Reservoir-Excess Pressure Parameters Independently Predicts Cardiovascular Events in Individuals with Type 2 Diabetes

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Short Title: Reservoir-excess pressure analysis in diabetes

Word Count for Manuscript: 7556 words
Word Count for Abstract: 246 words
Number of Figures: 3 figures

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ABSTRACT:

The parameters derived from reservoir-excess pressure analysis (RPA) have prognostic utility in several populations. However, evidence in type 2 diabetes (T2DM) remains scarce. We determined if these parameters were associated with T2DM, and whether they would predict cardiovascular events in individuals with T2DM. We studied 306 people with T2DM and cardiovascular disease (CVD) (DMCVD:70.4±7.8yrs), 348 people with T2DM but without CVD (DM:67.7±8.4yrs) and 178 people without T2DM or CVD (CTRL:67.2±8.9yrs). RPA-derived parameters including reservoir pressure integral (INTPR), peak reservoir pressure (MAXPR), excess pressure integral (INTXSP), systolic rate constant (SRC) and diastolic rate constant (DRC) were obtained by radial artery tonometry. INTPR was lower in DMCVD and DM than CTRL. MAXPR was lower, and INTXSP was greater in DMCVD than DM and CTRL. SRC was lower in a stepwise manner among groups (DMCVD<DM<CTRL). DRC was greater in DMCVD than CTRL. In the subgroup of individuals with T2DM (n=642), 14 deaths (6 cardiovascular and 9 non-cardiovascular causes) and 108 cardiovascular events occurred during a 3-yr follow-up period. Logistic regression analysis revealed that INTPR [odds ratio 0.59 (95%CI:0.45-0.79)] and DRC [odds ratio 1.60 (95%CI:1.25-2.06)] were independent predictors of cardiovascular events during follow-up after adjusting for conventional risk factors (both $p<0.001$). Further adjustments for potential confounders had no influence on associations. These findings demonstrate that altered RPA-derived parameters are associated with T2DM. Furthermore, baseline values of INTPR and DRC independently predict cardiovascular events in individuals with T2DM, indicating the potential clinical utility of these parameters for risk stratification in T2DM.

Key Words

aging; arterial stiffness; blood pressure; cardiovascular disease; ventricular/vascular coupling hemodynamics.

INTRODUCTION:

Improved management of cardiovascular risk factors[1] has led to a significant reduction in cardiovascular incidence in type 2 diabetes (T2DM), but cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in individuals with T2DM.[2] The prevalence of T2DM has doubled during the past 20 years and CVD in people with T2DM is likely to cause a significant burden on the health care system in the near future.[3] Therefore, an improvement in CVD risk prediction in those with T2DM is essential.

Alterations in macro- as well as microvasculature are evident in T2DM,[4, 5] and thus altered central hemodynamics could play an important role in the development of CVD in this condition. It has been suggested that central blood pressure (BP) and its morphological parameters may provide prognostic information on cardiovascular risks and subsequent cardiovascular events beyond those obtained from brachial artery BP alone.[6] Indeed, central BP is closely associated with subclinical biomarkers of cardiovascular risk such as carotid intima-media thickness (CIMT) and left ventricular mass (LVM),[6] and the reduction in CIMT and regression of LVM are more closely associated with the reductions in central pulse pressure (PP) than brachial PP.[7, 8] However, the evidence to support the proposition that central BP and its morphological parameters may provide better prognostication on future cardiovascular events has been equivocal in a hypertensive population and the general population.[9, 10] This is particularly relevant in T2DM because, although brachial PP has previously been shown to predict cardiovascular events in T2DM,[11-13] the prognostic utility of central BP and its morphological parameters is unclear in this context. Furthermore, augmentation index, a proxy for wave reflection that is commonly used as a morphological parameter of central artery, has not exhibited consistent associations with T2DM.[14, 15] These

issues may point to a need for an alternative approach that could be utilised for the refinement of CVD risk prediction in individuals with T2DM.

Reservoir-excess pressure analysis is an approach to conceptualise components of conduit artery pressure waveform. In this analysis, the measured pressure waveform can be considered to have two components: the reservoir pressure component that reflects the theoretical minimum hydraulic work required to generate a given stroke volume; and the excess pressure component provides an index of unnecessary work done by the ventricle in each cardiac cycle.[16] Both components are related to wave phenomena.[17] The prognostic utility of the parameters derived from reservoir-excess pressure analysis has been demonstrated in several different populations, including patients with hypertension,[18, 19] suspected coronary artery disease,[20] end-stage renal disease,[21, 22] heart failure[23] and in the general population.[24] However, the utility of these parameters in T2DM is limited[25, 26] and their prognostic utility in the population remains unknown.

Therefore, we aimed to determine the prognostic utility of reservoir-excess pressure parameters in T2DM. We first determined whether these parameters were associated with T2DM, and subsequently determined whether the reservoir-excess pressure parameters would independently predict cardiovascular events in this population. Conventionally obtained central and peripheral artery hemodynamic parameters were also included in these analyses alongside the reservoir-excess pressure parameters to compare the prognostic utility in individuals with T2DM.

METHODS:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participants

This is an ancillary study of the SUrrogate markers for Micro- and Macro-vascular hard endpoints for Innovative diabetes Tools-Vascular Imaging Prediction (SUMMIT-VIP) study. Participants were 832 individuals recruited for the SUMMIT-VIP study from Exeter, Dundee (both United Kingdom) and Malmö (Sweden) sites. Of those, 306 had T2DM and CVD (DMCVD: 70.4±7.8yrs, 94F), 348 had T2DM without CVD (DM: 67.7±8.4yrs, 142F) and 178 had neither T2DM nor CVD (CTRL: 67.2±8.9yrs, 83F). A detailed description of the SUMMIT-VIP study, including inclusion/exclusion criteria, has been described elsewhere,[4, 27] and summarised in the Supplemental Material. UK National Research Ethics Service South West Committee, East of Scotland Research Ethics Service and the Institutional Ethics Committee at the University of Lund approved all study procedures, and written informed consent was obtained from all participants.

Acquisition of radial pressure waveforms and derivation of conventional central artery hemodynamic parameters

Applanation tonometry of the radial artery was performed using a SphygmoCor system (AtCor Medical Pty Ltd, West Ryde, Australia). Participants lay supine on an examination bed and rested for 10 min before assessment. Right radial artery pressure waveforms were recorded over 10 seconds with a high-fidelity micromanometer (SPT-304, Millar Instrument, Houston, TX) attached to the SphygmoCor system. Waveforms were then processed through dedicated software (SphygmoCor version 8.2) to calculate an ensemble-averaged

radial pressure waveform calibrated by brachial systolic and diastolic pressures (as per the manufacturer's suggestion), and a corresponding aortic pressure waveform was derived using a previously validated generalised transfer function.[28, 29] The following central artery hemodynamic parameters were obtained for analysis in this study: central systolic and diastolic BP, central PP, central augmented pressure (AP), central augmentation index adjusted for a heart rate of 75 beats per min. Three separate waveform data were acquired for each participant and the average of these acquisitions was used as representative for statistical analysis.

A supine brachial BP was measured three times at 1-min intervals using validated semi-automated oscillometric devices (Omron M6, Hoofddorp, Netherlands). The average of the last two measurements was used as a representative brachial systolic pressure, diastolic pressure and PP.

