Cardiovascular benefits of controlled isometric training may be due to an improvement in endothelial function via up regulation of nitric oxide synthase through shear stress induced transcriptional mechanisms

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SUMMARY Essential hypertension is associated with a reduced functioning of endothelial release of nitric oxide. Impaired endothelium-dependent vascular relaxation has been documented in virtually all cardiovascular disorders and appears to occur early in the course of cardiovascular disorders such as arteriosclerosis, diabetes mellitus, hypercholesterolemia, hypertension, and heart failure.

Endothelium-dependent vasodilatation is most actively driven by the release of nitric oxide (NO) in response to shear stress on the arterial wall. The exposure to shear stress is also a regulating factor in the transcription of endothelial nitric oxide synthase (eNOS); an increase in shear stress upregulates the production of eNOS. These regulating mechanisms are initiated at the onset of an increase in shear stress, and produce structural changes through a signaling cascade that involves transcription factor activation, gene regulation and protein synthesis, and ends in a remodeling of the vessel to align with the applied shear stress.

If there is a deficiency of eNOS activity/availability, then the basal release of NO will not properly dilate the arteries, and the basal sympathetic activity will allow the vascular smooth muscle to constrict the vessel to a smaller diameter. This results in a net increase in total peripheral resistance (TPR), increase in systemic blood pressure, a net increase in wall shear stress, and eventually a balanced regulation of eNOS and release of NO to hold the dilation to the new diameter. This feed back provides homeostasis, but at the price of elevated systemic pressures.

A transient increase in systemic mean arterial pressure (MAP) increases the mean shear stress in vivo throughout the entire arterial tree. Sustained, brief (one minute), increases in MAP may be able to initiate the signaling cascade that leads to an upregulation in eNOS in the entire arterial tree, an improved basal release of NO, a reduction in total peripheral resistance (TPR), and a reduction in arterial blood pressure.

A simple method for eliciting a transient increase in MAP is through the use of acute controlled isometric efforts greater than 15% maximum voluntary contraction (MVC). During such a sustained effort, MAP rises constantly (pressor response). At higher levels of sustained force, MAP rises faster. A predictable level of MAP increase can be obtained by holding a set percentage of MVC for a set amount of time. This type of sustained isometric effort has been shown to reduce blood pressure over a four-week period and may be due to a systemic upregulation in eNOS. This type of training also maintains the benefit of reduced blood pressure, probably through maintenance of the new level of eNOS activity.

The cardiovascular benefits of chronic controlled isometric training may be due to an improvement in endothelial function; a common treatment goal for conditions such as arteriosclerosis, diabetes mellitus, hypercholesterolemia, hypertension, and heart failure.

Introduction

Essential hypertension is associated with a reduced functioning of endothelial release of nitric oxide.[171, 238, 239, 242, 249] Clinically effective antihypertensive therapy does not restore the impaired endothelium-dependent vascular relaxation of patients with essential hypertension.[250] This indicates that such endothelial dysfunction is either primary or becomes irreversible once the hypertensive process has become established. Impaired endothelium-dependent vascular relaxation has been documented in virtually all cardiovascular disorders and appears to occur early in the course of cardiovascular disorders such as arteriosclerosis, diabetes mellitus, hypercholesterolemia, hypertension, and heart failure.[153, 158]

Preservation or restoration of normal endothelial function has become a target for therapy and may even be considered as a surrogate for clinical events at later stages of cardiovascular disorders. Any therapy that can improve whole body endothelium-dependent vascular relaxation will have a significant application in a wide range of cardiovascular disorders. The restoration of proper local vasodilation action allows the arterial system to adapt to changes in flow requirements, without having to elicit increases in systemic blood pressure, to maintain proper blood perfusion.

The cardiovascular system

Classic descriptions of blood flow through the human body have focused on the major organs and the heart.[351] (Fig 1) This model illustrate the fundamental task of the circulatory system which is to provide oxygenated blood to the entire body. The system is comprised of several major divisions of blood flow arranged in a parallel combination. High pressure blood flows through a distribution of arteries of increasingly smaller diameter (Fig 2), through capillary beds in each organ, into small veins, and finally into large veins to be returned to the heart.

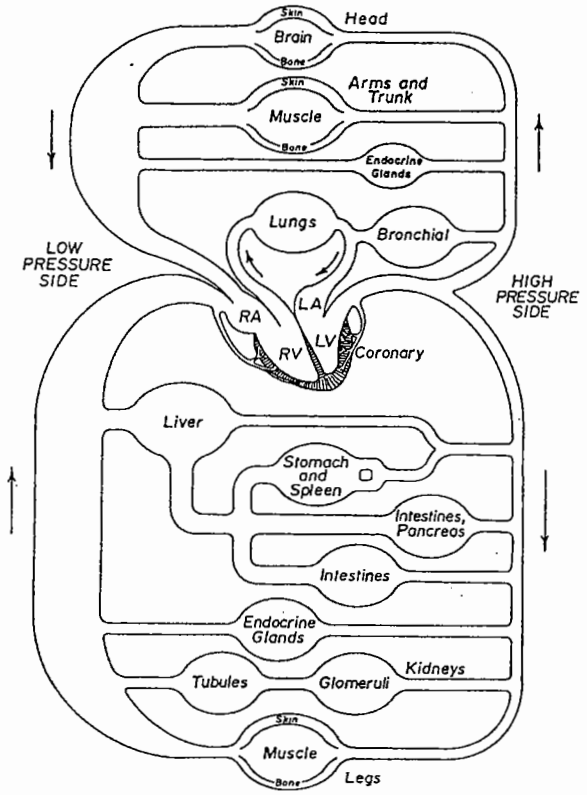

Figure 1. Distribution of blood to the systemic vascular beds.

