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## Brief Communication: Radiographic Contrast Infusion and Catecholamine Release in Patients With Pheochromocytoma

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### Abstract

**Background**—Contrast-enhanced computed tomography (CT) is useful for localizing pheochromocytoma. However, in patients with suspected pheochromocytoma, CT is often canceled or not performed because of the strong belief that intravenous contrast may induce hypertensive crisis.

**Objective**—To examine whether intravenous low-osmolar contrast administration during CT induces catecholamine release that increases blood pressure or heart rate.

**Design**—Prospective study.

**Setting**—Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland.

**Participants**—22 patients with pheochromocytoma (15 nonadrenal and 7 adrenal) and 8 unmatched control participants without pheochromocytoma.

**Measurements**—Plasma catecholamine levels, blood pressure, and heart rate.

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**Potential Financial Conflicts of Interest:** None disclosed.

**Reproducible Research Statement:** *Study protocol:* Précis available at [http://pqs.cc.nih.gov/protocol\\_query/protocol/1442](http://pqs.cc.nih.gov/protocol_query/protocol/1442). The complete protocol is available from Dr. Pacak (karel@mail.nih.gov). *Statistical code:* Available from Dr. Wesley (bwesley@mail.nih.gov). *Data set:* Available from Dr. Pacak (karel@mail.nih.gov).

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Collection and assembly of data: S.K. Baid, E.W. Lai, H.J.L.M. Timmers, K. Pacak.

**Results**—Plasma catecholamine levels within and between groups did not significantly differ before and after intravenous administration of low-osmolar CT contrast. Patients with pheochromocytoma experienced a clinically and statistically significant increase in diastolic blood pressure that was not accompanied by corresponding increases in plasma catecholamine levels. The difference became non-statistically significant after adjustment for use of  $\alpha$ - and  $\beta$ -blockers.

**Limitation**—The study lacked a placebo group, and the sample was relatively small.

**Conclusion**—Intravenous low-osmolar contrast-enhanced CT can safely be used in patients with pheochromocytoma who are not receiving  $\alpha$ - or  $\beta$ -blockers.

Computed tomography (CT) is used to localize pheochromocytoma once it has been biochemically diagnosed. Noncontrast CT has high sensitivity (approximately 90%) in various types of pheochromocytoma, and contrast can increase both the sensitivity and specificity of CT (1).

It is commonly believed that the contrast media used for CT can induce hypertensive crisis in patients with pheochromocytoma. Reports of complications (such as hypertensive crisis) are well described in patients who underwent angiography for diagnosis and localization of pheochromocytoma in the 1960s and 1970s (2). However, these invasive procedures used high-osmolar (ionic) contrast agents, which are associated with more adverse events than low-osmolar (nonionic) contrast agents (3). Low-osmolar contrast agents are now used for most invasive and noninvasive radiologic procedures, including contrast-enhanced CT.

Since 2003, more than 200 patients with pheochromocytoma have been evaluated with contrast CT at the National Institutes of Health, Bethesda, Maryland. In our experience, there have been no reports of hypertensive crisis after injection of intravenous low-osmolar CT contrast in patients with pheochromocytoma, although we did not routinely record vital signs initially. We report the effect of intravenous administration of low-osmolar contrast during CT on plasma catecholamine release, blood pressure, and heart rate in patients with and without pheochromocytoma, to determine whether it induces catecholamine release that increases blood pressure or heart rate.

## Methods

The protocol for this study was approved by the institutional review board of the Eunice Kennedy Shriver National Institute of Child Health and Human Development at the National Institutes of Health. All patients provided written informed consent.

## Patients

We evaluated plasma catecholamine levels, blood pressure, and heart rate responses in 30 patients who received oral and intravenous low-osmolar contrast (Iovue 300 [Bracco Diagnostics, Princeton, New Jersey; ALTANA Pharma AG, Singen, Germany]), 30 mL at 1.8 to 2.0 mL/h, for whole-body CT at the Warren G. Magnuson Clinical Center, National Institutes of Health. Twenty-two patients had histologically confirmed solitary adrenal or metastatic pheochromocytoma. Eight patients in whom pheochromocytoma had been ruled out served as a control group. The Appendix Figure (available at [www.annals.org](http://www.annals.org)) provides details on sampling and recruitment.

