Blood velocity measurement in human conjunctival vessels

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The bulbar conjunctiva is one of the few areas in which blood flow in the peripheral vasculature can be directly and noninvasively observed in the human. Although extensive literature exists describing morphological changes which correlate with a variety of systemic diseases in this vasculature, little quantitative data is available on hemodynamics in either normal or abnormal states. The hemodynamic data available are primarily subjective assessments of "low flow." Approaches to place the subjective assessment on more quantitative grounds have usually been based on photographic techniques that have intrinsic inadequacies. The objective of the work reported here was to develop a system capable of providing sequential blood velocity data potentially useful for providing quantitative information on blood flow and its change in the microvessels of the human conjunctiva. The method that has evolved uses a standard Zeiss slit-lamp to image a subject's conjunctival vessels by using a 1-inch Newvicon TV camera with an electronic magnification of 2x. The video image is simultaneously recorded on a video tape recorder (VTR) to an overall system magnification of approximately 4 μm/raster line. The data acquisition phase requires approximately 5 minutes of patient time, whereas the actual determination of

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blood velocity in individual vessels is done offline through a modification of the dual-slit videodensimetric method. Two independently controllable video cursors are placed axially over the vessel image with the VTR in the still-frame mode. For each consecutive video field, the position of two reference points on the vessel and the position of each cursor relative to these and to each other are encoded into a computer to track the moving image caused by normal eye movement. The computer then determines new cursor coordinates to ensure a constant position within the vessel. The electrical signals obtained for each cursor site and for each video field are cross-correlated to yield the average blood velocity over the sampled time interval. The system has been calibrated *in vitro* from 0.2 to 2.5 mm/sec, evaluated in experimental animals, and used to measure blood velocity (0.3 to 1.5 mm/sec) in human conjunctival venules with diameters ranging from 20 to 50 μm. At this writing, blood velocity has been recorded during a period of about 3 months in the same vessel of several postmyocardial infarction patients. Thus, the method appears suitable for determining sequential changes in small vessel blood flow in patients over extended periods of time.

The bulbar conjunctiva is one of the few regions of the body in which the circulation of the blood can be directly and noninvasively observed in the human. The vascular supply of the conjunctiva derives from branches of the ophthalmic artery, particularly the anterior and posterior ciliary arteries, the former being the terminal branch of the lachrymal. Biomicroscopic examination of the bulbar conjunctival vessels has long been an indicator of the extent to which small vessels are altered in various pathological states,[1-3] and attempts to place conjunctival morphometry on a more quantitative basis have recently been developed.[4] Although such morphological data are important,[5] the dynamic aspects associated with blood flow change could provide a new dimension in using the conjunctival vessels as an indicator of the development or presence of disease.

Lee[1] attempted to measure blood velocity in arterioles, capillaries and venules by tracking individual red cells with a stop watch and timing the transit over a long distance. The results of these studies indicated that in the normotensive adult, the mean linear blood velocity in venules was only 0.06 mm/sec. The highest blood velocity recorded was 0.11 mm/sec in arterioles. These values are probably in the lower limits of true blood velocity, for in order to visualize moving cells or plasma gaps, an investigator would invariably choose the slowest moving particles because they are most clearly seen. In spite of the probable inaccuracies of these absolute values of velocity, Lee showed a dramatic decrease in all velocities in patients with hypertensive vascular disease. A variety of photographic techniques have been employed in an attempt to measure red blood cell velocity in the human conjunctival vessels.[6] Wells and Edgerton[7] used microcinephotography in conjunction with stroboscopic lighting to measure blood velocity, and they utilized this data as quantitative diagnostic

criteria. Results of their study, which relied on the identification of the movement of specific cell groups or plasma gaps, yielded data indicating that normal venule velocity ranged from 0.375 to 0.425 mm/sec; according to the authors, corresponding arterioles had velocities that were approximately three times higher. By using a similar approach, Monroe[6] quoted a venous velocity range of 0.1 to 0.5 mm/sec and arteriole velocities usually below 1.0 mm/sec. He and his colleagues reported slower and more erratic flow patterns in patients with coronary artery disease. He also reported a considerable improvement in blood velocity in patients with recent myocardial infarction evaluated within 48 hours and followed sequentially for approximately 3 weeks. It should be emphasized that in this study no systematic quantified values of blood velocity were reported. However, these subjective findings are consistent with those of Bloch,[8] who studied the conjunctival vessels in patients who had sustained a myocardial infarction within the previous 24-hour period. He noted reduced sludging during the first 2 to 3 weeks after infarction. The reduction in sludging was accompanied by some reversal of venule tortuosity. Because of technical problems, our present knowledge of the human microcirculation in health and disease has been mostly on morphological description.[2] Observation of the human bulbar conjunctival circulation has been a very effective adjunct to understanding the human microcirculation. And although extensive information is available concerning the relationship between vascular morphology and its change in a variety of disease states, there is still very little in the way of quantitative information on hemodynamics. The most reasonable approach to obtaining this kind of quantitative information in earlier studies involved the use of photographic methods from which single-point velocity measurements could be made. Recent advances in methodology and instrumentation[9-15] now make possible the accurate determination of blood velocity in small vessels.

Appropriate application of these techniques makes it possible to provide an accurate assessment of the alterations in microvessel hemodynamics with the human bulbar conjunctiva as a test tissue. The purpose of the present paper is to describe a system which has been developed for this purpose.

