

Involvement of Renin–Angiotensin System in Pressure–Flow Relationship

Role of Angiotensin-converting Enzyme Gene Polymorphism

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Background: The renin–angiotensin system is involved in blood pressure regulation. The insertion/deletion (*I/D*) polymorphism of the angiotensin-converting enzyme (*ACE*) gene is known to be associated with variation of plasma and cellular *ACE* concentrations. Furthermore, changes in arterial function have been suggested to be associated to the *DD* genotype. The aim of the study was to investigate the arterial vascular response to a physiologic stimulus (*i.e.*, flow) according to the *I/D* *ACE* gene polymorphism.

Methods: Sixty patients scheduled for coronary artery bypass grafting (*n* = 24) or valve surgery (*n* = 36) under normothermic cardiopulmonary bypass were genotyped in a blind manner by polymerase chain reaction. Mean arterial pressure was measured at pump flows ranging from 1 to 3 l · min⁻¹ · m⁻² by 0.25 l · min⁻¹ · m⁻² step each 15 s, to obtain a pressure–flow relation. Independent factors associated with the variation of the slope of the pressure–flow relation curve were assessed by multivariate analysis.

Results: We found a *D* allelic frequency of 0.54. Patients were separated in two groups (*DD*, *n* = 16; *ID/II*, *n* = 44). There were no significant difference with regard to preoperative and intraoperative data between the two groups. *DD* patients had their pressure–flow relation curves shifted upward (with higher pressures as flow increased), indicating a lesser decrease in vascular resistance. Furthermore, *DD* genotype was the only independent predictor of the slope of the curves (21.5 ± 4.2 *vs.* 18.1 ± 5 mmHg/[l · min⁻¹ · m⁻²] for *DD* and *ID/II*, respectively; *P* = 0.02; values are mean ± SD).

Conclusion: These results show that vasomotor properties are influenced by the *I/D* polymorphism of the *ACE* gene.

BLOOD pressure regulation involves three different vasopressor systems: sympathetic, renin–angiotensin, and

vasopressin systems. The renin–angiotensin system plays a key role during anesthesia because of reduction of sympathetic tone and induced decrease in vascular capacitance.¹ Moreover, the renin–angiotensin system may be activated during cardiac surgery under cardiopulmonary bypass (CPB) as assessed by either increased plasma renin activity^{2–4} or high angiotensin II plasma concentration.³ However, there is a great variability between patients concerning hemodynamic stability and vascular response during anesthesia.

Plasma and cellular angiotensin-converting enzyme (*ACE*) concentrations are partially determined by the insertion/deletion (*I/D*) polymorphism of the *ACE* gene.⁵ Several changes in arterial phenotype have been previously reported in homozygote patients for the *D* allele (*DD* patients), known to be associated with highest concentrations of *ACE*⁵ and an increased risk of cardiovascular diseases.⁶ We previously reported an increased vascular response to phenylephrine in *DD* patients during CPB.⁷ Other studies have explored the association between this genetic polymorphism and endothelial function. Impaired endothelial-dependent vasodilation has been described *in vitro* in human internal mammary arteries from *DD* patients, probably because of a smaller sensitivity for nitric oxide in response to pharmacologic stimuli.⁸ However, *in vivo* studies showed conflicting results. Endothelium-dependent dilation in response to pharmacologic stimulation has been shown to be impaired in *DD* patients in some studies,^{9,10} but others led to different conclusion.¹¹ Furthermore, endothelium-dependent dilation in response to hyperemia (*i.e.*, shear stress), a more physiologic stimulus of nitric oxide release, was not impaired in *DD* patients.¹²

Faced with these divergent reports, it seems to be worthwhile to investigate *in vivo* the vascular response to flow, in accordance with the *I/D* polymorphism of the *ACE* gene. Therefore, in the current study, we assessed this vascular response in cardiac surgery patients using the CPB resistive model. We determined the pressure–flow relationship (PFR) by recording changes in arterial pressure induced by stepwise increases in flow, according to the *ACE* genotype.

