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EXPERIMENTAL OSTEOARTHRITIS IN THE RABBIT

II. A NEW METHOD TO ESTIMATE THE OXYGEN CONSUMPTION AND DIFFUSION CAPACITY IN THE SYNOVIAL MEMBRANE OF THE KNEE

By

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SVALASTOGA, EILIV and JØRGEN GRØNLUND: *Experimental osteoarthritis in the rabbit. II. A new method to estimate the oxygen consumption and diffusion capacity in the synovial membrane of the knee.* Acta vet. scand. 1985, *26*, 326—339. — The oxygen supply to the joint cartilage depends on the oxygen transport from the capsular arteries to the capillaries, the oxygen diffusion across the synovial membrane and the oxygen transport through the synovia. In osteoarthritis the resistance to transport across all 3 barriers may be increased because of the joint effusion, the elevated intraarticular pressure and the inflammatory changes of the synovial membrane.

In the present study we describe a method to determine 2 important parameters affecting the oxygen transport through the synovial membrane: the oxygen consumption and diffusion capacity of the membrane. The principle of the method is to perfuse the joint cavity of the knee by saline saturated with air and to record the relationship between the oxygen partial pressure in the outflowing perfusate and the perfusion rate.

The values found for the diffusion capacity and oxygen consumption were 0.039 ± 0.013 µl O_2/min/Torr and 0.93 ± 0.90 µl O_2/min (mean ± s).

joint perfusion; joint model; nonlinear least square technique.

The degenerative changes characterizing the joint cartilage in osteoarthritis have hypothetically been ascribed to oxygen deprivation of the chondrocytes (*Lane et al.* 1977, *Ahlqvist* 1984). Oxygen consumed by the joint cartilage penetrates 3 serially arranged transport barriers between the capsular arteries and the chondrocytes. First, oxygen is carried by the convective

blood stream from the arteries to the capillaries of the joint capsule and then diffuses across the synovial membrane into the joint cavity, where it is transferred to the joint cartilage by the diffusive and convective gas transport in the synovia. In osteoarthritis the resistance to oxygen transfer across all 3 barriers may be increased because of the joint effusion, the elevated intraarticular pressure (*Jayson & Dixon* 1970) and the inflammation of the synovial membrane (*Svalastoga & Reimann* 1985). Joint effusion leads to an increase in the length of the transport path between the synovial membrane and the surface of the joint cartilage. The increased intraarticular pressure may cause compression of the vascular structures in the joint capsule and thus hamper the convective transfer of oxygen from the arteries to the capillaries. The inflamed synovial membrane is characterized by edema and hypercellularity (*Svalastoga & Reimann* 1985), due to proliferation of the lining cells and infiltration with leukocytes. These alterations may cause a decrease in the oxygen diffusion capacity across the synovial membrane and an increase in the oxygen consumption of the membrane, and thereby inhibit the oxygen transfer from the capillaries to the synovia. Hence, a possible explanation for the degenerative changes observed in the joint cartilage of the osteoarthritic bone is that the chondrocytes are partially deprived of their oxygen supply due to an increase in the resistance to the oxygen transport from the capsular arteries to the surface of joint cartilage.

In order to aid the experimental investigation of this hypothesis we have developed an in vivo method to estimate the oxygen consumption and diffusion capacity of the synovial membrane in the knee joint of the rabbit.

MATERIALS AND METHODS

The principle of the method utilized here to determine the oxygen consumption and the diffusion capacity of the synovial membrane is to perfuse the joint cavity with a 0.9 % NaCl solution, which is saturated with atmospheric air. The oxygen flow from the perfusate to the joint at different perfusion rates is equal to the product of the perfusion rate and the difference between the inflow and outflow O_2 concentrations. Oxygen flowing from the perfusate is either consumed by the cells of the synovial membrane or diffuses across the membrane into the capillaries

of the joint capsule. The two components can be discriminated experimentally by assuming that the oxygen partial pressure difference across the membrane is equal to P_{02} in the perfusate less the arterial P_{02}, and that the oxygen consumption is a zeroth order process. Application of these assumptions in the analysis of a model of the oxygen transport across the synovial membrane allows derivation of an expression for the relationship between the perfusion rate and the oxygen partial pressure in the perfusate flowing out of the joint cavity. Since the oxygen consumption and diffusion capacity are formal parameters of the derived expression, the numerical values of these parameters can be determined by using a non-linear least square technique to fit the expression to the experimental data.

