Effect of Acute Increase in Blood Pressure on Intraocular Pressure in Pigs and Humans

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PURPOSE. To study the effect on intraocular pressure (IOP) of a sudden increase in blood pressure (BP) and of changes in partial pressure of CO2 (pCO2).

METHODS. Two experimental studies were conducted: in pigs (n = 7), where BP was reduced by intravenous injection of sodium nitroprusside and increased by injection of angiotensin II; and in humans (n = 17 healthy subjects), where BP was increased by two types of isometric exercise (squatting and handgripping) performed for 2 minutes; IOP and pCO2 were measured every 30 seconds during separate tests (rest, hyper-ventilation, isometric exercise) and then after 1, 3, 6, and 10 minutes of rest.

RESULTS. In pigs, there is a linear relationship between BP and IOP variations: ΔIOP = 1.21 ΔBP − 0.14 (P < 0.001). In humans, this linear relationship is as follows: ΔIOP = 0.40 ΔBP + 0.85 (P < 0.001) for squatting and ΔIOP = 0.54 ΔBP + 0.55 (P = 0.02) for handgripping. BP and IOP increases are greater with squatting than with handgripping (53% vs. 46%, P = 0.05 and 46% vs. 35%, P = 0.03, respectively). Handgripping causes a greater fall in capnia than squatting does (P = 0.02). Capnia and IOP are positively correlated (P < 0.001).

CONCLUSIONS. The pharmacological approach in animals and the study of isometric exercise in humans show that IOP rises significantly and rapidly with kinetics close to those of BP, and the two values are linearly related. The absence of variation in capnia and the greater increase in BP during squatting may explain the greater increase in IOP during this exercise compared to handgripping. (Invest Ophthalmol Vis Sci. 2010;51:1599–1605) DOI:10.1167/iovs.09-4215

Several epidemiologic studies of humans have reported a correlation between a chronic increase in blood pressure (BP) and an increase in intraocular pressure (IOP).1–3 However, the close relationship between BP and IOP has been studied mainly in animals and especially rats, cats, and rabbits.4–6 These pharmacological studies show a positive correlation between BP and IOP, but which varies according to the animal studied.

Studies of humans mainly consider the effect on IOP of BP increases obtained by dynamic exercise, particularly during the post-exercise period.7,8 Isometric exercise9–10 causes a greater rise in mean BP than that obtained by dynamic exercise,11–13 principally by stimulating the sympathetic nervous system.14 But published results on isometric exercise are contradictory, with IOP falling,14 rising,9–15–19 and not varying significantly.20–22 Partial pressure of CO2 (pCO2) has been reported to fall24–26 during isometric exercise and to change IOP.25,27 Further, cardiovascular response differs according to the type of isometric exercise, with, in particular, a greater increase in BP and in heart rate (HR) during squatting compared with handgripping.28

To better define the effects of a sudden increase in BP on IOP, we did an experimental study on animals (pigs) by pharmacologically inducing variations in BP and on healthy humans, by increasing BP during 2 minutes of isometric exercise and by measuring pCO2. The latter experiment served to compare handgripping and squatting.

METHODS

Animal Experimentation

The animal procedures were approved by the Institutional Animal Care and Use Committee and conducted in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. The experimentation phase concerned seven pigs (Sus scrofa domesticus, weight 20 kg). The animal received food with drink ad libitum for at least 15 days before the experiment. At the end of the experiment, the animal received a lethal dose of anesthetic (Pentothal; Abbott, Chicago, IL).

Animal Preparation

On experiment day, the animal received 2.5 mg azaperone (Stressnil; Merial, Victoriaville, PQ, Canada) intramuscularly before being anesthetized via a mask by inhalation of isoflurane 2%. The animal was then intubated and was ventilated throughout fitting of the pressure sensors.

As the animal was in dorsal decubitus, a cutaneous incision was made above the sternocleidomastoid muscle, allowing catheterization of the left common carotid artery to the origin of the aortic arch. The carotid artery was ligatured upstream. The same maneuver was performed for the left internal jugular vein, which was catheterized as far as its confluence with the superior caval vein.

