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Effects of catheterization on artery function and health:
When should patients start exercising following their coronary intervention?

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Key points:

- Coronary interventions can result in artery dysfunction and acute injury, potentially leading to thrombosis and stenosis.
- Due to the arterial injury, a period of relative arterial vulnerability post-coronary interventions may exist.
- Acute exercise during this period, particularly at higher intensities, may result to an increase in oxidative stress, inflammation, transient endothelial dysfunction and a pro-thrombotic milieu, contributing to elevated event susceptibility.
- Patients following coronary interventions can start an exercise-training program between 2 and 4 weeks post-PTCA and/or PCI, recognizing that there may be a “grey area” for functional recovery between 2-12 weeks post-catheterization.
- Individual characteristics of patients (age, severity of disease, comorbidities) and parameters of exercise (intensity, duration, frequency) should all be considered when prescribing exercise following coronary interventions.

Abstract:

Coronary artery disease (CAD) is a leading cause of death worldwide, and percutaneous transluminal coronary angiography (PTCA) and/or percutaneous coronary intervention (PCI; angioplasty) are commonly used to diagnose and/or treat the obstructed coronaries. Exercise-based rehabilitation is recommended for all CAD patients; however, most guidelines do not specify when exercise training should commence following PTCA and/or PCI. Catheterization can result in arterial dysfunction and acute injury, and given that fact that exercise, particularly at higher intensities, is associated with elevated inflammatory and oxidative stress, endothelial dysfunction and a pro-thrombotic milieu, performing exercise post-PTCA/PCI may transiently elevate the risk of cardiac events. This review aims to summarize extant literature relating to the impacts of coronary interventions on arterial function, including the time-course of recovery and the potential deleterious and/or beneficial impacts of acute versus long-term exercise. The current literature suggests that arterial dysfunction induced by catheterization recovers 4-12 weeks following catheterization. This review proposes that a period of relative arterial vulnerability may exist and exercise during this period may contribute to elevated event susceptibility. We therefore suggest that CAD patients start an exercise-training program between 2 and 4 weeks post-PCI, recognizing that the literature suggest there is a "grey area" for functional recovery between 2-12 weeks post catheterization. The timing of exercise onset should take into consideration the individual characteristics of patients (age, severity of disease, comorbidities) and the intensity, frequency and duration of the exercise prescription.

1.0 Introduction:

Cardiovascular disease (CVD) is the leading cause of death worldwide with 17.8 million deaths per year [1]. Atherosclerosis, the inflammatory process which underlies most CVD, results in thickening of the artery wall, plaque development and, sometimes, plaque rupture. Endothelial dysfunction is an early atherogenic event, with subsequent transmigration and accumulation of white blood cells and vascular smooth muscle cells (VSMC) into the intima [2-4], resulting in plaque formation and stenosis.

Coronary artery disease (CAD) is the most common cause of cardiovascular deaths [5, 6]. The presence and extent of coronary artery plaque and associated stenosis is commonly determined using percutaneous transluminal coronary angiography (PTCA), a technique that utilizes contrast agent and X-ray based detection to visualize the vessel lumen [7]. Treatment for an obstructed artery can include angioplasty (PCI; percutaneous coronary intervention); where a catheter with balloon tip is inserted and advanced to the stenosed coronary artery. A balloon is inflated to restore the blood flow and a stent (expandable tube-shaped device), is commonly deployed inside the artery to keep it open. PCI is the most common treatment of CAD [8] and one of most widely performed medical procedures in Western world; with 97,376 PCI reported in UK in 2015 [9], although it is worth noting that critical appraisal of the benefits of PCI, relative to conservative medical management, has only recently begun to emerge [10, 11].

Guidelines released by representative bodies recommend that all patients with CAD should receive a program of structured exercise-based cardiac rehabilitation (CR) [8, 12, 13, 6]. However, these guidelines do not typically specify a time for the onset of rehabilitation following PCI, reflecting the relatively weak and conflicting data in regards to the effects of acute exercise in patients following coronary interventions. The UK National Institute for Health and Care Excellence (NICE) is the only body that provides guidance, recommending that programs start 2 weeks post-PCI, and 6 weeks after coronary artery bypass graft (CABG) surgery [14]. The basis for this recommendation regarding timing is, however, unclear and PCI can result in artery dysfunction and/or acute injury [15-17], the extent of which may vary according to procedure and patient characteristics. The time-course of recovery from the “insult” of catheterization, and whether exercise during this period presents a risk, has not been fully considered. The purpose of this review is to summarize extant literature relating to the impacts of coronary interventions on arterial function, including the time-course of the recovery and the potential deleterious and/or beneficial impacts of acute versus long-term exercise. Our aim is to raise consciousness among clinicians and exercise scientists regarding the acute impacts of catheterization on arterial function and to develop an evidence-based approach to recommendations pertaining to the optimal timing to safely begin rehabilitative exercise-based programs following PCI.

2.0 Do coronary interventions cause arterial injury?

PTCA/PCI are commonly utilized in the management of CAD, resulting in reduced angina [18], and are considered safe and effective [19, 20]. However, vascular dysfunction and other complications such as re-stenosis and thrombosis are well recognized [21]. There is clear evidence that invasive procedures mechanically disrupt and can damage the vascular endothelium. Acutely, endothelial dysfunction or damage can convert dilator responses to increased flow and shear stress into constriction and possibly even spasm. Chronically, an injured or denudated endothelium permits the development of atherosclerosis, as it no longer provides an anti-thrombotic surface, and VSMC are exposed to the circuiting blood, resulting in platelet binding and activation of the clotting cascade,

possibly leading to thrombosis [21-23]. In addition, loss of endothelial function and cytokine release by platelets and macrophages further stimulate migration and proliferation of VSMC to the intima, contributing to the formation of neo-intima layer and restenosis [24] (Figure 2).

2.1 What are the effects of catheter insertion, balloon inflation and stent implantation on arterial structure and function?

