Exercise Response in Children and Adolescents Late After Kawasaki Disease According to Early Coronary Status

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Conflict of Interest

- Data are from a Pharmaceutical sponsored multicenter study

- Independent analysis
- No conflict of interest
- No financial relationship

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Introduction

- KD classified under the **vasculitis** nomenclature

- Severity of cardiovascular sequelae associated with the severity of coronary artery (CA) lesions.
- Endothelial dysfunction; Impaired myocardial flow reserve; abnormal SN and AV node function; QT interval dispersion; Autonomic dysfunction; ventricular dilation; Histologic myocardial alterations.

- KD causes **inflammatory myocarditis** in all patients

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Exercise testing in KD

- Most patients → no obvious clinical functional limitations with exercise after the convalescent stage:
  - A similar **exercise capacity** between KD and healthy children of the same age (*Rhodes 1996; Gravel 2012*)
  - A similar **exercise capacity** with or without **CA aneurysms** or **perfusion defects** (*Paridon 1995; Gravel 2012*)

- Recent studies:
  - Exercise-induced perfusion defects (*Kashyap 2011; Zanon 2008*)
  - Exercise-induced ECG abnormalities (*Gravel 2012*)

Even in subjects without CA lesions

Research Questions

Does exercise challenge highlight chronotropic or barotropic alterations following KD?
Is it associated with CA aneurysm status?

Besides exercise “duration” and “ischemic” changes, valuable information can be obtained from stress tests:

- Blood pressure response
- Chronotropic response
- Heart-rate recovery

Objectives

- Cardiolite-301, a multicenter study conducted in 2006-2008: «*A Study to Evaluate the Use and Safety of Cardiolite™ in Pediatric Patients with Kawasaki Disease*»

- Post-hoc analysis describing response to exercise challenge late after KD to determine response according to coronary artery status at onset:
  1. Exercise capacity **late during childhood** after KD
  2. Heart-rate and blood-pressure response **during exercise** and **during recovery**
  3. Evaluate if the ***severity of CA disease*** upon onset affects these parameters

Methods

- Inclusions:
  - Treadmill test
  - >6 years old
  - >1 year after the acute phase

- Exclusion:
  - Stationary cycle ergometer testing
  - Medication affecting exercise response
  - History of CA intervention
  - Uncertain presence/absence of aneurysm

Final study population (450 C-301 → **250 pts**):

- KD without CA aneurysm: n=117
- KD with CA aneurysm(s): n=133

Analysis

- Exercise challenge measurements:
  - Endurance time
  - Heart Rate, systolic BP and diastolic BP
  - At the following time points: **Rest**, **3-minute stages**, **peak exercise**, and **recovery** (1min, 3min, 5min and 10min)
- Myocardial perfusion defects
  - Assessed by Tc-99m Sestamibi SPECT imaging
  - Core-lab analysis by 3 independent readers

Analysis

- Raw data were compared between groups

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- Normalized to Z-scores calculated for gender and age, using available reference values:
  - Chatrath et al. 2002 «*Physical Fitness of Urban American Children*»
  - Ahmad et al. 2001 «*Responses of Non-Obese White Children to Treadmill Exercise*»

