Cardiovascular Function in Hypothermic Anesthetized Man

By John C. Rose, M.D., Thomas F. McDermott, M.D., Lawrence S. Lilienfield, Ph.D., M.D., Frank A. Porfido, M.D., and Robert T. Kelley, M.D.

Although hypothermia is being used as an adjunct to general anesthesia, its cardiovascular effects in man are not fully known. In this report the authors present the hemodynamic changes observed in patients undergoing hypothermia under the clinical conditions of its practical usage in the operating room. Considerable variability in vasomotor and cardiac responses was encountered, indicating that uniform behavior of patients to this agent is not to be expected in the relatively uncontrolled operating room setting; therefore, it should be used conservatively, particularly in critically ill patients in whom unexpected reactions may be disastrous.

The use of hypothermia as an adjunct to general anesthesia is becoming increasingly common. The indications for its application, and the various techniques by which patients may be cooled have been reviewed in many publications and recently summarized by Virtue. However, aside from electrocardiographic studies, measurements of the physiologic alterations produced by the artificial induction of hypothermia in man have not been made in the operating room.

With regard to cardiovascular function, it is generally assumed that those physiologic changes that occur in dogs in the controlled environment of the experimental laboratory also occur in patients in the variable atmosphere of the operating room. The work of Pree's group, Bigelow and his colleagues, Edwards and co-workers, and Sabiston, Theilen, and Gregg indicates that in cooled dogs, heart rate, blood pressure, and cardiac output are frequently almost linear functions of body temperature. However, Hegnauer and D'Amato have demonstrated marked elevations of cardiac output and oxygen consumption in dogs due to only moderate shivering during the cooling period.

There seemed, then, a need for more detailed observations of the circulatory alterations produced by hypothermia in man, under the conditions found in the operating room. In anesthetized patients, measurements were made in the normothermic and hypothermic state of heart rate, cardiac output, mean arterial pressure, total peripheral resistance, mean circulation time, cardiac work, central blood volume, plasma volume, and hematocrit. Measurements were made prior to any surgical procedure, and an attempt was made to exclude influences other than hypothermia, such as drugs or fluids.

Materials and Methods

Ten patients were selected for this study. Their ages, diagnoses, preoperative drugs, and anesthetic agents used are shown in table 1. No patient had clinical evidence of cardiovascular disease. Studies were performed in the following manner:

After the induction of anesthesia and tracheal intubation, a 17-gage thin-wall needle was inserted in a femoral artery and taped in place. Rectal temperature was continuously recorded with a telethermometer. When the patient's condition appeared stable, as evidenced by level blood pressure, pulse, and clinical depth of anesthesia, the electrocardiogram was recorded simultaneously with the direct femoral arterial pressure contour. Arterial pressures were obtained with a strain-gage transducer, carrier-wave type amplifier and 2-channel, direct-writing oscillograph. Mean pressures were determined by planimetric integration of the pulse wave.

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\* Yellow Springs Instrument Company, Yellow Springs, Ohio.
\† P-23D, Statham Laboratories, Beverly Hills, Calif.

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Table 1.—Summary of Patients, Drugs and Anesthetic Agents

