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Cardiac Anaphylaxis in Isolated Guinea Pig Hearts Perfused at Constant Flow or Constant Pressure (42534)

J. F. REGAL AND L. J. HELLER

Departments of Pharmacology and Physiology, University of Minnesota, School of Medicine, Duluth, Minnesota 55812

Abstract. Acute responses to antigen–antibody interactions (anaphylactic reactions) in isolated guinea pig hearts are reported to include decreases in coronary flow, increases in heart rate, prolongation of impulse propagation, development of arrhythmias, and transient increases followed by substantial decreases in ventricular contractile force. It is not clear from these studies, however, whether all of the changes are direct effects of the mediators released by the antigen–antibody reaction or whether some of them are indirect results of the severe reduction in flow evoked by coronary vasoconstriction. Therefore, the present study was designed to assess cardiac anaphylactic events in isolated hearts of guinea pigs passively sensitized with IgG antibody to ovalbumin under conditions in which coronary perfusion pressure was maintained constant and to compare the responses to those of hearts in which coronary flow was maintained at a constant rate. Our data indicate that when coronary flow decreased during anaphylaxis (constant pressure perfusion), hearts responded to antigen challenge with greater (i) prolongation of the PR interval, (ii) duration of arrhythmias, (iii) suppression of left ventricular systolic pressure, and (iv) release of histamine and adenosine plus inosine into the venous effluent than when coronary flow was maintained during anaphylaxis (constant flow perfusion). The data suggest that maintenance of coronary flow during cardiac anaphylaxis may attenuate the severity of the functional derangement.

An immediate hypersensitivity reaction (i.e., anaphylaxis) is associated with significant alterations in cardiac as well as pulmonary function (1–3). Studies from isolated guinea pig hearts indicate that antigen/antibody-induced changes in cardiac function include increases in coronary vascular resistance and heart rate, prolongations in PR intervals with arrhythmia generation, and minor increases followed by large decreases in myocardial contractile force (3–9). However, it is not clear from these previous studies of preparations perfused at constant pressure to what extent the changes are a result of the severe reduction in flow that accompanies coronary vasoconstriction.

Therefore, the present study was designed to examine the anaphylactic reaction in isolated hearts under conditions where coronary flow was maintained at a constant value throughout the experiment. These results were compared with those obtained from hearts perfused at a constant pressure in which the coronary flow decreased during anaphylaxis. Variables examined included coronary vascular resistance, atrial and ventricular beating rates, left ventricular pressure, and PR interval. In addition, we monitored release of histamine, one of the known mediators of the cardiac anaphylactic reaction. The release of adenosine and its deamination product, inosine, was also measured to determine the extent of mismatch between oxygen supply and oxygen demand (10, 11) during anaphylaxis.

Materials and Methods. *Antibody production and passive sensitization of guinea pigs.* IgG antibody to ovalbumin was prepared and separated from other immunoglobulins as previously described (10). Briefly, 12 guinea pigs were immunized by a regimen which produced both IgG- and IgE-type antibodies to ovalbumin; the serum was harvested, pooled, and passed over a protein A–Sepharose affinity column to separate guinea pig IgG from other serum constituents. The ovalbumin-specific content of this IgG preparation was assessed using a passive cutaneous anaphylactic reaction (12). For this procedure, normal guinea pigs were injected intradermally with dilutions of IgG. After a latent period of 4 hr, the animals were anesthetized with ether and challenged by intracardiac administration of 2 mg of ovalbumin and 25 mg/kg Evans blue in normal saline. The diameter and intensity of

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bluing was evaluated 30 min after ovalbumin challenge on the undersurface of the skin and results were expressed as the smallest quantity of antibody giving at least a 5-mm bluing reaction in three of five guinea pigs. For the present studies, 270 ng IgG gave a 5-mm bluing reaction in three of five guinea pigs. Untreated ether-anesthetized guinea pigs were then passively sensitized by intracardiac administration of 0.32 mg of this IgG, 12–24 hr prior to removal of the heart for perfusion.

