Cardiac Dynamics during Hemorrhage

Relative Unimportance of Adrenergic Inotropic Responses

Thomas H. Hintze and Stephen F. Vatner

From the Departments of Medicine, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Massachusetts, and the New England Regional Primate Research Center, Southboro, Massachusetts

SUMMARY. We examined, in conscious dogs, the effects of acute hemorrhage on measurements of mean arterial and left ventricular (LV) pressures, LV diameters, LV dP/dt, LV dP/dt/P40, LV dP/dt/circ, i.e., LV dP/dt divided by LV circumference, and LV dD/dt, i.e., velocity of myocardial fiber shortening. Hemorrhage (30 ml/kg) over 1 hour reduced mean arterial pressure (31 ± 4.3%), LV end-diastolic (21 ± 3.2%) and end-systolic (13 ± 1.6%) diameters, and LV end-diastolic pressure (69 ± 4.6%). Heart rate increased by a maximum of 37 ± 7.5% at 20 ml/kg of blood loss. Indices of myocardial contractility rose slightly (~10%) during the initial normotensive hemorrhage, but then fell. Hemorrhage (30 ml/kg) reduced LV velocity by 31 ± 2.6%, LV dP/dt by 37 ± 2.9%, LV dP/dt/P40 by 34 ± 3.5%, and LV dP/dt/circ by 17 ± 7.2%. More rapid hemorrhage, 30 ml/kg at a rate of 1 ml/sec, induced similar effects. After β-adrenergic receptor blockade, the indices of myocardial contractility failed to rise initially and then fell with hemorrhage. The changes in indices of myocardial contractility were only slightly different (~10%) from those in dogs without blockade. Responses of mean arterial pressure and LV end-diastolic diameter to hemorrhage were essentially identical in the presence and absence of either selective β1- or combined β1- and β2-adrenergic receptor blockades. After hemorrhage, 30 ml/kg, when LV end-diastolic diameter was returned to pre-hemorrhage values by aortic constriction in dogs without β-adrenergic receptor blockade, LV dP/dt returned to, but not significantly above, control levels. Thus, activation of the sympathetic nervous system results in only small increases in cardiac contractility during acute hemorrhage, which are relatively unimportant in cardiovascular control. (Circ Res 50: 705–713, 1982)

ACUTE hemorrhage, by reducing blood volume and arterial pressure, induces arterial baroreceptor reflex-mediated increases in heart rate and peripheral vascular resistance. These adjustments to hemorrhage have been documented repeatedly in a variety of preparations (Chien, 1967; Vatner, 1974; Kirchheim, 1976). Textbooks of physiology indicate that enhanced cardiac contractility is another major compensatory response to hemorrhage (Selkurt, 1971; Folkow and Neil, 1971; Mountcastle, 1974; Berne and Levy, 1978). This concept derives considerable indirect support from experiments in anesthetized animals, where increases in circulating catecholamines (Hall and Hodge, 1971) and sympathetic neural activity (Chien, 1967) have been shown to occur with hemorrhage and where arterial baroreceptor unloading leads to an important inotropic effect (Sarnoff and Mitchell, 1961; DeGeest et al., 1964; Glick, 1971). Moreover, the reflex increases in heart rate, which occur during hemorrhage, should result in further positive inotropic increases through the Bowditch mechanism (Bowditch, 1871), an important myocardial control mechanism in anesthetized preparations. Finally, the renin-angiotensin system is also activated during hemorrhage, (Dempsey et al., 1971) which would contribute to a positive inotropic effect (Dempsey et al., 1971; Heyndrickx et al., 1976). Despite the preponderance of indirect evidence from anesthetized animals which would predict an important inotropic response to hemorrhage, supportive direct evidence in conscious animals is lacking.

The goal of this investigation was to study the left ventricular (LV) dynamics and, in particular, inotropic responses to hemorrhage. Since a positive inotropic effect would be most likely mediated by activation of the sympathetic nervous system, responses to hemorrhage were repeated on another day after β-adrenergic receptor blockade. In addition, since LV preload falls with hemorrhage, which could act to mask a positive inotropic effect, (1) indices of myocardial contractility were utilized that are considered to be relatively insensitive to changes in preload, (2) experiments were conducted in which preload was returned to control levels by inflating an aortic occluder, and (3) isoproterenol was infused to demonstrate that the utilized indices of myocardial contractility can demonstrate a rise, despite a fall in preload. Finally, norepinephrine was injected in the presence and absence of hemorrhage to determine whether hemorrhage prevented expression of an inotropic response to the neurotransmitter. All of these experiments were conducted in conscious animals where the unknown

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mitigating influence of general anesthesia and recent surgery were not present (Vatner and Braunwald, 1975).

