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ORIGINAL ARTICLE

Access

# Evaluation of partial pressure $CO_2$ change in the dialyzer blood inlet during hemodialysis as a measure of vascular access recirculation

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## Abstract

**Introduction:** Vascular access recirculation during hemodialysis is associated with reduced effectiveness and worse survival outcomes. To evaluate recirculation, an increase in $pCO_2$ in the blood of the arterial line during hemodialysis (threshold of 4.5 mmHg) was proposed. The blood returning from the dialyzer in the venous line has significantly higher $pCO_2$, so in the presence of recirculation, pCO2 in the arterial blood line may increase ($\Delta pCO_2$) during hemodialysis sessions. The aim of our study was to evaluate $\Delta pCO_2$ as a diagnostic tool for vascular access recirculation in chronic hemodialysis patients.

**Methods:** We evaluated vascular access recirculation with $\Delta pCO_2$ and compared it with the results of a urea recirculation test, which is the gold standard. $\Delta pCO_2$ was obtained from the difference in $pCO_2$ in the arterial line at baseline ($pCO_2T1$) and after 5 min of hemodialysis ($pCO_2T2$). $\Delta pCO_2 = pCO_2T2 - pCO_2T1$.

**Findings:** In 70 hemodialysis patients (mean age: 70.52 ± 13.97 years; hemodialysis vintage of 41.36 ± 34.54, KT/V 1.4 ± 0.3), $\Delta pCO_2$ was 4 ± 4 mmHg, and urea recirculation was 7% ± 9%. Vascular access recirculation was identified using both methods in 17 of 70 patients, who showed a $\Delta pCO_2$ of 10 ± 5 mmHg and urea recirculation of 20% ± 9%; time in months of hemodialysis was the only difference between vascular access recirculation and non-vascular access recirculation patients (22 ± 19 vs. 46 ± 36, $p$: 0.05). In the non-vascular access recirculation group, the average $\Delta pCO_2$ was 1.9 ± 2 ($p$: 0.001), and the urea recirculation % was 2.8 ± 3 ($p$: 0.001). The $\Delta pCO_2$ correlated with the urea recirculation % ($R$: 0.728; $p < 0.001$).

**Discussion:** $\Delta pCO_2$ in the arterial blood line during hemodialysis is an effective and reliable diagnostic tool for identifying recirculation of the vascular

access but not its magnitude. The $\Delta pCO_2$ test application is simple and economical and does not require special equipment.

**KEYWORDS**
hemodialysis, $pCO_2$, recirCO2lation test, vascular access recirculation

# INTRODUCTION

## Background

The quality and effectiveness of hemodialytic therapy depend largely on the function of hemodialysis vascular access. The first choice for vascular access in terms of dialytic quality is the arteriovenous fistula (AVF).[1] Considering the importance of the AVF, the guidelines recommend the continuous monitoring of vascular access to evidence any alterations in its function,[1] such as the development of stenosis, which reduce its performance. To highlight these alterations, the guidelines propose the monitoring of AVF with various instruments, including the measurement of vascular access recirculation.[1] If the intra-access blood flow rate (Qa) is pathologically reduced up to values close to the extracorporeal blood flow (Qb) set during hemodialytic treatment, vascular access recirculation appears, the measurement of which can highlight the problem.[2] Vascular access recirculation during hemodialysis sessions consists of the passage of blood, already dialyzed, directly back from the venous to the arterial needle. This is a sign of a reduction in Qa linked to decreased dialysis adequacy, reduction in KT/V, and possibly a negative outcome for the patients.[3] At the moment, the evaluation of vascular access recirculation is limited by the available methods (urea recirculation, thermodilution, ionic dialysance, and glucose infusion tests)[4–8] that invariably require one of the following elements: more work for nursing staff, specific dialysis monitors, expensive external devices, or extreme accuracy to avoid measurement errors.[9] For these reasons, vascular access recirculation is usually not used as a monitoring tool of the AVF but as a diagnostic confirmation tool when an alteration in the AVF performance is already evident, this limits its possible preventive role. Marano et al.[9] proposed a new test to evaluate vascular access recirculation called the "RecirCO2lation test." This is based on the evidence that the partial pressures of carbon dioxide ($pCO_2$) in the post-dialyzer blood (called venous) is high and, if recirculation is present, it may increase the $pCO_2$ value in the pre-dialyzer blood (called arterial)[10] (Figure. 1). These alterations can be detected using blood gas analysis (BGA). The authors found in an artificial recirculation model that an increase in $pCO_2 > 4.5$ mmHg ($\Delta pCO_2$) with respect to the baseline value in the pre-dialyzer blood with a test performed 5 min from the start of dialysis session marks the presence of vascular access recirculation. At the moment, clinical studies evaluating the efficacy of this recirculation test are lacking.

