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## Estimated versus achieved maximal oxygen consumption in severely burned children Maximal oxygen consumption in burned children

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### Abstract

**Purpose**—In burned children, exercise training increases maximal oxygen consumption ( $VO_2$  max) and can be combined with the nonspecific beta-blocker propranolol to decrease cardiac work.  $VO_2$  max is estimated if indirect calorimetry is not available. We compared measured and estimated  $VO_2$  max in severely burned children treated with or without propranolol to determine the suitability of commonly used formulas in these populations.

**Methods**—Patients received propranolol or placebo (control) during acute hospitalization.  $VO_2$  max was measured during a modified Bruce treadmill test at discharge and compared to values obtained using the Cooper, Bruce, American College of Sports Medicine, and Porro formulas. Pearson correlations and Bland-Altman analyses were used to compare measured and estimated values.

**Results**—Ninety-nine children (propranolol  $n=46$ , control  $n=53$ ) admitted at our facility between 2003 and 2016 were analyzed. Age at burn (propranolol  $12\pm 4$  years, control  $12\pm 3$  years,  $p=0.893$ ) and total body surface area burned (propranolol  $44\pm 15\%$ , control  $49\pm 14\%$ ,  $p=0.090$ ) were comparable between groups. Measured  $VO_2$  max was higher in the propranolol group ( $25.5\pm 6.0$

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#### Author's contributions

Study conception and design: CT, DNH, LKB, OES; acquisition of the data: CT, DP; statistical analysis: CT, OES; analysis and interpretation of the data: CT, OES; drafting of the manuscript: CT, DP, LKB, RPM, OES; critical revision: DNH, LKB, RPM, OES. All authors approved the final version of the manuscript.

#### Declarations of interest

None

mL/min/kg vs.  $22.0 \pm 4.7$  mL/min/kg,  $p=0.002$ ) and was generally lower than estimated values. Age, sex, inhalation injury, body mass index, exercise time, and maximal speed were predictive of measured  $\text{VO}_2$  max in the control group. Age, sex, and maximal speed were predictive in the propranolol group. Backward selection yielded the formula  $[7.63 + 2.16 \times \text{sex}(\text{females}=0, \text{males}=1) + 0.41 \times \text{age}(\text{years}) + 0.15 \times \text{maximal speed}(\text{m/min})]$  ( $R^2=0.6525$ ).

**Conclusions**—Propranolol seems to have beneficial effects on cardiorespiratory capacity in burned children. However, estimated  $\text{VO}_2$  max with common formulas were too high. The  $\text{VO}_2$  max formula reported here is suitable for propranolol-treated children and the Porro formula for non-propranolol-treated children.

### Keywords

Physical activity; oxygen uptake; exercise; burn injury; pediatric

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### Introduction

Severe burns affect multiple organ systems and result in a loss of muscle mass, increased cardiac work, and protein catabolism [1–4]. We have previously shown patients also experience decreased cardiorespiratory exercise capacity for up to 2 years post burn [5]. Pharmacological treatments are sometimes used to counteract increased cardiac work. One such treatment is the administration of propranolol, a nonselective  $\beta$ -adrenergic receptor antagonist, which can reduce cardiac work and burn-induced hypermetabolism [1]. When combined with exercise training, propranolol (in combination with oxandrolone) has been shown to increase cardiorespiratory fitness [6].

A key outcome for exercise rehabilitation and prognosis is a patient's maximal oxygen consumption ( $\text{VO}_2$  max [mL/kg/min]), since it indicates cardiorespiratory fitness and endurance and remains attenuated for several years post-burn [7–9]. A commonly used method for measuring  $\text{VO}_2$  max during exercise is indirect calorimetry. At our center, indirect calorimetry during a (modified) Bruce treadmill protocol is used [10]. However, indirect calorimetry may not be possible because of the cost of calibration gases, mouthpieces, and calorimeters needed for measurement. Another limitation to assessing gas exchange using calorimetry is the inability of some patients with severe burn injuries to be fitted with a respiratory mouthpiece or mask. Thus, more general means of measuring  $\text{VO}_2$  max or formulas for estimating  $\text{VO}_2$  max are important. Most of the commonly used formulas were developed in healthy adults [11, 12]. In addition, our group has reported on formulas for predicting  $\text{VO}_2$  max in severely burned children not receiving propranolol [13]. However, to our knowledge, no formula exists for severely burned children treated with propranolol.

