Detection of early central circulatory transits in patients with cirrhosis by gamma variate fit of indicator dilution profiles

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Henriksen, Jens H., Søren Møller, Stefan Fuglsang, and Flemming Bendtsen. Detection of early central circulatory transits in patients with cirrhosis by gamma variate fit of indicator dilution profiles. Am J Physiol Gastrointest Liver Physiol 288: G677–G684, 2005. First published December 4, 2004; doi:10.1152/ajpgi.00201.2004.—Patients with cirrhosis have hyperdynamic circulation with abnormally distributed blood volume and widespread arteriovenous communications. We aimed to detect possible very early (i.e., before 4 s) and early (i.e., after 4 s) central circulatory transits and their potential influence on determination of central and arterial blood volume (CBV). Thirty-six cirrhotic patients and nineteen controls without liver disease undergoing hemodynamic catheterization were given central bolus injections of albumin with different labels. Exponential and gamma variate fits were applied to the indicator dilution curves, and the relations between flow, circulation times, and volumes were established according to kinetic principles. No significant very early central circulatory transits were identified. In contrast, early (i.e., 4 s to maximal) transits corresponding to a mean of 5.1% (vs. 0.8% in controls; \( P < 0.005 \)) of cardiac output (equivalent to 0.36 vs. 0.05 l/min; \( P < 0.01 \)) were found in cirrhotic patients. These early transits averaged 7.7 vs. 12.7 and 17.2 s of ordinary central circulatory transits of cirrhotic patients and controls, respectively \( (P < 0.001) \). Early transits were directly correlated to the alveolar-arterial oxygen difference in the cirrhotic patients \( (r = 0.46, P < 0.01) \) but not in controls \( (r = 0.04; \text{not significant}) \). There was good agreement between the CBV determined by the conventional indicator dilution method and that determined by separation of early and ordinary transits by the gamma variate fit method \( (1.51 \text{ vs. 1.53 liter; not significant}) \). In conclusion, no very early central circulatory transits were identified in cirrhotic patients. A significant part of the cardiac output undergoes an early transit, probably through pulmonary shunts or areas with local ventilation–perfusion ratios in cirrhotic patients. Composite determination of CBV by the gamma variate fit method is in close agreement with established kinetic methods. The study provides further evidence of abnormal central circulation in cirrhosis.

central blood volume; exponential fit; indicator dilution technique; kinetic principles; pulmonary shunts; ventilation-perfusion ratio

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Early Circulatory Transits in Cirrhosis

Table 1. Clinical and biochemical data of patients with cirrhosis and controls

<table>
<thead>
<tr>
<th></th>
<th>Controls, n = 19</th>
<th>Cirrhosis, n = 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>59 ± 2.6</td>
<td>50 ± 1.4</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>11/8</td>
<td>26/10</td>
</tr>
<tr>
<td>Ascents</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Child-Turcotte, A/B/C</td>
<td></td>
<td>8/17/11</td>
</tr>
<tr>
<td>Diuretics, n/yes</td>
<td>12/7</td>
<td>19/17</td>
</tr>
<tr>
<td>Hemoglobin, mmol/L</td>
<td>8.8 ± 0.2</td>
<td>6.9 ± 0.2‡</td>
</tr>
<tr>
<td>Serum albumin, μmol/L</td>
<td>604 ± 11</td>
<td>456 ± 11‡</td>
</tr>
<tr>
<td>Serum alanine aminotransferase, μmol/L</td>
<td>40 ± 23</td>
<td>56 ± 5</td>
</tr>
<tr>
<td>Alkaline phosphatase, μmol/L</td>
<td>149 ± 14</td>
<td>349 ± 26§</td>
</tr>
<tr>
<td>Serum bilirubin, μmol/L</td>
<td>10 ± 1</td>
<td>27 ± 4*</td>
</tr>
<tr>
<td>Coagulation factors, 2.7,10, index: 0.70–1.30</td>
<td>1.06 ± 0.01</td>
<td>0.62 ± 0.03‡</td>
</tr>
<tr>
<td>Serum Na, mmol/L</td>
<td>139 ± 1</td>
<td>135 ± 1†</td>
</tr>
<tr>
<td>Serum K, mmol/L</td>
<td>4.0 ± 0.1</td>
<td>4.1 ± 0.1</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>86.5</td>
<td>91 ± 9</td>
</tr>
</tbody>
</table>

Values are means ± SE. Numbers following the units are reference intervals. Significant difference from controls: *P < 0.02, †P < 0.005, ‡P < 0.001, §P < 0.0001.

