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Avoidance of Perioperative Acute Renal Failure: Land in Sight?

To the Editor:—Acute renal failure (ARF) is a severe perioperative complication and, until today, strategies to avoid it remain controversial.[1] Kheterpal *et al.*[2] performed an informative retrospective analysis on this topic, underlining the impact of perioperative ARF on patient mortality. Moreover, they identified several independent predictors of ARF in noncardiac surgery. To have them in mind will be useful for our daily practice.

However, the authors' conclusions regarding intraoperative risk factors drawn in the abstract, despite being markedly attenuated in the main text, seem somewhat misleading to us, especially in combination with the title announcing a study on "Patients with Previously Normal Renal Function."[2] To prevent general confusion regarding the perioperative use of vasopressors and diuretics, it is important to clearly stress that one major shortcoming limits a direct transfer of the findings to the healthy individual: More than 65,000 patients were primarily screened to evaluate the propensity of patients with certain risk factors to ARF. Unfortunately, not only those 6,534 patients without preoperative renal function measures were excluded from the study,[3] but in addition 25,537 outpatient cases. In all, the investigators excluded the healthier part of their primary collective. To draw an overall conclusion questioning the use of vasopressors and diuretics in healthy patients from this preselected collective seems a bit overreaching to us. But a careful look into their subgroup analysis does not lower our concerns: In the low-, medium-, and medium–high-risk groups, only 0.8% of the patients receiving vasopressors and 1.5% of the patients receiving diuretics developed ARF. The authors themselves state that ARF occurs in 1–5% of all hospitalized patients,[2] meaning that diuretics seem to have no influence and that vasopressors seem to even lower the risk of ARF. This picture is slightly changed when taking the high-risk patients into account. However, even now, the overall risk (vasopressors 4.8% and diuretics 2.3%) is still within the range anticipated in hospitalized patients.[2]

To make such a striking statement in the abstract is an unnecessary overinterpretation and falls short of this otherwise very well-performed retrospective analysis.

In addition, an extremely interesting finding is only scarcely discussed by the authors: Urine output was not associated with ARF in this study. Eighty-eight percent of the patients not developing ARF had a urine output of less than 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$, surprisingly significantly more patients than those with ARF (75%). Above that, mean urine production in patients developing ARF was not significantly different from that in the other patients. This is in clear contrast to the common assumption that "logic suggests"[1] urine output has to be maintained above a certain level to prevent ARF and, therefore, should be treated with crystalloid boluses.[4] From our point of view, the authors made an important contribution to the current discussion on the practicability of a modern approach to perioperative fluid therapy, aiming at limiting the total crystalloid amount to reduce perioperative complications.[5]

We would like to congratulate Kheterpal *et al.* on this interesting retrospective analysis. Their work not only will contribute to our patient's safety, but, more importantly, it marks several starting points for further prospective investigations.

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The above letter was sent to the authors of the referenced editorial. The authors did not feel that a response was required.—James C. Eisenach, M.D., Editor-in-Chief

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Use of Cockroft and Gault Formula for Estimation of Creatinine Clearance

To the Editor:—We read with interest the recently featured article "Predictors of Postoperative Acute Renal Failure after Noncardiac Surgery in Patients with Previously Normal Renal Function" by Kheterpal *et al.*[1] in ANESTHESIOLOGY. We congratulate the authors on this excellent article. The importance of alterations in renal function in the perioperative period is not widely recognized by anesthesiologists. Hence, we appreciate the contribution of the authors on this subject.

During our own work on renal function, we have noticed a recent change away from using the Cockroft and Gault formula for estimation of Creatinine Clearance toward using the Modification of Diet in Renal Disease formula in view of the many drawbacks with the Cockroft and Gault formula.[2,3,4,5] We noted in the article significant findings related to renal function and obesity. These results may have looked different with the Modification of Diet in Renal Disease formula with respect to the obese patients in their population.

We would be curious if the authors could comment on their choice of formula for estimation of creatinine clearance in their article.

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In Reply:—We thank Dr. Chappell *et al.* for their interest in our article and insightful review. They first question the abstract's conclusion that "The use of vasopressor and diuretics is also associated with acute renal failure," and specifically highlight concern regarding the applicability of the conclusion to "healthy individuals."[1] Dr. Chappell *et al.* seem to be using the concepts of "healthy patients" and "patients with previously normal renal function" interchangeably. We agree that the patient population we examined does not represent "healthy patients," as demonstrated by the variety of comorbidities affecting the patients and delineated in table 1 of the original article.[1] However, the data are explicitly based on patients with normal preoperative renal function, given that we excluded patients with preexisting renal dysfunction or the failure to demonstrate a preoperative estimated creatinine clearance of 80 ml/min or greater. As we stated in the limitations section, although these criteria do exclude patients with renal dysfunction, they probably also exclude healthy patients who did not warrant preoperative serum creatinine testing. Our article does not attempt to make commentary regarding "healthy patients," simply those with normal renal function.

