Altered vascular function in boys with hypospadias- role of reactive oxygen species

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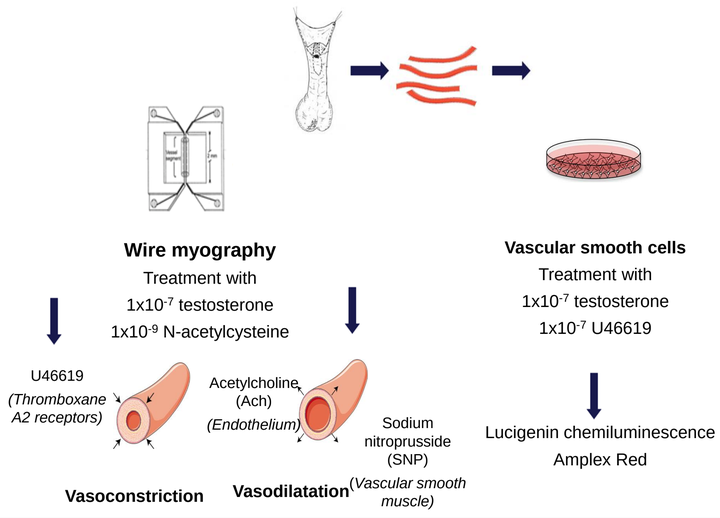
Introduction

- Hypogonadism, defined as clinical or biochemical evidence of low circulating testosterone, leading to abnormalities of the external genitalia occurs in approximately 1 in 300 live births.
- Animal models have demonstrated that there is a programming window during which androgens are required for normal masculinisation of the genital tract, without which hypospadias and other genital abnormalities occur.
- In recent years, multiple studies have demonstrated that low endogenous levels of testosterone increase the risk of cardiovascular morbidity and mortality in adult men. To date there is no data regarding this relationship in children.
- Here we determine if young boys with hypospadias, which are often associated with hypogonadism, exhibit vascular dysfunction through altered vascular androgen signaling, which may be ameliorated by testosterone.

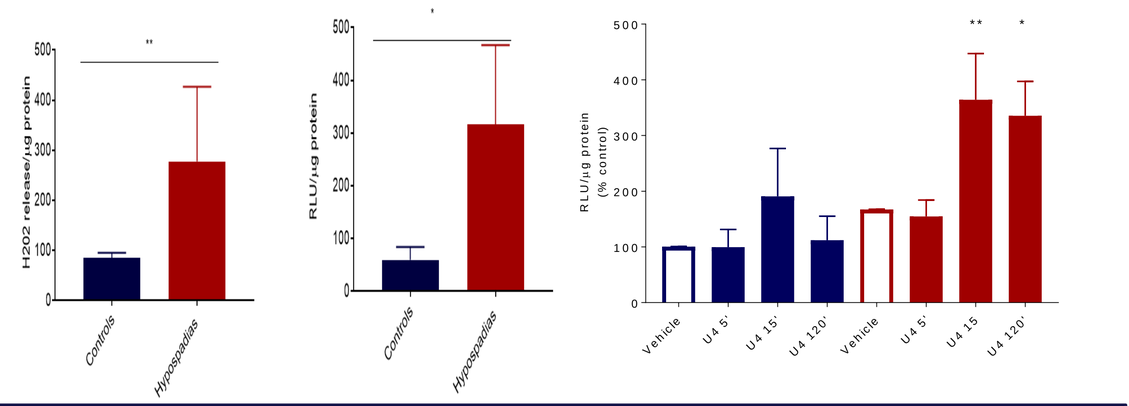
Methods



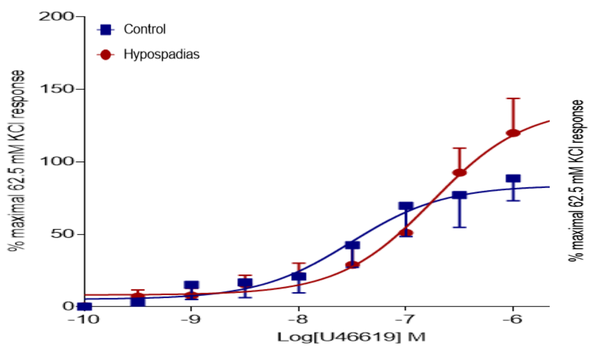
We hypothesised that boys with hypospadias exhibit vascular dysfunction through altered vascular androgen signaling, which will be improved by testosterone.