All patients had blood samples obtained through an indwelling forearm venous cannula at baseline (approximately 1 hour before the start of CT with the patient at rest and the intravenous line placed at least 20 minutes before blood draw); prescan (immediately before the start of CT, with the patient instructed to lie on the CT table for 10 minutes before the blood draw and start of CT); and at 5, 10, 15, and 20 minutes after contrast injection. Heart

rate and blood pressure were measured at all time points. Patients were supine during all measurements. Contrast was administered intravenously between the prescan and 5-minute post-contrast administration time points. Patients who were receiving antihypertensive medications continued to take these medications.

Plasma was analyzed for concentrations of catecholamines, including norepinephrine and epinephrine by high-pressure liquid chromatography, as described elsewhere (4).

### Statistical Analysis

We used the 2-sample *t* test to compare preinjection and postinjection changes in patients with pheochromocytoma and control participants, comparing the change from the average of the 2 preinjection values with the average of the 4 postinjection values. We also used the 2-sample *t* test to compare preinjection and postinjection changes in patients with solitary adrenal pheochromocytoma with those in patients with nonadrenal pheochromocytoma. Paired analyses within groups were done by using paired *t* tests. We used 2-way analysis of variance to test for differences between the patient groups while adjusting for whether the patients were or were not receiving adrenoreceptor blockade medications. For norepinephrine and epinephrine end points, log values were used because the raw values for these 2 variables were heavily skewed. All *P* values are 2-sided, and a value less than 0.05 was considered statistically significant. Summary values are presented as means.

### Role of the Funding Source

This study was supported by the Eunice Kennedy Shriver National Institute of Child Health and Development, National Institutes of Health. The funding source played a role in the decision to submit the manuscript.

### Results

We studied 22 patients with pheochromocytoma (12 women and 10 men; mean age, 46 years [range, 27 to 64 years]) and 8 control participants (4 women and 4 men; mean age, 49 years [range, 35 to 60 years]). The biochemical profile of pheochromocytoma was noradrenergic in 12 patients, adrenergic in 2 patients, mixed noradrenergic and adrenergic in 7 patients, and dopamine-secreting tumor in 1 patient (Table). Values were not available for every variable at each time point (Figure). However, for each variable except epinephrine (28 participants), values were sufficient for all 30 participants to be included in the comparisons of average values obtained before and after contrast administration.

Compared with preinjection values, epinephrine levels were significantly lower after contrast injection in patients with pheochromocytoma (mean change,  $-1$  log pmol/L [95% CI,  $-3$  to  $0$  log pmol/L];  $P = 0.041$ ). Norepinephrine values did not statistically significantly differ. Systolic blood pressure (mean change, 10 mm Hg [CI, 3 to 16 mm Hg];  $P = 0.005$ ) and diastolic blood pressure (mean change, 5 mm Hg [CI, 2 to 9 mm Hg];  $P = 0.005$ ) were significantly higher after contrast in the pheochromocytoma group. There was no statistically significant change in heart rate. In the control group, no statistically or clinically significant differences before and after contrast injection were observed in norepinephrine or epinephrine level, systolic or diastolic blood pressure, or heart rate.

Average preinjection norepinephrine levels were about 3 times higher in patients with pheochromocytoma than in control participants (Figure). However, the average change in norepinephrine levels from before to after contrast injection did not statistically significantly differ between the groups (mean change, 0.0010 log nmol/L [CI,  $-0.0004$  to 0.0024 log nmol/L];  $P = 0.148$ ). Average preinjection epinephrine levels were similar in both groups. The between-group difference in average change in epinephrine levels before and after

contrast injection was not significant (mean change, 0 log pmol/L [CI, -3 to 2 log pmol/L];  $P=0.69$ ).

Preinjection systolic and diastolic blood pressures were similar in patients with pheochromocytoma and control participants. The  $t$  tests did not show a significant effect of contrast administration on systolic blood pressure ( $P=0.142$ ) but did show a borderline significant effect on diastolic blood pressure ( $P=0.045$ ).