<table>
<thead>
<tr>
<th>Patient, age and sex</th>
<th>Surface area (M²)</th>
<th>Preoperative diagnosis</th>
<th>Preoperative medication</th>
<th>Anesthetic* agents</th>
<th>Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>D. T. 72, M</td>
<td>1.69</td>
<td>Carcinoma, esophagus</td>
<td>Demerol, atropine</td>
<td>pentothal, nitrous oxide</td>
<td>Resection esophagus</td>
</tr>
<tr>
<td>J. C. 60, M</td>
<td>1.93</td>
<td>Carcinoma, esophagus</td>
<td>morphine, atropine</td>
<td>pentothal, nitrous oxide</td>
<td>Resection esophagus</td>
</tr>
<tr>
<td>B. T. 37, F</td>
<td>1.46</td>
<td>Uterine myomata</td>
<td>Phenergan, Demerol</td>
<td>pentothal, nitrous oxide</td>
<td>Hysterectomy</td>
</tr>
<tr>
<td>E. F. 48, F</td>
<td>1.61</td>
<td>Carcinoma, colon</td>
<td>pentobarbital, morphine, scopolamine</td>
<td>pentothal, ether, nitrous oxide</td>
<td>Laparotomy</td>
</tr>
<tr>
<td>F. R. 62, F</td>
<td>1.78</td>
<td>Carcinoma, colon</td>
<td>pentobarbital, scopolamine</td>
<td>pentothal, ether, nitrous oxide</td>
<td>Abdomino-perineal resection</td>
</tr>
<tr>
<td>E. J. 78, F</td>
<td>1.54</td>
<td>Carcinoma, colon</td>
<td>pentobarbital, morphine, scopolamine</td>
<td>pentothal, ether, nitrous oxide</td>
<td>Hemicolecctomy</td>
</tr>
<tr>
<td>M. W. 48, F</td>
<td>1.78</td>
<td>Carcinoma, rectum</td>
<td>pentobarbital, morphine, scopolamine</td>
<td>pentothal, cyclopropane</td>
<td>Abdomino-perineal resection</td>
</tr>
<tr>
<td>M. C. W. 36, F</td>
<td>1.45</td>
<td>Portal cirrhosis</td>
<td>pentobarbital, Demerol, scopolamine</td>
<td>pentothal, cyclopropane</td>
<td>Portocaval anastomosis</td>
</tr>
<tr>
<td>J. V. 67, M</td>
<td>1.86</td>
<td>Carcinoma, pancreas</td>
<td>pentobarbital, Demerol, scopolamine</td>
<td>pentothal, ether</td>
<td>Cholecystoduodenostomy</td>
</tr>
<tr>
<td>W. P. 48, M</td>
<td>1.80</td>
<td>Carcinoma, larynx</td>
<td>pentobarbital, morphine, scopolamine</td>
<td>pentothal, ether, nitrous oxide</td>
<td>Laryngectomy and node dissection</td>
</tr>
</tbody>
</table>

* All patients maintained on continuous positive pressure respirations.

Immediately following pressure recording, indicator-dilution curves were obtained with radioiodinated human serum albumin (5 cases), T-1824 dye (2 cases), or a mixture of red blood cells tagged with Cr⁴⁺ and radio-iodinated human serum albumin (3 cases).

The indicator-dilution curves were obtained following a rapid injection into an antecubital vein and femoral artery sampling, modified from the method of Werko and his associates.⁸ Two-second blood samples were collected into paraffined tubes containing dried heparin continuously for 80 seconds following injection. Methods for chromating red blood cells, the preparation and analysis of injectates, and the analysis of blood samples for radioactivity of plasma and red blood cells have been described in a previous communication from this laboratory.⁹ Following the sample collection, rectal temperature was noted and direct pressure recording repeated. In several instances, 10 minutes following injection of indicator, a blood sample was obtained for determination of plasma volume.

The patient was then cooled by packing him with ice enclosed in cloth or plastic bags. The indwelling arterial needle was left in place. No fluids or drugs were administered during the cooling period, which averaged 2 hours in duration (range 1.0 to 2.5 hours). Although shivering was occasionally noted for brief periods during cooling, no shivering was detectable during measurement periods. At rectal temperatures between 31 C. and 32.5 C. the ice was removed and the patient dried. At this time the measurements made prior to cooling were repeated in an identical manner, and the rectal temperature at the time of the observations was noted (table 2). After collection of a 10-minute sample for plasma volume determination, the patient was prepared for surgery.

Semilogarithmic plots of indicator concentration or radioactivity were constructed against time. The curves were analyzed by a recently described method¹⁰ and calculations made of cardiac output, mean circulation time, and central blood volume.¹¹ In 3 cases the mean circulation times of red blood cells and plasma were independently but simultaneously measured after cooling. Total peripheral resistance was expressed in peripheral resistance units¹² and cardiac work calculated by the formula of Starling and Visscher.¹³ Hematocrit values were determined in Wintrobe tubes. For plasma volume calculations, the amount of indicator injected was corrected for the amount removed in obtaining the dilution curves.

Results

The measurements made and the corresponding rectal temperatures are given in table 2. Figure 1 shows graphically the results of several of the measurements.

