B-Type Natriuretic Peptide and Hemoglobin are Two Major Factors Significantly Associated With Baseline Cerebral Oxygen Saturation Measured Using the INVOS Oximeter in Patients Undergoing Off-Pump Coronary Artery Bypass Graft Surgery

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Abstract

Objectives: To investigate an association between the preoperative plasma B-type natriuretic peptide (BNP) concentration and cerebral regional saturation (rSO_2) measured using the INVOS oximeter (Medtronic, Minneapolis, MN).

Design: A retrospective data analysis.

Setting: Single university hospital.

Participants: Patients undergoing off-pump coronary artery bypass (OPCAB) surgery. Interventions: None. Measurements and Main Results: Associations of variables obtained from preoperative blood laboratory tests and transthoracic echocardiography with baseline rSO_2 before induction of general anesthesia were investigated using bivariate and multivariate regression analyses in 330 OPCAB patients. With bivariate analyses, age; body size–related variables such as weight and body surface area; hematologic function–related variables such as blood hemoglobin (Hb) concentration and arterial oxygen saturation; renal function–related variables including estimated glomerular filtration rate, creatinine, and blood urea nitrogen; hepatic function–related variables including cholinesterase, albumin, total bilirubin, and alanine aminotransferase; serum electrolytes including sodium, chloride, and phosphorus; BNP or log-transformed BNP; and 13 transthoracic echocardiography variables such as left ventricular ejection fraction highly significantly correlated with baseline rSO_2 ($p < 0.0001$). However, the multiple regression analysis revealed that only BNP and Hb remained major factors significantly associated with baseliner SO_2 ($p < 0.0001$), while estimated glomerular filtration rate, arterial oxygen saturation, and body surface area remained minor factors ($p < 0.05$). Baseliner SO_2 correlated better with log-transformed BNP than with BNP, indicating that rSO_2 correlated with BNP in an exponential fashion.

Conclusions: Preoperative BNP and Hb concentrations were 2 major factors associated with INVOS rSO_2 in patients undergoing OPCAB.

Key Words: B-type natriuretic peptide; cerebral oxygen saturation; hemoglobin; INVOS; near-infrared spectroscopy

CEREBRAL TISSUE OXIMETRY with near-infrared spectroscopy (NIRS) is used widely to monitor cerebral oxygen saturation during cardiac surgery.[1,2] Although various NIRS values have been used, regional cerebral oxygen saturation (rSO_2) derived from the INVOS oximeter (Medtronic, Minneapolis, MN) has been one of the most widely used NIRS values.[1,2] In clinical practice, however, there are wide inter-individual variations in absolute INVOS rSO_2 values, even at baseline.[3–12] Hence, it generally is accepted that trends rather than absolute values of rSO_2 should be relied on in clinical practice.[1,2]

To conquer such limitations of the INVOS oximeter, it seems crucial to recognize factors affecting such inter-individual variations. Previous studies most consistently have demonstrated that INVOS rSO_2 values correlate positively with blood hemoglobin (Hb) concentration.[3–10] In addition, previous studies have identified factors associated with INVOS rSO_2 values suchasage,[4,8,11] body size,[7,8,11] blood urea nitrogen (BUN),[10] creatinine,[8,9] estimated glomerular filtration rate (eGFR),[8] total bilirubin (T.Bil),[9] albumin,[10] electrolytes,[9,10] N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP),[8] and cardiac function–related variables other than NT-proBNP.[8,12] B-type natriuretic peptide (BNP) is synthetized and released from the heart in response to volume or pressure overload.[13] It is released as an active hormone—BNP—and as an inactive fragment—NT-proBNP—after proteolysis of proBNP. BNP decreases afterload by relaxing vascular smooth muscles while decreasing preloadbyinducingdiuresis.[13] Plasma BNP concentration increases in patients with cardiac dysfunction,[14–19] chronic kidney disease (CKD),[15,19,20] and/or liver cirrhosis,[21] whereas cerebral INVOSrSO_2 values decrease in patients with cardiac dysfunction,[8,12,22,23] CKD on hemodialysis (HD),[10,24] and/or liver cirrhosis.[9,25] Therefore, the authors hypothesized that BNP would have a significant association with INVOS rSO_2. To the authors' knowledge, a relationship between BNP and INVOS rSO_2 has not been studied in adults undergoing off-pump coronary artery bypass graft (OPCAB) surgery, although 1 previous study reported a negative correlation between NT-proBNP and INVOS rSO_2 in adults undergoing on-pump cardiac surgery.[8] Furthermore, the relationship between NT-proBNP and rSO_2 was not described in detail in that previous study.[8]

In the study presented here, the authors retrospectively investigated associations among preoperative plasma BNP concentration, other clinical variables, and baseline INVOS rSO_2 in patients who underwent OFCAB to explore factors associated with baseline INVOS rSO_2. The authors also attempted to closely characterize the relationship between BNP and rSO_2.

Methods

Before this retrospective study, approval was obtained from the Institutional Review Board of Juntendo University Hospital (approvalnumber16-193). Because of the retrospective fashion of the study, the Institutional Review Board waived the need for patient consent.

Patients

Consecutive patients who underwent OPCAB surgery between January 2013 and June2015 were included in the study.

Anesthesia Management

Patients were not premedicated. In the operating room (OR), monitoring with noninvasive blood pressure, pulse oximeter, electrocardiogram, bispectral index, and cerebral rSO_2 using the INVOS-5100C oximeter was started. After an arterial pressure line was established with the patient under local anesthesia, arterial blood gas on room air was analyzed. Anesthesia was performed in accordance with institutional standards with midazolam (0.1-0.2mg/kg), fentanyl (5-10 μg/kg), and rocuronium bromide for induction and sevoflurane (1%-1.5%) and remifentanil (0.5-1.0 μg/kg/min) for maintenance. Then, a transesophageal echocardiography probe and pulmonary artery catheter were placed. Coronary vasodilators nitroglycerin (0.5 mg/kg/min) and nicorandil (3-4 mg/h) were infused throughout surgery. During coronary artery bypass grafting, the ß-blocker landiolol (10-40 μg/kg/min) and the vasoconstrictor phenylephrine (0.5-5 mg/h) were infused to reduce heart rate and to maintain arterial pressure, respectively. Boluses of phenylephrine (0.05-0.2 mg) were given as necessary. When all anastomoses were completed, infusions of landiolol and phenylephrine were replaced by dopamine (3-5 μg/kg/min) and noradrenaline (0.01-0.1 μg/kg/min) to increase cardiac output and to maintain arterial pressure. Before ending surgery, anesthesia was switched to an infusion of propofol (2-3 mg/kg/h) and fentanyl as incremental boluses (5-10 μg/kg) for sedation for postoperative mechanical ventilation in the intensive care unit (ICU).

