

Blood Volume Response to Physical Activity and Inactivity

VICTOR A. CONVERTINO, PHD

ABSTRACT: Data from both cross-sectional and longitudinal studies provide compelling evidence that circulating blood volume can be influenced by regular physical activity or inactivity. Expansion or contraction of plasma volume can account for most of the alteration in circulating blood volume during the initial 1 to 2 weeks of changing physical activity patterns; after this time, altered blood volume may be distributed equally between plasma and red cell volumes. Alterations in circulating blood volume that accompany changes in physical activity represent a net change in total body water and solutes that are associated with increased or decreased water intake and urine volume and solute output. The mechanism of altered urine output appears to be a modified renal tubular reabsorption of sodium. The expansion of blood volume that accompanies physical activity provides advantages of

greater body fluid for heat dissipation (sweating) and thermoregulatory stability as well as larger vascular volume for greater cardiac filling and stroke volume and cardiovascular stability during exercise and orthostatic challenges. The opposite is true when blood volume is reduced during periods of relative physical inactivity. The observation that underlying mechanisms for alteration in blood volume with physical activity and inactivity are similar but respond directly opposite suggests that they are intricately related. These relations have implications as to a mechanism by which physical activity and fitness may be protective against reduced blood volume and subsequent development of cardiovascular disease associated with aging. **KEY INDEXING TERMS:** Physical fitness; Cardiovascular; Thermoregulation; Exercise; Bed rest. [*Am J Med Sci* 2007; 334(1):72-79.]

There is compelling evidence in the scientific literature that the level and regularity of physical activity has a significant impact on the regulation of circulating blood volume. Historically, an emphasis has been placed on the study of responses and mechanisms underlying adaptations of blood volume associated with increasing physical activity through exposure to exercise. However, less attention has been given to the lower end of the activity continuum, that is, the deconditioning induced by chronically reduced activity and its implications for health and rehabilitation in diseased patients. Since blood volume plays an important role in mechanisms that dictate cardiovascular function(s), it is not unexpected that individuals who undergo regular physical activity generally have larger blood volumes and benefit from greater physiological capacities compared with more sedentary people. Such hypotheses have motivated numerous investigators to conduct studies aimed at providing a better understanding about the relation between blood volume and physical activity or inactivity. The purpose of this report

is to describe our current knowledge about the relation between blood volume and physical activity, underlying mechanisms for alterations in blood volume with changes in physical activity, and physiological advantages and clinical implications of maintaining an active life style. A review is presented that focuses on mechanisms of blood volume regulation, with an emphasis on responses to regular exercise as a model of elevated physical activity and chronic exposure to bed rest as a model of reduced physical activity.

Relation of Blood Volume to Physical Activity

The association of expanded blood volume with physical activity was initially reported more than 50 years ago when average blood volumes of 90 mL/kg measured in 8 exercised-trained women and 14 exercise-trained men were compared with average blood volumes of only 62 to 75 mL/kg in 92 nontrained women and 174 nontrained men.¹ Average blood volumes were even higher in 23 men (103 mL/kg) who were trained for competitive sports. Similar results have been reported in subsequent investigations.^{2,3} In more recent studies, high correlations have been reported between aerobic capacity or maximal oxygen uptake ($\dot{V}O_2\text{max}$) as a marker of physical activity and blood volume (Figure 1).⁴⁻⁶ Thus, cross-sectional comparisons clearly demonstrate that athletes and

From the Remote Triage Research Laboratory, US Army Institute of Surgical Research, Fort Sam Houston, Texas.

Correspondence: Dr. Victor A. Convertino, US Army Institute of Surgical Research, 3400 Rawley E. Chambers Avenue, Building 3611, Fort Sam Houston, TX 78234-6315 (E-mail: victor.convertino@amedd.army.mil).

