Cardiorespiratory Fitness, Exercise, and Blood Pressure

Peter Kokkinos

Findings from well-designed large epidemiological studies and diverse populations support a robust, inverse, and independent association between physical activity, cardiorespiratory fitness, and cardiovascular and overall mortality risk. The association is independent of age, race, sex, documented cardiovascular disease, or comorbidities, including hypertension. In prehypertension and hypertension, cardiorespiratory fitness exhibits preventive, prognostic, and therapeutic properties. Thus, appropriate lifestyle interventions, including increased physical activity designed to enhance cardiorespiratory fitness, are recommended by the Eight Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) and the European Society of Hypertension/European Society of Hypertension of Cardiology recent guidelines as initial therapy to prevent, treat, and control hypertension. This review presents evidence on the preventive, prognostic, and therapeutic aspects of exercise and fitness status of the individual on blood pressure (BP).

Preventive Aspects of Fitness on Blood Pressure

The age-related progressive increase in BP is accompanied by an incremental increase in cardiovascular risk evident beyond BP levels of 115/75 mm Hg. Evidence suggests that this increase in BP is preceded by arterial stiffness, an important and independent contributor to hypertension. To some extent, the age-related increase in arterial stiffness and BP is inevitable (biological aging). However, a substantial portion of the pronounced increase observed in industrialized societies is pathological and more likely a consequence of lifestyle characterized by high-fat and salt diets and physical inactivity than an inevitable outcome of aging. Indigenous populations living a relatively traditional hunter-gatherer lifestyle exhibit only a modest and substantially lower increase in arterial stiffness and BP compared with individuals living in westernized environments. Additionally, vascular health is improved by habitual physical activity and exercise intervention programs implemented in westernized populations and diminished by inactivity and bed rest. The exercise-induced increase in shear stress appears to provide the physiological stimulus for the adaptations in endothelial function and vascular remodeling observed after exercise training in healthy subjects.

Prehypertension, defined as systolic BP levels of 120 to 139 mm Hg or diastolic BP of 80 to 89 mm Hg, is frequently a precursor of hypertension. The aforementioned findings suggest that cardiorespiratory fitness may attenuate the rate of progression from prehypertension to hypertension. This concept was investigated in 2303 prehypertensive, middle-aged, male veterans followed for 9.2 years. Higher cardiorespiratory fitness, as reflected by peak metabolic equivalents (METs; 1 MET=3.5 ml of oxygen consumption per kg of body weight per minute), achieved during a standardized exercise test, was inversely associated with the rate of progression to hypertension. Compared with the individuals with the highest exercise capacity (>10 METs), the multivariate-adjusted risk for developing hypertension was 36% higher for those with an exercise capacity of 8.6 to 10 METs; 66% for those with 6.6 to 8.5 METs, and 72% higher for individuals who achieved ≤6.5 METs. Similar findings have been reported by others, and a recent meta-analysis of 13 prospective cohort studies confirmed an inverse, dose–response association between levels of recreational physical activity and risk for developing hypertension.

Collectively, these studies support that the age-related insidious increases in arterial stiffness, systolic BP, and incident hypertension are not entirely inevitable and that increased physical activity or a physically active lifestyle that leads to increased cardiorespiratory fitness can attenuate and even reverse the process.

Prognostic Aspects of Exercise Blood Pressure

Physiological rise in BP occurs during acute exercise. However, in some individuals, systolic BP rises disproportionally to the workload. This disproportionate BP rise is adversely associated with end-organ damage. For example, in our study of 790 middle-aged, prehypertensive individuals, exercise systolic BP at the workload of ≈5 METs was the strongest predictor of left ventricular hypertrophy (LVH). Systolic BP ≥150 mm Hg was the threshold for LVH. Individuals who achieved a systolic BP ≥150 mm Hg had significantly greater cardiac wall thickness, left ventricular mass (LVM) index (Figure 1), and lower exercise capacity compared with those with systolic BP <150 mm Hg. Furthermore, the risk of LVH increased 4-fold for every 10-mm Hg incremental rise in
systolic BP >150 mm Hg. The resting BP in the 2 groups (systolic BP ≥150 mm Hg and <150 mm Hg) was similar. These findings suggest that the BP response to exercise may be used to identify individuals at risk for LVH.

**Exercise Blood Pressure, Fitness Status, and Clinical Significance**

The exaggerated rise in BP during exercise may be modulated by the fitness status of the individual. Systolic BP of fit individuals at ≥5 METs and ambulatory BP were significantly lower when compared with the BP of low-fit. Also, in a randomized controlled study of hypertensive individuals who completed 16 weeks of aerobic exercise training, systolic BP was <27 and <32 mm Hg from pretraining values at the absolute workloads of 3 and 5 METs, respectively.

