Immunoglobulin Binding
in Cardiomyopathic Hearts

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SUMMARY
Bound gamma globulin was demonstrated by the direct immunofluorescent tech-
nique in heart tissue from three patients with severe congestive cardiomyopathy. In
two of these patients complement (β1C) was also bound to the heart muscle. Heart
tissue from one of six patients who died of myocardial infarction showed a trace of
bound gamma globulin, but no bound complement. During life, the heart in advanced
cardiomyopathy may preferentially fix heart-reactive immunoglobulins to specific
sarcolemmal and subsarcolemmal antigens, and antiheart antibody may not be detectable
in the serum.

Additional Indexing Words:
Cardiomyopathy       Gamma globulin
Immunofluorescence   Complement

SERUM ANTIBODY directed against heart
muscle (HAb) has been reported in
patients with various forms of heart disease.1-3
It has been postulated that HAb is the result
rather than the cause of the injury in these
conditions. Despite severe cardiac disability
in patients with idiopathic cardiomyopathy, HAb
surprisingly is not found in increased fre-
quency. Thus Fletcher and Wenger4 and Camp et
al.,5 with an indirect immunofluorescent tech-
nique, found no increase in prevalence of
HAb in the sera of cardiomyopathic patients
compared with that of control subjects.
Similarly, we found no increase in prevalence
of HAb in 35 patients with cardiomyopathy.6
An explanation for this enigma may be
provided by the observations of Sanders and
Ritts,7 who found bound gamma globulin in
the hearts of five of nine patients with
cardiomyopathy. In the present study, the
hearts of three patients with the severe
congestive form of cardiomyopathy, whose
sera were negative for HAb, were examined
for bound gamma globulin.

Methods
Heart muscle was obtained from three male
patients (age range 39 to 48 years, mean 44
years) with the congestive form of cardiomyop-
athy who underwent cardiac transplantation. A
summary of their clinical data is shown in table 1.
The diagnosis of idiopathic cardiomyopathy was
confirmed in each following detailed histopath-
ologic examinations of the hearts. Heart tissue was
obtained at autopsy from seven individuals who
died of noncardiac causes. This group included
four adults (age range 18 to 33 years) and three
infants. Heart tissue was also obtained from six
older patients (age range 66 to 78 years) who
died within 1 week of acute myocardial infarction.
In the majority of cases in the control groups,
heart tissue was obtained within 4 hours of death
and in all cases within 6 hours of death.
All tissues were studied in a comparable
manner. A section of heart was frozen rapidly
with a mixture of dry ice and acetone and stored
at −70°C. Four-micra sections were cut on a
cryostat and placed on microscope slides. The
Clinical Data in Three Patients with Cardiomyopathy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Duration of symptoms</th>
<th>ECG</th>
<th>Chest X-ray</th>
<th>LV pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P.B.</td>
<td>48</td>
<td>M</td>
<td>Dyspnea</td>
<td>8 years</td>
<td>BP 110/70</td>
<td>Complete LBBB</td>
<td>Marked cardiomegaly, pulmonary congestion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Orthopnea</td>
<td></td>
<td>Cardiomegaly</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>PND</td>
<td></td>
<td>Ss, Ss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D.K.</td>
<td>39</td>
<td>M</td>
<td>Dyspnea</td>
<td>3 years</td>
<td>BP 110/75</td>
<td>Intraventricular block, LVH</td>
<td>Cardiomegaly, pulmonary congestion</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>Orthopnea</td>
<td></td>
<td>Cardiomegaly</td>
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<tr>
<td></td>
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<td></td>
<td>PND</td>
<td></td>
<td>Ss, Ss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.R.</td>
<td>47</td>
<td>M</td>
<td>Fatigue</td>
<td>7 years</td>
<td>BP 112/72</td>
<td>Complete LBBB</td>
<td>Cardiomegaly, pulmonary congestion</td>
</tr>
<tr>
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<td></td>
<td>Cardiomegaly</td>
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<td>PND</td>
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<td>Ss, Ss</td>
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</tbody>
</table>

Abbreviations: BP = blood pressure; LBBB = left bundle-branch block; LV = left ventricular; LVH = left ventricular hypertrophy; PND = paroxysmal nocturnal dyspnea.
shown in table 2. Heart tissue from two of the three patients with severe congestive cardiomyopathy contained abundant bound gamma globulin predominantly in subsarcolemmal sites (fig. 1). The heart from the third patient showed a moderate degree of subsarcolemmal and sarcolemmal staining. The predominant type of immunoglobulin bound to heart muscle was found to be IgG. Bound gamma globulin was not present in heart tissue obtained from any of the seven patients dying of noncardiac causes (fig. 2). However, a weak sarcolemmal staining was present in one of the six patients who died of myocardial infarction; this woman had suffered two previous myocardial infarctions. Complement was bound in moderate degree particularly in sarcolemmal sites in the hearts of the first two patients with cardiomyopathy, but was not observed in any of the other hearts in this study.

