Evaluation of Effects of Intra aortic Balloon Counterpulsation on Autonomic Nervous System Functions by Heart Rate Variability Analysis

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Background: In patients with acute myocardial infarction (AMI), intraaortic balloon counterpulsation (IABC) may improve cardiac performance, decrease the incidence of recurrent ischemia, and improve survival. Although there have been several reports concerning circulatory maintenance with the IABC, response of the autonomic nervous system to these hemodynamic changes is not clear. Heart rate variability (HRV) analysis has been extensively used to evaluate autonomic modulation of sinus node and to identify patients at risk for an increased cardiac mortality. In this study, we evaluated effects of the IABC on autonomic nervous system functions by HRV analysis.

Methods: The study group was composed of 32 consecutive patients (13 female, 19 male aged 61.8 ± 8.8 years) undergoing IABC. Transthoracic echocardiography and 1-hour Holter recordings for HRV analysis in each IAB pumping mode were obtained.

Results: The IABC improved left ventricular diastolic and systolic functions as well as caused an increase in SDNN1, PNN50(1), RMSSD1, and HF1 and a decrease in LF1, LF/HF1, mean heart rate, and the number of ventricular extrasystoles. The improvements in HRV parameters were correlated with some hemodynamic changes such as the increase in MAP and CO during counterpulsation. The only independent factors affecting in-hospital mortality were the change in LF/HF1 ratio (Δ LF/HF1) and the change in the number of ventricular extrasystole (Δ VES). The decrease in LF/HF1 ≥ 4.9 decreased the mortality by 1.7-folds (RR = 0.6, P = 0.04, 95% CI: 0.1–2.3). The decrease in VES $\geq 27/15$ minutes resulted in mortality reduction by 16-folds (RR = 0.06, P = 0.02, 95% CI: 0.01–0.4).

Conclusions: As a result, the IABC, especially in 1:1 support, causes an increase in HRV, decrease in sympathetic overactivity, and improvement in sympathovagal balance besides the favorable hemodynamic changes, and these electrophysiologic changes may explain the role of the IABC in the treatment of ventricular arrhythmias.

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Intraaortic balloon counterpulsation (IABC) represents a successful clinical application of the principle of counterpulsation^{1–3} with appropriate timing to the cardiac cycle. Although there have been several reports concerning circulatory maintenance with the IABC, response of the autonomic nervous system to these hemodynamic changes is not clear. Heart rate variability (HRV) analysis has been extensively used to evaluate autonomic modulation of sinus node and to identify patients at risk for

an increased cardiac mortality.^{4–7} In this study, we evaluated effects of the IABC on autonomic nervous system functions by HRV analysis.

MATERIAL AND METHODS

The study group was composed of 32 consecutive patients undergoing intraaortic balloon pumping. An informed written consent was obtained from all patients and local ethics committee approved the

trial. An IAB (Datascope, Montvale, NJ, USA) was inserted percutaneously in all patients in the catheterization laboratory. Pumps were set on automatic R wave deflation with manual deflation and inflation adjustments. Right-sided hemodynamic measurements were obtained by a Swan-Ganz catheter. Cardiac output was determined using injections of 10-mL iced saline solution and 3 measurements were averaged for analysis. Arterial pressure was monitored via an intraarterial cannula inserted into the radial artery. Measurements were obtained with "pump-on" and "pump-off" status. The IAB was set to full augmentation and recordings were made at pumping cycles 1:1, 1:2, and 1:3 (from 1:1 counterpulsation to 1:2) and when the pump was on stand-by, leaving a minimum of 15-minute interval between pumping modes to achieve stable hemodynamic conditions. All the patients underwent coronary angiography. Cardiogenic shock was defined as (1) persistent systolic blood pressure <90 mmHg or vasopressors required to maintain blood pressure at >90 mmHg, (2) evidence of end-organ failure, and (3) evidence of elevated filling pressures (pulmonary capillary wedge pressure $\geq$ 18 mmHg).

Transthoracic echocardiography was performed to assess the left ventricular ejection fraction (EF). Measurements were made according to the recommendations of the American Society of Echocardiography.⁸ Left ventricular inflow velocities were measured by the pulsed-wave Doppler technique in the apical 4-chamber view under 2-dimensional guidance. The sampling volume was placed near the tips of the mitral leaflets to measure the mitral inflow velocities. Left ventricular diastolic function was assessed using transmitral flow parameters. The E and A filling velocities, E wave deceleration time, and E/A ratio were measured. The isovolumic relaxation time was also recorded from the apical 4-chamber view simultaneous recording of the aortic and mitral flows.⁹ All the patients were in sinus rhythm at the time of study.

