

## ABSTRACT

**Background:** Through various molecular pathway, obesity may also lead into a condition of insulin resistance which play a major role in cardiovascular diseases as it is associated with endothelial dysfunction. Insulin stimulates the signal transduction on endothelial cells by disrupting the balance of vasodilator agent (eNOS) and vasoconstrictor agent (ET-1) regulated by phosphatidylinositol 3-kinase dependent (PI3K) and mitogen-activated protein kinase (MAPK), respectively which resulted in vascular remodeling.

**Objective:** To determine the effect of obesity on vascular remodeling of rat's heart tissue by measuring the intracardiac vascular wall thickness, lumen/wall ratio, eNOS mRNA expression, and ppET-1 mRNA expression.

**Methods:** Male Sprague Dawley rats (n=24, age 3 months, weight 200 g) were divided into 4 groups: control, rats fed on high fat diet for 1 month (OB1), rats fed on high fat-diet for 2 months (OB2), and rats fed on high fat-diet for 4 months (OB4). The rats were terminated, and the hearts were harvested for histological examination and quantification of mRNA expression. Vascular wall thickness and lumen/wall ratio were measured in histological preparation with Sirius Red staining. Upon RT-PCR the mRNA expression of eNOS and ppET-1 was observed.

**Results:** Obesity-induced high fat diet stimulated higher Lee index in obesity groups compared to control group. Augmentation of Lee index is followed by upregulation of ppET-1 ( $p<0.05$ ) and downregulation of eNOS ( $p<0.05$ ) mRNA expression. Histological changes showed that during obesity, the vascular wall thickness and lumen area were higher in obesity groups compared to the control group ( $p<0.05$ ). Meanwhile the lumen/wall ratio was lower in obese groups compared to the control group ( $p<0.05$ )

**Conclusion:** Obesity resulted in vascular remodeling of rat's heart tissue due to imbalance of vasoconstrictor and vasodilation agent resulting in increase of vascular wall thickness.

**Keyword:** vascular remodeling, obesity, high fat-diet, eNOS, ET-1, heart

## INTISARI

**Latar Belakang:** Obesitas dapat memicu kondisi resistensi insulin melalui berbagai jalur molekuler yang berperan penting dalam kejadian penyakit kardiovaskular melalui mekanisme disfungsi endothel. Insulin menstimulasi transduksi sinyal pada sel endothel dengan menyebabkan ketidakseimbangan agen vasodilator (eNOS) yang diregulasi oleh *phosphatidylinositol 3-kinase* (PI3K) dan agen vasokonstriktor (ET-1) yang diregulasi oleh *mitogen-activated protein kinase* (MAPK) sehingga terjadi *vascular remodeling*.

**Tujuan:** Mengetahui *vascular remodeling* pada tikus model obesitas melalui pengukuran tebal dinding vasa, rasio luas lumen/dinding, ekspresi eNOS, dan ekspresi ppET-1

**Metode:** Tikus Sprague Dawley jantan (n= 24, usia 3 bulan, berat 200 g) dibagi menjadi 4 kelompok: kontrol, tikus dengan pakan tinggi lemak selama 1 bulan (OB1), tikus dengan pakan tinggi lemak selama 2 bulan (OB2), dan tikus dengan pakan tinggi lemak selama 4 bulan (OB4). Tikus diterminasi untuk diambil jantungnya dan diamati secara histologis dan dikuantifikasi untuk ekspresi mRNA. Tebal dinding vasa dan *lumen/wall ratio* diukur paada preparat histologis dengan pewarnaan *Sirius Red*. Ekspresi mRNA eNOS dan ppET-1 diukur melalui RT-PCR.

**Hasil:** Obesitas meningkatkan *Lee index* pada kelompok obese dibanding kelompok kontrol. Peningkatan *Lee index* diikuti dengan peningkatan ekspresi mRNA ppET-1 ( $p<0.05$ ) and penurunan ekspresi mRNA eNOS ( $p<0.05$ ). Perubahan histologis menunjukkan peningkatan tebal dinding dan luas vasa ( $p<0.05$ ) serta penurunan *lumen/wall ratio* ( $p<0.05$ ) pada kelompok obesitas dibanding dengan kelompok control.

**Kesimpulan:** Obesitas menyebabkan *vascular remodeling* pada jaringan jantung tikus karena ketidakseimbangan agen vasokonstriktor dan vasodilator yang mengakibatkan peningkatan ketebalan dinding vasa.

**Kata Kunci:** *vascular remodeling*, obesitas, diet tinggi lemak, eNOS, ET-1, jantung