2.1.1 Structural changes**.**

Whilst catheterization on its own (i.e. PTCA) may damage the artery, the addition of balloon inflation and stent deployment may cause a greater degree of injury, resulting in neo-intima thickening [25]. Neo-intima thickening appears to depend on the degree of endothelial denudation [26], a small denuded area results in little intimal hyperplasia [27], while larger denuded areas lead to greater intima thickening [28]. Newer, 2nd generation bioresorbable drug-eluting stents (DES), with anti-inflammatory and anti-proliferative properties, have shown lower neo-intima thickening [29], and superior clinical outcomes [30] including reduced mortality, morbidity [31], and revascularization rates [32]. However, the incidence of in-stent restenosis [33, 34] and late thrombosis [35, 36] is still an issue. Recently, stents with seeding cells, endothelial progenitor cells (EPC) or endothelial cells (EC), have been studied utilizing *in vitro* and *in vivo* models, with promising outcomes regarding in-stent restenosis [37, 38]. Further research and clinical trials are needed in this area.

Transradial PTCA/PCI has become increasingly popular [39], and the radial artery represents a useful surrogate for epicardial arteries as they are comparable in histopathology and size [40]. Radial artery injury has been identified in approximately one-fifth of patients following transradial procedures, one-third of which have significant dissection extending into the media layer [17]. Moreover, greater vascular injury is associated with repeated catheterization [15]. The radial artery can therefore provide insight into acute and long-term structural changes, post-catheterization.

Intima media thickness (IMT), a non-invasive assessment of atherosclerosis, has been shown to increase at 1- [41], 3- [42] and 4-months [43] following radial procedures, potentially indicating a chronic impact on the structure of the artery wall. Interestingly, IMT has also been shown to increase after only 1 day [41], which likely reflects the acute impact on smooth muscle contraction, which itself can increase wall thickness measures [44]. Previous catheterizations may result in long-term structural remodeling, either due to an increased IMT or a decreased diameter [41, 42, 45, 46], which may have consequences for the long-term patency of the vessel. If the radial artery is removed and used as a graft for CABG, the stenosis-free graft patency is higher if the artery had not been previously catheterized for angiogram/PCI [46].

To summarize, there is evidence for an initial increase in artery diameter due to catheter insertion. Long term, further IMT thickening and decreases in diameter may evolve. In additional to structural changes, PCI may also affect arterial function. Structure and function interact [47], as reduced endothelial function post-injury has been associated with the degree of intimal thickening [48, 49].

2.1.2 Functional changes.

Numerous methods can be used to assess vascular function, either invasively or non-invasively, in both coronary and peripheral arteries. The most common method to evaluate coronary artery function to date has involved intracoronary infusion of endothelium-dependent and –independent

dilators and quantitative angiography. More recently, non-invasive techniques (cardiac magnetic resonance imaging, positron emission tomography, and computed tomography) have been used to assess changes in coronary diameter.

Impaired endothelium-dependent and -independent dilation, and paradoxical constriction are major functional complications following PTCA and/or PCI in coronary arteries [50, 48, 25, 51-54] and in other catheterized arteries [55-58, 16, 59, 17, 60]. The grade of endothelium-dependent dysfunction may depend on the severity of denudation [56], whereas VSMC function appears not to be related with the extent of denudation [48]. Plain-balloon injury, bare-metal stents (BMS) and drug-eluting stents (DES) all result in acute endothelial and VSMC dysfunction [25, 61]. In addition to the directly stented section, proximal and distal segments may experience impaired vascular responses [62-64]. Greater dysfunction occurs distal than proximal to stented area [65-68], resulting in greater vasoconstriction [53] and distal coronary vasospasm [69], potentially increasing thrombotic risk. Moreover, endothelial dysfunction assessed in this distal section of the vessel has been associated with poor endothelial coverage in this area [67].

Direct measurement of coronary artery function can be difficult and is highly invasive. Over the past few decades, a non-invasive assessment, called flow-mediated dilation (FMD), has emerged to assess endothelium-dependent function in humans, usually in the brachial artery. The change in artery diameter in response to sublingual-glyceryl-trinitrate spray (GTN) is also commonly used to evaluate endothelial-independent, but nitric oxide (NO)-mediated, VSMC function. FMD has been shown to be acutely lower in catheterized radial arteries compared to the non-catheterized arteries [70, 59, 60, 17, 16]. In general, equivocal findings regarding radial artery function post-catheterization are reported, with a reduction noted at 4- [17], 9- [60] and 12-weeks [70] in some studies, whereas others suggest that vascular function returns to baseline at 3- [59, 17, 16] and 12-months [71]. This may mirror coronary function as patients who experienced coronary artery stenosis post-PCI had lower coronary blood flow at 3 months [72]. In addition to dilatory function, the ability of the artery to constrict is also reduced 24h and 7-weeks post-catheterization [73]. However, VSMC function appears to recover earlier than endothelial function, with reduced function at 24h [17, 70, 59, 60], and 1-week [17] but not 1 and 3 months [17] (Figure 1).

Whilst change in function is likely due to direct damage, there may also be a systemic effect. Lower brachial artery function following PCI, assessed in the non-catheterized vessel, was associated with late in-stent restenosis at 1-month [74], 6-month [49] and 12-month [75, 76]. In contrast, VSMC function was unrelated to the incidence of in-stent restenosis [74]. Such vascular responses were independent of stent type [76]. Given that preserved function is often reported in a non-catheterized control limb [16, 17], further work is needed to determine if there is a systemic effect of PCI and whether inflammatory or oxidative stress mechanisms are involved.

In general, evidence suggests that endothelial denudation following endovascular procedures impairs vasomotor function, while VSMC function is often relatively preserved. It remains unclear whether such interventions result in systemic vasomotor dysfunction, but some indicative evidence suggests that this may be the case. Endothelial dysfunction in coronary arteries, assessed by ACh infusion has been associated with 9-13% cardiac event risk and 21% revascularization requirement in 8-year follow-up [77]. Similarly, a 1% decrease in peripheral endothelial function (FMD) has been associated with 8-

22% increase in risk of future CVD events [78], and risk prediction appears to be stronger in diseased than healthy individuals [79]. Nonetheless, FMD post-PCI might also be considered an independent marker to predict late restenosis or revascularization rates induced by coronary stenting [80].

