Filtration, pulse and permeability. An update on Pulse Reverse Osmosis

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Abstract

PRO is an update to the Starling hypothesis of fluid exchange which incorporates permeability and pulsatility. It suggests that fluid balance occurs when the mean capillary pulse pressure (MCPP) is equal and opposite to the membrane osmotic pressure (MOP) down the length of the capillary. The pulse drives fluid exchange.

The physico chemistry of osmosis, and research into the pulsatile nature of the capillary bed support the principals underlying PRO.

PRO suggests that imbalance between MOP and MCPP results in either oedema, shock and hypertension. Preliminary clinical studies support these proposed mechanisms.

PRO suggests that the shape of the pulse wave is critical to fluid exchange in order for the volume of fluid filtered out during systole to be equal and opposite to the volume reabsorbed during diastole. Arrhythmias and arterial stiffening both result in change in the pulse shape. Further research is required to investigate the impact of change in pulse shape on fluid exchange.

PRO is a new model of fluid balance and exchange which offers a simple model for the development of oedema, shock and hypertension. It suggests that arrhythmias and arterial stiffening have a profound effect on fluid exchange. Further research is required to investigate the full implications of this hypothesis on the development and treatment of cardiac disease.

Key words Pulse Reverse Osmosis, osmolality, COP, MOP, pulsatility, fluid balance, fluid exchange, oedema, shock, hypertension

Introduction

Pulse Reverse Osmosis [1] (PRO) is a new theory of blood pressure which incorporates permeability and pulsatility into the Starling hypothesis of fluid exchange. PRO suggests that fluid balance is achieved when the mean capillary pulse pressure (MCPP) is equal and opposite to the membrane osmotic pressure (MOP) across the capillary membrane. Fluid exchange is achieved by the pulsing of the blood pressure above and below this fluid balance equilibrium. Imbalances between the MCPP and the MOP are predicted to result in either oedema, shock or hypertension. This review looks at studies investigating the principles underlying PRO and the clinical studies investigating its relevance in the diagnosis and treatment of cardiac disease.

The Starling hypothesis of fluid exchange

In 1896 Starling and Baylis [2-4] proposed that fluid balance and fluid exchange were driven by the interaction of two pressures across the semi permeable

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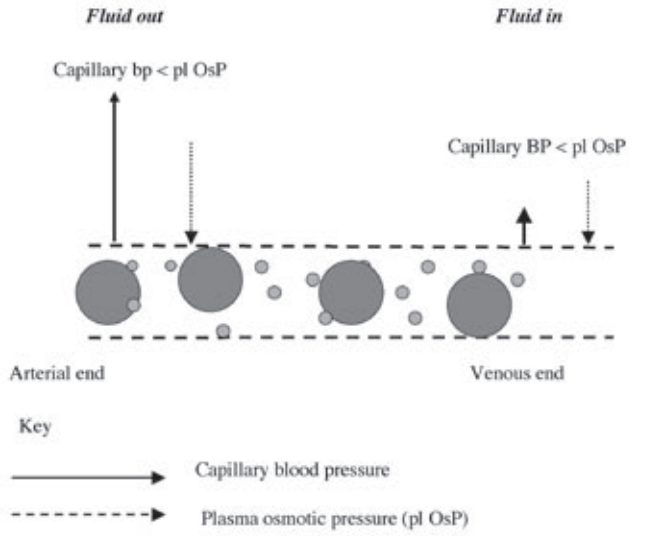

Fig 1 The Starling hypothesis of capillary fluid exchange

Principles of the Starling hypothesis

The capillary blood pressure drops from the arterial to the venous end of the capillary. The osmotic pressure remains constant down the length of the capillary. At the arterial end of the capillary the capillary blood pressure is greater than the osmotic pressure resulting in filtration of fluid out of the capillary. At the venous the osmotic pressure is greater than the capillary pressure resulting in reabsorption of the fluid from the interstitium. To maintain fluid balance the volume filtered out must be equal to the volume reabsorbed.

capillary wall. The hydrostatic (or capillary blood pressure) was suggested to filter fluid out of the plasma while the osmotic pressure drew fluid back into the circulatory system. Their measurements suggested that the blood pressure was about 30mmHg at the arterial end and about 10mmHg at the venous end of the capillary. The osmotic pressure of plasma, when measured across a piece of bladder as a membrane, was about 20mmHg. From these results they proposed their hypothesis of fluid exchange. This suggested that the blood pressure exceeded the osmotic pressure at the arterial end of the capillary. This resulted in filtration of fluid out of the capillary. At the venous end the blood pressure was less than the osmotic pressure resulting in osmotic re-absorption of fluid (see Fig 1).

There are two major problems with this hypothesis;
1 The osmotic pressure is dependent on capillary pore size
2 Capillary pressure is pulsatile not constant.

PRO has been put forward as a new theory of fluid exchange which incorporates these two factors. It suggests that fluid balance is achieved when the MCPP is equal and opposite to the MOP. During the systolic phase of the pulse wave the capillary pressure exceeds the MOP resulting in fluid being filtered out of the

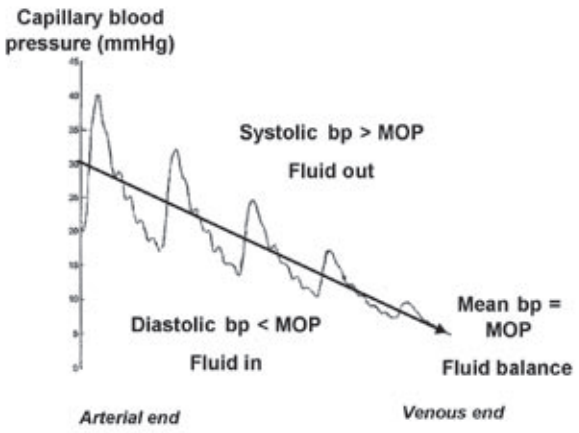

Fig 2 Pulse Reverse Osmosis

PRO suggests that fluid balance is achieved when the mean capillary blood pressure is equal and opposite to the MOP. During the systolic phase of the pulse wave the capillary pressure exceeds the MOP resulting in fluid movement out of the capillary. During diastole the MOP exceeds the capillary pressure resulting in fluid being drawn back into the capillary.

plasma. During diastole the osmotic pressure is greater resulting in fluid return into the capillary (Fig 2).

PRO was first published in 1991. This review looks at subsequent research on the physico-chemistry of osmosis, pulsatility in the capillary bed and the predictions of PRO into the diagnosis and treatment of oedema, shock and hypertension.

1 Physico-chemistry of osmosis

Osmosis is the movement of fluid through a semi permeable membrane from an area of low to an area of high concentration. The osmotic pressure is the pressure developed across the membrane during this process. In medicine, a number of terms are used to describe osmotic pressure. These include osmolality, osmolarity, colloid osmotic pressure, oncotic pressure, osmotic gradient and membrane osmotic pressure. Such an abundance of terms for the description of one pressure results in confusion. The two most meaningful terms are osmolality and membrane osmotic pressure.

Osmolality

Osmolality is the measurement of the number of particles per kilogram weight of solution. The osmolarity is the number of particles per litre of solution. Dissolved protein or fat affects the relative density (specific gravity) of solutions. In plasma

(relative density 1.024-1.028) the osmolarity is less than the osmolality. Osmolality is the more appropriate measurement to use in medicine.