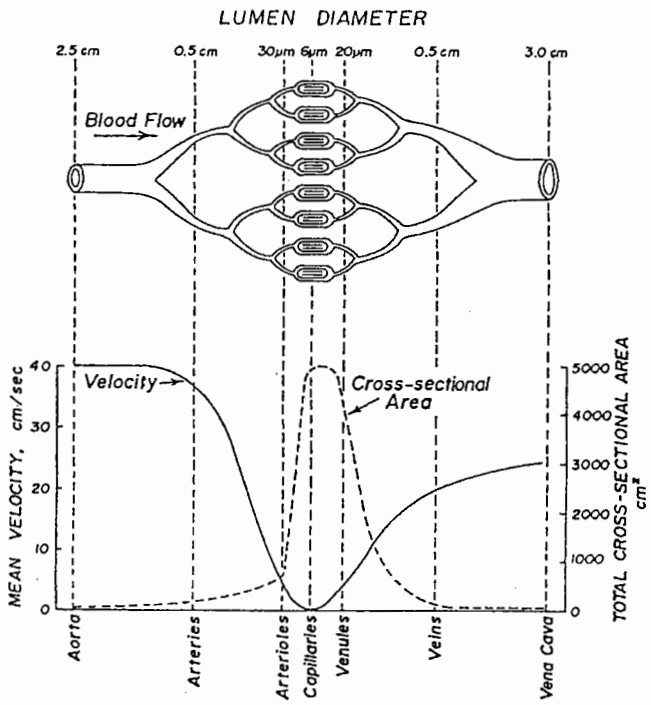

Figure 2. Changes in estimated total cross-sectional area and mean velocity of flow in consecutive segments of the systemic blood vessels.

Although individual arteries become smaller in diameter as the branching occurs, their number multiplies to such an extent that the total cross-sectional area of each consecutive section of vascular tree increases, to reach a maximum at the capillary level. As the total cross section increases, the relative resistance increases as well (Fig 3).

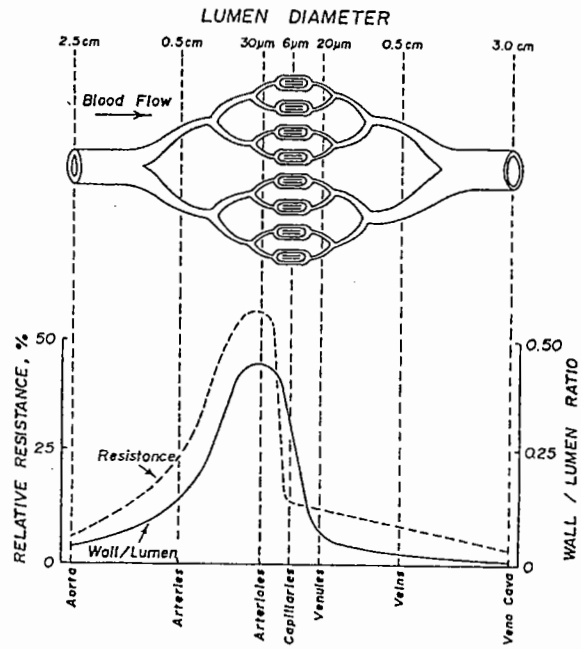

Figure 3. Changes in wall-to-lumen ratio and in relative resistance to blood flow.

At the level of the arterioles the resistance is highest. These 'resistance arterioles' therefore provide the most powerful modulators of blood flow throughout the body; a small percentage change in diameter will provide a large percentage change in resistance. These arteriole beds act as a large system of 'valves' that determine total blood flow through the body and through the individual organs (Fig 4). Total peripheral resistance is the circuit combination of the individual resistances.

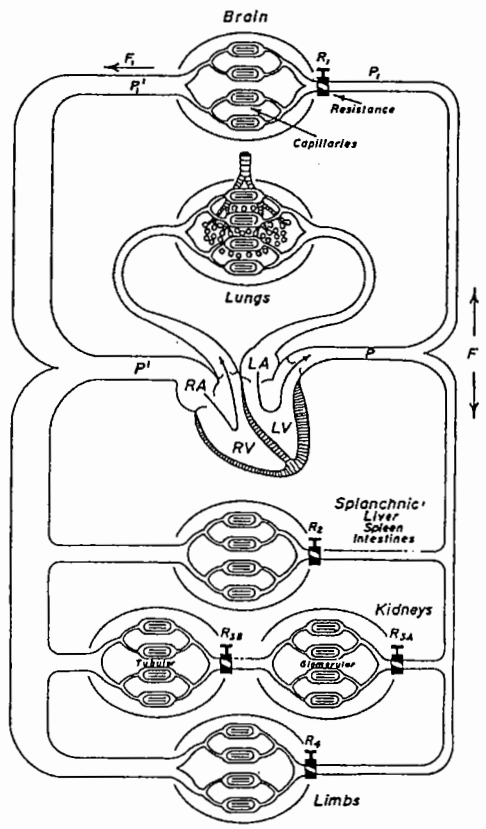

Figure 4. Interdependence of pressure, flow, and resistance to flow.

System pressure is then determined by the stroke volume, heart rate, and total peripheral resistance (Fig 5). An increase or decrease of resistance in a single arteriole bed will not drastically change the arterial blood pressure, but an increase of resistance in all arteriole beds definitely will increase systemic arterial pressure. Peripheral resistance changes in response to a wide host of influences (Fig 6), most notably the activation of sympathetic nerves.

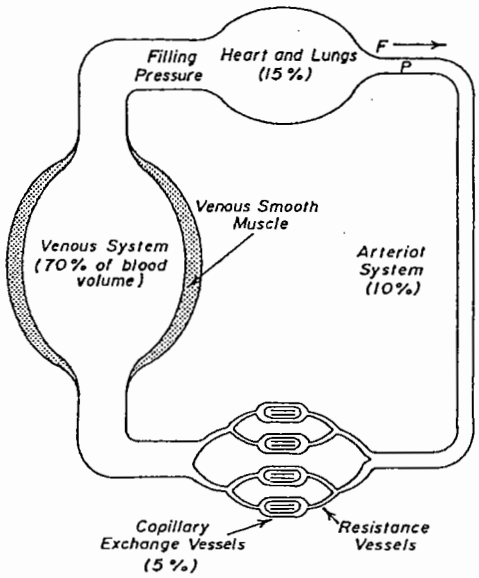

Figure 5. Distribution of blood volume and the role of the venous system in regulating the filling of the heart.

When the sympathetic nerves to a vessel are stimulated, norepinephrine (NE) is released, smooth muscle cells are activated to constrict, vessel diameter is decreased, and vessel resistance is increased (Fig 7). When the heart receives NE the rate of beating is increased. These combine to produce higher pressures and increased flow rates. This is the main control output of the brain to the cardiovascular system. There are many inputs to the control system, the most obvious being the baroreceptors; these provide direct information to the brain on the flow of blood from the heart and to the head. Flow of blood to the brain being the single most important controlled variable. Other input variables include chemoreceptors that detect levels of carbon dioxide, oxygen, and the metabolites of muscle activity.

