

# A Study of Biogenic Amines In Central Aortic And Coronary Sinus Blood In Ischemic Heart Disease

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## Summary:

We studied aortic and coronary sinus epinephrine (E), nor-epinephrine (NE), dopamine (DA) and serotonin (5-HT) in fourteen patients with stable angina (SA), six patients with vasospastic angina (VA) and six control subjects (C). SA patients were studied at rest and during incremental atrial pacing. VA patients were studied at rest and during various stages of vasospasm. E and DA were same in SA, VA and C subjects and did not rise with pacing or during vasospasm. NE was also same in all three subgroups but increased during vasospasm ( $p < 0.01$ ) but not with atrial pacing. 5-HT was, however, higher in SA and VA patients as compared to C subjects ( $p < 0.05$ ) and increased further during vasospasm ( $p < 0.01$ ) but not with atrial pacing. This increase in NE and 5-HT during vasospasm was seen before EKG changes manifested or angina occurred. Thus NE and 5-HT play an important causative role in vasospasm, and are not released as a secondary phenomenon in angina. Serotonin is elevated even during resting state in SA and VA. The role of E and DA could not be established.

## Introduction:

Increased sympathetic activity is postulated to be an important determinant of the pathophysiological events associated with ischemic heart disease. Increased peripheral catecholamine concentrations have been documented in acute myocardial infarction<sup>1-4</sup> and in angina pectoris<sup>5-6</sup>. But it is well known that ischemic attacks come on not only with emotion or exertion, but also while the patient is at rest when sympathetic activity is expected to be low. This is further supported by reports of normal peripheral catecholamine levels in some patients<sup>7</sup>.

These opposing lines of evidences may be because peripheral sympathetic activity is not a

true reflector of the actual sympathetic activity in the myocardium effecting the coronary tone. Its activity in the central aortic blood and coronary sinus could provide an insight on the real status of the biogenic amines operating in the myocardium.

We measured levels of epinephrine, nor-epinephrine, dopamine and serotonin in stable angina patients at rest and during atrial pacing and in vasospastic angina patients during rest and during spontaneous coronary spasm. Pacing was preferred to exercise as exercise is known to alter levels of these biogenic amines in absence of myocardial ischemia.

## MATERIAL AND METHODS

### Methods:

The study group consisted of 26 patients undergoing coronary angiography for evaluation of

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angina. They included 14 patients of TST positive stable angina who were studied at rest and after incremental atrial pacing, and 6 patients of vasospastic angina having spontaneous coronary spasm. The two groups were age and sex matched (mean age  $49.2 \pm 5.7$  years). None had ECG or enzymatic evidence of myocardial infarction in the past or during the period of these studies.

The control group consisted of 6 patients of suspected angina who were admitted in intensive care unit, but subsequently on investigations were found to have non-cardiac cause for their chest pain and angiographic evidence of normal coronary arteries. They were age and sex matched to the study group.

All patients were kept fasting for 12 hours before catheterisation and no patient was given aspirin, dipyridamole or beta-blockers for at least 3 days.

#### Experimental Procedure:

Right femoral vein and artery puncture were done by Seldinger Technique. A 7F Multipurpose A<sub>2</sub> catheter was advanced into the coronary sinus by reverse loop technique and a 7F Pigtail catheter was advanced into ascending aorta. In SA patients in whom incremental right atrial pacing was done, a USCI bipolar lead was advanced through femoral vein into high right atrium. Pacing was started at 100 beats/minute and increments of 10 beats/min were given till angina and ST depression more than 1 mm appeared. In 10 patients the pacing was stopped at 160 beats/minute while in 4 patients it was stopped at 130 beats/minute. Pacing at each rate was done for 5 minutes and then blood samples were taken out. In the 6 patients of VA the procedure was prolonged till the patients had evidence of coronary vasospasm. 4 of these 6 patients showed ST elevation of 2 mm in v2-v6 on EKG, while in the other two, the combination of mild coronary stenosis and occurrence of angina at minimal double product led to the presumptive diagnosis of vasospasm.

#### Biochemical Analysis:

Norepinephrine, epinephrine, dopamine and 5-HT were determined in coronary sinus and aortic blood using reverse phase High Performance Liq-

uid Chromatography (HPLC) with electrochemical detection according to method described by Lackovic et al<sup>8</sup>. Analysis of the samples was done on Millipore's (U.S.A.) Water's HPLC system containing Water's 501 HPLC pump, an automated gradient controller, Water's 740 data module and a Water's 460 electrochemical detector. A reverse phase C-18 Bandapack column (10 u 300 mm x 4 mm) was used for the separation of the amines. Electrochemical detector with a glassy carbon electrode was set to a potential of +0.7V versus a Ag/AgCl reference electrode.

#### Statistical Analysis:

Mean value was calculated for each group. Data are given as Mean  $\pm$  S.D. The statistical significance of differences between groups was determined by the student's 't' test.

#### Results:

The concentrations of central aortic and coronary sinus epinephrine, nor-epinephrine, dopamine and 5-HT of control group, stable angina group at rest and at peak pacing, and vasospastic angina at rest and during spontaneous vasospasm are presented in Tables I and II.

