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Cardiac anaphylaxis in isolated working guinea pig heart[1]

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ABSTRACT Three distinct phases of response were seen after antigen challenge in isolated working guinea pig heart sensitized with crystallized ovalbumin: 1) Phase of augmentation, characterized by sinus tachycardia and augmentation of cardiac function parameters; 2) Phase of arrhythmias, characterized by severe arrhythmias, decrease of coronary flow, and attenuation of cardiac functions; 3) Phase of recovery, characterized by the recovery of sinus rhythm and progressive decrease of the pump function. These results strongly demonstrate that the sequence of events during cardiac anaphylaxis are connected with the direct action of mediators released (histamine and other bioactive endogenous substances) on the heart solely, independent of pulmonary distress and peripheral vasomotor collapse.

KEY WORDS cardiac anaphylaxis; isolated working heart; histamine; albumins; arrhythmia; coronary circulation; cardiac hemodynamics; cardiac output

When systemically immediate anaphylactic reaction was provoked, severe arrhythmias and pump failure were usually the reasons of death, and the symptoms could not be explained by the asphyxiating effects of bronchospasm and laryngeal edema, as it could occur without being preceded by respiratory distress[1]. It was put forward that the heart is an important target organ in systemically immediate anaphylactic reaction and this was proved by many experimental researches. "Cardiac anaphylaxis" is a term coined by Feigen *et al*[2]. Generally, there are 3 characteristics: arrhythmia, decrease of cardiac function, and decrease of coronary flow. Because the responses of guinea pig are similar with that of human being, Langendorff heart of guinea pig is often used for research, that is to perfuse heart retrogradely and it cannot reflect the pump function parameters. In this study, we chose isolated working guinea pig heart to reproduce cardiac anaphylaxis and observed its characteristics, especially the influence on pump function, and compared with the results obtained by Langendorff method. When cardiac anaphylaxis took place, histamine was released from sensitized heart ($3.1 \pm$SD 0.9 μg/g)[3]. So 5 μg histamine were used in our experiment in order to imitate and compare the effect with endogenous histamine. This will be worthy of approaching the mechanism of cardiac anaphylaxis and searching for the antagonist drugs.

MATERIALS AND METHODS

Sensitization Guinea pigs of both sexes, weighing $202 \pm$SD 20 g, were used. Three successive doses of 5 mg ovalbumin (obtained from Shanghai Institute of Biochemistry) were given ip to a guinea pig every other day. The experiment was started 20-30 d after the last injection.

Isolated working heart[4] The perfusion solution was Krebs-Henseleit solution contained EDTA-Na[5]. Hearts, removed from the sensitized guinea pigs, were perfused for 20 min prior to challenge. 5 mg ovalbumin in 0.1 ml of warm oxygenated K-H solution were injected to the heart rapidly via atrial cannula for challenge. Left ventricular pressure (LVP), dP/dt, left ventricular end diastolic pressure (LVEDP), aortic blood flow (ABF), coronary blood flow (CBF), ECG were recorded by an 8-channel polygraph.

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Langendorff isolated heart The heart was perfused for 40 min before challenge at a constant flow of 4–5 ml/min. Ventricular contractile force (VFC), coronary perfusion pressure (CPP), and ECG were recorded.

Histamine administration Guinea pigs of both sexes, weighing 355±SD 47 g were used. Histamine 5 μg (Sigma), was given into an isolated working heart via atrial cannula with bolus injection, and the cardiac function parameters were recorded.

Data were processed by an IBM computer. Statistical evaluations were performed by paired *t* test.

RESULTS

Phasic characteristics of cardiac anaphylaxis 10 working hearts were used. As seen in Fig 1 and Tab 1, 3 distinct phases of response were discernible: Phase of augmentation (phase I): Sinus rate increased at 20±3 s and reached its peak at 60±31 s after challenge. HR, LVP, $+dP/dt_{max}$, $-dP/dt_{max}$ and ABF increased by 30, 17, 38, 44, 46% ($p<0.01$) respectively. LVEDP and CBF decreased 17 and 14% ($p<0.01$), respectively. The increase of $-dP/dt_{max}$ was larger than that of $+dP/dt_{max}$. Phase of arrhythmia

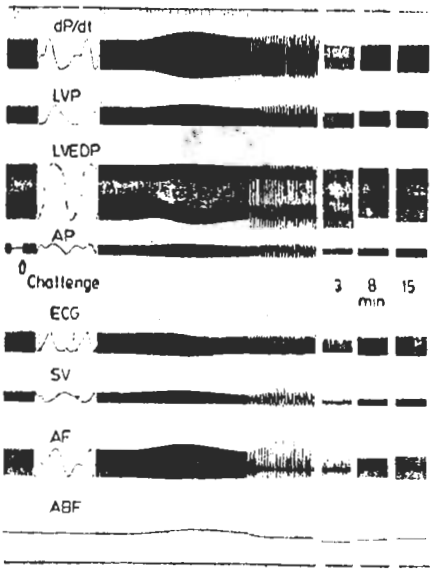

Fig 1. Characteristics of cardiac anaphylaxis in isolated working guinea pig heart, tracing from an 8-channel polygraph, showing the phasic changes after challenge with 5 mg ovalbumin.

