Cardiac thermal acclimation and adaption of the heart to extreme temperatures

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Key points

- An acute reduction in temperature decreases heart rate, and the rate and strength of muscle contraction. An increase in temperature has the opposite effect.
- There are multiple temperate species of fish that are exposed to seasonal changes in environmental temperature but maintain cardiac function.
- Thermal acclimation can affect the density and isoforms of K^+ channels expressed in the sarcolemma. This alters the duration of the action potential and helps to regulate heart rate.
- Thermal acclimation can alter the sensitivity of the heart to adrenergic stimulation, and thus, influence the rate and strength of contraction.
- Thermal acclimation can affect the amount of collagen in the ventricle and alter the thickness of the compact myocardium. Such changes are thought to help regulate the biomechanical properties of the muscle.
- Thermal acclimation influences the Ca^{2+} sensitivity of the myofilament, and affects relative heart size. These changes compensate for the effect of temperature changes on force and pressure generation.
- Energy production pathways are modified with thermal acclimation, including the type of metabolic fuel utilized.
- Adaptations to improve cardiac function at low temperature in Antarctic nototheniids include a significant increase in relative heart size and stroke volume, a reduction in hematocrit, and an increase in the diameter of the blood vessels that results in reduced arterial pressures.

Glossary

Acclimatization (acclimation) The inherent physiological response of an organism to environmental change, allowing it to maintain fitness across a range of environmental conditions.

Active properties of the heart ATP-dependent properties that affect muscle contraction, including the rate of cross-bridge cycling and Ca^{2+}sensitivity.

Cardiac contractility Ability of the heart to contract and generate force when intracellular Ca^{2+} levels rise.

Cardiac myofilaments Primarily composed of actin thin filaments and myosin thick filaments, and responsible for force generation in striated muscle.

Cardiac stiffness When cardiac muscle resists stretching, as determined by both active and passive properties of the muscle. Inverse of compliance.

Cardiac output Blood volume pumped by the heart per unit time, calculated as the product of heart rate and stroke volume.

Compact myocardium The outer layer of fish myocardium characterized by tightly packed and circumferentially arranged myocytes. This muscle layer encases the spongy myocardium.

Connective tissue A group of tissues that maintain the form of the body and the arrangement of its organs, and provide cohesion and internal support.
Diastole The period of the cardiac cycle when the ventricle is relaxed or relaxing. It is associated with filling of the ventricle with blood.
Differential protein isoform expression Changes in the expression of protein variants in a tissue as a result of a change in gene expression.
Eurythermal Describes an organism that can live in environments that undergo large changes in temperature.
In situ Being in the original position; used to describe experiments where measurements are taken on an organ (tissue) while it is still located within the animal.
Passive properties of the heart Non-contractile properties that affect the stiffness of the heart and influence the ability of the heart to relax and fill with blood between heart beats. This is affected by collagen composition and the sarcomere protein titin.
Protein isoforms Proteins that have different amino acid sequences, and may have similar, or different, functional characteristics. These different proteins are encoded by different genes or gene transcripts.
Pumping capacity The product of contraction rate (frequency) and force developed by isolated myocardial preparations.
Sarcolemma Plasma membrane of a muscle cell.
Specific heat capacity The amount of heat that must be added to one unit of mass of a substance in order to raise temperature by one unit.
Spongy myocardium The inner layer of fish myocardium characterized by a fine arrangement of muscular trabeculae that span the heart's chamber.
Stenothermal Describes an organism that cannot live in environments that undergo large changes in temperature.
Stroke volume (S_V) The amount of blood pumped by the heart per beat.
Temperature quotient (Q_{10}) A measure of the rate of change of a biological or chemical system as a consequence of increasing the temperature by 10 °C. The Q_{10} is calculated as: $Q_{10} = R1/R2^{10(T2-T1)}$, where R is the rate at a particular temperature and T is the temperature in degrees Celsius (°C).
Upper incipient lethal temperature (UILT) Maximum temperature at which 50% of the fish acclimated to a temperature survive after a defined period of exposure to the test temperature.

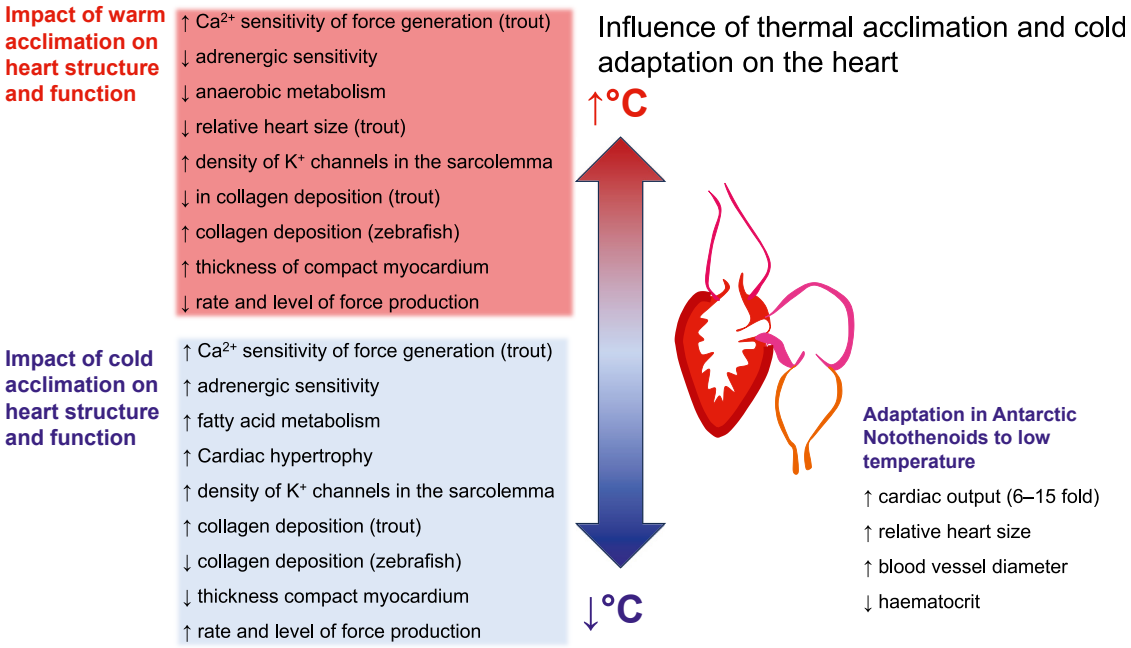
Nomenclature

AP Action Potential
ATP Adenosine Triphosphate
Ca^{2+} Calcium
CCO Cytochrome C Oxidase
CPT Carnitine Palmitoyl Transferase
CS Citrate Synthase
f_H Heart Rate
FKBPs FK-506 Binding Proteins
HOAD 3-Hydroxyacyl-Coa Dehydrogenase
I_{CaL} Primary Ca^{2+} Influx Pathway In The Fish Heart
K^+ Potassium
LDH Lactate Dehydrogenase
Na^+ Sodium
Q_{10} Temperature Quotient
RBC Red Blood Cells
ROS Reactive Oxygen Species
RyR Ryanodine Receptor
SERCA Sarco(Endo)Plasmic Reticulum Ca^{2+} ATPases
SR Sarcoplasmic Reticulum
S_V Stroke Volume
T_aO_2 Arterial Blood Oxygen Transport
UILT Upper Incipient Lethal Temperature

Abstract

An acute change in temperature has a significant effect on the contractile function of the heart. This is because of changes in the function of multiple cellular components including ion channels and transporters, metabolic enzymes and the contractile machinery. There are, however, multiple fish species that remain active in environments where temperature changes seasonally by at least 10 °C, or that live in Antarctica where temperatures do not increase over 0 °C. Being able to do so requires significant phenotypic plasticity/adaptation in the cardiovascular system of these species. Studies with e.g., rainbow trout and zebrafish demonstrate that thermal acclimation causes multiple changes to the heart thought to help maintain contractile function. This includes increased densities of ion channels in the sarcolemma, increased sensitivity of the myofilament to Ca^{2+}, increased reliance on fatty acids for energy production, increased sensitivity to adrenergic stimulation and changes to the size and composition of the heart. Study of Antarctic notothenioid fish demonstrates that the hearts of these fish have a much larger relative chamber volume, that the blood of some species contains no hemoglobin and that the diameter of some blood vessels are significantly larger than that in temperature species. These adaptations are thought to help maintain cardiac function in the subzero temperatures of Antarctic waters.