All subjects consented to take part in the study, which was approved by the Ethics Committee for Medical Research in Copenhagen and was carried out in accordance with the guidelines established in the Helsinki Declaration II. No complications or side effects were encountered during the study.

Catheterization

Catheterization was performed in the morning after an overnight fast for at least 1 h in the supine position, as described elsewhere (18). In brief, a Swan-Ganz catheter (7 Fr) was guided to the hepatic veins and right atrium through the femoral route under fluoroscopic control with the patient under local analgesia (15, 18, 32). A small indwelling polyethylene catheter (5 Fr) was introduced into the femoral artery by the Seldinger technique and was placed with the tip at the aortic bifurcation.

Measurements of pressures, cardiac output, and CCTs have been described elsewhere (15, 17, 18, 32). Cardiac output was determined by the indicator dilution technique after a bolus injection of 150 KBq of 125I-labeled human serum albumin (IFET 20S; Institute of Energy Technique, Kjeller, Norway) into the right atrium followed by arterial sampling. In addition, cardiac output was determined independently by a quantitative injection of 0.5 MBq of 99mTc-labeled human serum albumin (Vasculocis; CIS Biointernational, Griffe-sur-Yvette, France) from a catheter depositing directly into the right atrium followed by automatic arterial sampling for 60 s, as described recently (32). In this way the technetium indicator was injected straight away, immediately followed by the iodine indicator. Separate control experiments disclosed an interval (i.e., that between the mean time of the catheter outflow profiles of the two indicators) of 0.6 s. Arterial blood samples and standards were counted in a well-type scintillation detector (Compugamma 1210 Wallac; LKB, Helsinki, Finland). 99mTc was counted after sufficient decay to avoid overflow and dead-time problems in the scintillation counter. After an interval of at least 4 days, the samples were recounted in the 125I spectrum. At least 10,000 counts were recorded and were corrected for background activity and decay. Simultaneous collection of counts in the 99mTc spectrum showed no activity above the background here.

Arterial compliance was determined from pulse pressure and stroke volume as described elsewhere (17). Systemic vascular resistance was assessed as 80 × (mean arterial pressure – right atrial pressure)/cardiac output.

The CCT (mean indicator transit time), which represents the mean indicator sojourn in the central vascular bed (i.e., heart cavities, lung vasculature, and central arterial tree up to points that are temporarily equidistant to the aortic bifurcation), was determined from the indicator dilution curve as the time-weighted average of outflow at the aortic bifurcation (16, 22, 31) (see Determination of CCTs and Initial Short Circulation Transits). All transit times were corrected for catheter transit time by the formula: t_cath = catheter volume/catheter flow (9.68–11.88 s).

CBV was assessed in accordance with the kinetic theory as cardiac output multiplied by CCT (15, 25, 32).

Determination of CCTs and Initial Short Circulation Transits

Indicator dilution curves were determined at sample intervals of 1 s. At least 10,000 counts were obtained in each sample (coefficient of variation < 1%). A characteristic curve is shown in Fig. 1. Both equidistant and semilogarithmic presentations were available. After reaching a peak radioactive blood concentration, but before recirculation, several samples showed a linear fall in the semilogarithmic presentation. This constitutes the basis of exponential extrapolation of the part of the indicator dilution curve affected by recirculation (25). The area under the extrapolated part of the total curve constituted <12% of the total area curve. The area under the curve and the time-weighted area were determined by the combination of numerical analysis and exponential integration, as previously described (15, 32). All curves were inspected thoroughly for the presence of very early (i.e., before 4 s) and early (i.e., 4 s to maximum) transit times, reflecting fast anatomic shunts before the upstroke of the indicator dilution curve.

