with the important proviso that the calculated plasma concentration has been maintained for a sufficient period to permit equalibration with the effect site.

References


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The Lower Limit of Autoregulation: Time to Revise Our Thinking?

To the Editor:—I am concerned that the popular conception regarding the normal lower limit of cerebral blood flow autoregulation (LLA), frequently identified as 50 mmHg, may be substantially in error. Clinically, one encounters frequent reference to the LLA in discussions regarding minimal acceptable blood pressures for patient management.¹ It has been argued that this relevance has been overemphasized (see below).² Nonetheless, the LLA is a widely quoted physiologic limit to which the anesthesiology community, rightly or wrongly, has assigned considerable importance.

Depictions of autoregulation in many standard texts show an auto-regulatory plateau between mean arterial pressures of 50 and 150 mmHg. It is likely that the common choice of a mean arterial pressure (MAP) of 50 mmHg as the LLA was significantly influenced by a figure in a review article by Lassen.³ Lassen’s depiction of an LLA of 50

mmHg was in turn an estimate based on data from an investigation by McCall (see table 1) published in 1953.⁴ That investigation was performed in pregnant volunteers at or near term, in whom blood pressure was lowered with hydralazine and veratrum virede. The former is a cerebral vasodilator,⁵ and the effects of the latter on the cerebral circulation are undefined. Yet, despite of the meager database that identified 50 mmHg as the LLA for healthy humans, the definition has remained widely accepted without thorough confirmation. In part, this may be because the LLA for several animal species is also approximately 50 mmHg. Nonetheless, a review of the literature more recent than McCall’s 1953 publication does not confirm that an LLA of 50 mmHg actually prevails in humans. The majority of data derived in healthy, normotensive, nonanesthetized adults argues that the LLA is not less than an average value of 70 mmHg. In

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Table 1. Data Regarding the Lower Limit of Autoregulation in Nonanesthetized, Normotensive Adults

<table>
<thead>
<tr>
<th>Author</th>
<th>Hypotensive Technique</th>
<th>CBF Method</th>
<th>LLA Mean (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCall††</td>
<td>Hydralazine</td>
<td>K-S/N2O</td>
<td>&lt;64 (33–80)</td>
</tr>
<tr>
<td></td>
<td>Veratrum viride</td>
<td>K-S/N2O</td>
<td>&lt;57 (40–72)</td>
</tr>
<tr>
<td></td>
<td>Trimethaphan</td>
<td>K-S/N2O</td>
<td>&gt;57 (44–75)</td>
</tr>
<tr>
<td></td>
<td>Pendiomide</td>
<td>K-S/N2O</td>
<td>&gt;61 (54–72)</td>
</tr>
<tr>
<td>Stranggaard§</td>
<td>Trimethaphan/titl</td>
<td>1/A-VDO2</td>
<td>73 ± 9</td>
</tr>
<tr>
<td>Waldemar, et al.‖</td>
<td>Trimethaphan/lower body negative pressure ± captopril</td>
<td>1/A-VDO2</td>
<td>79 (57–101)</td>
</tr>
<tr>
<td>Larsen, et al.‖</td>
<td>Lower body negative pressure/labetalol</td>
<td>1/A-VDO2</td>
<td>79 (53–113)</td>
</tr>
<tr>
<td>Olsen, et al.‖</td>
<td>Labetalol/lower body negative pressure</td>
<td>CBFVmca 91 (41–108)</td>
<td></td>
</tr>
<tr>
<td>Olsen, et al.‖</td>
<td>Lower body negative pressure/labetalol</td>
<td>1/A-VDO2</td>
<td>88 (76–101)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A-NIRS diff</td>
<td>73 (73–101)</td>
</tr>
</tbody>
</table>

Data are presented as mean values with ranges (when available) or standard deviations.

* The subjects were 42 pregnant women near term, 24 of whom had toxemia of pregnancy.

