Baroreflex function in a patient with Bartter's syndrome

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There is little information regarding circulatory responses in Bartter's syndrome, with the exception of marked resistance to vasopressors. We investigated baroreflex function in a 40-year-old woman with this syndrome. The patient showed oscillation of heart rate even with a small increase in blood pressure after administration of vasopressor agents. Variations in heart rate and blood pressure were exaggerated during halothane, nitrous oxide and oxygen anaesthesia. Although the mechanism of the unstable baroreflex in this syndrome remains to be proved, the instability may be attributable to many factors such as prostaglandins, hypovolemia, hypokalemia, halothane, nitrous oxide and positive pressure ventilation.

Bartter's syndrome is rare, although the exact incidence is not known.[1] The syndrome is characterized by hypokalemic hypochloremic alkalosis, hyperreninemia, hyperaldosteronism and hyperplasia of the juxtaglomerular apparatus of the kidneys. Patients with this syndrome have normal blood pressure and show marked resistance to the pressor actions of angiotension II and norepinephrine.[1-7] Because treatment with prostaglandin synthetase inhibitor tends to correct many of the abnormalities of the syndrome, a primary physiologic defect in Bartter's syndrome has been suggested to be an over production of prostaglandins, causing vascular insensitivity to vasopressors,[1-4,6,7] and enhanced vagus-mediated depressor effects.[8] However, baroreflex functions in this syndrome has never been investigated in a patient awake or during anaesthesia. We report studies of the baroreflex function in a patient with Bartter's syndrome.

Key words

COMPLICATIONS: Bartter's syndrome; HORMONE: prostaglandins; REFLEX: baroreflex; SYMPATHETIC NERVOUS SYSTEM: sympathomimetic agents.

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Case report

A 40-year-old woman, weighing 39.5 kg, with a clinical diagnosis of Bartter's syndrome, was scheduled for a renal biopsy, for definitive diagnosis. On admission, blood pressure was 90/60 mmHg, heart rate 80 beats·min^{-1}. The chest roentgenogram revealed a small heart (cardiothoracic ratio 32 per cent). An electrocardiogram revealed no abnormality except prolongation of the PR interval (0.22 sec). The patient was extremely resistant to vasopressors; a pressor test with angiotensin II and norepinephrine at doses of 0.015 and 0.3 μg·kg^{-1}·min^{-1} respectively produced only a 10 mmHg rise of mean blood pressure. The normal response is more than 35 mmHg and 25 mmHg, respectively. Biochemical examinations demonstrated hypokalemia (3.1 mEq·L^{-1}), hypochloremia (89 mEq·L^{-1}), normal serum sodium (133 mEq·L^{-1}) and serum calcium (4.8 mEq·L^{-1}). Blood urea nitrogen and serum creatinine were 21 mg·dl^{-1} and 1.2 mg·dl^{-1}, respectively. The pHa was 7.55, $PaCO_2$ 40 mmHg, PaO_2 91 mmHg, and base excess 10.6 mEq·L^{-1}. Endocrine studies revealed increased plasma renin activity of 41.9 ng·ml^{-1}·h^{-1} and a plasma aldosterone level of 195.5 pg·ml^{-1} (normal range 1–2.5 ng·ml^{-1}·h^{-1} and 10–50 pg·ml^{-1}, respectively). Preoperative medications consisted of a potassium supplement, 200 mEq·day^{-1}, and indomethacin 75 mg·day^{-1}.

Informed consent was obtained from the patient.

