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Assessment of cerebral hemodynamics before and after revascularization in patients with occlusive cerebrovascular disease by means of quantitative IMP-SPECT with double-injection protocol

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The purpose of this study was to validate a double-injection (DI) method with *N*-isopropyl-[^{123}I]*p*-iodoamphetamine (IMP) to measure regional cerebral blood flow (rCBF) twice in a single session of dynamic SPECT and to elucidate a possible role of this method to identify patients with occlusive disease of major cerebral arteries, who might benefit from cerebral revascularization procedures (CR). ***Materials and Methods:*** Fourteen patients with occlusion or severe stenosis of the internal carotid or middle cerebral artery were studied before and after CR to assess hemodynamic changes after revascularization treatment. We quantitatively measured rCBF before and after acetazolamide (ACZ) challenge along with cerebrovascular reserve capacity (CVR) with two injections of IMP in a single session of dynamic SPECT scans (DI method). The reliability and reproducibility of the DI method were validated by means of a simulation study and in eight patients who were examined without ACZ challenge to measure baseline rCBF twice. ***Results:*** The analysis of simulated noisy data with realistic noise levels showed that the errors of the estimates for the first and the second rCBF and for the increase in rCBF were 2.6%, 8.1% and 10.4%, respectively. In the 8 patients examined by the DI method to measure baseline rCBF twice, the mean and the SD of percentage differences between the two consecutive measurements in rCBF were −1.3% and 5.5%, respectively. Eight out of 14 patients with occlusive disease had at least one region with a CVR less than 10%. They showed a significant increase in resting rCBF after CR, not only in the ipsilateral hemisphere (from 26.1 ± 6.4 to 33.4 ± 4.7) but also in the contralateral one (from 28.3 ± 7.0 to 34.7 ± 4.7) with a recovery of the ipsilateral CVR from 9.3 ± 17.2 to 41.2 ± 20.1%. The remaining six patients with good-moderate CVR did not show an increase in rCBF after CR (from 28.0 ± 2.7 to 28.3 ± 3.4). The three of them with a moderate CVR (10–25%) before CR showed normalization of CVR after CR. ***Conclusion:*** Patients with decreased rCBF and reduced CVR benefited from CR in terms of an increase in rCBF and recovery of CVR. The quantitative double-injection IMP-SPECT has the ability to identify those patients who may benefit from CR.

Key words: ^{123}I-IMP, cerebral blood flow, single photon emission computed tomography (SPECT), cerebrovascular reserve capacity

INTRODUCTION

RECENT STUDIES have reported with increased evidence that, in occlusive disease of major cerebral arteries, patients with uncoupled blood supply/metabolic demand or impaired cerebrovascular reserve capacity (CVR) have a high risk of recurrent stroke.[1–5] Those patients with reduced metabolic and hemodynamic reserve capacity may

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benefit from the external carotid to internal carotid artery (EC-IC) bypass surgery, although a randomized trial failed to show the efficacy of such procedure.[6] To identify these patients, it is essential to devise a method that can accurately assess the regional cerebral hemodynamics in each patient. Although positron emission tomography (PET) is the only established method providing information on oxygen metabolism, it is not easily accessible in routine clinical settings.

Single photon emission computed tomography (SPECT) and *N*-isopropyl-[^{123}I]*p*-iodoamphetamine (IMP) have been proved to yield reliable values of regional cerebral blood flow (rCBF)[7,8] and are commonly used to measure absolute values of rCBF, especially in Japan. Comparative studies with PET also showed that CVR as measured by means of IMP-SPECT or stable xenon-enhanced CT with acetazolamide (ACZ) challenge could identify stage II hemodynamic failure.[9,10] Moreover, the double-injection (DI) method with IMP-SPECT and ACZ challenge provides consecutive rCBF measurements in a single session of dynamic SPECT scans, and therefore has the advantage of decreasing the within-subject error in estimated rCBF for the two measurements, enabling a more accurate determination of CVR.[11]

The aim of this study was to validate a DI method with IMP-SPECT and to elucidate a possible role of this method to identify patients with occlusive disease of major cerebral arteries, who might benefit from CR.

