

**SHORT REPORT**
*Muscle Mechanics and Ventricular Function*
**Structural and functional remodeling for elite cyclists during exercise; pressure-volume loops and hemodynamic forces analysis**

 **Alessio Pellegrino**,<sup>1,2</sup>
 **Loira Toncelli**,<sup>1</sup>
 **Simone Vanni**,<sup>2</sup>
**Alessandra Modesti**,<sup>3</sup>
 **Gianni Pedrizzetti**,<sup>4</sup> and
  **Pietro Amedeo Modesti**<sup>1,2</sup>

<sup>1</sup>Sport Medicine Unit, Careggi University Hospital, Florence, Italy; <sup>2</sup>Department of Clinical and Experimental Medicine, University of Florence, Florence, Italy; <sup>3</sup>Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy; and <sup>4</sup>Department of Engineering and Architecture, University of Trieste, Trieste, Italy

**Abstract**

The study was designed to investigate the pattern of intraventricular hemodynamic forces (HDFs) and myocardial performance during exercise in elite cyclists (ECs). Transthoracic stress echocardiography was performed on 19 ECs and 13 age-matched sedentary controls (SCs) at three incremental exercise intensities based on heart rate reserve (HRR). Left ventricular (LV) HDFs were computed from echocardiography long-axis datasets using a novel technique based on endocardial boundary tracking, both in apex-base and latero-septal directions. Pressure volume (PV) loops were noninvasively investigated using the single-beat approach. Differences between groups were investigated using mixed model analysis. At PV loops, EC showed a steeper increase in stroke work compared with SC, without acute changes in ventricular capacity (EDVI<sub>20</sub>). Contractility, measured as ventricular elastance ( $E_{es}$ ), increased during exercise with no difference between groups ( $P = 0.625$ ). At rest, EC had significantly lower heart rates and generated lower HDF than SC. However, during exercise, the pressure gradient developed by EC in systole, and therefore systolic HDF, was significantly higher than that developed by SC ( $P < 0.009$ ), also showing a greater elastic rebound in late systole compared with SC ( $P < 0.032$ ). Importantly, during early diastolic filling, EC showed lower HDF deceleration than SC ( $P < 0.043$ ), indicating a facilitated relaxation of the left ventricle. Analysis of the HDF pattern during exercise shows the functional changes that occur in EC, characterized by increased HDF generation in systole, and facilitated relaxation in early diastole. This is the first time LV structural and functional remodeling is reported for elite cyclists during exercise.

**NEW & NOTEWORTHY** Analysis of the hemodynamic forces shows that the functional changes that occur in elite cyclists during exercise are characterized by increased hemodynamic forces generation in systole, and facilitated relaxation in early diastole.

*echocardiography; elite cyclists; hemodynamic forces; pressure-volume relationship; speckle-tracking echocardiography*

**INTRODUCTION**

Several pilot studies have directly investigated cardiac function during exercise in athletes using echocardiography (1, 2). For endurance-trained athletes, the proposed mechanisms for the progressive increase in stroke volume (SV) to maximal oxygen consumption ( $\dot{V}O_{2max}$ ) are increased diastolic filling, increased contractility, larger blood volume, and decreased cardiac afterload (1–3). A limitation of these studies is that the echocardiographic parameters studied (fractional shortening or ejection fraction) depend on cardiac load, which increases significantly during exercise. Therefore, most echocardiographic parameters are not suitable to describe myocardial performance and cardiac reserve during exercise. Furthermore, most literature focused on the analysis of wall mechanics, ignoring the effects of ventricular

geometry (especially of the shape dynamics) on the genesis of intraventricular pressure gradients (IVPGs) and therefore of the hemodynamic forces (HDFs), which are their surrogates.

The gold-standard measure of load-independent contractility is end-systolic elastance ( $E_{es}$ ) assessed with pressure-volume curves (4). This parameter has been used to invasively investigate contractility responses to exercise in the animal model (5) and in patients, by altering the force-frequency relationship using either inotropy, exercise, or pacing, in several classic studies (6–8). Important advances in echocardiographic imaging have permitted the noninvasive study of pressure-volume curves (9–10). Recent developments in cardiac fluid-dynamics imaging have also heightened interest in HDF patterns associated with cardiac adaptations (11). HDF analysis represents a novel approach to quantifying IVPG, which may permit the detection of changes in athletes (11).



Correspondence: P. A. Modesti (pa.modesti@unifi.it).

Submitted 18 December 2024 / Revised 28 December 2024 / Accepted 10 January 2025



Detailed study of HDF during exercise may provide new insights into the normal physiology of the healthy heart. The study of the heart of an endurance athlete is made complex by the fact that cardiac remodeling has different characteristics in different sports (12). A previous study failed to show any differences in HDF between healthy volunteers and elite endurance athletes at rest, suggesting that cardiac force expenditures are tuned to accelerate blood similarly in small and large hearts to provide adequate cardiac output at rest (13). However, no information is available on HDF changes during exercise in athletes, and there is a lack of data on cycling, the sport characterized by the most marked structural adaptations of the LV (14, 15).

Therefore, the aim of this study was to investigate the cardiac function and HDF during exercise in elite road cyclists (ECs), and the relationship between increased hemodynamic load and functional changes of the left ventricle.

## MATERIALS AND METHODS

### Study Cohort and Ethics

Nineteen male professional ECs (Polti Kometa team) were investigated. Thirteen age-matched male participants who had volunteered to undergo cardiac evaluations between January 2024 and May 2024 were enrolled as sedentary controls (SCs).

All participants underwent clinical and instrumental investigations to exclude any underlying disease. The Ethics Board approved the study (Ref. 22843\_oss), and written informed consent was received from every participant.

### Procedures

Body height and body weight were measured, and body surface area (BSA) and body mass index (BMI) were calculated. Resting systolic (SBP) and diastolic blood pressure (DBP) were measured, and clinical information was collected.

Participants refrained from moderate/vigorous physical activity, caffeine, and alcohol for 24 h before each testing visit and fasted for 2 h before each test.

