Title: **Regulation of oxygen saturation in retinal blood vessels in response to dynamic exercise**

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Abstract:

Purpose: To evaluate the impact of dynamic exercise on retinal vessel oxygen saturation in healthy individuals.

Methods: Twenty-six healthy participants underwent moderate dynamic exercise (modified Master's two step exercise). All subjects intraocular pressures (IOP), systolic and diastolic blood pressure (SBP and DBP), retinal vessel calibres and retinal arterial and venous oxygen saturation was measured at baseline, immediately following exercise and 15 minutes post exercise.

Results: Moderate dynamic exercise increased systolic and diastolic blood pressures immediately post exercise (SBP: 116 (+/-13) mmHg to 150 (+/-21) mmHg; $p<0.001$ and DBP: 69 (+/-10) mmHg to 74 (+/-10); $p<0.001$) while IOP decreased by an average of 2 mmHg (baseline: 13 (+/-3) mmHg)) immediately post exercise (11 (+/-2) mmHg). Oxygen saturation in retinal arteries remained unchanged (baseline= 93 +/-8%; immediately post exercise=94 +/-9% and 15 minutes post exercise=96 +/-8%; $p=0.069$) but increased in retinal veins immediately post exercise and did not return to baseline values within 15 minutes post exercise (baseline=54 +/-12%; immediately post exercise=56 +/-15%; 15 minutes post exercise=57 +/-12%; $p=0.036$).

Conclusion: There is a mild increase in retinal venous oxygen saturation and a trend towards an increase in arterial saturation in otherwise healthy individuals following dynamic exercise.

Introduction:

Retinal vessel oxygen saturation measurements are a novel imaging modality to examine the metabolic regulation in health and disease. The non-invasive nature of this technique has helped its uptake in clinical research exploring the oxygen delivery and consumption in patients suffering from glaucoma (Vandewalle et al. 2014, Olafsdottir et al. 2014, Mordant et al. 2014, Ramm et al. 2015), Diabetes Mellitus (Khoobehi et al. 2013) , and diabetic retinopathy (Hardarson & Stefánsson 2012, Hammer et al. 2012, Jørgensen et al. 2014) as well as patients with systemic vascular and respiratory pathology (Palkovits et al. 2013, Türksever et al. 2014).

The results of these studies along with those conducted in healthy subjects has provided not only information on normative values (Geiersdottir et al. 2012) and reproducibility (Hammer et al. 2008, Goharian et al. 2014, Türksever et al. 2015) but also in regards to confounding factors such as age, blood pressure (BP) (Geiersdottir et al. 2012), image acquisition (Palsson et al. 2012, Patel et al. 2013, Heitmar & Attardo 2015) and location of measurement (Heitmar & Safeen 2012, Shahidi et al. 2013).

Changes in vascular haemodynamics which arise through pathology and normal physiological function (such as ageing) are thought to play a role in the pathogenesis of retinal vascular diseases such as glaucoma, hypertensive and diabetic retinopathy.

While a number of studies have explored the autoregulatory range and factors contributing to maintain stable ocular blood flow (OBF) parameters, little is known with regard to retinal vessel saturation and its regulation during physical activity.

Dynamic exercise techniques such as walking, jogging, running, cycling and knee bends have been used to study its impact on intraocular pressure (IOP) and OBF parameters (Marcus et al 1970, Myers 1974, Orguel & Flammer 1994, Qureshi 1995, Okuno et al 2006, Devi & Babu 2014). Acute dynamic exercise leads to a decrease in IOP of 2 mmHg – 13 mmHg depending on resting IOP levels, age and fitness of the individual studied (Gale et al. 2009). Exercise increases systemic BP depending on the type and duration. We know from published work that physical activity alters retinal vessel calibres (constricting vessels immediately post exercise and dilating vessels during recovery phase following dynamic exercise) depending on age and intensity (Nussbaumer et al. 2014, Kergoat & Lovasik 1995). It can be hypothesised that these alterations in vessel diameter and OBF in combination with changes in IOP could impact on retinal vessel saturation and possibly extraction. This study was designed to capture the systemic and ocular pressure changes following dynamic exercise to study possible alterations in vessel calibre and saturation in the peripapillary retina.

