

Rationale and design of the PROspective ATHletic Heart (Pro@Heart) study: long-term assessment of the determinants of cardiac remodelling and its clinical consequences in endurance athletes

Ruben De Bosscher ^{1,2}, Christophe Dausin,³ Kristel Janssens,⁴ Jan Bogaert,⁵ Adrian Elliott,^{6,7} Olivier Ghekiere,^{8,9} Caroline M Van De Heyning,^{10,11} Prashanthan Sanders,^{6,7} Jonathan Kalman,¹² Diane Fatkin,¹³ Lieven Herbots,^{8,9} Rik Willems,^{1,2} Hein Heidbuchel,^{14,15} André La Gerche,¹⁶ Guido Claessen,^{1,2} on behalf of the Pro@Heart Consortium

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For numbered affiliations see end of article.

Correspondence to

Dr Ruben De Bosscher; ruben.debosscher@uzleuven.be

ABSTRACT

Background Exercise-induced cardiac remodelling (EICR) results from the structural, functional and electrical adaptations to exercise. Despite similar sports participation, EICR varies and some athletes develop phenotypic features that overlap with cardiomyopathies. Training load and genotype may explain some of the variation; however, exercise ‘dose’ has lacked rigorous quantification. Few have investigated the association between EICR and genotype.

Objectives (1) To identify the impact of training load and genotype on the variance of EICR in elite endurance athletes and (2) determine how EICR and its determinants are associated with physical performance, health benefits and cardiac pathology.

Methods The Pro@Heart study is a multicentre prospective cohort trial. Three hundred elite endurance athletes aged 14–23 years will have comprehensive cardiovascular phenotyping using echocardiography, cardiac MRI, 12-lead ECG, exercise-ECG and 24-hour-Holter monitoring. Genotype will be determined using a custom cardiomyopathy gene panel and high-density single-nucleotide polymorphism arrays. Follow-up will include online tracking of training load. Cardiac phenotyping will be repeated at 2, 5, 10 and 20 years.

Results The primary endpoint of the Pro@Heart study is the association of EICR with both training load and genotype. The latter will include rare variants in cardiomyopathy-associated genes and polygenic risk scores for cardiovascular traits. Secondary endpoints are the incidence of atrial and ventricular arrhythmias, physical performance and health benefits and their association with training load and genotype.

Conclusion The Pro@Heart study is the first long-term cohort study to assess the impact of training load and genotype on EICR.

Trial registration number NCT05164328; ACTRN12618000716268.

INTRODUCTION

‘Exercise-induced cardiac remodelling’ (EICR) comprehends the structural,

Key messages

What is already known on this topic

- ▶ There is a large unexplained variability in the extent of exercise-induced cardiac remodelling among highly trained endurance athletes.
- ▶ Endurance athletes may present with structural, functional and electric features that overlap with cardiomyopathies.
- ▶ Endurance athletes have an increased risk of developing atrial fibrillation.

What this study adds

- ▶ Insights on the impact of training load and genotype on the variability of exercise induced cardiac remodelling and its prognostic impact.
- ▶ A new gold standard for training load quantification in the field of sports cardiology.
- ▶ Knowledge on the phenotypic features that predispose endurance athletes to a higher physical performance and more health benefits; but also to cardiac disease and arrhythmias such as atrial fibrillation.

How this study might affect research, practice or policy

- ▶ Stimulate other long-term prospective collaborative trials in the field of sports cardiology that combine comprehensive cardiovascular phenotyping, training load quantification and genotyping.
- ▶ Provide a better understanding of the normal spectrum and variability of the athlete’s heart for clinicians.
- ▶ Aid clinical practice in identifying athletes at risk of cardiac disease and arrhythmias.

functional and electrical adaptations of the heart in response to the metabolic and mechanical demands of exercise.¹ Although cross-sectional and some short-term prospective studies have enhanced our understanding

of EICR, numerous questions concerning the spectrum, determinants and the prognosis of EICR remain unanswered.

The determinants of EICR

Training load

Athletes participating in highly dynamic and static sports (eg, cycling and rowing), accomplishing more training hours per week and performing at the highest level have the largest hearts.^{2,3} However, not all athletes engaging in the same sport and competing at a similar level remodel equally. In a group of 174 non-elite male runners for example, 16% had concentric left ventricular (LV) remodelling, 11% had non-dilated concentric LV hypertrophy (LVH), 4% had non-dilated eccentric LVH, 9% had dilated eccentric LVH and the remaining 60% had normal LV geometry.⁴ A 2004 study by Abergel *et al* showed a wide scatter of LV internal diameter at end-diastole, maximal wall thickness and LV ejection fraction (LVEF) in professional cyclists before participating in the 1995 and 1998 Tour de France with 11% having a reduced LVEF $\leq 52\%$, 51.4% having a dilated LV of $>62\text{mm}$ and 8.7% having a LV wall thickness of $>13\text{mm}$.⁵

Subtle differences in training load may at least partially explain some of the variability. In well-conducted longitudinal trials with supervised exercise programmes, endurance training in sedentary individuals increased biventricular volumes and mass.⁶⁻⁸ In seasoned athletes, intensification of training induced significant cardiac structural adaptations, suggesting that acute changes in training regimens significantly influence cardiac structure beyond the already present remodelling from extensive long-term training load.⁹⁻¹² The evidence of training load as a determinant of EICR also extends towards cardiac pathology. More days and hours per week or the cumulative lifetime distance, hours or years of training, have been associated with atrial fibrillation (AF), myocardial fibrosis and exercise-induced arrhythmogenic right ventricular cardiomyopathy (ARVC) in athletes.¹³⁻¹⁸