An IOP sensor was fitted in the right eye of each animal. Under biomicroscopic examination, a self-scaling intracorneal tunnel was made and a 20G catheter was inserted into the anterior chamber to 1 mm from the limbus.

All catheters (neck vessels and anterior chamber) were connected to piezoelectric pressure sensors (Edwards Lifescience, Irvine, CA).
Once the sensors were fitted, gas anesthesia was replaced with anesthesia by intravenous injection of 2 mL/kg propofol (Diprivan; AstraZeneca, Wilmington, DE) to keep the animal under spontaneous ventilation throughout the experiment.

Pharmacological Experiment

For each animal, BP was reduced by injecting sodium nitroprusside (0.25 mg/mL) in rising doses, to obtain at least three BP levels. BP was then increased by intravenous injection of angiotensin II (0.05 mg/mL). The drug infusion rate was controlled at the syringe pump. BP levels corresponded to stable pressure plateaus of at least 1 minute. For example, BP plateaus of 50 mm Hg and 100 mm Hg were obtained after intravenous injection of, on average, 8 mL/h sodium nitroprusside and 12 mL/h angiotensin II, respectively.

Data Analysis

All data were collected by an acquisition software program (AcqKnowledge; Biopac Systems, Goleta, CA) with 50 Hz frequency. For each BP level in each animal, mean BP and IOP values were calculated.

Human Experiment

This study received the consent of the local Institutional Review Board (IRB 6705) and adhered to the tenets of the Declaration of Helsinki. After having the study objectives and possible side-effects explained, and signing the informed-consent forms, 17 healthy subjects aged 21 to 32 years took part in the experiment.

The inclusion criteria were: any non-smoker aged 18 to 40 years having approved and signed the consent form. The exclusion criteria were: under local or general medication; ocular or systemic disease; pregnancy; infection; and/or being bedridden or having reduced mobility. The inclusion inspection comprised a full ophthalmological examination (visual acuity, slit lamp examination, funduscopy, pachymetry), a general examination with reeling and standing BP measurement, and an electrocardiogram.

IOP was measured in one eye (right eye) using a calibrated Goldmann tonometer, after instillation of one drop of oxybuprocaine (Novatis Pharma, Rueil-Malmaison, France) and one of fluorescein (Novatis Pharma, Rueil-Malmaison, France) 29A monitor with a pneumatic transcutaneous route (tcpCO2) using a radiometer (TINA TCM3; Radiometer, Copenhagen, Denmark). 29A monitor with a pneumatic transcutaneous route (tcpCO2) using a radiometer (TINA TCM3; Radiometer, Copenhagen, Denmark). The mean values measured after a stabilization phase, before injection of sodium nitroprusside or angiotensin, 63 stable levels were obtained in the seven animals, varying from 40 to 150 mm Hg.

In Test 1 (rest), subjects remained seated during measurement, to allow analysis of physiological variations in the measured parameters. Test 2 (hyperventilation) consisted of deep inspiration followed by deep expiration every 6 to 7 seconds. In test 3 (squatting), the subject maintained a static position with knees flexed to 90°, with no leaning on a table or chair. Test 4 (handgripping) consisted of static contraction of the finger flexors to 30% of maximum contraction force using a hand dynamometer (MSD, Londerzelle, Belgium). The subject then sat resting, facing the slit lamp.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD), normalized according to the baseline value, and defined as ΔX in the linear regression formula. The IOP–BP relationship was analyzed with a nonparametric test (Pearson). Mean comparisons were done with nonparametric tests (Friedman, Wilcoxon, and Mann–Whitney). Paired comparisons of factors during and after the exercise were done against baseline values. The IOP–BP relationship was modeled using a linear model (generalized estimating equations taking account of repeated values). With this model, R² is not calculated. Statistical analysis was done using commercial software (SPSS 12.0 for Windows; SPSS, Chicago, IL). A P value of 0.05 or less was deemed significant.

RESULTS

In Animals

The mean values measured after a stabilization phase, before injection of BP-changing drugs, were 76.2 ± 10.1 mm Hg for BP and 14.1 ± 2.2 mm Hg for IOP in the right eye. After injection of sodium nitroprusside or angiotensin, 63 stable levels were obtained in the seven animals, varying from 40 to 150 mm Hg.