Materials and Methods:

The present study was conducted adhering to the Declaration of Helsinki after receiving a favourable opinion of the Aston University Ethics Committee. All subjects provided written informed consent following explanation of the nature of the study.

We included twenty-six healthy participants (mean age 27 SD ±6 years). All participants were free from systemic disease, ocular abnormalities (including lenticular changes (Patel et al. 2013, Heitmar & Attardo 2015)), and had no history of previous ocular surgery or trauma. All measurements were undertaken with the participants having abstained from caffeinated and carbonated beverages, alcohol, chocolate, red meat, vitamin C or participated in any form of exercise for a minimum of 4 hours prior to testing. All participants underwent the following tests in one unselected eye.

IOP was measured using non-contact tonometry (rebound tonometry using I-CARE, Midoptic, Birmingham, UK). This type of tonometer was chosen because of its ease to use and minimizing patient movement which could have delayed the "immediately post exercise" measurement. Reproducibility of IOP (i.e. non-pathologic) is good across the normal range of IOP compared to Goldman contact tonometry (GAT) (Pakrou et al. 2008). Absolute IOP values as measured with the I-Care rebound tonometer overestimate IOP compared to GAT slightly (Davies et al. 2006, Tamcelik et al 2016). To minimize errors and to ensure stable IOP we obtained six individual IOP measurements at each time point.

Participants pupils were dilated using one drop of Tropicamide 1% (Minims, Chauvin Pharmaceuticals Ltd, UK). After resting in a sitting position for a minimum of 20 minutes to acclimatise to a room temperature of 22 °C, baseline systemic blood pressure (BP) was measured using a digital BP monitor (UA-779, PMS Instruments, UK) adhering to best practice guidelines (Williams et al. 2004).

After these baseline measurements, all participants underwent retinal vessel oximetry and photography as detailed below. This was followed by six minutes of dynamic exercise (modified Master's double step test) (Master 1968). In brief, participants were instructed to step up with both feet onto a stepper (height: 9 inch [22.86cm]) and down again for 6 minutes.

All baseline measurements were repeated immediately following exercise and again 15 minutes post exercise. The recovery period of 15 minutes was chosen to reflect most current clinical practice scenarios in regards to BP, IOP and ocular haemodynamic measurements, where most practice guidelines suggest that patients should be seated in a chair with back support, both feet flat on the floor for a minimum of five minutes prior to BP measurements being taken (Frese et al. 2011).

Ocular perfusion pressure (OPP) was calculated for all three measurement conditions according to the following equation: *OPP = (2/3*mean arterial pressure) - IOP.*

It is important to note that although IOP was measured prior to dilation to ensure safe practice, all BP and IOP measurements detailed in table 1 for the three conditions (baseline, immediately post exercise and 15 minutes post exercise) were taken with participants' pupils fully dilated. After completing the examination, a final IOP measurement was taken to ensure that an upward spike in IOP had not occurred and participants were safe to leave.

Retinal vessel oxygen saturation measurements:

Once full pupil dilation was reached, 5 images were obtained per condition i.e. "baseline", "immediately post exercise" and"15 minutes post exercise" with the camera angle set at 30° and the optic nerve head (ONH) centred. Oxygen saturation measurements were performed using the "oxygen tool" and VesselMap software (Version 2, Imedos Systems, Imedos GmbH, Jena, Germany) as described elsewhere (Hammer et al. 2008). In brief, retinal images were taken with a customized dual wavelength filter (transmission bands at 548 and 610 nm; bandwidth 10 nm each) inserted in the illumination pathway of the fundus camera (Zeiss FF450+). Optical densities of retinal vessels were measured as the logarithmic ratio of the fundus reflection at the vessel centre and its surrounding tissue. The optical density ratio (ODR) at 610 and 548 nm has been found to be inversely proportional to the vessel haemoglobin oxygen saturation when compensating for the vessel diameter and fundus pigmentation (Hammer et al. 2008).

