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The Temporal Emergence of Cardiovascular Pathology in American-Style Football Players

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The Temporal Emergence of Cardiovascular Pathology in American-Style Football Players

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ABSTRACT

The Temporal Emergence of Cardiovascular Pathology in American-Style Football Players

By: Jonathan H. Kim, M.D.

Background

Collegiate American-style football (ASF) participants are at increased risk for pathologic cardiovascular phenotypes. However, ASF participation rates are highest among high school athletes compared to other levels of ASF competition and data characterizing this population are lacking. This study sought to compare the cardiovascular response to high school versus collegiate ASF participation.

Methods

ASF participants (High School, N = 61; Collegiate, N = 87) were studied longitudinally at pre- and post-season time points with 2-D echocardiography and vascular applanation tonometry. Primary outcome variables included: left ventricular mass index, left ventricular diastolic function (early relaxation velocity [E′]), and arterial stiffness (pulse wave velocity).

Results

High school (17.1 ± 0.4 years old) and collegiate ASF participants (18 ± 0.4 years old) experienced similar left hypertrophy (Δleft ventricular mass high school = 10.5 ± 10 vs. collegiate = 11.2 ± 13.6 g/m^2, P = 0.97). Among high school participants, left ventricular mass increased due to eccentric remodeling, which was associated with stable diastolic (ΔE′ = -0.3 ± 2.9 cm/s, P = 0.40) and vascular function (Δpulse wave velocity = -0.1 ± 0.6 m/s, P = 0.13). In contrast, collegiate ASF participants demonstrated concentric left

ventricular remodeling with concomitant reductions in diastolic function (Δ E′: -2.0 ± 2.7 cm/s, P <0.001) and increased arterial stiffness (Δ pulse wave velocity: Δ0.2 ± 0.6 m/s, P = 0.002), changes that were driven by linemen position players who had the highest post-season weight (124 ± 10 kg) and systolic blood pressure (138.8 ± 11.2 mmHg). In multivariable linear mixed models adjusted for weight and systolic blood pressure and accounting for subject-specific random effects, increased weight predicted decreased E′ (mean difference in E′ from pre- to post-season estimated at -0.02 cm/s, P = 0.02) and increased pulse wave velocity (mean difference in PWV from pre- to post-season estimated at 0.01 m/s, P <0.0001), while increased systolic blood pressure predicted increased left ventricular mass index (mean difference in indexed left ventricular mass from pre- to post-season estimated at 0.15 kg/m^2, P = 0.008) and increased pulse wave velocity (mean difference in PWV from pre- to post-season estimated at 0.01 m/s, P <0.001).

Conclusions

The transition from high school to college represents a clinically important temporal data point after which pathologic cardiovascular phenotypes are more evident among collegiate ASF participants. Future work aimed to clarify modifiable underlying mechanisms and long-term clinical implications is warranted.

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INTRODUCTION

While the benefits of exercise on reducing cardiovascular morbidity and mortality are well established (1), recent data suggest that there may be increased cardiovascular risk in certain populations of athletes (2,3). American-style football (ASF) is the most popular organized team sport in the United States (US) with approximately 1 million high school (HS) (4), 70,000 collegiate (5), and 2,000 professional participants annually (6,7). Although youthful competitive athletes are classically regarded as the paradigm of health and vitality, uncertainties surrounding the long-term health implications of ASF participation have recently become a topic of considerable controversy (8,9). Specifically, concerns about the impact of ASF participation on cardiovascular and neurocognitive health (10) have generated debate in the scientific literature, mainstream media, and within governing bodies that oversee ASF rules and regulations.

The physiology inherent in ASF participation is complex and differs from most other forms of sport. Factors including high loads of static hemodynamic stress, relatively low amounts of aerobic conditioning, deliberate body mass gain, psychological stress, and routine non-steroidal anti-inflammatory medication (11) use carry potential negative implications for cardiovascular health. In healthy non-athletic populations, early onset cardiovascular risk and attendant sub-clinical pathology at ages typical of ASF athletes predict later life cardiovascular morbidity and mortality (12-14). While this phenomenon has not been firmly established among ASF participants, a growing body of observational data documents associations between large body mass (15,16), early life hypertension (2,15), and sub-clinical pathologic cardiovascular phenotypes (3,17-19) among ASF athletes. In addition, epidemiologic outcomes data among former professional ASF

athletes suggest accelerated cardiovascular mortality among former lineman (LM) position players (20,21). While the precise relationship between early life ASF participation and subsequent cardiovascular health remains incompletely understood, multiple lines of evidence suggest that ASF participation may impart increased risk for the development of cardiovascular disease.

Healthy, sport-specific cardiovascular adaptations occur in response to the hemodynamic stressors inherent in strenuous exercise training (22). ASF participants are exposed to considerable amounts of isometric hemodynamic stress. As such, the development of concentric left ventricular (LV) hypertrophy among ASF participants has been demonstrated by several longitudinal observational studies (2,18,23). However. the observation that the development of concentric LV hypertrophy is associated with intra-season changes in systolic blood pressure (SBP) and absolute post-season SBP (2) suggests an element of sub-clinical hypertensive cardiac remodeling contributes to the development of these phenotypes rather than simple benign exercise-mediated adaptive remodeling. The development of concentric LV hypertrophy among ASF LM has since been reproduced in several distinct longitudinal collegiate cohorts and has also been associated with relative myocardial functional impairment (18) and sub-clinical vascular dysfunction (3). Arterial stiffening, an important mechanistic precursor to the development of overt hypertension (24), has been observed among collegiate ASF athletes (3).

An important current knowledge gap is the temporal progression of maladaptive cardiovascular phenotypes observed among ASF athletes. Importantly, ASF participation rates in the United States are highest at the HS school level with an estimated 1 million

athletes each year (25). Whether early cardiovascular risk and maladaptive cardiovascular phenotypes occur in the HS ASF population is unknown.

To address this knowledge gap, we sought to examine longitudinally acquired cardiovascular phenotypes among HS and collegiate ASF participants after one season of competitive ASF participation. In addition, despite differences in baseline body size between HS and collegiate ASF athletes, we sought to compare the change in specific measures of cardiovascular structure and function after seasonal ASF participation between these groups. The hypothesis tested was that cardiovascular remodeling patterns would differ as a function of participation level with collegiate ASF athletes developing a within-person, higher burden of adverse cardiac and vascular remodeling compared to HS ASF athletes. To address this hypothesis, HS and collegiate ASF participants were studied with 2-D echocardiography and vascular applanation tonometry before and after seasonal ASF participation.

BACKGROUND

ASF athletes appear to be uniquely at risk for the development of cardiovascular pathology during sport participation (2,3,15,17,18). Specifically, prior studies document a high prevalence of hypertension among both collegiate (2,3,17,18) and professional (15) ASF athletes and associations between increased blood pressure and sub-clinical pathologic cardiovascular remodeling have been documented (2,3,18). Data characterizing ASF-associated hypertension commenced with a study from Tucker and colleagues investigating the prevalence of cardiovascular risk factors in a cohort of 504 active professional ASF athletes (15). In this cross-sectional analysis (first year "rookie" players were excluded), hypertension (13.8%, 95% CI: 11 to 16.7%) and pre-hypertension (64.5%, 95% CI: 58.3 to 70.7%) were significantly more common in the ASF cohort compared to age-matched controls (5.5%, 95% CI: 4.6 to 6.6%, and 24.2%, 95% CI: 22.3 to 26.1%, respectively) despite a 30% prevalence of active tobacco use in the controls.