Local control is modulated by the immediate response of resistance arterioles to these metabolites through vasodilatation. The dilation allows a greater flow of blood and carries away the increased concentration of metabolites, thus restoring nominal concentrations. As the metabolites are washed away, the normal vessel diameter is returned, and the system is ready for the next release of metabolites.

This is the fundamental view of the cardiovascular system: smooth muscles allow for constriction by command from the nervous system and they are relaxed in the presence of metabolites. This basic view of dilation is useful, but it is missing an important element, vessel dilation in response to blood flow. Blood vessels respond to an increase in flow by dilating, not due to metabolites, not due to an increase in pressure, but simply due to the fact that the blood is flowing past the vessel walls. This phenomenon is a recent discovery.[379, 386]

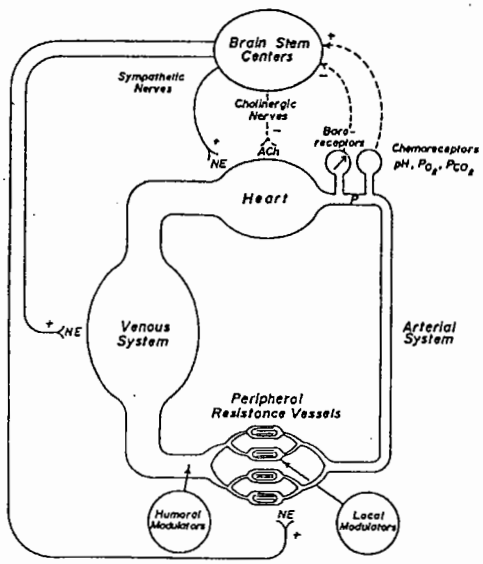

Figure 6. Nervous, humoral, and local regulation of the cardiovascular system.

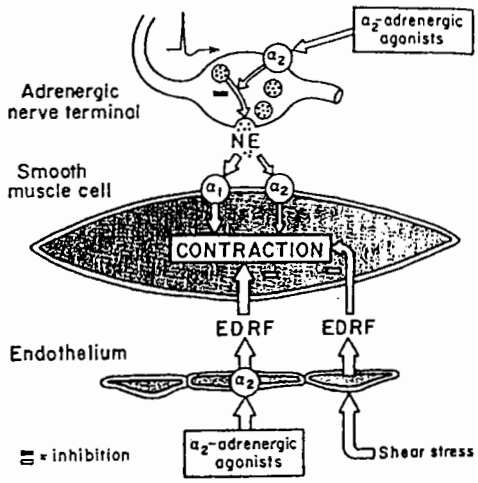

Figure 7. Schematic illustration of stimuli present for the contraction and relaxation of smooth muscle.

Endothelium-dependent vascular relaxation

The endothelium is located between flowing blood and the vascular wall.[357] Cells lining the arterial circulation are exposed to fluid forces of much greater magnitude than those experienced by other mammalian tissues. Consequently, mechanically related responses controlled by the endothelium have evolved as part of normal vascular physiology, most notably in the control of vascular tone where mechanisms responsible for the transmission and transduction of hemodynamic information from the blood to the underlying vessel wall reside in the endothelium.

Forces acting on an artery due to blood flow can be resolved into two principal vectors.[357] One is perpendicular to the wall and represents blood pressure, and the other acts parallel to the wall to create a frictional force, shear stress, at the surface of the endothelium. Although all of the vessel wall, including the endothelium, smooth muscle cells, and the extracellular matrix (collagen, elastin, proteoglycans), is subjected to stretch as a consequence of pulsatile pressure, the shear stress is received

principally at the endothelial surface. In large arteries, the mean wall shear stress is typically in the range of 20-40 dyn/cm^2 in regions of uniform geometry and away from branch vessels, however, the velocity profile varies with the cardiac cycle to produce a range of shear stress and shear stress gradients.

Shear stress transmission/transduction from the surface of the endothelial cells to the inner portions of the cell structure are mediated by mechanical connections of F-actin fibers, as well as through chemical messengers from shear stress response elements (SSRE). (Fig 8)

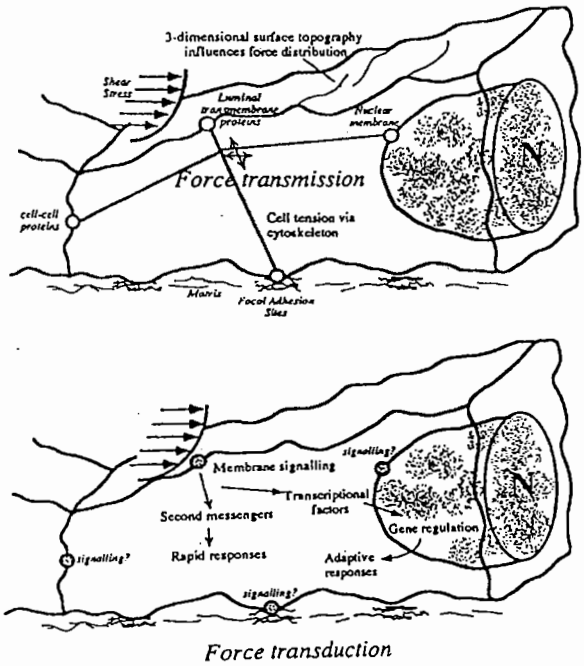

Figure 8. Separation of concepts of force transmission and force transduction.

One of the results of shear stress on endothelial cells is an activation of constitutive nitric oxide synthase (cNOS) to convert L-arginine to nitric oxide (NO) and L-citrulline. (Fig 9) Released NO then interacts with the smooth muscle cells nearby, and causes relaxation. (Fig 10) Continuous release of NO from endothelial cells in vivo modulates vascular tone, and provides immediate feedback for maintaining blood flow through the vessel. An increase in pressure will cause an increase in flow. The increase in flow will cause an increased shear stress, which causes an increased release of NO. The increased release of NO will provide a higher activation of smooth muscle relaxation, which provides a net dilation of the vessel, and reduces local pressure and returns the shear stress to nominal values. Thus, the endothelium acts to maintain a constant wall shear stress.[341]

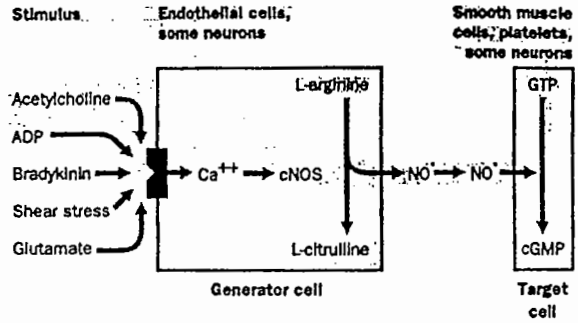

Figure 9.Scheme showing constitutive release of NO.

