Blood vessel remodeling and physical inactivity in humans

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Thijssen DH, Green DJ, Hopman MT. Blood vessel remodeling and physical inactivity in humans. J Appl Physiol 111: 1836–1845, 2011. First published July 7, 2011; doi:10.1152/japplphysiol.00394.2011.—Physical inactivity is associated with an increase in cardiovascular risk that cannot be fully explained by traditional or novel risk factors. Inactivity is also associated with changes in hemodynamic stimuli, which exert direct effects on the vasculature leading to remodeling and a proatherogenic phenotype. In this review, we synthesize and summarize in vivo evidence relating to the impact of local and systemic models of physical inactivity on conduit arteries, resistance vessels, and the microcirculation in humans. Taken together, the literature suggests that a rapid inward structural remodeling of vessels occurs in response to physical inactivity. The magnitude of this response is dependent on the “dose” of inactivity. Moreover, changes in vascular function are found at resistance and microvessel levels in humans. In conduit arteries, a strong interaction between vascular function and structure is present, which results in conflicting data regarding the impact of inactivity on conduit artery function. While much of the cardioprotective effect of exercise is related to the nitric oxide pathway, deconditioning may primarily be associated with activation of vasoconstrictor pathways. The effects of deconditioning on the vasculature are therefore not simply the opposite of those in response to exercise training. Given the importance of sedentary behavior, future studies should provide further insight into the impact of inactivity on the vasculature and other (novel) markers of vascular health. Moreover, studies should examine the role of (hemodynamic) stimuli that underlie the characteristic vascular adaptations during deconditioning. Our review concludes with some suggestions for future research directions.

endothelium; cardiovascular risk; shear stress; remodeling

The first evidence for detrimental effects of physical inactivity was provided by the landmark study of Morris and colleagues, published in Lancet in 1953 (11, 59). They observed that bus conductors had a lower risk for myocardial infarction than bus drivers, who were less active during working hours. Several subsequent studies have established physical inactivity as an independent risk factor for atherosclerosis and cardiovascular diseases (4, 53), while impaired cardiopulmonary fitness is a strong predictor of all-cause mortality (100). Sedentary living is estimated to be responsible for approximately one-third of deaths (67). Given the low daily energy expenditure that is characteristic of modern living (10), the consequences of physical inactivity seem likely to get worse.

Recent data have provided a basis for assessing the nexus between risk factor modification and the impact of physical activity on cardiovascular risk (58). A significant portion of the impact of physical activity cannot be explained through modification of risk factors (58). An alternative mechanistic explanation for the link between physical inactivity and vascular events relates to the direct effects of inactivity on vascular remodeling and vascular function (41). In this review, we summarize evidence, from studies performed in humans, for structural and functional changes in conduit arteries, resistance vessels, and the microcirculation in response to distinct models of physical inactivity. We also summarize recent data that support the presence of a strong interaction between vascular function and structure, which may help to explain adaptation to physical inactivity. Finally, the impact and importance of (hemodynamic) stimuli that may contribute to vascular remodeling are discussed.

Physical inactivity and vascular remodeling

Most of our current knowledge about the impact of physical inactivity in humans is derived from studies that examined the effect of physical inactivity in healthy volunteers subjected to local (e.g., lower limb suspension, cast immobilization) or systemic models (e.g., bed rest, space flights) of extreme
vascular inactivity. It is important to acknowledge that these models induce sudden and extreme local and/or systemic physical inactivity and do not reflect typical human sedentary behavior that may be associated with more gradual (inexorable) effects. Nonetheless, these models have proven useful to study the direct, physiological impact of physical inactivity on the vasculature in humans. Specific limitations associated with each model of inactivity are discussed in detail elsewhere (87) but in general relate to the difficulty in quantifying levels of physical inactivity.

Another frequently used model to examine extreme physical inactivity involves the study of subjects with complete spinal cord injury (SCI). An important caveat in this group is that denervation, rather than physical inactivity per se, may affect vascular remodeling and caution is therefore warranted when extrapolating such data to human sedentary behavior. Nonetheless, sympathectomized patients do not exhibit the same forms of vascular remodeling as those observed in SCI subjects. In addition, vascular adaptations in SCI are partly reversible by electrical stimulation training of the paralyzed legs in SCI (87), suggesting that vascular adaptations observed in paralyzed legs primarily result from physical inactivity.

