Acetyl Glycerol Ether Phosphorylcholine (AGEPC): A Putative Mediator of Cardiac Anaphylaxis in the Guinea Pig

Roberto Levi, James A. Burke, Zhao-Gui Guo, Yuichi Hattori, Carol M. Hoppens, Linda M. McManus, Donald J. Hanahan, and R. Neal Pinckard

SUMMARY. Platelet-activating factor is a novel phospholipid that has been implicated as an important mediator of acute allergic reactions. The intravenous administration of acetyl glycerol ether phosphorylcholine, a pure, synthetic platelet-activating factor, causes electrocardiographic changes in the rabbit similar to those which are characteristic manifestations of systemic anaphylaxis. To determine whether platelet-activating factor contributes to anaphylactic cardiac dysfunction, we measured platelet-activating factor release from the sensitized guinea pig heart challenged in vitro with specific antigen and compared the resulting cardiac dysfunction with that induced by the injection of acetyl glycerol ether phosphorylcholine into nonsensitized hearts. The results of these studies document that, during anaphylaxis in the isolated guinea pig heart, a platelet-activating factor is released into the coronary effluent that has physicochemical and functional properties similar to those of acetyl glycerol ether phosphorylcholine. The intracardiac administration of acetyl glycerol ether phosphorylcholine (10^{-14} to 3 \times 10^{-9} \text{ mol}) induced dose-related decreases in left ventricular contractile force (−5 to −85%) and coronary flow (−5 to −85%), as well as impaired atrioventricular conduction. The negative inotropic effect of acetyl glycerol ether phosphorylcholine also was present in hearts perfused at constant flow. Although, in these hearts, acetyl glycerol ether phosphorylcholine increased coronary resistance, which may have caused regional shunting and ischemia, it is unlikely that the negative inotropic effect of acetyl glycerol ether phosphorylcholine was secondary to changes in coronary flow, since acetyl glycerol ether phosphorylcholine also caused a dose-dependent negative inotropic effect in the electrically paced, noncoronary-perfused left atrium and right ventricular papillary muscle. Moreover, the cardiac effects of acetyl glycerol ether phosphorylcholine were not modified by indomethacin or FPL 55712, indicating that they were not mediated by various cyclooxygenase or lipoxygenase products of the arachidonic acid cascade. These data suggest that platelet-activating factor may contribute to the contractile failure, reduced coronary flow, and conduction arrhythmias of cardiac anaphylaxis. (Circ Res 54: 117-124, 1984)
these changes could have been secondary to pulmonary hypertension, systemic hypotension, and reduced cardiac output (Halonen et al., 1980), a model of anaphylaxis was required in which cardiac dysfunction could be studied independently of systemic vascular and platelet-mediated changes. The isolated, sensitized guinea pig heart provided such a model. Indeed, many of the cardiac abnormalities characteristic of systemic anaphylaxis are manifested in vitro when hearts from sensitized guinea pigs are challenged with specific antigen ["cardiac anaphylaxis" (Feigen et al., 1961)]. Sinus tachycardia, arrhythmias, decreased coronary flow, and left ventricular contractile failure are characteristic of cardiac anaphylaxis (Capurro and Levi, 1975). Concurrently, endogenous substances known to mediate systemic anaphylaxis (Beaven et al., 1982), and highly purified PAF was assayed for histamine and PAF.

Coronary effluent were assayed for histamine and PAF. Hearts from sensitized animals were challenged intraaortically with specific antigen [1 mg of DNP-bovine serum albumin (DNP-BSA)]. The 2-minute samples of coronary effluent were assayed for histamine and PAF. Histamine was assayed by a radioisometric method (Beaven et al., 1982), and highly purified PAF was assayed as described below.

**Methods**

**Cardiac Anaphylaxis**

Male Hartley guinea pigs (250–300 g) were passively sensitized by intravenous injection of 0.4 mg of guinea pig anti-dinitrophenyl-bovine-γ-globulin IgG (anti-DNP-BGG) (Levi and Burke, 1980). This dose of anti-DNP-BGG was shown by the method of Ovary (1964) to be 2000 PCA units. Twelve hours after sensitization, the animals were killed by cervical dislocation, and the hearts were excised and mounted in a Langendorff apparatus (Levi and Allan, 1980; Levi et al., 1982).