In the present study, we compared  $\text{VO}_2$  max achieved during a treadmill exercise with predicted  $\text{VO}_2$  max in severely burned children treated with or without propranolol. We anticipated that children receiving propranolol would require a different formula for estimating  $\text{VO}_2$  max because of the cardiac effects of propranolol.

## Methods

### Patients

Severely burned children who were admitted to our institution between February 2003 and July 2016 and treated with propranolol were included in this study and compared to those not treated with propranolol. Patients were included if they performed a treadmill exercise test at discharge. Patients with a history of cardiac disorders or events, leg amputation, or psychological disorders were excluded from the analysis. Demographic and clinical data included sex, age at burn, percent total body surface area (%TBSA) burned, presence of inhalation injury, height, weight, resting heart rate (RHR), peak heart rate, and body mass index (BMI, kg/m<sup>2</sup>). The study was approved by the Institutional Review Board of the University of Texas Medical Branch, Galveston, Texas (Protocol 04-157). Informed consent was obtained from all individual participants or their parents prior to study participation.

### Treadmill exercise test (modified Bruce protocol) and VO<sub>2</sub> max measurement

Cardiovascular exercise capacity was assessed during modified Bruce treadmill tests [10, 14]. The maximal rate of VO<sub>2</sub> was measured using the Ultima CardiO2 Combined Cardiorespiratory Exercise and 12-Lead ECG (Medgraphics Cardiorespiratory Diagnostics, St. Paul, MN, USA). Prior to the test, the metabolic cart was calibrated with an oxygen and carbon dioxide mixture of known concentration. The exercise test was performed as follows. Patients were fitted with an airtight mouth piece, and inspired/expired gas, flow, and gas volumes were measured while the patients were sitting. At the start of the test, treadmill speed was set at 1.7 mph with a 0% grade elevation. Every 3 minutes, speed (2.5, 3.4, 4.2, 5 mph) and elevation (5%, 10%, 12%, 14%, 16%) were increased. The patients were encouraged to give their maximum effort to reach VO<sub>2</sub> max, but a respiratory exchange ratio (RER) >1.1 was also required. VO<sub>2</sub> max was calculated as the mean of the last 30 seconds of each state. The test was stopped once the patient was unwilling to continue or volitional fatigue was achieved and when the RER threshold was met. The following parameters were recorded during the test: duration of the test (minute), maximum speed (mph), maximum grade (%), peak heart rate, and RER.

### Estimated VO<sub>2</sub> max

Measured VO<sub>2</sub> max, as assessed using the Ultima CardiO2 System, was compared with predicted values obtained using the Cooper, Bruce, American College of Sports Medicine (ACSM), and Porro [13] formulas. The Cooper formula was as follows: VO<sub>2</sub> (mL/min) = 43.6 × height (cm) – 4547.1 for males and VO<sub>2</sub> (mL/min) = 22.5 × height (cm) – 1837.8 for females. Both formulas are in use for children under 16 years [11]. For VO<sub>2</sub> max, VO<sub>2</sub> is divided by weight [kg]. The Bruce formula was as follows: VO<sub>2</sub> max (mL/kg/min) = 14.76 – (1.379 × T) + (0.451 × T<sup>2</sup>) – (0.012 × T<sup>3</sup>) for males and VO<sub>2</sub> max (mL/kg/min) = 4.38 × T – 3.9 for females [12]. T is the time of exercise expressed as decimals of a minute. The ACSM mentions the following formula for prediction of VO<sub>2</sub> max while walking: VO<sub>2</sub> max (mL/kg/min) = 3.5 + 0.1 × speed (m/min) + 1.8 × speed (m/min) × grade (percent grade expressed as decimal format). One mile per hour is 26.82 m/min [12]. We used this formula since most, if not all of our patients, were unable to run. Porro and coworkers developed a formula for severely burned children at 6 months after discharge from the burn intensive care

unit [13].  $VO_2 \text{ max} = 10.33 - 0.62 \times \text{age (years)} + 1.88 \times \text{treadmill time (min)} + 2.3 (\text{sex; females} = 0, \text{males} = 1)$ .

