Impact of **angiotensin converting enzyme activity** on exercise training sensitivity

A randomized placebo-controlled trial

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Background

The insertion/deletion (I/D) polymorphism of the human angiotensin converting enzyme (ACE) gene was the first genetic component shown to impact substantially on the adaptation pattern to exercise training in humans. Briefly, intervention studies have demonstrated an 11-fold greater training-induced improvement in muscular endurance for ACE I/I homozygotes compared to ACE D/D homozygotes (Montgomery et al., 1998).

In support, cross-sectional studies have reported an overrepresentation of the ACE I/I genotype among elite endurance athletes (Hruskovicová et al., 2006)

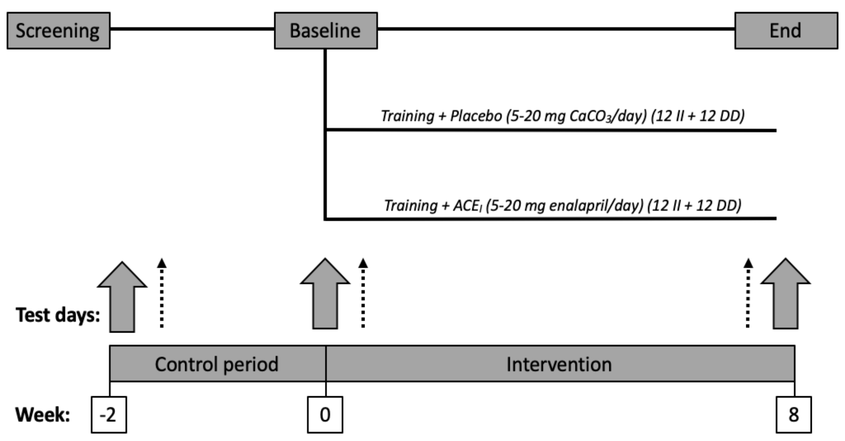
Importantly, the ACE I/D polymorphism causes large inter-individual differences in serum ACE activity (Rigat et al., 1990).

Because the ACE D/D genotype is characterized by high serum ACE activity and potentially blunted endurance exercise training response, it appears likely that ACE inhibitors (ACE_i) have the potential to improve the outcome of exercise training for ACE D/D homozygotes.

Aim and hypothesis

The main aim of the present study is to investigate whether pharmacological inhibition of ACE activity can amplify the exercise training response in healthy humans carrying either the ACE D/D or ACE I/I genotype.

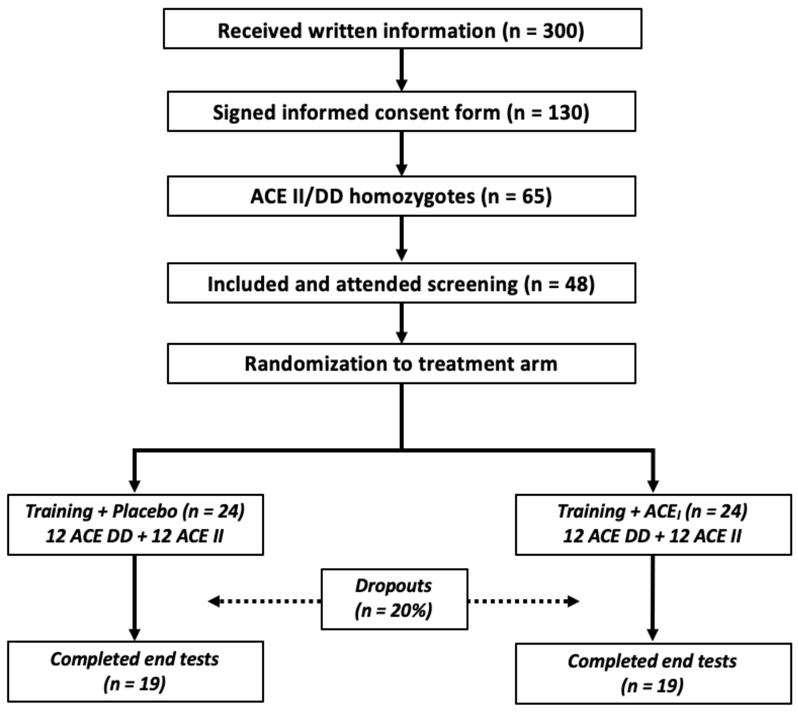
The hypothesis, that inhibition of ACE activity in humans with the ACE D/D genotype will amplify the health beneficial effects of exercise training in contrast to carriers of ACE I/I genotype, will be tested.



The ACE study is a randomized double-blind placebo-controlled longitudinal study involving 48 participants. Fat arrows mark test days and includes resting blood pressure, resting blood samples, total blood volume, muscle biopsies from m. vastus lateralis and m. deltoideus posterior, cardiac magnetic resonance imaging, echocardiography, dual-energy x-ray absorptiometry scan, measurement of resting and exercise metabolism including determination of maximal oxygen uptake and measurement of skeletal muscle endurance and strength.
Dotted arrows mark measurement of endurance performance determined by a 2000 meter time trial on an indoor rowing ergometer.

Inclusion criteria

- ACE I/I or ACE D/D homozygote
- Aged 20-50 years
- Healthy



Expected *flow chart of participation in the ACE study.*

Methods

A randomized double-blind placebo-controlled longitudinal design is applied. The intervention period consists of a 2-week control period and an 8-week training period (3x1 h mixed intensity rowing-ergometer weekly training session). Participants will be randomly assigned to daily administration of placebo ($CaCO_3$) or ACE_i (Corodil® 'Enalapril'). In total, 12 males and 12 females aged 20 to 50 years representing each genotype (I/I and D/D) are recruited (in total 48 participants). Recruitment of ACE II / DD carriers is conducted in collaboration with the FarGen-project. Clinical investigations will be performed before and after the 2-week control period and subsequent to the training period.

The primary outcome variable is maximal oxygen uptake and the most important secondary outcomes are endurance performance, total blood volume, muscle endurance and muscle oxidative capacity.

Project significance

The projects scientific relevance relates to the mechanistic understanding of how exercise training provokes physiological adaption. In this context, the project will clearly unravel the impact of ACE genotype for exercise adaptation.

Because the applied pharmacological intervention targeted at the ACE phenotype is a worldwide used anti-hypertensive drug (Enalapril) the project will also clarify if a general interaction between blood pressure and exercise training response exists.

If the hypothesis is verified, follow up studies will be performed to evaluate if the effect of ACE_i also can manifest in humans carrying the ACE I/D genotype and as such be a step towards personalized exercise and pharmacological prescription.

Acknowledgements

The project is funded by the Novo Nordic Foundation.

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References

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