Effects of Norepinephrine on the Coronary Circulation in Man

By Peter M. Yurchak, M.D., Ellis L. Rolett, M.D., Lawrence S. Cohen, M.D., and Richard Gorlin, M.D.

The sympathomimetic amine l-norepinephrine is extensively used in the treatment of hypotensive states, and is considered by many to be the pressor agent of choice.\(^1\)\(^-\)\(^3\) Shock associated with myocardial infarction is one of the more important of these hypotensive states.\(^1\)\(^-\)\(^8\) Therefore, it seemed relevant to examine the effects of infusion of this agent upon the coronary circulation in the human subject.

Materials and Methods

Twenty-one patients were studied in conjunction with diagnostic cardiac catheterization. Their ages ranged from 15 to 61 years, with a mean of 39 years. There were 13 women and eight men. The cardiac rhythm was sinus in 12 and atrial fibrillation in nine. The group was subclassified as follows: (1) "Normal" left ventricle (13 subjects); these subjects had no evidence of left ventricular hypertrophy by electrocardiogram\(^9\) or by x-ray. The left ventricular end-diastolic pressure was less than 12 mm. Hg. Five of this group had mitral stenosis. (2) Left ventricular failure (eight subjects); the left ventricular end-diastolic pressure was 12 mm. Hg or greater at rest.

Patients were studied after a light breakfast. Premedication consisting of a mixture of 37.5 mg. of meperidine hydrochloride and 3.75 mg. of prochlorperazine was given intramuscularly to 15 of 21 patients. Polyethylene cannulae were placed in a brachial artery and vein by the Seldinger technic. A no.-7 Goode-Lubin catheter was introduced deep into the coronary sinus where sampled blood reflected events in the left ventricular myocardium.\(^9\) In the 16 patients in whom diagnostic transeptal left heart catheterization had been performed previously, the catheter was left in the left ventricle. This was well tolerated for long periods of time, and arrhythmias were uncommon. Pressures were measured with Statham P23-D strain gages and recorded on a Sanborn 150 direct-writer. Cardiac output was measured by the indicator-dilution technic with indocyanine green, with injection into the left ventricle (pulmonary artery in five patients), and sampling from the brachial artery.\(^1\) Coronary flow was measured by intravenous or left ventricular infusion of \(\text{I}^{131}\) iodoantipyrine\(^1\) or left ventricular injection of krypton-85 in saline,\(^1\) with simultaneous sampling from brachial artery and coronary sinus. Blood samples for lactate and pyruvate were taken during coronary flow studies with appropriate precautions, and determined enzymatically in duplicate.\(^1\)\(^4\) Systolic ejection period and systolic and diastolic mean pressures were measured from phasic brachial arterial pressure pulses. Myocardial oxygen consumption per 100 Gm. left ventricle was calculated as the product of coronary flow and myocardial arteriovenous oxygen difference (ml./L.). Coronary vascular resistance was calculated as described elsewhere.\(^1\)\(^5\) Myocardial and total body excess lactate were calculated as described previously.\(^1\)\(^4\)

Observations were made at rest and during steady intravenous infusion of l-norepinephrine * in a dose ranging from 2 to 17 mg. of base per minute (average 7.5 mg./min.) at a time when pulse and blood pressures (including left ventricular end-diastolic) had been stable for at least 3 minutes. The dose varied widely from subject to subject, but enough was given to raise arterial peak systolic pressure by approximately 40 mm. Hg above control level. Sequential measurements were made with graded doses of norepinephrine in six subjects. In these, the set of data corresponding most closely to a peak rise in systolic pressure of 40 mm. Hg was chosen for purposes of calculating group averages.

Results

The data on results are shown in table 1. Norepinephrine raised average peak arterial

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* Available as Levophed, Winthrop Labs, 1450 Broadway, New York, N. Y.

From the Medical Clinics, Peter Bent Brigham Hospital and Harvard Medical School, Boston, Massachusetts.

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systolic pressure by 38 mm. Hg and average diastolic pressure by 11 mm. Hg. There was a slight but insignificant slowing of heart rate. This was true regardless of the basic cardiac rhythm. Cardiac output was unchanged. Coronary flow rose an average of 16 per cent pari passu with rise in perfusing pressure (arterial diastolic mean pressure). Coronary vascular resistance was calculated to have remained essentially unchanged. Average myocardial oxygen consumption increased 30 per cent, being met by both increased coronary flow and increased oxygen extraction. Myocardial arteriovenous oxygen difference widened from both a slight rise in arterial oxygen content and a major decrease in venous oxygen content (fig. 1). There was no consistent appearance of "excess lactate" in coronary venous blood, but three of the five subjects who did produce "excess lactate" were among those with the most severe heart disease. A fourth, with proven coronary heart disease, exhibited "excess lactate" during both control and norepinephrine states.

