Use of Catheter-tip Velocity–Pressure Transducer to Evaluate Left Ventricular Function in Man: Effects of Intravenous Propranolol

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SUMMARY A catheter-tip velocity transducer with two high-fidelity pressure manometers was used to evaluate the left ventricular (LV) hemodynamic effects of intravenous propranolol (10 mg). Nine patients without clinical evidence of heart failure were studied. Pulsatile ascending aortic blood flow velocity and pressure and LV pressure were measured continuously during drug administration. Beat-to-beat changes in stroke volume index, stroke work index, LV end-diastolic pressure, maximum blood flow velocity and acceleration, and maximum LV dP/dt were determined. Propranolol produced a decrease in maximum blood flow velocity (from 58 ± 4.7 to 42 ± 5.1 cm/sec, p < 0.002), and acceleration (from 1181 ± 130 to 847 ± 117 cm/sec², p < 0.002), max dP/dt (from 1361 ± 70 to 1146 ± 63 mm Hg/sec, p < 0.002), stroke volume index (from 47 ± 3.0 to 38 ± 3.2 ml/m², p < 0.002) and total stroke work index (from 702 ± 33 to 603 ± 44 ml/sec, p < 0.04), with little change in mean aortic pressure, peak systolic pressure and LV end-diastolic pressure. Depression in myocardial function was detectable within 1 minute after initiation of propranolol and persisted when negative chronotrophic effects were eliminated by atrial pacing. The multisensor catheter technique allows rapid and safe detection of changes in cardiovascular function during propranolol administration in conscious man.

THERAPEUTICALLY, the most important actions of \( \beta \)-adrenergic blocking agents in general and propranolol in particular are their effects on cardiovascular performance. Effects of propranolol on left ventricular (LV) function represent a complex interaction between myocardial contractile state, end-diastolic fiber length and vascular loading. In addition, due to varying levels of sympathetic stimulation, individual responses may be widely variable. While certain aspects of the functional effects of propranolol have been studied in detail in patients with and without coronary artery disease,1–11 some areas have not been fully evaluated.

One such area is analysis of LV functional effects of \( \beta \)-blockade in terms of pulsatile ascending aortic blood flow and pressure and their relations. The basis for this approach to the analysis of LV function has been recently presented in detail by us and others.12–17 Briefly stated, because the ventricle is acting as a pulsatile generator of blood pressure and flow waves, a more complete understanding of its overall function and interaction with the systemic vascular system can be obtained from an analysis of continuous measurements of pulsatile blood flow and pressure.18–20 A necessary prerequisite to the study of more complex functions, such as blood flow velocity, acceleration, input impedance and total LV external work, is determination of pulsatile blood flow and pressure in the ascending aorta. Most pulsatile hemodynamic studies have been performed in dogs with implanted perivascular electromagnetic velocity probes.21 However, recent advances in the design of catheter-mounted miniature blood flow velocity sensors provide a technique to make measurements of pulsatile aortic blood flow feasible in conscious man.12–17, 21–22 Application of this technique to quantitate effects of various interventions on pulsatile ascending aortic blood flow and pressure was recently described.15–17, 23, 33

In this presentation we describe the effects of propranolol on pulsatile aortic root hemodynamics and related indexes using a catheter-mounted velocity sensor with two high-fidelity pressure manometers. These studies were done in awake, unsedated patients and effects of propranolol on cardiovascular function, independent of heart rate effects, were assessed using atrial pacing.

Methods

Patients

The study group included nine patients who underwent diagnostic cardiac catheterization for further evaluation of chest pain. Informed consent was obtained from each patient. All patients were men who ranged in age from 44–66 years (mean age 57 years). At the time of study no patient had valvular heart disease, recent myocardial infarction, current treatment with \( \beta \)-blocking drugs, or clinical evidence for heart failure. Table 1 presents the pertinent clinical data for this study group.