A model of the oxygen transport across the synovial membrane

The joint model (Fig. 1) has 3 elements: the joint cavity, which contains the perfusate, the synovial membrane and the capsular capillaries. The contents of the joint cavity and the capillaries are assumed to be completely mixed (i.e. without internal concentration gradients) and the concentration gradients of the synovial membrane in directions other than the x-axis

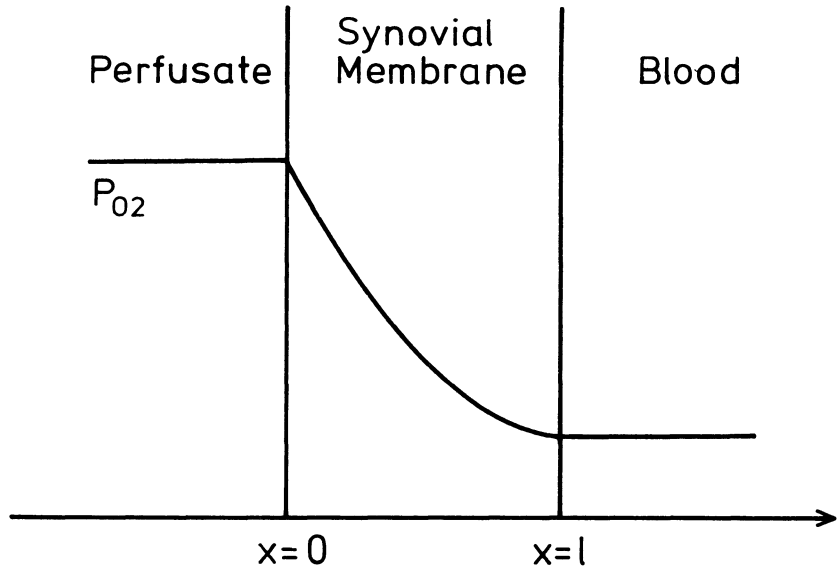

Figure 1. The model of the joint utilized to derive the expression for the relationship between P_{02} in the perfusate and the perfusion rate.

(Fig. 1) are neglected. The equation of continuity for oxygen dissolved in the synovial membrane is given by:

$$dj_{02}(x)/dx^2 = -k_{02} \quad (1)$$

where $j_{02}(x)$ is the oxygen flux in the x-direction (μl O_2/min/m^2) and k_{02} is the rate of oxygen consumption (μl O_2/min/l).
Application of Fick's 1. law yields:

$$D_{02} \cdot d^2c_{02}(x)/dx^2 = k_{02} \quad (2)$$

where $c_{02}(x)$ is the oxygen concentration (μl O_2l) and D_{02} is the diffusion coefficient in the synovial membrane (m^2/min).
According to Henry's law eq. (2) can be written as:

$$D_{02} \cdot \alpha_{02}(S) \cdot d^2P_{02}(x)/dx^2 = k_{02} \quad (3)$$

where $\alpha_{02}(S)$ is the solubility coefficient of oxygen in the synovial membrane (μl O_2/l/Torr) and $P_{02}(x)$ is the oxygen partial pressure (Torr).
If it is assumed that the oxygen consumption is a zeroth order process, (i.e. independent of $P_{02}(x)$), eq. (3) is a linear second order differential equation, the solution of which is:

$$P_{02}(x) = ((1/2) \cdot k_{02} \cdot x^2 + a_1 \cdot x + a_2) \cdot (D_{02} \cdot \alpha_{02}(S))^{-1} \quad (4)$$

where a_1 and a_2 are integration constants.
At the membrane side of the perfusate/membrane interface ($x = 0$, Fig. 1), the oxygen partial pressure is equal to that of the perfusate and at the other interface ($x = l$) the partial pressure is equal to the capillary gas tension:

$$P_{02}(0) = P_{02}(P) \quad (5)$$

$$P_{02}(l) = P_{02}(C) \quad (6)$$

where l is the thickness of the synovial membrane, and $P_{02}(P)$ and $P_{02}(C)$ are the average oxygen partial pressures in the perfusate and the capillaries, respectively.
Eqs. (5) and (6) comprise a set of boundary conditions that allow determination of the integration constants a_1 and a_2:

$$a_1 = D_{02} \cdot \alpha_{02}(S) \cdot (P_{02}(C) - P_{02}(P))/l - (1/2) \cdot k_{02}\, l \quad (7)$$

$$a_2 = D_{02} \cdot \alpha_{02}(S) \cdot P_{02}(P) \quad (8)$$

The oxygen flow across the interface at $x = 0$ is equal to the flux multiplied by the membrane area:

$$J_{02}(0) = A \cdot j_{02}(0) \quad (9)$$

where $J_{02}(0)$ is the oxygen flow from the perfusate (μl O_2/min) and A is the area of the synovial membrane (m^2).
According to Fick's 1. law and eqs. (4), (7), (8) and (9), $J_{02}(0)$ is given by:

$$J_{02}(0) = (A \cdot D_{02} \cdot \alpha_{02}(S)/l) \cdot (P_{02}(P)—P_{02}(C)) + (1/2) \cdot A \cdot k_{02} \cdot l \quad (10)$$

The factor $A \cdot D_{02} \cdot \alpha_{02}(S)/l$ in eq. (10) to the diffusive gas flux through the synovial membrane in the case where the oxygen consumption is zero ($k_{02} = 0$) and the partial pressure difference across the membrane is 1 Torr. This parameter of the synovial membrane is the oxygen diffusion capacity, which we denote by the symbol DC_{02}. The term $A \cdot k_{02} \cdot l$ is the product of the membrane volume ($A \cdot l$) and the rate of oxygen consumption per unit volume, and this product is equal to the total oxygen consumption of the synovial membrane. We denote this parameter by M_{02}. Thus:

$$J_{02}(0) = DC_{02} \cdot (P_{02}(P)—P_{02}(C)) + (1/2) \cdot M_{02} \quad (11)$$

If the amount of oxygen consumed by the synovial membrane approximates the net oxygen flow from the perfusate, the capillary oxygen partial pressure is equal to the arterial value, P_{a02}, i.e.:

$$P_{02}(C) = P_{a02} \quad (12)$$

Furthermore, in view of the linear solubility of 0_2 in the perfusate, the average oxygen partial pressure in the perfusate is likely to be close to the mean value of the partial pressures in the perfusate flowing in and out of the joint cavity:

$$P_{02}(P) = (P_{02}(in) + P_{02}(out))/2 \quad (13)$$

where 'in' and 'out' refer to the perfusate before and after the passage of the joint.

Insertion of eqs. (12) and (13) into eq. (11) yields:

$$J_{02}(0) = DC_{02} \cdot ((P_{02}(in) + P_{02}(out))/2—P_{a02}) + (1/2) \cdot M_{02} \quad (14)$$

The total oxygen flow from the perfusate is equal to the perfusion rate multiplied by the inflow to outflow O_2 concentration difference:

$$J_{02}(0) = \alpha_{02}(P) \cdot (P_{02}(in)—P_{02}(out)) \cdot PR \quad (15)$$

where PR is the rate of joint perfusion (ml/min).

