Factors Which Initiate or Influence Edema in the Isolated Dog's Heart

By Peter F. Salisbury, M.D., Ph.D., Cecil E. Cross, Kimiko Katsuhara, M.D., Ph.D., and P. Andre Rieben, B.S.

EDEMA of the heart muscle appears to be a nonspecific response to various types of cardiac injury, as pointed out in several publications recently reviewed. The evolution of myocardial edema has not been studied in controlled experiments, although the increased water content or the edematous appearance of certain postmortem heart-muscle specimens has elicited comment and speculation, widely scattered through the literature. The present report describes the production and evolution of myocardial edema in isolated dog hearts.

Methods

Isolated dog hearts were perfused in a nonpulsatile fashion through the left coronary artery from a system of reservoirs. In some experiments, the fresh blood for coronary perfusion came from the femoral artery of a heparinized (1.5 mg./Kg.) donor dog and, after passing through the coronary vessels, was returned to the donor's femoral vein. In other experiments, the "Pulmo-Pak" disposable oxygenator (Abbott Laboratories, North Chicago, Illinois), the "Perfuso-Pac" (Travenol Laboratories, Morton Grove, Illinois) disposable oxygenator, or a rotating-disk oxygenator (Pemco Inc., Cleveland, Ohio) was used to arterialize the blood. The hearts were weighed on a balance before and after the experiments; they were mounted on a wire platform, as already described, so that heart weight and coronary perfusion pressure could be recorded simultaneously on a direct-writing oscillograph recorder. Blood temperature was kept between 35 and 37 C, but was steady in individual experiments. Arterial blood pH was between 7.35 and 7.40 in individual experiments. The heart rate was controlled by a pacemaker. Whenever necessary, the heart was defibrillated either electrically or with 3.0 ml. of 25 per cent potassium citrate injected directly into the coronary perfusion conduit. Drugs or chemicals could be added to the system as a whole, or could be injected into the coronary perfusion line and removed from the system after transit through the heart muscle by collecting the coronary venous blood.

In three experiments, chromium-tagged red cells were added to the perfusion system at the beginning of the experiment; at the end of the experiment the residual blood content of edematous heart muscle was measured from the radioactivity of weighed samples of coronary venous blood and of the empty, whole heart, which had been homogenized in a Waring blender.

Results

Criteria for Detecting the Presence and Observing the Evolution of Myocardial Edema

When isolated dog hearts were perfused with arterialized blood from a donor dog and the mean coronary perfusion pressure was below 150 mm. Hg, the recorded heart weight was stable for prolonged periods (maximal period here, three hours). Whenever perfusion pressure, heart rate, or left ventricular volume was changed within "physiological" limits, the heart weight shifted in a rapid, stepwise transition from one stable plateau to another. These stepwise changes of the heart weight were attributed to variations of the coronary blood volume, as described in another report.

Edema of the heart muscle was distinguished from changes of coronary blood volume by the appearance of a slope, which represented a steady weight gain of the perfused heart. During edema, the "bleeding volume" (decrease of heart weight during 60 seconds of coronary inflow) did not vary, but the baseline weight (heart weight after 60 seconds arrest of coronary inflow) increased in proportion with fluid accumulation. Weight gain was not referable to blood accumulation in the cardiac chambers, when these were open. Perfusion with radioactive red cells and subsequent measurements of the bleeding volume and of the residual
Figure 1

Influence of coronary perfusion pressure on rate of edema accumulation in isolated, beating hearts. (HW) = heart weight, (CP) = coronary perfusion pressure. Edema initiated by perfusion with bag oxygenator. Note typical "edema" slopes of weight registration with coronary pressure at 100 mm. Hg and absence of "edema" slopes with lower coronary pressures. Rapid stepwise changes of heart weight caused by changes of coronary blood volume.

The radioactivity of heart muscle homogenate ruled out interstitial hemorrhage or increased coronary blood volume as the sole cause of weight gain (table 1). Continuous weight gain of perfused hearts, indicated by a slope of the heart-weight registration, could only be attributed to accumulation of transudate in heart muscle. The maximal increase in heart weight (balance) observed here was 62 per cent of the initial weight. When edema was present, the heart muscle appeared paler than normal and was wet when sectioned at the end of the experiment. The presence of myocardial edema was also characterized by clear, yellowish droplets of transudate on the epicardial surface. Interstitial or subendocardial hemorrhages were noted occasionally after coronary perfusion with pressure above 200 mm. Hg.

