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Low Serum Dopamine β-Hydroxylase Activity: *A MARKER OF CONGESTIVE HEART FAILURE*

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To gain information about the nature of disturbances in sympathetic nervous system control in congestive heart failure, serum dopamine β-hydroxylase (DBH) activity was measured in 30 patients with heart failure of diverse etiologies and 29 healthy normotensive controls. The heart failure patients had been symptomatic for at least 6 wk and had elevated filling pressures, low cardiac indices, low ejection fractions, and wide arteriovenous oxygen differences. DBH activity was 47.1±4.7 (mean±SE) for the controls and 14.4±2.7 IU for the heart failure patients ($P < 0.001$). Sera from some patients with heart failure had potent inhibitory effects on DBH activity of normal sera. The inhibitor was heat stable and dialyzable and could be demonstrated despite presence of *N*-ethylmaleimide or Cu^{++} in the reaction mixture. However, some inhibitory activity was also present in sera of normal patients; this inhibitory property was not demonstrable in unheated normal serum, but was unmasked when DBH was heat inactivated. It is proposed that although the inhibitor may have been a factor in low serum DBH activity in some patients with heart failure, the major cause of the low activity in the heart failure group was a reduced rate of synthesis or release of the enzyme by sympathetic nerves. This may reflect a dissociation between rates of neural release of norepinephrine and release of DBH in chronic, […]

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A MARKER OF CONGESTIVE HEART FAILURE

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ABSTRACT To gain information about the nature of disturbances in sympathetic nervous system control in congestive heart failure, serum dopamine β-hydroxylase (DBH) activity was measured in 30 patients with heart failure of diverse etiologies and 29 healthy normotensive controls. The heart failure patients had been symptomatic for at least 6 wk and had elevated filling pressures, low cardiac indices, low ejection fractions, and wide arteriovenous oxygen differences. DBH activity was 47.1±4.7 (mean±SE) for the controls and 14.4±2.7 IU for the heart failure patients ($P < 0.001$). Sera from some patients with heart failure had potent inhibitory effects on DBH activity of normal sera. The inhibitor was heat stable and dialyzable and could be demonstrated despite presence of *N*-ethylmaleimide or Cu^{++} in the reaction mixture. However, some inhibitory activity was also present in sera of normal patients; this inhibitory property was not demonstrable in unheated normal serum, but was unmasked when DBH was heat inactivated. It is proposed that although the inhibitor may have been a factor in low serum DBH activity in some patients with heart failure, the major cause of the low activity in the heart failure group was a reduced rate of synthesis or release of the enzyme by sympathetic nerves. This may reflect a dissociation between rates of neural release of norepinephrine and release of DBH in chronic, severe heart failure. The observation of low serum DBH levels in patients with heart failure suggests that measurement of DBH levels may serve as a useful indicator of cardiac dysfunction.

INTRODUCTION

The nature and extent of the alterations in sympathetic nervous system tone in patients with congestive heart failure has not been clear. There is evidence that both in humans, and in animal models, heart failure is associated with depletion of cardiac norepinephrine stores and augmented generalized sympathetic activity (1–4). Marked increases in rates of norepinephrine turnover have been reported in this disorder (5). Under normal conditions the rate-limiting step in the biosynthesis of norepinephrine is the hydroxylation of tyrosine, which is catalyzed by the enzyme tyrosine hydroxylase (6). However in a recent study of cardiomyopathic Syrian hamsters with heart failure, the hydroxylation of dopamine, rather than the hydroxylation of tyrosine, appeared to limit norepinephrine synthesis (7). If the accumulation of dopamine observed in this animal model is characteristic of heart failure in other species, including man, then it is reasonable to hypothesize that there may be a reduction in activity levels of the enzyme dopamine β-hydroxylase (DBH), which catalyzes conversion of dopamine to norepinephrine.

DBH is released from the synaptic vesicles of postganglionic sympathetic neurons along with norepinephrine (8, 9). Because the enzyme has a relatively long half-life and amounts released from sympathetic nerves are small (10, 11), DBH levels are much less sensitive to acute stresses than are catecholamine levels and tend to remain stable from day to day. Although there have been numerous studies of DBH activity in systemic hypertension, little is known about blood or cardiac levels in patients with heart failure or other forms of cardiovascular disease. Accordingly, we measured serum DBH activity in a group of patients with severe, chronic congestive heart failure.