Combination of eqs. (14) and (15) gives an expression for the relationship between $P_{02}(out)$ and PR:

$$P_{02}(out) = \frac{(PR \cdot \alpha_{02}(P)—DC_{02}/2) \cdot P_{02}(in) + P_{a02} DC_{02} + 1/2 \cdot M_{02}}{DC_{02}/2.0 + PR \cdot \alpha_{02}(P)} \quad (16)$$

Table 1 summarizes the assumptions made to derive eq. (16).

Table 1. Assumptions made to derive the expression for the relationship between P_{02}(out) and the perfusion rate (eq. (16)).

Negligible O_2 concentration gradients in the perfusate and the capillary blood.
Negligible O_2 diffusion flux in the synovial membrane in directions other than the x-axis.
Zeroth order kinetics for the oxygen consumption in the synovial membrane.
Identical oxygen partial pressures in the capsular arteries and capillaries.

Experiments

Fig. 2 shows the setup utilized in the experiments. The glass syringe (GS) of the infusion pump (*Harvard Apparatus*, Millis, U.S.) is connected to the stainless steel tube (T1), which is kept at 37°C by a heated concentric water circulation. The outlet of the steel tube is connected to the two-way valve (V1), the setting of which determines the direction of the flow from the infusion pump. In one of the positions the flow by-passes the joint cavity via the shunt tube (T2), and in the other position the perfusate flows through the joint cavity via the flexible polyethylene tubing (P1 and P2). In both cases, the perfusate flows through the second two-way (V2) valve into the trunk of the T-tube (T3).

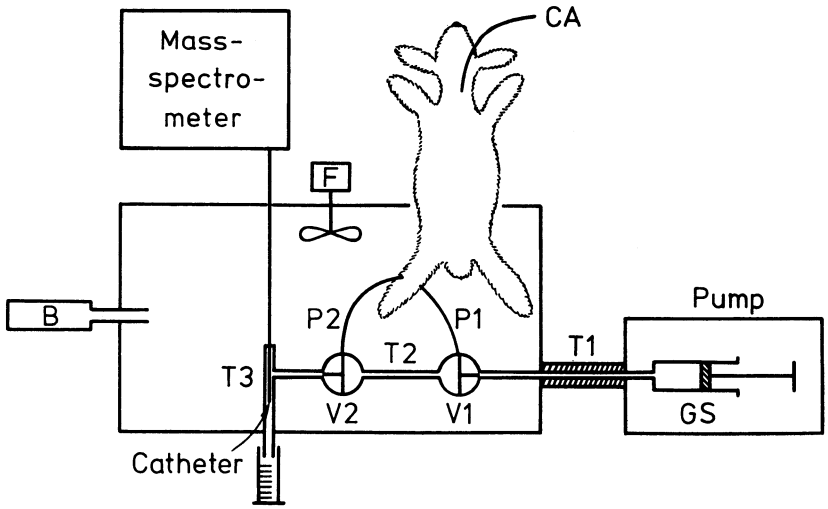

Figure 2. Experimental setup. See detailed description in text.

The bar of this tube contains a membrane covered catheter connection to the mass spectrometer (VG *Micromass,* SX 200, Middlewhich, England). The construction and performance of this catheter, which enables continuous measurement of P_{02} has been described in detail elsewhere (*Lundsgaard et al.* 1980). At the outlet of the T-tube the perfusate is collected in a graduated glass. In order to avoid cooling of the joint by the perfusate, the setup is placed in a box manufactured in plexiglass. The temperature of the box is kept at 37°C by the blower (B), the heating element of which is controlled in a negative feedback loop. The temperature sensor (Ellab Instruments, TE3, Copenhagen) of this loop has an optic display, which is converted to an on/off signal by a photo cell. The maximum temperature difference between 2 locations in the box was kept below 0.5°C by the stirring of the fan (F).