Monitoring of INVOS rSO_2

Monitoring of bilateral rSO_2 with the INVOS5100C oximeter was started as soon as patients were placed on the operating table while breathing room air. Thereafter, rSO_2 values were monitored and recorded every 5-to-6 seconds in the USB memory stick until the end of anesthesia. Duration of patients' stay in the OR was divided into the following 6 phases: the baseline phase before induction of general anesthesia; the preoperative phase from anesthesia induction to the start of surgery; the pre-grafting phase from the start of surgery to the beginning of cardiac manipulation; the intra-grafting phase from the beginning of cardiac manipulation for bypass grafting to completion of the last anastomosis; the post- grafting phase from the last anastomosis to the end of surgery; and the postoperative phase from the end of surgery to the end of anesthesia immediately before transfer to the ICU. A representativerSO_2 value in each phase was determined by averaging all rSO_2 values recorded during the corresponding period. A temporary, minimal rSO_2 value during surgery also was determined in each patient.

Preoperative Data on Blood Laboratory Tests, Echocardiography, Radiography, and Pulmonary Artery Catheterization

In scheduled OPCAB patients, routine preoperative blood tests were performed, at least twice, before hospitalization and within 2 days before surgery; whereas in emergency OPCAB patients, tests were performed once, on the day of surgery. The authors also collected, from the electronic medical record, results of the latest blood tests data, including white blood cell count, red blood cell count, Hb, hematocrit, platelet count, activated partial thromboplastin time, international normalized ratio of prothrombin time, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, γ-glutamyl transpeptidase, creatine kinase, choline esterase (ChE), T.Bil, direct bilirubin, total protein,

albumin, BUN, creatinine, eGFR, uric acid, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, sodium (Na), potassium, chloride (Cl), calcium, phosphorus (P), magnesium, hemoglobin A_{1c}, C-reactive protein, serum osmolarity, and BNP. The authors collected, from the electronic anesthesia records, arterial blood gas data on room air, including pH, partial pressure of carbon dioxide, base excess, partial pressure of oxygen, oxygen saturation (SaO_2), and glucose concentration. The authors reviewed reports of preoperative transthoracic echocardiography, which were examined and reported on by a pair of an expert ultrasonographer and a cardiologist, and collected data including left atrial diameter, left ventricular (LV) diastolic diameter (LVDd), LV systolic diameter, LV end-diastolic volume, LV end-systolic volume, inferior vena cava diameter, LV wall thickness (LVWT),LV fractional shortening, LV ejection fraction (LVEF), early transmitral velocity (E), late transmitral velocity, the E/late transmitral velocity ratio, E deceleration time, early diastolic mitral annular velocity (e´), late diastolic mitral annular velocity, systolic mitral annular velocity, and E/e´ ratio, for which dimensional data, including left atrial diameter, LVDd, LV systolic diameter, LV end-diastolic volume, LV end-systolic volume, inferior vena cava diameter, and LVWT were indexed to body surface area (BSA), LVWT was an average of LV posterior and septal wall thicknesses, and the systolic mitral annular velocity, e´, late diastolic mitral annular velocity, and E/e´ ratio were averages of those at the medial and lateral sides, respectively, as described previously.[18,26] The authors also measured the cardiothoracic ratio on a preoperative chest x-ray. Furthermore, the authors collected, from the electronic anesthesia record, pressure data just at the time of pulmonary artery catheter placement, including mean arterial pressure (MAP), central venous pressure, mean pulmonary artery pressure, and the mean pulmonary artery pressure/MAP ratio.

Statistical Analyses

One of the main objectives of the study was to identify factors significantly associated with baseline rSO_2 using multiple regression analysis, for which the general rule of thumb is that10-to-20 observations per independent variable are needed to be able to detect reasonable-size effects with reasonable power.[27] Therefore, a sample size of 300 was considered sufficient for multiple regression analyses including 15 independent variables. Because many continuous variables examined, except for 13 variables such as Hb and partial pressure of arterial oxygen, were non-normally distributed after Shapiro-Wilk testing, demographic, anesthetic, and surgical data are presented as median (quartiles) or median (quartiles) [range].Because BNP was non-normally distributed in an extreme way, log-normal transformed BNP (log BNP) also was used for statistical analysis, as reported previously.[15–17] Sex difference in baseline rSO_2 was examined using the Mann-Whitney U test. To examine the relationship between baseline rSO_2 and clinical outcomes, patients were divided into 2 groups based on whether their baseline rSO_2 values were >50% or ≤50%, according to the criterion set by the previous authors.[8] Comparison between groups was performed with the Mann-Whitney U and Fisher exact tests, as appropriate. Changes in rSO_2 in the OR were examined with the Wilcoxon signed-rank test with Bonferroni correction. Correlation between any of 2 variables was analyzed with Spearman's correlation coefficient. However, Pearson's correlation coefficient

also was used to characterize relationships between BNP and any other variables and to select candidate-independent variables to be included in the multiple regression analysis. A p value < 0.05 was considered to be statistically significant, except for multiple comparisons among representative rSO_2 values in 6 phases, for which p < 0.008 was considered to be significant. Data were analyzed with JMP12 (SAS Institute Inc, Cary, NC). Scatter plots with linear or exponential regression lines were generated by Excel 2013 (Microsoft, Redmond, WA).

Results

During the study period, 365 patients underwent scheduled (n = 334) or emergency (n = 31) OPCAB. Excluded were patients in whom rSO_2 was not monitored throughout anesthesia (n = 35). Consequently, 330 OPCAB patients (283 males and 47 females) aged 34 to 87 years were included. Demographic, anesthetic, and surgical data are shown in Table 1. No patient had valvular disease indicated for concomitant valve repair.

Baseline rSO_2 was not different between males and females (62.5% [53.9%/68.8%] *v* 61.0% [53.0%/66.2%], p > 0.05). Tables 2 and 3 show the variables that significantly correlated with baseline rSO_2 using Pearson's correlation coefficient, not only between each variable and baseline rSO_2 but also between each variable and BNP or Hb because many of the variables listed also correlated closely with BNP and/or Hb, which were 2 major factors associated with baseline rSO_2, as described later. The results of Spearman's correlation were quite similar to those with Pearson's correlation in most variables (data not shown). Among these variables, a number of them related to the patients' body size; cardiac, renal, hepatic, or hematologic function; and serum electrolytes highly significantly correlated with baseliner SO_2 (p < 0.0001 [see Tables 2 and 3]). However, multiple regression analysis, incorporating 15 independent variables including BSA; Hb and SaO_2; alanine aminotransferase, ChE, T.Bil, and albumin; eGFR; Na, Cl, and P; log BNP; LVDd; LVEF; and E/e′ ratio, as representatives variables related to body size, hematologic function, hepatic function, renal function, electrolytes, hydration status, cardiac volume load, systolic function, and diastolic function, respectively, revealed that only Hb and log BNP remained as major factors associated with baseline rSO_2 (p < 0.0001), while eGFR, SaO_2, and BSA remained minor factors (p > 0.05) (Table4). On the other hand, variables related to cardiac function other than BNP, hepatic function, or serum electrolytes did not remain significant factors (p > 0.05) (see Table 4), all of which closely correlated with log BNP and/or Hb with Pearson's correlation coefficient (p < 0.0001) (see Tables 2 and 3). With Pearson's correlation coefficients and on scatter plots, baseline rSO_2 linearly correlated with many variables examined, such as BSA, Hb, SaO_2, ChE, albumin, eGFR, Na, Cl, P, LVDd, LVEF, and E/e′ ratio (see Tables 2 and 3; Fig 1, C and D). On the other hand, baseline rSO_2 correlated more closely with log BNP than with BNP, indicating that rSO_2 correlated with BNP in an exponential rather than linear fashion (Fig 1, A and B). Likewise, cardiac variables and Hb correlated with BNP in exponential fashions (see Tables2 and 3; Fig2).