METHODS

Characteristics of the subject populations. The 30 subjects with congestive heart failure reported dyspnea on exertion, orthopnea, or paroxysmal nocturnal dyspnea for at least 6 wk before the study. Each had been observed by a physician to have a third heart sound, distended neck veins, or pedal edema within 2 wk before the study. Diagnoses included coronary artery disease in 11 subjects,

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TABLE I
Clinical Characteristics of the 30 Heart Failure Patients

Patient	Age	Sex	Diagnosis	LVEDP	WEDGE	CI	AP	SVR	EF	AVO_2 difference
	yr			*mm Hg*	*mm Hg*	*liters/m²*	*mm Hg*	*dyn-s-cm⁻⁵*	*%*	*vol%*
1	50	M	CAD, mitral regurgitation	—	30	—	—	—	—	—
2	64	M	RHD, mitral stenosis & aortic regurgitation	7	28	2.1	120/70	1740	65	7.1
3	42	M	CAD, hypertension	20	14	2.5	130/85	1616	31	3.6
4	58	M	CAD, mitral regurgitation, hypertension	26	24	1.6	110/65	2093	42	6.0
5	61	M	AR, due to endocarditis	16	16	3.5	120/45	786	—	—
6	51	M	CAD	18	19	1.9	136/75	1984	45	4.9
7	60	M	ASD	15	14	1.8	120/70	1939	40	6.5
8	53	M	RHD, mitral stenosis & regurgitation, hypertension	16	30	1.6	130/80	2152	50	6.4
9	39	M	RHD, mitral stenosis & regurgitation	23	23	2.0	120/75	1794	21	6.5
10	64	M	CAD, hypertension	26	36	1.5	120/60	1920	31	6.2
11	50	M	RHD, mitral stenosis, aortic stenosis & regurgitation	9	14	1.9	105/55	1829	40	6.3
12	63	F	RHD, mitral stenosis, aortic stenosis	12	26	1.5	120/60	2660	60	4.7
13	66	M	PMD	5	5	1.9	120/70	1900	27	5.0
14	53	F	ASD	8	8	3.6	160/70	1447	—	5.1
15	55	M	AR due to endocarditis	—	35	2.0	115/38	1131	—	5.5
16	51	M	RHD, aortic & mitral regurgitation	20	23	3.0	145/45	1360	51	—
17	31	M	CAD, mitral regurgitation	21	26	1.7	85/58	1624	23	—
18	58	M	CAD, hypertension, diabetes mellitus	20	24	1.4	120/78	1200	18	5.9
19	59	M	CAD, mitral regurgitation	27	22	1.4	130/80	1644	—	7.6
20	58	M	AS, mitral regurgitation	18	25	1.8	170/80	1930	35	4.0
21	54	M	CAD, hypertension	43	42	1.1	120/80	2430	13	9.7
22	44	M	RHD, mitral stenosis	5	40	2.1	90/60	983	69	6.9
23	41	M	RHD, mitral stenosis, aortic regurgitation	10	20	2.5	130/70	1565	57	5.7
24	22	F	PMD, mitral regurgitation	38	—	2.0	95/75	2125	16	4.8
25	63	M	PMD, mitral regurgitation	18	20	1.6	140/80	2571	8	6.1
26	28	M	PMD	30	32	2.2	110/80	1644	11	8.1
27	42	F	RHD, mitral stenosis	22	30	1.8	140/80	2533	50	—
28	62	M	CAD, aortic regurgitation	20	25	1.9	120/65	1946	62	6.1
29	54	M	PMD, aortic regurgitation & mitral regurgitation	16	14	1.2	110/60	2966	27	6.8
30	74	M	CAD	—	27	1.2	110/70	3268	—	—

Abbreviations used in this table: LVEDP, left ventricular end-diastolic pressure at *y* point; WEDGE, mean pulmonary wedge pressure; AP, peak systolic and diastolic catheter aortic pressures; SVR, systemic vascular resistance; EF, left ventricular ejection fraction; AVO_2, pulmonary artery-systemic artery oxygen difference; CAD, coronary artery disease; RHD, rheumatic heart disease; AR, aortic regurgitation; ASD, atrial septal defect; PMD, primary myocardial disease; AS, aortic stenosis.

