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ORIGINAL RESEARCH

Hypertension and Ventricular–Arterial Uncoupling in Collegiate American Football Athletes

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BACKGROUND: Ventricular–arterial (VA) coupling is defined as the ratio between arterial elastance (EA) and left ventricular elastance (ELV). VA uncoupling, as occurs in hypertensive heart disease, is associated with adverse outcomes. This study sought to determine the relationship between American football (AF)–associated hypertension and VA uncoupling.

METHODS AND RESULTS: This was a multicenter, longitudinal, and repeated measures observational study of collegiate AF athletes across 3 years of AF participation. Of 200 freshman athletes initially enrolled, 142 (67 Black [47%]/75 White [53%], 58 linemen [41%]/84 nonlinemen [59%]) were prospectively studied with echocardiography and applanation tonometry. Primary echocardiographic VA coupling outcome measures were EA/ELV and ΔEA/ELV, with increased EA/ELV indicating VA uncoupling. Adjusting for race and player position, AF athletes demonstrated increased EA/ELV (mean [95% CI]Δ, 0.10 [0.04–0.15]; P=0.001) and systolic blood pressure (SBP) (mean [95% CI]Δ, 11.4 [8.3–14.5] mm Hg, P<0.001) over their collegiate AF careers. In combination with longitudinal VA uncoupling, hypertension prevalence (including both stage 1 and 2) increased from 54% at baseline to 77% (44% stage 2) at the end of the study period (P<0.001). In multivariable mixed-effects linear regression analysis, higher SBP (β=0.021, P=0.02), lower E′ (β=−0.010, P=0.03), and worse global longitudinal strain (β=0.036, P<0.001) were associated with higher EA/ELV. Increased SBP (ΔSBP, β=0.029, P=0.02) and worsened global longitudinal strain (Δglobal longitudinal strain, β=0.045, P<0.001) also predicted increased ΔEA/ELV.

CONCLUSIONS: VA uncoupling is associated with pathologically increased SBP and subclinical impairments in left ventricular systolic function in collegiate AF athletes, indicating a key mechanism underlying maladaptive cardiovascular phenotypes observed in this population. Future studies analyzing whether targeted clinical interventions improve VA coupling and health outcomes are warranted.

Key Words: American football ■ echocardiography ■ exercise ■ global longitudinal strain ■ hypertension

The physiologic interaction between the left ventricular (LV) and arterial system, defined as ventricular–arterial (VA) coupling, facilitates optimal cardiac workload and cardiovascular performance.[1,2] When uncoupled, the efficient interaction between cardiac contractility and vascular compliance is lost, which occurs in numerous cardiovascular disease states.[3,4] Importantly, the presence of VA uncoupling predicts adverse clinical cardiovascular outcomes, including increased all-cause and cardiovascular mortality, particularly in older patient populations with hypertensive heart disease and other cardiovascular conditions.[5–8] Although VA coupling measurements are typically considered via invasive pressure-volume loops,[9] noninvasive echocardiographic VA coupling estimates have been validated[10,11] and can predict long-term health outcomes.[5–7]

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CLINICAL PERSPECTIVE

What Is New?

- In this longitudinal multicenter study, collegiate American football athletes over the course of their competitive collegiate careers are likely to develop hypertension and subclinical ventricular–arterial uncoupling
- Among American football athletes, ventricular–arterial uncoupling is associated with increased systolic blood pressure and impaired left ventricular systolic function, as assessed by global longitudinal strain.

What Are the Clinical Implications?

- American football players are at risk for early development of hypertension.
- Ventricular–arterial uncoupling seen among collegiate American football athletes may represent an important mechanism underlying adverse cardiovascular health and outcomes prevalent among retired professional American football players.
- Future studies implementing behavioral and pharmacologic strategies are warranted to investigate whether early intervention may deter ventricular–arterial uncoupling and improve long-term health outcomes in this population.

Nonstandard Abbreviations and Acronyms

AF	American football
DBP	diastolic blood pressure
EA	effective arterial elastance
ELV	left ventricular end-systolic elastance
GLS	global longitudinal strain
PWV	pulse wave velocity
SBP	systolic blood pressure
VA	ventricular–arterial

Among adolescents and young adults with cardiovascular risk, previous analyses of VA coupling are limited. In addition, the assessment of changes in VA coupling as a consequence of intense athletic training have not previously been conducted. American football (AF) athletes represent a unique athletic population in which acquired cardiovascular risk is prevalent despite engagement in intense exercise training.[12] In particular, the development of hypertension has been observed in AF athletes at both the collegiate and professional levels.[13–15] Hypertension present among high-risk AF athletes has been associated with early arterial stiffening,[16,17] subclinical decrements in diastolic[17–19] and systolic LV function,[20] and pathologic concentric LV hypertrophy.[17] Whether early perturbations in VA coupling also occur in AF athletes has not previously been affirmed.

We therefore sought to assess whether noninvasive surrogates of VA uncoupling progress during the collegiate AF career and to analyze the relationship between VA coupling and other key determinants of cardiac and vascular function. We hypothesized that AF athletes would demonstrate longitudinal VA uncoupling, and that VA uncoupling would be associated with increased systolic blood pressure (SBP) and impaired LV systolic function as estimated by global longitudinal strain (GLS). To address this hypothesis, we conducted a longitudinal and multicenter analysis of collegiate AF athletes across their college career with repeated blood pressure measurement, transthoracic echocardiography, and vascular applanation tonometry.

METHODS

AF athletes ≥18 years of age were recruited from National Collegiate Athletic Association Division I program at Georgia Institute of Technology (Atlanta, GA) and Furman University (Greenville, SC) and studied between 2016 and 2019. Clinical characteristics, anthropometric measurements, 2-dimensional and speckle tracking echocardiography, and vascular applanation tonometry were prospectively and longitudinally captured for all study participants over this time period. The Emory Institutional Review Board approved all aspects of this study, and subjects provided written informed consent. Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author.