Although the importance of training load on EICR is evident, the field of sports cardiology has only scratched the surface of this association. In contrast to the accurate and extensive evaluation of EICR, training load has been poorly defined and has mostly relied on the history of training hours, distances and amount of completed races gathered through screening questionnaires that are prone to inaccuracy and fail to quantify the internal training load. Training load encompasses multiple variable such as type, frequency, intensity and duration of exercise which can be brought back to two measurable components: external and internal loads. External loads are objective measures of the athlete's work during exercise (eg, time, distance, altitude, speed and power). By contrast, internal loads represent the athlete's physiological and psychological responses to the imposed external loads (eg, heart rate, blood pressure, serum lactate levels). Over recent decades, wearables have become omnipresent in athletes

and record a wealth of data including time, distance, speed, power output and heart rate during exercise. With an electronic training diary linked to the athlete's heart monitoring and sports GPS device, external and internal training loads from every single training session can be exported and expressed across multiple time domains (eg, per week, month, years).

Genotype

Where training load fails to explain the variability in cardiac structure and function between athletes, genetics may provide insights.

Genetic make-up plays an essential role in cardiac structure and function. The most notable impact of genetics on cardiac morphology is in cardiomyopathies such as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM) and ARVC. These are typically caused by single rare variants in genes that encode cardiomyocyte components such as sarcomere and desmosomal proteins.¹⁹ However, the genetic heterogeneity, pleiotropy, variable penetrance and the variable impact environmental factors result in an important phenotypic variability.

Exercise-induced ARVC serves as a prime example. Our research group has contributed to the recognition of exercise-induced ARVC, characterised by a combination of potentially life-threatening ventricular arrhythmias originating from a dilated and mildly dysfunctional right ventricle (RV) at rest or during exercise.²⁰⁻²³ Genetic testing in these athletes revealed a lower than expected prevalence of desmosomal gene mutations, thereby implying a significant contribution of intense exercise to the resulting phenotype.²⁴ Furthermore, in patients labelled with 'gene-elusive' ARVC a higher prevalence of athletes and more intense exercise history was reported.²⁵ The terms 'exercise-induced' and 'gene-elusive' ARVC may be considered synonyms, with the former Australian/Belgian terminology emphasising the common feature of high doses of intense endurance exercise and the latter Baltimore terminology emphasising the observation that genetic mutations are seldom identified. As not all endurance athletes develop exercise-induced/gene-elusive ARVC, a solely exercise-induced ARVC is disputed. It remains to be investigated which factors, including genotype, predispose certain athletes towards a phenotypic expression of ARVC when exposed to exercise. The gene-exercise relation is already evidenced by the exacerbated disease progression in genotype positive ARVC due to the mechanical stress of exercise.^{26,27} Interactions between mechanical stress and genetic susceptibility have also been reported for peripartum cardiomyopathy. Although assumed an acquired disorder, recent data have shown an increased prevalence of rare cardiomyopathy gene variants, including truncating TTN variants (TTNtv), in women with peripartum cardiomyopathy compared with a reference population.²⁸ Further, studies in a zebrafish TTNtv model have shown reduced tolerance of mechanical stress in titin-deficient hearts.²⁹ Aside from rare gene

variants, the potential role of more common variants should be emphasised. As an example, common polymorphisms associated with cardiac structure and function have been linked to incident DCM in the general population and may influence the phenotype among carriers of TTN truncating variants.³⁰

Genetics also play an essential role in the onset of arrhythmias. There is growing evidence on the role of a genetic predisposition in the onset of AF. Research in cases of early-onset AF and families with AF has identified numerous variants in genes coding for ion channels, transcription factors and myocardial structure, which could be a primary cause of AF, regardless of exercise.³¹ Genome-wide associations studies in large populations with AF and controls have identified >100 chromosomal loci associated with AF in which common variants are present. As the prevalence of AF in athletes exceeds that of the general population, the interaction between genetics and environmental factors (eg, exercise) is thought to play a crucial role in phenotypic expression. Of particular interest are the genes encoding for mechanical stress-sensitive cardiac ion channels in which stimuli such as hypertension or endurance exercise alter channel activity. The KCNQ1 gene for example encodes for the cardiac I_{Ks} channel and a missense mutation was detected in a family with hypertension, atrial dilation and atrial fibrillation.³² Other mechanical stress-sensitive ion channels include two-pore domain K⁺ channels (eg, TREK1, TREK2, TRAAK), transient receptor potential channels (eg, TRPM4, TRPC3, TRPC6) and the Piezo1 channel.³³

Sex

Besides training load and genetics, cross-sectional studies suggest sex-differences in the type and extent of EICR. Absolute measures of LV and RV dimensions and mass are smaller in females, but when corrected for body surface some echocardiographic studies have reported larger indexed end-diastolic diameters in female athletes than in males.^{34 35} A recent study using cardiac MR (CMR) showed lower indexed LV and RV volumes in adolescent and adult female athletes with a higher tendency towards eccentric remodelling as evaluated by volume to mass ratios.³⁶ Functionally, while no sex-differences were noted for LVEF and RVEF in adolescent athletes, RVEF was lower in adult males compared females. The latter could suggest that RV function remains stable from adolescence to adulthood in females but decreases in males. Using deformation imaging, LV and RV global longitudinal strain was higher at rest and increased more during exercise in female athletes compared with males, thus further supporting a potential higher susceptibility towards RV dysfunction in male athletes.³⁷ Whether the sex-differences in EICR contribute to the reduced arrhythmogenic risk in female athletes remains unclear.^{20 21 24}

