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ORIGINAL ARTICLE

# Three-dimensional regional bi-ventricular shape remodeling is associated with exercise capacity in endurance athletes

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## Abstract

**Aims** Endurance athletes develop cardiac remodeling to cope with increased cardiac output during exercise. This remodeling is both anatomical and functional and shows large interindividual variability. In this study, we quantify local geometric ventricular remodeling related to long-standing endurance training and assess its relationship with cardiovascular performance during exercise.

**Methods** We extracted 3D models of the biventricular shape from end-diastolic cine magnetic resonance images acquired from a cohort of 89 triathlon athletes and 77 healthy sedentary subjects. Additionally, the athletes underwent cardiopulmonary exercise testing, together with an echocardiographic study at baseline and few minutes after maximal exercise. We used statistical shape analysis to identify regional bi-ventricular shape differences between athletes and non-athletes.

**Results** The ventricular shape was significantly different between athletes and controls ($p < 1e{-}6$). The observed regional remodeling in the right heart was mainly a shift of the right ventricle (RV) volume distribution towards the right ventricular infundibulum, increasing the overall right ventricular volume. In the left heart, there was an increment of left ventricular mass and a dilation of the left ventricle. Within athletes, the amount of such remodeling was independently associated to higher peak oxygen pulse ($p < 0.001$) and weakly with greater post-exercise RV free wall longitudinal strain ($p = 0.03$).

**Conclusions** We were able to identify specific bi-ventricular regional remodeling induced by long-lasting endurance training. The amount of remodeling was associated with better cardiopulmonary performance during an exercise test.

**Keywords** Exercise physiology · Athlete's heart · Cardiac remodeling · Statistical shape analysis

## Abbreviations

| | |
|---|---|
| AUROC | Area under receiver operator characteristic |
| ARVC | Arrhythmogenic right ventricle cardiomyopathies |
| BSA | Body surface area |
| CO | Cardiac output |
| CPET | Cardiopulmonary exercise testing |
| HR | Heart rate |
| LH | Left heart |
| LOO-CV | Leave one out cross validation |
| LV | Left ventricle |
| LVGLS | Left ventricular global longitudinal strain |
| LVOT | Left ventricular outflow tract |
| MRI | Magnetic resonance imaging |
| PCA | Principal component analysis |
| PER | Pulmonary extraction ratio |
| PLS | Partial least squares |
| RA | Right atria |
| RH | Right heart |
| RV | Right ventricle |
| RV-FW | Right ventricular free wall |
| RVGLS | Right ventricle global longitudinal strain |
| RVOT | Right ventricle outflow tract |
| SA | Short axis |

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| | |
|---|---|
| SSA | Statistical shape analysis |
| STD | Standard deviation |
| $VO_2$ | Oxygen uptake |

## Background

As reported in the literature, extensive periods of physical exercise result in chronic exposure to volume and pressure overload, inducing cardiac remodeling (La Gerche et al. 2013; Schmied and Borjesson 2014). This cardiac remodeling includes a set of morphological and functional changes to obtain a better cardiovascular response to exercise. Known remodeling includes left ventricle (LV) hypertrophy and dilatation, dilated right ventricle (RV) and atria (RA), decreased resting heart rate (HR) and a slight decrease in myocardial deformation at rest. These changes vary importantly among individuals, but the right heart (RH) has shown more propensity for mal-adaptation and fibrosis (Rhodes et al. 1990; La Gerche et al. 2012; D'Andrea et al. 2015), as it is exposed to a bigger relative pressure increase during exercise in comparison to baseline than the left heart (LH). Exercise-induced remodeling is known to be influenced by lifestyle parameters such as sport discipline, training load, and individual-specific parameters such as age, gender, and ethnicity (Sanz-de la Garza et al. 2017; Sitges et al. 2017). However, the details and spectrum of physiological adaptation to sport are not yet completely understood.

Overall, this eccentric remodeling helps to increase cardiac output (CO) during exercise, and previous authors have established a relationship between structural size remodeling and exercise performance in endurance athletes (Scharhag et al. 2002). However, it was also reported that this remodeling can become mal-adaptative in a subset of elite athletes with high training doses (La Gerche and Prior 2007; Sanz-de la Garza et al. 2016).