2.2 Does contrast media using during PTCA/PCI cause vascular dysfunction?

Contrast media (CM) is a chemical substance used to enhance visibility of structures or fluids within the body, improving the medical imaging and allowing diagnosis of stenosis. However, the intravascular administration of CM can be associated with vasoconstriction [81] and nephrotoxic effects (contrast-induced nephropathy; CIN). Interestingly, CM may change vascular tone differently, depending on the health of the artery. CM normally induces dilation in healthy subjects [82, 83], however, in CAD patients who typically exhibit endothelial dysfunction, coronary vasoconstriction or even vasospasm may occur [83, 84]. *In vitro* studies have demonstrated that CM may exert negative effects on both EC [85, 86] and VSMC [87, 88]. CM is more likely to exert dose-dependent [89] vasoconstriction in segments close to a stenotic lesion [83, 90], emphasizing a possible involvement of endothelial dysfunction, and constriction occurs more frequently following ionic CM than the currently used non-ionic CM [91]. Ionic CM has greater cytotoxic effects on VSMC, compared with non-ionic CM as it is likely to release of tissue plasminogen activator inhibitor (PAI) from platelets and ECs, contributing to intimal hyperplasia following coronary interventions [92].

CM volume is negatively correlated with subsequent FMD, but positively correlated with von willebrand factor (vWF), thiobarbituric acid reactive substances (TBARS), C-reactive protein (C-RP), interleukin (IL)-6), inferring increased oxidative stress and inflammation induced by CM [93]. CIN may be associated with increased oxidative stress and inflammation [94, 93, 95] and lower level of circulating EPC [96], which may underlie the increased major adverse cardiac events [96, 97]. Collectively, these studies suggest that PCTA with CM alone may negatively affect vascular function, potentially due to increased oxidative stress.

2.3 Mechanisms leading to neo-intima formation and vasomotor dysfunction post PTCA and PCI

Increased oxidative stress and inflammation post PTCA/PCI has been associated with restenosis and vascular dysfunction [98-105]. Neo-intima formation (and VSMC proliferation) within the first week [106, 27] may be a consequence of the release or synthesis of growth factors by VSMC, including PDGF (platelet-derived growth factor; a potent VSMC mitogen), while the elevated VSMC proliferation in the following weeks [24, 27] may be explained by reduced NO production due to endothelial damage [107]. Loss of eNOS and reduced NO production post-injury initially occurs due to the actual damage/death of EC during the procedure, and subsequently due to increased production of reactive oxygen species (ROS) [100, 99, 108-110], which appears to follow a similar time course to proliferation post-injury [111]. ROS production and inflammation increase immediately after vascular injury (following both PCI and PTCA [102]) and remain elevated for hours [100] or even days (1-15 days) [112, 113, 104, 98], returning close to baseline levels at 1-month [114]. Inflammation, oxidative stress and platelet adhesion are associated with endothelial dysfunction in CAD patients [115] and increased radial IMT in post-PCI patients [43]. In further support of this, some studies indicate that antioxidant treatments in both animals and patients are associated with reduced neo-intima formation [116, 112, 117, 104, 118, 119, 114], greater luminal diameter, and lower risk of major adverse cardiac events [118]. Finally, lower antioxidant capacity in post-PCI patients is a predictor for cardiac event risk [120].

2.4 Recovery of function and structure following catheterization.

In animal models, impaired endothelium-dependent dilation of catheterized arteries is evident in the first days to 4 weeks [25, 48, 54, 58] and tends to recover by 4-8 weeks [57, 51]. In contrast, reduced VSMC function is apparent only the first week post-denudation [54, 25, 51]. Similarly, reduced endothelium-dependent constriction observed the first 1-2 weeks post-injury [56, 25], recovers at 1 month [25, 57].

In humans, reduced endothelium-dependent function at 4 weeks [17, 60, 70] typically returns to baseline at 3-12 months [59, 17, 71], whereas VSMC function is generally preserved or appears to recover more quickly, with improved function at 1 month post-catheterization [65, 17, 16]. In addition, marked endothelium-dependent constriction has been reported in denuded radial arteries at 6 months post-PCI, compared to the control vessel. Structural remodeling seems to be more complicated and persistent; with increased IMT still reported 1-4 months post-PCI [41-43] (Figure 1).

EPC derived from bone marrow have been proposed as a source in endothelial regeneration following vascular injury [121-124]. EPC have been shown to decrease in count [125] and function [126] following PCI. However, EPC cannot predict recovery of vessels [17] and do not enhance re-endothelialization or reduce restenosis [127, 128]. Therefore, further research is needed to define the role of EPC in vascular recovery post coronary intervention. Alternatively, following endothelial denudation, re-endothelialization begins to cover and repair the denuded area. Endothelial repair is predominantly a result of replication and migration of intact adjacent non-injured endothelial cells, close to the denuded area. In support of this, endothelial repair tends to begin from the edges of the denuded zone (close to intact endothelium) and then converge on the center [129-132].

Regenerating endothelium appears to re-establish the capacity for arterial constriction before the ability to induce dilation [57]. This may result in a greater long-term contractile capacity, increasing the risk for vasospasm and thrombotic events. Indeed, paradoxical vasoconstriction in coronary arteries (treated and non-treated) has been reported [53, 133] at 1 to 6 months post-PCI. Interestingly, incomplete re-endothelialization is apparent at 1-month post-PCI only in DES-treated arteries, while complete recovery is reported in arteries treated with balloon-inflation only or BMS [25]. DES induces non-specific anti-proliferative effects; not only reducing the VSMC proliferation rate but also influencing the growth of other cell types, including EC. It may negatively affect the recovery of the endothelium post-denudation.

