RECORDINGS OF APPLANATING FORCE AT CONSTANT INTRAOCULAR PRESSURE
Development of a new technique and results obtained from a study of human eyes.

AKADEMISK AVHANDLING

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This doctoral thesis is based on the following six papers, which will be referred to in the text by their Roman numerals:


III. Thorburn, W. Recordings of applanating force at constant intraocular pressure. II. Procedures applied on living human eyes. *Acta Ophthal.* (Kbh.) In press.


V. Thorburn, W. Recordings of applanating force at constant intraocular pressure. IV. Intraocular volume changes due to changes in blood content. *Acta Ophthal.* (Kbh.) In press.

VI. Thorburn, W. Recordings of applanating force at constant intraocular pressure. V. Intraocular volume changes due to changes in the content of aqueous humour. *Acta Ophthal.* (Kbh.) In press.
Introduction
In 1953, Becker and Friedenwald\textsuperscript{1} discussed sources of error in determination of facility of outflow with a Schiötz tonometer by Grant's method\textsuperscript{6}. Among other things, they stressed the uncertainties due to assumptions of a constant flow of aqueous humour, of unchanged blood content of the eye, and of facility of outflow being independent of outflow pressure. The error due to variations in ocular rigidity was pointed out. Further, they described wave-like variations in the intraocular pressure at the rate of three to six per minute, which were related to variations in the diastolic blood pressure. These waves were considered a large source of error.

During recent years, some of these problems have been investigated further. The pressure-dependence of the net inflow of aqueous humour is estimated in man by Goldmann\textsuperscript{4} and by Kupfer & Sandersson\textsuperscript{7}. The pressure-volume relationship in the living eye has been investigated by several authors. Langham & Eisenlohr\textsuperscript{8}, comparing the open manometric studies found good agreement between the different reports. The results deviated from the average value of ocular rigidity observed by Friedenwald\textsuperscript{2,3} in such a way that larger volumes of fluid than expected were necessary to get a certain increase in intraocular pressure.

Abbreviations:
\begin{itemize}
\item \( P_{a2} \) : applanation tonometry, final reading;
\item \( P_t \) : intraocular pressure during the experiment.
\end{itemize}
By keeping the intraocular pressure constant during the experiment, several uncertainties in the estimation of facility of aqueous outflow can be avoided. The influence of the ocular rigidity is eliminated. The effects of the pressure-dependence of the net inflow of aqueous humour and possible pressure-dependence of the blood content of the eye are avoided. Further, the fluid involved in the waves described previously can be observed. It is not known if the facility of aqueous outflow is sensitive to the outflow pressure, and a method of keeping the intraocular pressure at a constant level gives the possibility of studying effects of different pressure levels.

**Basic considerations (I, II).**

Some procedures aimed at keeping the intraocular pressure constant during the experiment have been reported. Among these, the reports by Moses\textsuperscript{11,12,13} deserves to be mentioned. He developed applanation tonography at constant intraocular pressure by use of a Mackay-Marg tonometer. However, the method had certain limitations\textsuperscript{12}. The purpose of the present study was to develop an apparatus based on another principle, and by means of this apparatus to make it possible to measure continuously the applanating force and intraocular pressure. From these, the applanated area can be calculated according to the general relationship called the Imbert-Fick law. However, the cornea's resistance to deformation and the surface tension cause forces which act in opposite directions. Previous studies on enucleated human eyes indicate that there might be a small deviation from the Imbert-Fick law at large (> 3 mm) applanated areas, but
An applanation of the cornea causes a displaced volume, and the relationship between applanated area and displaced volume can be estimated in different ways. Calculation of the displaced volume as if it is a spherical segment with the base area equal to the applanated area disregards possible additional deformation of the eye ball besides the applanation of the cornea. The experimental results of Linnér⁹, based on observations on intact enucleated human eyes, showed larger values than those calculated as spherical segments when the measured applanation diameter was used for the calculation. The relationship between applanated area and displaced volume calculated as a spherical segment probably represents the lower limit value, and that according to Linnér the upper limit value. In the present study the displaced volume is calculated as a spherical segment resulting in arbitrary units and giving the possibility of estimating the displaced volume, and used mainly for comparative purposes.

