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Influence of OATP1B1 and OATP1B3 mutations and glomerular filtration rate on trough serum digoxin concentration in the Chinese population

A prospective cohort study

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Abstract

Polymorphisms of organic anion transporting polypeptides (OATPs) have been reported to affect trough serum digoxin concentration (SDC). However, the association of these polymorphisms with trough SDC in Chinese heart failure patients has not been studied. We aim to explore whether OATP1B1 388A>G, OATP1B1 521T>C, and OATP1B3 699G>A influence trough SDC in Chinese heart failure patients and to make clinical recommendations.

Chinese patients (n = 104) diagnosed with heart failure under long-term digoxin therapy (0.125 mg daily) were enrolled in this study. Blood samples were collected for the analysis of trough SDC (immunofluorescence) and the polymorphisms of OATP1B1 388A>G, OATP1B1 521T>C, and OATP1B3 699G>A (PCR-RFLP and Sanger sequencing).

Patients with glomerular filtration rate (GFR) under 30 mL/min had significantly higher trough SDC (1.20 ± 0.50 ng/mL) than recommended trough SDC for heart failure patients. Trough SDC was not significantly influenced by mutations of OATP1B1 388A>G ($P = .890$), 521T>C ($P = .054$), and OATP1B3 699G>A ($P = .854$). Patients with OATP1B1 521T>C mutant-type carrier had slightly higher trough SDC (0.98 ± 0.53 ng/mL) than those with wild-type carrier (0.74 ± 0.40 ng/mL) when they have repaired renal function.

Heart failure patients with severe renal dysfunction (GFR<60 mL/min) and/or OATP1B1 521T>C mutant-type carriers are recommended a smaller dosage of digoxin and strict therapeutic drug monitoring.

Abbreviations: ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, BNP = brain natriuretic peptide, GFR = glomerular filtration rate, LDL-C = low-density lipoprotein cholesterol, NHYA = New York Heart Association, OATPs = organic anion transporting polypeptides, PCR-RFLP = Polymerase chain reaction–restriction fragment length polymorphism, SDC = serum digoxin concentration, TG = Triglycerides.

Keywords: digoxin, heart failure, organic anion transporting polypeptide, mutation

1. Introduction

Digoxin is one of the oldest compounds used in cardiovascular diseases.[1] Even though there are some conflicting reports, digoxin is still an irreplaceable medicine for the treatment of heart failure with reduced ejection fraction.[2] The PROVED and the RADIANCE studies proved that continued usage of digoxin, diuretics, and angiotensin-converting-enzyme inhibitors improves heart failure.[3,4] The DIG trial showed that digoxin can reduce heart failure-related death or hospitalization in patients with reduced systolic function.[5] However, some physicians refuse to use digoxin because of its narrow therapeutic window and toxicity risk, which can sometimes be fatal. The chance of digitalis intoxication is related to the serum digoxin concentration (SDC), which is affected by dosage, age, renal function, use of concomitant drugs, and genetic polymorphisms.[6] Digoxin clearance can be largely affected by renal function. However, clinical studies have shown that even in patients with similar renal function, digoxin clearance varies 7- to 8-folds.[7] The reason for such inter-individual difference might be genetic diversity.

The members of the organic anion transporting polypeptide (OATP/SLCO) represent a family of important proteins involved in the membrane transport of endogenous and xenobiotic compounds. OATP can be found in the liver, kidney, brain, small intestine, blood brain barrier, etc.[8,9] The subfamily member OATP1B consists of OATP1B1 and OATP 1B3, which are mostly expressed in the basolateral membrane of hepatocytes.[10] Thus, these transporters are considered to be important for drug disposition in the body. A number of single nucleotide polymorphisms have been identified in association with OATP1B1 and OATP1B3 genes among different populations.[11] OATP1B1 388A>G, OATP1B1 521T>C, OATP1B 699G>A,

Editor: Yan Li.

This study was founded by National Natural Science Foundation of China (no. 81373487), the National Key Technologies R&D Program under Grant (no. 2016YFC0904900) and Scientific Research Seed Fund of Peking University First Hospital (no. 2018SF081). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The authors declare they have no conflict of interest.