Data from the six subjects receiving graded doses of norepinephrine are shown in table 2 and figure 2. Rise in flow was usually less than, or equal to, rise in perfusion pressure. In only one subject (L.B.) did flow increase more than pressure. In general, except for patient L.B., vascular resistance was unchanged or increased, despite progressively increasing myocardial oxygen and blood flow requirements. Coronary venous oxygen content fell progressively with increasing doses of catechol in five of six subjects. These differences were beyond the rather narrow range of random variation described previously from this laboratory 10. 15 in normal subjects undergoing various forms of stress, e.g., exercise, tachycardia, hypertension. Patients D.B. and A.H. actually showed a fall in coronary venous oxygen content before arterial pressure rose appreciably.

In most respects, the two subgroups behaved like the group as a whole (table 1). Myocardial oxygen consumption and coro-

Figure 2
Effects of graded infusion of norepinephrine. Note the increase in both blood pressure and myocardial oxygen consumption and the unchanged coronary flow. Coronary resistance increased while myocardial arteriovenous oxygen difference increased. Excess lactate remained negative, suggesting no anaerobic metabolism.

Figure 1
Effect of norepinephrine on the coronary venous oxygen content. This figure shows that the majority response was reduction in coronary venous oxygen content during norepinephrine infusion.
Table 1

Effects of Norepinephrine on Coronary Circulation (Average Results)

<table>
<thead>
<tr>
<th></th>
<th>Entire group (21 subjects)</th>
<th>Heart rate (beat/min.)</th>
<th>Effective cardiac index (L./min./M.²)</th>
<th>Systemic arterial pressure (mm. Hg)</th>
<th>Coronary flow (ml./min./100 Gm. LV)</th>
<th>Systemic arterial mean diastolic pressure (mm. Hg)</th>
<th>Diastolic filling period (sec./min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>82</td>
<td>2.5</td>
<td>118/64</td>
<td>92</td>
<td>78</td>
<td>39.0</td>
<td>38.2</td>
</tr>
<tr>
<td>± SD</td>
<td>19</td>
<td>0.8</td>
<td>15/10</td>
<td>32</td>
<td>10</td>
<td>3.6</td>
<td></td>
</tr>
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<td><strong>Norepinephrine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>79</td>
<td>2.6</td>
<td>156/75</td>
<td>106</td>
<td>93</td>
<td>39.6</td>
<td>3.9</td>
</tr>
<tr>
<td>± SD</td>
<td>24</td>
<td>0.7</td>
<td>75/12</td>
<td>32</td>
<td>11</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>NS*</td>
<td>NS</td>
<td>&lt;.001</td>
<td>.025&lt;p&lt;.05</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
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</table>

“Normal left ventricle” group (13 subjects)

<table>
<thead>
<tr>
<th></th>
<th>Left ventricular failure group (8 subjects)</th>
<th>Heart rate (beat/min.)</th>
<th>Effective cardiac index (L./min./M.²)</th>
<th>Systemic arterial pressure (mm. Hg)</th>
<th>Coronary flow (ml./min./100 Gm. LV)</th>
<th>Systemic arterial mean diastolic pressure (mm. Hg)</th>
<th>Diastolic filling period (sec./min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>81</td>
<td>2.7</td>
<td>114/64</td>
<td>82</td>
<td>77</td>
<td>39.0</td>
<td>2.7</td>
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<tr>
<td>± SD</td>
<td>16</td>
<td>0.9</td>
<td>11/7</td>
<td>21</td>
<td>7</td>
<td>2.7</td>
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<tr>
<td><strong>Norepinephrine</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>76</td>
<td>2.7</td>
<td>149/73</td>
<td>99</td>
<td>92</td>
<td>40.1</td>
<td>3.9</td>
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<tr>
<td>± SD</td>
<td>20</td>
<td>0.8</td>
<td>21/8</td>
<td>24</td>
<td>11</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>NS*</td>
<td>NS</td>
<td>&lt;.001</td>
<td>.01&lt;p&lt;.025</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* NS, not significant.
† A-V O₂/A O₂, oxygen extraction fraction.

Cardiovascular flow, however, rose to a greater percent in the “normal” left ventricle group, and less in the “failure” group than in the group as a whole.