Theory of Operation

When blood flows in small vessels, the difference in optical density between the red cells and plasma creates a temporal variation in the vessel opacity. By sensing this variation with an electro-optical sensor, an electrical signal is produced which may be thought of as a "signature" characterizing the intravascular cellular-plasma pattern. If the sensor is chosen to receive light from only a small segment of the vessel, then the signal obtained from it represents the signature of the pattern at a particular spatial site. When two such sensors are used and separated axially by a

known distance, with one sensor monitoring the upstream and the other monitoring the downstream signature, it is possible to determine the blood velocity by detecting the transit time of the measured signals. For signals derived from microvessels other than those close to capillary dimensions, the degree of similarity of the upstream and downstream is not adequate to resolve the transit time in a simple fashion, and further signal processing is required. One procedure that has proved effective for this purpose is the mathematical process of cross-correlation, which is used to estimate the transit time based on an analysis of the degree of similarity of the upstream and downstream signals. The operating principle of this technique is that the degree of similarity between upstream and downstream signals will be maximum when the elapsed time is precisely equal to the inter-sensor transit time. The cross-correlation of the upstream and downstream signals yields this transit time by producing a maximum in the resulting function at a time delay that is equal to the unknown transit time. The demonstration of the applicability of this technique to the measurement of blood velocity in microvessels originated with Wayland and Johnson[9] in 1966 and was refined and implemented as an on-line system by Intaglietta and co-workers[10] in 1970. These initial methods utilized phototransistors as the electro-optical sensing elements and were used exclusively for studies in experimental animals. A major advancement occurred with the introduction of video methods for blood velocity measurements and their applications to human nailfold capillaries.[10-13] As differentiated from discrete photosensors, the use of the closed circuit television camera as the primary electro-optical convertor allowed an entire image to be viewed on a television monitor and stored on video tape or disk. Subsequently, any part of the image could be analyzed and, if necessary, reanalyzed. Although several methods are available for extracting the video information pertinent to blood velocity, it is the "double window" technique that has received the most attention. In this method, the video signal is routed through an electronic processing device that can select any area of the monitored image and produce an output voltage proportional to the scene brightness within that area. The particular region of the vessel image to be analyzed is indicated by a white cursor or "window" that is inserted into the video signal for identification purposes. To measure blood velocity, two cursors are used that bear the same relationship to the television image of the blood vessel as the photosensor methods previously described.

System Description

Data Acquisition

The bulbar conjunctival blood vessels are observed with a Zeiss model 70 slit lamp equipped with a 70/30 beam splitter and photo adapter. Prior

to video recording, the microscopic field is photographed with a 35 mm Nikon FE equipped with an automatic winder to prevent the microscope from moving during rapid sequential shooting. All photography is accomplished without flash by using a green filter to minimize heating effects. Kodak Tri-X pan black and white film rated at ASA 400 is routinely employed and, when necessary, is processed to an effective ASA rating of 1600. The photographs obtained provide an effective "road map" to identify those vessels in which blood velocity is determined for subsequent examinations. Video recording is accomplished with a 1 inch Newvicon TV camera (MTI model VC-65), expressly selected for its spectral response, light sensitivity, and its ability to produce an operator-controlled electronic magnification of 2x. Overall magnification is 4μm/TV raster line. The video output is coupled to a special effects amplifier (GBC model MEA-5100) that has the capability of synchronously mixing multiple TV camera inputs. The special effects amplifier provides simultaneous video recording of the patient's blood vessel image and arterial pulse, which is subsequently available for timing purposes during blood velocity analysis. This is accomplished by obtaining pulse information from a finger photoptic plethysmograph and Medsonics model PA 13 Photopulse Adapter. The adapter output is displayed on a chart recorder, and the pulse waveform is imaged with a second TV camera. This video is then mixed with the conjunctival image in the special-effects amplifier. Prior to recording the composite image on video tape (Sanyo model VTR1200), timing information (date and time to 0.0001 minutes) is inserted into the video with an Odetics model G-77A video timer. The composite video is viewed on a TV monitor (Koyo model TMC-17T) and recorded on the VTR. In addition to the video information, the audio channel of the VTR is used to record the patient's pulse wave form electronically. This is done by modulating the baseband photopulse adapter output with a Vetter model 2 FM adapter and recording it on the audio channel of the video tape. This information is easily recovered during analysis by demodulating the recorded signal.

The initial photography prior to video recording provides the examiner with an opportunity to observe closely the vascular topography of the conjunctival vessels. Upon initial examination of a patient, vessels for subsequent analysis are chosen. Because the same vessels must be relocated at future examinations, they should have reasonable clarity and good background contrast, and should be readily identifiable, or in proximity to a readily identifiable landmark. Vessel segments close to branching points are reasonable choices, since they are more easily identified than straight segments. The video recording of these regions provides the opportunity of determining blood flow in three vessel segments with visually different blood flow; that is, one vessel with a subjectively "medium-high" flow and another with a "low" flow. Although blood flow velocity has been determined principally in the venous vessels, it is desirable to include *both* arterial and venous vessels in the video recording

whenever possible. Postcapillary vessels are usually larger in diameter than their precapillary counterparts by a factor that ranges from 1.5 to 3.0 in most circumstances, and are more amenable to blood flow analysis. The entire data acquisition phase schematically illustrated in Figure 1 requires less than 10 minutes of the patient's time and is accomplished without pain or discomfort.

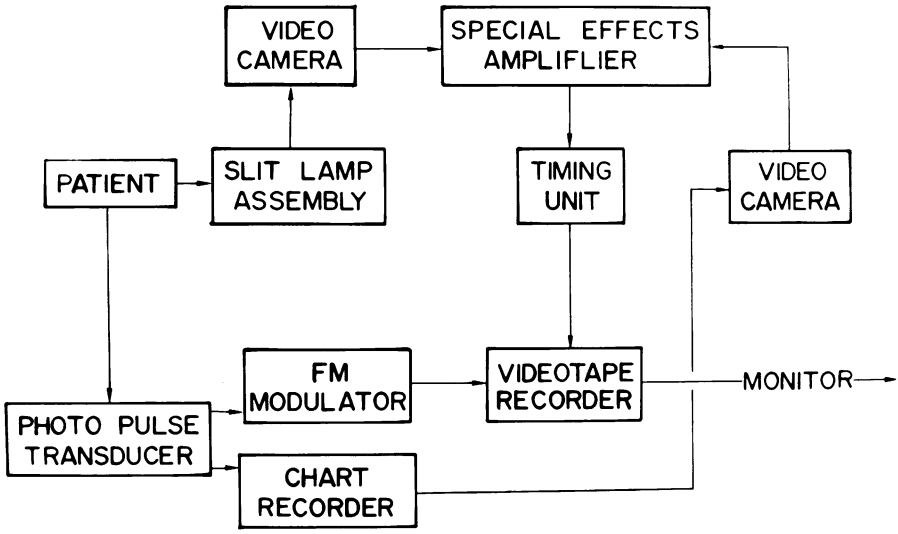

Fig. 1 Block diagram illustrating data acquisition of conjunctival blood vessels and pulse information.

