Normal and abnormal trans-oxygenator pressure gradients during cardiopulmonary bypass

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A prospective study was conducted with the aims of 1) determining the normal trans-oxygenator pressure gradient characteristics for a range of oxygenators and 2) determining the characteristics, incidence and outcome of abnormally raised gradients. The trans-oxygenator pressure gradient was monitored in 3684 patients undergoing open-heart surgery in eight different hospitals. When the normal pressure gradient was measured during cardiopulmonary bypass in mmHg/L blood flow, a constant figure was obtained which was specific for each oxygenator. This gradient was abnormally raised in 16 cases (one in every 230 cases) and was raised to such an extent in three of these cases that an emergency oxygenator changeout was required (one in every 1228 cases). Among the 16 reported incidents, three different patterns of gradient changes occurred, suggesting the possibility that there were three different aetiologies. In nine of these incidents, the pressure gradient was normal immediately upon going on bypass, but rose rapidly to a plateau value, which then returned to the normal value within 40 minutes. In three cases, the pressure gradient was raised immediately upon going on bypass and then rapidly returned to the baseline. In one case, the pressure gradient was raised immediately upon going on bypass and stayed raised throughout the operation. *Perfusion* (2003) **18,** 25–30.

Introduction

A failing or failed device in the cardiopulmonary bypass circuit is a potentially serious complication during open-heart surgery. One such problem that has only been relatively recently reported is the generation of an abnormally raised pressure gradient across the oxygenating and heat exchanging sections of a membrane oxygenator. This appears to be caused by the generation of a platelet-fibrin thrombus that has developed despite adequate anticoagulation.[1] Reports suggest that this thrombus is initially attached to the heat exchanger.[1–3] In the extreme case, the thrombus will completely block off the blood pathways. Alternatively, it may either break away or grow into the oxygenating compartment and compromise oxygenation to the extent that the device will fail. In either extreme case, emergency oxygenator changeover must be performed. The aetiology of this phenomenon is unknown. It has been suspected that it is due to the presence of cryofibrinogen,[1] but it appears to occur whether patients are cooled or not and, therefore, it is unclear as to whether the initial event is the activation of fibrinogen or the activation of platelets due to an as yet unknown activating agent or agents.

The reported incidence of this problem varies from one in every 40 cases to one in 239 cases (Table 1).[1,4–7] The incidence of a resulting emergency oxygenator changeout varies from one in every 346 cases to one in 954 cases. There is a suggestion that the incidence not only varies from hospital to hospital,[8] but also between different countries. In addition, there are multiple names and methods used to describe and define this pathological event,

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Table 1 Reported incidence of raised trans-oxygenator pressure gradient and resulting emergency oxygenator changeout

Author	*Study size*	*Overall incidence*	*Incidence of oxygenator changeout*
Blomback (1995)[1]	1800 (s)	1 in 164	1 in 600
Wahba (1997)[4]	1959 (s)	42	490
Svenmarker (1998)[5]	6918 (m)	239	346
Stensved (1999)[6]	11 451 (m)	89	954
Wendel (2001)[7]	5617 (s)	51	374

m = multicentre study; s = single centre study

which may result in false positive or false negative event reporting. Finally, it is important to appreciate that, unless the trans-oxygenator pressure gradient is measured, the only evidence that a pathological event has occurred will be in the extreme case of oxygenator failure.

The normal trans-oxygenator pressure gradient is usually presented in graphical form, by the manufacturer, as pressure drop against flow under controlled conditions. In modern oxygenators, this results in a straightline graph showing a linear relationship between the two principle variables. The major factors affecting the trans-oxygenator pressure gradient, apart from blood flow, will be blood viscosity and the physical dimensions of the device (including the tubing connecting it to the site of pressure monitoring). During cardiopulmonary bypass, changes in viscosity will be due primarily to changes in haematocrit and temperature.

The first part of this study was to test the hypothesis that the value of the pressure gradient per litre blood flow (mmHg/L) during clinical work was relatively constant and could be used as an accurate baseline from which to establish whether a pathological situation has occurred.

The second part of this study was to determine the frequency of occurrence of raised pressure gradients and to look at some possible underlying factors in a time-controlled, prospective, multicentre study.

