Small Artery Structure in Hypertension
Dual Processes of Remodeling and Growth

Anthony M. Heagerty, Christian Aalkjaer, Stuart J. Bund, Niels Korsgaard, and Michael J. Mulvany

Although the causes of high blood pressure vary, it is becoming clear that sustained hypertension is associated with changes in cardiovascular structure: left ventricular hypertrophy and increased wall thickness:lumen diameter (wall:lumen) ratio of the blood vessels. To some extent, these alterations are natural physiological responses and are protective. However, the risk of circulatory death is closely related to left ventricular hypertrophy, and therefore, it is suggested increasingly that effective antihypertensive treatment requires normalization not only of blood pressure but also of cardiac structure. This may be the case also for the vascular changes, in particular at the level of the “resistance arteries” (defined here as pre-capillary arteries with diameters less than 500 μm; see Reference 2), these vessels being responsible for the increased peripheral resistance of essential hypertensive patients. Until recently, this possibility remained speculative because there were few quantitative data concerning resistance artery structure. However, over the past 10 years such data have become available, in particular with regard to the more proximal resistance vessels, so-called “small arteries” (see Reference 2). The purpose of this Brief Review is to identify the type of structural change that is found in small arteries in hypertensive individuals. In particular, we will discuss whether the altered structure can be ascribed to growth alone or whether it is due to “remodeling,” that is, a rearrangement of otherwise normal material, which Baumbach and Heistad first noted in cerebral small arteries of spontaneously hypertensive rats (SHR) that are stroke-prone.

Essential Hypertension

Human studies of forearm blood flow have demonstrated that established essential hypertension is associated with an abnormally high peripheral vascular resistance. Indeed, this increased resistance to blood flow is distributed throughout all tissues, and Pickering observed that the so-called “minimum vascular resistance” (the resistance to blood flow after maximal vasodilation) remained increased in hypertensive patients. Furthermore, Doyle and Black showed that hypertension is associated with an increased “reactivity” of the forearm, i.e., infusion of agonists caused greater pressor responses in forearms of essential hypertensive patients. However, it was Folkow who showed quantitatively that the observed increases in vascular resistance and reactivity could be explained fully in terms of an alteration in vascular wall architecture without any need to postulate a change in excitation-contraction coupling in hypertension. He demonstrated that the observed increases in minimum vascular resistance and reactivity could be explained by alterations in vascular structure if there were encroachment of the tunica media into the lumen, thus decreasing the lumen diameter and increasing the media thickness:lumen diameter (media:lumen) ratio.

The information from any approach to the measurement of vascular structure is limited by the technique used, whether it be indirect as in plethysmography or more direct as in examination of vascular tissue in vitro by myography or histology. Nevertheless, the available data from these methods are in general agreement. Evidence from plethysmography has suggested that the lumen diameter of resistance arteries is moderately reduced (e.g., by 7–8%), whereas (with certain assumptions) the data predict an increased media:lumen ratio, and these findings have in general been confirmed by in vitro examination of small arteries (see Table 1) using the myograph technique. With this technique the vessels are examined when extended to a diameter equal to 90% of the diameter they are estimated to have when relaxed and subjected to a transmural pressure of 100 mm Hg. Histological examination of autopsy material also has indicated that, under standardized conditions, the media:lumen ratio of small arteries is increased in hypertension. On the other hand, studies that have looked for altered vascular sensitivity in essential hypertension have been negative for the most part. Earlier plethysmographic studies in essential hypertensive patients, and in vitro studies of large arteries showed little or no change in excitation-contraction coupling properties. Likewise, more recent in vitro studies on small arteries taken from essential hypertensive patients have shown unaltered or indeed decreased sensitivity to various agonists.