Ethnicity

As ethnic diversity in sports has grown over the years so has the relevance and understanding of the role of ethnic background on EICR. While ventricular dilation is common in white athletes with 14% having an LV diameter of >60 mm on transthoracic echocardiography, significant hypertrophy such as an LV wall thickness of >12 mm is uncommon.^{38–40} In black athletes the degree of ventricular dilation is similar to white athletes whereas an increased LVWT >12 mm is more frequent and seen in up to 12% of black athletes.^{41–43} Black athletes generally present with a higher systolic blood pressure at rest and during exercise which could explain the higher prevalence of LVH.⁴⁴ Additionally LV hypertrabeculation is more frequent in black athletes than in white athletes.⁴⁵ These differences in structural remodelling between white and black athletes is also illustrated on the ECG with anterior T-wave inversions being more common in black athletes and considered a normal ethnic variant.⁴⁶ With regard to East Asian athletes a slight distinction can be made between Chinese and Japanese athletes. The former have shown similar cardiac dimensions as compared with white athletes whereas the latter have greater LV end diastolic dimensions.^{47–50} In Arab athletes, in comparison to white and black athletes, smaller cardiac dimensions have been measured with a similar degree of LVH as white athletes.⁵¹ Finally in Pacific Islanders a higher LV mass was seen when compared with white athletes.⁵² Whether differences in cardiac remodelling between ethnic population is based on differences in genotype, training load or other factors remains to be explored.

The prognosis of EICR

Despite the many health benefits of endurance exercise, athletes are not granted immunity from cardiovascular disease.

Atrial fibrillation

Atrial fibrillation is the most common arrhythmia and has a U-shaped dose–response relationship with endurance exercise. On the one hand, low to moderate intensity exercise has been associated with a decreased risk of AF.^{53 54} On the other hand, a higher incidence of AF was seen when endurance exercise was performed more frequently (ie, >4/week) and longer (ie, >5 hours/week) or when a lifetime exercise history of >2000 hours was met.^{13–15} A 2009 meta-analysis calculated that endurance athletes are 5.3 times more likely to develop AF than controls.^{55 56} Part of the propensity for AF in high-level endurance athletes is thought to arise from the structural and functional atrial adaptations. A recent study by Trivedi *et al* investigated the differences in atrial structural and functional properties between healthy non-athletes, non-athletes with paroxysmal AF, healthy endurance athletes and athletes with paroxysmal AF. Diastolic dysfunction, LA dilation and reduced LA strain characterised non-athletes with AF whereas athletes, regardless of AF, had a normal diastolic function, increased LA volumes and



decreased LA strain. However, athletes with AF had lower LA emptying fraction and LA expansion index, which are suggestive of atrial cardiomyopathy.⁵⁷ This study highlights the difficulties in distinguishing the healthy athlete's dilated atrium for one that is predisposed to AF.

Ventricular arrhythmias and sudden cardiac death

Sudden cardiac death (SCD) is an uncommon event in athletes and occurs primarily through ventricular arrhythmias. The incidence of SCD ranges between 0.4 and 8.4 per 100 000 athlete-years.⁵⁸ ARVC and other inherited cardiomyopathies such as HCM and DCM can be highly arrhythmogenic and are among the most common causes of SCD in young athletes.^{59 60} A particular challenge in sports cardiology is the overlapping phenotype of EICR and these cardiomyopathies. Although research has granted clinicians strategies to distinguish disease from physiological adaptation a better understanding of the extent and mechanisms of EICR is required.^{23 61–65}

Another putative risk factor associated with SCD in athletes is myocardial fibrosis.⁶⁰ Reports on myocardial scarring in athletes are heterogeneous regarding prevalence, location, extent, aetiology and clinical significance. Coronary artery disease (CAD)-patterns and non-CAD subepicardial/midmyocardial fibrosis have been associated with potentially life threatening arrhythmias such as non-sustained ventricular tachycardia but also ventricular tachycardia leading to sudden death or an appropriate shock by an implanted defibrillator.^{66 67} In contrast, hinge point fibrosis associated with cumulative exercise exposure, such as years of training and the lifetime number of races and race distances is considered a benign consequence of RV overload.^{16–18}

The majority of SCD in athletes are classified as sudden unexplained deaths in which the role of plain EICR as potential triggers and/or substrates of arrhythmias is unknown.^{59 60}

Physical performance and health benefits

Despite the increased risk of arrhythmias in some highly trained individuals, there is no denying the numerous health benefits associated with endurance exercise in the general population. Endurance exercise is associated with a lower prevalence and better control of cardiovascular risk factors such as arterial hypertension, dyslipidaemia, obesity and diabetes mellitus.^{68–71} Increased longevity is the strongest health outcome associated with exercise. Regular physical exercise at low to moderate intensity, even in small doses, reduces all-cause and cardiovascular mortality.^{72 73} These findings can be extended to higher levels of exercise with Olympic athletes demonstrating an increased life expectancy of up to 6.5 years compared with the general population.^{74–78} Research in Tour de France participants from 1947 until 2012 has similarly reported a 41% lower mortality rate in cyclists for both malignancies and cardiovascular causes.⁷⁹ However, the cited research is limited by its retrospective design and focus on elite athletes who on average were over 20 years

old thereby being potentially affected by the 'survival of the fittest' selection bias.