Study Population

AF athletes were recruited each year of this study, in parallel with the academic school calendar, beginning with the respective freshman season. Athletes were then prospectively studied at prespecified longitudinal time points until the end of the study period. For the freshman season, this included the preseason (baseline) and the immediate conclusion of the season (postseason year 1), approximately 5 to 6 months later. For the sophomore season, this was postseason year 2, approximately 1 year after postseason year 1, and for the junior season, this was postseason year 3, approximately 1 year after postseason year 2. Two time points for freshman AF athletes were chosen because of the significant cardiovascular plasticity previously

demonstrated among first-year college athletes in response to athletic training.[18] Because AF athletes at the participating institutions engage in consistent levels of AF training throughout the calendar year after the freshman season, only annual postseason study time points were captured beyond the first year (postseason years 2 and 3). Athletes with known hypertension on pharmacotherapy were excluded. Only athletes with complete clinical data and echocardiographic images sufficient to determine VA coupling at ≥2 time points were included in the final analysis.

Subjects were required to abstain from exercise for at least 24 hours before data collection. Clinical data including age (years), height (centimeters), family history of hypertension, current medication use, and self-reported race were collected at baseline. Player position was classified as either lineman or nonlineman as previously proposed.[21] Linemen engage in pure isometric training and are at increased risk of developing hypertension and adverse cardiac remodeling compared with nonlinemen.[12,17,20] All athletes were subject to performance-enhancing drug testing protocols as per National Collegiate Athletic Association guidelines. Weight (kilograms), SBP (millimeters of mercury), and diastolic blood pressure (DBP) (millimeters of mercury) were collected at all time points. Blood pressure was measured after ≥15 minutes of rest using a manual aneroid sphygmomanometer and an appropriately sized cuff and recorded as the average of 3 measurements. At each time point for each subject, blood pressure was categorized as normal (SBP <120 mm Hg and DBP <80 mm Hg), elevated (SBP 120–129 mm Hg and DBP <80 mm Hg), stage 1 hypertension (SBP 130–139 mm Hg or DBP 80–89 mm Hg), or stage 2 hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg) in accordance with contemporary guidelines endorsed by the American College of Cardiology and American Heart Association.[22]

2-Dimensional Transthoracic Echocardiography

Transthoracic echocardiography was performed using a commercially available system (Vivid-I; GE Healthcare, Milwaukee, WI) at all study time points. Two-dimensional and tissue-Doppler imaging from standard parasternal and apical positions were performed by experienced sonographers, who were consistent throughout the years of this study. Frame rates were individualized per study for optimal image quality between 60 and 100 Hz. All information was stored digitally, and poststudy offline data analysis (EchoPAC version 7; GE Healthcare) was performed by study investigators (J.V.T., J.H.K.). Definitions of normality for cardiac structure and function were adopted from the most recent guidelines.[23] LV mass was calculated using the area-length method (accounts for left ventricle morphology in both the short and long axis) and indexed to body surface area, and LV ejection fraction was calculated using the modified biplane technique. Comprehensive assessment of cardiac diastolic function using tissue-Doppler imaging was performed, and tissue velocities (E′, A′, and S′) were measured from color-coded images at the lateral and septal mitral annulus. E′ was then reported as the average value between the 2 measurements. GLS was measured in the apical 4-chamber view using commercially available speckle-tracking software (EchoPAC version 7; GE Healthcare).[24] Briefly, the endocardium was manually traced from the highest quality apical 4-chamber view, and tracing width was adjusted to include the full thickness of the myocardium. The software automatically separated the myocardium into 6 segments (n=2 apical, n=2 septal, and n=2 lateral segments) with suitable speckles selected for tracking. The reliability of tracking was confirmed by the software, with the observer adjusting the endocardial tracing until tracking was deemed acceptable. GLS measurements were obtained after 3 consecutive cardiac cycles and reported as an averaged value. GLS was presented in the conventional manner as a negative percent, with more negative GLS values representing greater longitudinal shortening. In those participants in which values could not be obtained in the full 6 segments as described, GLS measurements were excluded in the final analysis.

GLS Measurement Variability

GLS values in 62 of 448 (14%) studies across all study time points were deemed insufficient in quality; thus, the respective GLS measurement was not included in the final analysis. For quality consistency, interobserver variability for GLS was assessed in a group of 40 randomly selected echocardiographic studies (10 studies at each time point) by a separate study investigator (B.R.W.) who was blinded to all previous measurements. Correlation analysis yielded a Pearson correlation coefficient of r=0.88, and a paired t test used to assess discrepancies among observations revealed no significant variability among observers (mean difference, 0.05%; P=0.73).

Assessment of Ventricular–Arterial Coupling

VA coupling is a marker of cardiovascular efficiency and overall cardiovascular performance (Figure S1). It is generally assessed in the pressure-volume plane and defined as the ratio of effective arterial elastance (EA), a comprehensive measure of afterload, and LV end-systolic elastance (ELV), which is generally

a load-independent marker of ventricular performance.[25,26] VA coupling can be quantified noninvasively as EA/ELV,[1,2] and expressing VA coupling as a ratio of elastances allows for direct comparison of the arterial and LV systems in identical units (millimeters of mercury per milliliter).[1,2] EA is defined as the ratio of LV end-systolic pressure and stroke volume.[2] Noninvasively, end-systolic pressure is estimated as 0.9×brachial SBP, and stroke volume is calculated from the LV outflow tract area and velocity time integral.[11,27] This noninvasive estimation of EA closely approximates invasive pressure-volume measures of arterial load.[2,11] ELV estimates LV stiffness and contractility and was originally proposed as the slope of the end-systolic pressure-volume relationship obtained from invasive pressure-volume loops.[28] Noninvasively, ELV can be estimated using the single-beat method proposed by Chen and colleagues.[10] This guideline-endorsed method (Data S1: Supplemental Methods), which has been validated against invasive assessments and used in clinical studies,[5,29,30] incorporates brachial SBP and DBP and echocardiography-derived stroke volume, ejection fraction, and ejection timing intervals.[10,30]

Vascular Applanation Tonometry

Arterial stiffness was measured at all time points using high-fidelity applanation tonometry (SphygmoCor; Atcor Medical, Sydney, Australia), which records sequential high-quality pressure waveforms at peripheral pulse sites. The primary measure of arterial function was the carotid–femoral pulse wave velocity (PWV), the gold-standard index of arterial stiffness,[31] measured as previously described.[16,17]