Evidence also suggests that the BP response to exercise or physical exertion may modulate left ventricular structure. In the aforementioned study of prehypertensive individuals, the exercise capacity–LVM index association was strong and inverse. The risk for LVH was 42% lower for every 1-MET increase in exercise capacity. When the cohort was stratified based on cardiorespiratory fitness, the least fit individuals exhibited higher exercise systolic BP and LVM index than the moderate and high-fit (Figure 2). Moreover, the exercise BP at the workload of ≥5 METs was the strongest predictor of LVM, whereas resting BP was a substantially weaker predictor. Exercise intervention studies have also reported significant reductions in LVM index in older individuals with stage 1 and 2 hypertension.

Collectively, these findings suggest (1) the exercise BP at the workloads of ≥3 to 5 METs reflects BP during daily activities; (2) an abnormal BP response at these relatively low workloads (3–5 METs) provides the impetus for increases in LVM and progression to LVH; (3) the exaggerated BP response is attenuated by regularly performed moderate intensity exercises or increased physical activity; and (4) the lower daily BP leads to LVM regression. However, these assumptions are based on prospective epidemiological data and interventional exercise studies are needed to substantiate these findings.

The clinical significance and public health effect of the exercise systolic BP–LVM relationship is 2-fold. First, exercise BP may be a marker for present and future LVH and hypertension. Second, the lower exercise BP and LVM index associated with higher fitness suggest that the progression to hypertension and LVH can be attenuated by increased fitness status. Thus, exercise programs designed to improve fitness can be used to attenuate the progressive increase in arterial stiffness, BP, and LVH.

**Therapeutic Aspects of Cardiorespiratory Fitness**

The consensus of meta-analyses and several reviews is that structured aerobic exercise training programs or increased physical activity of moderate intensity and adequate volume result in an independent reduction of 4 to 10 mm Hg in systolic and 3 to 8 mm Hg in diastolic BP for individuals with stage 1 hypertension regardless of age or sex. Relatively little is known on the effects of exercise in individuals with stage 2 hypertension or those with resistant hypertension. We noted significant reduction in BP in male veterans with stage 2 hypertension and LVH after 16 weeks of moderate-intensity aerobic exercise training. At 32 weeks, BP reduction was more pronounced even after a 33% reduction in antihypertensive medication in the exercise group, whereas BP in the no-exercise group increased substantially. We also noted a significant reduction in cardiac wall thickness and LVM, similar to that observed with most antihypertensive medications. This finding was unprecedented and clinically significant because LVH is considered an independent risk factor for mortality.

Similar findings were observed in individuals with resistant hypertension, defined as BP that remains above goal in spite of the concurrent use of 3 antihypertensive agents of different classes, one of which is a diuretic. In this study, moderate exercise was effective in significantly lowering 24-hour ambulatory BP. The reduction was similar to that reported by previous studies in individuals with mild to moderate hypertension.

Almost all of the information on exercise and BP are derived from aerobic exercises. Information available on the effects of resistance or strength training on resting BP is limited, conflicting and suggesting that resistance training is less efficacious than aerobic exercise in lowering resting BP. The reasons for this are not known. However, resistance exercise studies do not consistently support improvements in systemic
Exercise Capacity and Mortality Risk in Hypertensive and Prehypertensive Individuals

Findings from large and well-controlled epidemiological studies support an inverse, independent, and graded association between exercise capacity and mortality risk in prehypertensive and hypertensive individuals. For example, in a cohort of 4631 hypertensive veterans with multiple cardiovascular risk factors, who successfully completed a graded exercise, test mortality risk was 13% lower for every 1-MET increase in exercise capacity. When compared with the least-fit individuals (exercise capacity ≤5 METs), mortality risk was 34% lower for those in the next fitness category (5.1–7.0 METs) and progressively declined to over 70% for individuals with the highest exercise capacity (>10 METs). When the presence or absence of additional risk factors within fitness categories (least-fit to most-fit) was considered, the least-fit individuals (≤5 METs) with additional risk factors had a 47% higher mortality risk than those without risk factors. This increased risk was eliminated in the next fitness category (5.1–7.0 METs) and declined to ≥50% in those with an exercise capacity ≥7.0 METs, regardless of cardiovascular risk factor status.

The interaction between exercise capacity, body mass index, and mortality risk was also evaluated in hypertensive veterans. Progressively lower mortality rates with increased exercise capacity were observed within each body mass index category. The mortality risk reduction ranged from ≥40% in those with an exercise capacity of 5.1 to 7.5 METs to 70% in those with ≥7.5 METs.