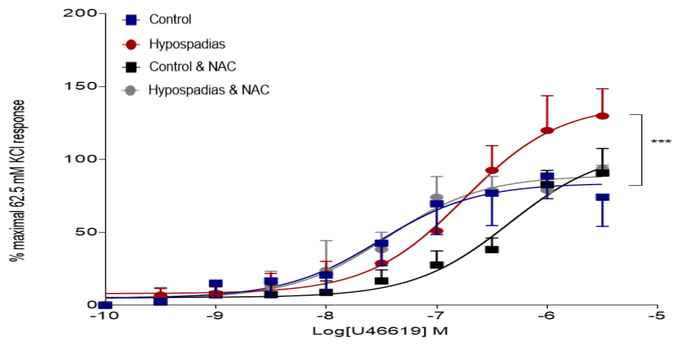
Results

Median (range)	Hypospadias (n=20)	Controls (n=29)	p
Age	1.84 (1.2-6.4) yrs	2.0 (1.2-12.9) yrs	0.23
Gestation at birth	39 (35-40) wks	40 (26-42) wks	0.09
Birthweight	3.3 (0.7-4.0) kg	3.5 (1.5-4.6) kg	0.28
External masculinisation score (EMS)	10 (3-11) Proximal 6 (30%) Mid 5 (25%) Distal (45%)	12 (12-12)	<0.00001
Heart rate (bpm)	118 (90-155)	120 (70-168)	0.69
Systolic blood pressure (mmHg)	90 (75-100)	90 (70-105)	0.36
Diastolic blood pressure (mmHg)	40 (30-60)	45 (35-60)	0.27
Cholesterol (mmol/l)	4.4 (3.2-4.5)	4 (2.0-4.7)	0.44
Triglycerides (mmol/l)	1.1 (0.6-1.8)	0.8 (0.5-1.7)	0.09
Fasting glucose (mmol/l)	4.3 (3.4-5.3)	4.7 (3.5-6.8)	0.29
LH (range) (U/l)	0.1 (0.1-1.4)	0.1 (0.1-0.5)	0.91
FSH (range) (U/l)	0.7 (0.1-3)	0.5 (0.2-1.8)	0.61
Testosterone (nmol/l)	<0.5	<0.5	>0.99
AMH (pmol/l)	875 (421-1472)	987 (371-1725)	0.98

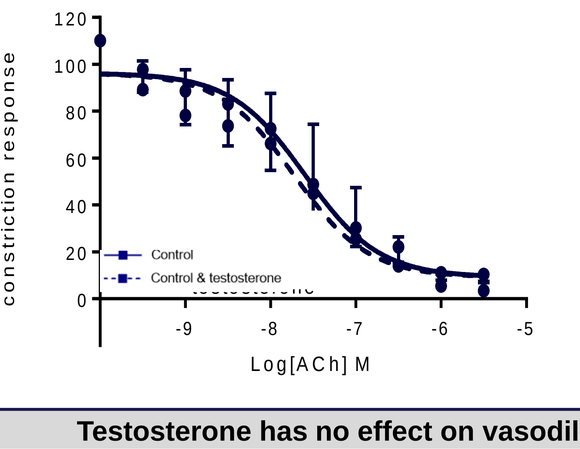


VSMCs from boys with hypospadias produce more ROS than controls.

