Uniformity of intracarotid drug distribution with diastole-phased pulsed infusion

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Drug streaming has been implicated in the development of focal necrotic lesions in perfused tissues following intracarotid chemotherapy of brain tumors at low infusion rates. The narrow infusate path characteristic of streaming within laminar blood flow is not observed at high infusion rates such as are typical in contrast injection for angiography. By periodically pulsing the infusate at a high rate, the mechanisms of rapid mixing can be exploited while retaining the practicality of low average infusion rates. This in vitro study demonstrates the effects of the pulse-controlling parameters and the catheter characteristics and placement on mixing effectiveness. An internal carotid artery model including eight cerebral branches was infused with dye through various indwelling catheters, and individual branch effluents were collected and analyzed spectrophotometrically for dye concentration. While catheter placement dominates the factors that control infusate distribution, judicious selection of the pulse parameters can alleviate that dependence. A primary advantage is gained by phasing the pulse to occur during that period of the cardiac cycle when the blood flow is lowest at the injection site. The data clearly showed that diastole-phased pulsed infusions are highly effective in producing a uniform infusate distribution at low average infusion rates.

Key Words • drug streaming • chemotherapy • brain neoplasm • drug delivery

Significant pharmacokinetic advantage in chemotherapy of isolated tumors can be gained by selective arterial perfusion techniques in concert with local venous drug extraction. Several catheter systems have been developed to achieve these superselective delivery positions and are in clinical use. With notable exceptions, these systems have limited flow capacity and have contributed to the establishment of low-infusion-rate protocols. Recent investigations in animals have shown evidence of drug streaming at these low infusion rates. The result is maldistribution of the drug among critical distal branches of the selected perfusion bed: that is, extreme drug concentration in branches where the drug has channeled, and ineffective treatment in tissues perfused by vessels with subtherapeutic concentrations or total lack of drug. In addition, the highly selective placement of the catheter tip aggravates the mixing problem by precluding from drug distribution the long downstream vessel lengths which are conducive to infusate stream break-up and drug/blood mixing.

Typical arteriography, performed at a high infusion rate, gives little evidence of the streaming phenomenon. Indeed, these rates produce a very uniform downstream concentration of contrast medium, as is required for accurate angiographic visualization. During chemotherapy, the inherent mixing capability of high infusion rates can be exploited (while retaining the practical value of low average infusion rates) by repeatedly pulsing the infusate between no-flow and high-flow conditions, effectively eliminating the periods of low flow where streaming may occur. As will be seen, substantial additional advantage is gained by phasing each infusion pulse to occur during the period of lowest local blood flow. This report describes the physical character and governing parameters of this infusion technique. The accompanying article describes use of this technique for intracarotid radioisotope infusion in rhesus monkeys, and the resulting tissue concentration uniformity is analyzed by autoradiography.

Materials and Methods

Systems and Calculations

The infusate flow is a series of precision off-on-off pulses. The onset of each pulse derives from the R-wave of the electrocardiogram (EKG) so that only a single pulse occurs during each cardiac cycle. By means
Uniformity of intracarotid drug distribution

of a controllable delay between the R-wave and the pulse onset, the pulse can be made to occur at any desired time during the local blood flow cycle. Figure 1 shows, on a single time scale, a simulated display of the EKG, the local blood flow waveform, and the infusion flow pulse which has been positioned by the controllable delay to occur during "local diastole." To implement phasing in vivo, the audio output of a Doppler flow detector is converted from frequency to voltage to reveal the blood flow waveform. On palpating the common carotid artery for a few seconds with the Doppler probe, this waveform displays concurrently with the EKG. The pulse, triggered by the R-wave, is then electronically delayed to occur during blood flow diastole. The infusion system was developed through modifications made to a standard angiographic injector and an ultrasonic Doppler flow detector.*

During infusion, the pulse width is automatically modulated by the heart rate to maintain the average and pulse infusion rates (the delay is also modulated to maintain the pulse position at local diastole). As the heart rate increases, the pulse width decreases. For reasons discussed below, a minimum pulse width is specified. When that threshold is crossed, the frequency of the pulse is decreased to every second cardiac cycle, then to every third cycle, and so on, as required. The ratio of the heart rate to the pulse frequency is called the beat:pulse ratio, and assumes integer values. From another perspective, the beat:pulse ratio can be used to control the pulse width and to decouple it from the infusion rate. The relationships between these parameters, which become available for broad control in this pulsed-infusion scheme, are:

\[
\text{pulse width (sec)} = \frac{160\alpha}{HR^2}
\]

\[
\text{pulse volume (ml)} = \frac{I\alpha}{HR^2}
\]

\[
\text{total infused volume (ml)} = IT.
\]

where \(I\) = average infusion rate (ml/min); \(i\) = pulse infusion rate (ml/min); \(\alpha\) = beat:pulse ratio (beats/pulse); HR = heart rate (beats/min); and \(T\) = total infusion time (min). The interplay of these parameters with the catheter and blood flow characteristics to effect a uniform drug/blood concentration is revealed in the in vitro experiments that are described below.

