Effects of Nucleosides on Acute Left Ventricular Failure in the Isolated Dog Heart

By N. M. Buckley, M.D., K. K. Tsuboi, Ph.D., and N. J. Zeig, M.D.

The effect of nucleosides on acute left ventricular failure was studied in 15 isolated dog hearts. The unilateral failure was produced by exposure of the isolated left ventricle to elevated aortic pressure. Parameters of left ventricular function used to evaluate the control, failure, and nucleoside periods included ventricular stroke work and output, contractility and distensibility. Adenosine and cytidine were found to be negative inotropic substances. Guanosine, inosine, thymidine and uridine were found to be positive inotropic substances, restoring the control level of ventricular function.

We have found that acute left ventricular failure following prolonged exposure of the isolated left ventricle to elevated aortic pressure is characterized by progressive loss of contractility and distensibility of the ventricle wall. Since work load and the duration and extent of filling were controlled in the experiments, changes in these properties would be expected to occur on the basis of chemical changes in the myocardium. The contribution to such effects by variations in distribution of coronary flow is still under investigation. The present study was suggested to us by a preliminary report of work by Cook, Greene and Lorber who found that certain nucleosides halt the progressive deterioration of the electrically-driven frog ventricle strip. It seemed possible that nucleosides might be involved in the development of or recovery from the acute unilateral ventricular failure produced in our experiments. We chose to study the inotropic behavior of these compounds in the isolated mammalian ventricle preparation in which the working muscle was perfused by its own coronary circulation and the hemodynamic factors determining stroke work could be controlled. In such a preparation, stroke work and the distensibility and contractility of the ventricle could be evaluated directly.

Methods

Experiments on the Isolated Left Ventricle

The isolated left ventricle preparations were made as previously reported. Aortic resistance was controlled by the use of the Starling peripheral resistance unit. The hydrostatic pressure available for filling the left ventricle was kept constant throughout diastolic filling. Blood was oxygenated on passage through the device described previously. Blood temperature at the sino-atrial node region was regulated so that variations in heart rate could occur only in response to chemical stimuli.

Control period observations were begun within 1 to 1 1/2 hours after a dog had been anesthetized for dissection. Then acute left ventricular failure was produced by elevating the aortic resistance to 90 per cent beyond the control level. Decreased stroke volume and stroke work became apparent within 15 to 20 min., at which time the resistance was returned to the control level. Observations during the period of failure were then made at the same aortic resistance, filling pressure and heart rate as in the control period. Finally, a single dose of nucleoside was injected into the ventricular inflow circuit and observations repeated at intervals thereafter.

The nucleosides examined included the naturally occurring purine ribosides adenosine, guanosine and inosine; the pyrimidine ribosides cytidine...
and uridine; and the deoxyriboside thymidine.* All compounds were dissolved to minimum volume in saline and added directly to the circulating blood in 10 μM amounts in all experiments. The final concentration of nucleoside did not exceed 4 × 10⁻³ molar, varying somewhat with the volumes of blood employed among experiments. Since circulation in the left ventricle preparation does not involve the lungs, metabolism of the administered nucleoside was restricted to the myocardium and blood. Metabolic studies with dog blood are included to show that all or most of each administered nucleoside remains available to the myocardium. Pilot studies were carried out to determine the time of onset and duration of action of each of the nucleosides, as well as to study the effects of administration of more than 1 test compound in the same heart.

Ventricular function was evaluated during control and failure periods and after the administration of a nucleoside. In 2 experiments on each nucleoside found to have positive inotropic action, ventricular function was further tested by volume loading at 5 increments of filling pressure during each period. Since this procedure required 20 min., an infusion was necessary to maintain suitable concentrations of certain nucleosides.

Recordings and Calculations

The hemodynamic determinants of left ventricular stroke work were controlled as closely as possible. As a guide for aortic pressure adjustments, a damped mercury manometer was attached to the outflow cannuula. The hydrostatic pressure available for filling the ventricle was measured from the height of the blood reservoir above the inflow cannula. Aortic outflow was collected for 3 sec., coronary drainage from the right heart for 30 sec. at the time of recording. Stroke volume was calculated from total ventricular outflow divided by heart rate. Aortic and left ventricular pressure were registered by Statham no. P23D arterial pressure transducers. Simultaneous pressures, or left ventricular pressure and electrocardiogram, were displayed on a Tektronix dual-trace oscilloscope and photographed by a Grass oscillographic camera at a film speed of 25 mm/sec. The film was magnified by anastigmatic projector to twice the area of the oscilloscope screen to facilitate detailed analysis of the records. Ventricular function was evaluated from calculations of stroke work, diastolic impedance, and rates of isometric intraventricular pressure change.