The objective of the present study, therefore, was to determine whether PAF might contribute to anaphylactic cardiac dysfunction. To this end, we measured the release of PAF from isolated sensitized guinea pig hearts during anaphylaxis, we assessed the physiological effects of exogenously administered AGEPC on the isolated nonsensitized guinea pig heart, and we compared these effects with the cardiac dysfunction observed during anaphylaxis.

**Methods**

**Cardiac Anaphylaxis**

Male Hartley guinea pigs (250–300 g) were passively sensitized by intravenous injection of 0.4 mg of guinea pig anti-dinitrophenyl-bovine-γ-globulin IgG (anti-DNP-BGG) (Levi and Burke, 1980). This dose of anti-DNP-BGG was shown by the method of Ovary (1964) to be 2000 PCA units. Twelve hours after sensitization, the animals were killed by cervical dislocation, and the hearts were excised and mounted in a Langendorff apparatus (Levi and Allan, 1980; Levi et al., 1982).

After a period of stabilization (30–45 minutes), the hearts from sensitized animals were challenged intraaortically with specific antigen [1 mg of DNP-bovine serum albumin (DNP-BSA)]. The 2-minute samples of coronary effluent were assayed for histamine and PAF. Histamine was assayed by a radioisometric method (Beaven et al., 1982), and highly purified PAF was assayed as described below.

**Response of Isolated Hearts to Exogenous AGEPC**

Hearts from nonsensitized male Hartley guinea pigs were mounted in the Langendorff apparatus and perfused at 37°C, either at constant pressure, as described above, or at constant flow. Under constant flow, Krebs-Henseleit solution continuously aerated with 95% O₂/5% CO₂ was perfused through the heart. The composition of the Krebs-Henseleit solution was (mm): Na⁺, 142.5; K⁺, 5.4; Ca²⁺, 2.5; Mg²⁺, 1.2; Cl⁻, 128; HCO₃⁻, 24.9; HPO₄²⁻, 1.0; SO₄²⁻, 1.2; glucose, 11.1; and HSA, 2.5 mg/ml. The solution was delivered by a peristaltic pump (Buchler Instruments, Polystaltic pump). The flow rate was adjusted to give a control perfusion pressure of 40 mm of Hg. The perfusion pressure was continuously monitored with a physiological pressure transducer (Statham model P23AA). Under both conditions, isometric ventricular contraction and bipolar surface electrogram were recorded as noted above.

AGEPC (1-O-hexadecyl/octadecyl-2-acetyl-sn-glycero-3-phosphorylcholine) and lyso-GEPC (1-O-hexadecyl/oly-sr-glyceryl-3-phosphorylcholine) were synthesized, purified, and structurally characterized, as described previously (Demopoulos et al., 1979). Under constant pressure conditions, a single dose of AGEPC (10⁻⁶ to 3 x 10⁻⁸ mol) or its deacylated derivative, lyso-GEPC (10⁻⁶ to 10⁻⁸ mol), dissolved in a constant volume of warm oxygenated Ringer's containing 2.5 mg/ml HSA, was injected intraaortically to determine dose-response relationships. To avoid the possibility of tachyphylaxis, only one dose of AGEPC was administered to each heart. Under constant flow conditions, AGEPC (10⁻¹² to 10⁻⁸ mol) in Krebs-Henseleit solution) was continuously perfused through the heart. The hearts were exposed to each concentration to AGEPC for 10 minutes, followed in turn by the next higher concentration.

In some experiments, AGEPC also was administered to the hearts in the presence of indomethacin or compound FPL 55712. In these studies, indomethacin (Sigma Chemical Co.) (1 µg/ml in Ringer's solution) or FPL 55712 (donated by Fisons Pharmaceuticals, U.K.) (250 ng/ml in Ringer's solution) was continuously perfused through the heart from 30 minutes before AGEPC administration to the end of the experiment. This concentration of indomethacin had been previously documented by us to abolish the synthesis of cyclooxygenase products during cardiac anaphylaxis (Allan and Levi, 1981). The concentration of FPL 55712 used here had been shown by us to shift the dose-response curves for the negative inotropic and coronary-constricting effects of leukotrienes C₄ and D₄ in the guinea pig heart to the right by one to two log units (Burke et al., 1982a).