Statistical Analysis

Continuous variables are presented as the mean±SD and categorical variables as percentages. Separate linear mixed-effects models were constructed to evaluate for longitudinal changes in clinical and cardiovascular measurements, with time being the categorical (baseline, year 1, 2, and 3) independent variable adjusting for race (White or Black) and player position (nonlineman or lineman), and the least squares means were reported for each metric at each time point. The prevalence of normal blood pressure, elevated blood pressure, stage 1 hypertension, and stage 2 hypertension[22] at each time point were calculated and are reported. Mixed-effects ordinal logistic regression analysis was used to evaluate categorical hypertension development[22] over the study period, with time as the continuous independent variable to assess the overall trend of change in hypertension status. Compared with baseline, we calculated the change of metrics at each follow-up time point. Primary outcome VA uncoupling measurements were EA/ELV and ΔEA/ELV (also log-transformed). To assess for factors associated with EA/ELV, a linear mixed-effects model was constructed with independent variables including player position, race, height, weight, SBP, PWV, E′, LV mass index, and GLS. To assess for factors associated with ΔEA/ELV, a second mixed-effects model was constructed including independent variables of player position, race, height and Δ weight, SBP, PWV, E′, LV mass index, and GLS. Similar models were also constructed to evaluate factors associated with log-transformed EA/ELV and ΔEA/ELV. In all mixed-effects models, participant-specific random intercepts were incorporated to account for within-participant correlations. Analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC). A *P* value of ≤0.05 was considered significant.

RESULTS

Baseline Characteristics

Between June 2016 and June 2019, 200 collegiate freshman AF athletes were serially enrolled in this study, with 142 eligible for final analysis and prospective follow-up (Figure S2). Of the 58 excluded athletes, 34 were lost to follow-up because of sport-related attrition (significant AF-related injury or leaving the team for any reason), and 24 did not have the appropriate Doppler images obtained to estimate EA/ELV at ≥2 time points. Because of the rolling nature of study enrollment aligned with the collegiate academic calendar, 142 athletes were analyzed at baseline and postseason year 1, 100 were analyzed at postseason year 2, and 64 were analyzed at postseason year 3. At baseline, the final study cohort (Table 1) was evenly distributed by self-identified race (67 Black athletes [47%]/75 White athletes [53%]) and consisted of 84 nonlinemen (59%) and 58 linemen (41%).

Table 1. Baseline Characteristics

Characteristic	American football athletes, n=142
Age, y	18 ± 0.2
Race	
Black	67 (47%)
White	75 (53%)
Family history of hypertension	46 (32%)
Height, cm	186 ± 6
Weight, kg	100.2 ± 19.6
Body mass index, kg/m^2	28.8 ± 4.7
Systolic blood pressure, mm Hg	126 ± 11
Diastolic blood pressure, mm Hg	76 ± 9

Values are presented as mean±SD or n (%).

Longitudinal Changes in Cardiovascular Phenotypes and VA Coupling

Adjusting for race and player position, athletes demonstrated increased weight (cumulative mean [95% CI] Δ, 5.0 kg [3.9–6.2 kg]; *P*<0.001), SBP (cumulative mean [95% CI] Δ, 11.4 mm Hg [8.3–14.5 mm Hg]; *P*<0.001), and PWV (cumulative mean [95% CI] Δ, 0.45 m/s [0.31–0.60 m/s], *P*<0.001) across the collegiate AF career (Table 2). Athletes also demonstrated LV structural and functional changes with increased LV mass index (cumulative mean [95% CI] Δ, 21.7 g/m^2 [19.5–23.9 g/m^2]; *P*<0.001) and decreased diastolic function as estimated by E′ (cumulative mean [95% CI] Δ, –2.2 cm/s [–2.7 to –1.7 cm/s]; *P*<0.001). There was no change in GLS across the study period (cumulative mean [95% CI] Δ, 0.3% [–0.9% to 0.3%]; *P*=0.22). In parallel with SBP, EA/ELV and the log-transformed EA/ELV increased over the study period (cumulative mean [95% CI] Δ, 0.10 [0.04–0.15]; *P*=0.001 and 0.111 [0.052–0.169]; *P*=0.003, respectively, Figure 1), signifying longitudinal VA uncoupling. Longitudinal change in cardiovascular phenotypes were similar among linemen and nonlinemen, with the exception of SBP, which increased more among linemen than nonlinemen (cumulative respective means [95% CI] Δ, 18.5 mm Hg [13.5–23.5 mm Hg] versus 5.8 mm Hg [3.8–7.8 mm Hg]; *P*=0.001). Additionally, linemen demonstrated increases in EA (cumulative mean [95% CI] Δ, 0.15 mm Hg/mL [0.05–0.25 mm Hg/mL]; *P*=0.03) and EA/ELV (cumulative mean [95% CI] Δ, 0.14 [0.06–0.22]; *P*=0.006) (Table S1).

Hypertension Progression

AF athletes developed clinically significant hypertension, which increased in severity over the study period (Table 3, Figure 1). At baseline, the prevalence of hypertension in the AF athletes was 54% (76/142), stage 1 (32%), or stage 2 (22%). By postseason year 3, the prevalence of hypertension increased to 77% (49/64), with stage 2 hypertension being most common, present in 44% (28/64) of athletes (*P*<0.001 overall trend).

Factors Associated With VA Uncoupling

In univariate analysis, higher SBP (β=0.017, *P*=0.02), lower E′ (β=–0.016, *P*<0.001), and impaired GLS (β=0.037, *P*<0.001) were associated with higher EA/ELV. In addition, decreased E′ (ΔE′, β=–0.020, *P*=0.004) and worsened GLS (ΔGLS, β=0.041, *P*<0.001) were associated with increased ΔEA/ELV (Table 4). In multivariable mixed-effects linear regression analysis, higher SBP (β=0.021, *P*=0.02), lower E′ (β=–0.010, *P*=0.03), and impaired GLS (β=0.036, *P*<0.001) were associated with higher EA/ELV. Increased SBP (ΔSBP, β=0.029, *P*=0.02) and worsened GLS (ΔGLS, β=0.045; *P*<0.001) also predicted increased ΔEA/ELV (Table 4).

