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Original article

Effects of human atrial natriuretic peptide on myocardial performance and energetics in heart failure due to previous myocardial infarction

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ABSTRACT

Background: Human atrial natriuretic peptide (hANP) and spontaneous nitric oxide (NO) donor share cyclic guanosine monophosphate (cGMP) as a second messenger, but their effect on myocardium may differ. We compared the effect of hANP and sodium nitroprusside (SNP) on left ventricular (LV) mechano-energetics in heart failure (HF).

Methods: Ten patients with HF due to previous myocardial infarction (LV ejection fraction: 45 ± 3%) were instrumented with conductance and coronary sinus thermodilution catheters. LV contractility (E_{es}: slope of end-systolic pressure–volume relation) and the ratio of LV stroke work (SW) to myocardial oxygen consumption (SW/MVO_2 = mechanical efficiency) were measured in response to intravenous infusion of ANP (0.05 μg/kg/min) or SNP (0.3 μg/kg/min) to lower blood pressure by at least 10 mmHg, and changes in plasma cGMP.

Results: SNP had no effect on E_{es}, SW, or MVO_2, thus SW/MVO_2 remained unchanged (40.54 ± 5.84% to 36.59 ± 5.72%, $p = 0.25$). ANP increased E_{es}, and decreased MVO_2 with preserved SW, resulting in improved SW/MVO_2 (40.49 ± 6.35% to 50.30 ± 7.96%, $p = 0.0073$). Infusion of ANP (10.42–34.95 pmol/ml, $p = 0.0003$) increased cGMP levels, whereas infusion of SNP had no effect (10.42–12.23 pmol/ml, $p = 0.75$).

Conclusions: Compared to SNP, the ANP-dependent increase in cGMP may ameliorate myocardial inotropy and energetics in HF.

Introduction

Congestive heart failure (CHF) is a complex syndrome that results from various underlying conditions, including acute and chronic ischemic heart disease, cardiomyopathies, myocarditis, and pressure overload, that lead to an inability to pump blood at an output sufficient to meet the requirements of tissues in the body. Current therapies for CHF include loop diuretics to reduce intravascular volume, vasodilators to reduce vascular resistance, and inotropic agents to increase myocardial contractility.

Vasodilatation using a nitric oxide (NO) donor such as nitroglycerin and sodium nitroprusside (SNP) is a widely used therapeutic strategy for CHF. NO has vasodilatation effects in vascular smooth muscle cells via the activation of soluble guanylate cyclase and an increase in intracellular levels of guanosine 3′,5′-cyclic monophosphate (cGMP), an intracellular messenger. In addition to vasodilatation, several experimental studies have suggested that NO donors affect cardiac contractility. De Mulder et al. demonstrated that SNP enhances the left ventricular (LV) contractile response to β-adrenergic stimulation [1]. In contrast, Shinke et al. demonstrated that inhibition of endogenous NO synthase enhances the LV contractile response to β-adrenergic stimulation [2]. The precise effects of NO on cardiac function and mechano-energetics in patients with CHF, however, have not been investigated clinically.

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Atrial natriuretic peptide (ANP) induces various biologic responses via binding the particulate guanylate cyclase-coupled receptor, that is, the natriuretic peptide receptor-A (NPR-A) [3], and this natriuretic peptide utilizes cGMP as a second messenger similarly to NO. In addition to its potent natriuretic and vasodilatory properties, ANP has various other beneficial effects, such as anti-inflammatory effects, suppression of sympathetic tone and catecholamine production, and inhibition of the renin–angiotensin system [4–6].

The effect of ANP on myocardial contractility, however, is controversial. Ohte et al. reported that ANP had a negative inotropic effect in both normal dogs and dogs with CHF [7]. On the other hand, Lainchbury et al. demonstrated that ANP had a positive inotropic effect in normal dogs, and no inotropic effect in dogs with CHF [8]. Mizuno et al. demonstrated that ANP administration increased E_{es}, an index of contractility, in patients with CHF [9].

Given these various potent biologic activities, clarification of the effects of ANP on contractility and cardiac mechano-energetics is important toward establishing a therapeutic strategy for CHF. In the present study, we examined the effects of an NO donor and ANP on cardiac performance and mechano-energetics in patients with LV dysfunction.

Methods

Patient population

Studies were performed in 10 patients (mean age 68.1 ± 9.5 years, men/women = 5/5) with prior myocardial infarction (MI). They underwent diagnostic cardiac catheterization for evaluation of heart function at least 1 month after the onset of MI.

All patients received percutaneous coronary stenting within 48 h of the onset of symptoms and had no residual epicardial coronary stenosis, dyskinetic LV wall motion, or more than moderate mitral valve regurgitation at the time of this study protocol. All patients were in sinus rhythm and were diagnosed with New York Heart Association functional class II CHF. Before cardiac catheterization, angiotensin-converting enzyme inhibitors and β-blockers were withheld for at least for 24 h and more than 72 h, respectively. Written informed consent was obtained from all patients, and the study protocol was approved by the Institutional Committee on Human Research at Kobe University Hospital.