Data Extraction

The pertinent information for determining vessel blood velocity is contained in the recorded video signals. The basic method used to extract this data is the "double window" technique. The first step in this process is in selecting the vessel segments to be analyzed. In the patient's first examination, a larger degree of freedom is available for this selection, since in a follow-up examination, the vessel segments have already been chosen and velocity determinations have been made. Follow-up velocity measurements are most useful when made in the same vessel segments. The most important technical criteria is that the vessel to be analyzed is in good focus for at least 20 consecutive video fields. Since the video field rate is 60 per second, this requirement is equivalent to good focus for at least 1/3 of a second. Defocusing during the data acquisition phase is principally attributable to involuntary eye movement. Suitable sequential video fields are selected by the operator through a frame-by-frame scan of the video tape recorder. The initial and final fields to be used for the analysis are specified by the time information superimposed on the video during the original recording.

Conversion of the intravascular optical density within the selected vessel sites to an electrical signal is accomplished by using two video integrators (CVI model 310), which serve as electronic cursors for optical sensing. The horizontal and vertical size of each cursor and its X and Y coordinates is manually controlled by the operator. The video signal corresponding to the selected region defined by each cursor is electronically integrated, and an output voltage proportional to the average vessel opacity is obtained for each video field. The set of these voltage values obtained simultaneously from upstream and downstream cursor locations for N consecutive video fields constitutes the data that are subsequently cross-correlated to determine blood velocity. In actual operation, each of the consecutive 1/60 of a second discrete voltage samples is fed directly to a 12-bit analog-to-digital converter (Xerox model MD40-4), which communicates directly with the main computer (Xerox Sigma 9).

In applying this technique to the measurement of blood velocity in the human conjunctival vessels, the most difficult problem is movement of the vessels associated with involuntary eye movement. For the method to yield reliable velocity information, the position of the cursors relative to the vessel and their separation must be invariant. This is accomplished by encoding the position of two reference points on a vessel and the initial position of each cursor relative to these and to each other. As subsequent video fields are analyzed, the change in the coordinates of the reference points due to vessel movement is detected and used to determine the required new coordinates of each cursor to ensure that the position within the vessel is constant. The determination of the required cursor coordinates is done automatically by the computer, whereas the actual positioning of the cursors according to the specified coordinates is done manually. The implementation of this technique requires the ability to determine the coordinates of the reference points and cursors and to display these to the operator. This is achieved in the present system by using a video analyzer (CVI model 321), a device which is capable of inserting a cross-hair on the video image and producing an output voltage that denotes the horizontal and vertical coordinates of the cross-hair center. This device is used to pinpoint each reference point and the initial cursor positions. Subsequent repositioning of the cursors, based on movement of the reference points, is achieved by using the cursors' own coordinate readout system. The video analyzer and a calibration slide also permit accurate determination of the vessel diameters in the recorded image, and thus enable a calculation of blood flow with the measured values of blood velocity. The main elements of the data extraction phase are illustrated in Figure 2.

The chief aspect of the data processing is the time series cross-correlation of the signals obtained from the two video cursors. These computations are carried out numerically with a suitable algorithm. The result of this analysis is to yield a cross-correlation function which reaches its maximum value at a lag interval that corresponds to the inter-cursor

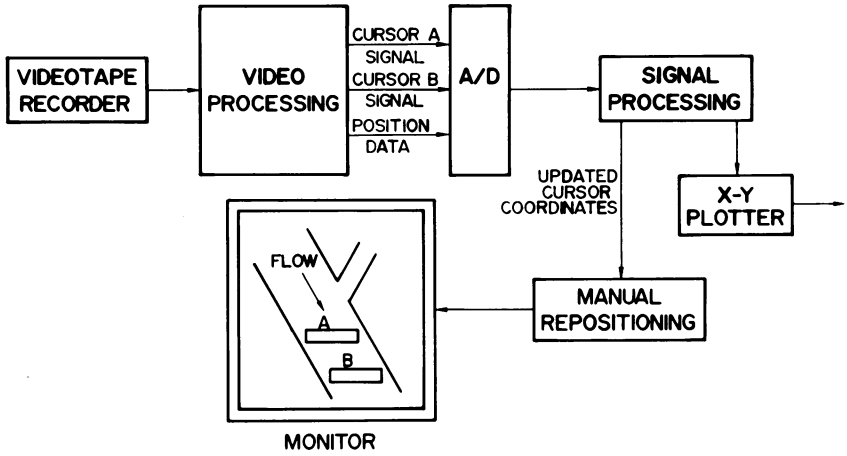

Fig. 2 Block diagram illustrating blood velocity data extraction from videotaped conjunctival vessels.

transit time. Since the inter-cursor separation referred to the vessel is known, a simple computation yields the blood velocity, which is the average velocity over the sampling interval.

