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Running Head: Cardiovascular Activity and Vaccine Response

Cardiovascular Activity and the Antibody Response to Vaccination

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Abstract

Objective: To examine the relationship between cardiovascular activity in response to acute psychological stress and the antibody response to vaccination.

*Method*s: Fifty-seven healthy participants were vaccinated with the trivalent influenza vaccine and meningococcal A+C polysaccharides. Antibody levels were measured at baseline and 5-weeks post-vaccination. Cardiovascular activity was measured at rest, during and following a mental arithmetic stress task in 54 participants.

Results: Participants demonstrating a four-fold increase in antibody titre to the A/Panama and B/Shangdong influenza strains and to meningococcal A showed greater blood pressure reactions toward the end of the acute stress task. In addition, there was some evidence of delayed diastolic blood pressure recovery in those who were responders to A/Panama and B/Shangdong influenza strains.

Conclusion: The present results suggest that heightened cardiovascular reactivity to stress and delayed recovery may not necessarily be detrimental to all aspects of health, and may be associated with an enhanced immune response to antigen challenge.

*Keywords***:** acute stress; cardiovascular reactivity; influenza vaccination; meningococcal A+C vaccination;

Examining the antibody response to medical vaccination is considered a useful model for studying the impact of psychological stress on *in vivo* immune function (1). The results of numerous studies now testify to an association between high levels of psychological stress, whether measured as life events exposure or perceived stress, and poorer antibody response to a range of vaccinations including hepatitis A (2), hepatitis B, (e.g. (3)); influenza (e.g. (4)), rubella (5), and pneumococcus (6).

The mechanisms by which psychological factors might affect antibody response to vaccination remain relatively unclear. However, functional relationships between the neuroendocrine system, including the autonomic nervous system, and the immune system have been demonstrated for some time (for a review see (7)). One method by which autonomic nervous system activity can be indirectly assessed is by measuring cardiovascular reactivity to acute stress (8). There is now evidence that the magnitude of cardiovascular reactivity is correlated with the extent of stress-elicited variations in both enumerative and functional immune measures (see e.g. (9)). Importantly, the magnitude of the immunological changes to acute stress are associated with antibody response to vaccination; *in vitro,* reduced T-cell proliferation to phytohaemaglutinin following an evaluative speech task was associated with lower antibody responses to the hepatitis B vaccine (10).

As far as we are aware, to date only two small studies have investigated the association between cardiovascular reactions to acute stress and antibody response to vaccination. In the first, elderly women with lower T-cell responses three months following influenza vaccination were reported to exhibit relatively large cardiac reactions to standard laboratory stress tasks (11, 12). In the second, a study of hepatitis B vaccination, participants with lower antibody titres following vaccination showed larger cardiac output and contractility reactions, but smaller increases in total peripheral resistance to mental

arithmetic stress (13). Thus, the evidence linking cardiovascular reactivity to psychological stress and vaccination response is, as yet, limited.

The present study examined the association between cardiovascular reactions to and recovery from acute laboratory stress and antibody status following a thymus-dependent influenza and a thymus-independent meningococcal A+C vaccination. The choice of these immunologically distinct vaccines allowed comparison of the association between cardiovascular reactivity and both thymus-dependent (antibody response involving T- and B-cells) and thymus-independent (antibody response without T-cell involvement) processes within the same population (for a fuller description of these processes, see (4)). This should shed light on the generality of any such association between cardiovascular reactivity and vaccination response. Given preliminary evidence from the two previous vaccination studies, it was hypothesised that those showing greater cardiovascular reactions to the acute stress task would exhibit a poorer antibody response to vaccination.