In animal models of essential hypertension, such as the SHR, similar changes in the structure of small arteries have been inferred or observed (Table 2), regardless of the technique used: decreased lumen and increased media:lumen ratio irrespective of the vascular bed examined. Here, however, there is some evi-
TABLE 1. Characteristics of Small Arteries From Hypertensive Individuals and Corresponding Control Subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Vessel</th>
<th>Internal diameter</th>
<th>Media thickness</th>
<th>External media diameter</th>
<th>Decrease in lumen (%)</th>
<th>Increase in m:l (%)</th>
<th>Remodeling index (%)</th>
<th>Growth index (%)</th>
<th>Cell hypertrophy (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>EH</td>
<td>15</td>
<td>subcutaneous</td>
<td>167±10</td>
<td>16.4±0.7</td>
<td>199.8</td>
<td>7</td>
<td>32</td>
<td>62</td>
<td>16</td>
<td>...</td>
<td>13</td>
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<tr>
<td>NT</td>
<td>15</td>
<td></td>
<td>180±11</td>
<td>13.4±0.4</td>
<td>206.8</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>EH</td>
<td>14</td>
<td></td>
<td>190±9</td>
<td>14.9±0.7</td>
<td>219.8</td>
<td>8</td>
<td>26</td>
<td>83</td>
<td>9</td>
<td>...</td>
<td>14</td>
</tr>
<tr>
<td>NT</td>
<td>14</td>
<td></td>
<td>200±10</td>
<td>12.8±0.8</td>
<td>231.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EH</td>
<td>16</td>
<td></td>
<td>186±10</td>
<td>15.4±0.8</td>
<td>216.8</td>
<td>17</td>
<td>27</td>
<td>110</td>
<td>10</td>
<td>-10</td>
<td>16</td>
</tr>
<tr>
<td>NT</td>
<td>16</td>
<td></td>
<td>223±10</td>
<td>14.5±0.8</td>
<td>252.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EH</td>
<td>8</td>
<td></td>
<td>304±26</td>
<td>24.8±2.2</td>
<td>353.6</td>
<td>24</td>
<td>62</td>
<td>102</td>
<td>-4</td>
<td>...</td>
<td>16</td>
</tr>
<tr>
<td>NT</td>
<td>8</td>
<td></td>
<td>401±39</td>
<td>20.2±1.4</td>
<td>441.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values for internal diameter and media thickness show reported mean±SEM. External media diameter equals internal diameter plus twice media thickness. Remodeling and growth indexes calculated as defined in "Addendum." Cell hypertrophy indicates the difference in volumes of the smooth muscle cells in the arteries in the hypertensive individuals and the normotensive individuals as a fraction of the corresponding volume in the arteries from the normotensive individuals. m:l, Media thickness:internal diameter; EH, subjects with essential hypertension; NT, normotensive control subjects.

Hypertension, Hyperplasia, and Remodeling

The increased media:lumen ratio of small arteries has often been interpreted as synonymous with growth. This is not necessarily the case. Increased media:lumen ratio (Figure 1) can be due to addition of material onto either the abluminal or luminal side of the vessel. Clearly, both of these situations will involve growth. However, an increased media:lumen ratio can also be brought about by rearranging the existing material.
around a smaller lumen, without the need to invoke a growth response or change in media cross-sectional area. This process has been defined as remodeling. In accord with accepted usage, it should be noted that the word "remodeling" does not involve growth, but rather a refashioning and thus realignment of pre-existing tissue elements in the vascular wall. Unfortunately, in current literature, the term is frequently used to describe any type of alteration in structure. We would strongly urge that the meaning of this word not be used indiscriminately. As originally suggested by Baumbach and Heistad, it should define a development distinct from, but which can take place in conjunction with, the growth process. Furthermore, this usage is consistent with the terminology used by molecular biologists. Thus, in practice, both remodeling and growth may be involved in the hypertensive process.