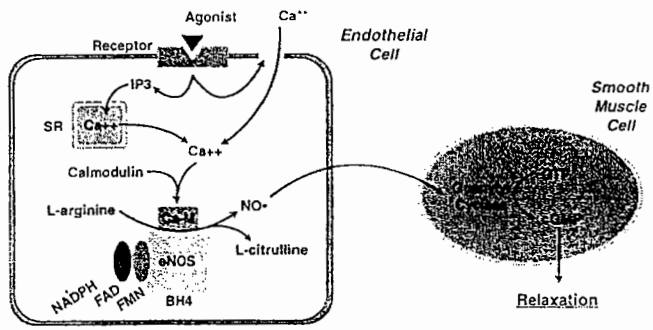

Figure 10.Receptor-stimulated NO biosynthetic pathway in endothelial cells and effects on vascular smooth muscle.

Systemic consequences of endothelium-dependent relaxation are the maintenance of blood perfusion to all parts of the body. During exercise, when metabolic demands change in specific parts of the body, local adaptations in each vessel provide the control mechanisms necessary to maintain local perfusion for local metabolic needs. (Fig 11) Nitric oxide release in response to shear stress provides an important 'negative feedback' element in the maintenance of cardiovascular function.

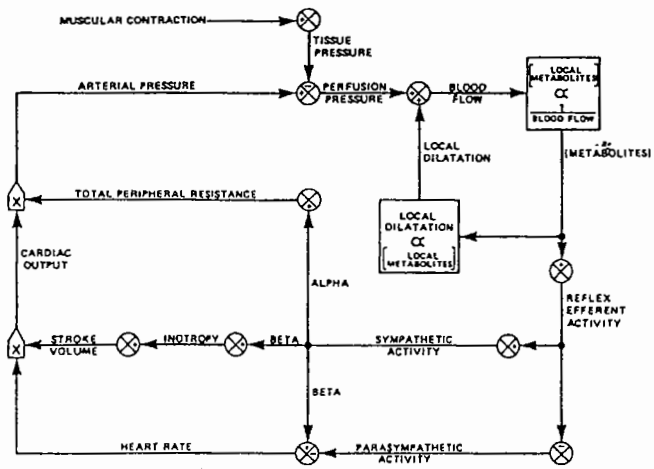

Figure 11. The principle mechanisms available for arterial pressure elevation as a result of isometric contraction.

Shear stress modulation of gene expression

The exposure to shear stress is also a regulating factor in the transcription of endothelial nitric oxide synthase (eNOS); an increase in shear stress upregulates the production of eNOS.[140, 159, 165] These regulating mechanisms are initiated at the onset of an increase in shear stress, and produce structural changes through a signaling cascade that involves transcription factor activation, gene regulation and protein synthesis, and ends in a remodeling of the vessel to align with the applied shear stress. (Table 1) (Fig 12)

Within 1 min	
K^+ channel activation IP_3 and DAG elevation cGMP increase Calcium increase	Initiation of signaling
Acute end responses (NO, neurotransmitter, and PGI_2 release)	
1 min to 1 h	
G protein activation MAP kinase signaling NFκB activation SSRE-dependent gene regulation: PDGF-B, c-*jun* bFGF upregulation Pinocytosis stimulated	Signaling cascades Transcription factor activation and initiation of gene regulation
1–6 h	
SSRE-dependent gene regulation: eNOS, tPA, TGF-β, ICAM-1, c-*fos*, MCP-1 Stimulation of HSP 70 Downregulation of ET-1 Cytoskeletal rearrangement Focal adhesion rearrangement Transient rearrangement of Golgi and MTOC	Gene regulation and protein synthesis Beginning of cell-wide adaptive responses
>6 h	
Reorganization of luminal surface Cell alignment Completion of cytoskeletal rearrangement Increased mechanical stiffness Decreased fibronectin synthesis Changes of TM expression Stimulation of histidine decarboxylase Enhanced LDL metabolism Induced MHC antigen expression	Adaptive responses to new hemodynamic conditions

Table 1. Endothelial responses to unidirectional shear stress: temporal groupings.

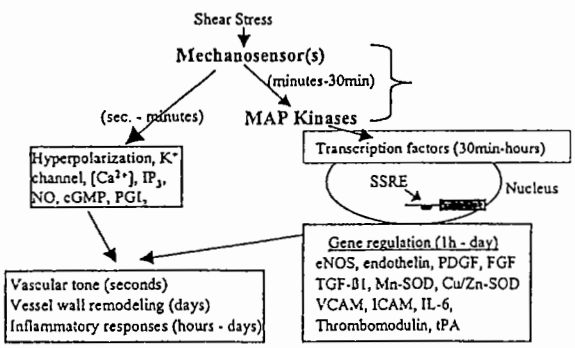

Figure 12. Shear stress is a key regulator of endothelial cell function.

These processes are active constantly. They are what allow the cardiovascular system to grow as an individual grows. When the system is insufficient for proper delivery of blood, then the system is stimulated to remodel its structure through activation of increased growth factor secretion and other stimulator mechanisms that allow the structure to adapt to a new equilibrium point. These are also the mechanisms that allow the system to repair itself when damaged. A physical puncture of a vessel results in a gap in the endothelial cells, which results in platelet adhesion and aggregation, which leads to a closure of the gap. Decreased NO concentration in the area of the platelet covered area allows smooth muscle cell growth to run unchecked, thus growing new material over the plugged hole. Eventually the nearby endothelial cells grow over the new smooth muscle cells, and the repair is complete.