Similar associations were identified when the log-transformed EA/ELV was analyzed. In univariate analysis, higher SBP (β=0.018, *P*=0.02), lower E′ (β=–0.018, *P*<0.001), and impaired GLS (β=0.041, *P*<0.001) were associated with log(EA/ELV). In addition, decreased E′ (ΔE′, β=–0.023, *P*=0.002) and worsened GLS (ΔGLS, β=0.046, *P*<0.001) were associated with increased

Table 2. Longitudinal Changes in Select Clinical and Cardiovascular Measurements

Characteristic	Baseline, n=142	Year 1 postseason, n=142	Year 2 postseason, n=100	Year 3 postseason, n=64	*P* value*
Weight, kg	100.6 (98.4–102.7)	102.0 (99.9–104.1)	104.0 (101.8–106.2)	105.6 (103.4–107.8)	<0.001
Body mass index, kg/m^2	28.9 (28.4–29.5)	29.3 (28.8–29.9)	29.9 (29.3–30.5)	30.4 (29.8–30.9)	<0.001
Systolic BP, mm Hg	126.5 (124.5–128.5)	130.8 (128.9–132.8)	132.4 (130.1–134.7)	137.9 (135.1–140.7)	<0.001
Diastolic BP, mm Hg	76.2 (74.7–77.7)	75.8 (74.3–77.3)	76.9 (75.1–78.6)	78.6 (76.4–80.8)	0.19
PWV, m/s	5.1 (5.0–5.2)	5.3 (5.2–5.4)	5.5 (5.4–5.6)	5.5 (5.4–5.7)	<0.001
LV mass/BSA, g/m^2	89.0 (87.3–90.7)	100.3 (98.6–102.0)	105.8 (103.9–107.8)	110.7 (108.5–113.0)	<0.001
E′, cm/s	15.9 (15.5–16.3)	15.1 (14.7–15.5)	14.6 (14.1–15.0)	13.7 (13.2–14.2)	<0.001
Ejection fraction, %	61.1 (60.2–61.9)	60.5 (59.7–61.3)	60.2 (59.2–61.2)	60.2 (59.0–61.4)	0.47
GLS, %	–18.6 (–18.9 to –18.2)	–18.6 (–19.0 to –18.2)	–18.1 (–18.5 to –17.6)	–18.3 (–18.8 to –17.8)	0.22
EA, mm Hg/mL	1.29 (1.25–1.34)	1.30 (1.25–1.34)	1.31 (1.26–1.37)	1.35 (1.29–1.42)	0.32
ELV, mm Hg/mL	1.57 (1.50–1.63)	1.51 (1.44–1.58)	1.49 (1.41–1.57)	1.45 (1.36–1.54)	0.08
EA/ELV	0.854 (0.822–0.885)	0.899 (0.866–0.933)	0.905 (0.866–0.945)	0.949 (0.903–0.995)	0.001
log(EA/ELV)	–0.181 (–0.216 to –0.147)	–0.131 (–0.167 to –0.094)	–0.116 (–0.159 to –0.073)	–0.071 (–0.121 to –0.020)	0.002

Values are mean (95% CI), adjusted for race and player position. BP indicates blood pressure; E′, tissue-Doppler averaged mitral annular early diastolic velocities; EA, effective arterial elastance; ELV, end-systolic left ventricular elastance; GLS, global longitudinal strain; LV mass/BSA, left ventricular mass indexed to body surface area; and PWV, pulse wave velocity.

**P* value reported for fixed effects of time points (baseline, year 1, 2, and 3).

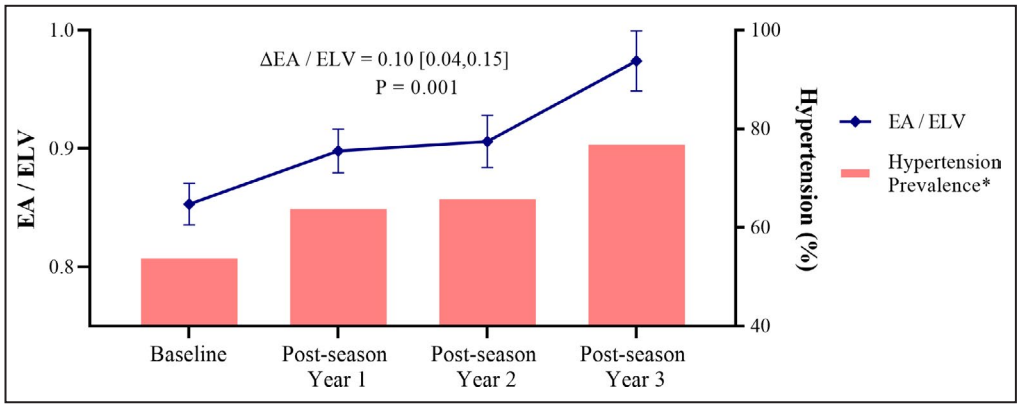

Figure 1. Ventricular–arterial uncoupling (ΔEA/ELV) occurs in parallel with progressively increasing systolic blood pressure in collegiate American football athletes.
ΔEA/ELV is presented as the adjusted mean with 95% CI. CV indicates cardiovascular; EA, effective arterial elastance; ELV, end-systolic left ventricular elastance; GLS, global longitudinal strain; and SBP, systolic blood pressure. *Stage 1 or 2 hypertension as defined by the 2017 American College of Cardiology/American Heart Association hypertension guidelines.

Δlog(EA/ELV) (Table 5). In multivariable mixed-effects linear regression analysis, higher SBP (β=0.020, *P*=0.03), lower E′ (β=−0.012, *P*=0.02), and impaired GLS (β=0.040, *P*<0.001) were associated with log(EA/ELV). Increased SBP (ΔSBP, β=0.027, *P*=0.04) and worsened GLS (ΔGLS, β=0.050, *P*<0.001) also predicted increased log(ΔEA/ELV) (Table 5).