The three best images per condition were used for the subsequent analysis of retinal vessel saturation parameters. The measurement area consisted of a concentric annulus around the optic nerve head (ONH) which was half a disc diameter (DD) distant from the ONH and of ½ DD in width (see Figure 1). This distance and length was chosen in order to obtain results which could be used for comparison to earlier publications using the same device. Oxygen saturations were obtained and averages taken separate for all three conditions of each participant, using the software's "multi-measurement tool" (Visualis software (Imedos Systems, Jena, Germany)). Oxygen saturation parameters for retinal arteries and veins were used for further analysis along with arterial minus venous oxygen saturation to obtain A-V saturation. While in previous publications A-V is often referred to as oxygen extraction or oxygen consumption this is strictly speaking incorrect. In order to calculate retinal oxygen extraction one also needs to measure the ocular blood flow (for more information on the calculation of retinal oxygen extraction please see Werkmeister et al. 2015) which was not carried out in this study.

Summarised retinal vessel calibre measurements:

Average retinal vessel diameters were calculated by averaging the vessel diameters (separately for arteries and veins) of the vessels included for saturation measurement. As these vessel diameter measurements are limited to be used for study comparisons due to the different measurement sizes reported, we calculated vessel parameters as detailed next using a standardized approach:

Retinal vessel calibres were measured using semi-automated software (VesselMap 2, Imedos, Germany) by a single observer (RH). Following image selection, the six largest retinal arteries and six largest veins passing through the created ring segment (see Figure 1) were included in the analysis as described in more detail by Hubbard and colleagues (Hubbard et al. 1999). Summarised retinal vessel calibres of retinal arteries (CRAE) and retinal veins (CRVE) were then calculated from images obtained at the three conditions: “baseline”; “immediately post exercise” and“15 minutes post exercise” for each participant.

Statistical analyses:

Study sample size was calculated based on IOP changes through dynamic exercise: for alpha 0.05 and a power of 0.80 to detect a 2mmHg change in IOP. This calculation yielded a sample size of 18, however, we recruited in excess of this to account for drop out and possible lack of sufficient image quality.

All data was analysed using Statistica version 12.4 (Dell, Dublin, Ireland). Data was normally distributed. Differences between the three conditions: “immediately post exercise” and “15 minutes post exercise” were analysed using a repeated measures ANOVA followed by Tukey’s post hoc testing, where applicable. Stepwise forward multiple regression analyses was used to explore any interaction between vessel calibres (CRAE and CRVE), BP, IOP and oxygen saturation measurements. Statistical significance was set at $p<0.05$.

Results:

Data of summarised vessel calibres (CRAE and CRVE), saturation parameters and pressure values for all three conditions can be found in table 1. Moderate dynamic exercise significantly increased systolic and diastolic BP immediately post exercise ($p<0.001$) while decreasing IOP by on average 2 mmHg ($p<0.001$; individual participant data on IOP, SBP and DBP changes can be found in figure 2). Systolic BP and IOP returned to baseline values within 15 minutes post exercise, whereas diastolic BP remained elevated compared to baseline ($p=0.001$). All blood pressure and saturation values is also presented graphically in Figure 2 and 3.

Retinal vessel calibres (CRAE and CRVE), the arterio-venous ratio (AVR) and averaged retinal vessel diameters of the vessels included in the oxygen saturation measurement remained unchanged throughout the experiment (all $p>0.05$, see table 1).