The mean IOP amplitude related to the cardiac cycle was 2.5 ± 1.4 mm Hg. The mean IOP amplitude related to the respiratory cycle was 3.7 ± 1.8 mm Hg. The relationship between the IOP and BP variations was linear:

\[ \Delta IOP = 1.21 \Delta BP - 0.14 \]  

(P < 0.001; Fig. 2).

In Humans

Eight men and nine women (mean age, 29.3 ± 3.4 years) took part in the study. Mean corneal thickness was 542.4 ± 25.6 μm. Mean sitting IOP at rest was 11.1 ± 1.5 mm Hg. Mean sitting BP and HR were 84.6 ± 8.5 mm Hg and 70.5 ± 4.6 bpm respectively. Mean tcpCO2 at rest was 37.4 ± 3.7 mm Hg.

Test 1 (Rest)

No significant variation in BP (P = 0.35), HR (P = 0.53), IOP (P = 0.45), or tcpCO2 (P = 0.22) was highlighted.
**Test 2 (Hyperventilation)**

There was no significant variation in BP during hyperventilation and post-hyperventilation ($P = 0.1$; Fig. 3A). HR rose by 8–11% during hyperventilation ($P = 0.007$; Fig. 3C), then fell to its baseline value after 1 minute of rest ($P = 0.09$).

IOP fell significantly by 10% to 22% during hyperventilation ($P < 0.001$; Fig. 3B), then regained its baseline value after 5 minutes of rest ($P = 0.09$).

TcpCO$_2$ fell by 4% to 28% ($P = 0.001$; Fig. 3D) during hyperventilation, reaching −32% 1 minute after exercise ceased ($P < 0.001$). TcpCO$_2$ gradually returned to its baseline value after 10 minutes of normal ventilation.

**Test 3 (Squatting)**

BP rose significantly during squatting by 29% to 53% ($P < 0.001$; Fig. 3A), then quickly normalized after exercise ceased, regaining its baseline value 3 minutes later ($P = 0.4$). HR rose significantly by 40% to 52% during squatting ($P < 0.001$; Fig. 3C), then normalized 3 minutes after exercise ceased ($P = 0.1$).

IOP rose significantly by 31% to 46% during squatting ($P < 0.001$; Fig. 3B). After squatting ceased, IOP fell as far as 23% below its baseline value ($P < 0.001$) after 1 minute of rest, then rose again to its baseline value after 6 minutes of rest ($P = 0.07$). The linear relationship between IOP and BP variations was: $\Delta$IOP = 0.40 $\Delta$BP + 0.85 ($P < 0.001$; Fig. 4A).

No significant variation in tcpCO$_2$ was highlighted during squatting ($P = 0.6$; Fig. 3D) or the rest period ($P = 0.2$).

**Test 4 (Handgripping)**

BP increased significantly by 21% to 46% during handgripping ($P < 0.001$; Fig. 3A), then normalized after 6 minutes of rest ($P = 0.4$). HR rose significantly by 14% to 27% during exercise ($P < 0.001$; Fig. 3C). One minute after handgripping ceased, HR had regained its baseline value ($P = 0.7$).

IOP increased by 18% to 35% during handgripping ($P < 0.001$; Fig. 3B). After a significant drop in IOP 1 minute after exercise ceased (−17%; $P < 0.001$) compared to its baseline value, IOP normalized after 3 minutes of rest ($P = 0.1$). The significant relationship between IOP and BP variations was linear: $\Delta$IOP = 0.54 $\Delta$BP + 0.55 ($P = 0.02$; Fig. 4B).

TcpCO$_2$ fell significantly by 3% at the end of exercise ($P = 0.01$, Fig. 3D) and by 6.4% at 1 minute after cessation ($P = 0.001$), before returning to its baseline value.