**Methods**

Mongrel dogs of either sex, weighing between 18 and 30 kg, were sedated with propriopromazine HCl (Travnet; Diamond Lab) and anesthetized with sodium pentobarbital (J. A. Webster), 25 mg/kg, iv. Using sterile technique through an incision in the left 5th intercostal space, Tygon (Norton Plastics and Synthetic Division) catheters were implanted in the descending thoracic aorta and left atrium, piezoelectric transducers were implanted on opposing anterior and posterior endocardial surfaces of the left ventricle, and a solid state pressure gauge (P 22, Königsberg Instruments) was inserted into the left ventricle via an apical stab wound. In five of these dogs, an aortic occluder (26 mm i.d.) was placed around the aortic root, and pacing electrodes were sutured to the right atrium and the outflow tract of the right ventricle. The incision then was closed in layers, the pneumothorax reduced, and the animals allowed to recover.

Arterial and left atrial pressures were measured using the implanted catheters and Statham P23Db strain gauge manometers (Statham Instruments). LV pressure was measured with the solid state miniaturized pressure gauge and calibrated in vitro against a mercury manometer and in vivo against the arterial and left atrial pressure measurements. An improved ultrasonic transit-time dimension gauge (Patrick et al., 1974; Pagani et al., 1978) was used to measure LV diameter. The instrument generates a voltage linearly proportional to the transit time of acoustic impulses traveling at the sonic velocity of $1.5 \times 10^5$ mm/sec between the 3 MHz piezoelectric crystals, thus giving a record of instantaneous LV diameter. The frequency response of the dimension gauge is flat to 60 Hz. At a constant room temperature, the thermal drift of the instrument is minimal, i.e., less than 0.01 mm in 6 hours. Any drift in the measurement system, in the instrument electronics, the data tape recorder, and the oscillograph that displayed the data were eliminated during the experiment by periodic calibrations. This involved substituting pulses of known duration from a crystal-controlled pulse generator having a stability of 0.001%. The position of all transducers was confirmed at autopsy. Arterial blood gases ($P_{O_2}$, $P_{CO_2}$, and pH) were measured with a blood gas analyzer (Radiometer BCM 3MK 2) in six dogs. Blood samples for plasma catecholamines were collected prior to hemorrhage and after 30 ml/kg of blood loss in six dogs. Plasma catecholamines were determined according to the method described by DaPrada and Zurcher in 1976.

The experiments were conducted 3–6 weeks after operation, when the animals were vigorous, healthy, and trained to lie in the left lateral position. In 14 dogs, blood was withdrawn with a calibrated syringe pump (Harvard model no. 901) at a constant rate (0.5 ml/kg per min) for 60 minutes from a catheter positioned in the inferior vena cava. Blood was stored in an evacuated bottle during the hemorrhage and returned to the animal at the end of each experiment. In five dogs, hemorrhage was continued to 50 ml/kg to provide a more severe stimulus. In six dogs, hemorrhage (30 ml/kg) was repeated on a separate day, when heart rate was held constant by electrical stimulation. On a separate day, at least 2 days apart, hemorrhage (30 ml/kg) was carried out after β-adrenergic receptor blockade with propranolol, 1 mg/kg, iv, in 14 dogs. In 11 dogs, on a separate day, hemorrhage was carried out after selective β₁-adrenergic receptor blockade with atenolol, 1 mg/kg. In six of these dogs, heart rate was maintained constant at 150 beats/min, and LV end-diastolic diameter was returned to the pre-hemorrhage level by inflation of the aortic occluder. The dose of atenolol utilized blocks inotropic responses, but not decreases in arterial pressure and iliac vascular resistance, in response to isoproterenol (Manders et al., 1980). The adequacy of combined β₁ and β₂ adrenergic receptor blockade was confirmed by the injection of norepinephrine, 0.2 μg/kg, iv. The sequence of hemorrhage in the presence and absence of β₂-adrenergic receptor blockade was randomized. In all dogs, norepinephrine, 0.2 μg/kg, iv, was injected prior to and after 30 ml/kg of hemorrhage. In five dogs, effects of norepinephrine (0.2 μg/kg) were also examined after LV end-diastolic diameter was returned to the pre-hemorrhage level by inflation of the aortic occluder. In six dogs, isoproterenol was infused, 0.5 μg/kg per min for 10 minutes. In four dogs, hemorrhage was examined after α-adrenergic receptor blockade with phentolamine, 2.0 mg/kg, administered as an intravenous bolus, initially, and followed by a continuous infusion, 1 mg/min. Finally, more rapid hemorrhage (1.0 ml/sec to 30 ml/kg) was also examined in eight dogs.