Heart Rate. Heart rate fell significantly in 7 patients and showed no significant change in 3. The average decrease in the 7 patients was 31 per cent (range from 21 to 47 per cent). No pa-
CARDIOVASCULAR FUNCTION IN HYPOTHERMIC ANESTHETIZED MAN

Table 2.—Results of Studies in Ten Patients before and after Surface Cooling to Rectal Temperatures Shown

<table>
<thead>
<tr>
<th>Patient</th>
<th>Rectal temperature (°C)</th>
<th>Heart rate (1/min.)</th>
<th>Stroke volume (ml.)</th>
<th>Cardiac output (L./min.)</th>
<th>Mean arterial pressure (mm. Hg)</th>
<th>Total peripheral resistance (F.R.U.)</th>
<th>Cardiac work (Kg. m./min.)</th>
<th>Mean circulation time (sec.)</th>
<th>Central blood volume (L.)</th>
<th>Hema-tocrit (%)</th>
<th>Plasma volume (L.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D. T.</td>
<td>36.8</td>
<td>120</td>
<td>33</td>
<td>3.94</td>
<td>135</td>
<td>2.05</td>
<td>7.23*</td>
<td>40</td>
<td>2.63</td>
<td>3.95</td>
<td>40</td>
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<tr>
<td>J. C.</td>
<td>37.0</td>
<td>80</td>
<td>48</td>
<td>3.80</td>
<td>101</td>
<td>1.57</td>
<td>5.22</td>
<td>61.3</td>
<td>3.95</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>B. T.</td>
<td>31.0</td>
<td>44</td>
<td>54</td>
<td>2.39</td>
<td>95</td>
<td>2.39</td>
<td>3.09</td>
<td>58.6</td>
<td>2.33</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>E. F.</td>
<td>32.3</td>
<td>66</td>
<td>50</td>
<td>3.30</td>
<td>140</td>
<td>2.55</td>
<td>6.28</td>
<td>19.9</td>
<td>1.09</td>
<td>41</td>
<td>2.03</td>
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<tr>
<td>F. R.</td>
<td>35.6</td>
<td>55</td>
<td>51</td>
<td>2.80</td>
<td>98</td>
<td>2.10</td>
<td>3.73</td>
<td>37.1</td>
<td>1.73</td>
<td>38</td>
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<td>M. W.</td>
<td>30.5</td>
<td>50</td>
<td>51</td>
<td>2.55</td>
<td>77</td>
<td>1.81</td>
<td>2.36</td>
<td>37.8</td>
<td>1.61</td>
<td>41</td>
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<tr>
<td>M. C. W.</td>
<td>32.5</td>
<td>62</td>
<td>69</td>
<td>4.25</td>
<td>132</td>
<td>1.86</td>
<td>7.63</td>
<td>46.1</td>
<td>3.27</td>
<td>42</td>
<td>2.39</td>
</tr>
<tr>
<td>J. V.</td>
<td>36.5</td>
<td>68</td>
<td>44</td>
<td>2.97</td>
<td>115</td>
<td>2.32</td>
<td>4.65</td>
<td>31.0</td>
<td>1.54</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>W. P.</td>
<td>31.0</td>
<td>60</td>
<td>82</td>
<td>4.94</td>
<td>70</td>
<td>0.85</td>
<td>4.70</td>
<td>18.4</td>
<td>1.51</td>
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<tr>
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<td>60</td>
<td>41</td>
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<td>2.20</td>
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<td>56.8</td>
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<tr>
<td></td>
<td>37.4</td>
<td>80</td>
<td>53</td>
<td>4.21</td>
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<td>0.78</td>
<td>3.15</td>
<td>31.8</td>
<td>2.23</td>
<td>38.5</td>
<td>2.74</td>
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<td>31.0</td>
<td>45</td>
<td>52</td>
<td>2.36</td>
<td>72</td>
<td>1.83</td>
<td>2.31</td>
<td>36.7</td>
<td>1.44</td>
<td>42</td>
<td>2.52</td>
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<tr>
<td></td>
<td>36.3</td>
<td>85</td>
<td>46</td>
<td>3.95</td>
<td>85</td>
<td>1.29</td>
<td>4.57</td>
<td>35.4</td>
<td>2.33</td>
<td>35.5</td>
<td>4.13</td>
</tr>
<tr>
<td></td>
<td>31.5</td>
<td>67</td>
<td>76</td>
<td>5.12</td>
<td>103</td>
<td>1.21</td>
<td>7.18</td>
<td>31.8</td>
<td>2.72</td>
<td>38</td>
<td>3.89</td>
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<tr>
<td></td>
<td>37.0</td>
<td>65</td>
<td>70</td>
<td>4.58</td>
<td>74</td>
<td>0.97</td>
<td>4.61</td>
<td>33.7</td>
<td>2.57</td>
<td>41</td>
<td>3.85</td>
</tr>
<tr>
<td></td>
<td>31.2</td>
<td>60</td>
<td>94</td>
<td>5.63</td>
<td>104</td>
<td>1.10</td>
<td>7.96</td>
<td>29.5</td>
<td>2.39</td>
<td>44</td>
<td>3.38</td>
</tr>
</tbody>
</table>