Normal plasma osmolality[5] is in the range 285-297 milliosmol/Kg. As little as a 2milliosmol/kg change in plasma osmolality result in change from maximal to minimal output of antidiuretic hormone (ADH).

Osmolality represents the concentration of the major ions, glucose and urea in the plasma. Sodium, potassium, chloride, bicarbonate, urea and glucose contribute 280 milliosmol/Kg to the total value[6]. Total protein contributes less than 1.2 milliosmol/kg to the total[1,6]. Changes in osmolality represent changes in small molecules rather than protein in the plasma. Osmolality can be calculated from the formula;

$$= R \times T \times (M/V) \times \nu \times m$$

Where R = gas constant, T = temperature in ˚K, M = molar mass of water, V molar volume of water, ν = the dissociation number (the number of particles into which the solute dissociates), m = molar mass of the solute in millimol (From Geigy Scientific Tables ed Lentner C Basel 1984)

Changes in osmolality are the major trigger for fluid balance mechanisms. An increase in plasma osmolality (dehydration, increase in ions, glucose or alcohol) results in release of ADH from the pituitary. This decreases the excretion of water from the kidneys and increases the volume of water in the circulation. A reduction in plasma osmolality inhibits the release of ADH increasing urine excretion.

An osmolality of 1milliosmol/kg is equivalent to 19.8 mmHg of osmotic pressure across a membrane [1,6]. Small changes in osmolality therefore represent large changes in the osmotic pressure across membranes.

Colloid osmotic pressure

The term colloid osmotic pressure (COP) has generally been used to describe the osmotic pressure operating in the capillary. The COP is the measurement of the osmotic pressure generated across a membrane with a pore size of 10-20kDalton.

Starling proposed that the difference between the plasma osmolality Πc and the interstitial osmolality Πi must be equal and opposite to the difference between the blood pressure in the capillary Pc and the interstitium Pi in order to achieve fluid balance.

$$Pc - Pi = \Pi c - \Pi i$$

In 1951 Staverman[7] recognised that not all the protein was retained by the capillary membrane, a little leaked out into the lymph. He proposed that a factor should be added to the Starling equation to account for this leakage. He called this factor the reflection coefficient (α) a term that represents the amount of protein leakage.

$$Pc - Pi = \alpha (\Pi c - \Pi i)$$

This leakage is dependent on the permeability of the capillary membrane.

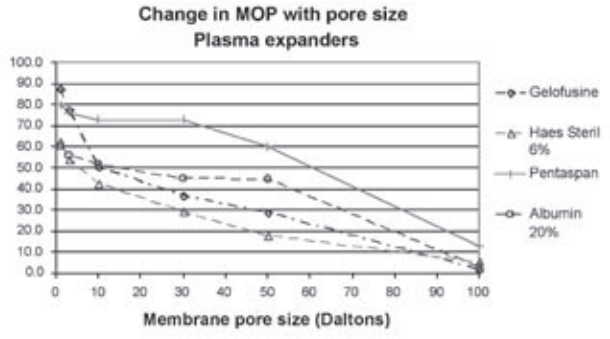

Fig 3 change in the osmotic pressure of plasma expanders with membrane pore size

Solutions containing a solute with a uniform particle size such as albumin demonstrate a plateau between 3 and 50kDalton. The MOP then decreases as the pore size reaches the molecular size of the molecule. Materials that have a wide range of particle sizes such as Gelofusin and Haes Steril have less of a plateau between 10 and 50kDalton.

Following the development of membrane osmometers, the osmotic pressure of solutions across membranes with different pore sizes has been measured. Prior and Barnett [8] demonstrated large changes in osmotic pressure with pore size for a number of commonly used plasma expanders (Fig 3).

Plasma expanders contain molecules with a range of particle sizes. The large changes in MOP with pore size for fixed concentrations of these solutions, highlights the fact that pore size has a major effect on the osmotic pressure of mixtures. Human plasma is also a complex mixture of particles with a wide range of molecular sizes. The osmotic pressure of human plasma has also been demonstrated to vary in a non linear manner with pore size[6,9,10,11].

To date, the osmotic pressure of plasma has been assumed to be equivalent to the colloid osmotic pressure (COP). This is the measurement of the osmotic pressure across a membrane with a pore diameter of 10-20kDalton. However, none of the pores in the capillary are this size. COP is therefore a poor measurement of capillary osmotic pressure. The term Membrane Osmotic Pressure (MOP) has been suggested as an alternative[6,9].

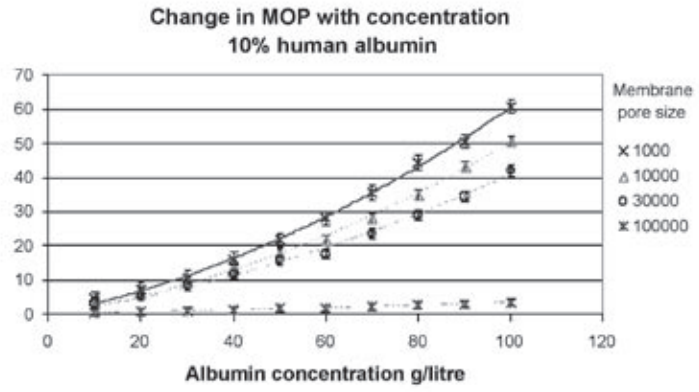

Fig 4 Change in MOP with concentration for 10% albumin solution across membranes with pore sizes ranging from 1K to 100kDalton.
MOP is curvelinear with increasing concentration. For a given concentration MOP increases with decreasing pore size.

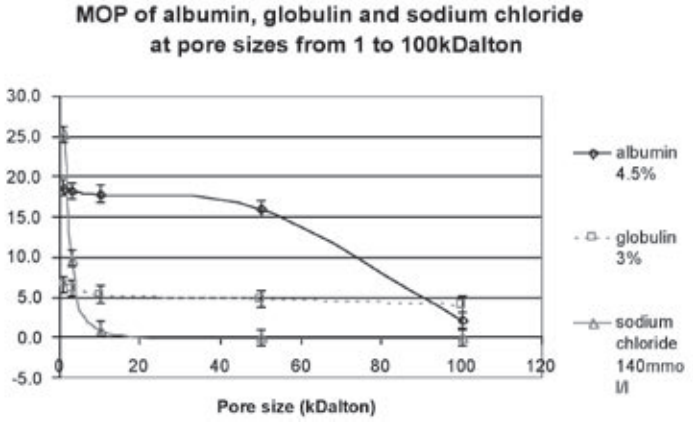

Fig 5 Change in MOP with pore size for albumin, globulin and sodium chloride at normal plasma concentrations
Albumin demonstrates a plateau at 18mmHg this falling off as the pore size reaches the molecular size of the molecule (69kDalton). Globulin demonstrates a plateau between 10 and 100 kDalton. Sodium chloride shows no measurable MOP until the pore size is below 10kDalton. As the pore size approaches the molecular size of sodium the MOP rapidly increases.

