
Study of Adrenomedullin in Children with Heart Failure

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Abstract:

Congestive heart failure (CHF) is the end stage of many diseases of the heart and is a major cause of morbidity and mortality among children. CHF is a common, serious and treatable disease so great efforts should be made to manage it correctly. Adrenomedullin (ADM) is a multifunctional peptide with a wide range of actions related to cardiovascular homeostasis. ADM receptors are highly expressed in the heart. ADM may play some important role in the pathophysiologic make up of CHF.

This study was conducted on 50 infants and children with CHF of cardiac etiology divided into 3 groups: Group I, rheumatic heart disease patients (RHD), Group II, congenital heart disease patients (CHD) and Group III, myocardial heart disease patients (MYHD). Ten healthy matched age and gender children were taken as controls. All patients were subjected to; full history taking, clinical physical examination, chest X-ray, ECG, echocardiography and routine laboratory investigations including complete blood count, blood gases, PH, sodium, potassium, serum calcium, AST and ALT. Adrenomedullin was assayed using enzyme immunoassay method.

Results revealed that plasma level of ADM was highest in Group I (RHD) patients followed by Group II (CHD) then Group III (MYHD) indicating a role played by underlying etiological cardiac disease in the pathophysiology of CHF and ADM level. As regards to Group I (RHD) the plasma level of ADM was significantly higher in patients with combined mitral and aortic valve affection than those with isolated valve affection. The mean level of ADM was also higher when there was isolated mitral valve affection rather than isolated affection of aortic valve. In Group II (CHD) the cyanotic patients had significantly higher plasma ADM level than the acyanotic patients. Concerning Group III (MYHD) ADM level was significantly higher in patients with dilated cardiomyopathy compared to those with myocarditis. The plasma level of ADM was significantly elevated in proportion to the severity of CHF; cases with NYHA (New York Heart Association) Class IV (Severe CHF) had the highest plasma ADM levels followed by NYHA Class III (moderate CHF) cases then NYHA Class II (mild CHF).

Conclusion: ADM is involved in the pathophysiologic make up of HF. It is not only a biochemical marker for evaluating the severity of HF, but also an independent prognostic indicator of this syndrome. An improved understanding of the role of ADM in HF might lead to the development of promising therapeutic agents for the treatment of patients with this syndrome.

Abbreviations: CHF: congestive heart failure, ADM: adrenomedullin, RHD: rheumatic heart disease, CHD: congenital heart disease, MYHD: myocardial heart disease, DCMP: dilated cardiomyopathy.

Introduction:

Heart failure is a clinical syndrome characterized by inadequate cardiac performance. The heart is unable to pump enough blood to meet the body's metabolic needs.¹ It is a common, serious and treatable problem, so great efforts should be made to improve its management.²

Heart failure is the end stage of many diseases and is a major cause of morbidity and mortality.³ Congenital heart disease (CHD) is the most common cause of heart failure among children. Acquired heart diseases and myocardial dysfunction such as; acute rheumatic fever, viral myocarditis and dilated cardiomyopathy can also cause heart failure.⁴

Adrenomedullin (ADM) is a multifunctional peptide with a wide-ranging actions related to cardiovascular homeostasis. It is produced in many tissues relevant to the cardiovascular and renal functions, such as the heart, adrenal medulla, kidney, aorta and brain. Its receptors are highly expressed in the heart.⁵

ADM may play an important role in the pathophysiologic make up of heart failure by its vaso-dilating effect against the concomitant exaggeration of humor pressor agents, as well as by its inotropic effect.⁶ It also attenuates cardiac hypertrophy in the myocytes and inhibits proliferation and collagen production in cardiac fibroblasts suggesting that ADM may be an anti-fibrotic and anti-hypertrophic factor in the failing and hypertrophied heart.⁷

Circulating concentrations of ADM are elevated in cardiovascular diseases in proportion to the severity of cardiac and hemodynamic impairment. An improved understanding of the role of ADM in heart failure might lead to the development of new therapeutic agents acting through the ADM receptors.⁸

The aim of this work is to assess the role of ADM in congestive heart failure among children, and its correlation with the etiological type of underlying heart disease, the severity of heart failure (NYHA classification) and the prognostic mortality rate.

Subjects and Methods:

A prospective one year (from August 2003 to August 2004) clinical study was carried out at the inpatient wards of the Children Hospital, Cairo University. The present study enrolled 50 infants and children with an age range from 3 days to 14 years with a mean of (33.78 months) admitted to the hospital with acute congestive heart failure of cardiac origin. They included 24 (48%) infants less than 2 years and 26 (52%) children more than 2 years. Ten healthy children with matched age and sex were taken as controls.

