The Physiological and Clinical Importance of Cardiorespiratory Fitness in People with Abdominal Aortic Aneurysm

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New Findings

What is the topic of this review?

This review focuses on the physiological impact of abdominal aortic aneurysm (AAA) on cardiorespiratory fitness, and the negative consequences of low fitness on clinical outcomes in AAA. We also discuss the efficacy of exercise training for improving cardiorespiratory fitness in AAA.

What advances does it highlight?

We demonstrate the negative impact of low fitness on disease progression and clinical outcomes in AAA. We highlight potential mechanistic determinants of low fitness in AAA and present evidence that exercise training can be an effective treatment strategy for improving cardiorespiratory fitness, post-operative mortality and disease progression.

1. Abstract

An abdominal aortic aneurysm (AAA) is an abnormal enlargement of the aorta, below the level of renal arteries, where the aorta diameter increases by over 50%. As an aneurysm increases in size there is a progressive increase in the risk of rupture, which ranges from 25% to 40% for aneurysms larger than 5.5 cm in diameter. People with AAA are also at a heightened risk of cardiovascular events and associated mortality. Cardiorespiratory fitness is impaired in people with AAA, and is associated with poor (post-operative) clinical outcomes, including increased length of hospital stay and post-operative mortality following open-surgical or endovascular AAA repair. While cardiorespiratory fitness is a well-recognised prognostic marker of cardiovascular health and mortality, it is not routinely assessed and it is not included in current clinical practice guidelines for the management of people with AAA. In this novel review we discuss the physiological impact of AAA on cardiorespiratory fitness, as well as the consequences of low cardiorespiratory fitness on clinical outcomes in people with AAA. Finally, this review summarises current evidence of the effect of exercise training interventions on cardiorespiratory fitness in people with AAA, including the associated improvements in post-operative mortality, AAA growth and cardiovascular risk. Based on this review we propose that cardiorespiratory fitness should be considered as part of the

routine risk assessment and monitoring of people with AAA, and that targeting improvements in cardiorespiratory fitness with exercise training may represent a viable adjunct treatment strategy for reducing post-operative mortality and disease progression.

2. Introduction

Abdominal aortic aneurysm (AAA) is characterised by an abnormal progressive dilatation of the aorta, below the level of the renal arteries, surpassing the normal aorta diameter by >50% (Upchurch and Schaub 2006). The burden of AAA is significant, with a reported global prevalence of ~6% and a mortality rate that accounts for ~2% of all annual deaths in males aged over 60 years (Ashton, Buxton et al. 2002). AAA development is regarded as a local manifestation of a systemic inflammatory disease where gradual degeneration of the aortic wall leads to weakening, enlargement and ultimately the high risk of rupture (Brady, Thompson et al. 2004). Aneurysm rupture is often life-threatening and the associated mortality rate surpasses 90% (Van 't Veer, Buth et al. 2008). To date, treatment options for AAA consist of open-surgical or endovascular aneurysm repair, which are generally only available for patients with large AAA (>5.5 cm diameter). People with small AAA (<5.5 cm) typically undergo regular imaging surveillance and there are no viable treatment options (Wanhainen, Verzini et al. 2018). Beyond the risk of AAA rupture, common causes of mortality among people with AAA are the postoperative mortality associated with AAA repair (Eslami, Rybin et al. 2017) and cardiovascular disease-related mortality (Bath, Saratzis et al. 2017). Of particular note, the prevalence of cardiovascular disease and associated events (e.g. ischaemic heart disease~45%, myocardial infarction~27% and stroke~14%) is very high in people with AAA and has been reported to increase by approximately 3% year-on-year after AAA diagnosis (Bath, Saratzis et al. 2017).

Cardiorespiratory fitness, measured as the maximum capacity to uptake and utilise oxygen, relies on the health and coordinated responses of various physiological systems and organs (Arena, Myers et al. 2007). Among the general population, there is a strong association between cardiorespiratory fitness and the risk of morbidity and mortality, particularly that associated with cardiovascular disease (Lee, Artero et al. 2010). Current evidence demonstrates that cardiorespiratory fitness is impaired in people with AAA, relative to those without AAA (Rose, Davies et al. 2018) and age-related normative reference values (Ferguson 2014). Moreover, the association between cardiorespiratory fitness and

cardiovascular related risk (Kodama, Saito et al. 2009) and factors related to AAA growth and rupture, such as increased arterial stiffness (Arena, Fei et al. 2007) and endothelial dysfunction (Montero 2015), raises the possibility that cardiorespiratory fitness may be a viable marker or determinant of clinical outcomes in people with AAA.

This review explores the premise that the inclusion of cardiorespiratory fitness as a treatment target has the potential to mitigate cardiovascular risk, aneurysm progression and the morbidity and mortality associated with AAA. The review aims to provide a comprehensive overview of the importance of cardiorespiratory fitness in people with AAA and includes three related sections: 1) the physiological impact of AAA on cardiorespiratory fitness, 2) the association of low cardiorespiratory fitness with clinical outcomes in AAA, and 3) the effect of exercise training interventions on cardiorespiratory fitness and cardiovascular risk in people with AAA.

3. The impact of Abdominal Aortic Aneurysm on Cardiorespiratory Fitness

3.1 The assessment of cardiorespiratory fitness

Cardiorespiratory fitness reflects the capacity of the body to uptake and utilise oxygen. It is dependent on the synergistic function of key organ systems, particularly the respiratory, cardiovascular and muscle-metabolic, to deliver oxygen from the ambient air to the mitochondria at the working skeletal muscles (Lee, Artero et al. 2010). Oxygen consumption is described by the Fick equation, where oxygen utilisation ($\dot{V}O_2$) = cardiac output x arteriovenous oxygen difference (a-vO_2D) (Levine 2008). These parameters provide an insight into the physiological determinants of oxygen consumption, where cardiac output is primarily dependent on central factors including heart rate, stroke volume, and aortic function, and a-vO_2D depends largely on peripheral factors such as peripheral blood flow, blood oxygen carrying capacity, capillary supply and mitochondrial volume and density, and the matching of oxygen perfusion and diffusion between the capillaries and the mitochondria (Del Torto, Corrieri et al. 2017).

Cardiopulmonary exercise testing (CPET) is used to assess functional capacity and cardiorespiratory fitness (Albouaini, Egred et al. 2007). During CPET, expired ventilatory gasses are collected and analysed while the test participant undertakes incremental exercise to their maximum effort, i.e., the point at which they are not volitionally able to sustain the

exercise load and continue. The *maximum* rate of oxygen uptake during exercise ($\dot{V}O_{2max}$) is considered to be the gold-standard measure of cardiorespiratory fitness. $\dot{V}O_{2max}$ is commonly defined as a plateau in oxygen consumption for a sustained period (e.g. 30-60s) during maximum incremental exercise. However, given that this plateau in oxygen consumption is often not observed, $\dot{V}O_{2peak}$, i.e. the *highest* rate of oxygen consumption during a test, is commonly used as a measure of cardiorespiratory fitness (Arena, Myers et al. 2007, Green and Askew 2018). CPET with expired gas analysis also enables an assessment of gas exchange thresholds, including (GET) the ventilatory threshold (VT), where expired ventilation ($\dot{V}_E$) increases disproportionately to the increase in $\dot{V}O_2$. The VT provides a submaximal measure of functional capacity, occurring at approximately 45-65% of the $\dot{V}O_{2peak}$ (Sato, Matsumura et al. 1989). Although its estimation can be subjective (e.g. using the V-slope, ventilatory equivalent or excess carbon dioxide methods) it has been shown to be reliably interpreted between clinicians (Vainshelboim, Rao et al. 2017). Exercise beyond VT is associated with metabolic acidosis, hyperventilation and reduced capacity to perform work, thus its assessment is useful in clinical populations when a maximal CPET may be contraindicated (Ferguson 2014).