Experiments

The effects of catheter compliance, diameter, and length were studied. The low-compliance catheters were of a high-durometer polyurethane; one set (No. 5 French) was 1.67 mm in outside diameter (OD) and 1.3 mm in inside diameter (ID), and the other set (No. 2 French) was 0.67 mm in OD and 0.5 mm in ID. Each set included three lengths: 45 cm, 90 cm, and 135 cm. The high-compliance catheters were of a low-durometer polyurethane with identical ID's but a wall thickness of about 0.06 mm; this series was heat-treated to produce tubing of collapsed cross section and so present a highly compliant lumen. All other characteristics were identical. All catheter tips were square-cut to form conventional end-hole configurations. This test matrix yielded copious data; the results reported here are only those data that showed significant effects on concentration uniformity.

The catheter tip position along the length of the artery was also studied. All studies were performed in an arterial model and flow circuit described previously. Briefly, the acrylic model is derived from orthogonal angiographic images and presents the full superior internal carotid artery; the ophthalmic, posterior communicating, and anterior choroidal branches; the anterior and middle cerebral arteries, including the M1 and the right and left M2 segments; and the lenticulostriate arteries. The balance of the flow system was precisely tuned to produce a physiologically accurate waveform of blood simulant within the cerebral model. For all studies, the system was set to 60 beats/min and 250 ml/min average flow rate. The infusate was a brilliant rose bengal dye. Effluents from all cerebral branches were individually and simultaneously col-
D. R. Shook, L. M. Beaudet and J. L. Doppman

FIG. 2. Histogram of the concentration index (CI) comparing the downstream concentration uniformities of infused dye at two steady continuous infusion rates: 1 ml/min and 50 ml/min. See text for further explanation. Op = ophthalmic artery; Ch = choroidal artery; AC = anterior cerebral artery; Ls = lenticulostriate artery; M2L and M2R = left and right M2 segments of the middle cerebral artery.

lected over a period of at least 20 cardiac cycles after flow was well established, and dye concentrations were determined spectrophotometrically. It is possible to define a concentration index (CI) that accounts for the differential in branch flow rates and any dye build-up (or background) in the recirculating flow system by means of the following equation: \( \text{CI} = \frac{(C_n - C_o)}{(C^* - C_o)} \), where \( C_n \) is the dye concentration of the branch in question, \( C^* \) is the average (or mixture) concentration, and \( C_o \) is the background dye concentration. A value of 1.0 for the index indicates a branch concentration equal to the average concentration; a value of 1.0 for all branches, then, implies complete concentration uniformity. Figure 2 presents a histogram of this index for each branch. In all subsequent figures, however, the absolute range of that index is shown by indicating its maximum and minimum values without reference to the two particular branch flows where those values were measured. This parameter is referred to as the concentration range (CR). In all experiments except one (the results of which are shown in Fig. 5), the catheter tip was placed 2 to 3 mm distal to the ophthalmic branch, where no dye concentration was detected or reported.

Results

Figure 2 shows the striking effect of high infusion rates on downstream concentration uniformity. These and all subsequent data are the result of at least three trials, with an average standard deviation of 0.040.

RESULTS

Figure 3 is a highly compact presentation of the effects of both the pulse placement (phasing) and the pulse infusion rate on the concentration range. The blood (simulant) flow waveform, centered on diastole, is depicted in Fig. 3 upper. Each boldface segment of that curve indicates the relative position of the infusate pulse for one individual study. Note that only one pulse occurred during each blood flow cycle, and the relative position of that pulse was not changed over the measurement period. The results of four such studies, at different pulse infusion rates, are shown in Fig. 3 lower.
Uniformity of intracarotid drug distribution

Fig. 4. Effects of pulse width on the concentration range (CR) at the four pulse infusion rates. A No. 5 French low-compliance catheter, 45 cm long, with a 4-ml/min average infusion rate was used for this test.

Fig. 5. Effects of catheter tip position on the concentration range (CR) at two pulse infusion rates. Position 1 is 2 to 3 mm distal to the ophthalmic artery branch point, with successive positions at 5-mm increments downstream along the internal carotid artery. This graph was generated using a No. 5 French low-compliance catheter, 45 cm long, with a 4-ml/min average infusion rate, 0.133-sec pulse width, and 4 beats/pulse.

Discussion

Streaming at low infusion rates can jeopardize the proven pharmacokinetic advantage of isolated intraarterial chemotherapy. Streaming is a natural phenomenon resulting from the laminar character of blood flow. Under such conditions, infusate introduced into a restricted set of laminae cannot cross over into adjacent laminae before those different streams may diverge into separate branches of the vasculature. The result is...
non-uniform infusate distribution in perfused tissues. Highly selective catheter placement only increases the likelihood that the infusate stream will substantially, if not fully, channel into a single branch at a branch point or bifurcation. Evidence indicates that streaming may persist even to the precapillary level. Catheter tip position across the lumen is by far the dominant factor in establishing the pathway of the infusate stream, although pulsatility of the arterial blood flow may redirect the stream or an infusate jet may relocate the stream origin away from the catheter tip. These problems are not evident, however, at high infusion rates.