The severity of CHF was classified according to New York Heart Association Functional Classification⁹ depending on the degree of dyspnea into:

- *NYHA Class II* (Mild): Patients having dyspnea on ordinary exercise.
- *NYHA Class III* (Moderate): Patients having dyspnea on mild exertion.
- *NYHA Class IV* (Severe): Patients having dyspnea at rest.

The studied cases were grouped according to the underlying etiological type of heart disease into 3 groups *Group I* patients with RHD, *Group II* patients with CHD, *Group III* patients with MYHD.

All patients were subjected to:

(1)-**Full history taking.**

(2)-**Clinical examination:**

- Vital signs: pulse, blood pressure, temperature, heart rate, respiratory rate.
- General examination: presence of cyanosis or pallor, congested neck veins, puffy eyelids, clubbing of fingers and oedema of the lower limbs.
- Local cardiac examination: to detect cardiac apex, precordial bulge, pulsations and thrills. Assessment of the heart sounds, murmurs; their type and intensity and the presence of additional sounds as gallop.

(3)- **Laboratory investigations:**

- Complete blood count and blood indices using Sysmex K-1000 automated blood cell counter.

- Blood gases, pH, sodium and potassium using 288 Ciba Corning blood gas analyzer.
- Serum calcium, AST & ALT on Express plus auto analyzer (Ciba Corning diagnostics, Halstead, England).
- Adrenomedullin assay: A 3 ml blood sample was collected on EDTA, transferred to a centrifuge tube containing Aprotinin (0.6 TIU/ml of blood), centrifuged and the plasma was separated, and kept frozen at -70°C till assay time.

Extraction of adrenomedullin from plasma was done using buffer (A): 1%trifluoroacetic acid (TFA) in water and buffer (B): 60%acetonitrile in 1% TFA. Plasma was acidified with an equal amount of buffer (A), mixed and centrifuged for 20 minutes at 4°C. A SEP-COLUMN containing 200 mg of C18 (code RK-SEPCOL-1) was equilibrated by washing with buffer B (1 ml, once) followed by buffer A (3 ml, 3 times).The acidified plasma solution was loaded onto the pre-treated C18 SEP-Column. The column was slowly washed with buffer A (3ml, twice) and the wash was discarded. Adrenomedullin was eluted slowly with buffer B (3 ml, once) and the eluant was collected in a polypropylene tube. The eluant was evaporated to dryness in a centrifugal concentrator. The dried extract was reconstituted with assay buffer before performing the assay.

Adrenomedullin was assayed using an enzyme immunoassay kit, DRG International, Inc. USA according to the following principle:¹⁰ The immunoplate in this kit is pre-coated with secondary antibody and the nonspecific binding sites are blocked. The secondary antibody can bind to the Fc fragment of the primary antibody whose Fab fragment will be competitively bound by both biotinylated peptide and peptide standard or targeted peptide in samples. The biotinylated peptide is able to interact with streptavidin-horseradish peroxidase which catalyzes the substrate solution to produce a blue color solution. The enzyme-substrate reaction is stopped by HCL and the solution turns to yellow which is read at 450 nm. The intensity of the yellow color is inversely proportional to the amount of the peptide in standard solutions or samples. Normal range of plasma adrenomedullin according to the manufacturer of the kit is 2.7- 18 pg/ml.

(4)-**Radiological Examination:** Plain chest X-ray: Postero-anterior and lateral views for assessment of cardiac size and pulmonary congestion.

(5)-**12-lead Electrocardiogram:** to detect ventricular hypertrophy, chamber enlargement, heart rate, or arrhythmia.

(6)-**Echocardiography:** M-Mode, 2-D echo, color flow mapping and Doppler imaging using Helwett-Packard

5500 Sonos ,using different sizes and resolution probes (7MHZ, 5MHZ and 3.5 MHZ) according to age.

Statistical Analysis:

Data were processed using the SPSS win version 9. The comparisons for independent groups were done using parametric analysis of variance (ANOVA) and non-parametric tests as Kruskal-Wallis test. P value of < 0.05 was considered significant.

Results:

The current study enrolled 60 children (50 patients and 10 healthy controls). Patients included 29 males (58%) and 21 females (42%). Their age ranged from 3 days to 14 years with a mean of (33.78 months). They included 24 infants less than 2 years and 26 children more than 2 years.