Evaluation of the System by Test and Calibration

In Vitro

Two separate procedures were used to evaluate the accuracy of the system. In one, blood flow was simulated by moving a microscope calibration slide and a blood smeared cover slip simultaneously at a controlled velocity. This was accomplished by placing the coverslip and stage micrometer calibration slide (Zeiss, M9-513106) on a lucite supporting assembly, which was then fixed to the stage of a trinocular microscope. The calibration slide and the blood smear were positioned so that each could be observed through the microscope and the motion of each could be videotaped via a TV camera fixed to the trinocular port. The entire stage was then moved in a horizontal direction with an infusion pump (Harvard Apparatus, Model 902) to push a steel rod against the microscope stage. Frame-by-frame, video replay was used to time the movement of the calibration slide and provide the standard to which cross-correlation determined velocity values obtained from the blood smeared slide could be compared. The calibration velocities ranged from 0.14 mm/sec to 1.5 mm/sec, a range which is thought to encompass blood velocities in most conjunctival vessels. An analysis of 23 separate determinations showed that the average deviation between calibration velocity and correlation velocity, as determined by the system under test, was 0.03 $\pm$ 0.007 mm/sec, with the largest difference being 0.08 mm/sec, occurring at a velocity of about 1.1 mm/sec.

The second procedure used a speed-controlled motor assembly to drive a rotating disc that was mounted in front of the slit-lamp microscope. The image of the rotating disc surface was videotaped at exactly the same magnification used for the conjunctival blood velocity measurements. The linear velocity of the rotating disc was determined by both calculation from its measured angular velocity and by tracking the motion of well defined objects on the rotating wheel. (An example of the raw signals obtained from each cursor and the resultant cross-correlation function is illustrated in Fig. 3.) The range of the calibration velocities used was from about 0.2 mm/sec to 2.4 mm/sec. At each calibration velocity, the velocity was determined with the cross-correlation method of the system under test. The results of this evaluation process indicated almost perfect agreement between the actual velocity and that which was calculated from the correlation method. (This data is shown graphically in Fig. 4.)

In Vivo

The ability of the system to accurately determine *in vivo* red blood cell velocity was determined by using the blood vessels in the Hamster cheek pouch preparation.[15] To carry out the velocity measuring procedure, a closed circuit TV camera secured to a tripod was positioned to view the blood vessel through one of the binocular eyepieces of a trinocular research microscope. Through this camera, the blood flowing in the hamster cheek pouch was recorded on video tape. Simultaneously, the blood velocity in the same microvessel was measured with an on-line cross-correlation dual slit system.[16] A comparison was then made between the red blood cell velocity as measured on-line, and that which was determined by using the system's frame-by-frame method of obtaining the cross-correlation function, and thence velocity. A variety of vessels in which velocities ranged from 0.1 mm/sec to 0.8 mm/sec were tested in this fashion. In our *in vivo* evaluation, both methods of velocity determination proved to yield similar data. (The results are graphically illustrated in Fig. 5.)

The ability of the system to accurately reposition and reproduce velocity in moving vessels was evaluated in two ways. Using the microvascular bed of the Hamster cheek pouch, a videotape was obtained by using two television cameras mounted on a microscope (Fig. 6). One television camera that was used to obtain an image of a still vessel with blood flow viewed the microvasculature through the eyepiece of the microscope. The other television camera was mounted on top of the microscope through the trinocular port; it was mounted so that it could be rotated or moved to simulate the image of a moving blood vessel. The video information from both cameras was directed into a special effects amplifier which could superimpose the images from both cameras side by side as split-image on a television monitor. Off-line analysis involved the comparison of calculated velocities for the two vessels during specified correlation intervals. These analyses were carried out on the stationary vessel