Analysis of RV structural morphology is difficult due to its complexity, and classical measurements, as used in current routine practice, might be ill-aimed to assess subtle regional remodeling occurring in many clinical conditions. Statistical shape analysis (SSA) denotes a set of techniques that allow to perform statistics directly on cardiac structures as a single object. This allows to assess shapes without having to define and standardize measurements beforehand, which is useful when the remodeling to assess is unknown, or many single measurements would be required to describe the complex shape. They compute a reference shape for a population and subsequently describe each individual shape with the transformation from the template to this individual. The individual deviation from the reference can subsequently be visualized for interpretability (Dryden and Mardia 1998). Cardiac imaging modalities are evolving towards routine 3D acquisition and current quantification software allows to automatically derive 3D-models of individuals' hearts, permitting the application of these techniques in clinical datasets to thus find regional morphology and deformation differences between two different populations (De Craene et al. 2012; Zhang et al. 2014; Varela et al. 2017; Varano et al. 2018).

We hypothesize that structural remodeling due to endurance sport is not limited to global size but also includes regional size, and that regional remodeling furthermore influences exercise performance. Identifying and understanding the physiological ventricular regional remodeling due to endurance sport are additionally important to differentiate it from pathological conditions that also cause a dilatation of the heart/cardiac mass, such as arrhythmogenic right ventricle cardiomyopathies (ARVC) or conditions associated with (bi-)ventricular hypertrophy.

Given the importance of the RH in endurance athletes, and the difficulty to assess regional remodeling using the current measurement-based techniques, we propose the use of SSA to assess regional structural remodeling. This paper uses SSA methods to find regional differences between bi-ventricular shapes, as retrieved from magnetic resonance imaging (MRI), of endurance athletes and non-athletes and relate these to exercise response and classical imaging parameters.

## Methods

### Population

Two gender-balanced cohorts of caucasian young adults (20–46 years), 1 of 89 healthy triathletes and another of 77 controls were retrospectively recruited from previous studies at Hospital Clínic, Barcelona, according to internal research protocols validated by the internal ethical committee. Written informed consent was available for each of the participants. Triathletes were originally recruited from local sports centers and inclusion criteria implied that they exercised at least 10 h weekly for at least 5 years, assessed via a physical activity questionnaire (Ainsworth et al. 2011). Controls were randomly selected among the population born in Barcelona and recruited via telephone. Controls who agreed to participate filled a physical activity questionnaire (Craig et al. 2003), and those who exercised 5 h or less weekly were included. All individuals included in this study were asymptomatic with no known nor suspected cardiovascular illnesses. All individuals were asked to avoid training, caffeine, exciting substances, and alcohol 24 h before the tests. Body surface area was calculated according to the DuBois formula (Du Bois and Du Bois 1916).

## Echocardiographic measurements

Echocardiographic images were acquired from athletes before and after a stress test using a commercially available ultrasound system (Vivid Q GE Medical; Milwaukee, USA) by an expert cardiologist. Images were acquired from the parasternal (long and short axes) and apical (RV-focused 4, 4, 3, and 2 chamber) views. Three consecutive cardiac cycles for each acquisition were digitally stored in a cine loop format for off-line analysis with commercially available software (Echo Pac, version 202.41.0, GE, Milwaukee, WI, USA). Myocardial deformation of both ventricles was evaluated by 2D-STE using loops with 60–80 frames per second. RV free wall peak systolic strain (RVFWLS) was measured as an average of the three free wall RV segments in an apical RV-focused view. Left ventricle global longitudinal strain (LVGLS) was calculated as an average of LV systolic strain in 2-, 3-, and 4-chamber apical views, according to the standards of the European Society of Echocardiography (Lang et al. 2015; Badano et al. 2018).

## Exercise test

All individuals performed a standard incremental cardiopulmonary exercise testing in an up-right position on an electrically braked cycle ergometer (range 6–999 W) using an Ergoselected 100 (Ergoline, Bitz, Germany). Over the course, of this test, they performed an increasingly demanding exercise until exhaustion, while their gas exchange parameters and HR were being monitored using a breath-by-breath and a 12 lead ECG. From this, the peak and basal oxygen uptake, as well as the HR were measured using the ExpAir software (Medisoft, Sorinnes, Belgium). All tests were performed and analyzed according to international guidelines by the same practitioner (Ross et al. 2003; Albert et al. 2008).