3.2 Cardiorespiratory fitness in people with AAA

Cardiorespiratory fitness has been demonstrated to be impaired in people with AAA. A recent large retrospective study reported a mean reduction of 13.6 $mL \cdot kg^{-1} \cdot min^{-1}$ (95%CI 12.0–15.2, P<0.001) in $\dot{V}O_{2peak}$ in people with AAA (*n*=124) compared with apparently healthy age-matched individuals (*n*=108) (Rose, Davies et al. 2018). In support of this finding, a recent comparative study reported that people with small AAA (<5.5cm) demonstrate significantly lower cardiorespiratory fitness (*n*=22, $\dot{V}O_{2peak}$:19.0 ± 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) when compared to those without AAA (*n*= 22, 24.5 ± 2.8 $mL \cdot kg^{-1} \cdot min^{-1}$, P≤0.001) (Perissiou, Bailey et al. 2019). These findings from comparative studies suggest there is at least a ~25% deficit in cardiorespiratory fitness in people with AAA. While to date these are the only two studies to directly compare cardiorespiratory fitness between people with and without AAA, overall there have been 17 studies that have reported estimates of cardiorespiratory fitness in patients with AAA. These studies are summarised in Table 1 and include cross-sectional and exercise-training investigations in people with small and large AAA. Across the 2259 study participants with small and large AAA (aged 69-76 years), these studies report $\dot{V}O_{2peak}$ means ranging between 13.3-20.0 $mL \cdot kg^{-1} \cdot min^{-1}$ and a VT range of 9.4-12.5 $mL \cdot kg^{-1} \cdot min^{-1}$.

According to age-related normative data, the $\dot{V}O_{2peak}$ and VT of people with AAA are categorised as "very poor", and within the lowest (25^{th}) percentile of the general population (Ferguson 2014, Vainshelboim, Arena et al. 2020). Importantly, current evidence demonstrates that a $\dot{V}O_{2peak}$ <15 $mL \cdot kg^{-1} \cdot min^{-1}$ and a VT< 10 $mL \cdot kg^{-1} \cdot min^{-1}$ are associated with reduced functional capacity and severe cardiovascular risk (Kodama, Saito et al. 2009). The reported mean $\dot{V}O_{2peak}$ in the eight studies that included people with a large AAA (*n*= 1859; $\dot{V}O_{2peak}$ 13.3-17.5 $mL \cdot kg^{-1} \cdot min^{-1}$, Table 1B) was generally lower when compared with the nine studies that included people with small AAA (*n*= 700; $\dot{V}O_{2peak}$ 18.0-20.0, $mL \cdot kg^{-1} \cdot min^{-1}$, Table 1A). To date there have been no studies directly comparing cardiorespiratory fitness levels between those with small and large AAA.

3.3 The potential impact of AAA on oxygen delivery and utilisation

While there have been no direct investigations to understand the impact of AAA on the physiological determinants of cardiorespiratory fitness, impairments in cardiorespiratory fitness can broadly be explained by limitations in factors associated with oxygen delivery and/or oxygen utilisation (Burtscher 2013). A primary physiological determinant of cardiorespiratory fitness is the ability of the blood and the vasculature to efficiently carry oxygen from the heart to the periphery in order to meet the oxygen requirements of working muscles (Levine 2008). Chronic systemic inflammation, a primary determinant of AAA (Dale, Ruhlman et al. 2015), plays a key role in the formation of vascular lesions and remodelling which consequently leads in endothelial dysfunction and increased arterial stiffness, both markers of arterial wall damage (Castellon and Bogdanova 2016) and main characteristics of AAA (Kadoglou, Papadakis et al. 2012, Siasos, Mourouzis et al. 2015). Importantly, vascular endothelial dysfunction and elevated arterial stiffness are factors known to directly impact blood flow and oxygen delivery (Kadoglou, Papadakis et al. 2012, Siasos, Mourouzis et al. 2015). We recently demonstrated that aortic stiffness and endothelial dysfunction are associated with lower cardiorespiratory fitness ($\dot{V}O_{2peak}$) in people with small AAA (Bailey, Perissiou et al. 2017, Perissiou, Bailey et al. 2019). There is evidence that increased arterial stiffness is directly associated with impaired muscle oxygenation during exercise in hypertensive patients (Dipla, Triantafyllou et al. 2017). In addition, endothelial dysfunction is widely associated with hypoperfusion of regional vasculature, including limb and muscle blood flow during exercise (Vallet 2002). Similarly, at the microvasculature, endothelial dysfunction and a disturbed production of nitric oxide derivatives is associated

with impaired capillary blood flow and altered oxy-haemoglobin binding (Iankovskaia and Zinchuk 2007), which potentially limit oxygen delivery to working muscles.

Impaired function and structure of the aorta is also associated with a deterioration in aortic Windkessel function (Belz 1995). The Windkessel effect dampens the phasic systolic surges in blood flow produced by ventricular ejection into a smoother, more continuous outflow to the peripheral vessels. Interestingly, Swillens et al. (2008) demonstrated in computer constructed models of AAA that the aneurysm itself is responsible for a deterioration in Windkessel wave-reflection, leading to an impairment in cardiac output and reduced blood flow to the periphery (Swillens, Lanoye et al. 2008). Reduced blood flow is commonly reported at the site of aortic aneurysms (White and Dalman 2008), and Suh et al. (2011) demonstrated a reduction in aneurysmal blood flow during cycling exercise (Suh, Les et al. 2011). This has been further interrogated with 3D computer models of large AAA, where during rest and exercise conditions there is recirculation of blood within the aneurysm which contributes to reduced blood distribution to the periphery throughout the cardiac cycle (Varshney, Haani Farooqi et al. 2020). These impairments in vascular function and haemodynamics are potentially compounded by an altered blood oxygen carrying capacity in people with AAA. Specifically, Zhang et al. (2012) retrospectively reviewed haemoglobin levels in 255 people with AAA and reported a high prevalence of anaemia (34.5%), and that haemoglobin concentration was independently and inversely associated with aneurysm diameter (Zhang, Zhang et al. 2012).