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Medicine (2019) 98:14(e15088)

Received: 9 October 2018 / Received in final form: 15 February 2019 / Accepted: 8 March 2019

http://dx.doi.org/10.1097/MD.0000000000015088

and OATP1B 344T>G have rather high variant allele frequencies in the Chinese population.[12,13]

Digoxin is one among the various substrates of OATP. Digoxin was proved to be uniquely transported by OATP1B3 and inhibitors of OATP1B1.[14–16] However, there is also a research states that digoxin is not a substrate for human OATP transporters. [17] Still, M. Tsujimoto[18] reported that hemodialysis patients with the 334T/699G allele have a lower trough concentration-to-dose ratio than those homozygous for the 334G/699A allele, but the differences were not statistically significant. There are no studies showing the relationship between SDC and OATP polymorphisms in the Chinese population. Therefore, the present study was conducted.

2. Materials and methods

2.1. Subjects population

Chinese patients (n = 104) diagnosed with heart failure and treated at Peking University First Hospital (Beijing, China) were enrolled in this study. Written informed consents were obtained from all participants in accordance with the ethics committees of Peking University First Hospital. Inclusion criteria: Patients diagnosed with chronic heart failure and have been taking digoxin 0.125 mg once daily for more than 30 days then measured SDC.

2.1.1. Exclusion criteria. Patients with abnormal serum potassium (<3.5 mmol/L or >5.5 mmol/L), liver dysfunction (ALT >150 IU/L or AST >120 IU/L), concomitant treatment with quinidine, verapamil, diltiazem, or amiodarone.

2.2. Trough SDC measurement

Trough SDCs were determined at the Therapeutic Drug Monitoring laboratory in Peking University First Hospital using ARTCHITECT iDigoxin Reagent Kit (Abbott Laboratories). The blood sample for trough SDC measurement were collected just before the next digoxin administration is due. The measurement range of the ARCHITECT iDigoxin assay is 0.3 to 4.0 ng/mL.

2.3. Blood sampling and DNA extraction

Venous blood samples were collected in a 4-mL EDTA-K2 BD vacutainer, transferred into cryogenic vials, and stored at −80°C. DNA was extracted from blood with a DNA Purification Kit (Wizard Genomic, Promega) according to the manufacturer's instructions and stored at 4°C until use.

2.4. Polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) assay for genotyping

The sequences of the primers used for the detection of 388A>G, 521T>C, and 699G>A are shown in Table 1. PCR was carried out in a reaction volume of 20 μL containing 2 μL of genomic DNA, 4 μL of 5 × Buffer (Promega, Madison, WI), 1.6 μL of 2.5 mM dNTP (Takara, Kusatsu, Japan), 0.4 μL front prime (BGI, Guangzhou, China), 0.4 μL reverse prime (BGI, Guangzhou, China), 0.1 μL Go Taq enzyme (Promega) and 11.4 μL H_2O. PCR amplification was performed using the Gene Amplification PCR System 9700 (Applied Biosystems, Shanghai, China) with initial denaturation step at 94°C for 5 minutes, followed by 30 cycles of denaturation at 94°C for 30 seconds, annealing at 48 to 55°C for 30 seconds, extension at 72°C for 30 seconds, and final extension at 72°C for 7 minutes. After amplification, the PCR products of 388A>G (274 bp) and 699G>A (274 bp) were digested with ClaI (Biolabs, New England) and Rsa I (Biolabs), respectively, for 2 hours at 37°C. PCR products of 521T>C and digested products of 388A>G and 699G>A were analyzed by electrophoresis (150 V, 35 minutes) on a 2.5% agarose gel in the presence of ethidium bromide.

Table 1

Primer sequence for tested SNPs.

Polymorphism	Exon	Position	Primer sequence
388A>G	exon 5	Asn130Asp	F: GCAAATAAAGGGGAATATTTCTC R: AGAGATGTAATTAAATGTATAC
521T>C	exon 6	Val174Ala	F: AAGTAGTTAAATTTGTAATAGAAATGC R: GTAGACAAAGGGAAAGTGATCATA inner1: CATACATGTGGATATATGT inner2: CATACATGTGGATATATGC
699G>A	exon 8	Met233Ile	F: ATGATTACATTCCCTGGATC R: ACTATCATGGTACCTTGTTC

2.5. Sanger sequencing

Blood samples with different genotypes detected with PCR-RFLP were verified by Sanger sequencing. Purified PCR products were placed in 96-well plates (Millipore) and sequenced using ABI3730XL DNA Analyzer (Applied Biosystems) with the initial denaturation step at 95°C for 15 seconds, followed by 35 cycles of denaturation at 94°C for 15 seconds, annealing at 50°C for 5 seconds, and extension at 60°C for 90 seconds to terminate the reaction.