The time required to cover a given distance defines physical performance of an endurance athlete. Physiologically, the latter can be brought back to the velocity and power generated by the athlete, with VO_2max being one of the major determinants. Elite endurance athletes have the highest VO_2max , with values of more than 70 and up to 85 mL/kg/min, equalling 150%–200% of the VO_2max seen in healthy active young individuals.⁸⁰ Alongside capillary density and mitochondrial density, the high levels of VO_2max have also been attributed to EICR such as increased cardiac size and stroke volume.⁸¹ For the elite athlete, the ultimate measure of physical performance is the level of competitiveness, the number of finals reached and Olympic Games participated in, or the amount of victories, trophies and medals obtained. It is unknown whether and/or which features of EICR, including pathology such as AF and myocardial fibrosis, affect VO_2max and physical performance. How much do alterations in training regimen explain differences in physical performance? To which extent does genotype play a role in predetermining gold medallists and Olympic champions? Finally, looking at both genotype and phenotype the question raises whether you can out-train unfavourable genetics?

In conclusion, much of the variability, determinants and the outcome of EICR has yet to be determined. Prospective long-term studies that investigate EICR in large cohorts of athletes are needed to improve knowledge in these areas of sports cardiology. The Pro@Heart study is a multicentre prospective cohort trial designed to assess and follow-up all aspects of EICR in young competitive endurance athletes. The interplay between training load and genotype will be investigated and insights on the long-term outcome of EICR will be gained.

THE PRO@HEART STUDY

Trial design

The Pro@Heart (Prospective Athlete's Heart) study is an international multicentre prospective cohort trial with collaborators in Australia (Baker Heart and Diabetes Institute Melbourne, St Vincent's Hospital Melbourne, University of Adelaide, Royal Adelaide Hospital, Royal Melbourne Hospital and Victor Chang Cardiac Research Institute) and Belgium (University Hospitals Leuven, University Hospital Antwerp and Jessa Hospital Hasselt). (ClinicalTrials.gov Registry Identifier NCT05164328—Australia New Zealand Clinical Trials Registry Identifier ACTRN12618000716268).

Objectives and hypothesis

The primary objective of the Pro@Heart study is to investigate the impact of training load (ie, accurately evaluated in term of type, frequency, duration and intensity) and genotype on the variability of structural, functional and electrical EICR in young competitive endurance athletes. The second objective is to determine how EICR,

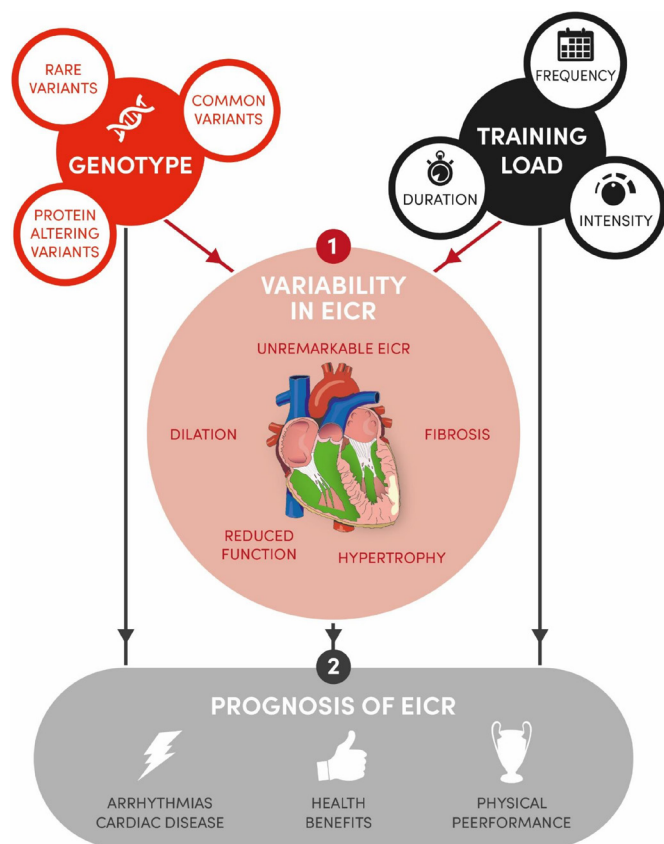


Figure 1 Study hypothesis of the Pro@Heart study. The first hypothesis is that genotype and training load are two major determinants in the variability of EICR. The second hypothesis is that cardiac disease and arrhythmias but also health benefits and physical performance are associated to specific (preclinical) phenotypes of EICR, training load and genotype. EICR, exercise-induced cardiac remodelling.

training load and genotype are associated with physical performance, health benefits and cardiac pathology (eg, exercise-related cardiomyopathies and arrhythmias) during follow-up over several decades.

The hypotheses are that: (1) Genetic factors contribute to variability in EICR beyond training load and, (2) Athletes with extreme EICR have a higher risk of arrhythmias. The study hypotheses are illustrated in [figure 1](#).

Study population and eligibility criteria

Athletes aged 14–23 years are recruited from elite endurance sports programmes and organisations including Cycling Vlaanderen, Triatlon Vlaanderen, Belgian Cycling, Cycling Australia, Rowing Australia and Athletics Australia and from sports performance centres including Nottebohm Antwerpen, Bakala Academy Leuven and Adlon Hasselt. Volunteers have also been recruited by means of ‘word of mouth’ and social media campaigns within elite endurance sporting circles. Non-athletes consist of age and gender matched university and college students recruited from Australian and Belgian universities in addition to social media campaigns. Subjects will be included based on the eligibility criteria listed in

Box 1 Eligibility Criteria for the Pro@Heart study

Inclusion criteria

1. Males and females aged 14–23 years old.
2. Athletes competing in endurance sports at national or international level for at least 2 years. Sports include:
 - Triathlon.
 - Cycling.
 - Distance running (≥ 1500 m).
 - Rowing.
 - Swimming (≥ 400 m).
 - Cross-country skiing (including biathlon and Nordic combined).
3. Non-athletes engaged in < 3 hours per week of physical activity.

