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Review

Coronary arteriosclerosis in salmon: growing old or growing fast?☆

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Abstract

A review is presented of what we know and what we suspect regarding the formation of coronary arteriosclerotic lesions in salmonids. Coronary lesions are a fact of life for both Atlantic and Pacific species of migrating salmon. Severe forms of lesions, usually restricted to the main coronary artery, are typically found in the majority of a salmon population when they are spawning. Vascular injury to the coronary artery, as a result of the bulbus arteriosus being excessively distended, is proposed as an initiating mechanism for coronary lesion formation, possibly explaining why severe lesions are restricted primarily to the main coronary artery. Evidence is presented that coronary arteriosclerosis in salmonids develops in immature fish, well before maturation, and progresses with age. Growth and growth rate are implicated in lesion progression. A faster growth rate could produce a more stressful life style, which in turn initiates more coronary vascular injury. Dietary factors, especially polyunsaturated fatty acids (and their metabolites), can significantly stimulate vascular smooth muscle proliferation in the salmon coronary artery, but a possible linkage to the progression of coronary lesions has yet to be studied. Whether coronary lesions negatively impact blood flow to the salmon heart has not been properly studied. Nevertheless, the coronary blood supply to the heart has functional importance when salmon exercise and the coronary flow reserve may be reached when fish swim under mild hypoxic conditions. If coronary arterial lesions do adversely affect blood flow to the heart, the selective effects would be most prominent in years when upstream migration conditions are particularly severe. © 2002 Published by Elsevier Science Inc.

Keywords: Coronary artery; Arteriosclerosis; Growth; Omega-3 polyunsaturated fatty acids; Vascular smooth muscle; Coronary blood flow; Salmon; Exercise; Hypoxia; Aging

1. Introduction

Robertson et al. (1961a) first described coronary arteriosclerosis in fish when adult Pacific salmon (Genus *Oncorhynchus*) were sampled during their spawning migration. Subsequently, adult steelhead trout (*Oncorhynchus mykiss*), Atlantic salmon (*Salmo salar*), sockeye salmon (*O. nerka*), chum salmon (*O. keta*), chinook salmon (*O. tshawytscha*) and coho salmon (*O. kisutch*) were also shown to suffer similar coronary artery degeneration (van Citters and Watson, 1968; Maneche et al., 1972; Moore et al., 1976a,b,c; McKenzie et al., 1978; Farrell et al., 1986, 1990a; Kubasch and Rourke, 1990). While migratory salmon have a propensity to possess coronary artery lesions as adults, coronary lesions are usually absent in non-salmonid teleosts (Vastesaeger et al., 1965; Santer, 1985). No lesions have been found in the main coronary artery of various adult elasmobranchs (Farrell et al., 1992a) and only small lesions occasionally appear in small coronary arteries (Eaton et al., 1984; Garcia-Garido et al., 1993). These observations can be construed as supporting the idea that salmon are more predisposed to

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coronary arteriosclerosis than other fish species. Therefore, coronary arteriosclerosis is a fact of life for mature spawning salmonids, but rarely the case in other fish species. As such, migratory salmon are an intriguing comparative model for the study of coronary arteriosclerosis.

Atlantic and Pacific salmon start their life in freshwater streams, migrate to the ocean for a period of growth and then return to their natural stream to spawn. They usually live for 3–6 years and undergo an extremely rapid, often spectacular senescence shortly after they mature and spawn. Therefore, the discovery of coronary lesions in mature salmon was initially thought to be one of the numerous histological changes that characterize senescence in salmon (Robertson and Wexler, 1960; Robertson et al., 1961b), a phenomenon that Finch (1990) placed in the context of the comparative biology of senescence. Nevertheless, the exact etiology of coronary arteriosclerosis in salmon was unknown. Questions were also raised concerning the impact of these lesions on coronary blood flow to the heart since migratory salmon perform what might be their most energetic feat [an upstream migration of up to 1000 km for some sockeye salmon (*Oncorhynchus nerka*) stocks], at least in terms of cardiac performance, at a time when they have severe coronary arteriosclerosis. The question of what happens to coronary arteriosclerotic lesions in kelts and in landlocked salmon was also of special interest. Two salmon species (steelhead trout and Atlantic salmon) do not necessarily die after spawning and a small percentage of survivors (kelts) return to the sea and repeat their spawning cycle the following year, while other salmon species remain in freshwater and do not migrate to the sea.

This review attempts to answer the questions raised above. In describing what is known concerning the etiology of coronary lesions in fish, we consider that coronary lesions are possibly related to age and growth rather than to senescence, and that the initiating factor could be vascular injury. Also, we suggest that lesions do not regress in kelts when they return to the ocean for subsequent spawning cycles. Lastly, we examine how coronary lesions might affect coronary physiology and cardiac performance in salmon based on the relatively limited information on coronary physiology in fish. However, before addressing each of these issues, a brief description of the coronary circulation and coronary lesions in fish is provided as a background.

2. The coronary circulation in fish

Without exception, adult mammals have an obligatory dependence on the coronary circulation to supply oxygen and nutrients to cardiac muscle. Any interruption in this supply can cause permanent cardiac damage and death. Only in the early stages of fetal development, when the coronary circulation has yet to be fully developed, does the mammalian heart rely on the blood that is pumped through the heart chambers for its own circulation, i.e. the cardiac circulation.

In contrast to mammals, the majority of fish species do not have a coronary circulation. These fish, like fetal mammals, rely entirely on the cardiac circulation. However, the blood that is pumped through the cardiac chambers in water breathing fish is deoxygenated venous blood. (The mammal fetal heart receives oxygenated venous blood from the placental circulation). Approximately one third of all teleost species, e.g. salmonids, scombrids and anguillids, have a coronary circulation (Tota, 1983; Davie and Farrell, 1991a,b; Farrell and Jones, 1992). All elasmobranchs, however, have a coronary circulation and so the coronary circulation has its roots early in the evolution of the vertebrate heart.