A strong association between ASF participation and incident hypertension has also been established in collegiate ASF athletes. In a longitudinal, repeated measures study of 113 freshman ASF athletes followed across seasonal training, there were significant increases in both SBP (116±8 vs.125±13 mmHg, $P<0.001$) and diastolic blood pressure (DBP, 64±8 vs. 66±10 mmHg, $P<0.001$) from the pre- to post-season with 61% of the cohort meeting criteria for either pre-hypertension or at least Stage I hypertension (2,26). Importantly, intra-season changes in SBP significantly correlated with increases in LV mass ($R=0.46$, $P<0.001$) among the LM. This finding suggests a mechanistic role of resting hypertension in the genesis of cardiac hypertrophy among ASF athletes.

Moreover, a growing body of observational data documents associations between large body mass (15,16), early life hypertension (2,15), and sub-clinical pathologic cardiovascular phenotypes (3,17-19) among ASF athletes.

In the general pediatric population, epidemiologic data obtained from separate cohorts of obese children and adolescents of various ethnicities and from separate geographic regions have demonstrated increased cardiovascular disease mortality later in adulthood (27-30). Similar to the observed data reported from adults, strong associations between increased body-mass index (BMI) and SBP have been demonstrated in large population-based pediatric studies such as NHANES III (31). Hypertension during young adulthood, the time-period that coincides with competitive ASF participation, is a well-established independent risk factor for later life cardiovascular disease morbidity and mortality (12,13,32). Finally, among non-athletic populations, concentric LV hypertrophy present at youthful ages is associated with increased risk of later life coronary heart disease and stroke (14).

While the accumulation of provocative cardiovascular outcomes and phenotypic data from competitive ASF athletes continues to grow, the populations studied have included only older, more elite-level collegiate and professional ASF athletes. ASF participation rates in the United States are highest at the HS school level with an estimated 1 million athletes each year (25). To date, data characterizing the cardiovascular impact of ASF participation at the HS level are lacking.

METHODS

Overview

We performed a prospective, observational cohort study of ASF athletes at the HS and collegiate level between 2014-16. This study was designed to test the hypothesis that cardiovascular remodeling patterns would differ as a function of participation level with collegiate ASF participants developing a higher burden of within-person adverse cardiac and vascular remodeling after seasonal ASF training. ASF participants from two National Collegiate Athletic Association (NCAA) Division-I programs [Georgia Institute of Technology (Atlanta, GA) and Furman University (Greenville, SC)] and three metropolitan high schools [Marist School, Woodward Academy, and St. Pius X (Atlanta, GA)] were recruited for this study. Study participants were followed across one competitive ASF season with repeated measures analyses obtained in the pre-season and the immediate beginning of the post-season. The Emory Institutional Review Board approved all aspects of the study and subjects provided written informed consent (subject assent with parental consent for participants <18 years old).

Study Population

Senior HS and freshman collegiate ASF participants were studied longitudinally at two predefined time points. Time point one was immediately prior to pre-season training and time point two was 5-6 months later at a program-specific date corresponding with the immediate conclusion of the ASF season (beginning of the post-season). We chose to confine the HS cohort to seniors (4^{th} year students) to minimize the impact of pubertal development and to maximize capture of the cardiovascular phenotype associated with complete HS football exposure. In contrast, we confined the collegiate

cohort to freshmen students, a time period previously shown to be marked by significant cardiovascular plasticity in response to the hemodynamic stress of athletic training (17). Participants were required to abstain from exercise for ≥24 hours prior to both data collection time points.

Field position for each ASF participant was classified as either LM or non-lineman (NLM) as previously proposed (33). Specifically, LM included players at the tackle, guard, center, or defensive end positions while NLM included quarterbacks, running backs, wide receivers, tight ends, linebackers, cornerbacks, safeties, kickers, and punters. In-season practice schedules, including strength training, differed between HS and collegiate ASF participants and were characterized as follows. HS practice sessions occurred, on average, 2 hours/weekday (10 hours/week) and collegiate practice sessions occurred, on average, 3 hours/weekday (maximum 20 hours/week of practice, weight training, film study, meetings, etc. per NCAA guidelines). Collegiate ASF participants were subject to testing for performance-enhancing drugs as dictated by NCAA standards.

Definition of the cohort

Eligible ASF athletes included any male student (HS senior or collegiate freshman) rostered on the official ASF teams included in the study at the time of initial recruitment. ASF athletes excluded were those who were unable to complete the season due to injury or other circumstances, diagnosed in the pre-season with a significant pre-existing cardiac condition (example, hypertrophic cardiomyopathy; arrhythmogenic right ventricular cardiomyopathy; Marfan's syndrome) which would disqualify the athlete from athletic participation, diagnosed with known mild cardiac abnormalities, but allowed to participate in sports (example, bicuspid aortic valve with no significant

stenosis / regurgitation or aortopathy; simple uncorrected congenital heart disease such as an atrial septal defect or ventricular septal defect with no significant shunt or right or left ventricular volume overload), diagnosed with significant co-morbid medical conditions requiring prescription medications (example, asthma classified as more than mild, intermittent; cancers; diabetes; systemic disease processes (such as lupus; rheumatoid arthritis; inflammatory bowel disease), and finally collegiate athletes who tested positive for anabolic steroids (NCAA mandated drug testing).

Exposures of interest and measured covariates

The exposure of interest was pre- to post-season competitive ASF participation at the HS and collegiate level. Prior work has demonstrated that intense athletic / sport training exposure yields sport-specific changes in cardiac structure and function (17). Moreover, we have previously expanded on these findings, specifically among ASF athletes, and demonstrated changes in the vasculature and the development of arterial stiffening occur as a consequence of ASF participation (3,19). In this study, we used a comprehensive array of non-invasive testing including cardiac imaging and vascular function analysis and recorded select clinical characteristics in phenotyping this cohort. Selected measured covariates included anthropometric and clinical data, specifically age (years), height (cm), weight (kg), current medication use, family history of hypertension, SBP, and diastolic blood pressure [(mmHg), measured using a manual aneroid sphygmomanometer and an appropriately sized cuff]. In addition, measurements from 2-D echocardiography and vascular applanation tonometry were obtained.

Vascular applanation tonometry (vascular function)

Indices of arterial stiffness and wave reflection were measured using high fidelity

applanation tonometry (SphygmoCor®, Atcor Medical, Australia), which records sequential high-quality pressure waveforms at peripheral pulse sites. Full details of tonometer technology and measurement algorithms have been previously detailed (34). Vascular function was characterized using validated surrogates of arterial stiffness and cardiovascular disease risk (24,35-37). The primary outcome variable for vascular function was pulse wave velocity (PWV), the gold standard index of arterial stiffness (34). PWV was measured by acquisition of pressure waveforms within the carotid and femoral arteries. The distance between measurement sites was recorded manually using the "foot-to-foot" method (38). Additional validated measures of vascular stiffness originating from the pulse wave analysis included the augmentation index (39) and subendocardial viability ratio (40). Pulse wave analysis derivation >80% of the operator index and PWV with <10% standard deviation were required for quality control.