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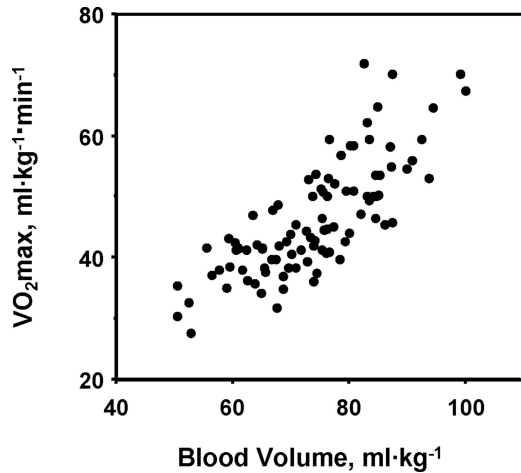


Figure 1. Cross-sectional relation between total blood volume and maximal oxygen uptake (VO_2max) in 97 male subjects. First-order correlation coefficient is 0.78 and linear regression of best fit is $\text{VO}_2\text{max} = 0.66 (\text{blood volume}) - 2.51$. Modified from Convertino (1991).

individuals who perform regular physical activity can exhibit 20% to 25% larger blood volume than more sedentary subjects, a finding that is evident in both women and men¹ and appears independent of age.⁴

Changes in Blood Volume Associated With Physical Activity

Increased Physical Activity: Exercise

It is important to appreciate that although cross-sectional comparisons provide some direction as to the underlying differences in blood volume between individuals who are physically active or sedentary, they fail to isolate the direct effects of physical activity from factors influenced by genetic endowment. Thus, demonstrating a cause-effect relation between blood volume and active life styles requires the use of longitudinal studies to examine changes before and after alterations of physical activity in the same individuals. Figure 2 presents a hypothesized time course relation (drawn lines) for changes in blood, plasma, and red cell volumes during exercise training based on a compilation of longitudinal studies from the literature.^{4,7} The striking rate at which exercise-induced blood volume expansion (hypervolemia) occurs is demonstrated by the observation that just one exposure to an exercise bout can increase blood volume by as much as 10% to 12% within 24 hours.^{8–10} Training-induced hypervolemia then appears to reach a plateau at around 10 to 14 days of training. Up to this time, virtually all of the blood volume expansion can be explained by increased plasma volume with virtually no change in red cell mass. As the duration of training continues beyond 2 to 4 weeks, the increase in blood volume is

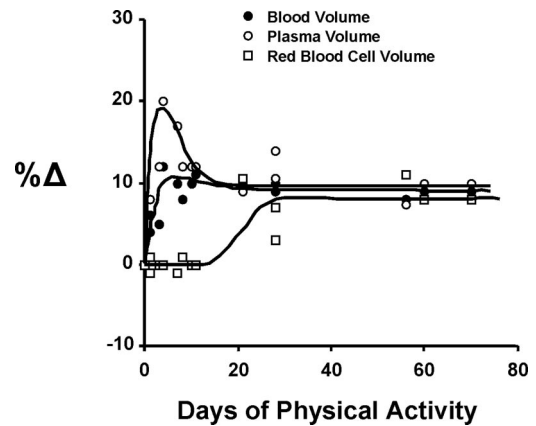


Figure 2. Estimated time course of relative change ($\% \Delta$) in blood volume (closed circles), plasma volume (open circles), and erythrocyte volume (open squares) during adaptation to regular physical activity (eg, exercise training). Each point represents the average change reported in a group of subjects from one investigation. Data were extracted from 18 independent investigations in which all three vascular volumes were reported. Modified from Sawka et al (2000).

distributed more equally between increases in the plasma volume and the red cell mass. Clearly, physical exercise provides a fundamental stimulus to mechanisms that regulate the expansion of blood volume. Although increased exercise capacity was associated with elevated hemoglobin and red blood cell volume in chronic heart failure patients receiving erythropoietin,¹¹ exercise training failed to increase erythropoietin and 2,3-DPG in healthy subjects¹². Therefore, less is known regarding the mechanisms underlying red blood cell adaptation to physical activity levels in the absence of longitudinal studies specifically designed to investigate the dynamics and interaction of acute and chronic exercise and circulating red blood cells. Consequently, the remainder of this review will emphasize the characteristics and mechanisms of alterations in plasma volume associated with changing physical activity.