Method

Eight hospitals situated throughout the UK were enrolled in this study. Multicentre ethical committee approval was obtained (MREC/99/4/020). Each centre was provided with suitable preoxygenator pressure-monitoring equipment (Airedale Instruments, UK) and with a conversion kit for their perfusion circuit (Dideco Ltd, Mirandola, Italy). One individual in each hospital was provided with standardized instructions and reporting forms to ensure that the monitoring was universally applied and was appointed to collate the results. Cardiopulmonary cases were monitored in the eight hospitals over the same specific six month period in order to reduce the effect of any changes in technology or techniques. In six hospitals, all cases were monitored. In the other two hospitals, only the cases performed by the appointed individuals were monitored.

The following parameters in every patient were recorded immediately upon going on bypass and then every 15 minutes for the duration of the bypass:

Pre- and postoxygenator pressures
Blood flow
Blood gases and haematocrit
Activated clotting time (ACT)
Patient, blood and water temperatures

Any case where the primary perfusionist suspected that the pressure gradient had risen to over double its normal level was reported. Twenty normal consecutive cases for each oxygenator used at each hospital were also fully reported on in order to establish baseline readings.

Results

Normal trans-oxygenator pressure gradients

The eight hospitals used nine different oxygenators, with five of these oxygenators being used in more than one hospital. Figure 1 shows the mean pressure gradient per litre blood flow during 20 routine bypass cases in two different hospitals for the Cobe Duo and the Sorin Monolyth oxygenators. This figure shows that the value for mean pressure gradient per litre flow remains reasonably constant during bypass, and the only difference between

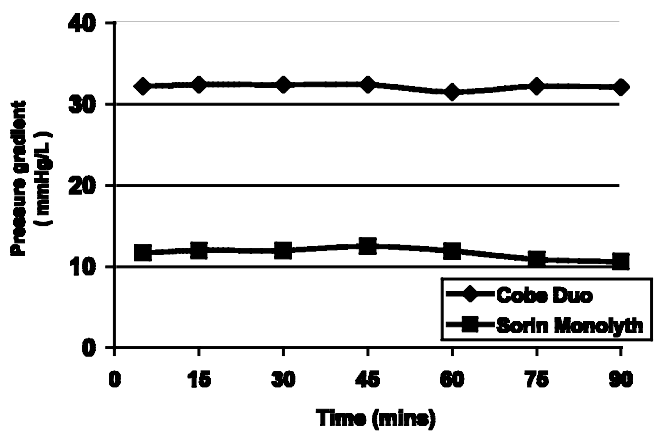

Figure 1 Normal trans-oxygenator pressure gradient for the Cobe Duo and Sorin Monolyth oxygenators (mean of 20 cases) during 90 minutes of cardiopulmonary bypass

different makes of oxygenators is the absolute value obtained. The pressure drop across the Cobe Duo was 32.2±1.6 mmHg/L while that across the Sorin Monolyth was 11.9±3.4 mmHg/L. If five litres of blood per minute were passing through a Cobe Duo, the expected normal pressure gradient would, therefore, be 161 mmHg, but would be only 59.5 mmHg across a Sorin Monolyth. The mean pressure gradients per litre blood flow for all the oxygenators used are shown in Table 2. While there was some variation in the measurements, there were no statistically relevant differences in the pressure gradient at any timepoint during any bypass. Also, there were no statistical differences in pressure gradient when a specific make of oxygenator was used in different hospitals.

Because of their consistency, these measurements were used as the baseline readings for the second part of this study, which was conducted to determine whether or not a pathological incident had occurred.

Raised trans-oxygenator pressure gradients

A total of 3684 patients were monitored. Nineteen cases of raised pressure gradients were reported. Two of these, when analysed against the normal gradient, although showing a raised gradient were substantially less than double the baseline. Both of these minor incidences occurred during cases that required high blood flow, so the premembrane pressure appeared to be higher than usual. Another reported incidence was shown to have a normal gradient, but with both pre- and postoxygenator pressures raised as a result of a restriction downstream of the oxygenator (possibly as a result of constriction or blockage in the arterial line filter or arterial cannula). In these three false positive reports (16% of reported incidents), the appearance of an unnaturally high premembrane pressure presupposed an occurrence of a raised gradient. The remaining 16 reported incidents were confirmed occurrences of abnormally raised pressure gradient – an incidence of one in every 230 cases, among which there were three emergency oxygenator changeovers – an incidence of one in every 1228 cases.

When analysed, nine of the 16 cases followed the same pattern: immediately after going on bypass, the pressure gradient was normal, but rose rapidly to a maximum value in an average of 16 minutes (range 5–25 minutes). This raised gradient eventually returned to the normal baseline over an average time of 40 minutes (range 25–60 minutes). Figures 2 and 3 demonstrate examples. We have classified these as Type I gradients. In addition, the three cases that resulted in emergency oxygenator changeovers also started as Type I gradients.