Shear stress effects on structure

Along with the gene expression dependencies on shear stress, structural adaptations are not only driven by the level of shear stress, but generally cause alignment with the average direction of blood flow. Endothelial cells cultured under no-flow conditions are polygonal in shape, and have no preferred orientation. (Fig 13a) After exposure to constant flow, the cells align with the direction of flow, and take on an elongated shape (Fig 13b). These changes not only affect the internal functioning of the endothelial cell, but have the net effect of reducing the resistance to flow on the outer surface. When the cells are aligned, the F-actin fibers are arranged in a mostly parallel fashion, and thus the fundamental mechanical properties of the endothelium is different than when under no flow conditions. There is also a difference in the cytoskeletal elements just beneath the membrane surface which result in a more rigid configuration when aligned with a flow direction.[357] These mechanical adaptations affect the passive response of the vessel to distention by pulse pressures.

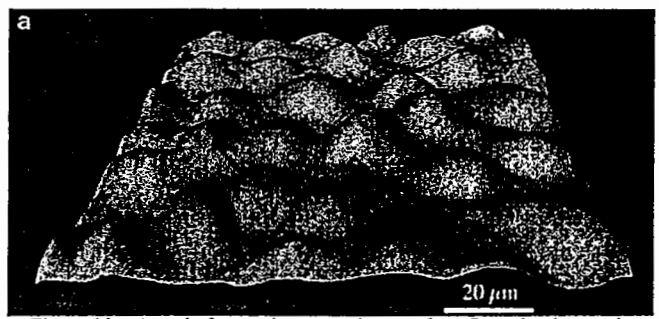

Figure 13a. Atomic force microscope image of confluent bovine aortic endothelial cells cultured under no flow conditions.

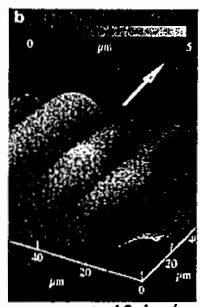

Figure 13b. After 24-h exposure to 12 dyn/cm^2 shear stress in steady laminar flow Arrow indicates direction of flow.

The nucleus of the endothelial cells elongate in the direction of flow[387], and are mobile enough that if the flow pattern is rotated 90 degrees, the structure remodels to align with the new flow direction in less than 10 days.

Time constants of adaptation to shear stress

Of the enzyme and structural adaptations to shear stress, there are definite stimulus times required for activation of changes. Certainly, a fraction of a second of exposure to shear stress is insufficient for aligning an entire system. On the other hand, a lifetime of exposure to shear stress is what keeps our bodies working the way they do. So what happens in between those two time extremes?

Initiation of signaling events begin within the first minute of exposure to shear stress (Table 1) (Fig 12). Signaling cascades and transcription factor activation occur over the next hour of exposure. Gene regulation and protein synthesis occur between 1 and 6 hours after exposure, and final structure adaptations are evident after 6 hours of exposure.

In hypertension, the average blood pressure is raised, the average shear stress is raised, and the exposure happens throughout the entire body. So, the question raised is this: shouldn't this long-term exposure to increased shear stress upregulate eNOS, thus causing an increase in NO release, thus relaxing the vessels, and automatically fixing the problem of the increased blood pressure? The answer is no. The response of endothelial cells to *steady laminar* flow is different than the response to *pulsatile laminar*flow.[357]

For example, pinocytosis rates that increase with steady shear stress (8 dyn/cm^2) were unaffected by 1-Hz oscillations of shear stress around the same mean value (8 ± 5 dyn/cm^2).[395] Endothelin-1 mRNA that normally down-regulates at 15 dyn/cm^2 failed to change when cells were subjected to back-and-forth reversing flow of root-mean-square shear stress magnitude 15 dyn/cm^2 but average magnitude of zero.[408] Thus, the endothelium provides different functionality of response depending on the type of flow conditions at any point in the cardiovascular system.

Further, shear stress responses are not always constant when exposed to a constant flow. The response to a 'step' change in shear stress may elicit a pulse response, a linear response, an increasing then decreasing response, or no response (Fig 14). These responses occur in both a step increase in shear or a step decrease in shear, indicating that the responses vary during the time of structural remodeling to the new shear level. Knowing these responses to sustained changes in shear stress, it is possible that a purposeful sustained, intermittent, change in shear stress may be used to 'push' the cardiovascular system to make desired, beneficial, changes in structure.

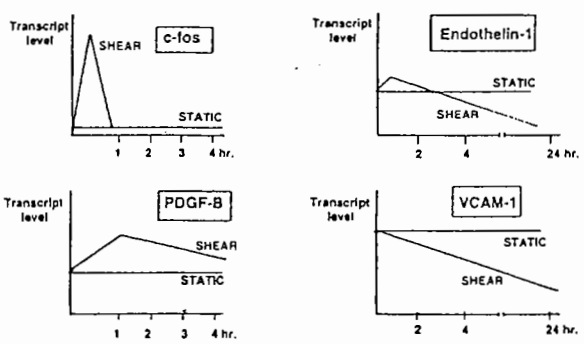

Figure 14. Patterns of endothelial gene regulation by laminar shear stress.

Implications of varied flow conditions

The flow experienced in the body is a complex combination of steady flow, pulsatile flow, separated flow (still laminar), and chaotic flow (non-laminar). These variations in flow can produce changes in endothelial alignment within a few cell distances[357] in regions of highly changing flow conditions (Fig 15).

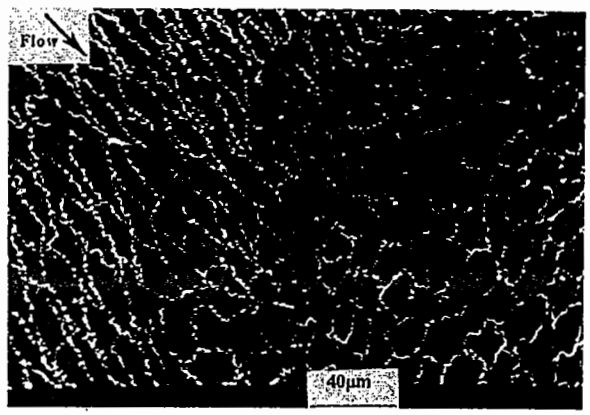

Figure 15. Outlines of endothelial cells in primate thoracic aorta adjacent to an intercostal branch artery.

