Effects of Adenosine Infusion on Renal Function, Plasma ANP and ADH Concentrations and Central Hemodynamics in Anesthetized Pigs

A. N. Elias,1,* R. C. Wesley,2
I. L. Gordon,2 M. R. Pandian1 and N. D. Vaziri1
1UNIVERSITY OF CALIFORNIA, IRVINE, CA 92717, USA;
AND 2VETERANS ADMINISTRATION HOSPITAL, LONG BEACH, CA, USA

ABSTRACT. 1. The effect of high-dose adenosine administration on atrial natriuretic peptide (ANP) and antidiuretic hormone (ADH) release is not completely understood, and data concerning the effect of adenosine on renal and systemic hemodynamics in the pig are lacking. Measurements of central hemodynamics, renal blood flow and urine production were made in anesthetized pigs during infusion of adenosine. The relationship between these parameters and the plasma concentrations of ANP, ADH and renal renin production was examined.

2. Adenosine infusion at the rate of 140 mg/kg per minute resulted in a significant decrease in systemic, diastolic and mean arterial blood pressure as well as pulmonary arterial pressure. However, cardiac output and renal blood flow remained unchanged during adenosine infusion. Likewise, heart rate remained unchanged until the end of infusion when it increased significantly. Plasma ANP and ADH concentrations increased significantly within 30 min after adenosine infusion, reaching peak levels at 30 to 60 min. However, despite the significant decrease in arterial blood pressure, renal renin production did not change significantly.

3. The adenosine-induced rise in ANP, which is normally released by atrial stretch, may represent a direct effect of adenosine on the cardiac myocytes. The increase in ADH may be a result of decreased arterial blood pressure triggering stimulatory signals from the aortic arch and carotid body receptors to hypothalamic-pituitary sites of ADH production/release. Urine flow decreased dramatically within 30 min of adenosine infusion. Thus adenosine infusion at the given rate led to marked reduction in systemic and pulmonary arterial pressures without significant change in cardiac output, heart rate and renal blood flow. This was associated with a marked increase in plasma ANP and ADH levels with no significant change in renal renin production despite a marked reduction in arterial blood pressure.


KEY WORDS. Atrial natriuretic peptide, antidiuretic hormone, plasma renin activity

INTRODUCTION

The endogenous purine, adenosine, has potent vasodilatory properties (Owall et al., 1988; Sollevi, 1986). For this reason adenosine is used in the treatment of patients with perioperative hypertension and coronary vasoconstriction to improve coronary blood flow (Torsell et al., 1989; Zall et al., 1991). Adenosine exerts its vasodilatory effects through specific adenosine receptors (Olsson and Pearson 1990; Spielman and Thompson, 1982; Spielman and Arend, 1991). Adenosine may be involved in the physiologic regulation of blood flow in various organs, including the kidney (Olsson and Pearson 1990; Spielman and Thompson, 1982; Spielman and Arend, 1991; Torsell et al., 1989), and heart (Berne, 1980; Torsell et al., 1989). When infused in humans adenosine produces a decrease in the systemic blood pressure, and when given in an appropriate dosage enhances coronary blood flow (Torsell et al., 1989; Zall et al., 1991). It reduces renal blood flow and glomerular filtration rate in a dose-dependent manner (Olsson and Pearson 1990; Spielman and Thompson, 1982; Spielman and Arend, 1991; Tagawa and Vander 1970; Zall et al., 1990). These renal effects of adenosine are believed to be due to its action as a vasoconstrictor in the cortical blood vessels of the kidney (Tagawa and Vander 1970; Zall et al., 1990).

Little is known about the effects of adenosine on renal and systemic hemodynamics in pigs. Moreover, the effects of adenosine on antidiuretic hormone (ADH) and atrial natriuretic peptide (ANP) secretion have not been fully addressed. Both these hormones play a significant role in regulating central and renal hemodynamics. We hypothesized that, in addition to its indirect blood-pressure-mediated actions, adenosine may directly modulate renal hemodynamics as well as ADH and ANP release and may confer renal protection against severe hypotension. We thus examined the effect of high-dose adenosine perfusion on central hemodynamics, and renal function and its relationship to the plasma concentrations of ADH and ANP.

*To whom correspondence should be addressed at: University of California at Irvine, Medical Center, Department of Medicine, 101 City Drive South, Orange, CA 92668, USA.
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Adenosine infusion

Adenosine was infused intravenously at a rate of 140 mg/kg per minute for 120 min. Measurements of systolic, diastolic and pulmonary artery pressures, cardiac output, renal blood flow, and urine volume were obtained prior to adenosine infusion, and at 30, 60, 90 and 120 min of continuous infusion. Posttreatment measurements were made 30 min after cessation of adenosine infusion.