Sera obtained prior to transplant operations from the three patients with cardiomyopathy were negative for flAb by the indirect immunofluorescent test. Sera obtained within a week of the episode from the 10 patients with myocardial infarction and from eight of

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
<th>Average age (years)</th>
<th>Negative</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyopathy</td>
<td>3</td>
<td>44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6</td>
<td>69</td>
<td>5</td>
<td>1*</td>
</tr>
<tr>
<td>No heart disease</td>
<td>7</td>
<td>14</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

*This patient had two previous myocardial infarctions.

Figure 1

Heart tissue from a patient with severe congestive cardiomyopathy showing bound gamma globulin in dense white streaks located predominantly in subsarcolemmal sites (A) and to a lesser extent in sarcolemmal sites (B).
these 10 patients 3 to 4 weeks later showed no HAb.

Discussion

Circulating antiheart antibody has not been reported to occur with increased frequency in patients with cardiomyopathy, although van der Geld et al. reported HAb in 23 of 43 patients with endomyocardial fibrosis, a disorder peculiar to Africa and other tropical countries. In our study, six of 35 patients with cardiomyopathy had HAb. Moreover, none of the nine patients in class IV functional state (New York Heart Association) had HAb by the direct immunofluorescent technique. One of the patients with HAb deteriorated symptomatically and 8 months later showed no evidence of HAb preterminally. It is possible that HAb may occur early in cardiomyopathy and disappear as the disease advances. It is also possible that not all patients with cardiomyopathy produce HAb. The heart may adsorb HAb in advanced disease and remove it from circulation. A somewhat analogous mechanism is thought to be operative in certain types of human glomerulonephritis in which gamma globulin is bound to the kidney while circulating antikidney antibody is absent. Finally, HAb may circulate periodically as an immune complex with antigen and thus remain undetected by the usual serologic methods.

Heart tissue from the control patients did not show bound gamma globulin except in one case (table 2). Although these tissues were obtained within 6 hours of death, while the operative cases were obtained fresh, there was no evidence of autolysis in the routine histologic sections of any of the tissues. It is unlikely that the differences in timing could have played any important part in the observed changes. The mechanism by which gamma globulin is bound within the heart muscle fiber is not clear. Cellular permeability appears to be an essential prerequisite as antibodies theoretically cannot enter living cells. Injury, such as rheumatic fever, could...

Figure 2

Heart tissue from an adult dying of a noncardiac cause showing nonspecific autofluorescence.
alter cell membrane permeability and enable gamma globulin to localize within the muscle fiber. Similarly, repeated myocardial infarctions might account for the gamma globulin binding that was observed in one patient in our study. Although there are no data that indicate that bound gamma globulin in the heart plays a causal role in the pathogenesis of cardiomyopathy, it is possible that it may interfere with cardiac function.

Complement was observed in the heart tissue of two of the three patients with cardiomyopathy in sites which corresponded to areas of bound gamma globulin localization. This finding is supportive evidence that autoimmune mechanisms might be operative. Serum complement was not assayed prior to transplant operations. However, other parameters of immunologic reactivity, such as precipitating antibodies to nuclear constituents, antinuclear antibodies, rheumatoid factors, and positive serologic tests for syphilis, were not present. An increase in the serum IgM concentration greater than the mean + 2 standard deviations was observed in two of the three patients.

Sanders and Ritts observed bound gamma globulin in the hearts of a majority of their patients; however, the prevalence of HAb prior to the immunopathologic study was not reported. Based on their findings, they speculated that an autoimmune mechanism might have pathogenic significance in cardiomyopathy. In their study the age of the patient at the time of examination did not appear to influence the likelihood of finding bound gamma globulin. Other investigators in studies of serologic factors in cardiomyopathy concluded that autoimmune mechanisms were not responsible for the disease in the majority of patients. The bound gamma globulin observed in cardiomyopathic hearts might be unrelated to autoimmunity, but rather might be related to some other pathologic process, possibly infection. Serial immunopathologic and serologic studies will be necessary to determine if immune mechanisms are indeed involved. An autoimmune etiology would be enhanced if eluted gamma globulin from these hearts produced cardiomyopathy in suitable animals.

Acknowledgments

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References

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