Retinal arterial oxygen saturation and arterial minus venous oxygen saturation (A-V saturation) remained unchanged immediately following exercise and 15 minutes post exercise. But retinal venous saturation was statistically significantly increased immediately post exercise and remained increased compared to baseline levels even after 15 minutes post exercise ($p=0.049$ and $p=0.013$ respectively).

Arterial and venous oxygen saturation measurements correlated with each other at the same magnitude throughout the experiment (baseline $r^2=0.74$; immediately post exercise $r^2=0.71$ and 15 minutes post exercise $r^2=0.70$).

Multiple regression analysis showed no association between changes in vessel calibres (CRAE and CRVE) and retinal vessel oxygen parameters.

Discussion:

To the best of our knowledge this is the first study reporting on the impact of dynamic exercise on retinal vessel oxygenation parameters. Retinal vessel oxygen saturation in veins and arteries increased significantly post exercise and remained elevated even after 15 minutes of recovery (p=0.036). Retinal arterial saturation increase too, but this was not statistically significant (p=0.069). The numerical increase was on average only 2-3% (saturation increase). While this increase is close to the documented test-retest variance (Hammer et al. 2008, Lasta et al. 2012) it provides only an insight on group average changes and average variability. Changes are dependent on individual factors and while group averages and variances are useful to define clinical cut-off values, it is equally important to look at changes in an individual form one to another time point. This is particularly useful as for many clinical decisions the absolute change in an individual across time is more powerful that their performance compared to a group mean.

The statistically insignificant changes of average retinal vessel diameters in the measurement annulus as well as CRAE and CRVE were unsurprising but were not related to the vessel saturation parameters. It is well documented that dynamic exercise reduces IOP whilst raising retinal arterial pressure. Vasoconstriction of retinal vessels in response to the increase in systemic BP and subsequent increase in OPP therefore induces an increase in vascular resistance. This compensatory autoregulation is known as the myogenic response and ensures the maintenance of normal blood flow in central retinal arteries and veins during dynamic exercise (Harris et al. 1996, Iester et al. 2007, Hayashi et al. 2011).

In fact, our cohort of 26 healthy individuals showed a significant increase in BP while IOP decreased on average 2 mmHg immediately post exercise. Intraocular pressure decreased in 18 out of the 26 participants but remained unchanged in four and increased by 1mmHg in four. This finding is in agreement with Myers KJ (1974) who also found a few study participants where IOP increased or remained at the baseline level following exercise. Systolic BP and IOP values returned to normal within 15 minutes post exercise, while DBP and OPP remained elevated. The decrease in IOP is in agreement with others which have shown similar decreases in IOP post exercise (Gale et al. 2009, Risner et al. 2009). The IOP changes observed in the present study were not related with the concurrent increase in SBP and DBP, concordant with the findings of Lanigan and colleagues (Lanigan et al. 1989). While the changes in systemic BP and IOP were unrelated, they both contribute to the increase in ocular perfusion pressure (OPP). Increases in OPP of up to 40-60% (Gale et al. 2009) are considered to be within the autoregulatory range of the ocular circulation. The

increases in OPP of the present study immediately post exercise were found to be within this autoregulatory range (23 (+/- 15) % increase). Vessel calibres along with retinal arterial vessel saturation and A-V saturation did not change significantly during the entire assessment.

While the term autoregulation implies no change in blood flow or rather a blood flow maintained within a certain level, i.e. over a wide range of OPP changes. The role of BP autoregulation could also be seen as to significantly dampen blood flow related changes. The fact that the A-V difference was stable could therefore reflect an interaction between BP autoregulation and metabolic autoregulation. Furthermore, resistance in a vascular network depends on the fourth power of the vessel radius, a 20% change in resistance requires only a modest 5% change in vessel diameter, highlighting that the smallest diameter changes can have a significant impact. A 5% change in vessel diameter in our case would relate to an approximately 4 microns change arteries and 4.5 microns in veins. While the change observed in our study was smaller, there might well have been a bigger change which might have been masked by the image resolution, vessel detection and diameter measurement algorithms.

