

Review Article

Aerobic Versus Resistance Exercise Training and Coronary Angiogenesis in Elite Football (Soccer) Players: A Systematic Review

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Abstract

Coronary angiogenesis, the formation of new micro vessels from pre-existing vasculature, is a crucial adaptive response enhancing myocardial perfusion and potentially reducing cardiovascular risk in athletes. Elite football (soccer) players experience unique hemodynamic loads combining aerobic endurance and anaerobic bursts. This systematic review critically evaluates current evidence comparing the distinct and synergistic effects of aerobic endurance training (AET) and resistance exercise training (RET) on molecular pathways and potential for stimulating coronary angiogenesis in this specific athletic cohort. Analysis of recent literature (primarily 2019-2024) reveals that AET predominantly enhances coronary angiogenesis through chronic elevation of laminar shear stress, significantly up regulating endothelial nitric oxide synthases (eNOS), vascular endothelial growth factor (VEGF), and hypoxia-inducible factor-1 α (HIF-1 α) expression. RET, characterized by intermittent high-pressure pulsatile flow, robustly activates mechanosensitive pathways (e.g., PI3K/Akt/mTOR) and increases circulating VEGF and angiopoietin-2, though its direct coronary effects are less documented. Football-specific training inherently blends both modalities, suggesting potential synergy. However, human in vivo evidence for direct coronary angiogenesis remains challenging to obtain; current conclusions rely heavily on peripheral vascular surrogates, animal models, molecular biomarkers, and advanced imaging (CMR perfusion). Future research utilizing novel molecular imaging and sport-specific exercise interventions is paramount to elucidate optimal training prescriptions for maximizing coronary vascular health in elite footballers.

Keywords

Coronary Angiogenesis, Aerobic Exercise, Resistance Training, Football Players, Soccer, Endothelial Function, VEGF, Shear Stress, Exercise Physiology, Cardiac Adaptation

1. Introduction

Elite soccer imposes extraordinary cardiovascular demands, integrating prolonged sub maximal aerobic activity with frequent high-intensity anaerobic bursts, sprints, jumps, and rapid changes of direction [1]. This complex loading pattern

subjects the coronary circulation to both sustained volume/pressure overload (aerobic component) and acute, high-magnitude pressure pulses (resistance/anaerobic component). Coronary angiogenesis – the formation of new ca-

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pillaries and arterioles within the myocardium – is a fundamental adaptive response enhancing oxygen delivery, substrate exchange, and overall cardiac efficiency and resilience [2]. While the cardio protective benefits of exercise are well-established, the specific contributions and molecular mechanisms by which distinct exercise modalities prevalent in football training – Aerobic Endurance Training (AET) and Resistance Exercise Training (RET) – stimulate coronary angiogenesis remain incompletely characterized and directly compared [3]. Understanding these modality-specific effects is critical for optimizing training regimens aimed at maximizing cardiac health and performance longevity in elite footballers. This review synthesizes recent experimental and clinical evidence to compare the mechanistic impact of AET versus RET on pathways driving coronary angiogenesis, specifically within the context of elite football players' physiology.

2. Methodology

This systematic review followed a structured approach to identify, evaluate, and synthesize relevant literature:

- 1) *Data Sources*: Comprehensive searches were conducted in Pub Med/MEDLINE, Scopus, Web of Science Core Collection, and SPORT Discus (January 2019 – May 2024).
- 2) *Search Strategy*: Key terms included: ("coronary angiogenesis" OR "myocardial angiogenesis" OR "cardiac capillarization") AND ("aerobic exercise" OR "endurance training" OR "resistance training" OR "strength training") AND ("soccer" OR "football") AND ("athletes" OR "players") AND ("mechanism" OR "pathway" OR "VEGF" OR "shear stress" OR "eNOS" OR "HIF-1 α "). Filters included English language and human/animal studies.
- 3) *Inclusion Criteria*: Original research (RCTs, cohort, cross-sectional, mechanistic animal/cell), systematic reviews, and meta-analyses focusing on AET/RET effects on coronary/cardiac angiogenesis or key molecular regulators in athletes (preference for football/soccer players) or relevant models. Emphasis on molecular pathways and recent publications.
- 4) *Exclusion Criteria*: Studies solely on peripheral angiogenesis, non-exercise interventions (e.g., pharmacological), reviews without novel synthesis, abstracts only, studies predating 2019 unless seminal.
- 5) *Quality Assessment*: Included studies were evaluated for methodological rigor using appropriate tools (e.g., Cochrane Risk of Bias for RCTs, SYRCLE for animal studies).
- 6) *Synthesis*: Findings were thematically synthesized, focusing on exercise modality (AET vs RET), molecular mechanisms, evidence level, and relevance to elite footballers. Direct comparisons were highlighted where possible.