Materials and Methods

Patients

After obtaining approval from the local ethics committee (Hôpital Bichat, Paris, France) and written informed

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Table 1. Preoperative Characteristics of Study Patients

	Genotype DD (n = 16)	Genotype II/ID (n = 44)
Age (yr)	66.8 ± 8.0	61.1 ± 12.7
Sex (M/F)	13/3	31/13
Body surface area (m ²)	1.84 ± 0.17	1.79 ± 0.16
Surgery (CABG/VS)	9/7	15/29
Normal LV function	12	39
History of hypertension	7	27
History of myocardial infarction	6	8
Preoperative Medications		
β-blockers	6	15
ACE inhibitors	7	14
Ca channel blockers	7	10
Nitrates	6	12

For all groups, comparisons according to genotype were not significant. Values are mean ± SD for age, sex, and body surface area.

CABG = coronary artery bypass grafting; VS = valve surgery; LV = left ventricular; ACE = angiotensin converting enzyme; Ca = calcium.

consent, we genotyped 60 adult white patients scheduled for cardiac surgery, either coronary artery bypass grafting or valve surgery. All experiments were performed in a blind manner. Taking into account the known factors acting on vascular response, patients with diabetes and untreated hypercholesterolemia, and those who were current smokers, were excluded. We also excluded emergent and infected patients and those who received intravenous vasoactive medications before CPB (catecholamines, nitroglycerin, or calcium channel blockers). To avoid deleterious effects of transient hypoperfusion, patients with carotid stenosis or history of ischemic stroke were also excluded. Patients with extreme values of hematocrit (< 20% or > 35%), pH (< 7.4 or > 7.6), carbon dioxide tension (< 3.0 kPa or > 5.3 kPa), glycemia (> 12 mmol/L), or temperature (< 35°C) during CPB were not included.

The patients' preoperative characteristics are shown in table 1. Left ventricular function was assessed by echocardiography (normal function corresponds to an ejection fraction ≥ 50%).

Anesthesia and Cardiopulmonary Bypass Management

Anesthesia management was standardized. Calcium channel blockers and ACE inhibitors were not given on the day of surgery. β-blocker medication was given on the morning of surgery, with the premedication (2 mg oral lorazepam and 0.1 mg/kg intramuscular morphine). Anesthesia was induced and maintained with fentanyl (bolus of 20–30 μg/kg, followed by repeated injections as needed) and midazolam (0.03–0.06 mg/kg and repeated injections); muscle relaxation was achieved using pancuronium bromide (bolus of 0.1 mg/kg followed by 0.03-mg/kg injections as needed). For the purpose of this study, neither propofol nor volatile anesthetics were used. CPB was normothermic and nonpulsatile. Myocar-

dial protection was achieved by intermittent cold-blood cardioplegia.

Pressure-flow Relation

Mean arterial pressure (MAP) was recorded through a radial artery catheter with a transducer maintained at mid-axillary level. The protocol was performed once CPB and MAP stabilized for a pump flow of 2.4 l · min⁻¹ · m⁻². Before this study, to establish the duration of each flow-increase step, we ensured that blood pressure was stabilized in less than 15 s after change in flow, as described by other investigators.¹³ The PFR was generated by first decreasing the pump flow to 1 l · min⁻¹ · m⁻² during 15 s and then increasing it up to 3 l · min⁻¹ · m⁻² by steps of 0.25 l · min⁻¹ · m⁻² each 15 s. MAP was recorded at each step. The protocol was stopped if MAP was less than 30 or more than 90 mmHg. The protocol was also stopped if the venous return was insufficient to increase flow (*i.e.*, a blood concentration < 300 ml in the reservoir). No injection of anesthetic drugs was performed for at least 20 min before the study protocol. Blood samples were drawn at the beginning of the CPB to control biologic parameters (table 2) and for polymerase chain reaction (PCR) analysis.

For each patient, the slope of the PFR curve, reflecting the change in vascular resistance, was calculated as follows: slope of the curve = (MAP_{max} - MAP_{min}) / (Flow_{max} - Flow_{min}). MAP_{max} was the value of MAP obtained at the highest flow (Flow_{max}); conversely, MAP_{min} was the value of MAP obtained at the lowest flow (Flow_{min}).