To quantify the remodeling process, Baumbach and Heistad have defined a "remodeling index," which is defined as the proportion of the change in lumen that can be ascribed to remodeling. Baumbach and Heistad observed that remodeling leading to an increased media:lumen ratio necessarily must involve a reduction in the external diameter, and therefore it is possible to calculate the change in lumen diameter that would have occurred if there had been no change in media cross-sectional area. Then the remodeling index is the ratio of this calculated change in lumen diameter (normotensive lumen diameter minus calculated remodeled lumen diameter) to the observed difference in lumen diameter (normotensive lumen diameter minus hypertensive lumen diameter) and in this review is expressed as a percentage (see "Addendum"). If the remodeling index is less than 100%, this indicates that the media cross-sectional area is greater, implying growth that is here expressed as a growth index equal to the percentage by which the hypertensive vessel has a greater cross-sectional area than the normotensive vessel (see "Addendum"). Situations in which media:lumen ratios decrease (for example, as a result of antihypertensive treatment) may also be the result of remodeling, atrophy, or both. This "reverse remodeling" can also be described by the remodeling index, where, in this case, a remodeling index less than 100% would imply atrophy.

In using this terminology, it is important to recognize its limitations. First, the terms "remodeling" and "growth" are misnomers if used to describe the difference between vessels from normotensive and hypertensive individuals. Remodeling and growth are processes that may have occurred in both normotensive individuals and individuals who have become hypertensive where, starting with similar dimensions when the individuals were young, the vessels have developed differently. Second, a comparison of the media cross-sectional area of hypertensive and normotensive vessels points only to the end result. A normal cross-sectional area, for example, could be the result of growth in one part of the vessel and atrophy in another. Third, the remodeling index should not be regarded as a precise measure of the remodeling process. As implied above, a remodeling index of 100% could in fact be due to concurrent growth and atrophy; a remodeling index of 0% could be the result of growth on the abluminal side of the vessel and subsequent remodeling to bring the outer diameter back to the original size. Fourth, an increase in the media:lumen ratio without growth could also be consequent to a decrease in the elastic modulus of the wall material. However, in the few studies where the elastic modulus of small arteries from hypertensive individuals has been studied, the indication is that the elastic modulus is decreased, not increased, at least in the rat models investigated. Fifth, it must be emphasized that the index is the fraction of the change in lumen that can be accounted for by remodeling and not an absolute value: high indexes may be obtained with minimal changes in lumen.

Table 1 shows the remodeling and growth indexes that may be calculated from data reported from in vitro investigations of subcutaneous small arteries taken from the gluteal region of essential hypertensive patients compared with age- and sex-matched control subjects. In all four investigations, increased media:lumen ratios were reported. In some cases there was a tendency to a small amount of growth, but in all cases the external diameter was less in the vessels from the hypertensive individuals, indicating remodeling indexes of between 62% and 102%. Similar findings have been reported concerning mesenteric small arteries from transgenic hypertensive rats (Table 2). By contrast, in SHR, most studies of small arteries demonstrate significant amounts of growth compared with WKY animals, although remodeling also plays an important role (Table 2).

The cellular basis of these morphological changes has been investigated. In essential hypertension, early evidence using the disector method suggests that myocyte size is normal in subcutaneous small arteries (Table 1), and this is also the case in one study of the mesenteric small arteries of transgenic hypertensive rats (Table 2). As regards small arteries from SHR, there have been several studies using different techniques, and there is a welcome degree of agreement. Although the abnormal
structure in large arteries of SHR is due largely to cellular hypertrophy, in small arteries the evidence all points to cell size being normal. This is the case, whether determined indirectly by measurements of cellular cross-sectional area or by percentage of cells containing nuclei, or determined more directly by measurements of cellular DNA content or by using the disector (Table 2). Therefore, the available evidence suggests the remodeling that is seen in small arteries in essential hypertension, in the transgenic hypertensive rats, and in SHR is due to a rearrangement of normalized cells. In the SHR, where growth also appears to be involved in the altered structure of small arteries, the lack of cellular hypertrophy indicates that the observed growth is in part due to an increase in the number of vascular smooth muscle cells, i.e., hyperplasia.