The data were recorded on a multichannel tape recorder (Hewlett Packard) and played back on a direct writing oscillograph (Gould-Brush). A cardio-tachometer (Beckman no. 9857B) triggered by the pressure pulse provided instantaneous and continuous records of heart rate. Continuous records of LV $dP/dt$ and $dD/dt$, i.e., the velocity of myocardial fiber shortening, were derived from LV pressure and diameter signals using Philbrick operational amplifiers (Teledyne Philbrick), operated as differentiators and having frequency responses of 700 and 140 Hz, respectively. A triangular wave signal was substituted for the pressure and diameter signals to calibrate the differentiators directly. Two additional indices of cardiac contractility, i.e., $dP/dt$ at a developed pressure of 40 mm Hg ($dP/dt/P_{max}$) and the quotient of $dP/dt$ and LV end-diastolic circumference, i.e., $\pi$ times LV end-diastolic diameter ($dP/dt/circ$), were calculated to normalize for changes in afterload and preload respectively (Quinones et al., 1975; Mahler et al., 1975; Braunwald, 1977). Although measurements were recorded continually, data were averaged at each 5 ml/kg blood loss for statistical analysis. Data were stored in a digital computer (PDP-11/34) and statistical evaluation was performed by a one-way analysis of variance for linear contrasts and a multiple-way analysis of variance to determine significance between groups. Significance was determined using Scheffe's test (Armitage, 1975).

**Results**

Control values as well as specific confidence levels for changes from control are shown in Table 1 for experiments in the presence and absence of β₂-adrenergic receptor blockade with propranolol.

**Effects of Hemorrhage on LV Dynamics (Fig. 1)**

**Effects in Intact, Conscious Dogs**

Mean arterial pressure was well maintained at 5 ml/kg of blood loss and then fell gradually (Fig. 1). It was $31 \pm 4.3\%$ (mean $\pm 1 \text{ SEM}$) below control at 30 ml/kg. Heart rate increased by a maximum of $37 \pm 7.5\%$ above control at 20 ml/kg and then declined slightly as hemorrhage continued. LV systolic pressure fell progressively with hemorrhage, falling by 27
Effects of Hemorrhage on LV Dynamics before and after β-Adrenergic Receptor Blockade

<table>
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<th>Table 1</th>
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<td>β-block (mm Hg)</td>
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<tr>
<td>LV systolic pressure</td>
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<td>No block (mm Hg)</td>
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<tr>
<td>LV end-diastolic pressure</td>
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<tr>
<td>Heart rate</td>
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<tr>
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<tr>
<td>LV end-systolic diameter</td>
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<tr>
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<tr>
<td>LV dP/dt/40</td>
</tr>
<tr>
<td>No block</td>
</tr>
<tr>
<td>β-block (sec⁻¹)</td>
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<tr>
<td>LV dP/dt/circ</td>
</tr>
<tr>
<td>No block</td>
</tr>
<tr>
<td>LV velocity</td>
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</tbody>
</table>

* Change significantly different from control (P < 0.05).
† Significantly different after β-blockade from no block (P < 0.05).

± 4.0%, while LV end-diastolic pressure fell by 69 ± 4.6% at 30 ml/kg of hemorrhage. LV end-diastolic diameter fell progressively, by a maximum of 21 ± 3.2% below control at 30 ml/kg, while LV end-systolic diameter decreased by 13 ± 1.6% at this point. At 5 ml/kg of hemorrhage, LV dP/dt increased by a maximum of 7.8 ± 1.4%, LV dP/dt/40 increased by 8.0 ± 1.3%, LV dP/dt/circ rose by 13 ± 2.0%, whereas LV velocity did not change significantly (~2.5 ± 1.4%). With further hemorrhage, these indices returned to baseline and then fell below control. By 25 ml/kg of hemorrhage, all indices were significantly reduced below control (Table 1). At 30 ml/kg, peak LV dP/dt fell by 37 ± 2.9%, LV dP/dt/40 fell by 34 ± 3.5%, LV dP/dt/circ fell by 17 ± 2.2%, and LV velocity fell by 31 ± 2.6%.

