Contribution of Prostaglandins to the Antihypertensive Action of Captopril in Essential Hypertension

THOMAS J. MOORE, M.D., FRANK R. CRANTZ, M.D., NORMAN K. HOLLENBERG, M.D., PH.D., RICHARD J. KOLETSKY, M.D., MERYL S. LEBOFF, M.D., STEPHEN L. SWARTZ, M.D., LAWRENCE LEVINE, SC.D., STEPHEN PODOLSKY, M.D., ROBERT G. DLUBY, M.D., AND GORDON H. WILLIAMS, M.D.

SUMMARY To determine whether prostaglandins contribute to the depressor response to the converting enzyme inhibitor, captopril, we measured the plasma prostaglandin levels by radioimmunoassay before and after captopril administration, and then examined the effect of prostaglandin synthetase inhibition on captopril's antihypertensive effect. When a single oral captopril dose (25-100 mg) was given to 31 sodium-restricted patients with essential hypertension, the levels of the stable transformation product of prostacyclin remained immeasurable and that of thromboxane A2 did not change, while the metabolite of PGE1 (PGE-M) increased by 53% (34 ± 4 pg/ml pre-captopril, 52 ± 5 pg/ml after; p < 0.001). As expected, blood pressure (BP) and angiotensin II (AII) levels fell, and kinin levels rose (all changes p < 0.001). We then blocked prostaglandin synthesis in 18 of these subjects for 24 hours with either indomethacin (n = 10) or aspirin (n = 8) before repeating the captopril dose, to assess the importance of these PGE-M increments. The PGE-M responses to captopril were effectively blocked in nine of 10 subjects receiving indomethacin and four of eight receiving aspirin. In these 13 patients, the depressor response to captopril was significantly blunted (−20 ± 3 mm Hg pre-synthetase inhibition vs −13 ± 2 mm Hg post; p < 0.05). When these agents did not block the PGE-M response to captopril, the BP response was also unchanged (−15 ± 4 mm Hg pre, −18 ± 5 mm Hg post). Neither indomethacin nor aspirin changed the AII or kinin responses to captopril. We conclude that the prostaglandins may be important mediators of captopril's antihypertensive effect in the sodium-restricted state.

Key Words · prostaglandins · captopril · essential hypertension

SINCE demonstrating that angiotensin-converting enzyme was identical to one of the kinin-degrading enzymes, kininase II, and that blocking this enzyme blocked both angiotensin generation and kinin degradation, investigators have debated the relative importance of angiotensin II vs the kinins in mediating the hypotensive response to converting enzyme inhibition (CEI). More recent evidence, however, suggests that still another class of hormones, the prostaglandins, may also be involved. It is known that bradykinin releases prostaglandins from several tissues,1-7 and it has been postulated that inhibition of kininase II with CEI could increase endogenous kinin levels, permitting more kinin-mediated prostaglandin release. Murthy et al.8 have provided indirect evidence in rabbits supporting this postulate by showing that prostaglandin synthetase inhibition partially blocks the hypotensive response to bradykinin after CEI. Vinci et al.9 found that the peptide CEI, SQ 20,881, increased plasma immunoreactive prostaglandin E levels in some hypertensive subjects.

In the studies reported here, we examined the potential importance of the prostaglandins in mediating the depressor response to the oral CEI, captopril, in hypertensive patients both by measuring the changes in plasma prostaglandin levels after CEI and by assessing the effect of prostaglandin synthetase inhibition on the response to CEI. Our results show that captopril does increase endogenous prostaglandin production and that prostaglandins contribute to captopril's antihypertensive effect.
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Methods

Thirty-one essential hypertensive patients were studied on the Clinical Research Center of the Peter Bent Brigham Hospital. All subjects had had documented hypertension (> 90 mm Hg diastolic) for at least 6 months of outpatient observation. Antihypertensive drugs were discontinued at least 10 days before hospitalization whenever possible, but, when the severity of the hypertension precluded this, the drugs were tapered gradually and then changed to hydralazine which was continued until the day before captopril was begun. The diagnosis of essential hypertension was based upon the absence of reversible etiologies as assessed by urinary catecholamine and 17-hydroxy steroid determinations, intravenous pyelogram, and, where indicated, renal arteriogram and renal vein renins.

Of the 31 subjects, 25 were men; their mean age (± SEM) was 46.4 ± 2.2 years; serum creatinine was 1.3 ± 0.1 mg/dl, and creatinine clearance was 70 ml/min or greater in all but one subject. Admission blood pressure (BP) was 157 ± 6/103 ± 2 mm Hg. Before captopril administration, all subjects ingested constant, isocaloric diets containing 10 mEq sodium and 100 mEq potassium per day until metabolic balance was achieved (usually by the fifth hospital day).

