



# The effect of flow and pressure on the intraoxygenator flow path of different contemporary oxygenators: an in vitro trial

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## Abstract

**Introduction:** This study analyzed the effect of different flows and pressures on the intraoxygenator flow path in three contemporary oxygenators and its consequences for oxygen transfer efficiency.

**Methods:** In an experimental setup, intraoxygenator flow path parameters were analyzed at post-oxygenator pressures of 150, 200, and 250 mmHg and at flows ranging from 2 L/min to the oxygenators' maximum permitted flow, with and without pulsatility. The oxygen gradient and the oxygen transfer per minute and per 100 mL blood were calculated using previously collected clinical data and compared with the flow path parameters.

**Results:** Increasing pressure did not affect the flow path parameters, whereas pulsatile flow led to significantly increased dynamic oxygenator blood volumes. Increased flow resulted in decreased values of the flow path parameters in all oxygenators, indicating increased flow through short pathways in the oxygenator. In parallel, oxygen transfer/100 mL blood decreased in all oxygenators (average  $2.5 \pm 0.4$  to  $2.4 \pm 0.3$  mL/dL,  $p > 0.001$ ) and the oxygen gradient increased from  $229 \pm 45$  to  $287 \pm 29$  mmHg,  $p > 0.001$ , indicating decreased oxygen transfer efficiency. Oxygen transfer/min increased ( $101 \pm 15$  to  $143 \pm 20$  mL/min/m<sup>2</sup>,  $p > 0.001$ ), however, due to the increased flow through the oxygenator.

**Conclusion:** Varying trans-membrane oxygenator pressures did not lead to changes in the intraoxygenator flow path, while an increased flow exhibited lower flow path parameters resulting in less efficient use of the gas exchange compartment. The latter was confirmed by a decrease in O<sub>2</sub> transfer efficiency during higher blood flows.

## Keywords

oxygenator; oxygenator blood volume; flow path; oxygenator efficiency

## Introduction

Contemporary oxygenators are designed to maximize gas transfer and heat exchange performance, increase biocompatibility, and minimize the passage of micro-emboli. Manufacturers have developed various oxygenator designs to do so, presumably leading to different blood flow paths through these oxygenators. In a previous study by our group, all contemplated oxygenators showed different relationships between shear stress and gas transfer.<sup>1</sup> Often, gas transfer efficiency seemed to increase with increasing shear stress, but only until a certain level. At shear stress above this level, gas transfer efficiency seemed to stagnate or even decrease. We hypothesized that this was an effect of increased blood flow velocity, lowering the residence time of blood in the oxygenator and thus allowing less time for gas exchange, decreasing oxygenator efficiency. Another

possibility could be that increasing flow or consequently system pressures causes changes in the blood flow path through the oxygenator. At higher flows, more blood might be pushed through the short pathways inside the oxygenator instead of spreading out across the whole gas exchange area. This would lead to less efficient use of the full volume of the gas exchange compartment and possibly lower gas transfer efficiency.

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The extracorporeal life support assurance (ELSA) monitor (Transonic systems, Ithaca, NY, USA) can, using saline bolus injections, accurately measure the effectively perfused volume of an oxygenator, a dynamic parameter called oxygenator blood volume (OXBV).<sup>2</sup> This OXBV is dynamic as it changes with alterations in intraoxygenator flow patterns, clot formation etcetera, in contrast to the static (priming) volume of an oxygenator. Besides calculation of the OXBV, the data from the ELSA monitor can be used to calculate three other parameters that give insight into the flow path through the oxygenator, that is, the ratio of the area below the dilution curve before and after maximum dilution in total (ratio BA) and starting from 30% and 50% of the maximum curve height (chord 30 and chord 50, respectively).

In this study, the effect of flow and pressure on the intraoxygenator flow path of three contemporary oxygenators was analyzed. In addition, the relation between changes in the flow path and changes in O<sub>2</sub> transfer efficiency were examined.