Coronary Perfusion Pressure as a Factor that Can Initiate or Influence Myocardial Edema

In 23 isolated hearts perfused with arterialized blood from a donor dog, the left ventricle was empty or minimally distended with a balloon, while the valves were open and the heart was paced. Edema of the heart muscle was not seen when the nonpulsatile perfusion pressure was below 150 mm. Hg. Myocardial edema occurred regularly when the hearts were perfused with pressures exceeding 200 mm. Hg, under otherwise identical conditions. Whenever fluid accumulation was evident, further increases of the perfusion pressure would accelerate the rate of myocardial edema formation. When coronary perfusion pressure in donor-perfused hearts was reduced below a threshold, variable in individual experiments, the heart weight decreased slowly; the rate of weight loss was dependent upon the level of the coronary perfusion pressure. In our acute experiments, the heart never returned to the original weight.

After myocardial edema had been initiated by factors other than excessive coronary pressure (table 2), the rate of edema formation could be varied by changes of the coronary perfusion pressure (fig. 1). Mean coronary perfusion pressures below 70 mm. Hg often resulted in prolonged periods of weight loss, which proceeded in an asymptotic manner. The rate of weight loss was inversely related to the coronary perfusion pressure (fig. 2) and directly related to the magnitude of the preceding fluid accumulation.

Edema of the Heart Muscle Influenced by Osmotic Pressure of the Perfusion Fluids

When Ringer's solution was infused into the donor dog in amounts equivalent to 30 per cent or more of the blood volume in the entire preparation, coronary flow increased.

Table 1

<table>
<thead>
<tr>
<th>Initial HW Gm.</th>
<th>Δ HW Gm.</th>
<th>CP mm. Hg</th>
<th>Residual blood content† Gm./100 Gm. initial HW</th>
<th>Edema content‡ Gm./100 Gm. initial HW</th>
</tr>
</thead>
<tbody>
<tr>
<td>111</td>
<td>56</td>
<td>225</td>
<td>11.6</td>
<td>42.9</td>
</tr>
<tr>
<td>146</td>
<td>55</td>
<td>225</td>
<td>14.0</td>
<td>28.5</td>
</tr>
<tr>
<td>206</td>
<td>25</td>
<td>120</td>
<td>4.5</td>
<td>12.0</td>
</tr>
</tbody>
</table>

*Blood content determined with tagged red cells. HW = heart weight, CP = coronary perfusion pressure.
†Residual blood content of nonedematous hearts is 3 to 5 Gm./100 Gm. HW.
‡Edema content = (Δ HW/100 Gm. initial HW) — (excess residual blood content/100 Gm. HW).

Excess residual blood content is residual blood content of edematous hearts minus residual blood content of nonedematous hearts.
Table 2
Comparison of Factors Causing Myocardial Edema at a Mean Coronary Perfusion Pressure of 125 mm Hg

<table>
<thead>
<tr>
<th>Experimental procedure</th>
<th>Number of experiments</th>
<th>Mean rate of edema formation (Gm./100 Gm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor dog perfusion alone (control)</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Clean, rotating-disk oxygenator</td>
<td>5</td>
<td>0.05</td>
</tr>
<tr>
<td>Overdistention of left ventricle (balloon)</td>
<td>8</td>
<td>0.27</td>
</tr>
<tr>
<td>Hemodilution</td>
<td>6</td>
<td>0.32</td>
</tr>
<tr>
<td>Disposable bag oxygenators</td>
<td>18</td>
<td>0.32</td>
</tr>
<tr>
<td>Multiple electrical defibrillation†</td>
<td>6</td>
<td>0.96</td>
</tr>
</tbody>
</table>

* HW = heart weight.
† In conjunction with the disposable bag oxygenators.

immediately when the "diluted" blood reached the heart, causing rapid weight gain, which we interpreted as reflecting the expanded coronary blood volume. Although coronary flow and blood volume soon stabilized after "hemodilution," the heart continued to gain weight. This increased at a steady slope for a period of about 30 minutes and then reached a plateau after gaining about 5.4 Gm./100 Gm. initial heart weight (six experiments). Transudate appeared on the epicardium as soon as the heart started to gain weight after hemodilution.

