Infarct size limitation triggered by excess ischemic arrhythmias in hypertensive rats

Jan Neckář

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C-reactive protein (CRP)

- ✓ CRP is a sensitive marker of acute phase of inflammation and a mediator of inflammation and immune response.
- ✓ CRP has direct cardiovascular effects.
- ✓ Increased levels of CRP are associated with an increased risk of cardiovascular events.

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Transgenic rat strain SHR-CRP

- ✓ The humanized C-reactive protein (CRP) transgenic rat strain with elevated the overall concentration of CRP (endogenous rat and transgenic human).
- ✓ They are characterized by:
  - ✓ multiple features of the metabolic syndrome including insulin resistance, hypertriglyceridemia, and increased blood pressure.
  - ✓ kidney injury
  - ✓ myocardial hypertrophy

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General Aim

To find out whether transgenic expression of human CRP affects cardiac susceptibility to ischemia/reperfusion injury in adult SHR-CRP rats.

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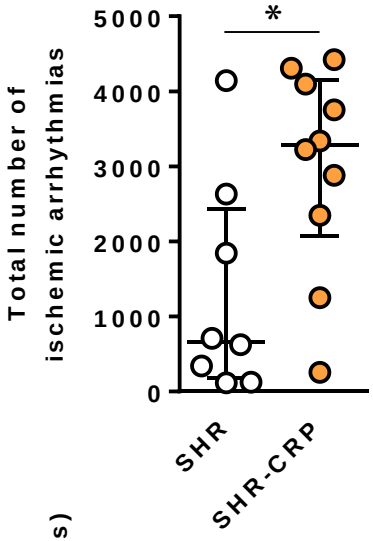
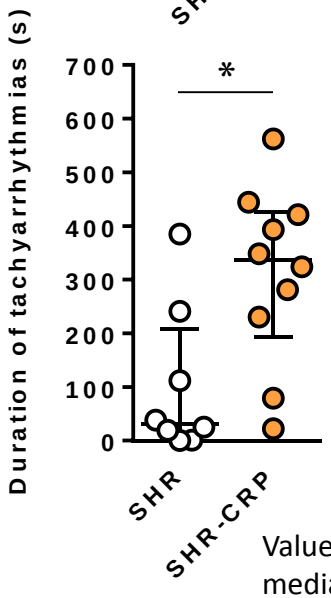
Cardiac ischemic tolerance – heart *in vivo*

Ischemic arrhythmias





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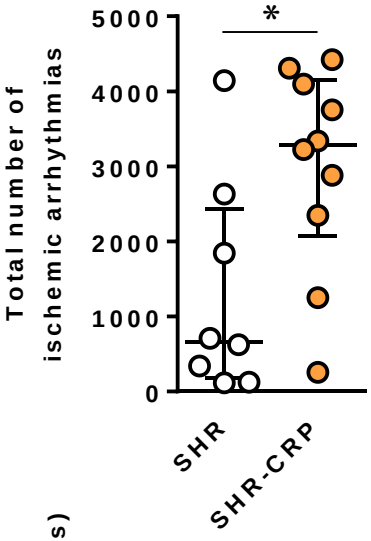

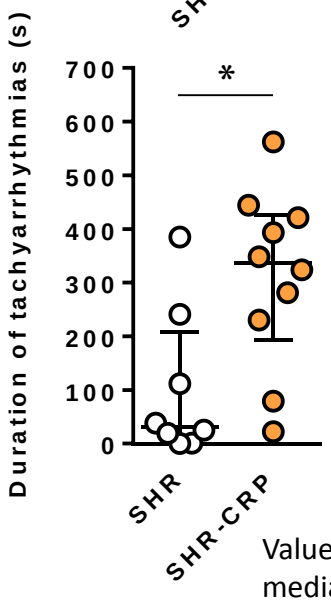

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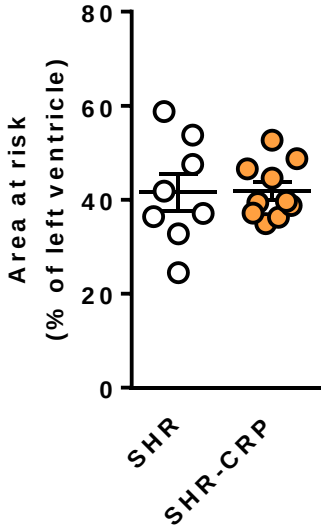
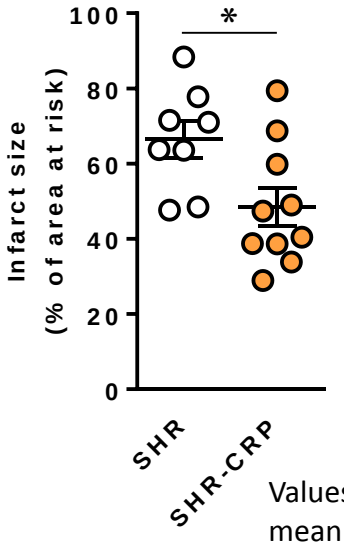
Infarct size





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To find out whether transgenic expression of human CRP affects cardiac susceptibility to ischemia/reperfusion injury in adult SHR-CRP.

Specific Aims

In SHR-CRP, to clarify the mechanism(-s) of:

i) severe ischemic tachyarrhythmias

ii) infarct size-limiting effect

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Summary

Severe ischemic tachyarrhythmias in SHR-CRP

Transgenic expression of human CRP predisposes SHR-CRP to excess ischemic ventricular tachyarrhythmias.

The proarrhythmic phenotype was associated with altered:

- ✓ myocardial composition of fatty acids in phospholipids
- ✓ heart and plasma eicosanoids
- ✓ autonomic nervous system balance

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General Aim

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In SHR-CRP, to clarify the mechanism(-s) of:

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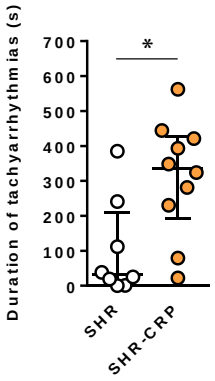
Ischemic arrhythmias vs. Infarct size



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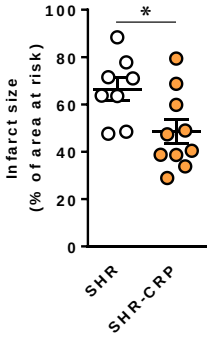

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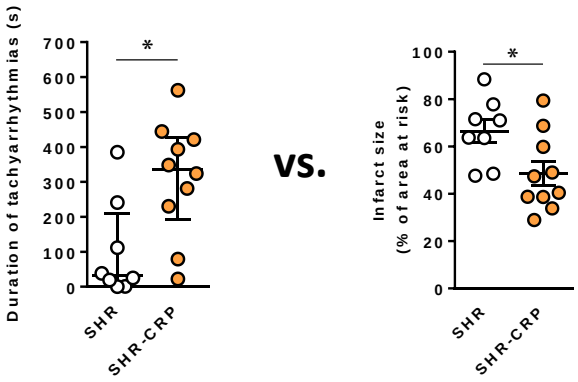

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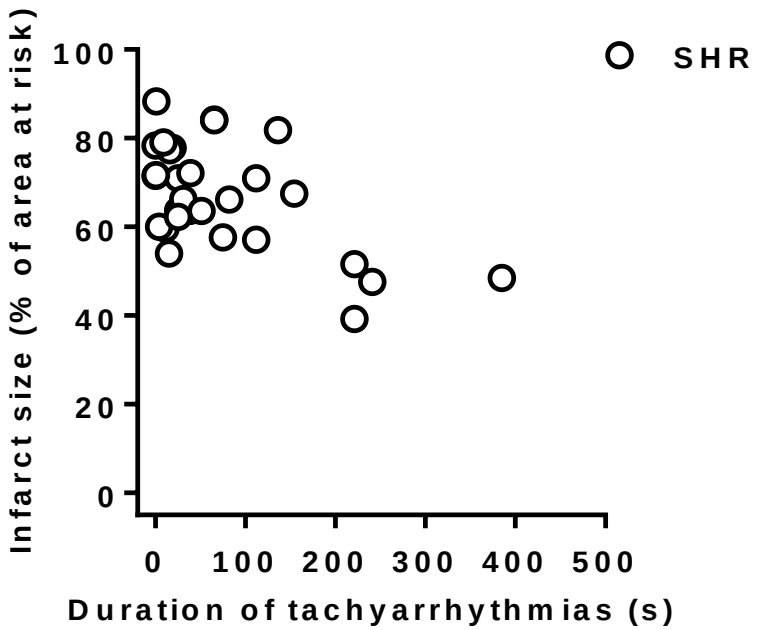

Physiol. Genomics 44, 183-92, 2012
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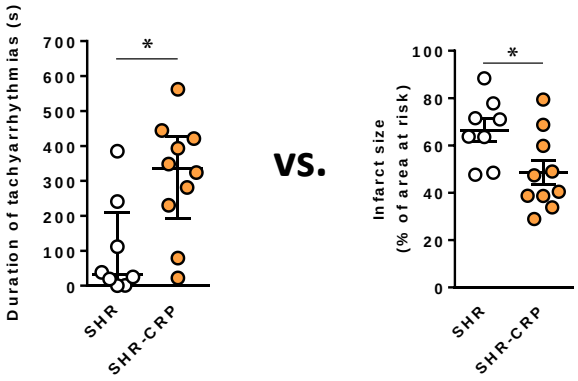

