Effect of Artificial Pacing of the Heart on Cardiac and Renal Function

By J. O. Humphries, M.D., E. J. Hinman, M.D., L. Bernstein, M.D.,
and W. G. Walker, M.D.

SUMMARY
Six patients with complete heart block provided an opportunity to study renal hemodynamic responses to increased heart rate produced by an artificial pacemaker. Observations were made at rest and following exercise during idioventricular rhythm and slow rates and were repeated after increasing the rate to 70/min by means of an artificial pacemaker. Ability to excrete a water load was impaired at the slow idioventricular rate; this was associated with a reduced glomerular filtration rate. No acute improvement in renal function occurred with pacemaker-induced increase in heart rate except in the presence of congestive heart failure. With long-term pacing (7 to 8 months), the glomerular filtration rate and the ability to excrete solute-free water increased in all patients studied. The acute increase in free water clearance which occurred with increased heart rate in the presence of congestive heart failure suggests that decreased renal perfusion may be responsible for the inability to excrete excess water. The dilutional hyponatremia in congestive heart failure may be explained on this basis. Changes in indices of cardiac function in these patients were similar to those reported by others. No change in resting cardiac output occurred at heart rates between 40 and 70/min in the absence of congestive heart failure. The response to exercise, however, was greater at the higher rates.

Additional Indexing Words:
Cardiac output       Artificial pacemakers
Dilutional hyponatremia Glomerular filtration rate
Renal blood flow

THE CLINICAL MANIFESTATIONS of complete heart block with a slow idioventricular rate result from failure to maintain adequate cardiac output. These manifestations may vary from acute Stokes-Adams seizures, due to acute cerebral vascular perfusion insufficiency, to profound congestive heart failure. To the extent that the heart is incapable of compensating for a decrease in rate by increasing stroke volume, hypoperfusion of the vascular bed of the major organ systems of the body results in various clinical manifestations of complete heart block. Hypoperfusion of the kidneys associated with very slow rates may result in impaired renal function. This impaired renal function may contribute to the development of congestive heart failure as well as to the development of azotemia and uremia.

We report herein hemodynamic studies on six patients who presented with complete heart block and slow idioventricular rate. Cardiac and renal function were assessed during acute stepwise increases in heart rate produced by an artificial pacemaker and again after a normal heart rate had been maintained with a permanent pacemaker for several months.

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These studies reveal that at rest venous return is much more important than heart rate as the determinant of cardiac output. In addition, it appears that inability to excrete a water load may be the most sensitive index of inadequate renal perfusion, an observation which may be of cardinal importance in explaining the mechanism of development of hyponatremia in congestive heart failure.

Methods

Six patients with complete heart block, idioventricular rhythm, and slow heart rate have been studied one or more times (table 1). Two patients (H.C. and H.H.) had Stokes-Adams attacks and no symptoms or signs of congestive failure and azotemia, and two patients (R.P. and H.D.) had lethargy and a history of easy fatigability and breathlessness on moderate exertion. No cases of congenital heart block were included; the etiology in each instance appeared to be idiopathic or degenerative. All six patients had received various medications in an effort to increase the heart rate, but administration of all drugs except digitalis was discontinued prior to the studies with the exception of corticosteroids in patient H.D. The studies were conducted without premedication or anesthesia.

The study protocols were designed to provide data on cardiac output and renal function at the initial slow idioventricular rate, and then as the heart rate was increased stepwise to a final rate of 70/min. Thirty minutes of pacing at each rate was allowed before cardiac and renal functions were assessed. On those patients who received permanent fixed rate pacemakers* following the initial studies, the studies were repeated after the pacemaker had been in place and in continuous operation for 7 or more months. For the acute studies prior to inserting a permanent pacemaker, a bipolar catheter electrode* was passed from a peripheral vein to the right ventricle and used to alter cardiac rate.

*Medtronic, Inc., Minneapolis, Minnesota.

Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Heart rate</th>
<th>Activity</th>
<th>Time of study</th>
<th>CI (L/min/m²)</th>
<th>SV (ml)</th>
<th>RPF (ml/min)</th>
<th>GFR (ml/min)</th>
<th>Clearance (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H.C.</td>
<td>40</td>
<td>Rest</td>
<td>Acute</td>
<td>2.2</td>
<td>100</td>
<td>259</td>
<td>61</td>
<td>1.7</td>
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<tr>
<td></td>
<td>70</td>
<td>Rest</td>
<td>Acute</td>
<td>2.2</td>
<td>57</td>
<td>236</td>
<td>64</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>Exercise</td>
<td>8 mo P.O.</td>
<td>1.8</td>
<td>128</td>
<td>76</td>
<td>88</td>
<td>4.6</td>
</tr>
<tr>
<td>B.P.</td>
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<td>Rest</td>
<td>Acute</td>
<td>2.6</td>
<td>80</td>
<td>295</td>
<td>42</td>
<td>-0.7</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>Rest</td>
<td>Acute</td>
<td>2.3</td>
<td>43</td>
<td>167</td>
<td>41</td>
<td>-0.9</td>
</tr>
<tr>
<td></td>
<td>62</td>
<td>Rest</td>
<td>8 mo P.O.</td>
<td>2.7</td>
<td>224</td>
<td>63</td>
<td>6.0</td>
<td>4.3</td>
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<td>62</td>
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<td>8 mo P.O.</td>
<td>3.3</td>
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</tr>
<tr>
<td>R.P.</td>
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<td>Rest</td>
<td>Acute</td>
<td>2.4</td>
<td>110</td>
<td>298</td>
<td>79</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
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<td>Acute</td>
<td>2.7</td>
<td></td>
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</tr>
<tr>
<td></td>
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<td>Rest</td>
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<td>3.4</td>
<td>87</td>
<td>202</td>
<td>80</td>
<td>-0.6</td>
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<td>Acute</td>
<td>3.9</td>
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<tr>
<td></td>
<td>70</td>
<td>Rest</td>
<td>7 mo P.O.</td>
<td>3.1</td>
<td>43</td>
<td>135</td>
<td>5.2</td>
<td>3.4</td>
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<td>227</td>
<td>4.7</td>
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<tr>
<td></td>
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<td>Rest</td>
<td>Acute</td>
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<td></td>
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<tr>
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<td>Acute</td>
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<td>82</td>
<td>206</td>
<td>60</td>
<td>3.7</td>
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<tr>
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<td>Acute</td>
<td>2.9</td>
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<tr>
<td></td>
<td>76, 79</td>
<td>Rest</td>
<td>Acute</td>
<td>2.5</td>
<td>53</td>
<td>194</td>
<td>61</td>
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<tr>
<td></td>
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<td>Acute</td>
<td>3.9</td>
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</table>

Abbreviations: HR = heart rate; CI = cardiac index; SV = stroke volume; RPF = renal plasma flow; GFR = glomerular filtration rate; C_H2O = free water clearance.

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ARTIFICIAL PACING

Cardiac Output

Cardiac output was determined in duplicate at each heart rate by the indocyanine-green (Cardio-Green) indicator-dilution method. Material was injected into the superior vena cava or right atrium through a no. 5 French cardiac catheter.

Renal Function

All renal function studies were done under a standard water load, the patient receiving 1,500 ml of water 2 to 3 hours prior to the beginning of the study; additional water was administered at the rate of 500 ml an hour throughout the study. Renal plasma flow and glomerular filtration rate were determined by standard para-aminobipirurate and inulin clearance techniques. Sodium, potassium, osmolar, and free water clearances were measured by techniques previously described from this laboratory. The cardiac and renal studies were carried out simultaneously in four patients, on consecutive days in one patient, and cardiac studies alone were done on one patient. The initial studies on all patients included studies at the idioventricular rate followed by studies while the patient was being maintained at one or more selected rates by an artificial pacemaker. In five of the patients the studies were repeated at various heart rates during exercise on a cycle ergometer with the patient in the supine position.

Results

A summary of the results obtained in the six patients is presented in table 1. The parameters of cardiac and renal function are presented for each heart rate studied for each patient. Renal clearance data represent averages of at least three consecutive 20-minute clearance periods; values for cardiac output are averages of two consecutive determinations.

Renal Function Studies

Studies on five patients during control periods at slow idioventricular rates revealed uniformly low glomerular filtration rates. It is also evident from the summary of data in table 1 that all five patients studied had impairment of ability to excrete water. Lowered glomerular filtration rate, lowered renal plasma flow, and blunted water diuresis were the characteristic features observed in these patients prior to increasing heart rate. Since the patients were not maintained on a constant sodium intake, no firm conclusions can be drawn from the data on sodium excretion. It is probably pertinent that the patients M.S. and B.P. who had the lowest rate of sodium excretion had the most severe exercise intolerance, with patient M.S. exhibiting marked evidence of congestive failure.