### Exercise echocardiography.

All participants underwent a semi-upright bicycle exercise stress echocardiography (Ergoselect 1200, Ergoline, Bitz, Germany), with a ramp protocol using an iE33 system, equipped with an X5-1 transducer (Royal Philips Electronics, Amsterdam, The Netherlands) according to recommendations (16). Twelve-lead ECG was monitored continuously throughout the exercise, and blood pressure (BP) was measured every 2 min. Three submaximal stages were targeted to achieve different exercise intensities based on heart rate reserve (HRR), calculated as the following formula:  $HRR = (220 - \text{age}) - HR_{\text{rest}}$ .

Stage 1, 20–40 HRR%; stage 2, 40–60 HRR%; stage 3, 60–80 HRR%. At each stage, echocardiographic images were acquired at 4-, 3-, and 2-chamber apical views. BP and HR were monitored as previously reported.

Each electrocardiographically gated full-volume dataset was digitally stored and exported to QLAB 3DQA software (Philips, Best, The Netherlands) for offline analysis. LV end-

diastolic (EDV) and end-systolic volumes (ESV) were measured using the biplane method of disk summation, and stroke volume (SV) and cardiac output (CO) were calculated. LV mass was calculated (16), and indexed to BSA. The ratio of the early mitral inflow velocity (E) over the early diastolic mitral annular velocity ( $e'$ ) was determined. Speckle-tracking echocardiography analysis was performed using commercial software (2 D CPA 1.4.0.158, Medis BV, Leiden, The Netherlands).

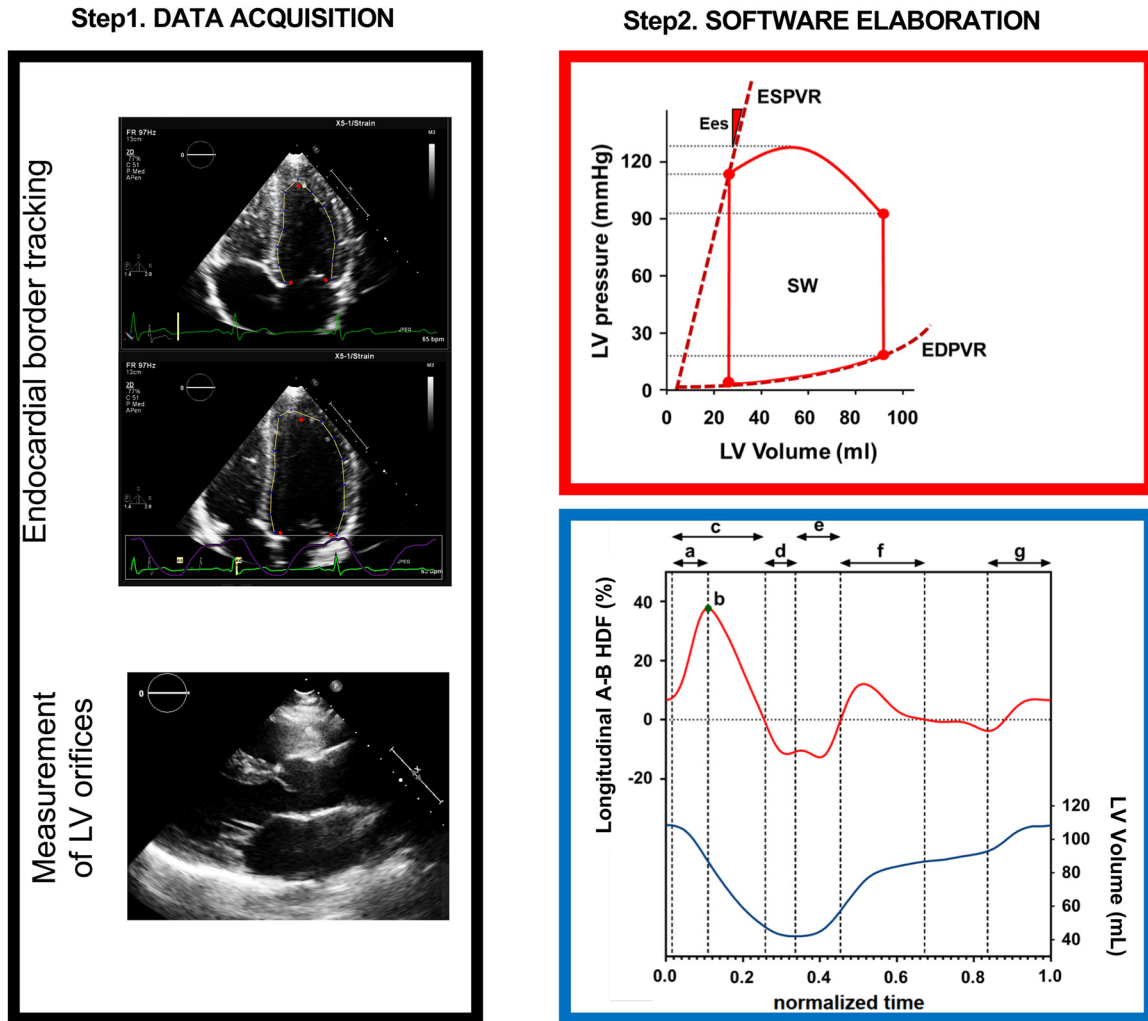
### Pressure-volume curves.

Pressure-volume (PV) loops were constructed using dedicated software (QStrain, Medis BV, Leiden, The Netherlands) using the single-beat approach according to Chen et al. (9) and Klotz et al. (10), respectively, as previously reported (17). To compare the entire position of the end-diastolic pressure-volume relationship (EDPVR), the calculated EDV at an EDP of 20 mmHg indexed to BSA ( $EDV_{20}$ , ventricular capacitance) was used.