From Prior FGR, The effect of pore size on membrane osmotic pressure. British Microcirculation Society 41st Scientific Meeting and Symposium 5-6 th Apr 2004 P26

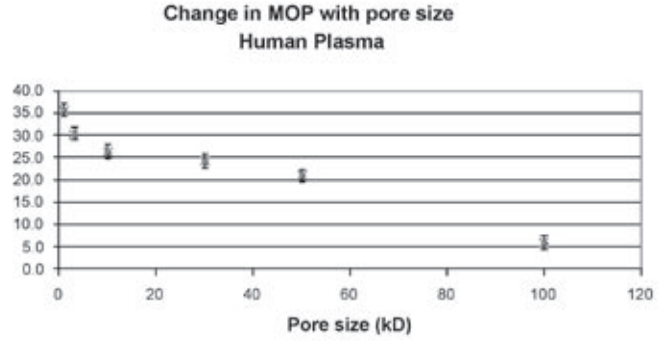

Fig 6 Change in osmotic pressure of human plasma with pore size
The MOP of human plasma varies with pore size, the smaller the pore the higher the MOP.

Membrane Osmotic Pressure

The Membrane Osmotic Pressure (MOP_{xK}) is the osmotic pressure of a solution generated across a membrane with a specific pore size, where the term $_{xK}$ represents the pore size in kDalton.
The two major factors that affect MOP are;
1 The concentration of non diffusible particles on either side of the membrane
2 Membrane pore size.

The effect of concentration on MOP

MOP has been shown to be curvelinear with concentration, the non linearity resulting from concentration polarisation at the membrane surface[12]. A typical concentration/ MOP curve for human albumin is shown in Fig 4.
Curve fitting suggests that MOP is related to concentration by the formula[6].
$MOP = ac^2 + bc + i$

where c is the concentration
a and b are factors dependent on the particle size and inter-particle attraction.
i is the integer.

The effect of change in pore size on MOP

In order to determine which plasma components contributed to the overall shape of the MOP/pore size curve for human plasma Prior [6,13] measured the change in MOP with pore size for albumin, globulin and sodium chloride at normal plasma concentrations. These relationships are shown in Fig 5.
Small molecules such as the ions, and glucose have little effect until the pore size is less than 3kD. At pore sizes below this, the increase in MOP is rapid with reducing pore size. Larger molecules such as albumin exhibit a plateau followed by a sharp fall when the pore size reaches the molecular size of the molecule (69kDalton). The MOP of globulin remains reasonably constant over the pore size range from 1 to 100kDalton. Summation of these three curves gives a close approximation to the MOP/pore size curve of human plasma (Fig 6).

Prior[13,14] has suggested that there are three periods of acute change in the MOP/pore size relationship for plasma (see fig 7).

The periods of acute change correspond to the three different species of pore sizes reported to exist in the capillary (see table 1).

Small changes in pore size in the region of 1-3kDalton or 60-80 kDalton produce large changes in MOP. Pore size is highly dynamic. The change in pore size also affects the MOP.

As long ago as 1934 Landis [38] demonstrated that the venous end of the capillary was twice as permeable as the arterial end. This increase in permeability has been demonstrated for every species of animal tested[39]. This suggests that the medium and large pores are at greater abundance at the venous end of the capillary [40,41]. Increasing pore size down the length of the capillary would result in decreasing MOP down the length of the capillary.

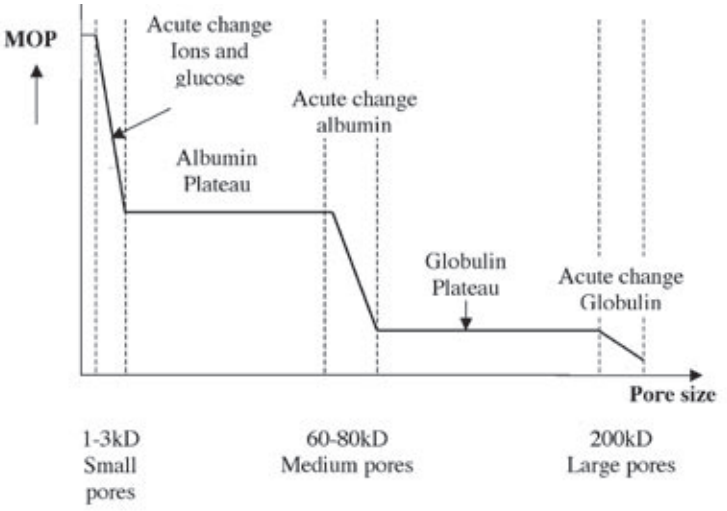

Fig 7 Relationship between pore size and MOP in human plasma. *Plasma exhibits a stepwise decrease in MOP with increasing pore size. This consists of an acute drop between 1and3kDalton, followed by a plateau. A second acute phase occurs between 60-80kDalton followed by a globulin plateau. It is assumed that there will be a third acute phase when the pore size reaches the molecular size of the globulins. The pore sizes corresponding to the acute change phases correspond to the known diameters of the three classes of pore in the capillary.*

Prior FGR Blood pressure, pore size and osmotic pressure. Proceedings of the Artery 4 meeting Royal College of Physicians London, 4&5th Oct 2004-09-27 PB3

Relevance to fluid balance and fluid exchange

As pore size is one of the major factors to affect MOP, the dynamic nature of pore size in the capillary, and its effect on MOP, must be included in theories that describe fluid balance and fluid exchange. The dynamic nature of MOP is central to the mechanisms proposed in Pulse Reverse Osmosis

2 Pulsatility in the capillary bed.

The second weakness of the Starling hypothesis is that it fails to consider the pulsatile nature of the capillary pulse. Starling and Bayliss believed that the pulsatility of the circulatory system was damped out before it reached the capillary bed. Indeed it was not until 1964 that Wiederheilm [42] demonstrated pulsatility in the capillaries of frogs. The pulsatility was a stepped down version of the normal cardiac pulse wave.

It is now recognised that pulsatility is an essential feature of the microvascular bed in all animal species [43-44]. If the normal cardiac pulsatility is compromised the capillary generates its own vasomotion pulse waves. Vasomotion is initiated when there is a 30% or greater reduction in blood volume [45], or if the blood pressure drops below a threshold pressure (usually 50% or less) [46]. The pulsatility is set up by rhythmical contractions of the precapillary musculature. Maximal flow motion coincides with the local arterial pressure and flow known to be critical for survival [47].

Type of pore	diameter	Relative ratio	Theoretical structure	Mediators known to affect pore size
Small pores	1-3kDalton	10,000	Aquaporins [15,16] or Glycoprotein matrix [17-19]	Hypertonicity [31] ADH [32,33] Insulin [32], Glucocorticoids[34], Thiazides[35], Aldosterone[35], ANP[36]. ANGII [33]
Medium pores	60-80kDalton	500	Tight junctions between endothelial cells [20-25, 28,29]	Bradykinin[23], Histamine[23-25], Serotonin[23] Prostaglandins [22] TNF[28], IL4[29], Nitric oxide [37]
Large pores	< 150 k Dalton	1	Trancellular pores and fenestrations[21,24,30]	Histamine [23] VEGF[30] INFbeta-1b[26]

Table 1 Pore sizes in the capillary

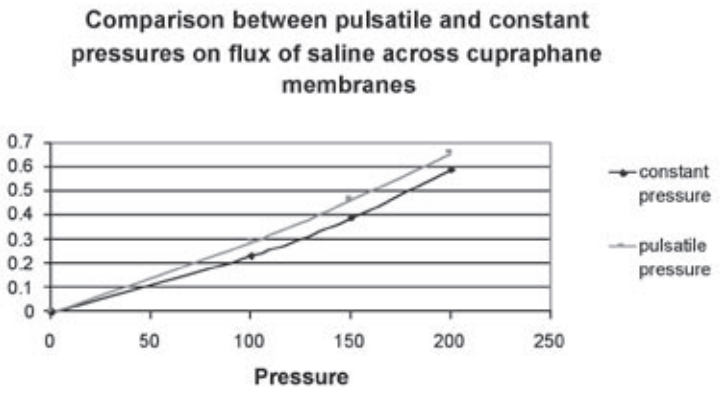

Fig 8 Increase in flux of saline with pulsatile pressure
Pulsatile pressure resulted in 30% greater flux of sodium chloride 0.9% across cupraphane membranes that equivalent constant flow pressure.

