Eighth Annual Scientific Meeting

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Pulmonary Vein Electrical Isolation for the Cure of Paroxysmal Atrial Fibrillation Guided by a Novel Geometry Mapping System

CAIYI LU, SHIWEN WANG, XINPING DU, YINLONG HOU, QIAO XUE, XINLI WU, RUI CHEN, PENG LIU

From The Institute of Geriatric Cardiology, 301 Hospital, Beijing, China

LU ET AL.: Pulmonary Vein Electrical Isolation for the Cure of Paroxysmal Atrial Fibrillation Guided by a Novel Geometry Mapping System. Objectives: The purpose of the study is to evaluate the feasibility and effect of left wall (LA) ablation guided by a novel geometry mapping system in the treatment of older patients with paroxysmal atrial fibrillation (PAF). Methods: Regular electrophysiological study was conducted to exclude atrioventricular reentrant tachycardia (AVRT) with accessory pathways, atrioventricular nodal reentrant tachycardia (AVNRT) and other inducible tachyarrhythmias. Twice transseptal puncture was achieved with L1 and R1 Swartz sheaths. Pulmonary vein (PV) angiographies were conducted to evaluate their orifices and branches. LA geometry was constructed under either sinus rhythm or PAF using Ensite3000 Navx system. Two lesion loops and three lines (see details in the text) for electrical isolation were outlined and created by radiofrequency catheter ablation on the three-dimension geometry of LA. Each lesion point was ablated in 30 seconds with preset temperature 50°C and energy 30W. The disappearance or 80% decrease of the amplitude of LA target potential and 10 to 20 Ω decrease of ablation impedance were used as effective index. Results: Three patients included two males and one female of age 67.3±3.6. PAF history was 7.4±5.1 years. Mean 3.5±1.2 antiarrhythmic agents were used in 5.7±2.3 years without PAF effectively prevention. No organic heart diseases and stroke complications were founded. Left atrium was 38.7±3.2 mm and LVEF was 58.6±4.3 on echocardiography. Altogether 59-126 (63.7±11.2) lesion points were created to complete two loops and three lines. Rapid burst pacing up to 600 beats per minute was delivered from the distal coronary sinus electrode pair without PAF provoked. The procedure time was 2.8±0.7 hours and fluoroscopy time was 19.6±8.3 minutes. Patients were discharged with long-term oral warfarin and without any antiarrhythmic agent. During the follow up of 5.6±2.3 months, one patient was free of symptom and PAF attacks were decreased more than 80% in the other two patients by evaluation of Holter monitoring. Conclusions: Ensite3000 Navx guided LA wall ablation near PV orifice to cure PAF in the elderly is safe and feasible and has the advantages of clear procedure endpoint, shorter X-ray exposure, less complication and satisfied long-term effect. Large number of cases and long-term follow up data are needed to validate these primary results. (J HK Coll Cardiol 2004;12: 58-63)

Electrophysiology, paroxysmal atrial fibrillation, radiofrequency ablation
PULMONARY VEIN ELECTRICAL ISOLATION FOR PAF

30秒, 預設溫度50°C, 能量30瓦, 消融點左房電位消失或振幅降低80%, 阻抗下降10~20Ω 爲放電終點。結果: 3例患者中男性2例, 女1例, 平均年齢67.3±3.6歲, PAF病史7.4±5.1歲, 服用抗心律失常藥物3.5±1.2種效果不佳。

無器質性心臟病, 左房直徑38.7±3.2mm, LVEF 58.6±4.3%。兩個環和三條共由59-126 (63.7±11.2)個消融點組成, 經冠狀動脈心房刺激不能誘發PAF。手術操作時間2.8±0.7小時, 透視時間19.6±8.3分鐘。隨訪5.6±2.3月, 1例病人無PAF發作, 2例病人Holter檢查。結論: Ensite3000 Navx 指導的肺靜脈口左房壁消融治療老年人PAF安全有效, 具有操作終點明確, 透視時間短, 併發症少和遠期效果好的優點, 這一初步結果需積累更多病例和隨訪結果加以驗證。

關鍵詞: 電生理 陣發性房顫 射頻消融

Paroxysmal atrial fibrillation (PAF) in elderly is usually triggered or driven by electrical foci originated from atrial muscle sleeves (AMS) mostly from pulmonary veins.1 PAF could be cured either by ablating AMS focus or isolating target AMS electrically.2,3 Due to the high recurrence rate of the former technique, later therapies are more frequently used in clinical interventive electrophysiology.4 Radiofrequency (RF) catheter ablation at the orifice of target pulmonary vein (TPV) was used at first in the cure of PAF, but early and long-term stenosis of TPV limited the usage of the method.3,5 Therefore, novel non-contact geometry mapping systems are used to guide the isolation of AMS in the left atrial wall just near their orifice.6 Ensite3000 Navx is one of these new systems. The main difference between Ensite3000 Navx and Carto quick map is the former adapts a regular RF large tip catheter to construct left atrial and AMS geometry and creates the RF lesion circles or lines at either sinus rhythm or PAF rhythm. Three older PAF patients were treated with Ensite3000 Navx and clinical effect and experience were reported.

**Clinical Data**

Three patients included two males and one female of age 67.3±3.6. PAF history was 7.4±5.1 years. Mean 3.5±1.2 antiarrhythmic agents (including amiodarone, propafenone, propranolol, sotalol, quinidine, etc.) were used in 5.7±2.3 yeas without PAF effectively prevention. One male case had controlled hypertension. No other organic heart diseases and stroke complications were founded in all patients. Left atrium was 38.7±3.2 mm and LVEF was 58.6±4.3 on echocardiography. Repetitive P’ on T atrial premature and PAFs were confirmed by regular ECG (Figure 1) and Holter monitoring.