Calculation of reservoir-excess pressure parameters

Reservoir-excess pressure parameters were calculated based on a pressure-alone approach from the ensemble averaged radial pressure waveforms without the application of a generalized transfer function. In the reservoir-excess pressure analysis,[17] the measured pressure waveform can be separated into 1) a reservoir pressure component which varies in magnitude through changes in the resistance to outflow from the reservoir, the reservoir compliance and the asymptotic pressure,[30] and 2) an excess pressure component which is the difference between the measured pressure waveform and reservoir pressure. The calculation of the reservoir pressure depends on determination of two rate constants: the systolic rate constant (SRC) which is the inverse of the product of the constant of

proportionality between the excess pressure and the arterial inflow and the total arterial compliance; and the diastolic rate constant (DRC) which is the inverse of the product of the peripheral vascular resistance and the total arterial compliance. **Figure 1** shows a schematic example of the reservoir-excess pressure separation. A review of the method including its theoretical basis and validation has been published recently.[17] The following reservoir-excess pressure parameters were obtained for analysis in this study: reservoir pressure integral (INTPR), peak reservoir pressure (MAXPR), excess pressure integral (INTXSP), SRC and DRC.

Follow-up

The participants with T2DM irrespective of the CVD status at baseline (n=654) were followed-up for a period of 3 years. Of those, 12 participants were excluded from the final analysis (n=642) due to the missing data that were used to adjust for multivariate logistic regression analysis (**Supplemental Figure S1**). Clinical events that occurred during this period were recorded as defined in the SUMMIT-VIP study.[27] These included cardiovascular mortality, myocardial infarction, unstable angina, cardiac arrest, revascularization procedures, peripheral arterial disease, cerebrovascular events (stroke and transient ischaemic attacks) and non-cardiovascular mortality.

Statistical analysis

Data are presented as means±SD, means [95% confidence intervals (CI)] or number (%). Skewed data were log-transformed for statistical analysis. A Chi-square test was used to compare categorical parameters between groups. An analysis of (co)variance (ANOVA/ANCOVA) with a Bonferroni post hoc test was used for between-group

comparisons of continuous data (after adjusting for age and sex for variables other than age and sex). Due to the unavailability of time-to composite cardiovascular event data, univariate and multivariate logistic regression analyses were used to determine associations between baseline values of reservoir-excess pressure parameters, and conventional central and peripheral artery hemodynamic parameters and incident cardiovascular events during the 3-year follow-up period in individuals with T2DM, and reported as odds ratio (OR) with 95% CI. Reservoir-excess pressure parameters, and conventional central and peripheral artery hemodynamic parameters were standardised before entering into the logistic regression analysis to allow comparisons across the parameters. Covariates were chosen *a priori* as being established risk factors for CVD and complete case analysis was performed as levels of missingness were minimal (<10%). All statistical analysis was conducted using IBM SPSS Statistics 25 (IBM, Armonk, NY) and statistical significance was set at $p<0.05$.

RESULTS:

Baseline characteristics of the study participants

Characteristics of the study participants are presented in **Table 1**.

Reservoir-excess pressure parameters, and conventional central and peripheral artery hemodynamic parameters between groups

Reservoir-excess pressure parameters stratified by group are presented in **Figure 2**. INTPR was lower in DMCVD [85.8 (83.9-87.6) mmHg·s] and DM [87.7 (86.0-89.4) mmHg·s] than CTRL [95.9 (93.5-98.3) mmHg·s]. MAXPR was lower in DMCVD [104.6 (103.0-106.2) mmHg] compared to DM and CTRL [107.9 (106.5-109.4) mmHg and 109.8 (107.7-111.8) mmHg, respectively]. INTXSP was greater in DMCVD [7.6 (7.4-7.9) mmHg·s] compared to DM and

CTRL [7.0 (6.8-7.2) mmHg·s and 6.7 (6.4-7.0) mmHg·s, respectively]. SRC was lower in a step-wise manner among the groups [DMCVD: 6.4 (6.2-6.6) 1/s, DM: 7.0 (6.8-7.3) 1/s, CTRL: 7.6 (7.3-7.9) 1/s). DRC was greater in DMCVD [2.4 (2.3-2.5) 1/s] than CTRL [2.2 (2.1-2.3) 1/s], but was similar between DMCVD and DM [2.3 (2.3-2.4) 1/s].

Conventional central and peripheral artery hemodynamic parameters stratified by group are also presented in **Table 1**. Central diastolic BP was lower and central PP was higher in DMCVD compared with DM and CTRL. DM showed a trend for lower central AP compared with DMCVD and CTRL. Brachial PP was higher in DMCVD and DM compared with CTRL. Other parameters were similar between the groups.

Incidence of cardiovascular event during the 3-year follow-up period in type 2 diabetes

In the subgroup of individuals with T2DM (n=642), 14 deaths (6 cardiovascular and 9 non-cardiovascular causes) and 108 composite cardiovascular events occurred during a 3-year follow-up period (see **Supplemental Table S1** for the breakdown of cardiovascular events that occurred). **Table 2** shows selected baseline characteristics of individuals with T2DM stratified by the incidence of cardiovascular event during the 3-year follow-up period. In those who had a cardiovascular event during the follow-up period, HbA1c level was higher and heart rate was faster than in those who had no event. In the group that had had a cardiovascular event during the follow-up period, smoking, a previous history of CVD and insulin treatment were more prevalent than in the other group. Other parameters were similar between the groups.

Reservoir-excess pressure parameters of individuals with T2DM stratified by the incidence of cardiovascular event during the 3-year follow-up period are presented in **Table 2**. At baseline, INTPR was lower, and DRC was greater in those with cardiovascular events than those without. INTXSP tended to be greater in those with cardiovascular events than in those without.

Conventional central and peripheral artery hemodynamic parameters of individuals with T2DM stratified by the incidence of cardiovascular event during the 3-year follow-up period is also presented in **Table 2**. Brachial PP was higher in those with cardiovascular events than in those without. Central PP tended to be higher in those with cardiovascular events during the follow-up period than in those without. Other parameters were similar between the groups.

Logistic regression analysis was performed to determine whether reservoir-excess pressure parameters, and central and peripheral artery hemodynamic parameters would independently predict the incidence of cardiovascular events during the 3-year follow-up period in individuals with T2DM. In a minimally adjusted (age and sex) logistic regression model (**Figure 3A**), INTPR (OR: 0.699, 95% CI: 0.545-0.897, p=0.005), INTXSP (OR: 1.238, 95% CI: 1.011-1.628, p=0.041), and DRC (OR: 1.499, 95% CI: 1.217-1.846, p<0.001) were significant independent predictors of the incidence of cardiovascular events during the follow-up period. In addition, in the same minimally adjusted logistic regression model (**Figure 3B**), central PP (OR: 1.281, 95% CI: 1.001-1.640, p=0.049) and brachial PP (OR; 1.332, 95% CI: 1.042-1.703, p=0.022) were significant independent predictors of the incidence of cardiovascular events during the follow-up period.