To explore the fitness–fatness and mortality risk relationship further, we compared normal weight–low-fit individuals to overweight or obese, but fit individuals. The mortality risk was 47% and 60% lower for the overweight–moderate-fit and overweight–high-fit individuals, respectively. Similarly, the risk was 55% lower for the obese–moderate-fit and 78% lower for the obese–high-fit individuals. These findings suggest that it is more beneficial to be fit and overweight or obese rather than normal weight and unfit. Furthermore, it appears that obese hypertensive individuals may benefit at least as much (if not more) from fitness than their overweight or normal weight counterparts.

Finally, similar trends in the fitness–mortality risk association were noted in 4478 prehypertensive individuals and those with high-normal BP (130–139/85–89 mm Hg), independent of risk factors. The most pronounced reduction in risk (40%) was observed in low-fit individuals (peak MET level ≤6.0) compared with the least-fit (peak MET level ≥6.0), suggesting that relatively low levels of cardiorespiratory fitness are necessary for exercise-related health benefits. Risk reduction was progressively greater in moderate-fit (58%) and high-fit (73%) individuals. The trends were similar, but more pronounced among younger than older individuals. For every 1-MET increase in exercise capacity, the adjusted risk was 18% lower for those ≤60 years of age and 12% for individuals >60 years.

In summary, strong evidence supports that regularly performed exercise or a chronic increase in physical activity that leads to increased cardiorespiratory fitness attenuates the age-related progressive increase in BP and prevents hypertension. In hypertensive individuals, habitual physical activity lowers BP and the risk of mortality, independent of other risk factors. Finally, some evidence suggests that increased cardiorespiratory fitness attenuates the 24-hour BP and the BP response to exercise or physical exertion, thereby lowering the risk for LVH. The dose–response association between increased cardiorespiratory fitness, BP, and mortality risk reduction supports the existence of a causal mechanism(s). However, the mechanism or mechanisms are not well understood. It is likely that the favorable effects cardiorespiratory fitness, exercise, and physical activity have on several biological systems and traditional risk factors are likely to share the credit.

Disclosures

None.
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心肺耐力、锻炼和血压

Cardiorespiratory Fitness, Exercise, and Blood Pressure

Peter Kokkinos

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计良好的大型流行病学研究和不同人群研究的结果，支持锻炼、心肺耐力（cardiovascular fitness）与心血管死亡及总死亡风险之间存在独立的强负相关关系。该相关性独立于年龄、种族、性别、有记录的心血管疾病或并存疾病，包括高血压[1,2]。在高血压前期和高血压阶段，心肺耐力具有预防、预后和治疗的特性[3-4]。因此，第8版美国高血压预防、检测、评估和治疗报告（Eight Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, JNC 8）和近期公布的欧洲高血压学会/欧洲心脏病学会指南均推荐了提高心肺耐力的合理生活方式干预（包括增加锻炼）作为预防、治疗和控制高血压的初始治疗[3,4]。本文将介绍个体的锻炼和心肺耐力状态对高血压预防、预后判断和治疗作用的证据。

心肺耐力对高血压的预防作用

随着年龄增大，心脏功率下降、伴随著心血管风险的增加，尤其是当血压超过115/75 mmHg时[5]。证据提示，动脉僵硬度增加在血压升高之前即出现，是导致高血压的重要、独立的因素[6-12]。在某种程度上，动脉相关的动脉僵硬度增加和血压升高是不可避免的（即生物老化）。不过，在工业化社会所观察到的动脉僵硬度明显升高，有很大一部分是病理性的，更可能由于高脂、高盐饮食和活动不足的生活方式所致，而非老化的不可避免的后果[13-15]。采取狩猎和采集这一相对传统生活方式的原住民其动脉僵硬度和血压的增幅均明显低于西方人群[14,15]。此外，在西方人群规律开展锻炼和实施锻炼干预计划能够改善血管健康[16-19]，而活动增加和跌床则使血管健康变差[18,19]。看起来，运动导致的切应力增加为在健康受试者中所观察到的内皮功能和血管重构的适应性提供了生理性刺激[20]。