rheumatic valvular disease in 10 subjects, primary myocardial disease in 5 subjects, atrial septal defect in 2 subjects, and aortic regurgitation caused by bacterial endocarditis in 2 subjects. There were 26 men and 4 women ranging from 22 to 74 yr in age with mean 52±2 (SE) yr. All 30 subjects were taking digoxin, 26 were taking furosemide, 3 were taking warfarin, 4 were taking methyldopa, 11 were taking potassium chloride solution, and 4 were taking diazepam. Other drugs, taken by one or two persons only, included antibiotics, nitrites or nitrates, other diuretics, drugs for diabetes therapy, or antiarrhythmic agents. There was pulmonary venous congestion by X ray within 2 wk of the time of study in all cases except the two subjects with atrial septal defect, both of whom had X-ray evidence of increased flow in the pulmonary circulation and clinical evidence of right heart failure.

Partial or complete cardiac catheterization, with methods described previously (12), were performed on each heart failure patient and results are shown in Table I. At the time of study, each patient had been treated optimally with appropriate medications and none had edema or evidence of pulmonary congestion. All were free of congestion for at least 3 days before catheterization and most were optimally diuresed for at least 1 wk. 28 of the 30 patients with heart failure had elevated (>12 mm Hg) pulmonary wedge or left ventricular end-diastolic pressures. Cardiac index was reduced (<2.5 liters/min-m²) in 23 of 29 subjects. Left ventricular ejection fraction was reduced (<52%) in 19 of 24 patients, arteriovenous oxygen difference was increased (>5.0 vol %) in 18 of 24 patients, and systemic vascular resistance was elevated (>1,500 dyn-s-cm⁻⁵) in 23 of 29 patients.

As controls, 29 healthy normotensive subjects were studied. They included 15 males and 14 females aged 21—53 yr with mean 32±2 yr. None were regularly taking medication. In five of the normal subjects who underwent cardiac catheterization because of a history or physical finding which raised the possibility of a subtle underlying heart disease, findings at catheterization were entirely normal.

Serum DBH assay methods. Bloods were drawn from a brachial artery or vein of fasting subjects. The samples were

drawn at the beginning of the procedure from those subjects who underwent cardiac catheterization. Sera was stored at −70°C.

DBH activity was measured by the spectrophotometric method of Nagatsu and Udenfriend (13). The reagents used were purified beef catalase (Boehringer Mannheim Biochemicals, Indianapolis, Ind.), *N*-ethylmaleimide and tyramine (Sigma Chemical Co., St. Louis, Mo.), pargyline (Saber Laboratories, Inc., Morton Grove, Ill.), and disodium fumarate (Calbiochem, San Diego, Calif.). Duplicate 10-μl serum samples were assayed. Subject serum boiled at 95°C for 5 min was used as a blank for each determination. Tyramine, which was added in saturating concentrations, was the substrate, and the octopamine produced as a result of enzymatic activity was oxidized to *p*-hydroxybenzaldehyde, which was quantitated spectrophotometrically. Endogenous inhibitors of DBH which interfere with the assay were inactivated by addition of *N*-ethylmaleimide. DBH activity was maximal in the presence of 30 mmol/liter of *N*-ethylmaleimide. Addition of Cu^{2+} to serum at this concentration of *N*-ethylmaleimide failed to increase activity further and substitution of Cu^{2+} for *N*-ethylmaleimide gave values which were lower than those obtained with *N*-ethylmaleimide alone. The optimum concentration of catalase was determined for each batch of enzyme. DBH activity in normal human serum was linear with time of incubation up to 60 min at 37°C, and was linear with concentration from 0 to 50 μl of serum (Fig. 1).