### Hemodynamic forces.

In the normal left ventricle, HDFs occur in the longitudinal (apex-to-base, A-B) and in the transversal (lateral-septal, L-S) direction, with the longitudinal direction being the most predominant force. HDFs, expressed in Newton, are divided by the fluid density and gravity acceleration after being initially normalized by the LV volume (11). HDFs were calculated using dedicated software (QStrain, Medis BV, Leiden, The Netherlands) (18), with endocardial tissue movement (tracking) and areas of the aortic and mitral orifices as inputs (17, 18). Two temporal landmarks were considered: end-diastole (synchronized to the ECG R wave) and end-systole (aortic valve closure coincident with the minimum LV volume). The endocardial border was traced at LV end-diastole and LV end-systole on the 4-, 3-, and 2-chamber apical views. The tracking algorithm was then applied to propagate the contours across entire cardiac cycles (17). The time profile of longitudinal HDF was used to extract some parameters (Fig. 1):

- 1) Left ventricular longitudinal force (LVLF): overall HDF strength calculated as the root mean square (RMS) of the HDF over the entire cardiac cycle (19, 20).
- 2) The systolic phase investigation comprised:
  - a) overall systolic longitudinal force: calculated as the LVLF above but limited to the systolic phase (19);
  - b) systolic peak: the peak of the HDF curve in systole (20);
  - c) early emptying: from the onset of LV volume reduction (aortic valve opening) to the peak of the HDF curve; this portion is characterized by a positive ascending phase due to the increase of the pressure gradient (A-B direction) (11);
  - d) systolic impulse: the mean longitudinal force during the systolic propulsive phase when the force was positive (A-B direction) (19);
  - e) elastic rebound: the negative portion of the HDF curve until aortic valve closure (coincident with the minimum LV volume); at this stage, ventricular flow is still exiting but decelerating (11).
- 3) The diastolic phase investigation included:
  - a) overall diastolic longitudinal force: calculated as the LVLF above but limited to diastole;



**Figure 1.** Procedures followed for data acquisition and software elaborations. Step 1: data acquisition. Representative tracing in systole and diastole of the endocardial border (top), and measurements of areas of the aortic and mitral orifices. Step 2: software elaborations. Top: red border: pressure-volume diagram. Left ventricular (LV) pressure (P) is plotted against the LV volume (V) at multiple time points during a single cardiac cycle. The pressure-volume (PV) loop area represents stroke work (SW). The slope between the hypothetical volume at zero pressure ( $V_0$ ), and the point of end-systolic pressure-volume relation (ESPVR), also called end-systolic elastance ( $E_{es}$ ), defines contractility; the end-diastolic PV relationship (EDPVR) describes the ventricular diastolic function. Bottom: blue border: time profile of longitudinal hemodynamic forces (red) and left ventricular volume (blue) used to characterize the various phases of the cardiac cycle for hemodynamic forces analysis. The vertical dotted lines represent the times selected from the two curves to define the following systolic (a–d) and diastolic (e–g) parameters: a) early emptying; b) systolic peak; c) systolic impulse; d) elastic rebound; e) filling impulse; f) diastolic deceleration; g) late diastolic filling. HDF, hemodynamic force.

- b) filling impulse: the negative portion of the HDF curve starting from aortic valve closure (the lowest LV volume); the force is directed from the base toward the apex (13);
- c) diastolic deceleration: from the positive change of the HDF curve after mitral valve opening to the change in the HDF curve direction (from reduction to increase) (20, 21);
- d) late diastolic filling: marked by the final pair of peaks (negative followed by positive) occurring during atrial contraction (11).

Early emptying, systolic impulse, elastic rebound, filling impulse, diastolic deceleration, and late diastolic filling are given as average values and were calculated from the area under the HDF curve normalized to the respective time interval.

### Statistical Analysis

Data are expressed as means  $\pm$  standard deviation for continuous variables. Normal distribution of continuous variables was checked using skewness and kurtosis. For the current analysis, group means were compared using the unpaired *t* test. The effect of exercise on each repeated measurement was analyzed using a linear mixed-effect model with random intercepts (level of exercise intensity and patient category fitted as fixed factors, patient as a random factor) and Bonferroni adjustment. The association between global longitudinal strain (GLS, dependent variable) and HDF (systole HDF A-B and systolic impulse included in the module) was investigated using multiple linear regression analysis. Statistical significance is a two-sided level of 0.05. Data were analyzed using the Statistical Package for the Social Sciences (SPSS Statistics v. 28, IBM, Armonk, NY).

## RESULTS

### Preliminary Investigations at Rest

EC had comparable age, and height, with lower weight than SC (Table 1). EC had lower resting HR, higher LV mass, larger SV and CO, and larger EDV and ESV than SC (Table 1). Parameters of contractility derived from echocardiography (EF, GCS, and GLS) were comparable between groups. Conversely, the load-independent parameter derived from PV loops,  $E_{es}$ , was lower in EC than in SC ( $P < 0.001$ ).  $EDVI_{20}$  was higher in EC than in SC ( $P < 0.001$ ). Longitudinal HDFs were lower in EC than in SC during the entire cardiac cycle ( $P < 0.001$ ), during systole ( $P < 0.021$ ), and during diastole ( $P < 0.008$ ). When more specific time intervals in diastole were investigated, no differences were observed between groups (Table 1).

### Myocardial Performance During Exercise

#### Echocardiography.

Hemodynamic changes during exercise are reported in Table 1. HR progressively increased during exercise with a different pattern between groups ( $P < 0.015$  for category  $\times$  intensity interaction at mixed model analysis). In particular, EC started from lower values than SC, whereas the maximum HR reached during exercise was not significantly different between groups. SV and CO increased progressively from rest to maximal exercise in both groups ( $P < 0.001$  for both). However, when compared with SC, SV of EC increased at a comparable rate from light to maximal exercise ( $P = 0.771$ ), whereas the rate of CO increase during exercise was higher in EC than in SC ( $P < 0.001$  for category  $\times$  intensity interaction). During exercise, two-dimensional LV longitudinal and circumferential strain progressively increased ( $P < 0.001$  for both) with no differences between groups.

#### PV loops.

At PV loop analysis (Fig. 2),  $E_{es}$ , a measure of contractility, progressively increased with exercise intensity ( $P < 0.001$ ), suggesting an exercise-induced improvement of inotropic state, with no differences between groups ( $P = 0.497$  for category  $\times$  intensity interaction at mixed model analysis) (Table 1). In addition, LVESP and stroke work (SW) increase during exercise were steeper in EC than in SC ( $P < 0.003$  and  $P < 0.001$ , respectively, for category  $\times$  intensity interaction) with no changes in ventricular capacitance ( $EDVI_{20}$ ) ( $P = 0.650$  for intensity and  $P = 0.098$  for category  $\times$  intensity interaction) indicating no acute changes of diastolic function.