## Objective

To evaluate the RecirCO2lation test ($\Delta pCO_2$) as a diagnostic tool for vascular access recirculation in real clinical practice.

# METHODS

## Study population

### Inclusion criteria

Age >18 years; patients in chronic hemodialysis for at least 3 months.

### Exclusion criteria

Acute respiratory disease, baseline $pCO_2$ greater than 45 mmHg, chronic obstructive pulmonary disease, acetate-free hemofiltration with potassium-profiled dialysate (AFB-K) dialysis, temporary vascular access, and central venous catheters.

## Study design

We performed a cross-sectional observational study to evaluate the ability to identify the presence of vascular access recirculation using the RecirCO2lation test. All eligible chronic hemodialysis patients were subjected to two methods to measure recirculation at the ICOT center in Latina (Polo Pontino Sapienza University of Rome): urea recirculation, the gold standard, and the RecirCO2lation test. These were conducted during the first hemodialysis session of the week (after a long interdialytic interval).

Urea recirculation % was evaluated with the "slow-stop flow" technique developed by Kapoian.[11,12] After the first 30 min of treatment, we stopped ultrafiltration,

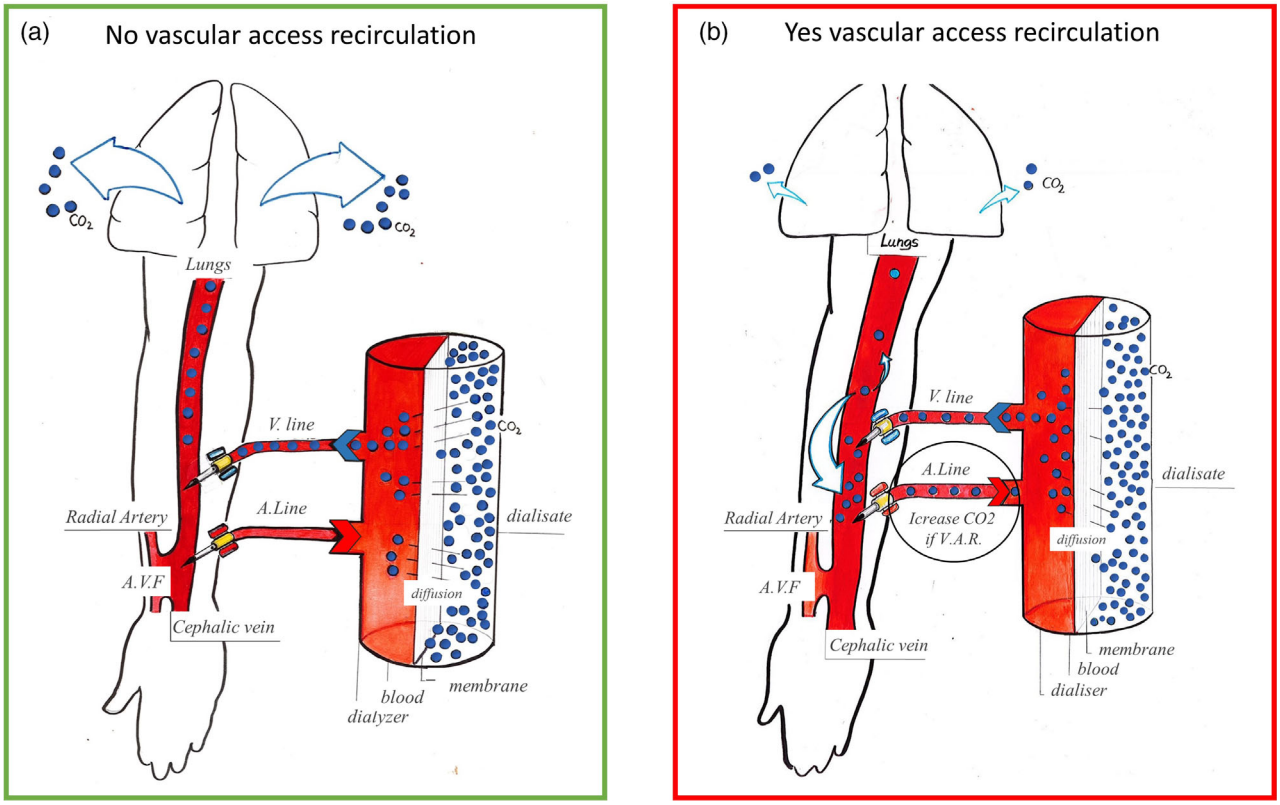


**FIGURE 1** Schematic representation of $CO_2$ evaluation to identify vascular access recirculation. (a): Patients' blood was taken during hemodialysis via the A. line. Dialysate $CO_2$ spreads into the blood during passage in the dialyzer. Blood returned to the patient V. line is rich in $CO_2$. $CO_2$ is removed from the lung in patients without vascular access recirculation. (b): If vascular access recirculation is present, the $CO_2$ in the V. line goes back to the A. line. This leads to a measurable increase in $CO_2$ in the A. line that can be used to identify the presence of vascular access recirculation. A. line, arterial line; A.V.F., artero venous fistula; V. line, venous line; V.A.R., vascular access recirculation. [Color figure can be viewed at wileyonlinelibrary.com]

increased the blood pump up to 500 mL/min (to the maximum allowed), and took blood samples from the arterial port (A) and the venous port (V) of the dialysis circuit. After collection, we reduced the blood flow to 120 mL/min, and after 10 s, we stopped the blood pump. We clamped the arterial line over the arterial port and took a blood sample (Sa); finally, the arterial line was first declamped and then the dialysis and ultrafiltration parameters were reset. The urea recirculation % was evaluated with the following formula:

$$[(\mathrm{Sa}-\mathrm{A})/(\mathrm{Sa}-\mathrm{V})]\times 100$$

The urea recirculation % was positive for vascular access recirculation if >10%.

The RecirCO2lation test was performed as described by Marano et al.[9]: we evaluated $pCO_2$ before the start of the hemodialysis session (T1) and 5 min after dialysis therapy (T2) with a BGA from the arterial line. We calculated the $\Delta pCO_2$ as the difference between T2 and T1 in the $pCO_2$:

$$\Delta pCO_2 = pCO_2T2 - pCO_2T1$$

The RecirCO2lation test was positive for vascular access recirculation if $\Delta pCO_2$ >4.5 mmHg.

In the same hemodialysis session, we evaluated the KT/V using the slow-flow method.[13] All patients received standard bicarbonate dialysis with the same acid concentrate to avoid possible bias in the results obtained (SoftPac C394: Na = 140 mmol/L, K = 3 mmol/L, Ca = 1.50 mmol/L, Mg = 0.50 mmol/L, CI = 110 mmol/L, $CH_3COO$ = 3 mmol/L; $C_6H_{12}O_6$: 5.55 mmol/L), according to their individual prescriptions of electrolyte concentrations ($HCO_3$: 29–31 mmol/L), dialysate temperature (35.5–36.0°C), and blood and dialysate flows.

## Statistical analysis

Data are expressed as means ± standard deviation (SD) for Gaussian variables or medians (25th–75th

percentiles) when normality was not tenable. We used the Shapiro test to evaluate the normality of continuous measurements. Chi-squared tests were used for qualitative variables. The *T*-tests were used to compare measurements between groups for quantitative variables. When a normality assumption was not tenable, Mann–Whitney tests were used to test for any significant differences. Spearman's correlation was used to assess the monotonic covariation of measurements. All tests were two-tailed, and (adjusted) *p*-values of <0.05 were considered statistically significant.

The diagnostic accuracy of $\Delta pCO_2$ was established using receiver operating characteristic (ROC) analysis and the corresponding Area under the ROC Curve (AUC). The optimal threshold was fixed as the one maximizing the sum of sensitivity and specificity.