In a multivariate logistic regression model after adjusting for age, sex, total and HDL cholesterol, current smoking, systolic BP, pharmacological hypertensive treatment and study centre (**Figure 3C**), INTPR (OR: 0.594, 95%CI: 0.446-0.792, *p*<0.001) and DRC (OR: 1.602, 95%CI: 1.246-2.059, *p*<0.001) independently predicted the incidence of cardiovascular events during the follow-up period. In the same logistic regression model (**Figure 3D**), however, none of the conventional central and peripheral artery hemodynamic parameters independently predicted the incidence of cardiovascular events during the follow-up period. These observations remained unaltered after further adjustments for body mass index, resting heart rate, haemoglobin A1c, previous history of cardiovascular disease, estimated glomerular filtration rate, duration of T2DM and insulin treatment (**Table 3** and **Supplemental Figure S2-S4**).

When INTPR and DRC were forced into the same multivariate logistic regression model together with age, sex, total and HDL cholesterols, current smoking, systolic BP, pharmacological hypertensive treatment and study centre, odds ratio were negligibly altered, and INTPR (OR: 0.642, 95% CI: 0.464-0.888, *p*=0.007) and DRC (OR: 1.434, 95% CI: 1.101-1.870, *p*=0.008) independently predicted the incidence of cardiovascular events during the follow-up period. The strength of these associations were essentially unaltered by further adjustments for body mass index, resting heart rate, haemoglobin A1c, previous history of cardiovascular disease, estimated glomerular filtration rate, duration of T2DM and insulin treatment [INTPR (OR: 0.566, 95% CI: 0.319-1.005, *p*=0.052) and DRC (OR: 1.397, 95% CI: 1.060-1.840, *p*=0.018)], although the 95% confidence intervals of the estimates were widened slightly.

DISCUSSION:

Each of the reservoir-excess pressure parameters explored in this study demonstrate a different association with T2DM and/or CVD. Furthermore, reservoir-excess pressure parameters, namely DRC and INTPR, independently predicted the incidence of cardiovascular events during the 3-year follow-up period in individuals with T2DM. This is the first study, to the best of our knowledge, to demonstrate the potential utility of reservoir-excess pressure parameters for cardiovascular risk stratification in individuals with T2DM.

Reservoir-excess pressure parameters are associated with type 2 diabetes and cardiovascular disease at baseline

Each reservoir-excess pressure parameter studied at baseline in this study has a different association with T2DM and the presence of CVD: INTPR was lower in T2DM than in CTRL irrespective of the presence of CVD. MAXPR was lower and INTXSP was greater in DMCVD compared with DM and CTRL. Interestingly, SRC and DRC exhibited stepwise alterations among DMCVD, DM and CTRL. From these observations, the information contained in the pressure waveform of the individuals with T2DM can be explained as follows. First, the lower INTPR in T2DM compared with CTRL indicates that a buffering capacity of central arteries, especially the aorta, is attenuated in T2DM due to stiffened central arteries, and this decline in the buffering capacity will result in a smaller proportion of stroke volume stored in systole and a faster discharge of blood from the aorta in diastole (consistent with the higher DRC). The proportionate increase in INTXSP compared with MAXPR in DMCVD may be interpreted as indicating an increase in excess work by the left ventricle and may be

an index of circulatory dysfunction.[16] Indeed, the association of INTXSP with subclinical biomarkers of target organ damage[18] and the prognostic utility of INTXSP has been demonstrated in several cohorts although not previously in people with diabetes.[18, 21-23] Finally, the stepwise alterations in SRC and DRC with increasing cardiovascular risk (cf. DM vs DM and CVD) is indicative of how the rate of reservoir filling and emptying linked to central artery stiffness may influence different aspects of the ventricular-vascular interaction. These alterations in SRC and DRC provide insight into the accumulation of cardiovascular risk and may have a utility for cardiovascular risk stratification in T2DM. The potential utility of SRC for risk stratification has been demonstrated in people with hypertension[19] and the general population,[24] and an association between DRC and kidney function has been reported.[31] Taken together with our observations that DRC and INTPR independently predicted the incidence of cardiovascular events over three years in T2DM, it is likely that the parameters derived from the diastolic phase, i.e. DRC and INTPR, may be more clinically relevant parameters than those derived from the systolic phase, at least in T2DM.

Reservoir pressure integral and diastolic rate constant predict cardiovascular events in type 2 diabetes

DRC and INTPR were both predictors of cardiovascular events in T2DM during the 3-year follow-up period, independent of conventional cardiovascular risk factors, and the prognostic ability of these parameters remained unaltered even after both parameters were forced into the same multivariate logistic regression model. These observations indicate that each parameter might possess unique prognostic information on the incidence of cardiovascular events in T2DM.

Diastolic rate constant

DRC in our T2DM population was associated with >60% increased odds of future cardiovascular events. DRC measures the rate of reservoir emptying during diastole, and with reference to a simple Windkessel model, can be interpreted as the inverse of the product of peripheral vascular resistance and total arterial compliance. Accordingly, it is challenging to separate individual contributions of each parameter to explain the greater DRC observed in those who experienced cardiovascular events in this study. However, because a greater central artery stiffness (i.e. a reduced arterial compliance) is a well-known observation in T2DM,[4] it is plausible that the reduced total arterial compliance may account for the greater DRC, and the observed association between DRC and increased cardiovascular events in T2DM.

A primary role of central arteries, especially of the aorta, is to accommodate and buffer the intermittent blood flow ejected from the left ventricle by expanding its calibre during systole so that an outflow continues by recoiling during diastole.[32] This buffering function becomes less effective with central arteries stiffening, resulting in a greater DRC. Therefore, the greater DRC may indicate a deleterious influence of central artery stiffness on highly perfused organs such as the brain, heart and kidneys, by increasing the penetration of excessive pulsatile energy into the microcirculation,[33] and also by reducing the amount of perfusion during diastole. The latter may be especially harmful for the heart since the majority of coronary artery perfusion occurs in diastole, potentially leading to subendocardial ischaemia.[34]

Contrary to our null finding, SRC has been demonstrated to independently predict cardiovascular events in an elderly hypertensive population.[19] The authors suggested that lower values of central artery stiffness and aortic characteristic impedance may account for a faster rate of reservoir filling and hence the protective effect of higher SRC in the elderly hypertensives. There are some methodological differences that could explain the divergent results between the studies, for example, use of carotid vs radial pressure waveforms. Alternatively, the discrepancies between the studies might imply differences in the importance of the systolic phase of ventricular-vascular interaction in hypertension and T2DM. Although this latter suggestion should be seen as speculative, the parameters describing the time-course of reservoir pressure changes (SRC and DRC) may provide more clinical utility than the conventional pulse waveform morphological parameters, such as augmentation index which did not differ markedly between groups in our study and failed to predict future events.