**Responses of Left Atria and Right Ventricular Papillary Muscles to AGEPC**

The left atrium and right ventricular papillary muscle were isolated from guinea pig hearts, as previously described (Burke et al., 1982a). Left atria and papillary muscles were mounted vertically in double-walled Pyrex chambers (2.5 ml volume) and perfused at 30°C with Tyrode's solution, containing 2.5 mg/ml HSA, aerated with 95% O₂/5% CO₂. The composition of the Tyrode's solution was (mm): Na⁺, 149.42; K⁺, 5.4; Cl⁻, 148.1; Mg²⁺, 1.05; Ca²⁺, 1.8; HCO₃⁻, 12; HPO₄²⁻, 0.42; glucose, 10. Changes in tension were measured with a force-displacement transducer (model TO3; Grass Instruments). Left atria and papillary muscles were paced with square pulses (duration, 5 and 10 msec for the left atrium and papillary muscle, respectively; voltage 1.5 times threshold) at a frequency of 1 and 2 Hz, respectively, with a pair of platinum electrodes placed in direct contact with the tissue and connected to a stimulator via a stimulus isolation unit.
Cardiac PAF was obtained from three guinea pigs passively sensitized with 3.3 mg rabbit anti-ovalbumin IgG (Levi, 1972) and three hearts passively sensitized with guinea pig anti-DNP IgG antibody (described above). In these studies, no PAF activity was detected in the crude coronary effluents after antigen challenge. Therefore, the coronary effluent samples, which were obtained prior to and up to 10 minutes after antigen challenge, were extracted and purified by methods previously shown to be necessary for the recovery of PAF from biological samples (Pinckard et al., 1979; Hanahan et al., 1980). For this lipid extraction, one volume of chloroform (CHCl₃) and two volumes of methanol were added to each 0.8 volume of crude effluent. After 1 hour of incubation at room temperature, the precipitated proteins were removed by centrifugation and one volume each of CHCl₃ and water was added to the supernatant to effect phase separation. The lower, CHCl₃-rich phase was then subjected to thin layer chromatography (TLC) of methanohwater, 2:1, vol/vol, Rf = 0.45-0.50. Subjecting this highly purified cardiac PAF, obtained from either anti-ovalbumin or anti-DNP-sensitized hearts, to base-catalyzed methanolysis (Demopoulos et al., 1979) destroyed all platelet-stimulating activity. Most important, platelets specifically desensitized to AGEPC did not respond to the purified cardiac PAF (see Table 1). These studies demonstrated that a PAF is released during in vitro cardiac anaphylaxis in the guinea pig which possesses physicochemical and functional properties similar to those of AGEPC.

The total amount of PAF released from the six hearts passively sensitized with anti-DNP and anti-ovalbumin during a period of time up to 10 minutes after antigen challenge corresponded to an average of 150 and 450 fmol of AGEPC, respectively. These estimated amounts of PAF were based upon the assumption that cardiac PAF is AGEPC. Moreover, they probably represented only a rough estimate, since losses of PAF were likely to have occurred during TLC purification. Indeed, we have observed 40-90% recoveries of [3H]PAF (New England Nuclear, 50 Ci/mM) after TLC purification, with variations in recoveries occurring between and within TLC plates. Thus, in subsequent studies performed using seven additional anti-DNP-sensitized hearts, trace quantities of [3H]AGEPC were added to each coronary effluent prior to initial lipid extraction and TLC, to serve as an internal standard to assess losses of PAF during purification (Fig. 1). The amount of [3H]AGEPC added (5000 cpm) was insufficient to affect the platelet release reaction assays and quantification of PAF (Demopoulos et al., 1979).