**Discussion**

There is general agreement that norepinephrine given systemically or into the coronary arteries increases coronary flow. Opinion differs sharply, however, as to whether this represents a primary dilator effect or an occurrence secondary to increased cardiac activity (and oxygen need) engendered by the agent. The latter view was first suggested by Folkow et al.16 and was supported by subsequent studies of others.17-23 In general, a biphasic response was observed, the initial brief fall in flow (interpreted as primary constriction) being followed by prolonged rise (secondary dilatation to supply increased amounts of oxygen required by the
NOREPINEPHRINE AND CORONARY CIRCULATION

Coronary vascular resistance (dyne sec. cm.\(^{-2}\) \(\times 10^3\)) | Myocardial oxygen consumption (ml./100 Gm. LV/min.) | Coronary arteriovenous oxygen difference (vol. %) | Coronary venous oxygen content (vol. %) | Myocardial "excess lactate" (mM./L.)
---|---|---|---|---
58 | 11.0 | 11.9 | 0.74 | 4.3 | +0.05
28 | 3.8 | 1.3 | 0.02 | 1.4 | 0.10
61 | 13.4 | 12.6 | 0.77 | 3.8 | +0.10
25 | 3.9 | 1.2 | 0.07 | 1.4 | 0.13
NS | .005<p<.01 | .01<p<.025 | .005<p<.01 | .001<p<.005 | NS
65 | 9.7 | 11.8 | 0.71 | 4.7 | +0.05
30 | 2.4 | 1.5 | 0.09 | 1.5 | 0.12
64 | 12.2 | 12.4 | 0.75 | 4.2 | +0.08
27 | 3.0 | 1.1 | 0.07 | 1.5 | 0.15
NS | .005<p<.01 | NS | .01<p<.025 | .025<p<.05 | NS
47 | 13.1 | 12.1 | 0.78 | 3.6 | +0.05
20 | 5.0 | 1.1 | 0.04 | 1.1 | 0.06
57 | 15.2 | 13.1 | 0.81 | 3.2 | +0.12
22 | 4.6 | 1.3 | 1.3 | 0.9 | 0.09
NS | NS | .025<p<.05 | .025<p<.05 | NS | NS

catechol-stimulated heart). Large doses of the agent elicited only a rise in flow. Studies in preparations in which no external work was done by the heart have shown solely the constrictor effect.\(^{21, 23}\) When cardiac oxygen consumption is increased by norepinephrine, however, the moot point is whether coronary flow rises pari passu with, in excess of, or less than that energy need.

The supply of adequate amounts of oxygen to the myocardium is usually accomplished by changes in coronary flow in normal subjects. Oxygen extraction, near-maximal at rest, changes little with increased oxygen demand. The unchanged venous saturation and pO\(_2\) probably reflect a constancy of myocardial pO\(_2\) which, for reasons currently not understood, may autoregulate coronary flow. Rise in extraction signifies oxygen demand outstripping oxygen supplied by change in flow. For proper assessment of the effects of any agent on the coronary circulation, one must measure changes in both oxygen consumption and extraction across the heart.\(^{24}\)