The coronary artery is functionally analogous in fish and mammals. In mammals the coronary artery is the first vascular branch of the ascending aorta and so the heart is the first organ of the body to receive oxygenated blood and at the highest possible blood pressure. Likewise in salmon, the anatomical origin of coronary circulation is such that it delivers oxygenated arterial blood directly to the heart at the highest possible blood pressure. Nevertheless, the anatomy differs in that in fish the heart must first pump venous blood through the gills to become oxygenated and the coronary artery is derived from branches of the efferent gill arteries. Consequently, the coronary artery is not developmentally homologous in fish and mammals. The anatomical origin of the coronary circulation among vertebrates, as well as developmental considerations and evolutionary perspectives, are well described in the older literature (Parker and Davis, 1899; Grant and Regnierm, 1926; Foxon, 1950; Halpern and May, 1958). The distribution pattern for coronary cir-

culation and its functional significance have been given more recent attention (Tota, 1973, 1983, 1989; de Andres et al., 1990; Davie and Farrell, 1991a,b).

The functional significance of the coronary circulation in fish differs from that in mammals in that it provides only a supplemental supply of oxygen to cardiac muscle. Therefore, the fish heart does not have an obligatory dependence on its coronary blood flow. This fact is demonstrated by the observations that rainbow trout and chinook salmon can survive surgical ligation or ablation of the main coronary artery (Daxboeck, 1982; Farrell and Steffensen, 1987; Farrell et al., 1990b; Gamperl et al., 1994). Gamperl et al. (1994) also found that routine cardiac function was unimpaired by coronary ligation in rainbow trout. This would not be the case in mammals where the coronary circulation supplies blood to over 95% of the myocardium. In fish, however, the coronary circulation rarely supplies more than 60% of the ventricle. In its simplest form, the fish coronary circulation is associated morphologically with an outer, compact layer of ventricular myocardium. Consequently, the compact myocardium is used as an index of coronary development among fish (but this is not to say that a somewhat larger portion of the ventricle might benefit from the coronary circulation). Compact myocardium ranges from as little as 5% of the ventricle in the primitive ratfish, to between 30% and 40% in salmonids, and up to 60% in skipjack tuna (see Tota, 1983; Davie and Farrell, 1991a,b). skipjack tuna, with the highest percentage of compact myocardium found in any fish species so far, might have an obligate dependence on its coronary circulation (Farrell et al., 1992b). Thus, the reduced functional significance of the coronary circulation in fish compared with mammalian hearts is most easily explained by the fact that the coronary circulation supplies a much smaller proportion of the ventricle in fish than in mammals.

In summary, by virtue of its presence among fish and especially elasmobranchs, the coronary circulation clearly appeared early in the evolution of the vertebrate heart. A coronary circulation is found in teleost species that swim long distances during their life. The finding that salmon can live without a functional coronary blood supply may have some significance to the etiology of coronary lesions.

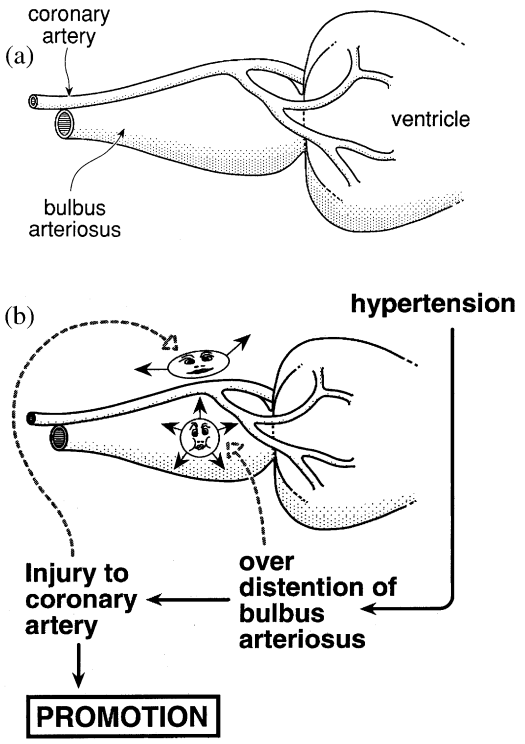

Fig. 1. (a) A schematic diagram of the arrangement of the main coronary artery in relation to the ventricle and elastic bulbus arteriosus. (b) A schematic diagram to illustrate how hypertension might lead to overdistention of the elastic bulbus arteriosus in salmon, thereby injuring the coronary artery and initiating coronary arteriosclerosis.

3. The coronary artery and coronary arteriosclerosis in salmon

Most of the work on arteriosclerosis in salmon has focused primarily on the main coronary artery. This vessel is accessed easily for histology study, surgical manipulations and in vivo blood flow measurement. The coronary artery forms as a branch of the hypobranchial artery, just outside of and anterior to the pericardial cavity. Within the pericardial cavity, the main coronary artery lies, often as an unbranched vessel, on the ventral surface of the ventral aorta and extends caudal over the surface of the bulbus arteriosus until it reaches the ventricular muscle that it supplies (Fig. 1a). Therefore, main coronary artery in salmon lies on the surface of elastic and highly distensible vessels. The main coronary artery is also where arteriosclerotic lesions appear to predominate in the fish's arterial system. Consequently, the main conduit for oxygenated blood to the fish heart that

is also the location of severe arteriosclerotic lesions.