Average preinjection heart rates were higher in control participants than in patients with pheochromocytoma, although not significantly so. The effect of contrast administration on heart rate also did not significantly differ between the groups ( $P=0.69$ ,  $t$  test).

Nine patients with pheochromocytoma and 2 control participants were taking  $\beta$ -blockers, and 9 patients with pheochromocytoma and 3 control participants were taking  $\alpha$ -blockers. Norepinephrine and epinephrine levels, systolic and diastolic blood pressure, and heart rate did not significantly differ before and after contrast administration between patients with pheochromocytoma and control participants after adjustment for use of  $\alpha$ - and  $\beta$ -blockers. The between-group differences in diastolic blood pressure became non-statistically significant after adjustment for  $\alpha$ -blocker use ( $P=0.058$ ) or  $\beta$ -blocker use ( $P=0.069$ ).

Changes in norepinephrine and epinephrine levels, systolic and diastolic blood pressure, and heart rate did not statistically significantly differ before and after contrast injection in patients with solitary adrenal pheochromocytoma and those with nonadrenal pheochromocytoma.

## Discussion

We found little evidence that oral or intravenous administration of low-osmolar contrast leads to catecholamine release or catecholamine-induced increases in blood pressure or heart rate in patients with pheochromocytoma, findings that support our clinical observations that intravenous low-osmolar CT contrast does not induce hypertensive crisis in pheochromocytoma patients. A few patients had clinically significant increases in systolic and diastolic blood pressure and moderate increases in heart rate; however, these results were incongruent with their respective change in catecholamine levels. Other factors, such as anxiety or nervousness, may have contributed to increases in these values in these patients.

In a study of 10 patients with pheochromocytoma (4 with metastatic disease), Mukherjee and colleagues (5) reported that occasional patients with pheochromocytoma showed unpredictable catecholamine responses to intravenous administration of low-osmolar CT contrast; however, they concluded that catecholamine release and intravenous administration of contrast were unrelated. Our results agree with this conclusion. In addition, our sample included patients with both norepinephrine- and epinephrine-secreting tumors, as well as more patients with metastatic pheochromocytoma, who have greater tumor burden and higher catecholamine levels than those with solitary lesions.

The primary limitations of our study are related to the relatively small sample and lack of a placebo group. Multiple comparisons without correction may have also had some effect, as evidenced by the borderline statistically significant result in the between-group comparison of diastolic blood pressure.

In conclusion, we found that intravenous low-osmolar CT contrast had no appreciable effect on norepinephrine and epinephrine release in patients with various types of pheochromocytoma. We therefore conclude that use of intravenous low-osmolar contrast-

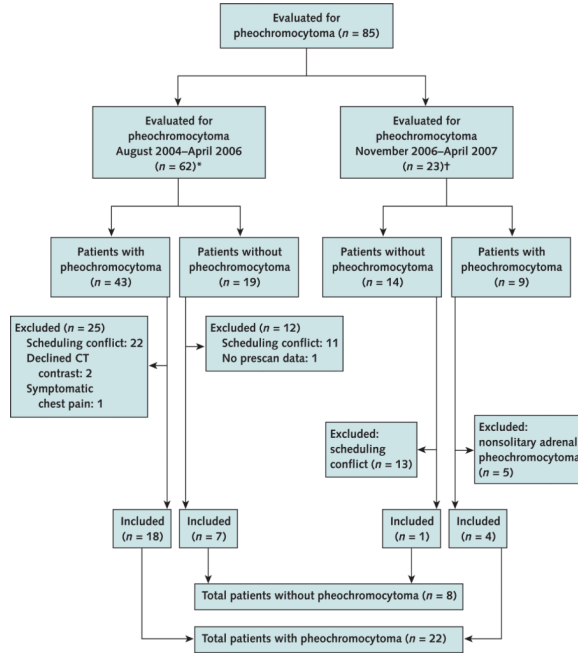
enhanced CT for localization of pheochromocytoma can be considered safe in these patients and that  $\alpha$ - or  $\beta$ -adrenergic blockade, which is often given to prevent hypertensive crisis, is not necessary.