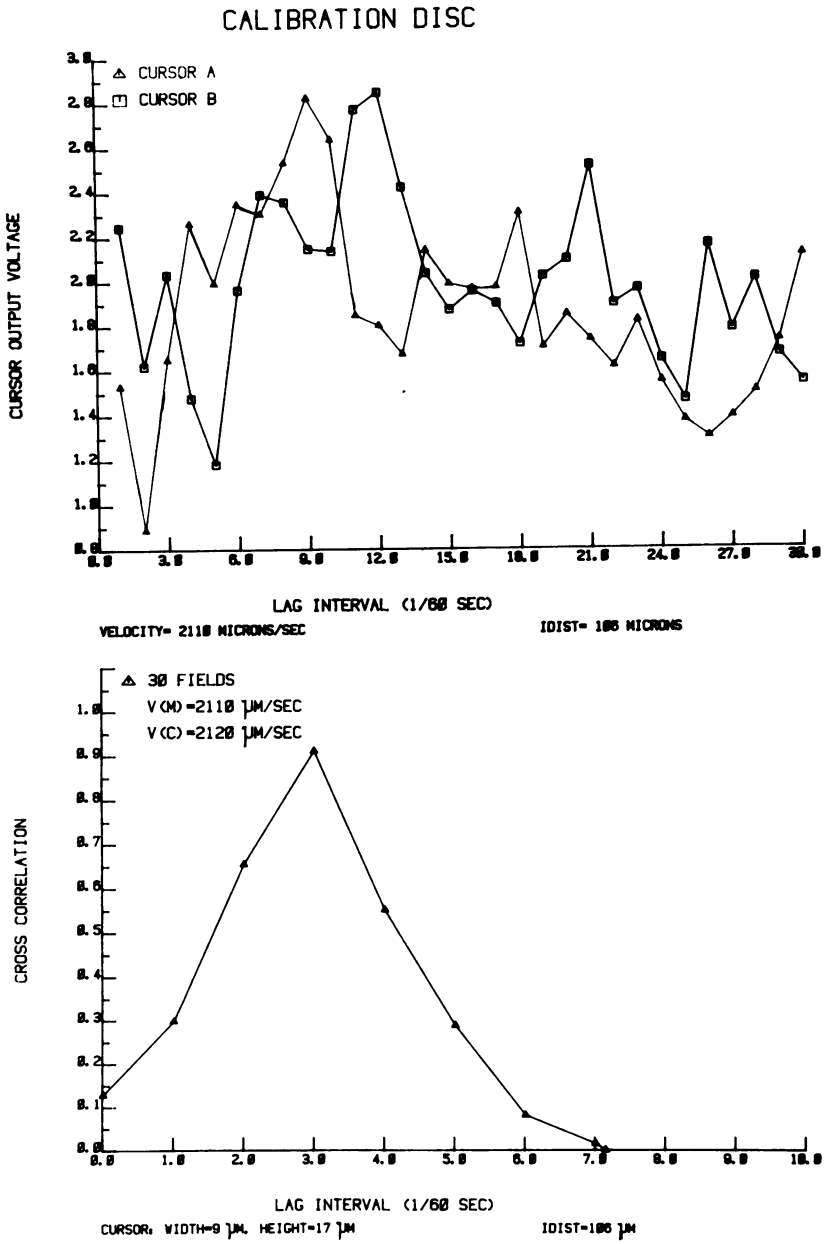

Fig. 3 An example of the sampled output signal from the upstream (A) and downstream (B) video cursors (top panel) and the resulting cross correlation function (bottom panel).

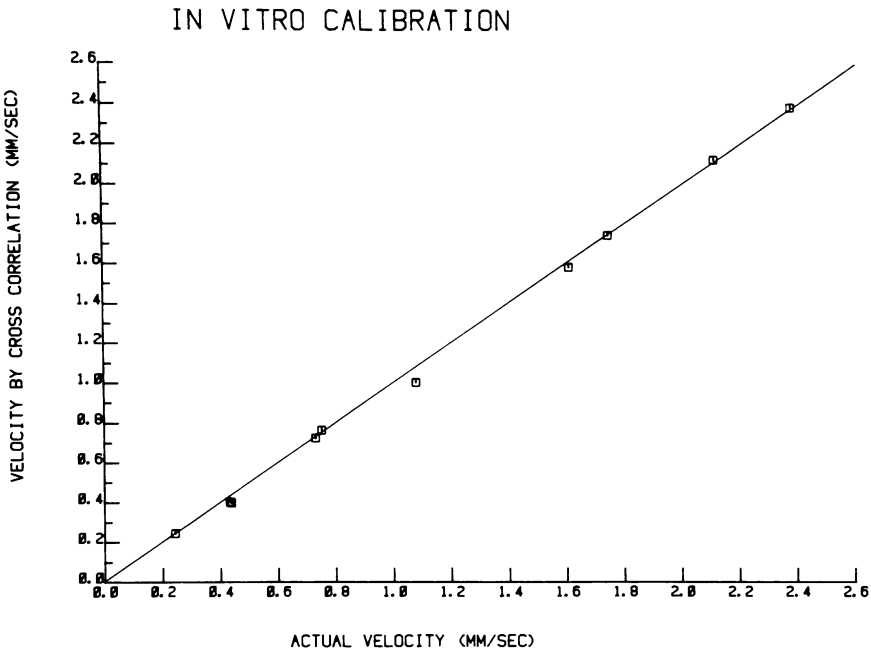

Fig. 4 Velocity determined by the video system (squares) compared with the actual velocity of a rotating disk. The solid line corresponds to equality of these two quantities.

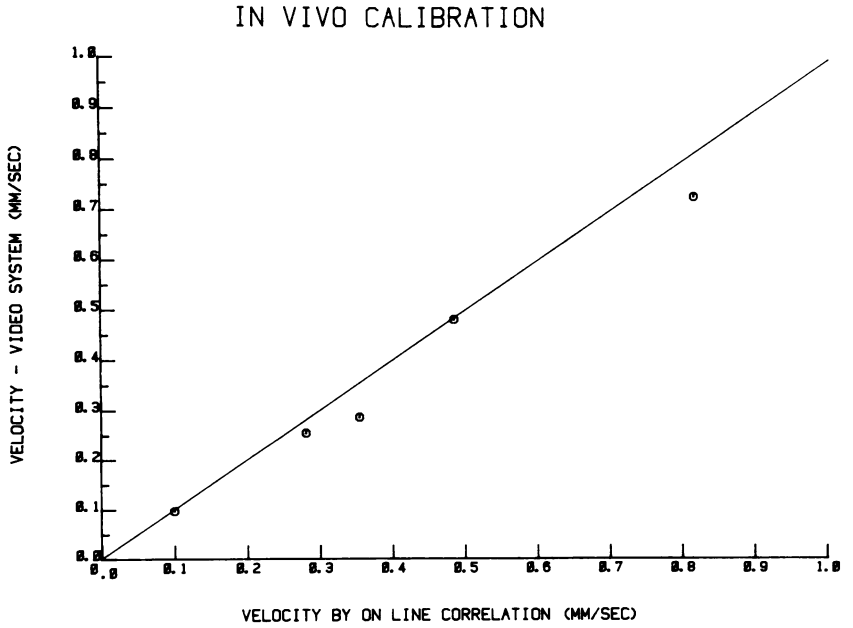

Fig. 5 Blood velocity determined by the video system (circles) compared with the on-line velocity of Hamster cheek pouch vessels. The solid line corresponds to equality of these two quantities.

