Effects of angiotensin II in the management of perioperative hypotension in kidney transplant recipients

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Abstract

Background: Due to the mechanisms of action of conventional catecholamine vasoressors, there is increased risk of renal allograft injury and adverse events in transplant recipients with fluid-refractory distributive shock during the perioperative period. As such, mechanistically alternative vasopressors like angiotensin II (ATII) may avoid these complications, but there is an absence of data supporting use in this population.

Methods: This was a single-center, single-arm, open-label, phase 4 study conducted as a 1-year pilot of 20 adult renal transplant recipients receiving ATII as their first continuous infusion vasopressor in the perioperative period. The study aim was to systematically assess the safety and hemodynamic effects of ATII. Safety was assessed based on the incidence of adverse events. Hemodynamic effect was assessed by the achievement of per protocol hemodynamic goals (i.e., SBP ≥ 120 mmHg) and the need for adjunct vasopressors.

Results: Most cases involved deceased donors (70%), with a corresponding mean (SD) cold ischemia time of 14.7 (8.6) h. Over a surgery duration of 5.3 (1.2) h, subjects received 3.2 (2.0) L of total volume resuscitation prior to ATII initiation. No adverse events were directly related to ATII administration. Throughout this period, ATII was utilized for a median of 1.0 (IQR, 1.5) h intraoperatively (N = 7), 26.5 (IQR, 84.8) h postoperatively (N = 4), and 63.8 (IQR, 57.8) h in subjects who required ATII both intra- and postoperatively (N = 9). Only one of the 20 patients needed adjunct continuous infusion vasopressors in addition to ATII.

Conclusions: Based on the observations of this pilot study, ATII is a safe and effective vasopressor option for renal transplant recipients requiring perioperative hypotension reversal.

KEYWORDS
allograft, angiotensin, hypotension, kidney, mean arterial pressure, perioperative, renal, systolic blood pressure, transplant
1 | INTRODUCTION

Hypoperfusion of the transplanted organ is a major hemodynamic consequence of prolonged hypotension during the perioperative phase of renal transplantation. Compensatory vasoconstriction of the renal afferent arterioles, reduction in nitric oxide production, and subsequent activation of proinflammatory pathways further contribute to unfavorable outcomes, such as acute tubular necrosis (ATN), delayed graft function (DGF), and allograft failure. Data from the United States Renal Data System 2020 Annual Report illustrate a significant correlation between rates of graft failure and mortality at 1-, 5-, and 10-years posttransplant in both deceased (DDRT) and living (LDRT) donor renal transplant recipients ranging between 1%–7%, 12%–23%, and 50%–65%, respectively. Therefore, rapid attainment and maintenance of hemodynamic goals such as systolic blood pressure (SBP) and mean arterial pressure (MAP) is crucial for the mitigation and prevention of these severe adverse events. Despite the absence of formal guidance defining specific SBP and MAP goals during the perioperative renal transplant period, several studies have suggested achieving and maintaining an SBP of ≥120 mmHg with a corresponding MAP of ≥95 mmHg. In the setting of perioperative fluid-refractory distributive shock, exposure to conventional catecholamine vasopressors (e.g., phenylephrine, norepinephrine, epinephrine, and dopamine) may compound renal vasoconstriction, further impede renal blood flow, and inadvertently exacerbate acute reperfusion injury due to the α1-adrenergic activity of these vasoactive agents. Multiple renal transplant studies have demonstrated a negative association with perioperative administration of catecholamine vasopressors, including decreased urine output (UOP), slower normalization of serum creatinine (Scr), and DGF in recipients, as well as increased rates of allograft rejection, tachycardia, hospital length of stay, and mortality. Conversely, non-catecholamine vasopressors such as angiotensin II (ATII) utilize alternative mechanisms to regulate SBP and MAP. As illustrated in Figure 1, the renin-angiotensin-aldosterone system (RAAS) helps maintain adequate perfusion pressure within the transplanted kidney by preventing excessive α1-agonism with more balanced afferent and efferent arteriolar vasoconstriction, theoretically decreasing the risk of ischemia and acute kidney injury (AKI).