## Methods

This *in vitro* study included three oxygenators: Capiiox FX25RW (Terumo, Tokyo, Japan); Inspire 8F (LivaNova, London, England), and Quadrox-i adult (Getinge, Gothenburg, Sweden). The oxygenators were built into an experimental setup consisting of a Capiiox hardshell reservoir (Terumo) and a Revolution centrifugal pump (LivaNova). A heater-cooler unit (HCU30, Getinge) was connected to the oxygenator for temperature regulation. Pressures in the system were regulated using a Hoffmann clamp and measured by Truwave pressure monitoring sets (Edwards Lifesciences Corporation, Irvine, CA, USA). A glycerol-water mixture was used as a blood surrogate, in a ratio that mimics the viscosity of whole blood with a hematocrit of 25% and a temperature of 37°C. This viscosity was estimated to be 0.00244 poise according to a formula by Einstein.<sup>3</sup> The corresponding ratio of glycerol-water mixture was found to be 1:2 at 37°, calculated according to a formula by Cheng, later corrected by Debue and Volk.<sup>4-6</sup> According to instructions for use, the ELSA monitor arterial probe was placed at the arterial oxygenator outlet and the venous probe was placed at the outlet of the hardshell reservoir. Bolus injections of 20 mL saline at the venous side of the oxygenator were used for the dilution measurements. Measurements were performed at post-oxygenator pressures of 150, 200, and 250 mm Hg and at flow rates of 2, 4, and 6 L/min, and the oxygenators' maximum permitted flow (7 L/min for the Capiiox FX25RW and Quadrox-i adult oxygenators, and 8 L/min for the Inspire 8F oxygenator). The effects of both continuous and pulsatile flow were considered. This resulted in 24 different measurement conditions, which were all

performed in threefold. The glycerol-water mixture was refreshed when changing the oxygenator type and between measurement series with continuous and pulsatile flow to prevent excessive dilution and consequent changes in viscosity.

## ELSA measurements

Following injection of a saline bolus, the ELSA monitor automatically calculates the OXBV using measured blood flow and the time between pre-oxygenator saline injection and post-oxygenator recording of the diluted glycerol-water mixture according to formula 1 (Appendix 1).<sup>2</sup> The dilution curves created by the ELSA monitor were used to calculate three more flow path parameters by splitting the area under the curve into two at the time of maximum dilution. The first parameter, the ratio BA, is calculated by dividing the area under the curve after maximum dilution by the area under the curve before maximum dilution. The other two parameters, the ratios chord 30 and chord 50, are calculated likewise, but using the areas after and before maximum dilution starting from 30% and 50% of the maximum curve height, respectively. All three parameters give an indication of the flow path through the oxygenator, with lower ratios indicating more of the injected saline flowing through shorter, preferential pathways inside the oxygenator. This decreases the effectively perfused volume of the oxygenator and will thus coincide with a lower OXBV value.

## Oxygen transfer parameters

To analyze if changes in the intraoxygenator flow path were related to changes in actual oxygen transfer efficiency, the following three oxygen transfer parameters were calculated: O<sub>2</sub> gradient ( $\Delta pO_2$ ; formula 2, Appendix 1), O<sub>2</sub> transfer in mL/min/m<sup>2</sup> membrane surface area (O<sub>2</sub> transfer/min; formula 3, Appendix 1), and O<sub>2</sub> transfer in mL/dL blood (O<sub>2</sub> transfer/dL; formula 4, Appendix 1). The latter parameter was calculated to exclude the effect of blood flow on O<sub>2</sub> transfer, as is the case when calculating O<sub>2</sub> transfer/min. As a glycerol-water mixture was used in this study, data from a previous clinical study were used and the O<sub>2</sub> transfer parameters were calculated from data with the same three oxygenators and at the same flow velocities as used in this experiment.<sup>1</sup>

## Statistics

Analysis was performed using SPSS Statistics version 23 (IBM Corp., Chicago, IL, USA). The Shapiro Wilk test was performed to test data on normality. Significance was set at a p value <0.05. Normally distributed data