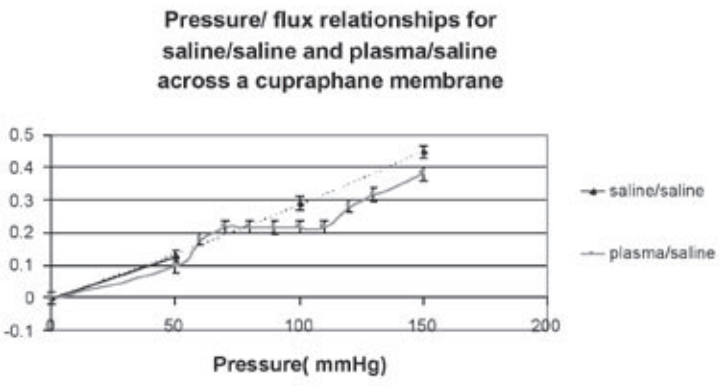

Fig 9 Flux of plasma with non pulsatile pressure
Flux of plasma across a cupraphane membrane was not linear with pressure. Plasma flux remained constant across the pressure range 70 and 120mmHg.

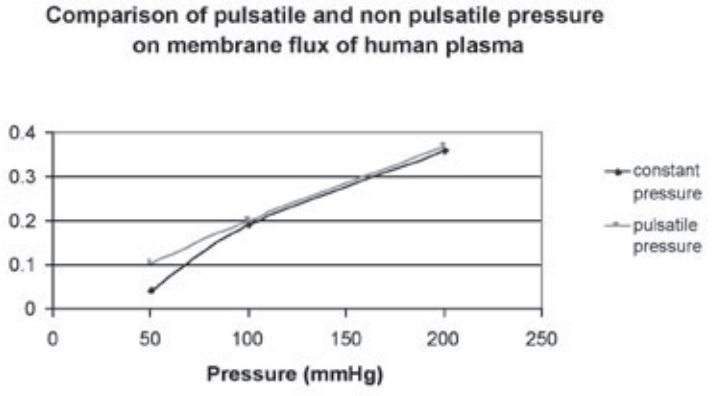

Fig 10 Pulsatile pressure flux relationships with human plasma
Pulsatile pressures only increase the flux of plasma by about 5% between 100 and 200mmHg. However there is a 120% increase at 50mmHg.

A stepped down version of the cardiac pulsatility has been recorded in human nailfold capillaries [48]. The pressure wave has a cardiac and respiratory component. The wave form is similar in health in adjacent capillaries (20.8+/-1.08mmHg) and remains relatively constant over a six month period. Pulsatility is a normal component of capillary pressure.

Physico chemical effects of pulsatile pressure on flux of solutions across membranes.

Pulsatile flow has been shown to increase the movement of plasma across membranes[6] The movement of a simple fluid (such as saline) through a cupraphane membrane (flux) has been shown to increase linearly with increasing pressure. Applying a pulsatile pressure with a mean pressure and amplitude the same as the non pulsatile pressure [6, 40,41] increases flux by about 30% (Fig 8).

When the same experiment was repeated using human plasma on one side of the membrane, and saline on the other, the flux of plasma across an identical membrane was non linear with a plateau between 60 and 120mmHg (Fig 9).

The finding that there is a flux plateau between 70 and 120mmHg, the normal blood pressure may be coincidental but requires further investigation. Comparison of pulsatile and non pulsatile flux for human plasma [6, 40,41] suggested little difference at pressures above 100mmHg but a 120% increase at 50mmHg (Fig 10).

The finding that pulsatile pressures, in vitro, double the flux of plasma at the pressures normally found in the capillary suggests that pulsatilty has a major effect on the fluid exchange. This requires to be tested in vivo.

The decay of pulse pressure down the capillary

Pulsatile wave forms can be generated using a one dimensional multi-branched transmission line model [49-50]. By applying superimposition of the linear transforms to fit the boundary conditions for the arterial amplitude of 40/20mmHg and a venous

amplitude of 10/5mmHg, Stroev [51] generated the capillary waveforms shown in Fig 11.

Interestingly the arterial notch in the waveform coincides with the mid point of the pressure wave. Changes in arterial stiffness change the shape of the pulse wave. Research is required to investigate the effects of this change in pulse shape on fluid balance and exchange. PRO predicts that minor changes in shape are likely to have major effects on fluid movement between the plasma and interstitium.
Applying Stroev's pulse wave prediction gives the following model of PRO (Fig 12).

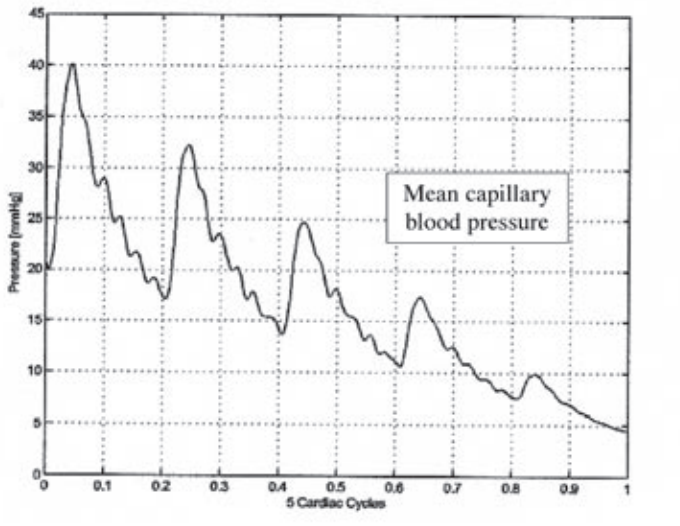

Fig 11 Predicted decay curve of capillary pulsatility.
Stroev's calculated fall off in pulsatility down the length of the capillary is shown above. The mean capillary pulse pressure (MCPP) corresponds roughly with the location of the aortic notch in the waveform.

3 Physiological Clinical studies relevant to PRO

Several physiological factors affect the MOP, these include posture, tourniquet compression, heat and change in external barometric pressure.

Posture

The body is approximately 60% water. Change from lying to standing increases the hydrostatic pressure by approximately 2 meters of water. One of mankind's major adaptations is the ability to adjust fluid physiology to counteract these hydrostatic changes. Change in MOP is one of the body's bipedal adaptive mechanisms.

Krough et al [52] demonstrated an increase in MOP_{10K} of 4.8- 12 mmHg between lying and standing. Hope and Prior[53] measured the changes in osmolality, MOP_{1K} and MOP_{10K} between lying and standing in 6 volunteers (see table 2).