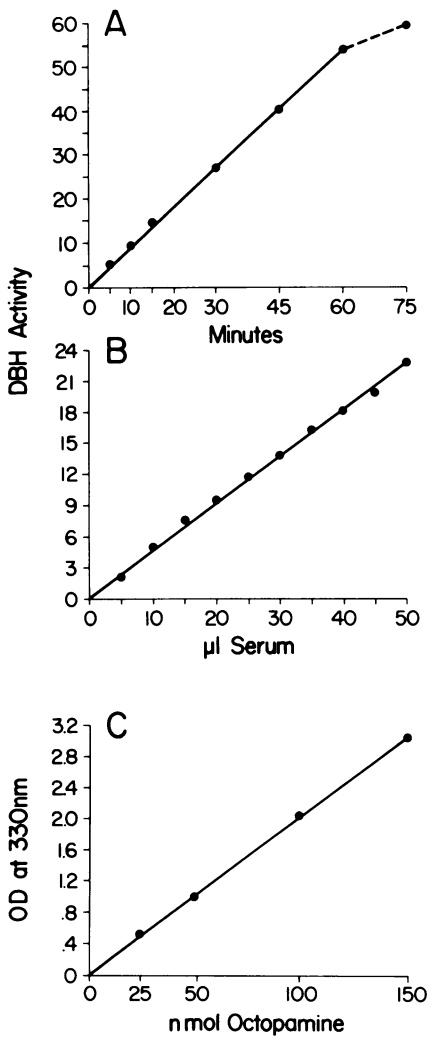

FIGURE 1 Linearity of DBH activity measurements. DBH activity expressed as nanomoles octopamine produced in 60 min of incubation at 37°C as a function of time (frame A) and volume (frame B), in a normal subject's serum. In frame C optical density at 330 nm with known concentrations of octopamine are shown.

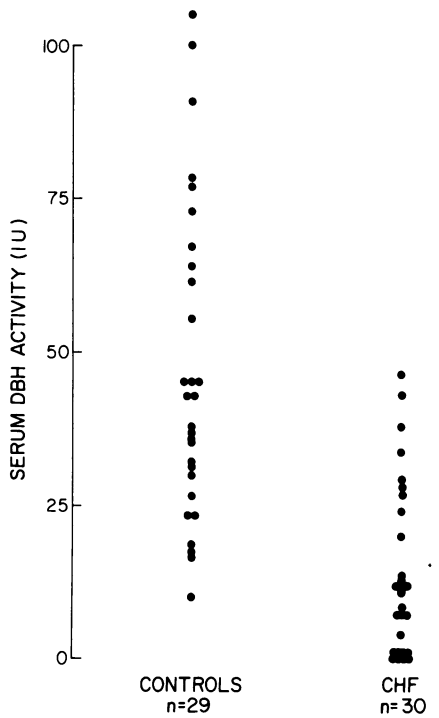

FIGURE 2 Individual DBH activities. Each dot represents serum DBH activity in international units in one of the 29 normal subjects (controls) or the 30 subjects with heart failure (CHF).

Results of DBH activity assays were expressed in international units, which are micromoles of octopamine produced per minute per liter of serum at 37°C. The intra-assay coefficient of variance was 2.4% and the interassay coefficient of variance was 3.6%. On repeated assays of frozen sera there was no loss of activity over a 6-mo period. All analyses were performed by one person who did not know the subjects' medical histories.

RESULTS

DBH activity in normal subjects and patients with heart failure. The individual levels of serum DBH activity are shown in Fig. 2. The mean value and standard error for the 29 normal controls was 47.3 ±4.8 IU. The mean and distribution of values in these normal subjects are similar to normal values reported by others using this technique (14). The mean value and standard error for the 30 subjects with heart

failure was 14.8±2.6. The difference between the two groups of subjects was significant by unpaired t test at $P < 0.001$.

Although there were some differences in age and sex distributions between the control and heart failure groups, these were unlikely to have influenced the results. Previous studies have found no differences between the sexes and little or no change in DBH activity with age after puberty (15, 16). Other differences between the populations were not apparent. Cachexia was not a feature of the heart failure cases. The heart failure patients were maximally diuresed and had normal or nearly normal extracellular fluid volumes at the time bloods were drawn.

Possible correlations between serum DBH activity levels and various clinical or hemodynamic factors within the heart failure group were examined. Three of the four highest DBH values in the heart failure group had a documented history of hypertension. Although the mean value for the 6 patients in the heart failure group with hypertension was higher (23.3±6.5 IU) than in the 24 nonhypertensive subjects with failure (12.6 ±2.7 IU), the difference was not statistically significant. Although some groups have postulated that DBH activity is high in hypertension (14, 17), other studies have not found a direct relationship (18, 19). There were no apparent differences in DBH activity levels among the various etiological categories of heart disease. There were no correlations between DBH levels and filling pressure (left ventricular end-diastolic or pulmonary wedge pressure), cardiac index, ejection fraction, arteriovenous oxygen difference, or systemic vascular resistance among the 30 heart failure patients. The subgroup of patients with near-zero serum DBH activity tended to have unusually severe heart failure clinically.

