direct | Doppler flowmeter | Stevens *et al.* (1972) |
| *Gadus morhua* | 9–10 | 2000–3000 | 20·8 | Direct | Electromagnetic flowmeter | Jones *et al.* (1974) |
| *Hoplerythrinus unitaeniatus* | 26–30 | 300–500 | 30·0 | Direct | Electromagnetic flowmeter | Farrel (1978) |

gradients and $\dot{Q}$ of Table 1. The $R_s$ value must underestimate the true figure, because the actual $\dot{Q}$ perfusing the systemic circulation will be reduced by the (unknown) amount of venous outflow from the gill (see Wood *et al.* 1978). Therefore the systemic vascular bed is obviously the major site of vascular resistance in the trout circulation. At least with respect to adrenergic controls (see below, and Wood & Shelton, 1975), it also appears to be the major site of variable resistance in the system. The trout deals with the problems of the single circulation by employing a small (though variable) $R_g$ and setting the general level of perfusion and pressure in the system by controlling the size of the much larger $R_s$, and the size of $\dot{Q}$.

## II. *Adrenergic mechanisms*

A varying balance between systemic and cardiac effects explained the considerable variability in the form of the pressor response to AD (Figs. 4–6). In turn, this probably reflected variability in the cardiovascular condition of the animals. *In vitro*, AD exerts a positive inotropic effect via cardiac $\beta$-adrenoreceptors (Bennion, 1968; Gannon & Burnstock, 1969; Gannon 1971). *In vivo*, this again seems to be AD's fundamental action on the heart manifested as a stimulation of stroke volume (Figs. 6, 9). Occasional small increases in heart rate did occur, but rate was probably already close to maximum in the present fish for there was generally no resting vagal tone (Wood & Shelton, 1980) and struggling activity did not cause tachycardia (e.g. Fig. 2C). However, superimposed on the stimulation of $\dot{Q}$ by AD was an inhibition associated with the systemic constriction caused by AD. A small and variable part of this inhibition was due to the activation of arterial baroreceptors causing an atropine sensitive bradycardia of reflex, vagal origin (cf. Randall & Stevens, 1967; Stevens *et al.* 1972; Helgason & Nilsson, 1973). However the major portion of the inhibition was coincident with

the pressor peak, abolished by pressor blockade, resistant to atropine, and therefore a passive consequence of the rise in total peripheral resistance caused by the constriction of $R_s$. Thus the trout heart is not a pressure-insensitive pump, and systolic emptying is reduced in the face of an elevated outflow pressure. A similar compound inhibitory effect, separable by atropine and pressor blockade, was reported by Stevens *et al.* (1972) in the ling cod *Ophiodon*, but these workers never saw an increase in $\dot{Q}$ in response to intra-vascular AD. The passive inhibitory effect probably predominates in those individuals where the contractility of the heart is already close to maximum prior to AD, and the direct stimulatory effect in more normal animals possessing a reserve of cardiac contractility.

Whatever the cardiac response, the dominant initial action of AD was elevation of $R_s$ by stimulation of the systemic $\alpha$-adrenergic constrictory receptors previously identified in the perfused trunk (Wood & Shelton, 1975; Wood, 1976). Some indications of branchial dilation were obtained, but the phenomenon could not easily be dissociated from the increase in $R_s$. A decrease in $R_g$ during a pressor response would in any case be expected simply because of the passive dilatory effect of the raised transmural pressure on the branchial vessels (Wood, 1974*a*; Wood *et al.* 1978). Branchial dilation in the absence of a systemic pressor response would be more convincing evidence of activation of the dilatory $\beta_1$-adrenoreceptors seen in the perfused gill (Wood, 1974*a*; 1975). As the perfused gill was much more sensitive to catecholamines than the perfused trunk (Wood & Shelton, 1975), we expected that a decrease in $R_g$ *in vivo* might occur at subpressor doses of AD. Such an effect was not generally seen. This may mean that the gills were already $\beta_1$-adrenergically dilated by endogenous catecholamines to the extent that subpressor doses of AD were also subthreshold for further gill dilation. However, the highly selective and potent $\beta$-agonist ISO did seem to decrease $R_g$ in the absence of a pressor effect (Fig. 11). In a few experiments (type 4 responses – Figs. 4D, 5D), AD actually increased $R_g$, probably by stimulating $\alpha$-constrictory receptors in the gills, an effect which would be most pronounced when the capacity for further branchial dilation was limited (Wood, 1975).