Teaching slide



Introduction

For fish to obtain sufficient O_2 from the water, fish blood must come into very close contact with it. As a result, the temperature of the blood and water equilibrate quickly. This means that the temperature of the heart is the same as that of the environment and can change by more than 20 °C over the course of the year (warming in summer and cooling in winter). Such a change in temperature has a significant effect on the heart's ability to contract and pump blood. For example, an acute (i.e., rapid, over minutes to days) lowering of temperature can decrease the strength and rate of heart contraction, and make it difficult for the fish to supply oxygen to meet their tissue oxygen requirements. However, if provided a sufficient amount of time to adjust to a new temperature (i.e., at least several weeks), there are some temperate and subtropical fish species that can largely maintain cardiac function relatively independent of seasonal temperate changes. These species include, for example, rainbow trout (*Oncorhynchus mykiss*) and brown trout (*Salmo trutta*), as well as the common carp (*Cyprinus carpio*) and zebrafish (*Danio rerio*). These eurythermal fish species undergo a seasonal, compensatory cardiac remodeling—based on differential and reversible gene expression—that maintains appropriate heart function across temperatures, a response called thermal acclimatization (Keen et al., 2016b). The ability of fish to modify or remodel their hearts to maintain function at the new environmental temperature will be the focus of the first part of this article.

Regulation of heart rate, and the ionic basis of contraction during thermal acclimation

Temperature directly influences the flux of ions that control heart function at the cellular level, and this impacts all contractile and electrical processes in the heart. The rainbow trout is a cold-active species, and much work has focused on the cellular adjustments that occur in this species' heart to counteract diminished functionality at colder temperatures. The previous articles: covered the concept of excitation-contraction (e-c) coupling, and explained how ions like Ca^{2+}, Na^{+} and K^{+} moving back and forth across the plasma membrane controls both the electrical activity and contractility of the cardiac muscle cell [also see (Vornanen et al., 2002)]; and explained how temperature directly impacts the open probability of the ion channels embedded in the membrane of heart cells. Warming increases the rate at which ions flow through the channels, but reduces the time the channels are open. Cooling has the opposite effect. Here, we describe how the heart remodels to compensate for this direct effect of temperature on ion flux, and how this is important for maintaining cardiac function when the temperature change is maintained for a long period of time (i.e., weeks to months).

Remodeling of heart rate (fH) and contractility

The intrinsic beating (pacemaker) rate of the rainbow trout heart at a given test-temperature is higher in cold-acclimated than warm-acclimated individuals (Shiels et al., 2002) (see **Fig. 1**A). However, at higher temperatures, the maximum f_H of cold-acclimated fish is lower than that of warm-acclimated fish, as reported for rainbow trout and roach (*Rutilus rutilus*). Indeed, acclimation of trout to warm temperature increases the maximum rate at which the myocardium can be stimulated to contract, and the amount of force developed at a particular contraction frequency (see **Fig. 1**B). This improves pumping capacity of the heart as compared to cold-acclimated fish, especially with regard to the acute effects of warming on myocardial function. Both of these observations are related to remodeling of cellular ion fluxes following thermal acclimation, which reset the pacemaker rate, modify the action potential of the atrial and ventricular muscle cells, and change cellular Ca^{2+} dynamics and the way that the myofilaments respond to Ca^{2+}.

As mentioned in the previous article, acute cooling prolongs the duration of the action potential (AP) and acute warming shortens it. These direct effects of warming and cooling can be compensated fully (e.g., in navaga, *Eleginus navaga*) (**Fig. 2**A), but more often only partially (e.g., in roach, pike, *Esox lucius*; burbot, *Lota lota*; and see **Fig. 2**B for bluefin tuna, *Thunnus orientalis*). These changes are largely related to alterations in the expression of cardiomyocyte sarcolemmal K^{+} channels. This change in K^{+} channel density, and in some cases K^{+} channel isoforms, shortens the duration of the AP during chronic cold and lengthens the duration of the AP after long-term exposure to warm temperatures. These effects offset the direct impacts of temperature on AP duration. Indeed, K^{+} channels are crucial for repolarizing the cardiomyocytes after contraction, and in contributing to the rhythm and rate of the heartbeat. When fish are exposed to chronic cooling, more delayed rectifier K^{+} channels, which carry the ion current I_{Kr}, are expressed in the membrane. K^{+} efflux through these channels repolarizes the cell membrane. Having more of these channels shortens the action potential duration and compensates for the direct effect of temperature. Thermal remodeling can also modify the kinetics of the K^{+} channels to ensure that the heart achieves proper repolarization despite the colder environment. By facilitating efficient repolarization, these K^{+} channels contribute to maintaining a stable and regular heart rhythm (Abramochkin and Vornanen, 2015).

Remodeling of cellular calcium flux

The changes in AP duration also counterbalance the potential increase in Ca^{2+} influx that occurs at colder temperatures during the extended AP plateau. For example, cooling directly decreases the amplitude and prolongs the kinetics of Ca^{2+} influx through the L-type Ca^{2+} channel (I_{CaL}, which is the primary Ca^{2+} influx pathway in the fish heart). The slowing of kinetics helps to compensate for the reduced amplitude of the I_{CaL}, meaning that the overall amount of Ca^{2+} influx is only slightly reduced in the cold (Shiels et al., 2000, 2015; Galli et al., 2011). However, because there is also a reduction in myofilament Ca^{2+} sensitivity in the cold (Gillis and Tibbits, 2002), ensuring adequate Ca^{2+} supply to the myofilaments is vital for ensuring strong contractions. Unlike with K^{+} channels, chronic temperature changes do not significantly alter the type or amount of Ca^{2+} channels in the cell membrane (Vornanen et al., 2002). Rather, the channels become more responsive to other modulators of ion flux like adrenergic stimulation. Adrenaline increases Ca^{2+} influx through the L-type Ca^{2+} channels by increasing the number of open channels and the time that they stay open. Indeed, chronic cooling increases the sensitivity of the rainbow trout heart to adrenergic stimulation, as an 8 °C decrease in temperature from 18 to 10 °C caused a 10-fold increase in sensitivity of the heart to adrenaline (Keen et al., 1993).

Ryanodine receptors (RyR) are responsible for the release of Ca^{2+} from the SR, and their opening is tightly controlled by mechanisms that act on both the cytosolic and luminal faces of these Ca^{2+}-release channels (Shiels and Sitsapesan, 2015). However, like L-type Ca^{2+} channels, thermal acclimation does not appear to modify the number of ryanodine receptors in the fish heart (Birkedal et al., 2009). SR Ca^{2+} release may be modulated by proteins that interact with the ryanodine receptor, including FK-506 binding proteins (FKBPs) and calmodulin with the cytosolic face, and junctophilin, triadin and CSQ2 with the luminal face (Shiels and Sitsapesan, 2015). Indeed, FKB12 expression in the trout heart was found to be higher in atrial than ventricular tissue, and after cold acclimation (Korajoki and Vornanen, 2014); although the relative role of RyRs and their modulators in the thermal acclimation of e-c coupling of fish hearts is still poorly understood.

Another way that cellular Ca^{2+} cycling can be maintained during chronic cold is by changing the expression and function of calcium-handling proteins such as the sarco(endo)plasmic reticulum Ca^{2+} ATPases (SERCA), which are responsible for pumping