Studies to exclude alterations in DBH activity caused by sampling technique or drugs. To rule out differences in DBH activity between arterial and venous blood, samples were drawn simultaneously from a brachial artery and a femoral vein in seven subjects. The mean difference between the paired samples was 0.4±0.8 (SE) IU. To examine the month-to-month variation in DBH activity, venous samples were drawn and examined from 1 to 8 mo after the initial arterial blood samples were assayed in seven patients with heart failure. The mean difference between samples in the same subject was 2.6±1.2 IU. Therefore, it was concluded by two-tailed t test that there were no differences in DBH activity between arterial and venous serum samples and that individual DBH activities remained constant for long periods of time.

Experiments were also done to exclude the possibility that drugs reduced measured DBH activity in the heart failure group. Only digoxin and furosemide were considered because no other drugs were being used by the majority of the heart failure subjects. In vitro studies were done in which clinically relevant dilutions of each drug were added to serum and the effect on measured DBH activity was assessed. Neither digoxin in dilutions from 0.5 to 2.0 ng/ml serum nor furosemide in dilutions from 0.001 to 0.1 μg/ml of serum altered DBH activity. Serum samples were obtained from five individuals who had been taking digoxin for long periods of time but had never been in heart failure and all had DBH activities greater than 20 IU. In another group of four subjects, blood samples were obtained before and after digitalization with digoxin for arrhythmias or heart failure; there were no changes in serum DBH activity between pretreatment samples and digoxin samples. In a recent study furosemide is reported to increase plasma DBH in normal subjects (20). It was concluded that the low DBH activity in the heart failure group was not caused by drugs.

Investigation of a possible circulating inhibitor of DBH activity. We noted that when increasing volumes of serum from some patients with heart failure were assayed the DBH activity was not linear. To explain this finding we considered the possibility that a circulating inhibitor of DBH activity was present

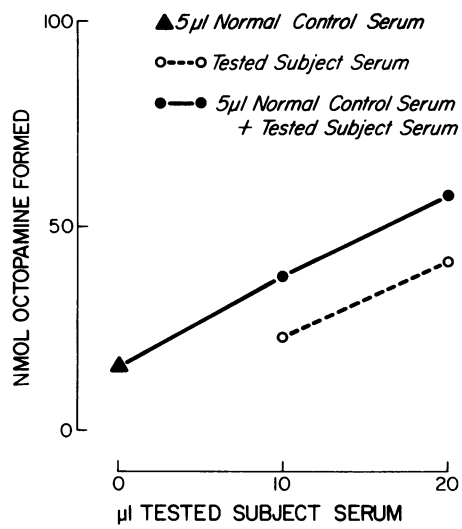

FIGURE 3 Results of a mixing experiment to test a normal subject's serum for inhibitory properties. 5 μl of a control serum were assayed for DBH activity alone (closed triangle) and when mixed with 10 and 20 μl of the tested subject's serum (closed circles). DBH activity in 10 and 20 μl of the tested subject's serum alone was also determined (open circles). DBH activity is reported as nanomoles of octopamine produced in 60 min of incubation at 37°C. The sums of the DBH activities in 5 μl of control serum and each volume of tested serum measured individually were equal to the activities measured in the corresponding mixtures. Thus, the tested subject's serum did not inhibit activity in the control serum when the two sera were mixed.