**Table 1.** Flow path parameters per oxygenator at three different post-oxygenator pressures during pulsatile flow.

Parameter	Oxygenator	Pressure (150 mm Hg)	Pressure (200 mm Hg)	Pressure (250 mm Hg)	p value
OXBV (mL)	Capiox	249 ± 7	248 ± 6	245 ± 8	0.397
	Inspire	280 ± 9	279 ± 10	279 ± 9	0.987
	Quadrox	288 ± 9	290 ± 10	292 ± 8	0.516
Ratio BA	Capiox	1.38 ± 0.16	1.46 ± 0.16	1.48 ± 0.10	0.247
	Inspire	1.86 ± 0.27	1.78 ± 0.24	1.84 ± 0.24	0.736
	Quadrox	2.45 ± 0.59	2.56 ± 0.58	2.66 ± 0.70	0.715
Chord 30	Capiox	1.23 ± 0.18	1.31 ± 0.17	1.31 ± 0.11	0.461
	Inspire	1.60 ± 0.26	1.55 ± 0.20	1.62 ± 0.22	0.739
	Quadrox	2.41 ± 0.70	2.50 ± 0.66	2.56 ± 0.77	0.882
Chord 50	Capiox	1.16 ± 0.14	1.23 ± 0.14	1.22 ± 0.09	0.328
	Inspire	1.45 ± 0.26	1.44 ± 0.22	1.44 ± 0.23	0.987
	Quadrox	2.22 ± 0.61	2.31 ± 0.63	2.38 ± 0.71	0.832

OXBV: oxygenator blood volume.

Ratio BA: ratio of the area under the dilution curve before and after maximum dilution in total; Chord 30: ratio of the area under the dilution curve before and after maximum dilution starting from 30% of maximum curve height; Chord 50: ratio of the area under the dilution curve before and after maximum dilution starting from 50% of maximum curve height.

**Table 2.** Flow path parameters per oxygenator at three different post-oxygenator pressures during continuous flow.

Parameter	Oxygenator	Pressure (150 mm Hg)	Pressure (200 mm Hg)	Pressure (250 mm Hg)	p value
OXBV (mL)	Capiox	237 ± 7	239 ± 4	239 ± 5	0.513
	Inspire	275 ± 6	275 ± 5	276 ± 5	0.776
	Quadrox	284 ± 9	284 ± 8	284 ± 7	0.968
Ratio BA	Capiox	1.49 ± 0.14	1.51 ± 0.13	1.46 ± 0.14	0.687
	Inspire	1.68 ± 0.10	1.65 ± 0.11	1.70 ± 0.13	0.552
	Quadrox	2.45 ± 0.58	2.44 ± 0.58	2.53 ± 0.47	0.901
Chord 30	Capiox	1.31 ± 0.14	1.33 ± 0.13	1.21 ± 0.11	0.559
	Inspire	1.43 ± 0.11	1.43 ± 0.10	1.45 ± 0.10	0.778
	Quadrox	2.37 ± 0.67	2.34 ± 0.66	2.42 ± 0.55	0.947
Chord 50	Capiox	1.22 ± 0.11	1.26 ± 0.12	1.21 ± 0.11	0.465
	Inspire	1.27 ± 0.09	1.28 ± 0.08	1.31 ± 0.11	0.616
	Quadrox	2.14 ± 0.61	2.16 ± 0.60	2.21 ± 0.48	0.949

OXBV: oxygenator blood volume.

Ratio BA: ratio of the area under the dilution curve before and after maximum dilution in total; Chord 30: ratio of the area under the dilution curve before and after maximum dilution starting from 30% of maximum curve height; Chord 50: ratio of the area under the dilution curve before and after maximum dilution starting from 50% of maximum curve height.

were analyzed using ANOVA tests, whereas a Kruskal-Wallis test was used for non-normally distributed data. Differences between continuous and pulsatile flow were tested using independent sample t-tests.

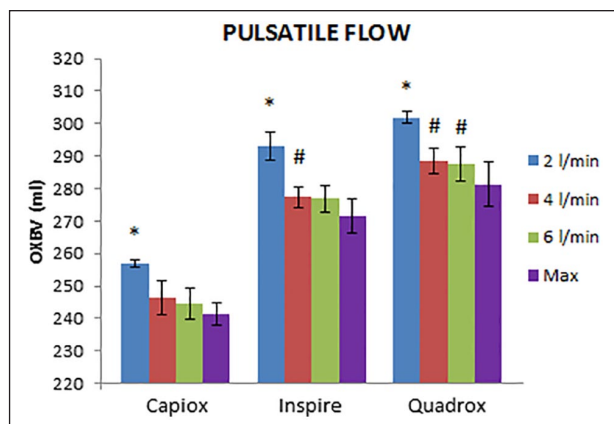
## Results

Different post-oxygenator pressures had no effect on any of the four flow path parameters. This showed to be the case for both the continuous and pulsatile flow mode, in all three oxygenators (Tables 1 and 2).