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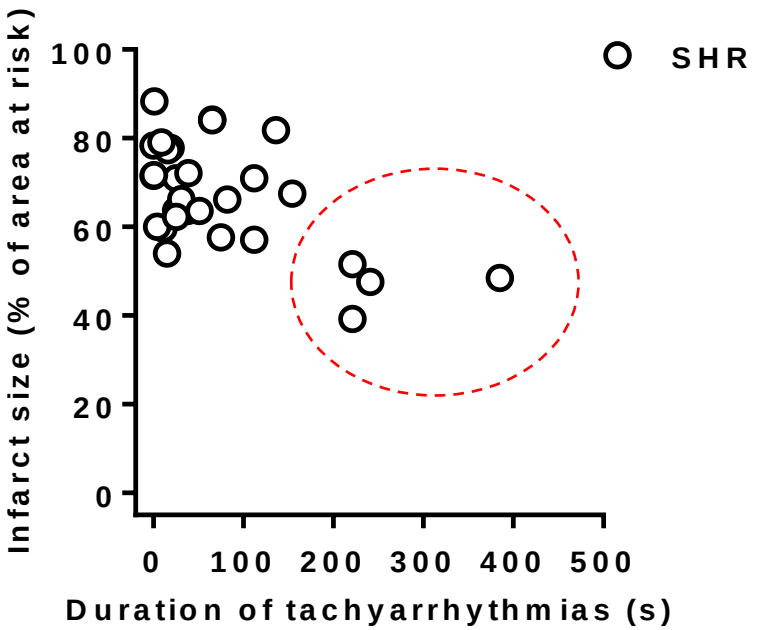

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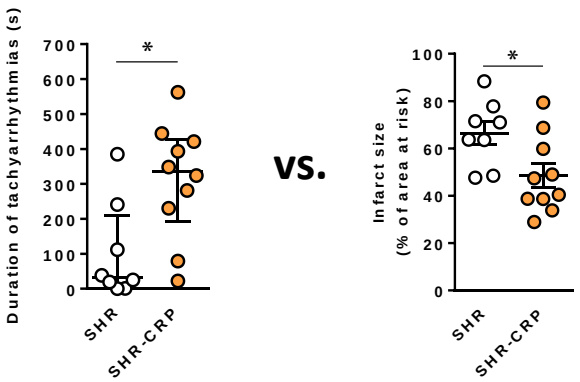

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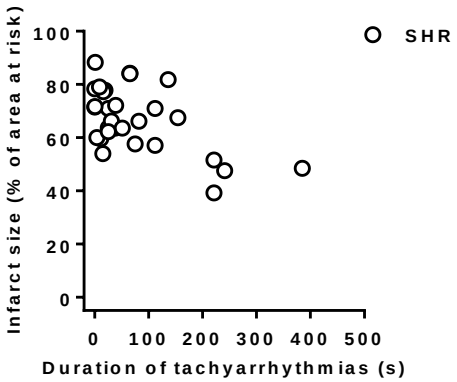

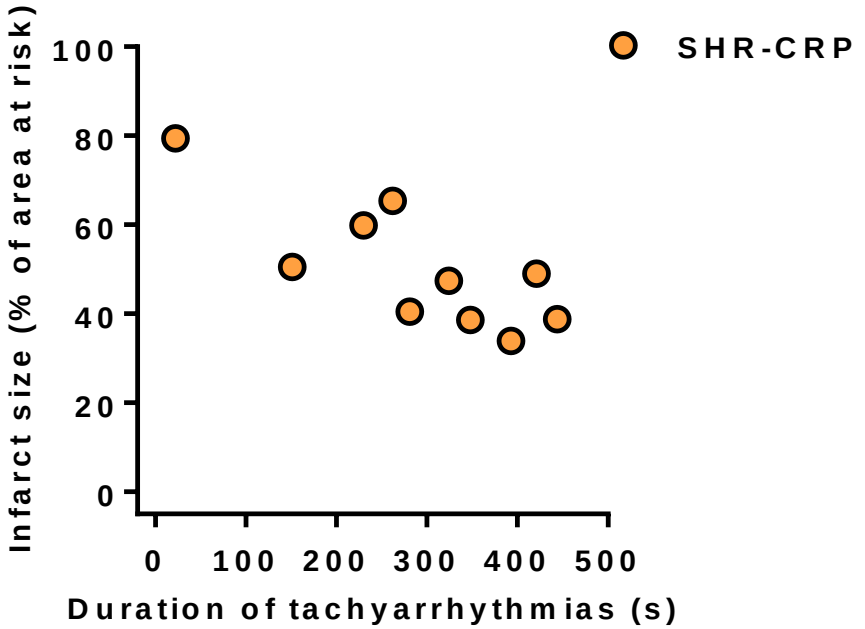

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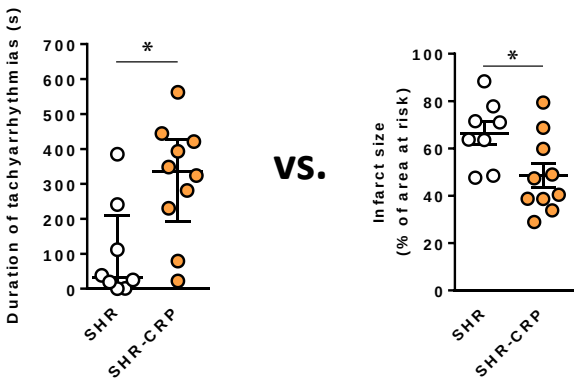

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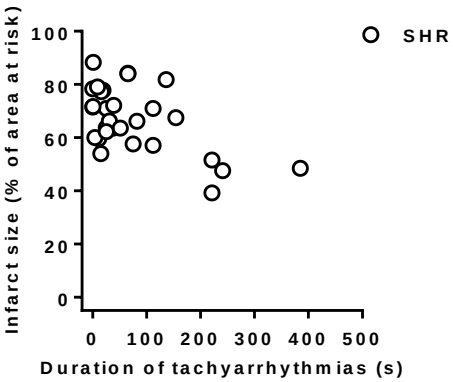

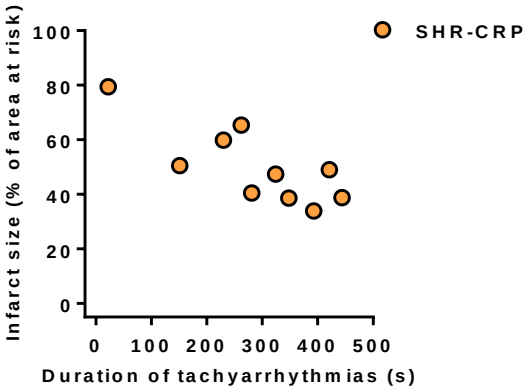

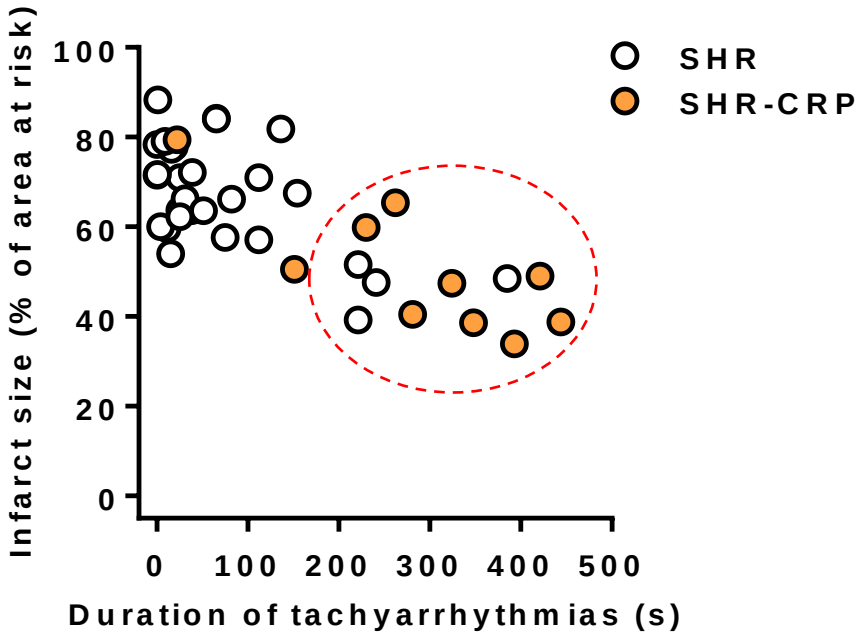

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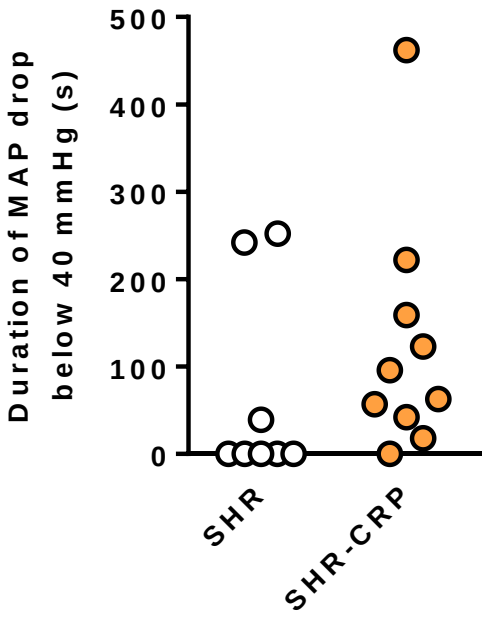
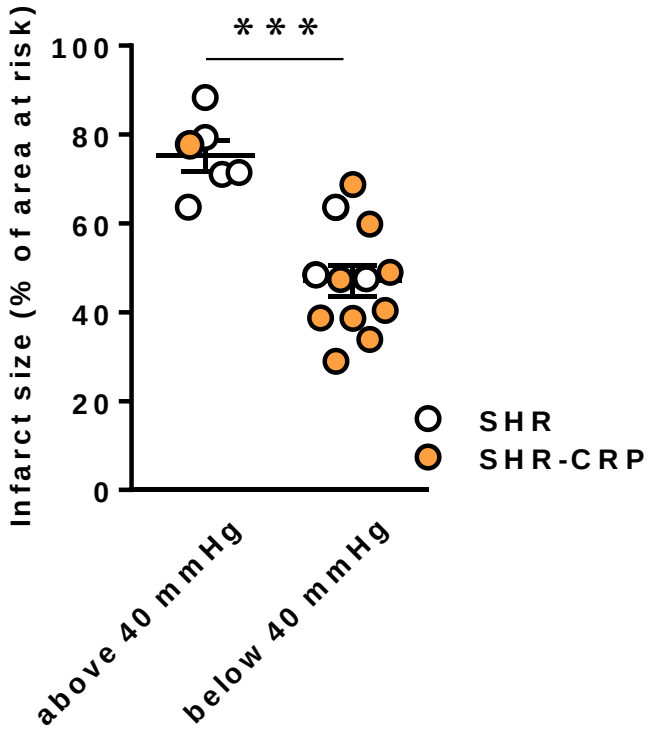
Severe ischemic arrhythmias lead to insufficient organ and tissue perfusion





