Dobutamine and Hydralazine: Comparative Influences of Positive Inotropy and Vasodilation on Coronary Blood Flow and Myocardial Energetics in Nonischemic Congestive Heart Failure

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Columbus, Ohio

Coronary blood flow and myocardial energetics were assessed after the administration of a parenteral inotrope (dobutamine hydrochloride) and an oral vasodilator agent (hydralazine) in 10 patients with nonischemic congestive heart failure. Dobutamine (5 μg/kg per min) and hydralazine (1 mg/kg) when group-matched elicited an identical increase in cardiac index and stroke volume index. Both agents augmented coronary blood flow while reducing coronary vascular resistance. Both forms of therapy elicited a significant increase in myocardial oxygen consumption. Dobutamine, demonstrating a balanced effect on the coronary circulation, induced a proportional increase in coronary blood flow and myocardial oxygen consumption, with the arterial-venous oxygen difference across the coronary vascular bed remaining unchanged. Hydralazine enhanced the myocardial oxygen supply versus demand ratio; despite a significant increase in myocardial oxygen consumption, the arterial-venous oxygen difference and the myocardial extraction ratio diminished. Both forms of therapy enhanced cardiac performance without inducing any electrocardiographic or clinical evidence of ischemia.

Dobutamine, a positive inotropic agent, elicited a balanced effect on the coronary circulation while hydralazine, a vasodilator agent, induced a greater increase in coronary flow than in myocardial oxygen demand.

Dobutamine and hydralazine are two frequently utilized agents in the treatment of congestive heart failure. Dobutamine, a synthetic catecholamine with β₁-adrenergic receptor agonist activity, is a potent myocardial inotropic agent (1–3). Hydralazine induces arteriolar relaxation with peripheral circulatory vasodilation and reduction in systemic vascular resistance and ventricular filling pressure (4–6). In the setting of congestive heart failure, both drugs have well documented salutary central hemodynamic effects with augmentation of cardiac output and reduction in ventricular filling pressure (7–12).

Nonischemic congestive cardiomyopathy is associated with diminished coronary blood flow per unit myocardial muscle mass and evidence of relative hypoperfusion of left ventricular subendocardium (13–16). Any agent that potentially augments myocardial oxygen consumption (inotrope) or diminishes the coronary perfusion pressure (vasodilator) may unfavorably alter the tenuous balance between oxygen demand and supply and induce myocardial ischemia. These deleterious effects might theoretically be mitigated by concomitant vasodilator- or inotrope-induced reduction in left ventricular wall stress secondary to decreased chamber size or increased coronary blood flow. This study was therefore designed to assess the effects of dobutamine and hydralazine on the coronary circulation and myocardial energetics in patients with chronic nonischemic congestive heart failure.

Methods

Study patients. Ten patients with congestive heart failure (New York Heart Association functional classes III and IV) were evaluated. Five women and five men with a mean age of 48 years (range 25 to 58) underwent cardiac catheterization and coronary angiography that documented nonischemic congestive cardiomyopathy. The left ventricular ejection fraction was less than 30% in all patients while eight demonstrated a left ventricular filling pressure greater than 20 mm Hg. The group had been maintained on conventional cardiac medications including digitalis, diuretics,
Table 1. Effects of Dobutamine and Hydralazine on Central Hemodynamic Measurements

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*p < 0.05, †p < 0.01, ‡p < 0.001 (versus control)

AP = mean systemic blood pressure, C = control, CI = cardiac index, D5 = dobutamine 5µg, D10 = dobutamine 10 µg, H = hydralazine, HR = heart rate, LVSWI

Table 2. Effects of Dobutamine and Hydralazine on Coronary Blood Flow and Myocardial Energetics

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*p < 0.05, †p < 0.01, ‡p < 0.001 (versus control)

(A – CS) O₂ = arterial-coronary sinus oxygen difference, AP – PCW = mean systemic blood pressure minus pulmonary wedge difference, C = control, CSF = arterial-coronary sinus oxygen difference, AP – PCW = mean systemic blood pressure minus pulmonary wedge difference, C = control.

and nitrites. Forty-eight hours before the onset of study, diuretics and nitrates were discontinued. Exclusion criteria included primary valvular heart disease, active myocarditis, uremia, primary hepatic dysfunction, anemia and pregnancy.