* Multiplied by 10^6.

Fig. 1. Alterations produced by hypothermia in several hemodynamic parameters.

Patient showed an increased heart rate following cooling.

Cardiac Output. Cardiac output fell significantly (more than 10 per cent) in 5 patients, at low temperatures. In these, the mean decrease was 36 per cent (range 11 to 57 per cent). In 3 cases there was a fall of less than 10 per cent (D. T., E. F., and F. R.). In 2 patients (J. V. and W. P.) cardiac output increased significantly at low temperatures (29 and 23 per cent respectively).

Stroke volume alterations were extremely inconstant. This quantity decreased significantly in 2 cases, showed changes of less than 10 per cent in 3, and increased in 5.

Pressure Pulse Contour. The femoral arterial pressure pulse contours showed consistent alterations at low temperatures. These were primarily a prolongation of the time required for systole and a more slowly rising anacrotic notch (figs. 2 and 3).

Analysis of tracings in 6 cases with clearly defined systolic periods (onset of systole to diastolic notch) revealed an average duration of systole of 32 per cent of the total cardiac cycle (range 24 to 41 per cent) in the normothermic state. At low temperatures, the mean duration of systole increased to 39 per cent of the cycle (range 37 to 48 per cent). Similar alterations have been noted in dog aortic pressure pulse contours in this temperature range.14, 15

Figure 3 illustrates the consistent finding that these alterations in pressure pulse contour...
Fig. 2. Femoral arterial pressure contours in 4 cases before and after cooling. The time required for systolic ejection after cooling is prolonged.

were unrelated to significant alterations in electric activity.

Mean Arterial Pressure. Mean arterial pressure rose significantly in 7 cases (mean 35 per cent, range 21 to 72 per cent) and fell in 3 (25, 11, and 21 per cent respectively in D. T., J. C., and E. F.).

Total Peripheral Resistance. These alterations were similarly inconstant. Resistance fell in 3 cases (D. T., E. F., and J. V.; 23, 13, and 6 per cent) and increased in 7 (mean 89 per cent, range 13 to 158 per cent).

Cardiac Work. Cardiac work was increased in 5 cases (mean increase 39 per cent, range 11 to 72 per cent) and decreased in 5 (mean decrease 37 per cent, range 26 to 62 per cent).

Mean Circulation Time. Mean circulation time was prolonged in 7 instances (mean prolongation 67 per cent, range 15 to 208 per cent), and shortened in 2 (J. V. 7 per cent and W. P. 12 per cent). It was not significantly altered in patient E. F.

In the 3 patients (B. T., E. F., F. R.) in whom simultaneous measurement of red blood cell and plasma mean circulation times were made, the ratio of these mean times averaged 1.05. This is higher than the 0.97 reported for normal subjects\textsuperscript{16} although the series is too small to determine a significant difference. This observation suggests that the velocity of red blood cells in relation to plasma may be decreased in the hypothermic state and requires further study.

Central Blood Volume. The central blood volume of Hamilton\textsuperscript{11} theoretically includes the volume of blood contained between the site of injection of indicator and the point of sampling. This volume thus includes the great vessels, heart, and lungs, and all vessels equidistant with the sites of injection and sampling. This volume was increased by more than 10 per cent in 5 cases, decreased by more than 10 per cent in 2, and showed no significant change in 3.

Hematocrit, Plasma Volume. Precooling hematocrit levels were not determined in D. T. and J. C. The remaining 8 patients demonstrated a consistent hemococoncentration. The mean hematocrit rise following cooling was 8 per cent (range 6 to 10 per cent).