Reservoir pressure integral

The reservoir pressure represents the theoretical minimum hydraulic work required to generate a given stroke volume,[16] and has a physiological foundation as corresponding to the instantaneous volume of blood stored in an artery.[35] In this study, INTPR demonstrated an association with future cardiovascular events in our T2DM cohort and, compared to DRC, the association with cardiovascular events was negative, indicating that a higher INTPR is *protective* rather than *detrimental* for the incidence of cardiovascular events. This observation seems somewhat at odds with the well-established view that high BP increases cardiovascular morbidity and mortality,[36] and a previous investigation has also demonstrated that a greater MAXPR was identified as a predictor for the incidence of

cardiovascular events in patients undergoing coronary angiography for suspected coronary artery disease.[20] Comparing our follow-up cohort at baseline (**Table 2**), INTPR was significantly smaller in those who experienced the cardiovascular events than those who did not, whereas MAXPR was similar between them. Furthermore, DRC was significantly greater in those who experienced the cardiovascular events than those who did not, whereas SRC was similar between them. Taken together with the notion that the reservoir pressure component makes a major contribution to the diastolic phase of the pressure waveform,[16] it is likely that the same mechanism responsible for the greater DRC may explain the smaller INTPR – that is, the increased central artery stiffness diminishes the buffering capacity of central arteries. It could also be plausible that the diminished buffering capacity may cause a smaller blood volume that can be stored in systole, although the effect of this will probably be marginal given the similarities in MAXPR and SRC observed between our groups. The smaller blood volume stored in central arteries in systole could in turn be discharged faster in diastole by the faster recoiling, potentially leading to a vicious cycle of diminished reservoir function and increasing cardiovascular risks in individuals with T2DM.

Conventional central and peripheral hemodynamic parameters did not predict the incidence of cardiovascular events in type 2 diabetes

In the minimally (age and sex) adjusted logistic regression model, both central and brachial PP were significantly associated with the incidence of cardiovascular events during the 3-year follow-up period. However, neither parameter was associated with the incidence of cardiovascular events after adjusting for conventional risk factors and study centre; and this was unaffected by further adjustment for other potential cofounders. Compared to these observations, earlier studies have reported that brachial PP is an independent risk predictor

for cardiovascular events in T2DM.[11-13] The reason for these divergent results is unclear, but could relate to well-controlled BP with pharmacological treatment in our T2DM participants. Nevertheless, given the prognostic utility of reservoir-excess pressure parameters along with the lack of prognostic utility with conventional central and peripheral hemodynamic parameters demonstrated in this study, these observations clearly suggest that the conventionally obtained central and peripheral artery hemodynamic parameters may not be capable of capturing clinical information from the pressure waveform sufficient to provide prognostic utility in T2DM. The lack of prognostic utility of conventional parameters analysed in this study could arise from the fact that they are derived either from extreme points on the pressure waveform (e.g. systolic and diastolic BP) or from derivatives calculated from specific points on the waveform (e.g. PP and AIx), rather than extracting information from the waveform morphology as a whole (e.g. DRC and INTPR). Conversely, the waveform analysis, such as reservoir-excess pressure analysis, could be useful in people with T2DM, even in those whose BP is well-controlled, as it may identify more subtle hemodynamic abnormalities.

Limitations

Data on left ventricular function by echocardiography are not available in this study. Because the systolic phase of ventricular-vascular interaction and hence INTXSP and SRC may be dependent on myocardial contractility and stroke volume, our findings should be interpreted in this context. Additionally, the data on peripheral vascular resistance are not available. However, the majority of our follow-up T2DM participants were taking vasodilating antihypertensive medications, and accordingly the inter-participant variability on vasomotor tone might have been limited. Therefore, the relative dependence of DRC is

shifted further toward central artery stiffness in our cohort and thus we think that our interpretation of the results is plausible. Lack of time to event data for the composite cardiovascular outcome meant that the evaluation of prognostic significance had to be performed by logistic regression analysis rather than survival analysis; however, given the low proportion of events, the loss of efficiency due to the use of logistic regression would be expected to have been very small.[37] Finally, all participants who were followed-up over three years were older people with T2DM. Therefore, the findings may not be applicable to other populations.

Perspectives

We demonstrate that each reservoir-excess pressure parameter has a different association with T2DM and/or CVD. Furthermore, we present evidence that reservoir-excess pressure parameters independently predict the incidence of cardiovascular events during the 3-year follow-up period in individuals with T2DM. Conversely, conventional central and peripheral artery hemodynamic parameters did not demonstrate the prognostic utility in the same cohort. These results support the concept that the conduit artery pressure waveform contains clinically meaningful information for cardiovascular risk stratification, and also suggest that reservoir-excess pressure analysis may provide an additional tool for cardiovascular risk stratification in individuals with T2DM, over and above conventional interpretation of pressure waveform.

ACKNOWLEDGEMENT:

a. Acknowledgements: The authors would like to thank all the participants who participated in the study.

b. Sources of Funding: This study was supported by the European Union's Seventh Framework Programme (FP7/2007-2013) for the Innovative Medicine Initiative under grant agreement number IMI/115006 (the SUMMIT consortium) and in part by the National Institute of Health Research (NIHR) Exeter Clinical Research Facility. The views expressed are those of the authors and not necessarily those of the UK National Health Service, the NIHR or the UK Department of Health and Social Care. ADH receives support from the British Heart Foundation, the Economic and Social Research Council (ESRC), the Horizon 2020 Framework Programme of the European Union, the National Institute on Aging, the National Institute for Health Research University College London Hospitals Biomedical Research Centre, the UK Medical Research Council and works in a unit that receives support from the UK Medical Research Council.

c. Disclosure: No potential conflicts of interest relevant to this article were reported.

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NOVELTY AND SIGNIFICANCE:

What Is New?

- The parameters derived from reservoir-excess pressure analysis, namely reservoir pressure integral and diastolic rate constant, independently predict the incidence of cardiovascular events in people with type 2 diabetes (T2DM), whereas conventional central and peripheral hemodynamic parameters do not in the same cohort.
- Additionally, each reservoir-excess pressure parameter has a different association with the presence of T2DM and/or cardiovascular disease.

What Is Relevant?

- The prognostic utility of conventional central blood pressure and its morphological parameters is unclear in people with T2DM.
- Reservoir-excess pressure analysis may provide useful information on cardiovascular risk stratification in people with T2DM that is not available from the conventional interpretation of blood pressure waveform.

Summary

- Reservoir-excess pressure parameters indicate disturbed cardiovascular function and independently predict cardiovascular events in T2DM.

FIGURE LEGENDS:

Figure 1. A schematic representation of reservoir-excess pressure separation in the radial artery. INTPR, reservoir pressure integral; MAXPR, peak reservoir pressure; INTXSP, excess pressure integral; SRC, systolic rate constant; DRC, diastolic rate constant. Adapted from Davies et al.[18]

Figure 2. Comparisons of reservoir-excess pressure parameters among the groups at baseline. The data are shown as medians (95% confidence intervals). DMCVD, type 2 diabetes with cardiovascular disease group; DM, type 2 diabetes group; CTRL, control group; INTPR, reservoir pressure integral; MAXPR, peak reservoir pressure; INTXSP, excess pressure integral; SRC, systolic rate constant; DRC, diastolic rate constant.

