The Postdialytic Plasma Cyclic Guanosine 3′:5′-Monophosphate Level as a Measure of Fluid Overload in Chronic Hemodialysis

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ABSTRACT
The postdialytic plasma level of cGMP, a marker for the release of atrial natriuretic peptide (ANP) in humans, is closely related to hypervolemia in chronic hemodialysis patients. In order to test the practicability of routine postdialysis cGMP determination for the detection of fluid overload, ANP and cGMP levels in the total hemodialysis population of 81 patients were measured with blood samples drawn immediately after hemodialysis. Twenty-three patients had a cGMP level of more than 20 pmol/mL. In 13 of these, pulmonary congestion was present on the chest roentgenogram. Two of these patients refused a gradual reduction of their dry body weight. In the remaining 21 patients, the weight reduction was associated with a decrease in cGMP levels in all cases and with a decrease in ANP levels in all but two cases. Fourteen of the 21 patients reached a cGMP level below 20 pmol/mL after weight reduction, and at that time, none of these showed signs of pulmonary congestion on chest x-ray. All seven patients, whose cGMP levels remained above 20 pmol/mL despite the reduction, had documented heart disease with impairment of left ventricular function. These results suggest that the plasma cGMP level after hemodialysis is more apt for the determination of dry body weight than is ANP or a chest roentgenogram.

Key Words: cGMP, atrial natriuretic peptide, hemodialysis, dry body weight, heart failure

The exact determination of dry body weight represents one of the central problems of maintenance hemodialysis therapy. Usually, dry body weight of hemodialysis patients is estimated by clinical symptoms and physical signs of hypervolemia or hypovolemia and by radiological features of pulmonary congestion. However, these criteria are relatively insensitive and, as a consequence, a considerable portion of hemodialysis patients remains overhydrated.

Both atrial natriuretic peptide (ANP) and cGMP, its second messenger, are elevated in chronic hemodialysis patients. Their levels decrease significantly during fluid removal by hemodialysis but remain well above normal after dialysis (1,2). Recently, it has been demonstrated that ANP and cGMP levels determined immediately after hemodialysis may reflect the hydration state of the dialysis patient and that these parameters are not influenced by clearance across the dialysis membrane (2,3). The postdialytic plasma cGMP level showed a particularly close relation to hyperhydration (3).

In order to test the reliability of routine postdialytic cGMP determination for the detection of fluid overload, we measured in a prospective study postdialytic cGMP and ANP levels in all 81 patients of our hemodialysis center and adjusted the dry body weight according to the measured cGMP levels.

PATIENTS AND METHODS
Study Population
All 81 patients with end-stage renal failure (34 women, 47 men; mean age, 53.7 ± 12.3 yr) maintained on regular hemodialysis at the Dialysis Department of the Medizinische Klinik, Klinikum Innenstadt, University of Munich (Munich, Germany) were enlisted for the study. Preexistent heart disease with impaired left ventricular function was known in nine patients. Two patients had persistent atrial
fibrillation. Antihypertensive drugs were administered to 30 patients (37%; beta-blockers, 9 patients; vasodilators, 9 patients; combination therapy, 12 patients), 68 patients received calcium carbonate, 45 patients were on aluminum-containing phosphate binders, and 15 patients had calcitriol. None of the patients showed clinical or radiological signs of uremia. The mean level of BUN was 73 mg/dL (±28; range, 28 to 110). Standard hemodialysis techniques were employed, and the patients were treated 4 to 5 h three times per week. Ultrafiltration was volumetrically controlled in all patients (dialysis machine, MTS 2008; Fresenius, Bad Homburg, Germany). The hollow-fiber dialyzers Hemoflow F6 (Fresenius), Hemoflow F 40 (Fresenius) and CA 130 (Baxter, Deerfield, IL) were used.

Study Plan

An electrocardiogram and a chest x-ray were performed in all patients before the study. Blood samples for the determination of cGMP and ANP levels were drawn immediately after the hemodialysis session with patients in the supine position. According to the results of our previous study (3), we considered a postdialytic cGMP level of 20 pmol/mL as the upper limit of the "normal range" in chronic hemodialysis patients. When cGMP levels were over 20 pmol/mL at the first determination, dry body weight was gradually reduced over a period of up to 3 wk until, in a repeated measure, the postdialytic cGMP level was below 20 pmol/mL. Thereafter, another chest x-ray was taken.

When patients exhibited clinical symptoms of excessive ultrafiltration during hemodialysis and did not tolerate a further dry weight reduction despite a cGMP level above 20 pmol/mL, an echocardiogram was performed to assess left ventricular function. Informed consent was obtained from all participants before the study.

Determination of ANP and cGMP

Blood samples were collected in EDTA tubes on ice at the end of the hemodialysis session before the final autotransfusion with the patient in the supine position.

Plasma was separated by centrifugation at 4°C at 2,000 g for 10 min. Plasma samples were stored at −70°C until determination of ANP and cGMP. ANP was measured by RIA after extraction with silica cartridges; cGMP was determined by RIA with alcohol-extracted plasma. Both methods have been described in detail previously (4,5).

Statistics

The influence of antihypertensive treatment upon ANP and cGMP levels was tested by the Mann-Whitney U test. For comparison between plasma ANP and cGMP levels, the linear regression was calculated. All statistics were done with the StatView SE program (Abacus Concepts Inc., Berkeley, CA).

RESULTS

The initial plasma cGMP levels ranged from 2.2 to 66.8 pmol/mL (Figure 1) with a median of 19.5 pmol/mL. The corresponding ANP values ranged from 10 to 350 pg/mL (Figure 2) with a median of 97.2 pg/mL.