高血压前期定义为收缩压120-139 mmHg或舒张压80-89 mmHg[21]，通常是高血压的早期形式[22]。上文提到的 research results 提示，心肺耐力有可能延缓从高血压前期进展为高血压的速度。通过对处于高血压前期的2303例中年男性退伍军人进行9.2年随访，研究者验证了这一概念。心肺耐力用最大代谢当量（metabolic equivalents, METs，1 MET=在标准运动试验中消耗氧气3.5 ml/min/kg）表示，在标准运动测试中其值越高，表明进展为高血压的速度越慢。相比运动能力最佳（>10 METs）的人群，METs为8.6-10、6.6-8.5和≤6.5的人群发生高血压的多变量校正风险分别增加36%、66%和72%[23]。其他研究报道了相似的结果，最近一项针对13项前瞻性队列研究的荟萃分析证实，娱乐性体育锻炼和高血压的发生风险之间存在负相关关系，且风险与体育锻炼的量相关[1]。

总的来看，支持随着年龄增长而潜在的增加的动脉僵硬度，收缩压和高血压发生并非完全不可避免[13-15]，增加体育锻炼或采取积极锻炼的生活方式来增加心肺耐力有助于延迟甚至逆转上述过程[18,20]。

运动时血压的预后意义

运动时会出现急性的生理性血压升高[1]。但是，在某些人，收缩压的升高与活动量成正比例。这一不成比例的血压升高与靶器官损害相关[24]。例如，我们开展的一项研究纳入了790例中年高血压前期受试者，发现在运动量约为5 METs时运动时收缩压是左室肥厚（left ventricular hypertrophy, LVH）的最强预测因子[25]。收缩压≥150 mmHg是预测LVH的阈值，收缩压≥150 mmHg的受试者相比收缩压<150 mmHg的受试者心脏壁更厚、左室重量指数（left ventricular mass index, LVMII）更大（图1）且

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运动能力更差。另外，当收缩压<150 mm Hg时，收缩压每升高10 mm Hg，LVH的发生风险增加4倍。低血压患者(收缩压≥150 mm Hg和<150 mm Hg)的静息状态下血压相似。上述结果提示，运动状态下的血压反应可用于发现有LVH发生风险的个体。

## 运动时血压、心肺耐力和临床意义

人体的心肺耐力可以调节运动时的血压过度升高。心肺耐力低的个体在运动量大约5 METs状态下的收缩压[23]和动态血压监测的收缩压[24]显著更低。此外，一项随机对照试验纳入了完成16周有氧运动训练的高血压患者，在运动量为3 METs和5 METs情况下，训练后收缩压相比训练前分别降低了27和32 mm Hg[27]。

证据还显示，锻炼或强度活动时的血压反应可能调节左室结构。在前文中提到的高血压前期人群研究中[25]，运动能力和LVM1之间存在弱的负相关性。运动能力每增加1个METs，LVH发生风险降低42%。基于心肺耐力对队列进行分层时，发现心肺耐力低的受试者比中等和高的受试者运动时收缩压和LVM1更高(图2)。此外，运动量约为5 METs时的运动时血压是LVM最强的预测因子，而静息时血压的预测作用要弱得多。锻炼干预研究也发现，1级和2级老年高血压患者的LVM1显著降低[25-30]。

总的来说，上述研究结果提示：(1) 运动量为3~5 METs情况下的人群运动时血压反应了日常生活中的血压；(2) 在相对较低运动量(3~5 METs) 情况下的异常血压反应促进了LVM的增加和进展至LVH；(3) 规律开展中等强度的体育锻炼或增加体力活动能够减弱过度的血压反应；(4) 日常血压较低可逆转LVH。但是，上述假设是基于前瞻性流行病学数据[23,26]，还需要开展干预性锻炼研究来验证上述结果。

运动时收缩压和LVM的相互关系对临床和公共卫生有两方面的影响。首先，运动时血压可能对目前和未来的LVH和高血压的预测因子。其次，心肺耐力更好的人群运动时血压和LVM指数更低提示改善心肺耐力有助于延缓延缓为高血压和LVH。因此，旨在改善心肺耐力的运动项目可被用于延缓动脉僵硬度和血压的进行性增加和LVH发生。

## 心肺耐力对治疗的意义

荟萃分析和几项综述对此已达成共识，即对于1级高血压患者，无论年龄或性别如何，系统性的有氧运动训练项目或增加适量的中等强度体力活动均能够独立地使收缩压大约降低4~10 mm Hg，使舒张压降低3~8 mm Hg[13,31,33]。至于锻炼对2级高血压或难治性高血压患者的影响，我们还知之甚少。我们发现，合并LVH和2级高血压的男性退伍军人在进行6周的中等强度有氧训练之后，血压显著降低。32周时，虽然训练组的降压药物应用减少了32%，但是该组血压降低更为明显，而对照组的血压显著升高[34]。我们还观察到锻炼可以显著降低左室壁厚度和LVH，与大多数高血压药物治疗时相似[34]。这是一个前所未有的发现，具有重要的临床意义，因为LVH被看作死亡的独立危险因素[35]。