Reduced Physical Activity: Bed Rest

If increased physical activity associated with regular exercise results in hypervolemia, it follows that a decrease in physical activity should produce lower blood volume (hypovolemia). This is clearly demonstrated by the observation that trained athletes who are normally involved in intense repeated physical activity demonstrate significant reduction in circulating blood volume within 10 days of the cessation of their training schedule.¹³ In addition, confinement of healthy human subjects to bed rest has provided an excellent clinical model for reduction in physical activity without the confounding effects of disease. A review of numerous investigations from the literature reveals that chronic restriction of physical activity resulting from confinement to bed rest caused significant decreases in plasma and

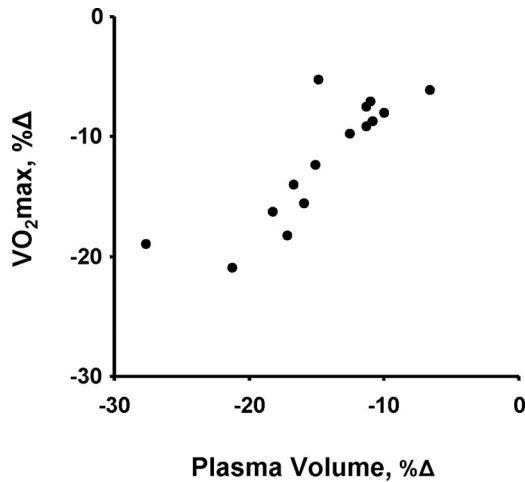


Figure 3. Relation between percent change (%Δ) in $\dot{V}O_{2max}$ on %Δ in plasma volume after bed rest. Data were obtained from 15 different experimental groups during 12 independent investigations. The linear regression equation is $\% \Delta \dot{V}O_{2max} = +0.3 + 0.82 [\% \Delta PV]$; $r = 0.84$. Modified from Convertino (1997).

blood volume by 10% to 30%, most of which is established within the initial 24 to 72 hours of confinement.¹⁴ The notion that a reduction in blood volume during bed rest was caused by restricted physical activity is supported by 3 fundamental observations: 1) a significant correlation exists between the relative (%) reduction in plasma volume and relative decrease in fitness level as measured by $\dot{V}O_{2max}$ (Figure 3)¹⁴; 2) the time courses for the relative reductions in plasma volume and $\dot{V}O_{2max}$ with bed rest confinement are similar (Figure 4)¹⁵; and 3) plasma and blood volume have been maintained in healthy subjects during confinement to bed rest when daily exercise is performed while remaining in the supine posture.¹⁵

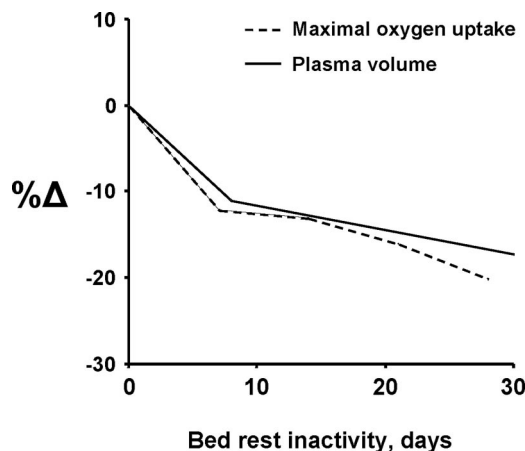


Figure 4. Time course of percent change (%Δ) in maximal oxygen uptake (solid line) and plasma volume (broken line) in 5 subjects during bed rest inactivity. Modified from Greenleaf et al (1989).