*Circulation, Volume XXX, August 1964*
Table 2

Effect of Graded Doses of Norepinephrine

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose of norepinephrine (µg. base/min.)</th>
<th>Systemic arterial pressure (mm. Hg)</th>
<th>Myocardial oxygen consumption (ml./100 Gm. LV/min.)</th>
<th>Coronary flow (ml./100 Gm. LV/min.)</th>
<th>Coronary venous O₂ content (vol. %)</th>
<th>Coronary A-V O₂/A O₂</th>
<th>Coronary vascular resistance (dyne sec. cm.⁻²) X 10⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>D.B.</td>
<td>—</td>
<td>106/55</td>
<td>6.8</td>
<td>55</td>
<td>4.5</td>
<td>0.74</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>119/52</td>
<td>6.9</td>
<td>54</td>
<td>4.0</td>
<td>0.76</td>
<td>91</td>
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<td></td>
<td>4</td>
<td>144/64</td>
<td>9.7</td>
<td>70</td>
<td>3.1</td>
<td>0.81</td>
<td>96</td>
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<td>8</td>
<td>177/76</td>
<td>11.9</td>
<td>82</td>
<td>3.0</td>
<td>0.83</td>
<td>85</td>
</tr>
<tr>
<td>A.H.</td>
<td>—</td>
<td>100/52</td>
<td>10.4</td>
<td>111</td>
<td>6.3</td>
<td>0.60</td>
<td>36</td>
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<td></td>
<td>2</td>
<td>107/53</td>
<td>13.1</td>
<td>135</td>
<td>5.5</td>
<td>0.64</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>127/57</td>
<td>14.2</td>
<td>135</td>
<td>4.6</td>
<td>0.69</td>
<td>36</td>
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<tr>
<td>L.B.</td>
<td>—</td>
<td>110/66</td>
<td>13.6</td>
<td>95</td>
<td>3.8</td>
<td>0.79</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>147/75</td>
<td>17.6</td>
<td>132</td>
<td>4.3</td>
<td>0.76</td>
<td>40</td>
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<tr>
<td></td>
<td>8</td>
<td>187/90</td>
<td>18.8</td>
<td>154</td>
<td>4.1</td>
<td>0.74</td>
<td>41</td>
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<tr>
<td>L.R.</td>
<td>—</td>
<td>105/75</td>
<td>10.4</td>
<td>75</td>
<td>2.6</td>
<td>0.84</td>
<td>53</td>
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<tr>
<td></td>
<td>2</td>
<td>135/90</td>
<td>9.9</td>
<td>75</td>
<td>2.4</td>
<td>0.85</td>
<td>63</td>
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<td></td>
<td>4.8</td>
<td>145/85</td>
<td>12.2</td>
<td>88</td>
<td>2.3</td>
<td>0.86</td>
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<tr>
<td></td>
<td>7.5</td>
<td>150/90</td>
<td>12.1</td>
<td>90</td>
<td>2.2</td>
<td>0.86</td>
<td>68</td>
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<tr>
<td>M.J.</td>
<td>—</td>
<td>110/60</td>
<td>10.4</td>
<td>110</td>
<td>6.3</td>
<td>0.60</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>143/74</td>
<td>12.2</td>
<td>110</td>
<td>4.7</td>
<td>0.70</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>161/82</td>
<td>11.4</td>
<td>110</td>
<td>4.8</td>
<td>0.69</td>
<td>64</td>
</tr>
<tr>
<td>E.F.</td>
<td>—</td>
<td>115/58</td>
<td>9.3</td>
<td>82</td>
<td>3.3</td>
<td>0.77</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>120/65</td>
<td>9.3</td>
<td>82</td>
<td>3.4</td>
<td>0.77</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>135/70</td>
<td>8.4</td>
<td>73</td>
<td>3.0</td>
<td>0.79</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>140/70</td>
<td>—</td>
<td>—</td>
<td>3.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>140/70</td>
<td>9.2</td>
<td>79</td>
<td>2.9</td>
<td>0.80</td>
<td>68</td>
</tr>
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</table>

To qualify as a vasodilator, an agent must produce an increase in flow out of proportion to the rise (if any) in perfusing pressure. Such was not the case here, for flow generally rose pari passu with pressure. Calculated vascular resistance was unchanged. Burton has suggested that an unchanged resistance at higher rates of flow and pressure implies increase in vascular tone. Otherwise, the greater pressure would passively distend the arteriolar vessel, and result in disproportionate rise in flow. In fact, this is seen in the coronary bed when experimental coarctation is produced. Vasodilatation is primary if the arteriovenous oxygen difference across a vascular bed narrows and secondary if it remains constant. The actual widening of the arteriovenous difference and absence of either primary or secondary dilator pattern suggests that in man norepinephrine has a primary coronary constrictor effect.

For an example of true primary coronary vasodilatation, one must turn to isoproterenol. Figure 3 compares the coronary effects of norepinephrine and isoproterenol. Note that both agents increase myocardial oxygen consumption, but this increased energy demand is met in different ways. With isoproterenol, flow rises far out of proportion to demand, and coronary venous oxygen content actually rises. With norepinephrine, as shown above, extraction increases and venous oxygen content decreases. This is a response seen thus far only in coronary insufficiency and with pitressin administration. It was most striking in the left ventricular failure group, in which 50 per cent of augmented myocardial oxygen consumption was supplied through increased extraction. One must conclude that suboptimal rise in coronary flow is provided by norepinephrine, undoubtedly due to competing primary vasoconstrictor effects.
Comparison of effects of norepinephrine and isoprote- 
erol on the coronary circulation. Average results of 
this study are compared with average results of 
a comparable group of patients who received iso- 
protenerol by constant intravenous infusion (0.8 to 
5.3 µg./min.). Particularly to be noted are the 
differences in response of heart rate and cardiac 
output and the different manner in which an increased 
myocardial oxygen consumption is met, i.e., coronary 
flow increased markedly and arteriovenous differ- 
ences decreased with isoprote-nerol, whereas with 
norepinephrine coronary flow rose only moderately 
and arteriovenous oxygen differences increased. The 
marked difference in the response of coronary vas- 
cular resistance is also shown.

