

Manukyan M.A., Falkovskaya A.Yu., Zyubanova I.V., Solonskaya E.I., Lichikaki V.A., Ryabova T.R., Vtorushina A. A., Hunkhinova S. A., Skomkina I. A., Yevtukh A. A., Gusakova A.M., Mordovin V. F.

Research Institute of Cardiology, Tomsk National Research Center of the Russian Academy of Sciences, Tomsk, Russia

## RENAL HEMODYNAMICS IN PATIENTS WITH RESISTANT HYPERTENSION AND TYPE 2 DIABETES MELLITUS

<i>Aim</i>	To study renal hemodynamics in patients with resistant arterial hypertension (RAH) in combination with type 2 diabetes mellitus (DM2) and to identify factors involved in the increase in intrarenal vascular resistance.
<i>Material and methods</i>	This study included 59 patients (25 men) with RAH in combination with DM2. Mean age of patients was $60.3 \pm 7.9$ years; 24-h blood pressure (24-BP) (systolic, diastolic, SBP/DBP) was $158.0 \pm 16.3 / 82.5 \pm 12.7$ mm Hg during the treatment with 4.3 [4.0;5.0] antihypertensive drugs; glycated hemoglobin (HbA1c) was $7.5 \pm 1.5\%$ ; estimated glomerular filtration rate (eGFR) was $73.1 \pm 21.8$ ml/min/1.73 m <sup>2</sup> (CKD-EPI equation). Measurement of office BP, 24-h BP monitoring, renal artery (RA) Doppler, routine lab tests including determination of GFR (CKD-EPI), 24-h urine albumin excretion, and ELISA measurement of blood lipocalin-2, cystatin C, high-sensitive C-reactive protein (hsCRP), and asymmetric dimethylarginine (ADMA) were performed for all patients.
<i>Results</i>	Incidence of increased RA resistive index (RI) was 39% despite the high rate of vasodilator treatment (93% for renin-angiotensin-aldosterone system inhibitors, 78% for calcium antagonists). According to a correlation and regression analysis, RA RI values were correlated with the kidney function ( $r = -0.46$ , $p < 0.001$ for eGFR, $r = 0.56$ ; $p = 0.006$ for lipocalin-2), age ( $r = 0.54$ , $p < 0.001$ ), increases in concentrations of hsCRP ( $r = 0.35$ , $p < 0.001$ ) and ADMA ( $r = 0.39$ , $p = 0.028$ ), the increase in vascular stiffness ( $r = 0.59$ , $p < 0.001$ for pulse BP (PBP) as well as DM2 duration, and HbA1c ( $r = 0.33$ , $p < 0.001$ for both). The independent association of RA RI with the age, PBP, and duration of DM2 was confirmed by the results of multivariate regression analysis. According to the ROC analysis, the threshold level of RA RI corresponding to a decrease in GFR $< 60$ ml/min/1.73 m <sup>2</sup> was $\geq 0.693$ conv. units.
<i>Conclusion</i>	In more than one third of patients with RAH in combination with DM2, increased renal vascular resistance was documented, which was closely associated with impaired kidney function, age, DM2 duration and severity, and markers of low-grade inflammation, endothelial dysfunction, and vascular stiffness. The value of RA RI $\geq 0.693$ conv. units was a threshold for the development of chronic kidney disease (CKD).
<i>Keywords</i>	Resistant arterial hypertension; type 2 diabetes mellitus; renal hemodynamics; renal arterial resistive index
<i>For citations</i>	Manukyan M.A., Falkovskaya A.Yu., Zyubanova I.V., Solonskaya E.I., Lichikaki V.A., Ryabova T.R. et al. Renal hemodynamics in patients with resistant hypertension and type 2 diabetes mellitus. <i>Kardiologiia</i> . 2023;63(8):42–49. [Russian: Манукян М.А., Фальковская А.Ю., Зюбанова И.В., Солонская Е.И., Личикаки В.А., Рябова Т.Р. и др. Почечная гемодинамика у больных резистентной артериальной гипертензией в сочетании с сахарным диабетом 2 типа. <i>Кардиология</i> . 2023;63(8):42–49].
<i>Corresponding author</i>	Manukyan M.A. E-mail: manukyan.musheg@yandex.ru

### Relevance

Type 2 diabetes mellitus (T2DM) and hypertension (RHTN) are the main causes of the development and progression of chronic kidney disease (CKD), which significantly increases the frequency of both renal and cardiovascular complications [1]. The combination of T2DM and drug-resistant HTN is associated with faster course of kidney damage process [2] and a progressive decrease in glomerular filtration rate (GFR). Renal resistive index (RRI) is a marker of subclinical kidney damage and reflects an increase in resistance renal [3]

and other vascular systems. Prognostic significance of higher intrarenal vascular resistance is determined by a close relation with adverse renal outcomes [4–6], including in patients with T2DM [7, 8], and damage to other target organs in the form of thickening of the intima-media complex of the carotid artery, increased vascular stiffness, and the development of left ventricular hypertrophy [9–14]. The features of renal blood flow and its relationship with the kidney functional state, and the factors involved in increasing intrarenal vascular resistance in patients with resistant hypertension

(RHTN) combined with T2DM, have not been sufficiently studied. At the same time, the knowledge of the pathophysiology of impaired renal hemodynamics can significantly change treatment approaches to improving both renal and cardiovascular prognosis.

This study is based on the hypothesis that the deterioration of renal blood flow is closely related in patients with RHTN combined with T2DM with the deterioration of the kidney functional state and depends not only on metabolic and hemodynamic disorders, but also on chronic low-intensity inflammation and endothelial dysfunction.

## Objective

Study the state of renal hemodynamics in patients with RHTN combined with T2DM and identify the factors involved in increasing the intrarenal vascular resistance.