We have discussed the impact of physical inactivity on conduit, resistance, and microvessels. Arteries are defined according to their size as conduit arteries (diameter: >1,000 μm), small arteries (diameter: 300–1,000 μm), resistance arteries and arterioles (diameter: 10–300 μm), and capillaries (diameter: ~6 μm; Ref. 13). Arteries that contribute to vascular resistance consist of small and resistance arteries and arterioles (13). Assessment of the microcirculation in humans refers to the capillaries and precapillary, smallest arterioles (13).

**Conduit arteries: structural adaptations.** Previous studies (93) have demonstrated that atherosclerosis leads to changes in structure and function of conduit arteries, which makes these vessels an attractive site of measurement to examine the impact of physical inactivity on the vascular system. Measuring conduit artery structural adaptations provides important and clinically relevant information. Indeed, measures of conduit artery structure, such as resting diameter (102) and wall thickness (50), have a strong and independent predictive value for future cardiovascular events. Interestingly, physical inactivity has a marked effect on conduit arterial lumen dimension and “dose-” and “time-dependent” decreases in arterial size are apparent in response to physical inactivity. For example, 7 days of leg casting (77), 28 days of lower limb suspension (5), 52 days of bed rest (6), and chronic paraplegia (20, 22, 24, 36) lead to reduction of the femoral artery of 6, 13, 17, and 30%, respectively (Fig. 1). Moreover, these adaptations in lumen diameter occur rapidly, as a 25% decrease in diameter is observed after only 18 days following spinal cord lesion (21). As physical inactivity also represents a potent stimulus for muscle atrophy, changes in lumen diameter may be associated with metabolic demands of the downstream (muscle) tissue. Indeed, differences in femoral artery diameter disappeared between SCI and controls after expressing the femoral artery cross-sectional area per unit muscle mass (64). Also, a comparable rate of change for the femoral artery and limb volume were observed: 1) during the first 6 wk after a SCI (21) and 2) during 4 (85) and 6 wk (84) electrostimulation exercise training in SCI. Hence, vascular structural remodeling and muscle atrophy in response to deconditioning may follow similar patterns.

Important changes in conduit arterial wall thickness are also apparent in response to physical inactivity. For example, a recent study (55) found a significantly larger carotid artery wall thickness in SCI. This difference was not present when comparing highly physically active SCI and able-bodied controls (39), suggesting that physical inactivity may relate to an increased arterial wall thickness. This is supported by the increase in carotid and superficial femoral artery wall thickness after 60 days of bed rest, which could be completely (carotid artery) or partly (superficial femoral artery) abolished by exercise countermeasures (Fig. 2) (18). This provides evidence that deconditioning leads to an increased wall thickness (Fig. 3). We believe it unlikely that these adaptations in wall thickness in response to models of physical inactivity represent atherosclerotic changes per se. Changes in wall thickness may instead represent (reversible) physiological adaptations, possibly present in smooth muscle cells that are abundantly present in the media layer. In support of this idea, we (79) recently demonstrated immediate changes in wall thickness (~10%) in response to pharmacological smooth muscle relaxation. Therefore, changes in vascular tone and “physiological” structural remodeling in the wall may contribute to the short-term changes in arterial wall thickness observed in studies of inactivity.

Collectively, the studies described above demonstrate that physical inactivity leads to a rapid, dose-dependent decrease in conduit artery lumen size, which may be related to skeletal muscle atrophy. Physical activity also leads to apparent thickening of the arterial wall. The early changes in wall thickness may reflect (reversible) physiological adaptations rather than atherosclerosis per se.

**Conduit arteries: functional adaptations.** Flow-mediated dilation (FMD) is a noninvasive technique that, assuming the appropriate methodology is adopted (80), represents largely nitric oxide (NO)-mediated, endothelium-dependent function in controls (26, 40, 43) and in SCI individuals (43). Lower FMD values are predictive of future cardiovascular events (29). Intriguingly, most previous studies have reported that physical inactivity is associated with increased conduit artery FMD (5, 6, 9, 19, 21, 22), a finding that was independent of the model and the duration of physical inactivity. This increase in FMD can be (largely) prevented by exercise countermeasure during bed rest (6, 19, 97), while electrostimulation training in SCI leads to a lower (i.e., reversed) conduit artery FMD (84, 85). However, results regarding the impact of deconditioning on the FMD are not universal (32, 76). Methodological differences for FMD assessment (29, 80) or different approaches peak diameter detection (32) may explain these conflicting results.