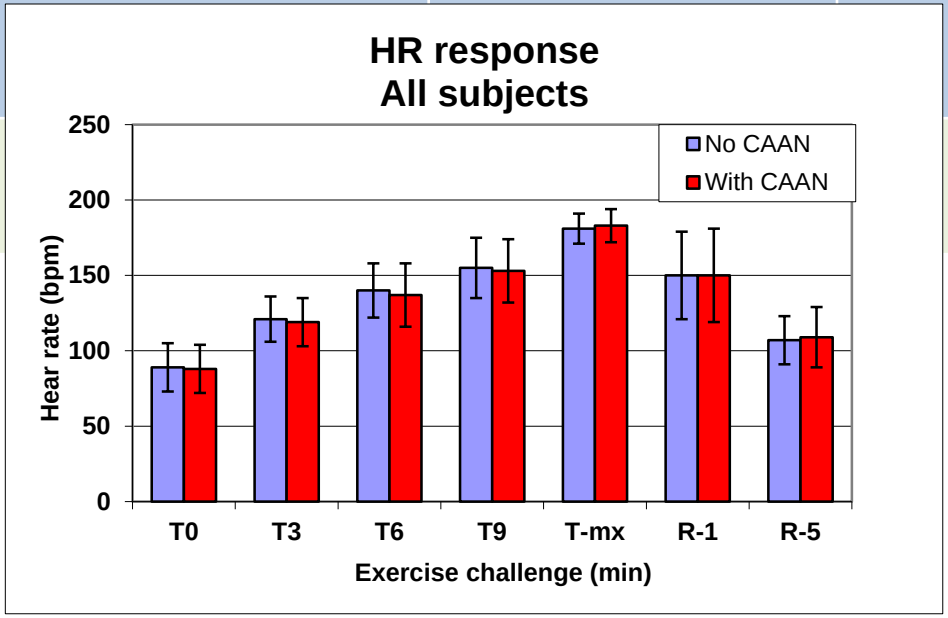
Results: Basic characteristics

	No CAAN	With CAAN
Age (years)	10.7±2.7	11.0±2.7
Height (cm)	143.6±16.4	145.5±17.3
Weight (kg)	41.7±16.7	42.3±16.8
BMI (kg/m^2)	19.6±4.7	19.3±4.1
Asian/Caucasian/other (%)*	47/40/13	65/27/8
Gender (male/female)	63/47	71/29
Time since diagnosis (yrs)	6.8±3.1	7.5±3.6
Reported cardiac symptoms (%)	17%	14%

* $p < 0.05$

Results: CAAN vs no CAAN

	No CAAN	With CAAN	*p value*
Endurance time (min)	11.3±2.6	11.0±2.6	0.343
Peak heart rate (% for age)	86.7±5.0	87.4±6.2	0.291
HR response & recovery			
BP response			