Mechanisms of Blood Volume Regulation With Changing Levels of Physical Activity

Increased Physical Activity: Exercise

Increased physical activity provides the stimulus for action of several mechanisms that promote the expansion of plasma and blood volume. During exercise, plasma volume is acutely reduced proportionate to metabolic and/or thermal demands.¹⁶ The resulting loss in circulating volume is accompanied by increased electrolyte concentrations and osmolality that initiate the activation of the renin-angiotensin-aldosterone cascade and the antidiuretic hormone vasopressin.¹⁶ These endocrine responses are accompanied by increased renal water and sodium retention, which in turn is associated with as much as a 20% reduction in the total urine output during the 24 hours of recovery after exercise.⁴ There is no change in glomerular filtration rate after exercise,⁴ suggesting that the mechanism of reduced urine excretion with physical activity must be postglomerular. Since free water clearance is actually more positive during physical activity, it is unlikely that vasopressin action on renal tubular water reabsorption can explain decreased urine output.¹⁷ However, physical activity reduces renal osmotic clearance mainly as a result of a 50% reduction in the clearance of sodium.⁴ Thus, a primary renal mechanism for increasing water retention and expanding body water initiated by physical activity involves an enhanced capacity for renal tubular sodium reabsorption. This notion is supported by the observation that introduction of an aldosterone antagonist (spironolactone) during exercise inhibits the normal expansion of plasma and blood volume as observed in a control group (no drug treatment).¹⁸ These data suggest that an aldosterone-sodium retention mechanism is an important factor in an expanded blood volume stimulated by physical activity. Since there is no change in 24-hour resting plasma aldosterone levels,¹⁹ enhanced renal tubular sodium reabsorption may represent an increase in the sensitivity of receptors to aldosterone as an adaptation to physical activity.

For an expansion of plasma and blood volume to occur, there must be mechanisms stimulated by physical activity that enhance water replacement (intake) in addition to reduced excretion (output). The 24-hour water intake after exercise exceeds that of the sweat loss incurred during exercise, suggesting that mechanisms underlying the stimulation of thirst contribute significantly to the chronic expansion of body water during adaptation to physical activity.⁴ It is clear that oral fluid replacement, in addition to renal actions that attenuate renal urine excretion, represents a fundamental mechanism that contributes to an increased body water balance and subsequent blood volume expansion associated with physical activity.

In the face of increased fluid intake and renal retention of water and electrolytes, elevated intravascular pressures resulting from increased volume would initiate transport of fluids across capillary membranes out of the vascular space in the absence of a counter force. Since capillary membranes are relatively permeable to plasma electrolytes, increased total circulating protein represents the primary mechanism for osmotic compartmentalization of fluid volume in the vascular space by increasing the oncotic pressure across capillary membranes. Since each gram of circulating plasma protein binds 14 to 15 mL of water, an increase in total circulating plasma protein would act to hold water in the vascular space and subsequently expand blood volume. In fact, there appears to be 2 phases of increased circulating plasma protein induced by physical activity. The initial phase occurs early after exercise and involves a transient protein and fluid shift from the interstitium into the vascular space.⁴ As physical activity continues for days, weeks, and months, a chronic hypervolemia develops that is associated with an increase in total body water.⁴ Indeed, plasma expansion with increased physical activity is accompanied by proportionate increases in the total circulating protein,^{4,20,21} as supported by the observation that plasma protein concentration is similar in athletes and nonathletes and unaltered by exercise training.^{4,18,20,21} The fact that total body water is chronically increased with regular physical activity without alterations in protein concentrations provides evidence that the mechanism for increased total circulating plasma proteins probably involves *de novo* synthesis.⁴

Despite increased water and electrolyte retention and circulating proteins, it is difficult to envision that the fluid volume within a given vascular space could increase without volume/pressure receptors providing feedback to promote volume excretion and maintain blood volume at its normal baseline level. Physical activity does not alter either arterial pressure or total vascular capacitance,⁴ so central venous pressure (CVP) becomes elevated. Although elevated CVP usually stimulates diuresis and prevents volume expansion, subjects who increase their activity level maintain an expanded blood volume despite a higher CVP. Thus, blood volume expansion that accompanies increased physical activity relies on a resetting of CVP to a higher operational range²² that allows greater intravascular volume without stimulating a feedback diuresis.