Immediately after the end of the exercise test, athletes were moved to a bed next to the ergometer and were subjected to a post-exercise echocardiographic exam to assess acute function and geometry changes. This post-exercise exam included an RV-focused apical 4-CV and the classical 2-, 3-, and 4- chamber apical views for strain analysis.

## MRI study

Cardiac MRI studies were performed using a 3 T (72 athletes and 77 controls) or 1,5 T (17 athletes) scanner (Magnetom Trio Tim and Magneton Aera, *Siemens* Medical Solutions, Erlangen, *Germany)* in all subjects involved in this protocol. Images were acquired during apnea. A cine sequence in short axis (SA) view was acquired with 8 mm slice thickness, an interslice gap ranging from 0 to 2.4 mm, and a pixel size ranging between 0.8 and 1.5 mm. All sequences were acquired by the same radiologist. The MRI was acquired within 3 months of the exercise test.

For each individual in our population, we generated a 3D surface by fitting a whole-heart deformable template, for all time instances, to the SA MRI, using the algorithm described and validated in (Ecabert et al. 2006; Peters et al. 2010). From this, we extracted the LV end-diastolic (ED) frame and selected the LV epicardial and endocardial surfaces as well as the RV endocardium. All contour points were in one-to-one correspondence due to the model-based segmentation.

An expert visually checked all automatic segmentations in the SA, and two individuals were discarded for inadequate tracing of the ventricular contour. In the Supplementary Material S1, we show randomly selected examples of the segmentation contours.

## Statistical shape analysis

We represented the surfaces/shapes by a point distribution model (PDM) (Cootes et al. 1995), and we used partial Procrustes analysis to rigidly align each individual to a common position, thus removing positioning-related variability.

Our framework is similar to the one used by (Zhang et al. 2014), consisting of a dimensionality reduction step followed by a logistic regression (LR) classifier. We used principal component analysis (PCA), and partial least squares (PLS) to build a dimensionality reduction that encoded most of the shape variability that correlated with the athlete label. First, we used PCA to obtain a dimensionality reduction that kept 95% of the shape variability, serving as a denoising step. Then, we used PLS to further reduce the shape space to four modes that maximized covariance with the athlete label. Finally, we used LR to find an optimal separation between athletes and controls in that reduced space, adjusting by BSA, age and gender as covariates. This LR corresponded to a certain shape pattern, the *athletic remodeling,* that subsequently could be quantified for each individual and expressed as a *remodeling score*.

To verify the model's invariance to age and gender, we used the same SSA method as described above to obtain the athletic remodeling shape pattern, after gender stratifying the population, as well as with an age-equalized subpopulation. We computed the Pearson's correlation coefficient between remodeling scores obtained with the restricted datasets and the remodeling scores derived from the full dataset.

## Statistical methods

We tested the difference of scalar variables using the Mann–Whitney *U*-test, and the Chi-square test for categorical variables. We used multivariate regression (MVR) to assess the relationship between the athletic remodeling

score and the scalar measurements, independently of the confounding variables (BSA, gender, and age) that are introduced as covariates in the model. To assess the results of the MVR, we report the $p$ value using the Fisher $F$ test, comparing with a model with only the confounding variables as predictors, and the standardized regression coefficient associated with the remodeling score and the $R^2$ determination coefficient of the model as effect size.

The performance of a logistic model was evaluated using the area under curve (AUC) of the receiver operator characteristic (ROC). We evaluated the models using leave one out cross validation (LOOCV) to split the data in a derivation and validation cohorts without loss of sample size. We compared the SSA model with a simple LR using the confounding variables via a DeLong test (DeLong et al. 1988).

We implemented the analysis in Python 2.7.14 (Enthought Inc, Austin USA), with the following packages: numpy (v1.13.0), scikit-learn (v0.18.1) and scipy (v0.19.0), and RStudio 1.1.423 (RStudio Inc, Boston MA) with package pROC (Robin et al. 2011). We set a threshold of 0.05 to determine statistical significance.

## Results

### Population characteristics

The population demographics are reported in Table 1, and Table 2 shows the comparison of geometric and functional MRI-based measurements between athletes and controls. Athletes had a lower deformation, BSA, and resting HR, which is consistent with chronic exercise, and were 2 years older than controls. Their CO indexed by BSA was maintained. We found an overall increase of the ventricular size. Table S2.1 of the Supplementary Material shows the difference between resting state and after maximal exercise in athletes.