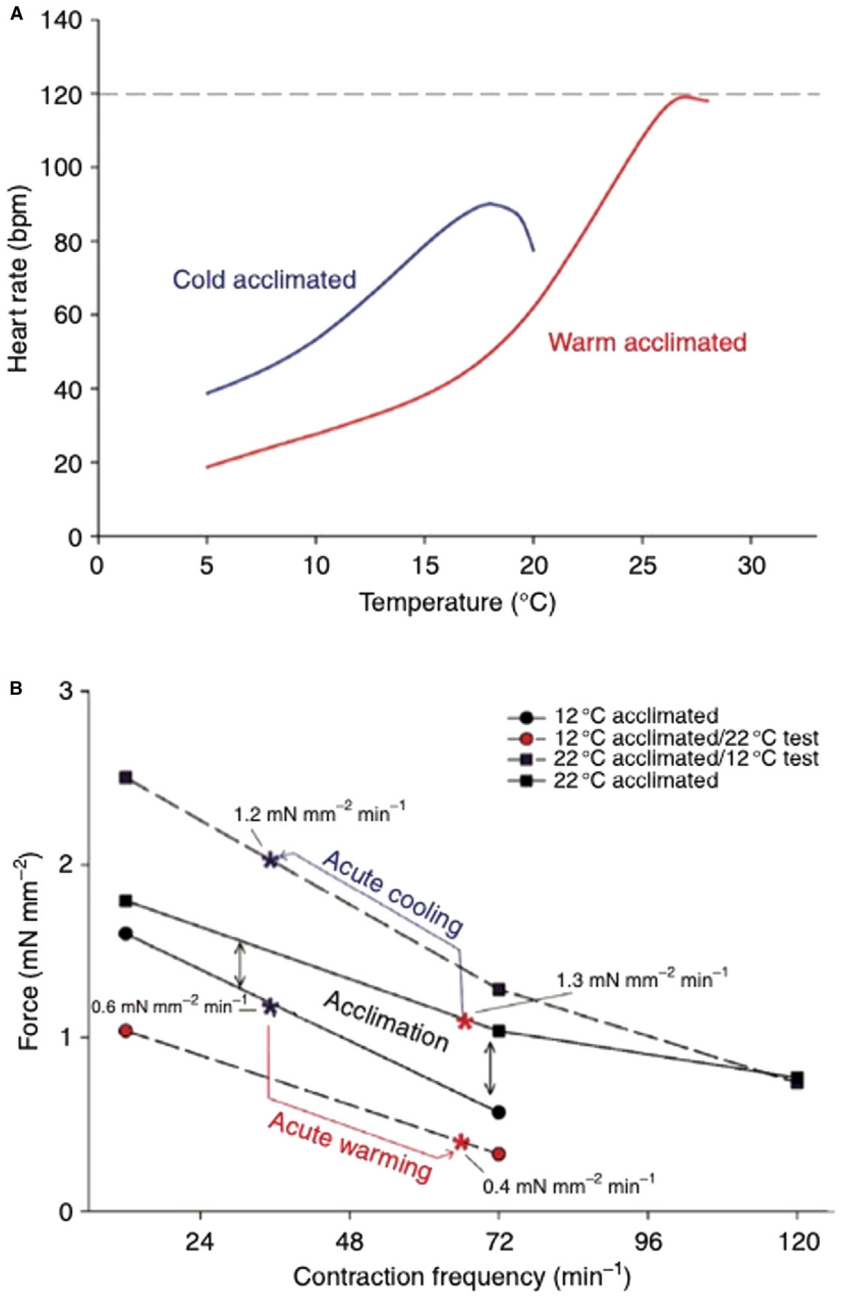


Fig. 1 (A) Effect of acute changes in temperature on the f_H of cold- and warm-acclimated rainbow trout. 120 beats per minute (bpm) represents the approximately upper limit of f_H in this species. (B) The effect of an acute temperature change and temperature acclimation on isometric force development by isolated ventricular muscle strips from the rainbow trout when paced at various contraction frequencies. The main points are as follows: cold- (12 °C) acclimated ventricular strips (irrespective of test temperature) cannot be paced faster than approximately 72 min^{-1}; acute warming (to 22 °C) severely compromises force development and pumping capacity; warm acclimation (at 22 °C) greatly increases forced developed at a particular temperature, and allows the trout heart to be paced up to approximately 120 min^{-1}; finally, acute cooling increases force development. Asterisk (*) indicates the approximate heart rate of live rainbow trout at each acclimation temperature, and the numbers associated with each asterisk indicate the heart muscle pumping capacity (product of force development and contraction frequency). (B) Modified from Shiels et al. (2002).

Ca^{2+} back into the SR after contraction. Changes in the activity of these proteins affect the rate of relaxation and the overall Ca^{2+} cycling within the myocytes. The SR is a membrane bound intracellular organelle that acts as a rapid storage and release site for Ca^{2+} in mammals, but its role in fish excitation-contraction coupling is more elusive (see Shiels and Sitsapesan, 2015). In some species of fish, including perch (Bowler and Tirri, 1990), burbot (Shiels et al., 2006) and tuna (Shiels et al., 2011), chronic cooling increases the amount of SR in the cardiomyocyte and the amount of Ca^{2+} available for binding to the myofilaments (Haverinen and Vornanen, 2009). SERCA controls the uptake of Ca^{2+} from the cytosol into the SR, and thus, its expression and activity are thought to be

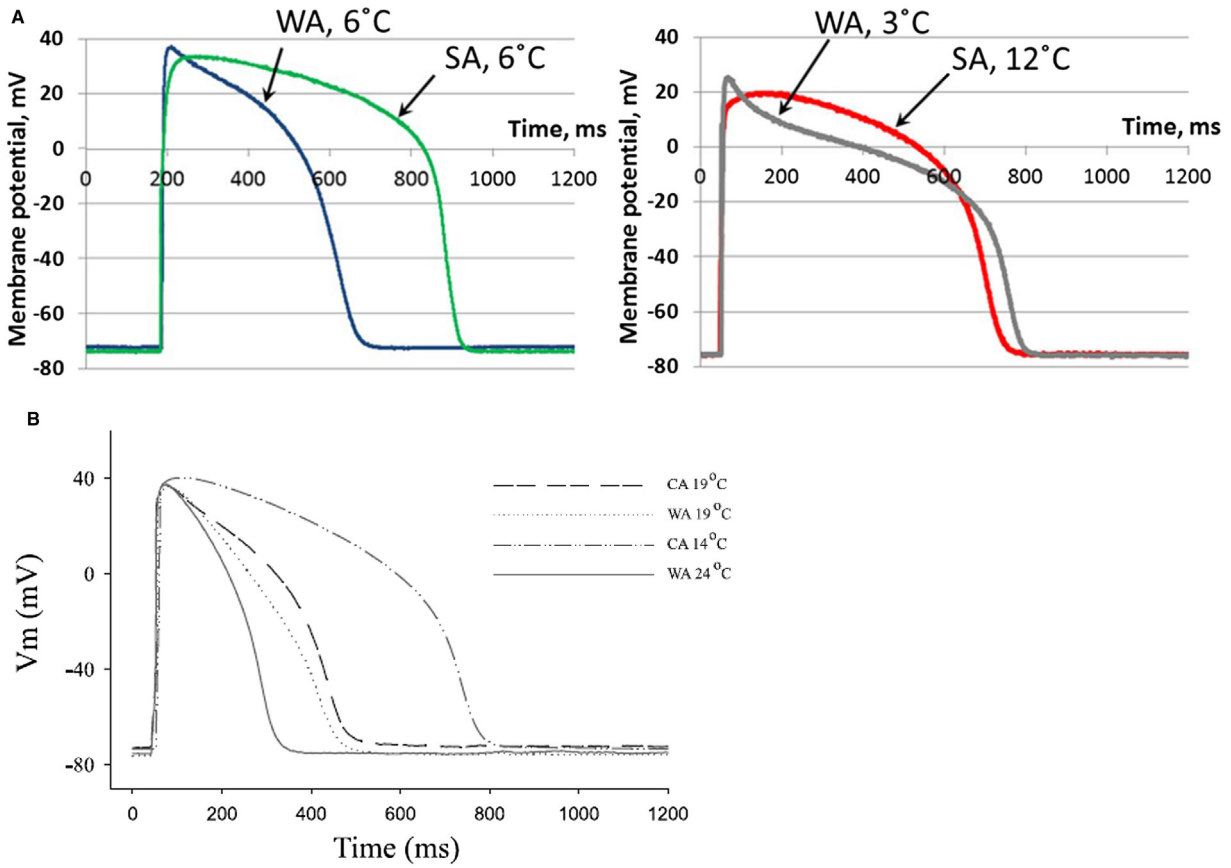


Fig. 2 Effect of thermal acclimation and acute temperature exposure on action potential characteristics in (A) AP waveforms in ventricular myocytes from winter-acclimatized (WA) and summer-acclimatized (SA) navaga (*Eleginus navaga*). Representative APs from single myocytes of WA and SA navaga at the same experimental temperature of 6 °C (left) and at the acclimatization temperatures (3 or 12 °C) of the fish (right). Note the almost complete thermal compensation of action potential duration (right). (B) Bluefin tuna (*Thunnus orientalis*) ventricular myocytes. Note the prolongation of action potential duration with acute cooling from 24 to 19 in the warm acclimated (WA, acclimated to 24 °C) myocytes and the acceleration of action potential duration with acute warming from 14 to 19 in the cold acclimated (CA, acclimated to 14 °C) myocytes. Also notice the minimal thermal compensation in this species with remodeling. This can be seen by the close match between the CA and WA traces when both are tested a common temperature of 19 °C. (A) From Abramochkin and Vornanen (2015). (B) Adapted from https://journals.physiology.org/doi/full/10.1152/ajpregu.90810.2008.

directly related to how much Ca^{2+} is in the SR. The activity of SERCA is regulated by an accessory protein called phospholamban which serves to slow SERCA Ca^{2+} pumping; thus, a reduction in phospholamban results in an increase in SERCA pumping and possibly more Ca^{2+} in the SR. Acclimation to cold increases the expression and activity of SERCA in the salmonid heart (Korajoki and Vornanen, 2012; Vornanen, 2021) (**Fig. 3**). This facilitates a faster rate of Ca^{2+} uptake into the SR (Aho and Vornanen, 1998), but it does not seem to increase the SR Ca^{2+} content in the rainbow trout heart (Haverinen and Vornanen, 2009). However, cold acclimation did increase SR Ca^{2+} content in the heart of the burbot (Haverinen and Vornanen, 2009) and increased SERCA content in the heart of seabass (Pettinau et al., 2022).