Severe hemorrhage, 50 ml/kg, induced significantly greater (P < 0.05) reductions in mean arterial pressure (53 ± 5.5%), LV end-diastolic diameter (29 ± 6.4%), LV end-systolic diameter (20 ± 6.5%), LV dP/dt/40 (66 ± 4.6%) (Fig. 2), LV dP/dt/P 40 (61 ± 7.0%), LV dP/dt/circ (50 ± 8.9%), and LV velocity (51 ± 3.3%).

The observed pattern of a slight rise in indices of myocardial contractility at 5 ml/kg of hemorrhage followed by a reduction below control levels was also observed in the six dogs with heart rate held constant. For instance, in these experiments, with hemorrhage 30 ml/kg, mean arterial pressure fell by 32 ± 6.7% from 98 ± 6.9 mm Hg, LV end-diastolic diameter fell by 12 ± 1.5% from 34.7 ± 1.5 mm, and LV dP/dt fell by 41 ± 5.7% from 2963 ± 196 mm Hg/sec.

Eight dogs were studied with more rapid hemorrhage (1 ml/sec) (Fig. 3). Hemorrhage induced similar changes in mean arterial pressure, LV end-diastolic diameter, heart rate, and LV dP/dt, as were observed in the experiments with slower hemorrhage. For instance, with rapid hemorrhage of 30 ml/kg, mean arterial pressure fell by 28 ± 2.0% from a control of 96 ± 5.2 mm Hg. LV end-diastolic diameter fell by 12 ± 1.5% from 34.7 ± 1.5 mm, and LV dP/dt fell by 41 ± 5.7% from 2963 ± 196 mm Hg/sec.
Effects of Hemorrhage in Conscious Dogs after β-Adrenergic Receptor Blockade

After combined β₁- and β₂-adrenergic receptor blockade, hemorrhage to 30 ml/kg elicited very similar effects on LV dynamics, as were observed in these dogs without autonomic blockade (Fig. 1). One different response was the attenuated peak response of heart rate (Table 1). Moreover, the initial slight but significant increases in LV dP/dt, LV dP/dt/P₄₀, and LV dP/dt/circ at 5 ml/kg of hemorrhage were not observed after β-adrenergic receptor blockade (Table 1). Although the reductions in mean arterial pressure and LV end-diastolic diameter during hemorrhage were almost identical (Fig. 1), the fall in all indices of cardiac contractility with hemorrhage appeared to be slightly greater (~10%) after β₁- and β₂-adrenergic receptor blockade. However, only the responses at 5 and 10 ml/kg of hemorrhage for LV dP/dt/P₄₀ were significantly different before and after combined β₁- and β₂-adrenergic receptor blockade.

After selective β₁-adrenergic receptor blockade with atenolol, hemorrhage elicited a similar fall in mean arterial pressure as occurred in dogs without blockade or after combined β₁- and β₂-adrenergic receptor blockade (Fig. 4). In the six dogs with heart rate maintained constant at 150 beats/min and pretreated with atenolol, 1 mg/kg, hemorrhage, 30 ml/kg, reduced mean arterial pressure by 27 ± 7.8% from 100 ± 5.8 mm Hg, LV end-diastolic diameter by 10 ± 1.3% from 35.8 ± 2.0 mm Hg, and LV dP/dt by 38 ± 2.5% from 2612 ± 132 mm Hg/sec. In these dogs, inflation of the aortic occluder returned LV end-diastolic diameter to the pre-hemorrhage level, while LV dP/dt returned to a level that was slightly, but not significantly, lower than the pre-hemorrhage values (Fig. 5). In these same six dogs, studied with heart rate constant at 165 ± 6.5 beats/min, but without β₁-adrenergic blockade, inflation of the aortic occluder after hemorrhage, 30 ml/kg, induced essentially similar results. Baseline LV dP/dt was slightly higher, P < 0.05, in the absence (2962 ± 196 mm Hg/sec) as
FIGURE 2. The effects of more severe hemorrhage are shown on mean arterial pressure (AP) and left ventricular (LV) dP/dt at each 5 ml/kg of blood loss up to a total depletion of 50 ml/kg. Significant changes from control are noted by the asterisks.

compared with the presence (2612 ± 132 mm Hg/sec) of β1-adrenergic receptor blockade. When preload was returned to control by inflation of the occluder, LV dP/dt remained 15 ± 4% greater in the dogs without blockade, compared with the results in the same six dogs pretreated with β1-adrenergic receptor blockade (Fig. 5).