Three of the 16 cases followed a different pattern, as shown in Figure 4. In these cases, the pressure gradient was maximal immediately on going on bypass, being up to five times greater than normal. The gradient rapidly returned back to baseline within a mean of 20 minutes (range 15–30 minutes). We have classified these as Type II gradients.

One case followed a third pattern, as shown in Figure 5. As with Type II gradients, immediately upon going on bypass the gradient was raised.

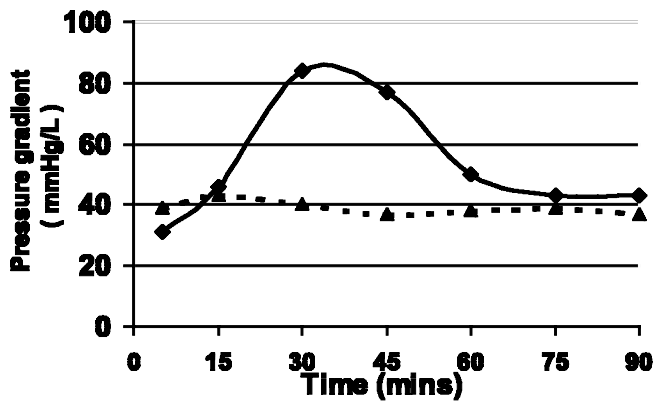

Figure 2 Type I raised trans-oxygenator pressure gradient in a Bard Quantum Oxygenator. Solid line = raised gradient event, dotted line = normal baseline reading for Bard Quantum.

Table 2 Normal pressure gradients and incidence of raised gradients in oxygenators

Oxygenator	*Manufacturer*	*Gradient; mmHg/L (Hosp 1)*	*Gradient; mmHg/L (Hosp 2)*	*Number oxygenators in study*	*Number of raised gradients*
Hilite	Medos	21.5±3.8		264	0
Monolyth	Sorin	11.9±3.4	12.5±3.5	128	2
Capiox SX 25	Terumo	22.4±3.8	21.0±3.2	317	1
Duo	Cobe	32.2±1.6	33.5±1.3	986	8
Optima	Cobe	25.0±4.2		208	0
Quantum	Bard	27.4±2.8	31.6±5.0	371	4
Avant	Dideco	28.5±2.5	30.8±6.4	982	1
Vision	Gish	18.1±5.5		87	0
Affinity	Avecor	11.7±3.7		341	0

Where the same oxygenator was used by a second hospital, the value is entered in column 4 under Hosp 2

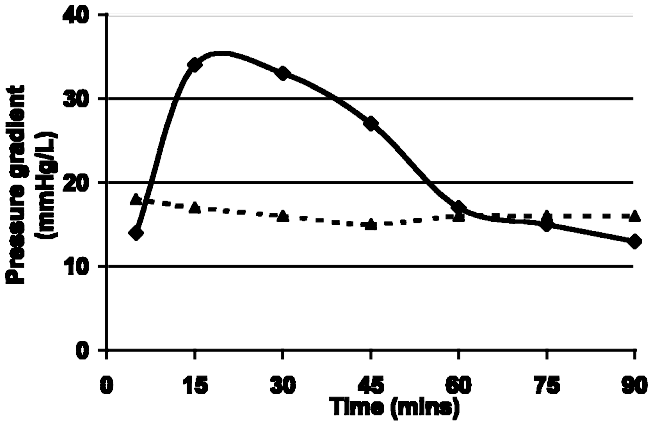

Figure 3 Type I raised trans-oxygenator pressure gradient with a Terumo SX25 Oxygenator. Solid line = raised gradient event, dotted line = normal baseline reading for Terumo SX25.

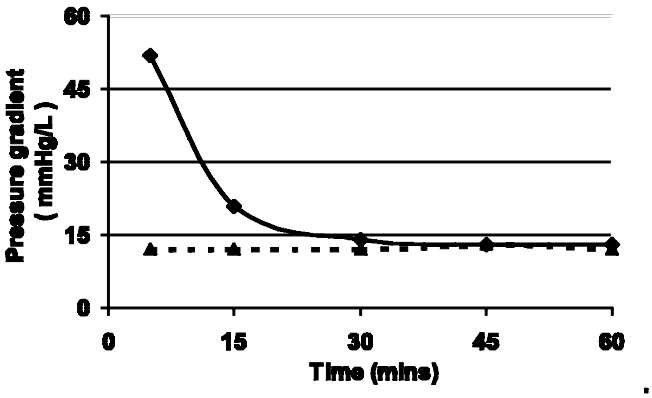

Figure 4 Type II raised trans-oxygenator pressure gradient in a Sorin Monolyth Pro Oxygenator. Solid line = raised gradient event, dotted line = normal baseline reading for Sorin Monolyth Pro Oxygenator.