K-S/N2O = Kety-Schmidt technique using nitrous oxide as the tracer, CBFVmca = mean CBF velocity in the middle cerebral artery; 1/A-VDO2 = the constancy of cerebral metabolic rate was assumed and that CBF was determined by the formula CBF = a constant × 1/arterial-jugular venous oxygen content difference; A-NIRS = the constancy of cerebral metabolic rate was assumed, and a decrease in CBF was inferred when the arterial to regional saturation difference (the latter determined by near infrared spectroscopy) increased; < = the LLA was not determined, but that CBF was unchanged from the control value at the MAP indicated; > = the LLA was not determined, but that CBF was less than the control value at the MAP indicated.

addition, one investigation concluded that the threshold for symptoms of cerebral ischemia in some normotensive nonanesthetized subjects was a MAP of 55 mmHg, i.e., above our accepted LLA threshold. Some of the available investigations, their methods, and the mean values for the lower limit of autoregulation are presented in table 1.

A review of the investigations in the table reveals other things about the LLA. The first is that the sharp inflection points of autoregulation curves are more a function of the statistical methods commonly used to calculate the LLA (linear regressions) than of normal physiology. These curves should probably be drawn with rounded "shoulders" rather than sharp "elbows." But, more important, these investigations demonstrate that there is enormous individual-to-individual variation in the LLA (see ranges noted in table 1)—so much so that a reviewer should wonder whether it can ever be appropriate to assume that any LLA value applies to a broad population of patients. If one insists on identifying an average value for a normotensive adult population to guide management, that average appears to be much higher than 50 mmHg.

If one rejects the concept of an average LLA as providing useful clinical guidance, what is the alternative? Using resting MAP as the basis for an estimate of a patient's LLA (if and when relevant) rather than assuming that the patient will conform to a population average may be more appropriate. There are data that support this approach. The investigations of Finnerty, et al. and Stranggaard indicate that the LLA for individual nonanesthetized patients occurs at a MAP of approximately 25% less than the resting value and that symptoms of cerebral hypoperfusion appear when BP reaches 40–50% of the resting value. The ideal, of course, is for contemporary investigators to test the validity of this approach before it can be advocated with conviction.

If the actual LLA in man is 70 mmHg or higher rather than 50 mmHg, what? At a minimum, for the various authors (including me) who present, in standard textbooks, figures depicting the LLA in healthy subjects, it will mean either redrawing their diagrams or specifying the precise pharmacologic circumstances to which they apply. For those clinicians who define minimal acceptable MAPs in their patients on the basis of the normal LLA, it also will have relevance. Not all would accept the validity of such an approach in the first place because there should still be a considerable CBF reserve at this level and because it has been amply demonstrated that many vasodilating agents, including anesthetic agents, lower the effective LLA. It may eventually be argued that the widely published autoregulation curves accurately depict not "normal" autoregulation but rather "anesthetized" autoregulation for patients receiving certain anesthetics or vasoactive agents. In general, it appears that agents with a direct cerebral vasodilating properties lower the effective LLA. However, there is certainly not sufficient dose-response information for the many anesthetic agents and combinations to permit the general conclusion that "anesthesia lowers the LLA." One might anticipate little effect on the LLA by ou commands total intravenous anesthesia regimens because the agents typically used lack cerebral vasodilating properties. The "bottom line" is that, if the LLA matters, it is unreasonable to assume that it is 50 mmHg for every normotensive adult in every anesthetic situation. The important clinical consequence is that in many patients, as MAP approaches 50 mmHg, we already may be well below the true LLA. Therefore, we may already be encroaching on the CBF reserve, and there may be a much smaller margin for error with respect to CNS ischemic injury than we have commonly believed.

The matter of the lower limit of autoregulation is more than a physiologic nicety. It is a concept that frequently influences clinical hemodynamic management. In that light, it may be appropriate for our community to adjust its thinking about the concept of the lower limit of cerebral autoregulation and, in particular, to escape the assumption that the lower limit of autoregulation is 50 mmHg in a majority of adults.

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