MATERIALS AND METHODS

Subjects

Fourteen patients (age: 64.1 ± 8.4) with occlusion or severe stenosis of the internal carotid or middle cerebral artery were included in the study (Table 1). All patients underwent CR: superficial temporal to middle cerebral artery (STA-MCA) bypass surgery in four (age: 62.0 ± 6.2), carotid endoarterectomy (CEA) in three (age: 55.7 ± 12.9) and percutaneous transluminal angioplasty with stent placement (PTA) in seven (age: 69.0 ± 3.6). Before and after CR, all patients underwent quantitative measurements of rCBF before and after ACZ challenge by using the DI method with dynamic IMP-SPECT scans in a single session.[11] Another 12 patients (age: 59.8 ± 23.2) without cerebral ischemia were studied by using the DI method before and after ACZ challenge and served as a control group. Also included in this study were 8 patients (age: 60.0 ± 10.3) with cerebrovascular disease, who were studied by means of the DI method without ACZ challenge to measure baseline rCBF twice.

The study was performed under the guideline of the Ethical Committee of Kyoto University Hospital and all subjects gave informed consent.

General procedure

We used a modified version of the DI method previously reported.[11] The method enables quantitative and serial measurements of rCBF before and after ACZ challenge in a single session of dynamic IMP-SPECT scans. Dynamic SPECT scans with continuous acquisition for 50 minutes (fifty 1-minute scans) were performed in all studies. Two injections of IMP (111 MBq each) at 0 and 30 minutes and an injection of ACZ (1 g) between 18 and 20 minutes after the start of the scans were given intravenously into the right antecubital vein. The dynamic SPECT scans were performed with a three-head gamma camera (PRISM3000, Picker International, Inc., Bedford Heights, OH). The fifty 1-minute raw data were reconstructed to obtain twenty-five 2-minute SPECT frames by adding two serial raw data. Data were acquired during clockwise and counterclockwise rotations of the detectors to compensate for changes in radioactivity in the brain during the rotation of the detectors. An input function was calculated for each patient from 29 arterial blood samples (21 in some patients) drawn through a small catheter inserted into the left brachial artery. The input function was corrected for the lipophilic fraction of IMP by using the standard time-course of the octanol extraction fraction previously determined in 15 patients.

Table 1 Patients' demographics

Case No.	Case age/sex	diagnosis	treatment
1	67/M	lt ICA stenosis	PTA + S
2	55/M	rt ICA occlusion	STA-MCA
3	66/M	rt ICA occlusion	PTA + S
4	65/M	lt ICA stenosis	PTA + S
		rt ICA occlusion (post STA-MCA)	
5	59/M	rt MCA stenosis	STA-MCA
6	69/M	lt ICA occlusion	STA-MCA
		rt ICA stenosis	
7	45/M	lt SCA occlusion	PTA + S
		lt ICA occlusion	CEA
8	70/M	bil ICA stenosis	CEA (lt)
9	65/M	rt ICA stenosis	STA-MCA
10	68/M	lt ICA stenosis	PTA + S
11	70/M	rt ICA stenosis	PTA + S
12	75/M	lt ICA stenosis	PTA + S
13	52/M	lt ICA stenosis	CEA
14	72/M	lt ICA stenosis	PTA + S
		rt ICA occlusion (post STA-MCA)	

ICA: internal carotid artery. MCA: middle cerebral artery. SCA: subclavian artery. STA-MCA: superficial temporal artery–middle cerebral artery bypass surgery. CEA: carotid endoarterectomy. PTA + S: percutaneous transluminal angioplasty + stent placement.

Calculation of rCBF and CVR

A two-compartment model analysis was used to estimate rCBF. In the measurement of baseline rCBF, dynamic brain data from 0 to 22 minutes and the arterial input function were used to estimate the influx rate (K_1) and the back diffusion rate (k_2) by means of a non-linear least squares fitting method with a simplex search algorithm.[11] We assumed the extraction of lipophilic IMP by the brain tissue to be unity (therefore, K_1 = rCBF). The equation for the first measurement was as follows:

$$C_B(t) = rCBF \int_0^t Ca(u) \exp(-k_2(t-u))du \quad [1]$$

In the measurement of the second rCBF, the third parameter (M_0), which represented the remaining radioactivity in the regional brain tissue at the time the second measurement started, was incorporated in the fitting procedure. Therefore, rCBF, k_2 and M_0 were estimated independently by using data from 26 to 50 minutes. The equation for the second measurement of rCBF was as follows:

$$C_B(t) - M_0 \exp(-k_2 t) = rCBF \int_0^t Ca(u) \exp(-k_2(t-u))du \quad [2]$$

where $C_B(t)$ is the radioactivity in the regional brain tissue and Ca(t) is the radioactivity in blood at t minutes after the start of the second measurement.