2-D Echocardiography (cardiac structure and function)

Trans-thoracic echocardiography was performed using a commercially available system (Vivid-I, GE Healthcare, Milwaukee, WI). 2-D, tissue-Doppler, and speckle-tracking imaging from standard parasternal and apical positions was performed by experienced hired sonographers. All data were stored digitally, and post-study offline data analysis (EchoPAC version 7, GE Healthcare) was performed. Definitions of normality for cardiac structure and function were adopted from the most recent American Society of Echocardiography guidelines (41). The primary outcome variable for LV structure was LV mass (calculated using the area-length method) indexed for body surface area. Diastolic function was estimated with the early tissue relaxation velocity (E′). LV ejection fraction, end-diastolic volume, and end-systolic volume were calculated

using the modified biplane technique. Relative wall thickness was calculated as: [interventricular septum thickness + posterior wall thickness (mm)] / LV end-diastolic diameter (mm)]. Measurements were adjusted for body surface area when appropriate (42). Comprehensive assessment of regional myocardial function using speckle-tracking and tissue-Doppler imaging was performed. Tissue velocities (E′, A′, and S′) were measured from color-coded images at the lateral and septal mitral annulus. E′ was reported as the average value between the 2 measurements. Global LV longitudinal strain was measured in the apical four-chamber view.

Outcomes

Three primary *a priori* outcome measures were chosen for this analysis, specifically to represent gold standard measures for LV structure, cardiac diastolic function, and arterial stiffness. The primary outcome variable for LV structure was LV mass indexed for body surface area. In addition, this measurement was coupled with relative wall thickness to estimate the type and degree of LV hypertrophy. As per American Society of Echocardiography guidelines, concentric LV hypertrophy was defined as: RWT >0.42 and LV mass index >102 g/m^2; concentric LV remodeling was defined as: RWT >0.42 and LV mass index ≤102 g/m^2; and eccentric LV hypertrophy was defined as: RWT ≤0.42 and LV mass index >102 g/m^2 (43). The primary outcome variable for diastolic function, as per American Society of Echocardiography guidelines, was the tissue-Doppler early relaxation velocity, E´ (44). Given the presence of structurally normal hearts and the presence of clinically preserved diastolic function in this cohort, we chose to report the average of the tissue-Doppler E´ velocities measured at the basal septum and lateral walls of the mitral valve annulus. Prior work has shown that

increased arterial stiffness precedes increases in blood pressure and serves as an important mechanistic precursor to overt hypertension (45). As such, the primary outcome measure for vascular function was PWV (34).

Statistical analyses

All statistical analyses were performed utilizing SAS software, Version 9.4 (SAS Institute, Cary, NC). Continuous variables are reported as means and standard deviation (SD). Categorical variables are reported as percentages. Repeated longitudinal measurements across the ASF season were assessed with the paired *t*-test for normally distributed variables. Comparison of post-season measurements between groups (HS vs. collegiate) was assessed with a 2-sample *t*-test for normally distributed variables. Comparisons between categorical variables were performed with the Chi-square test of homogeneity. P-values were calculated as two-sided and considered statistically significant when $P < 0.05$.

Correlation and mixed model analyses

The primary analysis was the construction of linear mixed models to identify factors associated with the predefined primary end-points: E′, PWV, and LV mass index in the total cohort. Mixed models included subject-specific random intercepts (one intercept for each subject) to account for within subject correlation due to 2 repeated measures in the dataset. In addition, the models were adjusted for weight and SBP. Pearson correlation coefficients were also determined for correlations between post-season weight and post-season SBP (cross-sectional) with PWV, E′, and LV mass index in the total, combined ASF cohort.

Comparison of the collegiate and HS cohorts stratified by player position

The collegiate and HS cohorts were also stratified by player position (LM versus NLM) and select continuous variable *post-season* outcomes (weight, SBP, indexed LV end-diastolic diameter, LV mass index, relative wall thickness, E′, and PWV) were compared using one-way ANOVA with Bonferroni correction for multiple comparisons using the collegiate LM group as the reference group (adjusted P-values are presented). The specific variables chosen were relevant to key clinical measures previously reported among ASF athletes (weight, SBP), key cardiac structural geometric measurements (indexed LV end-diastolic diameter, LV mass index, relative wall thickness), the primary cardiac functional outcome measure (E′), and the primary vascular function outcome measure (PWV). In addition, paired longitudinal analyses of the subset of HS and collegiate LM were performed.

Missing data

Data were obtained prospectively specifically for this analysis and quality control of our measurements was assessed at the time of data acquisition. For cardiac imaging and vascular function testing, measurements were repeated, if necessary, to obtain adequate images for processing and quality control for calculated PWV. As such, there were no missing data.

RESULTS

Baseline characteristics

Of the158 ASF participants initially enrolled in this study, 148 (HS seniors, N = 61; collegiate freshman, N = 87) completed the full season study period and were analyzed at both study time points. At baseline (**Table 1**), collegiate ASF participants were older, taller, heavier, and had higher diastolic blood pressures than HS participants. Caucasians accounted for the majority of HS participants while ethnicity was evenly distributed between Caucasians and African-Americans in the collegiate cohort. The distribution of NLM versus LM was similar between groups. For the three primary outcomes variables, baseline values for HS and collegiate participants at the pre-season time point were similar as follows (**Table 2**): LV mass: HS = 89 ± 11 vs. collegiate = 90 ± 16 g/m^2, P = 0.82; E′: HS = 15.2 ± 2 vs. collegiate = 16.2 ± 2.5 cm/s, P = 0.01; and PWV: HS = 4.6 ± 0.6 vs. collegiate = 4.7 ± 0.7 m/s, P = 0.31.

Longitudinal impact of HS versus collegiate ASF participation

At the post-season study time point, only collegiate ASF participants demonstrated significant increases in body mass and SBP (**Table 2**). Both HS and collegiate participants demonstrated significant increases in LV mass index during the study period but with significant differences in LV geometric remodeling patterns between groups. Specifically, HS ASF participants demonstrated balanced increases in LV diameter and LV wall thickness consistent with eccentric LV remodeling, while collegiate participants experienced increases in LV wall thickness with stable cavity size indicative of concentric LV remodeling. This translated to significantly higher rates of concentric LV hypertrophy among collegiate (21/87, 24%) versus HS participants (7/61,

11%, P=0.026). LV systolic function, as assessed by ejection fraction and global longitudinal strain, was unchanged among HS participants and showed a non-significant trend towards decline among collegiate participants. LV diastolic function, as assessed by E′, our primary diastolic function outcome variable, declined during the season among collegiate participants but was unchanged in the HS ASF cohort (**Table 2, Figure 1**). Finally, significant differences in vascular function were also observed between groups. While HS ASF participants demonstrated longitudinal enhancements in vascular compliance, collegiate participants demonstrated increases in PWV at the post-season time point. (**Table 2, Figure 1**).