Protocol and procedures. Written informed consent was obtained from each patient. Before the control period, a thin-walled, arterial cannula was placed in the radial artery for continuous monitoring of systemic arterial pressure and to provide a port for arterial blood samples. A balloon-tipped triple-lumen thermodilution catheter was placed in the pulmonary artery for monitoring central hemodynamic variables. The coronary sinus was cannulated under fluoroscopic control utilizing a dual thermistor coronary sinus catheter. Catheter position and stability during the study period were confirmed by contrast angiography and temperature assessment according to the techniques described by Ganz et al. (17).

In the supine resting state, central hemodynamic variables included pulmonary artery, pulmonary capillary wedge and systemic arterial pressure utilizing techniques previously reported by this laboratory (6). Cardiac output (thermodilution technique [18]) was measured in triplicate with less than 10% variation using an Instrumentation Laboratories 601 computer and 602 recorder. Coronary sinus blood flow measurements (thermodilution technique [17]) were performed with a 7 French model CCS-7U-90B dual thermistor coronary sinus catheter interfaced with a Wilton Webster CBA-210 two-channel Wheatstone bridge with self-contained
solid state preamplifiers (17,19). A multichannel Electronics for Medicine recorder transcribed simultaneous thermistor signals. Oxygen content was measured by the electrochemical technique (Lex-O2-Con, Lexington Instruments). A calibrated infusion pump (Harvard Apparatus) was utilized to provide intravenous dobutamine hydrochloride delivery. Coronary flow measurements and central hemodynamic variables were monitored during a 4 hour control period to ensure the stability of baseline data. Any patient displaying a coefficient of variation greater than 10% during the control period was excluded from the study.

After the control period, intravenous dobutamine hydrochloride infusion was instituted at 5 μg/kg per min (stage I), 10 μg/kg per min (stage II), a reequilibration control period (stage III) and then oral hydralazine, 1 mg/kg (stage IV). Measurements during stages I and II were made after a 15 minute equilibration period, stage III at a return to baseline levels and stage IV readings determined every 60 minutes over the ensuing 4 hours after oral hydralazine.

Central hemodynamic calculations (20) included cardiac index, stroke volume index, systemic vascular resistance and left ventricular stroke work index. Coronary hemodynamic and myocardial metabolic calculations included coronary sinus flow, coronary vascular resistance and myocardial oxygen consumption, using formulas previously reported by our laboratory (21).

Statistical analysis. Mean values and standard deviation were determined during control periods, dobutamine infusion (5 and 10 μg/kg per min) and hydralazine therapy (1 mg/kg). Control values

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Mean 27 34* 34* 37† 1747 1271† 1213† 1090† 24 30* 28† 34†
SD ±8.5 ±9.8 ±10.1 ±8.2 ±288 ±398 ±367 ±474 ±11.7 ±10.1 ±10.7 ±11.7
p(D5 vs H) NS NS NS

(A - CS) O₂ (ml/liter) O₂ (mJ/mm) MVO₂ (ml/min)

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Mean 104 104 94* 100 71 71 64* 69 15 18* 20† 21†
SD ±19.6 ±22.4 ±23.7 ±18.6 ±1.9 ±9.2 ±9.5 ±8.8 ±5.1 ±6.6 ±8.5 ±6.0
p(D5 vs H) 0.05 0.05 NS

coronary sinus blood flow; CSF/CO x 100 = percent coronary circulation; CVR = coronary vascular resistance. D5 = dobutamine 5μg; D10 = dobutamine 10μg, H = hydralazine, MVO₂ = myocardial oxygen consumption. NS = not significant, O₂ (% extraction) = myocardial extraction ratio. p = probability, SD = standard deviation.
represent the mean of the determinations made during the predrug control period and repeated during the second equilibration control period. Hydralazine values represent the average of the 2 and 3 hour responses. The Student’s t test for paired and unpaired analysis was used to compare data when appropriate. A probability value of p < 0.05 was established to indicate significant change.