ACE Genotyping

Blood was collected in EDTA, and genomic DNA was prepared from leukocytes by phenol extraction. Genotyping of all subjects for ACE was performed by PCR according to a previously reported procedure.⁵ Briefly,

Table 2. Intraoperative Characteristics of Study Patients

	Genotype DD (n = 16)	Genotype II/ID (n = 44)
Time from CPB (min)	41 ± 17	35 ± 15
Hematocrit (%)	26.1 ± 4	26.5 ± 4
pH	7.49 ± 0.05	7.50 ± 0.05
PO ₂ (kPa)	45 ± 6	47 ± 6
Pco ₂ (kPa)	4.4 ± 0.7	4.4 ± 0.6
Glycemia (mmol)	7.76 ± 2.04	6.82 ± 1.49
Temperature (°C)	36.5 ± 0.5	36.2 ± 0.5
Initial haemodynamic		
Pump flow rate (l · min ⁻¹ · m ⁻²)	2.36 ± 0.17	2.42 ± 0.21
SVR (UI)	16.2 ± 3.1	14.7 ± 3.5
Anesthetic agents		
Fentanyl (μg/kg)	92 ± 23	88 ± 19
Midazolam (mg/kg)	0.13 ± 0.06	0.11 ± 0.03

Values are mean ± SD.

For all groups, comparisons according to genotype were not significant.

SVR = systemic vascular resistance; UI = unit international.

the PCR products were separated by agarose gel electrophoresis, and DNA was visualized by ethidium bromide staining. Subjects were then classified according to the presence or the absence of the 287-base pair insertion in intron 16 of the *ACE* gene, as *DD*, *II*, or *ID*. In addition, to avoid possible mistyping of *ID* genotypes as *DD* genotypes, each *DD* genotype sample was confirmed by an additional PCR, with the same protocol but a separate sense primer specific for the insertion allele. The primers were those published by Shanmugan *et al.*¹⁴ The primers resulted in two amplified products: 84 base pairs (*D* allele) and 65 base pairs (*I* allele). All PCR products were separated by running them on a 1.5% agarose gel. No *ID* genotype was misidentified as *DD* in the current study.

Data Analysis

Data were expressed as mean \pm SD and examined according to a recessive genetic model (*DD* vs. *ID/II*). Comparisons between groups, defined as *DD* or non-*DD*, were made using a Student *t* test, a chi-square test, or a Fisher exact test, as appropriate. A two-factor analysis of variance for repeated measures was performed to compare the PFR curves within factor (*i.e.*, flow) and between factors (*i.e.*, *DD* genotype). Analyses of PFR were performed only for data sets without any missing values ($n = 55$). An additional analysis was conducted to ensure that the effect of genotype was not caused by confounding factors. For this purpose, analysis by a two-factor analysis of variance was performed, taking into account PFR curves and main clinical variables (*i.e.*, age, sex, hypertension, treatments, and type of surgery).

Furthermore, the link between the slope of the curve (dependent variable) and genotype, sex, age classified in two categories (≥ 65 and < 65 yr), history of hypertension, treatment with ACE inhibitors, and type of surgery (independent variables) was assessed by univariate analysis followed by multivariate regression analysis.

In all tests, the significance level was fixed at 5%; for the multivariate regression analysis, the threshold *F* value to accept a variable in the model was fixed at 4.0. All tests were performed with the Biomedical data package (BMDP; University of California-Los Angeles, Los Angeles, CA).

Results

ACE Genotype

We reported a 0.54 allelic frequency of the *D* allele and a genotypes distribution in the *DD*, *ID*, and *II* groups of 27, 55, and 18%, respectively. The overall genotype distribution was consistent with Hardy-Weinberg equilibrium. Patients were separated in two groups (*DD*, $n = 16$; *ID/II*, $n = 44$) since *DD* genotype is the one that is

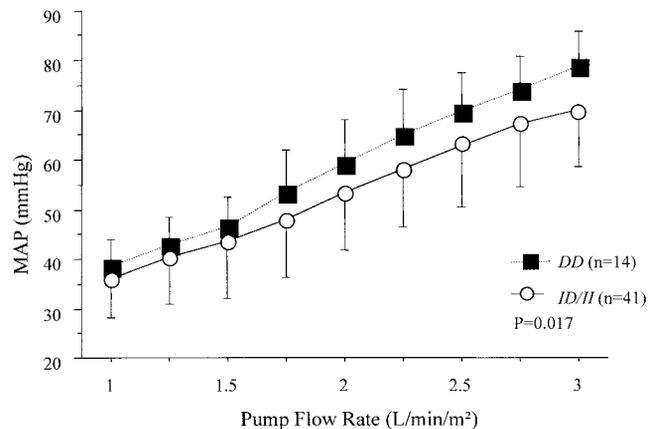


Fig. 1. Pressure-flow relation curves according to the *I/D* polymorphism of *ACE* gene. Values of mean arterial pressure are expressed as mean \pm SD for each pump flow step.

associated with the highest concentrations of ACE⁵ and an increased risk of cardiovascular disease.⁶

Patient Characteristics

No significant differences between *DD* and non-*DD* groups were found with regard to preoperative and intraoperative variables (tables 1 and 2). No patient had postoperative complications, either surgical or neurologic.