Measurement of plasma ANP, ADH and plasma renin activity (PRA)

Measurements of ANP, ADH, and PRA were made preinfusion and at timed intervals during adenosine infusion as previously noted. Postinfusion sampling was performed 30 min after stopping adenosine infusion. Blood for hormone measurements was collected in EDTA-containing tubes. The plasma was removed and stored at -80°C until assayed.

Immunoassay of ANP, ADH and PRA

ARTERIAL NATRIURETIC PEPTIDE (ANP). Plasma samples were extracted using a Sep-Pak column as previously described (Yandle et al., 1986). The antibody used in the assay recognizes the amino-terminal end of the ANP molecule (Pandian et al., 1986). The intraassay variation is 8.4% and the interassay variation 12.5%. The assay is sensitive to 10 pg/ml.

ANTIDIURETIC HORMONE (ADH). ADH was extracted from plasma with bentonite and assayed by radioimmunoassay (Skowsky et al., 1974). The sensitivity of the assay is 1 pg/ml. The intraassay variation is 9% and the interassay variation is 13.3%.

PLASMA RENIN ACTIVITY (PRA). Plasma renin activity was determined by generation of angiotensin I (AI) from endogenous substrate at 37°C at pH 5.7 (Osmond et al., 1974). The reported values of AI represent the PRA-generated AI minus the ungenerated AI in the sample. AI was determined by radioimmunoassay using anti-AI and 125I-AI (Taddei et al., 1992). Bound/free separation was achieved using goat anti-rabbit gammaglobulin as second antibody. PRA was expressed as nanograms per milliliter of AI generated per hour. The intraassay variation was 7.6% and the interassay variation 10.2%.

To avoid interassay variations all samples were tested in a single session for each of the aforementioned assays.

Statistics

Data were analyzed using analysis of variance (ANOVA). Where significant by ANOVA data were further analyzed using the
Mann–Whitney U test and Student’s t-tests for paired and grouped observations.

RESULTS
Values reported represent mean±SEM.

Central hemodynamics
Adenosine infusion resulted in a significant fall in systemic arterial, diastolic and mean blood pressure as well as pulmonary arterial pressure (Fig. 1). Systemic systolic, diastolic and mean blood pressure fell from 121±3.3 mmHg to 75.5±4 mmHg (P<0.02), 81.5±3 to 35.5±1.5 (P<0.001) and 93.8±2.8 to 47.3±1.9 mmHg (P<0.0001), respectively. Recovery to pretreatment levels occurred promptly after cessation of adenosine infusion. Pulmonary systolic arterial pressure fell from preinfusion levels of 31.3±0.5 mmHg to 24.8±1.1 mmHg (P<0.015). Cardiac output remained unchanged during adenosine infusion. Likewise, the heart rate remained constant until the end of the infusion when it rose significantly (Fig. 2).

Renal blood flow rate and urine flow
Renal blood flow rate did not change significantly during adenosine infusion. However, total urine flow (absolute amount) fell markedly within 30 min of infusion (38.3±10.6 ml to 8.3±3.4 ml, P<0.03), and remained low until after cessation of adenosine infusion at which point it increased to suprabasal levels (Fig. 3).

Plasma ANP, ADH concentrations and PRA
Plasma ANP and ADH concentrations rose significantly after adenosine infusion reaching peak values at 30 min after start of the infusion (Fig. 4). There was significant correlation between pulmonary arterial pressure at 30 min and plasma ANP concentrations (r=0.983, P<0.02). Renal arterial and venous PRA showed no significant change during adenosine infusion (Fig. 5), except for a minimal increase of renal arterial PRA at 120 min of infusion compared to preinfusion PRA (P=0.047, paired t-test).

DISCUSSION
Adenosine infusion at the rate given in the present study led to a significant decrease in systemic and pulmonary arterial pressure with no discernible change in cardiac output, heart rate or renal blood flow. This was associated with a significant fall in urine output coupled with marked increases in plasma ANP and ADH levels with no change in either renal arterial and venous PRA values.

The mechanisms responsible for the observed rise in plasma ANP level are unclear. Cardiac ANP production is primarily stimulated by increased atrial stretch. In view of the observed reductions in pulmonary and systemic blood pressures, coupled with an unchanged cardiac output, volume/pressure-mediated heart distention appears unlikely. However, adenosine may have promoted ANP release by either a direct effect or through modification of atrial stretch via an effect on cardiac myocyte tone. Alternatively, the rise in plasma

FIGURE 2. Heart rate (A) and cardiac output (B) before, during and after adenosine infusion.