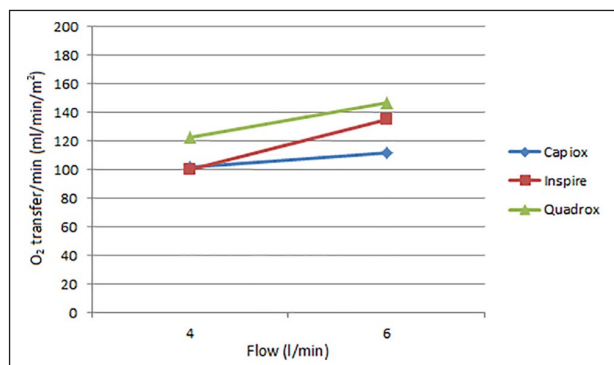
The OXBV during pulsatile flow, however, showed to be significantly higher than the OXBV during continuous flow in all three oxygenators (Capiox: 247 ± 7 mL vs.

238 ± 5 mL,  $p < 0.001$ ; Inspire: 280 ± 9 mL vs. 276 ± 5 mL,  $p = 0.020$ ; Quadrox: 290 ± 9 mL vs. 284 ± 8 mL,  $p = 0.003$ ). The other three flow path parameters were only significantly higher during the pulsatile flow mode in the Inspire oxygenator (ratio BA: 1.83 ± 0.25 vs. 1.68 ± 0.11,  $p = 0.001$ ; Chord 30: 1.59 ± 0.22 vs. 1.43 ± 0.10,  $p < 0.001$ ; Chord 50: 1.45 ± 0.23 vs. 1.29 ± 0.09,  $p < 0.001$ ).

The measurements at the different post-oxygenator pressures were grouped and average values for all four flow path parameters were calculated per measured flow per oxygenator. In most cases, the flow path parameters tended to decrease with increasing flow (Figure 1; OXBV changes during pulsatile flow mode, all other graphs can be found as online supplemental material).



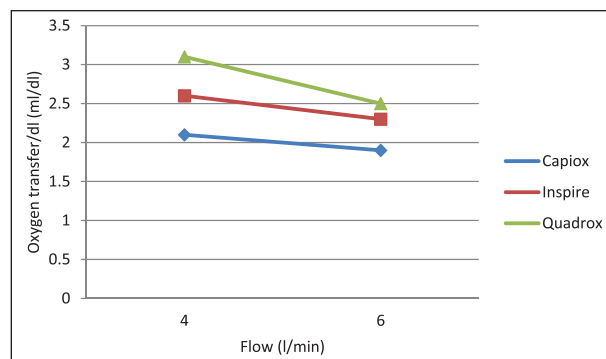
**Figure 1.** Oxygenator blood volume (OXBV) per oxygenator at a pulsatile flow of 2, 4, and 6 L/min and maximum permitted flow. An asterisk indicates a significantly higher OXBV compared to 4 and 6 L/min, and maximum flow; a hash tag indicates a significantly higher OXBV compared to the maximum flow.



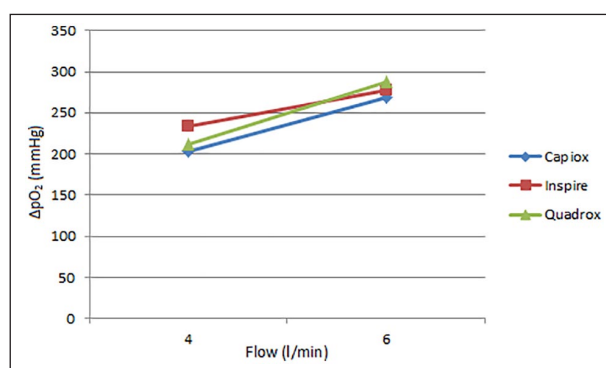
**Figure 2.** Oxygen transfer (mL/min/m<sup>2</sup>) per oxygenator at blood flows of 4 and 6 L/min.