**Results**

**Release of PAF during Cardiac Anaphylaxis**

Intravenous injection of DNP-BSA into isolated and perfused hearts from seven guinea pigs passively sensitized with guinea pig anti-DNP-BGG resulted in a typical anaphylactic crisis (Fig. 1). The heart rate (Fig. 1a) increased abruptly, reaching a peak within 1 minute after antigenic challenge. A transient increase in ventricular contractile force (Fig. 1b) was followed by a prolonged decrease, reaching its nadir 8 minutes after challenge. A prompt and prolonged decrease in coronary flow also occurred (Fig. 1c). Arrhythmias began about 1 minute after antigenic challenge and lasted 7.10 ± 2.68 minutes (mean ± SEM; Fig. 1a, inset); they consisted of idioventricular arrhythmias and conduction defects ranging from partial to complete AV block. In concert with the preceding, both histamine and PAF were released into the coronary effluent during the anaphylactic crisis (Fig. 1d), with maximal PAF release delayed.

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**Table 1**

**Functional Characterization of Cardiac PAF as Assessed by Platelet Secretion of [3H]-Serotonin**

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Control platelets</th>
<th>AGEPC-desensitized platelets</th>
</tr>
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<tbody>
<tr>
<td>Cardiac PAF</td>
<td>50.2 ± 2.6†</td>
<td>7.2 ± 0.5†</td>
</tr>
<tr>
<td>AGEPC (1.05 × 10⁻⁸ M)</td>
<td>57.9</td>
<td>7.0</td>
</tr>
<tr>
<td>α-Tenormbin (1.5 U)</td>
<td>56.4</td>
<td>51.8</td>
</tr>
<tr>
<td>BSA-saline</td>
<td>2.4</td>
<td>5.2</td>
</tr>
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</table>

*Expressed as percent of total [3H]-serotonin released from Triton X-100 lysed platelets (Demopoulos et al., 1979).
† Mean ± SEM; n = 7. Cardiac PAF was obtained from three anti-ovalbumin and four anti-DNP-sensitized hearts. The range of [3H]-serotonin secretion was 39.8—60.2% and 5.1—8.8% in control and AGEPC-desensitized platelets, respectively.
FIGURE 1. Changes in cardiac function and release of two mediators (histamine and PAF) during cardiac anaphylaxis. All values represent means ± SEM from seven hearts passively sensitized in vivo with guinea pig anti-DNP-BGG and challenged in vitro with DNP-BSA (antigen) at time = 0. Panels A and B: change in rate (panel A) and left ventricular contractility (panel B) at the time indicated, compared with the control period preceding antigenic challenge. Inset in panel A: ends of shaded bar indicate time of onset and termination of arrhythmias (second and third-degree A-V block and idioventricular rhythms). Panel C: changes in average coronary flow rate during 2-minute intervals compared with control period. Panel D: release of histamine and PAF into the coronary effluent during 2-minute intervals following challenge; PAF values have been corrected relative to the recovery of the internal AGEPC standard during TLC preparation, i.e., 68.6 ± 1.6% (mean ± SEM, n = 56). In the 2-minute interval preceding antigen challenge, histamine concentration in the coronary effluent was 3.0 ± 1.0 pmol (mean ± SEM, n = 7); there was no detectable PAF.

Effects of Exogenous AGEPC on the Guinea Pig Heart

Because the PAF released during cardiac anaphylaxis appeared by the criteria used to be physicochemically and functionally identical to AGEPC (see Methods), we assessed the possibility that PAF caused some of the concomitant functional changes by evaluating the effects of the administration of exogenous AGEPC in the nonsensitized isolated guinea pig heart. These studies documented that AGEPC reduced the force of contraction, reduced coronary flow, and caused arrhythmias when administered to isolated guinea pig hearts that were perfused at constant pressure. The response to AGEPC was prompt, reached a peak within 2 minutes and was long-lasting (Fig. 2). AGEPC (10^-14 to 3 x 10^-9 mol) reduced both the force of contraction and the coronary flow rate as a function of dose (Fig. 3). These effects were not blocked by the cyclooxygenase inhibitor, indomethacin (1 ug/ml; Fig. 3), nor by the end-organ SRS-A antagonist FPL 55712 (250 ng/ml; Table 2). In contrast to AGEPC, its deacetylated derivative lys-GEP caused minimal (less than 10%) decreases in contractile force and coronary flow rate in doses up to 10^-8 mol (Figs. 2C and 3).