We put a Holter recorder on the patients after balloon pump implantation. We got 1 hour-Holter recordings for HRV analysis in each pumping mode (after 15-minute interval necessary to achieve stable hemodynamics). The investigators were blinded to IAB settings during the analysis. All patients underwent 3 channel Holter ambulatory ECG monitoring (Biomedical System Century 2000/3000 Holter System, Version 1.32). Recordings were analyzed by "Biomedical Systems Century 2000/3000 HRV Package System," following

manual adjustment of RR intervals. Recordings with <85% of qualified sinus beats were excluded. The time and frequency-domain analysis of HRV were performed according to the recommendation of the task force.⁴ The mean heart rate (HR1), standard deviation of all NN intervals (SDNN1), root mean square of successive differences (RMSSD1), number of NN intervals that differed by more than 50 ms from adjacent interval divided by the total number of all NN intervals (PNN50(1)) for 1-hour interval were measured in the time domain analysis of HRV. A reduced SDNN has been considered reflecting diminished vagal and increased sympathetic modulation of sinus node. The power spectrum of HRV was measured using fast-Fourier transform analysis in 3 frequency bands: 0.0033–0.04 (very low frequency, VLF1), 0.04–0.15 (low frequency, LF1), and 0.15–0.40 (high frequency, HF1) during 1-hour recordings. HF was used a marker of parasympathetic nervous system and LF was used a marker of sympathetic activity.⁴ The power of these components was stated as normalized unit (nu). The normalization procedure is crucial for the interpretation of data.¹⁰ We also measured the ratio of low to high frequency power (LF/HF1) reflecting the sympathovagal balance. High values indicated dominant sympathetic activity.¹⁰ Normalized LF and HF components were defined dividing the corresponding raw power by total power minus the power in the VLF band [$LF_{nu} = LF/(TP-VLF)$].

Statistical Analysis

Continuous variables are presented as mean $\pm$ SD, and discrete variables are expressed as frequencies and percentages. When 4 groups were being compared, continuous variables were evaluated using analysis of variance. When a statistical difference among 4 groups was identified, paired *t*-test was used to test the difference of each parameter between two IAB settings. Pearson's correlation analysis was performed to show the correlation between the changes in hemodynamic and HRV parameters during intra aortic balloon pumping. Linear logistic regression and correlation analysis was performed to define the correlation between changes in echocardiographic, hemodynamic parameters and HRV after IABC. Binary logistic regression analysis was performed to find independent factors affecting in-hospital mortality. A *P* value <0.05 was considered to be statistically significant.

RESULTS

The study group was composed of 32 consecutive patients (13 female, 19 male aged 61.8 ± 8.8 years) undergoing intra aortic balloon pumping. Twenty-two patients had hypertension, 8 had DM, and 14 patients were smokers. Indication for the insertion of IABC was mostly cardiogenic shock (75%), and some complicated with mechanical complications of acute myocardial infarction (MI) (6 patients had ventricular septal defect and 4 patients had acute mitral regurgitation). IAB was implanted in 4 patients due to refractory hypotension, in 2 patients due to refractory ischemia after acute MI, and in 2 patients for refractory ventricular arrhythmias. No major complications (severe limb ischemia, bleeding, balloon leak or death due to IAB insertion or failure) occurred.

Mean duration of IABC was 3.8 ± 3.4 days and mean interval between insertion of IAB and HRV analysis was 18.9 ± 9.2 hours. Four patients were treated with beta-blockers, 2 patients with angiotensin converting enzyme inhibitors, 6 patients

with nitroglycerin, 18 patients with dopamine, 10 patients with dobutamine during the enrollment, 14 patients were treated with thrombolytic agents in our clinics or in the hospital that they were first admitted, and percutaneous coronary revascularization was applied in 2 patients.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and systemic vascular resistance (SVR) decreased, and mean arterial pressure (MAP) increased significantly during IABC support compared to those when IABC-off. Pulmonary capillary wedge pressure (PCWP) and systolic pulmonary arterial pressure (SPAP) decreased, and left ventricular EF (LVEF) and cardiac output (CO) increased with IABC. E/A ratio increased and isovolumic relaxation time (IVRT) prolonged, whereas deceleration time (DT) shortened during IABC. SDNN1, PNN50(1), RMSSD1, and HF1 increased, and mean HR1, LF1, LF/HF1 ratio, and VES count during 1-hour recording decreased during the counterpulsation (Table 1).