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### Appendix Figure. Study flow diagram



CT = computed tomography.

\* Initial enrollment period.

† Recommended to the authors to include more patients with solitary adrenal pheochromocytoma.

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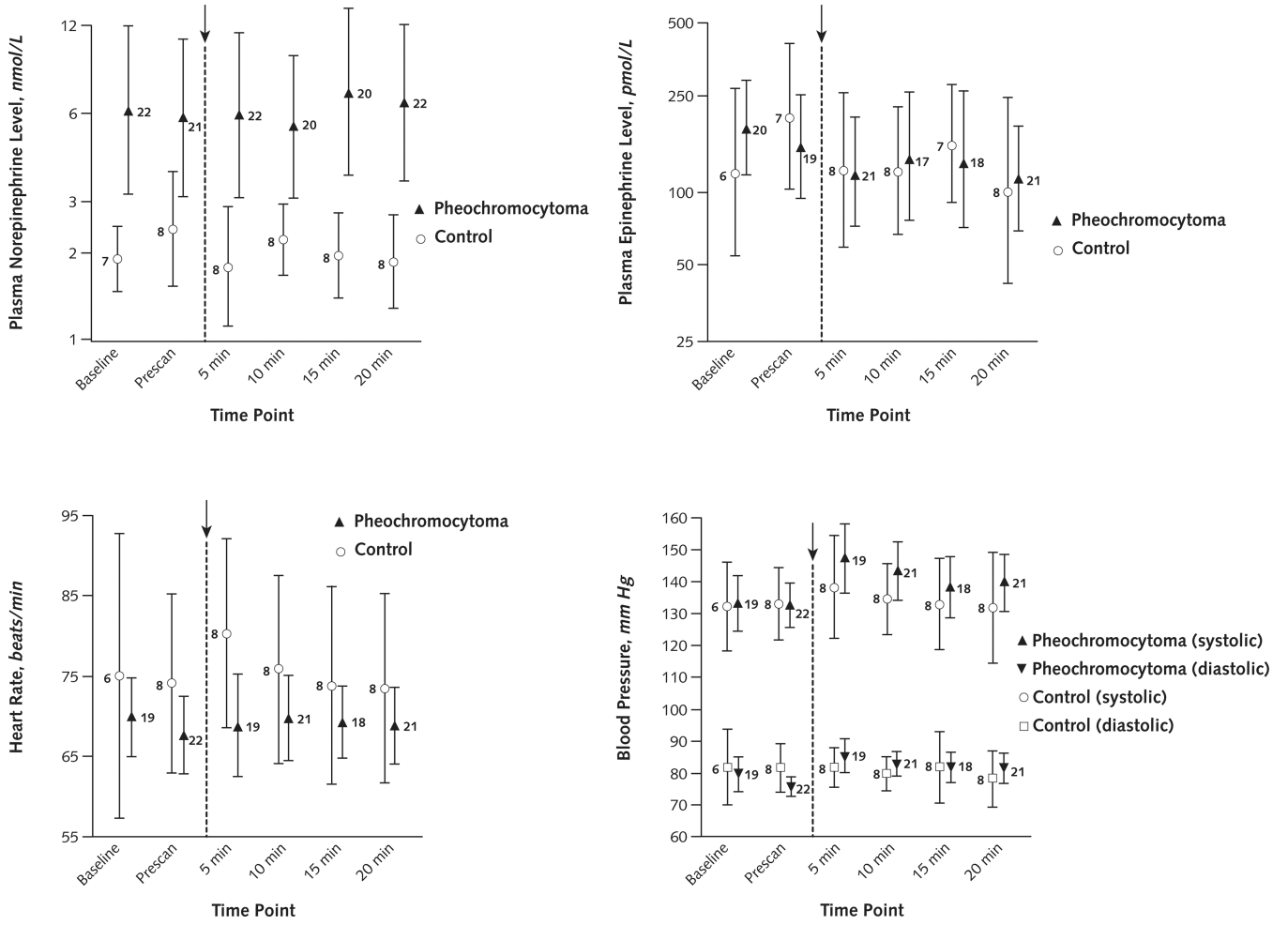
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**Figure.** Average norepinephrine and epinephrine levels, heart rate, and blood pressure in patients with pheochromocytoma compared with control participants before and after intravenous administration of computed tomography contrast. Arrows indicate the time of low-osmolar contrast injection. Bars represent 95% CIs. Number of patients with available data shown at each time point; there are no obvious outliers within the data.