**Electrophysiological Study**

After written informed consents were obtained, regular electrophysiological studies were conducted to exclude atrioventricular reentrant tachycardia (AVRT) with accessory pathways (AVAP), atrioventricular nodal reentrant tachycardia (AVNRT) and other inducible tachyarrhythmias. The methodology of standard electrophysiological study was reported elsewhere and briefly described as follows. A decapolar electrode catheter was placed in the distal coronary sinus via left subclavicle vein. A tetrapolar electrode catheter (Josephson curve) was put at His bundle branch and another catheter (Cournad curve) was settled at the high right atrium at first and then right ventricular apex. Both programmable and non-programmable electrical stimulations were conducted via high right atrium and right ventricular apex electrode pairs with two times of diagnostic threshold value and 0.5 ms pulse width. AVRT and AVNRT were not found according to their electrophysiological criteria. PAF could be induced with high rate burst pacing at distal coronary sinus in two patients.
Pulmonary Vein Identification and Geometry Creation

Twice transseptal puncture was achieved with L1 and R1 Swartz sheaths. A large-tip ablation catheter (Bard Co., 7F) and a non-contact balloon mapping catheter were introduced into left atrium (LA). The tip of the balloon mapping catheter was mounted at the left superior pulmonary vein with a 0.035 inch wire. Pulmonary vein angiographies were conducted to evaluate their orifices and branches (Figure 2A). LA geometry was constructed under either sinus rhythm or PAF using Ensite3000 Navx system (Figure 2B) and the large-tip ablation catheter as land mark in LA chamber. On the three-dimension geometry of LA, two ablation loops and two ablation lines for electrical isolation were outlined. The two loops encircled left and right sided pulmonary vein orifices respectively. The top line connected two loops on the roof of LA and the bottom line linked between the lower part of the left loop and the lateral part of mitral valular ring.

Radiofrequency Catheter Ablation

Along with the loops and lines, radiofrequency ablation was delivered to form continuous lesion by the direction of Ensite3000 Navx system. Each lesion point was ablated in 30 seconds with preset
temperature 50°C and energy 30W. The disappearance or 80% decrease of the amplitude of target potential and 10 to 20 Ω decrease of ablation impedance were used as effective index. Altogether 59-126 (63.7±11.2) lesion points were needed to complete the two loops and two lines (Figure 3). Then activation mapping in sinus rhythm on three-dimensional geometry was repeated to confirm the electrical disconnection between PVs and LA. Rapid burst pacing up to 600 beats per minute was delivered from the distal coronary sinus electrode pair to provoke PAF. After that, the geometry of right atrium was constructed by withdrawing the balloon and ablation catheter. Radiofrequency lesion line between tricuspid ring and inferior vena cava was achieved with another 6 lesion points (Figure 4). The procedure time was 2.8±0.7 hours and fluoroscopy time was 19.6±8.3 minutes. Total 10 mg morphine was injected intravenously during the period of energy delivery.

During the follow up of 5.6±2.3 months, one patient was free of symptom and PAF attacks were decreased more than 80% in the other two patients by evaluation of Holter monitoring.

**Discussion**

Most focal PAFs could be cured by completely isolating target pulmonary vein electrically.1-4 PV isolation could be achieved by spike potential guided catheter ablation at its orifice or by geometry mapping guided circular isolation on the LA wall just near its orifice.5,6 Different procedures have the different procedure end point and long-term effect.7,8

Spike potential guided ablation or segmental PV ostial ablation under X-rays suffered with technical challenges associated with identification of PV potential, complete electrical isolation, long distance of PV-LA junction, focus mapping within target PV, irregular PV orifice, long operation and X-ray exposure time, and potential PV stenosis.4,6-8 In contrast, left atrial wall ablation near PV orifice guided by non-contact electro-anatomical mapping,5 which includes two lesion loops around the left and

**Follow Up**

The patients were discharged with long-term oral warfarin and without any antiarrhythmic agent.

![Figure 2. (A) Left superior pulmonary vein angiography through a trans atrial septal sheath positioned at the pulmonary vein ostium. (B) Configuration of a novel three-dimensional electro-anatomical mapping system Ensite3000 Navx.](image)
Figure 3. Total 59 ablation points were used to complete two loops and two lines. The two loops encircled left and sided pulmonary veins respectively (A-G). The top line connected two loops on the roof of LA (D, E, G) and the bottom line linked between the lower part of left loop and the lateral part of mitral valular ring (C, D). (A) Lesion on RAO view. (B) Lesion on left lateral view. (C) Lesion on mitral isthmus. (D) Lesion on PA view. (E) Lesion on right lateral view. (F) Lesion on AP view. (G) Lesion on cranial view.

Figure 4. Posterior isthmus ablation. (A) A radiofrequency ablation line between tricuspid ring and inferior vena cava was achieved with 6 lesion points. (B) Three dimensional activation mapping showed posterior isthmus conduction block.
PULMONARY VEIN ELECTRICAL ISOLATION FOR PAF

right-sided PVs, one lesion line on the roof of LA between two loops, and one lesion line from left loop to the mitral valular ring, can overcome above disadvantages and achieve complete PV isolation. The two lesion lines also have the effect of LA atrial flutter prevention.

From these cases, it is found that Ensite3000 Navx guided LA wall ablation near PV orifice to cure PAF is safe and feasible and has the advantages of clear procedure endpoint, shorter X-ray exposure, less complication and satisfactory long-term effect. Large number case experience and long-term follow up data are needed to validate these primary results.

References

Prognostic Value of High-Sensitivity C-reactive Protein in Patients with Chronic Heart Failure

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XUE ET AL.: Prognostic Value of High-Sensitivity C-reactive Protein in Patients with Chronic Heart Failure. Objectives: To determine whether High-Sensitivity C-reactive Protein (hsCRP) has Prognostic value in patients with chronic heart failure. Methods: Serum hsCRP levels were measured with high-sensitivity assay (IMMAGE Immunochemistry Systems) in 128 patients with CHF and 25 healthy control subjects. Cardiac troponin T (TNT) was measured by Electrochemiluminescence immunoassay on Elesys1010 automatic analyzer. Cardiac events were defined as cardiac death and rehospitalization because of worsening heart failure during a mean follow up period of 378±26 days. Results: Circulating levels of hsCRP and TNT were significantly higher (3.85±4.25 mg/L, 0.21±0.15 mg/L, respectively) in patients with CHF than in 25 healthy people (p<0.01, p<0.01, respectively) and increased with severity of CHF. During a mean follow up period of 378±26 days, forty-two (32.8%) of the 128 patients had cardiac events. Levels of hsCRP and TNT were significantly higher (p<0.001, p<0.001, respectively) and left ventricular ejection fraction (LVEF) was significantly lower (p<0.01) in patients with cardiac events than in patients without cardiac events. When multivariate Cox proportional hazards analysis was performed, we could find that hsCRP, TNT, and LVEF were independent significant predictors of cardiac events in patients with CHF. (hsCRP: hazard ratio[HR], 3.81; 95%CI, 2.14-9.35; P=0.024; TNT: HR, 2.61; 95%CI, 1.96-4.31; P=0.012; LVEF: HR, 3.52; 95%CI, 2.36-10.37; P=0.024). A positive correlation was observed between hsCRP and TNT (r=0.493, p<0.01). A negative correlation was observed between hsCRP and LVEF (r=-0.354, p<0.01). Conclusion: Serum hsCRP concentrations were elevated in patients with CHF and increased with severity of CHF. It was an independent significant predictor of cardiac events in patients with CHF. (J HK Coll Cardiol 2004;12:64-69)