### Statistical analysis

All data are presented as mean  $\pm$  standard deviation (SD) if not indicated otherwise. Comparisons of the demographics of both groups were performed using paired t-tests. A p value less than 0.05 was considered to be significant. Estimated  $VO_2$  max calculated from the Cooper, ACSM, Bruce, and Porro formulas were correlated to the actual achieved values using Pearson's correlation. Agreement between measured  $VO_2$  max and predicted  $VO_2$  max values was assessed using the Bland-Altman method [15, 16]. A repeated measures ANOVA followed by Tukeys test was used to compare actual and predicted values for  $VO_2$  max. In addition, a linear regression model was used to find predictive variables for both groups. Based on the full model including age at burn, sex, %TBSA burned, inhalation injury, and BMI, a stepwise backward selection was performed. A new formula for estimated  $VO_2$  was then created for both groups based on these findings. Statistical analyses were performed using XLSTAT (Addinsoft SARL, New York, USA) and Graph Pad Prism 7.03 for Windows (La Jolla, USA).

### Results

A total of 99 patients (n = 46 propranolol, n = 53 control) with a mean age at burn of  $12.4 \pm 4.0$  years in the propranolol group and  $12.5 \pm 3.4$  years in the control group were included in the analyses. The two groups were well balanced in terms of age at burn, sex, %TBSA burned, presence of inhalation injury, height, weight, BMI, and length of hospital stay (Table 1).

Achieved  $VO_2$  max was  $25.5 \pm 6.0$  mL/min/kg in the propranolol group and  $22.0 \pm 4.7$  mL/min/kg in the control group (p = 0.002). Achieved  $VO_2$  max and predicted  $VO_2$  max derived from the different formulas are shown in Table 1. Predicted  $VO_2$  max was higher than the achieved value for all formulas in both groups, except for the Porro formula in the propranolol group.

ANOVA analyses showed significant differences between measured  $VO_2$  max and predicted values in both propranolol and control group (p < 0.001). Tukey's multiple comparison test then showed significant differences between measured  $VO_2$  max and Cooper's, Bruce's and ACSM's formulas (p < 0.001), but with Porro's in propranolol (p = 0.497) and control group (p = 0.427). Pearson's analysis revealed that, in the case of almost all formulas, poor correlations were present between predicted and achieved  $VO_2$  max for both the propranolol group (Cooper,  $R^2 = 0.14$ ; Bruce,  $R^2 = 0.23$ ; ACSM,  $R^2 = 0.21$ , Porro,  $R^2 = 0.32$ ) and the control group (Cooper,  $R^2 = 0.20$ ; Bruce,  $R^2 = 0.41$ ; ACSM,  $R^2 = 0.27$ , Porro,  $R^2 = 0.52$ ). The mean values predicted by the Porro formula were the closest to achieved values, with this formula having the highest  $R^2$  for both the propranolol and control groups and showing a mild-to-moderate correlation in the control group.

Results of the agreement analysis of achieved  $VO_2$  max and predicted values using the Bland-Altman method are shown in Table 2 and Figures 1 and 2. Poor agreement was found

between measured and predicted VO<sub>2</sub> max for all four formulas. Porro's formula showed the lowest mean difference in both the control and propranolol group.

RHR was  $101.8 \pm 19.5$  bpm in the propranolol group and  $119.8 \pm 16.5$  bpm in the control group ( $p < 0.001$ ), while peak heart rate was  $151.5 \pm 27.1$  bpm in the propranolol group and  $179.7 \pm 16.4$  bpm in the control group ( $p < 0.001$ ). RER was  $1.1 \pm 0.1$  in propranolol patients and  $1.1 \pm 0.2$  in control patients ( $p = 0.313$ ).