Results

Effects on hemodynamics. The central hemodynamic profile of this group is presented in Table 1. Before drug treatment, baseline cardiac index was depressed (2.3 ± 0.3 liters/min per m²), pulmonary capillary wedge pressure elevated (23 ± 6.9 mm Hg) and systemic vascular resistance increased (1747 ± 288 dynes·s·cm⁻²); all findings were commensurate with the diagnosis of moderate congestive cardiac failure. With low dose dobutamine infusion (5 µg/kg per min), heart rate and mean arterial pressure did not significantly change; however, systemic vascular resistance and pulmonary capillary wedge pressure decreased with a concomitant increase in cardiac index, stroke volume index and left ventricular stroke work index. Hydralazine (1 mg/kg) induced no appreciable change in heart rate but did diminish mean arterial pressure and systemic vascular resistance with reciprocal augmentation of cardiac index, stroke volume index and left ventricular stroke work index. Increases in cardiac index and stroke volume index were identically group-matched with low dose dobutamine and hydralazine. In this population, high dose dobutamine (10 µg/kg per min) elicited a significant increase in heart rate when compared with control, low dose dobutamine and hydralazine. The increase in cardiac index significantly exceeded that noted with low dose dobutamine and hydralazine; however, because of heart rate changes, there was no significant difference in stroke volume index when comparing the three modes of treatment. Dobutamine (10 µg/kg per min) markedly diminished systemic vascular resistance while left ventricular stroke work index was increased over both control and hydralazine therapy.

Effects of intravenous dobutamine and oral hydralazine on coronary blood flow and myocardial energetics (Table 2). Dobutamine in both dose ranges had no effect on the mean systemic blood pressure-pulmonary wedge pressure difference (a formulated estimate of coronary perfusion pressure), whereas hydralazine diminished the coronary vascular pressure gradient. At matched doses, both agents decreased coronary vascular resistance and augmented coronary blood flow, similar to the changes noted in the systemic vascular bed (Fig. 1A and B). Before drug treatment, 3.5% of cardiac output was distributed to the coronary circulation. After dobutamine (5 µg/kg per min) infusion, the relative flow distribution remained unaltered; however with hydralazine therapy, 4.3% of total cardiac output was directed into the coronary vascular circulation (Fig. 2A). The ratio of percent change of coronary flow to cardiac output remained constant with dobutamine (5 µg/kg per min) but increased significantly with hydralazine (Fig. 2B). Both agents elicited a significant increase in myocardial oxygen consumption (Fig. 3). Concomitant with the elevation of myocardial oxygen consumption, the arterial-venous oxygen difference and the percent myocardial ox-
Discussion

In the setting of congestive heart failure, the known salutary central hemodynamic effects of both dobutamine and hydralazine are well documented. However, the relative effects of these agents on coronary blood flow and myocardial energetics remain dependent on their ability to maintain an appropriate balance between myocardial oxygen demand and supply (21-25). Studies in both animal models and patients strongly suggest that cardiac hypertrophy adversely affects the coronary circulation with enhanced vulnerability of subendocardial muscle to ischemia and necrosis (14-16, 26, 27). Our patients with nonischemic cardiomyopathy demonstrated diminished coronary blood flow per unit mass of myocardium (40 ± 12 mill 00 left ventricle-min). Previous studies with the inotropic agents digoxin and amrinone have demonstrated diminution of myocardial oxygen consumption with concomitant augmentation of cardiac output in patients with significant heart failure (28, 29). Other investigators have speculated on the potential ability of vasodilator therapy to improve cardiac performance at a lower level of oxygen consumption than required by inotropic therapy (30-32). Dobutamine (5 μg/kg per min) and hydralazine (1 mg/kg) therefore were matched to induce an equal increase in cardiac index (35%) with a concomitant 51% augmentation of coronary blood flow.

Figure 2. Mean ratio of coronary versus systemic blood flow at baseline and after administration of dobutamine (5 μg/kg per min) and hydralazine (1 mg/kg). Panel A. The percent cardiac output (CO) directed to the coronary circulation (CSF) following drug therapy. Panel B. Dobutamine initiated a balanced effect on the coronary circulation while hydralazine augmented the relative flow to the coronary vascular bed. Abbreviations as before.

Figure 3. Mean indexes of myocardial energetics. Myocardial oxygen consumption (MVO2) increased with both agents. With dobutamine (5 μg/kg per min), the arteriovenous coronary sinus oxygen (Δ[AC- CSO2]) difference and percent oxygen extraction remained unaltered while hydralazine diminished these variables despite an overall increase in myocardial oxygen consumption. Abbreviations as before.
the relative effect on myocardial oxygen consumption and coronary supply.