Methods

Participants

Fifty-seven students (31 males) were recruited from the University of Birmingham. None of the participants had ever received influenza, meningococcal A, or A + C vaccines, neither had they suffered influenza in the winter prior to participation or meningitis ever. They also did not have a current acute infection, chronic medical condition, immune disorder (e.g. glandular fever), or any vaccine-related allergies or side-effects. Pregnant participants or those taking prescribed medication (excluding the contraceptive pill) were excluded. The mean age of the participants was 19.8 (*SD* = 2.3) years and mean body mass index, based on reported height and weight, was 23.9 (*SD* = 3.6). In terms of ethnicity, 50 described themselves as “white”, four as “Asian”, two as “black”, and one as “other”. Ninety-five

percent of the sample reported being non-smokers. The study was approved by the appropriate Research Ethics Committees and all participants provided written informed consent.

Study Design

The study comprised three sessions. In December / January, participants attended an initial session for 45 min, during which time they provided demographic information and completed psychosocial questionnaires (data reported elsewhere, see (4)). They were then medically screened for eligibility and vaccinated. Blood samples were drawn immediately prior to vaccination, and five weeks later in order to examine the baseline and peak post-vaccination antibody levels. Antibody titres were determined to each of the three influenza vaccine components and to meningococcal A and C polysaccharides. Participants attended an individual two-hour laboratory session for acute psychological stress testing approximately one month after the five week follow-up (mean = 29 days, SD = 15.4 days).

Blood Samples, Vaccinations and Immunological Assays

Blood was collected by venepuncture from an antecubital vein in plain tubes (BD Vacutainer, Meylan Cedex). Vaccinations were the Fluarix influenza vaccine (Glaxo SmithKline; Batch No: 18705B9) and an AC Vax meningitis A+C vaccination (Glaxo SmithKline; Batch No: N357A44D) via intramuscular injections into the upper arms. The Fluarix vaccine contained three viral strains: A/New Caledonia/20/99 (H1N1)-like strain – [A/New Caledonia/20/99 (IVR-116)]; A/Moscow/10/99 (H3N2)-like strain [A/Panama/2007/99 (RESVIR-17)]; and B/Hong Kong/330/2001-like strain [B/Shangdong/7/97]. The clotted blood samples were centrifuged after one hour and serum was frozen at –20 °C until assayed. Anti-influenza antibody titres were measured by the

serology laboratory of Glaxo Smith Kline Beecham at Dresden, Germany, using a haemagglutination inhibition test as described in the World Health Organisation Manual on Animal Influenza Diagnosis and Surveillance (14). Anti-meningococcal A and anti-meningococcal C antibodies were assayed at the Public Health Laboratory Service Meningococcal Reference Unit, Withington Hospital, Manchester. Serum Neisseria meningitidis serogroup A and C polysaccharide-specific immunoglobulin G levels were determined quantitatively, in μg/ml, by a standardised enzyme-linked immunosorbent assay (ELISA). A four-fold increase from pre-vaccination baseline is considered the clinical criterion of adequate protection (4, 15-17). Accordingly, the a priori intention was to classify participants as responders and non-responders to each viral strain on the basis of whether or not they registered a four-fold or greater increase in antibody titre from baseline to follow-up.

Laboratory Stress Task

The psychological stress task was the paced auditory serial addition test which has been observed in numerous studies to reliably perturb cardiovascular function and demonstrates high test-retest reliability (18). Participants were presented with a series of single digit numbers by audiotape and required to add a number to the number presented next, saying the answer out loud. They also had to retain the last number heard in order to add it to the next one. The 8-minute task consisted of four consecutive two minute periods of 50, 65, 75 and 100 digits at presentation rates of 2.4, 2.0, 1.6, and 1.2 seconds respectively. The experimenter sat 1 m distant from and adjacent to the participants and scored their answers. The task also involved elements of competition and social evaluation. A leader board was displayed prominently and participants informed that they should attempt to beat the five scores on the board. They were awarded 1000 points at the start of

the task but lost five points for every addition they failed to compute correctly. The final points total served as the performance score. Participants were videotaped and informed that the tapes would be assessed by "independent body language experts"; no such assessment was made. They were also able to see themselves live on a television screen in front of them throughout the task and were instructed to watch the television at all times. Finally, they received a brief burst of loud, aversive noise once during the first five of every ten trials, coincident with an error where one was made and at the end of the series of five if there were no errors. This ensured standardized exposure to these aversive stimuli among participants. The mean (SD) performance score, was 252.9 (176.2).