## Material and methods

The study included 59 patients with RHTN combined with T2DM admitted for severe HTN to the Hypertension Department, the Research Institute of Cardiology, the Tomsk Research Medical Center, from 2013 to 2021. The diagnosis of RHTN was verified following to the Russian Guidelines for the Treatment of Arterial Hypertension [15]. Pseudoresistance, secondary HTN, severe T2DM, glycosylated hemoglobin (HbA1c) > 10%, estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m<sup>2</sup>, pregnancy, chronic heart failure NYHA class III and IV were the exclusion criteria. Information on drug therapy was obtained by the survey.

All patients had office blood pressure and 24-hour blood pressure measured, renal Doppler ultrasound was performed and RRI was calculated. Automatic oscillometric measurement systems AVRМ-04 (Meditech, Hungary) and BPLab (Petr Telegin LLC, Russia) were used for 24-hour blood pressure monitoring. RRI was calculated by the following formula:

$$RRI = \frac{V_{sys} - V_{dia}}{V_{sys}},$$

where RRI is renal resistance index (peak systolic velocity – end-diastolic velocity)/peak systolic velocity measured at the level of segmental arteries [16].

Mean values of RRI in the upper, middle, and lower segments of the kidney were analyzed. RRI values of the left and right kidneys were also averaged given the absence of significant differences between the left and right kidneys. Patients with RRI differences > 10%

were excluded from the study. HbA1c was determined by enzymatic colorimetric method on an automatic biochemical analyzer Cobas 6000 c 501 (Roche Diagnostics, Japan). C-reactive protein (hs-CRP), asymmetric dimethylarginine (ADMA), lipocalin-2, and cystatin C were determined in blood serum by enzyme-linked immunosorbent assay using hs-CRP EIA test systems (Biomerica, USA), ADMA Xpress ELISA kit (Immunodiagnostik AG, Germany), Human Lipocalin-2/NGAL and Human Cystatin C ELISA (BioVendor, Czech Republic). 24-hour urinary albumin excretion was estimated by enzyme immunoassay using Micro-Albumin diagnostic kit (ORGENTEC Diagnostika GmbH, Germany). Measurement of optical densities, construction of calibration graphs, assessment, and accounting of the quantitative contents of all indicators of interest were carried out using Infinite f50 microplate reader and Magellan Tracker software (Austria).

The study was carried out following the Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the local ethics committee. All patients signed the informed consent and consent to personal data processing before the study.

The statistical analysis was carried out using the Statistica 10.0 and SPSS 26 for Windows. The normality of distribution was verified using the Shapiro-Wilk test. Normally distributed continuous variables were expressed as the means and standard deviations (M ± SD), non-normally distributed variables were expressed as the medians and the interquartile range (Me [25%; 75%]). The qualitative and categorical variables were presented as the absolute and relative values (n (%)). The standard methods of descriptive statistics were applied, differences between continuous variables in the independent samples were detected using the Student's t-test and the Mann-Whitney U-test. Qualitative indicators were compared by the conjugacy table analysis method using Pearson's chi-squared test or the Fisher exact test. Univariate and multivariate regression analysis were used to search for possible correlations. Non-normally distributed variables were logged before being included in the regression analysis. ROC analysis was performed to calculate the sensitivity, specificity and find a diagnostic cut-off point. The critical significance value p = 0.05 was used for all statistical analysis procedures.

## Results

The clinical characteristics of the examined patients are presented in Table 1, which shows that the majority of patients were over 60 years old and had a long course

of HTN and T2DM, a high incidence of obesity, left ventricular hypertrophy, and peripheral atherosclerosis; two of three patients had coronary artery disease.

As shown in Table 2, the majority of patients received beta-blockers, renin-angiotensin system inhibitors, calcium channel blockers, and diuretics, spironolactone was administered by two of three patients. Hyperglycemia was corrected in every third patient using insulin drugs.

24-hour urinary albumin excretion data available for 38 patients are presented in Table 3, according to which the majority of patients had normal or moderately elevated urine levels of albumin.

Mean RRI was  $0.68 \pm 0.08$ . A univariate correlation regression analysis was performed to identify factors associated with RRI (Figure 1). According to the data obtained, increased RRI was associated with age, parameters of renal dysfunction, elevated plasma hs-CRP and ADMA, vascular stiffness in the form of increased pulse blood pressure (PBP-24), long-term and severe course of T2DM, and decreased heart rate ( $r = -0.34$ ,  $p < 0.001$ ).

Multiple linear regression showed the correlation between RRI and PBP and T2DM duration remained

significant after being adjusted for age, sex, eGFR, and heart rate (HR) (Table 4).

A ROC analysis was performed to assess the prognostic significance of RRI in the development of CKD (Figure 2). Threshold RRI corresponding to CKD S3 ( $\text{GFR} < 60 \text{ ml/min/1.73 m}^2$ ) was 0.693. Area under the curve was 0.753 (CI: 0.630–0.876); the observed dependence was statistically significant ( $p < 0.001$ ), with sensitivity of 68.8% and specificity of 75.7%.

## Discussion

This work was first to provide information on the incidence of increased RRI in a selected group of patients with RHTN combined with T2DM. Despite the fact that the majority of patients took vasodilators, every third patient had increased intrarenal vascular resistance. It should be noted that the previous data concerned patients with RAH without T2DM or newly diagnosed T2DM, in whom this value was almost 2 times lower. For example, the incidence of increased RRI was 7.2% in the RESIST-POL study [17] and 18.8% in the work by Raff et al. [14]. In this work, the correlations of renal resistive indices and clinical and