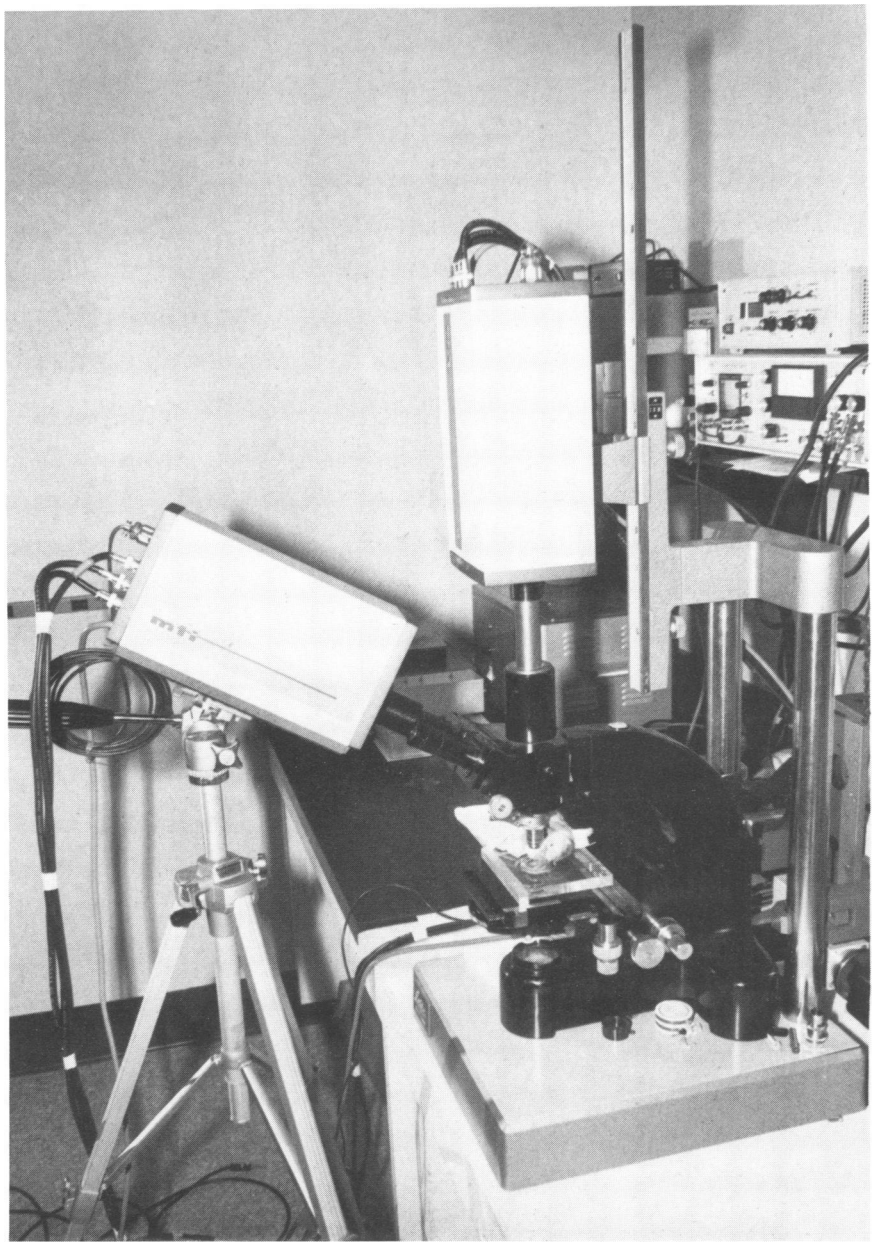

Fig. 6 Experimental setup for simulating blood vessel movement and accessing accuracy of velocity measuring system to track.

over a 30-field correlation interval, followed by a similar analysis of the moving vessel during the same correlation interval. Velocities measured in different vessels ranged from 0.35 to 1.95 mm/sec. The average absolute difference of velocities found was 0.08 ± 0.01 mm/sec, corresponding to an average overall percentage error of slightly less than 10%.

The second method used to evaluate the repositioning feature of the video system was to replace one of the TV cameras in the above experimental design with an on-line photo-optic sensing element so that blood velocity in the Hamster cheek pouch vessels could be determined by using an on-line cross-correlation method (IPM). The video camera, as previously described, was then moved to simulate vessel movement and to tape record for off-line processing. A comparison was then made between the measured on-line velocity read-out directly from the cross-correlator system and that which was determined with the frame-by-frame analysis of the moving vessel. Data points were obtained prior to movement, during movement, and after movement had ceased. This evaluation was carried out in a variety of vessels at different velocities (Fig. 7).

These procedures clearly substantiated the ability of the repositioning system to produce accurate velocity determinations.

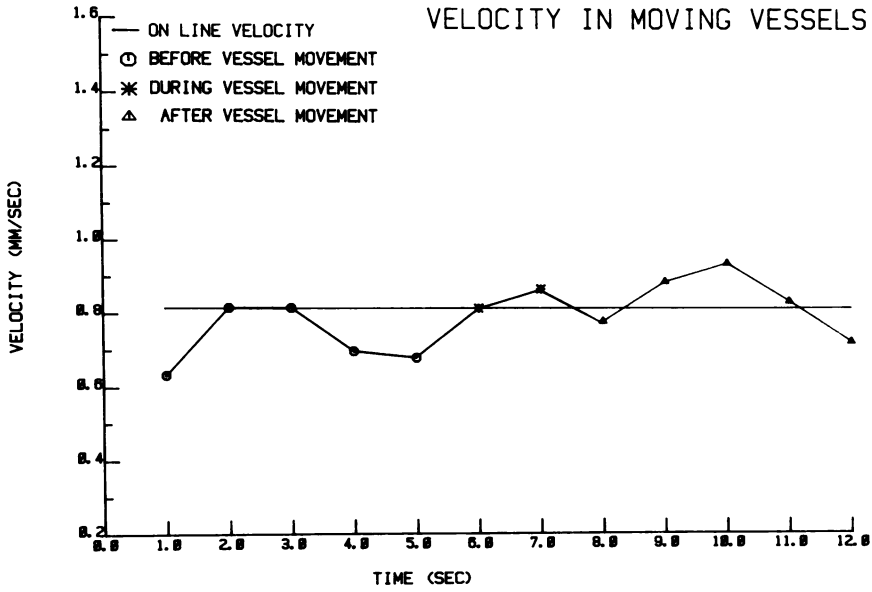

Fig. 7 Example of the blood velocity determined before, during, and after blood vessel movement by the tracking capability of the video processing system.