Results of the group comparisons according to baseline rSO_2 showed that the logistic EuroSCORE II was higher and that the postoperative intubation time, ICU stay, and hospital stay were longer in patients with

$rSO_2 \leq 50\%$ (n = 38) than those with $ScO_2 > 50\%$ (n = 298), although incidences of hospital mortality and postoperative cerebral complications did not differ between these patients (EuroSCORE 3.91 [2.14/6.97] *v* 1.61 [0.97/2.59], $p < 0.0001$; intubation time 7 [5/10] h *v* 5 [4/8] h, $p < 0.01$; ICU stay 2 [1/4] d *v* 1 [1/2] d, $p < 0.0001$; hospital stay12 [10/14] d *v* 10 [8/13] d, $p < 0.01$); hospital mortality 1/38 *v* 1/298, $p > 0.05$; and cerebral complications 0/38 *v* 2/298, $p > 0.05$).

rSO_2 values changed significantly during surgery (see median [quartiles] rSO_2 values shown on each panel of Fig3). The lowest recorded rSO_2 value occurred during the intra-grafting phase, when cardiac output could be most significantly depressed (see Fig3). Regardless of such significant changes, intraoperative rSO_2 values continued to correlate with baseline rSO_2 until the end of anesthesia (see Fig3), indicating that patients showing lower baseline rSO_2 values continued to record lower rSO_2 values throughout anesthesia.

Discussion

In this study, multiple regression analyses revealed that Hb and BNP were 2 major factors associated with baseline INVOS rSO_2, while eGFR, SaO_2, and BSA were minor factors. Lower baseline rSO_2 ($\leq 50\%$) was associated with a higher EuroSCORE and the need for longer postoperative care. Patients with lower baseline rSO_2 continued to record lower rSO_2 throughout anesthesia, irrespective of significant changes in rSO_2 during surgery.

As reported previously,[8,12,23] many cardiac variables closely correlate with rSO_2 on bivariate correlation analyses. However, only Hb and BNP, but not other cardiac variables, remained a factor significantly associated with rSO_2 using multiple regression analysis. Possibly, effects of other cardiac variables, which also closely correlated with BNP, on rSO_2 were masked by a stronger effect of BNP as a surrogate of cardiac function. Likewise, some hepatic variables and serum electrolytes correlated closely with rSO_2 on bivariate, but not multiple, regression analyses, suggesting that these variables just reflected underlying pathophysiology responsible for decreased rSO_2, such as cardiac dysfunction. In contrast, eGFR remained a significant factor, suggesting that rSO_2 values could be lower in patients with renal dysfunction, as reported previously,[8,10,24] independent of BNP and Hb levels. SaO_2 also remained a significant factor, as suggested previously.[10] Likewise, BSA remained a significant factor. Significant associations of body-size–related variables, such as weight, body mass index, and scull thickness, with rSO_2 have been reported previously.[7,8,11]

In the study presented here, Hb was a major factor associated with rSO_2. rSO_2 correlated positively with Hb in a linear fashion, as reported previously.[3–10] However, it remains unclear whether a decrease in INVOS rSO_2 with decreasing Hb reflects an actual decrease in cerebral oxygen saturation. Reportedly, induction of mild-to-moderate hemodilution did not decrease jugular venous bulb oxygen saturation (SjO_2), possibly due to compensation by increased cerebral blood flow (CBF),[6,28,29] whereas induction of even mild hemodilution decreased rSO_2.[3,5,6] Thus, changes in rSO_2 and SjO_2 were not parallel during hemodilution.[6] Although this discrepancy might suggest that rSO_2 was more sensitive than SjO_2 in detecting focal cerebral oxygen imbalance, it also might result from algorithms for calculating rSO_2.[6] The INVOS oximeter uses the modified Beer-Lambert method that includes optical path length in its formula as a constant, and a

change in actual optical path length that should be constant can cause a discrepancy between actual and calculated saturation values.[30] A decrease in Hb increases optical path length because NIR light travels a longer distance due to decreased absorption by Hb, which, in turn, results in overestimation of a decrease in oxyhemoglobin concentration, as measured using the modified Beer-Lambert method.[30] Such assumptions are supported by previous findings that INVOS rSO_2 correlated with factors influencing path length, including Hb, skull thickness, and the area of cerebrospinal fluid layer, whereas absolute cerebral oxygen saturation tissue oxygen index (TOI) did not, as measured with the NIRO oximeter (Hamamatsu Photonics, Hamamatsu City, Japan) using methodology independent of the modified Beer-Lambert method.[7] Previous findings that INVOS rSO_2, but not NIRO TOI, correlated positively with age and weight in children also might reflect the difference in effects on rSO_2 and TOI of age-related changes in skull thickness and thus in optical path length.[7,11] Likewise, a positive correlation between BSA and rSO_2 observed in the study presented here might reflect body-size–related changes in optical path length.

In the study presented here, BNP also was a major factor associated with rSO_2. rSO_2 correlated negatively with BNP in an exponential fashion. Possibly, this exponential relationship reflected biologic features of BNP because previous studies analyzed relationships between BNP and cardiac variables with Pearson's correlation after log-transforming BNP,[14–17] indicating that these relationships are better expressed in exponential models.[18]

Several explanations seemed plausible regarding mechanisms underlying the close negative correlation between BNP and rSO_2. First, it seemed unlikely that tissue BNP by itself affected absorption or optical path length of NIR light because its aqueous solution is transparent and uncolored.[31] Second, it also seemed unlikely that melanin pigmentation in HD patients affected rSO_2 because melanin in a superficial, thin epidermal layer of the skin does not affect NIRS light attenuation, unlike melanin in hair.[32,33] Third, cerebral tissue oxygenation actually might be impaired in patients with cardiac dysfunction presenting with high BNP because CBF can decrease in patients with severe congestive heart failure.[34,35] Indeed, previous investigators have attributed lower rSO_2 in cardiac patients to reduced CBF.[12] Even without reduced CBF, rSO_2 might decrease due to venous congestion from fluid overload because NIRS devices measure combined arterial and venous oxygen saturation.[1,2] Fourth, low rSO_2 in patients with cardiac and/or renal dysfunction associated with high BNP might reflect low extracranial tissue oxygen saturation resulting from extracranial tissue hypoperfusion and/or congestion even though adequate cerebral oxygenation might be maintained because of cerebral autoregulation at the cost of decreased peripheral blood flow because, reportedly, INVOS rSO_2 can be affected more profoundly by extracranial tissue oxygenation compared with NIRS values derived from newer-generation oximeters using more refined spatial resolution technologies.[36,37] Fifth, rSO_2 might be low as a result of fluid overload in patients with high BNP. In the study presented here, rSO_2 positively correlated with Hb in a linear fashion, whereas Hb negatively correlated with BNP in an exponential fashion, indicating that rSO_2 could correlate negatively with BNP in an exponential fashion via the aforementioned effect of Hb on rSO_2. Moreover, high BNP could be associated with generalized tissueedema,[16,38,39] which seemed, to the authors, to increase in an exponential fashion with increasing BNP.[40–43] This might decrease tissue Hb concentration more than blood

