The Role of Clonidine in Hypertensive Heart Disease*
Influence on Myocardial Contractility and Left Ventricular Afterload

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The hemodynamic and contractile effects of clonidine were studied in hypertrophied hearts of spontaneously hypertensive rats (Okamoto-Aoki strain, SHR). The hemodynamic pattern was characterized by dose-dependent decreases in systolic blood pressure and systolic wall stress, i.e., the afterload imposed upon the left ventricle, whereas left ventricular ejection fraction and stroke volume were unchanged. Even at extremely high doses (10^{-2} M/L) there was found no depression of isometric tension development and maximum isotonic shortening velocity of the isolated LV papillary muscle. It is concluded that clonidine may be beneficial in hypertensive heart disease, if ventricular unloading associated with a reduction in myocardial energy demand is desired.

If in arterial hypertension the left ventricular (LV) muscle mass is proportional to the hypertensive pressure in the left ventricle, systolic wall stress will remain within normal limits. However, in the case of an inappropriate low LV muscle mass or LV dilatation, systolic wall stress will be increased and LV ejection fraction impaired. Systolic wall stress is the quantitative equivalent of the LV afterload representing the result of LV systolic pressure and geometry and therefore reflecting the physical load imposed on the left ventricle.

Clonidine lowers blood pressure by activating α-adrenergic receptors in the CNS, resulting in a decrease in sympathetic outflow to the cardiovascular system. Furthermore, an increase in centrally mediated vagal tone may contribute to the hemodynamic changes associated with clonidine. An antihypertensive drug with such pharmacodynamic effects might be expected to exert both cardiac and peripheral arteriolar effects.

It was the aim of the study: (1) to investigate the acute effects of clonidine on LV ejection function and systolic wall stress; (2) to study the influence of clonidine on myocardial contractility with the effects of the sympathetic nervous system eliminated, and (3) to evaluate the role of clonidine in

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Figure 1. Influence of clonidine on left ventricular papillary muscle mechanics in vitro: Δl = muscle shortening; dl/dt = velocity of shortening; T = tension development; dT/dt = velocity of tension development.
the management of experimental hypertensive heart disease.

**METHODS**

**Left Ventricular Hemodynamics**

Experiments were performed on 16 male, 25- to 30-week-old, spontaneously hypertensive rats (SHR) of the Okamoto strain. Central hemodynamics were measured under ether anesthesia after placing an electromagnetic flow probe around the ascending aorta and direct puncturing of the left ventricle at the apex with a fluid-filled steel cannula connected to a Statham pressure transducer (P23Db) to determine LV pressures. Aortic pressure, LV systolic pressure and its first time derivative, LV end-diastolic pressure, and phasic and integrated mean aortic flow were simultaneously registered using a high-frequency recording system (Hellige Co). Central hemodynamics were measured at 20-minute intervals after clonidine was given intravenously (IV), beginning in a dosage of 10 μg/kg body weight, increasing to 30 μg/kg and 50 μg/kg every 30 minutes.

After having completed hemodynamic recordings, diastolic cardiac arrest was produced by intracardially injecting adenosine. Then a pressure-volume relationship of the left ventricle was assessed. On the basis of this relationship each end-diastolic volume could be related to a corresponding volume, ie, the end-diastolic pressure. Thus, by means of the direct measured stroke volume, ejection fraction was calculated. Systolic wall stress was determined from the peak systolic LV pressure and diastolic LV dimensions using a thin-walled, spherical model according to the LaPlace-relationship.

**Myocardial Contractility**

Mechanics of isolated LV papillary muscles in isolated afterloaded contractions at a temperature of 24°C and a stimulation frequency of 20/min were performed on eight SHRs. Methods have been reported in detail. Muscle shortening (Δl), first time derive of muscle shortening (dl/dt), tension development (T), and first time derive of tension development (dT/dt) were registered simultaneously. After having obtained constant mechanical values, clonidine was added beginning a molar concentration of 10⁻⁸ and stepwise increased to 10⁻⁴.

**Statistical Evaluations**

All values in tables and figures are means ± SEM. Statistical calculations were performed using the Student’s t test for paired data. Differences at the 95 percent level were considered to be significant.

**RESULTS**

**Left Ventricular Hemodynamics**

LV systolic pressure, LV systolic wall stress: There was a dose-dependent fall in LV systolic pressure from 183 to 138 mm Hg. Since the end-diastolic dimensions of the left ventricle remained nearly unaltered, systolic wall stress was lowered to the same extent by 24.7 percent (Table I).

Cardiac index, stroke index, heart rate, ejection fraction: With the highest dosage of clonidine cardiac index was diminished by 35.4 percent, stroke index by 12 percent, and heart rate by 23 percent. Left ventricular ejection fraction was unaltered, even after the highest dosage of clonidine (Table I).