ADM level ranged from 35.3 to 90.7 pg/ml in studied diseased cases with a mean of 57.63 ± 10.72 . It ranged from 3.9 to 17.8 pg/ml with a mean of 14 ± 3.46 in the control group. The difference was highly significant ($p < 0.001$) as seen in table I and figure A.

Table I: Comparison of plasma ADM levels in patients & controls.

Group	ADM pg/ml (Mean \pm SD)	p-value
Patients	57.63 ± 10.72	< 0.001
Control	14.00 ± 3.46	

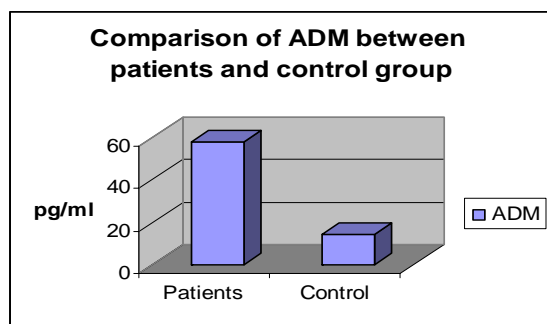


Figure (A): Comparison of ADM between patients groups and control

Comparative analysis of the ADM in relation to NYHA class II, III, and IV severity of CHF revealed highly statistical significance relationship (table II).

Table II: Correlation between plasma ADM level and the NYHA Classification of the severity of CHF

Severity	N°	ADM pg/ml (Mean \pm SD)	p- value
NYHA Class II (Mild)	8	41.0 ± 6.55	P1 = 0.02
NYHA Class III (Mod)	17	51.73 ± 6.15	P2 = 0.001
NYHA Class IV (Severe)	25	68.41 ± 12.14	P3 = 0.0001

P1: Comparison between Class II and Class III.

P2: Comparison between Class III and class IV

P3: Comparison between class II and class IV

The studied cases were grouped according to the underlying etiological type of heart disease into 3 groups **Group I** included 21 patients with rheumatic

heart disease (RHD); 10 of them had isolated mitral valve affection, 6 had combined mitral and aortic valves affection while 5 had single aortic valve affection. **Group II** included 16 patients with congenital heart disease (CHD); 11 of them with acyanotic CHD and 5 with cyanotic CHD. **Group III** included 13 patients with myocardial heart disease (MYHD); 8 of them had dilated cardiomyopathy and 5 had myocarditis.

In comparison between plasma ADM level and the underlying etiology of CHF; plasma ADM was significantly highest in Group I (67.82 ± 13.33 pg/ml) followed by Group II (57.38 ± 11.69 pg/ml) then Group III (47.5 ± 7.01 pg/ml) (table III and figure B).

Table III: Relation between plasma ADM and the underlying etiology of CHF

Group	N°	ADM (pg/ml) Mean \pm SD	p value
Group I (RHD)	21	67.82 ± 13.33	P1 = 0.02
Group II (CHD)	16	57.38 ± 11.69	P2 = 0.001
Group III (MYHD)	13	47.5 ± 7.01	P3 = 0.004

P1: Comparison of Group I (RHD) Vs Group II (CHD)

P2: Comparison of Group I (RHD) Vs Group III (MYHD)

P3: Comparison of Group II (CHD) Vs Group III (MYHD)

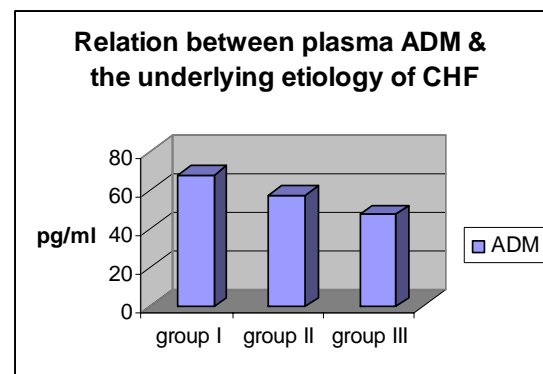


Fig. B: Relation between Plasma ADM & underlying etiology of CHF

Table IV: Relation between plasma ADM level and valvular affection among Group I (RHD)

Valve affected	N°	ADM (pg/ml) Mean \pm SD	p value
Isolated Mitral	10	65.57 ± 11.18	P1 = 0.025
Mitral + Aortic	6	90.00 ± 16.12	P2 < 0.05
Isolated Aortic	5	55.00 ± 4.95	P3 = 0.025

P1: Comparison of isolated mitral affection versus combined mitral + aortic.