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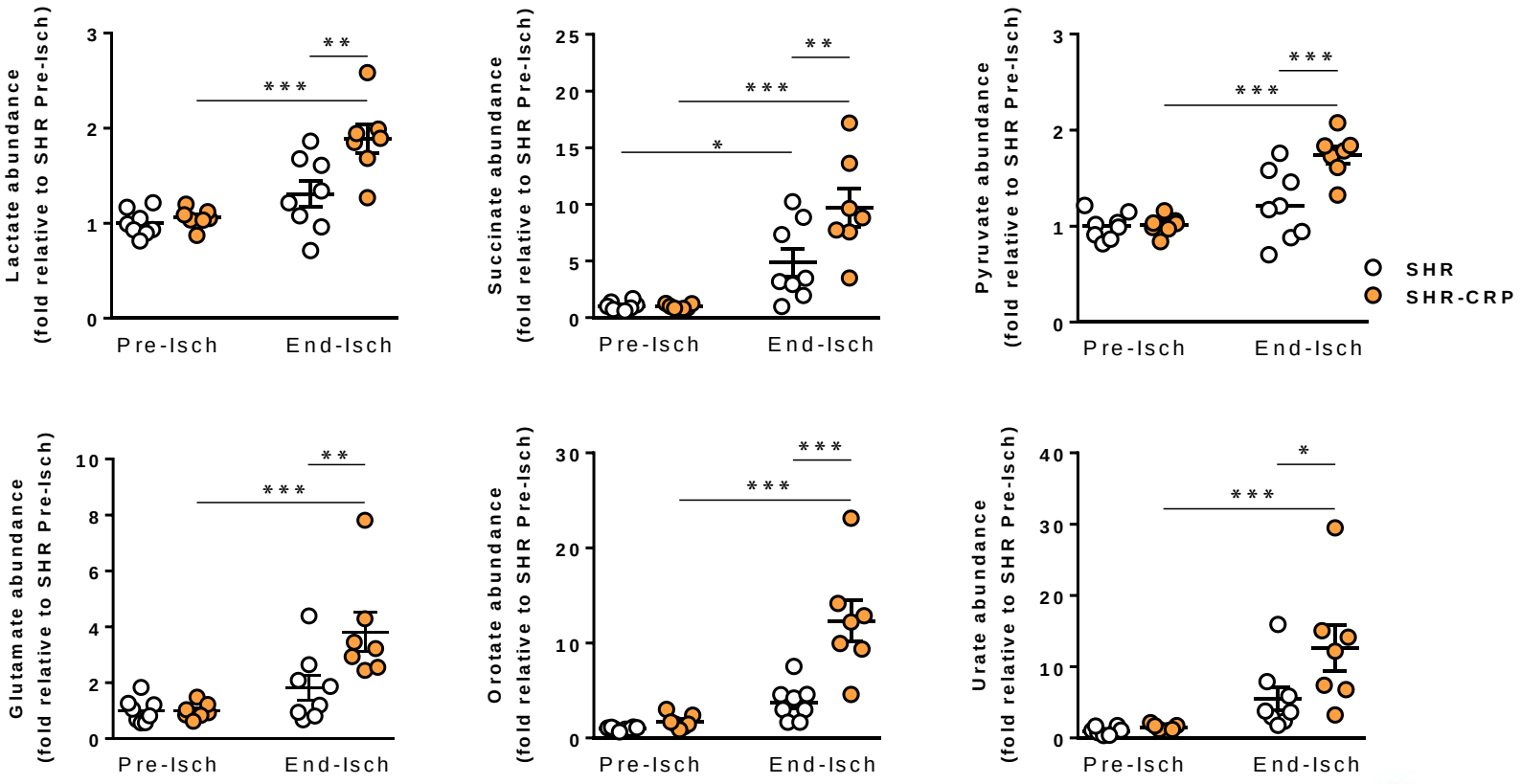
Severe ischemic arrhythmias lead to insufficient organ and tissue perfusion

Plasma metabolites associated with tissue hypoxia



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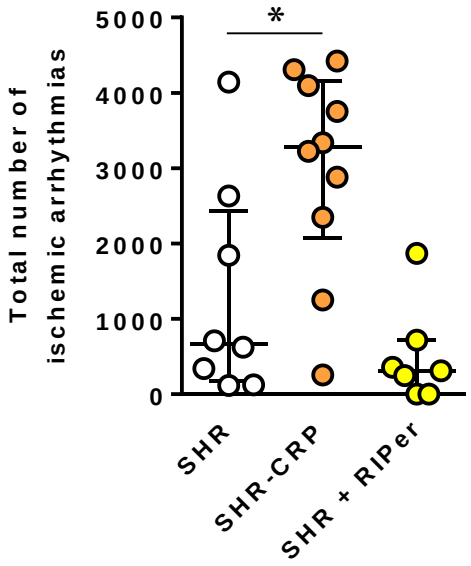
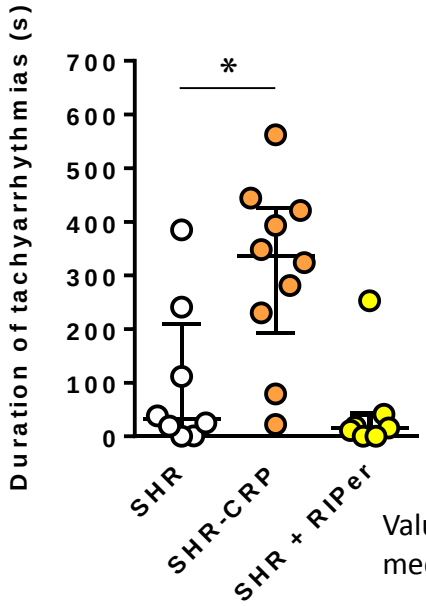
Remote ischemic perconditioning – heart *in vivo*

Ischemic arrhythmias





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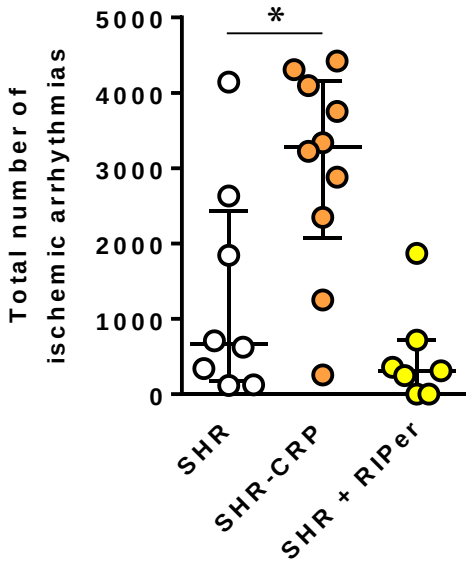

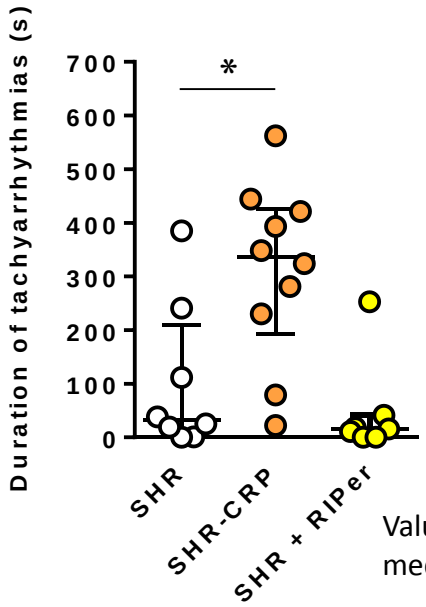

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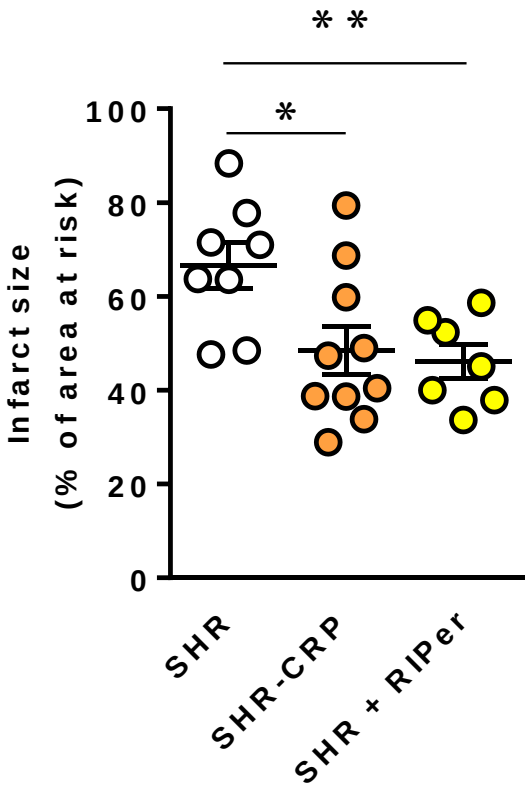
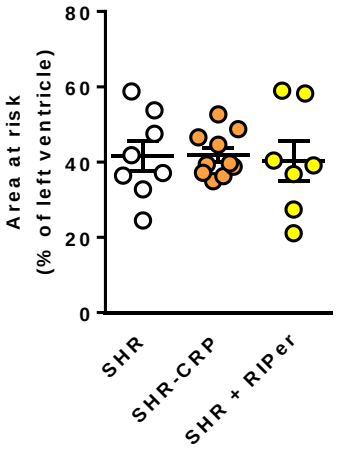
Infarct size





