Characterization of Subretinal Fluid Leakage in Central Serous Chorioretinopathy

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PURPOSE. The purpose of the study was to determine which category of hydrodynamic phenomena the smokestack in central serous chorioretinopathy (CSC) most likely belongs to: leakage by diffusion or bulk flow.

METHODS. Fluorescein angiograms of 13 eyes of 13 patients were reviewed and analyzed quantitatively. Two methods were used to assess the rate of fluid leakage. One was based on observation of the expansion rate of the bubble of stained fluid seen in the earliest phase of the angiogram, and the other one compared the area of the source of the leakage to the remaining area of retinal pigment epithelium (RPE) exposed to subretinal fluid, by using a standard value for RPE fluid resorption capacity per unit surface area and assuming that resorption equals leakage.

RESULTS. The mean rates of leakage were 16.2 μL/mm²/h (95% CI, 11.9–22.1) with the expanding-bubble method and 16.1 μL/mm²/h (95% CI, 12.0–21.7) with the area-of-resorption method (P = 0.95, linear correlation r = 0.94). The repeatability coefficient for both methods was 36.3%.

CONCLUSIONS. The study demonstrated sufficient overall agreement between the two methods of assessing leakage rates in smokestack CSC, with adequate repeatability. Leakage rates of the RPE lesions in smokestack CSC occurred at rates consistent with bulk fluid flow, rather than secretion and diffusion, indicating that the primary source of leaking fluid was not the RPE, but a segment of underlying choroidal vasculature. (Invest Ophthalmol Vis Sci. 2010;51:5853–5857) DOI:10.1167/iovs.09-4830

Central serous chorioretinopathy (CSC) is characterized by serous detachment of the neurosensory retina, secondary to focal retinal pigment epitheliopathy without detectable inflammatory, neovascular, or neoplastic components. Symptoms include blurred central vision, metamorphopsia, micropsia, dyschromatopsia, and the sensation of a transparent gray spot in the central visual field. The details of the pathogenesis of CSC have not been clarified.1,2 Several studies have implicated flow and permeability abnormalities in the choroidal vasculature in the pathogenesis of CSC. Indocyanine green angiography has shown localized angiographic filling delay and late-phase staining of choroidal vessels underlying the retinal pigment epithelium (RPE) lesions in CSC. Often, a serous pigment epithelial detachment can be found under the serous detachment of the neurosensory retinal detachment, and optical coherence tomography (OCT) may show an anatomic defect in the RPE associated with fluid that is leaking into the subretinal space.3–5 Except for the leakage site, the outer blood–retinal barrier is presumed to be intact in CSC, but it has been suggested that the metabolic active transport of fluid by the RPE is impaired and contributes to the formation and persistence of the serous detachment.6,7

The prognosis of CSC is not uniformly favorable and therefore it is of interest to gain better insight into its pathogenesis.4,8–12 The present study evaluated two different methods of determining the type of inflow in acute smokestack CSC in an attempt to understand the process of pathologic fluid formation.

METHODS

We retrospectively reviewed digital fluorescein angiograms of 348 patients with CSC examined between 1996 and 2008 at the Herlev Hospital, the Glostrup Hospital, and the Rigshospitalet, all in the Greater Copenhagen area. The diagnosis was based on the history, biomicroscopy, fluorescein angiography, and, when available, OCT. Eligible cases were those that presented a smokestack configuration of dye-stained fluorescein leakage on fluorescein angiography.2 Cases were excluded if the angiograms were of unacceptable quality or covered only some angiographic phases. OCT scans were available in only three cases and, being first-generation OCT scans, they were not of sufficient quality or multidirectionality to enable a reliable assessment of the volume of fluid under the retina. We therefore chose to base our analysis only on angiograms and fundus photographs, which were available in all cases. The confidentiality of the patients’ information was protected, in compliance with the Declaration of Helsinki.

The review identified 13 eligible cases involving 13 eyes of 13 patients, all of whom had presented with symptoms of recent onset and had not been seen by an ophthalmologist (Table 1). Color and/or grayscale fundus photographs were available in all 13 patients, all of whom were male. Their mean age was 40 years (range, 31–58) and their median best corrected visual acuity was 0.7 (range, 0.3–1.0). The ethnicity of all patients was Danish.