Oxygen extraction and the efficient utilisation of oxygen by the mitochondria is a fundamental determinant of cardiorespiratory fitness (Jacobs and Lundby 2013). To date, there have been no direct investigation of muscle oxygen utilisation in people with AAA. However, several studies have established that mitochondrial dysfunction is evident in the smooth muscle of the aneurysm wall. It has also been reported that there is differential expression of a number of genes associated with mitochondrial function and oxidative phosphorylation within the aneurysm wall (Yuan, Liang et al. 2015). The reduced mitochondrial function may also be accompanied by increased glycolysis and increased lactate production (Prado-Garcia, Campa-Higareda et al. 2020). Indeed, Tsuruda et al. (2012) reported an increased glycolytic activity in aneurysmal mouse models (Tsuruda, Hatakeyama et al. 2012), and Modrego et al. (2012) showed that in-vitro lactate content is elevated in AAA compared with control participants (Modrego, López-Farré et al. 2012).

Chronic inflammation, which characterises AAA (Dale, Ruhlman et al. 2015), is known to contribute further to a hypoxic microenvironment within tissues, a phenomenon known as inflammatory hypoxia (Biddlestone, Bandarra et al. 2015). Indeed, studies have reported that AAAs demonstrate inflammation induced tissue hypoxia and attenuated oxygen diffusion (Blassova, Tonar et al. 2019). In addition, systemic chronic inflammation in AAA has been shown to favour a pro-oxidant microenvironment in people with AAA (Meital, Windsor et al. 2020), a state that is associated with impairments in muscle oxygen utilisation and exercise capacity (König, Wagner et al. 2001). Indeed, Mentese et al. (2016) reported that compared to control, individuals with AAA demonstrate elevated oxidative stress levels with no change in antioxidant capacity (the ability of inhibiting molecules with high redox potential) (Menteşe, Turan et al. 2016).

Morphometric analyses of muscle biopsy samples from the anterior tibialis muscle show a predominance of atrophic type-I muscle fibres in people with AAA (Albani, Kiskinis et al. 2000). Interestingly, current evidence suggests that type I muscle fibre atrophy is a consequence of injury induced by reactive oxygen species and is associated with impaired oxygen utilisation (Bonaldo and Sandri 2013). Hence, we could speculate that muscle atrophy indirectly contributes to impaired muscle oxygen utilisation in people with AAA. Studies presented here only provide indirect evidence of the potential impact of AAA on muscle oxygen utilisation. There is a need for future studies to directly assess the determinants of muscle oxygen utilisation (e.g. mitochondrial volume and function, capillary supply, aerobic enzyme activities, muscle oxygen extraction) at rest and during exercise in people with AAA.

3.4 The potential impact of AAA comorbidities on the cardiorespiratory fitness of people with AAA.

There are several comorbidities that are commonly observed in people with AAA that may contribute to their impairment in cardiorespiratory fitness. Coronary artery disease (CAD) is one of the most prevalent co-morbidities, with 25 to 37 % of people with AAA reported to also have a diagnosis of CAD (Van Kuijk, Flu et al. 2009). There is a well-established impairment in cardiorespiratory fitness associated with CAD (Gander, Sui et al. 2015), as myocardial ischemia associated with the stenosis of coronary arteries leads to a reduction in cardiac output and therefore limits oxygen delivery to the working skeletal muscles. Similarly, peripheral arterial disease (PAD), which is present in approximately 20% of people

with AAA (Kent, Zwolak et al. 2010), is associated with low levels of cardiorespiratory fitness (Hou, Green et al. 2002). PAD is characterised by blood flow impairment to the muscle of the lower limbs. There is also evidence of skeletal muscle changes including alterations capillary supply, mitochondrial density and function, and changes to muscle fibre morphology and metabolism that all potentially contribute to impaired oxygen extraction and utilisation (Baum, Torchetti et al. 2016, Hamburg and Creager 2017). These skeletal muscle changes may also be exacerbated by the presence of type-2 diabetes, which is diagnosed in approximately 15% of people with AAA (Green, Askew et al. 2007, De Rango, Farchioni et al. 2014). Furthermore, diabetes potentially limits the efficient use of glucose as a substrate during exercise which is associated with impaired oxygen economy during exercise (Bauer, Reusch et al. 2007) and a reduction in cardiorespiratory fitness (Nesti, Pugliese et al. 2020). Finally, people with AAA commonly present with impaired pulmonary function, and chronic obstructive pulmonary disease (COPD) is reported in up to ~ 28% of AAA patients (Lederle, Noorbaloochi et al. 2015). COPD primarily causes a diffusion limitation at the lungs and has been shown to limit oxygen delivery capacity to peripheral tissues and working muscles (Nakamura, Tanaka et al. 2004) (Broxterman, Hoff et al. 2020).

Sections 3.3 and 3.4 in this review outline the systemic and local cardiovascular alterations that occur with AAA, as well several common comorbidities, that likely contribute to the impaired cardiorespiratory fitness in these individuals. A theoretical overview of the association between these mechanisms is depicted in Figure 1. While this provides a plausible basis for understanding the limits associated with AAA, studies that interrogate the physiological mechanisms of cardiorespiratory fitness in people with AAA are lacking, and there is a need for further research in this area.

4. Cardiorespiratory fitness as a predictor of clinical outcomes in people with AAA undergoing open surgical and endovascular repair

Open surgical or endovascular repair are currently the only recognised effective treatments for AAA, to prevent rupture and aneurysm-related death, according to the National Institute for Health & Care Excellence (NICE) AAA guidelines [NG156] (Care and Excellence 2020). Open repair is considered a major surgical procedure that requires an abdominal incision to be made in order to repair the aneurysm with a graft. Endovascular aneurysm repair (EVAR)

is considered less invasive. It involves a small incision in the groin and femoral artery where a stent-graft is deployed intraarterially in order to effectively exclude circulation from the aneurysm sac. Regardless of the method used, aneurysm repair is associated with a significant risk of mortality (open~3%; EVAR~1%), and for this reason it is generally reserved for those with a large AAA (>5.5 cm in diameter) and for those where the risk of rupture is greatest (Locham, Lee et al. 2017). AAA repair places considerable metabolic demands on patients during the repair procedure and the short-term (i.e. 3 month) postoperative period (Salartash, Sternbergh et al. 2001). This is thought to be due to a strong inflammatory response that leads to an increase in basal oxygen demand of ~110 to ~170 $mL \cdot min^{-1}$ during the postoperative period (Older, Hall et al. 1999). The increased energy requirements are reported to be necessary for wound healing and the resolution of inflammation, and are associated with significant elevations in ventilation and cardiac activity (Davies and Wilson 2004). Failure of the cardiorespiratory system to meet these increased metabolic requirements is suggested to contribute to intra- and post-operative complications and mortality in AAA (Struthers, Erasmus et al. 2008).

