REVIEW ARTICLE

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Arterial Prehabilitation

Can Exercise Induce Changes in Artery Size and Function that Decrease Complications of Catheterization?

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Contents

Abstract

Coronary angiography and angioplasty are common invasive procedures in cardiovascular medicine, which involve placement of a sheath inside peripheral conduit arteries. Sheath placement and catheterization can be associated with arterial thrombosis, spasm and occlusion. In this paper we review the literature pertaining to the possible benefits of arterial 'prehabilitation' – the concept that interventions aimed at enhancing arterial function and size (i.e. remodelling) should be undertaken prior to cardiac catheterization or artery harvest during bypass graft surgery. The incidence of artery spasm, occlusion and damage is lower in larger arteries with preserved endothelial function. We conclude that the beneficial effects of exercise training on both artery size and function, which are particularly evident in individuals who possess cardiovascular diseases or risk factors, infer that exercise training may reduce complication rates following catheterization and enhance the success of arteries harvested as bypass grafts. Future research efforts should focus directly on examination of the 'prehabilitation' hypothesis and the efficacy of different interventions aimed at reducing clinical complications of common interventional procedures.

1. Introducing the Concept of Arterial 'Prehabilitation'

Whilst the benefits of exercise in healthy individuals and patients with ischaemic heart disease and cardiovascular disease risk factors are well established[1] and include significant reduction in cardiovascular mortality,[2-4] the effects of exercise on traditional cardiovascular risk factors are relatively modest.[2] Indeed, a recent analysis of 27 000 subjects[5] demonstrated that risk factor modification is responsible for only ~50% of the cardiovascular benefit of exercise.[6] A potential explanation for the 'missing' cardioprotective benefits of exercise may relate to direct impacts of training on arterial function and size (i.e. remodelling).[6]

In this article we review evidence relating to the direct impact of different forms of exercise training on arterial function and structure. We propose that these benefits may be particularly important in decreasing complications of arterial catheter and sheath insertion, and in optimizing arteries used as bypass grafts.

2. Does Arterial Catheterization Cause Vascular Damage?

The vascular endothelium performs an array of homeostatic functions in normal blood vessels.[7] At the interface between the blood and vascular smooth muscle cells, the endothelium is a monolayer of cells capable of transuding blood-borne and haemodynamic signals. It senses mechanical forces within the lumen and regulates vascular tone through the production of vasoactive autacoids. Of these substances, nitric oxide (NO) is the most comprehensively studied. NO is a labile, lipid-soluble gas synthesized in endothelial cells from its precursor L-arginine, by the action of NO synthase (NOS).[7] The physiological stimulus to endothelial NO production is an increase in blood flow and shear stress,[8,9] subsequently leading to NO diffusion into smooth muscle cells and activation of intracellular cyclic guanosine monophosphate (GMP). This leads to decreased intracellular calcium, smooth muscle relaxation and consequent vasodilatation. Basal and stimulated production of NO tends to normalize the vascular shear stress via vasodilatation. Impaired endothelial NO-mediated vasodilator function predicts prognosis[10-14] and, enhancing endothelial function, decreases cardiovascular events.[15,16]

Endothelial injury due to sheath insertion during cardiac catheterization or percutaneous transluminal coronary angioplasty (PTCA) has been documented.[17-19] Although rare, this endothelial and artery wall damage can be associated with more serious complications, such as thrombosis and total or subtotal occlusion.[20-24] Such complications are more frequent in females, possibly due to their smaller arteries, which are predisposed to injury from sheath insertion.

Burstein et al.[17] demonstrated a significant loss of flow-mediated dilatation (FMD), a measure of endothelium-dependent NO function, in the radial artery following cardiac catheterization. Endothelial dysfunction persisted for 9 weeks post-procedure. Whilst it is possible that artery function recovers after a longer period, this study indicates that catheter and sheath placement is associated with damage to the artery wall. The authors suggested that the decreased FMD was due to direct endothelial damage during sheath insertion, resulting in impaired vasodilatation in response to a shear stimulus and severe vasomotor dysfunction. Sanmartin et al.[18] also concluded that transradial catheterization was associated with impaired vasoreactivity, although recovery was reported after 1 month.