To further emphasize the beneficial renal outcomes of synthetic ATII, a significant phase 3 trial, Angiotensin II for the Treatment of High-Output Shock’ (ATHOS-3), randomized subjects with catecholamine-resistant, fluid refractory distributive shock to receive either synthetic ATII or normal saline placebo to determine the incidence of MAP goal attainment within 3 h (defined as a MAP increase of ≥10 mmHg from baseline or an overall increase to ≥75 mmHg). In 70% of subjects receiving synthetic ATII, goal MAP was achieved within a median of 5 min, with sustained effects lasting throughout the duration of the study. Rapid MAP goal attainment within the synthetic ATII group allowed significant dose reductions to both study drug and catecholamine vasopressor therapy in 67% of subjects within 30 min of study drug initiation, until protocol discontinuation of the study drug at 48 h. Post-hoc analysis of ATHOS-3 later evaluated severe AKI patients without a history of end-stage renal disease (ESRD) who received renal replacement therapy (RRT) at the time of study drug initiation. In addition to a consistent MAP response, a greater proportion (38%) of subjects in the synthetic ATII group discontinued RRT within 7 days of study drug initiation. Though the underlying trigger of distributive shock from septic shock is different than that of hypotension surrounding perioperative kidney transplant, the resultant hemodynamic presentation is similar, and the renal benefit seen in sepsis may be magnified in the renal transplant population.

Aside from this landmark study prompting FDA approval of synthetic ATII (GIAPREZA®; La Jolla Pharmaceutical Company, San Diego, CA, USA) for the treatment of vasodilatory shock, no additional studies have evaluated the safety of this non-catecholamine vasopressor agent, nor described its utilization, in the renal transplant population. Therefore, this study aimed to pilot the use of synthetic ATII for the management of perioperative hypotension in kidney transplant recipients.

2 | MATERIALS & METHODS

2.1 | Study design & population

This single-center, single-arm, prospective, open-label, phase 4 study was conducted as a 1-year pilot (ClinicalTrials.gov: NCT04529005). The study was approved by the University of Illinois at Chicago (UIC) Office for the Protection of Research Subjects Institutional Review Board and conducted in accordance with good clinical practice. An independent institutional data safety monitoring board (DSMB) was also established to oversee the safety analysis of the study. This committee determined the relationship of adverse effects to study drug and graded the severity of any potential adverse events (AEs) as classified by the Common Terminology Criteria for Adverse Events (CTCAE, v5.0) and coded according to the Medical Dictionary for Regulatory Activities (MedDRA®, v24.0) under the guidance of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Based on the assessment of the DSMB, temporary suspension or termination of the study could occur in the event of any of the following if considered related to the study drug: documentation of the same Grade 3 AE in at least two subjects; documentation of the same Grade 3 AE in at least 20% of the subjects at the time of analysis; documentation of the same Grade 5 in any subject. Eligible subjects included adult renal transplant recipients >18 years of age with a pre-transplant ejection fraction of ≥50% who experienced intraoperative or postoperative distributive shock requiring vasopressor support. Exclusion criteria included allergy to mannitol, absolute neutrophil count <1000 cell/mm³ (within the preceding 18 months), and any history or active diagnosis of notable medical comorbidities such as mesenteric ischemia, aortic dissection, abdominal aortic aneurysm, Raynaud’s phenomenon, systemic sclerosis, or vasospastic disease. Vulnerable populations, including pregnant women, prisoners, and those with decision impairment were also excluded. Upon meeting eligibility criteria, written informed consent
FIGURE 1 Depicts the RAAS as an endogenous non-catecholamine hormonal feedback mechanism utilized by ATII to assist in the regulation of SBP and MAP. Episodes of hypotension stimulate renin release to promote cleavage of angiotensin (AT) I from angiotensinogen and subsequent conversion of ATI to ATII via angiotensin converting enzyme (ACE). The production of ATII then inhibits further renin release through negative biofeedback, resulting in direct vasoconstriction of both the afferent and efferent renal arterial vessels to increase capillary pressure within the glomerulus. In the setting of relative or absolute ACE deficiency, lack of this ATI conversion to ATII contributes to non-classical metabolism of ATI and produces the vasodilatory byproduct bradykinin.