Left ventricular stroke work (Gm. M.) was calculated as the product of stroke volume and mean aortic or ventricular ejection pressure. Mean pressures were obtained by planimetric integration of the recorded pressure curves. The contours of these curves were compared critically as a check against the occurrence of aortic valve incompetence during the period of ventricular failure.

Diastolic impedance³,⁴ was calculated during that apparently steady state in the cardiac cycle when diastolic intraventricular pressure and inflow were constant. This dynamic resistance to deformation was expressed as the diastolic pressure developed per unit inflow through a circuit of known resistance (dynes × sec/cm.²). Under the controlled hemodynamic conditions of these experiments, changes in diastolic impedance were interpreted to indicate changes in the visco-elastic properties determining the distensibility of the ventricle wall.

Rates of isometric pressure development and fall were calculated from the paired pressure records or by the slope method and found comparable to recent measurements in the intact dog.⁵ As long as the duration of the QRS and QT intervals of the electrocardiogram remained unaltered, the rate of change of intraventricular pressure during the period of isometric activity indicated the rate of isometric contraction or relaxation. Variations between control and experimental measurements were concluded to indicate changes in ventricular contractility.

In the more extensive experiments on each of the nucleosides found to have positive inotropic action, ventricular function was also evaluated from the responsiveness to volume loading. “Sarnoff curves”⁶ were constructed for each period of observation at 5 different filling pressures. Such curves are ordinarily shown as stroke work (ordinates) plotted against filling pressure (abscissas). However, for comparison of hearts working under different hemodynamic conditions, graphs were also made showing the ratio of each new work level to the initial control level (ordinates) plotted against changes in filling pressure beyond the control level (abscissas).

Experiments with Dog Blood

Freshly drawn dog blood was defibrinated and incubated directly with each of the nucleosides selected for investigation. Experiments were carried out separately in the presence of intact and laked red cells for comparative purposes. Incubation mixtures contained 1 ml. of freshly drawn dog blood.
NUCLEOSIDES IN VENTRICULAR FAILURE

dog blood, 4 μM of a nucleoside in 1 ml. of physiologic saline or water, and additional saline or water to a final volume of 4 ml. The saline and water series were for intact and laked red cell studies respectively. The incubation period was 3 hours at 35 C.

The metabolic products were separated by paper chromatography following initial removal of intact red cells by centrifugation, and deproteinization with perchloric acid. Excess removal of intact red cells by centrifugation, and cell studies respectively. The incubation period was 3 hours at 35 C.

chromatograms were developed by the ascending technic in stainless steel chromatography. Chromatograms were developed by the ascending technic in stainless steel chromatography. The solvents employed in this study were isobutyric acid—ammonium isobutyrate; ammonia water; and 77-propanol—ammonium butyric acid—ammonium isobutyrate, 77-propanol deproteinization with perchloric acid. Excess perchlorate was removed as the insoluble potassium salt and the remaining products concentrated to small volumes prior to chromatography.

RESULTS

Five single-dose experiments were performed using each nucleoside, in a total of 15 dog hearts. One purine and 1 pyrimidine compound were usually administered to the same heart since such a procedure had been shown to yield no difference in their individual effects. Two Sarnoff curve experiments were performed on each of the 4 nucleosides found to have a positive inotropic effect, in a total of 8 dog hearts. That significant amounts of unchanged nucleoside remained available to the myocardium in spite of degradative action by blood enzymes was assured on the basis of experiments detailed in a later section of this report.

Effect of Purine Nucleosides on the Acutely Failed Left Ventricle

Table 1 presents data from 9 experiments typical of all 15 in which adenosine, guanosine or inosine were administered after acute left ventricular failure had occurred. The values during the control and failure period were similar to those obtained previously for left ventricles working under these conditions. The increased impedance and the slow rates of isometric contraction and relaxation are as characteristic of the acute failure state as is the decreased stroke work. The decreased distensibility was observed when residual volume increases were restricted, and was therefore independent of ventricular size. The coronary drainage was a larger proportion of the cardiac output in the failure period, than in the control period.