Multiple linear regression analysis showed that there was no influence of %TBSA burned ( $p = 0.653$ ), BMI ( $p = 0.140$ ), or presence of inhalation injury ( $p = 0.985$ ) on measured VO<sub>2</sub> max in the propranolol group. The dependent variable "VO<sub>2</sub> max" could be predicted from a linear combination of the independent variables "maximal speed" ( $p < 0.001$ ), "age" ( $p = 0.026$ ), and "sex" ( $p = 0.046$ ) for the propranolol group ( $R^2 = 0.652$ ). In the control group, the dependent variable "VO<sub>2</sub> max" could be predicted from a linear combination of the independent variables "age" ( $p = 0.830$ ), "BMI" ( $p = 0.008$ ), "sex" ( $p = 0.359$ ), "presence inhalation injury" ( $p = 0.137$ ), "exercise time" ( $p = 0.087$ ), and "maximal speed" ( $p = 0.194$ ) ( $R^2 = 0.454$ ). This was the model with the highest  $R^2$  and contained nonsignificant variables as well. The linear regression models after variable selection are shown in Table 3. The formulas are as follows: VO<sub>2</sub> max (propranolol) =  $7.63 + 2.16 \times \text{sex}$  (females = 0, males = 1) +  $0.41 \times \text{age}$  (years) +  $0.15 \times \text{maximal speed}$  (m/min) and VO<sub>2</sub> max (control) =  $20.9 + 1.3 \times \text{sex}$  (females = 0, males = 1) -  $0.08 \times \text{age}$  (years) -  $2.16 \times \text{inhalation injury}$  -  $0.36 \times \text{BMI}$  +  $0.47 \times \text{exercise time}$  (min) +  $0.07 \times \text{maximal speed}$  (m/min). A comparison of predicted VO<sub>2</sub> max and achieved values for both groups is shown in Figure 3.

## Discussion

In the present study, severely burned children who received propranolol showed a higher cardiorespiratory capacity than control patients when assessed during a treadmill exercise at discharge. VO<sub>2</sub> max values derived from all predictive formulas were higher than achieved values. Linear regression analysis indicated age, sex, and maximal speed to be predictive parameters for VO<sub>2</sub> max in the propranolol-treated patients and age, BMI, sex, presence of inhalation injury, exercise time, and maximal speed to be predictive in control patients.

In both groups, achieved VO<sub>2</sub> max was lower than predicted VO<sub>2</sub> max determined using the Cooper, Bruce, ACSM and Porro formulas. Moreover, lower correlations were present in the propranolol group for all formulas except the Porro formula. Agreement analysis using the Bland-Altman method showed poor agreement between measured and predicted VO<sub>2</sub> max for all four evaluated formulas, with the Porro formula showing the lowest mean difference. These findings suggest that these formulas are not applicable to this particular study population. The Bruce protocol was originally developed for diagnosing coronary artery disease in middle-aged men [10], whereas the ACSM formulas are typically used for young and fit subjects and was originally developed for a submaximal steady state exercise [17, 18]. This may explain why the predicted VO<sub>2</sub> values are too high for the cohort in this study. Porro et al. developed their prediction formula in severely burned children at 6 months after discharge. They reported a  $R^2$  of 0.63 between measured and predicted VO<sub>2</sub> max [13]. In the present study, patients were evaluated at discharge, and one group received propranolol

during their stay. This could explain the discrepancies between predicted and achieved values in our cohort. However, it is not surprising that  $\text{VO}_2$  max values derived from the Porro formula were the closest to the achieved values in the present study because this formula was developed using data from severely burned children.

The significantly lower RHR and peak heart rate in the propranolol group is in line with several other studies. This finding is not surprising given that propranolol is a nonselective  $\beta$ -adrenergic receptor antagonist and has been shown to effectively reduce tachycardia and resting metabolic rate in burn patients [19, 20]. Owing to its high number of beneficial effects on post-burn recovery [6, 21, 22], propranolol recently became standard of care at our institution. Because propranolol may become the standard of care at other institutions, decreases heart rate, methods that use heart rate alone to predict  $\text{VO}_2$  max [23] are not appropriate for patients receiving this drug.

Linear regression models revealed age, sex, and maximal speed to be predictive of  $\text{VO}_2$  max in the propranolol group. Accordingly, all formulas evaluated contain one or more of these variables [10, 11, 13, 18]. Administration of propranolol seems to have a beneficial effect on cardiorespiratory capacity in severely burned children at discharge, and therefore these patients can hardly be compared to those who did not receive this drug. Since propranolol is now standard of care for children with severe burns at our institution, but not yet at other institutions, we suggest that different formulas be used to predict  $\text{VO}_2$  max in this group. For the control group, sex, age, presence of inhalation injury, BMI, exercise time, and maximal speed were predictive factors for  $\text{VO}_2$  max. These factors yielded the highest achievable  $R^2$ , even though not all were significant. The  $R^2$  of this formula was lower than that of the Porro formula and contains several parameters, making it impractical to use. Therefore, we recommend using the Porro formula for patients not receiving propranolol [13].