Response of the myofilament and contractile function to thermal acclimation

Myocytes contract when Ca^{2+} binds to the thin (actin) filament, and this results in the formation of force generating cross-bridges between actin and myosin. The level of force generation is determined by the number of cross-bridges formed, while the rate of force generation is determined by the rate of cross-bridge cycling. A reduction in temperature can decrease both of these factors by decreasing the Ca^{2+} sensitivity of the myofilament and the activity of actin-myosin ATPase (Keen et al., 2016b). The end result is a decrease in the capacity of the heart to pump blood around the body, and consequently, a reduction in whole animal aerobic energy production. Importantly, multiple studies have demonstrated that cold acclimation of the rainbow trout results in an increase in Ca^{2+} sensitivity of the myofilament (Klaiman et al., 2011, 2014). This response enhances the capacity of the myofilaments to generate force (Klaiman et al., 2014, **Fig. 4**, panels A and B), and occurs in concert with an increase in the activity of actin-myosin ATPase (Klaiman et al., 2011). In addition, work on isolated trout hearts shows that cold acclimation increases the rate and

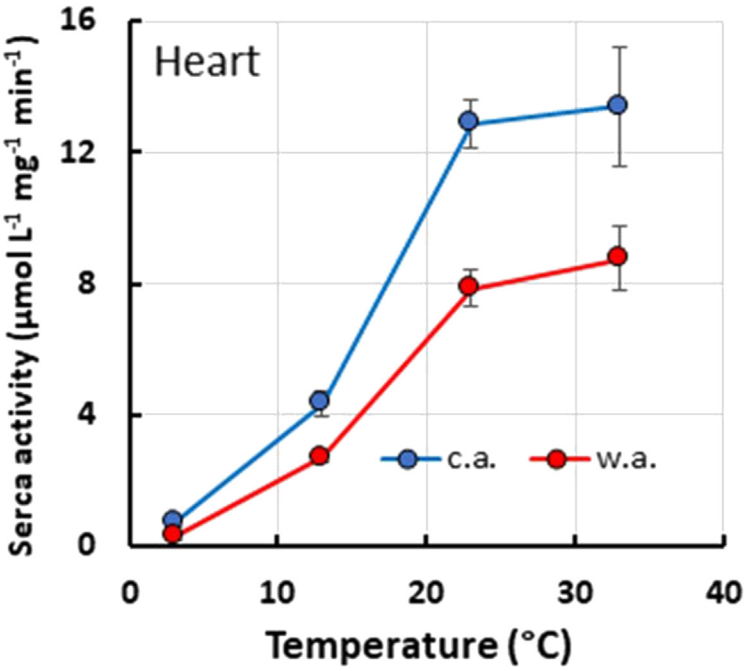


Fig. 3 Temperature dependence of SERCA activity in heart ventricle of brown trout (*Salmo trutta*) from cold- (+3 °C, c.a.) and warm- (+13 °C, w.a.) acclimated brown trout. SERCA activity is in μmols of inorganic phosphate liberated by mg tissue wet weight in 1 min as a function of temperature. Modified from Vornanen (2021).

level of pressure generation by the ventricle (Klaiman et al., 2014) (**Fig. 4**, Panel C). It is proposed that these changes, mediated through phosphorylation and/or differential isoform expression of the proteins involved, help to compensate for the effects of low temperature on the heart's contractile function (Alderman et al., 2012; Genge et al., 2013; Keen et al., 2016b; Klaiman et al., 2011, 2014). For example, Genge et al. (2013) demonstrated that cold acclimation of trout results in a switch in the type (isoform) of troponin C (TnC) expressed in the heart. TnC is the myofilament protein in striated muscle that binds Ca^{2+} and then initiates myocyte contraction. This result, therefore, suggests that changing the isoform of TnC expressed in the heart muscle actively regulates the capacity of the muscle to be activated by Ca^{2+}. Warm acclimation of some fish species can also result in changes to the function of the heart. For example, Klaiman et al. (2014) demonstrated that the magnitude of ventricular pressure generation by the hearts of warm acclimated trout (17 °C) was lower than that of control (11 °C) and cold-acclimated (4 °C) fish when measured at a common temperature of 15 °C (**Fig. 4**, Panel C). This suggests that the heart's function is actively tuned to the animal's thermal environment.

Influence of thermal acclimation on heart size, morphology and composition

In addition to altering heart function, thermal acclimation has also been reported to affect the size, morphology and collagen content of the hearts of some fish species. For example, cold acclimation has been reported to increase the relative heart mass of carp, *Cyprinus carpio* (Goolish, 1987); rainbow trout (Graham and Farrell, 1989); small mouth bass, *Micopterus dolomieui* (Sephton and Driedzic, 1991); and sea raven, *Hernitripterus americanus*, (Sephton and Driedzic, 1991). However, this is not a universal response as it does not occur in white perch, *Morone arnericana*, and yellow perch, *Perca flauescens* (Sephton and Driedzic, 1991). Cardiac hypertrophy with cold acclimation is mainly due to an increase in the size of the heart's myocytes (i.e., hypertrophy), and is hypothesized to increase stroke volume (S_V). This increase in S_V is needed to compensate for the negative effects of low temperatures on f_H and probably force development, and to overcome the increase in blood viscosity at cold temperatures. Importantly, while exposure of Atlantic salmon to very cold (<2 °C) temperatures increases relative ventricular mass, it also results in higher circulating levels of the stress hormone cortisol (Reid et al., 2002). This is relevant because cortisol-induced cardiac hypertrophy in trout has been associated with reductions in stroke volume and cardiac output, as well as the expression of biomarker genes for cardiac pathology (Johansen et al., 2011). This suggests that changes to the heart induced by extreme low temperatures, including cardiac hypertrophy, may sometimes be a pathological response.

For the heart to pump blood around the animal, it must first fill with blood during diastole. This function is controlled by the passive properties of the myocardium and central venous pressure, and is influenced by a number of factors including the thickness of the chamber walls and the stiffness of the myofilaments. If the heart is too stiff, the amount of blood that fills the ventricle between heartbeats is reduced, and this results in a decrease in cardiac output. For example, Keen et al. (2016a) demonstrated