A very complex flow situation is found in the carotid sinus.[409] (Fig 16) Here the flow separates into sheets of flow that recombine after the sinus. Flow patterns at the endothelium change with each cardiac cycle, and can have a net zero flow in some areas. The structure and mechanical response properties of the carotid sinus are particularly important, since this is the site of the baroreceptors having the most influence on the sympathetic outflow to the body. A small change in the elastic properties of the carotid sinus wall can have a large impact on sympathetic outflow, resulting in large changes in blood pressure.

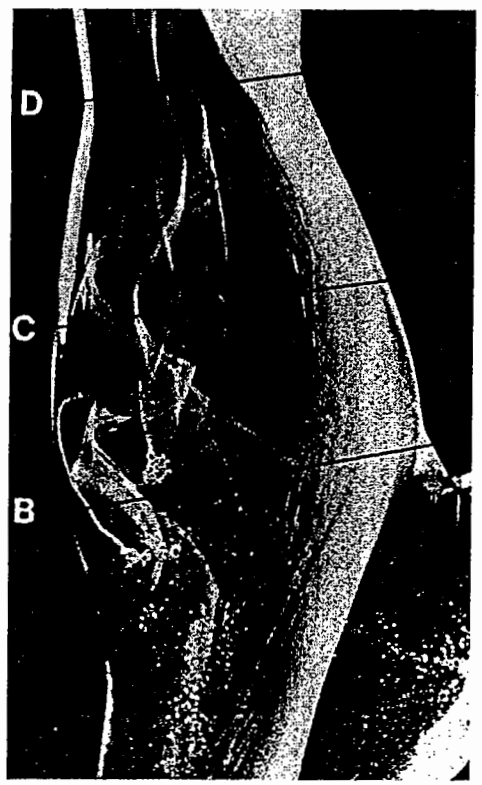

Figure 16. Glass model of human carotid sinus showing complex flow patterns visualized by hydrogen bubbles.

Nitric oxide is involved in the central regulation of sympathetic outflow in humans

Recent studies indicate that nitric oxide is involved in the central regulation of sympathetic outflow in humans.[161] The possibility exists that it is the vasodilatory action of nitric oxide release, in response to shear stress stimulation, in the carotid sinus that provides this modulation of sympathetic outflow.

Impaired eNOS activity

If there is a deficiency of eNOS activity, then the basal release of NO will not properly dilate the arteries, and the basal sympathetic outflow will allow the vascular smooth muscle to constrict the vessel to a smaller diameter. This results in a net increase in total peripheral resistance (TPR), increase in systemic blood pressure, a net increase in wall shear stress, and eventually a balanced regulation of eNOS and release of NO to hold the dilation to the new diameter. This feed back provides homeostasis, but at the price of elevated systemic pressures.

A deficiency, or complete lack, of the genetic transcription of endothelial nitric oxide synthase has been linked to essential hypertension.[130, 171] This may be the single defect that leads to all of the manifestations of hypertension, arteriosclerosis, diabetes mellitus, hypercholesterolemia; and exacerbates conditions such as chronic heart failure. Studies indicate that nitric oxide release accounts for insulin's vascular effects in humans[210, 211] and that abnormalities in insulin-induced NO release could contribute to altered vascular function and hypertension in insulin-resistant states.

Known inhibitors of endothelial function include smoking, and oxidized low density lipoproteins (oxLDL). Smoking causes a dose-related and potentially reversible impairment of endothelium-dependent arterial dilation, consistent with endothelial dysfunction.[204] Long-term smoking is associated with a diminished nitric oxide-dependent component of basal vascular tone and an impaired endothelium-dependent vasodilator response to low-dose endothelin-1 and short-term smoking enhances endothelin-1 induced vasoconstriction. Impaired endothelial control of vascular tone might reflect impairment of normal antiatherosclerotic endothelial functions in smokers, but the relevance of smoking-induced enhancement of endothelin-1 vasoconstriction remains to be determined.[226]

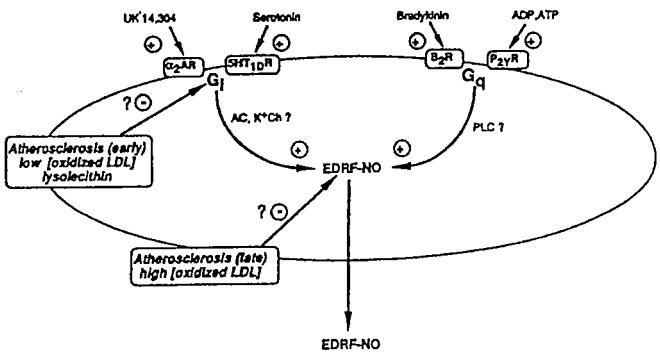

Figure 17. Schematic diagram of proposed mechanisms of endothelial dysfunction associated with atherosclerosis and with oxidized low density lipoprotein (LDL).

Oxidized LDL interferes with normal endothelial function[142] (Fig 17). Specifically, LDL cholesterol derivatives oxidized at position 7 constitute potent inhibitors of endothelium-dependent arterial relaxation.[197, 198] Efforts to reduce LDL levels, and more importantly oxidative stress, may reduce cardiovascular risk factors by improving nitric oxide function in the endothelium. Nitric oxide itself is a potent antioxidant.[392] (Fig 18) But this is its own undoing. The fact that it reduces oxidized LDL is the reason that it is not available, in part, for its role in vasodilatation. To improve function, the production of NO needs to be increased, so that it is available in sufficient quantities to perform adequately both as an antioxidant and as a vasodilator.

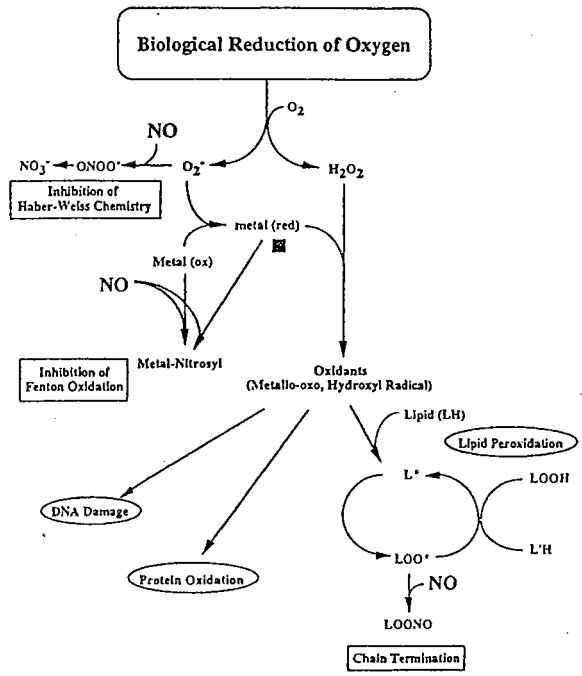

Figure 18. Protective mechanisms of NO against oxidative stress.