The general finding of an increase in FMD after deconditioning is counterintuitive, given the inverse relation between FMD and cardiovascular risk (29). A possible explanation may relate to differences in the eliciting shear stress stimulus for the FMD. As described above, inactivity leads to a marked inward structural remodeling of the artery diameter. Smaller sized conduit arteries are exposed, by virtue of their size, to greater shear stress stimuli during the reactive hyperemia associated with FMD testing (68). However, correcting for the magnitude of the shear stress stimulus does not fully explain the variation.
in FMD between arteries of different size within subjects (81). Therefore, the larger shear stress stimulus in the smaller, deconditioned vessels may not be fully explained by a larger shear stimulus (22). An alternative explanation relates to the strong interaction between arterial functional and wall architecture, which is discussed in detail later (see INTERACTION BETWEEN STRUCTURE-FUNCTION). Finally, increased sensitivity of smooth muscles to NO may relate to a larger FMD response after physical inactivity. However, a recent study (86) that examined smooth muscle cell NO sensitivity using incremental intrafemoral doses of a NO donor (sodium nitroprusside) in SCI subjects and able-bodied controls found no differences between groups.

Collectively, interpretation of increased conduit artery function (FMD) is difficult due to changes in the shear stimulus and arterial diameter in response to inward remodeling. Changes in conduit artery flow-mediated function do not simply represent the opposite to those observed during exercise training.

Arterial stiffness, which is defined as the change in diameter during a given increase in blood pressure, has an inverse relation with cardiovascular risk (48) and reflects functional and structural properties of the arterial wall. Previous studies (19, 57) found an increased arterial stiffness in SCI subjects compared with able-bodied controls. Such differences between groups were not found between endurance trained SCI and their age-matched able-bodied peers, while localized electrostimulation improved femoral arterial stiffness (39). These findings indicate that physical inactivity is associated with conduit artery arterial stiffening (Fig. 3).

**Resistance vessels: structural adaptations.** Characteristics of resistance vessels may contribute to systemic levels of vascular resistance and blood pressure as well as downstream supply of nutritive blood flow. Recent evidence indicates that hyperemic blood flow responses possess independent prognostic value to predict future cardiovascular disease (2, 49). Changes in this measure may therefore contribute to the increased cardiovas-
The resistance artery data described above are in general agreement with the structural remodeling described for conduit arteries, and the marked effects of deconditioning on peak reactive hyperemia may similarly relate to skeletal muscle atrophy. Olive et al (64) compared lower limb reactive hyperemia in SCI and controls. Although the reactive hyperemia was ~40% larger in able-bodied controls, this difference disappeared when the reactive hyperemia was corrected per unit for muscle volume. However, changes in lower limb volume and lower limb reactive hyperemia seem to follow a different time course when SCI subjects are exposed to 4- to 6-wk exercise training (84, 85), arguing against a common pathway between muscular atrophy and resistance artery structure.

**Resistance vessels:** functional adaptations. Abundant evidence indicates the presence of an increased basal vascular resistance in resistance vessels after physical inactivity (5, 7, 14, 15, 35, 42, 51, 66, 83, 99). The increased vascular resistance may relate to a reduced capillarization and a smaller peripheral vascular bed, apparent in smaller arterioles (<30 μm) (13). However, the larger upstream arterioles contribute importantly to the regulation of vascular resistance and changes in their circumference during remodeling are germane (13).

Changes in vascular function in these vessels may also be responsible for increased vascular resistance associated with inactivity. Local infusion of vasoactive substances and subsequent measurement of blood flow responses provide a tool to understand the mechanistic control of vascular tone in humans. A recent study (34) found that 13 days of bed rest impaired forearm resistance artery endothelium-dependent dilation (to acetylcholine). Interestingly, this change was not present when bed rest was performed under energy restriction (34), indicating that endothelial dysfunction may be due in part to decreased caloric intake rather than physical inactivity per se. Interestingly, lower limb resistance vessels of SCI individuals and healthy controls demonstrate no difference in the NO-mediated dilation, while also no differences in this measure were observed in young men after 4 wk of limb suspension (7). In another study, forearm responses to NO blockade immediately after and 6 wk after forearm cast treatment were similar within subjects but also comparable to uncasted controls (30). These studies suggest that the increased vascular resistance with physical inactivity is not explained by dilator pathways, such as NO.