Endothelial regeneration post-injury is associated with the incidence of thrombotic events [21], supporting the importance of early re-endothelialization. Delayed recovery may be associated with endothelial dysfunction [134, 135], explaining in-stent restenosis [33, 34] or late thrombosis [35, 36], post-PCI. However, it is important that the endothelial lining function well in order to reduce thrombosis and restenosis risk [136, 137, 67, 128]. Even in arteries with intact endothelial coverage [68], functional abnormalities may occur and are related to intimal thickening [48, 138, 51, 139]. Promoting functional re-endothelialization may be an important strategy to eliminate adverse complications following coronary interventions; however further research is required to understand the cellular and molecular mechanisms that drive EC to induce endothelial regeneration.

3.0 Can exercise limit the detrimental impacts of catheterization or artery function and structure: Generalized impacts of exercise training on vascular function and health.

Tradionally, the impact of exercise training in CAD patients has been focussed on improvements in fitness levels [140-143] and cardiovascular risk factors, such as hypertension and lipid profiles [143, 144]. However, this cannot fully explain the exercise-induced cardiovascular risk reduction [145, 144]. It has been suggested that this 'risk-factor gap', can be explained through exercise-mediated improvemnts in factors such as endothelial function [47, 146]. Indeed, there is compelling evidence that exercise in CAD patients directly improves vascular function [147-153, 140, 154-156, 143], in exercised limbs [149], non-exercised limbs [143, 157, 158] and in coronary arteries [159], all of which contribute to reduced ischaemic events [160]. This is found in traditional aerobic-based training sessions, combined circuit training with resistance exercise [161, 157] and high intensity exercise training (HIIT) [143].

The impact of exercise training can be profound. Exercise training has been shown to have superior outcomes at 1 year (event-free survival, re-hospitalization, and repeat revascularizations) in CAD patients, compared with those who had PCI [162] with reduced inflammation and ischaemic events still apparent at 2 years [163]. In contrast, no difference in the progression of *de novo* lesions [164] and plaque formation [165] have been found among exercised and non-exercised groups, although this may be related to efficacy of drug treatment and/or the short time-course for the development of atherosclerosis. However, exercised patients exhibited greater improvements in recurrent angina and maximum exercise tolerance than non-exercised patients [166]. More importantly, exercise training has been associated with lower 5-year all-cause mortality in post-PCI patients [167] and is recommended as a key treatment in CAD [8].

It is worthy of note that CAD patients are typically prescribed a range of CVD medications, including statins [168, 169], beta-blockers [170], angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers [171-174], and sometimes calcium channel blockers [175], all of which may positively impact upon the endothelial function. Few studies have directly assessed the combined impacts of exercise and CV medications on endothelial function, but Walsh *et al.* (2003) showed that basal NO bioactivity was increased following exercise in both treated (with statins) and untreated subjects, suggesting that exercise may benefit vascular function independently of the impact of statins per se [157]. To further support this, large-scale meta-analysis comparing medical treatment with and without exercise training, reported that the combination contributes to significantly lower cardiovascular risk and mortality [176, 177], indicating that some of the direct effects of exercise may be due to the impacts of shear stress and hemodynamics [146]. In conclusion, CVD medication and exercise may have independent effects on vascular function, mediated through distinct pathways that may culminate in synergistic enhancement in endothelial function.

A prominent mechanism through which exercise training leads to vascular adaptation is increase in shear stress. Shear stress is the tangential force of the flowing blood on the endothelial surface of the blood vessel, and it is known that high shear stress promotes EC survival, enhancing vasodilation. Conversely, low shear stress will result in EC apoptosis and to vasoconstriction, along with VSMC proliferation and platelet aggregation [178]. Hambrecht *et al.* demonstrated, in CAD patients, that exercise training results in upregulation of eNOS Ser1177, which is known to be related to shear stress transduction [179]. Upregulation of eNOS increases NO production and bioavailability, resulting in

vasodilation. To illustrate the relevance of shear stress in terms of exercise-mediated vascular adaptation, studies were performed in healthy people using an inflated cuff on one exercised limb, in order to blunt the shear stress that accompanied exercise compared to the contralateral unimpeded limb. Following 8 weeks of exercise training, the uncuffed (shear stressed) exercised limb exhibited significant improvement of endothelial function when compared with the cuffed limb [180, 47], supporting the proposal, that shear stress is the key stimuli during exercise to improve endothelial function (see recent review [47]). This was further supported by similar studies in which shear stress increases induced by passive heating (i.e. in the absence of exercise) induced identical adaptation, with similar levels of attenuation in the cuffed side [181].

Mechanisms other than shear stress, such as reduced inflammation and oxidative stress following exercise training, will all contribute to improved endothelial function [182, 152, 183]. This may also be associated with reduced platelet aggregation [184, 185], contributing further to decrease in the risk of thrombotic events [186] and reduced restenosis risk at 6- [152] and 9-month angiographic follow-up [187, 188]. In summary, improved endothelial function following exercise training may be a result of increased eNOS and NO production [189, 190, 151] and decreased oxidative stress [151] and NO scavenging, such that regular physical activity restores the balance between NO production and NO inactivation in CAD [156]. In addition, increased numbers of EPC following exercise training may be another mechanism by which exercise ameliorates endothelial function in CAD [191]. This supported by an association in EPC count and improved FMD and NO synthesis [154].

The studies outlined above indicate that there are profound direct and indirect effects of repeated exercise stimulation on the function, structure and health of conduit arteries in humans. Such benefits have been summarized in a recent review [47]. These effects would be expected to enhance the recovery from catheter related injury, but there is scant evidence regarding the most appropriate time to begin a preventive exercise program, or indeed whether pre-rehabilitation prior to catheterization maybe be as beneficial as post hoc training to enhance recovery [192]. Despite the evidence supporting that exercise-based CR benefits the event-free survival of patients post coronary interventions, the participation rate in both Europe and United States is far lower than desirable; approximately one-third of patients participate in cardiac rehab programs after a cardiac event [193-196]. In the United States, CR referral was remarkably lower in post-PCI than post-CABG patients; 48% and 91%, while the hospital performing the procedure was the strongest predictor of referral [197]. Therefore, an increase in referrals should be considered as a priority in CAD management.