Exclusion criteria

1. Medical history of cardiovascular disease.
2. Current smoker of past history of smoking.
3. Diabetes mellitus.

Eligibility criteria for the Pro@Heart study including both inclusion and exclusion criteria.

box 1. Informed consent will be obtained from the participants or their legal guardian.

A young age at inclusion will ensure a baseline evaluation at the beginning of the athlete’s career, at a time point of relative low cumulative training load. Moreover, it will allow close follow-up of the evolution of EICR over years, in correlation with training load, genotype, cardiovascular disease and athletic performance. The age range of 14–23 years was considered the best compromise between enrolling athletes with relatively low cumulative training load and sufficient commitment to high-level endurance training, minimising the risk of dropout.

To ensure a high level of athleticism, individuals must be competing at a national or international level for at least 2 years in a sport with a high dynamic and moderate-high static training components performed for sustained periods. Hence triathlon, cycling, distance running of 1500 m or more, rowing, swimming of 400 m or more and cross-country skiing (which includes biathlon and Nordic combined) were sports eligible for inclusion. The distances for running and swimming were selected based on the characteristic parabolic pacing profile of endurance exercise (ie, a fast-paced start, a slower and stable-paced middle section and finally a sprint).^{82 83} As cardiac volumes are similar between sedentary individuals and subjects exercising < 3 hours per week, a cut-off of < 3 hours per week of physical activity defined non-athletes.⁸⁴

Study procedures

Baseline evaluation includes medical history, review of medication and supplements, physical examination with blood pressure measurement on both arms and blood samples for biochemistry and DNA isolation. Genetic variants will be identified using a custom cardiomyopathy gene panel and the Axiom Precision Medicine Diversity Array (Thermo Fisher Scientific, Waltham, Massachusetts, USA). Rare variants will be assessed using the American

College of Medical Genetics and Genomics pathogenicity criteria.⁸⁵ Polygenic risk scores for various traits will be derived from suites of common variants. A resting 12-lead ECG will be recorded and interpreted in accordance with international recommendations.⁸⁶ Two-dimensional and three-dimensional transthoracic echocardiograms (TTE) and CMR with the administration of gadolinium as a contrast agent including native and postcontrast T1 mapping and will be performed at rest to assess ventricular systolic and diastolic function, atrial function, extracellular volume and myocardial tissue characterisation (ie, myocardial fibrosis). Cardiopulmonary exercise testing for maximal oxygen consumption measurement (VO₂max) including 12-lead ECG recording will evaluate athletic performance and exercise-related repolarisation abnormalities and arrhythmias. Dual-energy x-ray absorptiometry will assess body composition. Twenty-four-hour Holter monitoring will determine heart rate limits and the prevalence of arrhythmias. In addition to resting cardiac imaging, all recruits will also undergo exercise imaging to evaluate contractile reserve, using either two-dimensional TTE or CMR.

Follow-up will include annual telephone communication enquiring about clinical events as well as continuous monitoring of training load using an electronic training diary. The duration, distance, altitude, speed, power output and heart rate during training sessions recorded by sports GPS trackers will be exported to a big data platform. Measured external and internal training loads will be combined into a single parameter quantifying training load as a composite of duration and intensity, such as the Bannister training impulse (TRIMP) and derivatives.^{87–89} The permission to track all sports activities using a central coach profile will be asked to the athlete or their legal guardian. All exported raw data will be pseudonymised in accordance with current general data protection regulation guidelines.

The study flow chart is presented in figure 2. A detailed overview of study procedures is provided in online supplemental appendix.

Endpoints

The primary endpoint of the Pro@Heart study is the association of EICR (eg, ventricular hypertrophy, dilation, reduced function and/or myocardial fibrosis) with both training load, quantified as a combination of duration and intensity, and genotype such as the prevalence of rare and common variants in cardiomyopathy-associated genes and polygenic risk scores. Secondary endpoints are (1) the long-term incidence of arrhythmias such as AF and atrial flutter as well as ventricular ectopic beats, non-sustained and sustained ventricular tachycardia, (2) the physical performance (eg, VO₂max and race results) and (3) the health benefits (eg, longevity, cardiovascular risk factors) and their association with the different phenotypes of EICR, training load and genotype.