Effects of Norepinephrine (Fig. 6)

Norepinephrine increased peak LV dP/dt by 60 ± 11%, i.e., by 1962 ± 310 mm Hg/sec from a control of 3420 ± 162 mm Hg/sec (Fig. 6). After hemorrhage to 30 ml/kg, the same dose of norepinephrine increased peak LV dP/dt by 64 ± 9.9% or by 1258 ± 181 mm Hg/sec from a depressed baseline level of 2062 ± 134 mm Hg/sec. Thus, the actual increase in

FIGURE 3. The effects of rapid hemorrhage (1 ml/sec) in eight conscious dogs are shown at each 5 ml/kg of blood loss as percent change from control for mean arterial pressure (AP), heart rate (HR), LV end-diastolic diameter (EDD), and LV dP/dt. Significant changes from control are noted by the asterisks. These results with rapid hemorrhage are similar to those obtained with slower hemorrhage, as shown in Figure 1 and Table 1.

FIGURE 4. The effects of hemorrhage at each 5 ml/kg of blood loss are compared as percent decreases in mean arterial pressure in conscious dogs without autonomic blockade (circles), after combined β1- and β2-adrenergic receptor blockade with propranolol (squares), selective β1-adrenergic receptor blockade with atenolol (triangles), and α-adrenergic receptor blockade with phentolamine (diamonds). β1-adrenergic receptor blockade did not affect the maintenance of arterial pressure with hemorrhage. After α-adrenergic receptor blockade, mean arterial pressure could not be maintained well and the protocol had to be discontinued after 15 ml/kg of blood loss.
At Control After Hemorrhage Aortic Occlusion

<table>
<thead>
<tr>
<th>LV End-Dia. Diam (mm)</th>
<th>Control</th>
<th>Hemorrhage</th>
<th>Aortic Occlusion</th>
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<td>No Block</td>
<td>34.7 ± 1.5</td>
<td>30.6 ± 1.6</td>
<td>34.7 ± 1.3</td>
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<tr>
<td>Block</td>
<td>35.8 ± 2.0</td>
<td>32.3 ± 2.2</td>
<td>36.6 ± 2.0</td>
</tr>
</tbody>
</table>

At Control After Hemorrhage Aortic Occlusion

<table>
<thead>
<tr>
<th>LV dP/dt (mm Hg/sec)</th>
<th>Control</th>
<th>Hemorrhage</th>
<th>Aortic Occlusion</th>
</tr>
</thead>
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<td>No Block</td>
<td>35.8 ± 24</td>
<td>30.1 ± 1.0</td>
<td>36.2 ± 1.6</td>
</tr>
<tr>
<td>Block</td>
<td>34.2 ± 20</td>
<td>20.6 ± 1.2</td>
<td>32.3 ± 2.0</td>
</tr>
</tbody>
</table>

**FIGURE 6.** The effects of norepinephrine injection are compared prior to hemorrhage, after hemorrhage with preload reduced, and then with preload returned to control by inflation of an aortic occluder. The actual values for LV end-diastolic diameter (EDD) are noted above, while control values for LV dP/dt in mm Hg/sec are noted below the bars. The maximum increase in dP/dt during hemorrhage (5 ml/kg) is shown for comparative purposes by the inset striped bar.

**Discussion**

An increase in myocardial contractility is thought to be a major compensatory mechanism in response to hemorrhage (Folkow and Neil, 1971; Selkurt, 1971; Berne and Levy, 1972; Mountcastle, 1974). This concept is based on considerable, albeit indirect, evidence. For instance, it is known that the most prominent cardiovascular reflex response to acute blood loss involves arterial baroreceptor reflex unloading. Since experiments in anesthetized dogs with an open chest have indicated that this reflex can regulate myocardial contractility considerably (Sarnoff and Mitchell, 1961; DeGeest et al., 1964; Glick, 1971), it therefore follows by extrapolation that hemorrhage, which elicits this reflex, should increase myocardial contractility.