The exact mechanisms by which propranolol increases  $\text{VO}_2$  max need to be evaluated in further studies. The formula reported here for severely burned children receiving propranolol should also be evaluated further so that any needed adjustments can be made, and it should be validated in a larger cohort.

### Limitations of the study

One limitation of this study relates to %TBSA burned, which was higher in the control group, albeit not significantly. This may have influenced the performance of the children during the exercise test at hospital discharge. The same is true of localization of the burn injury, which was not taken into account. Our patients frequently suffer from pain or a limited range of motion, and the children studied here may not have reached their maximal effort, as assumed by the  $\text{VO}_2$  max formulas. However, an RER = 1.1 was part of the inclusion criteria and indicates maximal effort. Some of the patients also had inhalation injury, which can affect cardiorespiratory capacity. This could explain the discrepancy between estimated and achieved  $\text{VO}_2$  max to a certain extent.

However, this does not explain the higher  $\text{VO}_2$  max in the propranolol group, since both groups were well balanced in terms of presence inhalation injury and other demographics.

## Conclusion

Propranolol appears to have a beneficial effect on exercise performance in children with severe burns. This underscores the utility of this pharmacological treatment in this specific cohort. Prediction formulas for  $\text{VO}_2$  can be used if the equipment for indirect calorimetry is not available. However, the formulas commonly used to predicted  $\text{VO}_2$  max overestimate the actual achievable values in severely burned children. Therefore, we recommend using the Porro formula to determine  $\text{VO}_2$  max during exercise in severely burned children not receiving propranolol and our formula ( $7.63 + 2.16 \times \text{sex}$  (females = 0, males = 1) +  $0.41 \times \text{age}$  (years) +  $0.15 \times \text{maximal speed}$  (m/min)) in severely burned children treated with propranolol.