The addition of concentrated crystalloid solutions (5 ml of 50 per cent glucose in water; 3 ml of 5 per cent sodium chloride), injected into the coronary perfusion conduit, caused a rapid decrease in heart weight that was proportional to the transient increase of osmotic pressure in the perfusion fluid (fig. 3). The maximum weight loss caused by such osmotic transients was 16 per cent of the original heart weight. Coronary flow increased during the transit of hypertonic blood. After passage of the hypertonic blood, the heart weight returned slowly to the original level or a new plateau slightly above. When osmotic transients were observed during periods of edema formation, the rate of fluid accumulation was not permanently influenced.

Influence of coronary pressure on rate of myocardial edema formation in one experiment. Edema initiated by perfusion with bag oxygenator at CP of 125 mm Hg. Note fluid accumulation of 3.2 Gm./min. at 200 mm Hg coronary pressure (last observation) and loss of weight from the heart with coronary pressures below 60 mm Hg.

Edema of the Heart Muscle Initiated or Influenced by Myocardial Injury

Whenever the heart muscle had been injured, myocardial edema became evident at coronary perfusion pressures between 75 and 120 mm Hg (table 2). Cardiac injury was produced here by temporary overdistention of the left ventricle with a balloon (left ventricular diastolic pressure above 15 mm Hg), multiple defibrillation, or by the use of disposable bag oxygenators (fig. 4), but not by a carefully cleaned rotating-disk oxygenator. Whenever the heart was overdistended or when coronary perfusion was suddenly switched from the donor dog to a bag oxygenator, edema of the heart muscle appeared even though coronary perfusion pressure, blood pH, oxygenation, and other factors remained within normal limits. The continuous weight increase was initiated even when the disposable oxygenators were supplied with compressed air, and myocardial edema was, therefore, not referable to oxygen toxicity. When donor perfusion was resumed after the use of a bag oxygenator (four experiments), the
Figure 3
Influence of osmotic transient on weight of edematous heart. At (arrow) 3 ml. of 50 per cent glucose injected into coronary perfusion conduit (10 seconds injection time). Note weight loss with return of heart weight to previous slope after six minutes.

weight gain of the heart was arrested but not reversed during the period of observation, as long as the coronary perfusion pressure was not decreased. In six experiments, arterial blood from a donor dog was passed through a bag oxygenator into the coronary perfusion system while the coronary venous blood was returned to the donor. Edema of the heart muscle developed whenever the coronary perfusion blood passed through the disposable oxygenator. Repeated electrical or chemical defibrillation intensified myocardial edema formation.

Discussion
The potential role of myocardial edema as a pathogenetic mechanism in heart disease has been emphasized from time to time, most recently by Marchal and De Langen. The literature, already partially reviewed, demonstrates the need for more information concerning edema of the heart muscle. Post-mortem specimens from human patients show myocardial edema as an early morphological sign of acute infarction, and also in chronically ischemic regions. The water content of human heart muscle is increased in heart failure, hypoproteinemic states associated with liver disease, and when the plasma-protein pattern is altered by varied causes. In experimental preparations, increased myocardial water content has been demonstrated after acute or chronic cardiac injury, in failing heart-lung preparations, and in the ischemic territory previously supplied by an occluded coronary artery. Prolonged anoxia caused edema of the rat heart, but hemorrhagic shock in dogs did not change the extracellular water content of the heart muscle. Stubbs and Widdas recorded weight changes of the saline-perfused rabbit heart but could not investigate the relative contributions of interstitial fluid and of coronary blood volume to the observed changes. Intravenous hyaluronidase reduced the water content of ischemic regions of heart muscle, but unfortunately, it is not clear whether hemodynamic parameters or plasma proteins remained unchanged in the experiments; a fall in systemic arterial pressure or an increase of plasma osmotic pressure was not excluded as a possible explanation. From the literature, it can be concluded that edema of heart muscle is present in many injured hearts, that its cause and evolution are not well understood, that it may contribute to abnormal cardiac performance, and that the prevention or reversal of myocardial edema may be a therapeutic objective in the management of heart disease.