The system was tested for diffusional leaks to the surroundings by infusion of a 0.9 % NaCl solution equilibrated with N_2. There was no difference between the mass spectrometer signal of oxygen measured in the perfusate and the background signal. The mass spectrometer was calibrated with respect to oxygen by infusion via the shunt tube of a 0.9 % NaCl solution equilibrated with atmospheric air. The background signal was determined by infusion of the saline after equilibration with a nitrogen atmosphere.

Fourteen adult rabbits were anaesthetized by an initial dose of pentobarbitone (20 mg/kg) which was supplemented when necessary. An open ended catheter was inserted into the right carotid artery to allow blood sampling. The skin over the infrapatellar ligament and the medial collateral ligament was blocked with a local anaesthetic (0.5 ml lidocaine, 20 mg/ml). A 20 gauge cannula was inserted into the joint cavity through the infrapatellar ligament and firmly lodged under the patella with the tip in the suprapatellar pouch. A second cannula was inserted into the medial femoro-tibial joint compartment through the medial horizontal approach. The joint was flushed by 10 to 15 ml 0.9 % saline to remove synovia and debris from the joint. The rabbit was then moved through a rectangular window of 4×6 square inches into the box (Fig. 2). The 2 polyethylene tubes (P1 and P2) were connected to the cannules and the joint was perfused with a 0.9 % sodium chloride solution which was saturated with atmospheric air. The perfusion rate was varied in

the interval between 0.4 and 2.9 ml/min. The mass spectrometer signal of oxygen was displayed by a y-t recorder, and after attainment of a stable signal an arterial blood sample was taken from the catheter in the carotid/artery. P_{02}, P_{c02} and pH were measured by a blood gas and acid/base analyzer (BMS mk 2, *Radiometer*, Copenhagen). Experiments were terminated if blood was detected in the perfusate or the perfusate accumulated in the joint cavity. At the conclusion of the experiment the rabbit was sacrificed by an overdose of pentobarbitone. By following the described procedure we obtained 63 points on the P_{02}(out) vs. PR curve of normal joints in 14 rabbits, i.e. an average of 4.5 points per joint.

Statistical analysis

The expression for the relationship between P_{02}(out) and PR (eq. (16)) was fitted to the experimental points by the use of a non-linear square technique. The sum of squares, which was taken as the sum of the squared vertical distances between the theoretical and experimental points, was minimized with respect to DC_{02} and M_{02} by applying an iterative least square technique (*Gill & Murray* 1978). The standard deviations of the estimated parameters (DC_{02} and M_{02}) were determined by a previously described error analysis based on computer simulations (*Grønlund* 1982): A total of 100 'experiments' were simulated using the theoretical P_{02}(out) vs. PR curve fitted to the experimental points. A simulated experiment was produced by addition to each of the theoretical P_{02}(out) values of a random term obtained from a Gaussian random generator, whose mean value was set to zero. The standard deviation of the random generator was set to 27 % of the theoretical P_{02}(out) values in the joints. The value for the standard deviation was selected so that the sums of squares in the simulated experiments were equal to that of the real experiment. M_{02} and DC_{02} were calculated in each of the 100 simulated experiments by using the least square technique described above to procedure estimates of their standard deviations.

The calculation of the M_{02} and DC_{02} values and the error analysis were performed by a SPERRY 1100 processor*.

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* The program, which is written in FORTRAN IV, is available on request.

RESULTS

Fig. 3 shows the P_{02} tracing of a typical experiment recorded in the perfusate by the mass spectrometer. The figure shows that the extraction of oxygen from the perfusate increases when the perfusion rate is descreased.

Fig. 4 shows the 63 points (circles) on the P_{02}(out) vs. PR curve measured in 14 normal joints. Experimental points obtained in the same joint are connected. The theoretical P_{02}(out) values (crosses) were calculated by the use of a non-linear least square to fit the expression for the relationship between P_{02}(out) and PR (eq. (16)) to the experimental data. The solubility coefficient α_{02}(P) used in the calculations was 0.0326 µl O_2/ml/Torr (*Siggaard-Andersen* 1974). The scatter in the theoretical points is caused by the interindividual variations in the arterial oxygen partial pressure, which enters into the expression for P_{02} (out) (eq. (16)).