Figure 3. Logistic regression analysis of reservoir-excess pressure parameters, and conventional central and peripheral artery hemodynamic parameters for predicting cardiovascular events in individuals with type 2 diabetes. **A**: Results of a minimally adjusted (age and sex) logistic regression analysis of reservoir-excess pressure parameters. **B**: Results of a minimally adjusted (age and sex) logistic regression analysis of conventional central and peripheral artery hemodynamic parameters. **C**: Results of multivariate logistic regression analysis of reservoir-excess pressure parameters. **D**: Results of multivariate logistic regression analysis of conventional central and peripheral artery hemodynamic parameters. In **C** and **D**, age, sex, total and HDL cholesterol, current smoking, systolic blood pressure, pharmacological hypertensive treatment at baseline, and study centre were included in the model in addition to each reservoir-excess pressure parameter, and conventional central and peripheral artery hemodynamic parameters. INTPR, reservoir pressure integral; MAXPR, peak reservoir pressure; INTXSP, excess pressure integral; SRC, systolic rate constant; DRC, diastolic rate constant; CSBP, central systolic blood pressure; CDBP, central diastolic blood pressure; CPP, central pulse pressure; CAP, central augmented pressure; CAIx@HR75,

central augmentation index adjusted for heart rate 75 beat per min; BSBP, brachial systolic blood pressure; BPP, brachial pulse pressure.

Table 1. Selected baseline characteristics, reservoir-excess pressure parameters, and conventional central and peripheral artery hemodynamic parameters of the study participants stratified by group.

Parameter	1. Type 2 DM with CVD	2. Type 2 DM	3. Control	*p*	*p* (1 v 2)	*p* (1 v 3)	*p* (2 v 3)
Participants' characteristics							
Age, yrs	70.4±7.8	67.7±8.4	67.2±8.9	<0.001	<0.001	<0.001	0.999
Female, n (%)	94 (30.7)	142 (40.8)	83 (46.6)	0.001	-	-	-
BMI, kg/m^2	30.7 (30.2-31.2)	30.6 (30.1-31.1)	26.3 (25.6-27.0)	<0.001	0.999	<0.001	<0.001
Total CHOL, mmol/l	3.9 (3.8-4.0)	4.2 (4.1-4.3)	5.3 (5.2-5.4)	<0.001	<0.001	<0.001	<0.001
LDL CHOL, mmol/l	2.0 (1.9-2.1)	2.2 (2.1-2.3)	3.2 (3.1-3.3)	<0.001	0.001	<0.001	<0.001
HDL CHOL, mmol/l	1.2 (1.1-1.2)	1.3 (1.3-1.4)	1.6 (1.6-1.7)	<0.001	<0.001	<0.001	<0.001
Triglycerides, mmol/l	1.6 (1.5-1.6)	1.4 (1.3-1.5)	1.2 (1.1-1.3)	<0.001	0.016	<0.001	0.002
Fasting glucose, mmol/l	8.2 (7.9-8.5)	7.8 (7.5-8.1)	5.3 (5.1-5.6)	<0.001	0.221	<0.001	<0.001
HbA1c, mmol/mol	58.1 (56.6-60.0)	54.6 (53.3-55.9)	38.7 (37.4-40.0)	<0.001	0.002	<0.001	<0.001
Creatinine, µmol/l	87.3 (85.0-89.6)	79.3 (77.5-81.3)	79.2 (76.6-81.9)	<0.001	<0.001	<0.001	0.999
Brachial systolic BP, mmHg	134.9 (133.0-136.8)	135.8 (134.0-137.6)	133.2 (130.7-	0.262	-	-	-
Brachial diastolic BP, mmHg	73.0 (72.0-73.9)	76.0 (75.1-76.9)	76.5 (75.2-77.8)	<0.001	<0.001	<0.001	0.999
Heart rate, bpm	61.8 (60.7-62.9)	63.1 (62.1-64.2)	57.9 (56.4-59.3)	<0.001	0.273	<0.001	<0.001
eGFR, ml/min/1.73m^2	75.6 (73.4-77.9)	82.6 (80.6-84.6)	82.3 (79.5-85.1)	<0.001	<0.001	0.001	0.999
Current smoker, n (%)	31 (10.1)	28 (8.1)	15 (8.4)	0.627	-	-	-
HT-Rx, n (%)	283 (92.5)	241 (69.3)	55 (30.9)	<0.001	-	-	-
Statin, n (%)	267 (87.3)	238 (68.4)	38 (21.3)	<0.001	-	-	-

Glitazone, n (%)	**18 (5.9)**	**19 (5.5)**	**-**	**0.804**	**-**	**-**	**-**
Metformin, n (%)	**196 (64.1)**	**253 (72.7)**	**-**	**0.024**	**-**	**-**	**-**
Sulfonylureas, n (%)	**84 (27.5)**	**97 (27.9)**	**-**	**0.950**	**-**	**-**	**-**
DPP-4 inhibitors, n (%)	**22 (7.2)**	**29 (8.3)**	**-**	**0.614**	**-**	**-**	**-**
Insulin, n (%)	**100 (32.7)**	**63 (18.1)**	**-**	**<0.001**	**-**	**-**	**-**
Incretin analogues, n (%)	**16 (5.2)**	**19 (5.5)**	**-**	**0.907**	**-**	**-**	**-**
Conventional hemodynamic parameters							
Central systolic BP, mmHg	**125.7 (123.8-127.7)**	**126.3 (124.4-128.1)**	**126.3 (123.7-**	**0.913**	**-**	**-**	**-**
Central diastolic BP, mmHg	**74.2 (73.2-75.2)**	**77.5 (76.5-78.5)**	**78.0 (76.6-79.3)**	**<0.001**	**<0.001**	**<0.001**	**0.999**
Central PP, mmHg	**51.6 (50.1-53.0)**	**48.7 (47.4-50.1)**	**48.3 (46.4-50.2)**	**0.006**	**0.016**	**0.022**	**0.999**
Central AP, mmHg	**16.6 (15.9-17.4)**	**15.4 (14.6-16.1)**	**16.8 (15.8-17.8)**	**0.025**	**0.064**	**0.999**	**0.076**
Central AIx@HR75, %	**24.7 (23.9-25.6)**	**24.6 (23.8-25.4)**	**25.7 (24.6-26.7)**	**0.259**	**-**	**-**	**-**
Brachial PP, mmHg	**62.0 (60.6-63.5)**	**59.9 (58.5-61.3)**	**56.8 (54.8-58.7)**	**<0.001**	**0.123**	**<0.001**	**0.027**

Data are shown as means±SD, means (95% confidence intervals), or numbers (%). *p*-values shown for between-group comparisons (e.g. 1 v 2) are those that are corrected by a Bonferroni post hoc test. BMI, body mass index; CHOL, cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, haemoglobin A1c; BP, blood pressure; eGFR, estimated glomerular filtration rate; HT-Rx, pharmacological hypertensive treatment at baseline; DPP-4, Dipeptidyl peptidase-4; INTPR, reservoir pressure integral; MAXPR, peak reservoir pressure; INTXSP, excess pressure integral; SRC, systolic rate constant; DRC, diastolic rate constant; BP, blood pressure; PP, pulse pressure; AP, augmented pressure; AIx@HR75, augmentation index adjusted for heart rate 75 beat per minute.

Table 2. Selected baseline characteristics, reservoir-excess pressure parameters, and conventional central and peripheral artery hemodynamic parameters of individuals with type 2 diabetes stratified by the incidence of cardiovascular event during the 3-year follow-up period.