CVR was defined as the percentage increase in the second rCBF ($rCBF_{2nd}$) against the first one ($rCBF_{1st}$) as follows:

$$CVR = 100\ (rCBF_{2nd} - rCBF_{1st})/rCBF_{1st} \quad [3]$$

Validation of double-injection method

The feasibility of the DI method for the quantitative assessment of sequential rCBF in a single session of dynamic IMP-SPECT scans was validated by means of simulation and clinical studies. Two hundred simulated brain curves were generated with equations [1] and [2] by using an actual time-radioactivity curve of arterial blood that was taken from a subject of this study. Input values for the simulation curves were 20 to 60 m*l*/100 g/min with 0.2 m*l*/100 g/min step for the first rCBF, random values of Gaussian distribution with a mean of 40 m*l*/g and a SD of 12 m*l*/g for the partition coefficient (= K_1/k_2), and 0, 20, 40 and 60% for the percentage increase in the second rCBF against the first one. Noisy curves were generated by adding 3.5% Gaussian noise to the first part of the curve (0–30 min) and 2.5% to the second part (30–50 min). These noise levels were comparable to those of the actual brain curves from the ROIs used in this study. The reproducibility of rCBF was also evaluated in the eight patients who were studied with the DI method to measure rCBF twice in a baseline condition. The mean and SD of percentage differences between the first and the second rCBF were calculated.

Analysis in patients with occlusive cerebrovascular disease

Two pairs of regions of interest (ROIs) were manually drawn on the anterior and posterior part of the MCA territory on a SPECT image. As we selected two slices of SPECT images (at the levels showing the basal ganglia and corona radiata) for the analysis, eight ROIs were obtained for each patient. These ROIs were applied to dynamic SPECT images to obtain time-radioactivity curves that were used for the analysis.

We calculated the mean and the SD of rCBF before and after ACZ challenge and of CVR from the 12 control subjects. We tentatively assigned CVR before CR larger than the mean – 2SD as a 'good' response, CVR between the mean – 3SD and the mean – 2SD as a 'moderate' response, and CVR smaller than the mean – 3SD as a 'poor' response. According to this classification, we divided the 14 patients with occlusive cerebrovascular disease into three groups. We selected the ROI with the most impaired CVR among the eight ROIs for this classification. Resting rCBF and CVR before CR were compared in the 14 patients with those after CR. In the statistical analysis, we gathered the patients with the

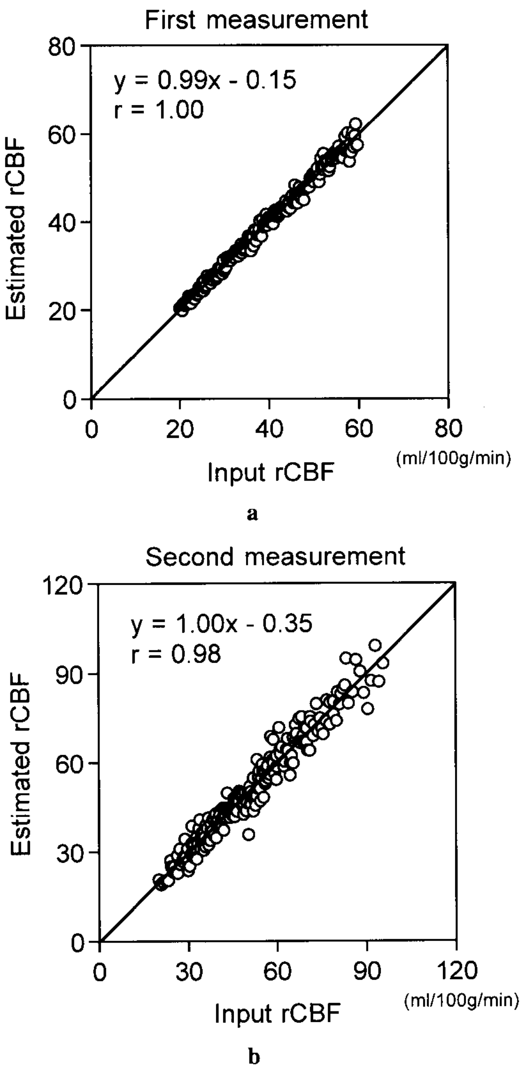

Fig. 1 Estimated values obtained from the simulation study are plotted against input values for the first (a) and second (b) measurement. Data points of each measurement are almost on the line of identity, indicating good agreement between the estimated and input values.