P2: Comparison of mitral versus aortic affection.

P3: Comparison of aortic versus mitral + aortic affection.

Table IV demonstrates the relation between the plasma ADM level and the valvular affection among Group I (RHD) patients. It was significantly higher in patients with combined mitral and aortic valve affection (90.0 ± 16.12 pg/ml) than those with isolated valve affection with a p-value < 0.05. Patients with isolated affection of mitral valve had significantly higher ADM level (65.57 ± 11.18 pg/ml) than those with isolated aortic valve affection (55.0 ± 12.45 pg/ml).

Table V compares the plasma ADM in the subgroups of Group II (CHD) cases; cyanotic patients had significantly higher ADM level (61.0 ± 11.65 pg/ml) than acyanotic patients (55.73 ± 12.45 pg/ml) with a p-value of <0.05 (table V).

Table V: Relation between plasma ADM level and CHD subgroups

CHD subgroup	N ^o	ADM (pg/ml) Mean \pm SD	p value
Acyanotic	11	55.73 ± 11.56	< 0.05
Cyanotic	5	61.00 ± 12.45	

Table VI: Relation between plasma ADM level and MYHD subgroups

MYHD subgroup	N ^o	ADM (pg/ml) Mean \pm SD	p value
Dilated cardiomyopathy	8	51.25 ± 2.98	< 0.05
Myocarditis	5	40.00 ± 7.07	

Table VII: Relation between plasma ADM and the age groups of the studied cases

Age group	N ^o	ADM (pg/ml) Mean \pm SD	p value
Neonates & infants	24	56.5 ± 11.95	0.017
Children	26	66.05 ± 13.27	

Regarding Group III (MYHD) subgroups; plasma ADM was significantly higher in dilated cardiomyopathy patients (51.25 ± 2.98 pg/ml) than myocarditis patients (40.0 ± 7.07 pg/ml) with a P-value < 0.05 as seen in table VI.

ADM plasma level was found to be significantly higher (p value =0.017) among children in comparison to infants (table VII).

Table VIII: Comparison of the mean values of PH, HCO₃, Na, K, ALT, AST and Ca between patient groups and the control group

Item	RHD (n = 21)	CHD (n = 16)	MYHD (n = 13)	Control (n = 10)
PH	$7.11 \pm 0.08^{**}$	$7.21 \pm 0.12^*$	7.33 ± 0.06	7.34 ± 0.05
HCO ₃ mmol/L	$7.65 \pm 3.0^{**}$	$15.75 \pm 0.5^*$	17.9 ± 3.18	19.6 ± 2.77
Na mmol/L	$145.2 \pm 4.9^*$	133.5 ± 14.2	135.8 ± 7.56	136.7 ± 4.64
K mmol/L	$2.95 \pm 0.2^{**}$	$3.04 \pm 0.34^{**}$	3.45 ± 0.04	4.13 ± 0.51
ALT U/L	$49.6 \pm 23.4^{**}$	25.8 ± 15.3	$34.4 \pm 20.8^*$	18.3 ± 2.51
AST U/L	$56.7 \pm 27.6^{**}$	19.8 ± 8.8	$27.72 \pm 12.32^*$	15.2 ± 8
Calcium mg/dl	$8.48 \pm 0.38^{**}$	$7.19 \pm 1.2^*$	$8.19 \pm 0.4^{**}$	9.78 ± 0.8

** Highly significant difference between patient group and control group.

* Significant difference between patient group and control.

Table VIII demonstrates a comparison of HCO₃, pH, Na, K, AST, ALT and calcium among various patients groups and control group.

Discussion:

Heart failure is a multi-system disorder, characterized by abnormalities of cardiac, skeletal muscle, and renal functions; stimulation of the sympathetic nervous system; and a complex pattern neuro-hormonal changes.¹¹ The overall prevalence of congestive heart failure (CHF) is 3-20 per 1000 live birth and its annual incidence is 1-5 per 1000 live birth.¹²

Adrenomedullin (ADM) is a 52-amino acid peptide that was found to be distributed widely in the body and throughout the cardiovascular system. ADM causes

vasorelaxation and influences vascular proliferation, and it may have a role in the pathophysiology of hypertension, ischemic heart disease, and cardiac and renal failure.¹³

The current study has demonstrated a highly statistical significant increase in ADM levels among the 3 patients' groups versus the control group (P value < 0.001 for each). The mean level of plasma ADM was highest in Group I (RHD patients) followed by Group II (CHD patients) then Group III (MYHD patients) signifying the role of the underlying etiological cardiac disease in the pathophysiology of CHF which is in agreement with the results of Joy et al.¹⁴ and Balat et al.¹⁵ This could be explained by the fact that ADM gene is highly expressed in endothelial cells and this has come to be regarded as a secretory product of the vascular endothelium, therefore ADM expression reflects varying degrees of tissue vascularity.