#### Hemodynamic forces.

In the apical-basal direction, three pairs of force peaks were found (Fig. 3). The first pair of peaks (positive followed by negative peak) was found during systole, corresponding to systolic ejection. In Fig. 3, the end of the systole (corresponding to aortic valve closure) is marked by a dotted line. The second pair (negative followed by positive peak) was found during elastic rebound/early rapid filling. The final pair of peaks (negative followed by positive) was found during atrial contraction. Table 1 reports LV HDF during each stage of exercise in SC and EC. HDF showed a significant increase

with exercise during the entire cardiac cycle, as well as during systole or diastole. Overall, the pattern of response to exercise of HDF during the entire cardiac cycle was not different between the two groups. However, during systole, the increase in the longitudinal component of force was significantly greater in EC than in SC ( $P < 0.009$  for category  $\times$  intensity interaction). Systolic-impulse increase was higher in EC than in SC ( $P < 0.017$  for category  $\times$  intensity interaction). The examination of the HDF pattern in late systole allowed us to detect an additional important peculiarity of LV response to intense physical exercise in EC, with a greater elastic rebound compared with SC ( $P < 0.032$  for group  $\times$  intensity interaction).

At the onset of diastole, there is a base-to-apex pressure gradient, which is reflected in the negative portion of HDF along the longitudinal axis. This force contributes to rapid ventricular filling. The filling impulse, achieved by integrating the negative portion of the apical-basal force acting after aortic valve closure, did not increase in EC during intense exercise (Fig. 3, Table 1). HDFs then reverse into a positive amplitude along the apical-to-basal direction, corresponding to the deceleration of flow. In this phase, EC showed a lower diastolic deceleration than SC ( $P < 0.043$ ), suggesting that the ventricular chamber offers less resistance to the entry of blood. No differences were observed in late filling.

Concerning the whole enrolled population at all exercise stages, GLS was associated with both A-B HDF calculated over the entire systole and systolic impulse ( $B = 0.151$ , 95% CL = 0.086 to 0.215; and  $B = -0.120$ , 95% CL =  $-0.217$  to  $-0.023$ , respectively) at multivariate linear regression analysis.

## DISCUSSION

This is the first time LV structural and functional remodeling is reported for elite cyclists during exercise. In particular, the present study describes for the first time the pattern of response to exercise of HDF in EC, showing an increased generation of the longitudinal HDF component during systole and a facilitated relaxation in early diastole.

According to the present results, the heart of EC appears to generate a lower resting intraventricular HDF than the SC heart. However, HDFs are indexed to the LV volume, which is significantly higher in our EC than in SC, and it is therefore reasonable to observe a lower HDF value in EC than in SC, both in the longitudinal and transverse directions. Indeed, increased cavity volume requires a lower contractile force to produce the necessary stroke volume (22). The only previous study investigating HDF in endurance athletes (13), failed to report any differences versus SC at rest. However, the group of athletes enrolled in that study performed a sport (orienteeering, long-distance trail running with map navigation) characterized by a less-marked LV remodeling than cycling (15), and the average LVEDV of investigated athletes was in fact not different from controls (13).

More importantly, the present study explored the HDF response to exercise for the first time, showing that when ECs face intense effort, intraventricular HDFs increase much more rapidly than in SC and reach much higher values. The increase is surprisingly consistent compared with SC in systole. The examination of the HDF pattern of the ejection

**Table 1. Characteristics of patients and hemodynamic changes at rest and during exercise in sedentary controls (controls) and elite cyclists (cyclists)**