**Table 1. Clinical characteristics of patients (M  $\pm$  SD, Me [Q25; Q75], n (%))**

Parameters	Total (n = 59)
Age, years	60.3 $\pm$ 7.9
Female, n (%)	34 (57.6)
Body mass index, kg/m <sup>2</sup>	35.2 $\pm$ 6.0
Duration of HTN, years	22.1 [15.0; 33.0]
Duration of T2DM, years	9.7 [5.0; 14.0]
Coronary artery disease, n (%)	37 (62.7)
History of myocardial infarction, n (%)	10 (17.0)
History of ischemic stroke, n (%)	11 (18.6)
Peripheral atherosclerosis, n (%)	54 (91.5)
Dyslipidemia, n (%)	58 (98.3)
Abdominal obesity, n (%)	49 (83.1)
Left ventricular hypertrophy, n (%)	52 (88.1)
Office SBP/DBP, mm Hg	170.7 $\pm$ 19.8/88.2 $\pm$ 14.5
Office HR, bpm	70 $\pm$ 9.2
SBP-24/DBP-24, mm Hg	158 $\pm$ 16.3/82.5 $\pm$ 12.7
HR, bpm	67.2 $\pm$ 10.2
HbA1c, %	7.5 $\pm$ 1.5
Basal glucose level, mmol/L	8.8 $\pm$ 2.7
eGFR (CKD EPI), mL/min/1.73 m <sup>2</sup>	69.7 $\pm$ 22.2
Chronic kidney disease, n (%)	30 (54.3)
S3A, n (%)	24 (40.7)
S3B, n (%)	6 (10.2)

AH, arterial hypertension; T2DM, type 2 diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; 24, mean 24-hour values; HbA1c, glycated hemoglobin; eGFR, glomerular filtration rate estimated by the CKD-EPI formula.

**Table 2. Characteristics of antihypertensive and hypoglycemic therapy**

Parameters	Total (n = 59)
<b>Antihypertensive therapy</b>	
Number of drugs	4.3 [4.0;5.0]
Beta-blockers	49 (83.1)
Renin-angiotensin-aldosterone system inhibitors	55 (93.2)
Diuretics, n (%)	57 (96.6)
Calcium channel blockers, n (%)	46 (78.0)
Spironolactone, n (%)	37 (62.7)
I1 imidazoline receptor agonists, n (%)	15 (25.4)
Alpha blockers, n (%)	8 (13.6)
<b>Sugar-lowering therapy</b>	
Diet therapy without hypoglycemic therapy	5 (8.47)
Metformin monotherapy	22 (37.3)
Combination oral hypoglycemic therapy	12 (20.3)
Insulin therapy + oral hypoglycemic therapy	20 (33.9)

**Table 3. Albuminuria grades (KDIGO 2020) in patients with resistant arterial hypertension combined with type 2 diabetes mellitus (Me [Q25; Q75], n (%))**

Parameters	Total (n = 38)
Albumin excretion, mg/day	20.1 [9.2–90.0]
A1	23 (60.5)
A2	10 (26.3)
A3	5 (13.2)