2.1. Aerobic Endurance Training (AET): Mechanisms Driving Coronary Angiogenesis

AET, characterized by sustained rhythmic activity (e.g., running, cycling), imposes chronic increases in cardiac output and coronary blood flow. This generates predominantly laminar shear stress (LSS) on the coronary endothelium, a potent mechanical stimulus for angiogenesis [4]. Key mechanisms include:

- 1) *Shear Stress & eNOS/NO Pathway*: Sustained LSS during AET consistently up regulates endothelial nitric oxide synthase (eNOS) expression and activity, leading to increased nitric oxide (NO) bioavailability [5]. NO is a master regulator promoting endothelial cell proliferation, migration, and survival – essential steps in angiogenesis [6]. Recent human studies using flow-mediated dilation (FMD) as a surrogate consistently show superior endothelial function in elite endurance athletes compared to strength athletes or sedentary controls [7].
- 2) *Hypoxia-Inducible Factor-1 α (HIF-1 α) Stabilization*: While systemic hypoxia is minimal during moderate AET, localized myocardial hypoxia during high-intensity intervals or near-maximal efforts can occur. This stabilizes HIF-1 α , a transcription factor directly inducing VEGF expression [8]. Furthermore, NO itself can stabilize HIF-1 α under normoxic conditions [9].
- 3) *Vascular Endothelial Growth Factor (VEGF) Up regulation*: VEGF is the most potent and specific direct stimulator of angiogenesis. AET robustly increases myocardial expression and circulating levels of VEGF [10]. This occurs via multiple pathways: HIF-1 α activation, increased shear stress, and potentially inflammatory cytokines (e.g., IL-6) released from exercising muscle [11].
- 4) *Other Growth Factors*: AET also modulates other pro-angiogenic factors like Fibroblast Growth Factor-2 (FGF-2) and Platelet-Derived Growth Factor (PDGF), and inhibits anti-angiogenic factors like endostatin and thrombospondin-1 [12].

Evidence in Footballers: Football involves significant aerobic components during training and matches. Studies comparing footballers to sedentary controls show enhanced endothelial function [13]. However, direct comparison of coronary capillary density or specific molecular responses exclusively to AET within footballers is limited, as their training is multimodal.

2.2. Resistance Exercise Training (RET): Mechanisms and Potential for Coronary Angiogenesis

RET involves brief, high-intensity efforts against resistance,

generating large, transient increases in blood pressure (pulsatile/oscillatory shear stress - OSS) and systemic hormonal responses. Its direct impact on *coronary* angiogenesis is less established than AET, but significant mechanisms exist:

- 1) **Mechano transduction Pathways:** High intramuscular tension and systemic pressure surges activate integrins and stretch-sensitive channels on endothelial and muscle cells. This strongly stimulates the PI3K/Akt/mTOR signaling pathway [14]. Akt phosphorylation activates eNOS (similar to LSS) and HIF-1 α , leading to VEGF production [15]. The magnitude of mechanical load appears crucial [16].
- 2) **VEGF Release:** RET significantly increases circulating VEGF levels acutely post-exercise and chronically with training [17]. This is likely driven by mechanical stress within the working muscle (local hypoxia, stretch) and systemic factors like lactate and catecholamines [18].
- 3) **Hormonal Factors:** Acute RET elevates growth hormone (GH), insulin-like growth factor-1 (IGF-1), and catecholamines. GH and IGF-1 have pro-angiogenic properties, while catecholamines can have complex, dose-dependent effects (potentially pro-angiogenic via β -adrenergic receptor signaling at moderate levels) [19].
- 4) **Angiopoietins:** RET may preferentially influence the Angiopoietin-Tie2 system. Some studies suggest RET increases Angiopoietin-2 (Ang-2), which, in concert with VEGF, promotes vessel destabilization and sprouting, a key step in angiogenesis [20].
- 5) **Shear Stress Profile:** The high-pressure, pulsatile flow during RET creates OSS, which generally has a less potent *direct* stimulatory effect on eNOS/NO compared to LSS and can even be pro-inflammatory at extremes [21]. However, the metabolic and mechanical stimuli appear dominant in RET-induced angiogenesis.

Evidence in Footballers: Football involves significant resistance-like elements (jumping, tackling, sprinting). RET is increasingly integrated into football training for performance. While RET improves peripheral vascular function [22], direct evidence for RET-induced *coronary* angiogenesis in foot-

ballers is scarce. Biomarker studies show acute increases in VEGF post-resistance sessions [23].

2.3. Comparative Analysis: AET vs RET in the Context of Football

- 1) **Primary Stimulus:** AET relies predominantly on chronic LSS and metabolic factors (local hypoxia/HIF). RET relies more heavily on high-magnitude mechanical tension/stretch and acute hormonal surges.
- 2) **Molecular Signature:** Both up regulate VEGF and activate eNOS/Akt pathways, but the initiating signals differ (Shear vs Stretch). RET may have a stronger influence on Ang-2 and IGF-1, while AET has a more consistent effect on systemic endothelial function via sustained LSS/eNOS [7, 22].
- 3) **Coronary Specificity:** Evidence for AET enhancing coronary capillarization in humans is strong, based on animal models, post-mortem studies in athletes, and CMR perfusion [24]. Direct evidence for RET specifically enhancing *coronary* angiogenesis is considerably weaker, relying more on peripheral surrogates and molecular plausibility. RET's high-pressure surges may pose different challenges/adaptations in coronary vessels compared to peripheral muscle beds.
- 4) **Synergy in Football Training:** The intermittent nature of football inherently combines AET and RETS elements. Aerobic base training provides the chronic LSS/eNOS/VEGF stimulus. High-intensity actions (sprints, jumps, challenges) provide the mechanical tension, pressure surges, and acute VEGF/IGF-1 spikes characteristic of RET. This combination may be uniquely potent, potentially explaining the robust cardiovascular adaptations observed in elite players [1, 13]. A recent RCT comparing different preseason training emphases in footballers suggested combined training optimized cardiac functional markers more than either modality alone [25].

Table 1. Key Molecular Pathways in AET vs RET-Induced Angiogenesis Relevant to Football.

Mechanism	Aerobic Exercise Training (AET)	Resistance Exercise Training (RET)	Relevance to Football
Primary Stimulus	Laminar Shear Stress (LSS), Metabolic Demand	Mechanical Tension, High Pressure	Match play provides both sustained effort (LSS) and frequent high-intensity bursts (Tension/Pressure).
eNOS/NO Activation	(Chronic, sustained via LSS)	(Acute, via Akt/PI3K, Ca ²⁺)	Crucial for endothelial health in both modalities. Sustained activity in football favors AET pathway.
HIF-1 α Stabilization	(Local hypoxia during intensity)	(Mechanical stress, metabolic)	High-intensity phases in matches/training activate HIF in both contexts.
VEGF Upregulation	(Shear, HIF, cytokines)	(Mechanical stress, HIF, hormones)	Major driver in both; likely synergistic in football.
PI3K/Akt/mTOR	(Downstream of	(Primary activation via	Key growth/survival pathway; RET provides strong

Mechanism	Aerobic Exercise Training (AET)	Resistance Exercise Training (RET)	Relevance to Football
Pathway	eNOS/VEGFR)	mechano sensors)	direct stimulus.
IGF-1/GH Influence	(Moderate increase)	(Significant acute increase)	RET stimulus prominent during strength/power actions.
Angiopoietin (Ang-2)	+/-	(Suggested by some studies)	Potential role in vessel sprouting, may be more RET-linked.
Shear Stress Profile	Predominantly LSS	Predominantly Oscillatory (OSS)	Football coronary endothelium exposed to complex, mixed profile.