Several studies have established that an impairment in pre-operative cardiorespiratory fitness is closely associated with the risk of death in the short-term (up to 3 months) period after open AAA repair (Table 2A). Specifically, Hartley et al. (2012) demonstrated that people with a $\dot{V}O_{2peak} \leq$ 15 $mL \cdot kg^{-1} \cdot min^{-1}$ and a VT $\leq$ 10.2 $mL \cdot kg^{-1} \cdot min^{-1}$ were at increased risk of both 30- and 90-day mortality following open repair (Hartley, Pichel et al. 2012). Similarly, Goodyear et al. (2013) found that people with a VT $\leq$ 11 $mL.kg^{-1}.min^{-1}$ demonstrated a 9.9% higher 30-day mortality rate after open repair compared to people that achieved a VT $\geq$11 $mL.kg^{-1}.min^{-1}$ (Goodyear 2013). Finally, Barakat et al. (2015) reported that different measures of fitness are associated with specific perioperative complications (Barakat, Shahin et al. 2015). A significant relationship was demonstrated between a $\dot{V}T \leq 10.2$ $mL.kg^{-1}.min^{-1}$ and cardiac complications, and a ventilatory equivalent for carbon dioxide $\geq$ 42 ($\dot{V}_E/\dot{V}CO_2$, a GET variable associated with elevated pulmonary pressures) and respiratory complications (Barakat, Shahin et al. 2015). These results highlight the clinical importance and impact of cardiorespiratory fitness on the short-term post-operative mortality and morbidity of people with AAA following open surgical repair.

Endovascular AAA repair (EVAR) was originally developed as a lower-risk non-invasive procedure that would also accommodate people who were considered physically ineligible

(unfit) for open surgical repair (Parodi, Palmaz et al. 1991). It is associated with a significantly lower rate of aneurysm related mortality than no-repair (Greenhalgh 2005). Indeed, studies to date have also reported that EVAR demonstrates significantly reduced short-term postoperative mortality (Hartley, Pichel et al. 2012, Goodyear 2013) and morbidity (Prentis, Trenell et al. 2012) in unfit ($\dot{V}T \leq 11$ mL.kg^{-1}.min^{-1}) people with AAA compared to open repair. However, it seems likely that the early benefit of EVAR with respect to short-term postoperative mortality is abolished in the long-term, due largely to fatal endo-graft leaks and ruptures (Patel, Sweeting et al. 2016). Indeed, a committee of clinicians appointed by the UK National Institute for Health and Care Excellence, recently published a scientific report recommending the use of open over EVAR repair (Bradbury, Davies et al. 2021). Interestingly, evidence demonstrates that besides endo-graft ruptures, cardiorespiratory fitness is one of the main determinants of the increased long-term post-operative mortality observed after EVAR. Specifically, Straw et al. (2020) assessed the 3-year postoperative mortality in people undergoing EVAR and reported that patients with a $\dot{V}O_{2peak} \leq 15$ mL.kg^{-1}.min^{-1} and a $\dot{V}_E/\ \dot{V}CO_2 \geq 42$ mL.kg^{-1}.min^{-1} have an increased risk of long-term postoperative mortality compared to patients with higher measures of fitness (Straw, Waduud et al. 2020). These results reinforce the impact of cardiorespiratory fitness as a significant determinant of long-term survival in people with AAA undergoing EVAR.

To date, several studies have demonstrated that cardiorespiratory fitness is associated with long-term postoperative mortality regardless of the AAA repair modality used (Table 2B). Specifically, a $\dot{V}T \leq 10.2$ mL.kg^{-1}.min^{-1} and a $\dot{V}O_{2peak} \leq 15$ mL.kg^{-1}.min^{-1} were found to successfully predict 3-year post-operative survival (Grant, Hickey et al. 2015) and length of hospital stay (Prentis, Trenell et al. 2012) regardless of whether EVAR or open repair was used. Importantly, using a combination of cardiorespiratory fitness and gas exchange threshold variables including $\dot{V}O_{2peak,}$ $\dot{V}T$ and $\dot{V}_E/\ \dot{V}CO_2$, may strengthen the prediction of mortality following AAA repair and help to assess the risk versus benefit prior to AAA repair (Grant, Hickey et al. 2015). Finally, in a large multicentre study (n=1,096), Carlisle et al. (2015) used pre-surgical values of $\dot{V}O_{2peak,}$ $\dot{V}T$ and $\dot{V}_E/\dot{V}CO_2$ in a survival calculator that strongly predicted 5-year post-operative mortality both in patients that underwent EVAR and open repair (Carlisle, Danjoux et al. 2015).

In summary, there is a plethora of evidence demonstrating that cardiorespiratory fitness is a significant predictor of short- and long-term post-operative mortality and morbidity,

regardless of the repair modality, in people with AAA. However, heterogeneity among available studies and the use of retrospective study designs does not allow for a suitable comparison as the reported CPET variables and cut-off values are not universally reported between studies. This is also noted in the latest guidelines for people with AAA from the National Institute of Health and Care Excellence, (NICE guideline 156), published in 2020, where it is highlighted that current evidence are not robust and homogenous enough to form official guidelines for using cardiorespiratory fitness in order to identify patients at risk for post-operative mortality (Care and Excellence 2020). Future studies should address the need for more homogenous fitness data that will aid in the development of universal clinical thresholds to aide in the management of people with AAA.

5. The beneficial effects of exercise training in people with AAA

Over the last decade, there has been growing interest in the use of exercise training (therapy) as an adjunct treatment for both surgical (large AAA) and non-surgical (small AAA) management of people with AAA. This is based on the multiple benefits that improved cardiorespiratory fitness seems to have on post-operative outcomes (as highlighted in section 4) and in reducing cardiovascular related mortality (Kodama, Saito et al. 2009). The current section provides a detailed review of evidence of the effect of exercise training on cardiorespiratory fitness, post-operative outcomes, cardiovascular health parameters and disease progression in people with AAA.

5.1. The effect of exercise training on cardiorespiratory fitness

Several studies have reported improvements in cardiorespiratory fitness after short-term (6-12 weeks) exercise training in patients with small AAA (Table 3). All studies have used aerobic or combined exercise (aerobic + resistance exercise) at a moderate intensity, with a frequency of 2 to 3 in-hospital exercise sessions per week. No exercise-induced adverse events have been reported in any of the studies to date. Overall, short-term exercise interventions were able to evoke significant increases in $\dot{V}T$ (Δ1.1 to 3.0 $mL.kg^{-1}.min^{-1}$) (Kothmann, Batterham et al. 2009, Tew, Moss et al. 2012) and $\dot{V}O_{2peak}$ (Δ1.2 to 1.7 $mL.kg^{-1}.min^{-1}$) (Tew, Moss et al. 2012, Lima, Vainshelboim et al. 2017) in patients with small AAA (<5.5 cm) when compared with a usual-care group. Importantly, the majority of the studies reported that the improvements in cardiorespiratory fitness met the criteria for a minimum clinically important difference (MCID) (i.e. 0.5 x SD of the reported change in $\dot{V}O_{2peak}$ or $\dot{V}T$), (Tew, Moss et al. 2012, Lima, Vainshelboim et al. 2017).