Tab 1. Cardiac function parameters of isolated working guinea pig hearts. C: cardiac anaphylaxis, n = 10; H: histamine injection, n = 6. $\bar{x}$±SD. *p>0.05, **p<0.05, ***p<0.01, *vs* before challenge or histamine injection

Parameter	Group	Control	Phase-Ⅰ (at 1 min) Augmentation		Phase-Ⅱ (at 5 min) Arrhythmia		Phase-Ⅲ (at 20 min) Recovery	
			Changes	%	Changes	%	Changes	%
HR(bpm)	C	236±22	71±32	30***	−17±51	−7*	−4±19	−2*
	H	234±24	45±18	18***	8±9	3*	−9±3	−4**
LVP(kPa)	C	8.2±0.7	1.5±0.7	18***	−0.3±0.7	−4*	0.8±11	−10*
	H	11.3±1.1	4.2±1.1	37***	0±0.4	−1*	−1±2	1*
LVEDP(kPa)	C	0.84±0.15	−0.15±0.19	−18**	−0.01±0.21	−1*	0.21±0.28	25**
	H	1.02±0.20	−0.29±0.21	−28**	0.15±0.21	14*	0.11±0.20	11*
dP/dt_{max}(kPa/s)	C	311±30	120±36	38***	−22±32	−7*	−49±50	−16**
	H	473±81	519±121	110***	15±57	3*	−45±38	−10**
$-dP/dt_{max}$(kPa/s)	C	218±34	97±44	44***	−20±27	−9**	−38±38	−17**
	H	391±96	310±81	79***	33±28	8**	−10±55	−2*
ABF(ml/min)	C	23±3	11±4	46***	−5±4	−23***	−9±10	−39**
	H	55±13	24±17	45**	−4±7	−7*	4±5	9*
CBF(ml/min)	C	6.6±1.3	−0.9±0.7	−14***	−1.0±0.6	−14***	−0.3±1.0	−5*
	H	14.0±3.9	2.9±1.5	8*	0.6±3.1	4*	0.9±3.3	5*

Tab 2. Cardiac function parameters during cardiac anaphylaxis of Langendorff isolated guinea pig hearts. n = 14, $\bar{x} \pm SD$. * $p > 0.05$, ** $p < 0.05$, *** $p < 0.01$

Parameter	Control	Phase-I (at 30 s)		Phase-I (at 1 min)		Phase-II (at 5 min)		Phase-III (at 20 min)	
		Change	%	Change	%	Change	%	Change	%
HR(bpm)	145±26	32±23	22***	48±40	33***	−32±21	−22**	15±30	11*
VCF(g)	2.8±2.4	0.2±0.3	7**	−0.03±0.7	−1*	−0.7±0.6	−27**	−0.8±0.4	28***
CPP(kPa)	6.2±0.7	−0.7±0.7	−11***	1.0±1.2	16**	1.9±0.9	31***	0.4±1.2	6*

(phase II): beginning at 1.2±0.5 min after challenge. Arrhythmias occurred and lasted for 8±4 min. In this phase, 2 prominent features were identified: (1) Arrhythmias: These included A-V block, ventricular extrasystole, ventricular tachycardia and idioventricular rhythm, with the incidence of 8/10. The remaining 2 hearts were of less severity or shorter duration. Because of the occurrence of A-V block, the atrial rate and ventricular rate were dissociated: atrial rate 306 ±30 bpm, ventricular rate 203±42 bpm. (2) Decrease of pump function: ABF, CBF, $-dP/dt_{max}$ decreased by 23, 14% ($p < 0.01$), 9% ($p < 0.05$) respectively at 5 min after challenge. At this time, there were no obvious changes on LVP, LVEDP. Phase of recovery (phase III): 20 min after challenge, arrhythmia ceased and sinus rhythm rertnued in most of the hearts (8/10), but pump function parameters continuously declined, concomitant with the elevation of LVEDP (26%, $p < 0.05$).

Effect of exogenous histamine Six working hearts were used. According to the phasic characteristics described above, action of exogenous histamine could also be divided into 3 phases. Phase I: sinus rate increased in 10 s after histamine injection. HR, LVP, $+dP/dt_{max}$, $-dP/dt_{max}$, and ABF increased by 18, 36, 110, 79% ($p < 0.01$) and 45% ($p < 0.05$), respectively. LVEDP decreased 28% ($p < 0.01$), but CBF did not reduce. Phase II: Sustained arrhythmias and attenuation of pump function could not be observed. Phase III: Apart form slight reduction of HR and $+dP/dt_{max}$, there were no obvious changes on cardiac function parameters.

Cardiac anaphylaxis in Langendorff heart Fourteen hearts were used. The phasic changes after challenge were similar with that in working heart, but augmentation in phase I was not so obvious. 30 s after challenge, a short decrease of CPP was seen, and then CPP increased gradually. At phase II, 5 min after challenge, CPP increased by 31% ($p < 0.01$). It began to reduce as soon as arrhythmias ceased. At phase III, 20 min aftre challenge, HR and CPP recovered to control. The incidence of severe arrhythmias was 12/14. When A-V block took place, atrial and ventricular rate were dissociated (atrial rate 178±37 bpm vs ventricular rate 113±29 bpm).