In addition, correction of recirculation was performed with a gamma variate fit that included curve points from two samples before peaking until recirculation (i.e., exclusion of the upstroke) (27, 28, 34) (see Appendix). The difference in area between the gamma variate fit and the upstroke of the indicator dilution curve was taken to represent possible early circulatory transits, and the flow through these was estimated as the relative area multiplied by the cardiac output. The radioactivity-time integral of the transits (area under the curve) and the mean transit time of this curve were determined and taken as the fast fraction of cardiac output and early mean CCT, respectively. Flow, flow fraction, and circulation time of early transits were related to the alveolar-arterial oxygen dioxide.

Fig. 1. Indicator dilution curve from patients with cirrhosis (○) after injection of 125I-labeled human serum albumin into the right atrium and arterial sampling at the aortic bifurcation. Exponential extrapolation for correction of recirculation (●) on the downward slope and the gamma variate fit (□) are illustrated. Early circulatory transits, obtained as the difference between measured values and gamma variate fit, are also shown (●). The x-axis represents sampling time (not corrected for catheter transit time), and the y-axis shows indicator concentration.
Measurement of Arterial Blood Samples

Arterial oxygen tension (PO$_2$), carbon dioxide tension (PCO$_2$), and pH were measured by an ABL-300 blood gas analyzer, and arterial oxygen saturation (SO$_2$) was measured by an OSM-2 hemoximeter (both from Radiometer, Copenhagen, Denmark). Coefficients of variation of PO$_2$, SO$_2$, and PCO$_2$ were determined from replicate arterial samples taken at an interval of $<15$ min: 0.7%, 2.1%, and 3.1%, respectively (33). The alveolar-arterial oxygen gradient (AaPO$_2$) was calculated from the alveolar gas equation

$$\text{AaPO}_2 = [\text{FiO}_2(\text{PB} - 6.3) - (\text{PCO}_2/R)] + \text{FiO}_2(1 - R)(\text{PACO}_2/R) - \text{PO}_2 \tag{1}$$

where FiO$_2$ is the inspiratory O$_2$ fraction, PB is the barometric pressure, and PACO$_2$ is the alveolar carbon dioxide tension, assumed to be equal to PCO$_2$. R is the respiratory exchange ratio, set at 0.80 as prescribed by the alveolar gas equation.

Statistical Evaluation

Comparisons between multiple data were performed by one-way ANOVA with Turkey’s test for multiple comparisons or by the Kruskal-Wallis test with Dunn’s correction for multiple comparisons. Bivariate paired or unpaired data were compared by Student’s paired or unpaired t-tests or by the Wilcoxon and Mann-Whitney tests, respectively. The nonparametric tests were applied in the cases of nonnormality. Correlations between independent variables were performed by the least squares method (Pearson). $P < 0.05$ was considered significant.

RESULTS

Physiological Variables in Patients with Cirrhosis and Controls

Hemodynamics. Cardiac output, stroke volume, heart rate, and arterial compliance were significantly higher in the patients with cirrhosis than in the controls (Table 2). Systemic vascular resistance, arterial blood pressure, CCT and CBV were either significantly reduced or equal to that of the controls.

Arterial blood gas analysis. A characteristic pattern with slightly decreased oxygen saturation and tension, and significantly reduced PCO$_2$ owing to hyperventilation, was seen in the cirrhotic patients (Table 3).