When the heart rate was acutely increased by means of an artificial pacemaker in these patients, repeat studies of renal function showed virtually no change in glomerular filtration rate, a modest fall in renal blood flow and, in three patients, in sodium excretion. One patient who behaved differently was the patient who was in congestive heart failure at the time of the studies (M.S.). Unfortunately, for technical reasons, glomerular filtration rate was not measured at the higher cardiac rate and so data are incomplete on this patient, but he demonstrated an increase both in cardiac output and in osmolar excretion. Since his renal blood flow increased during the study, it seems probable that an increase in glomerular filtration rate also occurred. This patient was hyponatremic at the outset of the study, his plasma sodium concentration being 126 mEq/L and his plasma, 254 mOsm/kg. He showed no tendency to increase his rate of water excretion with ingestion of the water load during the control period, but he did exhibit prompt water diuresis when his heart rate was increased acutely to 70 beats/min. Urinary flow rate increased, the increased flow being due in major part to excretion of excess water although not entirely since he also increased the output of sodium and potassium. Interestingly, the other patients all decreased the rate of sodium excretion in response to an acute increase in heart rate. Thus, in the presence of congestive heart failure and diuretional hyponatremia, artificial pacing produced an increase in cardiac output and in perfusion of the kidney with a resulting increase in rate of excretion of water and solute. No significant changes were observed in renal function of the other patients following acute increase in heart rate.

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The most striking finding in these studies was a significant increase in glomerular filtration rate in the patients who were studied after an interval of 7 months. Associated with this increase in glomerular filtration rate was a remarkable increase in their ability to excrete a water load. These data are summarized in Table 1 and shown in Figures 1 and 2. The follow-up data shown in Figure 2 are in striking contrast to the lack of any significant improvement shown during the acute studies in Figure 1. Although the number of patients studied is small, the changes in glomerular filtration rate and free water clearance are relatively large. Changes in sodium excretion could not be evaluated because dietary sodium intake was not controlled during these follow-up studies.

**Cardiac Function**

The hemodynamic data obtained were similar to those previously reported. In all six patients the cardiac output at the slow idioventricular rate was low, averaging 2.3 L/min/m², with a range of 2.1 to 2.6 L/min/m² (Fig. 3). When the heart was artificially paced at 70 beats per min or more acutely, there was essentially no change in cardiac output in four of the six patients; calculated stroke volume showed a marked decrease at the higher rate. Of the two remaining patients, M.L., who was in severe heart failure with peripheral edema, hepatomegaly, pulmonary congestion, and elevated venous pressure at the time the study was performed, doubled his cardiac output at the higher rate and his stroke volume remained essentially unchanged. R.P. did not have objective evidence of heart failure but gave a history of severe exercise intolerance. He also exhibited a significant increase in cardiac output. Patients

![Figure 1](attachment:image1.png)

*Figure 1*

Changes in the glomerular filtration rate (GFR) and free water clearance ($C_{H_2O}$) associated with an acute change in heart rate. (I) Idioventricular rate, and (P) artificially paced rate.

![Figure 2](attachment:image2.png)

*Figure 2*

Improvement in glomerular filtration rate (GFR) and free water clearance ($C_{H_2O}$) following 7 months of artificial pacing of the heart at a rate of 60 to 70/min. (I) Idioventricular rate and (P) artificially paced rate.

![Figure 3](attachment:image3.png)

*Figure 3*

Hemodynamic changes associated with increasing the heart rate. (I) Idioventricular rate and (P) artificially paced rate.
subjected to exercise showed an increase in cardiac output at both slow and fast heart rates. Although exercise-induced increases were only slightly greater with artificial pacing than at the idioventricular rate, this may only have been a reflection of the relatively mild exercise to which the patients were subjected. Only in patient H.D. was the increase in cardiac output with exercise much greater with pacing than at the idioventricular rate.

It is probably significant that, in those patients who were re-evaluated approximately 7 months after a permanent pacemaker had been implanted, the same level of exercise produced a much greater increase in cardiac output (fig. 4). These long-term studies also suggest that there was no significant increase in resting cardiac output, but observations are too few to be certain of this. Clinical follow-up on all patients indicated that there had been a substantial increase in functional capacity as judged by exercise tolerance.

**Discussion**

The hemodynamic abnormalities at a very slow heart rate and the changes in these hemodynamics with exercise and with an increase in heart rate noted in the six patients reported here are similar to those reported in animal studies and previous human studies. The cardiac output was low at rest and increased slightly with exercise even though there was no change in heart rate and even in the presence of overt heart failure in one patient. An increase in the heart rate resulted in essentially no change in the cardiac output except in the patient in congestive heart failure. Long-term pacing resulted in a greater increase in cardiac output with exercise than did a similar amount of exercise immediately after pacing had been initiated.

In the present study a remarkable concordance was seen between effects upon cardiac output and effects upon renal function. The acute studies showed no effect upon renal hemodynamics with the possible exception of a slight fall in renal plasma flow and a fall in sodium excretion. These changes may be significant, but the numbers are small and sodium intake was not controlled. The most important data provided by a study of renal function in the present group of patients pertain to the renal excretion of water in this and, by inference, similar cardiovascular disturbances where underperfusion of the kidney is a prominent feature. These data bear pertinent upon the problem of dilutional hyponatremia, hence, merit more detailed discussion.