Analyses were performed using R open-source software, version 3.4.0.

## RESULTS

Among 114 hemodialysis patients, 44 were excluded (15 patients did not give consent to the study, 15 had a CVC as vascular access, 4 had already undergone AFBK dialysis therapy, and 10 had basal pCO >45 mmHg). We enrolled 70 patients undergoing standard bicarbonate dialysis, with a mean age of 70.52 ± 13.97 years and hemodialysis duration of 41.36 ± 34.54 months; all the baseline characteristics are shown in Table 1. The urea recirculation % value was 7%±9% and the mean $\Delta pCO_2$ was 4 ± 4 mmHg. Vascular access recirculation was identified by both methods in the same 17 patients (24% of the population) who showed a $\Delta pCO_2$ of 10 ± 5 mmHg and a urea recirculation % of 21% ± 9%. Figure 2 shows the ROC curve for predicting true recirculation from $\Delta pCO_2$. The AUC is 1, and the sensitivity and specificity at the $\Delta pCO_2$ 4.5 threshold are both 100%. The characteristic of the two groups presenting recirculation versus no recirculation is shown in Table 1; the only clinical difference was the hemodialysis vintage (recirculation 22 ± 19 vs. no recirculation 46 ± 36 months, $p < 0.05$). Regarding the evaluation of vascular access recirculation, the average $\Delta pCO_2$ was significantly higher in the vascular access recirculation group (10 ± 5 mmHg vs. 1.9 ± 2 mmHg, $p < 0.001$), as was the urea recirculation % (20.9 ± 9 vs. 2.8 ± 3, *p*: 0.001). A positive correlation between $\Delta pCO_2$ and urea recirculation % (*R*: 0.728; $p < 0.001$;

**TABLE 1** Clinical and biochemical characteristics of the enrolled population and the two subgroups (no-recirculation and recirculation).

| | Enrolled population (*N* = 70) | No-recirculation (*N* = 53) | Recirculation (*N* = 17) | *p*< |
|---|---|---|---|---|
| Age, years | 70.52 ± 13.97 | 70.31 ± 15.71 | 71.45 ± 14.67 | 0.808 |
| M/F, n° (%) | 41/29 (58/42) | 33/20 (62/38) | 8/9 (47/53) | 0.521* |
| Hemodialysis vintage, months | 41.36 ± 34.54 | 46.35 ± 36.54 | 22.13 ± 19.43 | 0.016 |
| Kt/V | 1.41 ± 0.32 | 1.43 ± 0.31 | 1.31 ± 0.33 | 0.193 |
| Na, meq/L | 139.68 ± 3.16 | 140 ± 3.15 | 138 ± 3.16 | 0.176 |
| K, meq/L | 5.40 ± 1.25 | 5.36 ± 1.22 | 5.45 ± 1.32 | 0.779 |
| Ca, meq/L | 8.75 ± 1.18 | 8.7 ± 1.20 | 8.8 ± 1.16 | 0.779 |
| P, meq/L | 5.49 ± 1.35 | 5.5 ± 1.40 | 5.6 ± 1.32 | 0.775 |
| Hb, g/dL | 10.74 ± 1.12 | 10.7 ± 1.14 | 11.04 ± 1.10 | 0.164 |
| Qb, ml/min | 300 ± 20 | 300 ± 10 | 300 ± 25 | 1.000 |
| Pre-hemodialysis | | | | |
| $HCO_3$, meq/L | 22.43 ± 2.62 | 23.34 ± 2.23 | 22.52 ± 2.81 | 0.709 |
| $pCO_2$, mmHg | 39.45 ± 4.97 | 39 ± 5.86 | 40 ± 4.30 | 0.752 |
| After 5 min of hemodialysis | | | | |
| $HCO_3$, meq/L | 24.21 ± 3.21 | 24.74 ± 2.23 | 23.65 ± 4.42 | 0.08 |
| $pCO_2$, mmHg | 42.91 ± 6.37 | 40 ± 4.45 | 50 ± 7.86 | 0.001 |
| $\Delta pCO_2$, mmHg | 4 ± 4 | 1.9 ± 2 | 10 ± 5 | 0.001 |
| Urea recirculation, % | 7 ± 9 | 3 ± 3 | 21 ± 9 | 0.001* |

*Note*: Data are expressed as mean ± SD.