DISCUSSION

Key findings from this study are as follows. First, in this prospective multicenter collegiate AF cohort, coupled with hypertension progression, VA uncoupling occurred throughout the course of collegiate AF participation. Second, and equally important, subclinical reductions in LV systolic function were also associated with longitudinal VA uncoupling. Taken together, these novel data suggest that VA uncoupling represents an important mechanistic link between AF-associated hypertension and acquired maladaptive cardiovascular phenotypes, particularly worsened LV strain[20] (Figure 2). Our findings underscore the need to determine whether subclinical cardiovascular risk present among young, elite AF athletes improves after completion of their AF career or translates to later-life adverse health outcomes. Our results suggest that VA uncoupling may represent a clinically significant pathophysiologic end point in young patients with underlying cardiovascular risk. Finally, these data affirm an alarmingly high prevalence of untreated hypertension in youthful collegiate AF athletes. As such, coupled with a heightened emphasis on education and early treatment efforts in this higher-risk athletic population, proceeding with clinical intervention studies of AF athletes with hypertension, inclusive of both lifestyle modifications and pharmacologic treatments, remains a critical future direction.

To our knowledge, this study is the first to examine alterations in VA coupling in a young and athletic, but high-risk population. In normal human subjects, EA/ELV is physiologically preserved to maintain optimal cardiovascular mechanics.[3] For example, throughout natural aging, the progressive arterial and LV stiffening that develops is balanced; thus, EA/ELV remains unchanged to maintain efficient VA coupling.[3,32,33] In pathologic cardiovascular conditions, such as hypertension, obesity, and heart failure with preserved ejection fraction, EA/ELV may not be abnormal in the early stages of disease because of

Table 3. Longitudinal Clinical Hypertension Progression

Time point	Normal	Elevated	Stage 1 hypertension	Stage 2 hypertension
Baseline	24% (34/142)	23% (32/142)	32% (45/142)	22% (31/142)
Year 1 postseason	20% (28/142)	17% (24/142)	35% (49/142)	29% (41/142)
Year 2 postseason	15% (15/100)	19% (19/100)	36% (36/100)	30% (30/100)
Year 3 postseason	4% (3/64)	19% (12/64)	33% (21/64)	44% (28/64)

Blood pressure stages as defined by the 2017 American College of Cardiology/American Heart Association hypertension guidelines[22]:
Normal: systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg.
Elevated: systolic blood pressure 120 to 129 mm Hg and diastolic blood pressure <80 mm Hg.
Stage 1 hypertension: systolic blood pressure 130 to 139 mm Hg or diastolic blood pressure 80 to 89 mm Hg.
Stage 2 hypertension: systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg.

Table 4. Factors Associated With Ventricular–Arterial Uncoupling

Characteristic	Univariate		Multivariate	
	β (95% CI)	*P* value	β (95% CI)	*P* value
EA/ELV				
Position	0.032 (−0.010 to 0.074)	0.13	0.002 (−0.065 to 0.069)	0.95
Black race	0.027 (−0.014 to 0.068)	0.20	−0.002 (−0.046 to 0.042)	0.92
Height, cm	0.0003 (−0.0033 to 0.0039)	0.88	−0.002 (−0.007 to 0.003)	0.45
Weight, kg	0.0008 (−0.0002 to 0.0018)	0.13	0.0006 (−0.0015 to 0.0026)	0.58
Systolic BP, 10 mm Hg	0.017 (0.003–0.031)	0.02	0.021 (0.004–0.038)	0.02
PWV, m/s	0.010 (−0.015 to 0.035)	0.43	−0.028 (−0.059 to 0.002)	0.07
E′, cm/s	−0.016 (−0.023 to −0.008)	<0.001	−0.010 (−0.019 to −0.001)	0.03
LV mass/BSA, 10 g/m^2	0.014 (−0.0007 to 0.028)	0.06	0.005 (−0.010 to 0.020)	0.51
GLS, %	0.037 (0.028–0.045)	<0.001	0.036 (0.027–0.045)	<0.001
ΔEA/ELV				
Position	0.047 (−0.028 to 0.122)	0.22	0.093 (−0.002 to 0.188)	0.06
Black race	0.003 (−0.072 to 0.077)	0.95	0.003 (−0.080 to 0.086)	0.94
Height, cm	−0.002 (−0.008 to 0.005)	0.56	−0.005 (−0.013 to 0.004)	0.26
ΔWeight, kg	0.002 (−0.004 to 0.008)	0.44	0.00002 (−0.006 to 0.006)	0.996
ΔSystolic BP, 10 mm Hg	0.020 (−0.001 to 0.042)	0.06	0.029 (0.005–0.054)	0.02
ΔPWV, m/s	0.010 (−0.037 to 0.057)	0.67	−0.011 (−0.062 to 0.039)	0.66
ΔE′, cm/s	−0.020 (−0.033 to −0.006)	0.004	−0.010 (−0.025 to 0.005)	0.19
ΔLV mass/BSA, 10 g/m^2	−0.008 (−0.036 to 0.019)	0.55	−0.013 (−0.042 to 0.016)	0.38
ΔGLS, %	0.041 (0.028–0.054)	<0.001	0.045 (0.031–0.059)	<0.001

BP indicates blood pressure; E′, tissue-Doppler averaged mitral annular early diastolic velocities; EA/ELV, effective arterial elastance/end-systolic left ventricular elastance; GLS, global longitudinal strain; LV mass/BSA, left ventricular mass indexed to body surface area; and PWV, pulse wave velocity.

the corollary and balanced increases in LV contractility (ELV) that occur in response to the pathologic increases in arterial afterload (EA), and vice versa.[34–36] As such, it is noteworthy that although subclinical, we observed a significant increase in EA/ELV over a relatively short period of time, and this increase was associated with adverse changes in both vascular and ventricular function.