These results are consistent with the assumption that change in posture results in change in diameter of the medium sized pores. The changes took between 5- 10 minutes to stabilise.

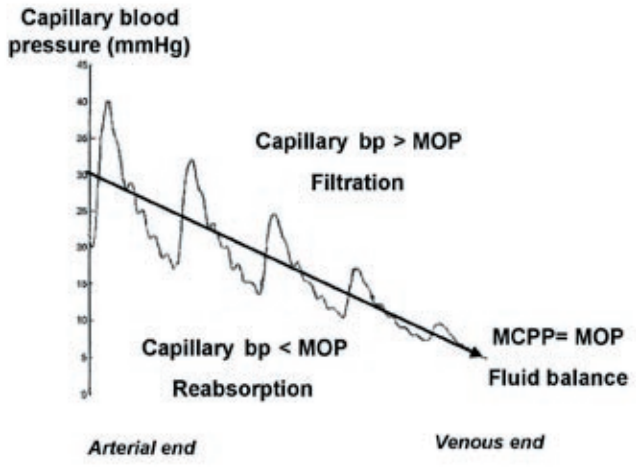

Fig 12 Pulse reverse osmosis related to the predicted decay of the capillary pulse.
During the systolic peaks the capillary pressure (MCPP) exceeds the MOP resulting in filtration. During diastole fluid will be drawn back into the capillary by Osmosis..
Fluid balance will be achieved when the MCPP is equal and opposite to the MOP.

Tourniquet Compression

Application of a tourniquet raised the MOP_{10K} from 25 to 28.4mmHg [54]. The MOP took longer than 10 minutes to return to baseline after the removal of the tourniquet. The finding that tourniquet compression changes the MOP must be taken into account when taking samples from patients. A blood pressure cuff should not be used.

	Osmolality Milliosmol/kg (SEM)	MOP 1K (mmHg) (SEM)	MOP 10K (mmHg)
Mean Lying	289 (1.1)	27.3 (0.61)	24.6 (0.59)
Mean standing	290 (1.0)	30.2 (0.56)	27.9 (0.62)
Change	1 (0.8)	2.9 (0.34)	3.4 (0.39)
P value	p = 0.3	p<0.01	p<0.01

Table 2 Change in osmotic pressure from lying to standing

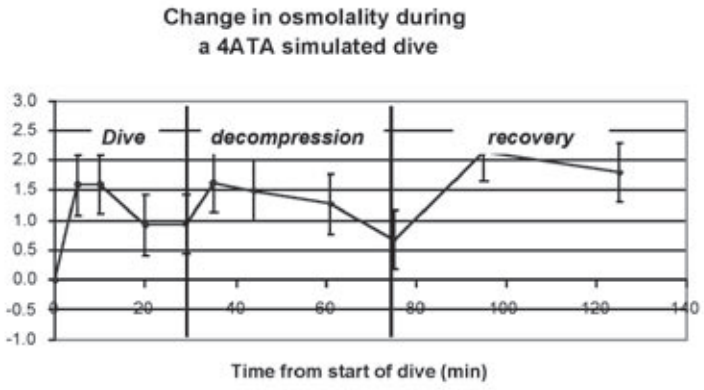

Fig 13 Change in osmolality during a 30 minute 4ATA simulated dive
The osmolality increased over the first 10 minutes of the dive phase and then fell. During decompression there was an initial rise followed by a prolonged fall. During recovery there was an initial rise followed by a slow fall. All of these results are consistent with the measurement of changing gas concentrations in the plasma.

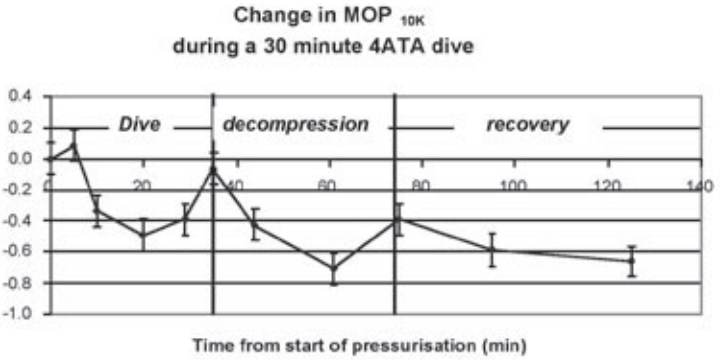

Fig 14 Change in MOP_{10K} during a 30 minute, 4ATA simulated dive.
In this study of 10 divers there was a decrease in MOP over the first 20 minutes of the dive followed by a small amount of recovery. During decompression the MOP fell again. During the recovery period there was a secondary fall in MOP.

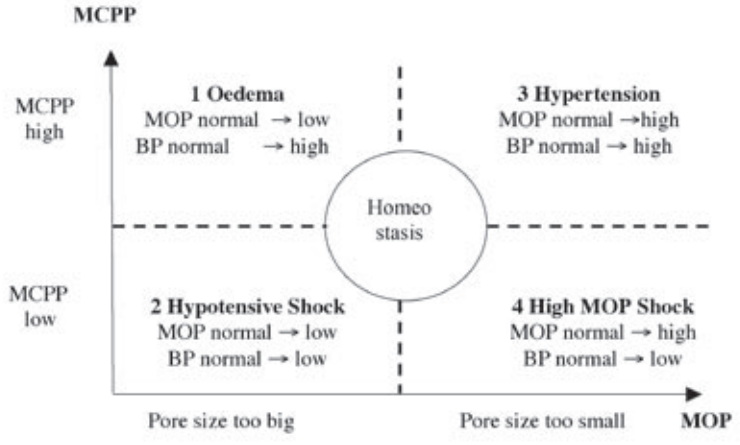

Fig 15 Fluid imbalance diseases as predicted by PRO

Effect of heat

Immersion of a hand into hot water raised the MOP_{10K} in that arm from 25.9 to 27.6mmHg [55].

External barometric pressure

Hypobaric exposure has been reported to increase plasma osmolality [56] decrease plasma volume [57-61] and increase MOP[62,68]. Hyperbaric exposure decreases plasma osmolality[63-65], increases plasma volume [65-67] and decreases MOP[68]. Results from the Diving Diseases Research Centre taken during simulated dives in a hyperbaric chamber[68] are shown in Fig 13.

The osmolality increased by 1.6 milliosmol/kg ($p<0.01$) during the first 10 minutes of pressurisation after which it fell towards the initial value. At the start of decompression the osmolality rose again for the first five minutes and then fell. During the recovery phase at the end of the dive, there was a 2 milliosmol/Kg rise ($p<0.01$) in osmolality 20 minutes after the end of the dive. The first two peaks of osmolality corresponded to periods where the volunteers were inhaling increased oxygen concentrations (increased partial pressure during compression, inhalation of 100% oxygen at the start of the decompression period to avoid decompression illness (DCI)). The cause of the rise during recovery is still under investigation.

The changes in MOP during the same controlled dive are Fig 14.

The changes in MOP were the mirror image of the changes in osmolality (See Fig 13). The changes are suggested to result from an increase in pore size of the medium sized pores.