FIGURE 3. Renal blood flow (A) and total urine output (B) before, during and after adenosine infusion.
FIGURE 5. Renal arterial and venous plasma renin activity (PRA) before, during and after adenosine infusion.

ANP may be due to enhanced release from extracardiac tissues or decreased ANP clearance. Further studies are required to explore the cause(s) of the adenosine-induced increase in plasma ANP.

Like ANP, plasma ADH concentration rose significantly with adenosine infusion in our animals. The observed rise in plasma ADH could not be attributed to increased osmolality since the animals' intake during the study was limited to intravenous infusion of isotonic solutions. Likewise, the phenomenon was not likely a consequence of general anesthesia since the rise in ADH was temporally related to the onset of adenosine infusion rather than the earlier induction of anesthesia. Alternatively, stimulation of a volume- or pressure-dependent regulatory pathway of ADH production/release seems more likely. In this regard a reduction in atrial filling volume or decreased stimulation of aortic arch and carotid body baroreceptors can trigger ADH release. In view of the lack of evidence of osmolality as the mechanism for ADH release, it is highly likely that ADH release may have been mediated by the adenosine-induced fall in arterial blood pressure triggering receptors in the great vessels. Volume depletion secondary to use of heat lamps to maintain body temperature also is an unlikely cause for the observed changes, because the animals' body temperature was strictly maintained within the euthermic range. A confounding effect of catecholamine release during the induction phase of barbiturate anesthesia cannot, however, be excluded.

It is of interest that, despite the significant decrease in arterial blood pressure, and hence renal artery perfusion pressure, renal venous blood renin activity did not change significantly during adenosine infusion. The reason for the lack of increase in renin release with the decrease in renal perfusion pressure is uncertain but is consistent with the previously demonstrated suppressive effect of adenosine on renin release (Kuan et al., 1990; Taddei et al., 1992).

The marked reduction in urine flow following adenosine infusion can be explained on the basis of ADH-induced antidiuresis as well as adenosine-induced reduction in glomerular transcapillary hydraulic pressure. It is of interest that, despite marked reduction in systemic arterial pressure, renal blood flow rate remained virtually unchanged during high-dose adenosine infusion. This indicates that renal vascular resistance decreases to maintain normal renal blood flow at greatly reduced perfusion pressure. Our demonstration that high-dose adenosine infusion causes renal vasodilation is different from a previous demonstration that adenosine causes afferent and efferent arteriolar vasoconstriction (Insahó et al., 1994). However, the renal constrictor effects of adenosine are transitory, and because our initial observations were made no sooner than 30 min after adenosine infusion, we may have lost the ability to detect the consequences of early adenosine-induced renal vasoconstriction. Our findings are, however, consistent with other studies which have shown that high-dose adenosine infusion protects kidneys from ischemia during cardiac bypass and spinal cord injury during surgery on the aorta in an experimental setting (Taddei et al., 1992). Consistent with other reports, our data show that sustained adenosine infusions do not decrease total renal blood flow, even when other cardiovascular parameters are affected, probably by an overall decrease in renal resistance (Edlund et al., 1993; Edlund and Sollevi, 1993; Haywood et al., 1992; Thompson and Spiehnan, 1992). Glomerular filtration during adenosine infusions has been noted to decrease, however, similar to our observation that overall urine production decreased (Edlund et al., 1993; Edlund and Sollevi, 1993). Of note, adenosine antagonists appear to increase glomerular filtration and urine production (Abels et al., 1992; Balakrishnan et al., 1993). The effects of adenosine infusion seen are probably unrelated to decreases in perfusion pressure, but may be in part secondary to redistribution of blood flow from the cortex to the medulla, which has been observed with adenosine agonists (Agmon et al., 1993).

FIGURE 4. Plasma atrial natriuretic peptide (ANP) (A) and plasma antidiuretic hormone (ADH) (B) concentrations before, during and after adenosine infusion.
Possible dilation of the efferent arteriole must also be considered, and needs to be investigated in future studies.

In conclusion, intravenous infusion of adenosine in anesthetized pigs at a rate of 140 mg/kg per minute led to a marked decrease in systemic and pulmonary arterial pressures without changing the cardiac output or renal blood flow. This was associated with a marked increase in plasma concentrations of ANP and AVP and no change in renal renin production rate despite a marked reduction in arterial blood pressure, and hence renal perfusion pressure.

References