Discussion of Results Obtained From Human Vessels

Because the video sampling method is constrained to discrete sampling intervals which are multiples of the video field scanning rate, the initial analysis of blood velocity may not yield a well defined peak in the correla-

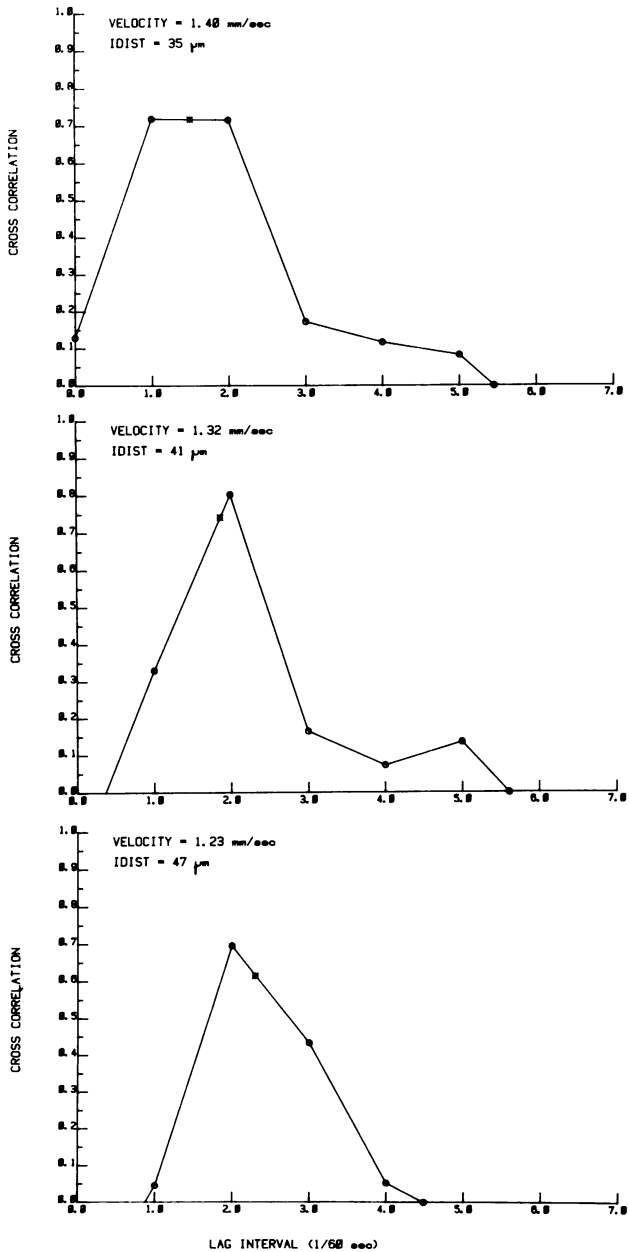

Fig. 8 Example of cross correlation functions obtained from a conjunctival venule, their dependence on cursor separation (IDIST) and the use of an interpolated lag, denoted by the asterisk.

tion function. This may occur because the initial separation of the cursors is less than optimal to produce a peak at multiples of the 1/60 of a second discrete sampling times. This field rate limitation may be overcome in two ways. One is to assume (based on theory) that the correlation function will tend to be symmetrical with respect to the points immediately adjacent to the peak. By using this criteria, an algorithm was developed that yields an interpolated lag for those situations in which a definite peak in the cross-correlation function is not obtained. A second method of dealing with this problem is to adjust the cursor separation so that the intersensor transit time is a multiple of 1/60 second. This concept is illustrated in Figure 8, which shows the correlation function obtained from a 30 μm venule of a 48-year-old patient at three different intercursor separations (IDIST). In each of the three panels, the interpolated lag interval is denoted by an asterisk and is the value used to calculate the blood velocity. At an IDIST of 35 μm it is clear that the true inter-sensor delay lies between one and two lags (1/60 to 2/60 of a sec). The interpolated lag yields a velocity of 1.40 mm/sec. Reanalyzing the same data, but now with an IDIST of 41 μm, results in a more definite peak in the correlation function and an interpolated lag that yields a blood velocity of 1.32 mm/sec. Further separation of the cursors to 47 μm produces a velocity value of 1.23 mm/sec. Based on *in vitro* studies, it is known that the true velocity will lie between the two latter values, and for the example illustrated, the velocity is determined as 1.27 mm/sec.

The ability to measure velocity and diameter simultaneously at venous confluences permits one to calculate and compare the sum of the flows entering and leaving based on the measured velocities at each site.

In Figure 9, a region of the vascular pattern is observed in a 25-year-old subject, together with the measured values of diameter, velocity, and

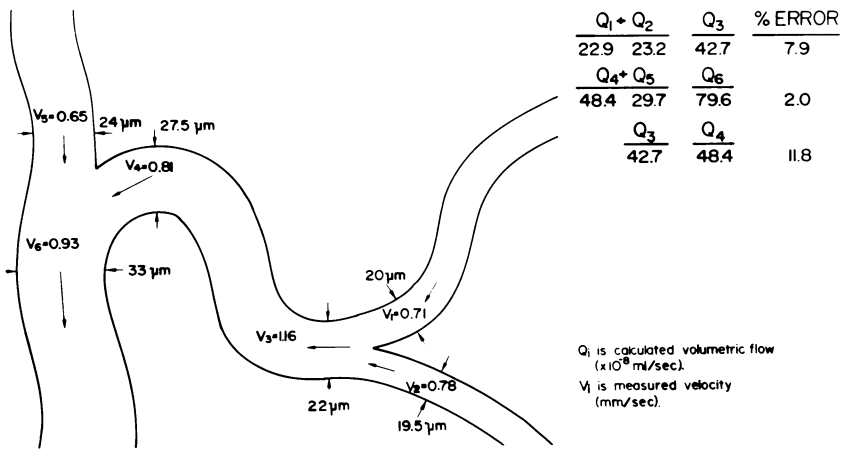

Fig. 9 Schematic representation of vascular pattern in conjunctival venous system and associated hemodynamic qualities. The sum of flows entering and leaving the venous confluences serve as an index of the system accuracy.