Acute hemorrhage also unloads low pressure baroreceptors. These reflexes could potentially augment inotropic responses as they do for peripheral reflex vasoconstrictor responses to hemorrhage (Pelletier and Shepherd, 1973; Hosomi and Sagawa, 1979) and to lower body negative pressure (Zoller et al., 1972). Studies also indicate that vagal activation may have an important negative inotropic response on the left ventricle (DeGeest et al., 1964; Priola and Fulton, 1969). However, it appears that the net vagal effect during hemorrhage is one of withdrawal, since the tachycardia that was observed after β-adrenergic receptor blockade is most likely attributed to withdrawal of vagal tone (Vatner et al., 1974). In addition, secretion of catecholamines from the adrenal gland

Plasma epinephrine rose with hemorrhage 30 ml/kg, by 1475 ± 266 pg/ml from a control of 342 ± 79 pg/ml.
should enhance reflex neural adrenergic mechanisms to increase myocardial contractility (Hall and Hodge, 1971). Furthermore, acute hemorrhage increases heart rate, which should add to the inotropic effect through the "treppe" phenomenon (Bowditch, 1871). The renin-angiotensin system is activated by hemorrhage (Dempsey et al., 1971), and also should increase myocardial contractility slightly (Heyndrickx et al., 1976). Finally, hemorrhage is thought to stimulate the peripheral arterial chemoreceptor reflex (Landgren and Neil, 1951; Biscoe, 1971) which has recently been shown to augment myocardial contractility (Pace, 1970; Vatner and Rutherford, 1978). Thus, a large body of indirect experimental evidence exists, which supports the hypothesis that myocardial contractility should rise substantially in response to hemorrhage.

In contrast to this widely held opinion and to the mass of indirect evidence, the results of the present experiments suggest that the inotropic response to hemorrhage in conscious dogs is relatively minor. During the early stage of hemorrhage, prior to a fall in mean arterial pressure, there is a small positive inotropic effect, as reflected by approximately a 10% rise in indices of myocardial contractility, despite a slight fall in LV end-diastolic diameter. The increases in LV dp/dt, LV dp/dt/P40, and LV dp/dt/circ, but not LV velocity were statistically significant (Table 1). Further support for the argument that a small positive inotropic response mediated by the adrenergic nervous system is elicited during hemorrhage, are the results showing slightly different (although generally not statistically different) reductions in indices of contractility with hemorrhage after β-adrenergic receptor blockade. It is important to note that these experiments were carried out in healthy, trained animals. If the animals were not healthy or were excited, quite different results might have been observed. Indeed, Goodyer (1967) studying anesthetized animals found an important role for sympathetic mechanisms in the cardiac contractile responses to hemorrhage.

Because both preload and afterload change with hemorrhage, no single index of cardiac contractility is ideal. In the present study, LV dp/dt and velocity of myocardial fiber shortening were examined. LV dp/dt/circ and dp/dt/P40 were also calculated. These latter indices are thought to be relatively insensitive to changes in preload and afterload, respectively (Mahler et al., 1975; Quinones et al., 1975; Braunwald, 1977). While all these indices demonstrated qualitatively similar findings (Fig. 1), it is noteworthy that LV dp/dt/circ demonstrated the least significant reductions with hemorrhage. This would suggest that the fall in preload was important in mediating the reductions in LV dp/dt and LV dp/dt/P40. It is also conceivable that changes in ventricular shape occur with severe hemorrhage. This could add inaccuracy to the correction factor for LV dp/dt/circ, i.e., the
circumference calculation. In any event, it is most important to keep in mind that none of the indices of contractility demonstrated an important positive inotropic effect with hemorrhage.

One might still argue that the fall in preload that occurred with hemorrhage prevented the full expression of the positive inotropic effect, which occurs with any of the indices of myocardial contractility utilized. The experiments with isoproterenol argue against this interpretation. Isoproterenol reduced preload, but still caused LV dP/dt to rise substantially (Fig. 7). In addition, if the fall in preload masked an important inotropic effect, then when LV end-diastolic diameter was returned to control by aortic constriction, LV dP/dt should have risen significantly above control, but did not. When preload was returned to control levels in the same six dogs studied in the presence and absence of selective β₁-adrenergic blockade and with heart rate constant, the difference in control levels of LV dP/dt were found to be 10%, whereas these differences were 15% after hemorrhage with preload returned to control. Thus, the β-adrenergic inotropic response to hemorrhage appears to be relatively trivial, regardless of whether preload remains depressed or is returned to the pre-hemorrhage control values (Fig. 5).