In spite of the “coronary insufficiency” pattern of 
response, evidence for anaerobiosis 
was unimpressive. There was no correlation 
between magnitude of fall in coronary venous 
oxgen and oxygen consumption of “excess lactate” 
(which, in fact was seen in only five of the 
21 subjects). Myocardial lactate production in 
the isolated perfused heart occurred when 
venous PO₂ fell to 9 mm. Hg or less. Average 
coronary venous PO₂ in the five above- 
mentioned studies approximated from oxygen 
saturation and pH of coronary venous blood 
decreased no lower than 14 ± 2 mm. Hg with 
norepinephrine.

It should be noted that no arbitrary dose of 
norepinephrine was used to achieve the 
hemodynamic response described, and no 
dose-response relationship was seen in the 
group as a whole. The majority of patients 
responded to a dose slightly higher than the 
range recommended for practical treatment 
of hypotensive states (2 to 4 µg. base/min.)31). 
In clinical studies of hypotension, enough 
agent is used to raise systolic pressure to a 
level of 100 mm. Hg. Caution has been urged 
against raising pressure to hypertensive levels 
because of the development of arrhythmias.32 
The peak systolic pressure seen in this study 
(156 mm. Hg) was certainly not excessively 
high, and arrhythmias were not a problem.

It is recognized that results obtained by 
making normotensive subjects slightly hyper- 
tensive cannot be applied directly to clinical 
shock, wherein perfusion pressure and often 
cardiac output are subnormal. At the same 
time, certain points from the data provide 
sobering counterpoise to the enthusiastic pro- 
motion of norepinephrine as the agent of 
choice for treatment of shock. If indeed 
proper oxygenation and presumably mainte- 
nance of PO₂ are important to the heart of a 
patient in shock, then the rise in both cardiac 
oxgen consumption and oxygen extraction 
with only a mechanically induced and rela- 
tively minor rise in coronary flow is a source 
of concern.

Although the mortality in untreated cardio- 
genic shock is 80 per cent, that of treated 
cases still approaches 60 per cent.7 8. 33 Could 
this high residual mortality reflect some ad- 
verse effect of the agent itself on myocardial 
oxgen supply? It is notable in this re- 
spect that Szakacs has described pathologic 
changes in the myocardium of norepineph- 
rine-treated animals that resemble subendo- 
cardial infarction.34–36 These ischemic 
changes may occur from excessive coronary vasocon- 
striction. Such changes seen in the heart of a 
patient who fails to survive his episode of 
cardiogenic shock “in spite of” treatment, are 
likely to be ascribed to the underlying coro- 
nary disease.

Summary
The effect of norepinephrine infusion on
the coronary circulation has been studied in 21 subjects. In doses ranging from 2 to 17 μg. base per minute norepinephrine caused a pari passu rise in perfusing pressure and coronary flow of 16 per cent above the control state. Despite an increase in cardiac oxygen consumption, coronary vascular resistance was unchanged, suggesting no vasodilation in the coronary bed. On the contrary, oxygen extraction across the heart increased, implying that oxygen needs were inadequately met by rise in flow. An increase in vascular tone induced by norepinephrine is inferred from the unchanged coronary resistance at a higher perfusion pressure.

Responses of the normal and failing left ventricle groups were qualitatively the same as for the group as a whole. The failure group showed greater tendency to meet oxygen needs by increased extraction than did the normal hearts.

Although these observations are not strictly applicable to the role and effects of norepinephrine in states of clinical shock, nonetheless it seems likely that norepinephrine induces a suboptimal rise in coronary flow that may set the stage for ultimate myocardial ischemia, particularly when coronary perfusion pressure is inadequate.

References
20. Gollwitzer-Meier, K., and Witzleb, E.: Die Wirkung von 1-Noradrenalin auf die Energie und die Dynamik des Warmblütener-
NOREPINEPHRINE AND CORONARY CIRCULATION


The Scientific Method

The guarantee of science is in the verification of experience, direct or indirect. It distrusts the validity of a priori conclusions, or of any explanation drawn solely from general ideas of Nature's order, unless those general ideas have themselves been rigorously demonstrated to be necessities of thought, or to represent the observed order. What must be, or may be, has to give place to what is. The general doctrines of Science are never, like those of Theology and Metaphysics, conceived to be final.—GEORGE HENRY LEWES, Aristotle: a Chapter from the History of Science (Smith, Elder and Co., London, 1864).
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