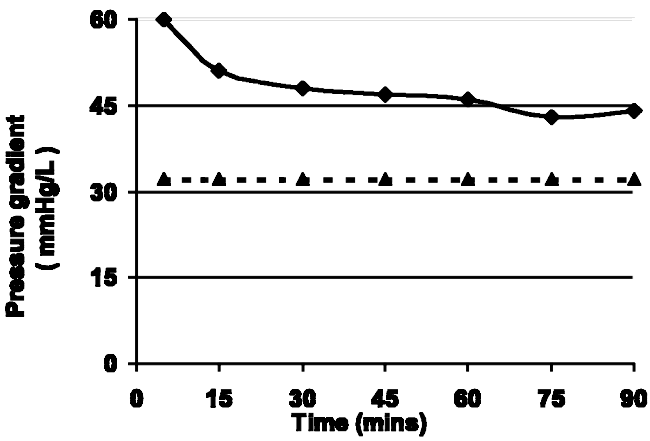

Figure 5 Type III raised trans-oxygenator pressure gradient in a Cobe Duo Oxygenator. Solid line = raised gradient event, dotted line = normal baseline reading for Cobe Duo Oxygenator.

Table 3 Incident rate per hospital

Hospital	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*
No. cases	602	730	982	498	400	144	87	241
No. incidents	1	4	1	2	1	2	2	3
No. of cases per incident	602	183	982	249	400	72	44	80

However, unlike Type II, the event was not reversible and the gradient remained raised for the duration of the bypass. We have classified this case as a Type III gradient.

Every hospital in the study experienced at least one pathological event (Table 3), although the rate of incidence varied between the hospitals from one in every 44 cases to one in every 982 cases. When analysed using the Yates corrected chi-squared test, there was a probability of less than 0.001 that this difference in incidence between hospitals was not a random event. The commonest difference in technique between different hospitals is in the selection of the brand of oxygenator, so the relationship between the incidence of abnormal pressure gradient to oxygenator type was examined (Table 2). The likelihood of an abnormal event occurring was significantly higher if a Cobe Duo was used ($p = 0.05$), but there were no significant differences between any of the other oxygenators.

There was no relationship between the occurrence of a raised pressure gradient and whether or not the patient was cooled.

Discussion

Because the trans-oxygenator pressure gradient is mainly dependent upon blood flow, the determination that a pathological event is occurring is, to some extent, subjective and may not be noted if low flows are used during bypass, but may be exaggerated during high flows. In addition, because it is generally inconvenient to do the required calculations during bypass, many perfusionists who are aware of this particular problem tend only to observe the preoxygenator pressure. In all previously reported work on this subject, there has been the potential for false positive and possibly false negative reports. In this study, 16% of reports were shown to be false positives. By removing the variable of blood flow, false positive and false negative reports are eliminated.

Schaadt reports a suggestion that there appears to be a difference in incidence between hospitals,[8] which is confirmed by the data reported here. In this study the incidence ranged from a very common one

in every 44 cases to a much rarer one in every 982 cases The most obvious difference between hospitals is in the selection of the brand of oxygenator. However, despite the relatively small numbers of abnormal events reported in this study, the results suggest that the particular oxygenator is probably not an influencing factor. It is reasonable to expect that, in a centre where there is a high incidence rate, there would be a great interest in this problem. In this multicentre study, the incidence of a raised pressure gradient was one in every 230 cases. This is very similar to the incidence reported by Svenmarker *et al.* of one in every 239 cases in another multicentre study,[5] but both these rates of incidence are much less than in all other reports (Table 1), three out of four of which were single-centre studies.

The results suggest that cooling the patient is not a contributing factor. The pressure gradient only ever rises at the very beginning of bypass, which is also the time commonly chosen to start cooling the patient. The gradient remains raised for an average of 40 minutes, which is also the time point at which the average surgeon starts rewarming. It is therefore quite possible that the suggested relationship between raised gradients and temperature is purely circumstantial.[1] Rewarming the patient while a raised gradient is occurring appears to slow down the rate of creation of thrombus. Whether this is due to de-activating cryofibrinogen or because of an action on the dynamics on the platelet-fibrin thrombus formation is unclear, but the latter action does seem more likely.