Δ PNN50(1) was correlated with Δ PCWP ($r = 0.4$, $P = 0.02$), Δ LF1 was correlated with Δ IVRT ($r =$

Table 1. Hemodynamic and Heart Rate Variability Parameters of the Patients

Variables	IABC-On			IABC-Off
	1:1	2:1	3:1	
SBP (mmHg)	104.3 ± 7.7	$103.8 \pm 7.2^*$	104.5 ± 7.4	104.6 ± 7.3
DBP (mmHg)	59.8 ± 4.9^a	60.0 ± 4.8^a	60.9 ± 4.5	61.8 ± 4.3
MAP (mmHg)	84.4 ± 6.8^a	83.8 ± 6.3^a	81.8 ± 5.5	80.6 ± 5.5
PCWP (mmHg)	21.4 ± 3.3^a	21.5 ± 3.2^a	21.9 ± 2.8	22.1 ± 2.7
SPAP (mmHg)	45.4 ± 4.9^a	45.5 ± 4.8^a	45.9 ± 4.6	46.2 ± 4.7
LVEF (%)	39.5 ± 8.7^a	39.1 ± 8.6^a	38.8 ± 8.3	38.5 ± 8.3
CO (L/min)	3.5 ± 0.83^a	3.46 ± 0.81^a	3.42 ± 0.82	3.36 ± 0.82
SVR (dynes s/cm ⁵)	1488.2 ± 436.9^a	1494.4 ± 441.8^a	1537.0 ± 469.2	1543.9 ± 472.3
E/A	0.94 ± 0.09^a	0.92 ± 0.09^a	0.84 ± 0.1^b	0.79 ± 0.1
IVRT (ms)	83.2 ± 9.4^a	83.1 ± 9.8^a	81.3 ± 8.4	81.2 ± 8.2
DT (ms)	229.3 ± 14.8^a	229.8 ± 14.9^a	232.4 ± 12.1	235.1 ± 9.1
Mean HR1 (beats/min)	100.1 ± 11.4	99.8 ± 11.4^a	102.3 ± 11.1^a	100.7 ± 10.8
SDNN1	79.3 ± 10.6^a	75.3 ± 14.5^a	70.9 ± 15.3^a	62.7 ± 16.8
RMSSD1	64.4 ± 21.4^a	60.2 ± 21.9^a	55.3 ± 21.7^a	49.7 ± 17.9
PNN50(1)	35.6 ± 19.4^a	32.3 ± 15.9^a	8.6 ± 14.1^a	2 1.9 ± 10.5
LF1 (nu)	42.1 ± 19.5^a	50.6 ± 20.3^a	56.2 ± 19.9^a	65.3 ± 19.8
HF1 (nu)	56.7 ± 22.7^a	49.1 ± 18.7^a	37.7 ± 15.6^a	24.9 ± 11.9
LF/HF1	1.9 ± 0.5^a	2.9 ± 0.7^a	6.1 ± 1.6^b	7.0 ± 2.2
VES count in 1 hour	8.9 ± 37.0^a	63.7 ± 39.9^b	69.5 ± 39.1^b	74.6 ± 38.8

^aP < 0.001 compared to IABP-off; ^bP < 0.01 compared to IABP-off; HT = hypertension; DM = diabetes mellitus; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; SPAP = systolic pulmonary arterial pressure; CO = cardiac output; LVEF = left ventricular ejection fraction; IVRT = isovolumic relaxation time; DT = deceleration time; PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance; VES = ventricular extrasystole; IABC = intra aortic balloon counterpulsation.

Table 2. The Variables Affecting the Change in SDNN1 after IABC

Variables	S.E.	β	t	P
Age	1.2	0.9	4.2	0.1
Gender	1.4	0.8	2.8	0.2
HT	1.1	1.2	0.8	0.5
DM	1.6	2.1	1.4	0.2
Smoking	1.1	1.2	1.6	0.1
Δ SBP	4.9	0.1	0.8	0.6
Δ DBP	6.9	0.02	0.2	0.7
Δ MAP	6.5	2.5	3.2	0.1
Δ SPAP	9.6	0.9	1.6	0.4
Δ CO	1.3	2.5	2.2	0.03
Δ E/A	0.1	0.3	0.1	0.3
Δ IVRT	0.1	-0.3	-0.9	0.7
Δ DT	0.1	0.9	0.7	0.5
Δ PCWP	4.6	-1.2	-1.8	0.1
Δ SVR	38.7	-3.2	-2.2	0.005

HT = hypertension; DM = diabetes mellitus; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; SPAP = systolic pulmonary arterial pressure; CO = cardiac output; IVRT = isovolumic relaxation time; DT = deceleration time; PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance; Δ = the difference between pre-IABC and post-IABC values.

0.4, $P = 0.04$), Δ VES was correlated with Δ MAP ($r = -0.4$, $P = 0.03$) and Δ SVR ($r = 0.4$, $P = 0.02$), and Δ SVR was correlated with Δ MAP ($r = -0.7$, $P = 0.001$) and Δ CO ($r = -0.8$, $P = 0.001$).

The independent variables associated with the change in LF/HF1 were the changes in CO ($\beta = -2.2$, $P = 0.04$) and PCWP ($\beta = 2.2$, $P = 0.045$); Δ IVRT ($\beta = 0.4$, $P = 0.04$) was the only independent determinant of the Δ LF1. The change in SDNN1 was significantly associated with the changes in MAP, CO, and SVR (Table 2).