The histology of the coronary artery has a similar design in fish and mammals. A medial layer of vascular smooth muscle (VSM) is surrounded by an external parenchyma. An internal elastic lamina separates the media from the intima, which is normally a single layer of endothelial cells (Fig. 2a). A difference is the much thinner medial layer of VSM in salmon compared with mammals, a feature that simply reflects a 2- to 3-fold lower arterial blood pressure in the coronary circulation of salmon.

Coronary arteriosclerotic lesions in mature salmon are characterized as an intimal proliferation of VSM with a disrupted elastic lamina (Fig. 2b). The lesions resemble the early forms of mammalian arteriosclerotic lesions, but lack the calcium and lipid inclusions typically found in mature mammalian lesions (Moore et al., 1976c; McKenzie et al., 1978; House and Benditt, 1981). Even so, the intimal proliferation of VSM can significantly encroach on the lumen of the coronary artery in salmon (Fig. 2b). Though other arteries have been examined, severe lesions are characteristically confined to the portion of the main coronary artery that lies on the ventral aorta and bulbus arteriosus (Robertson et al., 1961a; Moore et al., 1976a,b; Garcia-Garido et al., 1993). Furthermore, serial histological examinations have shown that between 66% and 80% of the length of the main coronary artery in mature salmon contained some form of severe lesion. These severe lesions would typically occlude 10 to 30%, and as much as 50% of the vessel lumen (Farrell et al., 1990a). To what degree coronary lesions might impair coronary blood flow has not been measured directly and is considered more fully in a subsequent section of the review. Less severe lesions are found in smaller coronary vessels (Eaton et al., 1984), but usually at locations where the vessel is subjected to mechanical stresses during cardiac contraction (Garcia-Garido et al., 1993).

As noted above, the early speculation was that coronary arteriosclerosis in salmon was related to senescence. The key observation in support of this idea was the $>90\%$ prevalence of severe coronary lesions among spawning populations of migratory salmon (Robertson et al., 1961a; van Citters and Watson, 1968; Maneche et al., 1972; Farrell et al., 1986, 1990a; Kubasch and Rourke, 1990). However, as shown below, the etiology is more complex than this.

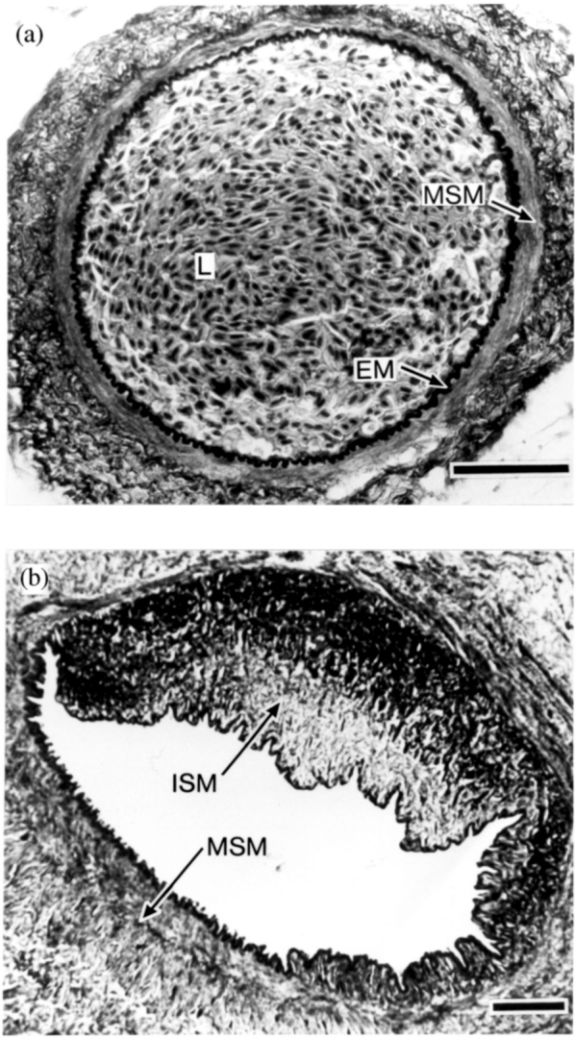

Fig. 2. (a) A cross-section of the main coronary artery to show the normal histological arrangement of the vessel wall. The lumen (L) is filled with nucleated red blood cells and is separated from the medial layer of vascular smooth muscle (MSM) by and intact and convoluted elastic membrane (EM). (b) A cross-section of the main coronary artery to show a severe lesion. The lumen is devoid of blood cells but the lesion containing mainly intimal smooth muscle cells (ISM) has occupied approximately 50% of the normal lumenal area. Calibration bars = 50 μm.

Several studies have found a high percentage of juvenile Atlantic and Pacific salmon, well before sexual maturation salmon, have well-developed coronary lesions (Moore et al., 1976b; McKenzie et al., 1978; House et al., 1979; Farrell et al., 1986; Kubasch and Rourke, 1990; Saunders et al.,