在难治性高血压患者中观察到了相似的研究结果。难治性高血压的定义为同时应用3种不同类型的降压药物时（其中含有一种利尿剂），血压仍不能达标[36]。一项研究显示，中度锻炼能够显著降低24小时动态监测血压[37]。血压降低与既往在轻至中等度高血压患者中开展的研究相似[33,34,35]。几乎所有有关锻炼和血压的数据都是来自有氧锻炼。

有关阻力训练或力量训练对静息血压影响的数据还很有限或互相矛盾。提示阻力降低静息时血压[38,39]不如有氧锻炼有效[41,33,31]。其原因尚不明确。此外，阻力训练研究尚未一致证实其能够改善血管阻力。内皮依赖性血管舒张和动脉顺应性。根据上述机制介导了有氧运动的降压效应[30]。因此，阻力训练被推荐作为有氧运动训练项目的补充，以降低
高血压[31,33]，同时阻力训练可以作为一种整套训练项目的一部分来实施[40,41]。

高血压和高血脂前期人群的运动能力和死亡风险

来自对照良好的大型流行病学研究的数据支持高血压前期和高血压人群的运动能力和死亡风险之间存在独立的、逐级的负相关关系[42,43]。例如，在一个有多种心血管危险因素、成功完成了逐级训练的退伍军人高血压患者队列（n=4631），观察到运动能力每增加1 METs，死亡风险降低13%[44]。心肺耐力较差的患者（运动能力为5.1-7.0 METs）相比心肺耐力较差的患者（<5 METs）死亡风险降低了34%，而心肺耐力最高的患者（>10 METs）死亡风险降低超过70%。当考虑不同心肺耐力水平时是否合并其他危险因素时，心肺耐力最低的患者（<5 METs）合并相比合并其他危险因素时死亡风险增加了47%。上述死亡风险的增加在心肺耐力较低的患者（5.1-7.0 METs）中消失，同时在运动能力>7.0的患者中，无论心血管危险因素情况如何，其死亡风险降低>50%。

在正常体重的退伍军人中，同样观察到了运动能力、体重指数和死亡风险的相关性。在相同的体重指数水平下，随着运动能力增加，死亡率逐步降低。运动能力为5.1-7.5 METs的患者死亡风险大约降低40%，METs>7.5 METs的患者死亡风险降低70%[44]。

为了进一步观察心肺耐力-肥胖和死亡风险的关系，我们比较了正常体重-心肺耐力低的人群和超重或肥胖但心肺耐力中等的人群。超重-心肺耐力中等和超重-心肺耐力高的人群相比正常体重-心肺耐力低的人群死亡风险分别降低47%和60%。同样地，肥胖-心肺耐力中等和肥胖-心肺耐力高的人群相比正常体重-心肺耐力低的人群死亡风险降低55%和78%。上述研究结果提示，超重或肥胖但同时心肺耐力高相比体重正常但心肺耐力低更加有益处。此外，看起来肥胖的高血压人群相比超重或正常体重的高血压人群能够从心肺耐力高当中至少同等程度（如果不是更大程度）的获益[44]。

最后，在4478例高血压前期人群和正常值血压人群中（130-139, 85-89 mmHg）中，观察到了心肺耐力与死亡之间相关性的相同趋势。并且相关性独立于危险因素[45,46]。心肺耐力较低（峰值METs 6.1-8.0）的人群相比心肺耐力最低的人群（峰值METs≤6.0）风险降低最为明显（40%），提示较低水平的心肺耐力对于锻炼相关的健康获益是必需的。心肺耐力为中度和高的人群死亡风险降低更大，分别降低58%和73%。年轻人群与老年人群具有同样的趋势，但是前者死亡风险降低更多。运动能力每增加1个METs，<60岁人群的校正死亡风险低18%，>60岁人群的校正死亡风险低12%。

综上所述，强有力的证据支持规律性锻炼或逐步增加体力活动能够提高心肺耐力，减少年龄相关的血压进行性增加，预防高血压的发生。在高血压人群，规律的体力活动能够降低血压和死亡风险，该作用独立于其他危险因素。最后，有一些证据提示，心肺耐力提高有利于降低24小时血压，同时减弱运动或体力活动时的血压反应，从而降低LVH的发生风险。提高心肺耐力与血压和死亡风险降低之间的剂量-反应关系，为这种因果关系提供了证据。不过，该机制尚不明确。或许，心肺耐力、锻炼和体力活动对各个生物系统和危险因素产生的积极作用可能是通过共同机制产生的。

利益声明

无。
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**Key Words:** exercise ■ hypertension ■ mortality ■ prevention