was obtained from each participant and documented in the electronic medical record prior to conducting any study-related procedures. Enrollment was completed on a rolling basis until a total of 20 adult kidney transplant recipients met the intraoperative and/or postoperative indication for vasopressor therapy. This number was determined a priori, to allow for adequate sampling and representation of the study population.

All non-vasopressor-related medical decisions were made at the discretion of the treatment team. Consenting subjects who experienced intraoperative hypotension, defined as a sustained SBP of <120 mmHg measured invasively via arterial line, were first assessed for hemorrhagic shock, and administered blood products, as indicated per institutional protocol (Figure 2). Any subject who remained hypotensive despite these initial measures also received a 2-L intravenous (IV) fluid challenge to definitively rule out hypovolemic shock. At this time, subjects were also assessed for cardiogenic shock via intraoperative transesophageal echocardiogram and given inotropes, as indicated by institutional protocol (Figure 2). Subjects ultimately diagnosed with fluid-refractory distributive shock (i.e., vasoplegia) were then indicated to receive ATII infusion as the initial vasopressor therapy per the study protocol. To achieve and maintain a target SBP goal of ≥120 mmHg (or per the discretion of the attending physician), ATII infusion was initiated at a rate of 20 ng/kg/min and titrated in increments of 5 ng/kg/min every 5 min, as needed. During the first 3 h of therapy, the maximum infusion rate of ATII was 80 mg/kg/min, followed by a maximum maintenance infusion rate of 40 ng/kg/min. If ATII was still required upon the conclusion of surgery, therapy was continued postoperatively until the target SBP goal was achieved and maintained without the need for vasopressor support. If ATII was not utilized intraoperatively, it could be started in the postoperative period (within 24 h of surgery) if indicated and described above.

2.2 Baseline data & clinical outcomes

The following baseline characteristics were obtained for every subject at the time of transplant: age, gender, race/ethnicity, height, weight, body mass index, comorbidities (e.g., hypertension, hyperlipidemia,
If perioperative hypotension occurs (i.e., SBP < 120 mmHg) the attending surgeon or anesthesiologist will screen the subject based on the above vasopressor usage protocol. If subject is deemed responsive (i.e., SBP ≥ 120 mmHg) at any step, then no additional therapy will be required. If diagnosed with hemorrhagic shock, blood products will be administered. If no source of bleeding is identified or SBP remains < 120 mmHg, intravenous fluids will be administered in the setting of presumed hypovolemic shock. If subject remains hypotensive despite volume expansion with blood products and/or IV fluids, the attending surgeon or anesthesiologist will assess for cardiogenic shock. If SBP remains < 120 mmHg at this stage (± inotropic therapy), then catecholamine vasopressors will be administered for the treatment of presumed distributive shock and titrated to goal SBP of ≥ 120 mmHg, or per physician discretion. Vasopressor therapy will be continued postoperatively in the ICU until SBP remains stable and vasopressor can be titrated off. If distributive shock does not occur during the perioperative period, then no continuous infusion vasopressors will be utilized throughout the perioperative period: duration of transplant surgery, baseline vital signs (systolic blood pressure, diastolic blood pressure, MAP, heart rate), total volume resuscitation (balanced crystalloids, colloids, blood products), and induction/maintenance immunosuppression regimens. All data points were manually extracted from the electronic medical record (Epic Systems Corporation, Madison, WI, USA) and

heart failure – reduced/preserved ejection fraction, arrhythmias – atrial fibrillation/other, peripheral vascular disease, coronary artery disease, pulmonary hypertension, and diabetes – type 1 or 2), duration of pre-transplant hemodialysis therapy, donor type, donor terminal SCr, kidney donor profile index, and cold ischemia time. The following transplant recipient characteristics were also obtained for each subject...
recorded using a REDCap electronic data tool (Vanderbilt University, Nashville, TN, USA) hosted by the study institution.23,24