Conversely, in studies of people with large AAA, findings from studies of short-term exercise are more variable. Tew et al. (2017) reported no significant increase in cardiorespiratory fitness after four weeks of high intensity interval aerobic exercise in people with large AAA (>5.5 cm) (Tew, Moss et al. 2012). The authors reported that only 63% of the study cohort was considered adherent to the exercise intervention and that during the intervention period the exercise intensity had to be occasionally reduced for the majority of the cohort (~74%) due to triggered exercise safety criteria, which may have resulted in limited exercise progression. In contrast, Barakat et al. (2015) reported significant increments in $\dot{V}O_{2peak}$ (Δ1.6 mL.kg^{-1}.min^{-1}) and $\dot{V}T$ (Δ1.9 mL.kg^{-1}.min^{-1}) after six weeks of combined moderate intensity exercise training in people with large AAA (>5.5 cm) compared to the usual care group (Barakat, Shahin et al. 2016). Importantly, it was also reported that people with large AAA randomised to the control group demonstrated a decrease of 1.2 mL.kg^{-1}.min^{-1} in their $\dot{V}O_{2peak}$ during the 6-week period, indicating that exercise training potentially mitigates a deterioration in cardiorespiratory fitness over time. Overall, studies to date indicate that exercise training may induce significant improvements in cardiorespiratory fitness in people with large AAA, however it may be that longer-duration moderate-intensity training is preferential and more feasible in this population.

The effect of long-term exercise training (>12 weeks) on cardiorespiratory fitness in people with AAA has only been assessed in one study to date. Myers et al. (2014) assessed the effect of long-term combined training program (up to 3 years follow up) on cardiorespiratory fitness in people with a small AAA (<5.5 cm) (Myers, McElrath et al. 2014). Results demonstrated significant increases in $\dot{V}O_{2peak}$ in the exercise group at the 3-month (Δ 0.9 mL.kg^{-1}.min^{-1}) and 1-year (Δ 1.3 mL.kg^{-1}.min^{-1}) evaluations. While at the 2nd and 3rd year evaluation $\dot{V}O_{2peak}$ remained stable in the exercise group, the authors reported a significant decrease for the usual care group (2nd year Δ -1.6 mL.kg^{-1}.min^{-1}; 3rd year Δ -2.3 mL.kg^{-1}.min^{-1}). A potential limitation of this study was the use of a home-based exercise intervention; however, current evidence in general clinical populations support the use of home-based programs compared with supervised in-centre programs (Anderson, Sharp et al. 2017). Importantly, these results demonstrate that despite advanced age (72±7) and multiple comorbidities (CAD, PAD, type 2 diabetes), training up to 3 years was well tolerated and feasible in patients with small AAA.

5.2. The effect of exercise training on post-operative outcomes

Exercise training induced improvements in cardiorespiratory fitness have been associated with favourable post-operative outcomes in people undergoing AAA repair (Barakat, Shahin et al. 2016). Barakat et al. (2016), was the first study to demonstrate that an increase of 1.6 $mL.kg^{-1}.min^{-1}$ in $\dot{V}O_{2peak}$ and 1.9 $mL.kg^{-1}.min^{-1}$ in $\dot{V}T$ in the exercise group, was associated with a lower rate of post-operative complications (cardiac 8.1%, pulmonary 11.3%, renal 6.5%) when compared with the usual care group who underwent open surgery alone. Similarly, Hayashi et al. (2016) reported that increased levels of pre-operative self-reported physical activity are associated with early ambulation and reduced length of hospital stay (LOS) after AAA repair (Hayashi, Hirashiki et al. 2016). Importantly, the authors also reported that individuals who engage in exercise at the earlier stages of the disease have superior post-operative outcomes (reduced mortality and LOS) compared to those who became physically active at a later stage. Conversely, Tew et al. (2017) reported no impact on post-operative mortality after four weeks of high intensity interval training in people with large AAA (Tew, Batterham et al. 2017). It is important to note that this was not a full-scale trial; authors characterised it as an external pilot trial, and that no significant increases in cardiorespiratory fitness were reported after the exercise intervention. To date, these are the only studies that have assessed the effect of an exercise intervention on post-operative clinical outcomes in people with AAA. A recent meta-analysis (Wee and Choong 2019) and a Cochrane review (Fenton, Tan et al. 2021) assessed the impact of preoperative exercise training for people with AAA. Both of the studies reported that preoperative exercise training appears to be beneficial for people with AAA however, due to methodological heterogeneity among studies, it remains premature to conclude that exercise training as a preoperative intervention improves postoperative outcomes.

5.3. The effects of exercise training on cardiovascular parameters and aneurysm progression.

Exercise training induced increases in cardiorespiratory fitness are accompanied by a cardiovascular health benefit in people with AAA. Tew et al. (2012) reported a decrease of 10 mmHg in systolic blood pressure in the exercise group after the completion of a short-term (12 week) exercise intervention in people with small AAA (Tew, Moss et al. 2012). In addition, the authors reported a corresponding decrease in high sensitivity C-reactive protein (hs-CRP) in the exercise group that was deemed clinically important. With these changes the exercise group's risk stratification changed from "moderate" to "low". Similarly, Nakayama

et al. 2018 reported that a reduction in hs-CRP, observed in people with small AAA that underwent cardiac rehabilitation, was associated with slower aneurysm growth (Nakayama, Morita et al. 2018). Recently, Niebauer et al. (2021) (Niebauer, Niebauer et al. 2021) reported sub-analysis data stemmed from the AAA Stop Trial (Myers, McElrath et al. 2014). The authors reported a significant reduction in systolic blood pressure and in lipid accumulation product (biomarker of atherosclerosis) in people with AAA after a year of exercise training compared to a usual care group. These results are promising, given that exercise-induced reductions in chronic inflammation are associated with corresponding improvements in endothelial function, blood flow and cardiorespiratory fitness in other chronic diseases such as, type 2 diabetes mellitus (Okada, Hiuge et al. 2010) and CAD (Cwikiel, Seljeflot et al. 2018). Interestingly, it was recently demonstrated that even a single bout of exercise is able to transiently improve the cardiovascular profile of people with small AAA by reducing aortic stiffness (Perissiou, Bailey et al. 2019) and inflammation (Windsor, Bailey et al. 2018) and improving endothelial function (Bailey, Perissiou et al. 2017). These parameters have all been associated with cardiovascular risk and aneurysm progression. It is apparent from current evidence that exercise can favourably influence markers of cardiovascular risk and aneurysm progression in patients with AAA; however, larger-scale clinical trials are needed in order to establish exercise as adjunct treatment modality for addressing cardiovascular risk in this population.

5.4. Risks and concerns of exercise in people with AAA

To date, the available studies report that only a low percentage of the AAA population is engaged in regular physical activity (Hayashi, Hirashiki et al. 2016), with a recent meta-analysis associating physical inactivity with the risk of AAA development (Aune, Sen et al. 2020). Concerns regarding the risks of exercise in people with AAA have been expressed in the past, although this is mostly based on opinion or medical concern rather than empirical evidence. Available data indicate that exercise is safe in people with AAA. In a total of 294 patients that underwent exercise training in the available 9 studies that were reviewed, only one adverse event (cardiac arrest) was reported in the exercise group, which was not aneurysm- or exercise-related (Kothmann, Batterham et al. 2009). A recent meta-analysis that assessed the safety of exercise training in patients with AAA reported that the cardiovascular event rate was 0.8% (Kato, Kubo et al. 2018), which is remarkably less than that reported (1.5%) for healthy older individuals without AAA (Goodrich, Larkin et al.