# Возвращение к активной жизни!

**Кораксан®**  
ИВАБРАДИН

## Симптоматическая терапия стабильной стенокардии и терапия хронической сердечной недостаточности<sup>1</sup>

**Краткая справочная информация по безопасности — ивабрадин**  
**СОСТАВ\*** Таблетки, покрытые пленочной оболочкой, содержащие каждая 5 мг или 7,5 мг ивабрадина в виде ивабрадина гидрохлорида. Содержит лактозу в качестве вспомогательного вещества. **ФАРМАКОТЕРАПЕВТИЧЕСКАЯ ГРУППА\*** Антиангинальное средство. **ПОКАЗАНИЯ К ПРИМЕНЕНИЮ\*** Симптоматическая терапия стабильной стенокардии. Симптоматическая терапия стабильной стенокардии при ишемической болезни сердца у взрослых пациентов с нормальным синусовым ритмом и частотой сердечных сокращений (ЧСС) не менее 70 уд/мин: при непереносимости или наличии противопоказаний к применению бета-адреноблокаторов; в комбинации с бета-адреноблокаторами при неадекватном контроле стабильной стенокардии на фоне оптимальной дозы бета-адреноблокатора. Терапия хронической сердечной недостаточности (ХСН) II класса по классификации NYHA с систолической дисфункцией у пациентов с синусовым ритмом и ЧСС не менее 70 уд/мин: в сочетании со стандартной терапией, включающей в себя терапию бета-адреноблокаторами, или при непереносимости или наличии противопоказаний к применению бета-адреноблокаторов. **РЕЖИМ ДОЗИРОВАНИЯ И СПОСОБ ПРИМЕНЕНИЯ\*** Симптоматическая терапия стабильной стенокардии. Начальная доза препарата должна превышать 5 мг 2 раза в сутки у пациентов младше 75 лет и старее рекомендованной начальной дозы препарата Кораксан® составляет 2,5 мг (по 1/2 таблетки 5 мг) 2 раза в сутки. Если симптомы сохраняются в течение 3–4 недель и если начальная дозировка хорошо переносилась и ЧСС в состоянии покоя остается более 60 уд/мин, доза может быть увеличена до следующего уровня у пациентов, получающих препарат в дозе 2,5 мг 2 раза в сутки или 5 мг 2 раза в сутки. Поддерживающая доза ивабрадина не должна превышать 7,5 мг 2 раза в день. Применение ивабрадина следует прекратить, если симптомы стенокардии не уменьшаются, или если не наблюдается клинически значимого снижения ЧСС в течение 3 месяцев терапии. Терапия хронической сердечной недостаточности. Рекомендованная начальная доза препарата Кораксан® для пациентов младше 75 лет составляет 10 мг в сутки (по 1 таблетке 5 мг 2 раза в сутки) для пациентов в возрасте 75 лет и старше. Если ЧСС в состоянии покоя стабильно более 60 уд/мин. В случае если ЧСС в состоянии покоя стабильно ниже 50 уд/мин или в случае проявления симптомов брадикардии, таких как головокружение, повышенная утомляемость или артериальная гипотензия, доза может быть уменьшена до 2,5 мг (по 1/2 таблетки 5 мг) 2 раза в сутки. Для всех показаний. Если в процессе применения препарата ЧСС в состоянии покоя стабильно менее 50 уд/мин или если у пациента отмечаются симптомы брадикардии, доза препарата должна быть снижена до более низкого уровня. Если ЧСС остается менее 50 уд/мин или у пациента сохраняются симптомы брадикардии, применение препарата следует прекратить. **ПРОТИВОПОКАЗАНИЯ\*** Повышенная чувствительность к ивабрадину или любому из вспомогательных веществ; ЧСС в покое ниже 70 уд/мин (до начала лечения); кардиогенный шок; острый инфаркт миокарда; тяжелая артериальная гипотензия (систолическое АД менее 90 мм рт.ст. и диастолическое АД менее 50 мм рт.ст.); тяжелая печеночная недостаточность (более 9 баллов по шкале Чайлд-Пью); синдром слабости синусового узла; синусовая блокада; нестабильная или острая сердечная недостаточность; наличие искусственного водителя ритма, работающего в режиме постоянной стимуляции; нестабильная стенокардия; атриовентрикулярная (AV) блокада II и III степени; одновременное применение с мощными ингибиторами ионных каналов системы щитовидной железы (тироксином, левотироксином), антиагрегантами группы гликопиринидов (калассином, элтрипсином) для приема внутрь, диализируемыми препаратами (инфузиями, инфузиями, инфузиями), ингибиторами ВПН (нефедина, ритонавира) и нефедина; одновременное применение с верапамилом или дилтиаземом, которые являются умеренными ингибиторами CYP3A4, обладающими способностью ускорять ЧСС; беременность, период грудного вскармливания и применение у женщин репродуктивного возраста, не соблюдающих надежные меры контрацепции (см. раздел «Применение при беременности и в период лактации»); возраст до 18 лет (эффективность и безопасность применения в данной возрастной группе не установлены); дефицит лактазы, непереносимость лактозы, синдром глюкозо-галактозной мальабсорбции. **ОСОБЫЕ УКАЗАНИЯ\*** Недостаточность положительного эффекта в отношении клинических исходов у пациентов с симптоматической стабильной стенокардией. Ивабрадин показан только в качестве симптоматической терапии стабильной стенокардии, поскольку ивабрадин не оказывает положительного влияния на частоту возникновения сердечно-сосудистых событий у таких пациентов. Контроль ЧСС. Перед началом терапии или при принятии решения о титрации дозы должно быть выполнено серийное измерение ЧСС одним из указанных способов: серийное измерение ЧСС, ЭКГ или 24-часовое амбулаторное наблюдение. Нарушения сердечного ритма. Ивабрадин не рекомендуется пациентам с фибрилляцией предсердий (мерцательной аритмией) или другими типами аритмий, связанными с функцией синусового узла. Во время терапии следует проводить клиническое наблюдение за пациентами на предмет выявления фибрилляции предсердий. У пациентов, принимающих ивабрадин, повышен риск развития фибрилляции предсердий. Если во время терапии возможна фибрилляция предсердий, соотношение ожидаемой пользы к возможному риску при дальнейшем применении ивабрадина должно быть рассмотрено повторно. Пациенты с синусовой сердечной недостаточностью и нарушениями внутрисердечной проводимости в желудочковой диссоциации ей должны находиться под пристальным контролем. Применение у пациентов с брадикардией. Ивабрадин противопоказан, если до начала терапии ЧСС в покое составляет менее 70 уд/мин. Если на фоне терапии ЧСС в покое уменьшается до значений менее 50 уд/мин или у пациента возникает симптом, связанный с брадикардией, необходимо уменьшить дозу препарата или прекратить прием, если ЧСС остается менее 50 уд/мин или сохраняются симптомы, связанные с брадикардией. Комбинированное применение в составе антиангинальной терапии. Применение препарата совместно с блокаторами медленных кальциевых каналов (БМКК), урежающими ЧСС, такими как верапамил или дилтиазем, противопоказано. Хроническая сердечная недостаточность. Следует с осторожностью применять препарат у пациентов с хронической сердечной недостаточностью II функционального класса по классификации NYHA. Инсулин. Не рекомендуется назначать препарат непосредственно после перенесенного инсульта. Функция зрительного восприятия. Пациентам с типичной дегенерацией сетчатки препарат следует принимать с осторожностью. Пациенты с артериальной гипотензией. С осторожностью у пациентов с легкой и умеренной артериальной гипотензией. Фибрилляция предсердий — сердечные аритмии: при возможности отсрочить плановую электрическую кардиоверсию, прием препарата следует прекратить за 24 часа до проведения электрической кардиоверсии. Применение у пациентов с врожденным синдромом удлиненного интервала QT или у пациентов, принимающих препараты, удлиняющие интервал QT. Не следует назначать. При необходимости такой терапии необходим строгий контроль ЭКГ. Пациенты с артериальной гипертензией, которым требуется изменение антигипертензивной терапии: при изменении гипотензивной терапии у пациентов с ХСН требуется мониторинг АД. Умеренная печеночная недостаточность: с осторожностью. Тяжелая печеночная недостаточность (класс < 15 баллов): с осторожностью. Вспомогательные вещества: в состав препарата входит лактоза, поэтому препарат не рекомендуется пациентам с дефицитом лактазы, непереносимостью лактозы, синдромом глюкозо-галактозной мальабсорбции. **ВЗАИМОДЕЙСТВИЕ С ДРУГИМИ ЛЕКАРСТВЕННЫМИ СРЕДСТВАМИ\*** Противопоказанные сочетания: мощные ингибиторы изофермента CYP3A4 (кетоназолов, итраконазола, клотримазола, эритромицина для приема внутрь, диализируемых препаратов (инфузиями, инфузиями, инфузиями), урежающие ЧСС (дилтиазем или верапамил). Нежелательные сочетания: трифлуоротетрацилин. Сочетание, требующее осторожности: прочие умеренные ингибиторы CYP3A4 (фуконазол). Индукторы изофермента CYP3A4 (рифампицин, барбитураты, фенитоин, растительные средства, содержащие зверобой продырявленный). **БЕЗОПАСНОСТЬ И ПЕРИОД ЛАКТАЦИИ\*** Противопоказано. **ВЛИЯНИЕ НА СПОСОБНОСТЬ УПРАВЛЯТЬ ТРАНСПОРТНЫМИ СРЕДСТВАМИ И ВЫПОЛНЯТЬ РАБОТУ, ТРЕБУЮЩУЮ ВЫСОКОЙ СКОРОСТИ ПСИХОМОТОРНЫХ РЕАКЦИЙ\*** Возможное возникновение временного изменения световосприимчивости должно приниматься во внимание при управлении автомобилем или другими механизмами при резком изменении интенсивности света, особенно в ночное время. **НЕЖЕЛАТЕЛЬНЫЕ РЕАКЦИИ\*** Очень часто: изменения световосприимчивости (фосфены). Часто: нечеткость зрения, брадикардия, AV-блокада I степени (удлинение интервала PQ на ЭКГ); желтуха, усиление экстрактуры, фибрилляция предсердий, головная боль, особенно в первый месяц терапии, головокружение, возможно связанное с брадикардией, неконтролируемое артериальное давление. Нечасто: ощущение сердцебиения, наддувательские экстрактуры, обморочное состояние, связанное с брадикардией, тошнота, запор, диарея, боль в животе, одышка, легкое дыхание, нарушение речи, кожная сыпь, эритема, астения, возможно, связанная с брадикардией, утомляемость, возможно, связанная с брадикардией, спазмы мышц, гипертермия, эозинофилия, повышение концентрации креатинина в плазме крови, удлинение интервала QT на ЭКГ, гипотензия, возможно, связанная с брадикардией. Редко: ангионевротический отек, кожный зуд, крапивница, недержание, возможно, связанное с брадикардией. Очень редко: AV-блокада II и III степени, синдром слабости синусового узла. **ПЕРЕДОЗИРОВКА\*** **ФАРМАКОЛОГИЧЕСКОЕ ДЕЙСТВИЕ\*** Ивабрадин — препарат, замедляющий ритм сердца, механизм действия которого заключается в селективном и специфическом ингибировании I<sub>Ca</sub>-каналов синусового узла, контролирующего спонтанную диастолическую деполаризацию в синусовом узле и регулирующий ЧСС. Кораксан дозозависимо снижает ЧСС. **ЛЕКАРСТВЕННАЯ ФОРМА\*** Таблетки, покрытые пленочной оболочкой, 5 мг и 7,5 мг.