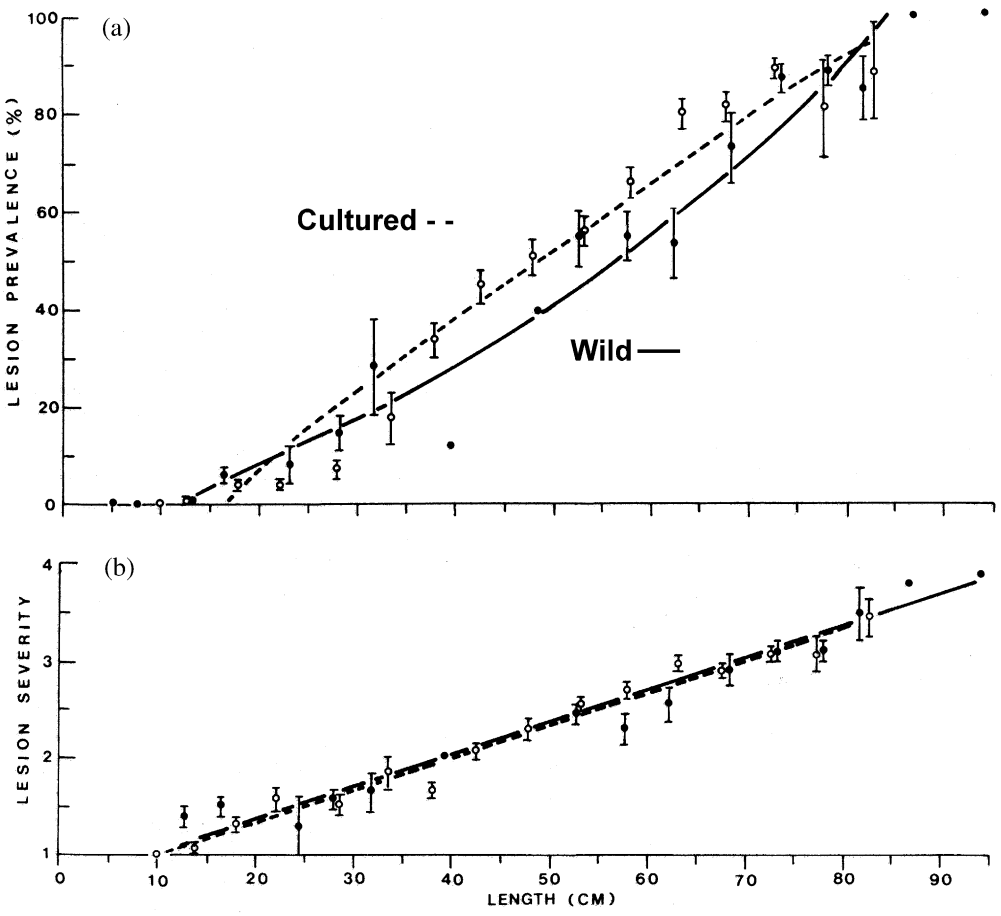

Fig. 3. Coronary arteriosclerotic lesions in cultured and wild-caught Atlantic salmon increase as a function of the fish's length. In fact, the Correlations with fish length illustrated account for at least 96% of the variability in lesion incidence (a) and lesion severity (b). [For cultured salmon: lesion incidence = 23.6 + 1.6(length) − 0.002 (length)^2, $R^2 = 0.960$ and lesion severity = 0.687 + 0.033(length), $R^2 = 0.978$; For wild salmon: lesion incidence = 4.68 + 0.46(length) + 0.009 (length)^2, $R^2 = 0.959$ and lesion severity = 0.707 + 0.033(length), $R^2 = 0.961$]. Lesion incidence is an expression of the percentage of the arterial cross-sections that possessed a lesion. Lesion severity is a ranking based on 0 = no lesion present and 4 = a very severe lesion that occluded part of the vessel lumen. (Adapted from Saunders et al., 1992).

1992). Consequently, the events associated with senescence and sexual maturation are likely only secondary factors in the etiology of coronary lesions in salmon. Nevertheless, sexual maturation apparently plays some role. Injections of sex hormones can promote a small increase in the number of coronary lesions in rainbow trout (House et al., 1979). Also, small lesions are reported in precocious salmon parr (Schmidt and House, 1979; Saunders et al., 1992).

The most comprehensive quantitative analysis of coronary histology for all life stages of Atlantic salmon, both wild-caught and hatchery-raised, is shown in Fig. 3. These data bring to light two very important findings with respect to the etiology of coronary lesions. Foremost, a direct correlation exists between fish size and lesion prevalence (and lesion severity). Thus, as salmon grow older and bigger, they accumulate more lesions. This correlation is true whether the salmon had been caught in the open ocean or whether they had been cultured in a fish farm because both have a similar prevalence and severity of coronary lesions when they reach maturity (Fig. 3). Clearly, these data are inconsistent with either sexually maturation or senescence being primary factors in the initiation of coronary lesions in salmon. Second, coronary lesions in salmon progress with age.

While coronary lesion development, to some degree, must be time-dependent and therefore age-

related as suggested by Fig. 3, other factors are involved in lesion progression. In fact, two observations suggest that coronary lesions in salmon are not strictly related to chronological age. Cultured Atlantic salmon grow at a faster rate than wild salmon. Therefore, while cultured and wild salmon are approximately the same size at maturity, cultured salmon are approximately 1.5 years younger when they reach this size. Consequently, cultured Atlantic salmon must also accumulate coronary lesions at a faster rate and at a chronologically younger age. This finding clearly argues against coronary lesion development being solely related to chronological age. Instead, an important component of coronary lesion development in salmon is tied in part to growth or growth rate.

Furthermore, evidence for a growth-related component of coronary lesion development comes from a comparison between a similar stock of Atlantic salmon cultured in either cold or warm water (Fig. 4). Cold-reared salmon reached sexual maturity at the same chronological age as warm-reared salmon, but grew slower and were considerably smaller in size at maturity. They also had significantly lower levels of coronary lesion prevalence and severity (Fig. 4). Interestingly, while coronary lesions are particularly prevalent and severe in all migratory salmon, they are less prevalent and severe in the land-locked freshwater form of *O. mykiss* (rainbow trout) compared with the migratory form (steelhead trout) (McKenzie et al., 1978). This suggests that factors associated with life at sea play an important role in lesion development. Rainbow trout grow much slower in their freshwater environment compared with steelhead trout in their marine environment. Therefore, the apparent influence of growth rate on coronary lesion development in salmon might help explain why lesion prevalence is lower in land-locked, slower growing freshwater salmonids.