Despite the increase in OPP, A-V saturation was maintained at a constant level throughout the experiment, which most likely reflects autoregulation. This finding is in agreement with Lovasik and colleagues (Lovasik JV et al. 2003) who reported that choroidal blood flow was maintained within 10 % of its baseline value throughout exercise and recovery phases (exercise by cycling). In their study, OPP increased more than in our study but also remained within the autoregulatory range of 40-60% increase. This study only examined moderate dynamic exercise, hence the calibre responses of the fundus vessels measured as well as CRAE and CRVE were on average decreasing during the period of study but only CRVE was showing a strong “trend” of constriction (decreasing on average 3 microns immediately post exercise; p=0.078). Our study is limited by the available technology used to assess retinal vessel saturation and calibre parameters which is currently not able to examine the choroidal or retinal capillary beds which most likely represent an important contribution to the maintenance of stable haemodynamic parameters. In fact, two recent studies just highlighted how smaller vessels in the retina are more reactive to flicker stimulation compared to larger vessels (Sharifizad M et al. 2016, Duan A et al 2016). While flicker stimulation increases vessel diameter and represents a different stimulus compared to an increase in systemic BP, these studies highlight that the smallest vessels display the largest change. In fact, this thought is supported by a study from Jeppesen and colleagues which have reported a stronger response of smaller retinal vessels in response to BP increases due to isometric exercise (Jeppesen et al.2007). Findings from their research

support the idea that the smaller, currently less accessible for measurements, vessels are responsible for a major proportion of the autoregulation and resistance of blood flow, possible due to their dense network. Patients with known vascular dysregulation (and compromised microcirculation), such as those suffering from diabetes, hypertension and vascular disease might exhibit a different response as their vascular system is compromised and less capable to maintain autoregulation.

In conclusion, assessments including vessel calibres and oxygen parameters warrant a resting period of more than 15 minutes prior to measurement to ensure stable and rested haemodynamic values. This is particularly important as IOP is returning to baseline/ resting level within 15 minutes as shown in this study and previous research (Myers 1974) and hence, short term exercise could possibly mask a borderline raised IOP. Besides resting long enough before commencing oxygen saturation measurements it is important to measure and document IOP and BP variables as this will be useful especially for long term observations. Future studies should, where possible aim to assess the retinal capillary bed to help further our understanding of the importance and contribution of these smaller vessels in maintaining autoregulation.

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Figure legends:

Figure 1: Schematic detailing the measurement zone for retinal vessel oximetry and retinal vessel calibre measurements.

Figure 2: Individual participants' changes of systolic, diastolic and intraocular pressure at (1) baseline, (2) immediately after exercise and (3) 15 minutes post exercise. The y-axis units refer to mmHg.

Figure 3: Individual participants' results forf retinal arterial, venous and A-V saturation at (1) baseline, (2) immediately after exercise and (3) 15 minutes post exercise. The y-axis units refer to percentage oxygen saturation.