\*Для получения полной информации, пожалуйста, обратитесь к инструкции по медицинскому применению лекарственного препарата.

1. Общая характеристика лекарственного препарата Кораксан®. РУ ЛП-№(000306)-(P-F-RU) от 15.07.2021 <https://servier.ru/wp-content/uploads/2018/11/Koraksan-OHL-Pdf>

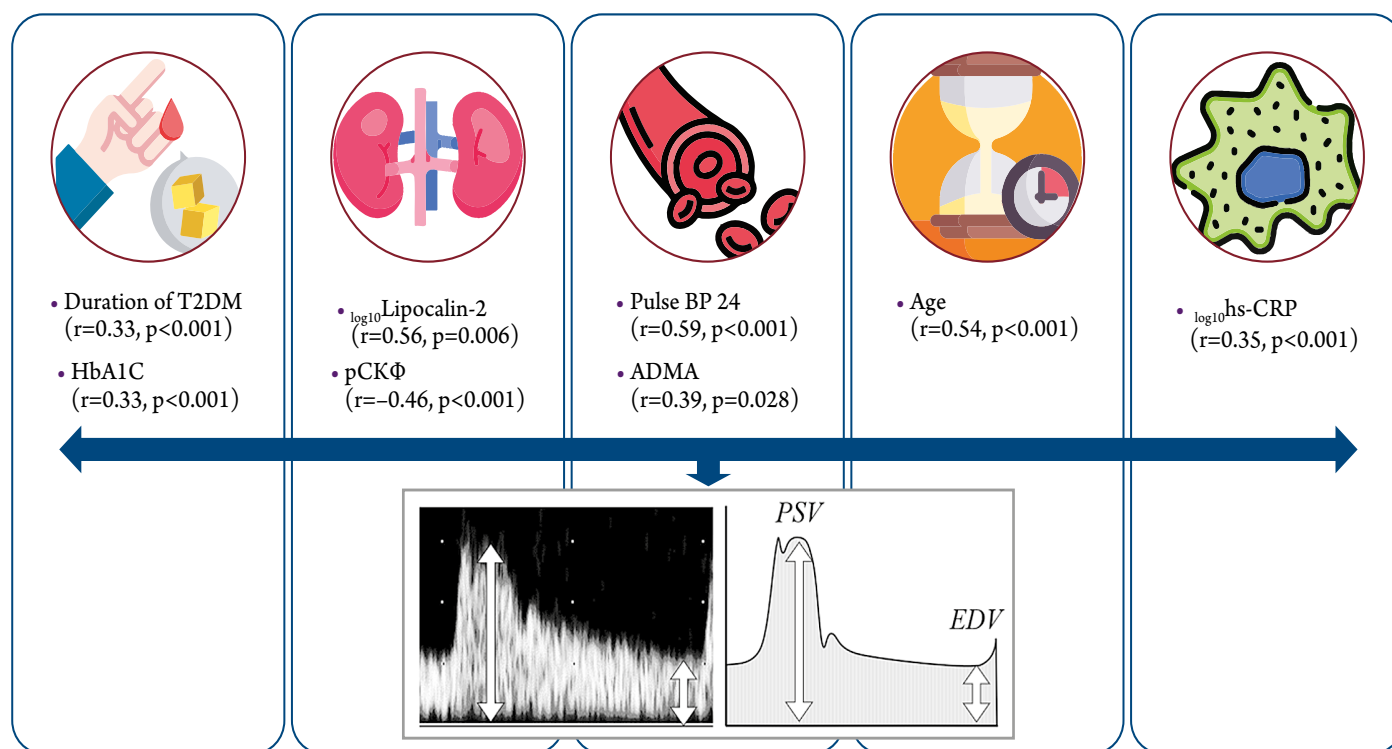
АО «Сервье». 125196, г. Москва, ул. Лесная, д. 7, этаж 7/8/9.  
Тел.: (495) 937-0700, факс: (495) 937-0701,  
[www.servier.ru](http://www.servier.ru)

Материал предназначен для специалистов здравоохранения

**SERVIER**



**Figure 1.** Results of univariate regression analysis of correlations between renal resistive indices and clinical examination data



T2DM, type 2 diabetes mellitus; HbA1C, glycated hemoglobin; log, logged value; eGFR, estimated glomerular filtration rate; ADMA, asymmetric dimethylarginine; hs-CRP, high sensitivity C-reactive protein.