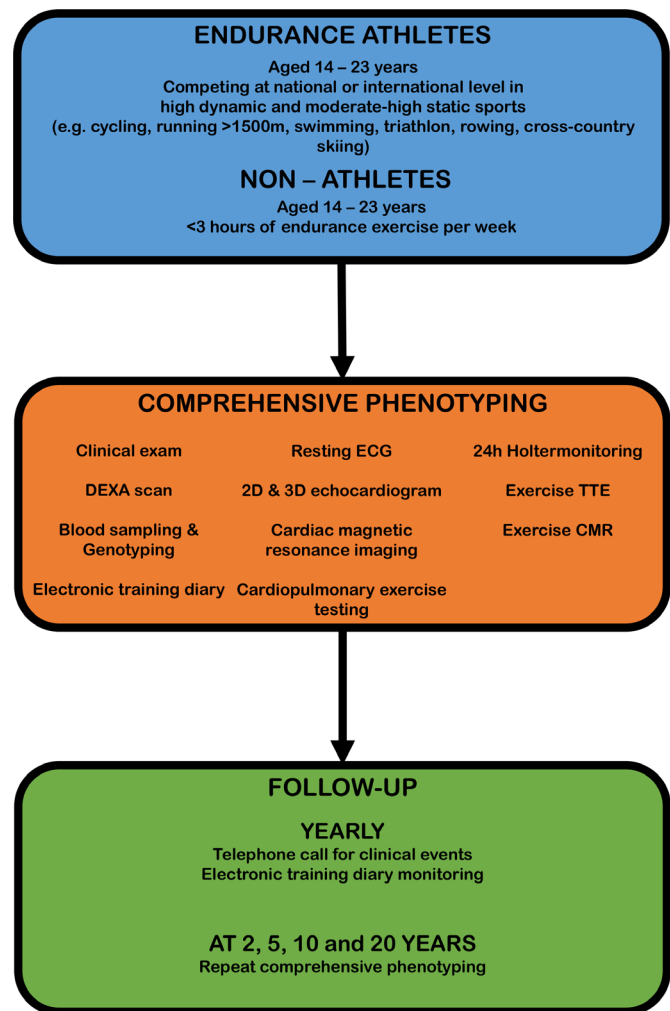


Figure 2 Design and flow chart of the Pro@Heart study. Endurance athletes are recruited from state and national sports programs from the age of 14 to 23 years. Baseline evaluation includes a clinical exam and intake of medical history, medication, supplements and exercise history, quantification of current training load through an electronic training diary, blood sampling, DEXA, resting 12-lead ECG, two- and three-dimensional resting TTE, cardiopulmonary exercise testing including 12-lead exercise ECG and maximal oxygen consumption measurement, CMR imaging at rest and during exercise and a 24-hour Holter monitoring. Follow-up consists of repeated testing at 2, 5, 10 and 20 years. CMR, cardiac magnetic resonance; DEXA, dual-energy x-ray absorptiometry; ECG, electrocardiogram; TTE, transthoracic echocardiograms.

STATISTICAL CONSIDERATIONS

Sample size and power calculations

The study is powered for primary and secondary objectives.

Regarding the primary objectives, using an average indexed LV end-diastolic volume of 113±19mL/m² from preliminary data and considering that 43% of the variance in LVEDV can be explained by all single-nucleotide polymorphisms (SNP) on a genotyping array, a population of 220 athletes would render a statistical power over >90%.³⁰ Likewise, using an average indexed right ventricular

end-diastolic volume of 125 ± 22 mL/m² and considering the same variance in RVEDV to be explained by all SNPs on a genotyping array, a population of 220 athletes would give a statistical power of >90%.

For the secondary objective of AF, based on the 2009 meta-analysis by Abdulla and Nielsen reporting a prevalence of AF of 23% in 655 athletes and 12.5% in 895 non-athletes aged 51 ± 9 years, a sample size of 300 endurance athletes and 150 non-athletic controls would provide 80% power and 5% probability of a type I error in detecting a difference in AF prevalence between athletes and non-athletes during long-term follow-up.⁵⁵

Statistical analysis

Groups will be defined based on the types of EICR being investigated. Differences between baseline and follow-up will be compared using either a related-samples Wilcoxon signed rank test or a paired-samples t-test. Independent samples will be compared using either a Mann-Whitney U test or an independent-samples t-test as appropriate. Categorical data will be compared using a Related-Samples McNemar test. In case of three or more groups being defined repeated-measures ANOVA or a Friedman test will be used to analyse the continuous outcomes. Cochran Q test will be used for dichotomous outcomes. The risk of type I errors due to multiple comparison will be assessed and corrections using the Bonferroni method or Benjamini-Hochberg procedure will be considered. Multiple linear, non-linear and logistic regression analysis will be used to determine the association between cardiac remodelling (including adverse remodelling), the presence of potential pathological variants in cardiomyopathy associated genes and training load. Differences between gender and ethnicities will be addressed either by subgroup analyses comparing athletes with different gender and ethnicity or by incorporating gender and ethnicity as an independent variable in multivariate analyses. Cumulative event rates will be calculated and presented using Kaplan-Meier time-to-event curves.

TRIAL STATUS

The Pro@Heart trial has been approved by the ethical committees of the University Hospitals Leuven, University Hospitals Antwerp, Jessa Ziekenhuis Hasselt and Baker Heart and Diabetes Institute. The first subject gave informed consent and took part in the trial on 23 June 2015. To date, over 220 athletes have been included, more than 70 athletes have had their 2-year follow-up appointment and the 5-year follow-up visits are being scheduled. Inclusions are ongoing. Trial results will be communicated through publications. Published articles will be available to the community on www.proatheart.be.

CONCLUSION

Cross-sectional and short-term longitudinal trials have offered a better understanding of EICR and exposed the large variability in clinical phenotypes, including cardiovascular pathology but also the health and performance

benefits. However, few studies have investigated the potential determinants and the long-term prognosis of EICR in a prospective manner. While training load may explain some of this variability, to date, the quantification of training load has primarily been reliant on subjective recall. The role of genotype in cardiomyopathies and certain cardiac arrhythmias is clear but its importance in EICR and arrhythmias in athletes remain to be investigated.