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Catheterization Procedures and Measurements

Right- and left-heart catheterization were performed from the right arm without premedication. A bipolar pacing catheter was used for right-heart catheterization and then positioned in the coronary sinus to provide a stable site for atrial pacing. Instantaneous ascending aortic blood flow velocity was measured with a #8 French multisensor catheter (Millar model VPC-684D) introduced via a brachial arteriotomy. In addition to the electromagnetic velocity sensor located 5 cm from the tip, the catheter also contains two sensors to measure high-fidelity aortic and LV pressures.13, 15, 16, 27-30 The pressure sensor at the catheter tip was positioned in the left ventricle so that the velocity sensor was located near the upper border of the sinuses of Valsalva (fig. 1). This arrangement tends to stabilize the probe in the central axis of the ascending aorta.21, 25 The velocity sensor was energized with a sine-wave electromagnetic flowmeter (Biotronex, model BL-613) and the signal amplified (Electronics for Medicine). The flowmeter was operated at a nominal frequency setting (50 Hz) that gives a constant amplitude response ± 5% from 0-23 Hz and a linear phase shift with frequency. This frequency response is adequate for obtaining accurate measurements of maximum blood flow velocity and acceleration30 (personal observation).

Calibration of electromagnetic catheter-tip velocity probes to measure pulsatile blood flow and their use in man have been described in detail previously.12-16, 22-29, 30-33 Briefly, because the velocity profile of blood flow in the ascending aorta is relatively flat,24-31 the product of measured velocity and vessel cross-sectional area is volume of blood flow per unit time.21 Therefore, if the vessel cross-sectional area is assumed constant, the velocity signal is equivalent to a volume-flow signal. Calibration of the pulsatile velocity signal was performed at the beginning of each study by equating the electronically integrated mean value of the signal to a simultaneous cardiac output determination using the indicator-dilution method.

**TABLE 1. Clinical Features and Baseline Hemodynamic Data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Presenting symptom</th>
<th>CI (l/min/m²)</th>
<th>LVEDP (mm Hg)</th>
<th>LVEF (%)</th>
<th>Coronary angiography</th>
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<td>WM</td>
<td>23</td>
<td>Dyspnea</td>
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<td>Normal</td>
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<td>HM</td>
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<td>Chest pain</td>
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<td>DJ</td>
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<td>51</td>
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<td>3-vessel CAD</td>
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</tbody>
</table>

Abbreviations: CI = cardiac index; LVEDP = left ventricular end-diastolic index; LVEF = left ventricular ejection fraction; CAD = coronary artery disease (vessel with ≥ 70% occlusion).

**Figure 1. Catheter containing pressure and velocity sensors positioned across the aortic valve, permitting simultaneous recording of aortic pressure, ventricular pressure and aortic root blood flow velocity.**
Zero blood flow was taken as the flat portion of the curve during late diastole and beat-to-beat stroke volume was obtained with a digital planimeter (Nunomics Model 254). Cardiac output (mean blood flow) was determined by multiplying average stroke volume by heart rate.

The velocity sensor was calibrated (cm/sec) in a hydraulic model using physiologic saline. Peak blood flow velocity was obtained from the maximum value of the measured flow curve using the velocity calibration. Blood flow acceleration (the rate of change of blood flow velocity) was calibrated as follows: 1) the maximum slope of the initial upstroke of the blood flow velocity curve was measured directly from a fast (200 mm/sec) polygraph (Electronics for Medicine) tracing of the flowmeter signal and 2) a continuous record of acceleration was obtained by electrical differentiation of the phasic velocity signal. The dynamic frequency response of the differentiator was flat (± 5%) from 0–43 Hz. The differentiated velocity signal (acceleration) was calibrated by correlating the peak differential with the graphically determined slope of the velocity signal.

High-fidelity ascending aortic and LV pressures were obtained from the solid-state pressure manometers. Resonant frequencies of these gauges are generally greater than 30–35 kHz. This frequency response is well in excess of that required to obtain dynamic LV pressure and its derivative (dP/dt). The rate of change of LV pressure (dP/dt) was obtained by electrical differentiation of the ventricular pressure signal. The dynamic frequency response of the differentiator was constant (± 5%) from 0–43 Hz. Continuous recording of dP/dt was calibrated in the same manner as blood flow acceleration.

Pressure and velocity signals were recorded on analog magnetic tape (Hewlett-Packard, model 3960) and later digitized at a sampling interval of 10 msec by an analog-to-digital converter (Biomation 1015). Data analysis was carried out on a programmable calculator (Hewlett-Packard Model 9820A), which converted pressure and velocity data to Fourier series, applied corrections for measured dynamic responses of the transducers, and computed total external LV hydraulic power as a function of frequency. Total external stroke work (steady flow work and pulsatile flow work) was obtained by dividing hydraulic power by heart frequency. Indexes of stroke volume, cardiac output and stroke work were obtained by dividing by body surface area.