Next, Dr. Chappell *et al.* suggest that it is inappropriate to claim an association between vasopressor or diuretic administration and acute renal failure (ARF) because of their analysis of the details in table 5 of the original article. They compared the 0.8% and 1.5% ARF incidences experienced by patients receiving vasopressor and diuretics, respectively, to existing literature documenting an ARF rate of 1–5% for hospitalized patients.[2–4] They conclude that an association cannot exist because 0.8% and 1.5% are less than the 1–5% incidence described in epidemiologic studies.[2–4] We disagree with this interpretation. The quoted 1–5% incidence is for an entirely different patient population: all hospitalized patients, without regard for their reason for admission. The 1–5% incidence presumably also includes patients at very high risk for ARF: urologic surgery patients, cardiac surgery patients, and patients receiving intravenous contrast postoperatively. Most importantly, that population and literature include patients with preexisting renal dysfunction, a group well known to be at high risk for postoperative ARF. A careful review of the original article's table 5 demonstrates that among low-, medium-, and medium–high-risk patients, 1.5% of those who received a diuretic experienced ARF, whereas only 0.3% of those who did not receive a diuretic experienced ARF. Similarly, among low-, medium-, and medium–high-risk patients, 0.8% of those who received a vasopressor infusion experienced ARF, whereas only 0.4% of those who did not receive a vasopressor infusion experienced ARF. We believe these are the most relevant comparisons. Most importantly, given that diuretic and vasopressor infusion administration were identified as independent predictors in a logistic regression analysis, they are independently associated with the ARF outcome. Our abstract conclusion only states this observation, without interpreting causation or speculating on pathophysiology.

Dr. Chappell *et al.* also highlight an important element of our data that may have warranted additional attention in the discussion section: the observation that intraoperative urine output is not associated with postoperative ARF. We completely agree with Dr. Chappell *et al.* that this is an important observation that contrasts existing clinical assumption and demands increased focus. We were reticent to expound more aggressively on this observation given that our data could not discern a causal relation or extract out the effect of fluid administration, preoperative fasting, or the timing of diuretics. We are uncomfortable concluding that these data suggest "limiting the crystalloid amount to reduce perioperative complication" as Dr. Chappell *et al.* suggest. In addition, Dr. Chappell *et al.* have brought to our attention a typographical error in table 5: The label of the second row from the bottom should include a greater-than symbol rather than a less-than symbol to read: "Urine >0.5 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}." This typographical error does not change the interpretation of the data: Urine output was not associated with ARF. In fact, most patients who experienced ARF did not demonstrate oliguria. We are delighted that Dr. Chappell *et al.* support our hypothesis-generating work. We hope these data will spur "further prospective investigations" as they suggest.

Dr. D'souza *et al.* raise an interesting point regarding the choice of the Cockcroft–Gault formula *versus* the Modification of Diet in Renal Disease formula when estimating creatinine clearance. As mentioned in the discussion section, the use of a single serum marker as a measure of renal function during a nonsteady postoperative state suffers from questionable accuracy, regardless of which formula is chosen. The Modification of Diet in Renal Disease formula was derived from data in patients with existing chronic kidney disease.[5] Later, it was modified to incorporate race-specific variations, providing additional accuracy in African-Americans. Conversely, the Cockcroft–Gault formula was derived using patients with and without chronic kidney disease.[6] The Cockcroft–Gault formula suffers from the absence of any race-specific measures. The Modification of Diet in Renal Disease formula suffers from the absence of any weight-based measures. We used the Cockcroft–Gault formula for several reasons: (1) It is more accurate across a broad range of renal function,[7] (2) it incorporates weight and the effect of weight on anticipated normal serum creatinine, (3) it is used more widely in pharmacologic dosing practice, and (4) the Modification of Diet in Renal Disease formula is known to underestimate glomerular filtration rate in patients with normal renal function.[7] Identifying patients with normal preoperative renal function was the foundation of our methodology and guided us to the use of the Cockcroft–Gault formula.

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