Changes in vasoconstrictor pathways may also contribute to increased vascular resistance following deconditioning. Although the α-adrenergic system cannot explain the increased vascular resistance in SCI individuals compared with able-bodied controls (42), recent studies support a role for vasoconstrictive substances. For example, increased plasma levels of endothelin-1 (ET-1), a powerful vasoconstrictor, have been reported after 4–8 wk of detraining in healthy persons (52) and in SCI individuals (98). In addition, 7–20 days of bed rest increased concentration of angiotensin II (ANG II; Refs. 3, 33), another powerful vasoconstrictor substance. Although these data suggest a role for vasoconstrictors to explain the increased vascular resistance induced by physical inactivity, plasma concentrations do not necessarily reflect a physiological change in these pathways. Indeed, the contribution of ET-1 to vascular resistance is related to baseline blood flow but not related to ET-1 plasma levels (88). This advocates the use of
direct assessment of the role of ET-1 by local infusion, rather than plasma concentrations.

Using local infusion of ET-receptor blockers, we found an increased contribution of ET-1 to baseline blood flow in the inactive legs of SCI individuals (83). This increased contribution of ET-1 to vascular resistance in SCI was reversed after 6 wk of functional electric stimulation (83). More recently, the contribution of ANG II to leg and forearm vascular resistance in SCI subjects and in able-bodied controls was examined with results indicating that blockade of ANG II reversed the increased leg vascular resistance in SCI but did not change forearm vascular resistance (31).

In summary, the findings above support the concept that localized upregulation of vasoconstrictor pathways (88) contribute to the elevated vascular resistance in resistance arteries during physical inactivity. Due to the proatherogenic properties of ET-1 and ANG II (47), these changes may contribute to changes in endothelial function and structural remodeling.

Microcirculation. The microcirculation mainly serves as an exchange site for nutrients between blood and the surrounding tissue. Microcirculatory changes in response to inactivity have been examined in the skin using laser Doppler responses. The effect of deconditioning has predominantly been examined after a period of whole body inactivity (i.e., bed rest and dry water immersion), which induces an impaired calf skin endothelium-dependent dilation (25, 60). The role of physical activity in mediating these changes is supported by the observation that treadmill exercise and resistance training during bed rest prevented the impaired skin microcirculation (25). In parallel, 14 days of 6° head-down tilt bed rest impaired forearm skin blood flow responses to heating, which was prevented by cycling ergometry during bed rest (16). Impaired skin microcirculation is also present in the inactive lower limbs of SCI subjects (62, 63, 96), while axon-reflex and NO-mediated responses of the leg skin blood flow to local heating are impaired in SCI compared with able-bodied controls (96). Six weeks of electrostimulation training could not reverse these responses (96), possibly due to an insufficient thermoregulatory stimulus during exercise in SCI. Taken together, these studies indicate that deconditioning leads to microvessel endothelial dysfunction in humans. To date, no previous study examined the potential role for vasoconstrictors (i.e., ET-1 and ANG II) or neural pathways to explain the change in microvessel function after inactivity.

INTERACTION BETWEEN STRUCTURE FUNCTION

In conduit arteries, most studies demonstrate no change or even an increase in vasomotor function after exposure to physical inactivity. These counterintuitive observations may relate to the marked inward remodeling of these arteries. A strong and inverse correlation between conduit artery size (i.e., lumen) and FMD responses has been described (69, 72, 73, 81), suggesting that inward remodeling of conduit arteries is associated with an increased FMD response. The larger shear stress stimulus evident in smaller sized arteries may contribute to an apparent increase in endothelial function. However, differences in FMD between arteries of different size cannot be fully explained by the shear stimulus alone (81). Alternatively, thickening of the arterial wall during physical inactivity may also contribute to a larger FMD (39, 95). In the 1950s, Folkow (27) proposed that heterogeneity in wall-to-lumen ratio could explain differences in vascular responsiveness. He provided indirect evidence that enlarged wall-to-lumen ratios in resistance arteries induce hyper-responsiveness to vasoactive stimuli (27). Recently, we (89) have tested this hypothesis in conduit arteries and confirmed the presence of a positive relation between wall thickness and FMD. Therefore, changes in conduit artery structural characteristics in response to remodeling influence conduit artery function via the shear stimulus but also through shear-independent mechanisms. This interaction between conduit artery function and structure must be taken into consideration when examining the effect of deconditioning on conduit arteries.