2.6. Data analysis

Normal distribution tests were conducted using SPSS software. Statistical significance was calculated with One-way ANOVA for normal distribution data and with Kruskal–Wallis test for not normal distributed data. The SPSS software package version 17.0 was used to perform the statistical analysis. A P value of less than .05 was accepted as significant.

3. Results

3.1. Genotyping results

The PCR-RFLP products of 388A>G, 521T>C, and 699G>A are shown in Figure 1 and the Sanger sequencing results are shown in Figure 2.

The homozygous variant 388GG produced 155-bp and 119-bp fragments, wild-type allele produced a 274-bp fragment, and heterozygous variant 388GA produced three fragments of 155, 199, and 274 bp.

Polymorphisms of 521T>C were identified by the electrophoresis strips from inner 1 and inner 2. The wild-type allele 521TT produced 260-bp and 179-bp fragments in inner 1 and a 260-bp fragment in inner 2, whereas the heterozygous mutant allele 521TC produced 260-bp and 179-bp in both inner 1 and inner 2.

The homozygous variant 699AA produced a 279-bp fragment, the wild-type allele 699GG produced a 242-bp fragment, and the heterozygous variant 699GA produced 279-bp and 242-bp fragments.

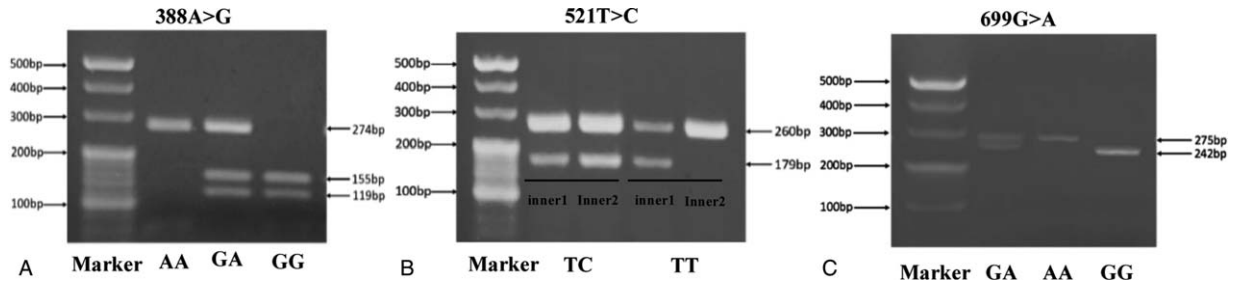

Figure 1. PCR-RFLP results of 388A>G (a), 521T>C (b), 699G>A (c) polymorphisms. Lanes show restriction fragmentation patterns for homozygous wild-type, heterozygous, and homozygous mutant subjects. PCR-RFLP = Polymerase chain reaction–restriction fragment length polymorphism.

3.2. Genotype and allele frequency

Polymorphisms of OATP1B1 388A>G, 521T>C, and OATP1B3 699G>A in subjects enrolled in this study are shown in Table 2. The allele frequencies for OATP1B1 388A>G, 521T>C, and OATP1B3 699G>A polymorphisms are shown in Table 2. The genotype frequencies for OATP1B1 388A>G, 521T>C, and OATP1B3 699G>A were in Hardy–Weinberg equilibrium.