Table

## Patient Characteristics

| Participant                   | Sex    | Type of Pheochromocytoma | Biochemical Profile of Tumor | Use of $\alpha$ - or $\beta$ -Blocker | Plasma Norepinephrine Level, $\log_{10}$ nmol/L |         |
|-------------------------------|--------|--------------------------|------------------------------|---------------------------------------|---|---------|
|                               |        |                          |                              |                                       | Mean Precontrast Value                          | Change* |
| <b>Pheochromocytoma group</b> |        |                          |                              |                                       |   |         |
| 1                             | Female | Metastatic               | Mixed                        | Both                                  | 0.056   | 0.0005  |
| 2                             | Male   | Metastatic               | Mixed                        | $\beta$ -Blocker                      | 0.061   | -0.0008 |
| 3                             | Male   | Metastatic               | Mixed                        | Both                                  | 0.057   | -0.0027 |
| 4                             | Male   | Metastatic               | NE                           | Neither                               | 0.039   | 0.0004  |
| 5                             | Female | Metastatic               | NE                           | Neither                               | 0.039   | -0.0008 |
| 6                             | Female | Metastatic               | NE                           | Neither                               | 0.043   | 0.0062  |
| 7                             | Male   | Extra-adrenal            | DS                           | Neither                               | 0.031   | 0.0005  |
| 8                             | Female | Metastatic               | NE                           | Neither                               | 0.034   | 0.0010  |
| 9                             | Female | Metastatic               | NE                           | $\alpha$ -Blocker                     | 0.041   | -0.0010 |
| 10                            | Male   | Metastatic               | NE                           | $\alpha$ -Blocker                     | 0.038   | -0.0015 |
| 11                            | Male   | Metastatic               | Mixed                        | Both                                  | 0.050   | -0.0008 |
| 12                            | Female | Metastatic               | NE                           | Neither                               | 0.038   | -0.0007 |
| 13                            | Female | Metastatic               | NE                           | Neither                               | 0.036   | -0.0013 |
| 14                            | Female | Metastatic               | NE                           | $\beta$ -Blocker                      | 0.034   | -0.0017 |
| 15                            | Female | Metastatic               | NE                           | Both                                  | 0.041   | 0.0012  |
| 16                            | Male   | Adrenal                  | Epi                          | Neither                               | 0.032   | 0.0017  |



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| Participant   | Sex    | Type of Pheochromocytoma | Biochemical Profile of Tumor | Use of $\alpha$ - or $\beta$ -Blocker | Plasma Norepinephrine Level, <i>log nmol/L</i> |                             |
|---|--------|--------------------------|------------------------------|---------------------------------------|--|-----------------------------|
|   |        |                          |                              |                                       | Mean Precontrast Value                         | Change*                     |
| 17  | Female | Adrenal                  | Epi                          | Neither                               | 0.036  | 0.0014                      |
| 18  | Female | Adrenal                  | Mixed                        | Both                                  | 0.048  | 0.0012                      |
| 19  | Male   | Adrenal                  | Mixed                        | Both                                  | 0.039  | 0.0009                      |
| 20  | Male   | Adrenal                  | NE                           | Neither                               | 0.035  | 0.0007                      |
| 21  | Female | Adrenal                  | Mixed                        | Both                                  | 0.038  | -0.0001                     |
| 22  | Male   | Adrenal                  | NE                           | Neither                               | 0.033  | -0.0012                     |
| Within-group summary  |        |                          |                              |                                       |  |                             |
| Average value (95% CI)                                      |        |                          |                              |                                       | 0.041  | 0.0001 (-0.0007 to 0.0009)  |
| <i>P</i> value for before vs. after contrast administration |        |                          |                              |                                       |  |                             |
| 0.71  |        |                          |                              |                                       |  |                             |
| <b>Control group</b>  |        |                          |                              |                                       |  |                             |
| 1   | Male   | NA                       | NA                           | Unknown                               | 0.037  | -0.0018                     |
| 2   | Female | NA                       | NA                           | Neither                               | 0.034  | -0.0002                     |
| 3   | Female | NA                       | NA                           | Neither                               | 0.033  | -0.0009                     |
| 4   | Male   | NA                       | NA                           | $\alpha$ -Blocker                     | 0.035  | 0.0016                      |
| 5   | Female | NA                       | NA                           | Both                                  | 0.039  | -0.0022                     |
| 6   | Male   | NA                       | NA                           | Neither                               | 0.031  | -0.0006                     |
| 7   | Female | NA                       | NA                           | Neither                               | 0.034  | -0.0018                     |
| 8   | Male   | NA                       | NA                           | Both                                  | 0.037  | -0.0011                     |
| Within-group summary  |        |                          |                              |                                       |  |                             |
| Average value (95% CI)                                      |        |                          |                              |                                       | 0.035  | -0.0009 (-0.0019 to 0.0001) |