Laboratory Session Procedure

Participants were instructed not to eat, drink, and smoke for one hour prior to arrival at the laboratory. They were also asked to refrain from drinking caffeine for two hours, and from exercise and alcohol for 12 hours before the session. Systolic and diastolic blood pressure and heart rate responses were measured using a semi-automatic oscillometric blood pressure monitor (Dinamap 1846, Critikon). A brachial blood pressure cuff was attached to the non-dominant arm and measurements were initiated manually every two minutes. On arrival, participants had the procedure explained, and the blood pressure cuff attached. They were allowed a brief practice at the mental arithmetic task. Participants were then exposed to three consecutive conditions: a 20-minute baseline rest period (rest), an 8-minute mental stress task (task), and a 30-minute recovery rest period (recovery). The last eight minutes of baseline were taken as the formal baseline for recording purposes, and a blood pressure reading was initiated every two minutes during this period, and every two minutes during the task and recovery periods. Sessions started at either 14:00 or 16:00 p.m. and lasted approximately two hours.

Data Reduction and Analysis

As indicated, systolic and diastolic blood pressure and heart rate data were available for every second minute of the laboratory session yielding 23 data points for each variable. Inspection of the raw data indicated that for heart rate and, to a lesser extent, diastolic blood pressure there was an anticipatory effect apparent in the final minute of the baseline period (minute 8). Accordingly, baseline was calculated from the average of minutes 2, 4, and 6, and minute 8 was designated as anticipation. Minutes 26, 36 and 46 were omitted from the analyses because of perturbations caused by movement during saliva sampling (data not reported here). From minute 22 onwards (during recovery), participants had returned to baseline and blood pressure and heart rate values were subsequently stable over time, i.e. there was substantial redundancy of values in the later part of recovery. Thus, these later recovery values were averaged across adjacent pairs of sampling points since fewer data points were required to depict the unchanging character of later recovery. This strategy also helped defend against the possibility that such homogeneity of values would mask any vaccine response effects during the task and earlier in recovery where temporal change was at its greatest. Cardiovascular change scores were computed by subtracting the average baseline from subsequent values, yielding 12 change score values, consisting of anticipation (minute 8), task reactivity (minutes 10, 12, 14, 16), and recovery (minutes 18 and 20, and the average of minutes 22 and 24, 28 and 30, 32 and 34, 38 and 40, and 42 and 44) for each cardiovascular variable. These change scores were analysed using repeated-measures multivariate analysis of variance (MANOVA) to compare the pattern of cardiovascular change over the 12 periods between responders and non-responders to each vaccine strain. Since attention has recently extended from cardiovascular reactions to acute stress to recovery patterns (19), it was deemed appropriate to maximize the number of data points

included in the analyses. Potential confounders (age, sex, body mass index, and task performance score) were examined for their effect on cardiovascular activity, again using MANOVA. Where a variable was significantly associated with the pattern of cardiovascular change, the original models comparing vaccine responders and non-responders were revisited adjusting for this variable, by entering it as a covariate in multivariate analyses of covariance (MANCOVA). Partial eta-squared is reported throughout as the measure of effect size. Fifty-five participants were available at five-week follow-up, and 54 attended for stress testing. Other minor variations in degrees of freedom reflect occasional missing data.

Results

Antibody Status

For all strains, participants responded with an initial increase in antibody titre from baseline at five weeks. Antibody titres for each vaccine strain are reported elsewhere (4). The number of participants with and without a four-fold increase to each of the viral strains at each follow-up is presented in Table 1. As only one participant was a non-responder to A/New Caledonia, analysis of four-fold response was not undertaken for this strain.