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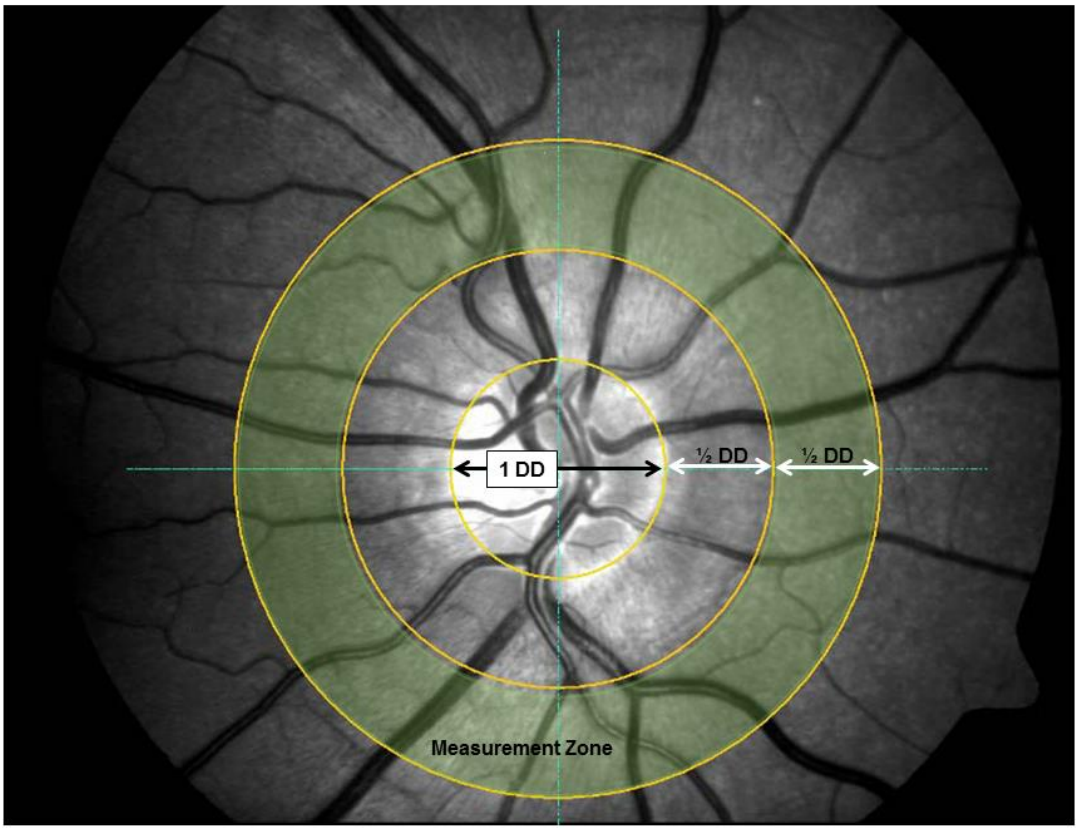
Table 1:

	Baseline	**Immediately Post-Exercise**	**15 minutes Post-Exercise**	**ANOVA D_f (2, 50)**	
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	*F*	*p-value*
Arterial Saturation [%]	93 (8)	94 (9)	96 (8)	2.82	0.069
Average arterial diameter [µm]	80 (28)	79 (27)	80 (27)	1.87	0.165
Venous Saturation [%]	54 (12)	56 (15)	57 (12)	**3.54**	**0.036**$^{+}$
Average venous diameters [µm]	90 (33)	89 (32)	90 (33)	**0.06**	0.942
A-V Saturation [%]	39 (7)	38 (9)	38 (7)	1.49	0.235
SBP [mmHg]	116 (13)	150 (21)	119 (12)	**86.04**	**<0.001**$^{*\#}$
DBP [mmHg]	69 (10)	74 (10)	73 (11)	**5.75**	**<0.001**$^{*+}$
IOP [mmHg]	13 (3)	11 (2)	14 (3)	**15.03**	**<0.001**$^{*\#}$
OPP [mmHg]	59 (10)	71 (10)	62 (10)	**47.64**	**<0.001**$^{*+\#}$
CRAE [mu]	166 (14)	165 (14)	167 (13)	2.21	0.120
CRVE [mu]	210 (16)	207 (16)	211 (15)	2.69	0.078
AVR	0.79 (0.05)	0.79 (0.04)	0.79 (0.04)	0.10	0.905