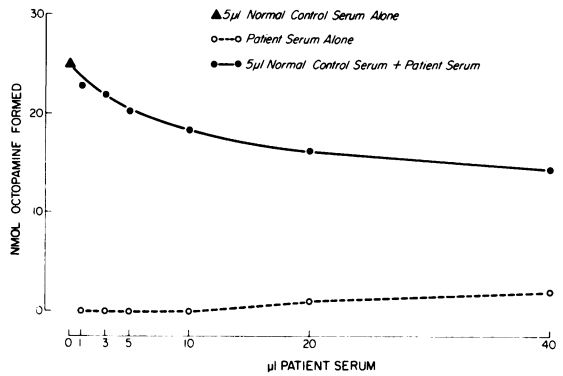

FIGURE 4 Results of a mixing experiment in which a heart failure patient's serum inhibited DBH activity in a control serum. 5 μl of control serum were assayed for DBH activity alone (closed triangle) and when mixed with a series of volumes of the patient's serum (closed circles). Activity was also measured in each volume of the patient's serum alone (open circles). When 5 μl of control serum was mixed with increasing volumes of patient serum DBH activity in the mixtures decreased progressively. Thus, addition of patient serum to control serum markedly inhibited DBH activity in the control serum.

in serum from these individuals. To detect such inhibition, experiments were performed in which increasing volumes (concentrations) of the serum to be tested were mixed with a fixed volume of a normal control serum and the DBH activity in each mixture was measured (17). For these studies DBH activity was expressed in nmol octopamine produced in 60 min. Fig. 3 shows the results when a serum from a normal subject was examined in this manner. The total activity in the mixture at each volume equalled the sum of the activities measured separately. Similar results occurred with sera from 10 other normal subjects, including sera with relatively low DBH activity.

Results from a study with serum from a patient with heart failure are shown in Fig. 4. When increasing volumes of the patient's serum were mixed with 5 μl of normal control serum, the DBH activity in the mixtures progressively decreased. Total activity in each mixture was less than in 5 μl of control serum alone. Thus, it appears that a substance in this patient's serum inhibited DBH activity in the control serum. When sera from 29 patients with heart failure were tested in this manner, 11 were inhibitory, 13 had normal responses (the activity of each mixture equalled the sum of activities in each of its components measured individually), and 5 had equivocal responses.

Studies were then done to partially characterize the inhibitor or inhibitors which appeared to be present in many of the patients with heart failure. Heating serum for 5 min at 95°C did not prevent the inhibition (Fig. 5). However, when 1 ml of serum from a

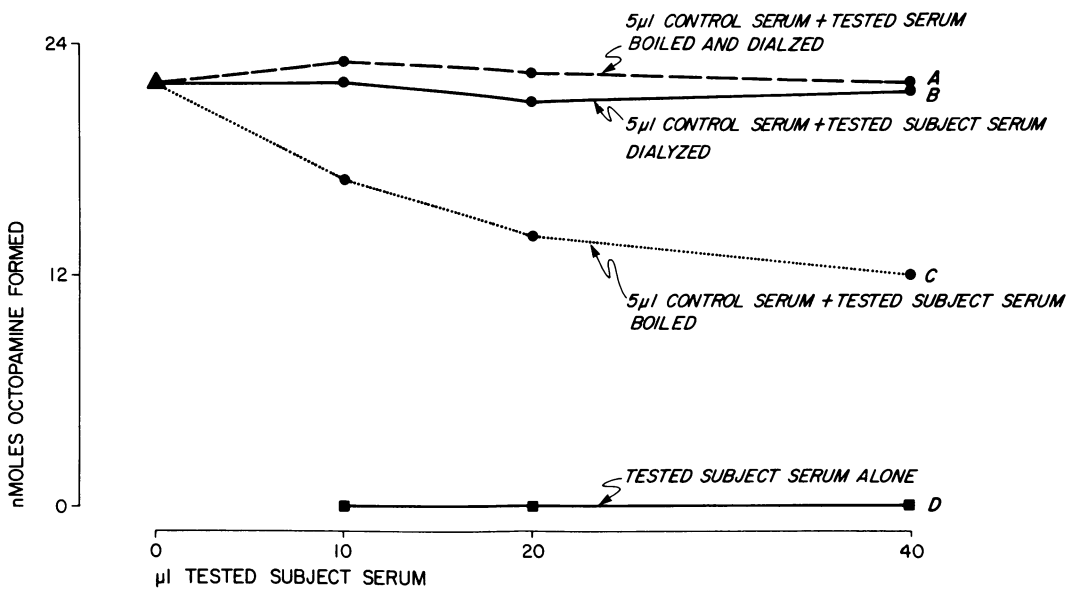

FIGURE 5 Effects of heat inactivation (boiling) and dialysis on inhibitory properties of a heart failure patient's serum. To accomplish heat inactivation serum was boiled at 95°C for 5 min and then centrifuged at 3,200 *g* for 10 min. For dialysis studies serum was vacuum dialyzed for 24 h at 4°C in 5 mM sodium phosphate buffer (pH 6.5) with three (1:1,000 ratio) changes of buffer and corrected for volume changes. Without heat inactivation or dialysis no DBH activity was measurable in the patient's serum (squares). Dialyzed serum whether or not heat inactivated did not inhibit activity in control serum. Heat-inactivated serum inhibited activity in control serum in a manner similar to results with untreated patient serum (shown in Fig. 4).