Apparatus (II)
The apparatus is based on the following principle: One wall of a pressure chamber is used as an applanating surface, the central part of which has an aperture. The surface including its aperture is covered with a flexible membrane. During applanation of the cornea, the curvature of the part of the membrane covering the aperture indicates any pressure difference between the pressure in the eye and that in the pressure chamber. The applanating force is regulated by means of an electric
signal indicating the degree of curvature of the membrane. In this way it is possible to keep the applanating force continually adjusted while, at the same time, the intraocular pressure is kept constant at a predetermined value, in principle equal to the pressure in the pressure chamber. Calibration studies on enucleated human eyes of the relationship between the intraocular pressure and the pressure in the pressure chamber are performed.

Methodological considerations and methods (III)
By use of several changes of the $P_t$ the displaced volumes corresponding to the intraocular pressures give information on the intraocular volume-pressure relationship. The recording of applanating force using one $P_t$-level gives information on the sum of changes in the intraocular content and changes due to the eye coats and extraocular factors. The possibility of a pressure-dependence can be studied by using several pressure levels.

Repeated measurements by applanation tonometry results in a gradual lowering of the readings. In the present study, the stabilized reading after repeated measurements was accepted as the basic intraocular pressure on which the choice of $P_t$ was based.

The main procedures were as follows: The intraocular pressure was measured by applanation tonometry for several minutes and the stabilized reading ($P_{at2}$) was accepted as the intraocular pressure on which the choice of $P_t$ was based. The above apparatus was then applied and recording of
the applanating force was performed with $P_t = P_{a2} + 6$ mm Hg for three minutes. Without interrupting the recordings the $P_t$ was raised to $P_{a2} + 10$ mm Hg for another three minutes, and finally a short recording with $P_t = P_{a2} + 15$ mm Hg was made (ascending pressure steps). Recording of applanating force was also performed using the $P_t$-values in opposite order, i.e. starting with a short recording with $P_t = P_{a2} + 15$ mm Hg and followed by a three min. recording with $P_t = P_{a2} + 10$ mm Hg and so on (descending pressure steps). To study a larger range of the volume-pressure relationship than obtained by the above procedures only short recordings were performed at each $P_t$-level. The values of $P_t$ were $P_{a2} + 6$ mm Hg and further stepwise increases by $4$ mm Hg. Recordings of applanating force with one $P_t$-level for a longer time were used for special purposes.

The recording of the applanating force showed a rapid oscillation, synchronous with and obviously induced by the pulse. Superimposed on the pulse induced amplitude there were oscillatory changes of lower frequency which were called waves. At every moment, the applanating force corresponded, within the errors of the method, to the displaced volume necessary to keep the intraocular pressure at a preset and constant level. Between the stepwise changes in $P_t$, the slope of the tracing corresponded to the continuous, steady increase in the displaced volume.

In principle, it was not possible to distinguish between the different factors causing changes in the intraocular volume (c.f. above). However, in
the present investigation, oscillatory changes in the intraocular volume were regarded as due to changes in the content of blood and a continuous, steady decrease in the intraocular volume was regarded as due to a decrease in the content of aqueous humour. Using the present method, any existing pressure-sensitive mechanism in the eye for controlling its content was suppressed by keeping the intraocular pressure constant.

In the analysis of a recording of applanating force with three pressure steps three main problems were considered:
1. The volume-pressure relationship in the living eye, i.e. the displaced volume at each change in intraocular pressure;
2. Volume changes due to changes in blood content, i.e. the fluid involved in waves;
3. Volume changes due to changes in aqueous humour content, i.e. continuous increase in displaced volume. This was not possible to estimate in all recordings because of pronounced waves.

Material (IV, V)
Three different groups of subjects were studied. Group A consisted of young healthy subjects, 30 subjects in all, aged between 23 and 33 years. Eighteen subjects (aged 23-29) were studied with recordings of applanating force with three pressure steps and varying number of the group were studied in other parts of the present investigation. Group B consisted of healthy subjects aged between 52 and 73 years with normal ocular tension, 51 subjects in all. Group C consisted of subjects with ocular hypertension without other signs of glaucoma,
from a group of people collected in 1960 and previously reported by Linnér and Strömberg. The subjects were now aged between 51 and 83 years, 67 subjects in all. In addition to these groups, some additional subjects were studied for special purposes.