The effects of adenosine were obvious within the 1 or 2 min. necessary for mixing and distributing the compound throughout

<table>
<thead>
<tr>
<th>Exp.</th>
<th>Period*</th>
<th>Parameters of ventricular function†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Work (X 10³)</td>
</tr>
<tr>
<td>1</td>
<td>control</td>
<td>6.0 .14</td>
</tr>
<tr>
<td></td>
<td>failure</td>
<td>5.8 .60</td>
</tr>
<tr>
<td></td>
<td>adenosine</td>
<td>5.7 .1.10</td>
</tr>
<tr>
<td>2</td>
<td>control</td>
<td>6.7 .04</td>
</tr>
<tr>
<td></td>
<td>failure</td>
<td>5.0 .07</td>
</tr>
<tr>
<td></td>
<td>adenosine</td>
<td>5.5 .10</td>
</tr>
<tr>
<td>3</td>
<td>control</td>
<td>5.7 .05</td>
</tr>
<tr>
<td></td>
<td>failure</td>
<td>3.5 .12</td>
</tr>
<tr>
<td></td>
<td>adenosine</td>
<td>1.9 .74</td>
</tr>
<tr>
<td>6</td>
<td>control</td>
<td>5.0 .02</td>
</tr>
<tr>
<td></td>
<td>failure</td>
<td>4.7 .15</td>
</tr>
<tr>
<td></td>
<td>guanosine</td>
<td>5.0 .02</td>
</tr>
<tr>
<td>7</td>
<td>control</td>
<td>5.3 .09</td>
</tr>
<tr>
<td></td>
<td>failure</td>
<td>3.5 .76</td>
</tr>
<tr>
<td></td>
<td>guanosine</td>
<td>4.7 .10</td>
</tr>
<tr>
<td>8</td>
<td>control</td>
<td>7.1 .04</td>
</tr>
<tr>
<td></td>
<td>failure</td>
<td>5.0 .10</td>
</tr>
<tr>
<td></td>
<td>guanosine</td>
<td>6.7 .04</td>
</tr>
<tr>
<td>11</td>
<td>control</td>
<td>8.5 .05</td>
</tr>
<tr>
<td></td>
<td>failure</td>
<td>6.0 .22</td>
</tr>
<tr>
<td></td>
<td>inosine</td>
<td>6.6 .05</td>
</tr>
<tr>
<td>12</td>
<td>control</td>
<td>6.7 .04</td>
</tr>
<tr>
<td></td>
<td>failure</td>
<td>4.5 .23</td>
</tr>
<tr>
<td></td>
<td>inosine</td>
<td>6.7 .04</td>
</tr>
<tr>
<td>13</td>
<td>control</td>
<td>6.6 .04</td>
</tr>
<tr>
<td></td>
<td>failure</td>
<td>4.8 .27</td>
</tr>
<tr>
<td></td>
<td>inosine</td>
<td>5.5 .14</td>
</tr>
</tbody>
</table>

*All at the initial control level of filling pressure and aortic pressure.
†Work, left ventricular stroke work (Gm. M.); Imp. (X 10⁹), diastolic impedance (dyne sec./cm.²); dPC, rate of isometric contraction (mm. Hg/msec.); dPR, rate of isometric relaxation (mm. Hg/msec.); HR, heart rate per minute.
the heart and artificial peripheral circulation. The heart slowed, often becoming irregular, but usually resumed its initial rate within 5 min. Figure 1 shows photographic records from an adenosine experiment. A marked dysrhythmia is illustrated in C. The subsequent period of regular slow heart rate in D was similar to that used in each adenosine experiment to calculate the data for table 1.

The decreased stroke volume and stroke work, increased impedance, and slower rates of isometric contraction and relaxation were more profound in some hearts than in others at this time. When heart rate returned to its initial control value, these changes typical of ventricular failure were seen to persist. In 3 of the 5 hearts (nos. 2, 3 and 5), the left ventricle eventually ceased to function. In 2 of these (3 and 5), coronary drainage approached 80 per cent of the total ventricular output.