PRO, oedema, shock and hypertension

PRO suggests that fluid balance is achieved when the capillary pressure is equal and opposite to the MOP across the capillary wall. There are four possibilities in which these pressures can be unequal;

1 MCPP high - MOP normal
2 MCPP low - MOP low
3 MCPP normal - MOP high
4 MCPP normal - MOP low

PRO suggests that these correspond to oedema, hypotensive shock, hypertension and high MOP shock (Fig 15). Clinical studies investigating these relationships are reported below.

1 Oedema

PRO predicts that oedema should occur when the MOP is normal to low and the blood pressure is normal to high. Prior et al [69] measured the MOP_{10K} and concurrent mean arterial blood pressures in a group of 50 patients with bilateral ankle oedema of any cause and 20 healthy volunteers [69]. The results are shown in Fig 16.

Oedema patients had MOP/mean BP points to the left of the normal controls, a finding that supports the predictions of PRO. Comparison of MOP_{10K} and mean blood pressure results against normals on a graph similar to Fig 16 may provide a useful diagnostic guide and a method of monitoring diuretic effectiveness in the treatment of oedema.

2 Hypotensive Shock

PRO predicts that hypotensive shock will occur when the MOP is normal to low and the MCPP is normal to low. Surgery is known to produce major falls in blood pressure but its effects on MOP are less well known. Bock et al[71] compared the drop in MOP_{10K} between normal controls and trauma patients over a 3 day period. The MOP_{10K} in the control group was 27.8 +/- 1.6 mmHg compared to 16.8 +/-3.3 mmHg in the trauma group. Cotton et al [72] demonstrated a drop in MOP_{10K} from 21.8 +/- 1.8 mmHg in maternity patients before delivery to 16.5 +/- 2.1 mmHg post partum. Moore and Clarke [70] demonstrated a decrease in MOP_{10K} from 25.5 +/- 3.4 to 21.05+/-2.2 mmHg following gastro intestinal surgery. The MOP_{10K} reached a minimum on the third postoperative day, returning to normal in most patients on the fifth post operative day. Fig 17 presents the typical pattern of change in MOP following GI surgery.

If treatment is required to raise the blood pressure in these patients it would be logical to administer plasma expanders to increase

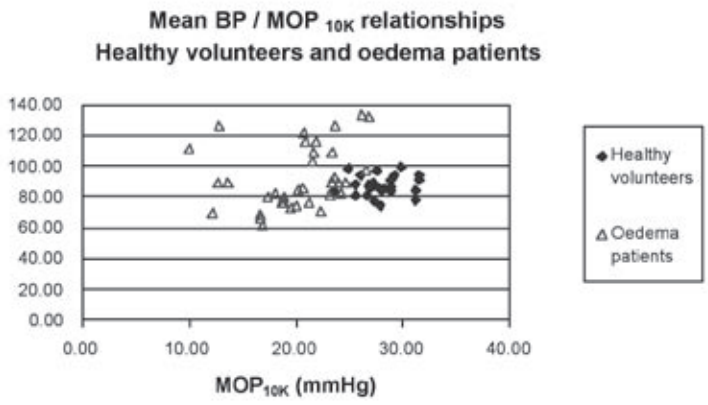

Fig 16 Comparison or mean arterial blood pressures and $MOP_{10K's}$ for oedema patients and healthy volunteers
The MOP_{10K} and mean blood pressures were measured for 50 patients with bilateral ankle oedema and 20 helthy volunteers. The oedema patients had BP-MO's in the predicted oedma area (se Fig 15)

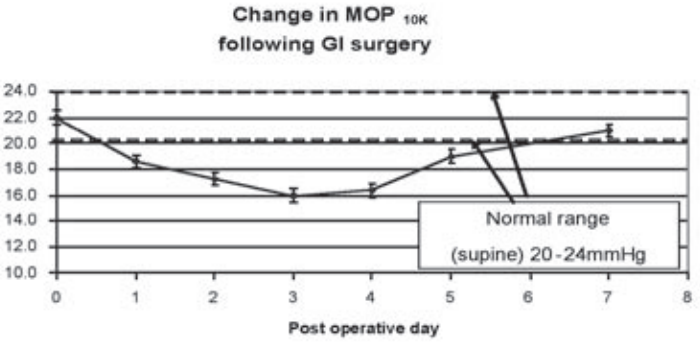

Fig 17 Typical MOP/time recovery period following gastro intestinal surgery
The MOP_{10k} typically drops following GI surgery to a minimum on day 3. Patients who undergo a non complicated recovery have MOP's that start rising on day 4 and return to the normal range 6-7 days after surgery.

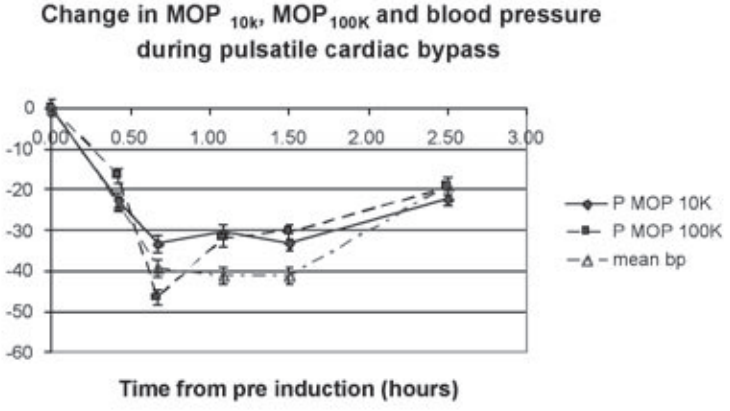

Fig 18 Change in MOP $_{10K}$ and MOP $_{100K}$ during cardiac bypass surgery
The study investigated mean blood pressure and MOP10 and 100kDalton in 19 patients undergoing pulsatile cardiac bypass surgery. There was a 20% drop in all three measurements before bypass was started. The maximum drop of 30-50% was observed in the samples taken 10 minutes into bypass. This drop corresponds to the area of hypotensive shock as predicted in Fig 15.

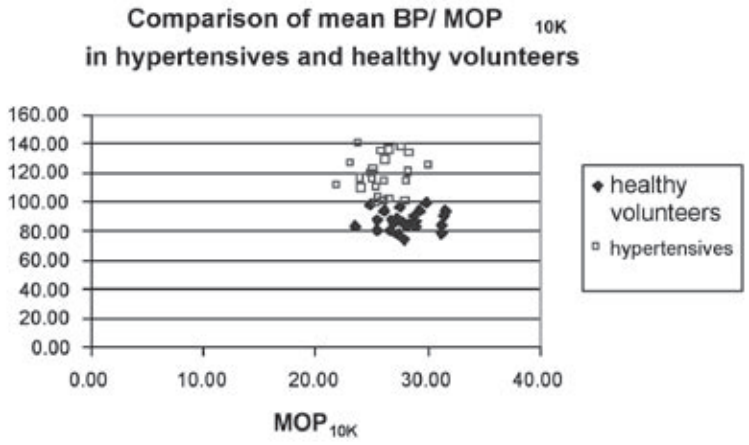

Fig 19 MOP_{10K} and mean arterial blood pressure for hypertensives compared to healthy volunteers
The mean bp/ MOP_{10K} plots for 25 hypertensives lay above the area of normals.