Congestive, C-reactive protein, heart failure, prognoses

摘要
目的：观察高敏C-反应蛋白（hsCRP）對慢性充血性心力衰竭病人是否有預後判斷價值。方法：本研究包括128例慢性充血性心力衰竭（CHF）病人和25例健康人。應用高敏法（IMMAGE Immunochemistry Systems）檢測病人及健康對照組血清hsCRP，同時應用電子化發光免疫分析法檢測肌酸蛋白T（TNT），並與hsCRP比較。隨訪病人，觀察其預後。心臟事件定為隨訪期內（378±26天）心源性死亡或因心力衰竭惡化再住院。結果：病人血清hsCRP和TNT濃度（分別為3.85±4.25 mg/L，0.21±0.15 mg/L）高於健康對照組（p<0.01，p<0.01），病情越嚴重其濃度越高。在隨訪期內（378±26天），128例病人中有42人(32.8%)發生心臟事件。發生心臟事件的病人，血清hsCRP和TNT濃度高於未發生心臟事件的病人（p<0.001，p<0.001），左室射血分數（LVEF）低於未發生心臟事件的病人（p<0.01），應用多變量Cox風險比例模型分析，發現hsCRP、TNT和LVEF是心力衰竭病人獨立的預後判斷標誌（hsCRP：風險比[HR]，3.81；

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PROGNOSTIC VALUE OF hsCRP IN PATIENTS WITH CHF

95% CI, 2.14-9.35; P = 0.024; TNT: HR, 2.61; 95% CI, 1.96-4.31; P = 0.012; LVEF: HR, 3.52; 95% CI, 2.36-10.37; P = 0.024. CHF病人血清hsCRP 和TNT存在正相關 (r = 0.493, p < 0.01)。hsCRP 和LVEF存在負相關 (r = -0.354, p < 0.01)。結論：慢性充血性心力衰竭病人血清hsCRP濃度升高，病情越嚴重其濃度越高。hsCRP是心力衰竭病人獨立的預後判斷指標。

Introduction

The serum concentration of C-reactive protein (CRP) is mildly elevated in patients with chronic congestive heart failure (CHF). Standard assay for CRP lack the sensitivity within the low reference range and thus cannot be used effectively for routine clinical risk prediction. Our study was aimed at investigating high-sensitivity assay of CRP (hsCRP), a marker of systemic inflammation, in the context of heart failure, and to determine if it has prognostic value in patients with CHF.

Methods

Patients

A total of 128 patients (Chinese) with chronic heart failure were enrolled in this study. The diagnosis of chronic heart failure (CHF) was based on the criteria below produced by the European Society of Cardiology:¹

1. Symptoms of heart failure (at rest or during exercise)
2. Objective evidence of cardiac dysfunction (at rest)
3. Response to treatment directed toward heart failure (in cases where the diagnosis is in doubt)

The characteristics of patients with CHF were summarized in Table 1.

All patients had a left ventricular ejection fraction (LVEF) <40% or had a mean left ventricular end-systolic dimension >55 mm by transthoracic echocardiography. Ischemic CHF was diagnosed by coronary angiography (>50% luminal diameter narrowing in at least 1 major epicardial coronary artery) or by the history of documented myocardial infarction.

Non-Ischemic CHF was caused by primary dilated cardiomyopathy (26 patients), valvular heart disease (15 patients), systemic hypertension (12 patients). We excluded patients with clinical or laboratory evidence of systemic infection, myocardial infarction within 8 months, pericarditis, cor pulmonale, inflammatory illness such as arthritis or connective tissue diseases, any malignancy tumor.

Control population consisted of 25 healthy Chinese people (men 15, women 10, mean age 59±16 years old). Blood samples from patients were obtained on the first day of admission. Control blood samples from 25 healthy people were obtained at fasting condition. Blood samples were allowed to clot for 30 minutes at room temperature and were centrifuged for 5 minutes. All blood samples were measured without

Table 1. The characteristics of patients with CHF

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>128</td>
</tr>
<tr>
<td>Age (y)</td>
<td>62±15</td>
</tr>
<tr>
<td>Sex M/F</td>
<td>79/49</td>
</tr>
<tr>
<td>No. of diabetics</td>
<td>19</td>
</tr>
<tr>
<td>No. of smokers</td>
<td>35</td>
</tr>
<tr>
<td>Cause of CHF</td>
<td></td>
</tr>
<tr>
<td>Ischemic CHF</td>
<td>75</td>
</tr>
<tr>
<td>Non-Ischemic CHF</td>
<td>53</td>
</tr>
<tr>
<td>NYHA n (%)</td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>57 (44.5%)</td>
</tr>
<tr>
<td>Class III</td>
<td>40 (31.3%)</td>
</tr>
<tr>
<td>Class IV</td>
<td>31 (24.2%)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td></td>
</tr>
<tr>
<td>All patients with CHF</td>
<td>0.37±0.11</td>
</tr>
<tr>
<td>Ischemic CHF</td>
<td>0.36±0.09</td>
</tr>
<tr>
<td>Non-Ischemic CHF</td>
<td>0.33±0.08</td>
</tr>
<tr>
<td>Class II</td>
<td>0.36±0.12</td>
</tr>
<tr>
<td>Class III</td>
<td>0.27±0.12</td>
</tr>
<tr>
<td>Class IV</td>
<td>0.19±0.13</td>
</tr>
</tbody>
</table>

¹ European Society of Cardiology.
Frozen within 3 hours after blood samples were obtained. All patients were followed up by telephone, or through regular outpatient visits, or when they were rehospitalized. Mean follow up period was 378±26 days. Cardiac events was defined as cardiac death and rehospitalization because of worsening heart failure.

**Measurements of hsCRP and TNT**

hsCRP was measured by immunoassay with an autoanalyzer (IMMAGE Immunochemistry Systems, Beckman Coulter, California). The intra-assay and inter-assay coefficients of variation for hsCRP were 5% and 10%, respectively. TNT was measured by Electrochemiluminescence immunoassay with Elecsys1010 automatic analyzer (Roche Company). Inter-assay and intra-assay coefficient of variation were <4% and <7% respectively. The level of sensitivity is <1 pmol. LVEF was obtained by 2-dimensional echocardiography with HDI 3000 echocardiograph (ALT Company America).