These studies indicated that immediately after catheterization, baseline artery diameter was significantly increased. This suggests that small arteries such as the radial are physically stretched and distorted by sheath placement. Other studies have indicated that the long-term effect of sheath placement in small arteries involves arterial wall thickening and concentric remodelling.[17,25-27] Collectively, these studies indicate that sheath insertion is associated with structural damage in smaller arteries, which triggers intimal hyperplasia, vascular remodelling[28] and a pro-atherogenic inflammatory cascade. Indeed,

assessment of the radial artery after it has been harvested has demonstrated that prior transradial catheterization induces intimal hyperplasia, medial inflammation and tissue necrosis at the puncture site.[29]

The studies described above indicate that arterial catheterization and sheath insertion can have a detrimental impact on arterial health, which may compromise the future use of such arteries as bypass grafts, particularly if the patient has undergone repeat catheterization of the artery. Specifically, catheter and sheath placement are associated with the immediate endothelial dysfunction, which may predispose the artery to spasm, thrombus formation, occlusion and the future development of focal atherosclerotic lesions. Increasing the size and function of conduit arteries prior to catheterization would, logically, help to minimize these complications. Although little research has directly addressed the efficacy of such 'arterial prehabilitation', we review evidence in the next section, which suggests that exercise training can enhance vascular function and increase the circumferential size of conduit arteries in humans.

3. Does Exercise Training Enhance Conduit Artery Function in Humans?

3.1 Localized Effects of Small Muscle Group Exercise Training

Although there have been few studies of the impact of small muscle group exercise on conduit artery function or structure in healthy volunteers (figure 1), all studies in patients with evidence of pre-existing endothelial dysfunction and/or cardiovascular disease have reported improved FMD (figure 2). Increases in endothelial function have been found following 4 weeks[44,65] and 8 weeks[41] of handgrip, or 10 weeks of localized leg training[43] with no changes in indices of smooth muscle function.[43,65]

Taken together, these studies strongly suggest that subjects with impaired conduit artery vasodilator function can derive benefit from localized exercise training programmes aimed at improving vascular endothelial function.[44]

3.2 Whole Body or Large Muscle Group Exercise Training Effects

To date, only a few studies have demonstrated an improvement in FMD in conduit arteries after whole body exercise in healthy subjects (figure 1). Whilst an increase in endothelial function has been demonstrated after 10 weeks of daily running,[38] other studies in healthy volunteers have found no change,[34,35] or slight and non-significant increases in FMD post-training.[36,37] In a recent study, 8 weeks of cycling exercise generated significant increases in FMD over the first 4 weeks of exercise, which returned to near baseline at the end of week 8.[33] This time course effect of training may resolve some of the previous disparity in the literature regarding the impact of whole body training in healthy volunteers. It suggests that initial changes in arterial function as a consequence of the shear stress increases associated with repeated bouts of exercise are ultimately superseded by shear-mediated increases in arterial size (i.e. remodelling), which consequently enable a normalization of artery function (see section 5).

Studies involving large muscle group exercise in subjects with evidence of endothelial dysfunction (e.g. existing cardiovascular disease or risk factors) have generally demonstrated improvement in endothelium-dependent function post-training (figure 2).

In subjects with coronary artery disease, significant improvements in FMD (endothelium-dependent function) were noted after exercise training.[39,43,56,57] Similarly, in patients with chronic cardiac failure, most of the studies that have examined the relationship between large muscle group exercise and endothelial function have demonstrated an improvement in vascular function.[58-60,66] This has also been found in patients with hypertension,[34,58] hypercholesterolaemia[56] and peripheral vascular disease.[42,47]

In summary, a beneficial effect of exercise training on NO-mediated endothelial function is

