Volume expansion and contrast-induced acute kidney injury

There is an ever-increasing population at risk of being exposed to intravascular iodinated contrast because of the increasingly popular practice of imaging techniques in medicine and surgery. Despite efforts to improve the safety of these agents, there has been no fundamental improvement in contrast product development since the introduction of iso-osmolar contrast more than 20 years ago.[1–3] Thus, clinicians have focused on strategies to decrease the risk of contrast-induced acute kidney injury by limiting contrast volume, giving adjuvant agents, and providing supportive care once the renal damage has occurred. It has been suggested that intravascular volume expansion with isotonic crystalloid solution can decrease the incidence and the severity of contrast-induced acute kidney injury.[4] This approach is attractive because the short-term administration of intravenous fluid results in an increase in renal blood flow, glomerular filtration, and increased volume of urine flow through the tubular segments of the nephron. Forced diuresis has been associated with a lesser rise in serum creatinine especially when higher rates (>150 ml/h) of urine flow have been achieved.[5]

In *The Lancet*, Estelle Nijssen and colleagues[6] present the primary results from a randomised trial comparing no-hydration protocol versus prophylactic intravascular volume expansion with normal saline in a high-risk group of patients receiving contrast for radiological or cardiovascular procedures. Serum creatinine was measured after the exposure in a standard fashion. This trial was unique in that it attempted to use a non-inferiority design, which is unusual for contrast-induced acute kidney injury, setting up the hypothesis that withholding prophylaxis would be non-inferior to the standard-of-care administration of intravenous normal saline. The method of computation of the non-inferiority margin and the revision of this statistical approach was unconventional and in the end had the assumptions that the contrast-induced acute kidney injury rate in the normal saline group would be 2·4% and the rate in the no saline prophylaxis group could be as high as 4·5% with relative risk or hazard ratio of less than 1·88 to meet non-inferiority. The upper bound of the 95% confidence limit for this construction is about 4·50, which exceeds all conventions for non-inferiority trials.[7,8] In other words, could one be comfortable accepting the non-inferior result knowing that withholding standard-of-care volume expansion could result in 4 to 5-fold increased hazard of contrast-induced acute kidney injury? Clearly this is questionable and represents an example on how clinical trials can go awry with hypothesis testing.

With the basis of clinical studies concerning volume expansion that have been published so far, how could a future trial add to our understanding of the problem and improve opportunities for patients? The first strategy is to guide the amount of intravenous fluid according to a personalised parameter such as left ventricular end-diastolic pressure or degree of total body water inferred by bioimpedance.[2,9,10] Degrees of precision are needed in terms of volume expansion for renal protection with avoidance of volume overload and renal congestion (appendix). In view of the low rates of contrast-induced acute kidney injury possible in some centres and patient groups, as Nijssen and colleagues learned, all efforts to reduce variation are necessary including restriction to similar procedures, setting a standard for appropriateness, the use of iso-osmolar contrast, and measurement of approved markers of kidney damage (eg, NGAL, TIMP2*IGFBP7) to achieve greater precision on the ascertainment of contrast-induced acute kidney injury.[11] We should strive for much larger trials and realistic effect sizes for interventions in the range of 20–30% risk reductions. In our view this field is not ready for non-inferiority trials until we have a reference standard intervention that is agreed upon as proven, and thus can be positioned as the control group and be compared with novel treatment or strategy.

This trial should stand as a signal to the community that attention should be shifted to large collaborative efforts that are patient-centred, rely on methods of precision medicine, and use the approved methods that allow us to better ascertain the outcome.

*Peter A McCullough, Jun Zhang, Claudio Ronco
Baylor University Medical Center (PAM), Baylor Heart and Vascular Institute (PAM, JZ), Baylor Jack and Jane Hamilton Heart and Vascular Hospital, Dallas, TX 75226, USA (PAM); The Heart Hospital, Plano, TX, USA (PAM); Department of Nephrology Dialysis and Transplantation, St Bortolo Hospital, Vicenza, Italy (CR); and International Renal Research Institute, Vicenza, Italy (CR)
peteramccullough@gmail.com

We declare no competing interests.

Living Art Enterprises,LLC/Science Photo Library

Published Online
February 20, 2017
http://dx.doi.org/10.1016/S0140-6736(17)30540-8

See Online/Articles
http://dx.doi.org/10.1016/S0140-6736(17)30057-0

See Online for appendix

1 McCullough PA, Choi JP, Feghali GA, et al. Contrast-induced acute kidney injury. *J Am Coll Cardiol* 2016; **68:** 1465–73.

2 McCullough PA, Brown JR. Effects of intra-arterial and intravenous iso-osmolar contrast medium (iodixanol) on the risk of contrast-induced acute kidney injury: a meta-analysis. *Cardiorenal Med* 2011; **1:** 220–34.

3 McCullough PA, Capasso P. Patient discomfort associated with the use of intra-arterial iodinated contrast media: a meta-analysis of comparative randomized controlled trials. *BMC Med Imaging* 2011; **11:** 12.

4 Brar SS, Aharonian V, Mansukhani P, et al. Haemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: the POSEIDON randomised controlled trial. *Lancet* 2014; **383:** 1814–23.

5 Briguori C, Visconti G, Donahue M, et al. RenalGuard system in high-risk patients for contrast-induced acute kidney injury. *Am Heart J* 2016; **173:** 67–76.

6 Nijssen EC, Rennenberg RJ, Nelemans PJ, et al. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. *Lancet* 2017; published online Feb 20. http://dx.doi.org/10.1016/S0140-6736(17)30057-0.

7 Dann RS, Koch GG. Review and evaluation of methods for computing confidence intervals for the ratio of two proportions and considerations for non-inferiority clinical trials. *J Biopharm Stat* 2005; **15:** 85–107.

8 Bethel MA, Sourij H. Impact of FDA guidance for developing diabetes drugs on trial design: from policy to practice. *Curr Cardiol Rep* 2012; **14:** 59–69.

9 Maioli M, Toso A, Leoncini M, et al. Pre-procedural bioimpedance vectorial analysis of fluid status and prediction of contrast-induced acute kidney injury. *J Am Coll Cardiol* 2014; **63**: 1387–94.

10 Larsen TR, Singh G, Velocci V, Nasser M, McCullough PA. Frequency of fluid overload and usefulness of bioimpedance in patients requiring intensive care for sepsis syndromes. *Proc (Bayl Univ Med Cent)* 2016; **29:** 12–15.

11 McCullough PA, Shaw AD, Haase M, et al. Diagnosis of acute kidney injury using functional and injury biomarkers: workgroup statements from the tenth Acute Dialysis Quality Initiative Consensus Conference. *Contrib Nephrol* 2013; **182:** 13–29.