**Comparison of Results of the Two Isometric-Exercise Techniques: Squatting versus Handgripping**

After 2 minutes of exercise, the BP increase was greater with squatting (+53%; +44.5 ± 11.6 mm Hg; Fig. 3A) than with handgripping (+46%; +37.2 ± 8.2 mm Hg; $P = 0.05$). The increase in HR was also greater with squatting (52%, 36.3 ± 10.1 bpm; Fig. 3C) compared with handgripping (+27%, +19.4 ± 10.4 bpm, $P = 0.001$) after 2 minutes of exercise and up to 3 minutes of rest ($P = 0.02$).

The rise in IOP at 2 minutes of exercise was greater with squatting than with handgripping (+46% vs. +35%; +4.6 ± 1.2 vs. +3.6 ± 0.9 mm Hg; $P = 0.03$; Fig. 3B). The transient fall in IOP after 1 minute of rest was also greater with the squatting test than with handgripping (−23% vs. −17%; −2.4 ± 0.9 mm Hg vs. −1.8 ± 1.1 mm Hg; $P = 0.03$). After 3 minutes of rest, there was no longer a difference between variation in IOP and in the rest values ($P = 0.4$) for the two types of isometric exercise.

TcpCO$_2$ also varied differently according to the type of isometric exercise: the falls in tcpCO$_2$ were 2.7% for handgripping and 0.7% for squatting ($P = 0.02$, Fig. 3D) at 2 minutes of exercise, and 6.4% vs. 1.6% after 1 minute of rest, respectively ($P = 0.005$). After 3 minutes of rest, there was no longer a significant difference in tcpCO$_2$ variation between the two groups ($P = 0.3$).

**Discussion**

This study of animals and healthy humans showed there is a close relationship between BP and IOP when BP rises rapidly. Squatting caused a greater increase in BP, HR, and IOP, and a lesser increase in tcpCO$_2$ than handgripping.
**FIGURE 3.** Variations during the hyperventilation, squatting and hand-gripping tests in mean blood pressure (BP) (A), in mean intraocular pressure (IOP) (B), in mean heart rate (HR) (C), and in mean transcutaneous partial pressure of CO₂ (tcpCO₂) (D). The data shown are normalized (relative to baseline values at rest). Error bars are SD. *P ≤ 0.001, #P < 0.05 (paired tests comparing the T values with baseline values). The *gray bar* represents the duration of the exercise or hyperventilation (2 minutes).
been reported for a mean increase in systolic BP of 74 mm Hg (the relationship was not modeled). In cats, this relationship is linear: \( \Delta IOP = 0.099 \Delta BP - 0.107 \) \((R^2 = 0.72)\). In rabbits, the IOP-BP relationship can also be modeled as an exponential relationship: \( IOP = 8.2 \times 10^{0.004 \times \text{mean BP}} \). In the latter model, BP was increased mechanically, not pharmacologically. The pig model is interesting, given its use in cardiovascular and ocular physiology, especially in glaucoma, cornea, and retina.

In physiological terms, two main hypotheses explain the BP-IOP relationship in the animal model. Kiel showed that IOP varies according to changes in the compliance of the ocular globe and pressure of CO2. This effect could be mediated by a change in choroidal blood volume. Further, our study shows that handgripping increases IOP response to isometric exercise.24 –26 This study allows the first-ever comparison of two isometric exercises, squatting and handgripping, in the same healthy subjects. Our results in humans show a greater increase in BP, HR, and IOP after squatting compared to handgripping. BP response to isometric exercise is known to be a function of maximal voluntary contraction (and is greater than with squatting) irrespective of muscle mass.

Further, our study shows that handgripping increases IOP during exercise, contrary to what previous studies suggested. Our squatting data also confirm that IOP rises markedly when BP rises. The increase in venous return related to venous compression in the lower limbs during squatting may partly explain the greater increase in IOP. The data obtained in post-exercise recovery phase, both in our experiment and in other studies, show a significant, temporary reduction in IOP.

In conclusion, this study shows a close temporal relationship between BP and IOP variations in pigs (using vasoactive drugs) and in humans (during isometric exercise). The differences obtained in IOP between squatting and handgripping (Table 1) are mainly associated with an increase in BP.
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At Rest Hyperventilation Squatting Handgripping

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BP, blood pressure; IOP, intraocular pressure; TcpCO2, transcutaneous partial pressure of CO2.