Previous studies conducted in anesthetized open-chest animals or pump-perfused canine hearts suggested that cardiac sensitivity to catecholamines decreases after hemorrhage as a result of hydrogen ion accumulation (Siegel and Downing, 1970). First of all, it is important to note that arterial pH remained normal during hemorrhage in these relatively acute experiments. However, some other myocardial depressant factor could also inhibit a rise in cardiac contractility. Our data indicate that the response to norepinephrine was identical (on a percent change basis) in the presence and absence of hemorrhage, while the actual rise in LV dP/dt with norepinephrine was less in the presence of hemorrhage. Furthermore, the present experiments suggest that the observed fall in LV dP/dt with hemorrhage was due to the fall in preload, rather than to the presence of a depressant factor, since when LV end-diastolic diameter was returned to control by inflation of the aortic occluder, LV dP/dt immediately returned to control and, then, under these conditions, the response to norepinephrine was identical both in terms of percent change and absolute values. If a depressant factor was circulating, there would have been a lag between the time LV end-diastolic diameter was returned to control and the time LV dP/dt returned to control. Moreover, the response to norepinephrine should have been depressed in the presence of a circulating depressant factor, and was not.

The stimulus of hemorrhage in the present study was sufficient to elevate plasma catecholamines considerably. However, these catecholamines, while potentially mediating the intense peripheral vasoconstriction (Vatner, 1974) and contributing to the reflex tachycardia, did not alter myocardial contractility substantially. Moreover, their β-adrenergic influence was not essential to the maintenance of arterial pressure during hemorrhage. Whereas, after α-adrenergic receptor blockade mean arterial pressure could not be well maintained with hemorrhage, after either selective β₁- or combined β₁- and β₂-adrenergic receptor blockades, responses of mean arterial pressure to hemorrhage were not significantly different from those obtained in dogs without autonomic blockade (Fig. 4).

The results of these studies in conscious dogs, as well as prior studies in this laboratory (Vatner, 1978), indicate that hemorrhage elicits important reflex chronotropic and peripheral vasoconstrictor responses, but trivial inotropic responses. The peripheral vascular responses appear to be mediated to a considerable extent by α-adrenergic pathways, whereas chronotropic responses are mediated by both β-adrenergic and vagal pathways. This finding that reflex sympathetic drive differs to peripheral vessels, the sinoatrial node and to myocardial contractile tissue, is somewhat surprising. However, there are other data supporting the concept that reflex sympathetic drive can vary in intensity to different organs and even within the heart. For instance, carotid chemoreceptor reflex stimulation in the conscious dog induces intense peripheral α-adrenergic vasoconstriction (Rutherford and Vatner, 1978), only modest β-adrenergic increases in myocardial contractility (Vatner and Rutherford, 1978), and actually no tachycardia, but bradycardia.

The results of the present investigation are consistent with prior studies conducted in this laboratory in that we have previously observed that carotid sinus baroreceptor regulation of myocardial contractility (Vatner et al., 1972) as well as the positive inotropic response due to activation of the Bowditch mechanism (Higgins et al., 1973) are relatively trivial in the intact, conscious animal. The present investigation extends these concepts by demonstrating that a physiological response involving both of these mechanisms, i.e., acute hemorrhage, also fails to elicit a substantial positive inotropic response. Furthermore, the defense of arterial pressure during hemorrhage was not affected significantly by β₁- or β₂-adrenergic mechanisms, indicating that the very slight difference in inotropic effects during hemorrhage in the presence and absence of β-adrenergic receptor blockade did not contribute to the maintenance of arterial pressure. This concept is teleologically appealing, since enhanced myocardial contractility in the face of depressed venous return and preload is not likely to be salutary.

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Address for reprints: Stephen F. Vatner, M.D., New England
Hintze and Vatner/Myocardial Contractility during Hemorrhage

Primate Research Center, One Pine Hill Drive, Southboro, Massachusetts 01772.

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T H Hintze and S F Vatner

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