Elevation of plasma angiotensin with the development of pulmonary arteriovenous malformations after cavopulmonary shunt

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Pulmonary arteriovenous malformation (PAVM) is a serious complication after cavopulmonary shunt. Although the etiology remains unclear, substances in the hepatic venous effluent are thought to play a crucial role in the formation of PAVM,¹ and reports have shown regression of PAVM after surgical inclusion of hepatic venous flow to the lung.^{2,3} Recently, neurohormonal abnormality was reported after cavopulmonary shunt.⁴ We measured neurohormones in 5 patients after cavopulmonary shunt and obtained evidence that angiotensin has some relation to the development of PAVM.

Clinical Summaries

A 7-year-old girl (patient 1), 1 year after Fontan completion, was admitted because of dyspnea on effort. Cardiac catheterization demonstrated that only the right lung received the hepatic venous flow, and diffuse PAVM existed in the left lung. An operation was performed to redirect hepatic venous flow to both lungs. Cardiac catheterization demonstrated complete regression of PAVM at 2 postoperative months and trivial PAVM in the left lung at 1 postoperative year. In this period, plasma renin, angiotensin I (AT-I), angiotensin II (AT-II), aldosterone, somatostatin, glucagon, vasoactive intestinal peptide, and atrial natriuretic peptide were measured in blood samples from the superior vena cava, the hepatic vein, the right and left pulmonary arteries, and the aorta at 4 intervals. Consonant with the development and regression of PAVM, AT-I and AT-II levels were increased and decreased in all regions (Table 1). Renin levels remained high even after the operation. Other parameters were within their reference ranges.

As a control group, 4 patients without PAVM after the Fontan operation (patients 2-5) were examined. Two (patients 2 and 3) had

Figure 1. Plasma angiotensin levels after cavopulmonary shunt. A and B, Angiotensin levels in superior vena cava blood (A) and hepatic venous blood (B) in each patient at various times after Fontan operation. C and D, Angiotensin levels in patient 1. Values are plotted according to intraoperative (C) and postoperative (D) hepatic venous flows. SVC, Superior vena cava; Pt, patient; lt, left; rt, right; HV, hepatic vein; PA, pulmonary artery; Ao, aorta.

elevated plasma concentrations of AT-I, but the other parameters remained within normal limits.

Discussion

Neurohormonal activation during the course of several years after cavopulmonary shunt has been demonstrated.⁴ In our study, similarly, 3 of 5 patients showed elevated AT-I (Figure 1, A and B). Moreover, in 1 of our patients AT-I and AT-II increased consonant with the development of PAVM and de-

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TABLE 1. Neurohormonal activity after cavopulmonary shunt

	Patient 1				Patient 2	Patient 3	Patient 4	Patient 5
	Preoperative	Intraoperative	2 PO mo	1 PO y	(3 PO y)	(7 PO y)	(10 PO y)	(17 PO y)
Diagnosis	SA, SV, CAVV, CoA, azygos continuation, left isomerism				SA, SV	MA	SA, SV	TA
Age (y)	7	8	8	9	13	44	22	22
PAVM	Develop (lt)	Develop (lt)	Regress	Trivial (lt)	None	None	None	None
Renin ($\mu\text{U/mL}$, normal <64)								
SVC	93	170	130	290	33	35	17	48
HV	49	120	170	210	34	22	12	38
RPA	77	170	160	280	45	37	15	49
LPA	88	180	160	430	35	22	14	49
Aorta	—	180	190	370	—	37	18	50
AT-I (pg/mL, normal <110)								
SVC	660	1200	330	700	300	440	39	67
HV	330	960	300	610	310	210	30	41
RPA	520	1700	490	560	350	480	30	62
LPA	670	1000	310	690	510	230	34	56
Aorta	—	1200	480	590	—	370	47	53
AT-II (pg/mL, normal <22)								
SVC	54	82	36	96	17	16	9	16
HV	13	15	8	20	12	7	3	5
RPA	32	130	17	46	17	11	4	13
LPA	36	61	23	110	12	5	10	10
Aorta	—	120	42	63	—	8	4	8
Aldosterone (pg/mL, normal 35-240)								
SVC	180	150	290	390	120	37	91	68
HV	200	180	84	75	76	17	39	41
RPA	290	180	220	330	110	43	110	66
LPA	220	160	160	310	120	19	72	67
Aorta	—	140	300	300	—	36	75	71
Somatostatin (pg/mL, normal 1-12)								
SVC	10	5.9	30	8.9	17	9.6	1.8	6.6
HV	28	7.6	9.8	11	26	3.9	10	11
RPA	15	<1	4.4	5.1	14	8	3.1	9.5
LPA	10	7	9.8	5.5	23	12	6.6	2.7
Aorta	—	<1	4.5	3.5	—	3.5	9	9

PO, Postoperative; SA, single atrium; SV, single ventricle; CAVV, common atrioventricular valve; CoA, coarctation of the aorta; lt, left; MA, mitral atresia; TA, tricuspid atresia; SVC, superior vena cava; HV, hepatic vein; RPA, right pulmonary artery; LPA, left pulmonary artery.

creased consonant with its regression. To the best of our knowledge, this is the first clinical evidence that angiotensin is elevated in relation to the development of PAVM. Experimentally, Malhotra and colleagues⁵ demonstrated elevation in the expression of AT-II receptors in an ovine model of PAVM. These data suggest that activation of the renin-angiotensin system plays some role in the development of PAVM after cavopulmonary shunt.

In patient 1, left PAVM developed as a result of the lack of hepatic venous flow. In this period, plasma AT-I and AT-II levels showed differences between the right and the left pulmonary arteries. We plotted these values according to the intraoperative and postoperative hepatic venous flows (Figure 1, C and D), demonstrating that AT-I and AT-II were activated mainly in the right lung preoperatively. After redirection of hepatic venous flow, both lungs received equal hepatic venous

flow and activated AT-I and AT-II. Abnormal circulation in which hepatic venous effluent bypasses one lung may induce abnormal metabolisms of neurohormones such as angiotensin, resulting in abnormal vascular changes after cavopulmonary shunt. It is still unclear whether this abnormal activation of angiotensin during the development of PAVM is primary or secondary. Further investigation, including measurement of angiotensinogen, is needed to clarify this phenomenon.

Conclusion

We demonstrated elevation of angiotensin during the development of PAVM. Circulation in which hepatic venous flow bypasses the lung seems to induce abnormal metabolism of the rennin-angiotensin system and to play some role in the development of PAVM.

References

1. Kawashima Y. Cavopulmonary shunt and pulmonary arteriovenous malformation. *Ann Thorac Surg.* 1997;63:930-2.
2. Knight WB, Mee RB. A cure for pulmonary arteriovenous fistulas? *Ann Thorac Surg.* 1995;59:999-1001.
3. Ichikawa H, Fukushima N, Ono M, Kita T, Matsushita T, Miyamoto Y, et al. Resolution of pulmonary arteriovenous fistula by redirection of hepatic venous blood. *Ann Thorac Surg.* 2004;77:1825-7.
4. Hjortdal VE, Stenbog EV, Ravin HB, Emmertsen K, Jensen KT, Pedersen EB, et al. Neurohormonal activation late after cavopulmonary connection. *Heart.* 2000;83:439-43.
5. Malhotra SP, Reddy VM, Thelitz S, He YP, Hanley FL, Suleman S, et al. Cavopulmonary anastomosis induces pulmonary expression of the angiotensin II receptor family. *J Thorac Cardiovasc Surg.* 2002;123:655-60.