		Characteristics of Patients										P Value	
		Controls (n = 13)					Cyclists (n = 19)						Unpaired t test
Age, yr		27.4±3.4					25.2±3.5					0.087	
Height, cm		179.0±5.6					178.0±6.3					0.650	
Weight, kg		77.1±8.8					67.5±6.3					0.001	
Body surface area, m <sup>2</sup>		1.9±0.1					1.8±0.1					0.013	
Body mass index, kg/m <sup>2</sup>		23.8±2.6					21.3±1.2					0.001	
V <sub>O<sub>2</sub>max</sub> , mL/kg/min		48.7±9.5					73.0±5.6					0.001	
		Hemodynamic Changes at Rest and During Exercise										P Value	
		Controls (n = 13)					Cyclists (n = 19)						Mixed Model
HRR		Rest	20%–40%	40%–60%	60%–80%	Rest	20%–40%	40%–60%	60%–80%	cat	int	cat × int	
Clinical parameters		64.6±11.6	100.6±2.4	129.0±4.2	155.3±5.0	49.1±4.9*	96.2±7.9	122.3±7.7	146.2±8.9	0.001	0.001	0.015	
HR, beats/min		124.2±17.7	145.8±13.1	173.8±17.2	187.7±17.9	118.7±10.4	174.1±30.7	185.4±28.7	190.0±18.3	0.043	0.001	0.003	
SBP, mmHg		73.5±10.5	70.8±10.6	67.1±12.5	64.2±14.1	69.5±10.0	59.6±12.7	57.9±11.2	62.5±15.0	0.012	0.001	0.161	
DBP, mmHg		Echocardiographic parameters											
LVESV, mL		30.2±3.7	26.4±9.0	24.3±7.9	25.3±6.8	53.8±7.2*	39.3±11.1	34.3±11.0	36.5±9.8	0.001	0.001	0.001	
LVEDV, mL		90.7±16.6	97.0±26.4	96.0±19.2	93.2±16.0	143.3±12.3*	142.6±16.4	134.9±18.6	137.6±14.3	0.001	0.061	0.009	
SV, mL		58.7±12.7	68.0±20.1	69.5±14.5	66.9±10.4	89.5±9.5*	103.3±11.7	100.6±10.9	101.0±8.2	0.001	0.001	0.771	
CO, L/min		3.68±0.43	6.83±2.01	8.95±1.81	10.37±1.47	4.38±0.55*	9.91±1.16	12.32±1.69	14.82±1.27	0.001	0.001	0.001	
CI, L/min/m <sup>2</sup>		1.89±0.26	3.50±1.16	4.56±0.98	5.32±0.83	2.38±0.24*	5.38±0.53	6.64±0.77	7.83±0.79	0.001	0.001	0.001	
EF, %		65.4±4.7	71.5±7.8	73.8±6.1	72.3±5.4	62.1±3.8*	72.5±6.1	75.0±4.8	73.8±5.3	0.964	0.001	0.065	
Strain and pressure-volume loop parameters													
GLS, %		24.7±3.8	30.0±6.0	28.8±3.6	31.1±3.1	23.9±2.5	30.3±3.5	31.1±4.7	28.5±2.9	0.934	0.001	0.167	
GCS, %		33.1±4.3	38.7±6.5	41.6±7.4	39.4±7.2	30.8±2.9	40.3±6.4	41.4±4.7	38.9±2.0	0.865	0.001	0.438	
E <sub>es</sub> , mmHg/mL		3.89±0.94	5.55±2.01	7.51±3.71	7.37±2.40	2.04±0.33*	4.75±2.13	4.81±1.57	5.09±1.10	1.000	0.001	0.625	
Beta		6.09±0.13	6.08±0.10	6.23±0.26	6.19±0.26	6.06±0.12	6.2±0.28	6.19±0.23	6.66±0.88	0.175	0.017	0.208	
EDV <sub>120</sub> , mL/m <sup>2</sup>		47.1±8.4	49.7±13.4	48.6±9.4	48.2±7.0	80.8±6.1*	79.3±7.8	76.6±4.8	77.5±5.5	0.001	0.650	0.098	
LVESP, mmHg		111.8±15.9	131.3±11.8	156.4±15.5	168.9±16.1	106.8±9.4	156.7±27.7	166.9±25.9	171.0±16.4	0.043	0.001	0.003	
LVEDP, mmHg		16.7±1.7	16.6±1.5	17.9±2.5	17.6±2.2	16.1±1.7	17.8±2.1	17.4±2.8	19.7±3.9	0.719	0.038	0.269	
SW, J		0.83±0.21	1.11±0.38	1.30±0.32	1.35±0.25	1.20±0.17*	1.97±0.45	1.98±0.38	2.15±0.06	0.001	0.001	0.001	
E <sub>a</sub> , mmHg/mL		1.99±0.51	2.07±0.57	2.34±0.57	2.55±0.40	1.21±0.20*	1.47±0.29	1.68±0.37	1.6±0.22	0.001	0.001	0.102	
VAC		0.52±0.10	0.40±0.15	0.35±0.10	0.37±0.10	0.59±0.10	0.35±0.12	0.36±0.05	0.40±0.10	0.830	0.001	0.244	
HDF entire cardiac cycle %		15.2±4.1	36.1±14.0	53.9±13.0	73.7±15.1	11.3±3.1*	44.2±18.2	58.3±15.6	79.7±23.9	0.174	0.001	0.086	
HDF A-B		3.1±1.1	7.1±1.9	10.8±4.0	16.8±6.4	2.2±0.6*	7.1±1.9	9.6±3.0	14.1±2.4	0.284	0.001	0.595	
HDF L-S		24.5±7.6	50.2±19.0	70.0±19.2	91.9±31.4	18.8±5.5*	66.4±30.8	85.0±26.7	108.7±37.3	0.013	<0.001	0.009	
HDF systole %		4.2±1.6	8.2±2.1	11.5±5.0	15.2±7.3	3.1±0.7*	8.0±3.7	11.8±3.1	16.6±4.8	0.531	0.001	0.448	
HDF A-B		22.5±6.0	56.2±22.1	81.1±22.2	114.2±46.5	19.0±4.9	70.5±32.7	99.4±34.9	144.0±44.6	0.052	<0.001	0.075	
Early emptying		22.6±6.4	48.1±17.8	68.1±23.5	82.9±34.2	18.2±5.6	62.0±30.2	85.9±31.7	119.4±37.3	0.025	<0.001	0.017	
Systolic impulse		43.8±15.0	89.9±45.6	123.5±38.2	161.0±70.4	33.7±10.1*	116.7±56.7	140.0±54.3	207.3±68.7	0.112	<0.001	0.068	
Systolic peak		-11.5±3.0	-25.4±10.3	-36.1±14.2	-40.7±16.9	-8.3±1.7*	-25.0±9.0	-37.8±9.9	-57.0±13.1	0.078	<0.001	0.032	
Elastic rebound													