AGEPC produced conduction arrhythmias ranging from second degree AV conduction block (Wenckebach phenomenon, 2:1 and 3:1 block) to compared with that of histamine. Histamine release was maximal within 2 minutes after antigen challenge and rapidly declined thereafter, whereas, PAF release, although detectable within 2 minutes, increased to a maximum between 4 and 6 minutes after antigen challenge and declined slowly thereafter. No PAF was released from sensitized hearts prior to antigen challenge or from nonsensitized hearts challenged with antigen. Minimal amounts of histamine were present in the coronary effluents of sensitized hearts prior to antigen challenge (3.0 ± 1.0 pmol; mean ± SEM, n = 7).
complete AV dissociation with junctional rhythms. The severity and duration of the conduction arrhythmias increased with the dose of AGEPC (10^{-12} to 3 \times 10^{-9} \text{ mol}; see Table 3). AGEPC and lyso-GEPC caused only slight increases in heart rate (10\%) which were not dose-related.

In isolated guinea pig hearts perfused at a constant flow, AGEPC (10^{-12} to 10^{-8} \text{ M}) decreased left ventricular contractile force and also increased perfusion pressures as a function of its concentration (Fig. 4). Reversible conduction arrhythmias similar to those observed when AGEPC was injected into hearts perfused at constant pressure also were observed when AGEPC (10^{-9} \text{ M}) was perfused through the hearts at constant flow. At 10^{-8} \text{ M}, AGEPC caused irreversible arrhythmias and normal sinus rhythm did not return even after prolonged perfusion with AGEPC-free medium. Since the negative inotropic and arrhythmogenic effects of AGEPC were present also in hearts perfused at constant flow, it is unlikely that the effects of AGEPC were secondary to reduction in coronary flow. On the other hand, the increase in perfusion pressure observed in hearts perfused at constant flow, indicated that AGEPC increased coronary vascular resistance. Because this could have produced regional shunting and ischemia, which may have contributed to arrhythmias and negative inotropism, we assessed the effects of AGEPC in the electrically paced, isolated left atrium and right ventricular papillary muscle of the guinea pig. In these preparations, changes in contractility were totally independent of changes in sinus rate and coronary flow. As a function of is concentration, AGEPC (10^{-11} to 10^{-5} \text{ M}) caused a negative inotropic effect in the left atrium (Fig. 5A) and in the right papillary muscle (Fig. 5B). Lyso-GEPC caused a minimal (about 5\%) decrease in the contractile force of the left atrium at a concentration of 10^{-5} \text{ M} (Fig. 5A).

**Figure 3.** Effects of AGEPC and lyso-GEPC on the normal isolated guinea pig heart perfused at constant pressure. AGEPC or lyso-GEPC was injected intraaortically. AGEPC was administered in the absence or presence of indomethacin (1 \text{ \mu g/ml}). Horizontal scale: dose of AGEPC or lyso-GEPC. Left panel: maximum percent change in left ventricular contractile force from control period before AGEPC. Right panel: maximum percent change in coronary flow. Points represent means (±SEM, n = 4-5 hearts).

**Table 2.** Lack of Modification of the Negative Inotropic and Coronary Constricting Effects of AGEPC by FPL 55712

<table>
<thead>
<tr>
<th>Condition</th>
<th>Untreated</th>
<th>FPL 55712</th>
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<tbody>
<tr>
<td>Left ventricular contractile force</td>
<td>-43 ± 8%</td>
<td>-44 ± 6%</td>
</tr>
<tr>
<td>Coronary flow rate</td>
<td>-50 ± 7%</td>
<td>-60 ± 6%</td>
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</table>

*AGEPC (10^{-11} \text{ mol}) was administered by bolus intraaortic injection in isolated guinea pig hearts. FPL 55712 (250 \text{ ng/ml}) was administered by continuous perfusion.

† Percent change from control (±SEM; n = 3-5).

**Discussion**

During anaphylaxis in the isolated guinea pig heart, a PAF is released into the coronary effluent which appears to have physicochemical and functional properties similar to AGEPC. AGEPC administered to isolated hearts mimicked many, but not all, of the pathophysiological changes observed during cardiac anaphylaxis. Our findings suggest that release of endogenous cardiac PAF may contribute at least in part to cardiac dysfunction during anaphylaxis in vitro.