The Pro@Heart study is a multicentre prospective cohort study that will combine comprehensive phenotyping with long-term follow-up to provide new insights on the spectrum and variability of EICR as well as how training load and genetics determine cardiac structure, functional and electrical properties, including arrhythmias in endurance athletes.

Author affiliations

- ¹Cardiovascular Sciences, KU Leuven, Leuven, Belgium
- ²Cardiology, KU Leuven University Hospitals Leuven, Leuven, Belgium
- ³Movement Sciences, KU Leuven, Leuven, Belgium
- ⁴Cardiology, Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia
- ⁵Radiology, KU Leuven University Hospitals Leuven, Leuven, Belgium
- ⁶Cardiology, Royal Adelaide Hospital, Adelaide, South Australia, Australia
- ⁷Centre for Heart Rhythm Disorders, The University of Adelaide, Adelaide, South Australia, Australia
- ⁸Cardiology, Jessa Hospital Campus Virga Jesse, Hasselt, Belgium
- ⁹Cardiovascular Sciences, University Hasselt Biomedical Research Institute Rehabilitation Research Center, Diepenbeek, Belgium
- ¹⁰Cardiology, University of Antwerp, Antwerpen, Belgium
- ¹¹Cardiovascular Sciences, University Hospital Antwerp, Edegem, Belgium
- ¹²Cardiology, The Royal Melbourne Hospital, Parkville, Victoria, Australia
- ¹³Inherited Heart Diseases, Victor Chang Cardiac Research Institute, Darlinghurst, New South Wales, Australia
- ¹⁴Cardiology, University Hospital Antwerp, Edegem, Belgium
- ¹⁵Cardiovascular Sciences, University of Antwerp, Antwerpen, Belgium
- ¹⁶Department of Cardiology, Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia

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Contributors All authors contributed to the design of the Pro@Heart trial. RDB, GC and ALG developed the sample size calculation and the statistical analysis plan. RDB, GC, ALG and HH drafted the manuscript. All authors read, gave final approval and agreed to be accountable for all aspects of the work, ensuring integrity. GC and ALG are joint last authors.

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Patient consent for publication Not applicable.

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ORCID iD

Ruben De Bosscher <http://orcid.org/0000-0002-3163-4781>

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Appendix

Physical examination and blood samples

A physical examination and blood samples are taken to evaluate cardiovascular risk factors (hypertension, dyslipidaemia, diabetes, smoking, and body mass index).

12-lead ECG

A resting 12-lead ECG will be recorded and interpreted in accordance to the Seattle Criteria by a cardiologist with experience in sports medicine.¹

Dual-X-ray absorptiometry

Subjects will undergo a dual-energy X-ray absorptiometry scan (Discovery W, Hologic Inc, Bedford, Massachusetts, USA - GE Lunar Prodigy Advance, GE Healthcare, Horton, Norway) to measure lean mass, fat mass, bone mineral content and bone mineral density of the whole body, trunk, legs and arms.

Exercise testing

Peak oxygen consumption (peak VO_2) will be determined in a sports-specific manner when possible. Cyclist and triathletes will perform a continuous bicycle stress test using either a dedicated ergometer (Lode Excalibur, Lode, Netherlands) or with the athlete's racing bicycle attached to a cycle ergometer (Avantronic Cyclus II, Leipzig, Germany). As we do not have the infrastructure to test swimmer, rowers and cross-country skiers in a sport-specific manner these athletes will also perform an bicycle exercise test. The protocol is determined at each site with either a ramp or incremental step of increased workload until exhaustion after a brief warm-up at low power. Runners performed a running test on an electronically controlled treadmill (Venus®

200/75, H/P/cosmos, Nussdorf, Germany). After a 5-minute warm-up, the starting will be 8 km.h⁻¹ and will increased by 1.5km.h⁻¹ every 8-min until exhaustion. Respiratory gas exchange will be analysed using a breath-by-breath open circuit spirometry system (Vyntus CPX Metabolic Cart, Vyair Medical, Germany). Peak VO₂ will be determined as the highest 30s average oxygen consumption. The first and second ventilatory threshold will be determined from respiratory gas analysis parameters. During this test, a continuous 12-lead ECG will be recorded at a speed of 25 mm/s. The exercise ECG will be interpreted for repolarization abnormalities and arrhythmias by a cardiologist with experience in sports medicine.

Two- and three-dimensional transthoracic echocardiography

Two- and three-dimensional TTE will be performed using a Vivid E9 or E95 ultrasound system (GE Healthcare, Horton, Norway) with an active matrix single-crystal phased array transducer (GE M5Sc-D probe, GE Healthcare, Horton, Norway) and 1.5-4MHz matrix-array transducer (GE 4Vc-D Matrix 4D cardiac probe, GE Healthcare, Horton, Norway). Cardiac morphology will be assessed, including end-diastolic (EDV), end-systolic volumes (ESV), rendering ejection fraction (EF) for both ventricles, as well as right and left atrial volumes. Diastolic function will be assessed using established Doppler and tissue-Doppler parameters such as the E wave velocity, the A wave velocity, the E/A ratio, septal, lateral and averaged E', E/E', tricuspid regurgitation flow velocity and the S-D-A waves at the pulmonary veins. In depth analysis of the intrinsic myocardial function will be performed by strain analyses. RV and LV strain and strain rate will be assessed as measures of systolic function. RV and LV early and late diastolic strain rate will be assessed for diastolic function. Time-to-peak shortening in all 18 segments of the LV and of the RV free wall will be measured to assess for differences in timing and mechanical dispersion. Atrial strain analysis will

be performed to assess the reservoir, conduit and contraction function of both atria. All measurements will be made following international guidelines.^{2,3}