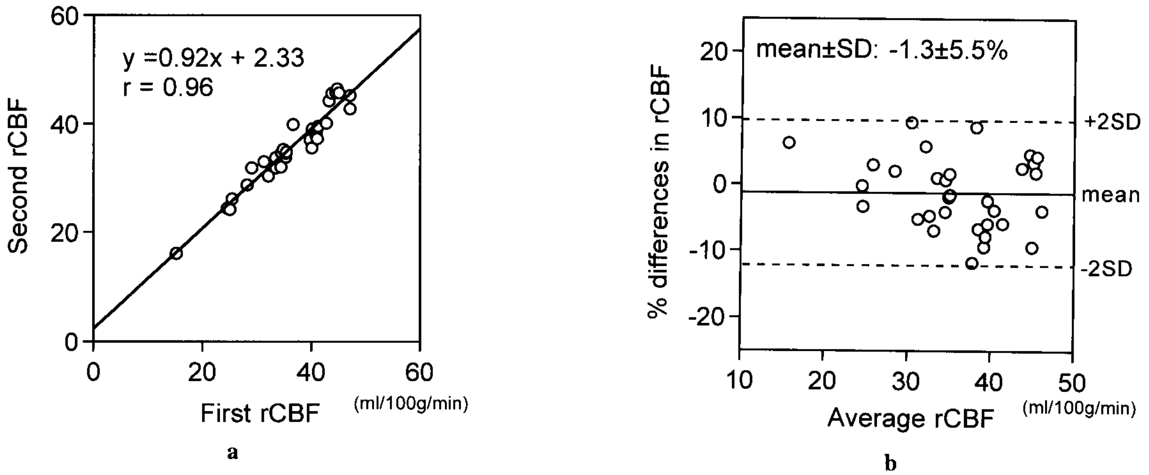

Fig. 2 (a) The plot shows the relationship between the first and second rCBF in patients who underwent two serial measurements of baseline rCBF with double-injection method of IMP-SPECT without injecting acetazolamide. (b) Percentage differences between the first and second rCBF are plotted against average rCBF of the first and second measurements, showing the negligible bias (the mean of differences: −1.3%) and the acceptable error (the SD of differences: 5.5%).

Table 2 Hemodynamic characteristics before and after cerebral revascularization procedures

	Pre-CR			Post-CR		
	rCBF-control	rCBF-diamox	CVR (%)	rCBF-control	CBF-diamox	CVR (%)
'Poor' response group (n = 8)						
affected	26.1 ± 6.3	28.6 ± 8.1	9.3 ± 17.2	33.4 ± 4.7[a]	46.7 ± 6.9[a]	41.2 ± 20.1[a]
non-affected	28.3 ± 7.0	38.0 ± 11.8	34.0 ± 22.7	34.7 ± 4.7[a]	48.3 ± 8.2[a]	39.2 ± 15.7
'moderate' and 'good' response groups (n = 6)						
affected	28.0 ± 2.7	40.4 ± 4.8	44.4 ± 11.1	28.3 ± 3.4	43.6 ± 3.9[c]	54.9 ± 13.6[b]
non-affected	29.0 ± 4.0	44.3 ± 7 8	51.9 ± 11.9	28.7 ± 2.8	43.5 ± 5.9	51.1 ± 11.6

Values in post-CR are statistically significant from those in pre-CR at a: $p < 0.001$, b: $p < 0.01$, c: $p < 0.05$.

'moderate' and 'good' response into one group because of the small number of patients.