The primary aim of this pilot study was safety, as assessed by the perioperative incidence of the following AEs from time of study drug initiation until discontinuation (up to a maximum of 30 days): arrhythmias confirmed via EKG, electronic medical record flowsheet, or note documentation (e.g., atrial tachycardia, supraventricular tachycardia, atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation, and/or bradycardia) of <50 bpm requiring intervention, ischemia as noted in chart documentation (e.g., visceral, digital, and/or peripheral), venous or arterial thrombosis as captured by ultrasound or other diagnostic imaging, postoperative fungal infections as documented by clinical care team notes, delirium as documented by clinical care team notes, hyperglycemia (requiring insulin infusion), acidemia (defined as pH < 7.2), and thrombocytopenia (defined as platelet count < 50,000). The selection of safety outcome measures was based on AEs documented in ≥4% of subjects receiving synthetic ATII as per the package insert.18,19 All safety outcomes were documented as standard of care, ICU-level monitoring data within the study institution’s electronic medical record and then assessed by the institutional DSMB after enrollment of every fifth subject.

The secondary aim of this study was to describe the hemodynamic effectiveness of ATII. This effectiveness was described by the dose, duration, attainment of hemodynamic goals (i.e., SBP > 120 mmHg), and need for adjunct continuous infusion vasopressors. Therefore, the following clinically relevant variables were collected: perioperative minimum and maximum infusion rates of ATII until study drug discontinuation, perioperative duration of ATII infusion until study drug discontinuation, frequency and type of non-ATII intraoperative IV push dose, or non-ATII perioperative continuous infusion vasopressor administration for up to 72 h. Additional exploratory short-term renal allograft outcome measures were also captured. These included the following: perioperative SCr, CrCL, and glomerular filtration rate (GFR) immediately after surgery (POD-0); POD-1, POD-5, and POD-30; average serum calcineurin inhibitor (CNI) trough level (in tacrolimus equivalents, ng/ml) at POD-5 and POD-30; incidence of DGF with or without the need for RRT during the first 5 days posttransplant. According to the institutional protocol, goal serum CNI trough levels for subjects up to 3 months posttransplant had a defined target range of 5–10 ng/ml tacrolimus equivalents.

### 2.3 | Statistical analysis

Descriptive statistics were performed using SPSS® version 27 software (IBM Corporation, Armonk, NY, USA). All normally distributed continuous variables were summarized using means with standard deviations (SD), non-normally distributed continuous variables and ordinal variables were summarized using medians and interquartile range (IQR), and categorical outcomes were summarized using counts and proportions.

### 3 | RESULTS

A total of 38 subjects meeting eligibility criteria provided written consent and 20 subjects were allocated and indicated to receive study drug during the perioperative period. The study population had a reported mean (SD) BMI of 33.2 (6.8) kg/m² and a corresponding total body weight of 95.1 (24.2) kg. A full list of comorbidities is provided in Table 1. Notable past medical conditions (in addition to all patients with ESRD requiring intermittent hemodialysis prior to renal transplantation) included 18 (90%) subjects with hypertension, 11 (55%) with type 2 diabetes, and two (10%) with atrial fibrillation at baseline. At the time of transplantation, the mean (SD) age of the study cohort was 56.3 (10.7) years, and the preoperative duration of hemodialysis therapy was 7.2 (4.4) years. Procurement and transportation times contributed to a mean (SD) cold ischemic time of 14.7 (8.6) hours, as most cases consisted of DDRTs (70%). Mean (SD) transplant surgery time was 5.3 (1.2) h for all cases (Table 1).