Table 2. Hemodynamics in patients with cirrhosis and controls

<table>
<thead>
<tr>
<th></th>
<th>Controls, $n = 19$</th>
<th>Cirrhotics, $n = 36$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output, l/min</td>
<td>5.36±0.46</td>
<td>7.85±0.46‡</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>71±2.4</td>
<td>79±2.5*</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>80±9</td>
<td>104±6.4†</td>
</tr>
<tr>
<td>Arterial blood pressure, mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>166±8</td>
<td>136±3.9†</td>
</tr>
<tr>
<td>Diastolic</td>
<td>75±2.8</td>
<td>64±1.9‡</td>
</tr>
<tr>
<td>Mean</td>
<td>105±4.4</td>
<td>86±2.5§</td>
</tr>
<tr>
<td>Right atrial pressure, mmHg</td>
<td>2.8±0.5</td>
<td>3.4±0.2</td>
</tr>
<tr>
<td>Systemic vascular resistance, dyn·s/cm$^5$</td>
<td>1803±215</td>
<td>955±723</td>
</tr>
<tr>
<td>Arterial compliance, ml/mmHg</td>
<td>0.94±0.11</td>
<td>1.46±0.11†</td>
</tr>
<tr>
<td>Central circulation time, s</td>
<td>17.2±1.0</td>
<td>12.7±0.6‡</td>
</tr>
<tr>
<td>Central and arterial blood volumes, ml/kg</td>
<td>21.8±2.2</td>
<td>21.2±0.7</td>
</tr>
<tr>
<td>Hepatic venous pressure gradient, mmHg</td>
<td>3.4±0.4</td>
<td>16.5±0.9</td>
</tr>
</tbody>
</table>

Values are means ± SE. Significant difference from controls: *$P < 0.05$, †$P < 0.005$, ‡$P < 0.001$

Table 3. Arterial blood gas analyses in patients with cirrhosis and controls

<table>
<thead>
<tr>
<th></th>
<th>Controls, $n = 19$</th>
<th>Cirrhotics, $n = 36$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial oxygen tension, kPa; 9.6–13.7</td>
<td>11.2±0.3</td>
<td>10.3±0.4</td>
</tr>
<tr>
<td>Arterial oxygen saturation, %; 92–99</td>
<td>95.9±0.3</td>
<td>94.9±0.5</td>
</tr>
<tr>
<td>Arterial carbon dioxide tension, kPa; 4.7–6.0</td>
<td>5.33±0.10</td>
<td>4.33±0.10*</td>
</tr>
<tr>
<td>Arterial pH 7.36–7.44</td>
<td>7.43±0.006</td>
<td>7.44±0.006</td>
</tr>
<tr>
<td>Alveolar-arterial oxygen gradient, kPa</td>
<td>1.23±0.38</td>
<td>3.57±0.31*</td>
</tr>
</tbody>
</table>

Values are means ± SE. Values following units are reference intervals. Significant difference from controls: *$P < 0.001$.

Analyses of Indicator Dilution Curves

An indicator dilution curve with exponential and gamma variate correction of recirculation is illustrated in Fig. 1. A close relation was found between the cardiac output determined by the two indicators ($r = 0.96$, $P < 0.001$) and cardiac output determined by the exponential extrapolation technique and the gamma variate fit technique ($r = 0.83$, $P < 0.001$). Likewise, CCTs determined by the two indicators and the two different techniques in each indicator were closely related (Fig. 2). CCT with $^{99m}$Tc label was 0.49 ± 0.16 s ($P < 0.001$) shorter than CCT with $^{125}$I label, owing to catheter deposit of the technetium-labeled tracer. A slight but statistically significant difference was found between the mean values (gamma variate CCT = 11.6 and exponential extrapolation CCT = 12.7 s, difference 1.06 ± 0.17 s; $P < 0.001$), owing to the presence of early transits. Correlations of CCT, cardiac output, and CBV determinations are summarized in Table 4.

Detection of Possible Very Early and Early Transit Times

A close inspection of the initial part of the indicator dilution curve showed that neither $^{125}$I-albumin nor $^{99m}$Tc albumin (which was shifted ~0.5 s) disclosed any very early peaks, which would indicate the existence of very early transits (see Fig. 1). When analytical error is taken into account, any very early transits would be $<0.4%$ of the cardiac output.