With coronary lesions already at a high level of prevalence and severity in steelhead trout and Atlantic salmon during their first spawning, scientists were intrigued by what would happen to coronary lesions in salmon that survived to become repeat spawners. If lesion regression occurred, it might represent a natural reversal coronary arteriosclerosis. To directly address this question, van Citters and Watson (1968) sampled previously spawned steelhead trout at high seas while Maneche et al. (1972) sampled Atlantic salmon kelts that were returning down river to the ocean after

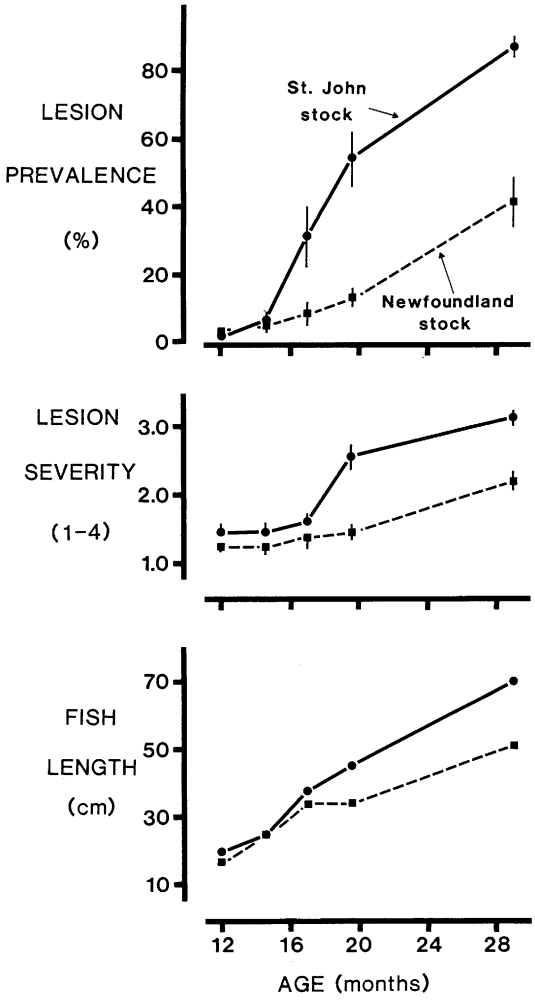

Fig. 4. Comparison of the appearance of coronary arterial lesions in two stocks of Atlantic salmon grown under different culture conditions. The Newfoundland stock was cultured in cold water and grew at a slower rate than the New Brunswick stock. As a result they accumulated fewer coronary lesions. (Adapted from Saunders, Saunders et al., 1992.)

spawning. Both studies found that repeat spawners had a lower lesion severity compared with first-time spawners that were sampled on the spawning ground and concluded that there was lesion regression. However, this conclusion was not confirmed in subsequent studies. In a more controlled study of cultured Atlantic salmon post-spawning, rather than regressing, coronary lesions were found to continue their development and parallel the resumption of growth after first spawning (Saunders and Farrell, 1988). Table 1 illustrates that the same situation likely exists for repeat spawning steelhead trout. Differences were either minor or

Table 1
Comparison of parameters used to describe the prevalence and severity of lesions in mature and repeat-spawning steelhead trout, *Oncorhynchus mykiss*

	High sea samples		Bamfield transfer		Squaxin island	Duncan hatchery
	Maiden spawners	Repeat spawners	Pre-transfer	Post-transfer	Post-maturation	Repeat spawners
Percent of sections with a lesion	80.2±1.8	71.9±4.5[a]	74.5±3.4	82.0±4.0	74.2±3.2	89.0±7.5[b]
Mean severity of lesions (1–5)	3.0±0.1	2.5±0.2	2.3±0.2	2.7±0.2	2.2±0.1	3.7±0.3[b]
Mean obstruction of lumen (%)	9.7±0.7	8.2±1.8	6.0±0.8	8.1±1.2	7.5±0.9	13.4±1.6[b]
Mean largest obstruction (%)	15.1±1.1	11.3±2.5	9.0±1.4	12.2±2.0	10.7±1.4	26.0±4.3[b]
Percent of fish with lesions	98% (n=161)	100% (n=36)	100% (n=38)	100% (n=29)	98% (n=72)	100% (n=5)

High sea samples represent fish that were captured as by-catch in commercial fisheries in the northern Pacific Ocean. The Bamfield transfer experiments represents mature fish that were transferred from Robertson Creek hatchery to a sea pen for recovery with the expectation that lesion severity would decline post-transfer. Squaxin Island samples represent a population of hatchery fish that had sexually matured and been left in sea pens for 1 year after maturation. Duncan hatchery samples represent repeat spawning fish that had returned to a hatchery on Vancouver Island. The following statistical comparisons were made: repeat vs. maiden spawners in the high-sea group (difference denoted by [a]); pre-transfer vs. post-transfer fish in the Bamfield transfer experiments; Squaxin Island fish vs. all other groups; and Duncan vs. all other fish groups (difference denoted by [b]). All comparisons were significant at $P<0.05$. (Table adapted from Farrell and Johansen 1992.)

non-existent between maiden spawners sampled on the spawning ground and fish that were caught at high sea after spawning (Farrell and Johansen, 1992). Similarly, lesion prevalence and severity remained elevated in post-spawned steelhead trout returning down river (Kubasch and Rourke, 1990). Repeat spawners on the spawning ground, however, had more lesions than maiden spawners (Table 1). Thus, the post-spawning rejuvenation process in Atlantic salmon and steelhead trout was not associated with any natural reversal of the coronary lesion accumulation, as was formerly thought. Why the recent studies of repeat spawning salmon are diametrically opposed to the earlier ones remains a mystery.