Plasma volume determinations were made in 5 instances in the normal and cooled state. All showed decreases. The magnitudes of the plasma volume alterations (6 to 12 per cent) were consistent with the hematocrit elevations, and suggest that an absolute loss of circulating plasma volume occurs in the hypothermic state. These phenomena have been well recognized in hypothermic dogs.\textsuperscript{17}
DISCUSSION

This investigation has afforded the opportunity to observe the circulatory effects of induced hypothermia as it is clinically employed. The results indicate that the information obtained from the study of dogs in the experimental laboratory cannot always be "literally translated" to hypothermia in man under conditions existing in the operating room.

In anesthetized man, hypothermia produced relatively consistent changes in heart rate, mean circulation time, and the pressure pulse contour, whereas alterations in other parameters differed qualitatively. Cardiac output and mean arterial pressure, and consequently total peripheral resistance and cardiac work alterations, were unpredictable.

Differences in arterial pressure responses, chiefly hypertensive, suggest that in the temperature range studied, homeostatic vasopressor reflexes are active to varying degrees from patient to patient. In most instances, when the operation was begun, the arterial blood pressure (auscultatory method) fell to and remained at levels lower than control. However, it is impossible to draw any conclusions from this phenomenon, since the level of the blood pressure must be related to cardiac output, blood loss, "drifting" of body temperature, and the reflexes and other influences that accompany extensive surgery.

Increased cardiac output may be related to somewhat variable levels of anesthesia, resulting possibly in subclinal shivering and increased oxygen consumption.7

The consequences of intense systemic vasoconstriction and increased cardiac output—increased work of the heart (observed in 5 of these 10 patients)—may be deleterious. Although this is a tenuous conclusion in the absence of observations of myocardial oxygen consumption and myocardial efficiency, it warrants mention, since so-called "poor risk" patients, who, presumably, include those with heart disease, have been considered candidates for hypothermic anesthesia.1

Controversy exists as to whether autonomic blocking agents are useful adjuncts to hypothermia.18, 19 The data described here may support their use. Reducing the intensity of the vasoconstrictor response to cold might conceivably relieve considerable stress on the cardiovascular system.

Although considerable data have been accumulated regarding the physiologic effects of experimental hypothermia, there is as yet insufficient data concerning the physiologic effects of "clinical" hypothermia induced in a patient about to undergo a formidable operation. Until our understanding of the hypothermic state in man is more complete, the indications for its use should be viewed conservatively. Measurements that will contribute further to our understanding of the hypothermic state in anesthetized man include oxygen consumption, both total and regional, regional blood flow measurements, and chemical and metabolic alterations.

SUMMARY AND CONCLUSIONS

Cardiac output, direct arterial pressure contours, and other measurements of circulatory function were made in 10 patients in whom hypothermia was induced prior to extensive noncardiovascular surgery. Measurements were made before cooling and again at rectal temperatures between 30.5 and 32.5 C. The results were characterized by considerable variability. The data suggest that vasomotor and cardiac responses to cold were active to varying degrees in individual patients and that uniform physiologic responses to hypothermia cannot be expected in the experimentally uncontrolled operating room setting.

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SUMMARIO IN INTERLINGUA

Le rendimento cardiac, le contornos del directe pression arterial, e altere mesurationes del function circulatori eseva determinate in 10 patientes in qui hypothermia habeva essite inducite in preparation de extente intervansiones chirurgic de character non-cardiovascu- lar. Omne le determinationes eseva effectuate ante le frigidation e de novo quando le sub-
jectos mostrava temperaturas rectal de inter 30,5 e 32,5 C. Le resultados esseva characteri-
sate per considerabile variationes. Le datos indica que le responsas vasomotori e cardiac al effecto de frigidation esseva active a varie
grados in le patientes individual e que un uniforme responsa physiologic non pote esser expectate sub le experimentalmente non-
regulate condiciones del sala de operation.

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Hyponatremia associated with medical or surgical shock may be due to extra renal salt loss or
deprivation and will show a decreased urinary salt concentration. Hyponatremia due to either renal
tubular damage or adrenocortical insufficiency is associated with increased urinary salinity. A
rapid simple test will differentiate between the two situations without delaying therapy. Studies to
extend this observation further and to use this method to predict the reserve status of adrenal
function are in progress.

Kitchell
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