Thus, the mechanisms underlying the increased blood volume that accompanies physical activity include increased thirst, reduced urine water and electrolyte excretion, greater total circulating plasma proteins, and elevated CVP.

Reduced Physical Activity: Bed Rest

In the same manner that increased physical activity promotes blood volume expansion by stimulation

of mechanisms underlying increased thirst, reduced urine water and electrolyte excretion, greater total circulating plasma proteins, and elevated CVP, the stimulus is withdrawn with inactivity. The role of physical activity as a primary stimulus in maintaining an expanded intravascular volume is underscored by the demonstration that the termination of exercise training results in the reduction of total circulating solutes, proteins, and blood volume.^{4,13,21} Consequently, lowered physical activity is accompanied by an absence of change in plasma electrolyte concentrations and osmolality with a subsequent inactivation of the renin-angiotensin-aldosterone cascade and vasopressin compared to normal ambulatory activity. When inactivity is associated with bed rest, aldosterone and vasopressin are acutely decreased.²³ These endocrine responses are accompanied by an acute increase in total urine and sodium excretion (diuresis and natriuresis) within the initial 24 to 48 hours of confinement without altering thirst and fluid intake.^{23,24} Similar to renal responses to exercise, there is no change in glomerular filtration rate associated with inactivity,^{23,25,26} again suggesting that the mechanism of increased urine and sodium excretion must be a postglomerular response. Since free water clearance is actually reduced (ie, more negative) with inactivity, an antidiuretic action associated with vasopressin cannot account for increased urine output.^{23,24} However, inactivity increases renal sodium clearance^{23,25} and total sodium excretion,²⁵ suggesting that reduced capacity for renal tubular sodium reabsorption represents a primary renal mechanism for the reduction in water retention and the subsequent contraction of blood volume. This notion is supported by the observation that infusion of aldosterone after a period of inactivity in monkeys was associated with less renal retention of sodium and osmotic solutes compared with a no drug control.²⁵ These data reinforce the concept that a renal tubular aldosterone-sodium retention mechanism contributes significantly to the regulation of blood volume during both physical activity and inactivity.

As a result of less renal retention of both water and electrolytes during inactivity, blood volume is reduced without alterations in plasma electrolyte and protein concentrations.^{23,25} However, a reduction in CVP accompanies the contracted intravascular volume with inactivity.^{23,26,27} A lower CVP would normally provide a feedback stimulus to cardiopulmonary baroreceptors and lead to the activation of neurohumoral mechanisms (eg, elevated aldosterone and vasopressin) designed to restore volume. In contrast to the response to physical activity, individuals who become less active maintain a smaller blood volume despite a lower CVP because of a resetting of CVP to a lower operating range, resulting in the regulation of intravascular volume at a new, contracted level.

Thus, opposite to those effects induced by increased physical activity, the mechanisms underlying decreased blood volume that accompanies physical inactivity include an acute inhibition of aldosterone leading to less renal tubular sodium and water retention and greater urine and electrolyte excretion, reduced total circulating plasma proteins, and a lower operating range for CVP.

Functional Implications of Physical Activity, Inactivity, and Blood Volume

Functional Advantages of Increased Physical Activity

Several longitudinal studies have demonstrated that hypervolemia associated with increased physical activity is related to increased sweat rate and evaporative cooling during exercise.^{4,19-21} Since an expanded blood volume associated with increased physical activity reflects an increase in total body water,⁴ more interstitial fluid is available to the sweat glands to provide water to the skin surface for evaporative cooling as well as greater vascular volume to provide optimal skin blood flow to enhance conductive heat exchange. Various methods including hypohydration,^{28,29} hyperhydration,^{28,30} saline infusion,^{31,32} and albumin infusion^{33,34} have been used to compare temperature regulation at different blood volumes during physical activity to determine if this relation was causal. In all cases, a reduction in blood volume or restriction of fluid intake resulted in higher core temperature during physical activity, particularly in the heat. Regular physical activity can promote increased recruitment and sensitivity of sweat glands.³⁵ However, enhanced heat dissipation associated with hypervolemia clearly demonstrates the contribution of intravascular volume to both increased sweating^{28,30,32} and greater skin blood flow^{30,32} during physical activity. Therefore, regular physical activity is associated with greater thermoregulatory stability, that is, lower body core temperature, during physical work at the same intensity.