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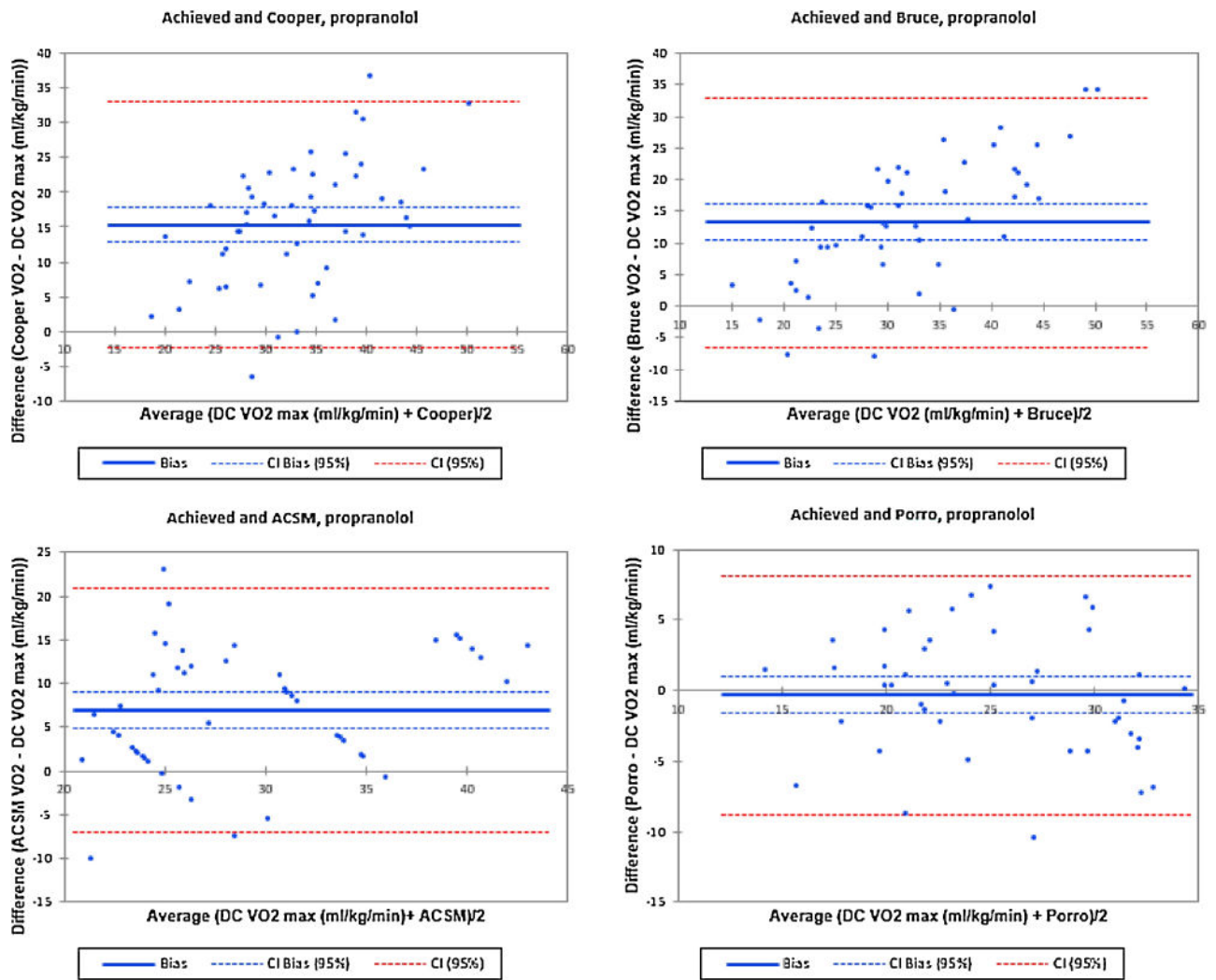
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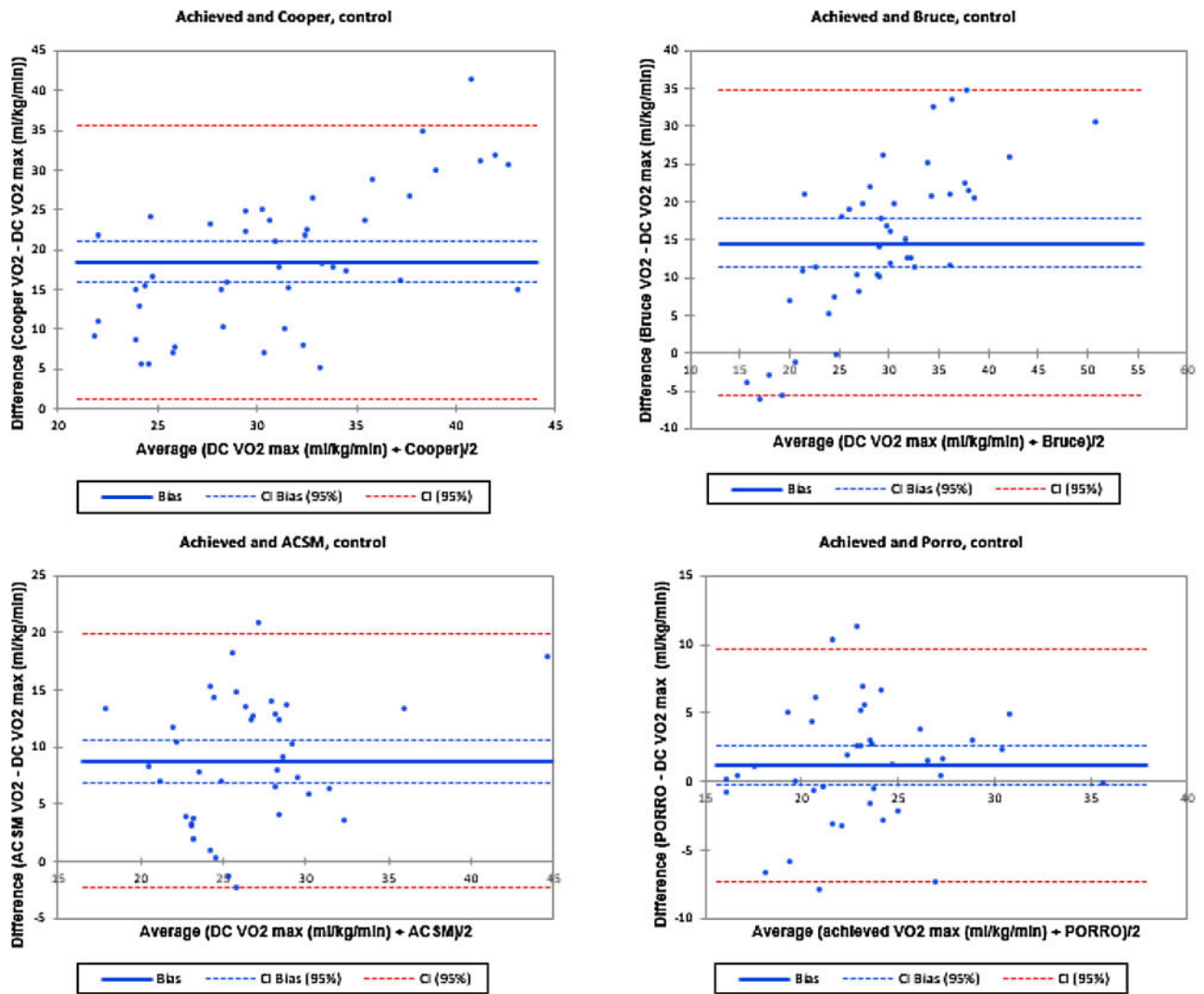