The method described here records changes of the weight of beating, isolated hearts. The tracing of heart weights integrates changes of the coronary blood volume and of myocardial liquid content; the blood content of the cardiac chambers did not contribute to the recorded heart weight, since the chambers were open and not filled with blood. Perfusion with tagged red cells showed that interstitial hemorrhage and other blood hold-up contributed not more than 15 per cent of the total weight gain in edematous hearts. Extensive interstitial hemorrhages were noted by visual inspection only after prolonged perfusion with extreme coronary pressures. The electrically recorded weight changes were in close agreement with the directly measured heart
MYOCARDIAL EDEMA

weights before and after perfusion. We believe, therefore, that the data reported here enabled us to distinguish sudden changes of heart weight caused by variation of coronary blood volume from the slow and progressive changes of heart weight that characterized the accumulation or disappearance of edema fluid.

It is generally known, but apparently not recorded in the literature, that perfusion of the coronary vessels with abnormally high pressures or flows causes edema of the heart muscle. This fact was confirmed here by the consistent observation that, in otherwise uninjured hearts, a nonpulsatile coronary pressure of 200 mm Hg or more produced myocardial edema. It thus appears improbable that edema of the mammalian heart muscle is initiated by "high blood pressure." However, it is clear that coronary artery pressure was an important determinant of the rate of fluid accumulation or disappearance after edema-provoking insults to the heart. Once myocardial edema formation had been initiated by any one of many different factors, the heart muscle continued to accumulate fluid when the coronary-artery pressure was as low as 100 mm Hg. In the same experiments, myocardial edema formation was arrested or reversed when the coronary pressure was decreased to 75 or 50 mm Hg, while other factors remained constant. Elevated coronary venous pressure may also enhance myocardial fluid accumulation; this possibility was not investigated here because of the difficulty of obtaining representative coronary venous-pressure measurements. The changes of myocardial fluid content with variation in coronary-artery pressure, after hemodilution and during osmotic transients, were expected, since they follow from Starling's concept of tissue-fluid formation and are analogous to similar observations on saline-perfused hearts and on hearts in situ from which the lymphatic drainage was collected.

Table 2 summarizes the rate of edema formation at a standard coronary perfusion pressure of 125 mm Hg. From earlier experiments, we had reason to expect that multiple defibrillation or distention of the left ventricle to a diastolic pressure exceeding 15 mm Hg would cause cardiac injury with resulting fluid accumulation. To our complete surprise, severe myocardial edema also appeared within a few minutes whenever arterialized perfusing blood was routed through a commercially available oxygenator, whereas myocardial edema was not initiated by donor-dog perfusion or by the use of a clean, rotating-disk oxygenator. Myocardial edema was not prevented when fresh blood from the femoral artery of the donor was passed through a bag oxygenator into the perfusion reservoir, even when the blood pH was normal and when air was used to aerate the blood; the toxic effect of bag oxygenators, therefore, cannot be referable to oxygen poisoning or other trivial explanations. It is likely that the appearance of myocardial edema in isolated, perfused hearts can be used as a criterion for detection and measurement of oxygenator toxicity, a subject deserving separate investigation.

Summary

Isolated dog hearts were perfused while the heart weight was electrically recorded. Arterialized blood was pumped into a coronary perfusion reservoir either from the femoral artery of a donor dog or from the arterial outlet of various oxygenators. The right heart was widely open. The presence of myocardial edema and the rate of fluid accumulation in heart muscle were observed from the slopes of the weight registration and from the dif-
ference of the directly measured heart weights before and after an experiment. Blood hold-up was measured in three experiments with tagged red cells: it accounted for 15 per cent or less of the observed weight gain.

When the heart was perfused from a donor dog and was not otherwise injured, myocardial edema fluid did not accumulate unless the coronary pressure exceeded 200 mm Hg. Myocardial edema also formed when blood was diluted with Ringer's solution or after cardiac injury; the rate of edema formation was then dependent on the coronary perfusion pressure. Edematous hearts could often be made to lose weight (i.e., edema fluid) when perfused at pressures below 100 mm Hg. Perfusion with blood from a disposable bag oxygenator initiated myocardial edema formation almost immediately.

References
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