Hb concentration due to decreased density of vascular beds in edematous tissues, thereby resulting in a further decrease in rSO_2. Of note, BNP itself could induce tissue edema through increased vascular permeability.[13,44]

As reported previously,[8] lower baseline rSO_2 ($\leq$ 50%) was associated with the higher EuroSCORE and need for longer postoperative care, suggesting that low baseline rSO_2 could be reflective of severity of preoperative systemic comorbidities and predictive of postoperative outcomes. Furthermore, patients exhibiting lower baseline rSO_2 continued to record lower rSO_2 throughout anesthesia and surgery, irrespective of changes in rSO_2 due to anesthesia- and/or OPCAB-related changes in cardiac output, MAP, CVP, Hb, partial pressure of carbon dioxide, and temperature [45] and effects of vasoactive agents.[46] Such phenomena suggested that lower rSO_2 reflects pathophysiology not readily modifiable intraoperatively, such as fluid overload associated with heart and/orrenalfailure.[47]

This study had several limitations. First, many CKD patients on HD were included, which could lead to a potential bias. In addition, measured BUN and creatinine levels and calculated eGFR in HD patients did not indicate actual renal function. However, these data in HD patients were not excluded because these variables were used as convenient, gross estimates of efficacy of renal replacement therapy and included in data analyses in previous studies.[10,48–50] Second, the aforementioned mechanisms underlying the close rSO_2-to-BNP relationship were only speculative, and the relationship just indicated that not high BNP itself but pathophysiology underlying high BNP was the cause of decreased rSO_2. Third, rSO_2 was measured only with the INVOS oximeter. Fourth, because of the retrospective fashion, there may have been problems with the accuracy of measurements of NIRS, echocardiographic, and other variables. Additional studies are required to elucidate exact mechanisms underlying the rSO_2-to-BNP relationship and to evaluate whether the results of this study would be reproducible with newer-generation NIRS devices more independent of extracranial contamination and/or path length factors.[7,36,37]

In conclusion, preoperative Hb and BNP concentrations were the 2 major factors associated with the baseline INVOS rSO_2 values in OPCAB patients. rSO_2 correlated positively with Hb in a linear fashion and correlated negatively with BNP in an exponential fashion. The exact mechanisms underlying close associations among these variables should be elucidated.

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Figure legend

Figure 1. Relationships between plasma B-type natriuretic peptide concentration (BNP) and baseline rSO_2 (A), between log-transformed BNP (log BNP) and baseline rSO_2 (B), between blood hemoglobin concentration and baseline rSO_2 (C), and between estimated glomerular filtration rate (eGFR) and baseline rSO_2 (D)

Pearson's correlation coefficient (r) is depicted on each panel. Note that the rSO_2-to-BNP relationship is better expressed in an exponential rather than linear fashion (A & B), whereas rSO_2-to-hemoglobin and rSO_2-to-eGFR relationships are better expressed in linear fashions (C & D). See also Table 2.

Figure 2. Relationships between plasma B-type natriuretic peptide concentration (BNP) and the left ventricular diastolic diameter (LVDd) (A), between log-transformed BNP (log BNP) and LVDd (B), between BNP and blood hemoglobin concentration (C), and between log BNP and hemoglobin (D)

Pearson's correlation coefficient (r) is depicted on each panel. Note that the LVDd-to-BNP and hemoglobin-to-BNP relationships are better expressed in exponential rather than linear fashions. See also Tables 2 and 3.

Figure 3. Relationships between baseline rSO_2 and rSO_2 in the preoperative (Pre-Op) phase (A), between baseline rSO_2 and rSO_2 in the pre-grafting (Pre-G) phase (B), between baseline rSO_2 and rSO_2 in the intra-grafting (Intra-G) phase (C), between baseline rSO_2 and rSO_2 in the post-grafting (Post-G) phase (D), between baseline rSO_2 and rSO_2 in the postoperative (Post-Op) phase (E), and between baseline rSO_2 and temporary, minimal rSO_2 during surgery (F)

Pearson's correlation coefficient (r) a p value are depicted on each panel. Note that patients exhibiting lower baseline rSO_2 continued record lower rSO_2 throughout anesthesia and surgery, irrespective of significant changes in rSO_2 during anesthesia and surgery, as shown by median (quartiles) values of rSO_2 depicted on each panel.

[a], $p < .0001$ vs baseline rSO_2 and rSO_2 in Pre-Op phases by Wilcoxon signed rank test ;

[b] $p < .0001$ vs baseline rSO_2 and rSO_2 in pre-Op, pre-G, Post-G, and Post-Op phases by Wilcoxon signed rank test

.

Table 1. Demographic, anesthetic, and surgical data of 330 patients (283 males and 47 females)

Age (years)	70 (64/76) [34-87]
Height (cm)	164 (159/168) [135-183]
Weight (kg)	63.0 (56.0/71.8) [36.5-115]
Body mass index (kg/m^2)	23.8 (22.0/26.2) [14.5-39.9]
Body surface area (m^2)	1.68 (1.57/1.81) [1.22-2.24]
Past and current comorbidities (Number of patients)	previous coronary stenting (91), previous cardiac surgery (5), acute coronary syndrome on intra-aortic balloon pumping (9), congestive heart failure (79; acute [13], chronic [37], previous [29]), hypertension (243), hyperlipidemia (211), diabetes mellitus (187), chronic kidney disease (141; pre-dialysis [93], on dialysis [48]), chronic lung disease (72), previous cerebrovascular disease or old cerebrovascular lesion (65), arteriosclerosis obliterans (38), carotid artery stenosis (20), aortic aneurysm (17), smoker (194; previous [156], current [38])
Logistic EuroSCORE II	1.67 (1.02/2.66) [0.50-31.7]
Baseline rSO2	62.3 (53.5/68.6) [25.9-85.5]
Duration of anesthesia (min)	292 (249/328) [155-462]
Duration of surgery	242 (198/279) [107-415]
Harvested graft vessels (Number of patients)	left internal thoracic artery (321), right internal thoracic artery (201), saphenous vein (124), gastroepiploic artery (100), radial artery (43)
Number of bypass grafts	3 (2/4) [1-7]
Concomitant surgery (Number of patients)	peripheral vascular surgery (9), endovascular aortic aneurysm repair (7), cholecystectomy (7), pulmonary vein isolation (5), mediastinal omentopexy (5), carotid endarterectomy (3)

NOTE. Data are shown as median (quartiles) [range] or number. Cholecystectomy was performed for gall stone in patients whose gastroepiploic arteries were harvested, pulmonary vein isolation was performed for treatment of atrial fibrillation, and mediastinal omentopexy was performed in an attempt to prevent mediastinitis in patients at high risk for postoperative infection.