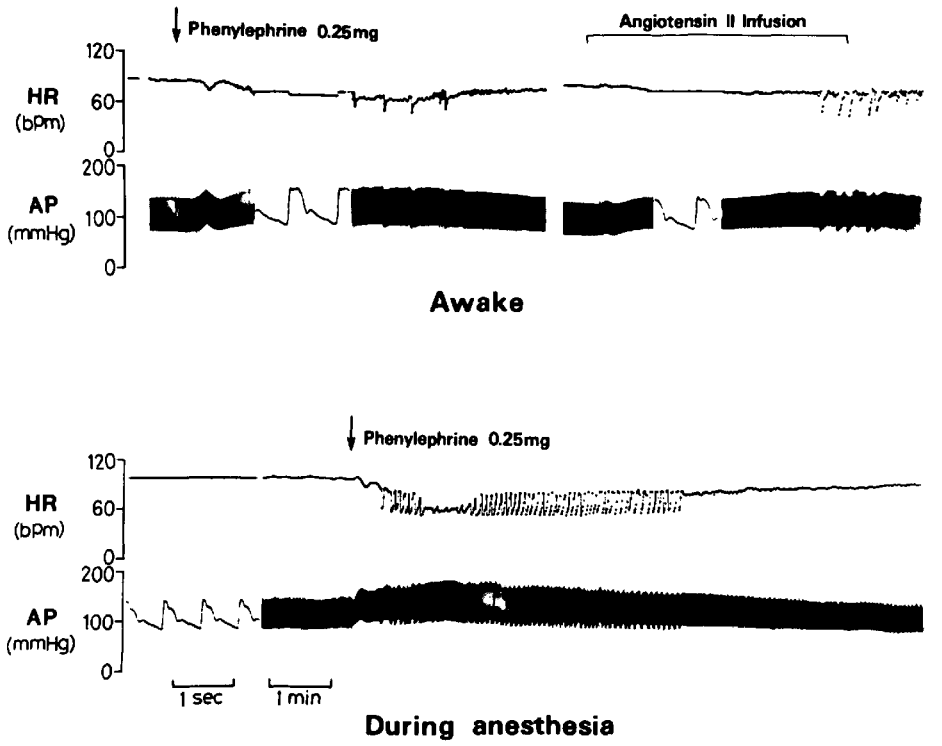

FIGURE Polygraph tracings of heart rate (HR) and arterial blood pressure (AP). Upper left panel: Note the repetition of bradycardia with the increases of blood pressure after phenylephrine 0.25 mg IV. Upper right panel: Angiotensin II produced the same phenomenon as pictured in the left panel. Lower panel: Note the considerably unstable heart rate and blood pressure after phenylephrine 0.25 mg IV during halothane, nitrous oxide, and oxygen anaesthesia. For further discussion, see the text.

On the operative day, hydroxyzine 100 mg and meperidine 35 mg were administered I.M. one hour before arrival in the operating room. A 16-gauge intravenous cannula was placed for infusion of lactated Ringer's solution and a 19-gauge cannula was placed in the left radial artery to permit continuous blood pressure monitoring and blood sampling. The latter was connected to a Statham P23ID transducer (Gould, USA); the signal was amplified and recorded on six-channel polygraph recorder (Polygraph 146 and Rectigraph-8H, Sanei Instrument, Tokyo). Baroreflex control of heart rate was assessed quantitatively by a pressor test as described in the literature.[9,10] Beat to beat systolic blood pressure (mmHg) and R-R interval (msec), obtained from simultaneous recording of direct arterial blood pressure and heart rate, were linearly related over the first period of blood pressure increase. The slope of this relationship was calculated in msec of R-R interval change per mmHg increase in systolic blood pressure, and this was defined as the baroreflex sensitivity.