In addition to thermoregulatory advantages, expanded blood volume is associated with reduced heart rate^{4,20,21,36} and elevated stroke volume^{13,37} when individuals participate in physical activity of the same intensity. The most likely explanation for the effects of hypervolemia on increased stroke volume and reduced heart rate during physical work is a Frank-Starling effect. Acute expansion of blood volume by intravenous infusion of dextran,³⁸ albumin,³⁹ or whole blood³³ produced increased cardiac stroke volume during physical activity but maintained cardiac output with a lower heart rate.

Figure 5 presents data obtained from 8 men who performed cycling activity for 2 hours each day for 8 consecutive days at an intensity of approximately

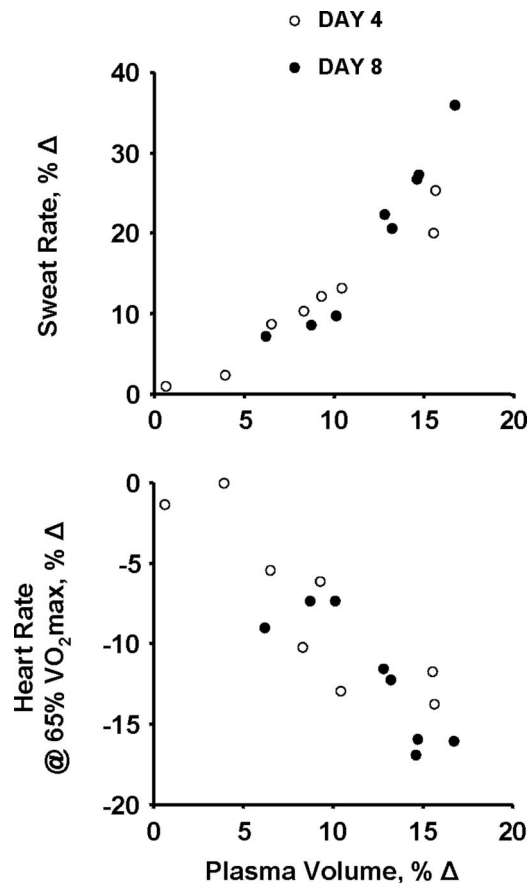


Figure 5. Relations between the percent increase (%Δ) in plasma volume (PV) and the percent increase in sweat rate (top panel) and percent reduction in heart rate at 65% of maximal oxygen uptake (HR, bottom panel) with adaptation at 4 days (open circles) and 8 days (closed circles) of increased physical activity through exercise training. Linear regressions are %Δ sweat rate = 2.01 [%ΔPV] - 5/22; r = 0.93 and %Δ HR = -0.97 [%ΔPV] + 0.26; r = -0.89. Modified from Convertino (1991).

65% of their maximal exercise capacity.^{4,36} The analysis demonstrates the close relations between the increase in intravascular volume caused by increased physical activity (exercise training) and the ability of an individual to perform equal intensities of physical work with greater sweating and lower heart rate. These relations support the notion that expanded blood volume resulting from regular physical activity provides protection against thermoregulatory and cardiovascular instability that could compromise the performance and well-being of individuals undergoing physiological stress.