Perfused heart preparation. Male guinea pigs (300- to 500-g Dunkin–Hartley descendants from Bio-Lab Corp., St. Paul, MN) received heparin (2.5 mg ip) and were anesthetized with sodium pentobarbital (35 mg/kg ip). Hearts were removed and placed in ice-cold Krebs–Henseleit solution containing (m*M*): NaCl, 118; KCl, 4.7; $NaHCO_3$, 25; $CaCl_2$, 3.0; $MgSO_4$, 1.2; KH_2PO_4, 1.2; glucose, 10.0; and Na_2EDTA, 0.5; and insulin, 10 U/liter; and heparin, 1000 U/liter. After trimming extraneous tissue from the heart, the distal end of the aorta was attached to the perfusion apparatus by a stainless-steel cannula and perfused through the coronary bed with Krebs–Henseleit solution bubbled with 95% O_2, 5% CO_2. Perfusion pressure was measured from a side arm in the perfusion line located at heart level.

For constant pressure perfusion, the perfusate reservoir was set so that coronary perfusion pressure was maintained at a constant 30 mm Hg. This pressure was the same as that used by Levi and co-workers, who have contributed substantially to the literature describing cardiac anaphylaxis (3, 5–7). For constant flow perfusion, a peristaltic pump (Gilson Minipuls 2) was used to hold coronary flow constant at a rate which produced an initial perfusion pressure of 30 mm Hg. Coronary vascular resistance was calculated by dividing the perfusion pressure by the flow rate per gram of heart weight. The wet weight of the heart was determined at the end of the experiment.

A temperature probe placed in the right ventricle via the pulmonary artery was used to record and maintain intracardiac temperature at 37 ± 0.5°C. In the case of constant pressure perfusion, where significant reductions in flow occurred, an external feedback-controlled heating lamp connected to the temperature probe was added to maintain intracardiac temperature at 37 ± 0.5°C. A fluid-filled balloon attached to a pressure transducer was placed through the mitral valve into the left ventricle. Balloon volume was adjusted to obtain a diastolic pressure (~5–10 mm Hg) that produced maximum systolic pressure development. Bipolar surface electrograms were continuously recorded from the right atrium and left ventricle. These procedures have all been used for previous studies of isolated rat hearts from this laboratory (13). Hearts were equilibrated for 45 min prior to antigen challenge.

Antigen challenge. For these experiments, 1.34 mg of ovalbumin in 0.2 ml of normal saline was administered as a bolus directly into the aortic cannula. Preliminary experiments with varying doses of antigen and antibody indicated that the combination selected resulted in consistent anaphylactic responses with maximal increases in left ventricular systolic pressure under constant flow conditions. Challenge of three sensitized hearts with bovine serum albumin in normal saline resulted in less than a 5% change in heart rate, perfusion pressure, PR interval, or left ventricular systolic pressure. Because of tachyphylaxis to ovalbumin, each heart was challenged with antigen only once. Changes in coronary vascular resistance, left ventricular pressure, heart rate, and PR interval of the EKG were monitored for 10 min after the antigen challenge. In addition, samples of venous effluent were collected before antigen challenge as well as during the 10 min following antigen challenge for analysis. In order to prevent enzymatic degradation of histamine, adenosine, and inosine, samples were collected on ice and 1.0-ml aliquots were acidified with 0.1 ml of 2 *N* perchloric acid. Samples were then stored at −20°C until they were assayed. Results are expressed as the concentration in the venous effluent. In addition, release of the various substances was calculated by multiplying the concentrations in the venous effluent by the coronary flow rate per gram of heart.

Histamine analysis. Histamine was analyzed by the manual fluorometric method of Shore *et al.* (14) as modified with respect to citric acid by Anton and Sayre (15). Histamine standards were included in each assay and carried through the extraction procedure to

correct for any losses incurred during the extraction and assay. Total histamine in the heart was determined as described by Anton and Sayre (15). Briefly, hearts perfused at constant flow for 45 min were homogenized in 2–3 ml of 0.4 *N* perchloric acid. The homogenate was centrifuged at 30,000*g*, 4°C, 15 min, and the supernatant was diluted with an equal volume of water and assayed as described above.

Adenosine and inosine analysis. Adenosine and inosine content of the venous effluent was determined using high-performance liquid chromatography (HPLC). The sensitivity of the HPLC assay was sufficient to determine adenosine concentrations directly from samples of venous effluent. The pumping system (Spectraphysics Model 8700 solvent delivery system) was programmed for gradient elution of 250-μl samples injected directly onto a reverse-phase, 5-μm C-18 HPLC column. A linear gradient changing from 95% 5 m*M* KH_2PO_4 and 5% of 100% methanol to 75% 5 m*M* KH_2PO_4 and 25% of 100% methanol over 25 min at a flow of 0.5 ml/min was used. Absorbance of the column eluate was continuously monitored at 254 n*M* using a Kratos 783 uv/vis detector and Shimadzu C-R3A integrator. Absorbance peaks were identified and quantified by comparison with retention times and peak magnitudes of acidified samples of known concentrations of adenosine and inosine.