4.0 What are the vascular effects of *acute exercise* after PTCA/PCI?

Whilst regular exercise has clearly associated with improved endothelial function and reduction of cardiac events, the acute response to a single bout of exercise remains a controversial issue, particularly exercise in patients following coronary interventions. It is proposed that strenuous exercise might acutely enhance the risk of events in cardiac patients, including thromboembolism and myocardial infarction [198]. Although such events are extremely rare; stent thrombosis risk 0-0.02% [199] and 1% [200], some isolated case-reports of sub-total or total occlusion of coronary arteries [198], and fatal acute stent-thrombosis [201-203], have been related with acute exercise following coronary interventions. The dichotomy between the increased acute risk of exercise and the well-established sustained benefits of prolonged exercise training is commonly known as the ‘exercise paradox’, whereby reduced endothelial function [204] and increased platelet aggregation [205] have

been shown in acute strenuous exercise, whereas improved endothelial function has been reported as a result of prolonged exercise training in CAD patients [143].

4.1 Endothelial function in healthy and CAD population. The impact of acute exercise on endothelial function (as assessed using FMD immediately following exercise) in healthy individuals is equivocal; studies showing an increase [206-208], a decrease [209-211], or no change [212-214]. This variation may relate to exercise intensity, type, duration and the subject's fitness level [215]. In particular, prolonged exercise has been shown to reduce endothelial function in healthy individuals [216] and result in negative effects on vascular stiffness in CAD patients [217]. Despite the duration, exercise intensity (typically defined as the % of maximal heart rate), has been considered as the 'key-factor' driving the vascular responses. In general, high intensity exercise (HIE) causes greater acute endothelial *dys*function than moderate intensity exercise (MIE) [215, 211, 218]. However, the role of exercise intensity on vascular responses in CAD population is unclear, with studies showing greater dysfunction in HIE [219], and others no difference compared to MIE [220-222]. The above controversy may be explained, in part, by the fact that each study had different exclusion criteria to define CAD patients; i.e. including or excluding patients with previous coronary interventions within 3 months. Differences in baseline FMD appears to affect the vascular responses acutely post-exercise; lower baseline FMD may result in increase in endothelial function post-exercise, while higher baseline-FMD may be associated with a decrease [222], further clouding the understanding of acute effects of exercise on endothelial function. Apart from non-invasive FMD data collected post-exercise, more invasive studies in animals have demonstrated an impairment in endothelial function to increased blood flow during exercise, paradoxical vasoconstriction to acetylcholine (ACh), but preserved VSMC dilation in atherosclerotic animals, whilst arteries from healthy animals dilate [223]. Similarly, Gordon *et al.* [224] suggested that vasoconstriction in response to ACh and exercise is apparent only in patients with atherosclerosis, while patients with angiographically smooth vessels appeared to preserve endothelial vasodilation.

Circulating EC, soluble E-selectin and vWf, (markers of endothelial dysfunction), are all elevated acutely post-exercise stress tests in CAD patients [225], suggesting that exercise bouts may impact on endothelial function in these patients. To our knowledge, only one study evaluated VSMC function immediately post a single bout of submaximal cycling exercise in CAD patients, showing a decrease at 15min post-exercise [222]. Whilst the above studies have examined peripheral arteries, changes in coronary artery function with isometric handgrip exercise has also been examined in patients with CAD [226, 227]. Isometric handgrip exercise resulted in abnormal coronary responses with reduced vasodilation and blood flow [226], supporting the incidence of coronary endothelial-dependent dysfunction [227].

4.2 Endothelial function post-denudation. Even less evidence exists regarding vascular responses of acute exercise in vessels that have been catheterized (Figure 1&2). Pohl *et al.* 1986 first illustrated i*n vivo* paradoxical vasoconstriction post-denudation in response to increased blood flow and ACh (endothelial-mediated function) in femoral arteries, whereas dilation appeared to be preserved in response to nitroglycerin (VSMC function) [58]. Following on from this, Berdeaux *et al.* 1994 reported marked vasoconstriction in response to exercise in canine epicardial arteries post endothelial denudation. This 'paradoxical' vasoconstriction in denuded arteries has also been observed following administration of ACh (endothelial-mediated function) and nitroglycerin (VSMC function). VSMC

function was restored at 3 days and endothelial-mediated function in response to exercise and ACh at 9 days [54].

More recently, studies in patients performing supine bicycle exercise during coronary catheterization reported an exercise-induced paradoxical vasoconstriction in coronary-treated artery, at 6 months post-PCI with 1st generation [228], and at 16 months with 2nd generation DES [229], with normal vasodilation in the non-catheterized vessel [229]. VSMC-induced dilation was abolished in the stented area, whereas vasodilation was still apparent proximally and distally to the stent [229]. Coronary vasoconstriction during exercise, 6-months post-PCI, has been implicated in chest-pain with the absence of significant stenosis in a recent case report [135]. Overall, these data suggest that coronary interventions result in impaired vascular responses to acute exercise, mainly in endothelium-dependent function, which may increase the risk for vasoconstriction, spasm and possibly cardiac events.

4.3 EPC. The role of EPC in post-catheterization injury and repair is unclear. Nonetheless, EPC count is increased immediately post exercise stress test in revascularized patients [230, 160], although this may only be apparent in patients who experienced exercise-induced myocardial ischemia [160]. In addition, the increase in EPC number appears to be delayed in CAD patients, compared to healthy controls, suggesting a delayed exercise-induced EPC mobilization in CAD patients [231]. More studies need to be done, to confirm whatever circulating EPC contribute the vascular remodeling post-PCI and to investigate their role (and time-course) post-acute exercise.