Early transits, as reflected by the difference between the measured indicator dilution upstroke and the gamma variate extrapolation, amounted to an average of 5.1 ± 0.89% in patients with cirrhosis and 0.8 ± 1.5% in controls ($P < 0.005$) (Fig. 3). These values correspond to 0.36 ± 0.065 l/min and 0.05 ± 0.08 l/min, respectively ($P < 0.01$) (Table 5). A Bland-Altman analysis indicates no relation to the level of cardiac output (not shown). There was no significant difference in the values obtained by $^{125}$I-albumin and $^{99m}$Tc-albumin. A significant relation was found between the fraction of early transits and early transit flow and the estimated alveolararterial gradient in patients with cirrhosis (Fig. 4) but not in controls.

“Composite” Determination of the CBV and Arterial Blood Volume

The CBV and arterial blood volume determined by the exponential and gamma variate techniques were directly correlated (Fig. 5A). However, a closer look at the individual patients revealed differences between 0.27 and 0.95 in 10 patients, which may be explained by early transits.
In the patients with cirrhosis, the mean time of the early transits was on average 7.7 ± 0.77 s. When CBV was determined as the sum of early transits (mean early transit time multiplied by its volume flow) and the CCT as obtained by the gamma variate function multiplied by cardiac output less early flow components, there was a good agreement to the CBV obtained in the conventional way (Fig. 5B and Table 6).

**DISCUSSION**

The present study shows that 1) extrapolation of indicator dilution curves for correction of recirculation by the exponential technique and the gamma variate fit technique give very similar results in patients with cirrhosis; 2) no very early transits (i.e., before 3–4 s) could be detected; 3) a significant contingent of early transits was identified in patients with cirrhosis, which may represent pulmonary vascular shunts or vascular areas with low ventilation-perfusion ratios, related to the size of the alveolar-arterial oxygen gradient; and 4) CBV determined from the sum of a shunt component and a nonshunt component show good agreement with the conventional determination of CBV.

It has been claimed on experimental and theoretical grounds that the gamma variate fit of indicator dilution curves would be better to determine cardiac output, owing to a better correction of recirculation (8, 14, 21, 40). However, any extrapolation procedure may underestimate the very long transits and may thereby lead to an erroneously low area under the late parts of the indicator dilution curve and thus to some reduction in the mean transit time compared with a “true” value (24). In keeping with this point of view, cardiac output, as determined by the Steward-Henriques-Hamilton technique, is often a few percent above that determined from oxygen uptake by the Fick principle (13). When the gamma variate fit technique is applied, the shortcomings of the indicator technique may be somewhat reduced (8, 14, 21). However, from the present results in patients with cirrhosis we found no substantial difference between the traditional exponential (or semilogarithmic) extrapolation and the more sophisticated gamma variate technique. One reason could be that patients with cirrhosis, even when they are resting in the supine position, are clearly hyperdynamic with short central and noncentral circulation times. Besides the cardiac output (which is simply reflected by dose relative to the area under the indicator dilution curve), the CCTs determined by the exponential technique and the gamma variate technique were also similar, and consequently almost identical CBV values were found. In addition, the present results confirm earlier observations in patients with cirrhosis of either normal or contracted CBV (15, 16, 32) and the presence of a low systemic vascular resistance and high arterial compliance (7, 9, 17).

Fitting of the gamma variate function to the indicator dilution curve can be performed with confidence, as described in

**Table 4. Correlations between variables obtained by ordinary correction for recirculation (exponential) and by the gamma variate method**

<table>
<thead>
<tr>
<th></th>
<th>Controls, n = 19</th>
<th>Cirrhotics, n = 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCT_{exp} vs. CCT_{v} (125I)</td>
<td>r = 0.89</td>
<td>r = 0.96</td>
</tr>
<tr>
<td>CCT_{exp} vs. CCT_{v} (99mTc)</td>
<td>r = 0.96</td>
<td>r = 0.90</td>
</tr>
<tr>
<td>CO_{exp} vs. CO_{v} (125I)</td>
<td>r = 0.93</td>
<td>r = 0.93</td>
</tr>
<tr>
<td>CO_{exp} vs. CO_{v} (99mTc)</td>
<td>r = 0.96</td>
<td>r = 0.69</td>
</tr>
<tr>
<td>CBV_{exp} vs. CBV_{v} (125I)</td>
<td>r = 0.93</td>
<td>r = 0.86</td>
</tr>
<tr>
<td>CBV_{exp} vs. CBV_{v} (99mTc)</td>
<td>r = 0.91</td>
<td>r = 0.70</td>
</tr>
</tbody>
</table>