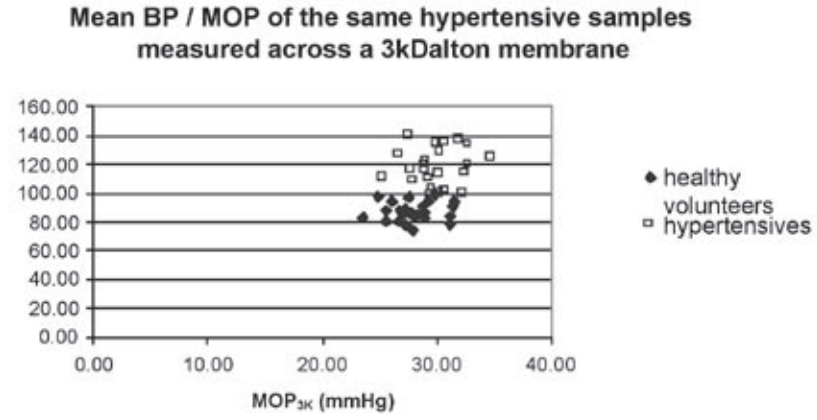

Fig 20 MOP/mean BP of the same hypertensive samples measured across a 3kDalton membrane
Measurement of the same samples of plasma across a 3K Dalton membrane shifted the mean BP/MOP plots to the right. This is the area predicted to indicate hypertension resulting from a decreased pore size in Fig 15.

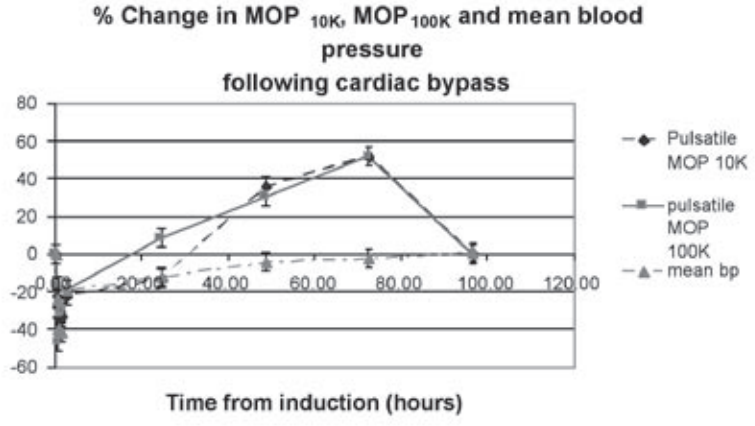

Fig 21 Changes in osmolality, MOP_{10K} and MOP_{100K} during the five post operative days following cardiac bypass surgery
Following surgery both the MOP_{10k} and MOP_{100K} increased to a peak between 60-80 hours after the bypass. This occurred while the blood pressure was still reduced. This corresponds to the high MOP low blood pressure shock suggested in Fig 15.

the MOP. Crystalloids should not be given in large volumes as the protein dilution that will result will lower the MOP further. This will result in oedema as soon as the blood pressure starts to recover (see Fig 16).

The pattern of low MOP with a concurrent low blood pressure is in agreement with the predictions of hypotensive shock outlined in PRO. Cardiac bypass surgery in adults[73] and in children[74] produces little change in osmolality, a drop of about 30% in MOP_{10K} and 50% in MOP_{100K} during the procedure (Fig 18).

Two thirds of the drop in MOP_{10K} and about a third of the drop in MOP_{10K} occurred before bypass started. This may be an effect of the anaesthetics or the release of mediators following opening of the chest wall. The effects would appear to be mediated through opening the tight junctions. Following connection to bypass there was a further 10% drop in MOP_{10K} but a 30% drop in MOP_{100K}. The fall in MOP_{100K} is consistent with opening of the large pores. In these situations plasma expanders with a molecular size of 70kDalton or less will not be retained in the plasma. If a plasma expander is required then one with a molecular weight greater than 200kDalton, such as Pentaspan, is probably more appropriate.

The changes observed in post surgical shock are in line with the predictions from PRO.

3 Hypertension

PRO suggests that hypertension will occur when patients have a MOP that is normal to high and a blood pressure that is normal to high [40,41]. This is consistent with the pores being too small or partially blocked.

Measurement of mean arterial BP and MOP_{10K} in 28 hypertensives and 20 healthy volunteers is shown in Fig 19.
In order to mimic the effect of a smaller pore on the MOP of these samples, the MOP_{3K} of the hypertensive samples

was measured across a 3 kDalton membrane (Fig 20).

A decrease in pore size shifts the MOP/BP to positions in the top right hand segment of Fig 15 placing them in the hypertensive segment. This suggests that hypertension results from decreased pore size in the capillary. This is consistent with the pharmacology of treatment of hypertension. Thiazide diuretics, ACE inhibitors and calcium antagonists all have an effect on the capillary bed. Thiazides, although classified as diuretics, increase capillary permeability. ACE inhibitors, as well as blocking ACE, block bradykininogen. This increases the levels of circulating bradykinin. Bradykinin increases the pore size of the medium pores the capillary. Calcium antagonists have an effect on calmodulin, the protein that holds the tight junctions together. Present treatments of hypertension increase the pore size of the capillary. This is in line with the mechanisms predicted in PRO.

4 High MOP shock

PRO predicts that high MOP shock will occur when the mean blood pressure is low and the MOP is high. Such a scenario is seen in certain patients after cardiac bypass surgery. As highlighted above these patients exhibit a profound fall of up to 50% in MOP_{10K} and MOP_{100K} (see Fig 18) which generally recovers within 24 hours of the surgery. There is then a large rise in MOP_{10K} and MOP_{100K} to double the normal levels on days 3-4 after surgery (Fig 21).

The increase in MOP concurrent with a low blood pressure suggests that these patients require crystalloids rather than colloids at this stage after surgery, It also suggests that the medium pores are too small. These patients demonstrate high MOP shock as predicted by PRO.

Pulse rate and blood pressure

PRO suggests that the pulse is driving force of fluid exchange. This is contrary to the current belief that pulse rate and blood pressure are synonymous. However, the circulatory system has evolved to control both fluid balance and fluid exchange. During exercise the body needs to increase the delivery of nutrients and gasses to the cells without compromising fluid balance. If the blood pressure during exercise increased 200-300% in line with the increase in pulse rate, fluid balance would be totally compromised. Increase in pulse rate increases the rate of fluid flux across membranes. It therefore appears logical that the pulse performs a function greater than pressure and flow in the capillary.

The concept that the pulse and blood pressure are two separate entities is supported by studies from the Diving Diseases Research Centre. Divers exposed to pressures equivalent to a 30 meter dive showed a 15% decrease in pulse rate with a 2-4% increase in blood pressure [75] (Fig 22).

In order to determine how much of this effect was due to increase in oxygen concentration and how much was to do with pressure, the same group of divers inhaled mixtures of oxygen from a face mask, the oxygen concentrations corresponding to the partial pressures they would have inhaled during the 30 meter dive. The effect of inspired oxygen on pulse rate and MOP is given in Fig 23

The inhaled oxygen was found to contribute about 6% to the decrease in pulse rate. The remainder of the 16% decrease during the dive is assumed to be a pressure effect. These results support the concept that the pulse rate depends on the metabolic requirement for dissolved oxygen and nutrients in the plasma.