4.4 Platelet activation. In addition to endothelial dysfunction induced by acute exercise, platelet aggregation may also be increased, contributing to increased thrombotic risk. HIE results in platelet activation and aggregation [205, 232], coagulation [233-235], platelet thrombus formation [236] and platelet-derived microparticles [237] in healthy and CAD populations, and this increase may be more pronounced in CAD patients [238]. Interesting, these effects may not fully reverse with aspirin treatment [239, 240], suggesting that post-PCI patients with prescribed anti-platelet therapy may continue to be at thrombotic risk post-exercise. Tokuue *et al.* (1996) suggested that platelet activation acutely post-exercise may be a result of high shear stress [241], while MIE appears to have some cardioprotective effects; resulting in decreased platelet activation, platelet adhesion [242], and platelet aggregability [232]. This increase in platelet activation following exercise is in line with the exercise paradox and could explain the increased risk of thrombotic events associated predominantly with acute high intensity exercise [198].

According to the most recent ACC/AHA guidelines [243], dual anti-platelet therapy (aspirin and $P2Y_{12}$ inhibitor) for 3-12 months (the duration depends on the severity of disease and other comorbidities, risk of bleeding etc.) has been recommended to CAD patients following catheterization. This decreases thrombotic risk and consequently adverse cardiac events following such procedures [244]. Given the evidence that acute exercise, especially at higher intensities, may induce platelet activation, it is important to emphasize that patients who aim to start exercise training following catheterization, should adherence to anti-platelet therapy.

4.5 Potential mechanisms. There are a number of different mechanisms underlying both the acute decrease in vascular function and increased platelet aggregation, explaining the risk of exercise-

related cardiac events (Figure 2). Changes in inflammation and oxidative stress can affect endothelial and platelet function. Inflammatory markers (C-RP, IL-6, IL-8, tumor necrosis factor alpha; TNF-a) are increased immediately following HIE, in healthy subjects [205] and CAD patients [245, 246], while no significant inflammation response appears following lower intensity exercise [205]. It is suggested that this acute immune response may stimulate thrombosis by enhancing both platelet activation and endothelial damage [205, 247]. Furthermore, a negative correlation between vascular function and platelet aggregation post-exercise has been reported in CAD [238], but not in healthy subjects [238] or pre-clinical populations [248], suggesting that existing endothelial dysfunction may be associated with attenuated platelet aggregation, resulting in increased thrombotic risk post-exercise. In addition, strenuous exercise leads to an immediate increase in oxidative stress in CAD patients [249], which appears to promote platelet responsiveness [250] and endothelial dysfunction by reducing NO bioavailability [205]. Vitamin C (an antioxidant) abolished the increased oxidative stress and endothelial dysfunction (FMD) post-exercise in CVD patients [251]. Interestingly, some *in vivo* studies have maintained that anti-oxidant therapy (ascorbic acid or glutathione) results in reduced coronary artery spasm [252], and platelet aggregation [253]. All of these mechanisms appear to follow a similar time-course, with an increase immediately post-strenuous exercise, followed by a normalization.

6.0 Conclusion:

Whilst coronary catheterization is a routine procedure widely used to manage obstructed coronary arteries, insertion of a catheter, CM, balloon inflation and stents, all lead to vascular injury and endothelial dysfunction. Endothelial denudation may result in impaired vascular responses and neo-intima formation, with further cardiac complications such as restenosis and thrombosis. Endothelium-dependent dysfunction is typically evident, while VSMC function is usually preserved. In general, PCI appears to cause greater damage than diagnostic PTCA, and therefore more time may be needed for vascular responses to recover [25]. Newer generations of DES are superior to 1st generation DES and BMS regarding in-stent restenosis, whereas the possibility exists that re-endothelialization may be delayed in DES, with an associated increased risk of late thrombosis.

Exercise training is an important intervention for CAD patients, resulting in improved exercise capacity, quality of life, reduced angina, improved vascular function and a lower risk of cardiac events and/or repeated revascularisation [166, 167, 162.]. More importantly, exercise training is generally considered safe for CAD patients with/without coronary interventions [143]. Exercise-based CR beginning at 8-10 days post-PCI has not been associated with adverse complications [254]. Similarly, a large-scale study, including more than 13,000 patients post-PCI, reported that stent-treated patients should start submaximal exercise at 7 days post-PCI and maximal exercise testing at 14 days [199], while another study with 1000 patients demonstrated that exercise was not associated with any cardiac events, even when exercise stress tests were applied the day after PCI with stenting [200]. Moreover, in a recent study, patients performed maximal exercise test immediately post-PCI, and demonstrated that PCI results in an immediate improvement of exercise tolerance, and increases epicardial and coronary microvascular responses to exercise [255]. Nonetheless, it is important to emphasize that the above studies were performed in a hospital environment, under close monitoring and supervision. Large-scale studies are required to examine the safety and benefits of exercise in a more ‘free-living’ environment, in order to establish the impact of exercise at different exercise intensities following catheterization. In the near future, the development of devices that track physical activity levels and also some cardiovascular parameters (i.e. heart rate and rhythm) may allow such a real world experiment to be ethically completed.

It is also clear that acute exercise, particularly at higher intensities, has been associated with elevated inflammatory and oxidative stress, transient endothelial dysfunction and a pro-thrombotic milieu [215, 205]. Therefore, caution should be applied when generalizing regarding the safety of exercise immediately post-catheterization. Studies suggest that impaired vascular function immediately following coronary intervenions [50, 55, 58, 54, 59, 17, 16], returns towards pre-catheterization levels 4 to 12 weeks post-PCI [59, 17, 71]. There is also evidence that these detrimental acute effects of exercise may be exacerbated in clinical populations.

Taking into account the above evidence, we propose that a period of relative arterial vulnerability may exist in the post-catheterization period and that increases in shear stress, oxidative stress and inflammation during this period may contribute to elevated event susceptibility. We suggest that patients should start an exercise-training program between 2 and 4 weeks post-PCI, recognizing that there is a grey area between 2-12 weeks post-catheterization and that discretionary judgement is called for in those at higher risk, related to the individual characteristics of the patients such as age, severity and sub-type of CAD (stable CAD, unstable CAD, non-ST-segment elevation myocardial infarction, ST-segment elevation myocardial infarction), comorbidities, controlled/uncontrolled medication (Figure 1). Consideration should be given to conducting exercise training, particularly that at higher intensity or load, in a supervised and controlled environment in the initial phases, especially in unstable patients and/or those with complicated PCI and/or patients with poor medication compliance. Even though some studies suggest that is safe to start higher-intensity exercise early post-PCI, we believe that the traditional prescriptive approach of beginning with lower and/or low-moderate intensity exercise, and gradually increasing the duration and/or frequency, followed by intensity, as tolerated by the patient under initial supervision, remains a valid and appropriate approach to progression and clinical exercise prescription.