Effects on myocardial oxygen demand and coronary blood flow. Heart rate, myocardial wall stress and contractility constitute the three major determinants of myocardial oxygen demand (33-35). Heart rate remained statistically unchanged with both agents. Myocardial wall stress was not directly assessed; however, the modest reduction in both left ventricular filling pressure and mean systemic pressure is consistent with an actual decrease in wall stress. Contractility, the third major myocardial oxygen consumption determinant, has been clearly shown to increase with dobutamine infusion in both normal hearts and heart failure models (1,3). The inotropic state of the ventricle was not directly measured in this study; however, the noted increase in stroke volume index at a diminished filling pressure would suggest that dobutamine did in fact augment myocardial contractility. Recent studies by our group have also demonstrated positive inotropic properties with hydralazine (36) and prominent coronary vascular effects (21) which may, in turn, account for the comparable increase in myocardial oxygen consumption noted with both the inotropic (dobutamine) and vasodilator (hydralazine) agents.

Coronary blood flow was greatly enhanced, and coronary vascular resistance significantly diminished with both agents. Hydralazine, however, demonstrated a more pronounced effect on the coronary vascular bed than on the systemic circulation while dobutamine initiated a more balanced circulatory response. Coronary perfusion pressure remained unaltered with dobutamine but decreased with hydralazine administration. The marked attenuation of coronary vascular resistance with hydralazine adequately compensated for the reduction in perfusion pressure and resulted in a significantly increased myocardial blood supply. Before pharmacologic manipulation, 3.5% of cardiac output was directed to the coronary vascular bed. The distribution of coronary blood flow remained unchanged with dobutamine, but after hydralazine, the balance shifted toward the myocardium with coronary flow then accounting for 4.3% of total cardiac output.

Balance between increased myocardial oxygen demand and augmented coronary blood flow. In this group of patients with moderately severe congestive heart failure, both inotropic and vasodilator intervention, group-matched to elicit a similar increase in cardiac performance, augmented myocardial oxygen demand. After dobutamine (5 \( \mu \)g/kg per min), the increased myocardial oxygen consumption was balanced by augmented coronary flow with the arteriovenous oxygen difference and myocardial oxygen extraction ratio remaining unaltered. High dose dobutamine resulted in further enhancement of central and coronary circulatory hemodynamic variables (increased cardiac output and coronary blood flow, decreased systemic and coronary vascular resistance) while myocardial oxygen consumption increased modestly and the arteriovenous difference across the coronary vascular bed remained unchanged. With hydralazine administration, the arteriovenous oxygen difference and myocardial extraction ratio actually decreased, suggesting that the enhanced coronary flow (increased proportion of total cardiac output) more than compensated for the increase in myocardial oxygen consumption.

Regional myocardial perfusion was not measured in this study and, therefore, one cannot exclude the possibility of relative subendocardial hypoperfusion or arteriovenous microcirculatory shunting in this group of patients with increased left ventricular muscle mass. However, the overall marked improvement in global left ventricular function (increased stroke volume index at decreased left ventricular filling pressure) without any clinical or electrocardiographic evidence of ischemia would suggest the maintenance of a favorable balance between myocardial supply and demand. Our data must be interpreted in the strict context of the patient group studied. The response of the coronary circulation may vary considerably in patients without elevated muscle mass and ventricular filling pressures and in patients with ischemic cardiomyopathy and fixed atherosclerotic lesions.

Implications. Both the inotropic and vasodilator agents enhanced the central hemodynamic function of this patient population with nonischemic congestive cardiomyopathy. Despite a marked reduction in both left ventricular filling pressures and systemic vascular resistance with no increase in heart rate or systemic blood pressure (no significant increase in rate-pressure product), both agents increased myocardial oxygen demand. Vasodilator therapy, at a paired level of cardiac performance, did not diminish myocardial oxygen consumption when compared with inotropic intervention. However, the hydralazine-induced shift in total cardiac output toward the coronary vasculature plus the greater increase in coronary flow than in myocardial oxygen consumption (55 versus 33%, \( p < 0.05 \)) suggest a more favorable balanced oxygen supply and demand. In a group of patients with attenuated myocardial flow per unit mass and diminished subendocardial perfusion, these coronary hemodynamic changes may, in part, account for the acute augmentation of global myocardial performance after hydralazine therapy.

We thank Max Bacher for her technical assistance.

References