### Oxygen transfer parameters

Sufficient clinical data to calculate O<sub>2</sub> transfer parameters were only available at blood flows of 4 and 6 L/min. O<sub>2</sub> transfer/min in the Capiiox oxygenators significantly increased from 102 ± 13 to 112 ± 21 mL/min/m<sup>2</sup> when flow increased from 4 to 6 L/min ( $p=0.019$ ). Similarly, the O<sub>2</sub> transfer/min in the Inspire oxygenators increased from 100 ± 15 to 135 ± 11 mL/min/m<sup>2</sup> ( $p<0.001$ ) and in the Quadrox oxygenators from 123 ± 36 to 147 ± 19 mL/min/m<sup>2</sup> ( $p=0.002$ ; Figure 2). O<sub>2</sub> transfer/dL, however, significantly decreased with increasing flow. In the Capiiox oxygenators an increase in flow from 4 to 6 L/min led to a decrease in O<sub>2</sub> transfer/dL from 2.1 ± 0.2 to 1.9 ± 0.4 mL/dL ( $p<0.001$ ). O<sub>2</sub> transfer/dL in the Inspire oxygenators decreased from 2.6 ± 0.4 to 2.3 ± 0.2 mL/dL ( $p<0.001$ ) and in the Quadrox oxygenators from 3.1 ± 0.9 to 2.5 ± 0.3 mL/dL ( $p=0.002$ ) (Figure 3). The  $\Delta pO_2$  in the Capiiox oxygenators increased from 203 ± 34 to 269 ± 31 mm Hg ( $p<0.001$ )



**Figure 3.** Oxygen transfer (ml/dL) per oxygenator at blood flows of 4 and 6 L/min.



**Figure 4.**  $\Delta pO_2$  (mmHg) per oxygenator at blood flows of 4 and 6 L/min.

when the flow increased from 4 to 6 L/min. Likewise,  $\Delta pO_2$  in the Inspire oxygenators increased from 233 ± 32 to 278 ± 38 mm Hg ( $p<0.001$ ) and in the Quadrox oxygenators from 212 ± 37 to 288 ± 23 mm Hg ( $p<0.001$ ) (Figure 4).

### Discussion

This study investigated the effect of flow and pressure on the flow path through three contemporary oxygenators. In addition, the relation between changes in the flow path parameters and changes in oxygenator O<sub>2</sub> transfer efficiency were examined.

Results showed that different pressures in the system did not influence the flow path through the oxygenators. Increasing flow, however, caused significant decreases in the flow path parameters, indicating that at higher flows a higher percentage of fluid flows through short, preferential pathways in the oxygenator. This might decrease gas transfer efficiency in two ways. First, the higher blood flow decreases the residence time of blood in the oxygenator, leading to less time for gasses to diffuse, possibly decreasing gas transfer efficiency. Second, the changed intraoxygenator blood flow path

with increased flow through the short, preferential pathways leads to an extra limitation in the time available for gas exchange. Moreover, it disturbs efficient use of the whole gas transfer membrane area.

These findings correspond with the observed decrease of the amount of O<sub>2</sub> transferred per 100 mL blood and the increase in the O<sub>2</sub> partial pressure difference at higher flows. It is therefore tempting to hypothesize that at higher flows the oxygen transfer efficiency of an oxygenator declines. The amount O<sub>2</sub> transferred per minute, however, did increase with increasing flow, suggesting that the decrease in oxygenator O<sub>2</sub> transfer efficiency at higher flow was repealed by the increase in total blood volume flowing through the oxygenator per minute.

Besides decreased O<sub>2</sub> transfer efficiency, a change in the intraoxygenator flow path could have more consequences, as it potentially makes the oxygenator more prone to the development of clots. Oxygenators with a large frontal area like the Quadrox already have low flow areas as a result of preferential pathways. If flow through these short, preferential pathways increases, the low flow areas will receive even less flow and are thus even more prone to clot development.<sup>7,8</sup> Clotting, in turn, adds to the decreased gas transfer efficiency by blocking part of the gas transfer membrane and might eventually lead to oxygenator failure necessitating oxygenator exchange, clot embolism or coagulation disorders.<sup>9-12</sup>

The results showed that pulsatile flow led to a significantly higher dynamic OXBV in all oxygenators compared with the continuous flow mode. A plausible explanation for this observation lies in the pulsatile flow mechanism, that is, an alternation of high and low flow. As lower flow led to higher OXBV measurements, the average OXBV during pulsatile flow is slightly higher than the OXBV during continuous flow. The other three flow path parameters were only significantly increased during the pulsatile flow mode using the Inspire oxygenator. Most likely this finding can be ascribed to the differences in design between the Inspire oxygenator and the other oxygenators.