The baseline blood pressure was 135/70 mmHg and heart rate 87 beats·min^{-1}. When phenylephrine, 0.25 mg, was rapidly injected intravenously, the blood pressure increased to 155/90 mmHg transiently, then rose slowly to 160/90, while the heart rate decreased to 72 beats·min^{-1} transiently, thereafter varying remarkably (from 48 to 72 beats·min^{-1}). During this period, the increase in systolic blood pressure was small (25 mmHg), and the heart rate was extremely labile, but no arrhythmia appeared (Figure, upper left panel). The baroreflex sensitivity was 7.1 msec·mmHg^{-1} (Table). A

TABLE Results of pressor test

	Pressor Agent		*Systolic blood pressure (mmHg)*	*R-R interval (msec)*	*Baroreflex sensitivity (msec·mmHg^{-1})*
Awake	Phenylephrine 0.25 mg	Pre	135	690	7.1
		Post	155	833	
	Angiotensin II 0.1 μg·kg^{-1}·min^{-1}	Pre	135	714	4.3
		Post	155	800	
Halothane/ nitrous oxide anaesthesia	Phenylephrine 0.25 mg	Pre	140	625	3.5
		Post	165	714	

pressor test with angiotensin II was performed after the blood pressure and heart rate had returned to baseline levels. Angiotensin II was infused intravenously at the rate of 0.1 μg·kg^{-1}·min^{-1}. Systolic blood pressure increased about 25 mmHg, while the heart rate was unstable, decreasing intermittently from 75 to 50 beats·min^{-1}; the oscillation of heart rate was observed periodically several times per minute (Figure, upper right panel). The baroreflex sensitivity was 4.3 msec·mmHg^{-1}.

Thereafter, general anaesthesia was induced with thiamylal 200 mg given slowly and the trachea was intubated after intravenous succinylcholine 50 mg. The blood pressure decreased from 130/75 to 95/55 mmHg and heart rate increased from 81 to 87 beats·min^{-1} after thiamylal administration, then changed to 145/90 mmHg and 84 beats·min^{-1}, respectively during laryngoscopy and endotracheal intubation. During this period the heart rate was relatively stable. Anaesthesia was maintained with halothane (0.5 to 1.0 per cent inspired) in nitrous oxide and oxygen (3 and 2 L·min^{-1}, respectively). Ventilation was controlled with the use of intravenous pancuronium 3 mg, maintaining $PaCO_2$ at about 35 mmHg.

The pressor test with phenylephrine was repeated 30 minutes later during a period of stable blood pressure and heart rate. Blood pressure rose transiently from 140/85 to 165/100, then increased slowly to 180/100 mmHg after phenylephrine 0.25 mg. Heart rate initially decreased from 96 to 84 beats·min^{-1}, then varied considerably from 51 to 81 beats·min^{-1}. The cycles of the oscillation of heart rate observed during halothane, nitrous oxide, and oxygen anaesthesia was about 12–13 per minute. A small oscillation of blood pressure (around 15 mmHg) was also observed; this being consistent with that of heart rate (Figure, lower panel). The baroreflex sensitivity was 3.5 msec·mmHg^{-1} (Table). The remaining anaesthetic course was uneventful. Microscopic examination revealed juxtaglomerular hyperplasia of the kidney.

Discussion

The baroreflex is one of the most important neuronal control systems for short-term regulation of blood pressure.[11] This patient's baroreflex control of heart rate was extremely unstable and the vasopressors induced a remarkable oscillation of heart rate, even with a small increase in blood pressure, and these oscillations were aggravated in the presence of halothane, nitrous oxide and oxygen.

Although the mechanism of the unstable baroreflex control system remains to be proved, it is evident that vagus-mediated bradycardia is notable even with a very small increase of blood pressure. The sensitivity of the baroreflex was 7.1 and 4.3 msec·mmHg^{-1} before anaesthesia, and 3.5 msec·mmHg^{-1} during anaesthesia. These values in the unanaesthetized state and during anaesthesia are comparable to those reported previously.[9,10,12] Presumably, the unstable baroreflex in this patient may be explained due to an impaired resetting of the baroreceptors, or a defect of central modulation of the reflex.