Protocols

Captopril Administration

All subjects were studied supine after an overnight fast. At 7 a.m. an indwelling venous catheter was placed for blood sampling. Between 8:30 and 9:00 a.m., a single oral dose of captopril was given. The dose ranged from 25 to 100 mg, the larger doses being given to patients with more severe hypertension and/or larger body mass. Blood samples were drawn just before the captopril dose and at 30, 60, 120, and 360 minutes thereafter. Samples were analyzed for plasma renin activity (PRA), angiotensin II (AII), kinins, and prostaglandins (except prostaglandins that were not measured at 30 minutes). The prostaglandins measured included the stable 13,14-dihydro-15-keto metabolite of PGE_2, and the transformation products of prostacyclin (PGI_2) and thromboxane A_2 (see below). The BP was monitored every 2 minutes for a 30-minute control period and for the first 120 minutes after captopril with an automatic BP recorder (Arteriosonde, Roche) and then at 360 minutes thereafter. Hormonal and vascular responses to captopril represent peak responses unless otherwise noted.

Prostaglandin Inhibition

Eighteen patients in this series repeated this captopril protocol after pretreatment with a prostaglandin synthetase inhibitor. On the day following their first captopril dose, these patients were given oral doses of either indomethacin (25 mg every 6 hours, n = 10) or aspirin (600 mg every 6 hours, n = 8). The patients received five doses, the last at 7 a.m. At 9 a.m., 48 hours after the first captopril administration, the captopril protocol was repeated as outlined above. Patients were given the same captopril dose on both study days.

The protocols were approved by the human subjects committee of our hospital, and written consent was obtained from each subject after a complete description of the protocol.

Laboratory Procedures

All blood samples were collected on ice, spun immediately, and the plasma separated and frozen until time of assay. Samples of PRA, AII, and kinins were drawn with EDTA as the anticoagulant; heparin was used as the anticoagulant in the samples for prostaglandins. In addition, polybrene was present in the samples processed for kinins. Serum and urine sodium and potassium levels were measured by flame photometry using lithium as an internal standard. PRA and AII levels were measured by radioimmunoassay techniques as previously described. In this assay, AII cross reacts 0.09%. All AII levels are corrected for this cross reaction (never greater than 5 pg/ml). Plasma kinins were measured by a modification of the radioimmunoassay techniques of Talamo and colleagues.

Prostaglandin E_2 is rapidly metabolized in vivo to its 13,14-dihydro-15-keto derivative. This metabolite (PGE-M) is more stable than the primary prostaglandin and thus may more accurately reflect the cellular biosynthesis of prostaglandin E_2. The plasma concentration of PGE-M was measured by radioimmunoassay. Briefly, rabbit antiserum was raised by immunizing rabbits with PGE-M coupled to human albumin; in the homologous anti-PGE-M immune system, PGE-M cross reacts 5%. All radioimmunoassays were performed on unextracted plasma. The lower limit of sensitivity of this assay was 10 pg/ml, and the intraassay coefficient of variation was less than 10%.

For radioimmunoassay of prostacyclin (PGI_2), measurement of its chemically stable transformation product, 6-keto-PGF_M was determined by inhibition of ^H 6-keto-PGF_M (New England Nuclear Corporation, Boston, Massachusetts) anti 6-keto-PGF_M binding. In this radioimmunoassay, PGE_2, PGE_M, thromboxane B_2 (TXB_2), and PGE_T and PGE_M-metabolites cross react less than 1%. Radioimmunoassay of thromboxane B_2, the stable product of the pharmacologically active thromboxane A_2, was accomplished by inhibiting ^H thromboxane B_2 binding to antithromboxane B_2 antibody. In this TXB_2 radioimmunoassay, PGE_2, PGE_M, 6-keto-PGF_M, and PGE_T and PGE_M-metabolites cross react less than 1%.

Statistical Methods

Group means are presented with the standard error of the mean as the index of dispersion. Statistical
probability was evaluated using the paired *t* test for normally distributed data; for nonparametric data, the Fisher exact (FET) or χ² tests were used. For the time course responses, significant changes from control were computed by analysis of variance, obtaining *p* values from Dunnett’s tables.

**Results**

All patients had achieved metabolic balance at the time of captopril administration (urinary sodium 14 ± 2; potassium 79 ± 3 mEq/d). Prostaglandin determinations in the first eight patients had shown generally undetectable (< 10 pg/ml) levels of the prostacyclin transformation product, 6-keto-PGF₁α, which did not increase after captopril, and thromboxane B₂ levels that did not change after captopril (167 ± 27 → 207 ± 35 pg/ml; *t* = 0.78). We limited our attention to PGE-M in all subsequent patients.