3.3. Influence of OATP polymorphisms on trough SDC

The relationship between OATP1B1 388A>G, 521T>C, and OATP1B3 699G>A and trough SDC in Chinese heart failure patients is shown in Table 3. According to statistical analysis, serum digoxin is not significantly influenced by these three polymorphisms ($P > .05$). However, for OATP1B1 521T>C, patients with TC+CC carrier had higher trough SDC (0.92 ± 0.53 ng/mL) than those with TT carrier (0.67 ± 0.52 ng/mL). Although

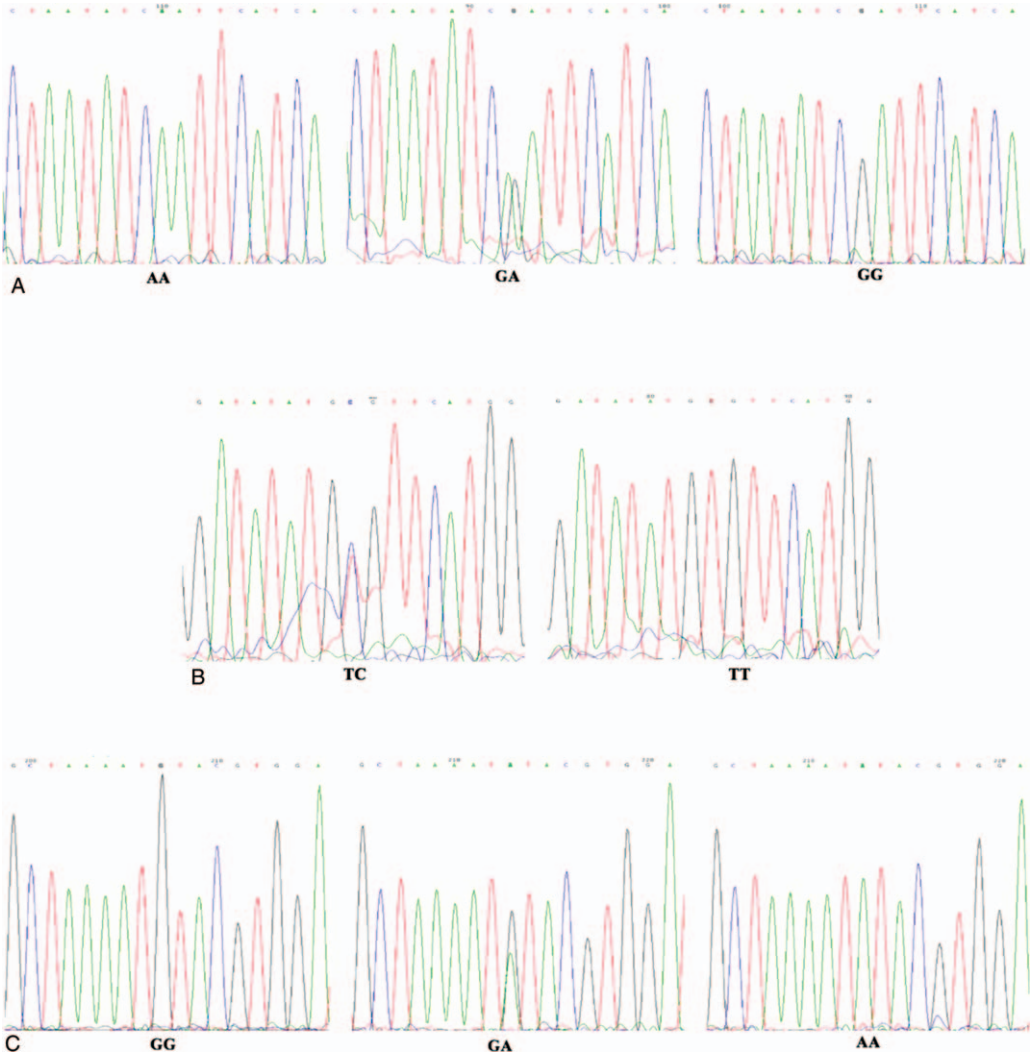

Figure 2. Sanger sequencing results for the OATP1B1 388A>G (A), 521T>C allele (B) and OATP1B3 699G>A.

Table 2

Genotype and allele frequency of the OATP1B1 388G>A, 521C>T and OATP1B3 699G>A.

OATP variant	Genotype	All subjects (n, %)	*P* value
388A>G	AA	10 (9.62%)	.053
	GA	58 (55.77%)	
	GG	36 (34.62%)	
521T>C	TT	86 (82.69%)	.333
	CT	18 (17.31%)	
	CC	0 (0.00%)	
699G>A	GG	7 (6.73%)	.898
	GA	39 (37.50%)	
	AA	58 (55.77%)	

P value obtained in the Hardy–Weinberg Equilibrium.

Table 3

Influence of OATP1B1 388G>A, 521C>T and OATP1B3 699G>A on trough SDC.