**Table 1** Demographics and echocardiographic functional measurements of the population, in the format of mean (STD)

| | Athletes | Controls | $p$ value |
|---|---|---|---|
| Age [years] | 35.4 (6.1) | 33.4 (3.8) | 0.01 |
| BSA [$m^2$] | 1.78 (0.19) | 1.86 (0.20) | 0.005 |
| Weight [kg] | 66.8 (11.3) | 73.5 (15.1) | 0.001 |
| Height [m] | 1.71 (0.09) | 1.73 (0.08) | 0.15 |
| Women [%] | 42 (48%) | 32 (44%) | 0.94 |
| Training intensity [MET*min/week] | 10,571 (3051) | NA | NA |
| Weekly ex. hours | NA | 1.62 (1.73) | NA |
| $VO_2$ peak [l/min/$m^2$] | 1.63 (0.28) | 1.11 (0.28) | < 0.001 |
| CO [l/min/$m^2$] | 3.4 (0.6) | 3.2 (0.8) | 0.59 |
| LV EF [%] | 60.3 (4.7) | 57.2 (4.6) | 0.03 |
| RV EF [%] | 54.9 (5.6) | 52.1 (5.0) | 0.67 |
| Heart rate [bpm] | 65.5 (10.2) | 54.5 (11.9) | < 0.001 |

*BSA* body surface area, *MET* metabolic equivalent of task, *$VO_2$ max* maximal oxygen uptake, *CO* cardiac output, *LV EF* left ventricular ejection fraction, *RV EF* right ventricular ejection fraction

**Table 2** Comparison of the MRI-based measurements between athletes and controls

| | Athletes | Controls | $p$ value |
|---|---|---|---|
| LV EDV [ml/$m^2$] | 101.7 (17.4) | 82.9 (12.1) | < 0.001 |
| LV mass (3D) [g/$m^2$] | 83.7 (14.0) | 71.7 (11.4) | < 0.001 |
| LV LA [mm/ $m^2$] | 53.9 (4.2) | 49.4 (4.2) | < 0.001 |
| LV OT [mm/ $m^2$] | 14.6 (1.0) | 13.4 (0.9) | < 0.001 |
| RV EDV [ml/$m^2$] | 108.3 (22.6) | 86.4 (15.7) | < 0.001 |
| RV EDA [$cm^2$/$m^2$] | 18.0 (2.6) | 15.7 (2.2) | < 0.001 |
| RV LA [mm/$m^2$] | 51.8(3.8) | 47.2(3.9) | < 0.001 |
| RV basal dimension [mm/$m^2$] | 28.1 (2.5) | 25.8 (2.4) | < 0.001 |
| RV OT [mm/$m^2$] | 16.6 (1.4) | 15.0 (1.1) | < 0.001 |

All measurements were computed from the MRI-derived 3D model

*LV EDV* left ventricular end-diastolic volume, *LV LA* left ventricular long axis, *LV OT* left ventricular outflow tract, *RV EDV* right ventricular end-diastolic volume, *RV EDA* right ventricular end-diastolic area, *RV LA* right ventricular long axis, *RV OT* right ventricular outflow tract

### Athletic shape remodeling

We built a model that captures the differences in 3D shape between athletes and non-athletes using our SSA technique described in the methodology. The model output is a shape pattern that best discriminates between athletes and controls and is, therefore, the remodeling acquired due to the practice of sport. To visualize that remodeling, in Fig. 1, we show the mean shape computed from the controls only, as well as the shape obtained by adding the remodeling with three STD of the found athletic shape pattern, thus representing the shape of an extreme athlete. We computed the local amount of remodeling in mm, which for each point measured the distance between the mean and the extreme shapes and subsequently represented this as a color map. A visual assessment of Fig. 1 shows that, in the RV, the outflow and apical regions presented high remodeling (> 15 mm), with the bigger remodeling affecting a region of the outflow below the valve level (> 20 mm). We found less remodeling in the basal lateral inlet (5–10 mm). In the LV, remodeling was distributed more homogeneously (10–15 mm). Supplementary Material S3 shows a continuous animation of this remodeling. Finally, for each athlete, we quantified how much of this athletic remodeling was present in their individual cardiac shape, to study the relation to acute exercise response. We normalized such score to have 0 mean and 1 STD in the controls.