2007). Further to this, it was reported that exercise training did not increase aneurysm diameter in patients with small AAA. Importantly, our recent study reported a similar acute hemodynamic response to moderate and higher intensity exercise between people with small AAA and older individuals without AAA (Perissiou, Bailey et al. 2019) suggesting that exercise can be undertaken safely to improve cardiorespiratory fitness and cardiovascular health in this population.

6. Summary and future directions

This review highlights the clinical and physiological importance of cardiorespiratory fitness in people with AAA. While we have identified several potential mechanisms and factors that likely contribute to the low levels of fitness observed in people with AAA, studies directly exploring the determinants of cardiorespiratory fitness in this population are lacking. Further studies are needed understand the impact of AAA on oxygen delivery and utilisation at the working muscles. Current evidence demonstrates that cardiorespiratory fitness is a significant predictor of short- and long-term post-operative mortality and morbidity in people undergoing AAA repair. Studies to date have used a wide range of gas exchange threshold methods for assessing and reporting cardiorespiratory fitness, and there is a need for more robust and homogenous reporting of data that will aid in the development of pre-operative fitness thresholds and inform clinical guidelines. Finally, this review synthesises the current available evidence of the benefits of exercise training on cardiorespiratory fitness for people with AAA. Exercise induced improvements in fitness are associated with markers of cardiovascular health and a reduction in post-operative mortality. However, current evidence regarding the safety and clinical effectiveness of exercise in people with AAA are still considered limited and there is a need for larger-scale clinical trials to establish clear exercise training guidelines for patients with AAA that take into consideration disease severity, high risk patients and the presence of co-morbidities.

7. Author contributions

All authors contributed to the intellectual content of the manuscript; MP, CDA and TGB conceived and planned the work; MP drafted the manuscript; all authors revised the manuscript and provided critical input to specific sections. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately

investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Figure 1: Theoretical impact of AAA on cardiorespiratory fitness.

(A) AAA affects oxygen delivery throughout the body. **(A1)** Increased arterial stiffness contributes to the reduced Windkessel function observed in AAAs leading to reduced cardiac output and blood flow to the periphery (Swillens, Lanoye et al. 2008, Kadoglou, Papadakis et al. 2012). Further, as AAA diameter increases, the recirculating fluid in the aneurysmal site leads to further disruptions of blood distribution to the periphery (Suh, Les et al. 2011, Varshney, Haani Farooqi et al. 2020). **(A2)** Endothelial dysfunction and disturbed production of NO derivatives contributes to a reduced oxygen carrying capacity by the blood, leading to reduced blood flow to the periphery (Iankovskaia and Zinchuk 2007). **(B)** People with AAA demonstrate increased systemic oxidative stress (Menteşe, Turan et al. 2016) and predominance in Type 1 atrophic muscle fibres (Albani, Kiskinis et al. 2000), factors associated with oxygen utilisation determinants, such as mitochondrial dysfunction (Handy and Loscalzo 2012), reduced oxidative phosphorylation and ATP synthase and increased lactate production(Bonaldo and Sandri 2013). **(C)** AAAs are characterised by co-morbidities that create an ischaemic environment in the central (CAD) (Kent, Zwolak et al. 2010) and peripheral circulatory system (PAD) (Kent, Zwolak et al. 2010) and affect oxygen distribution by the lungs (COPD) (Lederle, Noorbaloochi et al. 2015) and oxygen utilisation by the muscles (T2DM) (De Rango, Farchioni et al. 2014). AAA, abdominal aortic aneurysm; BF, blood flow; Hb, haemoglobin; NO, nitric oxide; ATP, adenosine triphosphate; CAD, coronary artery disease; PAD, peripheral arterial disease; COPD, chronic obstructive pulmonary disease; T2DM, type-2 diabetes mellitus. The figure was created with BioRender.com

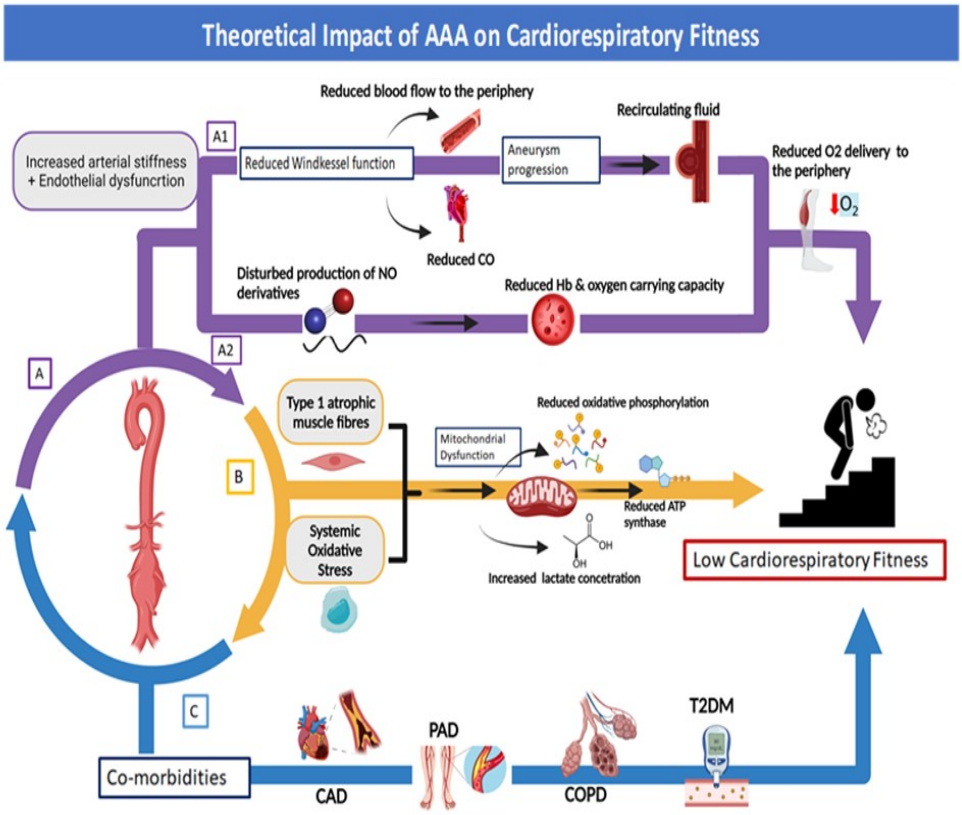

Table 1: Cardiorespiratory fitness in people with small (A) and large (B) abdominal aortic aneurysm (AAA).