Parameter	No Event (n=559)	Event (n=83)	*p*
Participants' characteristics			
Age, yrs	69.0±8.2	69.2±8.4	0.898
Female, n (%)	202 (36.1)	27 (32.5)	0.522
BMI, kg/m^2	30.4±5.1	30.9±5.4	0.391
Total CHOL, mmol/l	4.1±1.0	4.0±0.9	0.625
LDL CHOL, mmol/l	2.1±0.8	2.1±0.7	0.639
HDL CHOL, mmol/l	1.3±0.4	1.2±0.4	0.256
Triglycerides, mmol/l	1.4 (1.0-2.0)	1.4 (1.0-1.9)	0.843
Fasting glucose, mmol/l	7.9 (6.6-9.4)	7.8 (6.7-9.5)	0.858
HbA1c, mmol/mol	56.0 (48.0-64.0)	57.0 (51.0-70.0)	0.039
Creatinine, µmol/l	83.0 (69.0-96.0)	81.5 (71.0-98.0)	0.838
Brachial systolic BP,	135.2±18.2	138.0±17.1	0.202
Brachial diastolic BP,	74.6±8.9	74.1±8.9	0.630
Heart rate, bpm	62.0±10.3	64.6±11.2	0.032
eGFR, ml/min/1.73m^2	79.1±21.5	79.7±21.6	0.812
History of CVD, n (%)	247 (44.2)	54 (65.1)	<0.001
Current smoker, n (%)	42 (7.5)	13 (15.7)	0.018
HT-Rx, n (%)	446 (79.8)	71 (85.5)	0.216
Statin, n (%)	429 (76.7)	67 (80.7)	0.329
Glitazone, n (%)	31 (5.6)	6 (7.2)	0.494
Metformin, n (%)	386 (69.1)	54 (65.1)	0.632
Sulfonylureas, n (%)	160 (28.6)	16 (19.3)	0.088
DPP-4 inhibitors, n (%)	47 (8.4)	3 (3.6)	0.136
Insulin, n (%)	127 (22.7)	32 (38.6)	0.001
Incretin analogues, n (%)	30 (5.4)	2 (2.4)	0.258
Reservoir-excess pressure parameters			
INTPR, mmHg·s	87.8±16.7	82.4±15.7	0.006
MAXPR, mmHg	106.6±14.4	106.2±15.2	0.847
INTXSP, mmHg·s	7.3 (5.8-9.2)	7.5 (6.4-10.0)	0.056

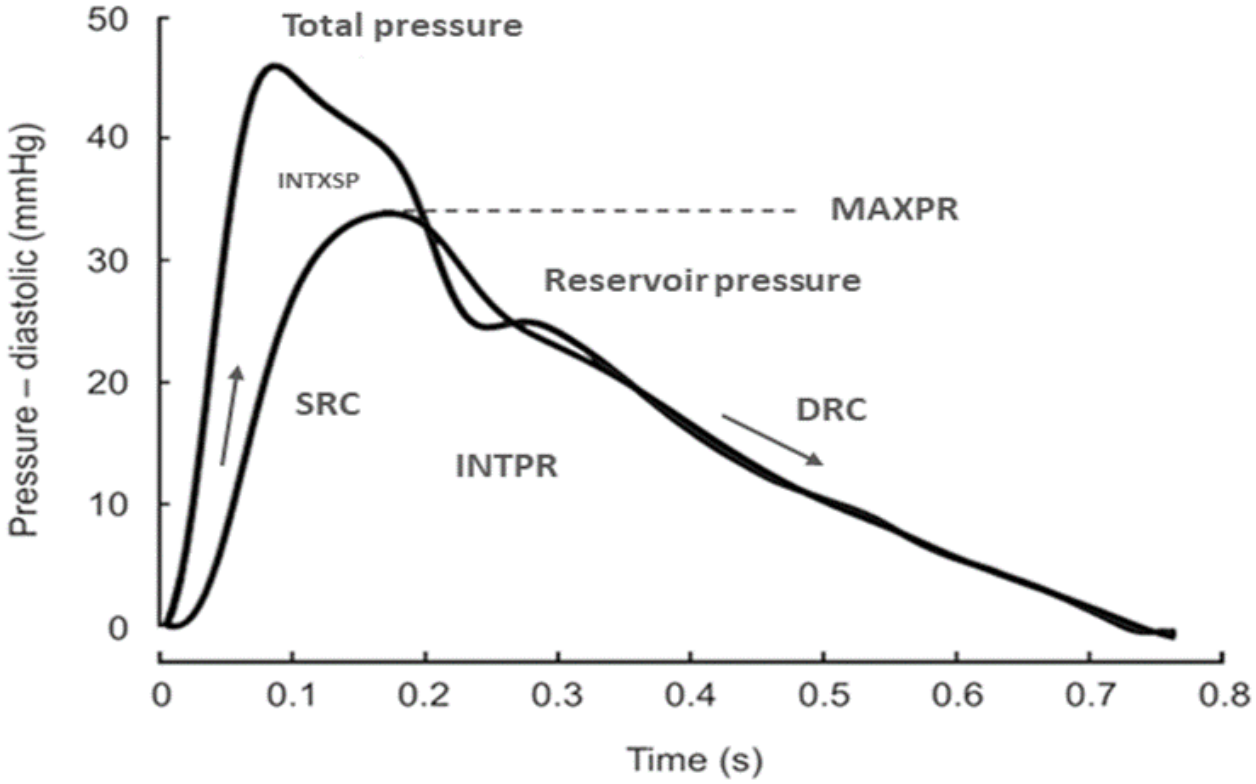
SRC, 1/s	**6.7 (5.7-7.8)**	**6.5 (5.4-7.8)**	**0.451**
DRC, 1/s	**2.4 (1.9-2.9)**	**2.7 (2.2-3.2)**	**<0.001**
Conventional hemodynamic parameters			
Central systolic BP,	**125.9±18.4**	**128.2±18.8**	**0.298**
Central diastolic BP,	**76.0±9.1**	**75.2±10.4**	**0.499**
Central PP, mmHg	**50.0±14.6**	**53.0±13.6**	**0.078**
Central AP, mmHg	**16.1±7.9**	**16.2±7.3**	**0.908**
Central AIx@HR75, %	**24.6±7.6**	**24.9±8.2**	**0.687**
Brachial systolic BP,	**135.2±18.2**	**138.0±17.1**	**0.202**
Brachial PP, mmHg	**60.7±14.8**	**64.3±14.5**	**0.042**

Data are shown as means±SD, median (interquartile range), or numbers (%). BMI, body mass index; CHOL, cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, haemoglobin A1c; BP, blood pressure; PP, pulse pressure; eGFR, estimated glomerular filtration rate; HT-Rx, pharmacological hypertensive treatment. BMI, body mass index; CHOL, cholesterol; HDL, high-density lipoprotein;HbA1c, haemoglobin A1c; BP, blood pressure; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; HT-Rx, pharmacological hypertensive treatment at baseline; DPP-4, Dipeptidyl peptidase-4; INTPR, reservoir pressure integral; MAXPR, peak reservoir pressure; INTXSP, excess pressure integral; SRC, systolic rate constant; DRC, diastolic rate constant; BP, blood pressure; PP, pulse pressure; AP, augmented pressure; AIx@HR75, augmentation index adjusted for heart rate 75 beat per minute.

Table 3. Multivariate logistic regression analysis of reservoir-excess pressure parameters, and conventional central and peripheral artery hemodynamic parameters for predicting cardiovascular events in individuals with type 2 diabetes.