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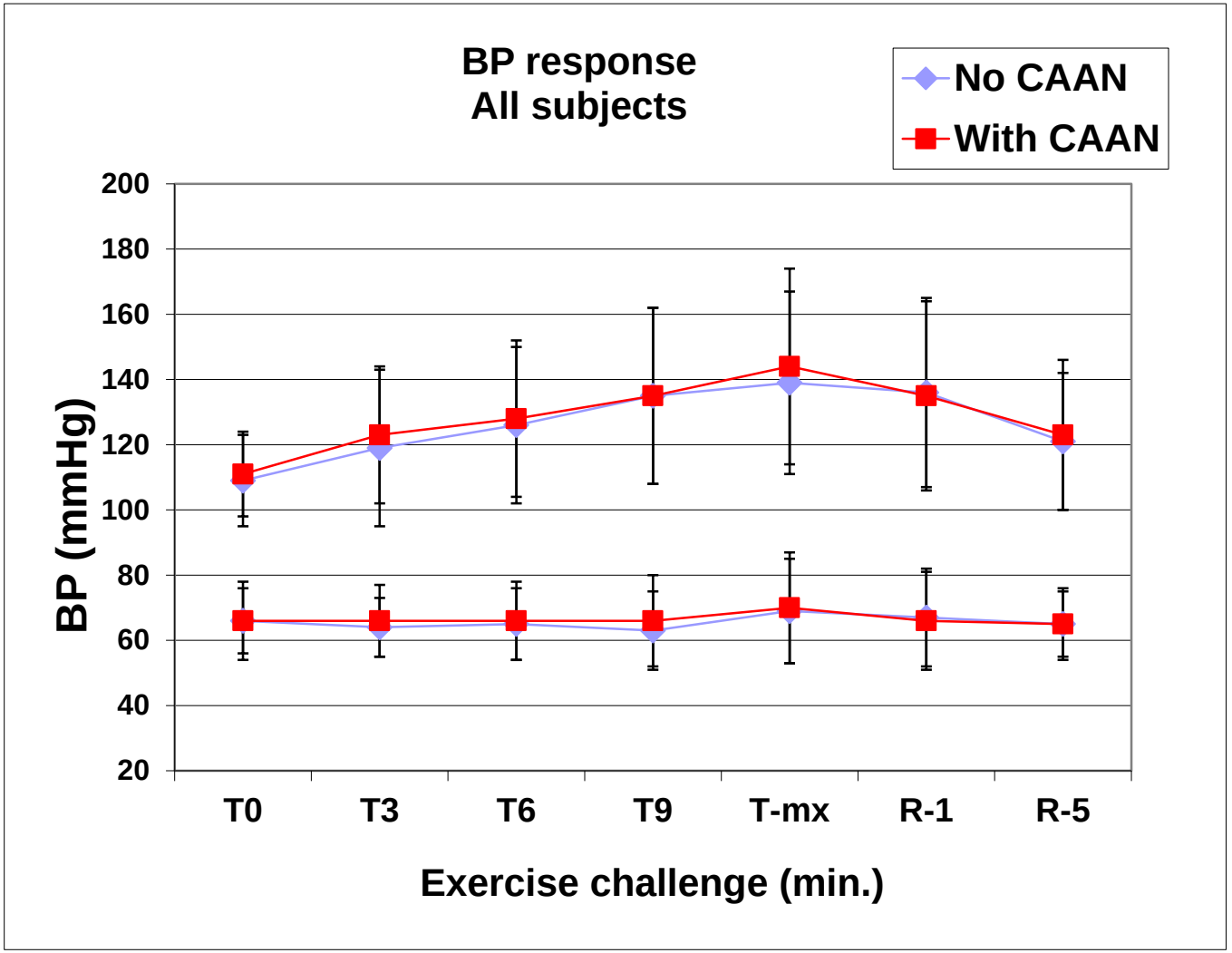
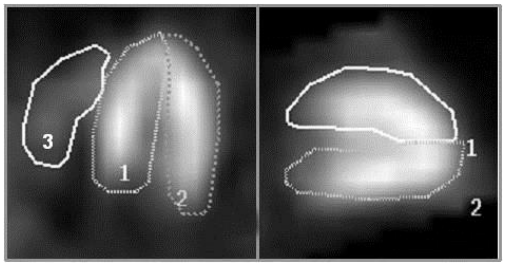
BP response: CAAN vs no CAAN



Myocardial perfusion



	No CAAN	With CAAN	*p value*
Fixed defects	12.8%	11.3%	0.708
Stress-induced defects	22.2%	16.5%	0.255