Table 2. Results of Pearson's correlation coefficient analyses between a variable related to patients' demography or blood laboratory test and baseline rSO_2, plasma BNP concentration, or blood hemoglobin concentration

Variables	n	Median (Quartiles)	Baseline rSO_2	BNP	Log BNP	Hemoglobin
			r (p) values	r (p) values	r (p) values	r (p) values
Age	330	70 (64/76)	-0.13 (< 0.05)	0.03 (> 0.05)	0.12 (< 0.05)	-0.22 (< 0.0001)
Height (cm)	330	164 (159/168)	0.20 (< 0.001)	-0.09 (> 0.05)	-0.11 (> 0.05)	0.32 (< 0.0001)
Weight (kg)	330	63.0 (56.1/71.8)	0.23 (< 0.0001)	-0.20 (< 0.001)	-0.20 (< 0.001)	0.38 (< 0.0001)
BMI (kg/m^2)	330	23.8 (22.0/26.2)	0.16 (< 0.01)	-0.20 (< 0.001)	-0.19 (< 0.001)	0.26 (< 0.0001)
BSA (m^2)	330	1.68 (1.57/1.81)	0.25 (< 0.0001)	-0.19 (< 0.001)	-0.20 (< 0.001)	0.40 (< 0.0001)
RBC ($10^6/\mu L$)	330	4.26 (3.85/4.67)	0.47 (< 0.0001)	-0.26 (< 0.0001)	-0.33 (< 0.0001)	0.90 (< 0.0001)
Hemoglobin (g/dL)	330	13.0 (11.6/14.3)	0.51 (< 0.0001)	-0.30 (< 0.0001)	-0.39 (< 0.0001)	1 (< 0.0001)
Hematocrit (%)	330	38.7 (34.7/41.9)	0.47 (< 0.0001)	-0.26 (< 0.0001)	-0.34 (< 0.0001)	0.98 (< 0.0001)
PT-INR	330	1.05 (1.01/1.09)	-0.20 (< 0.001)	0.14 (< 0.01)	0.24 (< 0.0001)	-0.13 (< 0.05)
pH	330	7.43 (7.41/7.45)	-0.13 (< 0.05)	-0.12 (< 0.05)	0.13 (< 0.05)	-0.09 (> 0.05)
PaO_2 (mmHg)	330	85.5 (77.0/93.6)	0.20 (< 0.001)	-0.21 (< 0.001)	-0.15 (< 0.01)	0.07 (> 0.05)
SaO_2 (%)	330	96.0 (94.9/97.0)	0.22 (< 0.0001)	-0.21 (< 0.001)	-0.15 (< 0.01)	0.03 (> 0.05)
ALP (IU)	330	200 (164/248)	-0.21 (< 0.001)	0.09 (> 0.05)	0.10 (> 0.05)	-0.09 (> 0.05)
ALT (IU)	330	17 (12/26)	0.23 (< 0.0001)	-0.20 (< 0.001)	-0.20 (< 0.001)	0.31 (< 0.0001)
ChE (IU)	330	275 (228/332)	0.44 (< 0.0001)	-0.44 (< 0.0001)	-0.52 (< 0.0001)	0.49 (< 0.0001)
T.Bil (mg/dL)	330	0.68 (0.48/0.92)	0.25 (< 0.0001)	-0.14 (< 0.01)	-0.16 (< 0.01)	0.41 (< 0.0001)
D.Bil (mg/dL)	324	0.05 (0.05/0.08)	-0.19 (< 0.001)	0.18 (< 0.01)	0.21 (< 0.001)	0.02 (> 0.05)
T.Protein (g/dL)	330	6.7 (6.3/7.0)	0.18 (< 0.001)	-0.19 (< 0.001)	-0.24 (< 0.0001)	0.25 (< 0.0001)
Albumin (g/dL)	330	3.9 (3.6/4.1)	0.40 (< 0.0001)	-0.35 (< 0.0001)	-0.46 (< 0.0001)	0.49 (< 0.0001)
BUN (g/dL)	330	16 (13/23)	-0.38 (< 0.0001)	0.45 (< 0.0001)	0.50 (< 0.0001)	-0.43 (< 0.0001)
Creatinine (mg/dL)	330	0.88 (0.74/1.23)	-0.43 (< 0.0001)	0.49 (< 0.0001)	0.51 (< 0.0001)	-0.37 (< 0.0001)
eGFR ($mL/min/1.73\ m^2$)	330	63.3 (44.2/80.5)	0.46 (< 0.0001)	-0.47 (< 0.0001)	-0.54 (< 0.0001)	0.34 (< 0.0001)
T.Chol (mg/dL)	330	159 (138/183)	0.15 (< 0.01)	-0.15 (< 0.01)	-0.18 (< 0.01)	0.23 (< 0.0001)
LDL-Chol (mg/dL)	330	88 (72/111)	0.17 (< 0.01)	-0.16 (< 0.01)	-0.16 (< 0.01)	0.25 (< 0.0001)
Na (mEq/L)	330	140 (138/142)	0.28 (< 0.0001)	-0.31 (< 0.0001)	-0.31 (< 0.0001)	0.19 (< 0.001)
Cl (mEq/L)	330	104 (101/106)	0.26 (< 0.0001)	-0.34 (< 0.0001)	-0.31 (< 0.0001)	0.06 (> 0.05)
P (mg/dL)	330	3.3 (3.1/3.8)	-0.27 (< 0.0001)	0.26 (< 0.0001)	0.30 (< 0.0001)	-0.24 (< 0.0001)
HbA_{1C} (%)	330	6.2 (5.7/6.8)	-0.13 (< 0.05)	-0.02 (> 0.05)	0.04 (> 0.05)	0.03 (> 0.05)
CRP (mg/dL)	330	0.1 (0.1/0.4)	-0.14 (< 0.01)	0.16 (< 0.01)	0.20 (< 0.001)	-0.22 (< 0.0001)
BNP (pg/ml)	330	66.9 (28.0/213)	-0.51 (< 0.0001)	1 (< 0.0001)	0.77 (< 0.0001)	-0.30 (< 0.0001)
Log BNP	330	1.83 (1.45/2.33)	-0.60 (< 0.0001)	0.77 (< 0.0001)	1 (< 0.0001)	-0.39 (< 0.0001)

NOTE. Variables data are shown as median (quartiles). Listed here are variables that showed significant correlation with baseline rSO_2 by Pearson's correlation coefficient. Correlation coefficient (r) and p value are shown.