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Cardiac ischemic tolerance – heart *ex vivo*

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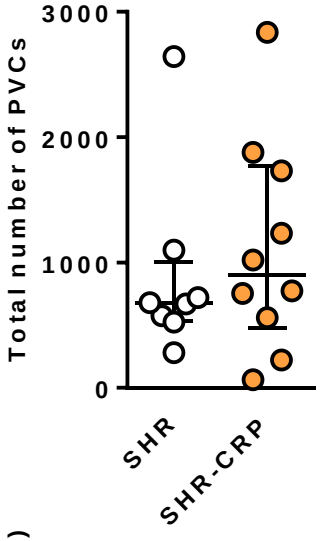

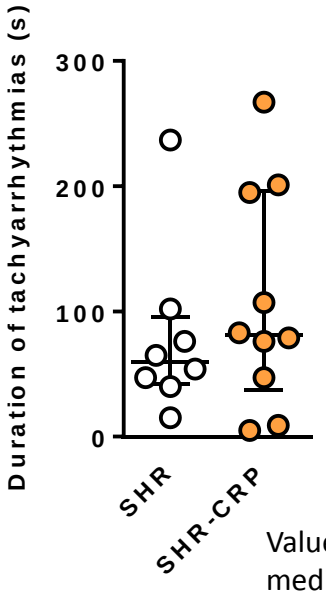

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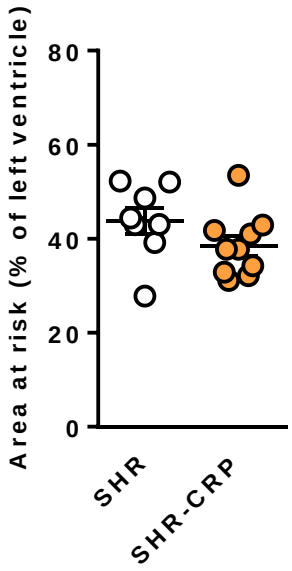

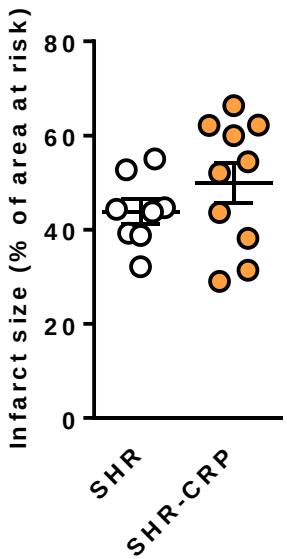

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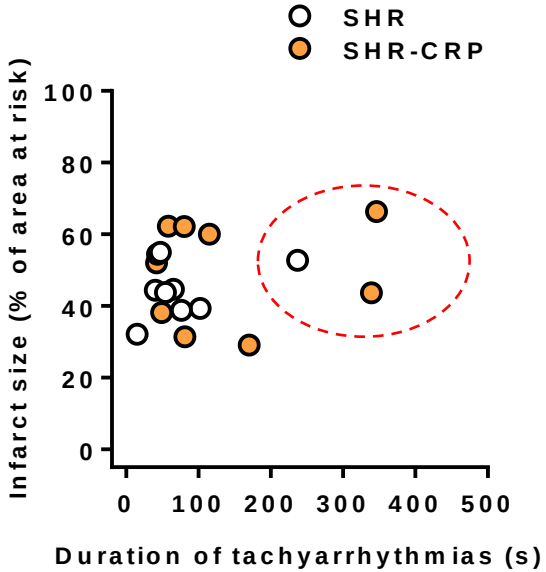

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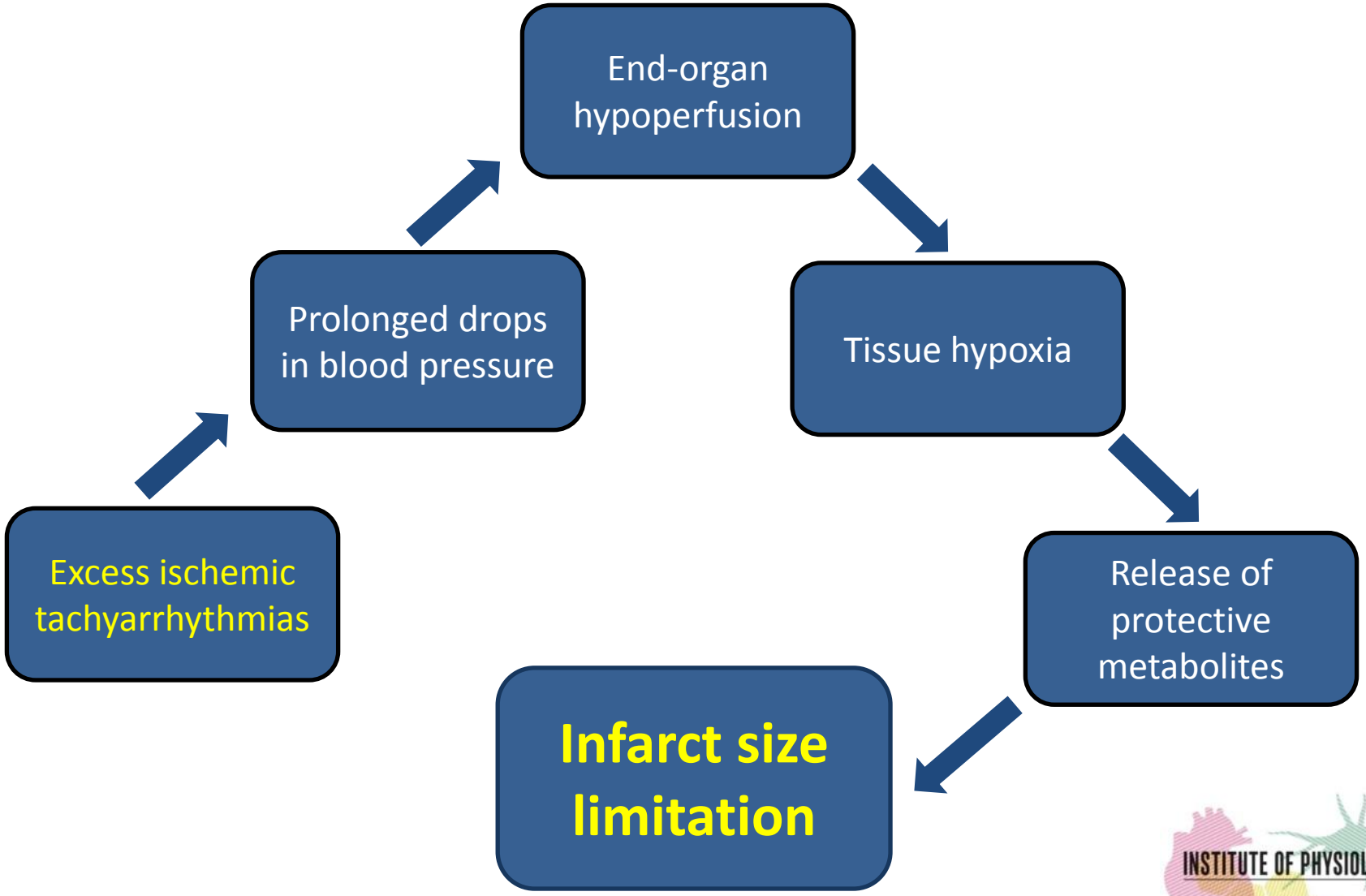
Summary

Infarct size-limiting effect in SHR strains



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Conclusion/Take home message

A new form of myocardial protection (conditioning) that is initiated by the heart itself without any external intervention, i.e. SELF-CONDITIONING, was demonstrated.

Practical recommendation: An analysis of arrhythmias occurring during ischemia/reperfusion experiments in vivo should always be performed in addition to infarct size determination.

It can help to avoid misleading interpretations of cardiac ischemic tolerance, in particular in transgenic animal models with various comorbidities.

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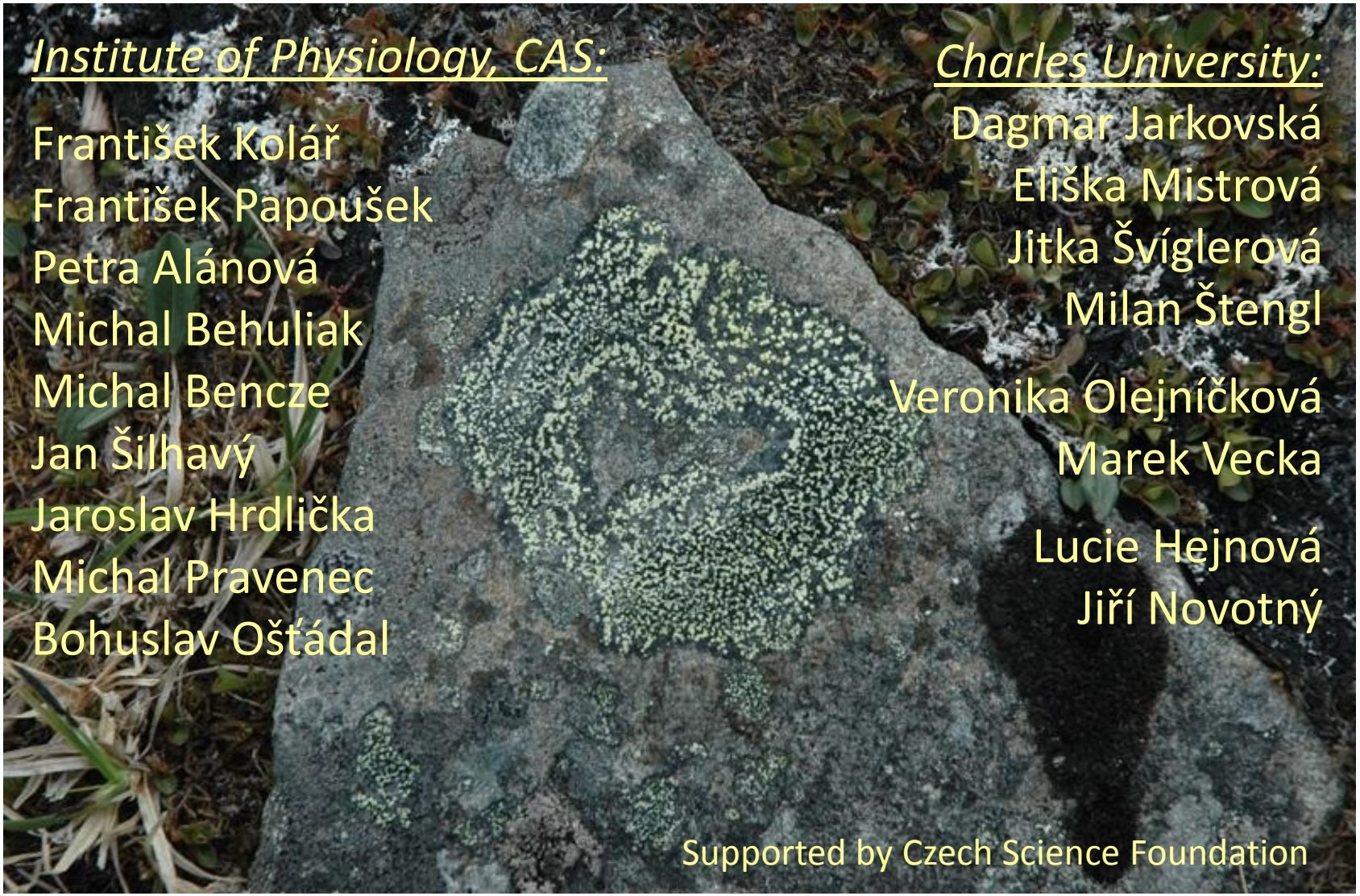
Acknowledgement