The uniformity of the NAD pressor responses (all type 2; Fig. 10) has been attributed to the relative absence of an increased $\dot{Q}$ in their genesis. NAD is about 10 times less potent than AD in stimulating the trout heart *in vitro* (Gannon & Burnstock, 1969). The mean maximum $\Delta P_v$/maximum $\Delta P_a$ was always less with NAD than with AD (Table 2). This phenomenon would result if NAD had a greater ratio of intrinsic potency than AD for gill dilation/systemic constriction and/or a lesser ratio of intrinsic potency than AD for heart stimulation/systemic constriction. The former is indicated by the results from perfused gill and trunk preparations (Wood, 1974, 1975, 1976; Wood & Shelton, 1975) and the latter by studies on the trout heart *in vitro* (Gannon & Burnstock, 1969; Gannon, 1971). Similar explanations would account for the greater pressor potency ratio (NAD/AD) in the dorsal aorta than in the ventral aorta (Table 2). The great variability in these NAD/AD pressor potency ratios from animal to animal probably resulted from differing degrees of vacancy of the $\beta_2$-dilatory receptors in the systemic vasculature (Wood, 1976). The greater the degree of $\beta_2$-activation in $R_s$ by endogenous catecholamines, the lower would be the potency of NAD relative to AD.

ISO (l-isoprenaline) effects in the present study were generally much less dramatic

than those reported in other teleosts (Chan, 1967; Helgason & Nilsson, 1973; Chan & Chow, 1976). However previous workers have used d,l-isoprenaline rather than the pure $\beta$-stimulant l-isoprenaline; the d-isomer in the racemate can cause $\alpha$-adrenergic blockade and therefore artificially high vasodepression (Wood, 1976). The initial elevation of $\dot{Q}$ and reduction in $R_g$ by ISO (Fig. 11) presumably represented stimulation of $\beta$-receptors in the heart and gills respectively. The final depression of stroke volume accounting for much of the vasodepressor effect of ISO (Fig. 11) was unexpected, because only positive inotropic actions of this catecholamine have been described on the *in vitro* trout heart (Gannon, 1971). Possibly both stimulatory and inhibitory $\beta$-receptors are present in the heart of the trout as in the rat (Broadley, 1972). The rapidly developing tachyphylaxis to ISO probably reflected accumulation and persistence of the drug's effects, for ISO is not accepted as a substrate by the neuronal transport mechanism which normally terminates catecholamine action (Iversen, 1973).

Yohimbine and phenoxybenzamine caused a large vasodepression *in vivo* by blocking systemic $\alpha$-receptors (Wood, 1976), confirming that $R_s$ is under a high degree of vasomotor tone in the trout (Wood & Shelton, 1975). This finding agrees with the work of Helgason & Nilsson (1973) and Wahlqvist & Nilsson (1977) on the cod *Gadus*. However in Pacific salmon, Randall & Stevens (1967) found that phenoxybenzamine caused only a very slight fall in $P_a$. In the present study, phenoxybenzamine caused a comparable vasodepression to yohimbine, but the effect developed much more slowly (1–2 h). Possibly the fish of Randall & Stevens (1967) developed compensations (e.g. increased $\dot{Q}$) masking the phenomenon. Recently, Smith (1978) using yet another $\alpha$-adrenergic antagonist, phentolamine, has reported a small but significant vasodepression of long duration. The point is important, for several investigators have used the data of Randall & Stevens (1967) to argue that since adrenergic tone is 'absent', a sympathetic mechanism for vasomotor control is lacking or rudimentary in fish (Burnstock, 1969; Campbell, 1970; Opdyke *et al.* 1972). While the present results demonstrate that an endogenous $\alpha$-adrenergic tone does occur in the systemic vasculature, the finding does not in itself reveal whether the tone is of neural or hormonal origin. However the results of Wood (1974*b*) and Smith (1978) strongly indicate that a sympathetic neural component is of great importance.

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