There was a highly significant correlation between basal plasma cGMP and ANP levels ($r = 0.7; P < 0.0001$). No significant correlation was apparent between ANP or cGMP levels and betablockers, vasodilators, combined antihypertensive therapy, or other medication ($P$ value was always <0.05).

Figure 1. Initial postdialytic plasma cGMP levels in patients without and with signs of pulmonary (pulm.) congestion on chest x-ray. A cGMP level below 20 pmol/mL was considered normal in hemodialysis patients.

Figure 2. Initial postdialytic plasma ANP levels in patients without and with signs of pulmonary (pulm.) congestion on chest x-ray.
None of the 58 patients with a cGMP level below 20 pmol/mL exhibited signs of pulmonary congestion on chest x-ray (Figure 1). Twenty-three patients (16 men, 7 women; mean age, 55.7 yr) had an initial cGMP level of more than 20 pmol/mL. Pulmonary congestion was present on chest x-ray (Figure 1) in 13 of these patients.

Two patients refused the reduction of their dry body weight. Dry weight was gradually reduced by a mean of 0.85 ± 0.5 kg in the remaining 21 patients. Figures 3 and 4 show the change in cGMP and ANP levels in relation to the weight reduction. Lowering the postdialytic body weight was associated with a decrease of cGMP levels in all cases (Figure 3) and with a decrease of ANP levels in all but two cases (Figure 4). There was a significant correlation between the decrease in plasma cGMP levels and the decrease in body weight \( P < 0.02 \). The correlation between ANP and cGMP values was again significant \( r = 0.5; P < 0.04 \) but was less close than before dry weight reduction. The decrease in cGMP did not correlate significantly with the decrease in ANP. Fourteen of the 21 patients reached a cGMP level below 20 pmol/mL after weight reduction, and at that time, none of these showed pulmonary congestion on chest x-ray. In the other seven patients, cGMP levels remained above 20 pmol/mL and further dry weight reduction was impossible because of clinical intolerance. These seven patients showed signs of impaired left ventricular function on echocardiogram. Six of the patients had known heart disease (coronary heart disease, two patients; hypertensive heart disease, two patients; mitral valve insufficiency, one patient; dilative cardiomyopathy, one patient), whereas impairment of left ventricular function was newly dis-

![Figure 3](image3.png)  
**Figure 3.** Change in cGMP levels after the reduction of dry weight in 21 patients. HF, patients with documented congestive heart failure.

![Figure 4](image4.png)  
**Figure 4.** Change in ANP levels after the reduction of dry weight in 21 patients. HF, patients with documented congestive heart failure.

**DISCUSSION**

The results of our investigation demonstrate that in an unselected hemodialysis population, the determination of the postdialytic plasma cGMP level is more sensitive for the assessment of fluid overload than is an x-ray of the chest. Only 60% of patients with an elevated postdialytic cGMP level exhibited signs of hypervolemia in the chest roentgenogram, but dry weight reduction by a various degree was clinically well tolerated by all of them.

Apart from chronic renal failure, the other major pathophysiological condition associated with markedly elevated plasma ANP and cGMP levels is heart failure (6,7). In fact, the majority of hemodialysis patients with impaired cardiac function showed high ANP and cGMP levels that could not be reduced to the normal range by dry weight reduction. However, this was not a universal finding, because three patients with documented impairment of left ventricular function had or reached normal basal cGMP values. Thus, a fixed normal range of the postdialytic cGMP level cannot be applied to hemodialysis patients with heart failure. In these patients, the intraindividual course of the cGMP levels may reflect changes in the body fluid status, whereas the absolute value is not helpful in this respect.

Antihypertensive drugs such as clonidine, dihydralazine, and \( \beta \)-blockers may affect plasma ANP and cGMP levels (8,9). However, the changes induced by these agents are small compared with the increase induced by hypervolemia. Thus, in our unselected hemodialysis population, antihypertensive medica-
tion, as well as other drugs commonly used in hemodialysis patients, had no detectable influence on ANP or cGMP levels.

It is known that nitric oxide (NO) and NO-containing substances increase intracellular cGMP formation in vitro by activation of the soluble guanylate cyclase, whereas the ANP-mediated generation of cGMP is catalyzed by the membrane-bound form of the guanylate cyclase (10). It has been shown that the plasma cGMP level does not increase significantly after the application of the NO-donor molsidomine in healthy subjects (11). Thus, an activation of the soluble guanylate cyclase obviously does not affect plasma cGMP levels in vitro. An influence of the NO system on the cGMP levels in our chronic hemodialysis patients seems therefore improbable but cannot be ruled out entirely.

In 1988, Talartschik and coworkers demonstrated that in chronic hemodialysis patients, ANP levels after dialysis can be used as a measure of fluid overload and that persistently high levels indicate congestive heart failure (12). Our results confirm these findings and extend the association between fluid overload, heart failure, and ANP levels to cGMP. In our study, the relation between hypervolemia and cGMP levels was considerably closer than between hypervolemia and ANP levels. Moreover, the cGMP determination is more suited for clinical routine, because blood samples do not need to be cooled because cGMP is stable under room temperature in EDTA-blood for at least 6 h (4).

We conclude from this study that the plasma cGMP level after hemodialysis is a sensitive marker for overhydration and is more apt for the determination of dry body weight than is ANP or a chest roentgenogram.

A postdialytic cGMP level of 20 pmol/mL may be considered as the limit of the normal range in hemodialysis patients. This limit does not apply to patients with congestive heart failure, where higher values are usually found.

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REFERENCES