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50. pracovní konference Komise experimentální kardiologie

4. – 6. října 2023 **Hotel Galant, Mikulov**

Thank you for your attention.

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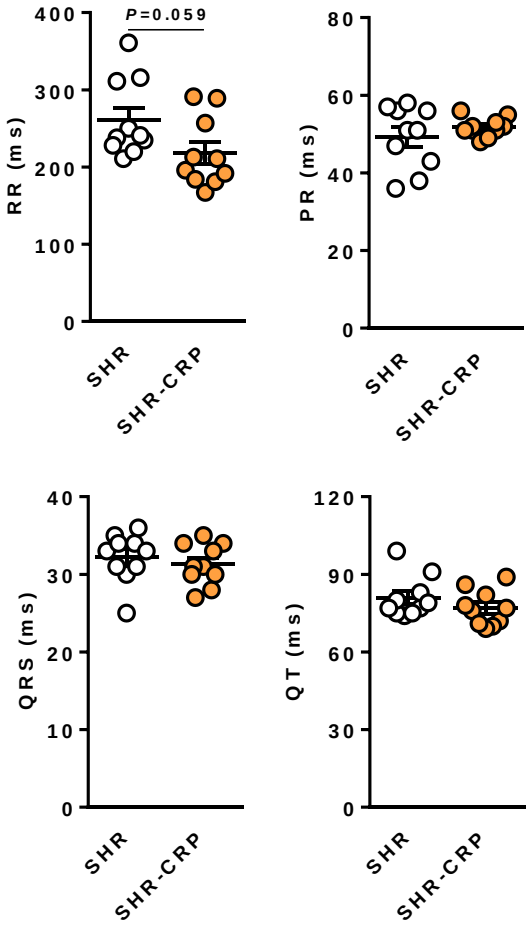
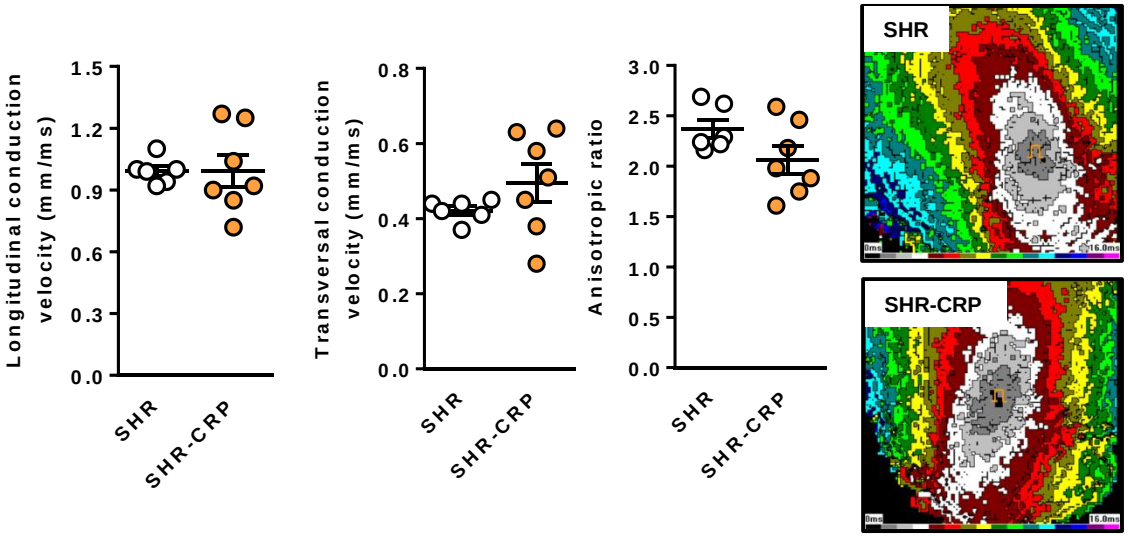
Electrophysiological measurements

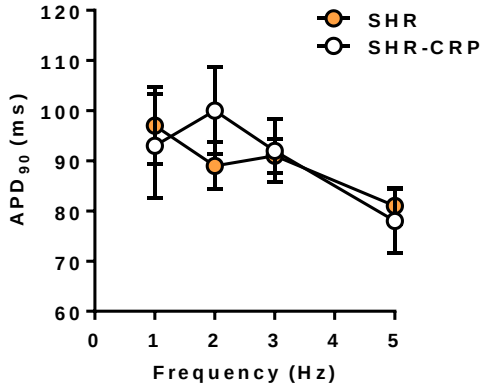
Heart *in vivo* – ECG analysis



Heart *ex vivo* – conduction velocities



LV trabeculae



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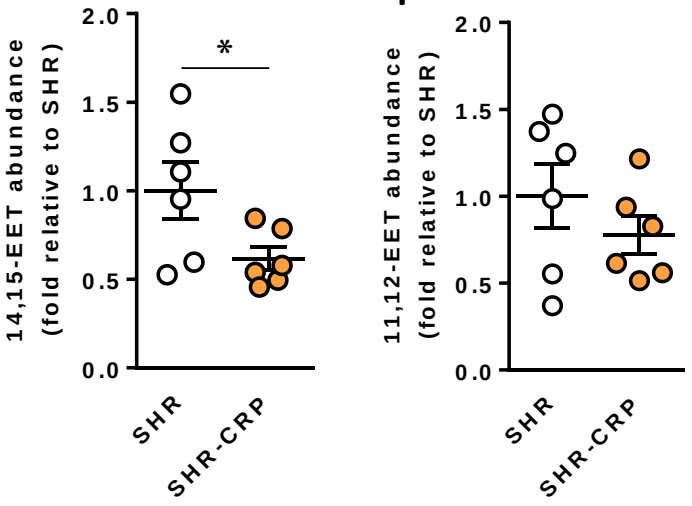
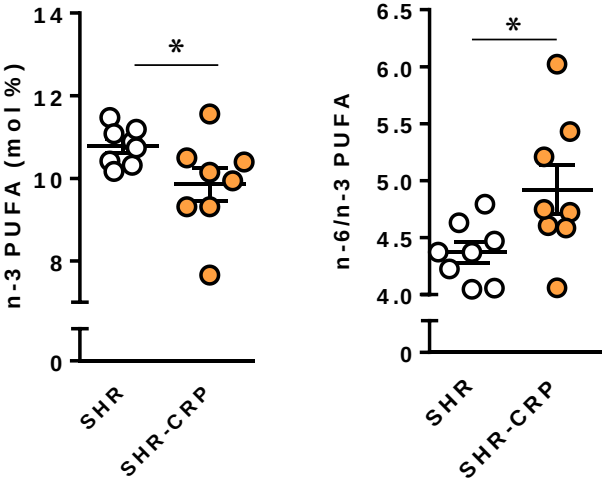
Pro- and antiarrhythmic lipid mediators