Although no negative safety outcomes documented from the time of study drug administration up to 30 days were determined to be directly related to ATII per the DSMB, the following AEs were documented by the clinical care team as grade 1 severity: hyperglycemia requiring insulin infusion therapy (N = 5, 25%), perioperative atrial fibrillation (N = 1, 5%), and thrombocytopenia (N = 1, 5%). All incidences of hyperglycemia requiring insulin infusion and perioperative atrial fibrillation occurred in subjects with baseline type 2 diabetes and atrial fibrillation, respectively. The single incidence of thrombocytopenia was accompanied by baseline thrombocytopenia and diagnosis of posttransplant lymphoproliferative disorder from a previous transplant. No incidences of acidemia, ischemia, thromboembolism, delirium, or fungal infections were observed throughout the study.

All subjects were initiated at an ATII infusion rate of 20 ng/kg/min, except for two cases in which subjects received a continuous ATII infusion of 5 mg/kg/min to maintain an SBP goal selected at the attending physician’s discretion. Sixteen (80%) subjects required ATII during the intraoperative period. Nine of those 16 required continuation into the postoperative period. Of the 16 with intraoperative use, 13 (81.3%) failed non-ATII vasopressor bolus dose prior to study drug initiation. One of these subjects was also erroneously initiated on an intraoperative phenylephrine infusion for 13 min (protocol violation) before transitioning to ATII. Four (20%) subjects required ATII only during the postoperative period. Of the 13 subjects who required ATII during the postoperative period, one (7.7%) received secondary postoperative continuous infusion vasopressor support with norepinephrine, which remained active for a total of 74 min. Angiotensin II usage characteristics are described in Table 2. To provide a visual representation of the observed perioperative SBP trends, population averages for the intraoperative and postoperative periods are plotted in Figures 3 and 4, respectively.

The incidence of DGF was documented in two subjects (10%); however, only one subject required RRT within the first five days posttransplant. All remaining renal allograft outcome data (including SCr,
TABLE 1  Baseline demographics and transplant recipient characteristics

| Characteristic                                      | Value     |
|-----------------------------------------------------|-----------|
| Age, years                                          | 56.3 (10.7) |
| Gender – male, No. (%)                              | 11 (55)   |
| Race/ ethnicity, No. (%)                            |           |
| Caucasian                                           | 6 (30)    |
| African American                                    | 7 (35)    |
| Hispanic                                            | 5 (25)    |
| Other                                               | 2 (10)    |
| Weight, kg                                          | 95.1 (24.2) |
| Height, cm                                          | 167.8 (9.6) |
| BMI, kg/m²                                          | 33.2 (6.8) |
| Comorbidities, No. (%)                              |           |
| Hypertension                                        | 18 (90)   |
| Hyperlipidemia                                      | 8 (40)    |
| Heart failure, preserved ejection fraction          | 2 (10)    |
| Arrhythmia – atrial fibrillation                    | 2 (10)    |
| Coronary artery disease                             | 7 (35)    |
| Diabetes – type 2                                   | 11 (55)   |
| Duration of pre-transplant HD therapy, yearsa       | 7.2 (4.4) |
| Donor type, No. (%)                                 |           |
| Deceased donor                                      | 14 (70)   |
| Living-related donor                                | 4 (20)    |
| Living-unrelated donor                              | 2 (10)    |
| Donor terminal SCr, mg/dl                           | 2.4 (3.3) |
| Kidney donor profile indexb                         | 48.6 (27.8) |
| Cold ischemia time, hoursc                          | 14.7 (8.6) |
| Duration of transplant surgery, hours               | 5.3 (1.2) |
| Recipient baseline vitals                           |           |
| Systolic BP, mmHg                                   | 145.2 (23.6) |
| Diastolic BP, mmHg                                  | 77.4 (13.4) |
| MAP, mmHg                                           | 98.7 (16.1) |
| Heart rate, bpm                                     | 83 (17.1) |
| Total volume resuscitation, liters                  | 3.5 (1.7) |
| Crystalloids, No. (%)                               | 18 (90)   |
| PlasmaLyte                                          | 18 (90)   |
| Lactated ringers                                     | 5 (25)    |
| Colloids, No (%)                                     | 16 (80)   |
| Albumin                                             | 7 (35)    |
| Mannitol                                            | 15 (75)   |
| Blood products, No. (%)                             | 6 (30)    |
| Red blood cells                                      | 5 (25)    |
| Fresh frozen plasma                                 | 2 (10)    |
| Induction agents, No. (%)                           |           |
| Steroids                                            | 17 (85)   |
| Thymoglobulin                                       | 13 (65)   |
| Basiliximab                                         | 7 (35)    |