Comparison of LM versus NLM

Post-season data comparing collegiate and HS ASF participants stratified by player position (NLM vs. LM) are shown in **Figure 2**. Differences in weight, SBP, cardiac structural geometry, diastolic function, and vascular function were most pronounced for the collegiate LM (N = 27) when compared to collegiate NLM (N = 60) and HS athletes at both field positions (HS NLM: N = 38; HS LM: N = 23). Specifically, collegiate LM demonstrated the highest weight (124 ± 10 kg) and SBP (138.8 ± 11.2 mmHg) among the groups. Differences in training-related LV remodeling, specifically increased concentric-type LV remodeling, were also more pronounced for the collegiate LM compared to the other groups as evidenced by significantly lower indexed LV end-diastolic diameter (collegiate LM = 20.8 ± 2 vs. collegiate NLM = 24.1 ± 2 vs. HS LM = 23.2 ± 1.8 vs. HS NLM = 25.5 ± 1.9 mm/m^2, P <0.001) without concomitant differences in LV mass index. Finally, collegiate LM demonstrated relative impairments in diastolic function (collegiate LM E′ = 13.2 ± 2.1 vs. collegiate NLM E′ = 14.7 ± 2.3 vs. HS LM E′

= 14.8 ± 2.5 vs. HS NLM E′ = 14.9 ± 2.7 cm/s, P = 0.03) and vascular compliance (collegiate LM PWV = 5.3 ± 0.7 vs. collegiate NLM PWV = 4.9 ± 0.6 vs. HS LM PWV = 4.7 ± 0.7 vs. HS NLM PWV = 4.4 ± 0.5 m/s, P <0.001) compared to the other groups.

Longitudinal comparison of the HS versus collegiate LM is reported in **Table 3**. While both groups developed concentric LV remodeling, only the collegiate LM gained significant weight and demonstrated reduced diastolic and vascular function.

Correlation and mixed model analyses

Correlation analyses in the combined ASF cohort were performed between post-season weight and SBP with our primary outcome variables of post-season PWV, LV mass index, and E′ (**Figure 3)**. For weight, there was a significant inverse correlation observed with E′ (R = -0.26, P = 0.001) and positive correlation with PWV (R = 0.52, P <0.001). For SBP, significant positive correlations were observed with PWV (R= 0.28, P <0.001) and LV mass index (R = 0.21, P = 0.009). No such correlations were observed between weight and LV mass index (R = 0.06, P = 0.48) or SBP and E′ (R = -0.06, P = 0.47). Linear mixed models were constructed to determine predictors of E′, PWV, and LV mass index (**Table 4**). After accounting for within subject correlation and subject-specific random effects, increased weight was a predictor of both reduced diastolic function (mean difference in E′ from pre- to post-season estimated at -0.02 cm/s, P = 0.02) and increased arterial stiffness (mean difference in PWV from pre- to post-season estimated at 0.01 m/s, P <0.001). Increased SBP was an independent predictor of both increased arterial stiffness (mean difference in PWV from pre- to post-season estimated at 0.01 m/s, P <0.001) and increased LV mass index (mean difference in indexed left ventricular mass from pre- to post-season estimated at 0.15 kg/m^2, P = 0.008). Finally,

independent associations between declining diastolic function and increasing arterial stiffness suggest an important element of ventricular-arterial uncoupling.

DISCUSSION

This study, designed to compare the cardiovascular response to ASF participation between HS and collegiate athletes, generated the following key findings. First, longitudinal cardiovascular remodeling patterns differed significantly between HS versus collegiate ASF participants. Specifically, collegiate ASF participants were more likely to develop concentric LV hypertrophy, to experience reductions in LV diastolic function, and to develop relative arterial stiffening than HS ASF participants. Importantly, these maladaptive findings were primarily driven by athletes who gained significant weight and therefore support the findings of prior studies, which suggest that collegiate LM, the largest ASF athletes, are uniquely at risk for the development of sub-clinical cardiac and vascular dysfunction (2,3,18). Second, this dataset establishes an important temporal data point, the initiation of the collegiate ASF experience, after which pathologic ASF cardiovascular phenotypes begin to emerge. Finally, our analyses suggest that intra-season weight gain and increased SBP represent synergistic biological mechanisms underlying the development of maladaptive cardiovascular remodeling. In aggregate, our findings suggest that HS ASF participants appear to be at comparatively lower risk than their collegiate ASF counterparts for the development of early life cardiovascular pathology (**Figure 4**).

Although the number of competitive ASF participants is highest at the HS level (25), cardiovascular health profiles among HS ASF participants have not been rigorously detailed. The rationale for the current study arises from a growing body of literature that documents evidence of hypertension, LV hypertrophy, and premature mortality among ASF participants, particularly LM, who participate in collegiate and professional ASF

(2,3,15,17,18,20,21). Results from this study provide a measure of clinical reassurance for HS ASF participants and for the practitioners charged with the clinical care of this pediatric and young adult athletic population. Our data suggest that ASF athletes at the HS level gain minimal weight, experience no significant increases in SBP, and develop eccentric LV hypertrophy, a clinically benign and physiologically adaptive remodeling phenotype common among other sport types, with stable diastolic function and vascular stiffness. In contrast, after the transition to the collegiate ASF ranks, pathologic sub-clinical cardiovascular phenotypes manifest more commonly, particularly for those who gain significant weight. As such, it seems prudent for ASF professional team and university physicians to consider the development of cardiovascular monitoring algorithms for high-risk ASF participants with an emphasis on LM position players and athletes who develop hypertension or gain significant weight during ASF participation.

Findings from this study may best be considered in the context of relevant long-term clinical outcomes data derived from non-athletic but otherwise similar populations (12,14,24,35,37,46-49). For example, hypertension and pre-hypertension present among ostensibly healthy young individuals, as measured at the time of college matriculation during the Harvard Alumni Health Study, predicted incident risk of later life cardiovascular disease (12). In the MESA cohort, concentric LV hypertrophy, the predominant structural cardiac remodeling pattern in collegiate LM, at young ages has been shown to increase the risk of later life attendant coronary heart disease and stroke (14). Similarly, both increasing PWV, and declining early diastolic relaxation velocity independently predict adverse cardiovascular outcomes when added to standard risk prediction models (37,46). Thus, the emergence of hypertension and substantial increases

in body weight, coupled with concentric LV hypertrophy, increased arterial stiffness, and declining diastolic function among youthful and otherwise healthy athletes is concerning and underscores the critical need for future studies aimed to clarify the long-term clinical outcomes in this potentially high risk population.