Assessment of the angiographic rate of leakage from the source of leakage, which was monofocal in all cases, was made manually with commercial digital image management software (Corel Paint Shop Pro X, ver. 10; Ottawa, Ontario, Canada) and two different methods that we developed for the purpose of the study.

All measures of fundus dimensions were made in pixels and converted, when necessary, to absolute dimensions assuming a vertical optic disc diameter of 1500 μm. The μm/pixel conversion ratio was determined from a fovea-centered image of the same angular subtense as the angiograms. All image analyses were made three times in random order at intervals of at least 1 week and by the same observer.

The expanding-bubble method (Figs. 1, 2) is based on the assumption that in the first phase of fluorescein angiographic leakage, freshly leaking fluid, densely stained by fluorescein, propagates into the subretinal cavity as a bubble that stands out in contrast to unstained fluid.
Smokestack Leakage

First frame of the angiogram: (4/3 of RPE that has been exposed by leaking fluid, opening and expanding source of leakage and outflow (resorption) through a surrounding area by the equilibrium between inflow (leakage) from a circumscribed

tion that a serous neurosensory detachment of stable size is maintained in the first 35 seconds of the angiogram. The marked areas of the initial hot spot and the area of detached retina were copied and pasted into new images, from which the area in pixels could be extracted by the software. Using a histogram func-

Distribution of fluorescence intensity at the center of the bubble. In all cases, vol-

Table 1. Clinical Characteristics of Patients with CSC with Smokestack Leakage

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Affected Eye</th>
<th>BCVA (Snellen)</th>
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<tr>
<td>1</td>
<td>M</td>
<td>45</td>
<td>Left</td>
<td>0.7</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>54</td>
<td>Right</td>
<td>0.8</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>56</td>
<td>Right</td>
<td>1.0</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>41</td>
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<td>0.5</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>40</td>
<td>Left</td>
<td>0.4</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>44</td>
<td>Right</td>
<td>0.7</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>55</td>
<td>Right</td>
<td>0.9</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>59</td>
<td>Left</td>
<td>0.8</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>42</td>
<td>Right</td>
<td>0.3</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>33</td>
<td>Right</td>
<td>0.6</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>31</td>
<td>Right</td>
<td>1.0</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>58</td>
<td>Left</td>
<td>0.7</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>42</td>
<td>Left</td>
<td>1.0</td>
</tr>
</tbody>
</table>

where \( \text{vol}_1 \) is the volume (in cubic millimeters) of a hemisphere in the first frame of the angiogram: \((\frac{4}{3} \pi \times r^3)/2\); \( \text{vol}_2 \) is the volume (in cubic millimeters) of a hemisphere in the second frame of the angiogram, according to the same formula: \( \Delta t \) the time elapsed between the recording of the two angiograms; and area is the area (in square millimeters) of the source of leakage in the first frame of the angiogram (area = \( \pi r^2 \)).

Circles corresponding to the outline of the hotspots in each frame of the angiogram were drawn manually (Fig. 1). The circumference of the expanding bubble was set quantitatively at the half-maximum fluorescence intensity at the center of the bubble. In all cases, volumetric expansion was calculated from two frames that were recorded in the first 35 seconds of the angiogram.

The area-of-resorption method (Figs. 3, 4) is based on the assumption that a serous neurosensory detachment of stable size is maintained by the equilibrium between inflow (leakage) from a circumscribed source of leakage and outflow (resorption) through a surrounding area of RPE that has been exposed by leaking fluid, opening and expanding

A cavity between the retina and the RPE to the point that equilibrium between leakage and resorption is established. The model assumes that the retina is not involved in the production or resorption of subretinal fluid. The rate by which the RPE resorbs subretinal fluid has been found to be 0.12 \( \mu L/mm^2/h \) in rabbits in which the rate of disappearance of fluid injected under the retina was observed. Because no comparable observations are available in humans, we have assumed that the data apply to humans with smokestack CSC, except at the point of leakage. The extent of the serous retinal detachment was determined by fitting of an oval overlying the rim of the retinal detachment, as seen on a late-phase fluorescein angiogram, and measuring its area. The rate of leakage was defined by

\[
\text{Leakage rate (\( \mu L/mm^2/h \))} = \frac{\text{area}_1 \times \text{resorption rate}}{\text{area}_1}
\]

where \( \text{area}_1 \) is the area of the source of leakage on the earliest angiogram, \( \text{area}_2 \) is the area of detached retina minus the source of leakage, and resorption rate is 0.12 \( \mu L/mm^2/h \). The marked areas of the initial hot spot and the area of detached retina were copied and pasted into new images, from which the area in pixels could be extracted by the software. Using a histogram func-