Prior studies of professional and collegiate AF athletes have established a high prevalence of hypertension.[13–15] Hypertension in this population is associated with maladaptive cardiovascular phenotypes, which include subclinical arterial stiffening, impaired LV systolic and diastolic function, and concentric LV hypertrophy.[17] Our findings demonstrate that hypertension severity significantly increases throughout collegiate AF participation and suggest concomitant VA uncoupling is a crucial maladaptive functional consequence that links the development of AF-associated maladaptive cardiovascular phenotypes. Although it is not unexpected that increased SBP, as an afterload surrogate, predicts VA uncoupling, our results suggest that matched, concomitant increased LV contractility does not occur as evidenced by the association with worsened GLS. In a separate single-season study of only freshman collegiate AF athletes from Lin and colleagues, worsened GLS was also observed in those athletes who became hypertensive. In that study, worsened GLS was more evident in those athletes who developed concentric LV hypertrophy.[20]

Clinical implications from this study should be first considered in the context of long-term outcomes data taken from retired professional AF athletes. Prior studies have established increased cardiovascular mortality, specifically in retired AF athletes who were linemen, compared with the general population.[37,38] In a more recent study accounting for a healthy-worker bias, retired professional AF athletes also demonstrated increased all-cause and cardiovascular mortality compared with retired professional baseball players.[39] To date, the compilation of observational data assessing pathologic cardiovascular phenotypes in active collegiate AF athletes suggests that early cardiovascular pathology may impart health risks later in life. However, the longitudinal progression of maladaptive cardiovascular phenotypes throughout the entire career of the elite AF athlete and after retirement from competitive AF participation remains unknown. Specific to VA uncoupling, it is also noteworthy that subclinical increases in EA/ELV have been associated with adverse outcomes in older patients in the general population.[7] Second, modifiable

Table 5. Factors Associated With log(EA/ELV)

Characteristic	Univariate		Multivariate	
	β (95% CI)	*P* value	β (95% CI)	*P* value
log(EA/ELV)				
Position	0.034 (−0.012 to 0.080)	0.15	−0.003 (−0.075 to 0.064)	0.93
Black race	0.031 (−0.014 to 0.077)	0.17	−0.0004 (−0.048 to 0.048)	0.99
Height, cm	0.0006 (−0.0034 to 0.0045)	0.77	−0.002 (−0.007 to 0.004)	0.57
Weight, kg	0.0008 (−0.0003 to 0.0020)	0.14	0.0007 (−0.0015 to 0.0029)	0.54
Systolic BP, 10 mm Hg	0.018 (0.002–0.033)	0.02	0.020 (0.002–0.039)	0.03
PWV, m/s	0.012 (−0.016 to 0.039)	0.39	−0.030 (−0.063 to 0.003)	0.07
E′, cm/s	−0.018 (−0.026 to −0.009)	<0.001	−0.012 (−0.021 to −0.002)	0.02
LV mass/BSA, 10 g/m^2	0.015 (−0.001 to 0.030)	0.07	0.005 (−0.012 to 0.021)	0.58
GLS, %	0.041 (0.032–0.051)	<0.001	0.040 (0.031–0.050)	<0.001
Δ log(EA/ELV)				
Position	0.038 (−0.043 to 0.120)	0.35	0.090 (−0.014 to 0.194)	0.09
Black race	0.015 (−0.065 to 0.096)	0.71	0.011 (−0.080 to 0.102)	0.80
Height, cm	−0.003 (−0.010 to 0.004)	0.45	−0.006 (−0.015 to 0.004)	0.23
ΔWeight, kg	0.003 (−0.004 to 0.009)	0.37	0.0007 (−0.006 to 0.008)	0.84
ΔSystolic BP, 10 mm Hg	0.019 (−0.005 to 0.042)	0.12	0.027 (0.001–0.054)	0.04
ΔPWV, m/s	0.007 (−0.045 to 0.058)	0.80	−0.015 (−0.070 to 0.040)	0.59
ΔE′, cm/s	−0.023 (−0.038 to −0.009)	0.002	−0.013 (−0.029 to 0.003)	0.12
ΔLV mass/BSA, 10 g/m^2	−0.012 (−0.043 to 0.018)	0.42	−0.017 (−0.049 to 0.015)	0.29
ΔGLS, %	0.046 (0.032–0.060)	<0.001	0.050 (0.035–0.065)	<0.001

BP indicates blood pressure; E′, tissue-Doppler averaged mitral annular early diastolic velocities; EA/ELV, effective arterial elastance/end-systolic left ventricular elastance; GLS, global longitudinal strain; LV mass/BSA, left ventricular mass indexed to body surface area; and PWV, pulse wave velocity.

behaviors and potential risks common within the competitive AF culture, including intentional and rapid weight gain, poor dietary choices, overused nonsteroidal anti-inflammatory drug use, and concussions may contribute to increases in resting SBP.[12,40,41] A critical emphasis on cardiac preventive education and counseling for competitive AF athletes is therefore essential, while also ensuring appropriate guideline-based

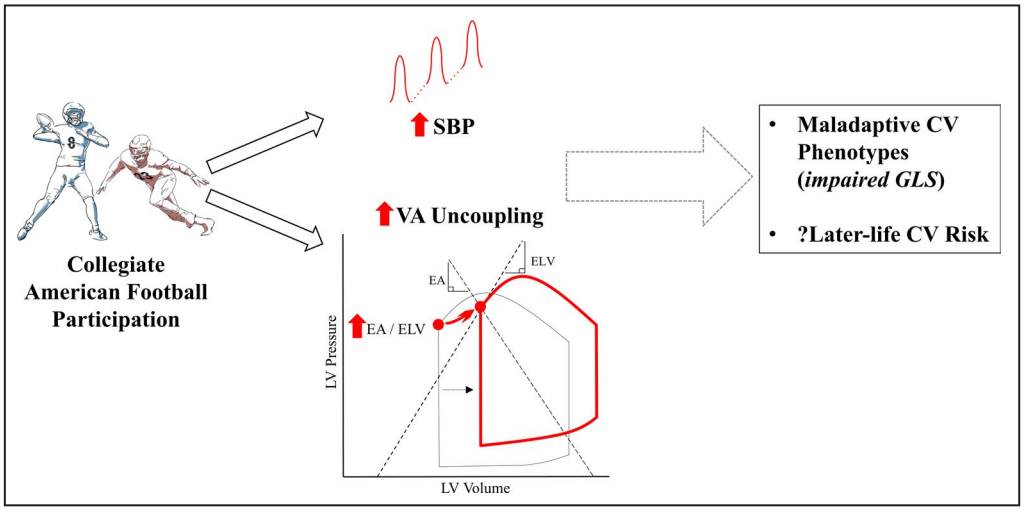

Figure 2. Hypertension and ventricular–arterial (VA) uncoupling in collegiate American football athletes lead to cardiovascular (CV) risk and pathology.
EA indicates effective arterial elastance; ELV, end-systolic left ventricular elastance; GLS, global longitudinal strain; LV, left ventricular; and SBP, systolic blood pressure.

pharmacologic interventions are offered to those athletes who are confirmed hypertensive.