While exact causal mechanisms underlying pathologic ASF-associated cardiovascular remodeling remain speculative, data from this study provide some novel advances. We observed 3 major factors differentiating HS from collegiate ASF participants in the current study: 1) intra-season weight gain, 2) intra-season increases in SBP and 3) ASF "dose" exposure. Our analyses suggest that increases in SBP and body weight are independent, yet synergistic determinants of sub-clinical cardiovascular pathology. Specifically, weight gain is associated with diastolic impairment and vascular stiffening while rising SBP is associated with vascular stiffening and LV hypertrophy. It is also intriguing that exercise load, particularly exposure to high intensity static exercise, differed as a function of competition level with collegiate ASF athletes experiencing a significantly higher level of exercise exposure. To what degree the amount of isometric activity (i.e. tackling drills, weight lifting), in combination with the absence of concomitant isotonic activity and other environmental factors (ex. diet, pharmaceuticals, etc.), impact longitudinal cardiovascular phenotypes is uncertain and represents an important area of future work. Future study addressing the impact of intense isometric physiology will require rigorously controlled study designs that include multiple variables (such as oxidative stress biomarkers) (50), invasive physiologic data collection, and detailed analyses of non-ASF strength athletes.

Several limitations of this study are noteworthy. First, we acknowledge that there were significant baseline differences in anthropometric data between groups and that we did not follow the same HS ASF athletes from senior year to freshman year of collegiate ASF. As such, it is possible that selection bias was present among the collegiate cohort. Perhaps the largest HS ASF athletes, if followed longitudinally from HS to college, would demonstrate maladaptive cardiovascular remodeling during both their senior HS and freshman collegiate year of ASF participation. However, the primary aim of this study was to compare generalized training-related cardiovascular differences between HS and collegiate ASF athletes. In addition, we did not observe maladaptive cardiovascular remodeling in the HS LM compared to collegiate LM. Finally, our analyses suggest weight gain, regardless of year of ASF participation, is associated with acquired maladaptive cardiovascular phenotypes and should therefore be flagged in the clinical assessment of any competitive ASF athlete. Second, the possibility of unrecognized confounders is acknowledged and may have limited our ability to precisely identify mechanisms underlying our findings. However, multi-center recruitment coupled with the use of a longitudinal repeated measures study design minimized the potential influence of single center bias and ensured that overall ASF participation, likely through numerous and discrete mechanisms, had a causal role in our findings. Third, we acknowledge there were a large number of statistical tests performed and therefore numerous observations. We therefore chose only 3 *a priori* primary outcomes and also adjusted for multiple comparisons in our ANOVA analyses. Fourth, this study did not assess temporal trends in cardiac remodeling and vascular function beyond first year collegiate ASF participants. As such, long term follow-up to include complete collegiate and professional careers is

warranted to further assess the potential synergistic mechanistic relationship between weight and SBP. Finally, we acknowledge that the HS and collegiate ASF cohorts were not ideally matched for ethnicity and that results of our analyses may have incompletely captured the impact of race, particularly for the HS ASF athletes.

In conclusion, compared to HS ASF participants, collegiate ASF athletes are at increased risk for the development of concentric LV hypertrophy with reduced diastolic function and concomitant arterial stiffening. These findings establish an important temporal data point along the continuum of ASF participation at which maladaptive cardiovascular remodeling appears to emerge. Future study designed to identify potentially modifiable underlying mechanisms and to establish long-term clinical implications of early life sub-clinical cardiac pathology in this athletic population are warranted.

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TABLES / FIGURES

Table 1. Baseline ASF participant characteristics.

	ASF Cohort N = 148		
Pre-Season Characteristics	**High School ASF (N = 61)**	**Collegiate ASF (N = 87)**	**P-Value**
Age (years)	17.1 ± 0.4	18 ± 0.4	<0.001
Ethnicity (%):			
Caucasian	89	53	<0.001
African-American	11	47	
Non-Linemen / Linemen (%)	62 / 38	69 / 31	0.40
Height (cm)	181 ± 6	184 ± 7	0.006
Weight (kg)	87 ± 17	99 ± 19	<0.001
Body Mass Index (kg/m^2)	41 ± 3	44 ± 4	<0.001
Family History Hypertension (%)	28	41	0.09
Family History Early CAD (%)	8	8	0.97
Systolic Blood Pressure (mm Hg)	129.6 ± 11	132 ± 12	0.30
Diastolic Blood Pressure (mm Hg)	70.4 ± 8	75 ± 10	0.005
Pulse Wave Velocity (m/sec)	4.6 ± 0.6	4.7 ± 0.7	0.31

ASF: American-style football; **CAD**: coronary artery disease

Measurements expressed as the mean ± standard deviation

Table 2. Comparison of the longitudinal impact of high school versus collegiate ASF participation

	Longitudinal ASF Data N = 148					
	High School N = 61			Collegiate N = 87		
Anthropometrics and Blood Pressure	**Pre-Season**	**Post-Season**	**P-value**	**Pre-Season**	**Post-Season**	**P-value**
Weight (kg)	86.7 ± 17	86.4 ± 16‡	0.47	97 ± 18	100 ± 18.5‡	<0.001
Body Mass Index (kg/m^2)	41 ± 3	41 ± 3‡	0.49	43.5 ± 3.5	44 ± 4‡	<0.001
Systolic Blood Pressure (mm Hg)	129 ± 12	131 ± 14§	0.29	131 ± 12	136 ± 12§	0.01
Diastolic Blood Pressure (mm Hg)	70 ± 8	74 ± 9	0.003	75 ± 10	76 ± 10	0.44
Cardiac Structure and Function						
Averaged LV Wall Thickness* (mm)	8.5 ± 0.7	8.9 ± 0.7‡	0.002	9.0 ± 0.9	10.0 ± 1.0‡	<0.001
LV Internal Diameter End-Diastole / Body Surface Area (mm/m^2)	24.1 ± 2	24.6 ± 2‡	0.02	22.8 ± 3	23.2 ± 2‡	0.16
LV Mass / Body Surface Area (gm/m^2)	89 ± 11	100 ± 12	<0.001	90 ± 16	102 ± 13	<0.001
Relative Wall Thickness	0.34 ± 0.04	0.35 ± 0.04‡	0.045	0.35 ± 0.04	0.39 ± 0.05‡	<0.001
EF (%)	59.4 ± 4	59 ± 4	0.37	62 ± 5	59 ± 5	<0.001
Global Longitudinal Strain (%)	19.6 ± 2	19.8 ± 2	0.69	20 ± 2	19.7 ± 2	0.41
Trans-Mitral E (cm/s)	94 ± 17	87 ± 13	0.003	89 ± 15	83 ± 15	<0.001
Trans-Mitral A (cm/s)	37 ± 11	37.4 ± 9§	0.66	43 ± 10	41 ± 8§	0.31
Trans-Mitral E/A Ratio	2.7 ± 0.9	2.4 ± 0.7‡	0.03	2.2 ± 0.7	2 ± 0.5‡	0.03
Tissue-Doppler LV Averaged E′† (cm/s)	15.2 ± 2	14.9 ± 2.6	0.40	16.2 ± 2.5	14.2 ± 2.4	<0.001
Vascular Function						
Pulse Wave Velocity (m/s)	4.6 ± 0.6	4.5 ± 0.6‡	0.13	4.7 ± 0.7	5 ± 0.7‡	0.002
Augmentation Index (%)	3.5 ± 17	-2 ± 14§	0.03	1.7 ± 13	3 ± 17§	0.62
SEVR	147 ± 37	160 ± 34§	0.004	157 ± 31	151 ± 28§	0.11