Author	Group/Site	N	Age (y)	AAA size (cm)	Body mass index (BMI)	Type of exercise	$\dot{V}O_{2peak}$ $mL \cdot kg^{-1} \cdot min^{-1}$	VT $mL \cdot kg^{-1} \cdot min^{-1}$
A. Reported cardiorespiratory fitness in people with small AAA (<5.5)								
Kothmann et al., 2009	Exercise	17	70	< 5.5	-	Cycling	-	10.5±2
	Usual care	8	70		-		-	10.4±2
Myers et al., 2011	-	306	72 ± 7.5	< 5.5	28.2 ± 4	Treadmill	20.0 ± 6.3	-
Tew et al., 2012	Exercise	11	71 ± 8	< 5.5	27.9 ± 3	Cycling	19.3 ± 4.5	-
	Usual care	14	74 ± 6		28.3 ± 3		18.0 ± 5.7	12.4±3.1
Barakat et al., 2014	-	20	75 ± 6	-	-	Treadmill	18.2 ± 2.8	12.2±2.1
Myers et al., 2014	Exercise	72	72 ± 7	< 5.5	29.1 ± 4	Treadmill	19.5 ± 5.8	-
	Usual care	68	71 ± 8		27.0 ± 3		20.0 ± 6.4	-
West et al., 2015	-	48	70 ± 6	< 5.5	28.7 ± 4	Cycling	18.2 ± 5.3	11.4 ± 2.7
Lima et al., 2018	Exercise	33	73 ± 6	< 5.5	28.8 ± 3	Cycling	18.8 ± 4.8	13.3 ± 3.3
	Usual care	32	73 ± 6		27.6 ± 3		19.7 ± 5.5	15.6 ± 4.7
Nakayama et al., 2018	-	49	72 ± 8	< 5.5	24.1 ± 3	Cycling	18.0 ± 6.0	12.0 ± 3.0
Perissiou et al., 2019	-	22	74 ± 6	< 5.5	28.0 ± 9	Cycling	19.0 ± 3.5	-

B. Reported cardiorespiratory fitness in people with large AAA (>5.5)

Prentis et al., 2012	-	185	74 ± 8	> 5.5	27.7 ± 4	Cycling	14.0 ± 3.5	11.3±2.7
Barakat et al., 2015	-	130	75 ± 7	> 5.5	27.8 ± 4	Treadmill	16.6 ± 2.2	11.8 ± 1.5
Carlisle et al., 2015	Newcastle	283	74 ± 8	> 5.5	27.8 ± 5	Cycling	14.7 ± 3.6	11.6 ± 2.6
	Sheffield	358	74 ± 7	> 5.5	27.5 ± 5	Cycling	17.8 ± 3.8	11.5 ± 2.5
	South Tees	153	74 ± 7	> 5.5	-	Cycling	13.3 ± 3.6	9.4 ± 2.3
	Torbay	302	73 ± 7	> 5.5	27.2 ± 4	Cycling	15.7 ± 3.7	11.0 ± 2.3
Barakat et al., 2017	-	124	73 ± 7	> 5.5	-	Treadmill	17.5 ± 4.5	12.5 ± 3.9
Tew et al., 2017	Exercise	27	75 ± 6	> 5.5	26.5 ± 4	Cycling	16.5 ± 3.7	11.0 ± 2.1
	Usual care	26	75 ± 6		26.8 ± 3		15.7 ± 3.1	10.9 ± 2.7
Weston et al., 2017	-	27	74 ± 6	> 5.5	-	Cycling	16.5 ± 3.7	11.0 ± 2.1
Rose et al., 2018	-	124	70 ± 7	> 5.5	27.1 ± 3	Cycling	14.4 ± 3.2	-
Straw et al., 2020	-	120	76 ± 8	> 5.5	-	Cycling	14.7 ± 3.6	10.9 ± 2.8

Data derived from studies that assessed cardiorespiratory fitness in people with AAA using measures peak oxygen consumption ($\dot{V}O_{2peak}$) and/or of Ventilatory threshold (**VT**). Data that are extracted from exercise training studies include separate sets of data for the exercise training group and the comparator group (usual care, control). The large study of Carlisle et al. 2015 reported separate sets of means for each of the four hospital sites.

Table 2: Cardiorespiratory fitness as a predictor of (A) short term (≤3 months) and (B) long-term (>3 months) postoperative clinical outcomes following AAA repair.

Author	*N*	Male (%)	AAA repair method assessed	Mean follow up (months)	Primary Outcome	Fitness threshold	Effect of fitness on post-operative outcome	Survival Analysis		*P*
								Odds ratio	*Hazard ratio*	
A.	***Cardiorespiratory fitness relation with short term, (≤3months) postoperative clinical outcomes***									
Hartley et al.,2012[a]	415	84	*OPEN+EVAR*	1	Post-op mortality	$\dot{V}O_{2peak} \leq 15.0$	*Both subthreshold CPET values identified patients at increased risk of early death following AAA repair.*	5.41	-	0.013
						VT ≤ 10.2		4.50	-	0.013
Hartley et al., 2012[b]	415	84		3	Post-op mortality	$\dot{V}O_{2peak} \leq 15.0$		8.00	-	0.001
Prentis et al., 2012	185	87	*OPEN+EVAR*	2	Post-op mortality	VT ≤ 10.2	*Fitness was associated with post-operative complications and mortality.*	3.46	-	0.013
Goodyear et al.,2013	230	-	*OPEN+EVAR*	1	Post-op mortality	VT ≤ 11.0	*A pre-operative VT ≤ 11.0* was associated with increased post-operative mortality and length of hospital stay.	3.06	-	0.015
Barakat et al., 2015	130	89	*OPEN+EVAR*	1	Post-op cardiac complications	$\dot{V}E/\dot{V}CO_2 \geq 42$	*A VT ≤ 10.2 was only associated with post-operative mortality and cardiac complications after AAA repair.*	1.02	-	0.054
						VT ≤ 10.2		0.55	-	0.005
						$\dot{V}E/\dot{V}CO_2 \geq 42$		0.96	-	0.540
					Post-op pulmonary complications	$\dot{V}O_{2peak} \leq 15.0$	*A $\dot{V}E/\dot{V}CO2 \geq 42$ was associated with pulmonary complications after AAA repair.*	0.89	-	0.363
						VT ≤ 10.2		0.85	-	0.317
						$\dot{V}E/\dot{V}CO_2 \geq 42$		1.18	-	0.005