Myocardial epoxyeicosatrienoic acids composition



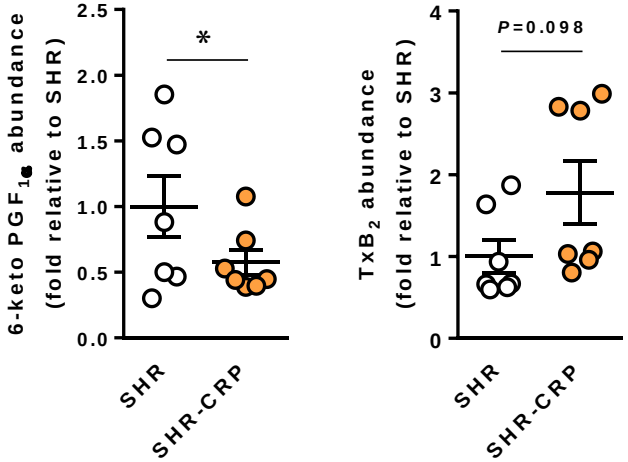
Myocardial fatty acid composition

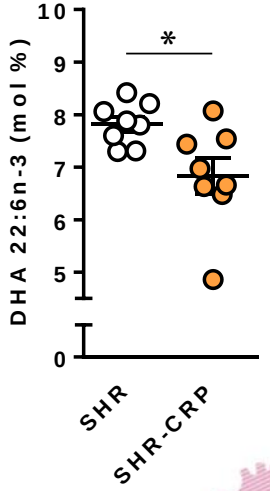


Plasma levels of antiarrhythmic PGI_2 and proarrhythmic TxA_2

PGI_2 → 6-keto $PGF_{1\alpha}$

TxA_2 → TxB_2





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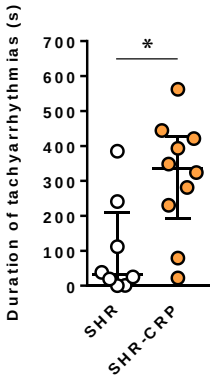
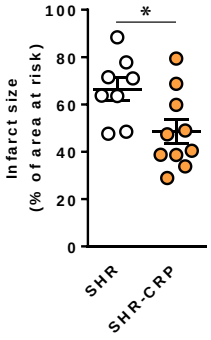
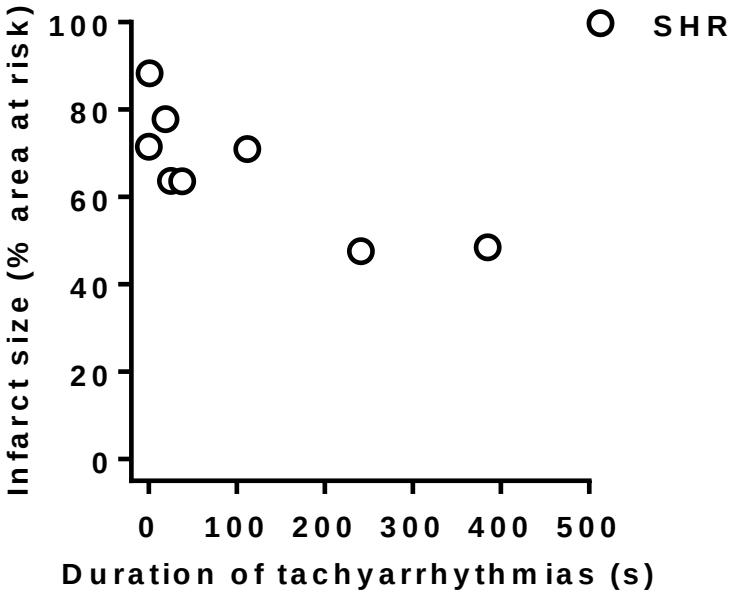
Ischemic arrhythmias vs. Infarct size



vs.





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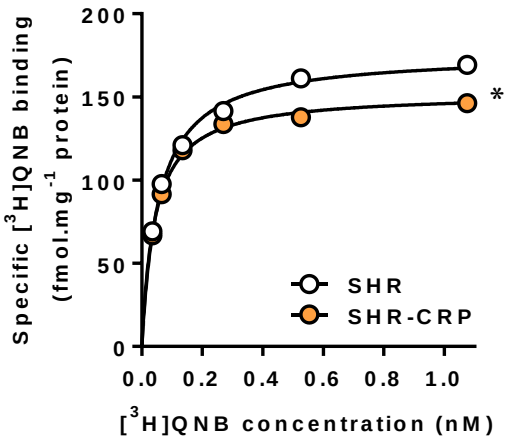
Autonomic nervous system activity

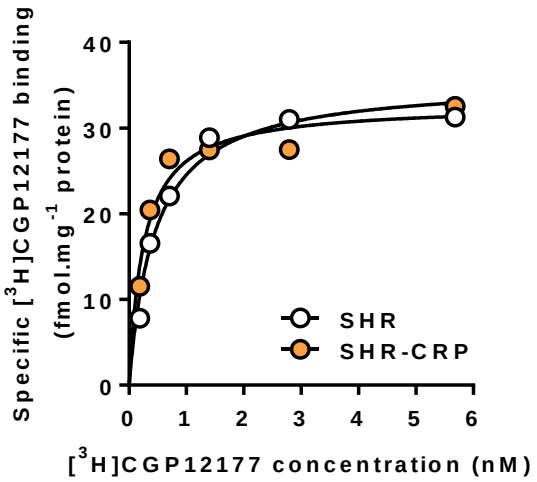
The total number of muscarinic cholinergic and β-adrenergic binding sites

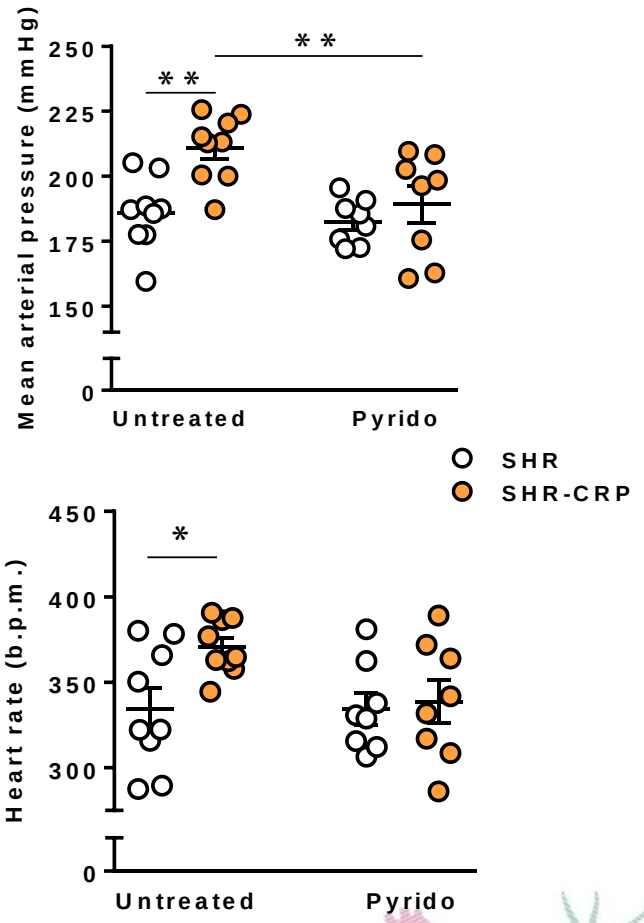
The effect of parasympathomimetic treatment

Muscarinic cholinergic receptors



β-adrenergic receptors





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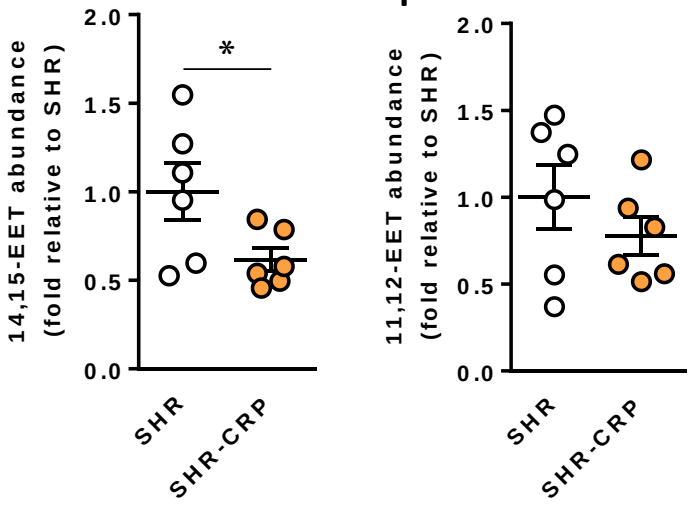

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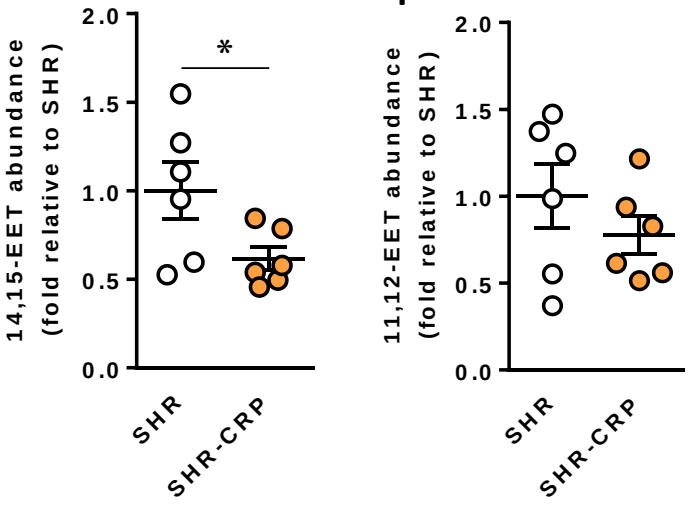
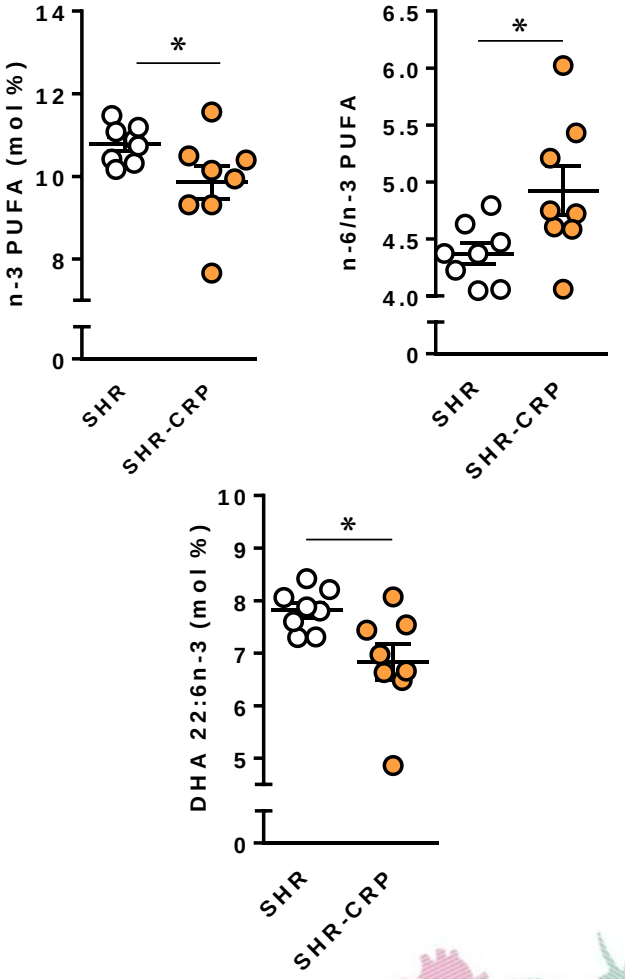