patient with heart failure was dialyzed at 4°C for 24 h against three changes of 1 liter 5 mM sodium phosphate buffer, pH 6.5, the inhibitory effect was lost (Fig. 5). Despite loss of the inhibitory property, the DBH activity in the dialyzed serum remained at its low predialysis level. When a normal subject's serum was dialyzed in this manner there was no change in DBH activity and a normal additive effect occurred when the dialyzed serum was mixed with control serum. We conclude that the inhibitor is heat stable and of sufficiently small molecular weight to be dialyzed. However, because removal of inhibitor did not increase DBH activity in patients with heart failure it seems likely that either the process by which the inhibitor binds with and inactivates DBH is not reversible or the total amount of bound inhibitor is extremely small.

We considered the possibility that the inhibitor in the subjects with heart failure was also present in normal subjects but in a bound rather than a free form. Since heat denatures DBH but does not affect the inhibitor, normal serum was heated for 5 min at 95°C. As shown in Fig. 6, addition of a series of aliquots of this heated normal serum to a fixed volume of control normal serum diminished DBH activity in the mixture below that in the control serum measured separately. Thus, the heated normal serum had an inhibitory effect on DBH activity. Dialysis of the heated normal serum abolished the inhibitory effect. Therefore, heat inactivation of normal serum results in appearance of an inhibitor which is not detectable in the same serum before heating and which closely resembles the inhibitor present in unheated serum from some of our patients with heart failure.

We also considered the possibility that *N*-ethylmaleimide, which was used in our studies, was not optimal for suppression of endogenous inhibitors in heart failure sera. Others have used Cu^{2+} for this purpose (9). An experiment was performed to evaluate the effects of adding Cu^{2+} to the assay to assure maximal inactivation of usual endogenous inhibitors. The DBH activity in serum from a patient with heart failure to which *N*-ethylmaleimide had been added was not altered by addition of Cu^{2+} between 200 nM and 10 μM. It appears likely that the inhibitor which we have demonstrated is distinctly different from the usual endogenous inhibitors in view of its lack of responsiveness to these substances.

DISCUSSION

We have found that serum dopamine β-hydroxylase activity is substantially reduced in patients with

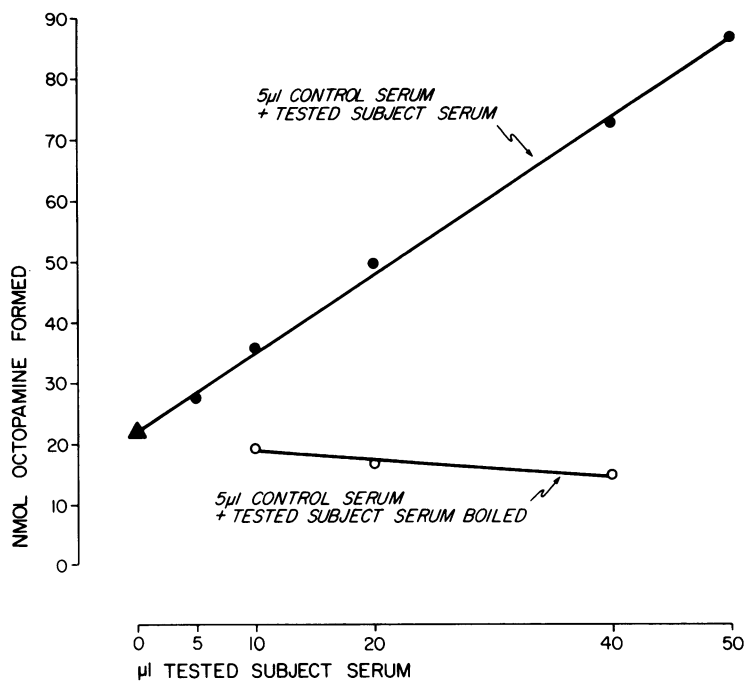

FIGURE 6 Results of mixing experiments with heat inactivated serum from a normal subject. 5 μl of control serum were mixed with increasing volumes of normal serum either heat inactivated or unheated. The unheated mixtures increased linearly with volume. However, when increasing volumes of heated serum were added to 5 μl of control serum a progressive decrease in measured activity occurred. Decreases as much as 50% of the initial control serum level were observed when heated serum from other normal subjects was added in this manner.