Pressure-flow Relation

We could not complete the study protocol in five patients because of too-high pressure in one patient in each group and an insufficient venous return in one *DD* and two *ID/II* patients.

Among the two groups, initial hemodynamic parameters (just before the onset of the study protocol) were similar (table 2). Baseline levels of MAP, for $1.1 \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ flow, were also similar (38 ± 5 vs. 36 ± 5 mmHg in *DD* and non-*DD* patients, respectively). By contrast, *DD* patients had higher MAP and calculated vascular resistance for $3.1 \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ pump flow rate (26 ± 3 vs. 23 ± 4 UI; $P = 0.03$).

Pressure-flow relation curves of *DD* patients were shifted upward (*i.e.*, with higher pressure values; $P = 0.017$; fig. 1), and slopes of their curves were different (21.5 ± 4.2 vs. 18.1 ± 5.3 mmHg/[$1 \cdot \text{min}^{-1} \cdot \text{m}^{-2}$]) in *DD* and non-*DD* patients, respectively; $P = 0.02$). Conversely, we found no difference in the response to flow according to the other clinical variables, particularly according to the type of surgery.

We found no interaction between the use of ACE inhibitors and the slope of PFR curve (20.6 ± 4.2 vs. 18.1 ± 5.6 for ACE inhibitors used or not used, respectively; $P = 0.07$).

As shown in table 3, *DD* genotype appeared as the only predictive variable of the slope of the PFR curve in multivariate regression analysis.

Table 3. Univariate and Multivariate Analysis of the Slope of the Curve According to Main Clinical Factors

	Slope of the Curve (UI)	Univariate Analysis (P=)	Multivariate Analysis
Surgery (valve/CABG)	19.2 ± 5.4/18.5 ± 5.1	0.6	ns
Sex (male/female)	19 ± 5.2/19 ± 5.6	0.98	ns
Age (≥ 65, < 65 yrs)	19.3 ± 5.6/18.7 ± 5	0.66	ns
History of hypertension (yes/no)	19.7 ± 5.2/18.4 ± 5.3	0.35	ns
History of MI (yes/no)	19.3 ± 4.9/18.9 ± 5.4	0.77	ns
ACE inhibitors (yes/no)	20.6 ± 4.2/18.1 ± 5.6	0.07	ns
Genotype (DD/non-DD)	21.5 ± 4.2/18.1 ± 5.3	0.02	< 0.05

Values are mean ± SD. See Materials and Methods section for multivariate analysis method. These analyses were performed for all 60 patients.

CABG = coronary artery bypass grafting; MI = myocardial infarction; ACE = angiotensin converting enzyme.

Discussion

The main goal of the current study was to provide the first evidence for an *in vivo* association between the PFR and the *I/D* polymorphism of the *ACE* gene. Furthermore, multivariate analysis showed that the homozygosity for the *D* allele was the only predictive variable of the slope of the curve. These findings indicate a modified vascular response to flow in *DD* patients.

Because during nonpulsatile CPB, vascular resistance mainly determines the relation between blood pressure and flow, our *in vivo* experimental model may be considered as a relevant model of purely resistive vascular behavior.¹³ Therefore, the differences in PFR curves reported in the current work suggest an impairment of vascular vasodilatory properties in *DD* patients. Indeed, the induced decrease in vascular resistance was lesser in *DD* than in non-*DD* patients. This could be a result of either an increased vascular smooth muscle tone or an endothelial dysfunction.