To conclude, although there is an extensive literature in regard to exercise training in CAD, there is a lack of quality evidence currently available with regard to the effects of acute exercise in arteries following catheterisation. Therefore, further studies are needed to investigate the mechanisms and time-course of vascular repair following catheterization, particularly the mechanisms associated with endothelial dysfunction which may occur following a single bout of exercise in denuded arteries. Further research is also required to characterize differences in the impacts of catheterization between sub-classes of CAD. We believe that the most recent and relatively less invasive techniques, such as MRI and PET, will be helpful in addressing vascular responses to exercise following invasive procedures in future. The guiding principal of "*primum non nocere*" should be observed when it comes to exercise prescription in high-risk patients and imprudent adoption of the notion that more pain (e.g. a higher intensity) equates with more "gain", threatens this abiding tenet.

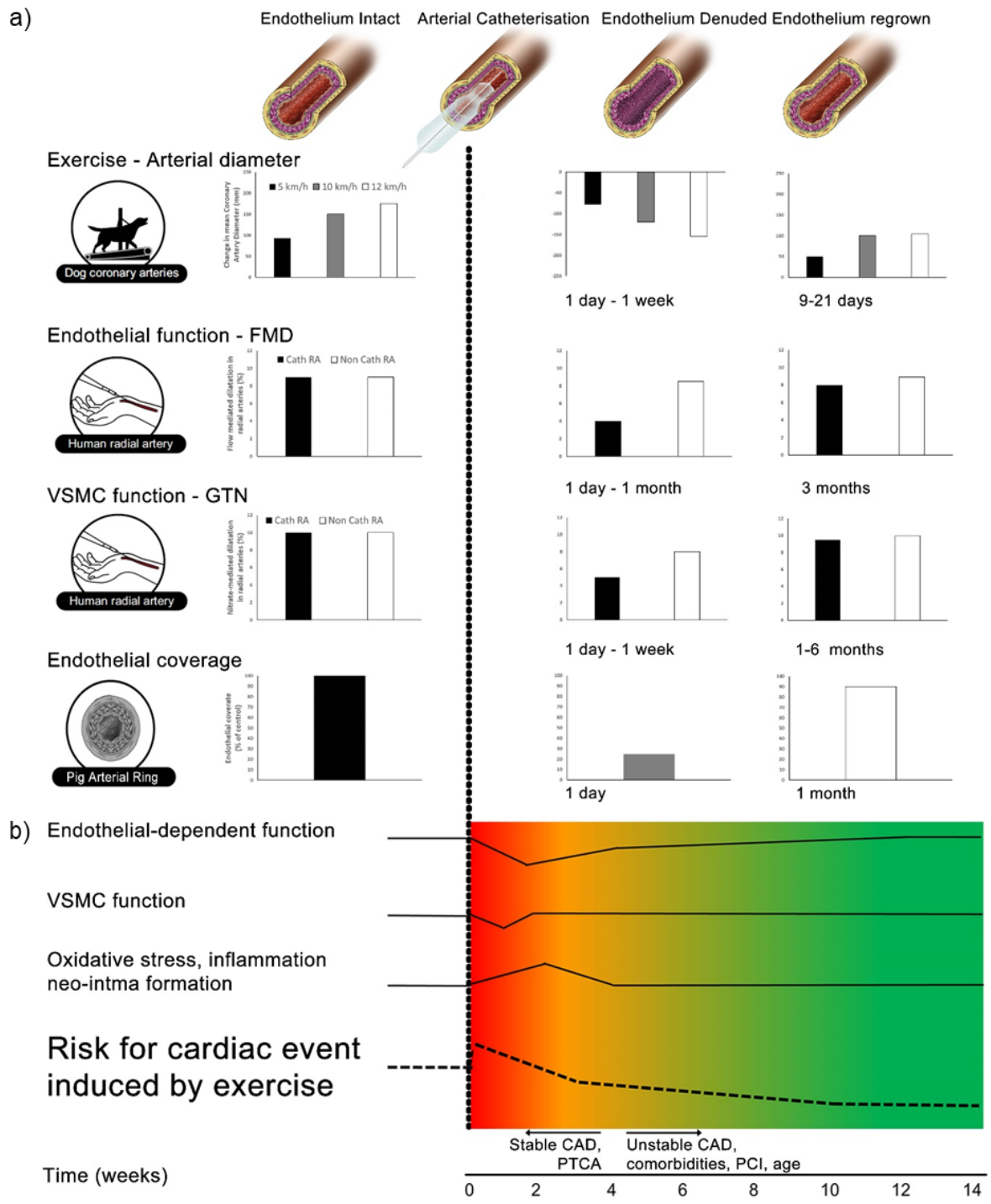

Figure 1: Time-course of arterial recovery following coronary interventions. Adapted from Figure 4 (Green *et al.* 2017) [47]. a) Summary of the outcomes of studies that investigated the effects of catheterization in arterial function and structure. Paradoxical vasoconstriction reported in *canine* denuded coronaries in response to exercise 3 days post-catheterization, and recovered at 9 days [54]. Endothelial dysfunction, assessed by flow mediated dilation (FMD), reported in patients' catheterized arteries 1 day to 1 month post-catheterization and tend to recover at 3 months [59, 17, 71]. Vascular smooth muscle cell (VSMC) function generally recovers more quickly; in humans reduced VSMC function is apparent only the first week post-denudation [65, 17, 16]. Endothelial coverage in pig's arterial rings was 25% at 1 day post-catheterization, when compared to the control-uninjured vessel,

and recovered up to 80% at 1 month [51]. b) Optimal time to onset exercise training post coronary interventions (PTCA: percutaneous transluminal coronary angiography, PCI: percutaneous coronary intervention). We proposed that patients who undertake PTCA and/or PCI should safely begin exercising at 4 weeks. Stable coronary artery disease (CAD) patients who undergo only PTCA may be able to start exercise training between 2-4 weeks post-PTCA, at a hospital setting, under supervision. Unstable CAD patients, including non ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI), with/without comorbidities, severe disease and/or those who undergo PCI should consider starting exercise training at somewhat later, under supervision if possible. Worth noting that oxidative stress, inflammation markers and neo-intima formation which related to the denudation [98-105], follows the same time pattern; increase immediately post denudation [102], remaining elevated for hours [100] or even days (1-15 days) [112, 113, 104, 98], and returning close to baseline levels at 1-month [114].