**Table 4.** Parameters of multiple linear regression analysis of age-adjusted correlations of renal resistive indices ( $n = 59$ )

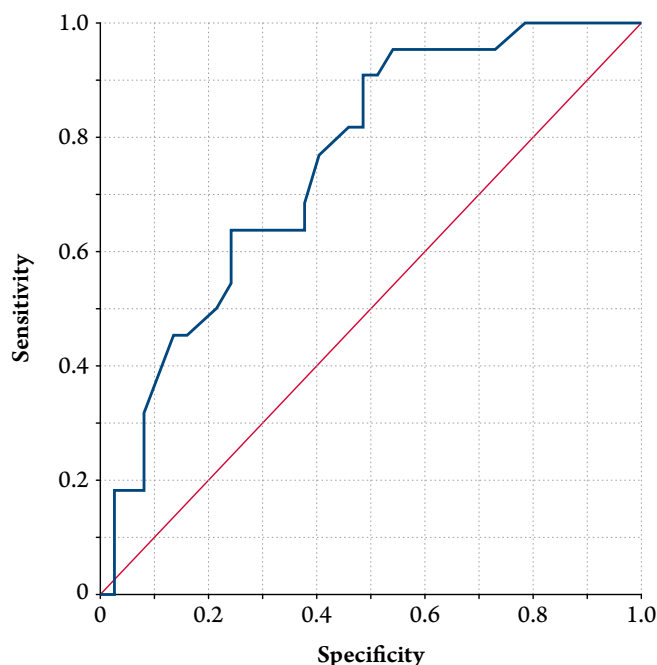
Variable	Coefficient $\beta$	Standard error $\beta$	B	Error B	t	p
Intercept	–	–	0.451	0.131	3.450	0.001
Age	0.106	0.109	0.001	0.001	0.978	0.333
Male	–0.059	0.112	–0.008	0.015	–0.530	0.599
eGFR, mL/min/1.73m <sup>2</sup>	–0.210	0.114	–0.001	0.000	–1.842	0.072
SBP 24, mm Hg	0.205	0.110	0.001	0.000	1.865	0.068
Pulse BP 24, mm Hg	0.379	0.108	0.002	0.000	3.513	0.001
Duration of T2DM, years	0.260	0.119	0.003	0.001	2.181	0.034
HR, bpm	–0.120	0.108	–0.001	0.001	–1.115	0.270

eGFR, estimated glomerular filtration rate; SBP 24, mean 24-hour systolic blood pressure; pulse BP 24, mean 24-hour pulse blood pressure; T2DM, type 2 diabetes mellitus; HR, heart rate.

laboratory data were analyzed. According to the current knowledge, both renal factors (peripheral renal vascular resistance, interstitial and venous pressure) and systemic vascular changes (aortic stiffness, PBP, atherosclerosis) affect RRI values. In this regard, RRI is considered as an indicator of increased vascular stiffness and systemic atherosclerosis, which allows predicting both renal and cardiovascular outcomes [14, 18]. However, it should be noted that RRI was evaluated in the previous studies in patients with untreated or well-controlled essential HTN, and studies including patients with RAH lacked patients with T2DM [14], or T2DM had not been previously diagnosed [17].

The established hemodynamic determinants of increased RRI include increased PBP, which was confirmed in our study including with age adjustment. Similar correlations were documented in several other works [10, 19, 20] including the Polish study RESIST-POL in patients with RHTN [17]. At the same time, Raff et al. did not find any correlation between PBP and RRI [14]. There was no direct correlation between RRI and systolic BP previously identified in patients with controlled HTN [10, 21, 22] in the cohort of patients examined by us. This may be due to the nature of antihypertensive therapy, and the fact that the degree of vascular damage is determined in

**Figure 2.** ROC curve characterizing the dependence of the presence of chronic kidney disease on renal resistive indices



uncontrolled HTN by the severity of the pulsatile load rather than systolic BP.

Since vascular endothelial dysfunction may be a cause of vasoconstriction, the direct correlation of RRI with levels of endogenous NO-synthase inhibitor ADMA appears quite reasonable and corresponds to the findings of Calabria et al. [23]. Moreover, endothelial dysfunction is accompanied by a decrease in the anti-inflammatory and antiproliferative potentials of the endothelium, which triggers vascular remodeling.

According to our findings, other factors associated with RRI were the severity and duration of the history of T2DM, which has a direct damaging effect on the vascular wall. The correlation between HbA1c and RRI was observed in patients with T2DM by Kawai et al. [21]. It is noteworthy that a direct correlation of RRI with basal glycemia in RAH was identified even in patients without T2DM [17].

Aging also leads to the remodeling and increased stiffness of vascular wall, which explains the correlation between RRI, and age documented in our study. Similar data were obtained in patients with controlled AH [10, 23–25], T2DM [4], and RAH [17]. The detected inverse correlation of RRI with HR was previously described by Mostbeck et al. [26]. It is based on a trivial inverse dependence of the blood flow velocity in diastole on its duration.

According to the data obtained, RRI was directly correlated with the levels of hs-CRP, which is consistent with the results in AH patients without T2DM [27] and

patients with CKD [28] and reflects the dependence of vascular resistance on the processes of low-intensity inflammation and the associated vasoconstrictor reactions and profibrotic changes.