CCT_{exp} and CCT_{v}, central circulation time (i.e., mean time of indicator sojourn in central circulation) determined by exponential and gamma variate correction, respectively, for recirculation with 2 different albumin-labeled isotopes (125I and 99mTc). CO, cardiac output. CBV, central and arterial blood volume. All r values are significantly different from 0.00 (P < 0.001).
However, no specific model is related to the concept of determination of flow and mean transit time from outlet registration (25). Other types of functions like the shifted random walk function or the lagged normal density function may also be fitted to the present data (23, 38). We tried out these functions on some of our patient data. The shifted random walk function and the gamma variate fit gave very similar results. (This could be expected, as the random walk function in some aspects is close to a gamma variate function). However, the lagged normal density function gave values of cardiac output and mean transit time that were 6–9% higher than that of the other two functions. The far greater experience with and ease in setting the starting conditions of the gamma variate function (see APPENDIX) are the main reasons for choosing this function in the present study.

We found no significant very early transits in our patients with cirrhosis. Very early transits are seen in patients with, for instance, intracardiac right/left shunts and persistent arterial duct and pulmonary malformations with anatomic shunts. Portopulmonary shunts have been described in some patients with cirrhosis (19). A portopulmonary shunt may reduce the arterial oxygen saturation somewhat but will not be detected by the present technique. Theoretically, a shunt could have a very short temporal dispersion and might thereby escape blood sampling at an interval of 1 s. However, in the present study we used two indicators that were shifted in time by about half a second. In this way, the temporal solution was increased, and from the present measurements any very early transit is insignificant, i.e., <0.4% of the cardiac output in patients with cirrhosis.

Estimated on the values of oxygen saturation in arterial blood and mixed venous and portal venous blood, right-to-left shunts of up to 20% of cardiac output may be present in patients with cirrhosis (33). According to the present study, a certain number of early transits may be present in patients with cirrhosis. The fraction was ~5%, corresponding to a flow rate of 0.36 l/min. These early transits did not show a significant relation to the level of cardiac output. The fact that they showed a direct relation to the alveolar-arterial oxygen gradient (Fig. 4) may suggest that they represent either anatomic shunts or areas with low ventilation-perfusion ratios.

Transit time analysis of vascular indications has been applied increasingly in the diagnosis and classification of cirrhosis. Thus Blomley and colleagues (1, 3, 4) have used a noninvasive technique with intravenous injection of ultrasound microbubble contrast agents and subsequent determination of appearance time in hepatic veins and the carotid artery. By this technique they found hepatic vein and carotid transit times consistently shorter with worsening cirrhosis, in agreement with the present findings and earlier reports on prognostic information of short transit times (29).

![Fig. 3. Indicator dilution curves from patients with cirrhosis. A: no evidence of early transits (gamma variate upstroke is identical to measured upstroke). B: small fraction of early transits (small area between gamma variate fit and measured upstroke). C: significant early transits (substantial area between gamma variate fit and measured upstroke).](image-url)
However, this noninvasive technique requires a change in the intensity of the baseline signal of 10% (4), rendering this method less suitable for detecting minor early circulatory transits. Moreover, at present the microbubble ultrasound technique is semiquantitative with focus on vascular appearance times. But with further development, quantitative data on transit curves can probably be obtained by a noninvasive method.