OATP variant	Genotype	Mean (ng/mL)	SD	*P* value
388A>G	GG	0.74	0.57	.890
	GA + AA	0.67	0.43	
521T>C	TT	0.67	0.52	.054
	CT + CC	0.92	0.53	
699G>A	AA	0.73	0.56	.854
	GA + GG	0.70	0.48	

P value obtained in the Kruskal–Wallis test for the comparison between genotypes.

Table 4

Influence of renal function on trough SDC.

GFR (mL/min)	All subjects (n, %)	Mean (ng/mL)	SD	*P* value
0~30	14 (13.46%)	1.20	0.50	.000
30~60	47 (45.19%)	0.71	0.40	
60~	43 (41.35%)	0.56	0.57	

P value obtained in the Kruskal–Wallis test for the comparison between genotypes. SDC = serum digoxin concentration.

Kruskal–Wallis test showed no significant difference ($P = .054$), SDC tended to be high in 521T>C mutant carriers, which requires further attention.

3.4. Influence of renal function on trough SDC

Renal function has been recognized as a vital determiner of digoxin clearance, which can be reflected by trough SDC. The influence of renal function on trough SDC is shown in Table 4. Patients were divided based on GFR calculated by the Schwartz formula. GFR under 30 mL/min is considered as severe renal dysfunction, GFR between 30 and 60 mL/min is considered as mild-medium renal dysfunction, GFR over 60 mL/min is considered of normal renal function. From Table 4 we can observe that with trough SDC markedly increases with decreasing GFR ($P = .000$).

3.5. Baseline information for patients with varied renal function

Since the digoxin concentration is strikingly influenced by renal function, we then divided the enrolled patients into 2 groups based on renal function: 43 patients with GFR $\geq$ 60 ml/L were classified into normal renal function, baseline information see in Table 5, and 61 patients with GFR $<$ 60 ml/L were classified as impaired renal function, baseline information see in Table 6. The baseline information for patients in each group were collected and were analyzed based on different polymorphisms. No significant difference was found in GFR between different genotypes in both groups, so the influence of renal function can be largely alleviated.

3.6. Influence of OATP polymorphisms on trough SDC for patients with varied renal function

The relationship between OATP1B1 388A>G, 521T>C, and OATP1B3 699G>A and trough SDC in Chinese heart failure patients with normal renal function is shown in Table 7, and those with impaired renal function is shown in Table 8. According to statistical analysis, serum digoxin is not significantly influenced by these 3 polymorphisms ($P > .05$). However,

Table 5

OATP 1B1 388A>G, 521T>C and OATP1B3 699G>A genotype and baseline characteristics for patients with normal renal function.

		388A>G			521T>C			699G>A		
Items (Unit)		GG	GA + AA	*P* value	TT	CT + CC	*P* value	AA	GA + GG	*P* value
N		12	31		41	2		26	17	
Gender (Male%)		75%	80.6%	.539	78.0%	100%	.478	76.9%	82.4%	.402
Age (yr)		61.5 ± 12.3	56.0 ± 12.6	.309	57.9 ± 12.8	51.0 ± 8.5	.391	56.4 ± 12.9	59.6 ± 12.3	.717
NYHA	I	6	11		18	0		11	7	
	II	3	11		13	0		8	5	
	III	1	6		6	1		5	2	
	IV	2	3		4	1		2	3	
GFR (mL/min)		81.9 ± 21.4	83.6 ± 28.6	1.000	82.6 ± 26.6	93.6 ± 31.8	.637	86.4 ± 30.6	77.9 ± 17.8	.604
K^+ (mmol/L)		4.0 ± 0.4	4.1 ± 0.3	.933	4.1 ± 0.4	4.2 ± 0.05	.124	4.0 ± 0.3	4.2 ± 0.4	.153
BNP (pg/mL)		279.0 ± 234.2	812.1 ± 860.6	.025	646.8 ± 760.4	1102.0 ± 1394.4	.046	592.2 ± 600.0	789.1 ± 1009.8	.873
AST (IU/L)		22.8 ± 7.6	23.4 ± 11.0	.759	23.4 ± 10.2	20.5 ± 10.6	.976	22.4 ± 9.9	24.7 ± 10.6	.516
ALT (IU/L)		24.6 ± 10.9	30.1 ± 27.9	.283	29.3 ± 24.3	31.5 ± 29.0	.906	25.0 ± 12.3	36.4 ± 35.4	.271
TG		2.2 ± 1.7	1.7 ± 0.9	.374	1.9 ± 1.2	1.7 ± 0.8	.364	1.8 ± 0.9	2.0 ± 1.6	.957
LDL-C		1.9 ± 0.5	2.4 ± 0.7	.048	2.3 ± 0.7	2.4 ± 0.5	.565	2.5 ± 0.7	1.9 ± 0.5	.013