Insertion of an oval overlying the rim of the retinal detachment, as seen on a late-phase fluorescein angiogram, and measuring its area. The rate of leakage was defined by

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\text{Leakage rate (\( \mu L/mm^2/h \))} = \frac{\text{area}_1 \times \text{resorption rate}}{\text{area}_1}
\]

where \( \text{area}_1 \) is the area of the source of leakage on the earliest angiogram, \( \text{area}_2 \) is the area of detached retina minus the source of leakage, and resorption rate is 0.12 \( \mu L/mm^2/h \).

The marked areas of the initial hot spot and the area of detached retina were copied and pasted into new images, from which the area in pixels could be extracted by the software. Using a histogram func-

Figure 3. Area of neurosensory retinal detachment determined from a midphase fundus fluorescein angiogram from an eye (case 3) with CSC and monofocal smokestack leakage. The detachment exposed 4.26 mm² of RPE to subretinal fluid emanating from a source of leakage covering 0.05 mm². Assuming equilibrium between leakage and resorption, with resorption occurring only over the RPE, the rate of leakage is 142 times higher per unit surface area than the rate of resorption. Inserting a rate of resorption found in animal studies enables estimation of the rate of fluid formation at the source of leakage.
tion, we extracted the number of marked pixels on the basis of the differences in grayscale intensities between marked and unmarked pixels. The area in number of pixels was converted to square millimeters, again by using the optic disc as a reference.

Initially, data were log transformed due to a positive skewed distribution and to enable comparisons between groups of data with a normal distribution. Analyses were conducted on log-transformed data by using a paired Student’s t-test and linear regression and after back-transforming into the original scale. The results are given in the original scale. Intraobserver reproducibility was determined by using repeatability coefficients and is expressed as a mean percentage of all measurements. Comparison between methods is shown in a Bland-Altman plot (see Fig. 6), equivalent to the log transformation used elsewhere. The difference between methods in the Bland-Altman plot is given as the ratio of the methods. The level of statistical significance was set at $P < 0.05$ (SPSS PC 12.0 software; SPSS Inc., Chicago, IL).

**RESULTS**

Trans-pigment epithelial fluorescein angiographic leakage was monofocal in all 13 cases, emanating from a minute circular focus, the extent of which ranged from 0.002 to 0.02 mm$^2$. The serous retinal detachment was circular or nearly circular in all cases, and no case showed subretinal granules, gravitational tracts, or other signs of chronic CSC.

**Repeatability**

Quantitative analysis in triplicate demonstrated intraobserver repeatability of 36.3% (corresponding to 95% CI, 5.90–44.6 μL/mm$^2$/hr with a mean of 16.2 μL/mm$^2$/hr) for the expanding-bubble method and 36.3% (corresponding to 95% CI, 5.87–44.3 with a mean of 16.1 μL/mm$^2$/hr) for the area-of-resorption method. Because of the moderate level of repeatability, subsequent results are based on the mean of triplicate results.

**Comparison of Methods**

The estimated rate of leakage using the expanding-bubble method averaged 16.2 μL/mm$^2$/hr (95% CI, 11.9–22.1) and 16.1 μL/mm$^2$/hr (95% CI, 12.0–21.7) by the area-of-resorption method ($P = 0.95$, paired t-test on log-transformed data; Table 2). The correlation between the two methods was $r = 0.94$ (Fig. 5). A Bland-Altman plot of mean leakage rates showed an even distribution around a horizontal line, with a mean ratio between the methods of 1.06 and 95% CI, 0.41–1.70 ($P = 0.52$; paired t-test; Fig. 6).

With mean rates of leakage of 197 and 151 μL/mm$^2$/hr with the respective methods, case 7 was the only one that reached rates higher than 40 μL/mm$^2$/hr (Table 2). A review of the fluorescein angiogram revealed no sign of a retinal pigment epithelial tear. OCT was unavailable.

**FIGURE 4.** The area-of-resorption method is based on a healthy pumping RPE. Arrows: direction of transepithelial fluid transport from the subretinal compartment into the choroid by the denuded RPE.