Administration of guanosine or inosine led to an increase in stroke volume and work within 2 to 5 min. There was no change in heart rate, nor in the duration of QRS and QT intervals of the electrocardiogram. The maximal effects of these compounds, in the amounts used, lasted for about 10 min. During this time, impedance decreased and the rates of isometric contraction and relaxation were faster in all but 1 inosine experiment. Normal intraventricular pressure curve contours were restored (fig. 3). Control values were obtained again after 20 min. Similar inotropic effects were obtainable on repeated administration of single doses of the same nucleoside.

is contrasted with the control (— — — — —) and failure (□ — — □) periods, at constant aortic resistance and heart rate.

Fig. 3 Bottom. Left ventricular pressure (LVP) and electrocardiogram recorded from a uridine experiment (no. 26): A, during the control period; B, during the failure period; and C, 5 min. after the administration of uridine. Time scale for all 3 records is shown below C. Filling pressure, 11.6 mm. Hg; aortic resistance, 90 mm. Hg; and heart rate, 83 beats/min.
Effects of Pyrimidine Nucleosides on the Acutely Failed Left Ventricle

Table 2 presents data from 9 experiments typical of all 15 in which cytidine, thymidine or uridine were administered after acute left ventricular failure had occurred. Again the control and failure period data were comparable to previous observations.

The effects of cytidine were noted within 2 to 5 min. and included a slowing of the heart without dysrhythmia. Stroke work and volume continued to decrease. The rates of isometric contraction and relaxation became slower and diastolic impedance increased. A low level of ventricular function was maintained in all hearts. The data of table 2 include those taken during the period of slower heart rate, but the changes persisted after the rate had returned to its initial value.

Administration of thymidine or uridine led to an increase in stroke volume and work within 2 to 5 min. There were no detectable changes in heart rate, nor in duration of QRS and QT intervals of the electrocardiogram. The effects of thymidine lasted about 10 min. while those of uridine persisted beyond 20 min. Diastolic impedance decreased and the rates of isometric contraction and relaxation were faster during this period. In 2 hearts (nos. 21 and 22), the proportion of coronary drainage to total ventricular output decreased 50 per cent after thymidine administration. Figure 3 shows the photographic records from an uridine experiment, illustrating the restoration of contour of ventricular pressure pulses observed also in the guanosine, inosine and thymidine experiments.

Figure 4 presents Sarnoff ventricular function curves which are typical for thymidine and uridine experiments. The control period curves are normal. The failure period curves are either "descending limb" (A) or "depressed" (B) types. Data for the uridine curves were obtained during the 20 min. period of that compound's effectiveness. Data for the thymidine curves were obtained dur-
TABLE 3.—Nucleoside Metabolism by Dog Blood

<table>
<thead>
<tr>
<th>Added nucleoside</th>
<th>Products resulting from in vivo incubation for 3 hours</th>
<th>% Products recovered</th>
<th>Products recovered %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intact whole blood</td>
<td>Hemolyzed blood</td>
<td></td>
</tr>
<tr>
<td>Adenosine</td>
<td>inosine</td>
<td>inosine</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>hypoxanthine</td>
<td>hypoxanthine</td>
<td>37</td>
</tr>
<tr>
<td>Inosine</td>
<td>inosine</td>
<td>inosine</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>hypoxanthine</td>
<td>hypoxanthine</td>
<td>34</td>
</tr>
<tr>
<td>Guanosine</td>
<td>guanosine</td>
<td>guanosine</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>guanine</td>
<td>guanine</td>
<td>46</td>
</tr>
<tr>
<td>Uridine</td>
<td>uridine</td>
<td>uridine</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>uracil</td>
<td>uracil</td>
<td>30</td>
</tr>
<tr>
<td>Cytidine</td>
<td>cytidine</td>
<td>cytidine</td>
<td>100</td>
</tr>
<tr>
<td>Thymidine</td>
<td>thymidine</td>
<td>thymidine</td>
<td>100</td>
</tr>
</tbody>
</table>

*The listed products account for, in each instance, more than 90 per cent of the initially added nucleoside.