After resting hemodynamic measurements were taken, propranolol was administered i.v. at 1.0 mg/min until 0.15 mg/kg (or a maximum 10 mg) had been given. The ECG, pressure and velocity signals were recorded continuously during administration of propranolol and for 15 minutes after the final i.v. dose of propranolol. When this 15-minute observation period was completed, if the patient's heart rate had decreased, atrial pacing was used to return heart rate to the control value. At least five consecutive beats were analyzed: 1) during the control period, 2) 15 minutes after the final injection of propranolol and 3) after heart rate was returned to control by atrial pacing. Angiographic evaluation of the left ventricle and coronary arteries was performed in all patients after hemodynamic and pharmacologic study. The mean ± SEM was calculated. The significance of comparisons between control data and propranolol response were examined using t test for paired data.

Results

The influence of i.v. propranolol on pertinent hemodynamic data is summarized for all patients in figures 2 and 3 and table 2.

Effects of Propranolol on Heart Rate, Mean Aortic Pressure and LV End-diastolic Pressure

Continuous recordings of the analog signals (ascending aortic blood and pressure and LV pressure) permitted detailed analysis of the progressive effects of propranolol on the cardiovascular system. An example of instantaneous flow and pressure signals recorded from a representative patient is shown in figure 4. By the end of the observation period, heart rate had decreased from 71 ± 1.9 to 67 ± 1.9 beats/min (p < 0.001). LV end-diastolic pressure increased slightly (from 12 ± 1.2 to 14 ± 1.0 mm Hg; p = NS) and mean aortic pressure decreased slightly (from 104 ± 3.4 to 102 ± 3.1 mm Hg; p = NS) with propranolol. The changes in pressure were not statistically significant either at the end of the 15-minute observation period or after heart rate returned to control. Data from each patient during control and after propranolol plus pacing to control are shown in figure 2.

Effects of Propranolol on LV Ejection Indexes

Propranolol administration produced a 19% decline in stroke index (from 47 ± 3.0 to 38 ± 3.4 ml/m2; p < 0.002), a 24% decrease in cardiac index (from 3.3 ± 0.2 to 2.5 ± 0.2 1/min/m2; p < 0.001) and a 16% reduction in total LV external work (from 702 ± 33 to 590 ± 43 mJ/m2; p < 0.03). No further change was observed in stroke index or stroke work index when heart rate was paced to control. However, cardiac index increased from 2.5 ± 0.2 to 2.7 ± 0.2 1/min/m2 (p < 0.05), but was still significantly (p < 0.002) depressed. Measurements of stroke index and stroke work index for all patients during the control period and after propranolol plus pacing are shown in figure 2.

Effects of Propranolol on Myocardial Contractile State

All three indexes of contractile state, maximum ascending aortic blood flow velocity and acceleration (ejection phase indexes) and maximum LV dP/dt (isovolumic phase index) declined with propranolol administration. Average max dP/dt decreased 17% (from 1361 ± 70 to 1123 ± 61 mm Hg/sec; p < 0.002) during propranolol, and average maximum velocity and acceleration decreased 26% (from 58 ± 4.7 to 43 ± 5.5 cm/sec, p < 0.002) and 23%
Figure 2. Individual data points for nine patients plotting control measurements on horizontal axis against postpropranolol values after pacing correction of heart rate. The points for each patient remain below the line of identity, showing postpropranolol depression of stroke volume and stroke work indexes with no significant change in mean aortic pressure or left ventricular (LV) end-diastolic pressure.

Figure 3. Individual data points for nine patients. Control values are plotted on the horizontal axis and postpropranolol plus pacing to control on the vertical axis. Propranolol administration resulted in a significant reduction in all three indexes of myocardial contractility (maximum ascending aortic blood flow velocity and acceleration and maximum left ventricular [LV] dP/dt) with no significant change in maximum LV systolic pressure.
Table 2. Hemodynamic Effects of Propranolol

<table>
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<tr>
<th>Patient</th>
<th>HR (beats/min)</th>
<th>BSA (m²)</th>
<th>SI (ml/m²)</th>
<th>CI (l/min/m²)</th>
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(P vs C) p < 0.001  0.002  0.001  NS
% change -6.0  -19  -24  NS

Abbreviations: HR = heart rate; BSA = body surface area; SI = stroke index; CI = cardiac index; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; AP = aortic pressure; MA = maximum ascending aortic blood flow acceleration; PV = peak blood flow velocity; Max dP/dt = maximum rate of rise of left ventricular pressure; SWI = stroke work index; C = control; P = propranolol; PP = propranolol/pacer.