Functional Disadvantages of Physical Inactivity

Opposite to the observations reported from investigations on expanded blood volume with increased physical activity, a reduction in plasma and blood volume is associated with compromised thermoregulatory capacities.⁷ The reduction in circulating blood volume after 14 days of bed rest inactivity was

accompanied by increased body heat storage during cycle exercise (45% $\dot{V}O_2$ max) at 22°C ambient temperature as indicated by excessive elevation in rectal temperature and a decrease in sweat rate for the same core temperature stimulus.⁴⁰ Thus, decreased blood volume with inactivity can be associated with impairment in thermoregulation that could exacerbate heat stress in sedentary individuals during performance of physical work.

Perhaps the most studied impact of reduced blood volume associated with inactivity is impaired cardiovascular function. The most pronounced clinical outcomes of hypovolemia due to inactivity are lower maximal functional capacity of the cardiovascular system (eg, reduced $\dot{V}O_2$ max) and orthostatic intolerance. Although several mechanisms contribute, there is compelling evidence that the most important factors underlying cardiovascular compromise after inactivity is the central circulatory effect of reduced blood volume on cardiac filling and output.^{13,14,41}

Patients who have been restricted to the inactivity of bed rest routinely develop orthostatic hypotension or frank syncope during their initial attempt at reambulation. Among contributing mechanisms, this orthostatic intolerance secondary to bed rest inactivity is accompanied by reduced circulating blood volume and manifested by lower cardiac output (central hemodynamics) and vasoconstrictor reserve (peripheral hemodynamics).⁴¹ These cardiovascular deconditioning effects of bed rest inactivity are independent of any disease state. The importance of physical activity on reversing the effects of inactivity was eloquently demonstrated when orthostatic intolerance and the underlying hemodynamics associated with reduced blood volume resulting from 16 days of bed rest were eliminated in subjects who performed a single bout of exercise designed to elicit maximal effort within 24 hours before reambulation.^{24,41}

Another adverse effect on the clinical function of patients who have been restricted to the bed rest inactivity is a 10% to 20% reduction in their $\dot{V}O_2$ max.¹⁴ Despite an elevated maximal heart rate, $\dot{V}O_2$ max is reduced primarily from decreased maximal stroke volume. An elevated ejection fraction during exercise despite lowered cardiac filling suggests that lower stroke volume results from lower circulating blood volume and decreased venous return rather than ventricular dysfunction (ie, Frank-Starling relation) after bed rest inactivity. The importance of a Frank-Starling effect caused by increased circulating blood volume was eloquently demonstrated by the experiments of Coyle and coworkers,¹³ who reduced blood volume in previously trained subjects by terminating their physical activity (detraining). They observed that the 10% reduction in circulating blood volume after 10 days of inactivity was associated with a 12% reduction in maximal stroke volume and 6% lower $\dot{V}O_2$ max. More importantly, a direct causal

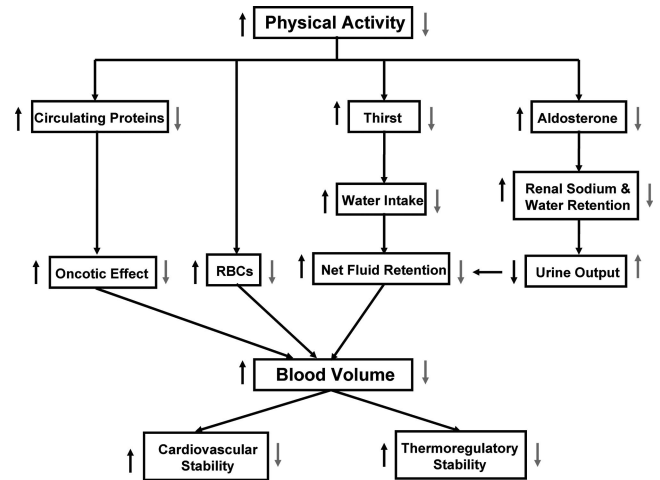


Figure 6. Diagrammatic summary of mechanisms and physiological functions associated with alterations in circulating blood volume induced by physical activity (black arrows) and inactivity (red arrows).

effect was demonstrated when acute restoration of blood volume (infusion) resulted in the complete restoration of maximal stroke volume and $\dot{V}O_2$ max.