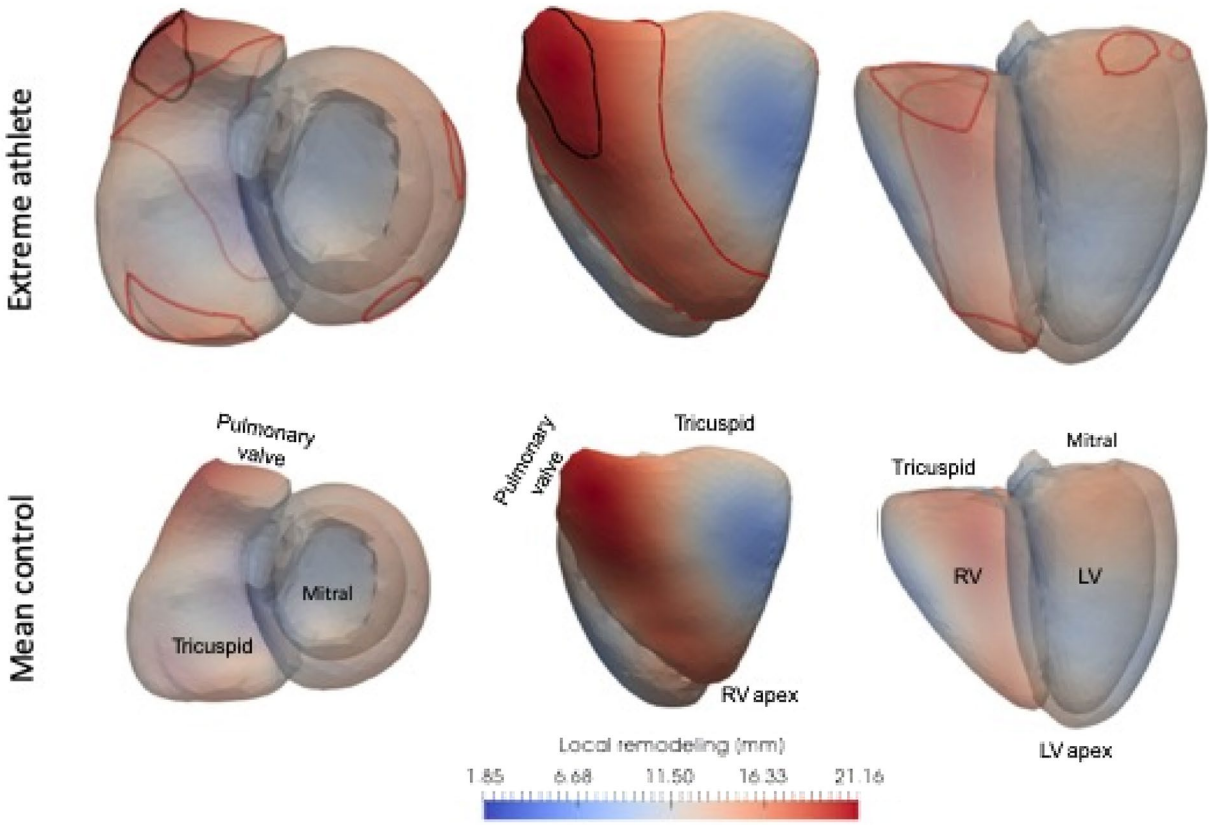


**Fig. 1** Most discriminant shape mode that distinguishes the RV from athletes and controls. The upper row corresponds to a representative extreme athlete (population mean + 3 STD of athletic remodeling), and the lower one to the mean shape of the non-athletes. The three views correspond to: a view of the base from the atria (left), a longitudinal view of the inferior RV and LV walls (center), and a longitudinal view of the LV free wall (center). The red–blue color map indicates the point-wise remodeling distance, in mm. The red contour line in the upper row marks the points that remodel 15 mm, and the black one corresponds to 20 mm. Both ventricles are very different from the controls, but while the LV mostly scale, more regional shape changes occur in the RV, especially in the outflow

Using MVR, we investigated in the athletes how different degrees of athletic shape remodeling corresponded to classical measurements at rest and cardiovascular performance in the stress test. Table 3 shows the regression coefficients of the remodeling score with $p$ values. All models used age, BSA, and gender as covariates.