Abbreviation: Ca, calcium; Hb, Hemoglobin; $HCO_3$, bicarbonates; K, potassium; M/F, men/female; Na, sodium; P, phosphate; $pCO_2$, partial pressures of carbon dioxide; $\Delta pCO_2$: Change $pCO_2$: $pCO_2$ (T2)−$pCO_2$ (T1); Qb, extra corporeal blood flow; VAR, vascular access recirculation.

*No recirculation versus recirculation *T*-test for quantitative variables was used to compare measurements between groups. Chi-squared test for qualitative variables.

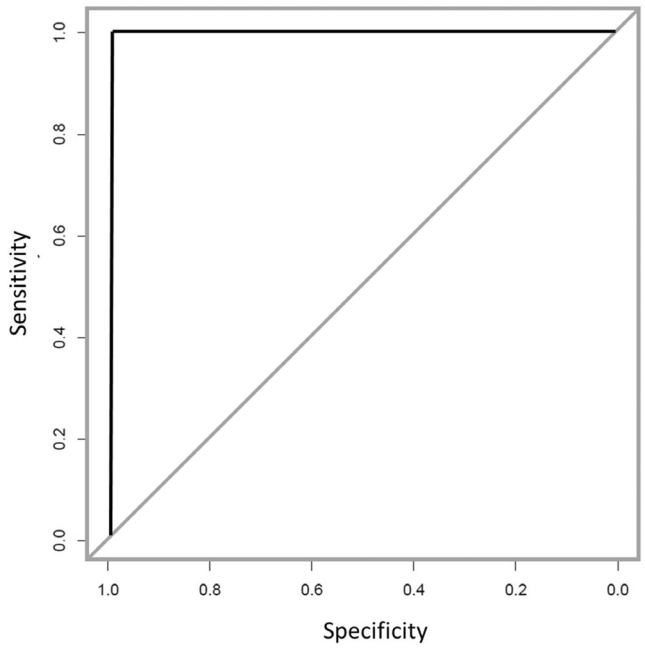


**FIGURE 2** Receiver operating characteristic (ROC) analysis. Diagnostic accuracy of $\Delta pCO_2$: AUC is 1, and the sensitivity and specificity at the $\Delta pCO_2$ 4.5 threshold are both 100%.

Figure 3a) was found in the enrolled population; no correlations were found in the no-recirculation and recirculation subgroups (Figure 3b,c). Urea recirculation % and $\Delta pCO_2$ showed no correlations with KT/V in the whole population (Figure 4a,b). In the group of patients with vascular access recirculation, we found a negative correlation between $\Delta pCO_2$ and KT/V (*R*: 0.505; *p*: 0.02; Figure 4c). Additionally, in this subgroup, no correlation was found between the urea recirculation % and KT/V (Figure 4d).

## DISCUSSION

The results show that the RecirCO2lation test identifies the presence of pathological AVF recirculation with the same effectiveness as the urea recirculation %. Moreover, the RecirCO2lation test correlates negatively with KT/V, identifying patients with reduced dialysis efficacy secondary to the presence of vascular access recirculation.

Good vascular access is essential for the quality of life and survival outcomes of patients receiving chronic hemodialysis.[14] Therefore, reliable and easy-to-use monitoring tools are needed in order to identify AVF