Parameter	Odds Ratio	95% CI	*p*
Reservoir-excess pressure parameters			
INTPR, mmHg·s	**0.489**	**0.280-0.853**	**0.012**
MAXPR, mmHg	**0.909**	**0.586-1.410**	**0.669**
INTXSP, mmHg·s	**1.121**	**0.744-1.688**	**0.586**
SRC, 1/s	**1.164**	**0.918-1.475**	**0.210**
DRC, 1/s	**1.488**	**1.134-1.952**	**0.004**
Conventional hemodynamic parameters			
Central systolic BP, mmHg	**1.083**	**0.582-2.015**	**0.801**
Central diastolic BP, mmHg	**0.783**	**0.554-1.108**	**0.168**
Central PP, mmHg	**1.558**	**0.914-2.657**	**0.103**
Central AP, mmHg	**0.989**	**0.623-1.569**	**0.962**
Central AIx@HR75, %	**0.991**	**0.733-1.339**	**0.951**
Brachial systolic BP, mmHg	**1.268**	**0.965-1.667**	**0.089**
Brachial PP, mmHg	**1.721**	**0.931-3.180**	**0.083**

Age, sex, total and HDL cholesterols, current smoking, systolic blood pressure, pharmacological hypertensive treatment, study centre, body mass index, resting heart rate, haemoglobin A1c, previous history of cardiovascular disease, estimated glomerular filtration rate, duration of T2DM and insulin treatment at baseline were included in the model in addition to each reservoir-excess pressure parameter, and conventional central and peripheral artery hemodynamic parameters. 95% CI, 95% confidence interval; INTPR, reservoir pressure integral; MAXPR, peak reservoir pressure; INTXSP, excess pressure integral; SRC, systolic rate constant; DRC, diastolic rate constant; BP, blood pressure; PP, pulse pressure; AP, augmented pressure; AIx@HR75, augmentation index adjusted for heart rate 75 beat per min.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INTXSP
MAXPR
Reservoir pressure
SRC
DRC
INTPR
Pressure – diastolic (mmHg)
Time (s)
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20
30
40
50
0
0.1
0.2
0.3
0.4
0.5
0.6
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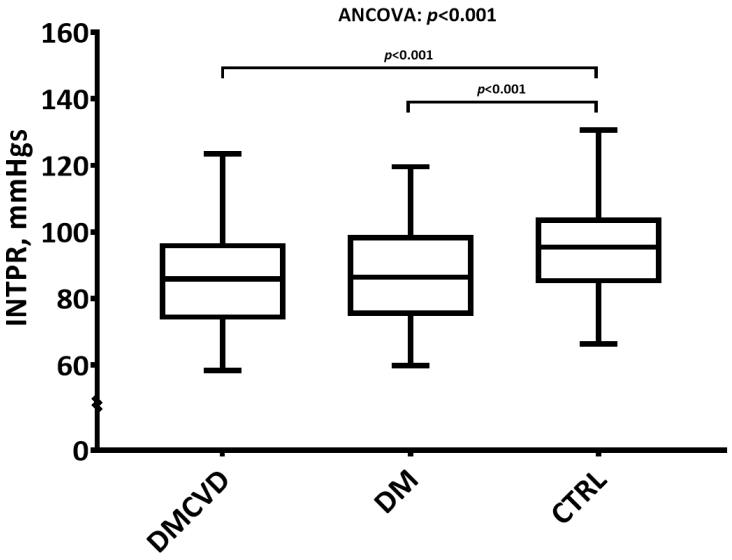
0.8