Shape remodeling was associated with bigger ventricular volumes ($\beta = 15.35$, $p < 0.001$, $\beta = 17.42$, $p < 0.001$ respectively) and LVM ($\beta = 7.78$, $p < 0.01$), showing a similar volume increment for both ventricles. This dilation affected function by leading to a bigger SV ($\beta = 6.46$, $p < 0.001$) and lower HR ($\beta = -3.18$, $p < 0.001$). Both RVOT and LVOT increased ($\beta = 0.97$, $p < 0.001$; $\beta = 0.64$, $p < 0.001$ respectively), with a bigger increase of the RVOT. We found no relationship between shape and neither strain, nor EF nor CO at rest.

While shape and CO at rest were unrelated, peak $VO_2$ had a positive association to shape ($\beta = 78.1$, $p = 0.003$), and lower HR ($\beta = -2.2$, $p = 0.08$): this resulted in athletes with more remodeling having higher $O_2$ pulse ($\beta = 0.6$, $p < 0.001$). A small association between shape and post-exercise RV FW LS was found ($\beta = 0.81$, $p = 0.03$). We found no association with neither acute RV/LV dilation during the maximal stress test nor post-exercise LV strain. We also didn't find any association between shape and exercise length/intensity.

## Validation

We compared the AUC of the shape's model (AUC = 0.91) and that of a LR that only takes confounding variables into account (AUC = 0.71). The improvement due to the inclusion of shape was statistically significant according to the DeLong test ($p < 1e{-}6$). The ROC of both models, as well as another model that uses the confounders and classical measurements (LV EDV, RV EDV, and LVM), can be found in Fig. 2. Supplementary Material S5 shows the full comparison of our shape score and these classical indices.

The gender-stratified models presented a very strong correlation with the pooled model ($\rho = 0.92$ for the

**Table 3** Results of the MVR to check the relationship between shape remodeling score to different functional parameters during exercise

| | Coef | $R^2$ | $p$ value |
|---|---|---|---|
| Rest morphology | | | |
| LV EDV [ml/m$^2$] | 15.35 | 0.76 | < 0.001 |
| LV mass [mg/m$^2$] | 77.78 | 0.72 | < 0.001 |
| LV long axis [mm/m$^2$] | 2.21 | 0.79 | < 0.001 |
| LV OT [mm/m$^2$] | 0.64 | 0.80 | < 0.001 |
| RV EDV [ml/m$^2$] | 17.42 | 0.69 | < 0.001 |
| RV OT [mm/m$^2$] | 0.96 | 0.73 | < 0.001 |
| Rest function | | | |
| HR [beats/min] | − 3.18 | 0.08 | 0.03 |
| SV (LV) [ml/m$^2$] | 6.46 | 0.44 | < 0.001 |
| CO (LV) [l/min/m$^2$] | 0.01 | 0.05 | 0.884 |
| LV EF [%] | − 0.60 | 0.09 | 0.325 |
| RV EF [%] | − 0.01 | 0.11 | 0.988 |
| LV GLS [%] | 0.10 | 0.32 | 0.613 |
| RV FW LS [%] | 0.02 | 0.20 | 0.957 |
| Exercise response | | | |
| Maximal HR | − 2.20 | 0.19 | 0.08 |
| $VO_2$ max [ml/min/m$^2$] | 2.2 | 0.49 | 0.003 |
| $O_2$ pulse [ml/m$^2$] | 0.6 | 0.51 | < 0.001 |
| LV GLS [%] | 0.35 | 0.30 | 0.23 |
| RV LS FW [%] | 0.81 | 0.34 | 0.03 |
| Delta RV EDA [%] | − 0.01 | 0.05 | 0.24 |
| Delta LV EDV [%] | 0.02 | 0.01 | 0.70 |
| Training | | | |
| Training duration [years] | − 1.05 | 0.04 | 0.35 |
| Training intensity [MET*min/week] | 76.11 | 0.34 | 0.78 |

Only athletes are included in this analysis. The $p$ values were obtained by comparing the regression model involving the athletic remodeling score and the confounders with a model that uses only confounders with a Fisher $F$ test