**FIGURE 5.** Correlation between two methods of estimating rates of fluid leakage from monofocal sources of fluorescein angiographic leakage in CSC with fluorescein angiographic smokestack leakage ($r = 0.94$). Black line indicates line of equality.

**TABLE 2.** Rates of Leakage from Monofocal Sources of Leakage in CSC with Smokestack Leakage

<table>
<thead>
<tr>
<th>Patient</th>
<th>Expanding Bubble Method (μL/mm$^2$/hr) Mean</th>
<th>95% CI</th>
<th>Expanding Bubble Method (μL/mm$^2$/hr) Mean</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>1</td>
<td>11.5</td>
<td>5.69–23.3</td>
<td>22.1</td>
<td>3.29–148.1</td>
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<tr>
<td>2</td>
<td>5.46</td>
<td>3.53–8.46</td>
<td>7.12</td>
<td>3.07–16.5</td>
</tr>
<tr>
<td>3</td>
<td>18.4</td>
<td>1.82–186.8</td>
<td>18.3</td>
<td>5.32–63.3</td>
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<tr>
<td>4</td>
<td>8.25</td>
<td>5.06–13.5</td>
<td>6.27</td>
<td>3.44–11.4</td>
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<tr>
<td>5</td>
<td>12.5</td>
<td>7.21–21.5</td>
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<td>4.11–37.8</td>
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<tr>
<td>6</td>
<td>6.04</td>
<td>2.17–20.4</td>
<td>9.23</td>
<td>4.94–17.2</td>
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<tr>
<td>7</td>
<td>197.3</td>
<td>96.0–405.4</td>
<td>151.2</td>
<td>78.2–292.4</td>
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<tr>
<td>8</td>
<td>16.0</td>
<td>9.31–27.5</td>
<td>9.20</td>
<td>4.03–21.0</td>
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<tr>
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<td>11.7</td>
<td>8.17–16.7</td>
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<tr>
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<td>11.3</td>
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<td>8.81</td>
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<tr>
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<td>39.8</td>
<td>34.7–45.7</td>
<td>37.3</td>
<td>30.3–45.8</td>
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<tr>
<td>12</td>
<td>12.7</td>
<td>7.48–21.6</td>
<td>11.8</td>
<td>5.16–27.1</td>
</tr>
<tr>
<td>13</td>
<td>32.9</td>
<td>21.6–50.1</td>
<td>38.2</td>
<td>22.6–64.7</td>
</tr>
<tr>
<td>Total</td>
<td>16.2</td>
<td>11.9–22.1</td>
<td>16.1</td>
<td>12.0–21.7</td>
</tr>
</tbody>
</table>

Mean and 95% CI of leakage rates for the two methods, calculated from the log-transformed data of triplicate measurements for each method. Data are presented as back-transformed values.

**DISCUSSION**

The present study demonstrated no significant difference between two semi-independent methods of estimating the rate of fluorescein angiographic leakage from monofocal sources in smokestack CSC from the RPE into the subretinal space. Repeatability coefficients of each method showed a similar repeatability of 36% of the mean results, as calculated from three measurements by the same observer, obtained at least 1 week apart. For both methods, the variability was minimized using the mean of the three measurements. The ratio between the methods presented as a Bland-Altman plot demonstrated an even distribution of a horizontal line with acceptable limits of agreement.
Transport of fluid can be driven by hydrostatic pressure gradients, active ion transport, and passive diffusion after osmotic gradients. The rates of leakage observed in this study exceeded more than one order of magnitude those known from the choroidal plexus, which secretes cerebrospinal fluid at a rate of 0.48 μL/mm²/h. This finding indicates that smokestack leakage in CSC represents bulk flow, rather than secretion by the RPE. Obviously, the angiographic sources of leakage need not represent the primary source of the leakage. It may simply be a bottleneck in a conduit for convective fluid flow that funnels fluid originating from a larger source behind the RPE into the subretinal space. The existence of such a source is suggested by several findings. First, fluorescein angiographic leakage in CSC often occurs in relation to pigment epithelial detachment, which could be driven by fluid pressure from behind Bruch’s membrane. Second, indocyanine green angiography in CSC sometimes shows localized delayed choroidal filling with subsequent choroidal vascular staining and leakage. These observations indicate the presence of choroidal vasculopathy in relation to CSC-lesions of the RPE, a vasculopathy that may be the primary cause of CSC.