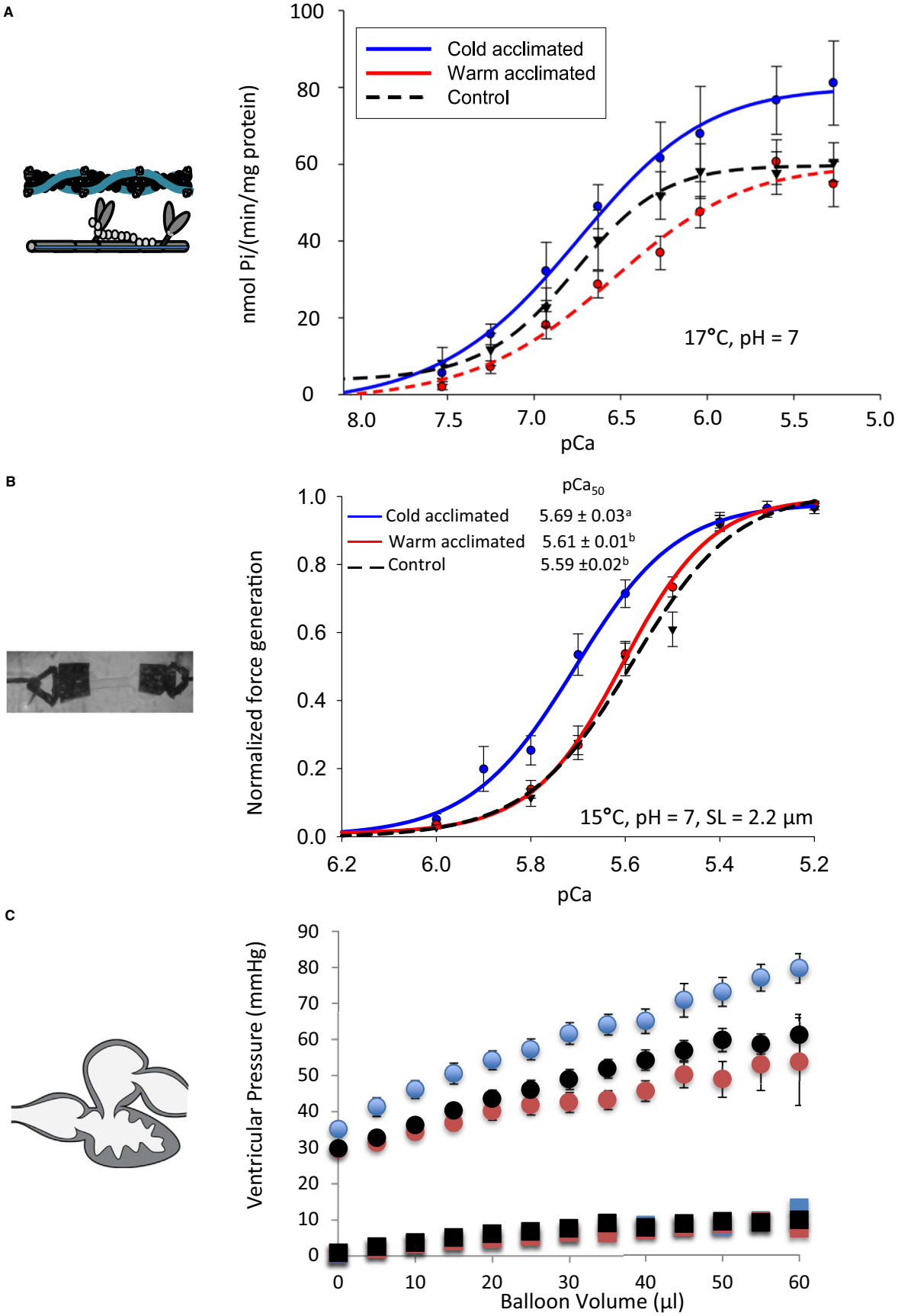


Fig. 4 Cardiac contractile properties of trout acclimated to 4 °C, 11 °C and 17 °C. (A) The maximal activity of actomyosin Mg^{2+}-ATPase isolated from ventricles is higher in preparations from cold-acclimated trout than those from warm-acclimated trout when measured at 17 °C. (B) The Ca^{2+} sensitivity of force generation by cardiac trabeculae from trout acclimated to 4 °C (blue line) is greater than that of trabeculae from trout acclimated to 11 °C (black line) or 17 °C (red line) when measured at 15 °C. pCa_{50} is the pCa at half-maximum force. SL, sarcomere length. (C) Developed pressures at ventricle volumes greater than baseline are higher for the 4 °C acclimated (blue symbols) fish than those for the 11 °C (black symbols) and 17 °C (red symbols) acclimated fish measured at 15 °C. Circles indicate ventricular developed pressures, while squares indicate diastolic pressures. All data are means ± s.e. Modified from Klaiman et al. (2011, 2014).

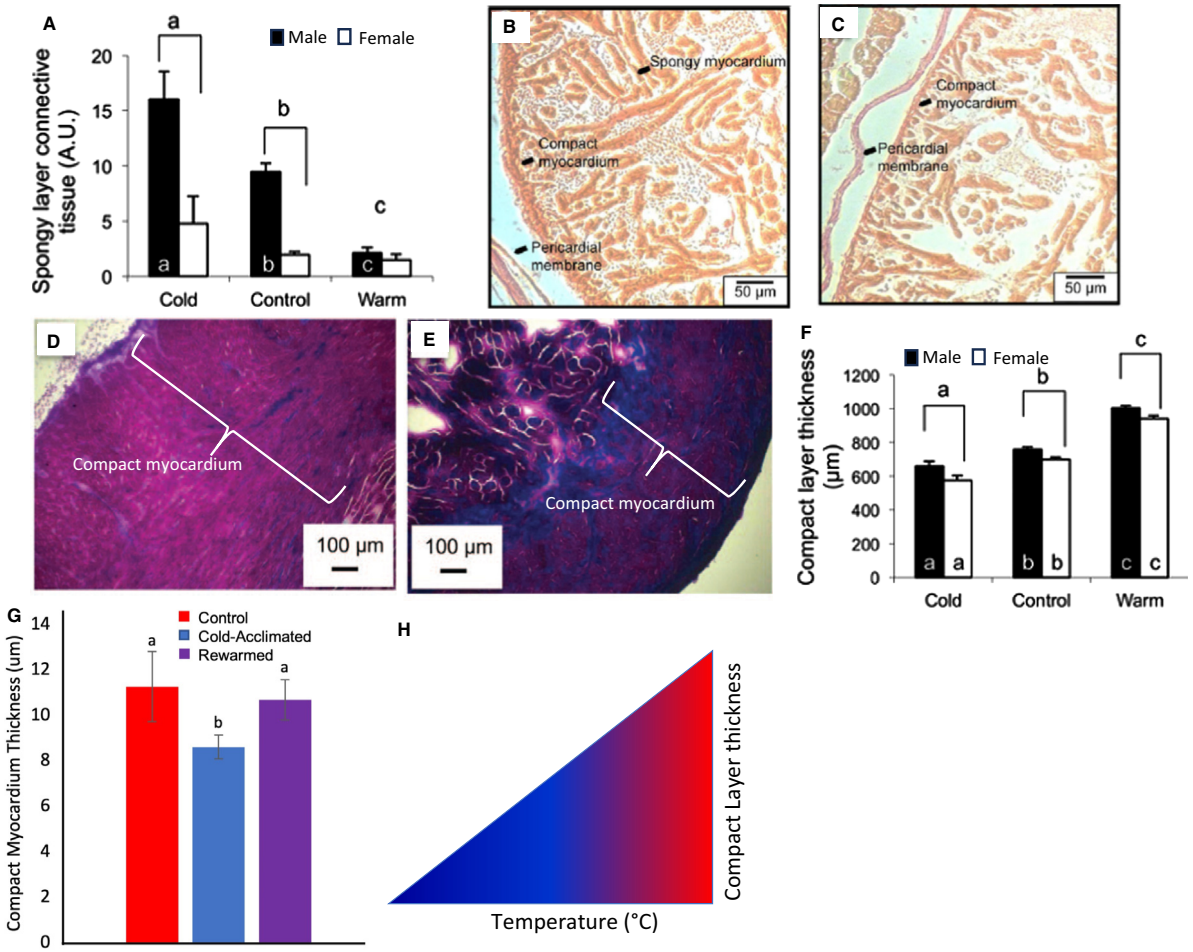


Fig. 5 Influence of thermal acclimation on the morphology and composition of the fish heart. (A) Cold acclimation of male trout caused an increase in connective tissue content in the compact layer compared to controls while warm acclimation of the male trout caused a decrease in connective tissue content compared to controls. The amount of connective tissue present is presented as arbitrary units (A.U.). Values are mean ± SEM. Brackets, indicate a significant difference between sexes within an acclimation group. Different letters above the bars indicate a significant difference between acclimation groups. Different letters within the bars indicate significant differences between acclimation temperatures when each sex is analyzed separately. (B) Micrograph of a heart from zebrafish acclimated to 28 °C. (C) Micrograph of a heart from zebrafish acclimated to 20 °C. (D) Micrograph of ventricular compact layer from rainbow trout acclimated to 17 °C. (E) Micrograph of ventricular compact layer from rainbow trout acclimated to 4 °C. Sections in panel A and B were stained with picro sirius red where pink indicates collagen. Sections in panel C and D were stained with Masson's trichrome where pink/purple is muscle, blue is connective tissue, and white or very pale pink is "extra bundular" space. (F) Influence of thermal acclimation on thickness of the compact myocardium in rainbow trout ($p < 0.05$). (G) Compact myocardial thickness of control, cold-acclimated, and rewarmed zebrafish at 23 weeks. (H) Relationship between acclimation temperature and the thickness of the spongy myocardium. (H) Adapted from Klaiman et al. (2011, 2014), Shaftoe et al. (2023).

that cold acclimation of rainbow trout increases the passive stiffness of the whole ventricle. It has been proposed that this response may help maintain the structural integrity of the heart as hemodynamic stress, caused by an increase in blood viscosity, increases at lower temperatures. This increase in passive stiffness of the trout heart is likely due to increases in the collagen content of the myocardium [(Keen et al., 2016a; Klaiman et al., 2011); **Fig. 5**A]. Collagen is the primary component of the extracellular matrix, and provides structural stability to the myocardium by helping the cells that make up this tissue adhere to each other, and resist deformation. However, excessive stiffening of the myocardium caused by an increase in collagen deposition in the mammalian heart has been shown to reduce diastolic filling, and in severe cases, lead to diastolic dysfunction (Collier et al., 2012). Changes in the collagen composition of the trout heart with cold acclimation are also proposed to help maintain structural integrity of the muscle as it undergoes hypertrophy (Keen et al., 2016b; Klaiman et al., 2011).