### Limitations

When interpreting these study findings one should consider the following study limitations. The manual injection of saline boluses possibly creates variability in the measurements. The ELSA monitor, however, has shown to be accurate independent of the operator and the precision of the injected volume.<sup>2</sup> Moreover, if an injection is truly incorrect, it results in a notification that the measurement should be repeated. No such notifications were given during this study, leading us to believe that the manual injection of saline did not significantly affect the results. The use of a glycerol–water solution as a surrogate for blood, only mimics the viscosity component of blood. For more accurate measurements of the flow path parameters actual

blood should be used. Moreover, the O<sub>2</sub> transfer parameters were not measured directly because of the use of glycerol–water solution, necessitating the extrapolation of data from a previous clinical study. But as the same three oxygenator types were used in both studies and all parameters were calculated at the same flows, the flow path parameters and the O<sub>2</sub> transfer parameters should be comparable. Finally, the possible effect of the arterial filters incorporated in the oxygenators on the flow path parameters was not considered. In Quadrox-i and Inspire 8F oxygenators, the filter compartment adds extra volume to the oxygenator and thus to the OXBV measurement. This additional volume, however, is added to every measurement and should not affect the changes in the intraoxygenator flow path parameters caused by changes in flow. Moreover, results of the Quadrox-i and Inspire 8F oxygenators show the same trends as those of the Capiox FX25 oxygenator that has no additional priming volume added by its arterial filter.

### Conclusion

In conclusion, varying trans-membrane oxygenator pressures did not lead to changes in the intraoxygenator flow path, while increased flow resulted in decreases in the flow path parameters indicating less efficient use of the gas exchange compartment. The latter was confirmed by a decrease in O<sub>2</sub> transfer efficiency at higher blood flows.

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### Supplemental Material

Supplemental material for this article is available online.

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## Appendix I

### Formulae

1. Calculation of the oxygenator blood volume by the ELSA monitor

$$\text{OXBV (mL)} = Q_b \times (\text{MTT}_a - \text{MTT}_{\text{inj}}) - V_{\text{in}} - V_s$$

where  $Q_b$  is the measured flow velocity (mL/s),  $\text{MTT}_a$  is the mean transit time of the bolus between place of injection and place of recording (s),  $\text{MTT}_{\text{inj}}$  is the mean transit time of the bolus injection (s),  $V_{\text{in}}$  is the priming volume between place of injection and the oxygenator (mL) and  $V_s$  is the priming volume between the oxygenator outlet and the arterial ELSA probe (ml).

2. Oxygen gradient

$$\Delta p\text{O}_2 \text{ (mm Hg)} = p\text{O}_{2\text{gas}} - p\text{O}_{2\text{art}}$$

where  $p\text{O}_{2\text{gas}}$  and  $p\text{O}_{2\text{art}}$  are the oxygen partial pressures in the gas compartment and in the arterial blood (mm Hg), respectively.

3. The amount of oxygen transferred per minute per square meter membrane surface area

$$\text{O}_2 \text{ transfer / min (mL / min / m}^2\text{)} = \frac{((\text{CaO}_2 - \text{CvO}_2) \times Q_b)}{\text{MSA}}$$

where  $\text{CaO}_2$  and  $\text{CvO}_2$  are arterial and venous blood oxygen content, respectively (mL/dL),  $Q_b$  is the blood flow (dL/min), and MSA is the oxygenator membrane surface area (m<sup>2</sup>).

4. The amount of oxygen transferred per 100 mL blood flowing through the oxygenator

$$\text{O}_2 \text{ transfer / dL (mL / dL)} = \text{CaO}_2 - \text{CvO}_2$$

where  $\text{CaO}_2$  and  $\text{CvO}_2$  are again arterial and venous blood oxygen content (mL/dL).