- Afterload reduction
- Negative inotropic interventions
- Clonidine

**Figure 2. Relationship between ejection fraction and systolic wall stress.** (1) Specific vasodilation leads to increase in function parallel with stress reduction. (2) Specific negative inotropism reduces ejection fraction at constant wall stress. (3) Clonidine causes a resultant action of both afterload reduction and diminished central sympathetic tone, mimicking reduced myocardial contractility.
LV end-diastolic pressure, LV end-diastolic volume, and LV diastolic wall stress: Clonidine administered at 10 μg/kg IV caused a decrease in LV end-diastolic pressure (~15 percent), LV end-diastolic volume (~5 percent), and diastolic wall stress (~21 percent). These effects were abolished at higher doses.

Myocardial Contractility

In experiments with isolated LV papillary muscles clonidine had no depressant effect on tension and shortening development nor on their first time derivatives, except for extremely high doses of 10^{-4} M/L (Fig 1).

Discussion

This study revealed that clonidine exerts marked systolic unloading of the heart by a reduction in LV afterload. Furthermore, the sympathetic drive to the heart is considerably diminished, whereas the intrinsic myocardial contractility remains unchanged.

With an increase in systolic wall stress parallel with an increase in heart size or end-diastolic volume a decrease in LV ejection fraction occurs. Patients with the largest wall stress, as in those with hemodynamically decompensated essential hypertension, had the lowest ejection fraction. A similar relationship was also found for chronic hypertrophic heart disease with aortic stenosis and aortic incompetence. This relationship is also valid for an acute increase in wall stress by an acute pressure load imposed on the left ventricle at nearly constant LV dimensions. The relationship between wall stress and ejection fraction is modified by the contractile state of the myocardium. Parallel with an increase in contractility (eg, by infusion of norepinephrine), an increase in LV function at comparable wall stress occurs. Corresponding negatively inotropic interventions (eg, by propranolol) depress LV function at the same instantaneous wall stress (Fig 2).

Clonidine caused a dose-dependent fall in systolic wall stress. Despite this striking decrease in wall stress, LV ejection fraction did not increase as expected, but remained unchanged (Table 1). It may be assumed that the lack of increase in ejection fraction in the event of lowered wall stress is caused by a downward shift of the wall stress-function regression line (Fig 2). This downward shift may have at least three causes: (1) decrease in end-diastolic muscle fiber length; (2) depression of myocardial contractility; and (3) decrease in central sympathetic tone (possibly also increase in vagal tone).

Only at the lowest dose, 10 μg/kg, were preload indexes such as end-diastolic volume, end-diastolic pressure, and diastolic wall stress reduced, indicating a decrease in end-diastolic fiber length. This may be related to a systemic venodilatation due to a centrally reduced sympathetic outflow to the capacitance vessels. However, at higher doses these effects were no longer observed, probably due to an arising α-adrenergic venoconstrictor action of clonidine. Even in very high doses of 10^{-4} M/L clonidine did not depress isometric and isotonic papillary muscle mechanics as studied in the isolated LV papillary muscle (Fig 1). From these in vitro experimental data it is reasonable to assume that clonidine produces no direct effects on the contractile behavior of the myocardium. Thus, the downward shift of the stress-function curve, at least at higher doses without any change in preload indexes, is most probably caused by a decrease in sympathetic drive to the heart and a possible increase in vagal tone.

A further indication of reduced cardiac sympathetic activity is the dose-dependent slowdown of the heart rate.

From the relationship between wall stress and LV ejection fraction, it is possible to discriminate between changes in ventricular loading conditions and myocardial contractility. By a systolic-only unloading—ie, reduction in LV afterload—ejection fraction would increase according to the relationship between stress and function (Fig 2). A decrease only in myocardial contractility by a negative inotropic intervention or a decrease in cardiac sympathetic drive, respectively, would reduce ejection fraction at a comparable systolic wall stress, causing a downward shift of the stress-function relationship. Regarding clonidine, the expected increase in LV ejection fraction by LV afterload reduction is prevented by the simultaneously occurring downward shift of the stress-function curve. Thus, the effect of clonidine on the stress-function relationship is represented as the result of both systolic unloading of the left ventricle and the decrease in myocardial contractility, based on the reduced sympathetic drive to the heart.

Due to the marked afterload reduction by clonidine, an equivalent decrease in myocardial energy demand has to be expected. This may be beneficial, especially in hypertensive heart disease with cardiac failure—ie, in dilated left ventricles with an increased wall stress. Clonidine at very low doses may reduce the sympathetic drive to the vascular periphery rather than to the heart. Thus, it might be expected that clonidine raises both ejection fraction and cardiac output in patients with ventricular dysfunction.

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