The possibility of nucleoside degradation by blood enzymes, leading to secondary products responsible for the observed cardiac effects, could not be discounted and was therefore separately examined. Adenosine metabolism by the human erythrocyte has been described in the early literature. The isolation of a purine nucleoside phosphorylase from these cells has been reported more recently and its specificity and kinetic characteristics defined. This enzyme does not act on adenosine. The extent to which similar or related enzymes capable of degrading nucleosides exist in dog blood was therefore investigated. Since the blood circulating in the isolated left ventricle preparation was unavoidably partially hemolyzed, the degradative capacities of both intact and laked blood were separately examined. Leukocytes were destroyed on passage through the perfusion circuit.

From the results summarized in table 3, it is apparent that the tested nucleosides were either not metabolized at all (cytidine, thymidine) or showed incomplete degradation following prolonged incubation (3 hours) with intact or hemolyzed red cells. Rapid deamination of adenosine to inosine, however, did occur and was found to be complete well within the 3 hour incubation period. Inosine and guanosine degradation was found to proceed rapidly to equilibrium by the action of the now familiar purine nucleoside phosphorylase catalyzing the following reversible reaction:

\[
\text{inosine} \rightleftharpoons \text{inorganic ribose-1-phosphate} + \text{guanosine} \rightleftharpoons \text{phosphate} \rightarrow \text{purine base}
\]

The extent of nucleoside degradation in this reaction is necessarily limited by the equilibrium which strongly favors the nucleoside as indicated by the arrows. Nucleoside degradation proceeds to a greater extent in the presence of intact as compared to hemolyzed red cells, due to a continued shift in the equilibrium to the right as the pentose-phosphate is metabolized and the free base extruded from the cell.

Uridine degradation also proceeds to a limited extent only, as observed with purine nucleosides. Whether a specific pyrimidine nucleoside phosphorylase or a single hydrolyase reaction is responsible for this degradation was not ascertained at this time.

DISCUSSION

Investigations on cardiac failure have been complicated by the number of variables contributing to the development and maintenance of this condition. Particular difficulty arises in attempting an evaluation of the apparent lack of complete agreement between our results and those in the recently published experiments on nucleoside effects on frog ventricle strips. It should be noted that the latter results were obtained after allowing a 3 hour deterioration of the ventricle strips, a situation associated with electrolyte shifts. In our experiments, no electrocardiographic changes characteristic of potassium ion concentration changes were seen during the 1 to 1½ hours of observation. The change in
plasma concentration of potassium from the beginning of the control period to the end of the experiment was of the order of magnitude of 0.5 mEq./L.

The type of acute ventricular failure following the relatively simple stress of high aortic pressure was chosen for the present study because it had been shown to be hemodynamically irreversible and to involve only the left ventricle. The levels of blood oxygen, glucose and insulin were maintained. The observed loss of contractility and distensibility associated with the decreased stroke work and output were independent of the size of the ventricle. They were reproducible from heart to heart, ensuring a relative uniformity of preparations in which to study the effects of nucleosides.

It seemed remarkable to us to find that each nucleoside examined, without exception, showed definable cardiac effects in the failing left ventricle. Administration of the various compounds consistently led to 2 contrasting patterns of ventricular response. Guanosine, inosine, thymidine and uridine as a group were positive inotropes on the basis of the generally accepted criteria of increased stroke work and output. In their presence, the left ventricle in failure regained or surpassed its original control level of function. Adenosine and cytidine were negative inotropes on the basis of decreased stroke work and output. In their presence, the left ventricle exhibited a further loss of function. The comparative effectiveness of the different compounds tested was not evaluated at this time. Further quantitative definition of the active chemical groupings is anticipated (see below).

The question of the amount of nucleoside available to the myocardium could be evaluated from the separate studies on their metabolism by dog blood. The negative inotropic effects of adenosine were even more striking in view of the evidence that rapid inosine formation from adenosine occurs in the blood. Cytidine and thymidine were unchanged by erythrocytes and thus completely available to the myocardium. Guanosine, inosine and uridine undergo only limited degradation to their respective bases and remain for the most part unchanged in the circulating blood.

The changes in rates of isometric contraction and relaxation observed in the failure and nucleoside periods of the experiments might be considered to be related to variations in synchronization of electrical activation or recovery and not to changes in contractility. However, prolongation of QRS or QT intervals was not associated with slower development and fall of intraventricular pressure during the failure period. Administration of positively inotropic nucleosides did not consistently shorten the duration of QRS or QT although the rise and fall of intraventricular pressure were always faster. Thus it was concluded that actual changes in contractility had occurred.