Data analysis. Results are expressed as means ± SEM. Antigen-induced alterations in variables within each group were assessed by ANOVA followed by Scheffe's test. Differences between groups at specific time intervals were determined by unpaired Student's *t* test with $P = 0.05$ as the limit of significance. In situations where the variances could not be assumed equal, a *t* test using Satterthwaite's approximation was employed (16) with a level of significance of $P = 0.05$. For both *t* tests, the Bonferroni correction for multiple comparisons was used (17). Fisher's exact test was used to determine whether the difference in the incidence of arrhythmias was significant.

Results. Mechanical characteristics of the two groups of isolated sensitized hearts determined 2 min prior to antigen challenge are described in Table I. Note that there were no significant differences in any of the initial values between the two groups.

TABLE I. CHARACTERISTICS OF THE ISOLATED PERFUSED GUINEA PIG HEARTS

	Perfused at constant flow ($n = 6$)	Perfused at constant pressure ($n = 9$)
Heart weight (g)	1.19 ± 0.06	1.20 ± 0.03
Initial control values of		
Perfusion pressure (mm Hg)	30.00 ± 0.40	30.00 ± 0.30
Coronary flow (ml/min/g)	6.10 ± 0.40	6.20 ± 0.40
Vascular resistance (mm Hg/ml/min/g)	5.00 ± 0.40	4.80 ± 0.40
Atrial rate (beats/min)	241 ± 10	237 ± 10
Systolic pressure (mm Hg)	80 ± 4	76 ± 5
PR interval (msec)	55 ± 1	58 ± 4

Data contained in Figs. 1A and 1B indicate that antigen challenge produced sustained increases in perfusion pressure or sustained decreases in coronary flow in hearts perfused at constant flow or constant pressure, respectively. The coronary vascular resistance was calculated in each group and the results are shown in Fig. 1C. The hearts perfused at constant pressure had a greater average increase in the coronary vascular resistance than those perfused at constant flow. However, statistical analysis of the data from both groups indicated that the coronary vascular resistance changes were not significantly different.

The changes in left ventricular systolic pressure, atrial rate, and PR interval that occurred with antigen challenge are shown in Fig. 2. In both groups, systolic pressure initially increased and then decreased below the control values (Fig. 2A). There was a significant difference in the systolic pressure changes between the two groups from 6 to 10 min after the antigen challenge. The decrease in systolic pressure was sustained significantly longer in hearts perfused at constant pressure than in those perfused at constant flow.

Antigen challenge produced arrhythmias in both groups. Analysis of the relationship between the atrial and ventricular electrical events on the EKG indicated that PR intervals were significantly prolonged and that there was a high incidence of second- and third-degree AV nodal conduction blocks, especially in hearts perfused at constant pressure. Seven of

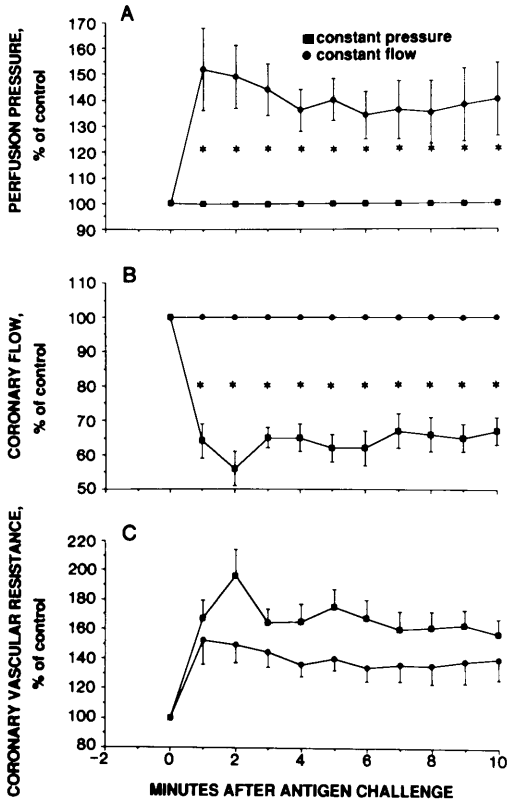

FIG. 1. Antigen-induced changes in perfusion pressure (A), coronary flow (B), and calculated coronary vascular resistance (CVR) (C) of isolated, passively sensitized guinea pig hearts perfused either at a constant pressure (n = 9) or at a constant flow rate (n = 6). Data indicate means ± SEM. *P < 0.05 constant pressure vs constant flow.