**Statistical Analysis**

Data were expressed as mean±SD. Patients were divided into 3 groups according to their NYHA functional classification. Analysis of variance test was used to compare the difference of the levels of hsCRP and TNT among these 3 groups and the 25 control subjects. The correlation between the levels of hsCRP and TNT, hsCRP and LVEF were assessed by using Linear regression analysis. Cox proportional hazards analysis was performed to determine the significance of age, sex, LVEF, presence of ischemic heart disease, the use of statin drugs, and circulating levels of hsCRP as independent predictors of CHF. Patients were divided in 2 groups, patients who had major adverse cardiac events and those who were event-free. T-test for measurement data and chi-square test for enumeration data were performed to compare clinical and hemodynamic characteristics in these 2 groups.

**Results**

Circulating levels of hsCRP and TNT were significantly higher (3.85±4.25 mg/L, 0.21±0.15 mg/L, respectively) in patients with CHF than in 25 healthy people (p<0.01, p<0.01, respectively) and increased with severity of CHF. These data were shown in Table 2. Patients with CHF were divided in 2 groups according to the causes of their CHF (ischemic vs non-ischemic), serum levels of hsCRP had no significant difference between the 2 groups (4.13±5.12mg/L vs 4.09±5.24 mg/L, p>0.05).

During a mean follow up period of 378±26 days, forty-two (32.8%) of the 128 patients had cardiac events. Patients with CHF were divided into 2 groups, patients with cardiac events and those who were event-free. There were no significant differences in age, sex, causes of CHF, or medications between the 2 groups. However levels of hsCRP and TNT were significantly higher (p<0.001, p<0.001, respectively) and LVEF was significantly lower (p<0.01) in patients with cardiac events than in patients without cardiac events. This data was shown in Table 3.

When multivariate Cox proportional hazards analysis was performed, we could find that hsCRP, TNT, and LVEF were independent significant predictors of cardiac events in patients with CHF. (hsCRP: hazard ratio [HR], 3.81; 95%CI, 2.14-9.35; P=0.024; TNT: HR, 2.61; 95%CI, 1.96-4.31; P=0.012; LVEF: HR, 3.52; 95%CI, 2.36-10.37; P=0.024). A positive correlation was observed between hsCRP and TNT (r=0.493, p<0.01). A negative correlation was observed between hsCRP and LVEF (r=-0.354, p<0.01).

<table>
<thead>
<tr>
<th>Table 2. The concentrations of hsCRP, TNT in patients with CHF and control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
</tr>
<tr>
<td>TNT (mg/L)</td>
</tr>
</tbody>
</table>
PROGNOSTIC VALUE OF hsCRP IN PATIENTS WITH CHF

Discussion

CHF is the final common pathway of a variety of cardiac disorder, including ischemic heart disease, idiopathic dilated cardiomyopathy, and valvular disease, and is usually progressive. Recent studies suggest that heart failure may, in part, be an inflammatory disease. CRP, an acute phase reactive protein that increases during the host response to tissue injury, including that caused by infection, trauma, malignant disease and chronic inflammatory conditions, is synthesized in the liver, and its serum concentration is a reliable index of overall inflammation activity. Several large-scale prospective epidemiological studies have shown that plasma levels of hsCRP are a strong independent predictor of risk of future myocardial infarction, stroke, peripheral arterial disease, and vascular death among individuals without known cardiovascular disease. Several studies have shown increased concentration of CRP in patients with heart failure, but clinical data about the prognostic value of CRP in patients with chronic heart failure have been sparse and inconsistent. Because standard assays for CRP lack the sensitivity needed to determine levels of inflammation within low reference range, and thus clinical utility of standard CRP is extremely limited to its prognostic values in patients with CHF. More recently, with the recognition that inflammation is one of the mechanisms of CHF and with the availability of highly sensitive assay systems, we thought that circulating concentrations of hsCRP may have prognostic value in patients with CHF.

Our study demonstrated that serum hsCRP concentration were elevated in patients with CHF and increased with severity of CHF. Furthermore, this study had shown that elevated serum hsCRP concentrations have independent significant predictive value. In our study we also found that hsCRP had a positive correlation with TNT and had a negative correlation with LVEF. The clinical and basic studies had shown that CRP has a fundamental role in atherogenesis. Coronary artery disease was present in 68% of patients with CHF, which cause, in part, elevated serum hsCRP in patients with CHF. This study also shown that increased hsCRP levels in patients with CHF was unrelated to the causes of heart failure, which suggests that CHF is the final common pathway of a variety of cardiac disorders, including ischemic heart disease, idiopathic dilated cardiomyopathy, and valvular heart disease.

Table 3. Characteristics of patients who had cardiac events and those who were event free

<table>
<thead>
<tr>
<th>Cardiac events (n=42)</th>
<th>Event free (n=86)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) 59±8</td>
<td>62±9</td>
<td>NS</td>
</tr>
<tr>
<td>Male (%) 26 (62%)</td>
<td>53 (62%)</td>
<td>NS</td>
</tr>
<tr>
<td>Causes of CHF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic 24</td>
<td>51</td>
<td>NS</td>
</tr>
<tr>
<td>Non-ischemic 18</td>
<td>35</td>
<td>NS</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic 39</td>
<td>84</td>
<td>NS</td>
</tr>
<tr>
<td>Digitalis 34</td>
<td>70</td>
<td>NS</td>
</tr>
<tr>
<td>β-blockers 22</td>
<td>43</td>
<td>NS</td>
</tr>
<tr>
<td>ACEI/ARB 32</td>
<td>68</td>
<td>NS</td>
</tr>
<tr>
<td>Statins 10</td>
<td>21</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF 0.22±0.14</td>
<td>0.36±0.15</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>hsCRP (mg/L) 6.59±7.69</td>
<td>2.46±3.25</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>TNT (mg/L) 0.48±0.11</td>
<td>0.11±0.02</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

NS: non significance
of TNT in patients with CHF, and their presence was associated with adverse outcome. Our results are consistent with the emerging concept that cardiac troponin elevations reflect ongoing myocardial cell injury associated with the progression of CHF. Also, the present study showed a positive correlation between TNT and hsCRP, speculating that markers specific for myocardial cell injury or inflammatory effect may detect different features of the pathophysiologic process of heart failure.