The inverse correlation of RRI and eGFR, which characterizes the dependence of the kidney functional state on their blood supply, is also quite natural. Deterioration of renal blood flow may be accompanied by a rarefaction of the vascular bed and violated tubular blood supply, which triggers the processes of tubular damage. This is confirmed by the direct correlation of RRI with lipocalin-2, the most well-studied indicator of tubular damage [29].

One of the important results of our work was the determination of the RRI threshold ( $\geq 0.693$ ), which determines the development of CKD. Similar results were obtained for patients with controlled AH [10, 21] including combined with T2DM [30].

We did not detect the correlation of RRI with albuminuria, unlike in the studies in patients with controlled HTN [10] and patients with T2DM [8]. This could be due to the small sample size and the nephroprotective effects of long-term therapy with renin-angiotensin system inhibitors and metformin [31].

There was no significant correlation between RRI values and sex, despite the fact that in some studies, female patients had higher RRI [5, 21, 22, 32], which could also be due to a small patient sample.

## Conclusion

Thus, increased renal vascular resistance was documented in more than a third of patients with RHTN combined with T2DM; it was closely correlated with renal dysfunction, age, duration of history and severity of T2DM, and markers of low-intensity inflammation, endothelial dysfunction, and vascular stiffness. RRI  $\geq 0.693$  can be considered as diagnosis cut-off point for CKD.

This study was limited to the small number of patients and the survey of treatment compliance.

The practical significance of this study is primarily the identification of RRI threshold associated with the progression of CKD in the selected group of patients with RHTN combined with T2DM. In future, studies may examine the efficacy of targeted therapy for kidney damage and renal and cardiovascular prognosis with the effects on vascular stiffness, endothelial dysfunction, and systemic low-intensity inflammation.