Coupled with the need to prospectively follow health outcomes in elite collegiate and professional AF athletes upon retirement from competitive AF, future research directions should include clinical trials focused on interventions to treat AF-associated hypertension. Noninvasive VA coupling measurements offer additional physiologic end points that could be included in future studies in combination with other key vascular and cardiac functional measures. In prior studies of patients with hypertension, pharmacologic lowering of SBP also led to improvements in EA/ELV.[29,42] Lifestyle interventions, such as aerobic exercise regimens, should also be tested in high-risk AF athletes, such as linemen who engage solely in primary static training. In prior studies of untrained individuals, aerobic endurance training led to improvements in VA coupling and aortic stiffness.[43,44]

We acknowledge several limitations with this study. First, a primary criticism of the EA/ELV pressure-volume model is that EA omits elements of the pulsatile arterial load.[45] However, we included PWV in our analysis, and despite the increase in PWV over time, the subclinical rise observed would not be expected to contribute to a significant rise in afterload. Second, despite the replication of findings from multiple prior studies,[15–18] we acknowledge the lack of a matched control group in this analysis. Third, because of the rolling nature of annual study enrollment and follow-up, we acknowledge incomplete cases, particularly at postseason year 3. In addition, athletes were not followed through the conclusion of their senior season because of logistic difficulties retaining graduating student athletes. Fourth, environmental factors and AF training regimens across collegiate programs may not be uniform, and thus may limit the generalizability of our results. Finally, we were unable to assess the impact of detraining on VA uncoupling in AF athletes who ceased competitive AF participation.

CONCLUSIONS

Coupled with the development of clinically significant hypertension, competitive collegiate AF athletes demonstrate progression of VA uncoupling throughout their collegiate AF career. VA uncoupling is associated with subclinical reductions in LV systolic function, indicative of the inability to appropriately increase LV contractility in response to chronic and pathologically increased afterload. These findings contribute to our understanding of acquired hypertension present among at-risk young collegiate AF athletes, and demonstrate novel mechanistic insight linking AF-associated hypertension with acquired pathologic cardiovascular phenotypes. Future investigations are necessary to determine the impact of VA uncoupling on long-term health outcomes in former AF athletes and whether therapeutic blood pressure interventions lead to improvements in VA coupling in at-risk collegiate AF athletes.

ARTICLE INFORMATION

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Author Contributions: Dr Kim was the principal investigator for this study and had access to all of the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. Drs Tso and Kim, and C. Liu performed statistical analyses. All authors contributed with acquisition of the data, conceptual design, analyses, and interpretation of the results. All authors contributed to drafting the article, providing critical revisions for intellectual content, and gave final approval for the version submitted.

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Supplemental Material

Data S1
Table S1
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Data S1. Supplemental Methods

ELV Estimation

End-systolic left ventricular elastance (ELV) was estimated using the single-beat method proposed by Chen et. al.[10] and described by the formula below:

$$ELV = (DBP - (E_{nd(est)} \times SBP \times 0.9)) / (SV \times E_{nd(est)}),$$

where diastolic blood pressure (DBP) and systolic blood pressure (SBP) were obtained from brachial blood pressure cuff readings, stroke volume (SV) was the Doppler-derived stroke volume, and $E_{end(est)}$ was the non-invasive normalized estimated LV elastance at the onset of ejection as calculated below:

$$E_{nd(est)} = 0.0275 - 0.165 \times EF \text{ (ejection fraction)} + 0.3656 \times (DBP / (SBP \times 0.9)) + 0.515 \times E_{nd(avg)},$$

where $E_{nd(avg)}$ was the group averaged normalized LV elastance at the onset of ejection (10) calculated using a polynomial equation, expanded below:

$$E_{nd(avg)} = 0.35695 - 7.2266 \times tNd + 74.249 \times tNd^2 - 307.39 \times tNd^3 + 684.54 \times tNd^4 - 856.92 \times tNd^5 + 571.95 \times tNd^6 - 159.1 \times tNd^7,$$

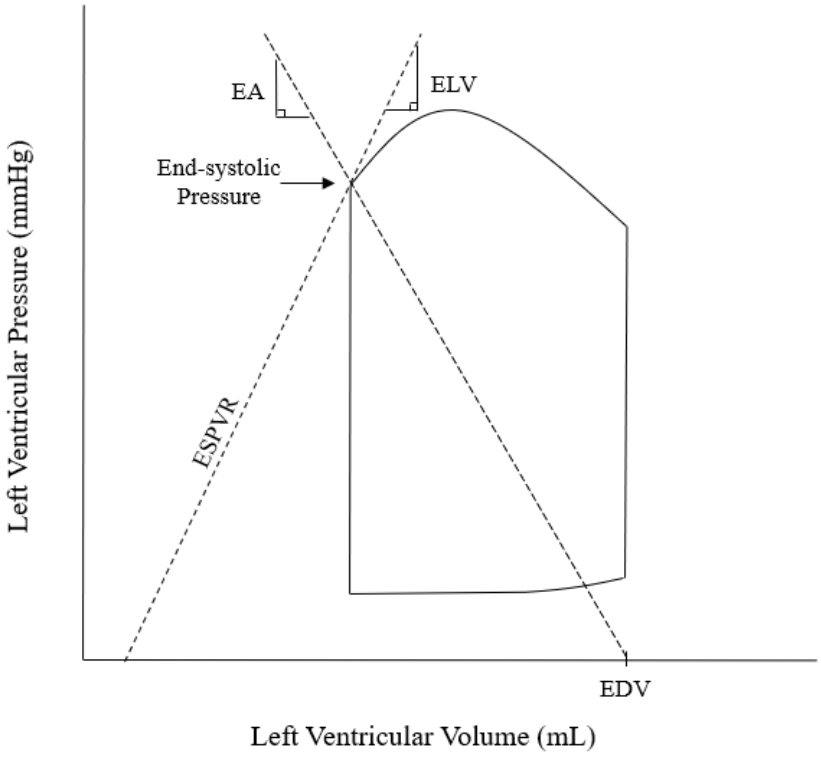
where tNd was the ratio of the pre-ejection period (R wave to the start of flow from the aortic Doppler tracing) to total systolic period (R wave to the end of flow from the aortic Doppler tracing).