P value obtained in the Kruskal–Wallis test for the comparison between genotypes.

ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, BNP = brain natriuretic peptide, LDL-C = low-density lipoprotein cholesterol, NHYA = New York Heart Association, TG = Triglycerides.

Table 6

OATP 1B1 388A>G, 521T>C and OATP1B3 699G>A genotype and baseline characteristics for patients with impaired renal function.

Items (Unit)		388A>G			521T>C			699G>A		
		GG	GA+AA	*P* value	TT	CT+CC	*P* value	AA	GA+GG	*P* value
N		24	37		45	16		32	29	
Gender (Male%)		45.8%	59.5%	.546	55.6%	50%	.704	50%	58.6%	.503
Age (yr)		74.6±11.9	72.0±11.2	.318	72.8±11.0	72.4±12.3	.743	72.8±10.3	72.5±12.5	.756
NYHA	I	5	6		9	2		6	5	
	II	10	23		24	9		17	16	
	III	7	8		10	5		7	8	
	IV	2	0		2	0		2	0	
GFR (mL/min)		41.5±10.0	39.7±13.9	.870	41.5±12.6	37.6±13.1	.145	41.8±12.8	38.9±12.3	.348
K^+ (mmol/L)		4.1±0.7	4.3±0.6	.364	4.3±0.8	4.2±0.6	.825	4.1±0.7	4.3±0.5	.023
BNP (pg/mL)		982.9±894.7	864.9±722.9	.847	926.0±792.0	867.8±829.1	.594	929.7±869.3	889.8±719.6	.691
AST		22.5±9.7	24.4±15.0	.628	23.62±13.8	23.9±12.0	.506	24.1±14.3	23.2±12.2	.592
ALT		19.3±13.3	20.6±16.4	.817	20.4±15.3	19.6±15.6	.389	21.2±15.8	19.1±14.9	.144
TG		1.2±0.5	1.9±2.0	.091	1.41±2.7	2.0±2.7	.356	1.8±2.0	1.4±1.1	.137
LDL-C		2.1±0.6	2.2±0.6	.854	2.11±0.6	2.27±0.6	.613	2.0±0.6	2.3±0.6	.069

P value obtained in the Kruskal–Wallis test for the comparison between genotypes. ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, BNP = brain natriuretic peptide, LDL-C = low-density lipoprotein cholesterol, NHYA = New York Heart Association, TG = Triglycerides.

when renal function is repaired, OATP1B1 521T>C mutant-type carrier had higher trough SDC (0.98±0.53 ng/mL) than wild-type carrier (0.74±0.40 ng/mL). It also much higher than 521T>C mutant-type carrier with normal renal function (0.56 ±0.58 ng/mL).

4. Discussion

This is the first study reporting the influence of OATP1B1 388A>G, 521T>C, and OATP 1B3 699G>A on trough SDC in Chinese heart failure population. Many factors may interfere with SDC, such as digoxin dose, age, gender, renal function, serum potassium, and the use of concomitant drugs that are known to alter SDC (e.g., amiodarone).[6] Therefore, these factors should be taken into account when digoxin is prescribed. In this study, dosage was unified to 0.125 mg once daily. The age, gender, and serum potassium values did not significantly differ among the genotype groups. Patients concomitantly treated with quinidine, verapamil, diltiazem, amiodarone, and antibiotics were excluded. Most of the patients are having a standard treatment regimen for heart failure, the usage rate of β-blocker, ACEI/ARB, and diuretics are 80.7%, 53.8%, and 71.2%.

Table 7

Association of OATP polymorphisms with SDC in patients with normal renal function.