At high infusion rates, several mechanisms of fluid dynamics interplay to uniformly distribute the infusate across the vessel lumen. In the clinical situation, infusate velocity and catheter diameter are available for control. Since streaming is much more sensitive to injection velocity than to diameter, velocity should be maximized, while only an optimally large exit lumen need be achieved. Figure 2 indicates the results of judicious control of exit velocity through the infusion rate. However, practical considerations in supraophthalmic intracarotid chemotherapy limit this variation and often preclude the rates required to overcome streaming. With the exception of the new everting catheter techniques, most existing catheters that can routinely achieve superselective positions offer severely limited flow capacity. On the other hand, assuming linear transport processes, simple dilution and continuous high-rate infusion of the drug would introduce massive fluid volumes. Use of extracorporeal extraction techniques capable of handling those volume flow rates would be mandatory. However, pulsing the infusion decouples mass infusion rate from jet velocity, allowing independent control of each.

Pulsing is the transient introduction and termination of a high-rate infusion into confined circumfluent (blood) flow. Just as a continuous high-rate jet can become a large percentage of the overall flow, a pulsed jet can combine in high concentration with the blood flow. Due to arterial elasticity and several hydrodynamic mechanisms that are operable during a transient pulse, a significantly higher infusate concentration can be deposited during the pulse period. Flow visualization shows the formation of this “bolus” and its propagation downstream. The bolus extends fully across the lumen and, as the overall flow divides at downstream branches, the bolus divides as well. In this way, all downstream branches receive essentially uniform infusate concentrations. Most residual non-uniformities can be traced to incomplete geometric formation of the bolus and to non-uniform concentration within the bolus itself.

Pulsing causes repeated establishment of flow. Each time the flow rises from zero to the pulse infusion rate, the catheter reacts to the accompanying thrust. To what extent the catheter recoils depends in part upon the flow acceleration and the rigidity of the catheter in its delivery position. During acceleration, streaming may occur at the lower velocities. Therefore, while it is desirable to attain the pulse infusion rate as quickly as possible, the acceleration is limited by the onset of appreciable catheter recoil. Since the time taken for the pulse to rise was essentially constant in our studies, flow acceleration varied directly with pulse infusion rate, and no recoil was observed in any catheter below 90 ml/min. In this regard, flow visualization showed that more rigid catheters began to recoil at greater accelerations than elastic catheters. Rigid catheters oscillated with each pulse, whereas the softer catheters recoiled on the initial pulse and remained stationary thereafter. Two explanations for this behavior were apparent. Elastic catheters had longer flexible free lengths, so that recoil was distributed, and rebound was hampered by sinuous vessels. Rigid catheters recoiled only at their tips, which were free to return to original positions. Where catheter recoil is expected, therefore, the catheter tip position must be verified radiographically under infusion conditions. Recoil had no measurable effect on mixing.

Compliant catheters have a reactive response to a change in flow. Final achievement of pulse infusion rate is delayed by a time characteristic of the system. This is observed at the catheter exit as a slow rise and fall from the pulse infusion rate for an otherwise square pulse input. Although this phenomenon may alleviate recoil, the lower exit velocities compromise mixing efficiency (Fig. 6). At short pulse widths, the pulse infusion rate may not be reached before the end of the pulse. At intermediate widths, the transients are a major
Uniformity of intracarotid drug distribution

proportion of the flow. During transient periods, low-flow-mediated streaming may occur. With a properly designed injection system, catheter compliance is the major reactive factor and may be significant for superselective catheters. A longer pulse width, therefore, allows the pulse infusion rate to be maintained and the transients to be relatively minimized.

The need for highest pulse infusion rates for mixing effectiveness can be alleviated by phasing. Diastolic placement of the pulse, as shown in Fig. 3, gains primary benefit from the drug:blood velocity ratio. But another factor is also important. Figure 3 shows the advantage of phasing during the period of falling blood flow rate. A pulse occurring at the same value of blood flow rate, but on the rising side of the curve, does not demonstrate this advantage. This is due to inherent instability produced by the adverse pressure gradients in pulsatile (blood) flow. Pulsing during rising blood flow rates, therefore, may stabilize an infusate stream, and should be avoided.

Conclusions

This in vitro study clearly demonstrates that infusion of diastolically phased, high-flow-rate pulses relieves the effects of laminar streaming while maintaining low average infusion rates. Diastolic phasing is simple to achieve and adds substantially to pulse effectiveness by exploiting the pulsatility of arterial flow. Several control parameters become available in phased pulsing and can be used to attenuate the influence of the catheter tip position, which is an overwhelming determinant of streaming effects. This technique was developed to address the streaming problem attributed to steady low-rate suprapahtalmic intracarotid chemotherapy of brain tumors. Treatment at other sites or with other systems, such as implantable infusion pumps, may benefit as well from this technique. Studies are underway to verify the effectiveness of high pulsed infusion rates in vivo. The success of those studies may further implicate streaming with drug heterogeneity in perfused tissues.

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References