Studies have shown that the incidence of a hepatopulmonary syndrome may vary considerably among study populations with cirrhosis (6, 10, 36). The hepatopulmonary syndrome is defined as a condition with dilation of pulmonary vessels, the presence of pulmonary shunts, and arterial oxygen desaturation. Only a few patients in the present study population meet these criteria in a strict sense, in accordance with the clinical selection of our patients. But several patients with cirrhosis showed signs of early transits, which may be identified as originating from areas with low ventilation-perfusion ratios or even minor shunts. Thus there may be a gradual transition from minor pulmonary abnormalities to a full-blown hepatopulmo-

Fig. 5. A: relation between central blood volume (CBV) determined by the gamma variate fit (CBVγ) and CBV determined by exponential correction (CBVexp) (r = 0.70, P < 0.001). Note that in most patients there is a good agreement between the two methods. However, in 10 patients the gamma variate method gave substantially lower values. B: relation between CBVexp and the sum of the CBVγ and shunt volume (r = 0.86, P < 0.001).
It can be shown (25) that this expression can be written as

\[ y(t) = A y_{\text{max}}^{x} \exp \left( -\frac{t}{\beta} \right), \quad t > 0 \tag{A1} \]

It can be shown (25) that this expression can be written as

\[ y(t) = y_{\text{max}} \left( \frac{t - t_0}{t_{\text{max}} - t_0} \right)^{x} \exp \left[ \alpha \left( 1 - \frac{t - t_0}{t_{\text{max}} - t_0} \right) \right], \quad t > 0 \tag{A2} \]

or, if the function begins in \( t = t_0 \), \( 0 < t_0 < t_{\text{max}} \):

\[ y(t) = y_{\text{max}} \left( \frac{t - t_0}{t_{\text{max}} - t_0} \right)^{x} \exp \left[ \alpha \left( 1 - \frac{t - t_0}{t_{\text{max}} - t_0} \right) \right], \quad t > 0 \tag{A3} \]

with \( A = y_{\text{max}} t_{\text{max}}^{x} \exp(\alpha) \) and \( \beta = t_{\text{max}}/\alpha \). Here \( \beta \) and \( A \) are

\[
\text{error} = \frac{1}{y_{\text{max}}} \sqrt{\sum(y_{\text{d}} - y_{\gamma})^2} \tag{A4}
\]

where the subscripts \( d \) and \( \gamma \) refer to the measured data and the gamma variate function, respectively.

In the case of early transit times, the gamma variate upward slope lags behind the upward slope of the measured data, so we only used curve points from two samples before peaking until recirculation in the fitting process.

When the parameters are estimated, the difference between the data and the gamma variate function is calculated. The mean transit time of early transits is the center-of-mass of the first nonnegative part of the resulting curve.

**Determination of Mean Transit Time**

For determination of the mean transit time, which is defined as

\[
\bar{t} = \frac{\int_{0}^{t_{\text{max}}} \frac{t}{y(t)} \, dt}{\int_{0}^{t_{\text{max}}} y(t) \, dt}
\]

we integrate the gamma variate function and the first moment curve from \( 0 \) to \( t_{\text{max}} \) (for \( t_0 = 0 \))

\[
\int_{0}^{t_{\text{max}}} y(t) \, dt = y_{\text{max}} t_{\text{max}} \exp(\alpha) x^{-\alpha - 1} \Gamma(\alpha + 1) \tag{A6}
\]

\[
\int_{0}^{t_{\text{max}}} \frac{t}{y(t)} \, dt = y_{\text{max}} t_{\text{max}}^{2} \exp(\alpha) x^{-\alpha - 1} \Gamma(\alpha + 2) \tag{A7}
\]

where the gamma function is defined as

\[
\Gamma(x) = \int_{0}^{\infty} t^{x-1} \exp(x) \, dt \tag{A8}
\]

By dividing Eq. A7 by Eq. A6 and using the fact that \( \Gamma(x + 1) = x \Gamma(x) \), the transit time can be expressed as

\[
\bar{t} = t_{\text{max}} \left( 1 + \frac{1}{\alpha} \right) = t_{\text{max}} + \beta \tag{A9}
\]

or for \( t_0 > 0 \)

\[
\bar{t} = (t_{\text{max}} - t_0) \left( 1 + \frac{1}{\alpha} \right) + t_0 \tag{A10}
\]
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