TIME COURSE OF STRUCTURAL AND FUNCTIONAL ADAPTATION

Data derived from animal studies introduced the idea that arterial remodeling during exercise training supersedes functional changes that occur in the shorter term (46), with some recent human evidence supporting this contention (90, 91). Accordingly, one may also expect a different time course of functional and structural vascular adaptations to physical inactivity. Unfortunately, no previous study has directly examined the time course of functional and structural vascular adaptations, while the sparse longitudinal data on conduit arteries present conflicting results.

Short-duration bed rest resulted in an impaired brachial artery FMD that was not accompanied by a change in baseline
diameter (9). Studies that adopt models of prolonged physical inactivity typically find the counterintuitive larger FMD but are also associated with a marked inward remodeling of the conduit artery diameter. If physical inactivity, in concurrence with exercise training (46, 90, 91), induces functional adaptations that precede structural remodeling, assessment of conduit artery FMD should take place before inward remodeling. The difficulty of detecting such changes is exemplified in a study that examined changes in femoral artery diameter and FMD immediately after a SCI. This study (21) found that femoral artery inward remodeling was completed within 3 wk after the SCI. The strong interaction between remodeling and functional characteristics makes assessment of the time course of functional and structural changes of conduit arteries to physical inactivity extremely difficult. Only studies that adopt a high sampling frequency could provide valuable information about the time course of functional and structural adaptation to physical inactivity.

Regarding comparisons between vessel beds, resistance, and conduit vessels may follow a different time course of adaptation to physical inactivity. The rapid decrease in femoral artery dimension after a SCI was not accompanied by an equally rapid decrease in reactive hyperemic flow (i.e., a reflection of arteriolar structural changes; Ref. 21). Also, 52 and 25 days bed rest resulted in a large decrease in femoral artery diameter, while the femoral artery reactive hyperemia did not change significantly (6). These observations suggest that conduit artery structural remodeling occurs earlier than changes in resistance artery structure, which may relate to the different hemodynamic stimuli associated with deconditioning.

PHYSIOLOGICAL STIMULI

Shear stress, perfusion pressure, and/or oxidative stress, but also other factors, may contribute to exercise-induced vascular adaptations (47). It is tempting to speculate that a decline in frequency and/or intensity of these signals contributes to physical inactivity-mediated vascular remodeling. However, to our knowledge, no previous studies (20) have directly examined such hypotheses.

Hemodynamic stimuli. Shear stress plays an important role in the regulation and adaptation of large arteries. Langille and O’Donnell (45) were the first to establish that a decreased blood flow (and therefore shear rate) mediates an inward remodeling within 2 wk. Moreover, this response was abolished when the endothelium was removed. This indicates that chronic changes in shear stress mediate vessel remodeling and that such changes are dependent upon an intact endothelial layer (45). It is believed that the inward remodeling homeostatically regulates wall shear (92).

Studies in humans demonstrate that deconditioning leads to an increase in mean shear stress (5, 22, 24). This suggests that arterial remodeling during deconditioning may not be driven by changes in resting shear stress. In addition to the mean shear levels, the pattern of the shear stress stimulus may be important for vascular health (61). Under resting conditions, blood flows in an oscillatory pattern through most peripheral conduit arteries, i.e., a large antegrade (i.e., forward) component during systole and a small retrograde (i.e., backward) part during diastole. It is currently thought that a shear pattern with a larger retrograde component produces a proatherogenic endothelial
cell phenotype (see reviews in Refs. 47, 61). Recently, we found that acute in vivo exposure to elevated levels of retrograde shear stress leads to a dose-dependent decrease in endothelial function (Fig. 4). It is assumed that higher resting retrograde shear stress results from an increase in peripheral vascular resistance (28). Indeed, a recent study (103) found that a higher leg peripheral vascular resistance was associated with a larger retrograde shear stress in the upstream femoral artery. The increased vascular resistance during physical inactivity may elevate retrograde shear stress, which, in turn, promotes a proatherogenic milieu. Future studies should characterize changes in shear stress patterns in response to deconditioning stimuli.