ANCOVA: p<0.001
p<0.001
p<0.001
INTPR, mmHgs
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140
120
100
80
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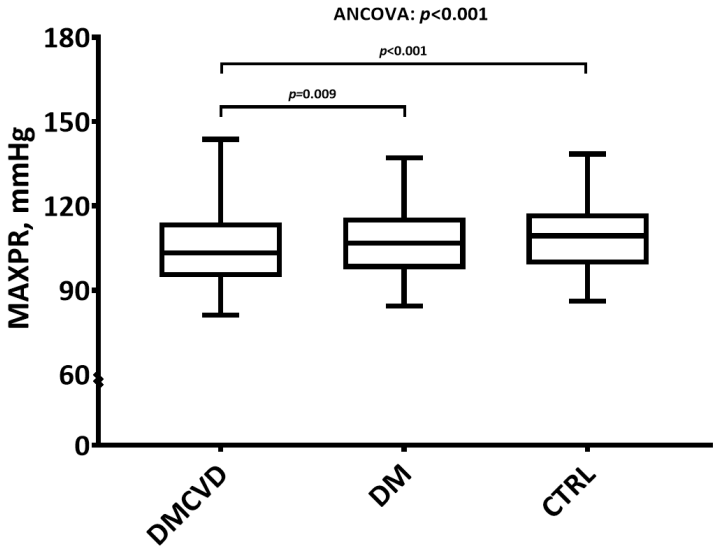
ANCOVA: p<0.001
p<0.001
p=0.009
MAXPR, mmHg
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DMCVD
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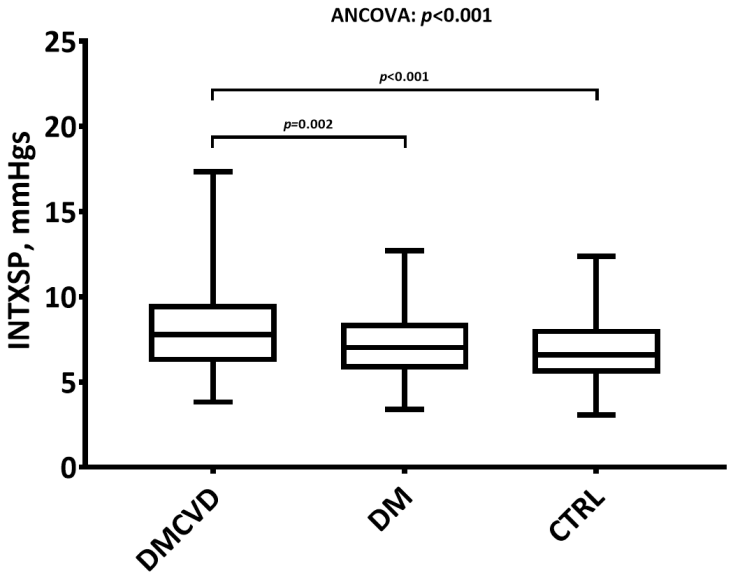
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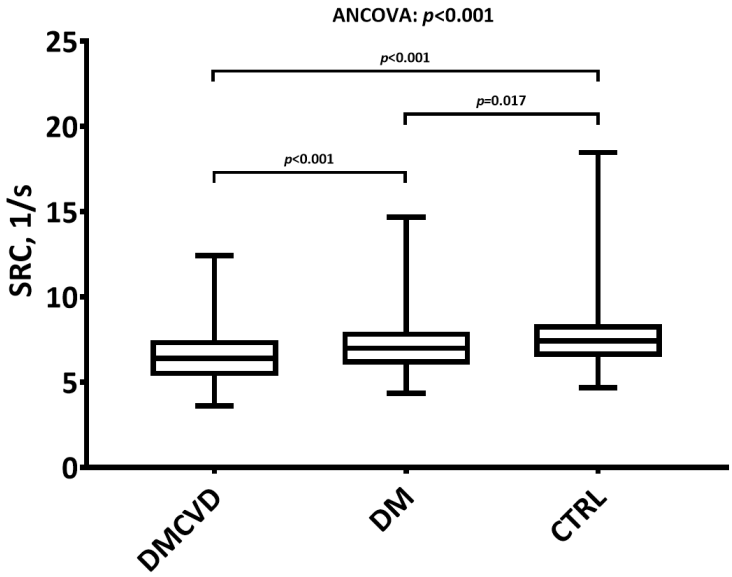
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p=0.017
p<0.001
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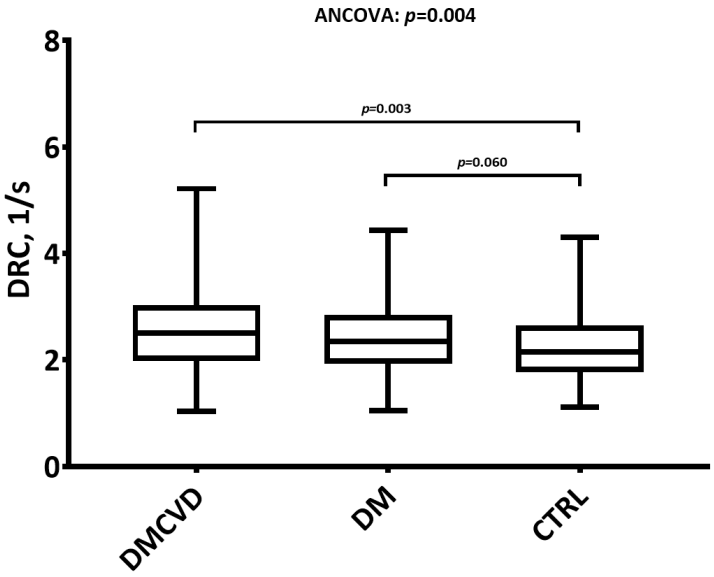
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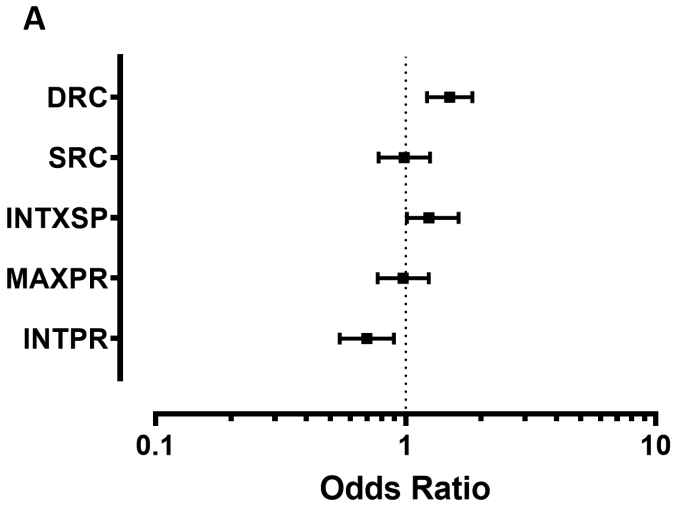
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SRC
INTXSP
MAXPR
INTPR
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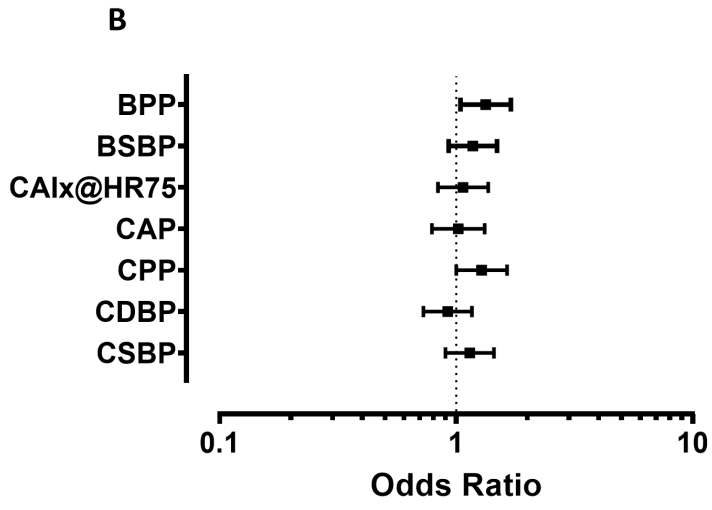
10
Odds Ratio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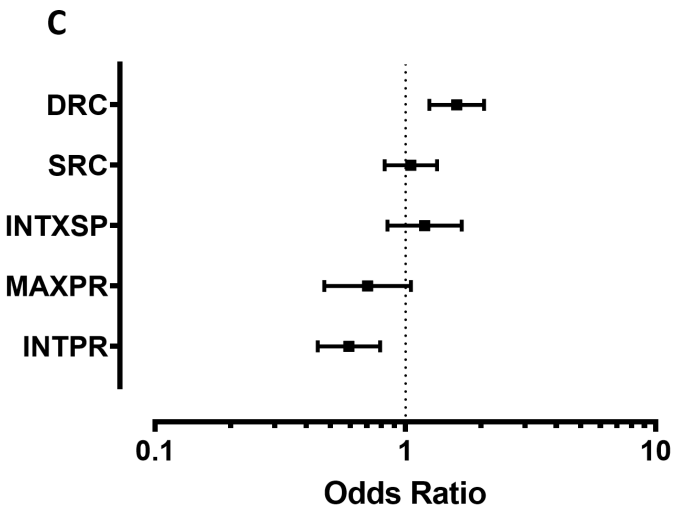
BSBP
CAIx@HR75
CAP
CPP
CDBP
CSBP
0.1
1
10
Odds Ratio


C
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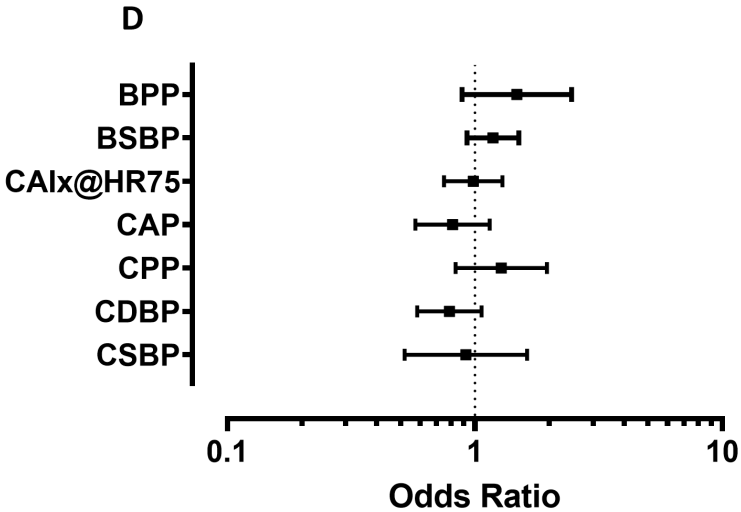
10
Odds Ratio


D
BPP
BSBP
CAIx@HR75
CAP
CPP
CDBP
CSBP
0.1
1
10
Odds Ratio