The patients who died during hospitalization ($n = 12$) were found to be older (64.5 ± 6.7 vs 60.4 ± 9.6 years, $P = 0.04$), have lower Δ MAP (3.1 ± 3.1 vs 4.2 ± 3.8 mmHg, $P = 0.03$), lower Δ CO (0.09 ± 0.09 vs 0.1 ± 0.3 L/min, $P = 0.04$), higher Δ LF/HF1 (6.2 ± 1.8 vs 4.5 ± 2.0 , $P = 0.02$), higher HT history (91.7% vs 55%, $P = 0.03$), lower baseline EF (33.8 ± 6.7 vs 41.3 ± 7.9 , $P = 0.08$), lower CO (2.9 ± 0.7 vs 3.6 ± 0.8 , $P = 0.01$) compared to those who did survive. Although both groups had similar VES counts during 1 hour when the IABC was off, the patients who died had a lower decrease in VES counts during IABC with 1:1 support (20.1 ± 8.6 vs 34.9 ± 16.5 , $P = 0.02$).

The only independent factors affecting in-hospital mortality were Δ LF/HF1 (RR = 0.6, $P = 0.04$, 95% CI: 0.1-1.3) and Δ VES (RR = 0.06, $P = 0.02$, 95% CI: 0.01-0.4).

DISCUSSION

The main findings of our study were that (1) the IABC, especially in 1:1 and 1:2 supports, caused an increase in HRV and improved sympathovagal balance besides the favorable hemodynamic changes in left ventricular systolic and diastolic functions in accordance with many previous reports,¹¹⁻¹³ (2) the improvements in HRV parameters were correlated with some hemodynamic changes such as the increase in MAP and CO during counterpulsation, (3) the number of ventricular extrasystoles decreased during counterpulsation and this decrease was correlated with the increase in MAP, and (4) in-hospital mortality was determined by the decrease in LF/HF and VES count.

In patients with acute MI, the IABC may improve cardiac performance, decrease the incidence of recurrent ischemia, and improve survival.¹⁴⁻¹⁷ Evidence may be cited supporting the use of the IABC in AMI patients with ventricular septal rupture and acute mitral regurgitation,^{17,18} progressive heart failure despite medical therapy,¹⁹ postinfarct angina,²⁰ and recalcitrant ventricular arrhythmias.²¹

The use of IABC can contribute to the management of medically refractory ventricular arrhythmias.^{3,21,22} There are several proposed mechanisms for the antiarrhythmic effects of IABP: (1) the

augmentation of the coronary perfusion,²³ (2) the decrease in myocardial wall tension and oxygen demand,²⁴ (3) the mechanical effects of the IABC (mechano-electrical feedback),^{25,26} and (4) the reduction in the adrenergic drive as a result of supporting the hemodynamic state.²¹ But, even though many studies have been performed to clarify the effects of IABC on hemodynamics, there is not much data about the effects of IABC on neural circulatory regulation.

Stanley TH et al.²⁷ showed that IABC reduces elevated circulating catecholamines after MI complicated by cardiogenic shock. IABC significantly reduced plasma epinephrine after 1 hour and norepinephrine after 2 hours of pumping. Tokunaga et al.²⁸ found that IABC driving inhibits renal sympathetic nerve activity and improves renal circulation in failing heart condition. Similarly, during left-ventricular assist device (LVAD) pumping, renal sympathetic nerve activity is found to be decreased with an increase in blood pressure and pulmonary artery blood flow and with a decrease in left atrial pressure probably mediated by both sinoaortic and cardiopulmonary baroreceptors.^{29,30} Since counterpulsation introduces a second positive wave in each cardiac cycle, it might be expected that the baroreceptors would receive increased stimulation during IABC and would, thereby, produce reflex decreases in peripheral resistance and in heart rate.³¹ Feola et al.³² reported that such a depressor reflex occurred in animals with normal or high systemic blood pressures at the initiation of IABC not in the animals with low arterial pressures. They claimed that the lack of this reflex in hypotensive animals was that the artificially produced diastolic waves were below the threshold level for stimulation of the baroreceptors that are located in the aortic arch and carotid sinus.³³

The adrenergic activation associated with AMI and ventricular dysfunction is the results of the complex interaction of several neural reflexes originating from different reflexogenic areas in addition to non-neural mechanisms. Unfortunately, HRV analysis does not allow the appraisal of individual mechanisms involved but our results demonstrated that the IABC counterpulsation yielded a decrease in this adrenergic overactivity in the early period.

Study Limitations

Since the order of testing was controlled (from 1:1 to 1:2 in order), a time dependent effect cannot

be excluded. The lack of neurohormonal measurements such as plasma catecholamines is another limitation of the study.

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