**Response to Captopril**

After captopril administration, BP and AII levels fell, while PRA and kinin levels rose as anticipated (all responses *p* < 0.001). The PGE-M levels also rose significantly (pre-captopril, 34 ± 4 pg/ml; post-captopril 52 ± 5 pg/ml; *p* < 0.001), and the responses represented a 53% increase over control levels (fig. 1). Neither the vascular nor hormonal peak responses were related to the captopril dose. However, because the doses were not assigned randomly and the higher doses were generally given to patients with the highest BPs, the significance of the dose response data is unclear.

The time course of the hormonal and BP responses in 21 patients given a single 25 mg dose of captopril is shown in figure 2. The BP fell significantly by 30 minutes (*p* < 0.01) and remained down through 2 hours, returning to near control levels at 6 hours. Concomitant with the depressor response, the AII levels fell significantly (*p* < 0.05) at 30 minutes and 1 hour, but were back to control by 2 hours and were actually higher than control at 6 hours. The rise in AII levels corresponded to the increase in PRA levels, which increased by 300% at 1 and 2 hours (from 3.3 ± 0.6 to 11.1 ± 2.1 and 10.2 ± 1.8 ng/ml/hr respectively, *p* < 0.01) and were still twice that of controls at 6 hours. Kinin levels increased early (but not significantly at any one time point) and were back to control level by 2 hours.

The PGE-M levels rose after captopril and were significantly above control at 2 hours (from 38 ± 6 to 49 ± 7 pg/ml; *p* < 0.05) — a time at which BP remained low but AII and kinins had returned to their basal levels. By 6 hours PGE-M levels were returning toward control.

**Inhibition of Prostaglandin Synthesis**

The administration of indomethacin or aspirin for 24 hours did not significantly alter the patients’ sodium balance (urinary sodium pre, 15 ± 3 mEq/d vs post 10 ± 2; weight pre, 84.2 kg vs post 84.0), nor did it alter the supine, pre-captopril BP or hormonal levels significantly although PGE-M did decrease by 8 pg/ml (0.1 > *p* > 0.05). Prostaglandin synthetase inhibition did alter the response to captopril, however (fig. 3). In the 10 patients given indomethacin, captopril’s hypotensive effect was blunted from −23 to −13 mm Hg — a decrease of more than 40% (*p* = 0.02). Concomitant with this, the PGE-M increase after captopril was eliminated completely. The captopril-induced changes in both BP and PGE-M were significantly different when the pre- vs post-indomethacin responses were compared (*p* < 0.05). However, indomethacin caused no significant change in either the AII or kinin responses to captopril although the PRA increase was significantly inhibited (*p* < 0.05). These data suggest that PGE₂ mediates some portion of captopril’s hypotensive effect, and that blocking prostaglandin synthesis also blunts the BP response.

Aspirin, in the doses we used, did not prove to be as effective at prostaglandin synthetase inhibition, blocking the PGE response to captopril in only four of eight patients treated (vs nine of 10 with indomethacin). If
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FIGURE 2. Time course of the blood pressure and hormonal responses to a single 25 mg captopril dose in 21 patients. Significant differences from control (p < 0.05) are shown (*).

FIGURE 3. Effect of indomethacin treatment on the peak responses to captopril in 10 patients. Significant differences between pre- vs post-indomethacin responses are indicated.

FIGURE 4. Comparison of the blood pressure responses to captopril before and after prostaglandin synthetase (PG-S) inhibition with either indomethacin (n = 10) or aspirin (n = 8). The patients are divided into two groups according to whether the PGE-M response to captopril was successfully blocked with the PG-S inhibitor or not. In the group with blocked PGE-M responses, the depressor response to captopril was also significantly blunted.

Discussion

We were encouraged to examine the importance of the prostaglandins in mediating the hypotensive response to converting enzyme inhibition because available data suggest that the observed changes in AII and kinin levels can account for only a portion of one compares the post-captopril PGE-M changes, the aspirin pretreated group had a mean increase in PGE-M (+ 4 ± 5 pg/ml) vs the mean decrease with indomethacin (−7 ± 3 pg/ml); the difference between the groups was significant (p < 0.02, FET). The blood pressure response to captopril was also not significantly blunted in the eight aspirin patients taken as a group. However, if all the indomethacin and aspirin patients were divided according to whether their PGE-M responses to captopril had been blocked or not (i.e., persistent PGE-M increase vs no change or decrease), the BP responses were blunted in the group whose PGE-M increments were blocked, and were significantly different from the nonblocked subjects (p = 0.015; fig. 4).
the vascular responses, and because changes in plasma prostaglandin levels after CEI have been demonstrated in two recent studies. Vinci et al. found increases in plasma immunoreactive PGE in hypertensive patients on a moderate sodium intake (109 mEq/d) and in some sodium-restricted patients in response to maximal doses of the peptide CEI, SQ 20,881. In addition, Swartz et al. in our laboratory documented PGE-M increases in response to captopril in normal subjects on both high and low salt diets. The results of our present study confirm the finding that captopril does increase PGE-M levels in hypertensive subjects. Moreover, our finding that inhibition of prostaglandin synthesis blunts the depressor response to captopril provides evidence that the prostaglandins are an important component of this agent's mechanism of action.