Cold acclimation of zebrafish (**Fig. 5**B and C) and rainbow trout (**Fig. 5**D–F) has also been reported to result in a decrease in the thickness of the compact myocardium (Johnson et al., 2014; Keen et al., 2016b; Klaiman et al., 2011); this layer of muscle encapsulates (surrounds) the heart and provides biomechanical stability. A reduction in its thickness is thought to facilitate easier filling during diastole, thereby helping to compensate for changes in biomechanical stiffness caused by a reduction in temperature (Keen et al., 2016b; Klaiman et al., 2011).

Warm acclimation has also been found to affect the structure and composition of the heart. However, the results are not consistent between experiments/species. For example, Keen et al. (2016b) and Klaiman et al. (2011) showed that warm acclimation of rainbow trout resulted in a decrease in ventricular mass, an increase in the thickness of the compact myocardium, and a decrease in connective tissue content. In contrast, Anttila et al. (2015) found that warm acclimation of Atlantic salmon, *Salmo salar*, resulted in a higher proportion of compact myocardium when it was combined with daily hypoxia, and that there was no response in Arctic char (*Salvelinus alpinus*) treated similarly. In addition, Gamperl et al. (2020) showed that while relative ventricular mass increased in Atlantic salmon held at temperatures above 20 °C for a prolonged period, there was no change in the proportion of compact myocardium.

The decrease in ventricular mass in trout with warm acclimation was due to a reduction in the amount of spongy myocardium, and this change is thought to reduce the volume of blood being pumped per beat (Keen et al., 2016b). However as heart rate in fish can increase with warm acclimation (Aho and Vornanen, 2001; Badr et al., 2016; Lee et al., 2016), the end result may be less blood being pumped per beat but at a faster rate (Keen et al., 2016b). Finally, recent work by Shaftoe et al. (2023) demonstrated that rewarming of zebrafish reverses changes to the structure and function of the heart associated with cold acclimation. For example, cold acclimation (from 27 to 20 °C) resulted in a decrease in the thickness of the compact myocardium, but an increase in the thickness of the myocardium was seen with rewarming to 27 °C. These data suggest that the structure and function of the hearts of these fish follow seasonal changes in environmental temperature (Shaftoe et al., 2023) (**Fig. 5**G).

Energy production

The heart is a highly metabolic (energy demanding) organ in fishes, as in other organisms, and the capacity to supply ATP to support its pumping capacity is key to fishes being able to tolerate long-term temperature changes. At cold temperatures biochemical reaction rates are depressed, and thus, the challenge is to produce enough ATP to meet cardiac energy demand. In contrast, mitochondrial function must be increased at temperatures that can impair the capacity for oxidative phosphorylation, and result in the production of reactive oxygen species (ROS) that can damage a number of cellular structures/components. As with many aspects of fish physiology affected by environmental temperatures, researchers have examined aspects of cardiac energy metabolism in species from different thermal habitats.

With respect to cold-water species, such studies have shown that the activity of carnitine palmitoyl transferase (CPT) and 3-hydroxyacyl-CoA dehydrogenase (HOAD)—key enzymes of fatty acid metabolism—are higher in cold- as compared to warm-adapted fish (Hunter-Manseau et al., 2019). This suggests that fish exposed to prolonged periods of cold rely more on fatty acids as a fuel source to meet cardiac energy demands. This finding is supported by some (but not all) studies that have acclimated fish species to different temperatures, again showing that the heart's temperature-dependent response can be species-specific. In 5 vs. 15 °C acclimated trout, Hicks et al. (1996) showed that fatty acid uptake was higher in fish acclimated to the lower temperature, and that while there was no difference in CPT enzyme activity, there was a 2-fold increase in fatty acyl-CoA synthetase—this is the first step in the biochemical pathway leading to the oxidation of fatty acids in the mitochondria. Also, the conclusion of a number of studies is that cardiac metabolism is more reliant on aerobic metabolism (as opposed to anaerobic glycolysis), and that fatty acid metabolism is favored over carbohydrate metabolism in fish (e.g., see Jayasundara et al., 2015; Rodnick and Gesser, 2017). Interestingly, however, this increased reliance on aerobic metabolism does not appear to be related to an increase in mitochondrial density, as has been observed in other tissues such as red skeletal muscle. With respect to energy usage by the heart, cold acclimation can result in cardiac enlargement, and this is hypothesized to decrease the amount of work that has to be performed by each heart cell, and result in an increase in the mechanical efficiency of the muscle (Rodnick and Gesser, 2017). Finally, protein synthesis in the heart is dramatically reduced (by >50%) in cold acclimated fish, and this allows more of the heart's ATP production to be directed to muscle contraction/cardiac performance (Rodnick and Gesser, 2017).

Cardiac failure is thought to be a primary determinant of the upper temperature tolerance of fishes, and there is evidence that ATP production in this critical organ may become impaired at high temperatures (Iftikar et al., 2014). Thus, it is important to understand how cardiac energy metabolism and mitochondrial function are affected by chronic exposure to warm temperatures, and may be impacted under climate change scenarios which predict that average water temperatures may increase by 2−4 °C by 2100. A number of studies have recently examined: (1) how high temperatures affect cardiac metabolism; and (2) whether acclimation to warm temperatures protects cardiac mitochondrial respiration (oxidative phosphorylation) at temperatures that approach a fish's tolerance limits. With regard to the effect of acclimation to warm temperatures, several studies have shown that this results in a decrease in protein levels or in the activity of enzymes that play central roles in cardiac metabolism and ATP production (e.g., Jayasundara et al., 2015; Ekström et al., 2017; Pichaud et al., 2019). This includes decreases in the activity of enzymes involved in anaerobic metabolism (lactate dehydrogenase, LDH) and the citric acid cycle (citrate synthase; CS), and in mitochondrial respiration associated with Complexes I and II of the electron transport chain. Some authors have suggested that this may be a form of thermal compensation by the heart that offsets Q_{10} effects on enzyme activity that would otherwise significantly elevate metabolic rate, and is associated with a decrease in cardiac mitochondrial density. Indeed, this may be why European perch (*Perca fluviatilis*) from an artificially heated ecosystem in the Baltic Sea ("Biotest" enclosure; ~23 °C in the summer) had lower values for CS and LDH, and a lower Complex-I catalytic capacity, at temperatures >30 °C as compared to fish from areas with typical Baltic sea summer temperatures (16 °C) (Ekström et al., 2017). However, these findings are not consistent with two recent studies on the Atlantic salmon (*Salmo salar*) (Gerber et al., 2020, 2021). These studies show that CS activity (also a marker of mitochondrial

density) is not affected by acclimation to warm temperatures (20 vs. 10 °C), and that Complex I catalytic capacity was greater and better coupled at 20 and 24 °C in salmon acclimated to the higher temperature. These differing results may be because the Atlantic salmon is a much more active species that has a higher aerobic/metabolic capacity than the other species examined. However, this hypothesis will require further testing. Nonetheless, the most important result of the Gerber et al. studies was that ROS production was 20–40% lower in mitochondria from 20 °C acclimated fish as compared to 10 °C acclimated fish when measured at temperatures between 20 and 28 °C. While this is the only study to make these specific measurements, this finding is supported by the reporting of a lower ratio for Complex I:Complex IV respiration in Ekström et al. (2017), which would theoretically result in less ROS production. Collectively, these data and that from others (also see Christen et al., 2018, 2020), suggest that: oxidative stress (ROS) management could be key to determining the high temperature limit of fishes; and may contribute to the increased cardiac and whole-animal thermal tolerance observed in perch from the artificially warmed "Biotest" enclosure.