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; IOP: Intraocular Pressure; OPP: Ocular Perfusion Pressure; CRAE: Central Retinal Artery Equivalent; CRVE: Central Retinal Vein Equivalent; AVR: Arterio-Venous Ratio. Differences between baseline and immediately post-exercise are marked by *; differences between baseline and 15 minutes post-exercise are marked by $^{+}$ and differences between immediately post-exercise and 15 minutes by $^{\#}$.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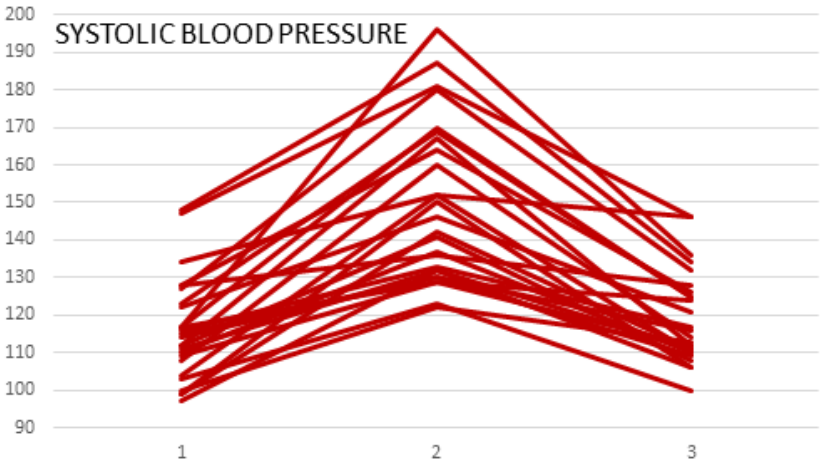