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging will be performed using a 1.5T MRI scanner (Magnetom Aera and Sigma 1.5T – Siemens Healthineers, Erlangen, Germany; Ingenia, Achieva or Ambition 1.5T - Philips Medical Systems, Best, The Netherlands) or a 3.0T scanner (Prisma, Siemens Healthineers, Erlangen, Germany) using a dedicated cardiac coil and electrocardiographic gating. Steady-state free precision (SSFP) short-axis cine imaging (8 mm slice thickness without gaps) will be obtained to analyse cardiac mass, function and volumes. In addition, native and post-contrast T1 mapping will be performed using the modified look-locker inversion recovery (MOLLI) sequence to calculate extracellular volume (ECV). Myocardial fibrosis (MF) will also be evaluated by means of delayed enhancement on breath hold phase-sensitive inversion recovery (PSIR) sequences 10 minutes after administration of gadolinium-DTPA. Analysis of CMR data will be performed in a central core lab. Assessment of cardiac volumes and mass will be performed using RightVol (KU Leuven, Leuven, Belgium). IntelliSpace Portal (Philips Medical Systems, Eindhoven, The Netherlands) will be used for T1 and ECV mapping and Suiteheart (Neosoft, Pewaukee, USA) is used for strain analysis (feature tracking). Our validated robust non-rigid motion correction will be used for accurate T1 measurements and ECV calculations.⁴

Exercise Cardiac Magnetic Resonance Imaging

In the University Hospital of Leuven and at the Baker Heart and Diabetes Institute Melbourne an exercise CMR will be performed using a cycle ergometer with adjustable electronic resistance (Lode, Groningen, The Netherlands). Images will be acquired using a Philips Achieva 1.5 T CMR

with dedicated cardiac coil during supine bicycle exercise at 25%, 50%, and 66% of maximal power determined by previous upright cardiopulmonary exercise testing. Steady-state free precession cine imaging was performed without cardiac gating. A 3D stack of 13–18 contiguous 8 mm image slices, covering both ventricles from apex to base, will be serially acquired in the short-axis plane and the horizontal long-axis plane. All image frames will be acquired during free breathing. Ventricular and atrial volumes and functional reserve during exercise will be measured using RightVol (KU Leuven, Leuven, Belgium). Our research group has previously demonstrated the feasibility, reliability and clinical utility of CMR to quantify cardiac volumes and function during exercise.^{5 6}

Exercise stress echocardiography

In the University Hospital Antwerp and Jessa Hospital Hasselt, exercise stress echocardiography (Vivid E95 ultrasound system - GE Healthcare, Horton, Norway) will be performed instead of exercise CMR in the subjects having undergone CMR at rest. An exercise table (ER900 and Oxycon Alpha, Jaeger, Germany) allowing backward and side tilt for optimal signal sampling will be used. Measurements will be performed at rest and during several stages of exercise depending on heart rate and respiratory gas analysis parameters. The following measurements and derived calculations will be collected: LVEF, RVEF, RV fractional area change, biventricular systolic and diastolic strain parameters, Doppler and tissue Doppler parameters to assess cardiac output, diastolic function and pulmonary artery systolic pressure. Using stress echocardiography we will assess how prolonged high intensity endurance training impacts pulmonary vascular resistance and diastolic function during exercise. All measurements will be made following international guidelines.⁷

Holter analysis

For the 24-hour Holter ECG monitoring, a Spiderview Holter device (Ela Medical, Paris, France) or a Pocket ECG (Device Solution, Belrose, New South Wales, Australia) will be attached to BlueSensor VL ECG electrodes (AmbuR, Penang, Malaysia). The ECG recordings will be analysed offline using SyneScope software (ELA Medical, Paris, France) to determine heart rate extremes, heart rate variability and the prevalence of arrhythmias.

Electronic Training Diary

Physiological data obtained with heart rate monitors during training sessions will enable quantification of exercise intensity during representative training bouts. Online tracking of sports activity will be performed using a dedicated web-based platform compatible with all current heart rate monitor and sports GPS devices (TrainingPeaks®, Peaksware, Boulder, USA).^{8 9} All athletes will receive a user profile upon study enrolment and permission will be asked to track all sports activities using a central coach profile. The recorded data on duration, distance, altitude, speed, power output and heart rate of from training sessions will be exported and transformed using a big data bioinformatics platform (RStudio 2020, Integrated Development for R, PBC, Boston, MA, USA). Finally, training load will be expressed by a parameter combining a factor of duration and intensity (e.g. Banister training impulse [TRIMP] and derivatives) will be further quantified for any relevant time period (week, month and year).^{10 11}

Genetic testing

Our primary genetic analyses will focus on (i) rare variants in cardiomyopathy associated genes, and (ii) polygenic risk scores (PRS) for various cardiac traits including DCM and AF.

Rare variants will be detected using a custom gene array comprised of protein-coding sequences of 24 genes that have been curated to show strong evidence of association with DCM, HCM or ARVC. Sequencing data will be analysed using an in-house pipeline at the VCCRI. Variant pathogenicity will be assessed according to standard clinical guidelines using the American College of Medical Genetics and Genomics scoring matrix.¹²

Genome-wide evaluation of single nucleotide polymorphisms will be obtained using the Axiom Precision Medicine Diversity Array (PMDA). Data will be used to derive PRS for various cardiac traits using validated scoring algorithms.

Finally, extracted DNA will be stored for potential future whole-genome sequencing.

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