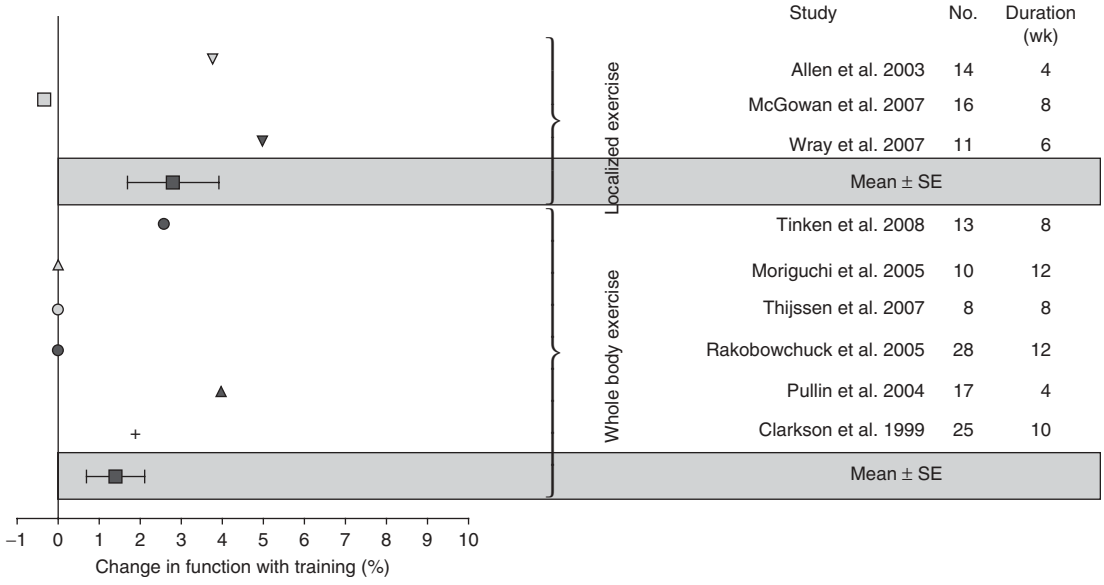

Fig. 1. Changes in flow-mediated dilatation (FMD) in the brachial or the femoral artery in healthy volunteers following local and whole body exercise. The number of volunteers, duration of exercise and the change in FMD post-exercise are identified next to each study. The absolute change in all studies is calculated and marked in the black square.[30-38] **SE** = standard error.

evident in individuals with impaired endothelial function *a priori*.[67]

4. Effects of Exercise Training on Conduit Artery Remodelling

In a classic study, Langille and O'Donnell[68] demonstrated that ligation of one carotid artery in rabbits led to a 70% reduction in flow and a subsequent decrease in arterial size over 2 weeks. This change in arterial size was dependent upon the presence of an intact and functional endothelial layer. Subsequent elegant studies further elucidated this finding. Tronc et al.[69] produced a chronic increase in blood flow and consequent shear stress through the common carotid artery in rabbits via an arteriovenous fistula with the external jugular vein. The diameter of the artery increased in order to restore the baseline shear rate in the experimental compared with the control group. Furthermore, they established that the arterial remodelling was, at least partially, NO-dependent as the increase in vessel calibre was attenuated in a subgroup treated with the NO synthesis inhibitor N^G-nitro-L-arginine-methyl ester (L-NAME). Later, Tuttle and colleagues[70] examined the correlation between the rate of arterial size expansion and blood flow/shear rate in Wistar rats (resistance) arteries by either increasing or decreasing the number of supply arteries to a given vessel. As expected, a reduction in shear rate and consequently a diminished expansion resulted in a reduced arterial luminal size, and vice versa. The increase in arterial lumen was associated with increased intimal and adventitial cell densities in arteries with the highest increase in shear rate. There was also an increased endothelial NOS (eNOS) expression in the arteries with increased flow, which led them to highlight the significant role of NO in this mechanism.[70] In summary, the study demonstrated that the rate of arterial size remodelling, arterial wall remodelling and gene expression is correlated with shear rate in the resistance arteries.[70]

In humans, cross-sectional studies in healthy volunteers have suggested that localized exercise of small muscle groups can induce structural vascular enlargement. For example, a demonstrable

increase in the capacity for peak blood flow, indicative of resistance arterial remodelling,[71] and a larger baseline artery diameter[72] have been reported in the preferred versus non-preferred limb of elite tennis players.[73,74] The adaptation of the vessels to specific and localized training is demonstrated by the finding of a larger subclavian artery in tennis players compared with road cyclists and untrained subjects, and a larger resting diameter of the common femoral artery in cyclists compared with tennis players and untrained subjects.[72] The 'trainability' of conduit arteries has been demonstrated even in athletes with prior evidence of vascular enlargement.[71] Data from longitudinal training studies have also demonstrated an increase in resistance vessel[75,76] and conduit artery diameter[35,71,77-79] following endurance training in healthy subjects.