Nervous control of cardiac function

The teleost heart receives autonomic innervation through the vagus nerve, which contains both excitatory adrenergic and inhibitory cholinergic fibers. This nervous innervation plays a significant role in regulating heart rate, and in some species the adrenergic fibers can also influence/regulate the ventricle's pumping capacity. As with many aspects of fish physiology, temperature appears to influence the extent to which these two antagonistic mechanisms (e.g., cholinergic tone, ↓ f_H; and adrenergic tone, ↑ f_H) affect heart function. Based on the measurement of cholinergic tone on a wide range of species inhabiting waters from −1 °C to >27 °C, Sandblom and Axelsson (2011) concluded that cholinergic tone is higher than adrenergic tone at both lower and higher ambient temperatures (**Fig. 6**). That cholinergic tone is higher in fish at warm temperatures is supported by recent studies on rainbow trout acclimated to 9 and 16 °C. Three weeks after the trout were transferred from the lower to the higher temperature, cholinergic tone increased from ~36 to 70% whereas adrenergic tone was unchanged at ~25% (Ekström et al., 2016). These authors suggest that this increase in cholinergic tone may reflect an adaptive mechanism. Having a high cholinergic tone would enable warm-acclimated fish to quickly increase f_H (and cardiac output) by releasing (decreasing) this tone, and may be fundamental to enabling fish to quickly meet the demands of energetically demanding processes at warm temperatures (e.g., swimming, digestion). The data at low temperatures (<5 °C) are dominated by Antarctic fish species, and thus, this high cholinergic tone may not be representative of other teleost fishes that experience temperatures down to ~0 °C (for example in winter). This is because there is some evidence that the heart of Antarctic fishes is not innervated by adrenergic nerves. Indeed, Porter et al. (2022) recently showed that while adrenergic tone doubled when 8 °C-acclimated Atlantic salmon were acutely (over 8 h) lowered to 1 °C, neither cholinergic or adrenergic tone were different when these fish were acclimated to 8 vs. 1 °C.

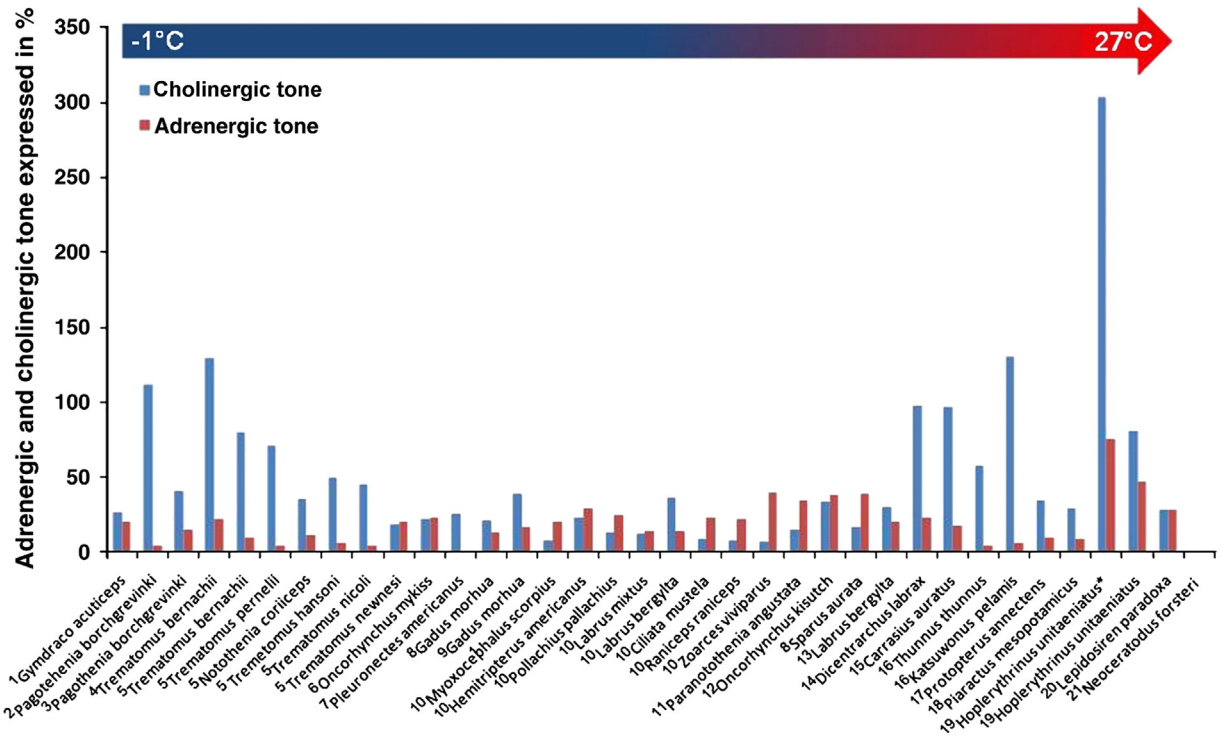


Fig. 6 Cholinergic and adrenergic tone on the heart in fish inhabiting cold (left end) to warm (right end) water temperatures. The numbers before the species names indicate the study where the data came from. Modified from Sandblom and Axelsson (2011).

Adaptations of the cardiovascular system to low temperatures

Fishes are a diverse taxonomic group, comprised of over 30,000 species, that employ a variety of life-history strategies, experience a range of thermal regimes/environments, and exhibit quite different thermal preferences and tolerances. Thus, it should be no surprise that the response of cardiac function to changes in temperature varies greatly among species (taxonomic groups). Unfortunately, there are few comprehensive studies of thermal sensitivity/adaptation of circulatory functions and their underlying mechanisms in species other than trout/salmon (with the exception of Antarctic fishes, see below). This makes it difficult to discern whether particular response patterns in cardiac function with temperature are characteristic of particular ecotypes (e.g., stenothermal vs. eurythermal, cold inactive vs. active). Regardless, a number of strategies have emerged that are utilized by fishes when temperature changes. For example, eurythermal species appear to have a lower f_H at equivalent temperatures, thus preserving their scope to increase f_H with temperature (Shiels et al., 2002). Although the Atlantic cod (*Gadus morhua*) heart does not exhibit cardiac enlargement at cold temperatures or cold-induced enhancement of intrinsic f_H that is typical of other fishes, and it is quite insensitive to adrenergic stimulation, a bell-shaped force–frequency relationship (i.e., positive at low contraction frequencies, negative at high contraction frequencies) appears to allow this species to elevate cardiac function at low temperatures and when acutely warmed (e.g., from 4 to 10 °C) (Lurman et al., 2012). Some species such as the sea raven (*Hemitripterus americanus*) and the crucian carp (*Carassius carassius*), which are inactive in winter and must conserve available energy, display a negative (inverse) thermal compensation of f_H (i.e., f_H is lower at a given temperature) (Graham and Farrell, 1989; Matikainen, 1992). Further, in the cold-acclimated crucian carp, action potential duration is prolonged, there is no contribution of the SR to cellular Ca^{2+} management, and myofibrillar adenosine triphosphatase (ATPase) activity (a major determinant of muscle contraction velocity) is greatly reduced (Vornanen, 1998). These adaptations appear to be critical to the survival of this species which experiences anoxia (a complete lack of oxygen), in addition to cold water temperatures, during the winter.

With regard to adaptations of the cardiovascular system to temperature, the Antarctic fishes are the only example where the influence of activity and temperature on cardiac function have been put into an appropriate phylogenetic framework. Fish in the Antarctic have been geographically and genetically isolated for approximately 25 million years, and live in frigid, glaciated waters characterized by constant temperatures (−1.8 to −1 °C) and high oxygen content. This exposure to permanent cold conditions has led to interesting phylogenetic specializations.

At these extremely cold temperatures, one of the greatest challenges faced by Antarctic fishes is to compensate for the inverse and exponential relationship between temperature and blood viscosity (a component of a fluid's resistance to flow). This increase in viscosity as temperature decreases is due to a number of factors, including:

1. A temperature-dependent increase in the viscosity of the plasma;
2. The accumulation of antifreeze glycoproteins in the blood to prevent the fish from freezing, the levels of these molecules reaching as high 3% (30 mg mL^{-1}); and
3. An increase in the stiffness of the erythrocytes (red blood cells, RBCs) that makes them less deformable and difficult to push through the vasculature.