In addition, it was found that the tissue damage that occurs to the valves in RHD patients is relatively more than that occurs in other heart diseases, therefore it may act as a strong stimulus for more secretion and release of ADM in this disease. On the other hand, in MYHD patients the suggested explanation for the relatively small degree of increase in ADM could be depletion of the viable myocyte population that release and secrete ADM. This coincides with the results found by Balat et al.¹⁵

On statistically reviewing the valvular affection of Group I (RHD), we found that the mean level of plasma ADM was significantly higher among patients with combined mitral and aortic valve affection than those with isolated mitral or aortic valve affection (p=0.025). The mean ADM level was also significantly higher when there is isolated affection of the mitral valve versus an isolated aortic valve affection (p= <0.05) reflecting a significant change in the level of plasma ADM in comparison to the number and type of the valves affected. This could be attributed to the occurrence of more endothelial damage when two valves were affected and may be also referred to the severity of CHF that usually become more with the increase in the number of the affected valves. That was consistent with what was found by Nicholls et al.,⁸ in their study, they proved that the level of ADM was correlated with the severity of hemodynamic dysfunction in CHF. A study conducted by Eto et al.¹⁶ added that the direct left ventricular wall stretch acts as a mechanical stimulus that activates ADM gene expression and secretion.

The elevation of ADM level among the cases with an isolated affection of the mitral valve than those with an isolated affection of the aortic valve may be referred to the double mitral valve affection (regurgitation and

stenosis) that occurred in some of those cases. This coincides with what was found by Joy et al.¹⁴ and Nishikimi et al.¹⁷

As regards Group II (CHD patients), the comparison of the mean levels of ADM between the acyanotic and the cyanotic subgroups showed a significant difference in which the level was higher in the cyanotic patients more than the acyanotic ($p < 0.05$). This may be referred to the higher degree of hypoxia among the cyanotic subgroup. Our results were in agreement with those elicited by Joy et al.¹⁴

In Group III (MYHD patients), the mean level of plasma ADM was significantly higher in dilated cardiomyopathy (DCMP) patients than myocarditis patients (P -value < 0.05). This could be verified by the fact that in patients with DCMP, the endothelium vasomotor system is disturbed so it may act as an additional factor for more stimulation of ADM gene expression. These results coincided with those obtained by Szekely et al.¹⁸ and by Klinik et al.¹⁹

Our study included only one case of arrhythmia. This case had supraventricular tachycardia, the level of ADM was high (48 pg/ml) because of the severity of CHF in that case.

On studying the relation between plasma ADM and the age of patients, we found that plasma ADM varied according to patients' age where it was significantly higher in children age group versus infant group (p value = 0.017). This could be attributed to the chronicity of heart disease which increases as the age passes and thus the severity of CHF. In addition most of the patients in the children age group were patients

having RHD, which in turn elevates the level of ADM. In contrast to our study, Joy et al.¹⁴ found no significant differences in the level of plasma ADM between different age groups.

Our study demonstrated that, as the severity of CHF increases, the plasma level of ADM increases in proportion to the severity of cardiac and hemodynamic impairment. The mean ADM level was significantly higher in severe HF than in moderate HF ($p = 0.02$) and even much higher than in mild HF ($p = 0.001$). This goes with what was found by Rademaker et al.,⁷ Nishikimi et al.²⁰ and Yoshihara et al.,²¹ who suggested that raised plasma ADM level in HF provide prognostic information on adverse outcomes. The level of plasma ADM was higher among the cases that died. That could be attributed to the severity of CHF among those cases. No significant correlation could be measured because of the small number of the mortality cases (3 cases).

Conclusion and Recommendations:

In conclusion ADM plays a compensatory role in heart failure. Not only could it be considered as a biochemical marker for evaluating the severity of CHF, but also as an independent prognostic indicator of this syndrome. An improved understanding of the role of ADM in HF might lead to the development of therapeutic agents acting through ADM receptors. Proper manipulation of the ADM system holds promise as a therapeutic strategy in cardiac diseases.

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