Taken together, these studies strongly suggest that conduit arteries adapt rapidly to chronic exercise training via structural enlargement, possibly to accommodate increased shear stress and flows associated with the repeated exercise bouts.[67] Vascular remodelling as a consequence of exercise may play an important role in enhancing vessel function and enlarging diameter prior to cardiac catheterization, potentially leading to a reduction in site complication rate. However, data pertaining to conduit remodelling are limited in patients with cardiovascular risk factors or diseases, and further research is required in this area.

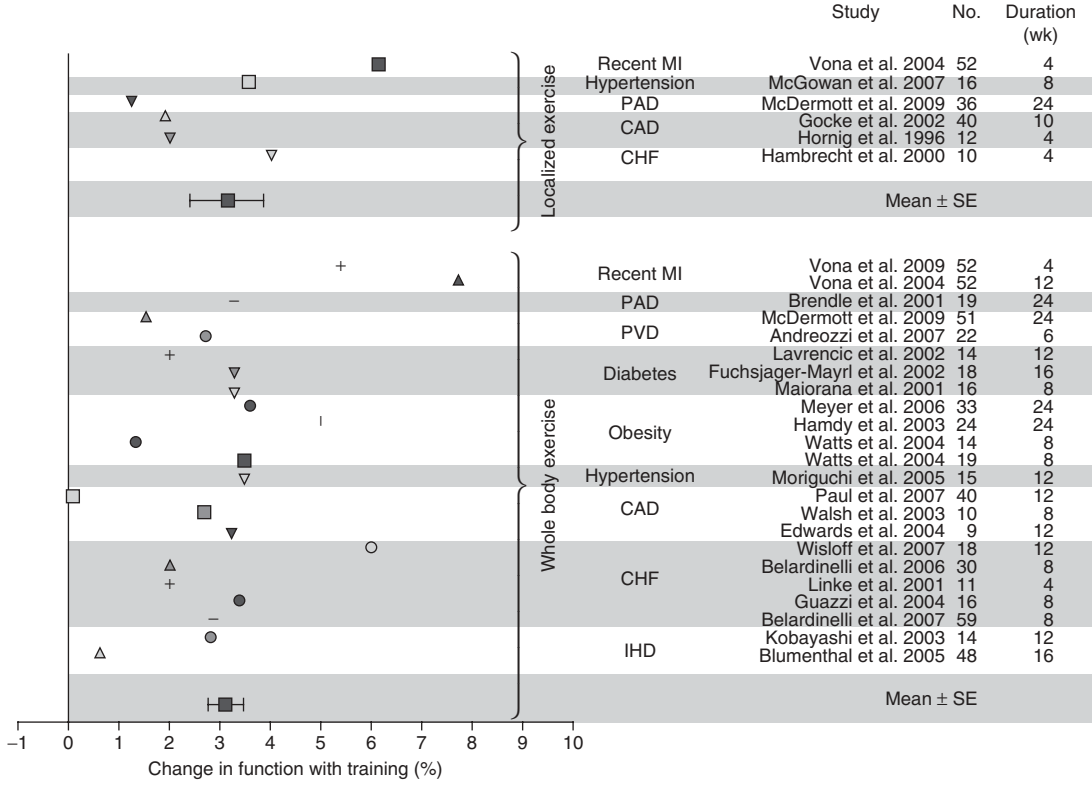

Fig. 2. Change in flow-mediated dilatation (FMD) in the brachial or the femoral artery in patients with recent myocardial infarction (MI), peripheral artery disease (PAD), peripheral vascular disease (PVD), diabetes mellitus, obesity, hypertension, coronary artery disease (CAD), ischaemic heart disease (IHD) and congestive heart failure (CHF) following local and whole body exercise. The number of volunteers, duration of exercise and the change in FMD are identified next to each study. The absolute change in all studies is calculated and marked in the black square.[34,39-64] **SE** = standard error.