The mechanisms underlying the pathogenesis and progression of CHF remain unclear. Different mechanisms may be involved, such as activations of sympathetic nerve and renin-angiotensin-aldosterone systems. Both experimental and clinical studies have also shown a role for inflammation in the pathogenesis of heart failure. There is evidence that chronic activation of the immune system exists during heart failure. Some patients present evidence of monocyte-macrophage and lymphocyte activation. It appears clear that patients have elevated levels of serum TNT in patients with CHF. In our study we found that hsCRP had a negative correlation with LVEF, this indicated a correlation between hsCRP and myocardial cell damage.

Whether CRP is simply a marker of chronic systemic inflammation or directly involved in the pathogenesis of CHF? Whether it can be used as a target for treatment of CHF? Further studies will be needed to answer this question.

In conclusion, serum hsCRP concentrations were elevated in patients with CHF and increased with severity of CHF. It was an independent significant predictor of cardiac events in patients with CHF.

References

Dynamic Characteristics of Heart Rate and Systolic Blood Pressure at Early Exercise Test after Myocardial Infarction in Predicting the Life Expectancy

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BLOZNELIENĖ ET AL.: Dynamic Characteristics of Heart Rate and Systolic Blood Pressure at Early Exercise Test after Myocardial Infarction in Predicting the Life Expectancy. During 11 years period submaximal exercise testing within 3 weeks of acute myocardial infarction was performed with 894 patients. Exercise induced ST segment depression appears to have prognostic significance of subsequent development of fatal coronary events at 6, 12, 24 months and 11 years post infarction. At follow-up at 2 years post infarction in the non survivores group there were only 45.2% exercise induced ST segment depression. This shows, that prognostic importance of ST depression is insufficient and demands of research of more consistent signs. The cardiovascular response to exercise was interpreted as transiting process of the self-regulation of cardiovascular system, and the new predictive signs were found on the basis of heart rate and systolic blood pressure curves during the exercise and after it. The prognostic value of these signs were established. The combined use both the new predictive signs and the usual data of early exercise test shows the high predictive possibility of test – the early cardiac death was predicted in 80% of cases. The patients after myocardial infarction can be divided into relative high and low-risk groups for subsequent cardiac events if all information available on the exercise test is used. (J HK Coll Cardiol 2004;12:70-74)

Early exercise test, myocardial infarction

Introduction

Despite the rise and spread of new diagnostic methods, exercise electrocardiography still remains the cornerstone of non-invasive evaluation and is almost uniformly performed after myocardial infarction (MI).
EXERCISE TEST AFTER MYOCARDIAL INFARCTION

This test is usually performed (in case of absence of contraindications) to all the patients after MI before the discharge. The prognostic value of the exercise test is not enough investigated despite of the high percentage of the persons dying suddenly after MI. The evaluation of depression of ST-segment in exercise test in predicting the prognosis after MI is not uniform.\textsuperscript{1-3} According to the literature and our data, sudden death during 6 months after MI is closely related to the life-threatening arrhythmias, detected in early exercise test after MI. This relation could not be established after MI later.\textsuperscript{4,5} It is considered the value of the exercise-induced QT dispersion (as a sign of ventricular depolarisation inhomogeneity) in predicting ventricular arrhythmias and sudden cardiac death.\textsuperscript{6} The data are contradictory in assessing which exercise test parameters are related with survival over 6 months after MI.\textsuperscript{7} Some authors regard to ST-depression as a borderline parameter and the main attention pay to the workload, which was obtained during the exercise. This sign is closely related to the survival over 10 as well as 15 years after MI.\textsuperscript{8} Heart rate (HR) and blood pressure (BP) changes represent the cardiovascular response to the exercise. The aim of our study was to evaluate the prognostic capability of these signs and to design the prognostic system capable to pick up patients with high risk of coronary death during 2 years time after MI, using the data of early exercise testing.

**Patients and Methods**

A total of 894 patients (aged 50.68±9.29 years; 827/92.5% males and 67/7.5% females) admitted to Kaunas Medical University Hospital have met the eligibility criteria and were put through submaximal exercise testing within 3 weeks of the onset of acute MI. Cases of noncardiac deaths, patients living outside Kaunas or those subjected to coronary bypass surgery were excluded from the further analysis. Kaunas Acute Myocardial Infarction Register was used for survival (12 months - 11 years) analysis. At the end of 2 years after MI there were 426 survivors (group I) and 42 cases of cardiac death (group II). After 11 years there were 98 coronary deaths.

The submaximal exercise testing (25 W incremental loading every 3 minutes) was performed within 3 weeks after acute myocardial infarction. A 12 lead ECG was continuously monitored throughout the test and 10 minutes after it. A blood pressure was measured before the exercise test and every minute during and 10 min. after the test. The occurrence of significant anginal pain, ventricular tachycardia, major conduction abnormalities, ST-depression ≥2 mm, limiting symptoms (such as dyspnoea, dizziness, fatigue, cramp in legs, etc.), an excessive increase (above 230 mmHg) or decrease (>30 mmHg) in systolic blood pressure were regarded as interruption criteria. Both ST depression in one or more leads, excluding aVR and V1, and ST elevation in leads without pathological Q waves were considered. The exercise-induced angina pectoris and/or the presence of horizontal or downsloping ST depression of 1 mm measured 80 ms after J point and of ST elevation of 1 mm measured 40 ms after the J point were regarded as positive criteria. Positive was defined as low-threshold if occuring at workload <75 W (450 kgm/min).

**Results**

Results of exercise testing 3 weeks after MI were as follows: mean peak workload differed significantly between the two groups: 44.5±0.9 W (267±5.4 kgm/min) in group I and 34.2±3.5 W (205.2±21 kgm/min) in group II (p<0.01). The exercise testing elicited angina and/or ST depression of >1 mm (ischemic response) in 132 (31%) patients of group I and in 24 (57.1%) patients of group II (p<0.01). The exercise testing positive ST-segment only was detected in 33 (7.8%) and in 19 (45.2%) cases respectively (p<0.01). Exercise test positive ST-segment only was detected in 17 (4 %) patients of group I and in 9 (21.4%) patients of group II (p<0.01). ST depression of >1 mm was detected in 33 (7.8%) and in 19 (45.2%) cases respectively (p<0.01). Indicators for electrical instability (exercise induced serious ventricular arrhythmias) showed no significant differences between the groups in 21 (4.9%) patients of group I and in 9 (21.4%) patients of group II (p<0.01). The patients of group I had better exercise capacity and ST depression was registered only in 7.8 % of patients as compared with 45.2% of patients of group II.
Our patients were in good functional state at entry (no patients had a contraindication to exercise); nonetheless, there were 8.5% of cardiac deaths within the first two years among the acute MI survivors. Among those dying within the first two years, only 45.2% had the exercise-induced ST segment depression. This shows that the prognostic value of ST depression is not sufficient and demands research of more consistent signs.