Caveats

There are important caveats concerning the conclusion that remodeling plays an important role in the altered structure of small arteries in essential hypertension. First, there is the question of sampling. Commonly, vessels from hypertensive and normotensive individuals are compared on the basis of specific branches or anatomic locations within the body. However, if the vascular architecture of hypertensive and normotensive individuals differs, then a systematic sampling error may be introduced, even though the operator concerned is unaware of whether hypertensive or normotensive samples are being examined. Therefore, the interpretation of observed differences between specific vessels from hypertensive and normotensive individuals is fraught with danger. In this respect, the method used by Short in 1966 remains the most clear-cut. In his small study, Short perfusion-fixed postmortem the mesentery from six patients who had been hypertensive and from six subjects who had been normotensive. To circumvent the sampling problem, Short made a histological analysis of all the arteries he could find within each preparation. He then ranked them according to the measured lumen diameter and ascribed each to the appropriate decile. Within almost every decile the wall:lumen ratio of the arteries from the hypertensive patients was increased, but in none of the deciles was the wall cross-sectional area increased. These data strongly support an important role for remodeling. Second, the recent data were obtained only in the one vascular bed that is at present readily accessible, and it is not clear if this is representative. Third, there is substantial variance in the data of each individual investigation, and there is still statistical room for 15-20% of the altered structure of the subcutaneous small arteries being due to growth. Fourth, the data have been obtained by an in vitro technique, and the extent to which they reflect the in vivo situation remains to be determined. Nevertheless, despite these caveats, the available evidence points toward remodeling as the major factor in accounting for the altered structure of small arteries, with a far less prominent but recognizable contribution also occurring from some form of growth process.

Cause or Effect?

Both in essential hypertension and in SHR, most of the available evidence points strongly to the changes in vascular structure occurring pari passu with the increase in blood pressure, although some workers have reported that there is altered vascular structure in the SHR in a "prehypertensive" phase. To examine the question of whether the altered vascular structure is a cause or a consequence of the increased blood pressure, Bund et al examined third-order branch femoral small arteries at 5, 12, and 24 weeks of age in SHR and WKY rats. In these studies, a loose ligature was placed around one iliac artery of SHR and WKY rats at the age of 5 weeks, and the development of vascular morphology was studied until the rats were 6 months of age. The ligature was such that, distal to it, the intravascular pressure was maintained at normotensive levels. It was found that in the femoral small arteries of SHR with the ligature, the media:lumen ratio and cell volume appeared to be the same as in WKY unprotected vessels. Comparison of the protected and unprotected arteries (Table 3) indicates that there was both remodeling and growth. Indirect histological evidence was also obtained indicating the growth was due to hyperplasia, not hypertrophy. The result is consistent with the premise that hyperplastic growth and remodeling of small arteries seen in SHR is an adaptive response to the increased blood pressure, a conclusion that is in contrast to cell culture data. Cultures of vascular smooth muscle cells from the superior part of the thoracic aorta from SHR tissues have an intrinsic ability to replicate more rapidly than those from WKY tissues. However, recent breeding studies using F1 generation SHR/WKY rats have failed to demonstrate cosegregation of this trait with blood pressure. Another approach is to study small arteries from animals with experimental hypertension (Table 4). The advantage is the independence of the response from genetic factors, but the disadvantage is that most experimental procedures induce profound neurohormonal effects on the body. For example, in rats coarctation of the abdominal aorta between the renal arteries increases the hemodynamic load on the proximal circula-
tion but also causes ischemia in the distal kidney with the attendant rise in circulating levels of angiotensin II. As one might anticipate, this procedure leads to hypertension within 30 minutes and is sustained for more than 4 weeks. Although there is evidence for remodeling, there is also a large increase in medial cross-sectional area of mesenteric small arteries, implying a growth response. In rats made hypertensive by the Goldblatt procedure, mesenteric small arteries showed a growth response (due to cellular hypertrophy) as well as a substantial remodeling index. A third example is the result of infusion of subpressor doses of angiotensin II to produce an increase in blood pressure over 10 days. The resulting increase in media:lumen ratio was due almost entirely to growth (also due to cellular hypertrophy) and not remodeling. Taken together, we suggest that even though both essential (genetic) hypertension and experimental hypertension are associated with an increase in media:lumen ratio, the basis of the altered vascular structure differs. In essential hypertension and in genetic models of hypertension, where remodeling appears to play an important role, the size of the vascular smooth muscle cells is normal, and any growth is due to hyperplasia. In the rat models of experimental hypertension that have been studied, although remodeling also occurs, much of the altered structure is due to vascular growth associated with hypertrophy of the vascular smooth muscle cells. The data of Bund et al suggest that the response of small arteries of SHR is adaptive. Therefore, it seems that the type of response depends either on when and how gradually the stimulus is applied or on the presence of genetic differences. In either case, the final result is a remodeling/hyperplastic response to increased intravascular pressure rather than cellular hypertrophy.