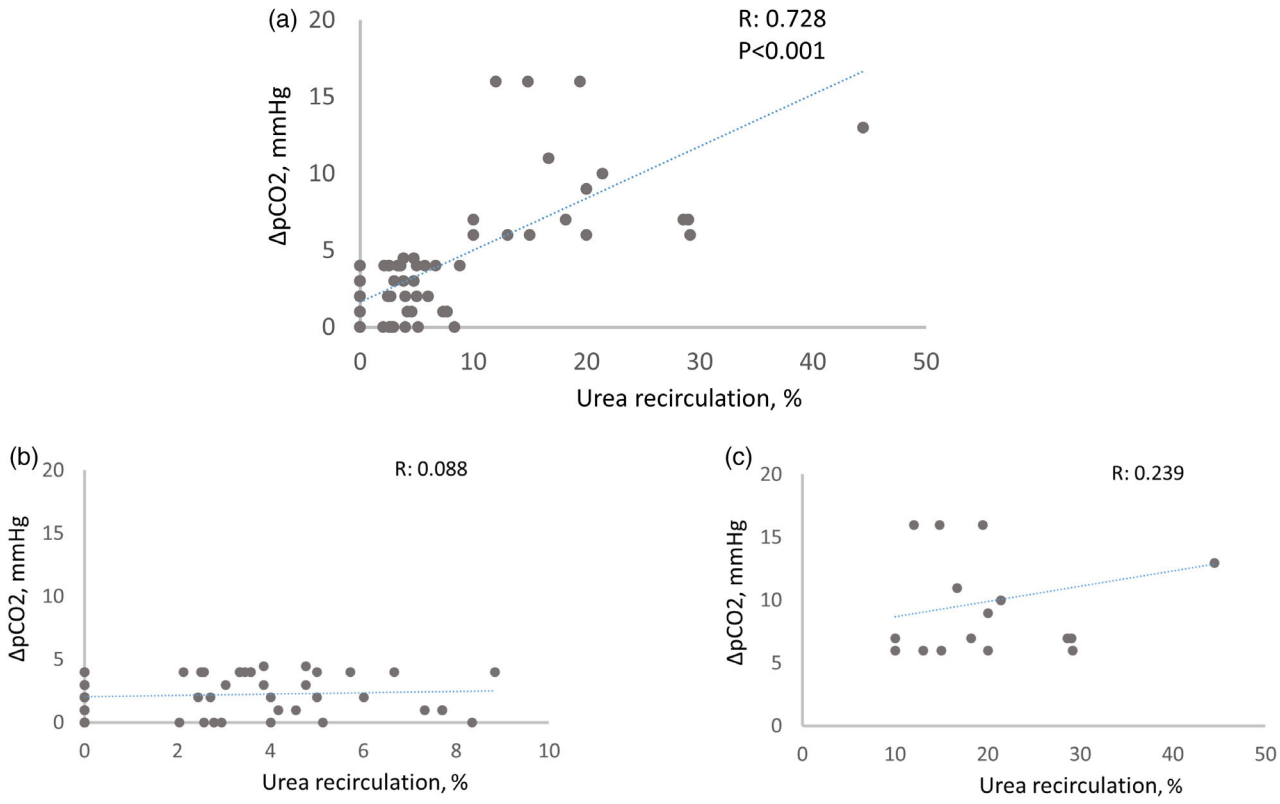


**FIGURE 3** Correlation test of urea recirculation, % with $\Delta pCO_2$, mmHg, in the enrolled population (a) and in the subgroups of no-recirculation (b) and recirculation (c). $\Delta pCO_2$: Change in $pCO_2$: $pCO_2$ (T2)−$pCO_2$ (T1). [Color figure can be viewed at wileyonlinelibrary.com]