The cardiovascular response to exercise was interpreted as a transition process in the self-regulation of cardiovascular system (system’s reaction to the stress). The survival was predicted by the shape of heart rate (HR) and systolic blood pressure (BP) curves (their dynamic characteristics) during exercise testing and after it. The signs specific to cardiovascular response to exertion were selected as follows: (1) the extent of systolic BP changes at the beginning of the exercise testing; (2) the extent of HR changes at the beginning of the exercise testing; (3) the character of HR changes one minute after the exercise discontinuation; (4) the character of systolic BP changes one minute after the exercise discontinuation (5) the correlation strength between the HR and systolic BP curves within the exercise test; (6) the character of HR curves at rest after the exercise; (7) the character of systolic BP curves at rest after the exercise; (8) the character of HR changes at the last minute of exercise; (9) the character of systolic BP changes at the last minute of exercise. The prognostic value of these signs was determined. A combined use of both, the usual data (indicators for residual myocardial ischaemia) and the new signs – dynamic characteristics of HR and BP curves considerably increased the predictive power of the test. Each sign included several manifestations. For example, the character of systolic BP and HR changes at the beginning of the exercise testing may be manifested by the different degrees of change intensity, BP and HR may increase and decrease, with or without delay. All these specific features are described as characteristic of sign. All the data obtained in exercise testing in the early period of MI was divided in two parts. One, named group C, was used as a learning assembly. In this C group we chose all cases of death in 0.5 year after MI and named this group A; all cases of death in the period between 0.5 and 2 years after MI and named this group B. So the remaining group D included the cases with no death in the period of 2 years after MI. D=C-(A+B).

Then the prognostic value in prediction of the high risk of coronary death of characteristics of signs was determined. For this purpose we computed the frequency rate of each characteristic of all the signs in group A, A+B, C and D, and denoted frequency rate of x-characteristic of i-sign in the group A as \( \varphi_A(x) \), in the group A+B as \( \varphi_{A+B}(x) \), in the group C as \( \varphi_C(x) \) and in the group D as \( \varphi_D(x) \). If the frequency rate of x-characteristic is the same or nearly the same in group A as in group C or D, this characteristic has no prognostic value. In contrast, if the value of frequency rate in group A is considerably greater in comparison with C or D, this characteristic has higher prognostic value, higher informativity. We denote informativity as a relation:

\[
\xi_i = \frac{\varphi_A(x)}{\varphi_D(x)}
\]

We reject \( \sigma(x) \) if \( \sigma(x) < 1.5 \).

We denote the prognostic power of characteristic of sign by following expressions:

\[
\psi(x) = 10 \cdot \sigma_i \cdot \varphi_A(x)
\]

\[
\psi_{A+B}(x) = 10 \cdot \sigma_i \varphi_{A+B}(x)
\]

After evaluation of separate characteristics of sign, the prognostic power of sign is determined as a set of selected prognostic powers of characteristics of this sign

\[
P_i = \sum_{j=1}^{n} \psi(x)
\]

\( x_j, x_i, \ldots \) are denominations of characteristics of sign. An example (for sign SAFP - the extent of systolic BP changes at the beginning of exercise test):

If

- \( \text{SAFP} (x = D1) \), then \( \psi_1 = 4.4 \)
- \( \text{SAFP} (x = D2) \), then \( \psi_2 = 3.5 \)
- \( \text{SAFP} (x = D5) \), then \( \psi_5 = 1.9 \)
- \( \text{SAFP} (x = m) \), then \( \psi_5 = 2.6 \)
EXERCISE TEST AFTER MYOCARDIAL INFARCTION

Here D1, D2,..., m - are concrete manifestations (characteristics) of sign.

The same method is used for evaluation of other signs:

\[ P_1, P_2,..., P_n \]

The full prognostic power

\[ \Pi_z = \sum_{j=1}^{n} P_j \]

n - the number of used signs, \( z \) - identifier of individual.

In accordance with this method, a programme for the computer was developed, and with this programme the values of

\[ \Pi_z^{\text{a}} \text{ and } \Pi_z^{\text{b}} \]

for each member of group "C" were estimated.

It was found that with increase of numeral quantity of prognostic power the risk of coronary death after MI increases.

After computation of prognostic power of each member in groups A, A+B, C and D, the arithmetical mean of prognostic power of each group \( V_A, V_{A+B}, V_C \) and \( V_D \) was estimated (obtained):

\[ V_A = 28.66; \quad V_{A+B} = 31.05; \quad V_C = 23.45; \quad V_D = 21.0. \]

These quantities may be used as criteria to pick up the patients with high risk of coronary death. The same method was applied for evaluation of prognostic values of widely accepted data of early exercise testing. The combined use of both the widely accepted data of early exercise testing and the dynamic characteristics of HR and systolic BP considerably increased the predictive power of the test. Computation of arithmetical mean of prognostic power gave following quantities

\[ V_A^{\text{a}} = 40.69; \quad V_{A+B}^{\text{a}} = 39.83; \quad V_C^{\text{a}} = 27.55; \quad V_D^{\text{a}} = 26.82. \]

After these investigations with the learning assembly and determination of prognostic power of signs, an examination on the other part of data of early exercise testing was performed. It demonstrate that early cardiac deaths were correctly predicted in 80% of cases.

Discussion

It is known that the double product (BPxHR/100) attained during the exercise test represents the survival prognosis and the decrease of BP during the exercise correlates with unfavourable outcomes. According to our data, exercise induced hypotension was registered more frequently in the group of survivors. The hypotension was established in 8.6% of the survivors and in 7.16% among those dying within the first 6 months after MI. In the group of 1-year survivors after MI, exercise hypotension was established in 9% of patients and in non-survivors – in 3.1% of cases. Two years after MI the results were 9.2% and 2.4% respectively. Hypotension in early exercise test was detected in 10% of patients in the group of 10 years survivors and in 5.1% of patients dying during this period after MI. Our patients undergoing early exercise test after MI were in relative good physical condition, without any contraindications for the test. In this case we can explain the relative rare hypotension cases in our early exercise tests after MI and no established correlation to the unfavourable outcomes. According to our data, dynamic of BP and HR during the exercise and after it were related to survival after MI.