ASF: American-style football; **EF**: ejection fraction; **LV**: left ventricle; **SEVR**: subendocardial viability ratio

Measurements expressed as the mean ± standard deviation

*Averaged LV Wall Thickness = Interventricular Septum + Posterior Wall Thickness / 2

†Averaged E′ (cm/s) = lateral E′ velocity + septal E′ velocity / 2

‡P<0.001 post-season high school vs. collegiate ASF

§P<0.05 post-season high school vs. collegiate ASF

Table 3. Longitudinal comparison of high school versus collegiate linemen

	Longitudinal ASF Linemen					
	High School N=23			Collegiate N=27		
	Pre-Season	**Post-Season**	**P-value**	**Pre-Season**	**Post-Season**	**P-value**
Body Mass Index(kg/m^2)	43.9 ± 3.6	43.7 ± 3.5‡	0.21	48.1 ± 2	48.5 ± 2‡	0.001
Systolic Blood Pressure (mm Hg)	133.2 ± 11	133.3 ± 16	0.79	134.8 ± 8	138.8 ± 11	0.06
Diastolic Blood Pressure (mm Hg)	72 ± 8.7	75.6 ± 10	0.16	78.2 ± 10	78.2 ± 11	0.80
Averaged LV Wall Thickness* (mm)	8.8 ± 0.6	9.4 ± 0.6‡	<0.001	9.4 ± 0.9	10.5 ± 1‡	<0.001
LV Internal Diameter End-Diastole / Body Surface Area (mm/m^2)	23.5 ± 2	23.2 ± 2‡	0.34	20 ± 4	20.8 ± 2‡	0.30
LV Mass / Body Surface Area (gm/m^2)	88.7 ± 11	99.5 ± 12	<0.001	93 ± 13	103 ± 14	<0.001
Tissue-Doppler LV Averaged E′† (cm/s)	14.5 ± 1.8	14.8 ± 2.5§	0.47	15.8 ± 2.5	13.2 ± 2.1§	<0.001
Pulse Wave Velocity (m/s)	4.8 ± 0.7	4.7 ± 0.7§	0.49	5 ± 0.6	5.3 ± 0.7§	0.003

ASF: American-style football; **LV**: left ventricle

Measurements expressed as the mean ± standard deviation

*Averaged LV Wall Thickness = Interventricular Septum + Posterior Wall Thickness / 2

†Averaged E′ (cm/s) = lateral E′ velocity + septal E′ velocity / 2

‡P<0.001 post-season high school vs. collegiate ASF

§P<0.05 post-season high school vs. collegiate ASF

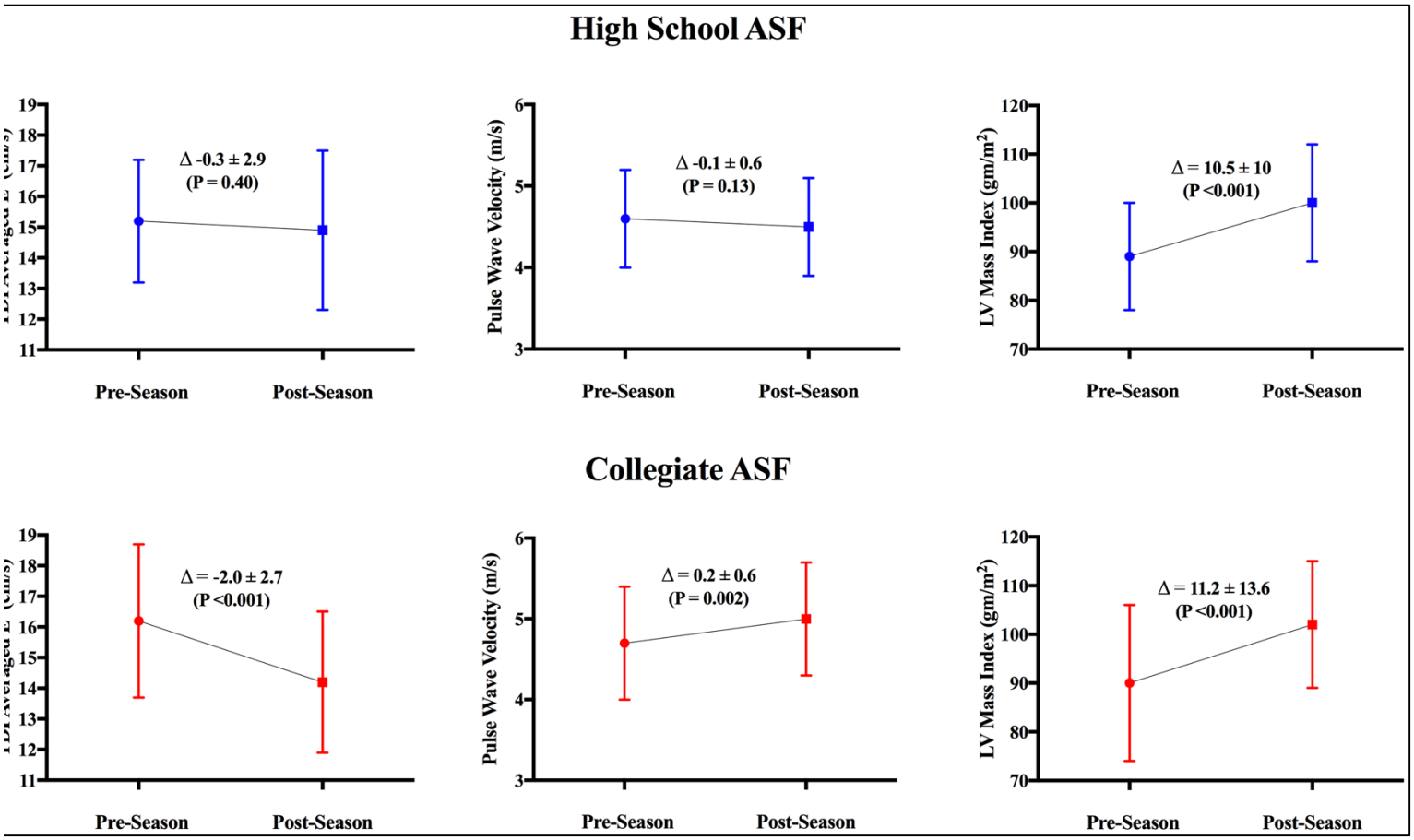
Table 4. Predictors of primary outcome cardiac and vascular indices