alterations, with the aim of making a pre-emptive diagnosis and correction before they become clinically relevant.[1,7] Among these tools, vascular access recirculation is often not performed as frequently or adequately as it should be, mostly due to the technical difficulties.[4] The RecirCO2lation test, from a theoretical point of view, is simple; it does not require access to the laboratory for analysis or the infusion of marker agents, and there is a low cost of performance[9] (Figure 1). This is based on evidence that post-filter blood (venous line) has elevated levels of $pCO_2$. This phenomenon is caused by the presence in dialysate of high levels of $pCO_2$ that derive from $HCO_3$ dissociation and the small amount of acetic acid that reacts with $HCO_3$. It is therefore known that the partial pressure of $CO_2$ in the dialysate is considerably higher than in the patient's blood, causing the diffusion of $pCO_2$ from dialysate to blood. As a result, post-filter blood has a higher $pCO_2$ than pre-filter blood.[15,16] As experimentally evidenced by Marano et al.,[9] in the presence of recirculation of vascular access, this causes an increase in $pCO_2$ in the pre-filter blood (Figure 1).We enrolled 70 patients in chronic hemodialysis treatment with AVF. The clinical characteristics of our population overlapped with the characteristics of the general hemodialytic population,[17] with an average age of 70 years (Table 1). Recirculation was identified by the RecirCO2lation test for 17 patients (24% of the population), in agreement with the urea recirculation % test. In particular, the ROC analysis showed an AUC of 1, and the sensitivity and specificity at the $\Delta pCO_2$ 4.5 threshold were both 100% (Figure 2). As shown in Figure 3a, the two methods were positively correlated ($p$: <0.001) in the whole population. These results emphasize that these methods can be considered alternatives in assessing the presence of vascular access recirculation. No correlation was shown between urea recirculation and $\Delta pCO_2$ in the population divided into the two subgroups according to the presence or absence of recirculation (Figure 3b,c). This result underlines that $\Delta pCO_2$ identified recirculation but not its magnitude. The lack of correlation between urea recirculation and $\Delta pCO_2$ in the recirculation subgroup also justifies the different correlations between the two methods and the KT/V (Figure 4). In fact, it is interesting to note that in the group of 17 patients with vascular access recirculation, there was a negative correlation between $\Delta pCO_2$ and KT/V (Figure 4c). These data agree with the idea that the presence of recirculation reduces the effectiveness of hemodialytic treatment, leading to a reduction in KT/V.[1] As shown in Figure 4d, this correlation was not present between the urea recirculation % and KT/V. This different relationship between the two methods of measurement of recirculation and KT/V is