The prostaglandins we measured included the metabolites of PGE2, and the stable transformation products of prostacyclin (PGI2) and thromboxane A2. We measured these compounds because the active prostaglandins have such short half-lives in plasma that their levels may not provide an accurate picture of tissue production rates. Although we found that only PGE-M increased after captopril, increases in PGI2 production may also be involved in captopril's effect. PGI2 is several times more potent than PGE2 as a vasodilator and is the major prostaglandin produced by human vascular tissue. It is possible that our inability to detect an increase in the PGI2 transformation product, 6-keto-PGF1α, may have been due to changes in the product below the sensitivity of our assay. In addition, recent work suggests that 6-keto-PGF1α can be further converted to 6,15-diketo-PGF1α, which is not detected in our assay. Thus, our measurements of 6-keto-PGF1α may have provided an incomplete estimate of prostacyclin production, and this compound, as well as PGE2, could be involved in captopril's depressor effect. The blunting of the BP response by indomethacin does not clarify which prostaglandin is involved, since it inhibits both PGI2 and PGE2 production.

Captopril could increase prostaglandin production either by a direct stimulatory action or indirectly via other factors. While there is no evidence to support a direct effect, a possible indirect mechanism has been described. Bradykinin has been shown to stimulate prostaglandin production in the kidney, heart, lungs, and vascular tissue, as well as from renal medullary interstitial cells in tissue culture. Murthy et al. applied this information when they demonstrated that indomethacin attenuated the hypotensive response to bradykinin infused after captopril pretreatment.

The time course of the hormonal responses to captopril in our study would support this concept, since the prostaglandin changes in our subject tended to be maximal 120 minutes after captopril while the peak bradykinin responses occurred earlier. In fact, because both the bradykinin and AII levels had returned to control levels at 120 minutes while BP remained depressed and PGE-M was increased, it is possible that the early response to captopril could be related to the AII and kinin changes while the sustained response is relatively more prostaglandin dependent. The fact that we measured a metabolite of PGE2 and not the active product itself must be considered, however, when interpreting the contribution of PGE2 at a given time point.

The state of sodium balance in which our studies were performed deserves further comment. We elected to study our patients in the sodium-restricted state because dietary sodium restriction and/or volume depletion with diuretics are such universal features of antihypertensive therapy. The work of Vinci et al. and Swartz et al. suggests that captopril also increases PGE levels in the sodium-loaded state, but the functional significance of those increases remains to be determined.

The fact that indomethacin blunted the PRA increase in response to captopril may provide some insight into the control of PRA secretion. It has been demonstrated that AII can inhibit PRA secretion directly, without acting through BP or altering sodium balance. The PRA increase after CEI administration could be due to inhibition of AII generation and release from this so-called "short-feedback" AII suppression, although the drop in BP that follows CEI could also stimulate renin production.

Our study raises still a third possible mechanism since the prostaglandins are also potent stimuli of renin secretion and the PGE2 response to captopril could be contributing to the PRA response. After indomethacin, we found that the PRA response to CEI was blunted without a concomitant change in the AII response. These results suggest that the PRA increase after captopril is not solely due to release from AII inhibition but also is regulated by the fall in BP and/or the increase in PGE2 production.

Finally, our finding that antiinflammatory drugs that inhibit prostaglandin synthetase and also blunt the depressor actions of captopril may be of some clinical importance, suggesting that these drugs should be avoided to maximize captopril's antihypertensive effect.

Acknowledgments

We are grateful for the assistance of Rita O'Donnell, Christine Barry, and Betty Mahoney in performing these studies, and for that of Diane Rioux in preparing the manuscript. The captopril used in these studies was generously supplied by Drs. D. McKinstry and R. Yvkovich of Squibb Pharmaceutical Company, Princeton, New Jersey.

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T J Moore, F R Crantz, N K Hollenberg, R J Koletsky, M S Leboff, S L Swartz, L Levine, S Podolsky, R G Dluhy and G H Williams

doi: 10.1161/01.HYP.3.2.168

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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