*No conflict of interest is reported.*

**The article was received on 23/03/2023**

## REFERENCES

- Demidova T.Yu., Kislyak O.A. Current Guidelines for the Treatment of Arterial Hypertension in Patients with Diabetes Mellitus and Chronic Kidney Disease. *Rational Pharmacotherapy in Cardiology*. 2021;17(2):323–31. [Russian: Демидова Т.Ю., Кисляк О.А. Современные рекомендации о лечении артериальной гипертензии у пациентов с сахарным диабетом и хронической болезнью почек. *Рациональная Фармакотерапия в Кардиологии*. 2021;17(2):323–31]. DOI: 10.20996/1819-6446-2021-04-06
- Cheung AK, Chang TI, Cushman WC, Furth SL, Hou FF, Ix JH et al. KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *Kidney International*. 2021;99(3):S1–87. DOI: 10.1016/j.kint.2020.11.003
- Heine GH, Reichart B, Ulrich C, Kohler H, Girndt M. Do ultrasound renal resistance indices reflect systemic rather than renal vascular damage in chronic kidney disease? *Nephrology Dialysis Transplantation*. 2006;22(1):163–70. DOI: 10.1093/ndt/gfl484
- Delsart P, Vambargue A, Ninni S, Machuron F, Lelievre B, Ledieu G et al. Prognostic significance of the renal resistive index in the primary prevention of type II diabetes. *The Journal of Clinical Hypertension*. 2020;22(2):223–30. DOI: 10.1111/jch.13819
- Doi Y, Iwashima Y, Yoshihara F, Kamide K, Hayashi S, Kubota Y et al. Renal Resistive Index and Cardiovascular and Renal Outcomes in Essential Hypertension. *Hypertension*. 2012;60(3):770–7. DOI: 10.1161/HYPERTENSIONAHA.112.196717
- Toledo C, Thomas G, Schold JD, Arrigain S, Gornik HL, Nally JV et al. Renal Resistive Index and Mortality in Chronic Kidney Disease. *Hypertension*. 2015;66(2):382–8. DOI: 10.1161/HYPERTENSIONAHA.115.05536
- Afsar B, Elsurur R. Increased renal resistive index in type 2 diabetes: Clinical relevance, mechanisms and future directions. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2017;11(4):291–6. DOI: 10.1016/j.dsx.2016.08.019
- Hamano K, Nitta A, Ohtake T, Kobayashi S. Associations of Renal Vascular Resistance With Albuminuria and Other Macroangiopathy in Type 2 Diabetic Patients. *Diabetes Care*. 2008;31(9):1853–7. DOI: 10.2337/dc08-0168
- Tedesco MA, Natale F, Mocerino R, Tassinario G, Calabrò R. Renal resistive index and cardiovascular organ damage in a large population of hypertensive patients. *Journal of Human Hypertension*. 2007;21(4):291–6. DOI: 10.1038/sj.jhh.1002145
- Adar A, Onalan O, Keles H, Cakan F, Kokturk U. Relationship between Aortic Arch Calcification, Detected by Chest X-Ray, and Renal Resistive Index in Patients with Hypertension. *Medical Principles and Practice*. 2019;28(2):133–40. DOI: 10.1159/000495786
- Geraci G, Mulè G, Geraci C, Mogavero M, D'Ignato F, Morreale M et al. Association of renal resistive index with aortic pulse wave velocity in hypertensive patients. *European Journal of Preventive Cardiology*. 2015;22(4):415–22. DOI: 10.1177/2047487314524683
- Geraci G, Mulè G, Costanza G, Mogavero M, Geraci C, Cottone S. Relationship Between Carotid Atherosclerosis and Pulse Pressure with Renal Hemodynamics in Hypertensive Patients. *American Journal of Hypertension*. 2016;29(4):519–27. DOI: 10.1093/ajh/hpv130
- Pontremoli R, Viazzi F, Martinoli C, Ravera M, Nicoletta C, Bertruti V et al. Increased renal resistive index in patients with essential hypertension: a marker of target organ damage. *Nephrology Dialysis Transplantation*. 1999;14(2):360–5. DOI: 10.1093/ndt/14.2.360
- Raff U, Schmidt BM, Schwab J, Schwarz TK, Achenbach S, Bär I et al. Renal resistive index in addition to low-grade albuminuria complements screening for target organ damage in therapy-resistant hypertension. *Journal of Hypertension*. 2010;28(3):608–14. DOI: 10.1097/HJH.0b013e32833487b8
- Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Journal of Hypertension*. 2013;31(7):1281–357. DOI: 10.1097/01.hjh.0000431740.32696.cc
- Boddi M. Renal Ultrasound (and Doppler Sonography) in Hypertension: An Update. *Advances in Experimental Medicine and Biology*. 2017;956:191–208. DOI: 10.1007/5584\_2016\_170
- Prejbisz A, Warchol-Celińska E, Florczak E, Dobrowolski P, Klisiewicz A, Szwench-Pietrasz E et al. Renal resistive index in patients with true resistant hypertension: results from the RESIST-POL study. *Kardiologia Polska*. 2016;74(2):142–50. DOI: 10.5603/KP.a2015.0114
- Nosadini R, Velussi M, Brocco E, Abaterusso C, Carraro A, Piarrulli F et al. Increased renal arterial resistance predicts the course of renal function in type 2 diabetes with microalbuminuria. *Diabetes*. 2006;55(1):234–9. PMID: 16380498
- Hashimoto J, Ito S. Central Pulse Pressure and Aortic Stiffness Determine Renal Hemodynamics: Pathophysiological Implication for Microalbuminuria in Hypertension. *Hypertension*. 2011;58(5):839–46. DOI: 10.1161/HYPERTENSIONAHA.111.177469
- Kuznetsova T, Herbots L, Lopez B, Jin Y, Richart T, Thijs L et al. Prevalence of Left Ventricular Diastolic Dysfunction in a General Population. *Circulation: Heart Failure*. 2009;2(2):105–12. DOI: 10.1161/CIRCHEARTFAILURE.108.822627
- Kawai T, Kamide K, Onishi M, Yamamoto-Hanasaki H, Baba Y, Hongyo K et al. Usefulness of the resistive index in renal Doppler ultrasonography as an indicator of vascular damage in patients with risks of atherosclerosis. *Nephrology Dialysis Transplantation*. 2011;26(10):3256–62. DOI: 10.1093/ndt/gfr054
- Ponte B, Pruijm M, Ackermann D, Vuistiner P, Eisenberger U, Guessous I et al. Reference Values and Factors Associated With Renal Resistive Index in a Family-Based Population Study. *Hypertension*. 2014;63(1):136–42. DOI: 10.1161/HYPERTENSIONAHA.113.02321
- Calabia J, Torguet P, Garcia I, Martin N, Mate G, Marin A et al. The Relationship Between Renal Resistive Index, Arterial Stiffness, and Atherosclerotic Burden: The Link Between Macrocirculation and Microcirculation. *The Journal of Clinical Hypertension*. 2014;16(3):186–91. DOI: 10.1111/jch.12248
- Alterini B, Mori F, Terzani E, Raineri M, Zuppiroli A, De Saint Pierre G et al. Renal resistive index and left ventricular hypertrophy in essential hypertension: a close link. *Annali Italiani Di Medicina Interna*. 1996;11(2):107–13. PMID: 8974435
- Sugiura T, Wada A. Resistive index predicts renal prognosis in chronic kidney disease. *Nephrology Dialysis Transplantation*. 2009;24(9):2780–5. DOI: 10.1093/ndt/gfp121
- Mostbeck GH, Gössinger HD, Mallek R, Siostrzonek P, Schneider B, Tscholakoff D. Effect of heart rate on Doppler measurements of resistive index in renal arteries. *Radiology*. 1990;175(2):511–3. DOI: 10.1148/radiology.175.2.2183288
- Berni A, Ciani E, Bernetti M, Cecioni I, Berardino S, Poggesi L et al. Renal resistive index and low-grade inflammation in patients with essential hypertension. *Journal of Human Hypertension*. 2012;26(12):723–30. DOI: 10.1038/jhh.2011.93
- Lai S, Ciccariello M, Dimko M, Galani A, Lucci S, Cianci R et al. Cardio-Renal Syndrome Type 4: The Correlation Between Cardiorenal Ultrasound Parameters. *Kidney and Blood Pressure Research*. 2016;41(5):654–62. DOI: 10.1159/000447934
- Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A. Accuracy of Neutrophil Gelatinase-Associated Lipocalin (NGAL) in Diagnosis and Prognosis in Acute Kidney In-

- jury: A Systematic Review and Meta-analysis. *American Journal of Kidney Diseases*. 2009;54(6):1012–24. DOI: 10.1053/j.ajkd.2009.07.020
30. Koshel'skaya O.A., Zhuravleva O.A. Markers of chronic kidney disease and disorders of renal hemodynamics in patients with medically-controlled arterial hypertension and high and very high cardiovascular risk. *Russian Journal of Cardiology*. 2018;23(10):112–8. [Russian: Кошельская О.А., Журавлева О.А. Маркеры хронической болезни почек и нарушения ренальной гемодинамики у пациентов с контролируемой артериальной гипертонией высокого риска. *Российский кардиологический журнал*. 2018;23(10):112–8]. DOI: 10.15829/1560-4071-2018-10-112-118
31. Halimi J-M. The emerging concept of chronic kidney disease without clinical proteinuria in diabetic patients. *Diabetes & Metabolism*. 2012;38(4):291–7. DOI: 10.1016/j.diabet.2012.04.001
32. Kuznetsova T, Cauwenberghs N, Knez J, Thijs L, Liu Y-P, Gu Y-M et al. Doppler Indexes of Left Ventricular Systolic and Diastolic Flow and Central Pulse Pressure in Relation to Renal Resistive Index. *American Journal of Hypertension*. 2015;28(4):535–45. DOI: 10.1093/ajh/hpu185