Table 2 shows the oxygen consumption and diffusion capacity obtained from the analysis of the experimental data shown in Fig. 4. The error analysis gave standard deviations on repeated

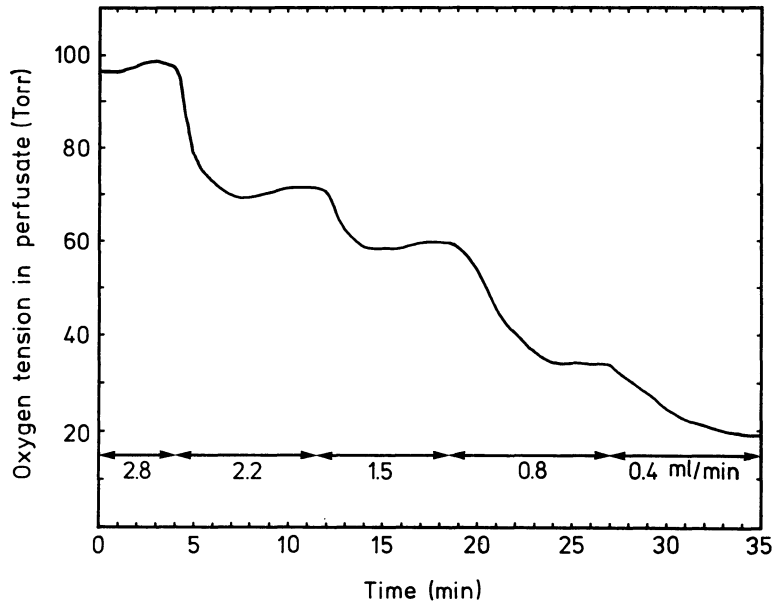

Figure 3. Typical P_{02} curve recorded in the perfusate at the outlet of the joint cavity. The different plateaus were obtained at the perfusion rates indicated at the bottom line.

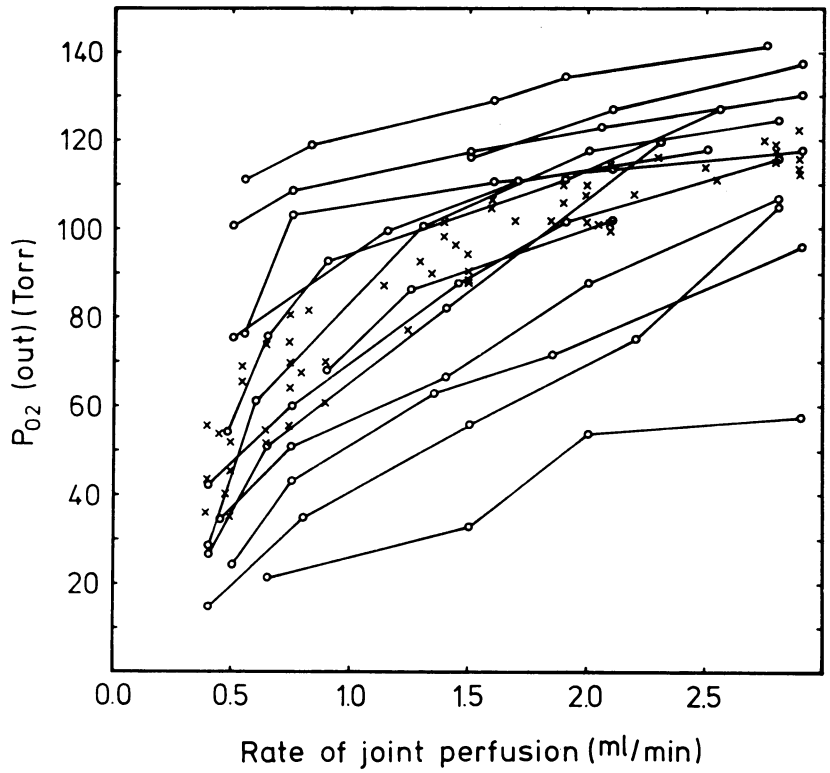

Figure 4. Experimental points (o) on the relationship between P_{02}(out) and the perfusion rate. Experimental points obtained in the same joints are connected. The theoretical points (x) were obtained by fitting the expression given in eq. (16) to the experimental data using a least square technique.