A cardinal feature of Bartter's syndrome is overproduction of prostaglandins such as PGD_2, PGE_2, and PGI_2.[1–4,6,7] There have been reports that pressor actions of sympathomimetics are counteracted by prostaglandins in this syndrome.[1–4,6,7] Staszewska-Barczak[8] demonstrated that the hypo-

tensive and bradycardia responses to nicotine were potentiated by intracoronary or intravenous infusion of PGI_2 and PGD_2 while the pressor effects evoked by bradykinin were potentiated by intracoronary infusion of PGE_2, and that indomethacin reduced this pressor effect. He also observed that PGE_2 had no effect on the nicotine-induced depressor effect, while PGI_2 reduced sympathetically-mediated reflex effects of bradykinin. In addition, because it has been reported that PGI_2 (not PGE_2) is a predominant active metabolite of arachidonic acid in blood vessels, it would be possible that PGI_2 plays a more important role in circulatory disturbances in this syndrome. Patients with Bartter's syndrome therefore seem to be in vagal dominant state, although preoperative indomethacin treatment might modify the effects of the prostaglandins.[8,13] The minimal change in heart rate, even with significant increases in blood pressure observed during laryngoscopy and tracheal intubation, support this speculation. Sympathomimetic responses such as tachycardia and hypertension usually occur during these procedures.

Normally, the heart rate responses to stimulation of the vagus nerve occur very rapidly, but sympathetic responses occur slowly.[11] In the resting condition, the increase of heart rate by complete vagolysis is much larger than the decrease produced by complete sympathetic blockade.[14] In Bartter's syndrome sympathetic tone is already decreased and sympathetic activities are not able to counteract the increased vagal tone, thus resulting in marked bradycardia. Because of impaired sympathetic responses in Bartter's syndrome, a depressor test may be more relevant, rather than a pressor test as in our patient. However, the remarkable oscillation of heart rate observed in our patient cannot be explained only on the basis of an imbalance in the autonomic nervous system. Hypovolemia, which can be present in Bartter's syndrome[15] may be also responsible for an unstable baroreflex, since the cardiovascular control system, including the baroreceptor response, oscillates considerably in hypovolemia.[16] In addition, hypokalemia, which is another feature of Bartter's syndrome,[1-6] may also be responsible for unstable baroreceptor responses, since hypokalemia has been reported to increase the pressure threshold at which baroreceptor discharges are initiated.[17,18]

In the presence of halothane, nitrous oxide, oxygen and pancuronium, the oscillation of heart rates induced by phenylephrine was obviously accentuated in this particular patient, though halothane and nitrous oxide have been reported to attenuate the baroreflex responses.[9,10,19-21] The reason for this is unclear. Phenylephrine per se may have an enhancing effect on the baroreflex responses,[22] and positive pressure ventilation could modify the baroreflex control of heart rate.[23] And it is possible that inhalation anaesthetics, such as halothane, could depress the sympathetic nervous system, intensifying the vagal dominant state produced by prostaglandins.

In summary, unstable baroreceptor responses exist in patients with Bartter's syndrome; this instability of the reflex responses may be attributable to many factors, including prostaglandins, hypovolemia, hypokalemia and positive pressure ventilation. Further the presence of halothane and nitrous oxide may aggravate the instability.

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Résumé

Il y a très peu d'information concernant les réponses vasculaires chez les patients atteints de syndrome de Bartter à l'exception de celle concernant une résistance marquée aux vasopresseurs. On a investigué la fonction des barorécepteurs chez une femme âgée de 40 ans atteinte de ce syndrome. La patiente a démontré une oscillation de la fréquence cardiaque même avec une augmentation minime de la tension artérielle suite à l'administration d'agents vasopresseurs. Les variations de la fréquence cardiaque et de la pression artérielle étaient exagérées lors de l'anesthésie à l'halothane, protoxide d'azote et oxygène. Même si le mécanisme de cette instabilité des barorécepteurs dans ce syndrome reste à prouver, cette instabilité peut-être attribuer à plusieurs facteurs dont les prostaglandines, l'hypovolémie, l'hypokalémie, l'halothane, le protoxide d'azote et la ventilation à pression positive.