3. Discussion

Challenges in Measurement & Current Evidence in Footballers

Directly quantifying coronary angiogenesis in vivo in living humans, especially athletes, remains a significant challenge:

- 1) *Invasive Techniques:* Endo myocardial biopsy is ethically unjustifiable in healthy athletes.
- 2) *Imaging:* While cardiac MRI (CMR) with quantitative perfusion mapping (e.g., myocardial perfusion reserve index - MPRI) provides an indirect functional correlate of micro vascular density/function [24], it does not directly count capillaries. PET offers high sensitivity but involves radiation.
- 3) *Biomarkers:* Circulating VEGF, Angiopoietins, soluble Tie2, endo statin, etc., provide systemic insights but may not directly reflect coronary-specific events [26]. Micro RNAs (miRNAs) regulating angiogenesis are emerging as potential biomarkers [27].
- 4) *Post-Mortem Data:* Limited availability and representativeness.
Consequently, most evidence for exercise-induced coronary angiogenesis in footballers is indirect:
- 5) Superior endothelial function (brachial FMD) compared to sedentary individuals [13].
- 6) Enhanced cardiac efficiency and diastolic function, potentially facilitated by better perfusion [1].
- 7) Biomarker studies showing training-induced changes in VEGF, etc. [23].

Extrapolation from robust animal models and studies in other endurance athletes.

4. Conclusions

Current evidence strongly supports AET as the primary driver of coronary angiogenesis, mediated through sustained laminar shear stress, eNOS/NO up regulation, HIF-1 α stabilization, and robust VEGF induction. RET contributes via distinct mechano transduction pathways (PI3K/Akt/mTOR), significant acute VEGF release, and hormonal influences

(IGF-1, Ang-2). While direct human coronary evidence for RET is less robust than for AET, its molecular signature suggests a significant pro-Angiogenic potential.

For elite football players, whose sports inherently combines the hemodynamic stimuli of both AET and RET, the training regimen likely provides a potent synergistic stimulus for coronary angiogenesis. The aerobic base generates the chronic LSS/eNOS/VEGF environment, while the frequent high-intensity actions characteristic of football delivers the mechanical and hormonal stimuli associated with RET.

5. Future Research Should Prioritize

Advanced Non-Invasive Imaging: Refining CMR and PET techniques to provide more direct quantification of myocardial capillary density/function in longitudinal athlete studies.

- 1) *Molecular Imaging:* Developing probes for key angiogenic targets (e.g., VEGF receptors, $\alpha v\beta 3$ integrin) for PET or SPECT imaging.
- 2) *Sport-Specific Interventions:* Conducting well-controlled RCTs comparing isolated AET, isolated RET, and combined training (mimicking football demands) on validated surrogates of coronary angiogenesis (e.g., MPRI, specific miRNA panels) in elite footballers.
- 3) *Omics Approaches:* Utilizing proteomics and transcriptomics (e.g., on circulating endothelial cells or exosomes) to identify football-specific angiogenic signatures.
- 4) *Long-Term Outcomes:* Investigating links between training modality emphasis, markers of coronary angiogenesis, and long-term cardiovascular health/performance in retired footballers.

Optimizing the balance between AET and RET within the football training paradigm holds promise not only for maximizing athletic performance through enhanced cardiac efficiency but also for fostering long-term coronary vascular health in this unique athletic population.

Abbreviations

ECA Exercise and Coronary Angiogenesis

Conflicts of Interest

The author declares no conflict of interest.

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