Abbreviations: BMI, body mass index; BSA, body surface area; RBC, red blood cell count; PT-INR, international normalized ratio of prothrombin time; pH, pH of arterial blood; PaO_2, partial pressure of arterial oxygen; SaO_2, arterial oxygen saturation; ALP, alkaline phosphatase; IU, international unit; ALT, alanine aminotransferase; ChE, choline esterase; T.Bil, total bilirubin; D.Bil, direct bilirubin; T.Protein, total protein; Albumin ; albumin; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; T.Chol, total cholesterol; LDL-Chol, low-density lipoprotein cholesterol; Na, sodium; Cl, chloride; P, phosphorus; HbA_{1C}, hemoglobin A_{1C}; CRP, C-reactive protein; BNP, B-type natriuretic peptide; Log BNP, log-transformed BNP.

Table 3. Results of Pearson's correlation coefficient analyses between a cardiac-function related variable and baseline rSO_2, plasma BNP concentration, or blood hemoglobin concentration

Variable	n	Median (Quartiles)	Baseline rSO_2	BNP	Log BNP	Hemoglobin
			r (p) values	r (p) values	r (p) values	r (p) values
LAD (mm/m^2)	329	22.7 (20.5/25.5)	-0.40 (< 0.0001)	0.45 (< 0.0001)	0.51 (< 0.0001)	-0.35 (< 0.0001)
LVDd (mm/m^2)	330	28.4 (26.4/31.7)	-0.41 (< 0.0001)	0.54 (< 0.0001)	0.59 (< 0.0001)	-0.30 (< 0.0001)
LVDs (mm/m^2)	330	18.5 (16.4/23.1)	-0.41 (< 0.0001)	0.59 (< 0.0001)	0.63 (< 0.0001)	-0.21 (< 0.001)
LVEDV (ml/m^2)	330	60.8 (51.9/79.5)	-0.36 (< 0.0001)	0.56 (< 0.0001)	0.60 (< 0.0001)	-0.19 (< 0.001)
LVESV (ml/m^2)	330	24.9 (17.4/40.7)	-0.38 (< 0.0001)	0.58 (< 0.0001)	0.63 (< 0.0001)	-0.13 (< 0.05)
IVCD (mm/m^2)	328	7.6 (6.5/8.7)	-0.30 (< 0.0001)	0.39 (< 0.0001)	0.40 (< 0.0001)	-0.19 (< 0.001)
LVWT (mm/m^2)	330	5.9 (5.3/6.5)	-0.33 (< 0.0001)	0.32 (< 0.0001)	0.34 (< 0.0001)	-0.25 (< 0.0001)
LVFS (%)	330	33.5 (26/38)	0.33 (< 0.0001)	-0.48 (< 0.0001)	-0.53 (< 0.0001)	0.05 (> 0.05)
LVEF (%)	330	60 (48/66)	0.33 (< 0.0001)	-0.49 (< 0.0001)	-0.58 (< 0.0001)	0.06 (> 0.05)
E (cm/s)	328	66 (54/81)	-0.27 (< 0.0001)	0.31 (< 0.0001)	0.36 (< 0.0001)	-0.24 (< 0.0001)
E/A ratio	318	0.84 (0.69/1.06)	-0.23 (< 0.0001)	0.32 (< 0.0001)	0.35 (< 0.0001)	0.001 (> 0.05)
e´ (cm/s)	327	6.4 (5.2/7.6)	0.26 (< 0.0001)	-0.34 (< 0.0001)	-0.43 (< 0.0001)	0.14 (< 0.05)
a´ (cm/s)	317	8.8 (7.4/10.1)	0.32 (< 0.0001)	-0.38 (< 0.0001)	-0.48 (< 0.0001)	0.09 (> 0.05)
s´ (cm/s)	327	6.7 (5.5/7.9)	0.33 (< 0.0001)	-0.41 (< 0.0001)	-0.53 (< 0.0001)	0.14 (< 0.05)
E/e´ ratio	327	10.7 (8.3/14.5)	-0.41 (< 0.0001)	0.54 (< 0.0001)	0.57 (< 0.0001)	-0.27 (< 0.0001)
CTR (%)	330	49 (46/53)	-0.30 (< 0.0001)	0.41 (< 0.0001)	0.51 (< 0.0001)	-0.16 (< 0.01)
MAP (mmHg)	330	78 (68/88)	0.18 (< 0.001)	-0.18 (< 0.01)	-0.20 (< 0.001)	0.14 (< 0.05)
CVP (mmHg)	330	8 (7/10)	-0.22 (< 0.0001)	0.19 (< 0.001)	0.22 (< 0.0001)	-0.08 (> 0.05)
MPAP (mmHg)	328	17 (14/20)	-0.21 (< 0.001)	0.22 (< 0.0001)	0.23 (< 0.0001)	-0.02 (> 0.05)
MPAP/MAP ratio	328	0.21 (0.18/0.26)	-0.30 (< 0.0001)	0.34 (< 0.0001)	0.36 (< 0.0001)	-0.15 (< 0.01)

NOTE. Variables data are shown as median (quartiles). Listed here are cardiac-function related variables that showed significant correlation with baseline rSO_2 by Pearson's correlation coefficient. Correlation coefficient (r) and p value are shown. See text for detailed explanations for cardiac-function-related variables.
Abbreviations: LAD, left atrial diameter; LVDd, LV diastolic diameter; LVDs, LV systolic diameter; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; IVCD, Inferior Vena Cava diameter; LVWT, LV wall thickness; LVFS, LV fractional shortening; LVEF, LV ejection fraction; E, early transmitral velocity; A, late transmitral velocity; e´. early diastolic mitral annular velocity; a´, late diastolic mitral annular velocity; s´, systolic mitral annular velocity, CTR; cardiothoracic ratio on preoperative a chest X ray; MAP, mean arterial pressure; CVP, central venous

pressure; MPAP, mean pulmonary arterial pressure; Baseline rSO_2, baseline regional cerebral oxygen saturation (%); BNP, plasma B-type natriuretic peptide concentration (pg/mL); Log BNP, log-transformed BNP; Hemoglobin, blood hemoglobin concentration (g/dL)

Table 4. Results of the multiple regression analysis for the objective variable baseline rSO_2 in 327 patients

Variable	R value	Standardized partial regression coefficient (β)	p value
	0.708		
log (BNP)		-0.287	< 0.0001
Hemoglobin (g/dL)		0.246	< 0.0001
eGFR (ml/min/1.73m²)		0.186	0.0020
SaO_2 (%)		0.131	0.0020
BSA (m²)		0.123	0.0464
ALT (IU)		-0.002	0.9718
ChE (IU)		0.012	0.8191
T.Bil (mg/dL)		0.015	0.7830
Albumin (g/dL)		0.019	0.7150
Na (mEq/L)		0.021	0.7744
Cl (mEq/L)		0.059	0.4255
P (mg/dL)		0.004	0.9786
LVDd (mm/m²)		-0.011	0.8687
LVEF (%)		0.042	0.5000
E/e´ ratio		-0.011	0.8308

NOTE: Data from 3 patients were excluded from the analysis because the E/e´ ratio was unavailable.