### Highlights

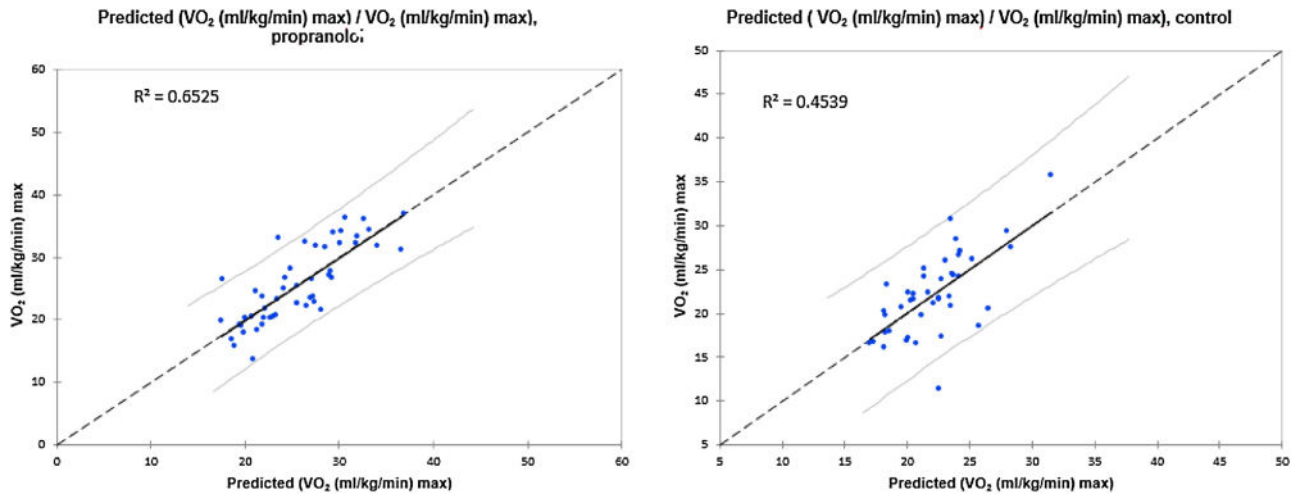
- Propranolol appears to have a beneficial effect on exercise performance in children with severe burns
- Estimation of maximal oxygen consumption is needed when indirect calorimetry is not accessible
- Established formulas for predicting maximal oxygen consumption overestimate the achievable value
- New formula for patients under propranolol is needed since this drug becomes more important in burn care



**Figure 1.** Differences between measured and predicted VO<sub>2</sub> max vs. mean of measured and predicted VO<sub>2</sub> max in propranolol-treated patients.



**Figure 2.** Differences between measured and predicted  $\text{VO}_2$  max vs. mean of measured and predicted  $\text{VO}_2$  max in control patients.