Continued

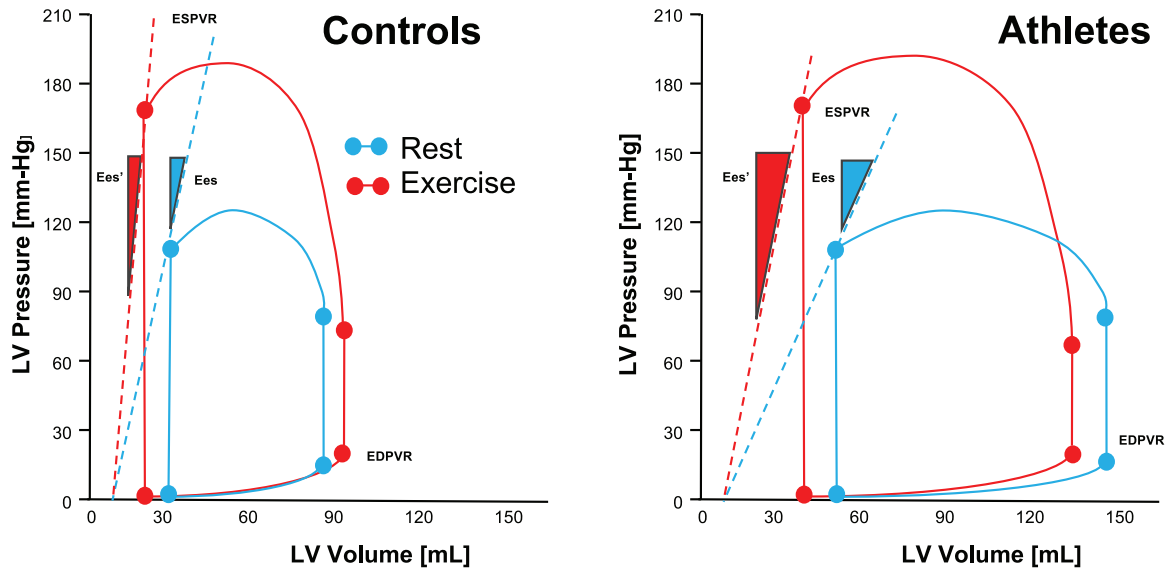
Table 1.— Continued

HRR	Hemodynamic Changes at Rest and During Exercise										P Value	
	Controls (n = 13)					Cyclists (n = 19)					Mixed Model	
	Rest	20%–40%	40%–60%	60%–80%	Rest	20%–40%	40%–60%	60%–80%	cat	int	cat × int	
HDF diastole %												
HDF A-B	6.5 ± 1.6	19.5 ± 7.8	33.1 ± 10.8	51.9 ± 11.1	5.0 ± 1.3*	19.4 ± 6.4	27.0 ± 5.3	41.4 ± 3.1	0.040	<0.001	0.223	
HDF L-S	2.2 ± 1.0	6.0 ± 2.3	9.7 ± 4.4	17.6 ± 8.8	1.6 ± 0.6	6.3 ± 2.1	7.5 ± 3.2	11.4 ± 1.4	0.093	0.001	0.192	
Filling impulse	-8.4 ± 2.6	-22.1 ± 9.5	-33.3 ± 16.1	-45.2 ± 18.9	-8.6 ± 2.6	-25.4 ± 13.5	-35.1 ± 14.9	-44.8 ± 11.4	0.826	<0.001	0.896	
Diastolic deceleration	5.0 ± 2.4	14.1 ± 9.6	22.2 ± 12.8	38.8 ± 18.3	5.0 ± 2.1	12.0 ± 6.0	17.4 ± 8.5	23.2 ± 13.0	0.014	<0.001	0.043	
Late diastolic filling	5.7 ± 2.3	12.6 ± 5.5	27.9 ± 8.9	46.4 ± 17.8	4.5 ± 1.0	12.5 ± 5.1	24.0 ± 8.3	31.2 ± 12.6	0.082	<0.001	0.411	

Units are means ± SD; n, subjects; CI, cardiac index; CO, cardiac output; DBP, diastolic blood pressure; E<sub>a</sub>, arterial elastance; EDV<sub>120</sub>, end-diastolic volume index at a pressure of 20 mmHg; E<sub>es</sub>, end-systolic ventricular elastance; EF, ejection fraction; GCS, global circumferential strain; GLS, global longitudinal strain; HR, heart rate; LVEDV, left ventricular end-diastolic volume; LVEDP, LV end-diastolic pressure; LVESD, LV end-systolic diameter; LVESV, LV end-systolic volume; SBP, systolic blood pressure; SV, stroke volume; SW, stroke work; VAC, ventricular arterial coupling; V<sub>O<sub>2</sub>max</sub>, maximal oxygen consumption. A-B, apical-basal longitudinal direction; L-S, latero-septal transversal direction. Mixed model analysis with Bonferroni correction: P for categories (cat = categories; athletes), zone intensity (int = intensity; 4 stages), and interaction between category and zone intensity (cat × int). \*P < 0.05 vs. Controls at rest.

phase during intense exercise in EC allows us to observe the appearance of a significant hemodynamic force directed along the apical-basal axis. In late systole, a marked increase in the negative deflection in the HDF curve compared with SC is also visible (ventricular elastic recoil). On the contrary, the study of pressure-volume curves showed that the load-independent contractility parameter E<sub>es</sub> was lower in EC compared with SC at rest and increased significantly during exercise, with no differences between the two groups. In the present study, longitudinal and circumferential strain increased significantly during exercise with no differences between the two groups, as also previously reported (23). During exercise, PV loops also highlight a significantly greater SW increase in EC compared with SC. Accordingly, during exercise, the study of pressure-volume curves detects a steeper increase in LVESP and SW in EC compared with SC, without acute changes in ventricular capacity (EDV<sub>120</sub>). This seems to indicate a greater reduction in afterload in ECs compared with SC during exercise.