In initial experiments (see Methods; Burke et al., 1982b), we detected the release of PAF also from hearts of guinea pigs sensitized with heterologous antibodies (i.e., rabbit antiovalbumin IgG). Subsequently, we have quantitatively defined the release of PAF from the heart of guinea pigs sensitized with homologous antibodies (i.e., guinea pig anti-DNP IgG_i). Thus, PAF release is a characteristic feature of cardiac anaphylaxis and is independent of the type of cytotoxic antibody.

We have demonstrated that the administration of AGEPC to nonsensitized isolated hearts mimics some of the functional changes observed during cardiac anaphylaxis. Low doses of AGEPC (10^{-14} to 3 \times 10^{-9} \text{ mol}) induced profound and long-lasting decreases in contractility, coronary flow, and slowed AV conduction. In contrast, 10^{-8} \text{ mol} of lyso-GEPC, the deacetylated derivative of AGEPC, which is devoid of any other known biological activity (c.f. Pinckard et al., 1982), had negligible cardiac effects. Although AGEPC reduced coronary flow and increased coronary vascular resistance, which could have caused shunting and regional ischemia, it is unlikely that the negative inotropic and arrhythmogenic effects of AGEPC were secondary to the
reduction of coronary flow. Indeed, we found that AGEPC induced a concentration-dependent negative inotropic effect in the left atrium and in the papillary muscle of the right ventricle (see Fig. 5). Both preparations were immersed in the perfusing medium, rather than being directly perfused through the coronary vasculature, as in the Langendorff preparation; thus, changes in contractility were independent of coronary flow. It was of no surprise that cardiac contractile responses were relatively independent of coronary flow changes; in fact, we had observed previously that negative inotropic responses to either histamine (Zavecz and Levi, 1978) or sodium arachidonate (Allan and Levi, 1980) could coexist with increases in coronary flow. Hence, although we cannot entirely rule out that the reduction in coronary flow caused by AGEPC might in part have contributed to its negative inotropic effects, our experiments indicate that this contribution was minimal.

AGEPC-induced reduction in coronary flow and contractility and slowing of AV conduction were independent of platelet aggregation or release of vasoactive amines from platelets, because they occurred in hearts perfused with platelet-free media. The finding that indomethacin (1 \( \mu \)g/ml, a concentration which effectively blocks cyclooxygenase in the heart; Allan and Levi, 1981) did not block the direct cardiac effects of AGEPC indicates that these effects were not mediated by cyclooxygenase products of arachidonic acid metabolism. This point is important, since AGEPC induces the release of thromboxane in vitro and in vivo (McManus et al., 1980, 1983), a substance which causes coronary vasoconstriction (Needleman et al., 1977; Terashita et al., 1978; Lewy et al., 1980). Moreover, recent studies in the perfused rabbit lung have shown that AGEPC-induced pulmonary hypertension and edema are platelet and thromboxane A\(_2\) dependent (Helfner et al., 1983). In the present study, the negative inotropic and coronary-constricting effects of AGEPC also were not modified by the leukotriene antagonist compound FPL 55712 (250 ng/ml, a concentration which shifts the dose-response curves for the cardiac effects of leukotrienes in the guinea pig heart to the right by 1–2 log units (Burke et al., 1982a)). This is important in view of recent evidence that AGEPC releases leukotrienes from isolated, perfused rat lungs (Voelkel et al., 1982); and leukotrienes C\(_4\) and D\(_4\) have been shown to cause negative inotropism and coronary constriction in the guinea pig heart (Burke et al., 1982a).