In summary, studies with both wild and cultured salmon clearly show that the accumulation of coronary lesions is cumulative over the life of the fish, i.e. an age-related progression rather than an association with specific events such as sexual maturity or senescence. Moreover, growth and growth rate significantly influence the rate of lesion accumulation, with sexual maturation possibly a secondary influence. The primary initiating factors in the etiology of coronary lesions in salmon remain unclear, but the VSM culture experiments described below point to vascular injury as a potential candidate for the initiating event.

4. Are coronary arterial lesions in salmon related to vascular injury and a stressful lifestyle?

In terms of lesion development, VSM proliferation represents a key morphological change during coronary lesion development in both fish and mammals. Consequently, initiation of a lesion must be followed by VSM proliferation. Therefore, studies of factors that stimulate coronary VSM mitosis in salmonids are useful in the expanding our understanding of the process of lesion initiation and development in salmon.

Mechanical abrasion of the coronary artery in vivo can significantly increase VSM mitosis. To demonstrate this response, the coronary artery of rainbow trout was surgically exposed and rubbed gently on the outside. Then fish were revived for up to 4 days before the coronary artery was removed so that an arterial explant could be cultured in vitro with [^{3}H]thymidine. VSM mitosis in the explant was significantly elevated compared with sham-operated fish 1 day after the mechanical abrasion (Gong and Farrell, 1995). Peak mitotic activity (a 3-fold stimulation) in the explant occurred 2 days after mechanical abrasion, with mitotic activity returning towards normal levels after 3 days. In view of this result, vascular intimal injury was suggested as a candidate for the primary

Table 2
Effect of various swimming regimes on [^{3}H]thymidine incorporation into explants of coronary arterial smooth muscle of chinook salmon

Fish group	*n*	Fish swimming Speed (bl/s)	Duration (months)	[^{3}H]thymidine (dpm/μg DNA)
Control	16	0.5	3–8	1435±242
Submaximal aerobic swimming	8	1.5	8	2116±326
Maximal aerobic swimming (U_{crit})	8	up to 2.8–2.9	3 (on alternate days)	3954±329[a]

Two control groups were tested, one lasting 3 months and the other 8 months. There was no significant difference in [^{3}H]thymidine incorporation between the two groups and the data were pooled for statistical purposes. (Table adapted from Gong et al., 1996.)
[a] Significantly different ($P<0.05$) from control.

initiating factor coronary arteriosclerosis in salmon (Gong and Farrell, 1995), as is the case in mammalian coronary arteriosclerosis (Ross, 1984). One mechanism of mechanical injury in mammals is that high blood pressure causes physical damage to the protective endothelium and elastic lamina through excessive shear stresses. This situation is unlikely to occur in fish because of the lower blood pressure in their coronary circulation. However, the elastic nature of the ventral aorta and bulbus arteriosus allows the superficial coronary artery to be excessively deformed during periods of stressful activity when the bulbus arteriosus is over-distended (Fig. 1b). Thus, it has been proposed that over stretching of the coronary artery with each heartbeat could cause vascular injury and this event could initiate lesion formation (Saunders et al., 1992). This mechanism could help explain why severe lesions are restricted to the main coronary artery in salmon. It could also explain why elasmobranchs do not have severe lesions in their main coronary artery because the artery is located on the much less compliant conus arterious. These suggestions have yet to be tested for the coronary artery in fish. However, a similar mechanical stress, a rhythmic distention of an artery surgically attached to the mammalian diaphragm muscle, has been shown to cause arterial lesions (Weibel, 1958).

If the mechanism of initiating coronary lesions is over-expansion of the bulbus arteriosus, as suggested above, it follows that stressful events that cause blood pressure to be raised in salmon would lead to lesion formation. It is interesting, therefore, that swimming to exhaustion, as a result of a critical swimming speed test, also significantly increased VSM mitosis in coronary artery explants (Gong et al., 1996). In contrast, continuous low speed swimming for 3 months had no significant effect on VSM mitosis in coronary explants (Table 2). Based on these findings, it was suggested that the more intense and stressful nature of the critical swimming speed test vs. the submaximal swimming challenge could have played a role in stimulating VSM mitosis.

Even if conclusive evidence is found to support the idea that vascular injury is an important factor in initiating coronary lesions in salmon, metabolic signaling will be involved in VSM proliferation. In this regard, polyunsaturated fatty acids (PUFA) seem to be important regulators of VSM mitosis in salmon. A low dose of arachidonic acid (AA; 20:4w6) in the culture medium caused a 5-fold stimulation of VSM mitosis in coronary explants from rainbow trout (Table 3). This powerful mitogenic effect of AA was striking because the level of stimulation was greater than that elicited by mechanical abrasion in vivo. Prostaglandin $F_{2\alpha}$ and analogues for prostacyclin and thromboxane A_2 were also mitogens (Gong et al., 1997).