*LV EDV* left ventricular end-diastolic volume, *LV OT* left ventricular outflow tract, *RV EDV* right ventricular end-diastolic volume, *RV OT*: right ventricular outflow tract, *HR* heart rate, *SV* stroke volume, *CO* cardiac output, *LV EF* left ventricular ejection fraction, *RV EF* right ventricular ejection fraction, *LV GLS* left ventricular global longitudinal strain, *RV FW LS* right ventricle free wall longitudinal strain, *$VO_2$* oxygen uptake, *Delta RV EDA* increment of right ventricle end-diastolic area, *Delta LV EDV* increment of left ventricular end- diastolic volume, *MET* metabolic equivalent of task

females-only model, and $\rho = 0.93$ for the males-only model). While we observed no gender differences in the most discriminative shape pattern, men presented a higher quantity of remodeling than women. The full experiments for the gender-stratified models can be found in the Supplementary Material S6. The age-equalized model presented an almost perfect with the pooled model ($\rho = 0.98$). The full results regarding age can be found in the Supplementary Material S7.

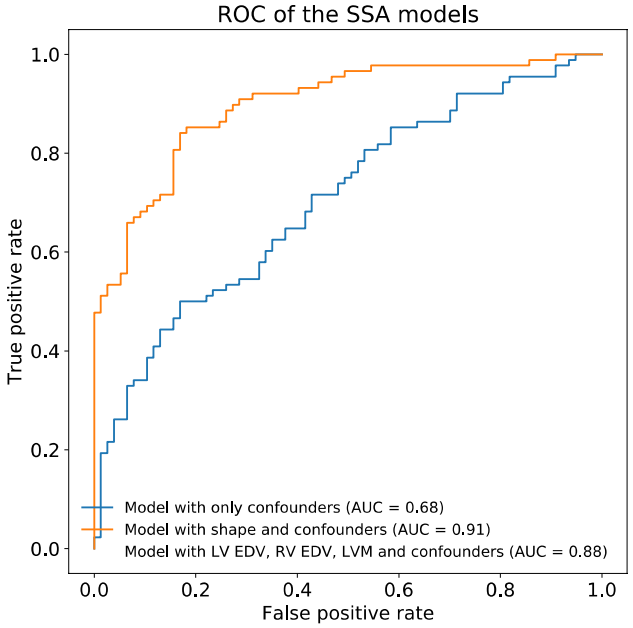


**Fig. 2** LOO-CV ROC of the triathlete-predictive model which considers shape and confounders (orange), compared to a simple model that only considers the confounders (blue) and another model that uses confounders and classical measurements (green)

## Discussion

Complementary to the well-known differences in size and mass, we found strongly significant statistical differences in resting ventricular regional shape between triathletes and controls. The relationship of this remodeling with exercise performance was found to be positive, as measured by $VO_2$ uptake and RV FW LS immediately after exercise. We found a negative association with maximal and resting HR and no association with baseline CO nor strain.

As analyzed using MVR, the identified remodeling consisted of a bi-ventricular dilation and increase of LV mass, coinciding with previous knowledge. The ventricular dilation is an adaptation to increase the stroke volume, and the higher mass helps to maintain wall stress limited when the pressure increases during exercise. The visual inspection of the shape remodeling allowed to see that the RV presents a more complex remodeling as compared to the LV: while both ventricles increase their volume, the LV increase is homogeneous distributed while the RV remodeling is more prominent in the outflow. RV shape becomes more elongated in the inlet, and there is a shift of volume from inlet to outflow, that is dilated and more curved. In conclusion, the RV remodeling corresponds more to a change in shape rather than in size, while the LV mostly dilates homogenously. The usage of SSA allows the analysis of complex structures: this is the first time that the dilatation of the outflow has been described to be more

prominent than the inflow. Since the most affected region is not in the valve annulus but below it, this remodeling cannot be easily assessed via classical measurements and, therefore, have remained unnoticed by previous authors. Moreover, previous work was mostly based on echocardiography, which offers a noisy and limited view on the RVOT.

The different behavior of the RV and LV can be explained from its intrinsic different morphological characteristics, as well as the changes in loading conditions induced by endurance exercise. The RV is more compliant and elastic than the LV since LV cavity has not been observed to increase acutely in size during extended submaximal endurance exercise, while RV size can increase up to 10% during moderate exercise (Claesen et al. 2014). Thus, the RV can change shape acutely. The pulmonary artery and aorta also have very different behavior and characteristics with the pulmonary artery being more compliant than the aorta (Slife et al. 1990; Marcus et al. 1994). Additionally, the pressure increases proportionally more in the pulmonary artery during exercise, which translates to RV loading (Kovacs et al. 2009; La Gerche et al. 2017). This is consistent with the observed remodeling in the RV outflow. Another contributing factor, which could not be assessed using the currently available data, might be the induced hypertrophy in the trabeculated RV apex, thus effectively reducing the potential apical stroke volume and forcing the base to remodel accordingly.