The former possibility is consistent with our previous work in which, using the same clinical model, we found an increased vascular reactivity to phenylephrine associated with the *D* allele of the *ACE* gene. We also showed *in vitro*, in human internal mammary arteries, an increased angiotensin II-induced potentiation of phenylephrine-mediated constriction associated with the *DD* genotype.⁷ Prasad *et al.*¹⁵ also suggested an increased vascular smooth muscle tone, counterbalanced by increased basal nitric oxide activity, in coronary arteries of *DD* patients. Involvement of the renin-angiotensin system in vascular smooth tone control has been demonstrated by Licker *et al.*,¹⁶ who showed that the chronic use of ACE inhibitors attenuates the vascular response to norepinephrine in the CPB model.¹⁶

The hypothesis of an endothelial dysfunction in *DD* patients led to divergent reports in the literature. Indeed, by using plethysmographic measurement of changes in forearm blood flow in response to intraarterial infusion of vasodilator substances, Perticone *et al.*⁹ and Butler *et al.*¹⁰ suggested a blunted response to nitric oxide vasodilation in *DD* patients. Nevertheless, Celermajer *et al.*,¹² using ultrasound measures and reactive hyperemia stimulation, found no difference in brachial artery flow-me-

diated dilation between genotypes. Schächinger *et al.*¹¹ reported that the *ACE* genotype was not associated with an altered acetylcholine-induced coronary blood flow increase. These discrepancies could reflect differences in methods, types of stimulus, or location of the blood flow measurement. For example, abnormal coronary arteries reactivity associated to a physiologic stress (pacing) was better represented by bradykinin infusion rather than by acetylcholine.¹⁷ In the same study, the *I/D* polymorphism did not influence acetylcholine response but was associated with an altered response to bradykinin.¹⁷ Moreover, endothelial dysfunction may occur in a patchy distribution, and it may therefore influence results obtained with methods investigating only the forearm vasculature or the coronary circulation rather than the global systemic circulation, as our model did. Whatever the potential vascular mechanisms, our results showed a global lesser decrease in vascular resistance in response to flow in *DD* patients.

Nevertheless, in the current model, other mechanisms should be considered. Changes in arterial structural and elastic properties of the vascular network could have occurred in the *DD* patients. However, because stiffness and thickness of arterial walls are not associated with the *D* allele, we can rule out this possibility.^{18,19}

The main limitation of the study is the small number of studied patients, which is a result of restricted inclusion criteria and the need for standardized anesthesia and CPB management. However, the frequency of the *D* allele of the *ACE* gene found in the 60 studied patients was not different from those previously reported in other large white populations.⁶ Furthermore, the *D* allele frequency reported here was consistent with the 0.58 frequency measured in a larger cohort of cardiac surgery patients (n = 528, personal data). This suggests that our study population may be representative of a true population sample. Another confounding factor could be the heterogeneity of our population of patients scheduled for coronary artery bypass grafting or valve surgery. However, we found no interaction between the type of cardiac disease and the PFR. Finally, the frequent use of cardiac medication in our patients is another potential bias, particularly concerning treatments known to inter-

fere with endothelial function such as ACE inhibitors. In our study, ACE inhibitors were associated with an unexpected higher slope of PFR curve (although not statistically significant). This could be the result of a modified vascular network linked to the patient's pathology. However, the absence of significant effect of this treatment is consistent with works showing no interaction with hemodynamic control in patients taking ACE inhibitors and undergoing cardiac surgery.¹⁶ Furthermore, other investigators have reported that hypotension observed in patients treated with ACE inhibitors occurred during hypothermic CPB,²⁰ and not during normothermia as in the current work.

Finally, the multivariate analysis showing no interaction with the other factors confirmed that vascular response to flow was impaired in *DD* patients independently of other confounding variables. One might then speculate that genetic determination, rather than pharmacologic modulation, of plasma and cellular ACE concentration is more important to predict vascular bed behavior.

In conclusion, in the current study we demonstrated that the *I/D* polymorphism of the *ACE* gene is associated with a modified PFR in patients undergoing CPB. The *DD* genotype is independently associated with a higher slope of PFR curve. The lesser decrease in vascular resistance showed in *DD* patients suggests an impaired flow-mediated vasodilatory properties associated to the *DD* genotype. These results and our previous studies^{7,21} underscore the implication of genetics in physiology. Further studies are needed to precisely explain the mechanisms involved (*i.e.*, increased vascular smooth cells tone or endothelial dysfunction). Furthermore, many other gene polymorphisms could be implicated in cardiovascular physiology and pathology.

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