Arterial blood pressure is another potent systemic hemodynamic stimulus that contributes to adaptations in the arterial wall. Although conflicting data exist, evidence from previous studies suggests that elevation in arterial pressure induces vascular remodeling towards a proatherogenic phenotype (see reviews in Refs. 47, 61). Despite the physical inactivity-mediated increase in vascular resistance, physical inactivity does not change mean blood pressure (5–7, 25, 66, 83, 95, 97). Models of physical inactivity may be too short to induce changes in mean arterial pressure, possibly due to compensation (via a decreased cardiac output; Refs. 23, 75) for the increased vascular resistance. Nonetheless, bed rest leads to an impaired baroreflex control (37, 38). Although the role for the baroreflex for long-term control of blood pressure is debatable (12), these data indicate that physical inactivity (via bed rest) impairs short-term blood pressure regulation.

Previous data from Laughlin’s group (101) indicate that short-term elevation in perfusion pressure, such as typically found during a bout of exercise, improves endothelium-dependent dilation in senescent muscle feed arteries via an enhanced NO bioavailability. Frequent exposure to these short-term elevations in perfusion pressure, such as present during exercise, may improve or maintain a healthy vasculature. However, physical inactivity is associated with a significant decline in the frequency and/or intensity of (cyclic/intermittent) elevations in blood pressure. Whether a decline in exposure to intermittent pressure oscillations or specific alterations in the pressure signal contribute to physical inactivity-mediated vascular remodeling is currently unknown. It should be borne in mind, however, that changes in arterial pressure are associated with changes in shear stress levels, which makes differentiation between shear and pressure difficult, especially when studying both stimuli in humans in vivo. Future studies should further examine the role of static or cyclic elevations in blood pressure for remodeling.

**Oxidative stress.** Oxidative stress, which refers to the balance between the production of reactive oxygen species and the efficiency of anti-oxidant enzymes, potentially impairs vascular health and may contribute to the development of atherosclerosis (56). Studies performed during bed rest demonstrate that humans are exposed to an increased oxidative stress (1, 17, 54, 104). In addition, bed rest also attenuates the capacity of antioxidant enzymes, which leads to a further oxidative stress for the vascular wall (17, 104). Moreover, lower fitness levels in healthy volunteers (8), but also in subjects with a SCI (94), are associated with higher expression in markers of oxidative stress. Therefore, it can be inferred that physical inactivity leads to increased levels of oxidative stress, possibly via impaired anti-oxidative enzymes, which may contribute to vascular remodeling in response to physical inactivity.

**SUMMARY**

Collectively, current data suggest that physical inactivity leads to a rapid and dose-dependent inward remodeling of conduit and resistance arteries and to a thickening of the arterial walls. At conduit artery level, complex interactions are present between measures of vascular function and structure, such that true changes in endothelial dysfunction may be masked by underlying and rapid structural remodeling. At least, vascular function in conduit and resistance vessels is not impaired. In resistance vessels, available data suggest that upregulation of vasoconstrictor pathways, rather than down-regulation of vasodilator pathways, is important in the vascular adaptation to physical inactivity. The effects of deconditioning on the vasculature are therefore not simply the opposite of those in response to exercise training. Inward remodeling, increases in wall thickness, and adverse effects on the balance between constrictor and dilator pathways are likely to produce a vascular milieu which has detrimental impacts on vascular health and favors atherosclerotic progression.

Future studies should provide better insight into the time course of functional and structural vascular adaptations to deconditioning but also differences between various vascular beds and the potential impact of gender. Moreover, to better understand the (patho)physiological impact of physical inactivity on the vasculature, future research should elucidate the role and importance of (hemodynamic) stimuli that underlie the characteristic vascular adaptations during deconditioning. Finally, little is known about the impact of deconditioning on novel markers of cardiovascular and/or endothelial health (e.g., micro RNAs and endothelial progenitor cells).

As pointed out by Booth et al. (10), the physiology of deconditioning has become the study of “typical” human behavioral exposure, given our historically unprecedented levels of sedentia. In future, the direct impacts of physical inactivity on vascular health will become the study of causation of a large proportion of cardiovascular death and morbidity.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

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