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| Participant   | Sex | Type of Pheochromocytoma | Biochemical Profile of Tumor | Use of $\alpha$ - or $\beta$ -Blocker | Plasma Norepinephrine Level, <i>log nmol/L</i> |
|---|-----|--------------------------|------------------------------|---------------------------------------|--|
|   |     |                          |                              |                                       | Mean Precontrast Value                         |
|   |     |                          |                              |                                       | Change*  |
|   |     |                          |                              |                                       | 0.078  |
| <i>P</i> value for before vs. after contrast administration |     |                          |                              |                                       |  |
| <b>Between-group summary</b>                                |     |                          |                              |                                       |  |
| Average value (95% CI)                                      |     |                          |                              |                                       | 0.0010 (-0.0004 to 0.0024)                     |
| <i>P</i> value for pheochromocytoma vs. control group       |     |                          |                              |                                       | 0.148  |

| Plasma Epinephrine Level, <i>log pmol/L</i> | Systolic Blood Pressure, <i>mm Hg</i> |         | Diastolic Blood Pressure, <i>mm Hg</i> |         | Heart Rate, <i>beats/min</i> |         |
|---|---------------------------------------|---------|--|---------|------------------------------|---------|
|   | Mean Precontrast Value                | Change* | Mean Precontrast Value                 | Change* | Mean Precontrast Value       | Change* |
| 25  | -2                                    | 135     | 38                                     | 77      | 14                           | 91      |
| 23  | -3                                    | 144     | 37                                     | 83      | 9                            | 56      |
| 22  | -7                                    | 138     | 34                                     | 84      | 25                           | 74      |
| 14  | 0                                     | 117     | 28                                     | 74      | 8                            | 58      |
| 18  | 0                                     | 132     | 27                                     | 84      | 4                            | 72      |
| 17  | -6                                    | 128     | 9                                      | 79      | -3                           | 86      |
| 18  | -2                                    | 132     | 8                                      | 71      | 12                           | 55      |
| 16  | -6                                    | 122     | 7                                      | 78      | 1                            | 66      |
| 12  | -4                                    | 99      | 5                                      | 62      | 0                            | 74      |
| 15  | -1                                    | 136     | -1                                     | 78      | 11                           | 64      |
| 21  | -1                                    | 157     | -3                                     | 86      | -3                           | 72      |
| 15  | -7                                    | 114     | -3                                     | 73      | -5                           | 86      |
| 12  | 1                                     | 115     | -5                                     | 75      | -3                           | 76      |
|   |                                       |         |  |         |                              | 0       |