B.	***Cardiorespiratory fitness relation with long-term postoperative clinical outcomes***									
Nugent et al., 1998	30	75	*OPEN*	12	Post-op complications	$\dot{V}O_{2peak} \leq 20.0$	*A $\dot{V}O_{2peak} \leq 20.0$ identified patients at increased risk of complications following AAA repair.*	2.33	-	0.001
Carlisle et al., 2007	130	-	*OPEN*	24	Post-op mortality	$\dot{V}O_{2peak} \leq 15.0$ VT ≤ 10.0 $\dot{V}E/\dot{V}CO_2 > 42$	*Subthreshold CPET variables identified patients unlikely to survive in the 24-month period following AAA repair.*		0.83 0.74 1.12	0.002 0.001 0.001
Thompson et al.,2011	102	93	*OPEN*	30	Post-op mortality	VT≤ 11.0	*A VT≤ 11.0 was successful in predicting 30-month mortality, following AAA repair.*	3.20		0.001
Grant et al., 2015	506	83	*OPEN+EVAR*	36	Post-op mortality	$\dot{V}O_{2peak} \leq 15.0$ $\dot{V}E/\dot{V}CO_2 \geq 42$	*Subthreshold CPET variables are independent predictors of reduced survival after AAA repair*	- -	1.63 1.68	0.046 0.049
Carlisle et al., 2015	1096	90	*OPEN+EVAR*	60	Post-op mortality	Age-expected $\dot{V}O_{2peak}$ Age-expected VT Age-expected $\dot{V}E/\dot{V}CO_2$	*Subthreshold CPET values identified patients at long-term (1-5 years) increased risk of death following AAA repair.*	- - -	0.88 0.88 1.05	≥0.001 ≥0.001 ≥0.001
Rose et al., 2018	124	83	*OPEN+EVAR*	24	Post-op mortality	$\dot{V}O_{2peak} \leq 13.1$ VT ≤ 10.2 $\dot{V}E/\dot{V}CO_2 \geq 34$	*A $\dot{V}O_{2peak} \leq 13.1$ and a $\dot{V}E/\dot{V}CO_2 \geq 34$ were associated with increased risk of post-operative mortality.*		0.81 0.74 1.11	0.010 0.030 0.010
Straw et al., 2020	120	86	*EVAR*	36	Post-op mortality	$\dot{V}O_{2peak} \leq 15.0$ $\dot{V}E/$	*A $\dot{V}O_{2peak} \leq 15.0$ and a $\dot{V}E/\dot{V}CO_2 \geq 42$ were associated with reduced survivorship*	- -	1.34 1.88	0.283 0.016

							$\dot{V}CO_2 \geq 42$	following AAA repair

Data are from published studies that assessed the risk using hazard ratio (the relative risk of an event happening at a specific time) or odds ratio (quantifies the strength of the association between two events) of mortality or adverse outcomes following open surgical (OPEN) or endovascular (EVAR) AAA repair based on preoperative cardiorespiratory fitness. VT and $\dot{V}O_{2peak}$ are presented in relative units ($mL \cdot kg^{-1} \cdot min^{-1}$) Hartley et al. 2015 reported mortality at 1 [a] and 3 [b] months after repair; CPET, cardiopulmonary exercise testing; VT, ventilatory threshold; $\dot{V}O_{2peak}$, peak oxygen consumption; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide.

Table 3. Summary of studies investigating the effect of exercise training in patients with small and large AAA.

Author(s)	Group	*N*	Age (yrs)	AAA size (cm)	Exercise Training	Exercise Intensity	Duration and frequency	Primary Outcomes (Reported change in the exercise group compared to usual care group*or baseline[#])
Kothmann et al. 2009	Exercise	17	70	< 5.0	30 min. of static bicycle	Moderate	6 weeks/ 2 per week	VT ↑ 1.1 $mL \cdot kg^{-1} \cdot min^{-1}$ *
	Usual care	8	70					
Tew et al. 2012	Exercise	11	71 ±8	< 5.0	35-45 min. of treadmill walking and cycle ergometry	Moderate	12 weeks/ 3 per week	VT ↑ 2.5 $mL \cdot kg^{-1} \cdot min^{-1}$ * $\dot{V}O_{2peak}$ ↑ 1.7 $mL \cdot kg^{-1} \cdot min^{-1}$ SBP ↓ 9.0 mm/Hg
	Usual care	14	74 ± 6					

								hs-CRP ↓ 0.8 mg/L *
Myers et al. 2014	Exercise	60	72 ± 7	< 5.0	60 min. of treadmill, cycle ergometry, stair climbing, elliptical training.	Moderate	3 months/ 3 per week	$\dot{V}O_{2peak}$ ↑ 1.1 mL·kg^{-1}·min^{-1} #
3 months	Usual care	61	71 ± 8					AAA growth N/A
	Exercise	53					12 months/ 3 per week	$\dot{V}O_{2peak}$ ↑ 1.7 mL·kg^{-1}·min^{-1} #
12 months	Usual care	58						AAA growth ↓ 0.03 cm
	Exercise	36					24 months/ 3 per week	$\dot{V}O_{2peak}$ ↑ 1.7 mL·kg^{-1}·min^{-1} #
24 months	Usual care	46						AAA growth - 0.06 cm#
	Exercise	21					36 months/ 3 per week	$\dot{V}O_{2peak}$ ↑ 2.5 mL·kg^{-1}·min^{-1} #
36 months	Usual care	24						AAA growth ↑ 0.07 cm#
Barakat et al. 2016	Exercise	33	74 ± 7	> 5.0	60 min. of cycle ergometer, knee extensions, biceps/arm curls, knee bends	Moderate	6 weeks/ 3 per week	$\dot{V}O_{2peak}$ ↑ 2.8 mL·kg^{-1}·min^{-1} #
	Usual care	15	73 ± 8					VT ↑ 2.1 mL·kg^{-1}·min^{-1} #
Tew et al. 2017	Exercise	27	75 ± 6	> 5.0	8 x 2 min cycling intervals with 2 min active recovery	High	4 weeks/ 3 per week	$\dot{V}O_{2peak}$ ↑ 0.5 mL·kg^{-1}·min^{-1}
	Usual care	26	75 ± 6					VT ↑ 0.3 mL·kg^{-1}·min^{-1}
Lima et al. 2018	Exercise	33	73 ± 6	< 5.0	45 min treadmill, cycle ergometry, stair climbing, elliptical rowing +resistance	Moderate	12 weeks/ 3 per week	$\dot{V}O_{2peak}$ ↑ 1.2 mL·kg^{-1}·min^{-1} #
	Usual care	32	72 ± 8					VT ↑ 3.0 mL·kg^{-1}·min^{-1} #

					exercises			
Nakayama et al. 2018	CR	44	72 ± 8	< 5.0	30-40 min bicycle ergometer and limb resistance training	Low	150 days/1-3 per week	AAA growth rate ↓ 0.24 cm/year*
	Non-CR	44	72 ± 8					hs-CRP ↓ 1.6 mg/L*
Nakayama et al. 2019	CR	15	77 ± 4	< 5.0	30-40 min bicycle ergometer and limb resistance training	Low	150 days/1-3 per week	AAA growth rate ↓ 0.13 cm/year*
	Non-CR	25	74 ± 6					
Niebauer et al. 2021	Exercise	42	73 ±8	< 5.0	60 min. of treadmill, cycle ergometry, stair climbing, elliptical training.	Moderate	12 months/ 3 per week	SBP ↓ 9.0 mm/Hg
	Usual care	54	74±8					LAP ↓ 9.61cm*mmol/L*

VT, ventilatory threshold; $\dot{V}O_{2peak}$, peak oxygen consumption; SBP, systolic blood pressure; hs-CRP, high sensitivity c-reactive protein; CR, cardiac rehabilitation; LAP, Lipid Accumulation Product. *Change in the exercise group is reported compared to usual care group, ($P<0.05$); $^{\#}$Change in the exercise group is reported compared to baseline.