It is important to pay attention to such easy detectable marker of sudden cardiac death – absence of T-wave pseudonormalisation during the early exercise test after MI. This sign is not enough investigated. There is an opinion, that this could be related to the absence of the metabolic myocardial activity. Necrotic myocardium has no metabolic and electrical activity, so in these cases negative T-waves can not undergo the changes (absence of pseudonormalisation). Our data revealed, that in the group of 11 patients dying suddenly during the first 6 months after MI, all of them had negative T-waves in the zone of infarction. Ten (90.9%) of them had no T-pseudonormalisation pattern during the exercise test. Negative T-waves at the third week after MI were detected in 58 (66%) of 87 patients dying during 10 years after MI. The early exercise test did not induce T-pseudonormalisation in 21 (36.2%) of these patients (significantly lower (p<0.01) as compared to the death cases during the first 6 months after MI). Thus, our data showed, that the absence of T-wave
pseudonormalisation during the early exercise test after MI may predict early sudden death after MI.

**Conclusion**

In conclusion, patients after MI can be divided into relative high and low-risk groups for subsequent cardiac events if all information available on the exercise test is used. The use of the dynamic characteristic of heart rate and systolic blood pressure considerably increase the predictive power of the test; the early cardiac deaths being correctly predicted in 80% of cases.

**References**

The Role of Adrenomedullin in the Cardiovascular System

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WONG ET AL.: The Role of Adrenomedullin in the Cardiovascular System. Adrenomedullin (AM) is a 52 amino acid peptide that was first isolated from human pheochromocytoma. Subsequently, AM and its receptors are found to be distributed widely in the body, including the cardiovascular system. It belongs to a family of peptides that include calcitonin gene-related peptide. In blood vessels, AM causes vasodilation and regulates proliferation. It interacts closely with nitric oxide and has a role in the pathophysiology of hypertension, ischaemic heart disease, cardiac and renal failure. A non-peptide analogue of AM or gene therapy may be of potential therapeutic use. The role of AM in septicemic shock also merits further investigation. (J HK Coll Cardiol 2004;12:75-81)

Adrenomedullin, cardiovascular system, nitric oxide, peptide, vasodilation

Introduction

Adrenomedullin (AM) was first discovered in 1993 by Kitamura and co-workers as a new peptide from human pheochromocytoma with its ability to raise cyclic adenosine 3’-5’-monophosphate (cAMP) levels in platelets.1 Subsequently, AM had aroused much interest because of its potent and long lasting depressor effect when injected intravenously into the rat.2 Human AM consists of 52 amino acids and has a ring structure formed by one intramolecular disulfide bond and an amidated carboxyl terminal, structures that are essential for its bioactivity. It belongs to a family of peptides that include calcitonin gene-related peptide (CGRP) and amylin.3 These peptides bind to either the calcitonin or the calcitonin receptor-like (CL) receptor.

The human AM gene is located at the single locus of chromosome 11 and consists of 4 exons and 3 introns.4 In the 5’-upstream sequence of the AM gene, several binding sites for activator protein-1 and activator protein-2, cAMP-regulated enhancer and a shear stress responsive element "GAGACC" are present, which play roles in the transcriptional regulation of AM gene.5 The circulating form of AM is formed from successive enzymatic cleavage of a 185-amino-acid preproadrenomedullin (preproAM) sequence (Figure 1). Cleavage of a 20-amino acid sequence in the N-terminal region of proadrenomedullin yields the proadrenomedullin N-terminal 20-peptide (PAMP),6 which is also a potent vasodilator. Recently, two other peptides in the family have been identified, namely long- and short-form intermedin which consist of a 47-
amino acid and a 40-amino acid peptide respectively.\textsuperscript{5} The long form intermedin is also known as AM2. They also have vasodilatory and hypotensive actions.

**Tissue Distribution and Synthesis**

AM was originally identified in pheochromocytoma, however, in the process of identifying AM-secreting cells, it has been shown to be widely distributed in many tissues and fluids. Immunoreactive AM is found in the human cardiovascular, renal, respiratory, gastrointestinal, reproductive, neurological, endocrine and immune systems.\textsuperscript{6} It circulates in plasma in the low fmol/ml range, and is also present in urine, cerebrospinal and amniotic fluid. The plasma half-life of AM in man is 22 minutes and the volume of distribution is 880 ml/kg.\textsuperscript{7}

Secretion of AM is influenced by physical and hormonal factors such as shear stress, ventricular wall stress, hypoxia, cytokines and endocrine and paracrine hormones. Inflammatory cytokines including tumour necrosis factor (TNF)-\(\alpha\), TNF-\(\beta\), interleukin (IL)-1\(\alpha\), IL-1\(\beta\), and lipopolysaccharide (LPS) strongly stimulate
ADRENO-MEDULLIN

the synthesis and secretion of AM in endothelial cells and vascular smooth muscle cells (VSMCs). Activation of NF-IL6 mediates the induction of AM expression by cytokines. In rat, LPS increases AM expression in various tissues including lung, heart, liver, and kidney. In VSMCs, AM production is also stimulated by glucocorticoids, thyroxine, angiotensin II, bradykinin and adrenaline.

Receptors and Signal Transduction

Specific binding sites for AM are present in rat heart, lung, spleen, liver, diaphragm, spinal cord and different parts of the brain, with the greatest density of binding sites in the heart and lung. Initially, AM was thought to bind to a CGRP receptor, as these related peptides have overlapping binding sites and vascular effects. It is now known that a functional AM or CGRP receptor consists of at least three proteins: the CL receptor, receptor-activity-modifying proteins (RAMPs) and a receptor component protein (RCP). Three subtypes of RAMPs, namely RAMP1, RAMP2, and RAMP3, have been identified. CL receptor can function either as a CGRP receptor or an AM receptor depending on the co-expression of different subtypes of RAMPs (Figure 2). Co-expression of CL receptor with RAMP1 forms a CGRP receptor while co-expression of CL

![Figure 2. CGRP and AM receptors.](image)
receptor with RAMP2 or RAMP3 results in binding of AM. These RAMPs may control the transport and glycosylation of the CL receptor to define the specificity of receptor. RAMP1 presents CL receptor as a mature glycoprotein at the cell surface to form a CGRP receptor, whereas the RAMP2 or RAMP3-transported receptors are core glycosylated AM receptors.12