Table S1. Clinical and Echocardiographic Characteristics Stratified by Player Position

	Linemen					Non-Linemen					
Characteristic	**Baseline (N=58)**	**Year 1 Post-season (N=58)**	**Year 2 Post-season (N=44)**	**Year 3 Post-season (N=29)**	**P-Value**	**Baseline (N=84)**	**Year 1 Post-season (N=84)**	**Year 2 Post-season (N=56)**	**Year 3 Post-season (N=35)**	**P-Value**	**P-Value (Δ LM vs NLM)**
Weight (kg)	118.2 (114.3,122.1)	119.9 (116.0,123.8)	122.4 (118.4,126.3)	124.5 (120.3,128.6)	**<0.001**	87.9 (85.6,90.1)	89.1 (86.9,91.4)	90.8 (88.4,93.1)	91.9 (89.5,94.4)	**<0.001**	0.3
BMI (kg/m^2)	32.9 (31.8,33.9)	33.3 (32.3,34.4)	34.0 (32.9,35.1)	34.6 (33.5,35.7)	**<0.001**	26.1 (25.5, 26.6)	26.4 (25.8,27.0)	26.9 (26.3,27.5)	27.2 (26.6,27.9)	**<0.001**	0.4
SBP (mmHg)	131.0 (127.8,134.2)	138.0 (134.8,141.2)	138.8 (135.2,142.4)	149.5 (145.1,153.9)	**<0.001**	123.2 (120.8,125.6)	125.7 (123.3,128.1)	127.8 (124.9,130.7)	129.0 (125.4,132.5)	**0.008**	**0.001**
DBP (mmHg)	79.1 (76.8,81.4)	78.1 (75.8,80.4)	81.0 (78.4,83.7)	82.2 (78.9,85.4)	0.14	74.0 (72.1,76.0)	74.0 (72.1,76.0)	73.7 (71.4,76.1)	75.8 (72.8,78.8)	0.7	0.6
PWV (m/sec)	5.5 (5.3,5.7)	5.8 (5.6,6.0)	5.9 (5.7,6.1)	6.1 (5.9,6.3)	**<0.001**	4.8 (4.6,4.9)	5.0 (4.9,5.1)	5.2 (5.1,5.4)	5.1 (4.9,5.3)	**<0.001**	0.3
LV mass/BSA (g/m^2)	87.2 (84.7,89.8)	99.5 (96.9,102.0)	105.2 (102.4,107.9)	110.5 (107.4,113.6)	**<0.001**	90.3 (88.0,92.6)	100.9 (98.6,103.2)	106.2 (103.5,108.9)	110.8 (107.6,114.1)	**<0.001**	0.6
E′ (cm/sec)	15.2 (14.6,15.8)	14.1 (13.5,14.7)	13.6 (12.9,14.3)	12.6 (11.8,13.3)	**<0.001**	16.3 (15.8,16.8)	15.9 (15.3,16.4)	15.3 (14.7,15.9)	14.6 (13.9,15.3)	**<0.001**	0.2
EF (%)	61.5 (60.2,62.8)	60.3 (59.0,61.6)	60.4 (58.9,61.8)	60.4 (58.5,62.2)	0.5	60.7 (59.7,61.8)	60.7 (59.6,61.7)	60.0 (58.7,61.3)	40.1 (58.5,61.7)	0.7	0.8
GLS (%)	18.1 (17.5,18.7)	18.9 (18.3,19.5)	18.0 (17.4,18.7)	18.2 (17.3,19.0)	0.1	18.9 (18.4,19.3)	18.4 (18.0,18.9)	18.1 (17.5,18.7)	18.4 (17.7,10.0)	0.2	0.1
EA (mmHg/mL)	1.24 (1.18,1.30)	1.27 (1.20,1.34)	1.31 (1.23,1.38)	1.39 (1.30,1.47)	**0.03**	1.32 (1.26,1.38)	1.31 (1.25,1.37)	1.32 (1.25,1.39)	1.33 (1.24,1.41)	0.9	0.2
ELV (mmHg/mL)	1.50 (1.40,1.59)	1.42 (1.32,1.52)	1.47 (1.36,1.59)	1.46 (1.33,1.58)	0.6	1.61 (1.52,1.70)	1.56 (1.47,1.66)	1.49 (1.39,1.60)	1.43 (1.30,1.56)	0.055	0.3
EA/ELV	0.851 (0.800,0.903)	0.936 (0.880,0.991)	0.910 (0.847,0.973)	0.991 (0.921,1.060)	**0.006**	0.855 (0.815,0.895)	0.875 (0.833,0.917)	0.901 (0.850,0.951)	0.916 (0.854,0.978)	0.3	0.4

DBP: diastolic blood pressure; **E′:** tissue-Doppler averaged mitral annular early diastolic velocities; **EA:** effective arterial elastance; **ELV**: end-systolic left ventricular elastance; **GLS:** global longitudinal strain; **LM:** linemen; **LV mass/BSA**: left ventricular mass indexed to body surface area; **NLM:** non-linemen; **PWV:** pulse wave velocity; **SBP:** systolic blood pressure

Figure S1. Ventricular-arterial coupling and the pressure-volume relationship.



VA coupling is defined as the ratio of effective arterial elastance (EA) and end-systolic left ventricular elastance (ELV). EA is the inverse of the slope of the line connecting the end-systolic pressure point and the end-diastolic volume (EDV) intercept on the volume axis. ELV is the slope of the end-systolic pressure-volume relationship (ESPVR), which is typically obtained through invasive pressure-volume loop studies.

Figure S2. Subject enrollment and prospective follow-up.