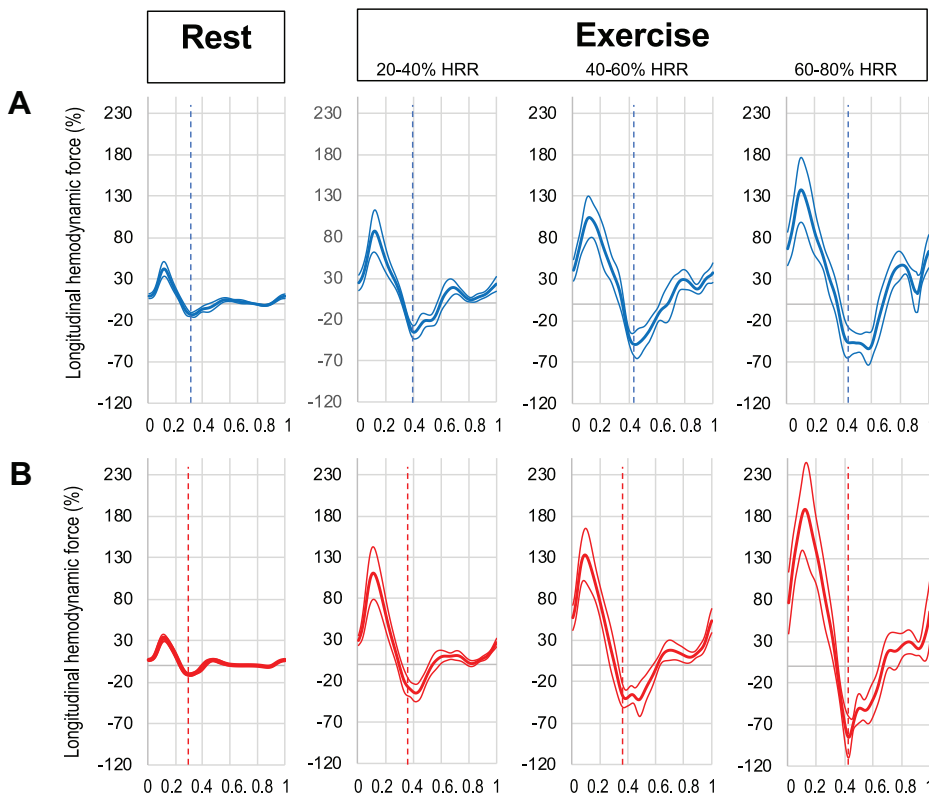
Furthermore, during exercise, EDV tends to reduce in athletes, whereas EDP does not behave differently compared with SC. It is therefore conceivable that the modifications of the LV induced by training have led to a greater capacity to accommodate blood flow in diastole. When examining the longitudinal impulse during early diastolic filling at rest, we found no difference between EC and SC. This was unexpected, given that diastolic function has consistently been found to increase in athletes (1, 21). The increased preload associated with the semi-supine position may obscure subtle physiological differences in diastolic function at rest within this cohort of healthy volunteers, but this hypothesis appears unlikely during exercise considering the significant hemodynamic effort generated. The process of filling the ventricle, which follows aortic valve closure is composed of different phases as can be seen in Fig. 3. At peak exercise, aortic valve closure is followed by a short first phase with a high negative filling gradient (due to the base-apex pressure gradient), followed by a second phase with a lower gradient. The filling impulse offers an overall measurement and probably does not allow the different phases of the filling process to be analyzed in detail. Conversely, present findings show that in EC during exercise it is possible to document a lower deceleration compared with SC immediately after early diastole. In this phase, once the initial moment of rapid entry coinciding with the opening of the mitral valve has passed, a reduction in the pressure gradient is observed, with a consequent lower slowdown in the speed of blood entry in EC. These data express a facilitated relaxation of the left ventricle in EC, offering important progress in current knowledge. Many studies investigating diastolic function using Doppler parameters observed no differences in peak E velocity between sedentary controls and athletes (24). On the contrary, the ratios of early to late diastolic filling (E/A-blood flow velocity, e'/a'-myocardial velocity) increased in endurance-trained athletes (14, 25), potentially due to enhanced early diastolic filling (25). Conversely, a recent study found decreased E and e' velocities in EC compared with nonathletes (14). Rather than indicating a lower diastolic function, this pattern was attributed to a significantly greater reserve volume and lower resting HR in comparison with nonathletes,



**Figure 2.** Left ventricular pressure-volume loop of one sedentary control and one elite cyclist at rest (blue) and during exercise (red). Ventricular pressure (P) is plotted against the ventricular volume (V) at multiple time points during a single cardiac cycle. The pressure-volume (P-V) loop area represents stroke work (SW). Slope between the hypothetical volume at zero pressure ( $V_0$ ), and the point of end-systolic pressure-volume relation (ESPVR), also called end-systolic elastance ( $E_{es}$ ), defines contractility. Dashed lines indicate the slopes of  $E_{es}$ ,  $E_{es'}$  and SW increase from rest to exercise.

resulting in a decreased need for enhanced relaxation/suction at rest (22). However, the Doppler parameters do not allow us to explore the different phases of rapid filling. On the contrary, the study of HDF highlights the presence of an increased relaxation capacity in the terminal phase of rapid filling (diastolic deceleration).

In conclusion, the present study shows that it is possible to noninvasively analyze the behavior of pressure-volume curves and HDFs during physical exercise. The simultaneous execution of these two methods offers the possibility of studying in an integrated manner the relationship between the changes in ventricular geometry that characterize cardiac



**Figure 3.** Average longitudinal hemodynamic forces (HDFs) in controls (A, blue lines) and elite cyclists (B, red lines) at rest and at different exercise stages (20%–40%, 40%–60%, and 60%–80% of heart rate reserve, HRR). Average HDFs over the entire cardiac cycle are presented as means with 95% confidence interval. The end of the systole (corresponding to the closure of the aortic valve) is marked by a dotted line.

remodeling, contractility, and the generation of HDFs in the EC. Analysis of the HDF pattern during exercise shows that the functional changes that occur in EC are mainly characterized by increased HDF generation in systole and facilitated relaxation in early diastole.

## DATA AVAILABILITY

Data will be made available upon reasonable request.

## DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

## AUTHOR CONTRIBUTIONS

A.P. and L.T. performed experiments; A.P., L.T., S.V., A.M., G.P., and P.A.M. interpreted results of experiments; A.P. and P.A.M. prepared figures; A.P. and P.A.M. edited and revised manuscript; A.P., L.T., S.V., A.M., G.P., and P.A.M. approved final version of manuscript; L.T., S.V., A.M., and P.A.M. analyzed data; P.A.M. conceived and designed research; P.A.M. drafted manuscript.