The vasodilatory and hypotensive responses elicited by AM are mediated via at least two mechanisms: a direct action on VSMCs to activate the adenyl cyclase-PKA pathway resulting in increase of intracellular cAMP, and an action on endothelial cells to stimulate nitric oxide (NO) release.13 Furthermore, potassium ion-ATP channel may also be involved in AM-induced vasodilation in isolatedperfused rat kidney in which the endothelium-derived hyperpolarizing factor (EDHF) opens the potassium ion channels.14

Cardiovascular Effects

AM plays a major role in the maintenance of cardiovascular and renal homeostasis.14,15 In addition, it modulates the hypertrophy of cardiomyocytes and the growth of fibroblasts, and also have antimicrobial effects.4 In transgenic mice with one AM allele deleted, there was increase in blood pressure and decrease in NO expression,15 suggesting that AM is involved not only in blood pressure regulation but also in endothelial function. Infusion of AM into human brachial artery significantly increases forearm blood flow via a NO-dependent pathway that can be blocked by L-NMMA.16 Infusion of AM in man also lowers pulse wave velocity.17 In sheep, intracoronary AM causes vasodilation, also through the release of NO.18 In Dahl salt-sensitive rats, AM restores NO-dependent vasodilatation, through upregulation of NO production and reduction in superoxide formation.19

Intravenous infusion of AM lowers blood pressure, and increases heart rate and cardiac output.20 A direct cardiostimulatory effect can also be demonstrated in the isolated perfused rat heart.21 However, AM is also negatively inotropic under other circumstances, such as in isolated rabbit cardiac ventricular myocytes, rat papillary muscle and human left ventricular myocytes.22 This negative inotropic effect may be mediated by NO.

Intravenous infusion of AM increases renal blood flow, glomerular filtration, urine flow and fractional urinary sodium excretion, and decreases distal tubular sodium reabsorption independent of blood pressure.23 The natriuresis and diuresis may be mediated via renal prostaglandin24 and NO.25

As well as regulating vascular tone, AM may also regulate vascular proliferation and remodelling. It dose-dependently inhibits thymidine incorporation and proliferation induced by platelet-derived growth factor in VSMCs.26 AM may also be an angiogenic factor. Vascular density and endothelial cell proliferation are stimulated by AM. Many tumours express AM; an antibody against AM or an AM antagonist suppresses tumour growth in animal models.27 Whether AM can be used to increase angiogenesis in ischaemia remains to be explored.

Neuroendocrine Effects

High levels of AM are found in the adrenal medulla and zona glomerulosa. Intravenous AM infusion lowers circulating cortisol and adrenocorticotrophic hormone (ACTH) levels in sheep.28 There appears to be a complex interaction between AM and the renin-angiotensin system; AM stimulates the release of renin,29 but inhibits aldosterone secretion.30 AM immunoreactivity is widely distributed in the central nervous system (CNS).31 In the supraoptic nucleus (SON) and in the magnocellular parts of the paraventricular nucleus (PVN), AM is expressed. As a neuropeptide, AM may regulate body fluid homeostasis by inhibiting water drinking and salt appetite. Blockade of the action of endogenous AM by passive immunoneutralization results in exaggerated sodium appetite.32 By restraining salt and water intake, AM's central actions complement its renal actions. AM expression is increased in the ischemic cerebral cortex in the rat after middle cerebral artery occlusion,33 where it may increase cerebral blood flow and promote collateral perfusion.
Plasma AM Levels in Diseases

Plasma AM levels are increased in a variety of diseases: congestive heart failure, myocardial infarction, renal diseases, hypertension, diabetes mellitus, the acute phase of stroke and septic shock. Plasma AM levels are elevated in patients with essential hypertension in proportion to the severity of hypertension, especially in those with left ventricular hypertrophy. However, neither acute nor chronic salt loading, nor anti-hypertensive therapy changes the circulating level of AM in patients with essential hypertension. Plasma levels of AM are increased in patients with congestive heart failure, whether systolic or diastolic. The failing human heart secretes increased amounts of AM. Plasma AM concentration correlates with pulmonary capillary wedge pressure and inversely with ejection fraction. It decreases after treatment of the heart failure. Plasma AM concentration is elevated in relation to the degree of renal failure.

Injection of LPS in the rat produces a marked increase in plasma AM, suggesting AM may be involved in sepsis. Circulating AM level is also increased in sepsis in man. In the early, hyperdynamic phase of sepsicaemia, there is upregulation of AM, followed by a reduction in vascular responsiveness to AM in the late, hypodynamic response. Administration of AM and its binding protein (AMBP-1) maintains cardiovascular stability and reduces sepsis-induced mortality. Transgenic mice overexpressing AM are resistant to sepsicaemic shock. Therefore, AM may be responsible for many of the changes in the circulatory system in septic shock.

AM as Therapeutic Agent

Infusion of AM lowers blood pressure in hypertension and lowers ventricular end-diastolic pressure and increases cardiac output in heart failure. Therapy based on increased stimulation of AM receptors may have potential application in hypertension and heart failure. In AM-knockout mice, there is accelerated cardiac hypertrophy and renal damage induced by angiotensin II, suggesting that endogenous AM protects against cardiac and renal damages. In the rat model of myocardial infarction induced by coronary artery ligation, a one-off early intravenous administration of AM prevents subsequent left ventricular remodelling. As AM is a peptide, it cannot be given orally. In patients with pulmonary hypertension, AM administered by inhalation reduced pulmonary vascular resistance. A non-peptide analogue is eagerly awaited for clinical studies. Neutral endopeptidase inhibitors increase the level of AM as well as other vasoactive peptides, but their use is limited by the increased likelihood of angiooedema. Expression of AM is known to be increased after angioplasty and stenting. AM gene delivery successfully inhibited neointimal formation after balloon angioplasty in a rat model. Gene therapy targeting the AM system is a novel and promising modality of treatment for the future.

Conclusions

In summary, AM and its receptor are distributed widely in the body, including the cardiovascular system. In blood vessels, AM causes vasodilation and regulates proliferation. It interacts closely with NO and has a role in the pathophysiology of hypertension, ischaemic heart disease, cardiac and renal failure. A non-peptide analogue of AM or gene therapy may be of potential use in these diseases. The role of AM in septicaemic shock, a condition characterised by high mortality, also merits further investigation.

Acknowledgements

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