5. Interaction between Functional Change and Structural Change Following Training

Evidence suggests that enhancement of function in conduit arteries with normal or abnormal endothelial function occurs rapidly following exercise training.[45,50,65,80-84] Laughlin and colleagues[85,86] have demonstrated, in animals, that adaptations in conduit artery structure occur subsequent to improved function following exercise training. This group was the first to suggest that arterial remodelling, which may be NO-mediated, decreases arterial shear levels, thereby resulting in normalization of NO-mediated endothelial function. Hence, structural remodelling supersedes functional adaptation. This proposal may explain some of the disparity in the human exercise training literature, since some studies that have employed longer durations of exercise training have not demonstrated enhanced NO endothelium-dependent vasodilatation.[87-89]

Whilst some indirect evidence has supported the notion of functional adaptation preceding structural change,[67] no study had directly tested this hypothesis until recently. In a study of 20 healthy males (13 who undertook 8-week cycling exercise training and seven who were controls), both brachial and popliteal arteries were examined every 2 weeks throughout the 8-week period. Improvement in arterial endothelium-dependent NO function (i.e. FMD) was observed in both arteries in the first 4 weeks of exercise training, but thereafter these values returned to baseline levels. Interestingly, the conduit dilator capacity (an index of conduit artery remodelling) followed the converse pattern, with an improvement in structure in the latter part of the exercise training programme. Therefore, this finding in humans reinforces the proposal of Laughlin et al.,[86] in that it appears that the initial improvement in function is followed by an outward remodelling of the arteries in humans.

6. Relevance of Functional and Structural Arterial Adaptation to 'Prehabilitation'

The studies above suggest that exercise training improves both artery function and structure. 'Prehabilitative' exercise may therefore be beneficial both before arterial cannulation and before removal of the artery as a bypass graft. The aim of 'prehabilitation' would be to reduce arterial injury and spasm and thereby improve success rates of transradial catheterization. Arterial spasm is more likely to occur in smaller arteries,[90,91] and an exercise training programme that triggers vascular remodelling would be beneficial to the patient by reducing painful arterial spasms as well as improving procedural success rates. If the artery is to be used as a graft then it is possible that 'prehabilitation' could increase artery size and thereby reduce damage induced by the catheter sheath insertion, which, in turn, could improve graft patency and potentially even improve clinical outcomes.

In the context of 'prehabilitation' before coronary artery bypass surgery, a final paper by the Hambrecht group deserves mention.[80] They examined male patients with stable coronary artery disease and preserved left ventricular function who were waiting for coronary artery bypass grafting surgery, during which the left internal mammary artery (LIMA) was employed as a graft. Patients were randomized into either a control or an exercise trained group. The exercise group completed a 4-week exercise programme prior to surgery, which included daily supervised exercise for 30 minutes on a rowing ergometer and 30 minutes on a bicycle ergometer. Exercise was set to the maximum intensity that could be tolerated in the absence of angina symptoms. An invasive *in vivo* assessment of the LIMA was carried out before and 4 weeks after the randomization. A small tissue sample was also obtained from the LIMA at the time of surgery. The group demonstrated that exercise training led to significantly enhanced endothelium-dependent vasodilatation (as assessed by an increase in mean peak flow velocity) following acetylcholine infusion, which was not evident in the control group. There was no significant change in endothelium-independent vasodilatation induced by glyceryl trinitrate (nitroglycerin) infusion. Furthermore, the exercise trained group had increased eNOS expression in the LIMA biopsy, which was correlated with the improved *in vivo* endothelial

function. The authors therefore concluded that exercise training resulted in enhanced endothelial function and that the mechanism behind this was associated with increased eNOS expression, which leads to an increase of NO activity.[80]

The above study demonstrates that an endurance exercise training programme can be undertaken in patients with stable coronary artery disease; however, this type of whole body exercise may not be suitable for all populations (figure 3). Localized exercise, such as handgrip training, has been shown to improve the function and structure of radial and brachial arteries (figure 2 and section 4). Interestingly, this mode of exercise, if submaximal values are employed, does not increase central blood pressure, and as such represents a low risk to patients with cardiovascular disease. Furthermore, localized training, in particular handgrip exercise, is a cheap mode of exercise training that could be carried out by the patients at home. In contrast, whole body exercise presents a higher risk and would require expert supervision.