[Insert Table 1 about here]

Cardiovascular Activity

Consistent with previous research, the stress task perturbed cardiovascular activity. Substantial main effects of period emerged for systolic blood pressure, $F(11,40) = 17.46$, $p < .001$, $\eta^2_p = .828$, diastolic blood pressure, $F(11,41) = 27.67$, $p < .001$, $\eta^2_p = .884$, and heart rate, $F(11,40) = 12.24$, $p < .001$, $\eta^2_p = .771$. Blood pressure rose at task onset and had largely recovered and stabilised by minute 23, i.e. after 7 minutes of recovery. Heart rate

increased in anticipation of the task, was further perturbed during it, and returned to baseline following its completion.

Antibody Status and Cardiovascular Change

The pattern of anticipation, reactivity, and recovery changes to the mental stress task was compared for responders and non-responders to the A/Panama, B/Shangdong influenza vaccination strains and meningococcal polysaccharides A and C. Group × period interactions were analyzed to assess whether cardiovascular change over time (i.e. period) was associated with antibody status after immunization (i.e. group). As revealed by significant antibody status group × period interaction effects, participants who responded with a four-fold increase to the A/Panama viral strain showed a different pattern of systolic, $F(11,39) = 2.26$, $p = .03$, $\eta^2_p = .390$, and diastolic, $F(11,39) = 2.64$, $p = .01$, $\eta^2_p = .427$, change than non-responders. Inspection of Figure 1 indicates that responders exhibited greater blood pressure increases during the second half of the stress task, i.e. during the final four minutes of mental arithmetic. They also showed greater diastolic blood pressure increases during anticipation and early in recovery. Responders and non-responders to the B/Shangdong influenza strain also differed in their diastolic blood pressure profile as revealed by a significant group × period interaction effect, $F(11,39) = 2.08$, $p = .05$, $\eta^2_p = .370$. Figure 1 indicates that the responders showed greater increases in anticipation, during early (first two minutes) and later (final four minutes) parts of the mental arithmetic task, and during the early part of recovery from the task.

[Insert Figure 1 about here]

For meningococcal A, there was also a group × period interaction effect for diastolic blood pressure, $F(11,39) = 2.07$, $p = .05$, $\eta^2_p = .369$; responders showed greater increases in the last two minutes of the stress task. For the meningococcal C polysaccharide, there was a group × period interaction effect for heart rate, $F(11,34) = 2.35$, $p = .03$, $\eta^2_p = .432$; responders showed higher heart rate in anticipation of the task. These effects are displayed in Figure 2. The only significant main effect of antibody response group to emerge was for the B/Shangdong influenza strain and DBP activity, $F(1,49) = 6.03$, $p = .02$, $\eta^2_p = .110$; responders had higher aggregate DBP change.

[Insert Figure 2 about here]

Potential Confounders

MANOVA indicated that there were no significant associations between the pattern of cardiovascular change and age, body mass index, and task performance score, treated as continuous variables. However, as indicated by a significant interaction between sex and systolic blood pressure change, men showed more pronounced systolic blood pressure reactions than women to the stress task, $F(11,39) = 2.31$, $p = .03$, $\eta^2_p = .394$. Accordingly, the significant associations between antibody status and systolic blood pressure change were revisited, adjusting for sex in MANCOVA. The difference in systolic blood pressure change profile between responders and non-responders to A/Panama remained significant, $F(11,38) = 2.14$, $p = .04$, $\eta^2_p = .383$.

Discussion

The present study examined whether cardiovascular reactivity to acute stress was associated with antibody response to influenza and meningococcal A+C vaccinations. The

most consistent result to emerge from these analyses was that participants categorised as responders, i.e. those who displayed a four-fold increase in antibody titre after vaccination, exhibited significantly greater cardiovascular responses during the second half of the stress task (the final four minutes of mental arithmetic) than non-responders. This was evident for three of the four antigen strains tested: A/Panama, B/Shangdong, and meningococcal A. In two instances in each case, there were also group differences in anticipation and recovery; again it was vaccine responders who had the higher values. Thus, the most compelling and consistent differences between vaccine responders and non-responders were evident for blood pressure reactivity. It is worth noting, however, that there was some evidence of delayed recovery in diastolic blood pressure change for responders to both A/Panama and B/Shangdong. This indicates that in studies of cardiovascular change and immune response to challenge, it is important measure both reactivity to and recovery from acute stress, as both heightened reactivity and delayed recovery have been linked prospectively to health outcomes (20).