Our data show that athletic remodeling at rest has a clear relationship with exercise response: triathletes with more remodeling can reach bigger $VO_2$ max and $O_2$ pulse. Via Fick's Principle, $O_2$ uptake can be used to obtain an estimate of the CO during exercise, even when the pulmonary extraction ratio (PER) is not known (Stringer et al. 1997). In La Gerche et al. (2010), La Gerche et al. reported that the PER interindividual variability was independent of physical training, so we can conclude that the differences in $VO_2$ max and $O_2$ pulse were due to differences in CO and SV respectively. Since we found no correlation of athletic remodeling and acute changes of ventricular geometry during exercise, we suggest that the higher SV might be caused by increased deformation during exercise, explained by the association between athletic remodeling and RV FW LS after exercise.

The long-term consequences of this remodeling are unknown, as follow-up is not available. Even if the found remodeling contains a dilatation of the outflow that overlaps with ARVC symptoms, remodeling seems positive, given that it is correlated with a better cardiovascular response. We think that a moderate dilatation of the outflow with a lower dilatation of the inflow is not per-se a sign of mal-adaptation if the exercise function is not impaired.

## Limitations

The SA MRI images had lower quality in the apical part due to the low resolution in the axial direction, and the presence of trabeculations making distinguishing between cavity and myocardium difficult. Therefore, while standard practice, using only MRI SA to construct the 3D model is not ideal to evaluate the apical region and apical differences between the populations might have stayed undetected due to this. Additionally, we did not manually correct the automatic segmentations contours in the images, to better maintain the point-to-point correspondence. We treated these segmentation errors as measurement error in the analysis. Finally, the atria were not included in the image and, therefore, we could not evaluate them using SSA.

The echocardiographic assessment was done pre- and post-exercise. Given the rapid recovery of athletes, moving them quickly from the exercise bike to the scanning table can affect the post-exercise analysis. While both ventricles need to increase their CO during exercise, we were only able to find post-exercise functional differences in the RV. The RV has been reported to experience more acute remodeling to exercise and suffer more ventricular fatigue. Assessing shape during exercise would allow to better understand the acute changes occurring during exercise and characterize the relationship between athletic shape remodelling and cardiovascular response to exercise.

Exercise doses were self-reported, and the population consisted only of high-intensity athletes. Therefore, our population is not well aimed to assess the relationship between exercise level and remodeling.

As stated, there is no follow-up data to confirm the positive effect of this remodeling. It must be studied if this remodeling, that dilates the RV outflow, has any relationship with ARVC outflow in the long term.

## Conclusion

This paper uses SSA to identify chronic resting regional shape remodeling induced by endurance sport in both ventricles, acquired via MRI. This remodeling consists of an LV increase in size and myocardial mass, and a shape change in the RV: a shift of the volume distribution from the inlet towards the outflow. Since RV remodeling is concentrated in the outflow, it adds more evidence to the importance of the pulmonary circulation in athletes. After quantifying the remodeling in all athletes, we found that during acute exercise, it is associated to maximal $O_2$ consumption, $O_2$ pulse and, weakly, to the post-exercise RV FW LS: athletes with more athletic remodeling showed better cardiovascular exercise performance.

As future work, SSA could be used to find regional shape differences induced by pathological remodeling (hypertrophic cardiomyopathies, ARVC) that might have an overlapping remodeling with the athlete's heart, and where current clinical measurements are not well discriminating.

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**Author contributions** ASM, MRL, and FC acquired and measured the echocardiography and MRI controls data. MSDG acquired and analyzed the echo data for the athletes. MSDG, FB, and IB acquired and analyzed the stress test. BDX, SPG, and RJP acquired and analyzed the MRI data. The SSA was done by GB, MAGB, CB, and MDC. All authors participated in the data interpretation, reading, and approval the final manuscript.

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## Compliance with ethical standards

**Conflicts of interest** GB and MDC were working for Philips at the time of the work.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Comité ético de investigación clínica del Hospital Clínic de Barcelona) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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