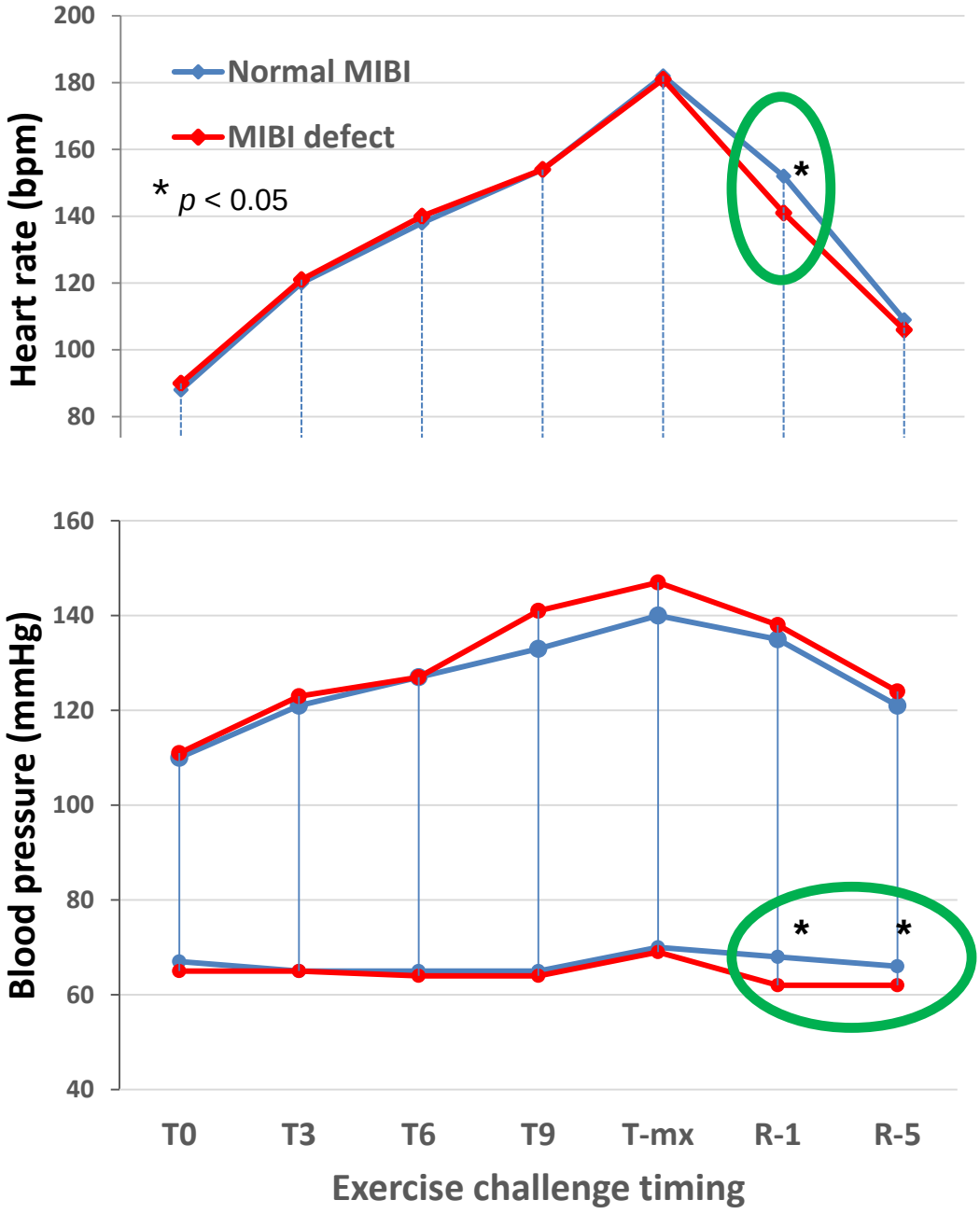
Subjects were redistributed based on perfusion scan, irrespective of CA status

Subsequent analysis

Abnormal perfusion imaging identified:

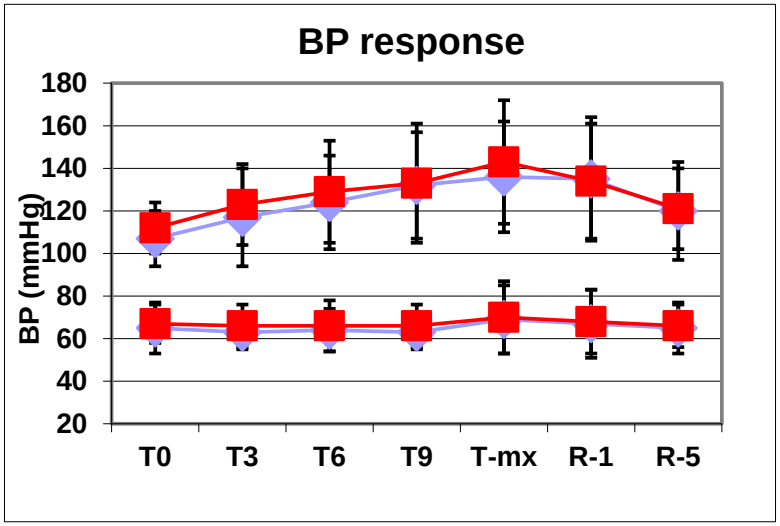
- lower HR
- lower diastolic BP

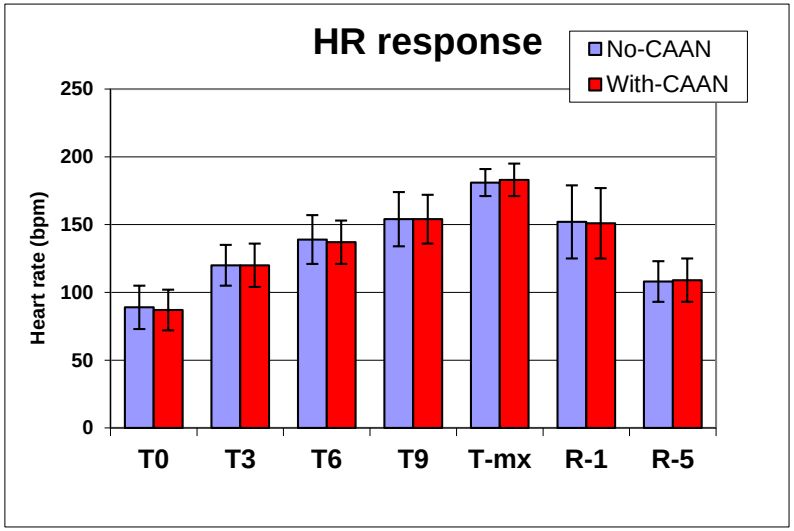
during recovery



Patients with normal MIBI