Table 2. Rate of oxygen consumption and diffusion capacity in the synovial membrane.

Diffusion capacity (± s) [µl O_2/min/Torr]	Rate of oxygen consumption (± s) [µl O_2/min]
0.039 ± 0.013	0.93 ± 0.90

determinations of M_{02} and DC_{02} of 0.90 µl 0_2/min and 0.013 µl 0_2/min/Torr, respectively.

DISCUSSION

The described method to measure the rate of oxygen consumption and the diffusion capacity of the synovial membrane

is based on the assumption that the mean oxygen partial pressure in the capillaries of the synovial membrane is equal to the arterial P_{02}. In the unperfused joint, this assumption is not correct because the oxygen consumed by the synovial membrane is extracted from the blood in the capillaries. However, in the perfused joint the situation is different because of the external oxygen supply from the perfusate. The quantitative evaluation of the assumption of equal arterial and capillary oxygen tensions reuires an estimate of the regional blood flow in the synovial membrane. Previous studies have given data on the perfusion coefficient for the joint capsule in dogs (*Phelps et al.* 1972, *Lucht et al.* 1983). However, these data do not differentiate between the perfusion of the capsule in its entirety and the local perfusion of the capillaries, which participate in the gas exchange with the synovia. We have therefore made supplementary experiments to estimate the blood flow in the capillaries of synovial membrane. The joints of 6 rabbits were perfused with a 0.9 % NaCl solution equilibrated with the inert gas helium. This gas has a very low solubility in both salt water and blood and therefore the helium partial pressures in the perfusate and the capillary blood rapidly reach a common value owing to the He diffusion across the synovial membrane. Under the assumption that complete equilibrium is attained between the two helium partial pressures the conservation equation for He in the joint gives the following expression for the blood flow, BF:

$$BF = PR \cdot (\alpha_{He}(P)/\alpha_{He}(B)) \cdot (P_{He}(in) - P_{He}(out))/P_{He}(out) \quad (17)$$

where P_{He} is the helium partial pressure and 'in' and 'out' refer to the perfusate entering and leaving of the joint cavity. $\alpha_{He}(P)$ and $\alpha_{He}(B)$ are the solibility coefficients of helium in the perfusate and the blood. The numerical values for $\alpha_{He}(P)$ and $\alpha_{He}(B)$ used in the calculation of the blood flow were 0.0113 and 0.0105 µl He/ml/Torr (*Weathersby & Homer* 1980).

If the equilibration is incomplete, eq. (17) underestimates the blood flow and therefore the expression provides a lower limit of the flow. Nine determinations in 6 rabbits gave a blood flow of 0.60 ± 0.09 ml/min (mean ± SEM). In the experiments described above the average oxygen flow to the joint from the perfusate was 2.30 µl/min and the oxygen consumption was to 0.93 µl 0_2/min, which gives a net rate of oxygen transfer to the

capillaries of 1.37 µl 0_2/min (2.30 minus 0.93). If the oxygen binding capacity of blood is set to 193.0 µl 0_2/ml blood the 0_2 transfer causes an increase in the oxygen saturation of 1.2 %. The average arterial oxygen tension in the experiments was 72 Torr. According to data on the hemoglobin oxygen binding curve of the rabbit (*Bartels & Harms* 1959) this partial pressure corresponds to an oxygen saturation of 95 % and the rise in the oxygen saturation by 1.2 % leads to an increase in the oxygen partial pressure by about 3 Torr. Thus, the assumption of identity between the arterial and mean capillary oxygen partial pressures is correct to within an error of 2 %. A renewed calculation of M_{02} and DC_{02} after correction of the capillary oxygen tension for this error gave values which differed from those given above by 12 % and 2 %, respectively.