	Multivariable Analysis	
Tissue-Doppler E′ Velocity*	**Estimate**	**P-Value**
Time	-1.35	<0.001
Weight (kg)	-0.02	0.02
Systolic Blood Pressure (mm Hg)	0.01	0.23
Ethnicity (0=white, 1=black)	-0.58	0.14
Pulse Wave Velocity (m/s)	-0.50	0.04
LV Mass Index (gm/m^2)	0.00	0.95
Post-Season Pulse Wave Velocity	**Estimate**	**P-Value**
Time	0.01	0.92
Weight (kg)	0.01	<0.001
Systolic Blood Pressure (mm Hg)	0.01	<0.001
Ethnicity (0=white, 1=black)	-0.10	0.23
TDI Averaged E′* (cm/s)	-0.03	0.04
LV Mass Index (gm/m^2)	0.00	0.64
Post-Season LV Mass Index	**Estimate**	**P-Value**
Time	10.17	<0.001
Weight (kg)	0.00	0.99
Systolic Blood Pressure (mm Hg)	0.15	0.008
Ethnicity (0=white, 1=black)	0.30	0.85
TDI Averaged E′* (cm/s)	0.16	0.59
Pulse Wave Velocity (m/s)	-0.17	0.88

*Averaged E′ (cm/s) = lateral E′ velocity + septal E′ velocity / 2

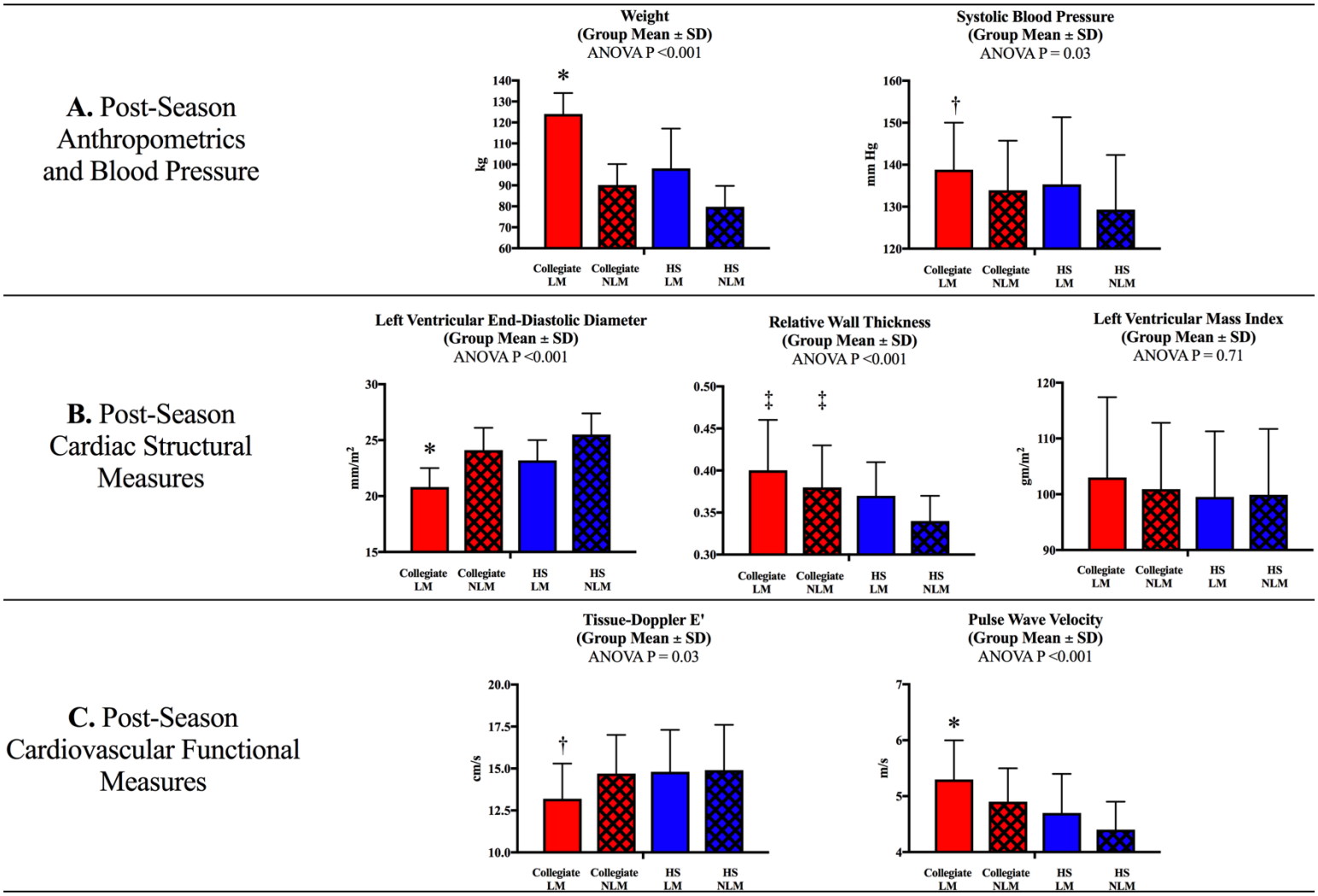
ASF: American-style football; **LV**: left ventricle, **TDI**: tissue-Doppler velocity

Figure 1. Pre- to post-season change in the group mean ± SD diastolic LV tissue-Doppler E′, PWV, and LV mass index in high school (top row, N = 61) and collegiate (bottom row, N = 87) ASF participants.



ASF: American-style football; **LV**: left ventricle; **PWV**: pulse wave velocity; **TDI**: tissue-Doppler imaging

Figure 2. One-way ANOVA comparison of post-season weight and SBP (**row A**), cardiac structural measures (**row B**), and cardiovascular functional measures (**row C**) by player position (LM and NLM).