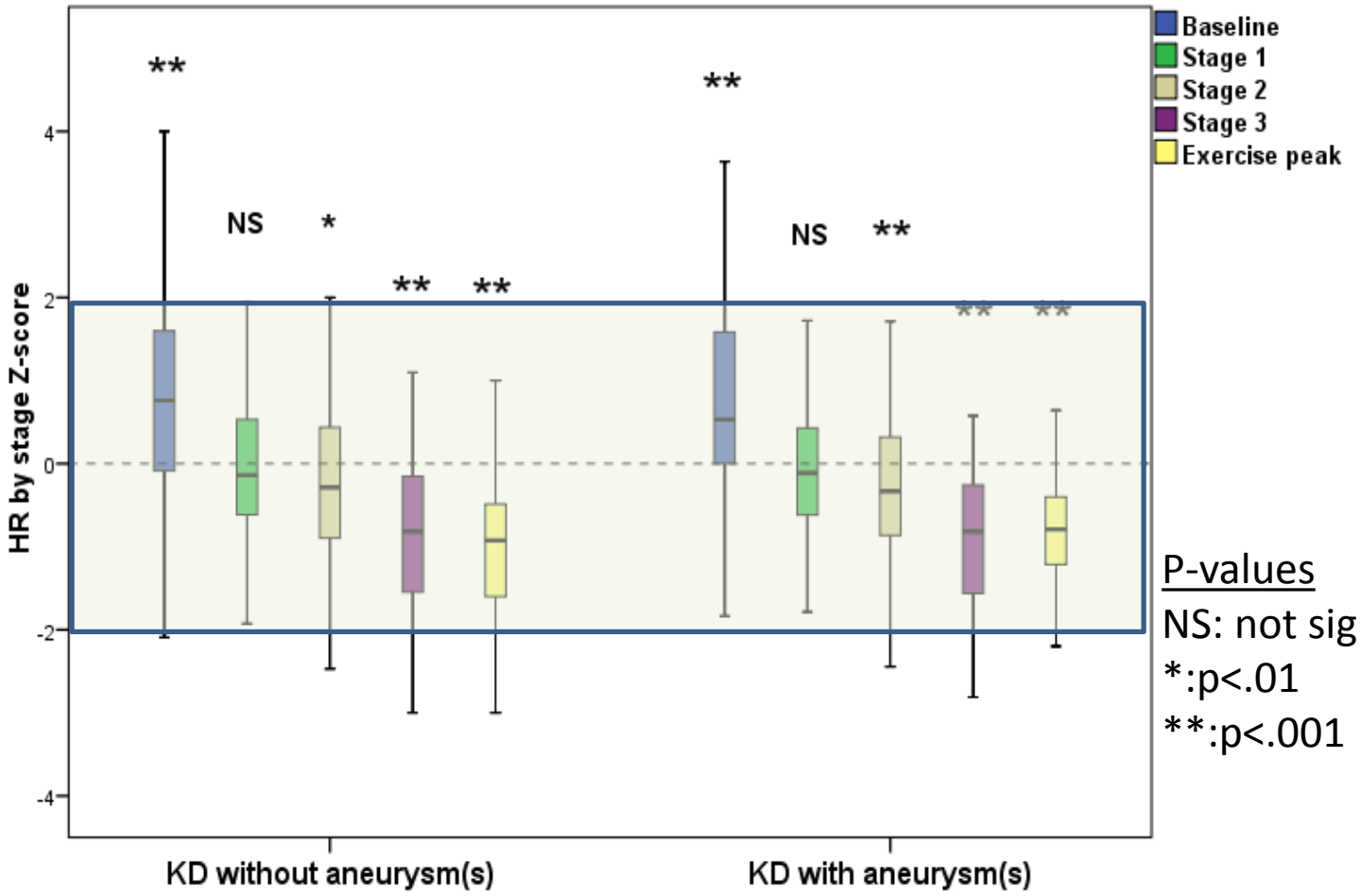
	No CAAN	With CAAN	*p value*
Endurance	11.47±2.7	11.1±2.6	NS
Peak HR (%-age)	86.6±5.2	87.6±6.2	NS