(from 1181 ± 130 to 908 ± 131 cm/sec²; p < 0.002), respectively, while LV systolic pressure was unchanged. When heart rate was paced to control, maximum velocity and acceleration decreased slightly while max dP/dt increased slightly (NS). Figure 3 shows individual data points for these variables during control and after propranolol plus pacing.

Discussion

Cardiovascular effects of propranolol in normal subjects and patients with LV disease have been reported. Propranolol administration usually caused significant reductions in cardiac index, LV external work and heart rate. We found that intravenous propranolol resulted in significant reductions in heart rate, stroke index, cardiac index and stroke work index, while aortic and LV end-diastolic pressure remained essentially unchanged. Ejection phase indexes of myocardial contractile state (maximum blood flow velocity and acceleration) and an isovolumic phase index (maximum LV dP/dt) were also significantly depressed with propranolol. The decrease in these indexes persisted even when chronotropic effects of the drug were overridden by atrial pacing. To our knowledge, these measurements, obtained from continuous recordings of ascending aortic blood flow velocity and high-fidelity aortic and LV pressure, represent the first reported in awake man during propranolol administration.
Certain limitations of these techniques require comment. When obtaining blood flow per unit time with an intravascular velocity transducer, certain assumptions are made regarding the cross-sectional area of the vessel. In this study aortic internal diameter was assumed to be constant during the cardiac cycle. In previous studies in man, changes in ascending aortic external diameter during ejection were estimated with an electrical strain gauge caliper. The change in aortic cross-sectional area during ejection was ± 5.5% of the mean value. This external cross-sectional area change was greater than previously reported internal area estimates made using angiographic techniques. We found that internal aortic diameter changes are less inside the pericardial reflection, where angiographic measurements are usually made, compared with outside, where caliper measurements are made. Therefore, the effect of cross-sectional area change on calculations of volume flow from blood flow velocity is probably minimal when velocity is measured near the upper border of the sinuses of Valsalva. Another assumption made was that the velocity profile of blood flow in the ascending aorta is flat. Previous measurements of blood flow velocity across the cross section of the ascending aorta of both dog and man show that the velocity profile is almost flat. This is because the inlet length of the vessel is short compared with its diameter and the nonflat velocity profile was not yet developed. The configuration of the profile may be influenced to some extent by the geometry of the aortic valves and ascending aorta. Motion artifact present in earlier studies using velocity catheters was minimized in this study by stabilizing the velocity sensor in the central aorta. This was accomplished by placing an extension at the end of the catheter. When the extension is through the aor-
otic valve in the ventricle, lateral motion is markedly reduced. We found excellent correlation \((r = 0.93)\) between cardiac output obtained with the electromagnetic velocity catheter and determinations by dye dilution. Although some error is introduced extrapolating catheter-measured blood velocity to volume flow rate, the error appears to be relatively small.

The ejection phase indexes derived from measurements obtained with the multisensor catheter and used to assess myocardial contractile state also require comment. Use of velocity and acceleration of ascending aortic blood flow to assess LV function was first suggested by Rushmer. Noble et al. showed in conscious dogs that coronary occlusion caused a decrease in maximum acceleration, although cardiac output and arterial pressure remained essentially unchanged. Furthermore, changes in posture, with the presumed associated changes in end-diastolic dimensions or preload, did not alter maximum acceleration. Similar observations were made in conscious dogs by Kezdi et al. during gradual coronary occlusion to induce myocardial infarction. Other investigators have used maximum acceleration to study the depressant effects of anesthetic agents on myocardial performance. In a recent study we showed that maximum blood flow velocity and acceleration were significantly reduced in conscious dogs with depressed myocardial performance due to phosphorus deficiency. Indexes derived from pulsatile aortic blood flow velocity signals have also been used to assess LV function in patients with coronary artery disease.