Myocardial fatty acid composition



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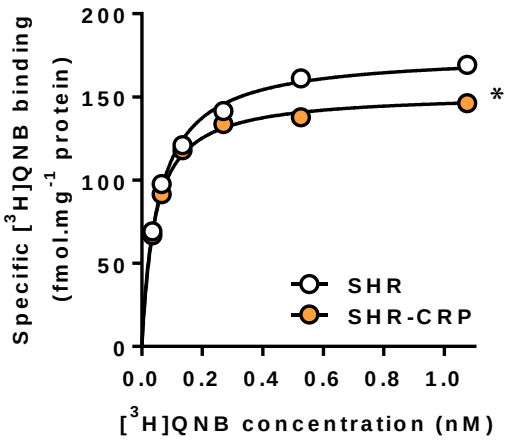
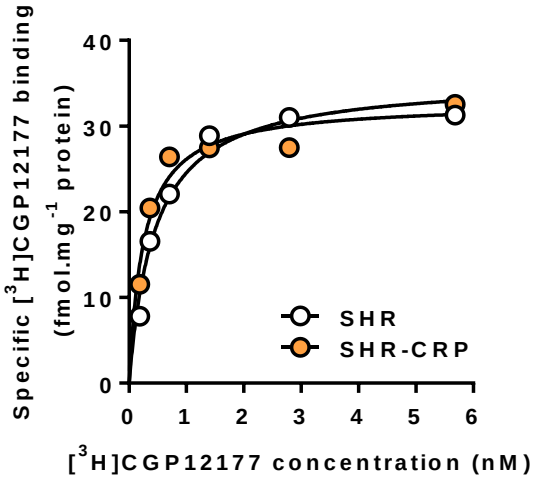
Autonomic nervous system activity

The total number of muscarinic cholinergic and β-adrenergic binding sites

Muscarinic cholinergic receptors



β-adrenergic receptors



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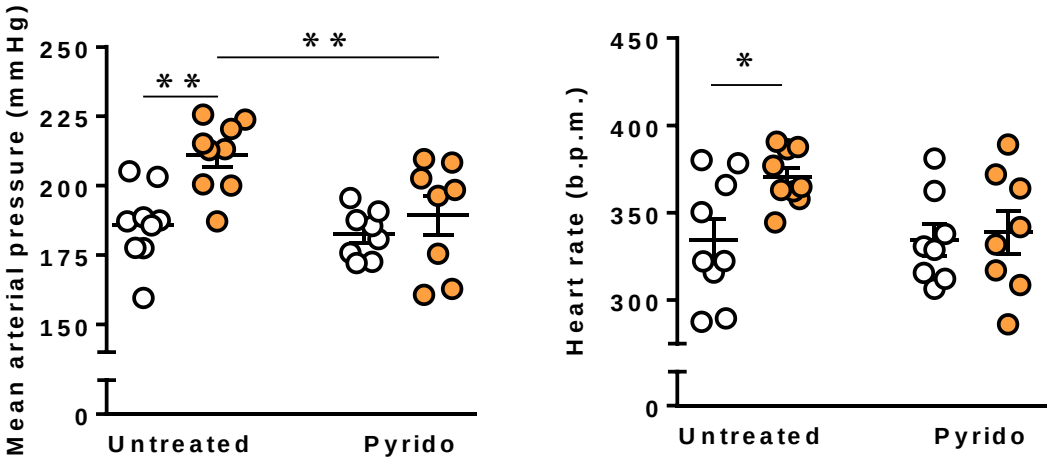
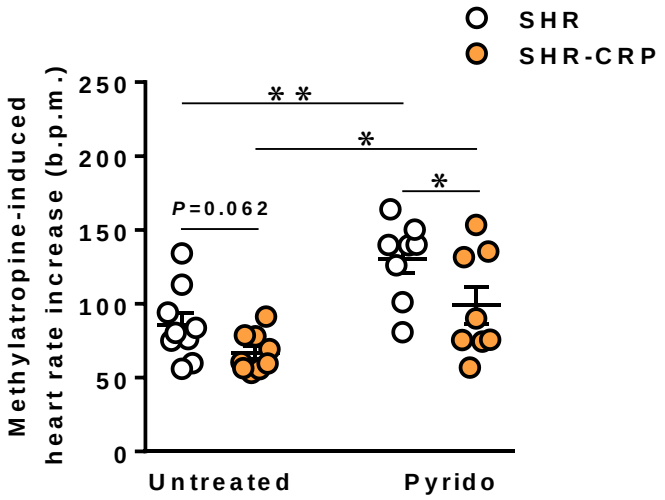
Autonomic nervous system activity

The effect of pharmacological modulators of parasympathetic activity





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Transgenic rat strain SHR-CRP

- ✓ The humanized C-reactive protein (CRP) transgenic rat strain with elevated the overall concentration of CRP (endogenous rat and transgenic human).
- ✓ They are characterized by:
  - ✓ multiple features of the metabolic syndrome including insulin resistance, hypertriglyceridemia, and increased blood pressure.
  - ✓ kidney injury
  - ✓ myocardial hypertrophy

CARDIAC ISCHEMIC TOLERANCE?

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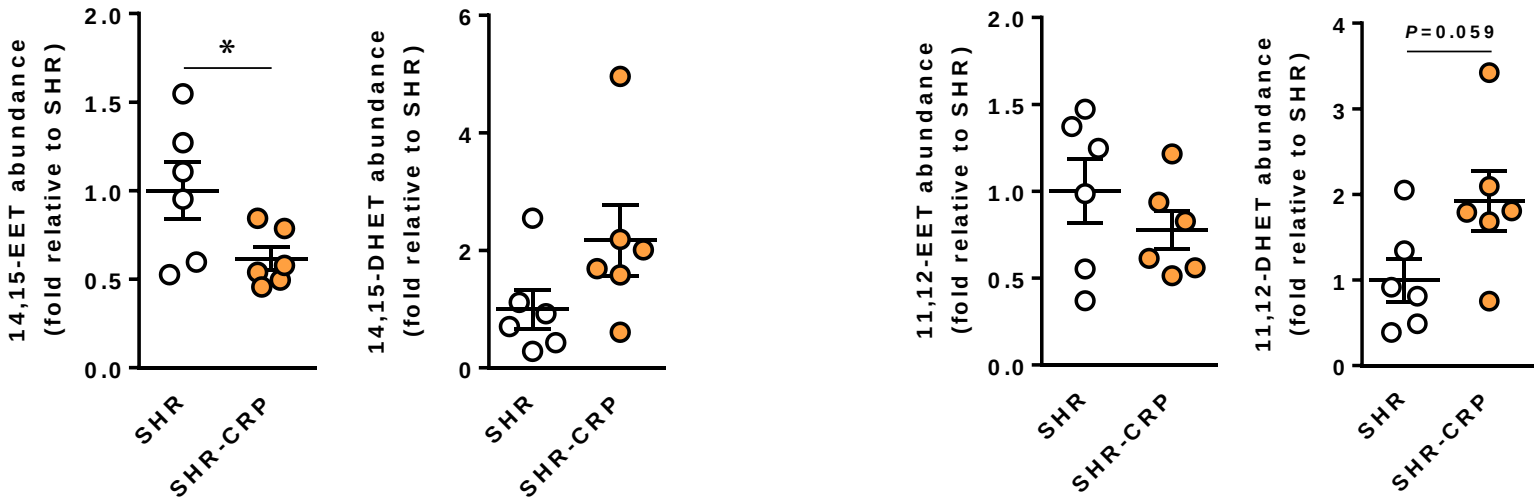
Pro- and antiarrhythmic lipid mediators

Myocardial epoxyeicosatrienoic acids composition



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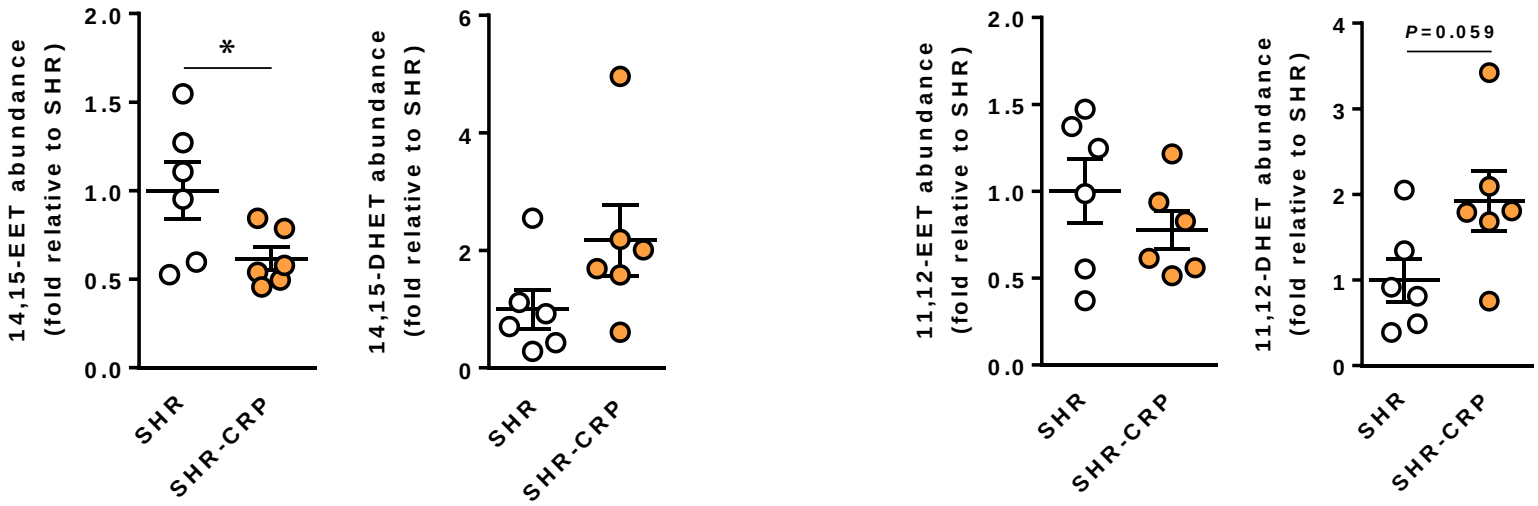
Pro- and antiarrhythmic lipid mediators