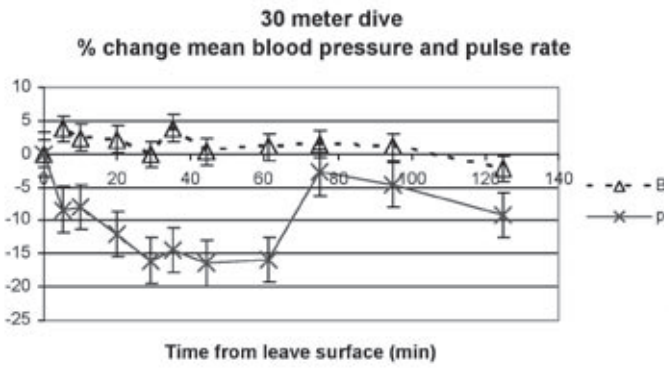

Fig 22 Change (%) in pulse rate and mean blood pressure during a simulated 30 meter dive.
During a 30 minute simulated dive in 10 volunteers the pulse rate dropped by 15% while the mean blood pressure increased by 5%.

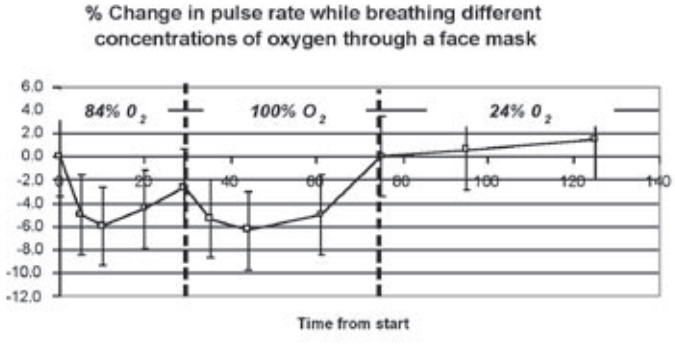

Fig 23 Change in pulse rate induced by oxygen content of inspired air
Increasing the inspired O_2 concentration to 84% resulted in a decrease in pulse rate for about 10 minutes. After this time the pulse rate started to return to normal. A second increase in concentration to 100% had a similar effect.

Discussion

Since its publication in 1991, evidence is growing to support the mechanisms proposed in PRO. Research into the physico-chemistry of osmosis confirms that MOP is dependent on the pore size in the capillary wall. There are three types of pore in the capillary with small (1-3kD), medium (60-70kD) and large diameter (> 100kD) pores. The pore size of each species of pore is dynamic with different mediators affecting different pore types. The periods of acute change in the MOP/pore size relationship of human plasma (Fig 7) corresponds to the three different pore diameters in the capillary. Small changes in pore size of the three types will have a large effect on the MOP of plasma. However, the ability to change the pore size enables the body to endure that the MOP=MCPP to maintain fluid balance.

PRO suggests that pore size increases down the length of the capillary This is in line with the doubling of permeability in all capillaries from the arterial to the venous end and that the medium sized tight junction pores are located principally in the venules. Increasing pore size down the length of the capillary will result in a decrease in MOP from the arterial to the venous end. As a result the MOP will decrease in line with the decrease in capillary pressure to ensure that MOP=MCPP down the length of the capillary.

Capillary flow is pulsatile, the pressure being a stepped down version of the cardiac wave with a secondary respiratory component. If the capillary is deprived of this pulse wave it sets up its own vasomotion waves. Vasomotion is triggered if the pulsatile pressure or flow falls below a critical level. The finding that pulsatility is an essential component of capillary flow gives suggests that pulsatility must have a role in the capillary. PRO suggests that this role is fluid exchange.

The concept that the pulse is an integral part of blood pressure is challenged by the finding that divers exhibit a 16% drop in pulse rate with a concomitant rise of 2-4% in blood pressure. This provides evidence that the pulse performs a function separate to that of mean pressure and flow in the capillary. This is consistent with the suggestion in PRO that the pulse drives fluid exchange while the balance between the MCPP and MOP controls fluid balance.

Pulsatile flow results in greater flux across membranes than constant flow. Pulsatile flow produces a 30% increase in saline flux across cupraphane membranes. The flux of plasma across membranes is non linear with a plateau between 70-120mmHg. As a result pulsatile flux at pressures lower than 50mmHg increase flux by 120%. Pulsatile pressures are therefore much more efficient at filtration than constant flow.

Prediction of the diminishing pulse wave shape in the capillary suggests that filtration corresponds with the pressure wave above the arterial notch. Reabsorption is a slightly longer phase below the notch. PRO suggests that the shape of the pulse wave is critical to fluid exchange. In this case, change in the shape of the pulse wave as a result of arterial stiffening or arrhythmias will have a major effect on capillary fluid exchange.

Fluid balance is one of the major achievements of the circulatory system. Imbalance is likely to seriously disturb homeostasis. PRO suggests that imbalances in MOP and MCPP result in either; oedema, shock or hypertension.

Oedema

Measurement of mean arterial blood pressure and MOP_{10K} in oedema patients shows an imbalance between the MCPP and MOP. Fig 16 offers a method of diagnosing oedema and a method of monitoring diuretic effectiveness.

Hypotensive Shock and High MOP shock.

Falls of 20-50% in MOP are routine following surgery. Following GI, trauma or obstetric delivery the MOP reaches a minimum on day 2-3 and returns to normal in those patients with an uneventful recovery after 5-7 days. After cardiac bypass the MOP rises by up to 50% on days 3-5 after surgery. These two situations correspond to hypotensive and high MOP shock as predicted by PRO. Therapeutically they suggest that expanders should be given to treat the hypotension of hypotensive shock whereas crystalloids should be used for high MOP shock.

Hypertension

Hypertensive patients have MOP/mean BP relationships that fall into the area suggested by PRO (Fig 16). Measurement of their plasma across membranes with smaller pore sizes gives an indication of the anticipated shift expected when the pore size in these patients is too small. These results are in line with the suggestion in PRO that hypertension is a condition in which the pore size in the capillary is too small.

Change in pulse shape

PRO suggests that the pulse drives fluid exchange.

In this case the shape of the pulse wave is critical to ensure that the volume filtered out during systole is equal and opposite to the amount reabsorbed during diastole. The shape of the pulse wave is therefore critical to achieving this balance. Arrhythmias and arterial stiffening both affect the shape of the pulse wave. Research is required to investigate the effects of change in pulse shape on capillary exchange.

Conclusion

PRO is an update to the Starling hypothesis which incorporates permeability and pulsatility. It suggests that fluid balance occurs when the MCPP is equal and opposite to the MOP. The pulse drives fluid exchange. The physico chemistry of osmosis and research into the pulsatile nature of the capillary bed support the principals underlying this hypothesis.

Imbalance between the MCPP and MOP are predicted to result in either oedema, shock or hypertension. Preliminary clinical studies support these predictions in oedema, shock and hypertension.

PRO is a new model of fluid balance and exchange which offers a simple model for the development of oedema, shock and hypertension. It suggests that arrhythmias and arterial stiffening have a profound effect on fluid exchange. Further research is required to investigate the full implications of this hypothesis on the development and treatment of cardiac disease.

Acknowledgements

P. Stroev was funded by the Overseas Research Students Awards Scheme and EPSRC (grant EPSRC/GR/19793/01), whose generous support is gratefully acknowledged.

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