Abbreviations: log BNP, log-transformed B-type natriuretic peptide (BNP); eGFR, estimated glomerular filtration rate; SaO_2, arterial oxygen saturation; BSA, body surface area, ALT, alanine aminotransferase; IU, international unit; ChE, choline esterase; T.Bil, total bilirubin; Na, sodium; Cl, chloride; P, phosphorus; LVDd, left ventricular (LV) diastolic diameter, indexed to BSA; LVEF, LV ejection fraction; E/e´ ratio, ratio of early transmitral velocity (E) to early diastolic mitral annular velocity (e´)

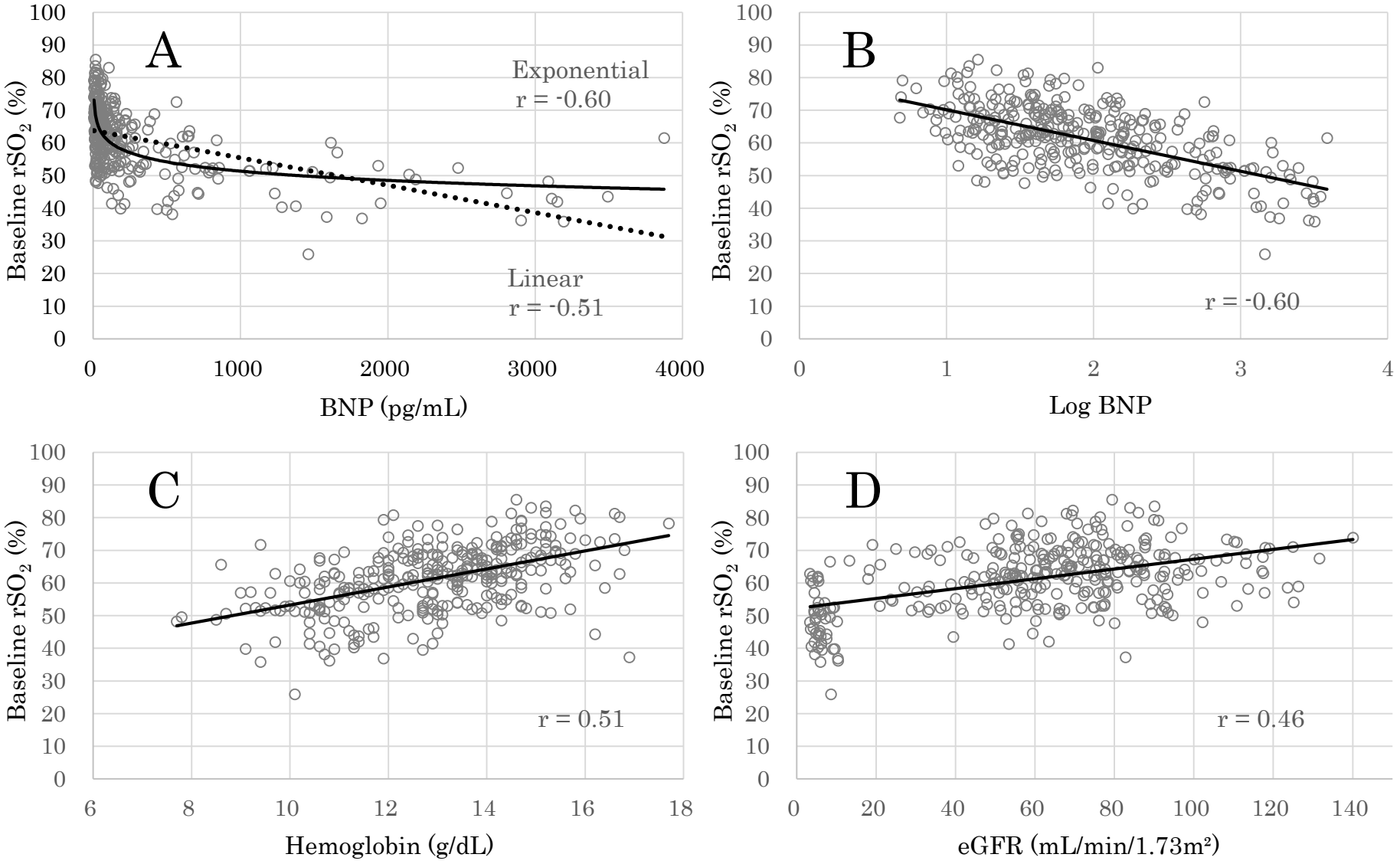
A
Exponential
r = -0.60
Linear
r = -0.51
Baseline rSO2 (%)
BNP (pg/mL)
B
r = -0.60
Log BNP
C
r = 0.51
Hemoglobin (g/dL)
D
r = 0.46
eGFR (mL/min/1.73m²)

Figure 1

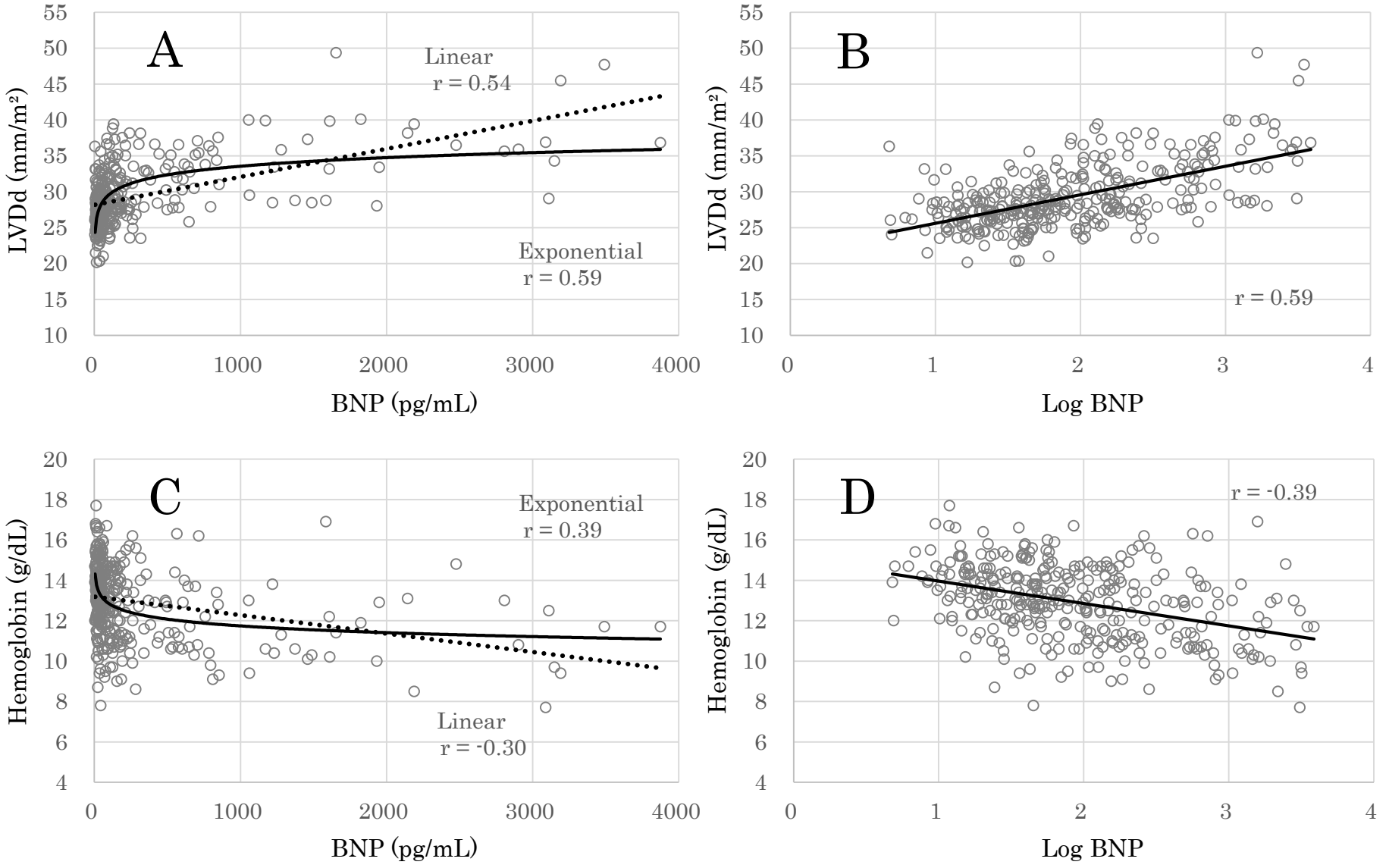
A
Linear
r = 0.54
Exponential
r = 0.59
LVDd (mm/m²)
BNP (pg/mL)
B
r = 0.59
LVDd (mm/m²)
Log BNP
C
Exponential
r = 0.39
Linear
r = -0.30
Hemoglobin (g/dL)
BNP (pg/mL)
D
r = -0.39
Hemoglobin (g/dL)
Log BNP