Myocardial epoxyeicosatrienoic acids composition



Plasma levels of antiarrhythmic PGI_2 and proarrhythmic TxA_2

PGI_2 ⇨ 6-keto $PGF_{1\alpha}$

TxA_2 ⇨ TxB_2

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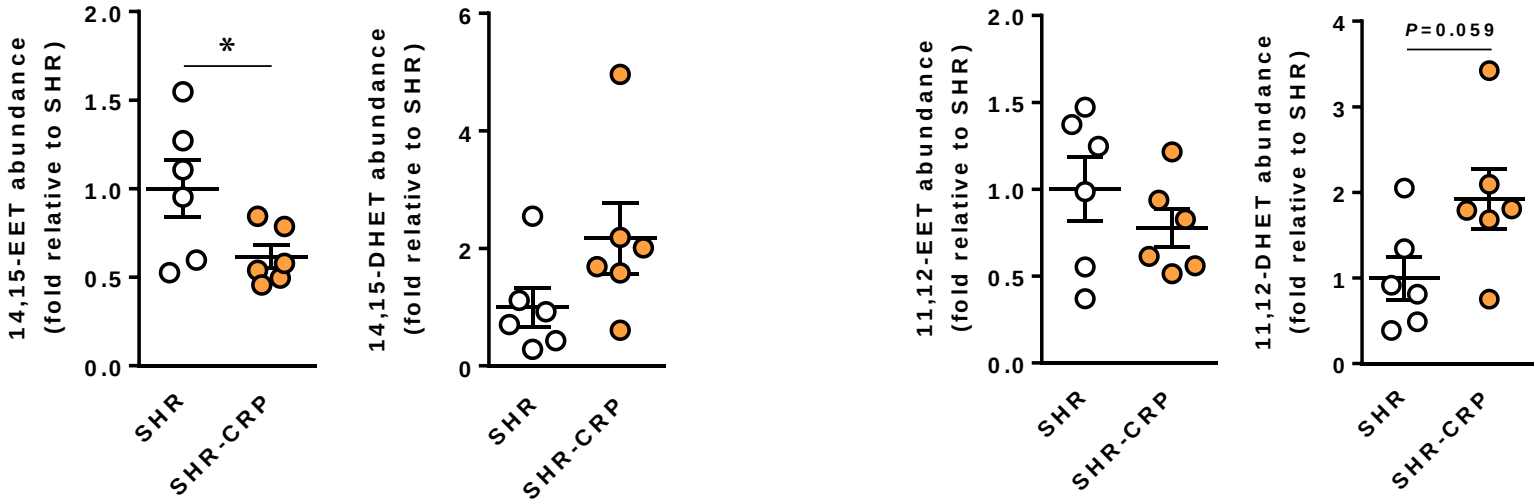
Pro- and antiarrhythmic lipid mediators

Myocardial epoxyeicosatrienoic acids composition



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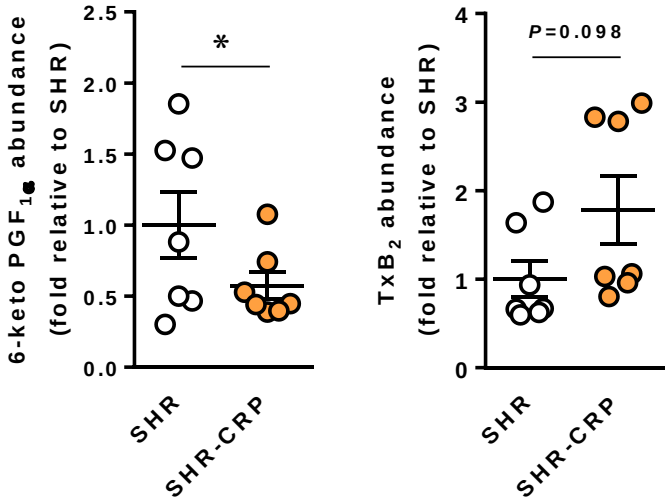

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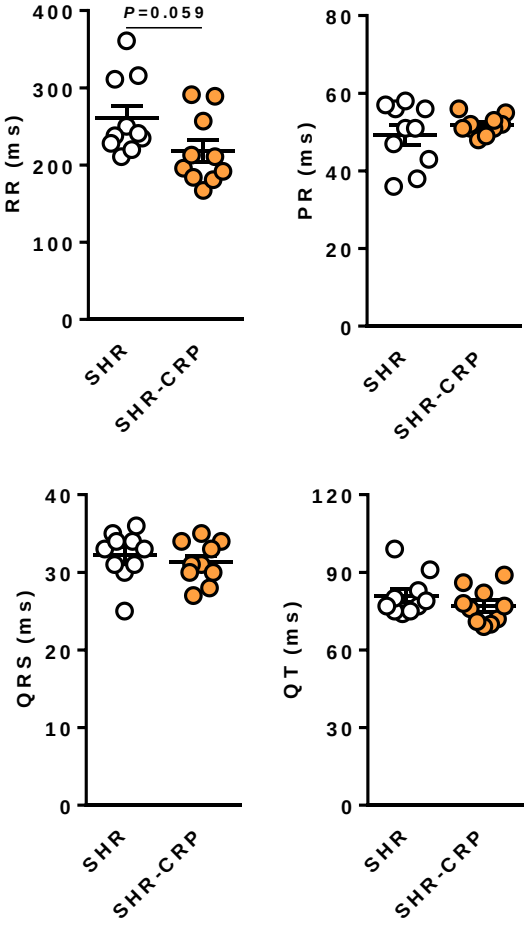
Electrophysiological measurements

Heart *in vivo* –
ECG analysis



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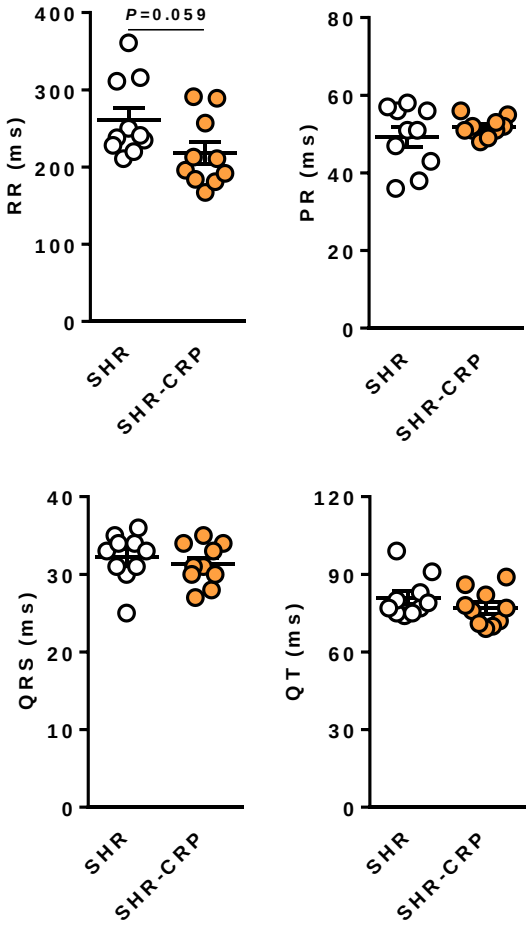
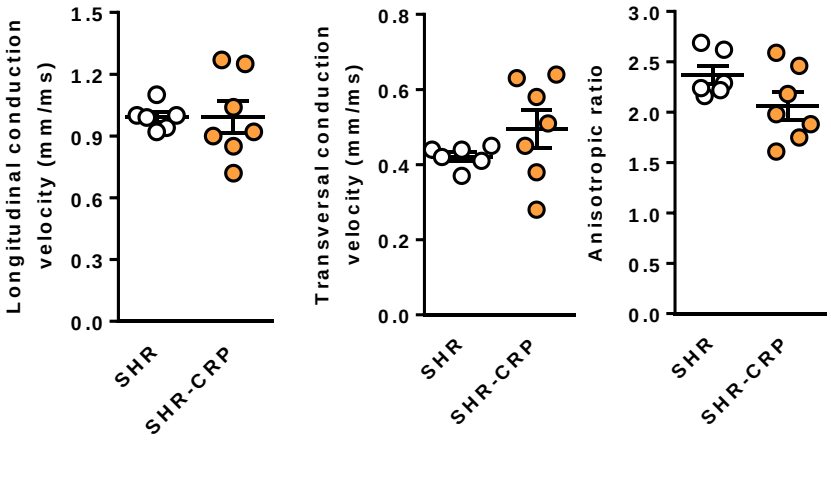
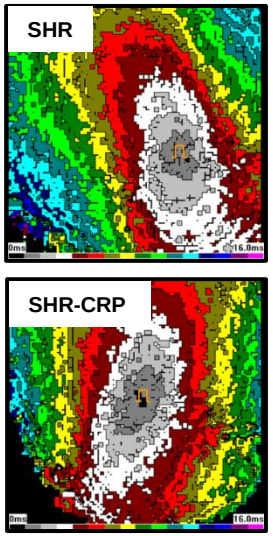
Electrophysiological measurements

Heart *in vivo* – ECG analysis



Heart *ex vivo* – conduction velocities





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General Aim

To find out whether transgenic expression of human CRP affects cardiac susceptibility to ischemia/reperfusion injury in adult SHR-CRP.

Specific Aims

In SHR-CRP, to clarify the mechanism(-s) of:

i) severe ischemic tachyarrhythmias
ii) infarct size-limiting effect

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