(Continues)

TABLE 1  (Continued)

| Maintenance agents, No. (%)                      |           |
| Tacrolimus                                         | 20 (100)  |
| Mycophenolate moffetil/ mycophenolic acid         | 19 (95)   |
| Steroids                                            | 11 (55)   |

Abbreviations: BMI, body mass index; HD, hemodialysis; SCr, serum creatinine; BP, blood pressure; MAP, mean arterial pressure. N = 20. Results reported as mean (SD), unless noted otherwise. The following baseline disease states were reported as none: arrhythmia – other, peripheral vascular disease, pulmonary hypertension, diabetes – type 1. The following concomitant fluids/ blood products were reported as none: normal saline, platelets, cryoprecipitate. The following induction/ maintenance agents were reported as none: alemtuzumab, belatacept, sirolimus.

4 | DISCUSSION

This pilot study primarily aimed to assess the safety and hemodynamic effectiveness of ATII as a non-catecholamine vasopressor agent for the management of hypotension in renal transplant. We did not observe any ATII-related side effects while maintaining goal hemodynamic parameters.

Due to the primary mechanism of ATII, the incidence of vasopressor-related AEs was anticipated to be low, as the study drug does not utilize α- and β-adrenergic pathways to regulate SBP or MAP, unlike its catecholamine counterparts. While the majority of catecholamine-associated AE data has been derived from septic shock literature and later extrapolated to other special populations, it is well-known that the α-adrenergic effects of phenylephrine can induce rebound bradycardia leading to reduced cardiac output, prerenal hypoperfusion, and microvascular ischemia. Likewise, the β-adrenergic effects of epinephrine and dopamine have been characterized as potentially arrhythmogenic in nature. Despite serving as an indirect comparison between these two therapeutic indications, the pathophysiologic response remains the same. Therefore, utilization of a vasopressor capable of bypassing these AE mechanisms could drastically improve renal outcomes in a population dependent on success. As we observed no study-drug related side effects, comparative studies are warranted to directly compare ATII to catecholamine vasopressors in this population to determine if ATII is a safer agent for perioperative hypotension surrounding renal transplant.

The absence of ATII-related AEs in this pilot study was also accompanied by the ability of ATII to achieve set hemodynamic goals with minimal use of adjunct vasopressors. As previously demonstrated in other distributive shock populations, this multimodal approach allows for a reduction in overall catecholamine exposure and any AEs associated with prolonged utilization. Due to its limited population size, any further parallels between the observations of this pilot study

CrCl, GFR, and serum CNI levels through POD-30 is provided in Table 3.
TABLE 2  Vasopressor characteristics

| Variable                        | Only intraoperative (N = 7) | Only postoperative (N = 4) | Both intra-/postoperative (N = 9) |
|---------------------------------|-----------------------------|---------------------------|----------------------------------|
| ATII infusion rate, ng/kg/min   | —                           | —                         | —                                |
| Maximum                         | 20                          | 40                        | 40                               |
| Minimum                         | 5                           | 5                         | 1                                |
| ATII infusion duration, hours,  | 1.0 (1.5)                   | 26.5 (84.8)               | 63.8 (57.8)                      |
| median (IQR)                    |                             |                           |                                  |

Abbreviation: ATII, angiotensin II.

n = 20. Results reported as raw value, unless noted otherwise.