the nine hearts perfused at constant pressure versus three of the six hearts perfused at constant flow developed arrhythmias. Statistical analysis of these data using Fisher's exact test indicated there was not a statistically significant difference in the *incidence* of arrhythmias. However, when the *duration* of the second- or third-degree AV nodal conduction blocks was examined, there was a statistically significant difference between the groups. The duration of arrhythmias after antigen challenge was 3.72 ± 1.17 min for hearts perfused at constant pressure vs 0.75 ± 0.28 min for hearts perfused at constant flow. The changes in PR intervals for the two groups are shown in Fig. 2C. Statistical analysis for differences in PR intervals was not carried out on data from the first 4 min because of the high incidence of conduction blocks. Note that the increase in PR interval of hearts perfused at constant flow was transient and had nearly returned to control values at the end of 10 min, whereas that of hearts perfused at constant pressure was significantly elevated above control values throughout the 10 min. The PR interval was significantly greater from 8 to 10 min after the antigen challenge in hearts perfused at constant pressure compared to those perfused at constant flow.

Venous concentrations (left panels) and release (right panels) of histamine, adenosine, and inosine from the hearts before and during anaphylactic reactions are shown in Fig. 3.

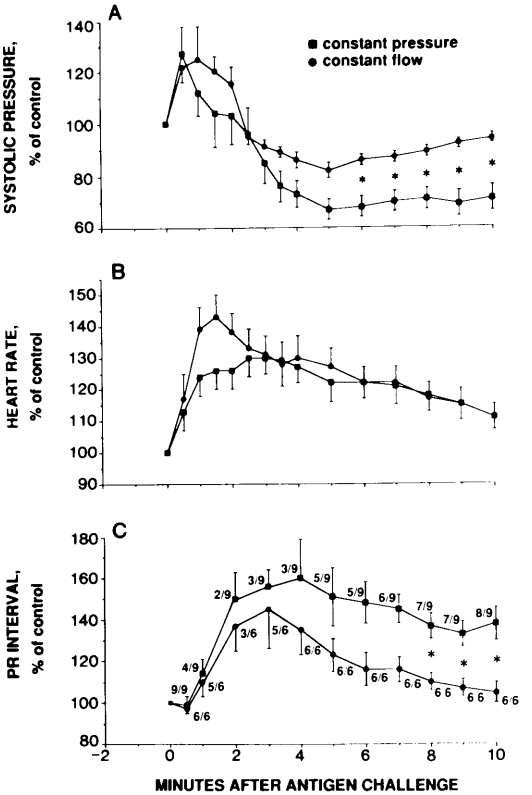

FIG. 2. Antigen-induced changes in left ventricular systolic pressure (A), atrial beating rate (B), and PR interval in the absence of arrhythmia (C) of isolated, passively sensitized guinea pig hearts perfused either at constant pressure (n = 9) or at constant flow (n = 6). Data indicate means ± SEM. In (C), the ratios shown by each data point represent the number of experiments out of the total that did not have arrhythmias and were used to calculate the means ± SEM. *P < 0.05 constant pressure vs constant flow.