The existence of blunted water diuresis in congestive heart failure has long been recognized and, more recently, it has become increasingly clear that this defect is related to the development of chronic dilutional hyponatremia, a constellation of findings in severely edematous patients characterized by severe symptoms of congestive heart failure and a low serum concentration.

The studies of Edelman and his colleagues establish that the serum sodium concentration reflects the ratio of total body solute to total body water. Since the principal cations of the body fluids are sodium and potassium, total body solute may be represented approximately as the sum of these cations plus their accompanying anions; the expression, $2 \times (\text{mEq of total body Na} + \text{mEq of total body K})$, approximates the total
body solute content. Thus, serum sodium concentration represents an estimate of the osmolality of body fluids, and hyponatremia may reflect either an excess of water or a deficit of potassium or sodium or both. In the patients studied by these investigators, pitting edema was always associated with a considerable increase in body sodium and, hence, the coexistence of hyponatremia and edema clearly establishes that hyponatremia in this situation is the result of a greater excess of body water.

Patients with chronic dilutional hyponatremia are often unresponsive to diuretics and, in general, the appearance of hyponatremia has ominous prognostic implications. It is unclear whether hyponatremia represents deterioration or failure of the physiological mechanism responsible for guarding the concentration and volume of body fluid, or whether these mechanisms have been reset to regulate at the lower level. The persistence of thirst, often quite severe despite the presence of severe hyponatremia, argues for the latter. The unresponsiveness to diuretics in the presence of marked hyponatremia and the return of responsiveness together with clinical improvement when the hyponatremia has been corrected tend to support the concept that the disorder results from an impairment of the normal regulatory mechanisms responsible for maintaining the osmolality of the body fluids constant. Such patients are frequently so severely ill that carefully controlled observations are not possible and, hence, considerable uncertainty remains about the mechanism responsible for the development of this disturbance.

The present studies appear to contribute information useful to the understanding of the mechanism underlying hyponatremia in certain cardiovascular abnormalities. As emphasized by Orloff and Burg, possible explanations for this blunted water diuresis include a persistent secretion or release of antidiuretic hormone with an associated disturbance in the thirst mechanism, a primary change in the intracellular solute concentration (potassium depletion), or a decreased rate of glomerular filtration.

The present group of patients had, in addition to their resting low cardiac outputs at the slow idioventricular rate, a depressed glomerular filtration rate and were all unable to excrete a significant quantity of solute-free water despite the presence of a considerable water load. Acute increase in heart rate produced no change in glomerular filtration rate and no change in any of the parameters in renal function, the inability to excrete solute-free water remaining unchanged under these circumstances. The one exception to this was observed in the patient with congestive heart failure at the time of study (M.S.). It is of interest that this patient was also hyponatremic and thus really represented an instance of chronic dilutional hyponatremia. When his heart rate was increased by means of an artificial pacemaker, his cardiac output increased, renal blood flow increased, and excretion of solute-free water promptly increased. Unfortunately, technical difficulties precluded measurement of the glomerular filtration rate after the heart rate was increased, but it seems reasonable to presume that this is also increased.

In contrast to the lack of response observed with acute pacing, studies after long-term pacing revealed a remarkable improvement in ability of the patients to excrete a water load (fig. 2). These observations establish that the low glomerular filtration rate in the presence of complete heart block is associated with a marked inability to excrete a water load. (A three to eightfold increase in rate of excretion of solute-free water was produced in these patients when the glomerular filtration rate was increased as a result of artificial pacing.) In view of the results in one patient with heart failure at the time of the acute study (M.S.), it seems likely that this defective perfusion of the kidney in a more exaggerated form may account for the dilutional hyponatremia of congestive heart failure.

While these studies serve to lend more weight to the importance of a decreased glomerular filtration rate in the pathogenesis of
of dilutional hyponatremia, they do not exclude additional contributions from the other factors, notably abnormal levels of circulating antidiuretic hormone. However, the presence of such marked impairment in solute-free water excretion in association with a severe reduction in glomerular filtration rate and underperfusion of the kidney, together with return of the ability to initiate water diuresis when renal perfusion is improved by means of artificial cardiac pacing, suggests that altered hemodynamics with poor renal perfusion represents a major part of the disturbance leading to dilutional hyponatremia. The acute increase in water clearance observed in the patient with heart failure and hyponatremia (M.S.) does suggest that there was no significant amount of circulating antidiuretic hormone in this patient at the time when dilutional hyponatremia was present.

Acknowledgment

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References

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