### Treatment of Essential Hypertension

Evidence from a number of sources has indicated that despite years of treatment, it is difficult to achieve normalization of vascular structure of essential hypertensive patients and plethysmographic studies have indicated that up to 6 years of antihypertensive treatment may be necessary to achieve normal vascular structure; in vitro studies with myography on subcutaneous small arteries have indicated that abnormal structure persists even after 1 year of effective antihypertensive therapy. In vitro data from SHR also support this finding. To understand the basis for this difficulty it may be useful, as discussed above, to recognize that it may be remodeling rather than growth that is primarily responsible for the abnormal small artery structure. Available data in both humans and SHR indicate that antihypertensive treatment results in reverse remodeling, i.e., decrease in media:lumen ratio without change in media cross-sectional area (Table 5), but it seems that the extent of this process may be insufficient.

### Table 4. Characteristics of Mesenteric Small Arteries From Rat Models of Experimental Hypertension

<table>
<thead>
<tr>
<th>Model</th>
<th>No.</th>
<th>Internal diameter</th>
<th>Media thickness</th>
<th>Increase in m:l (%)</th>
<th>Remodeling index (%)</th>
<th>Growth index (%)</th>
<th>Cell hypertrophy (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coarctation</td>
<td>10</td>
<td>223±10</td>
<td>12.7±1.0</td>
<td>8</td>
<td>75</td>
<td>56</td>
<td>51</td>
<td>NS</td>
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<tr>
<td>Sham</td>
<td>10</td>
<td>243±9</td>
<td>7.9±0.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1K,1C</td>
<td>14</td>
<td>189±7</td>
<td>19.8±0.9</td>
<td>16</td>
<td>89</td>
<td>68</td>
<td>39</td>
<td>23</td>
</tr>
<tr>
<td>Sham</td>
<td>14</td>
<td>226±7</td>
<td>12.5±0.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1K,1C</td>
<td>10</td>
<td>205±4</td>
<td>15.7±0.7</td>
<td>20</td>
<td>82</td>
<td>89</td>
<td>20</td>
<td>...</td>
</tr>
<tr>
<td>Sham</td>
<td>12</td>
<td>257±8</td>
<td>10.8±0.3</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2K,1C</td>
<td>12</td>
<td>216±4</td>
<td>14.5±0.6</td>
<td>13</td>
<td>51</td>
<td>87</td>
<td>16</td>
<td>...</td>
</tr>
<tr>
<td>Sham</td>
<td>13</td>
<td>249±5</td>
<td>11.1±0.4</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ang II infusion</td>
<td>12</td>
<td>256±3</td>
<td>13.2±0.5</td>
<td>2</td>
<td>30</td>
<td>7</td>
<td>25</td>
<td>30*</td>
</tr>
<tr>
<td>Saline</td>
<td>13</td>
<td>262±11</td>
<td>10.4±0.6</td>
<td></td>
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<tr>
<td>DOCA-salt</td>
<td>10</td>
<td>238±5</td>
<td>13.8±0.3</td>
<td>10</td>
<td>54</td>
<td>78</td>
<td>26</td>
<td>...</td>
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<tr>
<td>Uni-Nx</td>
<td>10</td>
<td>265±3</td>
<td>10.0±0.2</td>
<td></td>
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</table>