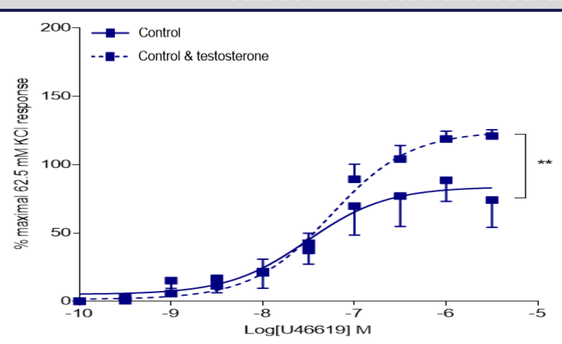


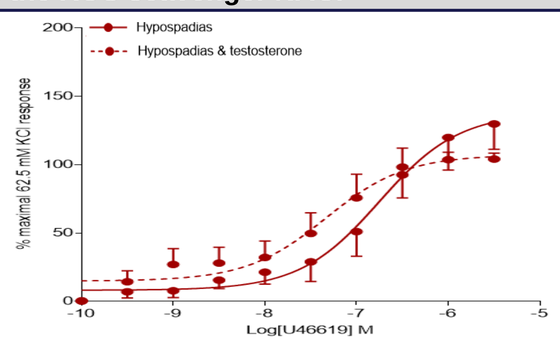


Genital skin arteries from boys with hypospadias contract more- than control arteries - an effect which is reduced with the ROS scavenger NAC.

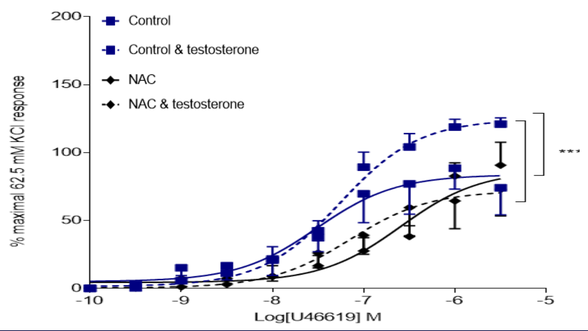


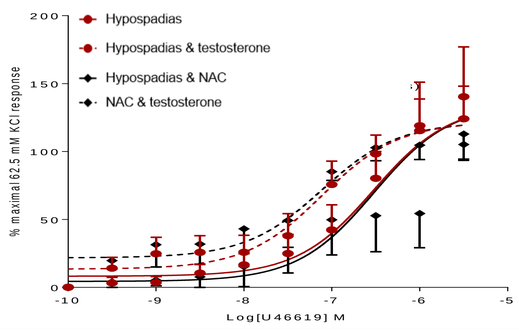
Genital skin arteries from boys with hypospadias have reduced endothelium dependent and independent vasodilatation compared to arteries from controls.



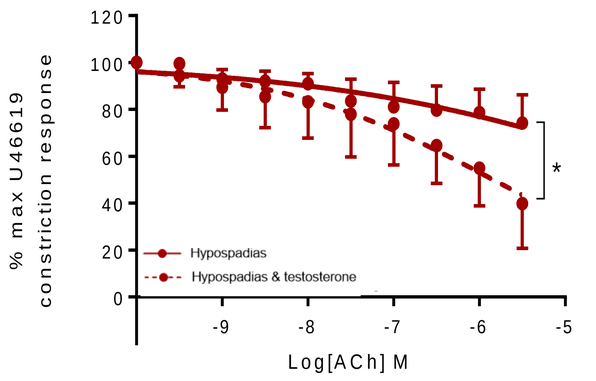


. Testosterone increases contraction in genital skin arteries from controls but not from boys with hypospadias.





. NAC attenuates the effects of testosterone in controls but does not alter contraction in boys with hypospadias.



***p≤0.0001, **p ≤ 0.001, * p ≤ 0.05. n= 7-13controls, 6-12 boys with hypospadias

Testosterone improves vasodilatation in arteries from boys with hypospadias.

Conclusions

- First study examining paediatric subcutaneous resistance arteries.
- Resistance arteries from boys with hypospadias are dysfunctional.
- Increased vascular contractility and reduced vasorelaxation may be due to increased ROS generation.
- Testosterone improves vasorelaxation but not contraction in hypospadias.
- Our findings indicate that hypogonadism is associated with vascular dysfunction and vascular oxidative stress in young boys. These phenomena may predispose boys with low testosterone levels to increased risk of cardiovascular disease later in life. Long-term studies are required to assess this.

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Sex differentiation, gonads and gynaecology or sex endocrinology

Angela Lucas-Herald

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