RESULTS AND CONCLUSIONS

Intraocular volume-pressure relationship (IV)

Within the pressure range investigated, a linear relationship seemed to be an adequate approximation. Previously, the relationship was estimated by Friedenwald being semilogarithmic, basing the observations on measurements on enucleated human eyes and thereby not including effects of the intraocular vascular bed. From the recordings of applanating force with three pressure steps, the displaced volumes at three intraocular pressure levels were used to calculate a regression line, the slope of which represented the volume-pressure relationship. No significant difference between the regression coefficients of ascending and descending pressure steps was found in eyes of young subjects. The average regression coefficient differed between eyes of young subjects (group A) and elderly subjects (group B and C) showing that the displaced volume at a certain pressure increase was larger in young subjects. This is compatible with the assumption of an increased scleral rigidity with increasing age, but it could also be due to a different amount of blood being expelled by the pressure increase between the young and the elderly subjects. No significant difference in regression coefficient was found between the groups B and C in spite of the fact that they represent
two different intraocular pressure levels. The change in volume displaced by applanation at a certain change in intraocular pressure was larger in all groups of subjects than expected if an average coefficient of ocular rigidity of 0.0215 was used. The results of groups A and B were compared with the figures of previous open manometric studies of the pressure-volume relationship in living human eyes. No certain conclusions could, however, be drawn from these comparisons. If the present results are applied to Grant's tonography the volume change due to the pressure change is underestimated when an average ocular rigidity coefficient of 0.0215 is used.

Intraocular volume changes due to changes in the content of the vascular bed (V)
The displaced volume at constant $P_t$ showed oscillatory changes, which were thought to be due to the vascular bed. They were sizeable under the present experimental conditions and the frequency pattern of these waves suggest that they are of the same nature as the waves of blood flow through muscles, which are due to vasomotor enervation. The average magnitude of the waves was larger in young subjects than in elderly subjects. Possibly, this might be due to decreasing vasomotor activity with increasing age, or there is a smaller content of blood in the elderly eye than in the young. No convincing change in the pattern nor in the magnitude of the waves occurred after retrobulbar anesthesia, neither after a blockade of the stellate ganglion. The magnitude of the waves is supposed to be at least partly due to the present method, as no changes in the intraocular pressure of corresponding magni-
tude, during regular measurements, are observed. There is a possibility of a pressure sensitive system in the eye which is suppressed by the present method. This is discussed in paper V.

To affect the vascular bed of the eye, a change of respiratory gas composition during recordings of applanating force was used. An average increase of the intraocular volume of 10 μl due to inhalation of 7% CO₂ (carbogen gas) was found, and a negligible effect followed inhalation of pure oxygen. The conclusion is drawn that increased carbon dioxide exercises a dilating effect on the choroidal vascular bed. As there was a simultaneous increase in the head of the blood pressure, it might then indicate an increased blood flow through the choroid.

**Intraocular volume changes due to changes in the content of aqueous humour (VI)**

The calculation of facility of aqueous humour outflow was based on the assumption of a linear relationship between the addition in outflow pressure and the increase in displaced volume per time unit as in Grant's method. The addition in outflow pressure was calculated as the difference between $P_t$ and $P_{a2}$ with no correction with regard to a possible change in episcleral venous pressure during the experiment. As mentioned above (page 9) the recordings sometimes showed pronounced waves and were therefore rejected for calculation of aqueous humour dynamics. In all groups of subjects facility of outflow observed at two $P_t$-levels suggested a pressure-dependence within the eye with a smaller facility of outflow at a higher outflow
pressure. This then tends to stabilize the rate of aqueous flow through the trabecular meshwork. A rise in the intraocular pressure by 15 mm Hg before the estimation of the facility of outflow, obtained by use of descending pressure steps, resulted in larger values than when ascending pressure steps were used, but the difference between the values obtained at two $P_\text{L}$-levels were the same. No age-dependent difference in the facility of outflow between eyes of young and elderly subjects with normal ocular tension (groups A and B) was found. Neither could any difference be established between subjects with normal ocular tension and those with ocular hypertension (groups B and C). These results indicate that the difference in intraocular pressure level cannot be due to the facility of outflow alone. Estimations of the facility of outflow with a Schiøtz tonometer showed a tendency towards lesser values in the elderly groups of subjects (B and C) as compared to the young group (A). Applying the conclusion above concerning the volume-pressure relationship this tendency would increase. Possibly, this difference from the results obtained by the present method might be due to the smaller pseudofacility in old people than in young man previously reported.^4^ To induce possible changes in the facility of outflow, accommodation and drugs were used in young subjects. Accommodation induced an increase in the facility of outflow. Thirty minutes after a single-dose of pilocarpine, no significant decrease in intraocular pressure but an increase in facility of outflow was found. Two hours after a single-dose of acetazolamide, a decrease in intraocular pressure but no significant change in facility of outflow was found.
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