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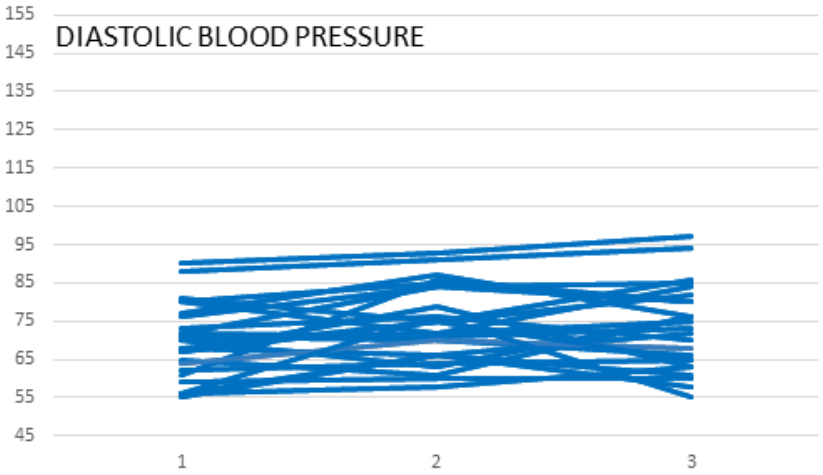
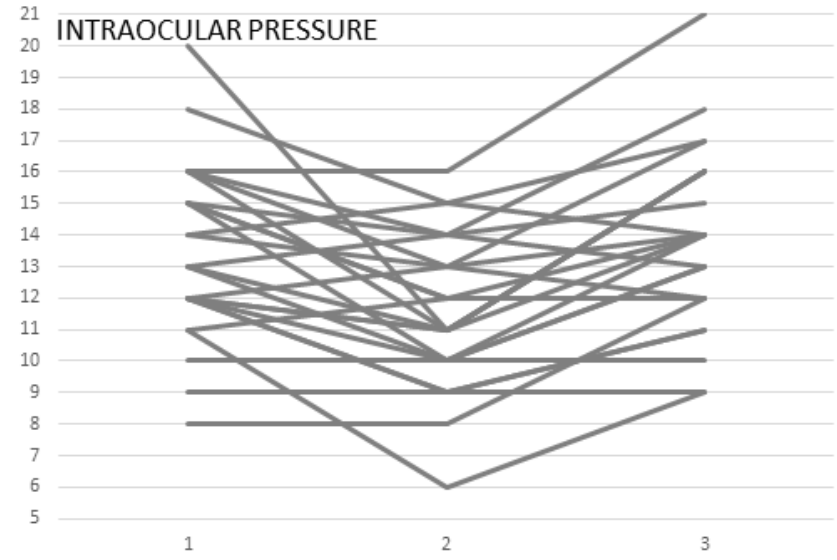
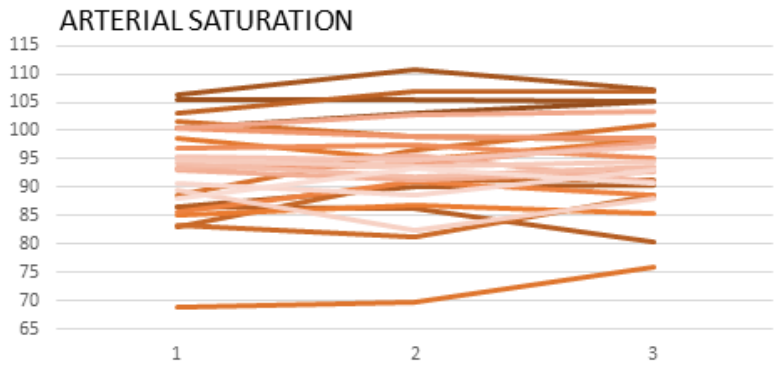
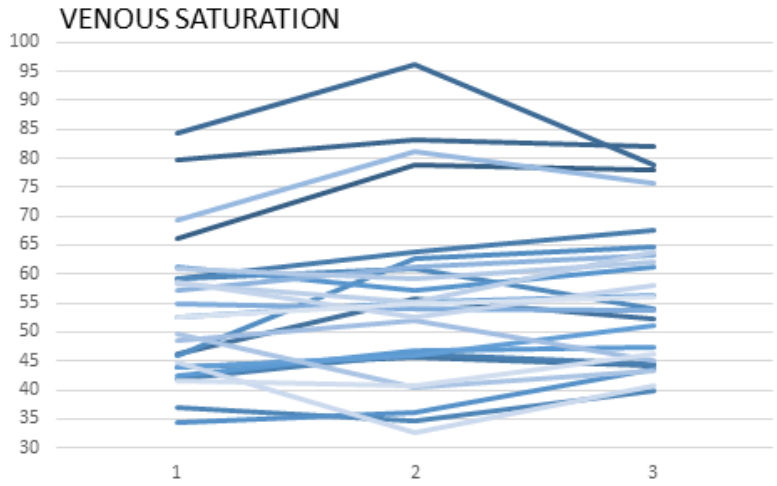
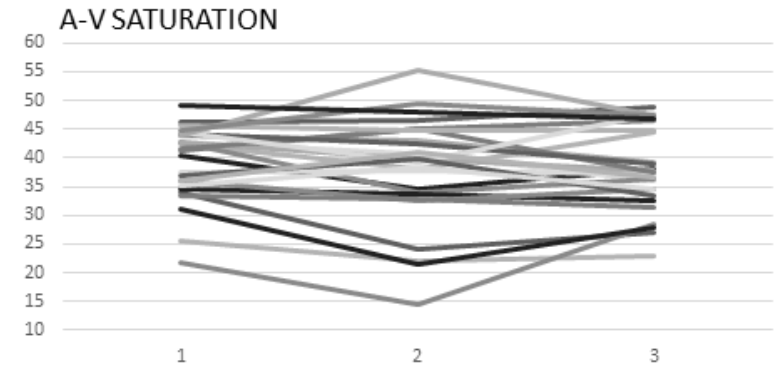
2
3


DIASTOLIC BLOOD PRESSURE
155
145
135
125
115
105
95
85
75
65
55
45
1
2
3


INTRAOCULAR PRESSURE
21
20
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
1
2
3


ARTERIAL SATURATION
115
110
105
100
95
90
85
80
75
70
65
1
2
3


VENOUS SATURATION
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
1
2
3


A-V SATURATION
60
55
50
45
40
35
30
25
20
15
10
1
2
3