That associations between reactivity and vaccine response emerged in the same direction for both thymus-dependent (influenza) and thymus-independent (meningococcal A) antigens testifies to the broad generality of this relationship. It also may indicate something of the mechanism underlying the association. Antibody responses to thymus-independent vaccines do not require or receive T-lymphocyte help. As both types of response were related to cardiovascular reactivity in the present study, this would imply that greater cardiovascular reactivity is associated with the healthy functioning of B cells in some way rather than just T cells.

These findings were contrary to initial expectations based on the results from the two small-scale studies of cardiovascular reactivity and response to vaccination. It has been reported that individuals with lower T-cell responses, measured by the influenza-virus-

specific IL-2 production *in vitro* three months following influenza vaccination, exhibited larger pre-ejection period reactions to mental arithmetic and speech tasks (11, 12). However, the analysis was based on eight female participants with a mean age of 67 years, clearly a very different sample in terms of size and characteristics to the present one. Further, a very different outcome measure, the cellular secondary response to antigenic re-challenge *in vitro,* was used; the present study monitored the humoral antibody response *in vivo*. Accordingly, the relevance of this study to the present one is unclear.

In a study of 30 medical students who had undergone the hepatitis B vaccinations on average almost a year earlier, participants with lower antibody titres exhibited larger cardiac reactions to mental arithmetic (13). However, those with higher antibody titres also showed greater total peripheral resistance, a marker of alpha-adrenergic activation, reactions to the stress task. This latter result is consistent with the direction of the current findings for diastolic blood pressure change. Other variations in results between our present and previous study may be due to the examination of different vaccines with different administration protocols. The hepatitis B programme comprises two initial injections one month apart, plus a booster injection at six months. Since blood sampling was undertaken subsequent to this booster injection, the antibody response measured in this study would have been a purely secondary response involving exclusively memory B cells. In the present study, the vaccines utilised would have elicited a mixture of primary and secondary antibody response, dependent on prior exposure, via both memory and naïve lymphocytes. Thus, it is possible that the nature of the association between cardiovascular activity and antibody status following vaccination varies with the type of antibody response mounted. Admittedly, this is speculative and only further study using novel antigen administration will help resolve whether an individual's general sympathetic nervous system responsiveness has differing consequences for primary and secondary antibody responses (21).

The present findings are consistent with the results of experimental animal studies showing that the optimal immune response is greatly enhanced by exposure to acute stress (22). Similarly, a recent human study from our laboratory exposed participants to mental arithmetic or exercise stress immediately prior to vaccination (23). Both stress tasks induced significant heart rate increases, and women exposed to the acute stressors had higher peak antibody responses to the A/Panama influenza strain than women in a no stress control condition (23). In addition, acute stress exposure prior to vaccination was also associated with an enhanced antibody response to meningococcal A in men (24). Finally, we have also found in this sample that responders to A/Panama showed a greater cortisol response to the acute stress task (25).

The present study suffered from a number of limitations. First, it was small in terms of the power to detect statistically significant effects, although it was noticeably larger than the two previous studies of cardiovascular reactivity and the antibody response to vaccination. Further, the effect sizes were substantial according the recommended criterion for large effects: $\eta^2 > .138$ (26). Second, the sample was healthy and relatively homogeneous. Indeed, the magnitude of the antibody response to vaccination was such for one of the influenza viral strains that it precluded analysis. Future studies would benefit from examining older populations, where reduced vaccine efficacy is observed and participants would be less likely to mount a four-fold antibody response (e.g. (27)), providing greater variation and hence more power to detect associations with variables such as cardiovascular reactivity. Third, it should be conceded that with the antibody response to four vaccine strains, and with three cardiovascular variables, a substantial number of statistical comparisons were undertaken. This clearly increases the likelihood of Type I errors. However, there were five statistically significant interaction effects, four telling a

broadly similar, from 12 interaction effects tested: an outcome that far exceeded chance. Finally, it is impossible to determine causation from a cross-sectional observational study.