chronic congestive heart failure. On the basis of our data and previous knowledge of the properties of this enzyme limited conclusions can be drawn regarding the mechanism of this decreased activity.

The presence of a detectable inhibitor or inhibitors, which is heat stable and dialyzable, could be a factor in the low DBH activity in the serum of some heart failure patients. Unlike usual endogenous inhibitors of DBH activity which are present in normal serum, this inhibitor was not inactivated by either *N*-ethylmaleimide or Cu^{2+}. Therefore, it is tempting to postulate that heart failure is associated with accumulation of a previously unreported inhibitor specifically related to cardiac decompensation. However, certain observations which we have made do not support this possibility. Forty-five percent of our patients with heart failure did not have detectable inhibitor in mixing experiments. In patients whose serum did demonstrate inhibitory properties the lack of a rise in DBH activity after removal of the inhibitor by dialysis makes it unlikely that the inhibitor is solely responsible for the low DBH activity levels. In most physiological settings inhibitor and an enzyme are loosely bound by reversible reactions and removal of free inhibitor would be expected to result in a rise in enzyme activity. The lack of an increase in DBH after dialysis may mean that the DBH-inhibitor complex is unusually tightly bound, that binding causes irreversible damage to the DBH molecule, or that the amount of bound inhibitor was extremely small.

Decreased sympathetic nerve synthesis or release of DBH could be the major cause of the low serum activity in patients with heart failure. According to a previous study in which serum DBH was measured by radioimmunoassay and by assay of enzyme activity (21), both active and inactive DBH molecules are present in the circulation. A hypothesis compatible with our data is that the inhibitor which we have described is a normal component of serum and is present in similar quantity in both normal subjects and those with heart failure. If in heart failure the amount of DBH released into the blood is markedly decreased, the ratio of inhibitor molecules to DBH molecules would be increased with the result that some inhibitor remains in the blood in unbound form. Our observation that heated normal serum has inhibitory properties similar to that of unheated serum from heart failure patients with very low DBH activity supports this hypothesis. If the quantity of DBH released in normal subjects is relatively high, the ratio of bound-to-free inhibitor would be high. However, heat inactivation of DBH molecules in normal serum could release previously bound inhibitor which then becomes detectable in mixing experiments. Although a reduced rate of release of DBH into the blood is the most likely cause of the low serum activity in heart failure, increased rates of metabolism or clearance of the enzyme cannot be excluded.

Why the amount of DBH released from sympathetic nerves would be low is an enigma. Circulating catecholamines in patients with heart failure have been reported to be either normal (22, 23) or to have a tendency to be high (3, 24). There are no reports of reduced blood levels of norepinephrine or other catecholamines in heart failure. It appears that in patients with chronic heart failure there may be a dissociation between rates of release of norepinephrine and rates of release of DBH. Alternatively, normal amounts of DBH are synthesized and released but the enzyme is peripherally inactivated. It is of considerable interest that in cardiomyopathic hamsters with heart failure there is accumulation of dopamine in the myocardium (5). This suggests that in this animal model there may be reduced availability of DBH to catalyze the hydroxylation of dopamine to norepinephrine.

The observation that serum DBH activity is low in patients with severe, chronic heart failure may prove to be of practical clinical value. Presumably these patients initially had normal serum DBH activity which had decreased because of the development of cardiac decompensation. If the fall in serum DBH activity procedes or occurs early in the course of development of heart failure it could be a useful predictor of impending dysfunction which would permit optimum timing of cardiac surgery or medical intervention. Determination of serum or plasma DBH activity might also be useful to distinguish pulmonary congestion due to heart failure from primary pulmonary disease.

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