Considerable evidence also indicates that in both conscious dogs and man the isovolumic phase index, maximum LV dP/dt, is a reliable index of the inotropic state of the myocardium. These studies showed an increase in max dP/dt with administration of positive inotropic agents and a decrease with cardiac depressant interventions. This index, which is the most easily measurable index of the speed of isovolumic contraction, appears to be useful in a subject in the assessment of acute changes in inotropic state because the magnitude of its response to abrupt changes in preload is small and to afterload insignificant. In a recent study of problems associated with the use of indexes of myocardial contractility, Van Den Bos et al. found in conscious dogs that both maximum blood flow acceleration and max dP/dt were less influenced than other contractile indexes by changes in preload and afterload.

A particular advantage of the multisensor catheter is that instantaneous high-fidelity ventricular and arterial pressures and blood flow velocity signals are provided continuously throughout each cardiac cycle. From these signals directional beat-to-beat changes in cardiovascular function may be quantitated during acute introduction of certain interventions. Since changes in aortic diameter are relatively small, stroke volume is essentially proportional to the area beneath each velocity pulse. Thus, relative changes in stroke volume can be derived rapidly in any patient without complicated calibration procedures. If absolute values for mean flow and stroke volume are desired, they may be obtained by in vivo calibration of the mean velocity signal using cardiac output determined independently by another method, as in this study. In vitro calibration of the velocity signal, in cm/sec, makes measurements of peak blood flow velocity, acceleration and LV and aortic pressure possible. These variables have been used previously in the assessment of LV function in man. Simultaneous measurements of pulsatile pressure and flow in the ascending aorta can be used to determine total external LV work.

Prior studies undertaken to assess the effects of propranolol upon myocardial function have produced various results. Patient differences in the degree of LV dysfunction have undoubtedly contributed to the conflicting results. Angiographic studies are complicated by problems of separating effects directly related to the drug from effects of contrast material upon myocardial function, and are also limited by the number and frequency of LV angiograms possible. Earlier hemodynamic studies have focused on measurements of heart rate and stroke volume without demonstrating consistent change.

In this study we have examined nine normotensive patients whose LV function appears comparable (ejec-
tension fractions ≥ 50% and cardiac index ≥ 2.51/min/m²). All hemodynamic measurements were made without sedation and before angiography. We also avoided problems of negative chronotropic effect by using atrial pacing to control heart rate after propranolol.

There is general agreement that acute administration of propranolol in doses comparable to those used in this study reduces heart rate, cardiac index and stroke work index, while LV end-diastolic and arterial pressures remain essentially unchanged. Peripheral resistance, therefore, increases.⁴ The magnitude of change in these hemodynamic indexes probably relates to the level of sympathetic activity present and the extent of LV dysfunction. These considerations may account for some of the variance reported relative to the hemodynamic effects of propranolol. This is particularly apparent considering the effect of propranolol on cardiac output at rest. Reduction in cardiac output is principally rate-dependent, although other factors play a part, as the decline in cardiac index after propranolol persisted when heart rate effects were controlled.⁴ In the present study when heart rate was controlled by atrial pacing after propranolol cardiac index increased from 2.5 ± 0.2 to 2.7 ± 0.2 l/min/m² (p < 0.05). The latter value was reduced (p < 0.002) compared with that before propranolol. This rate-independent reduction in cardiac index may in part be related to the loading effects attributable to the increase in peripheral resistance occurring after propranolol. These results are indicative of myocardial depression, in addition to the decrease in myocardial contractility reflected by decreases in maximum aortic blood flow velocity, acceleration and maximum LV dP/dt.⁵,⁶,⁷ To our knowledge, this is the first study to investigate the effects of propranolol administration on phasic aortic root blood flow velocity and acceleration. The decrease in these ejection phase indexes of myocardial contractility (maximum velocity and acceleration) with propranolol are similar to the decline in the more conventionally measured isovolumic phase index maximum LV dP/dt.

We stress the following observations: Intravenous administration of propranolol produced significant depression in myocardial performance independent of heart rate, aortic pressure and LV end-diastolic pressure. Myocardial depression was reflected by a reduction in beat-to-beat stroke index, stroke work index, maximum blood flow velocity and acceleration, and maximum LV dP/dt. These data were obtained from instantaneous and continuous signals recorded with a single, multisensor cardiac catheter. The results of this study suggest that this technique provides a rapid and safe method for assessment of a variety of interventions upon cardiovascular function in intact, awake man.

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