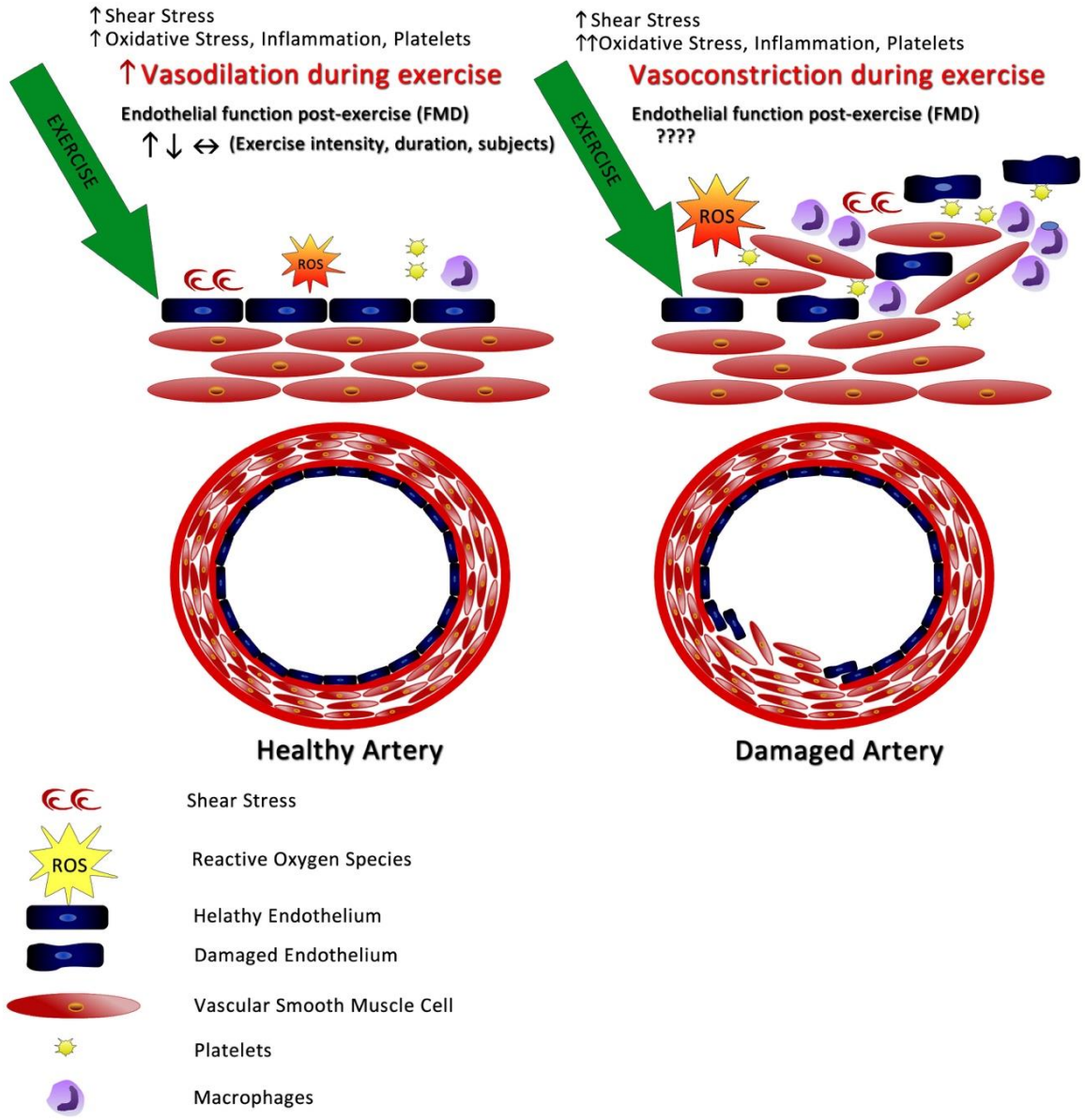

Figure 2: Mechanisms of artery responses to exercise with and without endothelial denudation. Exercise typically induced vasodilation (increase arterial diameter) in healthy arteries (left). Shear stress is elevated during exercise, which will result in increased dilation due to an increase in NO production [179]. Oxidative stress, inflammation and platelets (count/agreeability) may be increased during exercise, particularly following strenuous exercise. Endothelial function immediately post-exercise, assessed by flow mediated dilation (FMD), is equivocal and has been shown to increase, decrease or not change. This variation may relate to exercise intensity, type, duration and the subject's fitness level [215]. The damaged artery, following catheterization (right) will result in paradoxical vasoconstriction [54]. Even though there is an increase in blood flow and shear stress during exercise, the absence of endothelium in the damaged artery can abolish the dilatory response of artery to an exercise [58]. Higher levels of oxidative stress, inflammation and platelets are typically presented in damaged arteries post-catheterization. Endothelial denudation will also result in vascular smooth muscle cell (VSMC) proliferation and migration into the intima, leading to neo-intima formation. There is no information yet in regards to endothelial function post-exercise in damaged arteries.

Compliance with Ethical Standards:

Conflict of interest. Andrea Tryfonos, Daniel J Green and Ellen A Dawson declare that they have no conflicts of interest.

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