| Mean Precontrast Value | Plasma Epinephrine Level, $\log \mu\text{mol/L}$ |                        | Systolic Blood Pressure, $\text{mm Hg}$ |                        | Diastolic Blood Pressure, $\text{mm Hg}$ |                        | Heart Rate, $\text{beats/min}$ |                        |
|------------------------|--|------------------------|---|------------------------|--|------------------------|--------------------------------|------------------------|
|                        | Change*  | Mean Precontrast Value | Change*                                 | Mean Precontrast Value | Change*                                  | Mean Precontrast Value | Change*                        | Mean Precontrast Value |
| 16                     | 0  | 161                    | -10                                     | 79                     | 4  | 62                     | 3                              |                        |
| 6                      | 2  | 142                    | -12                                     | 78                     | -1                                       | 60                     | 2                              |                        |
| 24                     | 3  | 149                    | 5                                       | 79                     | 4  | 63                     | 6                              |                        |
| 19                     | -3   | 136                    | 2                                       | 80                     | 3  | 73                     | -4                             |                        |
| 20                     | 3  | 147                    | 7                                       | 90                     | 0  | 79                     | -4                             |                        |
| 30                     | 0  | 133                    | 13                                      | 64                     | 22                                       | 74                     | 9                              |                        |
| 15                     | 0  | 120                    | 2                                       | 78                     | 4  | 63                     | 2                              |                        |
| 26                     | 0  | 127                    | 19                                      | 72                     | 4  | 64                     | 2                              |                        |
| 16                     | -1   | 128                    | 8                                       | 81                     | 5  | 57                     | 9                              |                        |
| 18                     | -1 (-3 to 0)                                     | 132                    | 10 (3 to 16)                            | 77                     | 5 (2 to 9)                               | 69                     | 1 (-1 to 3)                    |                        |
| 0.041                  |  | 0.005                  |   | 0.005                  |  | 0.31                   |                                |                        |
| 19                     | 0  | 148                    | 3                                       | 94                     | -1                                       | 61                     | 9                              |                        |
| 11                     | 1  | 120                    | 2                                       | 71                     | 5  | 57                     | 4                              |                        |
| 21                     | -3   | 143                    | 4                                       | 84                     | 5  | 86                     | 5                              |                        |
| 21                     | 0  | 127                    | 25                                      | 73                     | 3  | 97                     | 3                              |                        |
| 24                     | -4   | 136                    | -19                                     | 79                     | -12                                      | 82                     | 0                              |                        |
| -                      | - <sup>†</sup>                                   | 138                    | 5                                       | 82                     | 4  | 71                     | -3                             |                        |
| 17                     | -2   | 119                    | -9                                      | 82                     | -7                                       | 80                     | -7                             |                        |
| 19                     | 2  | 139                    | -4                                      | 90                     | -7                                       | 73                     | -10                            |                        |
| 19                     | -1 (-3 to 1)                                     | 134                    | 1 (-10 to 11)                           | 82                     | -1 (-7 to 4)                             | 76                     | 0 (-5 to 6)                    |                        |

| Plasma Epinephrine Level,<br><i>log pmol/L</i> |                     | Systolic Blood<br>Pressure, <i>mm Hg</i> |                     | Diastolic Blood<br>Pressure, <i>mm Hg</i> |                     | Heart Rate,<br><i>beats/min</i> |                     |
|--|---------------------|--|---------------------|---|---------------------|---------------------------------|---------------------|
| Mean Precontrast<br>Value                      | Change <sup>*</sup> | Mean Precontrast<br>Value                | Change <sup>*</sup> | Mean Precontrast<br>Value                 | Change <sup>*</sup> | Mean Precontrast<br>Value       | Change <sup>*</sup> |
| 0.31   |                     | 0.85                                     |                     | 0.59                                      |                     | 0.93                            |                     |
| 0 (-3 to 2)                                    |                     | 8.8 (-3.12 to 20.74)                     |                     | 6.5 (0.16 to 12.79)                       |                     | 0.88 (-3.67 to 5.43)            |                     |
| 0.69   |                     | 0.142                                    |                     | 0.045                                     |                     | 0.69                            |                     |

DS = predominantly dopamine-secreting; Epi = predominantly epinephrine-secreting; NA = not applicable; NE = predominantly norepinephrine-secreting.

<sup>\*</sup> The average of 4 post-contrast administration values minus the average of 2 pre-contrast administration values.

<sup>†</sup> Data before or after contrast administration were unavailable because of interfering assay peak or values below the detectable range.