Cardiovascular response to acute exercise

There are two fundamental types of exercise: dynamic and isometric. Generally, normal daily activities and exercise regimens are combinations of both dynamic and static components. Dynamic training involves the changing of muscle length during effort. Static training involves the application of force, but no change in muscle length. Sustained static training involves an isometric effort that is held at a particular level for an extended period of time (greater than 10 seconds). Rhythmic static training involves the intermittent application of an isometric effort (2 to 3 seconds) with rest periods (2 to 3 seconds) and then repeated for an extended time period (minutes).

Generally, rhythmic static training elicits a similar cardiovascular response as dynamic training since the flow of blood to the working muscle is never restrained for a period longer than a few seconds.

Pure sustained isometric training elicits a cardiovascular response that can not be simulated by any other means. During sustained efforts at greater than 15% of maximum voluntary contraction (MVC): metabolites of the effort dilate the local muscle arteries to facilitate wash-out, but the mechanical contraction reduces the ability of the basal arterial pressure to eliminate the metabolites; local chemically sensitive muscle afferent nerves signal central command to increase sympathetic drive throughout the body causing systemic vascular constriction, increase in inotropy leading to increased stroke volume, and an increased heart rate; all of these factors combine to drive mean arterial pressure up (pressor response)[276,285] and

facilitate the wash-out of the metabolites of the effort. However, the exercising muscle is also subjected to the same vasoconstriction drive, and now requires even more pressure to wash-out the metabolites; this cycle continues as long as the effort is maintained at the same force level. During this constant drive of the body to maintain wash-out of the exercising forearm, the entire rest of the arterial tree is subjected to increased shear stress from the increase in MAP and the vasoconstriction of the sympathetic outflow.

A comparison of dynamic and isometric training is shown in Fig. 19. During static exercise both systolic and diastolic pressures rise, increasing mean arterial pressure (MAP). During dynamic exercise systolic pressures are driven up, but diastolic pressure drops due to the decrease in total peripheral resistance, thus MAP does not change significantly.

The normal measure of myocardial oxygen demand is the systolic pressure multiplied by the heart rate (rate pressure product or RPP). The RPP is driven up in both forms of exercise. The measure of blood supplied to the myocardium is given by the diastolic pressure multiplied by the heart rate; this decreases in dynamic exercise, but increases during isometric efforts. It is this imbalance between the two forms of exercise that allow dynamic exercise tests to be useful in forcing angina during effort, and the fact that isometric testing rarely produces angina, and is therefore not useful as a diagnostic in detecting angina[286, 290]. Isometrics can be safely performed by patients who exhibit angina.

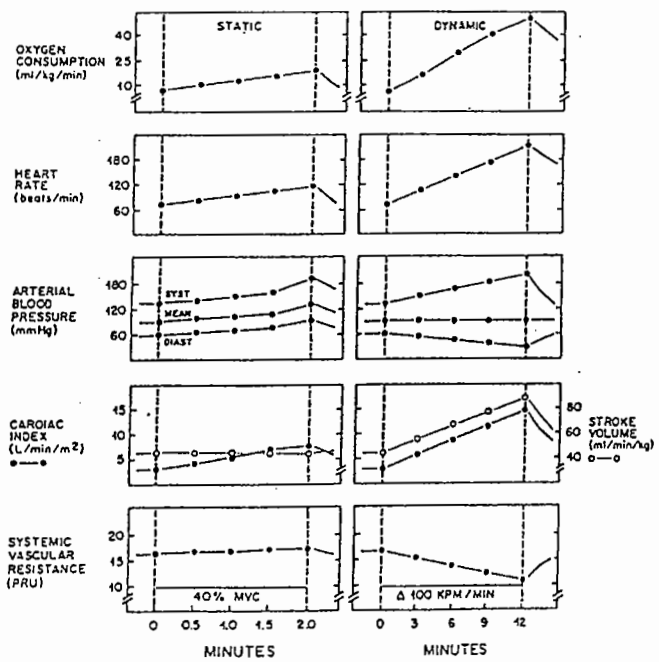

Figure 19. Cardiovascular responses to static and dynamic exercise.

Similarly, tests in other patients have shown isometrics to be a safe form of exercise after myocardial infarction.[62] In general the population normally subjected to treadmill stress tests report a 2.4% mortality rate while no reports of death during isometric testing was found.[93]

Sustained isometric exercise induces a high incidence of cardiac arrhythmia, more than dynamic exercise, in patients with heart disease and therefore may be hazardous form of exercise for those individuals with known arrhythmia.[292] However, isometric exercise can be an excellent diagnostic tool in the clinic, since it accentuates any existing arrhythmia; thus allowing early detection of a condition that would otherwise be too faint for detection.[350]

Rhythmic isometric arm training

Recent studies have shown that localized muscular training can elicit a local vascular improvement.[3] The implications of this are that dynamic training may provide cardiovascular benefit to *only* the trained muscle. This would indicate that to elicit a whole body conditioning, the whole body must be involved in the training. This is in contrast to localized pure isometric training which involves a whole body response, and a whole body cardiovascular conditioning.[279]

Pressor response effect on shear stress levels

A transient increase in systemic mean arterial pressure (MAP) increases the mean shear stress in vivo throughout the entire arterial tree.[87] (Fig 20) With an increase in blood pressure of 50 mmHg, wall shear rate nearly doubles in the 3A and 4A branches.

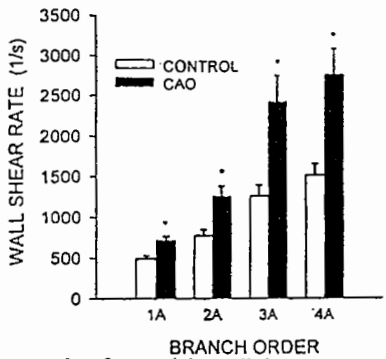

Figure 20. Summary data for arteriolar wall shear rate at rest (control) and in response to carotid artery occlusion (CAO).