Normalized heart-rate response

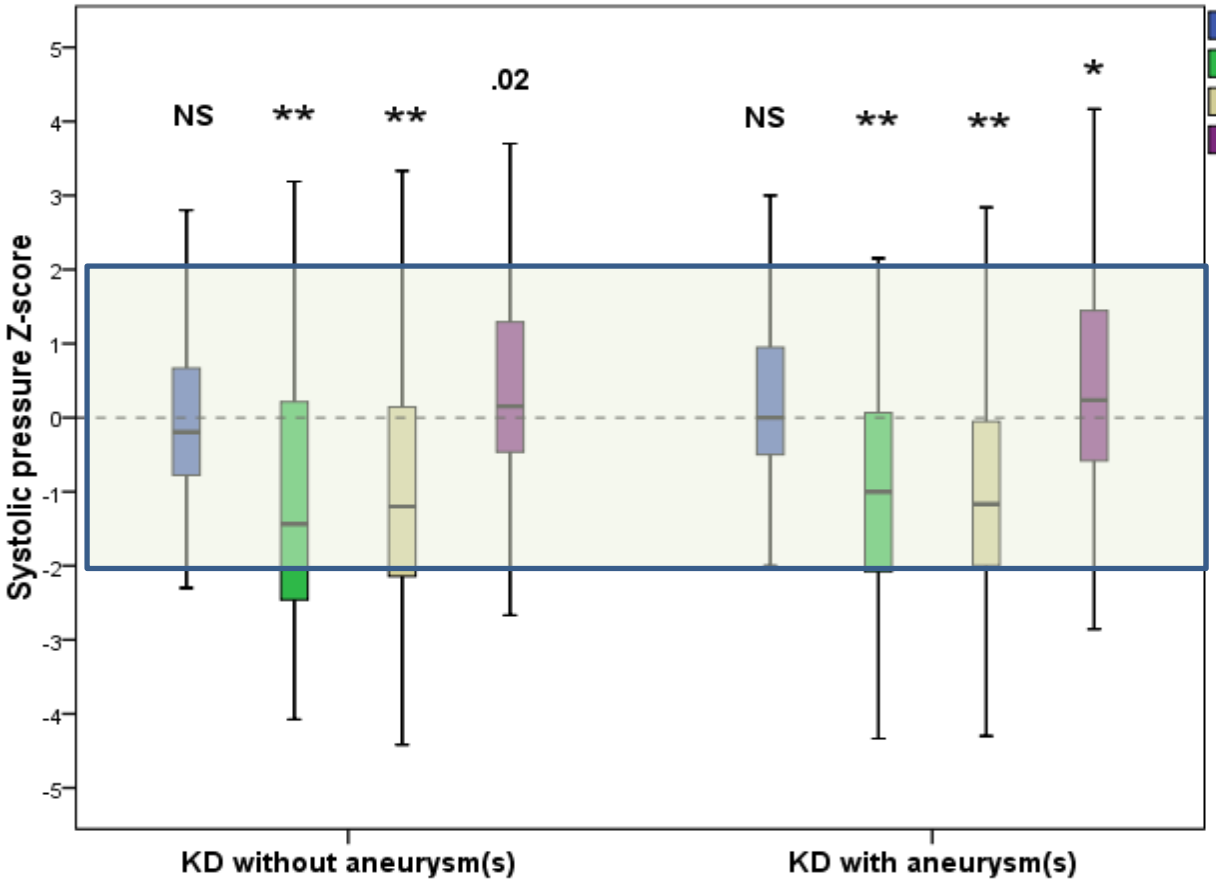
Comparable at all stages between CAAN+ and CAAN-