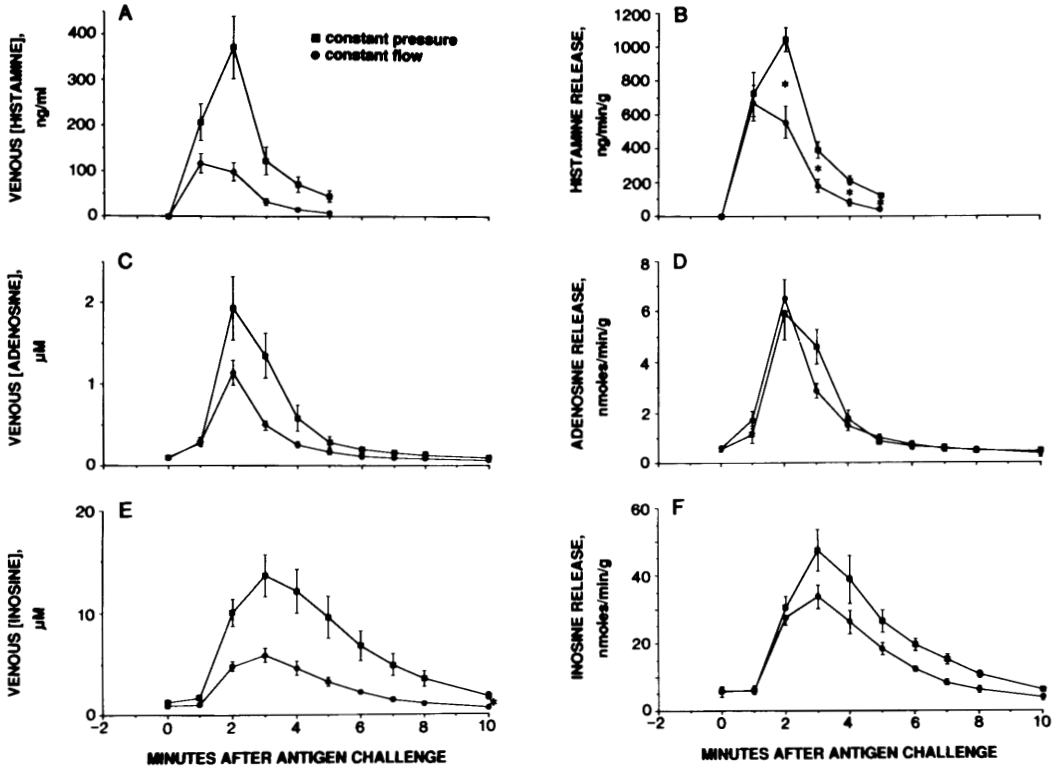

FIG. 3. Venous effluent concentration (left panels) and calculated release (right panels) of histamine (A and B), adenosine (C and D), and inosine (E and F) from isolated, passively sensitized guinea pig hearts perfused either at constant pressure (n = 5) or at constant flow (n = 5) before and during an anaphylactic reaction evoked by antigen challenge. Data indicate means ± SEM. *$P < 0.05$ constant pressure vs constant flow.

Prior to antigen challenge there was no detectable histamine in the venous effluent. Antigen challenge, however, evoked a transient release of histamine from tissue stores and venous levels increased. Hearts perfused at constant pressure tended to develop higher venous histamine concentrations than hearts perfused at constant flow. However, because of the unequal variances in the two groups and the multiple comparisons, the differences were not statistically significant according to our conservative tests. However, when histamine release rate was calculated from the venous concentration and the coronary flow, the variability of the data was reduced and statistical analysis indicated that histamine release rate was significantly greater from hearts perfused at constant pressure than from those perfused at constant flow (Fig. 3B). The total amount of histamine released 5 min after antigen challenge from hearts perfused at constant pressure was 2.50 ± 0.23 μg/g whereas that released from hearts perfused at a constant flow rate was 1.53 ± 0.23 μg/g ($P < 0.05$). These mean values represent 43 and 26%, respectively, of the average total tissue histamine content found in four unchallenged hearts (5.78 ± 0.37 μg/g).

Antigen challenge was also associated with a significant transient increase in venous adenosine concentration. The average increase was greater under constant pressure than constant flow conditions at all time points. However, the differences between the groups were not statistically significant. In addition, no difference in adenosine release rates between the groups was detected.

The inosine concentration of venous effluent from these hearts under control conditions was approximately 10-fold greater than

the adenosine concentration. The transient antigen-induced increase in venous inosine concentration or inosine release rate of hearts perfused at constant pressure was not significantly different from that of hearts perfused at constant flow.

The total amounts of histamine, adenosine, and inosine released after antigen challenge are shown in Table II. Under constant pressure perfusion, the totals of histamine, inosine, and adenosine plus inosine were significantly greater than under constant flow perfusion. The total adenosine released, however, was not significantly different between groups.