It was necessary to demonstrate that the changes in distensibility in the periods of failure and nucleoside administration were independent of variations in the size of the ventricle. Although the hemodynamic determinants of ventricular filling could be controlled in these experiments, it was inevitable that the altered contractility lead to changes in residual ventricular volume and the duration of filling at constant heart rate. In the previous report on ventricular failure it was shown that the observed loss of distensibility was not a mere consequence of the increased ventricular volumes, on the basis of separate cardiometric studies at experimentally restricted diastolic volumes. For the present report, the question was further investigated by determining the effects of nucleosides on the compliance of perfused quiescent rat hearts from measurements of the intraventricular pressure-volume relationships as volumes were added from a syringe. Perfusion with adenosine or cytidine always led to a decreased compliance, while perfusion with the other nucleosides always led to an increased compliance. It was therefore concluded that the nucleosides studied...
in the dog heart experiments had a direct effect on the distensibility of the left ventricle.

Administration of the positive inotropic nucleosides to the failing left ventricle was not accompanied by a change in heart rate, but by an increase in the duration of filling secondary to faster rates of contraction and relaxation. The somewhat longer filling time and consequently larger end-diastolic volume could contribute to the improvement of ventricular function. Evaluation of the further loss of distensibility and contractility following the administration of adenosine or cytidine was complicated by the initial slowing of the heart. However, the observed changes persisted after heart rate had returned to the control value. Furthermore, on the basis of previously reported experiments in which heart rate was controlled by electrical stimulation in the sino-atrial node regions, no loss in these properties would be expected at slower heart rates.

The development of acute left ventricular failure and the observed inotropic effects might be considered incidental to changes in coronary flow. In the isolated left ventricle preparation, coronary flow would be expected to be disproportionately distributed since the non-working right ventricle offers less resistance to flow through the myocardium. Elevation of aortic resistance to produce left ventricular failure would be expected to exaggerate this disproportion and thus lead to relative left ventricular coronary insufficiency. Electrocardiograms did not reveal any of the expected disturbances. Experiments in progress involving graded changes in blood oxygen saturation of coronary perfusion pressure show that electrocardiographic changes occur under these conditions before the appearance of changes in ventricular contractility or distensibility. Since the proportion of cardiac output estimated to be coronary flow was greater during the failure period of the present experiments, the conclusion was drawn that observations during this period could be only partly due to relative coronary insufficiency.

The effects of nucleosides and related compounds on left coronary artery flow have been reported for infusions of 0.1 to 1.0 µM/min. in the intact dog. The flow was increased by adenosine and unchanged by guanosine, inosine, cytidine or uridine. Thymidine was not studied. Coronary drainage was used as an index of coronary flow in full realization of the limitations of this method. Marked increases were observed in 2 of the 5 adenosine experiments and decreased in 2 of the 5 thymidine experiments. Improvement of coronary circulation in the presence of adenosine could be expected to increase the supply of nutrients to the ventricle, yet failure progressed. Impairment of coronary circulation in the presence of thymidine could be expected to decrease the supply of
NUCLEOSIDES IN VENTRICULAR FAILURE

nutrients to the ventricle, yet recovery from failure occurred. Thus the observed inotropic effects were concluded to be independent of variations in the general nutritional state of the ventricle due to alterations in coronary flow.

Examination of the chemical-structural relationships among the tested nucleosides reveals a remarkably consistent correlation between the observed cardiac effects and the specific substituents on the number 6 carbon of the pyrimidine rings. The relevant substituent groups appearing on the purine and pyrimidine bases of the nucleosides are illustrated in figure 5. Nucleosides containing a hydroxyl group on the number 6 ring-carbon were all found to be positive inotropes. On the other hand, nucleosides containing an amino group in this position showed a characteristic negative inotropic effect. Other substituent groups, including the nature of the carbohydrate moiety, did not appear to influence the particular inotropic effect exerted by the nucleoside. In this respect, preliminary experiments initiated in an attempt to further define the relationship between chemical structure and inotropic behavior reveal that the bases of the nucleosides alone exert similar inotropic action.