Values for internal diameter and media thickness show reported mean±SEM. External media diameter equals internal diameter plus twice media thickness. Remodeling and growth indices calculated as defined in Addendum. Cell hypertrophy indicates the volume of the smooth muscle cells in the arteries in the hypertensive individuals as a fraction of the corresponding volume in the arteries from the normotensive individuals. m:l, Media thickness:internal diameter; coarctation, rats with aortic coarctation; NS, indirect method indicated no significant cell hypertrophy, sham, sham-operated rats; 1K,1C, one-kidney, one clip Goldblatt renal hypertensive rats; 2K,1C, two-kidney, one clip Goldblatt renal hypertensive rats; Ang II infusion, rats made hypertensive by infusion of a nonpressor dose of angiotensin II for 10 days; DOCA-salt, uninephrectomized plus DOCA salt; Uni-Nx, uninephrectomized only.

*N. Korsgaard, unpublished data.
remodeling index can be calculated as follows.

Consider a "normotensive" vessel, with internal and external media diameters \((D_i)_{\text{norm}}\) and \((D_e)_{\text{norm}}\), respectively, and a "hypertensive" vessel with internal and external media diameters \((D_i)_{\text{hyp}}\) and \((D_e)_{\text{hyp}}\), respectively. The corresponding media cross-sectional areas are

\[
CSA_{\text{norm}} = \pi/4 \times ((D_i)_{\text{norm}})^2 - (D_i)_{\text{norm}}^2
\]

and

\[
CSA_{\text{hyp}} = \pi/4 \times ((D_i)_{\text{hyp}})^2 - (D_i)_{\text{hyp}}^2
\]

respectively. Remodeling of the normotensive vessel in which the cross-sectional area is kept equal to \(CSA_{\text{norm}}\) but its external diameter became \((D_e)_{\text{ remodeling}}\) would then give an internal diameter

\[
(D_i)_{\text{ remodeling}} = \sqrt{((D_e)_{\text{ hyp}})^2 - 4 \cdot CSA_{\text{ hyp}}/\pi}
\]

Thus, remodeling index equals

\[
100 \times ( (D_i)_{\text{ remodeling}} )/((D_i)_{\text{ hyp}} - (D_i)_{\text{ norm}})
\]

If the remodeling index is not equal to 100, then there will have been growth, which is here defined as

\[
\text{growth index} = (CSA_{\text{ hyp}} - CSA_{\text{ norm}})/CSA_{\text{ norm}}
\]

Equation 4 can also be used to quantify reverse remodeling, i.e., an increase in lumen without change in media cross-sectional area. Here a remodeling index less than 100% will be associated with a negative growth index, implying atrophy.

**Conclusion**

The available evidence suggests that the decreased lumen and increased media:lumen ratio of small arteries that is seen in essential hypertension may in large part be due to remodeling (a rearrangement of normalized cells) rather than growth. Similar results have been obtained with transgenic hypertensive rats. In SHR, although remodeling is present, growth (due to hyperplasia) appears to play a larger role. In experimental hypertension, the growth response (associated with cellular hypertrophy) is exaggerated, possibly because the induction of high pressure is more rapid. Antihypertensive treatment causes reverse remodeling, but this does not appear to be sufficient to bring about full normalization of small artery structure.

**Addendum**

The remodeling index, following the concept of Baumbach and Heistad, is here defined as the percentage of the observed difference in the internal diameter of hypertensive and normotensive vessels that could be accounted for by remodeling of the normotensive vessel. The remodeling index can be calculated as follows.

\[
\text{Remodeling index} = \frac{\text{CSA}_{\text{hyp}} - \text{CSA}_{\text{norm}}}{\text{CSA}_{\text{norm}} \times 100}
\]

**References**

37. Webster’s New World Dictionary. Cleveland, Webster’s New World, 1988, pp 871

Key Words • hypertrophy • hyperplasia • antihypertensive therapy • vascular resistance
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