Such responses to PUFAs are not unexpected given the knowledge base for mammalian VSM mitogens. However, given the protective effects of w-3 PUFA in the management of human atherosclerosis, and that salmon are thought to be a good source of w-3 PUFAs, it seems curious that salmon would develop severe coronary lesions. Interestingly, the w-3 PUFA eicosapentaenoic acid (EPA; 20:5w3) and eicosatrienoic acid (ETA; 20:3w6) were antimitogenic in that they completely or partially antagonized the mitogenic effect of low doses of AA (Table 3). EPA by itself had little effect on VSM mitosis in explants. Thus, autocoid release, perhaps associated with vascular damage, could have complex mitogenic and anti-mitogenic effects on coronary VSM in rainbow trout. The balance of these effects, in turn, might be influenced by dietary quality, which dictates what w-3

Table 3
The effect of some polyunsaturated fatty acids (PUFAs) and their metabolites on [^{3}H]-thymidine incorporation into coronary artery vascular smooth muscle from rainbow trout

PUFAs	Change compared with control	plus 20 μm AA
Arachidonic acid (AA) 20:4 *n*-6 (20 μM)	+4.5 X	
Eicosapaetenoic acid (EPA) 20:5 *n*-3 (20 μM)	NS	NS
Eicosatrienoic acid (ETA) 20:3 *n*-6 (20 μM)	−60%	+1.6 X
Metabolites		
Thromboxane A_2 analogue, U46619 (0.7 μg/ml)	+2.7 X	
Carbacyclin (1 μg/ml)	+2.4 X	
Prostaglandin $F_{2\alpha}$ (0.12 μg/ml)	+1.9 X	

Coronary vascular smooth muscle explants were incubated in culture medium with or without the PUFA or metabolite. In some cases, the interactive effects of eicosatrienic (ETA) and eicosapentaenoic acid (EPA) with arachidonic acid (AA) were measured to assess for antagonistic effects against the potent mitogenic effect of AA. (Adapted from Gong et al., 1997.)

and w-6 phospholipid substrates are available for autocoid synthesis. It is also known that a diet with elevated cholesterol stimulates lesion prevalence in Atlantic salmon (Farrell et al., 1986) and positive correlations exist between coronary lesions and low density lipoproteins in the plasma of salmon (Eaton et al., 1984; Farrell et al., 1986).

5. Is coronary arteriosclerosis in salmon a pathology and does it affect normal physiology?

The argument can be made that coronary arteriosclerosis in salmon is not a true pathology because of its extremely high prevalence in spawning salmon. Also, Moore et al. (1976c) suggested that 'extensive cardiovascular lesions alone apparently do not cause the death of salmon or impair the ability of trout to survive spawning.' One could then extend this line of reasoning and state that because routine cardiac performance is not affected by coronary ligation, then lesions are unlikely to affect routine cardiac performance. Be this as it may, life in the wild often requires outperforming predators and negotiating marginal environmental conditions, both of which can tax the heart to its limits. In addition, we have to be cautious with some of our field observations. In nature we rarely know why a particular salmon succumbs to predation or is captured by fishing. In the case of salmon, this unknown could have a strong biasing effect since as few as 1% of a year class of salmon return to their natal stream to spawn. Perhaps salmon that have a relatively low coronary lesion severity are more successful, and this is reflected in the fish we sample (i.e. the fish that are lost to natural mortality have an even higher lesion severity than we observe in the surviving fish). Beyond these speculative issues, there is clear and convincing evidence, as shown below, that the coronary blood supply is important in supporting swimming activity and maximum cardiac performance of salmon. Therefore, if it can be shown that coronary lesions impair coronary blood flow or its regulation in salmon, it would be likely that coronary arteriosclerosis could impair the success of salmon to spawn. In this way the selection for fish with a low lesion incidence on years when upstream migration conditions were particular severe could counteract a selective advantage of salmon with faster growth rates.

There have been relatively few studies of coronary physiology in fish. This is primarily because the arteries are small, less than 1 mm in diameter except in large fish, and this precludes most in vivo interventions to measure flows and pressures unless large fish are available. The available information comes from four types of study: in vivo coronary ligation and ablation studies, direct measurements of coronary blood flow in vivo, in vitro perfusion studies with isolated hearts, and in vitro studies of coronary arterial vasoactivity.

Even though laboratory fish do not die after the coronary is tied off, the coronary circulation clearly has longer-term importance because collateral

arteries can grow around ablation sites in as little as 14 days (Daxboeck, 1982; Farrell et al., 1990b). Furthermore, even though routine cardiac performance in vivo is unaffected by coronary ligation (Gamperl et al., 1994), a coronary circulation improves the maximal performance of in vitro perfused hearts (Davie and Farrell, 1991a,b; Davie et al., 1992). Therefore, the coronary circulation increases in its importance in situations where the heart is working harder (and increased myocardial oxygen demand) and when there are hypoxic conditions (there is less oxygen in the blood).

It has been estimated that the total oxygen consumption of the salmon heart under routine conditions could be supplied by as little as 4% of the oxygen contained in the venous blood (Farrell et al., 1985). Thus, unless there is a limitation on oxygen diffusion from the lumen to the compact myocardium, which will increase in likelihood as fish get larger, there is little need for a supplemental coronary circulation under routine conditions. During swimming, however, the oxygen demand of the heart may increase 4- to 6-fold and at the same time venous oxygen content may decrease 4-fold as a result of increased oxygen extraction by locomotory muscles. Thus, it is not surprising that the coronary supply of oxygen to the heart increases in importance when salmon swim. In fact, salmon with a ligated coronary artery and no collateral vessel formation cannot swim as fast (Farrell and Steffensen, 1987) and do not increase ventral aortic blood pressure nearly as much as control fish during swimming (Steffensen and Farrell, 1998). Furthermore, Farrell et al. (1992b) suggested that the poor maximum performance of in vitro perfused tuna hearts was a direct result of inadequate coronary perfusion because of the low oxygen content of the saline. This methodological problem has apparently been resolved by perfusing the tuna coronary circulation with blood (Barbara Block, pers. comm). Interestingly, when coronary-ligated trout were swum to exhaustion in hypoxic water, uncharacteristic arrhythmias developed in some fish while they were recovering in normoxic water (Steffensen and Farrell, 1998) and the heart could stop beating for periods of up to 40 s. Consequently, the coronary circulation may play just as important a role during the recovery from exercise, as well as during the exercise bout itself