**Figure 3.** Measured VO<sub>2</sub> max vs. estimated VO<sub>2</sub> max calculated using the prediction formulas for propranolol-treated and control patients.

**Table 1**

Patient demographics and maximal oxygen consumption

Characteristic*	Propranolol (n = 46)		Control (n = 53)	p value
Age at burn (years)	12 ± 4		12 ± 3	0.893
Sex, male, n (%)	32 (69.6)		40 (75.5)	0.510
%TBSA burned	44 ± 15		49 ± 14	0.090
Presence of inhalation injury (%)	33 (71.8)		37 (69.8)	0.834
Height (cm)	149.8 ± 17.6		147.7 ± 17.3	0.552
Weight (kg)	47.5 ± 18.1		43.7 ± 15.4	0.262
BMI (kg/m <sup>2</sup> )	20.4 ± 4.5		19.4 ± 3.5	0.217
Length of hospital stay (days)	47.5 ± 18.1		41.8 ± 17.7	0.117
Achieved VO <sub>2</sub> max (mL/kg/min)	25.5 ± 6.0		22.0 ± 4.7	0.002
Predicted VO <sub>2</sub> max (mL/kg/min)		p-value compared to achieved value		p-value compared to achieved value
Cooper	40.9 ± 9.9	< 0.001	40.3 ± 9.2	< 0.001
Bruce	38.9 ± 12.7	< 0.001	36.8 ± 11.5	< 0.001
ACSM	32.5 ± 7.9	< 0.001	31.0 ± 5.9	< 0.001
Porro	26.7 ± 3.7	0.497	23.8 ± 4.8	0.427

\* Data expressed as mean ± standard deviation unless noted otherwise.

%TBSA burned, percent total body surface area burned; BMI, body mass index; VO<sub>2</sub> max, maximal oxygen consumption; ACSM, American College of Sports Medicine

**Table 2**Agreement between achieved and predicted VO<sub>2</sub> max

Group/Formula	Mean difference measured vs. predicted (mL/kg/min)*	Limits of agreement	95% confidence interval for the bias (mL/kg/min)
<b>Propranolol</b>			
<b>Cooper</b>	18.4 ± 8.8	1.3 low, 35.6 high	15.8 – 21.8
<b>Bruce</b>	14.5 ± 10.3	-5.6 low, 34.7 high	11.4 – 17.7
<b>ACSM</b>	8.8 ± 5.7	-2.3 low, 19.8 high	6.9 – 10.6
<b>Porro</b>	1.2 ± 4.3	-7.3 low, 9.6 high	1.2 – 4.3
<b>Control</b>			
<b>Cooper</b>	15.3 ± 9.1	-2.4 low, 33.1 high	12.8 – 17.9
<b>Bruce</b>	13.3 ± 10.1	-6.4 low, 33.0 high	10.3 – 16.2
<b>ACSM</b>	6.9 ± 7.1	-7.1 low, 20.8 high	4.8 – 8.9
<b>Porro</b>	-0.4 ± 4.3	-8.8 low, 8.1 high	-1.6 – 0.9

\* Data expressed as mean ± standard deviation.

VO<sub>2</sub> max, maximal oxygen consumption; ACSM, American College of Sports Medicine

**Table 3**Linear regression model for prediction of VO<sub>2</sub> max in propranolol and control patients

Group	Estimate	Standard Error	P value
<b>Propranolol</b>			
(Intercept)	7.628	2.251	<b>0.001</b>
Sex (male)	2.165	1.265	<b>0.046</b>
Age (years)	0.407	0.176	<b>0.026</b>
Maximal speed (m/min)	0.153	0.024	<b>&lt; 0.001</b>
<b>Control</b>			
(Intercept)	21.153	3.206	<b>&lt; 0.001</b>
Age (years)	-0.038	0.174	0.830
Sex (male)	1.242	1.336	0.359
Presence of inhalation injury	-1.998	1.313	0.137
BMI at discharge (kg/m <sup>2</sup> )	-0.402	0.142	<b>0.008</b>
Exercise time (min)	0.505	0.287	0.087
Maximal speed (m/min)	0.299	0.225	0.194

VO<sub>2</sub> max, maximal oxygen consumption; BMI, body mass index