The computer technique used to estimate the standard deviation of M_{02} and DC_{02} relies upon a statistical model which assumes a Gaussian distribution of the measured P_{02}(out) values. Our data do not allow a definite test of this assumption but since the random variations in P_{02}(out) can be ascribed mainly to the noise of the gas analyser and the interindividual variation in the area of the synovial membrane exposed to the perfusate we believe that the normal distribution is a valid approximation to the true distribution. The computer technique to estimate the standard deviation from a single experiment was used by *Grønlund* (1982) and *Grønlund & Christensen* (1985) to evaluate the influence of measurement noise upon cardiac output determined by a single-breath method. The study of *Grønlund & Christensen* (1985) contains an experimental test of the technique showing the expected relationship between the standard deviation obtained by simulations and experiments.

In a previous study *Goetzl et al.* (1971) reported data on the half-time for the extraction of oxygen from a 60 ml bolus of saline infused into the knee joints of 29 patients with rheumatoid arthritis and 7 patients who served as a control group. The authors considered the disappearance curves exponential but the representative curves included in the paper show linear rather than exponential disappearance of oxygen from the joint cavity. This observation supports our assumption of zeroth order kinetics for the oxygen consumption of the synovial membrane. The data of *Goetzl et al.* (1971) do not allow calculation of the diffusion capacity because the circulation of the joint capsule was

stopped by a tourniquet on the thigh. However, a value for the oxygen consumption of about 7 µl 0_2/min can be calculated from the data obtained in the control group of patients. This value is about 8 times higher than the value estimated in the rabbit.

The relatively large interindividual variation observed in the P_{02}(out) vs. PR curves (Fig. 4) is probably caused by variations in the fraction of the total area of the synovial membrane exposed to the perfusate. However, since both M_{02} and DC_{02} are directly proportional to this area (eq. (10)) the ratio between the 2 parameters depends less on such variations. The oxygenation of the joint cartilage is impaired by an increase in M_{02} and improved by an increase in DC_{02}. The partial pressure difference across the synovial membrane required to overcome the oxygen consumption of the membrane can be estimated by insertion of $J_{02}(0) = 0$ into eq. (11):

$$P_{02}(C)—P_{02}(JC) = M_{02}/(2.0 \cdot DC_{02}) \quad (18)$$

where P_{02}(JC) in the oxygen partial pressure of the joint cavity in the case where the net oxygen flow across the synovial membrane is zero. Insertion of the estimated values for M_{02} and DC_{02} gives an oxygen partial pressure difference across the membrane of about 10 Torr. This value is small compared to the normal arterial value of about 90 Torr and thus leaves ample reserve diffusion capacity for the oxygenation of the joint cartilage. However, in osteoarthritis the unfavourable combination of an increase in M_{02} and a decrease in DC_{02} may occur. If for example M_{02} is increased by a factor of 3 and DC_{02} is decreased by the same factor the partial pressure difference required to overcome the oxygen consumption increases to 90 Torr and thus P_{02} in the synovia falls to a level approaching zero.

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SAMMENDRAG

Eksperimentel osteoartritis hos kaniner. II. En ny metode til bestemmelse af synovialmembranens diffusionskapacitet og metabolisme.

Iltforsyningen til den hyaline ledbrusk er afhængig af transport fra kapselarterierne til kapillærerne, diffusion over synovialmembranen, samt transport gennem synovi. Osteoartritis og andre effusive ledlidelser kan hypotetisk medføre en nedsat iltoverførsel over alle tre barrierer. I nærværende arbejde redegøres for en ny metode baseret på ledperfusion til bestemmelse af synovialmembranens metabolisme og diffusionskapacitet in vivo.

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