In conclusion, participants who showed a four-fold increase in antibody titre to both influenza and meningococcal A vaccine challenges demonstrated greater blood pressure reactivity towards the end of their exposure to acute mental stress. That this occurred for both thymus-dependent and thymus-independent vaccine strains indicates the consistency of the association. There was also some evidence of delayed diastolic blood pressure recovery in vaccine responders. As such, the present results challenge the contention that heightened cardiovascular reactivity and delayed recovery are necessarily detrimental to health since they appear to be related to an enhanced immune response to antigen challenge.

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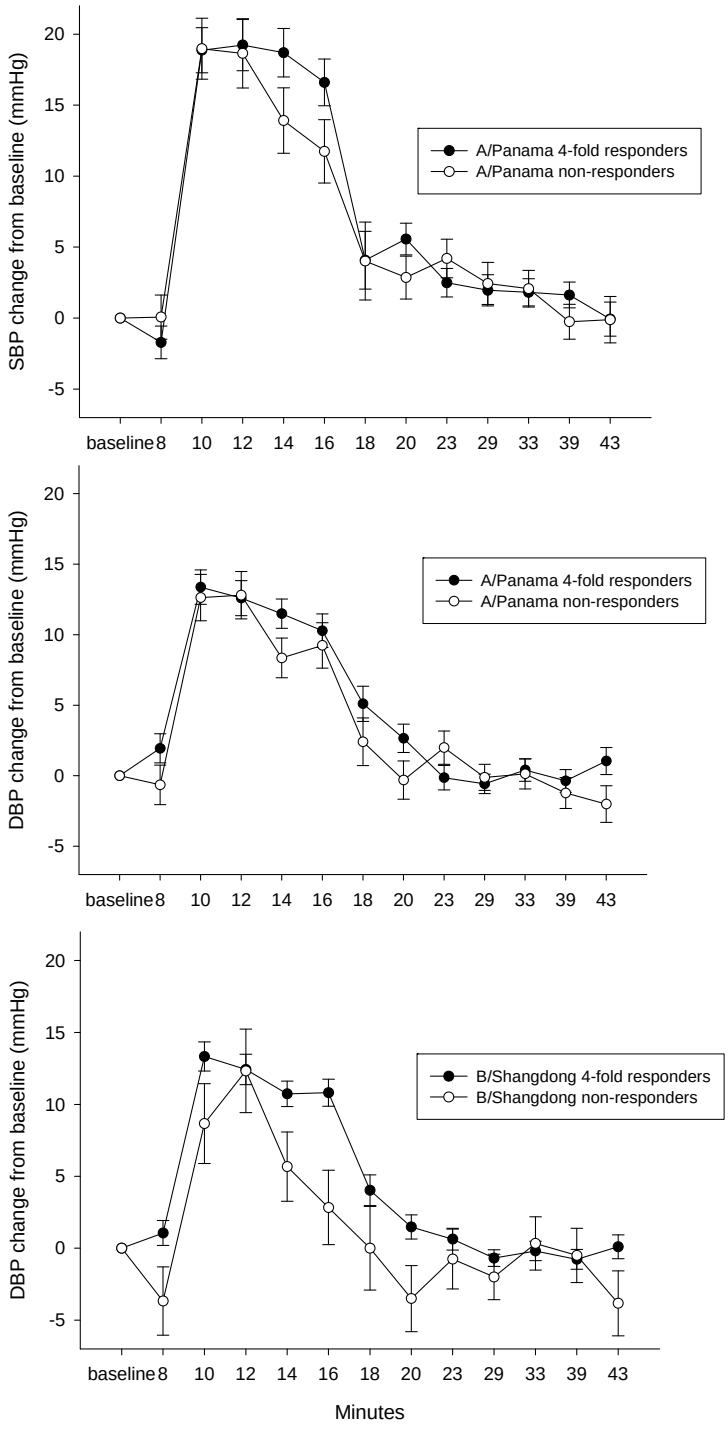
Table 1. Number (%) of participants with and without a four-fold response to each vaccine strain