TABLE 3  Renal allograft outcomes

| Variable          | POD-0     | POD-1     | POD-5     | POD-30    |
|-------------------|-----------|-----------|-----------|-----------|
| SCr, mg/dl        | 7.3 (3.3) | 6.1 (3.3) | 4.2 (3.1) | 2.3 (2.3) |
| CrCL, ml/min      | 13.9 (8.7)| 19.3 (15.6)| 25.7 (11.9)| 51.1 (27.1)|
| GFR, ml/min/1.73 m2 | 10.4 (9.5) | 16.0 (17.4) | 22.6 (14.1) | 42.1 (22.3) |
| Serum CNI level, ng/ml | —         | —         | 10.2 (6.0)a | 8.6 (3.6)b |

Abbreviations: POD, postoperative day; SCr, serum creatinine; CrCL, creatinine clearance; GFR, glomerular filtration rate; CNI, calcineurin inhibitors.

n = 20. Results reported as mean (SD).
aDenotes N = 19. b Denotes N = 17.

FIGURE 3  Depicts population median and range for each data point during the intraoperative period. The dotted line represents the SBP goal of ≥120 mmHg, per protocol.

Intraoperative Hemodynamics

and previously published data would likely be flawed, as there is a paucity of information regarding the acute and chronic outcomes of perioperative vasopressor use during kidney transplantation. As such, we were able to demonstrate that ATII is effective in reversing hypotension as a first-line continuous infusion vasopressor agent by achieving hemodynamic goals with minimal use of additional continuous infusion vasopressor support. As noted above, direct comparisons to catecholamine agents would be warranted to further explore the clinical efficacy of ATII in this population.

Though speculative without a comparator arm, this agent did not appear to negatively impact renal outcomes. As previously mentioned, RAAS is an endogenous non-catecholamine hormonal feedback mechanism utilized by ATII to assist in the regulation of SBP and MAP. Episodes of hypotension stimulate renin release to promote the cleavage of angiotensin (AT) I from angiotensinogen and subsequent conversion of ATI to ATII via angiotensin-converting enzyme (ACE). The production of ATII then inhibits further renin release through negative biofeedback, resulting in direct vasoconstriction of both afferent and
eff erent renal arterial vessels to increase capillary pressure within the glomerulus.16,17 In the setting of relative or absolute ACE deficiency, lack of AT1 conversion to ATII contributes to non-classical metabolism of ATI and produces the vasodilatory byproduct bradykinin.17 By avoiding preferential afferent arterial vasoconstriction and restoring AT1: ATII balance, supplementation with synthetic ATII may lessen the risk of reperfusion injury during renal transplantation and potentially avoid ischemia in the new allograft. In a study population of majority DDRT cases and a reported mean (SD) cold ischemia time of 14.7 (8.6) hours, the risk of DGF was estimated to occur in 12 of 20 cases (60%) based on a predictive model by Irish et al. However, DGF was only documented in 2 of 20 cases (10%), which is more indicative of a cold ischemia time of approximately 2.5 hours based on an anticipated increase of 4% for every 1-hour increase in cold ischemic time.25 These results are promising and deserve further investigation to determine if there is a renal protective effect of using ATII as a first line continuous infusion vasopressor in this population. Given the study design and power of our analysis, this possible benefit remains theoretical.

5 | CONCLUSIONS

Based on the observations of this pilot study, ATII may be a desirable vasopressor option in kidney transplant recipients requiring perioperative hypotension reversal, as it allows hemodynamics to be achieved with minimal additional vasopressor usage and side effects. To gain more conclusive insight into the global utility of ATII in this population, however, additional multicenter studies comparing prospective and retrospective outcomes are required to study the efficacy of ATII compared to other catecholamine agents, expand the universal census of available study data, explore potential pharmacoeconomic benefits, and determine potential differences in the therapeutic effect of ATII in populations with lower RAAS sensitivity.

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CONFLICT OF INTEREST

All authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Data not available due to restrictions. Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

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