Cardiac catheterization procedure

Patients had undergone routine right and left heart catheterization, left ventriculography, and coronary arteriography under fasting conditions without medication. A 6F conductance catheter (CardioDynamics, Rijnsberg, The Netherlands) was advanced into the LV through the right radial artery, and a 2F Millar Instruments catheter (Millar Instruments, Houston, TX, USA) was advanced into the LV through the lumen of the conductance catheter. An 8F coronary thermodilution catheter (Cordis Webster, Inc., Diamond Bar, CA, USA) was then advanced into the coronary sinus through the right jugular vein. The conductance catheter was attached to a stimulator/processor (Leycom Sigma-5, CardioDynamics). The electrocardiogram and hemodynamic parameters were recorded on a strip-chart recorder. Each measurement of the hemodynamic parameters was obtained as the mean value of 8–10 consecutive sinus beats.

Assessment of LV cardiac mechano-energetics

Coronary sinus blood flow (CSF) was measured with the previously described thermodilution technique [10]. Coronary blood was sampled from the distal lumen of the coronary thermodilution catheter for oximetry and determination of myocardial oxygen consumption (MVO_2). MVO_2 per minute was calculated as the product of CSF (ml/min) and the arterial-coronary sinus oxygen content difference (vol%) divided by heart rate to yield MVO_2 per beat (ml O_2/beat).

As previously described [11,12], pressure–volume loops for the sequence beats during the transient reduction in the preload by the Valsalva maneuver were recorded over 8–10 beats, and several pressure–volume loops were obtained from one subject. LV contractility is expressed as E_{es}, which is the slope of the linear end-systolic pressure–volume relation (ESPVR), as shown in Fig. 1 [13]. E_{es} is applied to the LV of the intact animal and humans as a load-independent index of myocardial contractility [14].

Effective arterial elastance (E_a) is a variable that incorporates the values of Windkessel model elements and heart rate as the ratio of end-systolic pressure to stroke volume, and corresponds to the slope of the line connecting the end-systolic pressure–volume point and the end-diastolic point on the volume axis [15]. The ratio of effective E_a to ventricular elastance (E_a/E_{es}) represents ventriculoarterial coupling. We normalized E_{es} and E_a (mmHg/ml/m^2) to the body surface area to permit comparison among patients in the present study, as described previously [13].

The rate of LV relaxation was analyzed using Tau. Tau is the time constant of LV pressure decay during isovolumic relaxation, quantified from a plot of $-dP/dt$ vs P ($P = P_0 e^{-t/T} + P_b$), where P is LV pressure, t is the time from peak $-dP/dt$, T is the time constant of isovolumic pressure decay, and P_0 and P_b are constants determined by the data [2,16].

Stroke work (SW) was calculated as the area bound by the pressure–volume trajectory of 1 beat. Systolic pressure–volume area (PVA) was calculated as the area bound by the ESPVR, end-diastolic pressure–volume relation (EDPVR), and the systolic pressure–volume trajectory of 1 beat. Mechanical efficiency was calculated as the ratio of SW (J/beat) to MVO_2 per beat (J/beat), where 1 mmHg/ml SW and 1 ml O_2 of oxygen consumption correspond to 1.33×10^{-4} and 20 J, respectively [17].

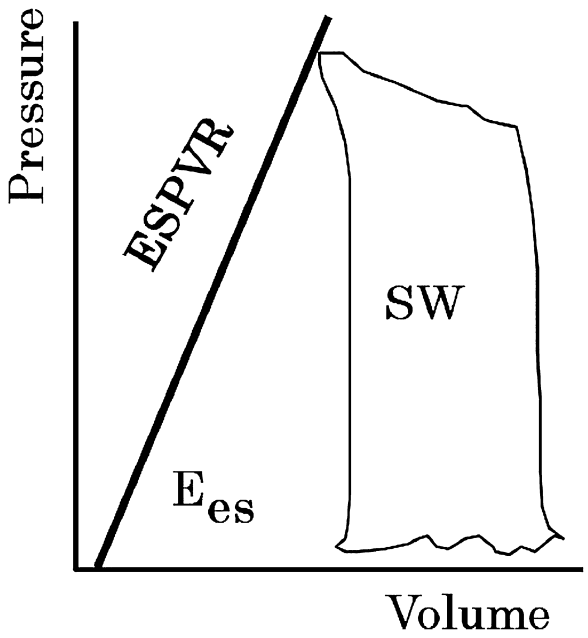

Fig. 1. LV pressure–volume relation. LV pressure–volume relation assessed by manometer-tipped LV conductance catheter. LV, left ventricular; E_{es}, slope of the LV end-systolic pressure–volume relation; SW, stroke work (J) calculated as the area bound by the pressure–volume trajectory of 1 beat; ESPVR, end-systolic pressure–volume relation.