Overview of Blood Volume to Physical Activity and Inactivity

Figure 6 represents a diagrammatic summary of the cascade of events that reflect the current knowledge of mechanisms and physiological advantages and disadvantages associated with alterations in circulating blood volume induced by physical activity and inactivity. With increased physical activity, an acute reduction in body water as a result of sweating stimulates thirst to allow oral replacement of fluids during recovery from exercise. Simultaneous activation of the renin-angiotensin-aldosterone mechanism increases renal tubular sodium reabsorption and subsequently reduces renal excretion of urine and electrolytes despite unaltered glomerular filtration of water and sodium. The combination of an increased water intake together with reduced renal excretion of water and electrolytes during the hours of recovery from each bout of physical activity results in a net body fluid expansion. Physical activity also activates de novo protein synthesis to increase total circulating proteins, which in turn elevate the oncotic pressure across capillary membranes to selectively compartmentalize fluid within the vascular space. With the added effect of increased vascular oncotic force due to circulating proteins, a greater proportion of the total body water expansion is distributed in the vascular space, thus increasing plasma and blood volume. In addition, there appears to be a stimulus for increased red cell mass, although this is less clear. The increase in total blood volume then increases the ability to maintain a high stroke volume and a lower heart rate for cardio-

vascular stability and to enhance heat dissipation (thermal stability) by increasing the amount of water available for sweating and the amount of blood flow to the skin. The net result is a protection against the health risks associated with cardiovascular and thermal stress during physical activity, particularly important in elderly populations.

Clinical Relevance of Physical Activity, Inactivity, and Blood Volume

In a recent investigation, a multiple regression model was constructed based on age, several anthropometric measurements, and $\dot{V}O_2\text{max}$ of 107 subjects to test the hypothesis that blood volume could be predicted from characteristics associated with fitness and physical activity.⁵ Results from the evaluation of the full model indicated that the most parsimonious result was obtained when age and $\dot{V}O_2\text{max}$ were regressed on blood volume expressed per kilogram of body weight (BV/kg). Both age and $\dot{V}O_2\text{max}$ were related to blood volume in the positive direction. These findings have particular implications for the effect of physical activity and fitness on aging. The model indicates that blood volume actually increases with age but that this relation may be masked by a sedentary “Western” life style that can often accompany the aging process. This relation is further supported by the observations that blood volume can be increased with regular physical activity in elderly individuals to the same relative degree compared with younger people⁴² and that reduction in blood volume associated with aging in sedentary subjects was removed in physically active subjects.⁴³ The contraction of blood volume may be associated with adverse effects on risk factors for cardiovascular disease such as elevated low-density lipoprotein cholesterol, increased whole blood viscosity, and stimulation of sympathetic nervous activity.⁴⁴ In turn, sympathetic hyperactivity is typically reported in patients with essential hypertension and chronic renal failure and is associated with poor prognosis and increased risk of sudden death.⁴⁵ The relations between blood volume, sympathetic activity, and progressive cardiovascular disease may reflect a protective nature of increased blood volume against development of coronary heart disease with aging. If it is true that blood volume increases with age when a sedentary lifestyle has been removed,⁴³ then perhaps a sedentary lifestyle is actually acting to remove a natural coronary heart disease protective factor. For example, if less viscous circulating blood or sympathetic activity results from increasing blood volume with regular physical activity during the aging process, then various risk factors associated with coronary heart disease such as platelet aggregation, arterial thrombosis, or cardiac arrhythmias are less likely to occur. The literature supports the observation that in the Western

world, blood volume decreases with age.^{43,46–49} However, this model developed from a robust data base provides compelling evidence that reduced blood volume with age may be a result of a sedentary, high caloric lifestyle rather than the aging process. Therefore, perhaps one of many important benefits of maintaining physical activity and fitness during aging is the resultant expansion of plasma and blood volume that provides a protective effect against development of cardiovascular disease.

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