Our findings raise the question as to whether sufficient PAF was released during cardiac anaphylaxis to account for the observed contractile failure, reduction in coronary flow, and arrhythmias. DNP-BSA-challenged hearts released \( 5.6 \times 10^{-13} \) mol of PAF (assuming that cardiac PAF is identical to AGEPC) during the first 14 minutes after antigen challenge. During this period, the maximum decreases in cardiac contractility and coronary flow were 37% and 28%, respectively, and conduction

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**TABLE 3**

Duration of Conduction Arrhythmias after AGEPC Injection* 

<table>
<thead>
<tr>
<th></th>
<th>AGEPC (mol)</th>
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<tbody>
<tr>
<td></td>
<td>( 10^{-12} )</td>
<td>( 10^{-11} )</td>
<td>( 10^{-10} )</td>
<td>( 10^{-9} )</td>
<td>( 3 \times 10^{-9} )</td>
</tr>
<tr>
<td>Second-degree AV block</td>
<td>0.5 ± 0.4†</td>
<td>0.7 ± 0.4</td>
<td>7.2 ± 3</td>
<td>23 ± 14</td>
<td>23 ± 5</td>
</tr>
<tr>
<td>Complete AV dissociation</td>
<td>0.2 ± 0.2</td>
<td>0</td>
<td>1.2 ± 0.7</td>
<td>10 ± 8</td>
<td>10 ± 5</td>
</tr>
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</table>

* AGEPC injected as an intravenous bolus into normal isolated hearts perfused at constant pressure. 
† Minutes (mean ± SEM, \( n = 4-5 \)).

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**FIGURE 4.** Effects of AGEPC on nonsensitized isolated guinea pig hearts perfused at constant flow. The flow rate was adjusted to give a perfusion pressure of 40 mm Hg before AGEPC. The indicated concentration of AGEPC was perfused through the heart for 10 minutes, followed in turn by the next higher concentration. Left panel: maximum percent change in left ventricular contractile force during AGEPC perfusion compared with the control period before AGEPC. Right panel: maximum percent change in coronary perfusion pressure during AGEPC perfusion. Points represent means (±SEM, \( n = 6 \) hearts).
arrhythmias developed. In comparison, significant decreases in cardiac contractility and coronary flow occurred in normal, unsensitized hearts after bolus administrations of $10^{-11}$ mol of AGEPC; moreover, $10^{-11}$ mol of AGEPC caused cardiac arrhythmias and decreases in contractility and flow of severity comparable to those observed during anaphylaxis (Fig. 3). Since the coronary flow rates decreased during cardiac anaphylaxis to approximately 2–5 ml/2 minutes, the molar concentration of PAF in the coronary effluents would have approximated $1.4-2.0 \times 10^{-11}$ M AGEPC; this concentration of AGEPC administered continuously at constant flow induced significant reductions in left ventricular contractility and increases in coronary perfusion pressures (Fig. 4). Thus, it would appear that the quantity of AGEPC released from the heart during anaphylaxis was sufficient to cause cardiac dysfunction, although it may not be enough to entirely account for all the changes observed. Furthermore, the amount of detectable PAF released into the cardiac effluent during anaphylaxis may underestimate the total amount of PAF synthesized at the site(s) of action within the myocardium. Since PAF is a phospholipid, significant amounts of newly synthesized PAF could have become tightly bound and retained within the myocardium, possibly in association with its chemoreceptor, thus preventing its release into the coronary effluent.

It should be stressed that several other mediators with cardiac effects similar to AGEPC are also released concurrently during cardiac anaphylaxis. For example, several arachidonic acid metabolites released during cardiac anaphylaxis have negative inotropic effects (e.g., PGF$_{2\alpha}$, PCD$_{2}$, and leukotrienes (Anhut et al., 1978; Allan and Levi, 1980; Levi et al., 1982; Burke et al., 1982a)). The leukotrienes and thromboxanes are likely contributors to the decreased coronary flow during anaphylaxis (Alan and Levi, 1981), and histamine is a major cause of the conduction arrhythmias (Levi and Allan, 1980). Thus, the contractile failure and reduced coronary flow would not unexpectedly be due to the combined effects, possibly synergistic, of these other mediators and AGEPC.

In summary, our results suggest that AGEPC may contribute, at least in part, to the contractile failure, reduced coronary flow, and conduction arrhythmias of cardiac anaphylaxis. Whether inhibition of AGEPC synthesis or pharmacological antagonism of its effects would significantly attenuate these cardiac abnormalities during anaphylaxis is a critical question for future research.


INDEX TERMS: Cardiac anaphylaxis • Platelet-activating factor (PAF) • Acetyl glyceryl ether phosphorylcholine (AGEPC) • Immediate hypersensitivity reactions of the heart • Acute allergic reactions of the heart • Histamine
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