The appearance of three types of event suggests that there may be three different aetiologies. When Type I gradients occurred, the trans-oxygenator pressure gradient was always normal immediately on going on bypass. Therefore, it seems reasonable to suggest that the activation of the platelet-fibrin thrombus is related to the use of the bypass circuit. However, when Type II gradients occur the thrombus appears to have already formed and immediately starts to block the oxygenator. The activation, most probably, must have started before going on bypass and is, therefore, independent of the bypass circuit, but must be related to anaesthetic or surgical techniques. In both these types, the thrombus was reversible and, when it had dissipated, the oxygenator acted perfectly normally. The thrombus never appears later on during the bypass or, if an emergency oxygenator changeover has been implemented, it never appears with the new oxygenator.

Although all these events occur in the apparent presence of adequate heparinization – the activated clotting time (ACT) during all the reported events was always over 480 seconds – the Type III gradient appeared to be a non-reversible thrombus. It is reasonable to presume that this may have been caused by a small quantity of unheparinized blood being sucked into the bypass circuit. This is supported by the circumstantial evidence that only one Type III event occurred in this study, giving an incidence of about one in 4000 cases and this incidence rate is in the same order as the reported appearance of blood clots in the CPB circuit.[9–11]

In order to reduce the incidence of raised gradients occurring, perfusionists may either add albumin to their prime[12] or use coated equipment.[4] The presence of at least three different mechanisms to produce the same raised gradient effect may explain why using these techniques do not appear to eliminate the problem, only reduce it.

There is one final consideration. If one does not monitor the premembrane pressure, then the first time the perfusionist knows that there is a problem is when the oxygenator fails. Because there is no other evidence, it will be reported as a 'failed oxygenator'. Table 4 lists the reported incidence of 'Failed Oxygenator' from the four surveys that have used this descriptor. It is remarkable how relatively constant the occurrence of failed oxygenators has been over the years, staying at about one in every 2000 cases. What is even more remarkable is that these reports are based on different types of oxygenators. During the surveys by Stoney *et al.*[13] and Wheeldon[14] in the late 1970s, only bubble oxygenators were available. During the Kurusz *et al.*[15] survey in 1986, about half of the oxygenators used were bubble oxygenators while the other half were membrane oxygenators and, during the Mejak *et al.*[11] survey in 2000, only membrane oxygenators were used. These reports demonstrate that bubble and membrane oxygenators appear to fail at about the same rate. Traditionally, perfusionists were taught that bubble oxygenators fail because the holes in the sparger plate become blocked off. While this is a potential possibility, it is not only unlikely, but in the event that it occurred, gas pressure would build up and tend to rupture the piping – the combined event of ruptured gas line and failed oxygenator is a very rare occurrence. About half of the oxygenating in a bubble oxygenator occurs in the defoamer. If the defoamer became coated with a

Table 4 Reported incidence of failed oxygenators

Author	*Year*	*Incidence of failed oxygenators*
Stoney[13]	1979	1 in 3022 cases
Wheeldon[14]	1981	2063
Kurusz[15]	1986	1134
Mejak[11]	2000	2458

platelet-fibrin thrombus, then the ability of the device to oxygenate decreased and had the appearance of a failed oxygenator. Thus, it is an interesting hypothesis that bubble oxygenators failed due to the development of this thrombus but, because of an inability to monitor for this problem, it always went undetected. Although bubble oxygenators are still being used in some parts of the world, it would be very difficult to substantiate this theory. However, if it were true, then the development of platelet-fibrin thrombi is not a recent problem, but one that has always been with us. It is quite possible that it is because of the development of low prime membrane oxygenators and the technical ability to monitor for it that this particular problem has only been reported recently.

While it has been assumed by other workers in this field that the underlying causes are both complex and multifactorial, the data presented here suggest that an even more complex picture needs to be described.

Conclusion

Abnormally raised trans-oxygenator pressure gradients occur once in every 230 bypass cases. In about one in five of these (one in 1228 cases), the thrombus becomes so large that the oxygenator fails and requires an emergency changeout. There are at least three different causes. One occurs immediately before going on bypass, the second within the first 10 minutes of going on bypass and the third as a result of the suction of unheparinized blood. The events always happen only at the beginning of bypass and never later on or after the addition of a replacement oxygenator. The incidence varies between different hospitals, but this difference appears to be unrelated to the brand of oxygenator used or whether or not patient cooling is employed.

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