At least 2 different directions of inquiry are suggested in attempting to establish a mechanism of action of this group of inotropic substances. Participation in cell membrane function is indicated by the onset, magnitude and duration of cardiac effects of such small concentrations of nucleosides as reported here. Further examination of this question is also indicated by the recent findings that adenosine, inosine and guanosine alter the electrical properties of the rat atrium.17 Other recent work has revealed that there are alterations in the physical properties of actomyosin prepared from failing hearts.18, 19 Since such changes could account for the loss of distensibility and contractility observed in the failure periods of our experiments, further examination of the effect of nucleosides on contractile proteins is warranted. Reversal of ventricular failure by the nucleosides tested indicates the possibility that they and/or their degradation products may be involved in some manner in the maintenance of the integrity of the contractile system.

SUMMARY

A reproducible type of acute unilateral ventricular failure was produced in 15 left ventricle preparations. Administration of the nucleosides selected for investigation was accompanied in each case by reproducible effects on stroke work and ventricular distensibility and contractility. The concentration of nucleoside available to the myocardium was estimated to be about $4 \times 10^{-5}$ molar. On the basis of separate metabolic studies with dog blood, it was concluded that only limited degradation of administered nucleosides by blood enzymes could have occurred.

Adenosine and cytidine slowed the heart initially. Persistent negative inotropic effects included decreased stroke work, slower rates of isometric contraction and relaxation, and increased diastolic impedance. In all 5 cytidine experiments, the left ventricle continued to function at a failure level. In 3 of the adenosine experiments, failure progressed until ventricular function ceased. Guanosine, inosine, thymidine and uridine did not alter heart rate. Their positive inotropic effects included increased stroke work, faster rates of isometric contraction and relaxation, and decreased diastolic impedance. Saroff ventricular function curves constructed in 2 experiments on each of these compounds showed loss of response to volume loading during the failure period, followed by restoration during the period of nucleoside administration.

The observed inotropic effects were shown to be independent of heart rate, chamber size or coronary supply. These effects were correlated with the chemical structure of the compounds, from the observation that they could be identified as positive or negative inotropes according to the substituent group on the 6-carbon of the pyrimidine ring.
Acknowledgments

The authors wish to thank Drs. Charles W. Frank and Sam Seifter for critical evaluation of the methods used.

Summario in Interlingua

Un reproducibile typo de acute disfallimento ventricular esseva producite in 15 preparatos sinistro-ventricular. Le administration del nucleosidos seligite pro iste studio esseva acompaniate in omne caso pro reproduicibile efectos in le labor pulsatil e in le distensibilitate e contractilitate ventricular. Le concentration de nucleosido disponibile al myocardio esseva estimate como circa 4 × 10^{-5} molar. Super le base de separate studios metabolic in sanguine canin, il esseva concludite que solmente un degradation limitate del nucleosidos administrate poteva haber essite effectuate per enzymas in le sanguine.

Adenosina e cytidina relentava le action del corde initialmente. Persistente effectos inotropic negative esseva reduction del labor pulsatil, relentation de contraction e relaxation isometric, e augmentos del impedantia diastolic. In omne le cinque experimentos con cytidina, le ventriculo sinistre continuava funcionar a nivellos de disfallimento. In tres del experimentos con adenosina, le disfallimento progredeva usque le function ventilcular cessava. Guanosina, inosina, thymidina, e uridina non alterava le frequentia cardiaca. Lor positive effectos inotropic includeva augmento del labor pulsatil, acceleration del contraction e relaxation isometric, e reduction del impedantia diastolic. "Curvas Sar-noff de function ventilcular," construite in duo experimentos pro cata un del compositos mentionate revelava un perdita de responsa a cargaition in volumine durante le periodo de disfallimento, sequite per restauramation durante le periodo administration del nucleosidos.

Le observe effectos inotropic se monstraiva independente de frequentia cardiaca. dimension del cameras, o provision coronari. Iste effectos esseva correlatoate con le structura chimic del compositos, i.e., iste com-posit os poteva esser identificate como isotropos positive o negative secundo le identi-tate del gruppo substituted in le position del seste carbon del anulo de pyrimidina. Investigations additional es necessari pro determinar le participantes in le mecanismo de action e le sito de su occurrentia.

References


Effect of Nucleosides on Acute Left Ventricular Failure in the Isolated Dog Heart

N. M. BUCKLEY, K. K. TSUBOI and N. J. ZEIG

Circ Res. 1959;7:847-857
doi: 10.1161/01.RES.7.6.847

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1959 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/7/6/847