DISCUSSION

With the ovalbumin active sensitization, we reconstructed a cardiac anaphylaxis model tein isolated working guinea pig heart. The advantages of this model are: the observations can be made at the working and energy consuming condition with preload and after load kept constant and it sensitively reflected the slight changes of cardiac function. Langendorff heart was perfused at a constant flow, from which we could find out the constriction or dilatation of coronary artery. These 2 models could supplement to each other. On the other hand, because there is an individual variability of antibody amounts produced among guinea pigs leading to the difference of sensitizing degree, the duration of arrhythmias and the severity of heart

failure may be different.

Sensitized heart released histamine after challenge[6]. Histamine was thought to mediate all of the changes of cardiac anaphylaxis. In the phase I, which was very similar with the effect of histamine with bolus injection, the positive inotropic and chronotropic action were mediated by H_2 receptors. Histamine is an important initiative factor causing arrhythmias in the phase II. The negative dromotropic effect mediated by H_1-receptors, and enhancement of automaticity mediated by H_2-receptor joined together and were most liable to elicit ventricular arrhythmias[1]. H_1 and H_2 antagonists could partially inhibit arrhythmias, but here were some phenomena which can not be explained merely by the release of histamine. 1) When 5 μg histamine were injected directly into an isolated working heart, obvious positive inotropic and chronotropic effect were noted, but sustained arrhythmia did not occur. 2) When a sensitized heart was challenged in the presence of cimetidine and pyrilamine, only augmentation in phase I was abolished, A-V block and ventricular arrhythmia in most hearts were not inhibited (Fig 2). 3)There was some correlation between arrhythmias and diminution of coronary flow. We have observed that accompanying arrhythmias there was a gradual increase of CPP, and when arrhythmias ceased, it gradually recovered too. Histamine is a vasodilator. Thus this effect must be connected with some other substances released. 4) Another important change in phase II was the obvious reduction of pump function. This effect was not related to histamine since exogenous histamine did not have this action. There is a release of leukotrienes and prostaglandins from allergic heart[7]. Leukotrienes, together with $PGF_{2\alpha}$, PGD_2 and TXA_2, caused a coronary constriction during cardiac anaphylaxis. Myocardial ischemia decreased cardiac contraction and was an important cause of arrhythmias[8].

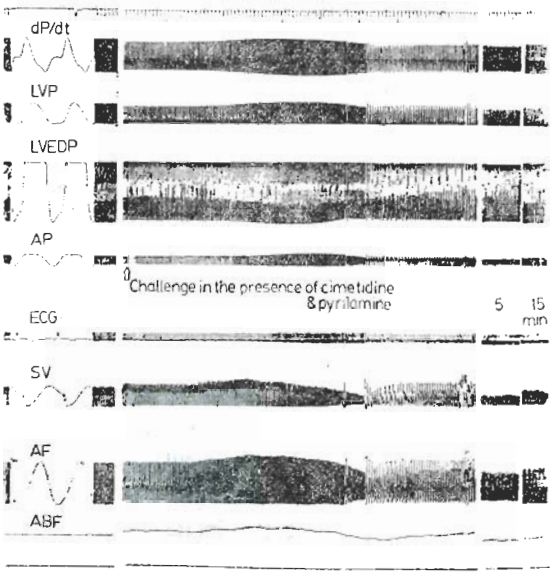

Fig 2. Response of sensitized isolated working guinea pig heart upon challenge in the presence of cimetidine 3 μmol/L and pyrilamine 3 μmol/L. The augmentation in phase I was abolished, but arrhythmias were not inhibited

In systemic anaphylaxis produced in guinea pig *in vivo*, cardiac and respiratory events occurred at the same time when challenged intravenously. When antigen was given by intracardiac injection, changes in tachycardia preceeded bronchoconstriction[9]. This method still can not completely rule out the secondary effects following respiratory distress during the whole course of cardiac anaphylaxis. The results in our experiments strongly demonstrate that the sequence of events in cardiac anaphylaxis was due solely to the direct attack of the mediators released (histamine and other bioactive endogenous substances) on the heart, independent of pulmonary distress and peripheral vasomotor collapse.

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豚鼠离体工作心脏的心性变态反应[1]

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提要　用卵清蛋白抗原致敏后豚鼠制备离体工作心脏。抗原攻击后出现三相反应：增强相，表现为窦性心动过速和各项心功能指标增强；心律失常相，表现为严重的心律失常和冠脉血流量降低，心功能抑制；恢复相，窦律恢复，但泵功能仍持续降低。本实验采用离体豚鼠工作心脏模型，排除了肺及外周的作用。结果提示心性变态反应时上述各时相变化，是组胺及其它内源性活性物质的释放，直接对心脏打击的结果。

关键词　心性变态反应；　离体工作心脏；　组胺；　白蛋白；　心律失常；　冠状动脉循环；　心脏血液动力学；　心排出量

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