**Table I**  
Central Aortic and Coronary Sinus  
Biogenic amines in Control and  
Stable Angina patients

Biogenic (pg/ml) Amine	Control Group		Stable Angina Group			
	Ao	Cs	Resting		Peak Pacing	
	Ao	Cs	Ao	Cs	Ao	Cs
Epinephrine	104 $\pm$ 18	102 $\pm$ 12	107 $\pm$ 14	115 $\pm$ 16	102 $\pm$ 15	114 $\pm$ 13
Nor-epinephrine	296 $\pm$ 13	365 $\pm$ 22	284 $\pm$ 30	342 $\pm$ 11	261 $\pm$ 14	350 $\pm$ 26
Dopamine	57 $\pm$ 11	53 $\pm$ 18	49 $\pm$ 7	57 $\pm$ 13	51 $\pm$ 2	48 $\pm$ 9
Serotonin	4153 $\pm$ 279	5147 $\pm$ 91	6834 $\pm$ 729*	7847 $\pm$ 342*	6742 $\pm$ 756*	7407 $\pm$ 478*

Abbreviations: Ao = Ascending aortic blood.

Cs = Coronary Sinus blood.

\*Resting and peak pacing serotonin levels of Ao and Cs differ from control group at  $p < 0.05$ .

Central aortic and coronary sinus levels of epinephrine and dopamine were same in all patient subgroups. The heart neither extracted nor produced these amines at rest or during pacing or during attack of vasospasm. However, nor-epinephrine and serotonin levels were higher in coronary sinus than in central aorta in all patient subgroups, though the difference was not significant. This could imply production of these two amines by the heart.

There was no difference in central aortic and coronary sinus epinephrine and dopamine levels between controls, stable angina patients during rest and at peak pacing and vasospastic angina patients at rest and during vasospasm. Nor-epinephrine levels were also the same in controls, stable angina patients at rest and during peak pacing and vasospastic angina patients during rest. But a rise ( $p<0.05$ ) in its level was seen both in central aortic and coronary sinus blood during vasospasm, returning back to baseline levels in about 20 min-

utes. However, serotonin levels were raised in stable and vasospastic angina patients over controls ( $p<0.05$ ) both in central aortic and in coronary sinus blood. While it failed to rise further during atrial pacing, it increased ( $p<0.01$ ) over resting state during vasospasm. A rise was seen even before ST elevation on ECG manifested or angina occurred and returned to baseline in about 20 minutes.

### Discussion:

Angina pectoris is generally associated with pain and emotion and a rise of plasma catecholamines is expected in such patients. But reports of their levels in arterial blood have been variable<sup>5,6,7,9,10,11</sup>. An attempt at measuring their levels in coronary sinus blood has not much solved this confusion<sup>12,13</sup>. The response to pacing has similarly been variable<sup>12</sup>.

Our values for resting biogenic amine concen-

**Table II**  
Central Aortic and Coronary Sinus Biogenic Amines in Vasospastic Angina patients

Biogenic (pg/ml) Amine	Stages of Vasospasm							
	Resting		Onset of ST elevation/ angina		During ST elevation/ angina		After 20 min. of relief of angina	
	Ao	Cs	Ao	Cs	Ao	Cs	Ao	Cs
Epinephrine	110± 28	103± 13	99± 18	102± 16	102± 20	110± 5	107± 13	108± 18
Nor-epinephrine	301± 17	351± 11	552± 17*	586± 32*	536± 18*	580± 22*	320± 17	365± 12
Dopamine	48± 5	52± 13	53± 16	50± 2	55± 3	49± 14	45± 12	53± 3
Serotonin	6947± 379	7608± 322	10524± 686**	12475± 572**	11087± 601**	11052± 358**	7101± 242	7907± 478

Abbreviations: Ao = Ascending aortic blood.  
Cs = Coronary Sinus blood.

\*

Differs from their resting values at  $p<0.01$ .

\*\*

tration in aortic and coronary sinus blood correspond closely to basal values reported by others<sup>1-16</sup>. Levels of epinephrine and dopamine were the same in angina patients as in controls and did not rise with atrial pacing or with spontaneous vasospasm. Levels of nor-epinephrine were also the same in controls and angina patients and did not rise with atrial pacing, but showed marked increase both in central aortic and coronary sinus blood during vasospasm. A significant increase was found before onset of angina or ST changes in ECG. Levels of serotonin were raised in angina patients and increased further during spontaneous vasospasm in a manner similar to nor-epinephrine. However, they failed to rise with atrial pacing.

Taken together these findings suggest an important role of nor-epinephrine and serotonin in episodes of vasospasm. Their rise before the onset of episode and failure to rise during atrial pacing suggests primary causative role of nor-epinephrine and serotonin rather than a secondary effect resulting from vasospasm itself. The role of epinephrine and dopamine in vasospasm could not be established. An increase in serotonin was also seen in resting state in angina patients. Serotonin is stored in dense bodies of platelets and its rise suggests an activated state of platelets as reported by other workers also<sup>17</sup>.

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