Connection

Sustained, brief (one minute), increases in MAP may be able to initiate the signaling cascade that leads to an upregulation in eNOS in the entire arterial tree, an improved basal release of NO, a reduction in total peripheral resistance (TPR), and a reduction in arterial blood pressure.

Chronic isometric exercise training

Chronic training with sustained, brief, interrupted, isometric efforts has been shown to reduce blood pressure over a four-week period in normotensive individuals.[279] Using 4 acute, 30% MVC, 2 minute efforts in the dominant arm, chronically 3 days a week for 8 weeks, statistically significant blood pressure reductions of 12.7 mmHg systolic and 13.9 mmHg diastolic were achieved as compared to a control group (Fig 21). No significant change in resting heart rate was seen in either group.

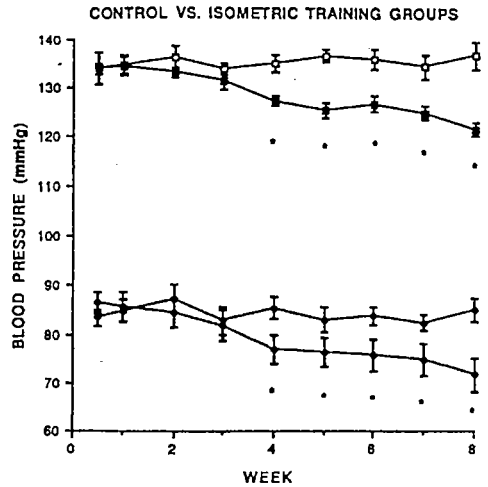

Figure 21. Blood pressure responses by control subjects (open) and by isometric exercise trained subjects (closed).

A subsequent study showed that the reduction in blood pressure could be achieved in a 5 week period using a protocol of alternating arms, 2 efforts per arm, 50% MVC, 45 second efforts, with 60 second rest periods, performed 5 days per week. (Fig 22) Statistically significant reductions of 9.5 mmHg systolic and 8.8 mmHg diastolic were achieved in 5 weeks. The subjects were then allowed to 'detrain' over a 5 week period, and blood pressures returned to pre-training levels.

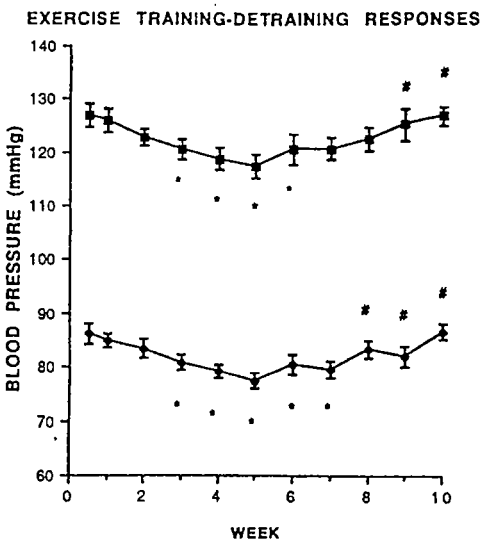

Figure 22. Blood pressure responses to isometric training (wk 0 to 5) and detraining (wk 5 to 10).

Wiley et al[279] proposed that a change in total peripheral resistance (TPR) was the most probable mechanism involved in producing these reductions in blood pressure, however, no evidence was available to support or refute this postulation. It now appears that the evidence is available to make this connection, and further to propose that the change in TPR is due to a systemic upregulation of eNOS, increased basal release of NO, increased basal vasodilatation, leading to the net reduction in TPR.

Training was also performed with hypertensive patients.[411, 412] Data from these studies (Fig 23) show that training conditions the cardiovascular system towards a normal blood pressure range.

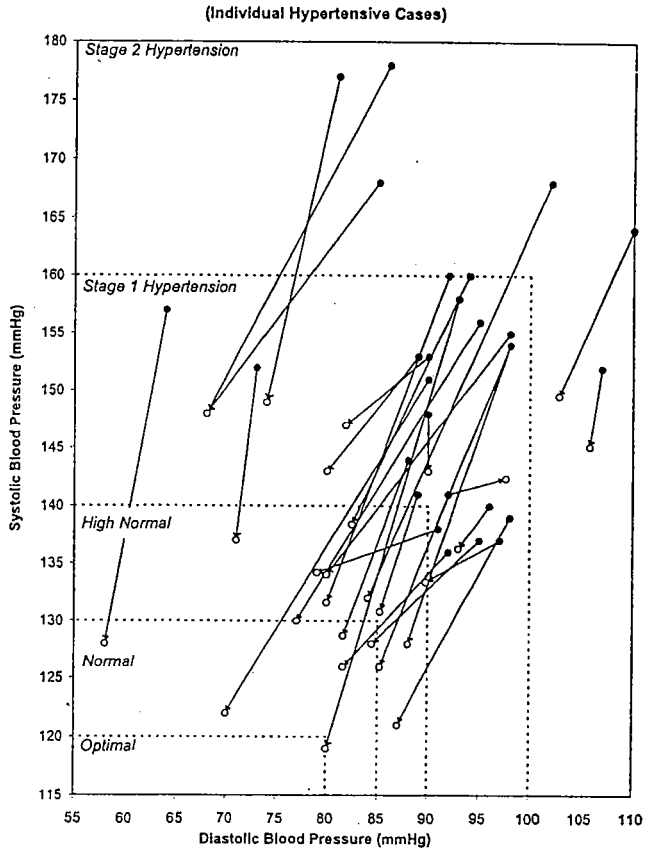

Figure 23. Blood pressure responses by individuals undergoing chronic isometric training: blood pressures are before training (closed) and after at least 5 weeks of training (open).

Sustained benefits with continued training

This type of training also maintains the benefit of reduced blood pressure[411], probably through maintenance of the new level of eNOS activity. Patients who trained for a period of one year were able to achieve significant blood pressure reductions in the first few weeks of use, and then maintained this new fitness level by continuing to train 3 days per week.

Conclusion

The cardiovascular benefits of controlled isometric training may be due to an improvement in endothelial function; a common treatment goal for conditions such as arteriosclerosis, diabetes mellitus, hypercholesterolemia, hypertension, and heart failure. This is important because a specific treatment of the process leading to endothelial dysfunction has the potential for improving the clinical outcome of hypertensive patients.[235]

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