OATP variant	Genotype	Mean (ng/mL)	SD	*P* value
388A>G	GG	0.43	0.30	.511
	GA+AA	0.60	0.63	
521T>C	TT	0.56	0.58	.976
	TC+CC	0.48	0.25	
699G>A	AA	0.61	0.69	.814
	GA+GG	0.56	0.57	

P value obtained in the Kruskal–Wallis test for the comparison between genotypes. ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, BNP = Brain Natriuretic Peptide, LDL-C = Low-density lipoprotein cholesterol, NHYA = New York Heart Association, TG = Triglycerides.

Table 8

Association of OATP polymorphisms with SDC in patients with impaired renal function.

OATP variant	Genotype	Mean (ng/mL)	SD	*P* value
388A>G	GG	0.78	0.46	.682
	GA+AA	0.82	0.46	
521T>C	TT	0.74	0.40	.094
	TC+CC	0.98	0.53	
699G>A	AA	0.77	0.37	.682
	GA+GG	0.83	0.53	

P value obtained in the Kruskal–Wallis test for the comparison between genotypes. SDC = serum digoxin concentration.

Ali et al[19,20] reported that digoxin at low doses and at low trough SDC (0.5–0.9 ng/mL) reduced major natural history endpoints, including overall mortality and cardiovascular hospitalizations. Rathore et al[21] reported that patients under digoxin therapy with trough SDCs of 0.5 to 0.8 ng/mL had a 6.3% lower mortality rate than patients receiving placebo. Considering the crucial impact of renal function on digoxin clearance, we divided the patients into normal renal function and mild-medium and severe renal dysfunction groups based on GFR. We found that with decreasing GFR, trough SDC strikingly increased. Besides, when GFR is less than 30 mL/min, trough SDC reach to 1.20±0.50ng/mL, which is much higher than the upper recommended limit of 0.9 ng/mL.

In this present study, OATP polymorphism did not significantly affect trough SDC, and mean trough SDCs were within the range of 0.5 to 0.9 ng/mL for wild-type + homozygous mutant / heterozygous mutant-type carriers of 388A>G (0.74±0.57/0.67 ±0.43 ng/mL), 699G>A (0.73±0.56/0.70±0.48 ng/mL), and wild-type carriers of 521T>C (0.67±0.52 ng/mL). The trough SDC of 521T>C mutant-type carriers was slightly higher (0.92± 0.53 ng/mL) than the recommended range. Besides, it is interesting to observe that the rough SDC of 521T>C mutant-type carriers is only 0.48±0.25 ng/mL when patients with normal renal function, while when GFR declines to less than 60 mL/min, the trough SDC then raised up to 0.98±0.53 ng/mL. Although the difference is not significant ($P = .094$), it is still a tendency which may require extra cautious. Besides, the number of patients in sub-groups is rather small and some of the significance might not be detected.

When the kidney is fully functional, liver metabolism plays a comparatively less important role in digoxin elimination.

However, when the renal function is impaired, the importance of liver metabolism becomes evident. Although digoxin is largely excreted unchanged in urine (about 50–70%), hydrolysis, oxidation, and conjugation in the liver also contribute to digoxin metabolism. The half-life time to steady state varies with different renal function capacities. The half-life time to steady state is shorter in patients with normal renal function than in patients with impaired liver function, in whom the elimination of digoxin occurs through the liver.[22] OATP1B1 and OATP1B3 are all expressed on sinusoidal membranes of hepatocytes. Thus, the OATP gene may have a bigger effect on digoxin under conditions of impaired renal function. However, the small sample size of this study may limit the generalization of the finding.

5. Conclusion

Our study suggests that patients with severe renal dysfunction (GFR<30 mL/min) may achieve significantly high trough SDC; therefore, we recommend a smaller dosage of digoxin and intense monitoring in these patients. There is no clear association between OATP polymorphisms and trough SDC, except that OATP1B1 521T>C mutant-type carriers have a slightly higher trough SDC than wild-type carriers when patients with impaired renal function (GFR<60 mL/min). Until now, there are no former reports or evidence to show that OATP1B1 can interfere with trough SDC. Therefore, further studies are needed.

Author contributions

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Project administration: Shu-qing Chen.
Supervision: Qian Xiang, Yi-min Cui, Xia Zhao.
Writing – original draft: Shu-qing Chen.
Writing – review & editing: Xia Zhao.

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