RESULTS

Reliability of the double-injection method

The simulation study with noiseless data revealed no bias or error between input values and estimated values both for the first and the second rCBF. The simulation study with noisy data also showed that estimated values agreed well with the input values both for the first and the second rCBF (Figs. 1a and 1b). The mean ± SD of percentage differences between the input and estimated values of the first and the second rCBF and of CVR were −0.2 ± 2.6%, −0.9 ± 8.1% and −0.7 ± 10.4%, respectively. The reproducibility of rCBF was also confirmed in patients who were studied with the DI method during a baseline condition, showing the mean and the SD of percentage differences between the first and the second rCBF to be −1.3% and 5.5%, respectively (Figs. 2a and 2b).

Hemodynamic alteration in occlusive cerebrovascular disease

In the 12 control subjects, rCBF before and after ACZ challenge and CVR were 38.0 ± 4.3 ml/100 g/min, 59.0 ± 7.3 ml/100 g/min and 55.8 ± 15.0% (mean ± SD), respectively. We therefore tentatively assigned CVR before CR larger than 25.8% (mean – 2SD) as a 'good' response, between 10.8 and 25.8% as a 'moderate' response, and smaller than 10.8% (mean – 3SD) as a 'poor' response.

The results in 14 patients with occlusive cerebrovascular disease are summarized in Table 2. Representative rCBF and CVR values before and after CR from one pair of ROIs, one of which showed the most impaired CVR on the affected side, are shown for each patient in Table 3. The 'poor' response group showed a significant increase in baseline rCBF after CR, not only in the ipsilateral hemisphere (from 26.1 ± 6.3 to 33.4 ± 4.7, $p < 0.001$) but also in the contralateral one (from 28.3 ± 7.0 to 34.7 ± 4.7, $p < 0.001$) with recovery of ipsilateral CVR from 9.3 ± 17.2 to 41.2 ± 20.1%. One patient with normal rCBF before CR in this group (case 8, Table 3) showed a

Table 3 Alterations of cerebral hemodynamcs in each patient

Case		baseline rCBF (ml/100 g/min)		CVR (%)	
No.	age	pre-CR	post-CR	pre-CR	post-CR
'poor' response group					
1†	(67)	20.9/24.1	30.8/35.7	−6.6/52.7	45.2/46.2
2*	(55)	27.9/28.0	33.2/33.3	8.5/31.4	15.9/29.3
3†	(66)	17.9/20.0	30.3/31.0	−5.5/38.1	67.1/45.5
4†	(65)	24.4/21.9	29.6/28.8	8.5/52.0	63.4/45.9
5*	(59)	25.9/29.5	37.1/34.8	−15.9/48.9	10.1/35.2
6*	(69)	27.6/26.5	35.5/33.6	0.8/10.1	29.7/15.9
7**	(45)	32.5/38.0	45.4/43.5	3.9/56.9	35.4/40.8
8**	(70)	37.3/40.8	31.0/32.7	9.8/33.2	66.0/66.9
'moderate' response group					
9*	(65)	29.3/31.7	32.9/31.3	25.2/55.9	42.3/48.4
10†	(68)	27.7/32.2	23.3/27.6	24.4/38.5	81.6/41.4
11†	(70)	27.6/28.3	30.9/28.5	20.0/63.9	49.3/55.0
'good' response group					
12†	(75)	28.9/31.4	26.5/28.7	42.5/43.4	62.2/54.9
13**	(52)	28.7/31.3	33.7/31.4	62.5/39.5	52.2/61.0
14†	(72)	24.9/26.1	27.3/27.9	41.9/39.6	54.4/56.1

Values are from the representative pair of ROIs, which included the most impaired CVR on the affected side (affected cortex/ contralateral cortex). CR: cerebral revascularization procedures. *: STA-MCA bypass, **: CEA, †: PTA

recovery of CVR but failed to have an increase in rCBF after CR. In the 6 patients in the 'moderate' and 'good' response groups, there was no significant increase in baseline rCBF (from 28.0 ± 2.7 to 28.3 ± 3.4) after CR. The three of them in the 'moderate' group showed normalization of CVR after CR.