Methodologic aspects must be discussed in the interpretation of the results of both methods. In the expanding-bubble method, diffusion may contribute significantly to the observed expansion of fluorescein and thus lead to overestimation of leakage rates. We calculated a quantitative estimate of the role of diffusion, as in a previous study. We considered the potential role of diffusion in producing the early concentric expanding bubble. The concentration of fluorescein in a serous detachment was estimated with a mathematical model, based on Fick’s law of diffusion, assuming a constant concentration at the pore of inflow and a diffusion rate of 6 × 10⁻⁶ cm²/s. The diffusion gradient throughout the detachment was assessed with several hemispheric cells, all a radius of 10 μm, and diffusion occurred bidirectionally. No active transport through the RPE was included. The model indicates that approximately 20% of the observed flow may be attributable to diffusion. Diffusion is driven only by osmotic gradients, presumably uniform in the serous detachment, and as the observed volume flow is larger than the flow from diffusion, we still believe that the smokestack phenomenon represent additional bulk flow. The observed upward direction of flow in smokestack CSC may be caused by differences in density or thermal gradients between newly formed fluid and fluid that has remained longer in the subretinal cavity.

Given the retrospective nature of the study and the limited frame rate of the initial angiography sequence, we cannot be certain that we have captured the area of the source of leakage at its minimum, nor can we be certain that the size of the initial hot spot matches that of the RPE defect through which fluorescein enters the subretinal space. Nevertheless, an erroneous estimate affects calculation of convection and diffusion to the same extent and therefore has little effect on the ability to distinguish between the two phenomena. Video angiography may provide a better estimate of the extent of the leakage points.

The area-of-resorption method is valid only if there is equilibrium between production and resorption of fluid and if the serous detachment is not expanding, shrinking, or undergoing hydrostatic pressure changes during the period of observation. We do not have data to demonstrate that our cases were in a state of equilibrium and can only refer to the clinical impression that visible expansion or shrinkage did not occur over the time frame of the angiographic recordings. The reference data for resorption rates over the RPE were drawn from studies of the rabbit, and the data may not be representative of humans, much less humans with CSC. Ultrasonographic investigations in humans suggest that the rate of resorption of subretinal fluid in rhegmatogenous retinal detachments are nearly identical with the value in the rabbit, but we favor the data from the rabbit experiments because the extent of the area of detachment and other methodologic aspects were better defined than in the more pragmatic clinical observations made in humans. Another issue is that the RPE may be diffusely dysfunctional in CSC, with the dysfunction potentially including an impaired capacity to resorb subretinal fluid because of metabolic dysfunction or abnormal hydrostatic pressure in the choroid. We cannot entirely exclude this possibility, but it is worth noting that all our cases had small, focal smokestack lesions and a short duration of symptoms and no case had the more extensive RPE abnormalities associated with chronic CSC.

Previous studies have suggested that the osmotic drag from proteins in the subretinal fluid in CSC is minimal and that its potential role in maintaining a serous detachment of the neurosensory retina is negligible. Clinical observation of the precipitation of macromolecules within and underneath the
retina after closure of vascular leakage strongly suggests that the RPE can overcome osmotic drag.\textsuperscript{27}

One of our cases had a leakage rate considerably higher than did the rest of the study sample. His lesion may have been a profuse blowout tear of an RPE detachment.\textsuperscript{28} It remains to be determined, by detailed OCT examination of smokestack leakage in CSC, whether a tear in the RPE is an essential or an occasional feature of this condition.

The prevalence in this study of smokestack leakage in CSC was 4.5\% of all cases of CSC—slightly less than the rate of 7\% found in a comparable setting before the advent of OCT. A hypothetical explanation is that OCT has facilitated the detection of CSC presenting with a shallow detachment and has widened the spectrum of CSC in clinical practice, whence the relative contribution of smokestack cases has decreased.\textsuperscript{29,30}

The results of this study support that bulk flow is the major component of the fluorescein angiographically visible expansion of fluid from a smokestack source of leakage into the subretinal space in CSC. This theory may be seen to fit the hypothesis that the primary lesion in smokestack CSC involves leakage from the choroidal vasculature. Both methods used in this study have methodologic limitations, and the predicted flow rates should therefore be interpreted with caution.

References