Whilst we cannot give exact times required for prehabilitative exercise to be effective, improvements in arterial function have been found after as little as 4 weeks of training,[44] and increases in artery size have been reported after 4–8 weeks.[33,35,78] Within the authors' hospital, the current waiting time for coronary artery bypass graft surgery is 6 weeks and the waiting time for coronary angioplasty in patients with stable angina is approximately 4 weeks. Given the previous literature, this may be sufficient time to produce improvements in both arterial function and structure.

As there are no data on improved outcomes from either transradial catheterizations or long-term graft survival with 'prehabilitation', we cannot conclusively comment on cost-benefits. However, Hambrecht and colleagues[15] reported that exercise training was more cost effective (over half the cost) over 12 months compared with PTCA. This was related to the cost of angioplasty and also to the higher number of re-hospitalizations and coronary re-interventions that were required in the PTCA (non-exercise trained) group. If exercise training is able to improve artery function and size prior to catheterization or removal of the artery as a graft, then this may reduce arterial spasm, improve success rates of transradial catheterization or positively affect graft longevity following bypass surgery. If this is the case, then it may be a viable option for patients awaiting these procedures.

There are limitations with our proposed model of 'prehabilitation'. First, exercise training, particularly whole body exercise training, is contraindicated in some populations (figure 3). This type of training is obviously not viable in patients who require immediate angiography or coronary artery bypass surgery. Nor do we suggest that it is undertaken by patients with unstable angina, since an acute bout of exercise in untrained individuals might result in plaque rupture, myocardial infarction and arrhythmias. Second, we do not propose delaying necessary interventional procedures in favour of prehabilitative exercise, although the data of Hambrecht et al.[15] suggest relative benefits of exercise compared with PTCA in some patients. Rather, we propose to make use of redundant waiting time in patients with stable coronary disease.

7. Conclusions

This review of the literature pertaining to vascular adaptation to exercise reveals that:

1. Exercise training is associated with decreased cardiovascular risk, in large part due to the direct beneficial impact of repeated acute bouts of exercise on endothelial function and arterial remodelling.
2. Endothelial cells possess antiatherogenic and antithrombotic properties. Endothelial dysfunction predisposes to increases cardiovascular events, and improvement in endothelial function is cardioprotective.
3. Percutaneous coronary interventional procedures involve placement of a sheath inside peripheral conduit arteries and this procedure is associated with entry site complications and predisposition to endothelial damage, denudation and dysfunction.
4. Exercise training is a potent stimulus to arterial adaptation and repair. Both localized