Coronary blood flow has been measured as 1.1% of total cardiac output in coho salmon (Axelsson and Farrell, 1993). This value is apparently much lower than that reported for mammalian hearts (coronary blood flow 4–5% of routine cardiac output). However, if account is made for the fact that only 40% of the coho salmon ventricle received coronary blood flow, the tissue specific flow rate for ventricular muscle in coho salmon is closer to that in mammals. When rainbow trout swim, a 2.1-fold increase in cardiac power output was matched by a 2.1-fold increase in coronary blood flow (note that these fish were not swum maximally; Gamperl et al., 1995). Mild hypoxia (9 kPa) increased routine coronary blood flow by 35%, presumably to compensate for decreased arterial blood saturation and/or increased tissue oxygen extraction that decreased venous oxygen content. Moreover, when rainbow trout swim under hypoxic conditions, coronary blood flow increased 2.3-fold but no further, suggesting that this is the maximum coronary blood flow reserve.

Given the above, the prediction is that the effect of coronary lesions on coronary blood flow, if there is any affect at all, would manifest itself in situations where fish were swimming hard, and when they were exposed to hypoxic water. It is also possible that coronary lesions could alter the vasoactive control mechanisms that contribute to increases in coronary blood flow (Axelsson and Farrell, 1993; Gamperl et al., 1995). The vasoactive mechanisms present in fish coronary artery vascular rings have been summarized (Farrell and Jones, 1992). In addition, coronary arterial vasoactivity was studied in adult rainbow trout and steelhead salmon that possessed coronary lesions, but none of the qualitative species differences could be related to any differences in lesion severity (Farrell and Johansen, 1995). Instead, prostanoids, including prostaglandin $F_{2\alpha}$, were shown to exert powerful controls over coronary vasoactivity, adding to their potential roles in coronary VSM mitosis.

Phasic measurements of coronary blood flow have given us insight into how coronary blood flow maybe disturbed. When cardiac output is low, diastolic runoff in the coronary artery is quite normal, based on simultaneous recordings of ventral aortic blood flow and coronary blood flow (Fig. 5). When cardiac output is elevated, however, the coronary flow pattern is interrupted in phase with ventricular contraction (Axelsson and Farrell, 1993). This disruption could come about because of compression of myocardial vessels during ventricular contraction. Alternatively, it could be that

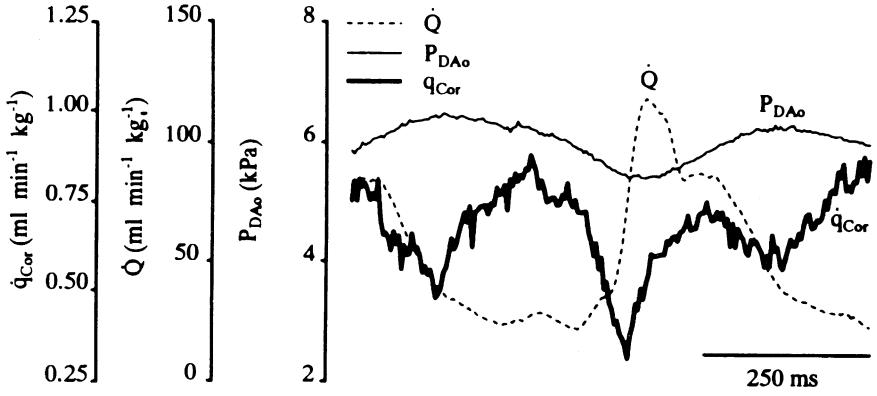

Fig. 5. Phasic recordings of coronary blood flow (q_{cor}), ventral aortic blood flow (Q) and dorsal aortic blood pressure (P_{da}) in an unaesthetised coho salmon. This example was taken from a fish with a particularly high cardiac output to illustrate how the pattern of coronary blood flow was disturbed. Here the coronary flow is interrupted, resulting in a double peak. Normally, with low cardiac outputs there is a single peak. (Adapted from Axelsson and Farrell 1993.)

in these high flow and blood pressure states, the elastic bulbus arterious is over-distended, as suggested earlier, and thus disrupts blood flow in the coronary artery.

In summary, coronary blood flow in salmonids can more than double in situations where oxygen demand of the heart increases and venous oxygen content decreases, i.e. exercise and environmental hypoxia. Therefore, coronary blood flow has increasing importance during swimming and during hypoxic exposure. However, the impact of lesions on coronary blood flow to the heart and its control has received too little study to draw any firm conclusions.

6. Conclusion

An overview has been presented of what we know and what we suspect regarding the formation of coronary lesions in salmonids. Severe lesions become a fact of life for Atlantic and Pacific species of migrating salmon. Coronary arteriosclerosis in salmonids is age-related and starts well before maturation. Vascular injury to the coronary artery, as a result of the bulbus arteriosus being excessively distended, is proposed as an initiating mechanism for coronary lesion formation, possibly explaining why severe lesions are restricted primarily to the main coronary artery. Growth and growth rate are implicated in lesion progression. A faster growth rate could produce a more stressful life style, which in turn initiates more coronary vascular injury. Polyunsaturated fatty acids (and their metabolites) stimulate coronary artery VSM mitosis in salmon and could therefore be implicated in the progression of coronary lesions. Whether coronary lesions negatively impact blood flow to the salmon heart has not been properly studied, but if they do, it would be most significant when the fish exercise. If coronary arterial lesions do adversely affect blood flow to the heart, the selective effects would be most prominent in years when upstream migration conditions are particularly severe. As a closing thought, one is left wondering whether a faster growth rate is associated with a more stressful life style that in turn initiates more coronary vascular injury and coronary lesions, which in some years may prevent successful migration and spawning.

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