P-values
NS: not significant
*:p<.01
**:p<.001

Normalized Systolic BP response

Comparable at all stages between CAAN+ and CAAN-



P-values

NS: not significant

*:p<.01

**:p<.001

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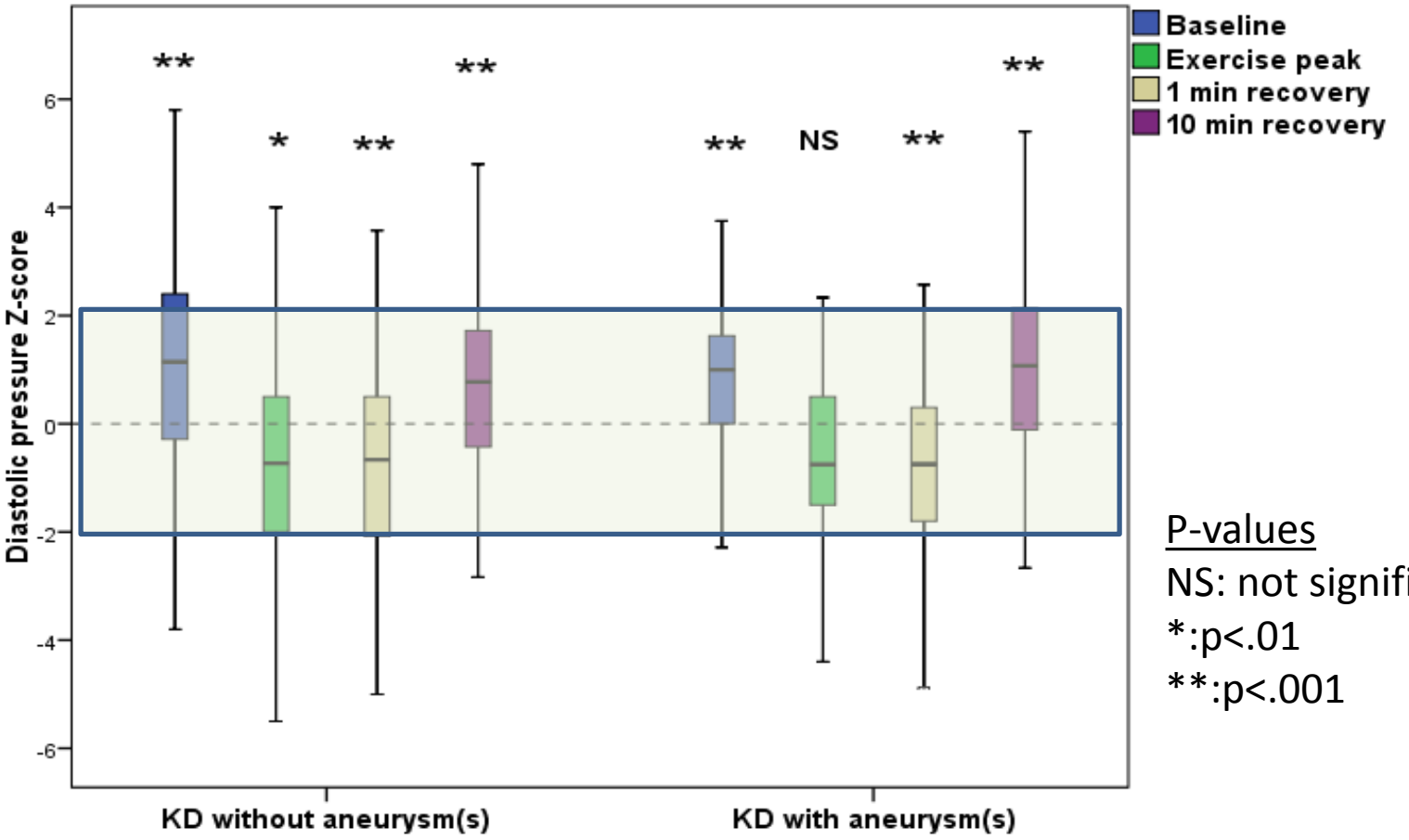
Normalized Diastolic BP response

Comparable at all stages between CAAN+ and CAAN-



P-values

NS: not significant

*:p<.01

**:p<.001

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Conclusion

- **Exercise capacity is preserved:**
  - Irrespective of CAAN status
  - Irrespective of myocardial perfusion status
- **Chronotropic response**:
  - **HR acceleration is NOT affected** by **CAAN** or **perfusion status**
  - **Faster HR recovery** in subjects with **abnormal perfusion**
- **Blood pressure response**
  - **Is NOT affected** by the **CAAN status**
  - **Diastolic BP is lower** at recovery in subjects with abnormal perfusion
- **Normalized** HR and BP response **sub-normal** vs. published pediatric series of healthy children

Questions ?

Lessons and future directions

- Assess autonomic system behavior post KD
- Assess response to exercise based on NT-proBNP profiling at onset.

Introduction

- KD classified under the **vasculitis** nomenclature

- Severity of cardiovascular sequelae associated with the severity of coronary artery (CA) lesions:

  -aneurysms → the most severe complications

  -stenosis → Incremental prevalence during youth

  -Primary myocardial infarction: first year after onset

  -Secondary myocardial infarction: pre-adolescence and up

- KD causes **inflammatory myocarditis** in <u>all patients</u>

BP response: all normal MIBI scan

		No CAAN (n=111)	With CAAN (n=91)	*P* value
SBP/DBP (mmHg)	Baseline	107±13/65±12	112±12/67±9	**0.005/NS**
	3 min	117±23/63±8	123±19/66±10	**NS/0.045**
	6 min	124±22/64±10	129±24/66±12	NS / NS
	9 min	132±25/63±8	133±28/66±10	NS / NS
	Peak	136±26/69±16	143±29/70±17	NS / NS
	Rec.1min	135±29/67±16	134±27/68±15	NS / NS
	Rec.5min	120±23/65±12	121±19/66±10	NS / NS