Discussion. The results of this study indicate that myocardial perfusion conditions significantly influence certain characteristics of the anaphylactic reaction. The results confirm previous findings indicating that isolated, sensitized guinea pig hearts respond to antigen challenge with release of histamine; increases in coronary vascular resistance, heart rate, and PR intervals; development of arrhythmias; and transient increases followed by decreases in myocardial contractile force (3–9). However, our data clearly indicate that, when coronary flow is maintained during the anaphylactic reaction, histamine release rate and total histamine released are lower, total adenosine plus inosine is lower, myocardial contractile depression 6 to 10 min after antigen challenge is less severe, arrhythmias are of significantly shorter duration, and PR intervals are not as prolonged 8 to 10 min after antigen challenge as when coronary flow decreases during the anaphylactic reaction.

TABLE II. ANTIGEN-INDUCED RELEASE OF HISTAMINE, ADENOSINE, AND INOSINE FROM ISOLATED, PERFUSED, SENSITIZED GUINEA PIG HEARTS

	Perfused at constant flow ($n = 5$)	Perfused at constant pressure ($n = 5$)
Histamine[a] (μg/g wet wt)	1.53 ± 0.23*	2.50 ± 0.23
Adenosine[b] (nmole/g wet wt)	16.17 ± 1.02	16.81 ± 1.82
Inosine[b] (nmole/g wet wt)	149 ± 13*	211 ± 19
Adenosine + inosine[b] (nmole/g wet wt)	166 ± 14*	227 ± 19

[a] Total histamine released in the 5 min following antigen challenge expressed per gram heart, wet weight.

[b] Total adenosine and/or inosine released in the 10 min following antigen challenge expressed per gram heart, wet weight.

* Significantly different from release from hearts perfused at constant pressure ($P < 0.05$).

Histamine is only one of several substances that have been implicated as mediators of the cardiac anaphylactic reaction (4–9, 18). Its actions, however, are quite well defined and it has been suggested to be the primary mediator responsible for the antigen-induced changes in rate, rhythm, and impulse conduction (5, 6, 8, 18). Histamine content of these hearts was found to be similar to that reported by others (see (18) for review). Our studies indicate that more than 40% of this histamine is released by antigen challenge from hearts perfused at a constant pressure and that substantially less is released from hearts in which flow is maintained during the anaphylactic reaction. It seems likely that such differences in histamine release could contribute to the observed differences in arrhythmia duration and PR interval prolongation. It is also possible that there could be perfusion-dependent alterations in release of other mediators as well.

Release of adenosine (and its deamination product, inosine) has been shown to increase whenever myocardial oxygen demand exceeds myocardial oxygen supply (10, 11). Our data have demonstrated increased release of adenosine and inosine during cardiac anaphylaxis, suggesting that myocardial oxygen demand exceeds myocardial oxygen supply in this situation. Since we found that total adenosine plus inosine release is greater under circumstances in which the coronary flow actually decreases, this suggests that oxygen imbalance is more severe in this situation.

Release of adenosine and inosine into venous effluent under control conditions is seven- to ninefold higher than that reported by others (10, 19). This difference may result from differences in perfusate constituents (10, 19) or from our preparations having lower flow rates (10) and higher left ventricular systolic pressure development (10, 19), the latter two conditions being known to significantly increase adenosine and inosine release from perfused hearts (10, 19, 20). Because of rapid uptake and degradation of adenosine by myocytes and vascular endothelium (11, 21, 22),

it is not possible to determine interstitial levels of adenosine accurately. However, from our measurements of venous adenosine and inosine concentrations, we suggest that increases in interstitial adenosine levels probably did occur and that these increases were greater when hearts were perfused at a constant pressure than at a constant flow. Since adenosine is known to have a variety of physiological effects (13, 20, 23–28), it is possible that differences in interstitial adenosine could contribute either directly or indirectly to some of the flow-dependent differences in the anaphylactic reaction. For example, greater increases in interstitial adenosine and inosine concentrations under constant pressure perfusion might have contributed to the enhanced histamine release found under these conditions (26–28). In support of this suggestion, we have recently reported that if levels of adenosine in the isolated, constant flow-perfused heart are increased by adding either exogenous adenosine and/or an adenosine deaminase inhibitor, then histamine release is increased during an anaphylactic reaction (29). In addition, increases in tissue adenosine levels might account for the longer PR interval (23), longer duration of arrhythmias (23), and greater suppression of ventricular contractile force (24, 25) observed during anaphylaxis under constant pressure perfusion. Our studies certainly do not define specific roles for adenosine in modulating these variables but do raise the possibility that such roles may exist.

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