To compensate for the increase in viscosity with temperature many Antarctic species have a reduced hematocrit (the proportion of the blood composed of RBCs), approximately one-half that of other teleosts (8–15% vs. ~20–40%) (Wells et al., 1990). Further, these fishes increase the fluidity of the RBC's cell membrane (by altering fatty acid composition) and decrease the amount of hemoglobin per cell (both of these changes increasing the ease at which the cells can be deformed) (Palmerini et al., 2009). Finally, they have arteries and veins that are considerably larger than normal for vertebrates. Collectively, these changes reduce the blood pressure that the heart must generate, while still providing sufficient oxygen transport to meet the fish's low metabolic demand at these frigid temperatures.

The challenge of increased blood viscosity also appears to have led to a very unique group of fish, the icefish (family Channichthyidae), which some scientists suggest represent an evolutionary dysadaptation permitted only because of the extremely stable Antarctic environment. The icefish have a hematocrit <1%, and thus the blood's oxygen-carrying capacity is only approximately 10% of red-blooded Antarctic fish species. In addition, some of them even lack the oxygen binding/transporting protein myoglobin in their heart and muscles (Sidell et al., 1997). This presents them with a distinct problem—how to deliver enough oxygen to the tissues?

The Channichthyidae have solved this problem by having a cardiac output 6–15 times greater than other teleosts, a blood volume 2–4 times that seen in red-blooded Antarctic fishes, and a heart and vasculature that are well suited to function as a high-flow, low-pressure system (Hemmingsen et al., 1972). For example, because f_H is no higher in icefish as compared to other fishes at these temperatures, the relative ventricular mass (i.e., g kg^{-1} of body mass; 0.4%) and S_V of icefishes are 3–4 times greater than those of most teleosts and the red-blood Antarctic fishes (**Fig. 7**A). Correspondingly, the bulbus arteriosus (see **Fig. 7**A) is greatly enlarged so that it can accommodate the ejection of such a large S_V. Channichthyids have increased the diameter and density of their vasculature, even more than observed in red-blooded Antarctic species. Finally, to overcome the difficulty of oxygen diffusion in the heart due to the lack of myoglobin, the cellular proliferation of mitochondria is appreciable (i.e., mitochondrial volume density is twice that measured in Antarctic red-blooded fishes; ~18% vs. 40%) (O'Brien and Sidell, 2000).

Given the specializations in cardiorespiratory function/morphology that have accompanied adaptation to cold temperatures in the Antarctic (<0 °C year round), one would expect that these fishes have a very limited capacity to tolerate or adapt to temperatures outside their normal thermal range. Although there is limited data, this appears to be true for aspects of cardiac metabolism. For

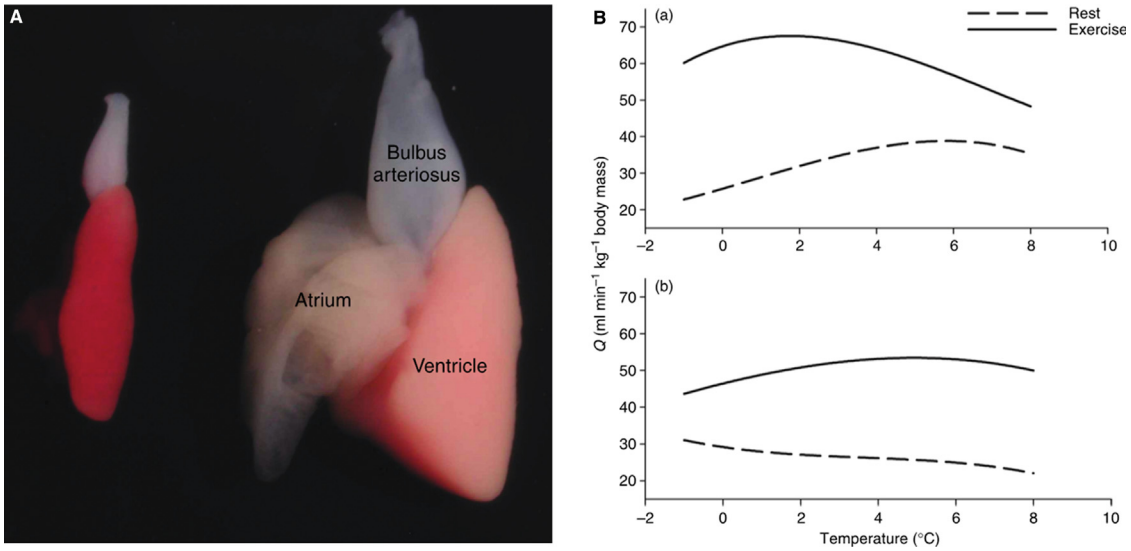


Fig. 7 Morphological and functional adaptations of hearts from Antarctic fish species. (A) Hearts from approximately 0.25 kg specimens of the red-blooded fish *Trematomus bernacchii* (left) and *Chionodraco hamatus* to illustrate the dramatic increase in heart size displayed by Antarctic icefishes. (B) The effect of an acute increase in temperature on resting and maximum (exercise induced) cardiac output (*Q*) in the Antarctic fish *Pagothenia borchgrevinki* acclimated to −1 °C (a) and 4 °C (b). Note the difference in cardiac scope (difference between resting and maximum *Q*) at the higher temperatures in fish acclimated to −1 vs. 4 °C. (A) Photograph courtesy of Dr. Bruno Tota. (B) Modified from Franklin et al. (2007).

example, warm acclimation leads to decreases in cardiac enzyme activity (CS, LDH and 3-hydroxyacyl CoA dehydrogenase), and it appears that the plasticity of mitochondrial function of Antarctic notothenioids is limited as compared to temperate fish species. For example, O'Brien et al. (2022) showed that there were no significant differences in cardiac mitochondrial State 2 or State 3 respiration, or in maximal oxidative phosphorylation or cytochrome C oxidase (CCO) activity in *N. coriiceps* acclimated to 0 vs. 5 °C. In fact, the only metabolic benefit of warm acclimation appears to be a reduction in oxidative stress. Transcript levels and the activity of catalase (a key antioxidant enzyme) were lower in the heart of *Notothenia coriiceps* when acclimated to warmer temperatures (O'Brien et al., 2021, 2022). However, Franklin et al. (2007) did show that red-blooded Antarctic fish *Pagothenia borchgrevinki* acclimated to 4 °C displayed compensatory adjustments in cardiovascular function (e.g., see **Fig. 7**B) that allow these fish to maintain their locomotory performance and cardiac scope until 8 °C. Further, Joyce et al. (2018) reported that cardiac performance can be improved in *N. coriiceps* with warm acclimation (5 °C for 6−9 weeks), and that this was associated with an increase in the temperature at which cardiac failure occurs when their hearts are acutely warmed (17.7 vs. 15.0 °C). These novel findings for *P. borchgrevinki* and *N. coriiceps* suggest that the circulatory system of at least some Antarctic fishes has retained a significant degree of functional plasticity, and that they may not be as severely impacted by accelerated climate change (global warming) as previously thought.

Summary

A change in water temperature impacts the ability of the fish heart to pump, and thus, to support the oxygen requirements of the animal. However, there are a number of fish species that undergo significant cardiac remodeling in response to prolonged changes in environmental temperature. In some species these changes are thought to help maintain cardiac output and are considered beneficial, such as those in rainbow trout. However, remodeling of the heart induced by thermal acclimation can be potentially detrimental in other species. For example, acclimation of Atlantic salmon to temperatures near their lower thermal limit may induce pathological changes in the heart. These data suggest that the response of the fish heart to temperature acclimation is species specific, and related to the range of their thermal niche over which the temperature change occurs. Significant adaptation of cardiac physiology is also evident in Antarctic fish species, those that lives in water at <0 °C throughout the year. These modifications to extreme conditions do not, however, prevent the hearts of these fish from showing considerable functional plasticity when exposed to variations in water temperature.

See Also: Anatomy in fishes and the associated coronary circulation; Cardiac morphology; Case study: The desert pupfish; Cellular ultrastructure of cardiac cells in fishes; Control of cardiovascular function; Effects of climate warming; Effects of temperature: An introduction; Electrical excitation, action potential and impulse conduction; Excitation-contraction coupling in fish cardiomyocytes; Integrated responses of the heart to acute changes in temperature; Measures of thermal tolerance; Physiology of cardiac pumping; Temperature and fish biology: Insights from metabolism.

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