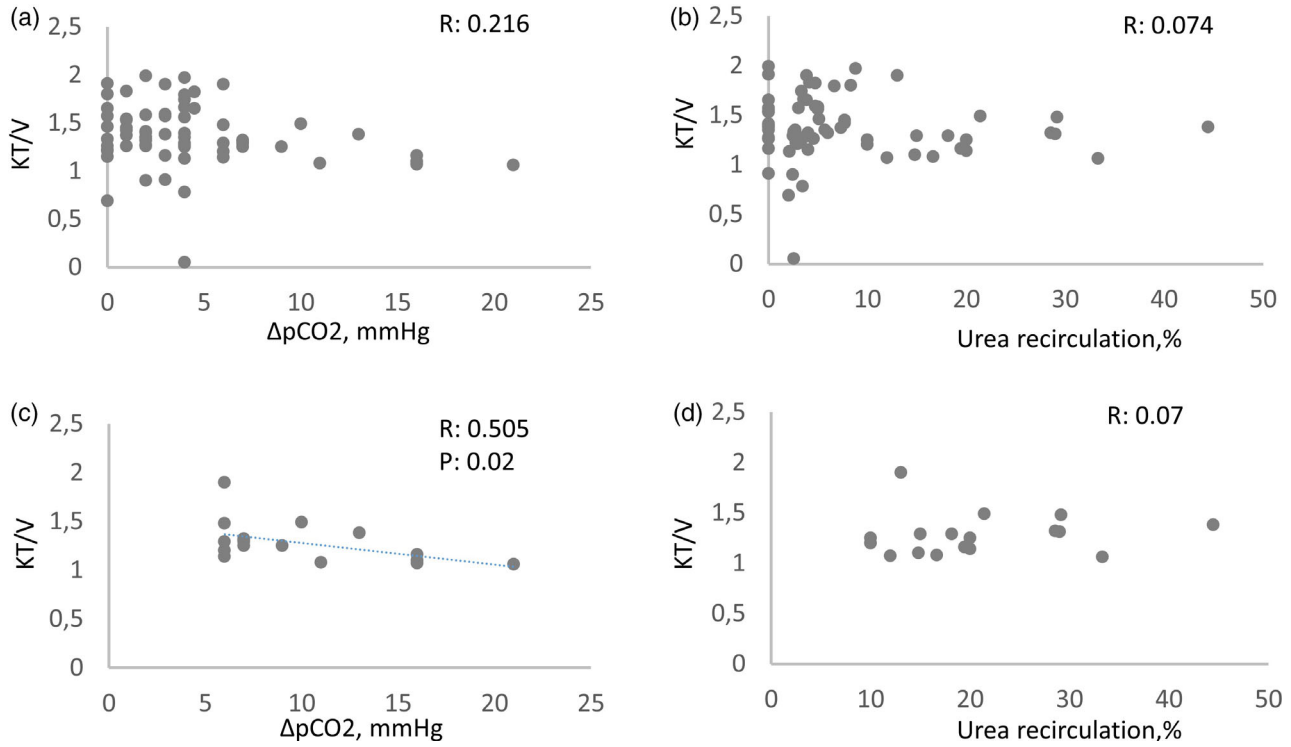


**FIGURE 4** Correlation test of KT/V and recirculation measurement methods ($\Delta pCO_2$ and urea recirculation, %) in the enrolled population (a–b) and the subgroup with recirculation (c–d). $\Delta pCO_2$: Change in $pCO_2$: $pCO_2$ (T2)−$pCO_2$ (T1). [Color figure can be viewed at wileyonlinelibrary.com]

probably linked to the different methodologies used for the measurement of recirculation. The RecirCO2lation test was measured without changing Qb during the hemodialysis session, representing the actual recirculation present during a dialysis session. The urea recirculation % is measured by increasing Qb to 500 mL/min to show early Qa reduction. In fact, the recirculation of vascular access occurs when the Qa and the Qb are similar.[2] The increase in Qb to 500 mL/min should highlight, with the appearance of urea recirculation %, the reduction in Qa to below 600 mL/min, which is considered an appropriate threshold.[1] This, however, makes the measurement of the vascular access recirculation with the urea recirculation % not identifiable of the recirculation actually present during a standard hemodialysis session with Qb at 300 mL/min (average Qb of our patients, Table 1). It is important to note that the different Qb used in the two methods may alter the ability to show recirculation. Conversely, the RecirCO2lation test identifies vascular access recirculation in the same patients as the urea recirculation % despite not increasing the Qb for its measurement. This suggests equal reliability but an increased ability of the RecirCO2lation test to identify the presence of vascular access recirculation in a standard hemodialysis session. The result may be linked to two different point. First, the RecirCO2lation test is not affected by cardiopulmonary recirculation,[9] and $\Delta pCO_2$ is due only to vascular access recirculation. Second, the post-dialyzer blood $pCO_2$ is considerably higher (about 70 mmHg)[16] than the patient's $pCO_2$ (39 mmHg in our population). This significant concentration gradient may identify small but significant recirculation. These two points can explain why the RecirCO2lation test identified vascular access recirculation with a standard Qb of 300 mL/min. Accordingly, only the RecirCO2lation test showed a correlation between KT/V and vascular access recirculation. Additionally, our recirculation subgroup did not show a difference in the $HCO_3$ concentration before and after 5 min of hemodialysis. The $HCO_3$ difference before and during hemodialysis was proposed as a test to identify vascular access recirculation,[18] but accordingly, with other evidence,[9] $HCO_3$ was unable to identify recirculation in our patients. There are various reasons for this result: the $HCO_3$ concentration gradient between post-dialyzer blood and pre-dialyzer blood is lower than the $pCO_2$ gradient, the $HCO_3$ concentration may change during hemodialysis treatment, and $HCO_3$ is calculated and not directly measured from blood-gas analysis software.

In conclusion: Our data suggest that the RecirCO2lation test effectively identifies vascular access recirculation. It is simple in its application and does not require dedicated preparation and equipment.

## Study limits

This study has some limitations: it is a single-center study with no sample-size calculation; the hemodialysis $HCO_3$ prescription may affect the dialysate $CO_2$ level, possibly modifying the $\Delta pCO_2$. The study was performed with an $HCO_3$ prescription of 29–31 meq/L; further study may investigate if lower or higher $HCO_3$ prescriptions may affect the $\Delta pCO_2$; the RecirCO2lation test indicates the presence or absence of recirculation, but it is not able to show the magnitude of recirculation; the results cannot be applied to patients with respiratory problems or undergoing AFB-K dialysis, showing the need for specific additional studies.

## ETHICS STATEMENT

This study was a sub-analysis of protocol N°0027769/2019, which was approved in 2017 by the "Comitato Etico Lazio 2." All procedures performed in the study were in accordance with the Helsinki Declaration and received informed consent approval from all involved patients.

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