## REFERENCES

- Gledhill N, Cox D, Jamnik R. Endurance athletes' stroke volume does not plateau: major advantage is diastolic function. *Med Sci Sports Exerc* 26: 1116–1121, 1994.
- Vella CA, Robergs RA. A review of the stroke volume response to upright exercise in healthy subjects. *Br J Sports Med* 39: 190–195, 2005 [Erratum in *Br J Sports Med* 39: 688, 2005]. doi:10.1136/bjism.2004.013037.
- Carrick-Ranson G, Doughty RN, Whalley GA, Walsh HJ, Gamble GD, Baldi JC. The larger exercise stroke volume in endurance-trained men does not result from increased left ventricular early or late inflow or tissue velocities. *Acta Physiol (Oxf)* 205: 520–531, 2012. doi:10.1111/j.1748-1716.2012.02430.x.
- Katz AM. Influence of altered inotropy and lusitropy on ventricular pressure-volume loops. *J Am Coll Cardiol* 11: 438–445, 1988. doi:10.1016/0735-1097(88)90113-1.
- Miura T, Miyazaki S, Guth BD, Kambayashi M, Ross J. Influence of the force-frequency relation on left ventricular function during exercise in conscious dogs. *Circulation* 86: 563–571, 1992. doi:10.1161/01.cir.86.2.563.
- Feldman MD, Alderman JD, Aroesty JM, Royal HD, Ferguson JJ, Owen RM, Grossman W, McKay RG. Depression of systolic and diastolic myocardial reserve during atrial pacing tachycardia in patients with dilated cardiomyopathy. *J Clin Invest* 82: 1661–1669, 1988. doi:10.1172/JCI113778.
- Inagaki M, Yokota M, Izawa H, Ishiki R, Nagata K, Iwase M, Yamada Y, Koide M, Sobue T. Impaired force-frequency relations in patients with hypertensive left ventricular hypertrophy. A possible physiological marker of the transition from physiological to pathological hypertrophy. *Circulation* 99: 1822–1830, 1999. doi:10.1161/01.cir.99.14.1822.
- Izawa H, Yokota M, Nagata K, Iwase M, Sobue T. Impaired response of left ventricular relaxation to exercise-induced adrenergic stimulation in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 28: 1738–1745, 1996. doi:10.1016/S0735-1097(96)00378-6.
- Chen CH, Fetits B, Nevo E, Rochitte CE, Chiou KR, Ding PA, Kawaguchi M, Kass DA. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. *J Am Coll Cardiol* 38: 2028–2034, 2001. doi:10.1016/s0735-1097(01)01651-5.
- Klotz S, Hay I, Dickstein ML, Yi GH, Wang J, Maurer MS, Kass DA, Burkhoff D. Single-beat estimation of end-diastolic pressure-volume relationship: a novel method with potential for noninvasive application. *Am J Physiol Heart Circ Physiol* 291: H403–H412, 2006. doi:10.1152/ajpheart.01240.2005.
- Vallelonga F, Airale L, Tonti G, Argulian E, Milan A, Narula J, Pedrizzetti G. Introduction to hemodynamic forces analysis: moving into the new frontier of cardiac deformation analysis. *J Am Heart Assoc* 10: e023417, 2021. doi:10.1161/JAHA.121.023417.
- Mihl C, Dassen WR, Kuipers H. Cardiac remodelling: concentric versus eccentric hypertrophy in strength and endurance athletes. *Neth Heart J* 16: 129–133, 2008. doi:10.1007/BF03086131.
- Arvidsson PM, Töger J, Carlsson M, Steding-Ehrenborg K, Pedrizzetti G, Heiberg E, Arheden H. Left and right ventricular hemodynamic forces in healthy volunteers and elite athletes assessed with 4D flow magnetic resonance imaging. *Am J Physiol Heart Circ Physiol* 312: H314–H328, 2017. doi:10.1152/ajpheart.00583.2016.
- Brown B, Millar L, Somauroo J, George K, Sharma S, La Gerche A, Forsythe L, Oxborough D. Left ventricular remodeling in elite and sub-elite road cyclists. *Scand J Med Sci Sports* 30: 1132–1139, 2020. doi:10.1111/sms.13656.
- Pelliccia A, Culasso F, Di Paolo FM, Maron BJ. Physiologic left ventricular cavity dilatation in elite athletes. *Ann Intern Med* 130: 23–31, 1999. doi:10.7326/0003-4819-130-1-199901050-00005.
- Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 16: 233–270, 2015 [Erratum in *Eur Heart J Cardiovasc Imaging* 17: 412, 2016]. doi:10.1093/ehjci/jev014.
- Pellegrino A, Toncelli L, Pasquini L, Masini G, Mecacci F, Pedrizzetti G, Modesti PA. Left ventricular remodeling in twin pregnancy, noninvasively assessed using hemodynamic forces and pressure-volume relation analysis: prospective, cohort study. *Am J Physiol Heart Circ Physiol* 326: H426–H432, 2024. doi:10.1152/ajpheart.00699.2023.
- Pedrizzetti G. On the computation of hemodynamic forces in the heart chambers. *J Biomech* 95: 109323, 2019. doi:10.1016/j.jbiomech.2019.109323.
- Faganello G, Collià D, Pagura L, Croatto E, Tosoni LM, Toritto P, Pedrizzetti G, Lenarda AD. Impact of left ventricular hemodynamic forces in adult patients with treated aortic coarctation and preserved left ventricular systolic function. *Echocardiography* 41: e15742, 2024. doi:10.1111/echo.15742.
- Backhaus SJ, Uzun H, Rösel SF, Schulz A, Lange T, Crawley RJ, Evertz R, Hasenfuß G, Schuster A. Hemodynamic force assessment by cardiovascular magnetic resonance in HFpEF: a case-control sub-study from the HFpEF stress trial. *EBioMedicine* 86: 104334, 2022. doi:10.1016/j.ebiom.2022.104334.
- Yang W, Wang Y, Zhu L, Xu J, Wu W, Zhou D, Sirajuddin A, Arai AE, Zhao S, Lu M. Unravelling the intricacies of left ventricular haemodynamic forces: age and gender-specific normative values assessed by cardiac MRI in healthy adults. *Eur Heart J Cardiovasc Imaging* 25: 229–239, 2024. doi:10.1093/ehjci/jead234.
- Claessen G, Schnell F, Bogaert J, Claeys M, Pattyn N, De Buck F, Dymarkowski S, Claus P, Carré F, Van Cleemput J, La Gerche A, Heidebuchel H. Exercise cardiac magnetic resonance to differentiate athlete's heart from structural heart disease. *Eur Heart J Cardiovasc Imaging* 19: 1062–1070, 2018. doi:10.1093/ehjci/jey050.
- D'Andrea A, Radmilovic J, Carbone A, Mandoli GE, Santoro C, Evola V, Bandera F, D'Ascenzi F, Bossone E, Galderisi M, Cameli M; Echocardiography Study Group of the Italian Society of Cardiology. Speckle tracking evaluation in endurance athletes: the "optimal" myocardial work. *Int J Cardiovasc Imaging* 36: 1679–1688, 2020. doi:10.1007/s10554-020-01871-z.
- Utomi V, Oxborough D, Whyte GP, Somauroo J, Sharma S, Shave R, Atkinson G, George K. Systematic review and meta-analysis of training mode, imaging modality and body size influences on the morphology and function of the male athlete's heart. *Heart* 99: 1727–1733, 2013. doi:10.1136/heartjnl-2012-303465.
- George KP, Naylor LH, Whyte GP, Shave RE, Oxborough D, Green DJ. Diastolic function in healthy humans: non-invasive assessment and the impact of acute and chronic exercise. *Eur J Appl Physiol* 108: 1–14, 2010. doi:10.1007/s00421-009-1233-0.