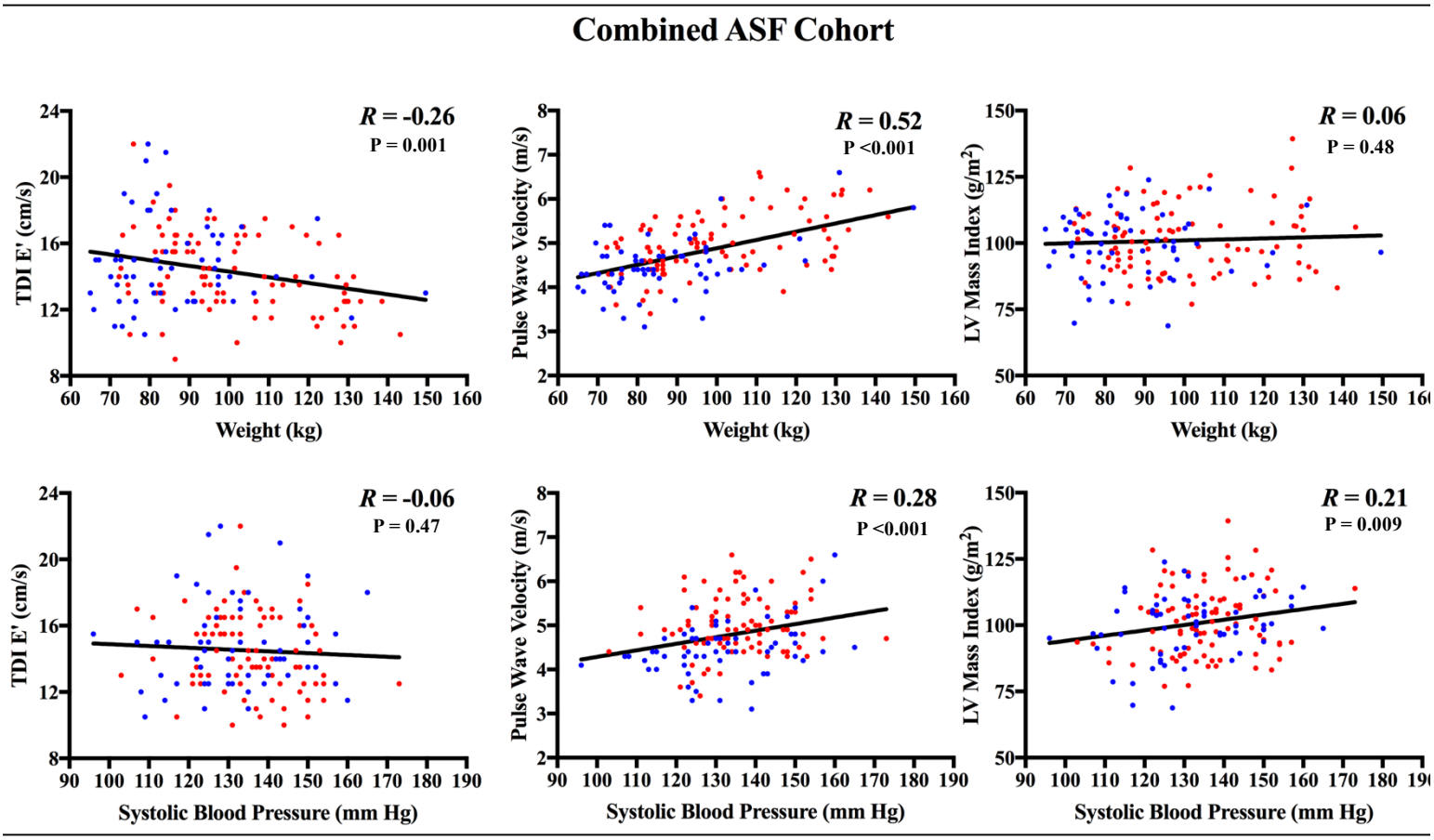
HS: high school; **LM**: linemen; **NLM**: non-linemen; **SBP**: systolic blood pressure

* Adjusted P <0.001 (multiple comparisons) collegiate LM versus all other groups

† Adjusted P <0.05 (multiple comparisons) collegiate LM versus HS NLM

‡ Adjusted P <0.05 (multiple comparisons) collegiate LM and collegiate NLM versus HS NLM

Figure 3. Correlation analyses between post-season weight and post-season diastolic function, PWV, and LV mass index (**top row**); and post-season SBP and post-season diastolic function, PWV, and LV mass index (**bottom row**) in the combined high school and collegiate ASF cohort.

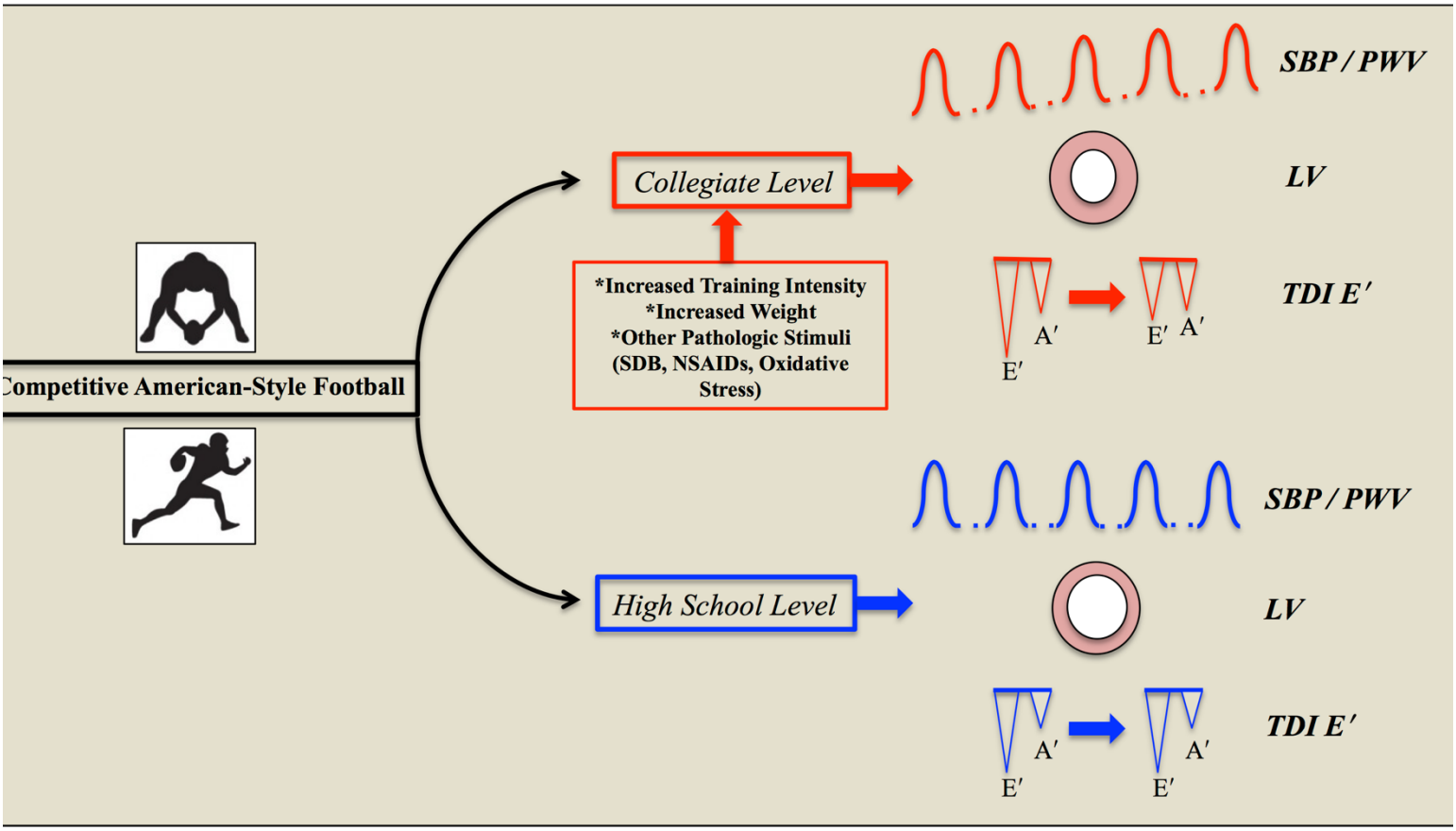


ASF: American-style football; **LV**: left ventricular; **PWV**: pulse wave velocity; **SBP**: systolic blood pressure; **TDI**: tissue-Doppler imaging

Blue: High School ASF

Red: Collegiate ASF

Figure 4. High school versus collegiate ASF participation and differences in cardiac and vascular phenotypes with proposed potential underlying mechanisms.



ASF: American-style football; **LV**: left ventricle; **NSAIDs**: non-steroidal anti-inflammatories; **PWV**: pulse wave velocity; **SBP**: systolic blood pressure; **SDB**: sleep disordered breathing; **TDI**: tissue-Doppler imaging