Strain	Responders	Non-Responders
A/New Caledonia/20/99	54 (98%)	1
A/Panama/2007/99	36 (66%)	19
B/Shangdong/7/97	49 (89%)	6
Meningitis A	44 (80%)	11
Meningitis C	28 (58%)	20

Figure 1: Cardiovascular change by influenza A/Panama and B/Shangdong antibody status post-vaccination.

Figure 2: Cardiovascular change by meningococcal A and C antibody status Post-Vaccination.



6-min baseline

2-min anticipation

8-min task (minutes 9-16)

30-min recovery (minutes 17-46)

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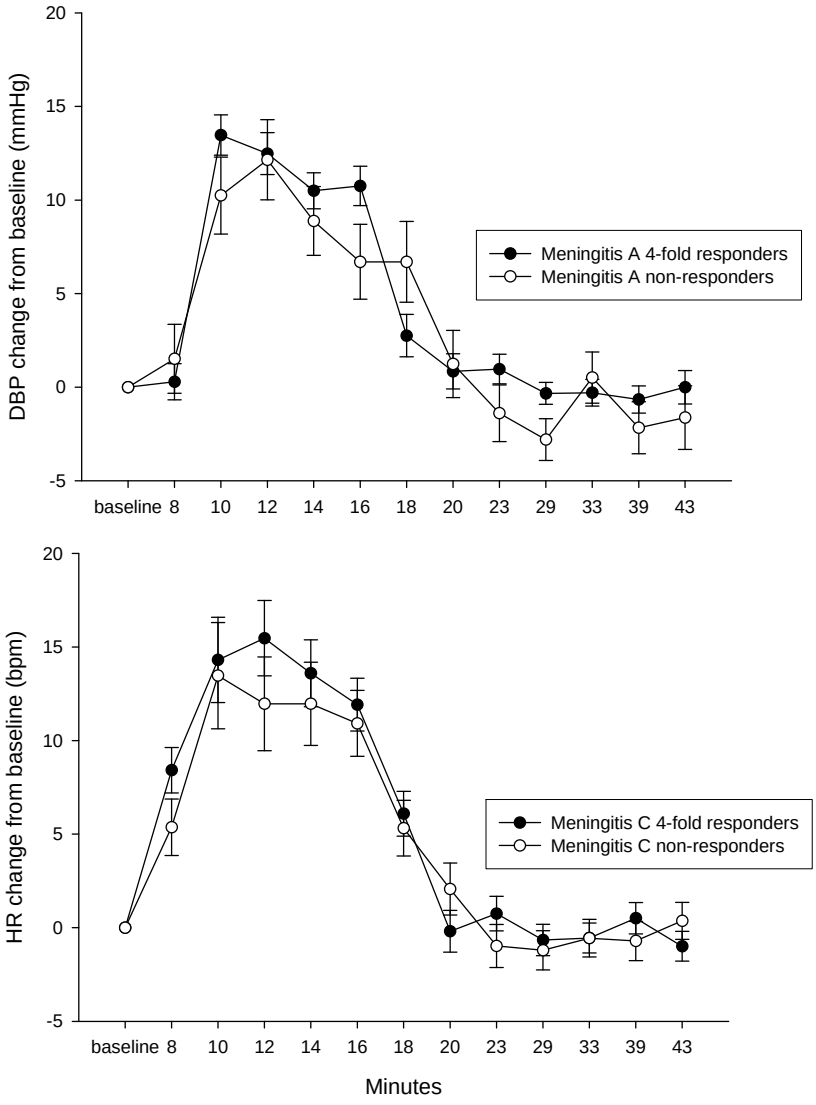

6-min baseline

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