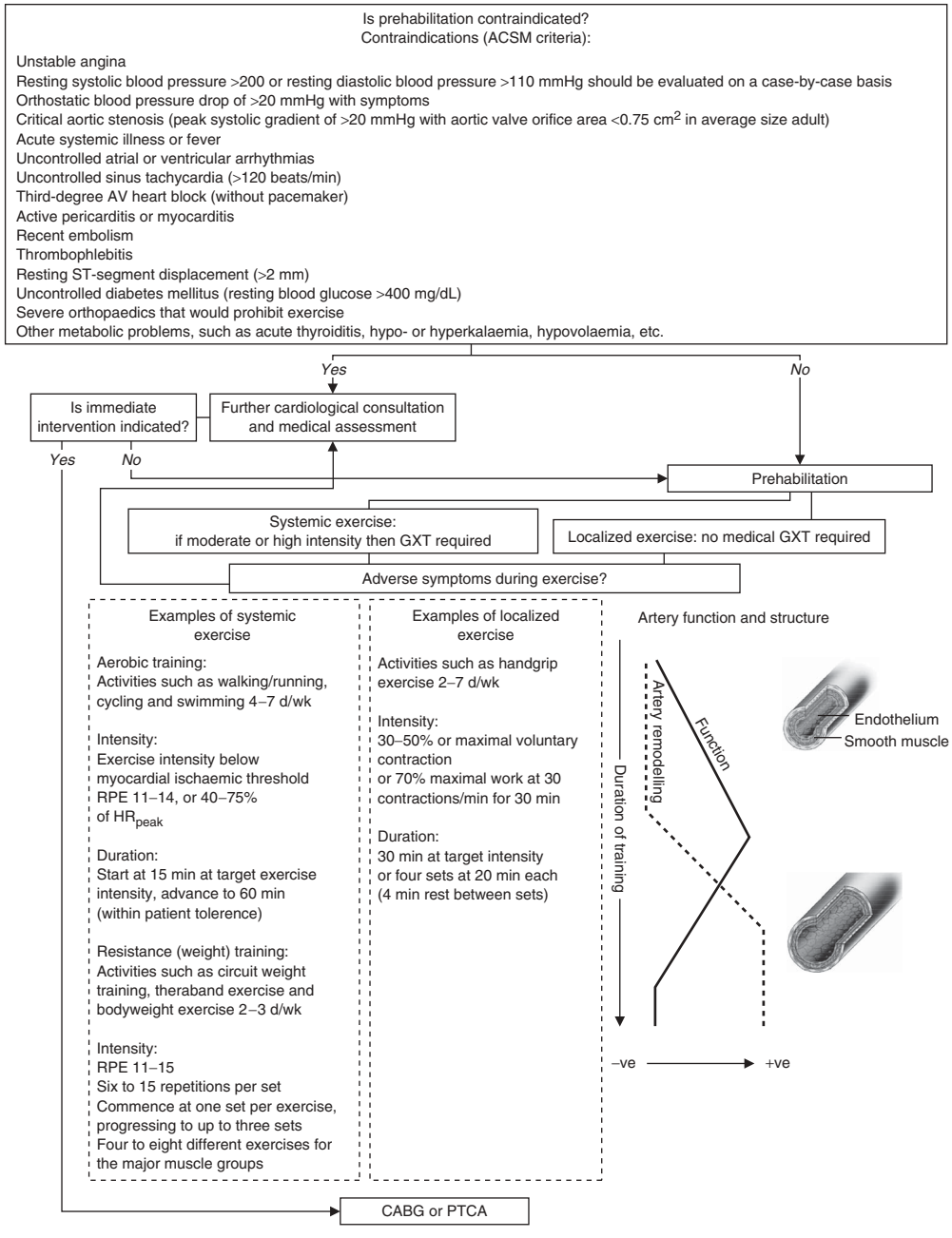

Fig. 3. Risk stratification, examples of exercise training and changes in vascular function with proposed 'arterial prehabilitation'. Moderate exercise: 40–50% of maximal oxygen consumption ($\dot{V}O_{2max}$); 3–6 metabolic equivalents (METs); "an intensity well within the individuals capacity, one which can be comfortably sustained for a prolonged period of time (~45 minutes)."[92] High intensity exercise: >60% of $\dot{V}O_{2max}$; >6 METs; "exercise intensity enough to represent a substantial cardiorespiratory challenge."[92] Examples of systemic exercise[15,80,93-95] and localized[30,41,44] exercise in patient populations in the literature. **ACSM** = American College of Sports Medicine; **AV** = atrioventricular; **CABG** = coronary artery bypass graft; **GXT** = graded exercise test; **HR_{peak}** = peak heart rate; **PTCA** = percutaneous transluminal coronary angioplasty; **RPE** = rating of perceived exertion; **ST** = ECG derived ST segment; **–ve** = negative; **+ve** = positive.

small muscle group exercise and whole body exercise can enhance endothelial function, enlarge conduit arteries and modulate endothelial progenitor cell number and function.

5. Based on the above evidence, we propose 'arterial prehabilitation', the concept that interventions aimed at enhancing arterial function, remodelling and repair should be undertaken prior to cardiac catheterization, or artery harvest for bypass graft surgery, in order to optimize subsequent outcomes and minimize complications such as artery spasm and occlusion or graft patency post-bypass surgery.

6. Future research effort should focus directly on examination of the hypothesis that beneficial effects of exercise training may be evident prior to routine procedures and that 'prehabilitation' may serve as an effective strategy in reducing clinical complications of common interventional procedures.

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