Figure 2

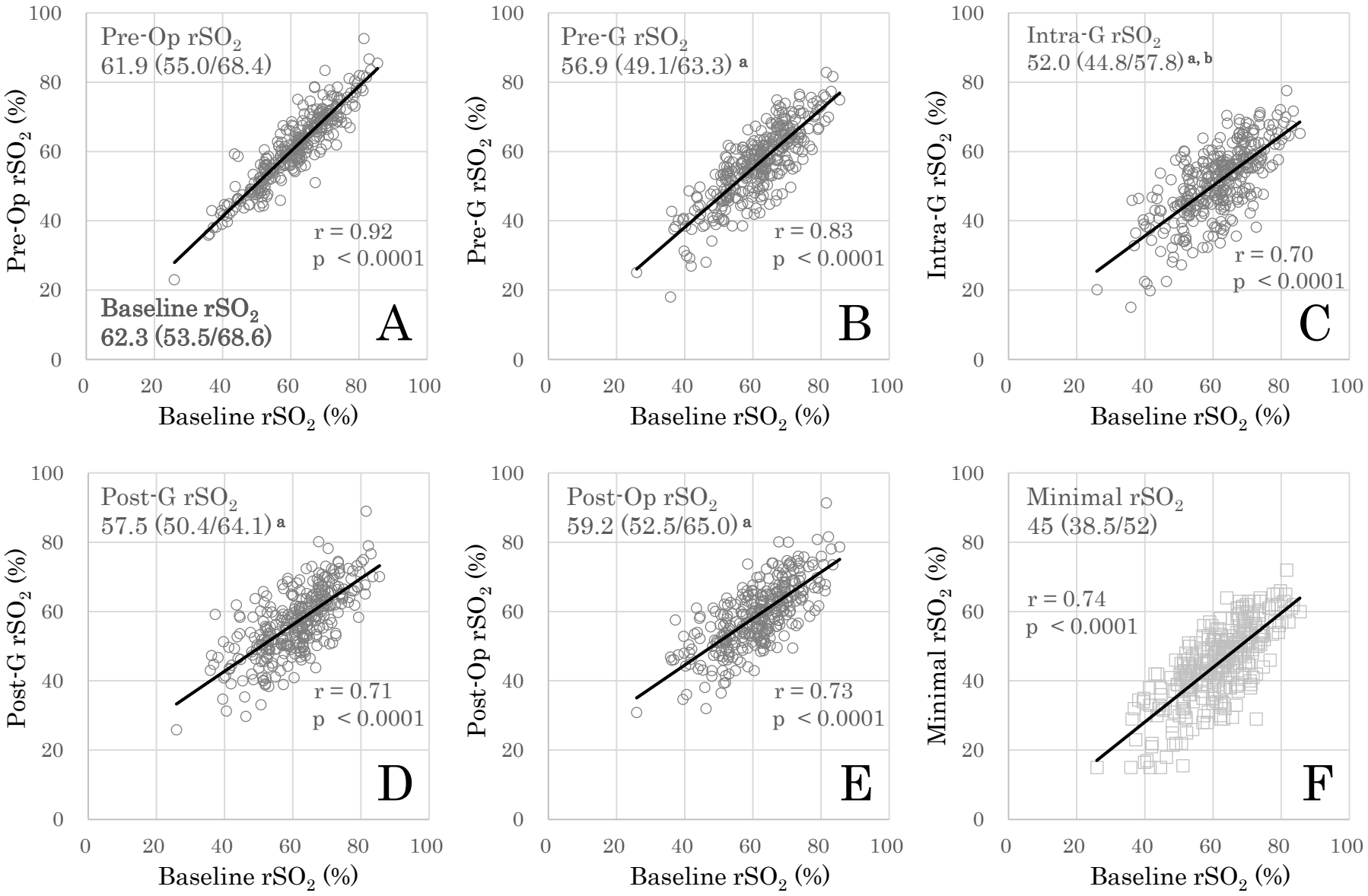
Pre-Op rSO2
61.9 (55.0/68.4)
r = 0.92
p < 0.0001
Baseline rSO2
62.3 (53.5/68.6)
A
Pre-G rSO2
56.9 (49.1/63.3) a
r = 0.83
p < 0.0001
B
Intra-G rSO2
52.0 (44.8/57.8) a, b
r = 0.70
p < 0.0001
C
Post-G rSO2
57.5 (50.4/64.1) a
r = 0.71
p < 0.0001
D
Post-Op rSO2
59.2 (52.5/65.0) a
r = 0.73
p < 0.0001
E
Minimal rSO2
45 (38.5/52)
r = 0.74
p < 0.0001
F
Pre-Op rSO2 (%)
Pre-G rSO2 (%)
Intra-G rSO2 (%)
Post-G rSO2 (%)
Post-Op rSO2 (%)
Minimal rSO2 (%)
Baseline rSO2 (%)
0
20
40
60
80
100

Figure 3