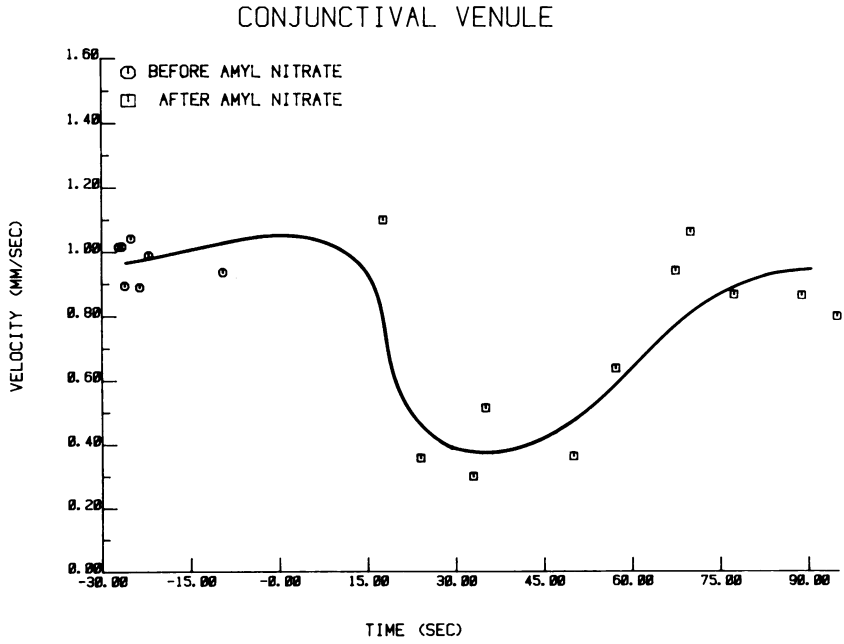

Fig. 10 Dynamic blood velocity change detected by the video system after inhalation of amyl nitrate.

calculated blood flow. The largest difference detected was 11.8%, and this may have been because there was some spatial flow variation at the proximal and distal ends of the vessel in which these measurements were made.

The ability of the system to follow rather rapid changes in blood velocity is accessed by inducing a blood flow change through inhalation of a small quantity of amyl nitrate. The effect is quite dramatic as evidenced by the response illustrated in Figure 10. During this particular procedure, no significant change in venule diameter was noted, thus the flow change depicted was characteristic of a significant blood flow reduction in the vessel under study.

A long-term follow-up study of hemodynamic changes is illustrated in Figure 11, which is an example of the overall system capability. This data was obtained from a 32-year-old patient who suffered a myocardial infarction 12 days before entering into a study designed to evaluate the efficacy of a beta-blocking agent as a postmyocardial infarction treatment procedure. Conjunctival data was first obtained 4 weeks after the patient entered the double blind study, and we will continue to gather and evaluate information for the next 3 years.

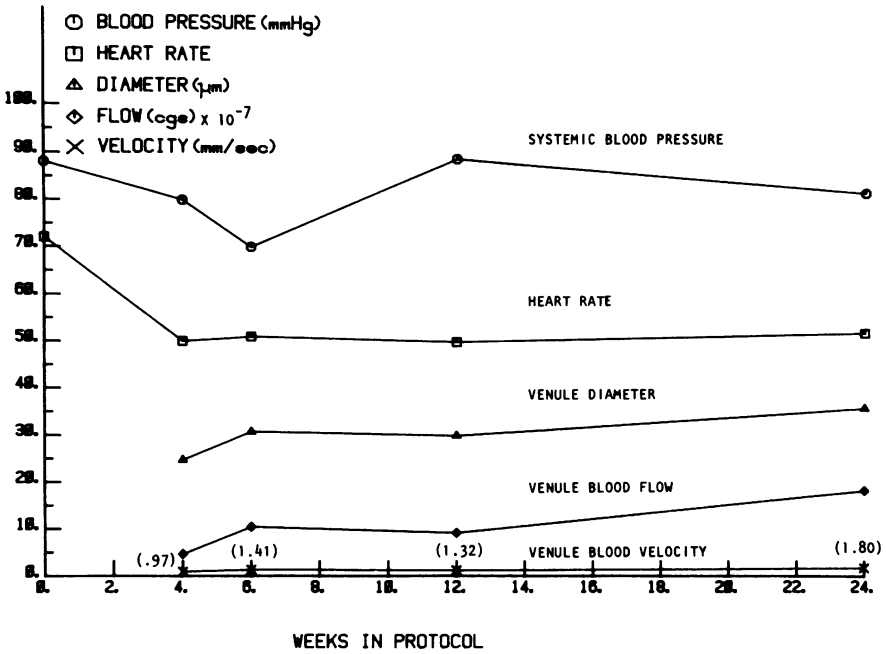

Fig. 11 Hemodynamic data from a post-myocardial infarction patient followed during a period of 24 weeks. Numbers in parentheses are the measured values of blood velocity in the same vessel segment.

Conclusion

Partly due to previous technical limitations, our current state of knowledge concerning the hemodynamics within the human microvasculature is quite sparse. Few "windows" into the human microcirculation are available for noninvasive, direct study of these circulatory dynamics. The use of recently devised video processing methods and their application to obtain blood velocity data from human conjunctival vessels is viewed as a major step forward in filling an obvious void in this important physiological and clinical area. The use of blood velocity data as an index of microcirculatory function provides a dynamic and physiologically significant parameter to supplement standard photographic methods. The use of the video tape recording facility allows the investigator to study and measure flow patterns and velocities of multiple sites and, in retrospect, to examine and study features which time does not permit during the actual patient examination. The method is completely noninvasive and requires little patient preparation, time, or discomfort. The information so obtained is one of the few ways in which direct and quantitative characterization of the human microcirculation can be meaningfully made.

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