DISCUSSION

This study demonstrated that quantitative IMP-SPECT by the DI method could identify those patients who would benefit from CR in terms of recovery from hemodynamic compromise. Recent reports, in which oxygen metabolism was analyzed by means of ^{15}O labeled gases and PET, revealed that patients with an increased oxygen extraction fraction had an increased risk of recurrent stroke,[1–3] so that appropriate preventive treatment would be needed for these patients. Although a randomized trial designed to test the efficacy of EC-IC bypass surgery failed to show benefits of this procedure in preventing recurrent stroke, the assessment of cerebral hemodynamic status was not adopted as inclusion criteria for the study. When selecting surgical candidates according to the cerebral hemodynamic status, the bypass surgery might be beneficial to those with impaired cerebral hemodynamic status.

The condition of reduced rCBF with impaired CVR demonstrated by IMP-SPECT is probably identical to that of stage II hemodynamic failure, as shown by recent reports,[9,10] in which PET and SPECT findings were directly compared in patients with occlusive disease of major cerebral arteries. Patients with decreased rCBF and impaired CVR would be possible candidates for bypass surgery as many previous reports suggested[12,13] and patients considered to be at stage II hemodynamic failure in our study actually demonstrated an increase in rCBF and normalization of CVR after CR. Although we included three different revascularization procedures in this report, hemodynamic changes seemed not to be dependent on the procedures themselves. Patients without impairment of CVR did not show an increase in rCBF after CR even if they had decreased rCBF in the affected side. In these patients, oxygen demand probably decreased as a result of reduced metabolism due to chronically low oxygen supply, and rCBF was consequently set at a lower level and matched to the reduced oxygen demand.

The reproducibility of rCBF by serial measurements in a single session of the DI method was 5.5% (expressed by the SD of percentage difference between the two measurements). This value was comparable to that of cerebral glucose utilization measured with ^{11}C-deoxyglucose and PET repeated within a few hours[14] or with FDG and PET by using a double-injection method in a single session.[15] The reproducibility of absolute rCBF obtained by using IMP-SPECT on separate days, when expressed by the SD of percentage differences between two measurements, was about 7.5% if the measurements were done a week apart,[16] and about 17% if the measurements were done about 3 months apart.[17] Even in the FDG PET measurements for cerebral glucose utilization repeated a month apart, a discrepancy of −25% was reported.[18] In addition to uncertainty of the comparability of baseline rCBF on separate days, errors may also be introduced through the repositioning of the head. The patient is not moved out of the scanner during the single SPECT scanning session in the DI method. This ensures minimal movement of the head and small fluctuations in the baseline physiological state. CVR measurements as assessed by the DI method would therefore be more reliable than those assessed by two measurements of rCBF performed on separate days.

It is important to discriminate patients at stage II hemodynamic failure from those at stage I, at which rCBF is maintained by means of compensatory vasodilatation in response to a decline in cerebral perfusion pressure. Although CVR is also impaired at stage I, it has not been proved whether patients at stage I have an increased risk of recurrent stroke. By means of non-quantitative SPECT studies, it may be difficult to identify those at stage II from those at stage I. In this study, even in patients with unilateral occlusion or stenosis, it was difficult in most cases to assess the decrease in rCBF on the affected side by using the uptake ratio of the affected to normal cortices, which was more than 0.85 in all cases. Most of the cases, even with a unilateral occlusive disease, showed a bilateral decrease in rCBF and the quantitative value of rCBF was needed for accurate assessment of the hemodynamic status.

Non-invasive procedures to measure CVR can be used as a screening test. Transcranial Doppler ultrasound and magnetic resonance imaging techniques combined with vasodilatory testing are available for this purpose.[5,19–21] Nevertheless, data obtained by these techniques are still semiquantitative and/or some of them provide only information about large vessel flow rather than tissue perfusion that may be maintained through collateral vessels. Quantitative assessment of rCBF and CVR seems to be needed to clarify the significance of hemodynamic changes in each patient. The quantitative DI method for serial rCBF measurements is a useful tool for identifying patients in stage II hemodynamic failure, who benefit from CR in terms of an increase in rCBF and a recovery in CVR.

CONCLUSION

In this study we showed the feasibility of the DI method with IMP for serial measurements of rCBF in a single SPECT session. By this method, we demonstrated that patients having decreased rCBF with reduced CVR benefited from CR in terms of an increase in rCBF and a recovery in CVR. The quantitative DI method with IMP-SPECT has the ability to identify those patients with stage II hemodynamic failure who may benefit from CR.

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